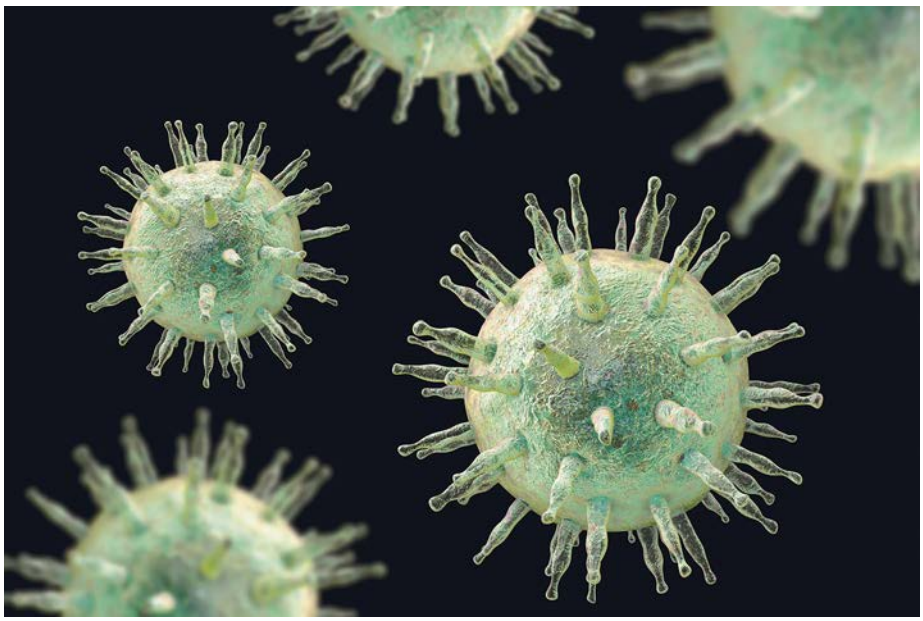
nature reviews
rheumatology

February 2026

Systemic lupus erythematosus

Mechanistic link uncovered between EBV infection and SLE



Epstein–Barr virus (EBV) has long been associated with systemic lupus erythematosus (SLE) but the mechanisms linking infection to autoimmunity have remained unclear. A new study reveals that EBV infection reprogrammes autoreactive B cells into pathogenic antigen-presenting cells that amplify systemic autoimmunity.

Using a single-cell RNA sequencing platform designed to detect EBV transcripts (EBV-seq), the researchers identified EBV-infected B cells in the blood of patients with SLE, noting that these cells were present at a higher frequency than in healthy individuals and were also transcriptionally distinct from uninfected counterparts.

The EBV-infected B cells were predominantly $CD27^{+}CD21^{low}$ memory cells and showed upregulated expression of genes involved in antigen processing and presentation, B cell activation, interferon responses and T cell activation. The EBV-infected $CD27^{+}CD21^{low}$ memory B cells were also primed to differentiate into plasmablasts, linking viral infection to the expansion of antibody-secreting cells.

Integrative analyses combining EBV-seq with ChIP–seq (chromatin immunoprecipitation followed by sequencing), ATAC-seq (assay for transposase-accessible chromatin using sequencing) and RNA polymerase II occupancy revealed that the EBV protein EBNA2 binds regulatory elements near *ZEB2*, *TBX21*, antigen-presentation genes and other genes that are upregulated in EBV-infected B cells, reprogramming EBV-infected B cells towards enhanced survival, activation and antigen-presenting cell functionality. The EBV-infected B cells also had upregulated expression of immunoregulatory molecules such as CD73, CD39 and TGFβ1, potentially enabling immune evasion and persistence.

Functionally, the EBV-infected B cells produced autoantibodies against nuclear antigens and activated T peripheral helper cells, which in turn stimulated uninfected autoreactive B cells, amplifying systemic immune responses.

Given that EBV infects more than 94% of the human population and yet only a small fraction develop SLE, these findings establish a mechanistic link between infection and disease initiation and persistence. This work also highlights EBV-infected B cells as a therapeutic target and raises the possibility that similar virus-driven reprogramming could contribute to other autoimmune conditions.

Jessica McHugh

Original article: Younis, S. et al. Epstein-Barr virus reprograms autoreactive B cells as antigen-presenting cells in systemic lupus erythematosus. *Sci. Transl. Med.* **17**, eady0210 (2025)

Related article: Robinson, W. H. et al. Epstein–Barr virus as a potentiator of autoimmune diseases. *Nat. Rev. Rheumatol.* **20**, 729–740 (2024)

Rheumatoid arthritis

ExT$_H$17 cells maintain chronic inflammation in RA

T helper 17 (T$_H$17) cells occasionally lose expression of IL-17 and convert into exT$_H$17 cells that sustain inflammation via IL-17-independent mechanisms. A study published in *Science Immunology* uses a mouse model of rheumatoid arthritis (RA) to track the fate of arthritogenic T$_H$17 cells over time and to investigate the involvement of exT$_H$17 cells in chronic disease.

"This paper was inspired by the fact that T$_H$17 cells are not found in biopsies from patients with established RA and [that] anti-IL-17 agents have limited efficacy in established RA, [despite the fact that] arthritis onset in several mouse models of RA is T$_H$17 cell dependent and [that] a T$_H$17-like signature appears in a subset of patients with pre-RA or early RA," notes Nunzio Bottini, corresponding author of the study.

Bottini and colleagues tracked the fate of arthritogenic CD4$^+$ T cells from SKG mice after their adoptive transfer into immunodeficient *Rag2*$^{-/-}$ mice and subsequent induction of inflammatory arthritis. The frequency of T$_H$17 cells in the joints and lymph nodes of recipient mice was highest at the peak of arthritic disease. In the chronic phase of inflammatory arthritis, the number of T$_H$17 cells was found to decrease, and the most prominent CD4$^+$ T cell subset was marked by previous expression of IL-17, expression of the T$_H$17-lineage transcription factor RORγt, the pro-inflammatory cytokines TNF and IL-6, and lack of IL-10 or IFNγ. Importantly, when transferred alone into new *Rag2*$^{-/-}$ recipient mice, exT$_H$17 cells induced more-severe disease than T$_H$17 cells did.

The exT$_H$17 transcriptional signature included upregulation of CD44 and the sphingosine 1P receptor S1PR4. Analyses of transcriptional profiles from human RA joint biopsies identified T cells with similar transcriptional profiles, suggesting exT$_H$17 cells as potential targets in RA.

The authors next investigated the mechanisms of exT$_H$17 cell differentiation and function. In vitro co-cultures with mouse exT$_H$17 cells and fibroblast-like synoviocytes (FLSs) indicated that FLSs promote the differentiation of exT$_H$17 cells in an S1PR4-dependent manner. Consistent with that, spatial transcriptomics using human biopsies from RA joints indicated that T cells with an exT$_H$17-like transcriptional profile were in close proximity to FLSs. "This is a classic case where local T cell behavior is determined by the microenvironment," highlights Bottini, who next plans to confirm the mechanisms that drive exT$_H$17 cell formation in patients with RA.

Lastly, TNF and IL-6 were verified as mediators of exT$_H$17 cell-driven inflammation in the SKG–*Rag2*$^{-/-}$ mouse model of RA. Strikingly, blockade of CD44 was even more efficient than IL-6 receptor inhibition in controlling disease, and CD44 expression on arthritogenic exT$_H$17 cells was required for the upregulation of TNF and IL-6. Together, these findings highlight CD44 as a potential target in exT$_H$17 cell-driven RA. "[Another] key implication for patients is that perhaps we should revisit IL-17 blockers for pre- or early RA," adds Bottini.

Maria Papatriantafyllou

Original article: Zoccheddu, M. et al. T$_H$17 cells converted into exT$_H$17 cells sustain rheumatoid-like IL-17-independent inflammatory arthritis. *Sci. Immunol.* https://doi.org/10.1126/sciimmunol.adm7800 (2025)

Personalized medicine in 2025

https://doi.org/10.1038/s41584-025-01337-3

Advances in AI-based patient stratification for rheumatic diseases

Rachel Knevel

Advances in artificial intelligence (AI) are transforming patient stratification in rheumatology. In 2025, three landmark studies demonstrated how multimodal AI approaches spanning clinical, molecular and longitudinal data can uncover distinct disease subtypes and predict therapeutic response, advancing the field towards precision rheumatology.

The past year has seen artificial intelligence (AI) move from proof of concept to practical frameworks for stratifying patients with rheumatic diseases. AI is defined as models that learn complex, often nonlinear patterns from data with limited human supervision, such as deep neural networks, transformers or large multimodal architectures. These systems perform inference or prediction beyond explicit programming. Building on decades of work in clinical clustering and molecular profiling, researchers are now integrating complex, multimodal data — from transcriptomes to electronic health records (EHRs) and longitudinal registries — to define coherent patient subgroups. Three studies published in 2025 exemplify this progress (Table 1), showcasing different types of AI methods and tasks, collectively marking a pivotal step towards precision rheumatology.

At the molecular scale, Lewis et al. leveraged synovial RNA sequencing from the STRAP precision medicine trial ($n = 208$ people with rheumatoid arthritis (RA)) to train machine learning models to predict the response to three classes of biologic drugs: etanercept, tocilizumab and rituximab[1]. The resulting algorithms showed good performance and were externally validated using the independent R4RA cohort, confirming robustness in performance.

Across treatments, those who responded to treatment showed coordinated B cell and T cell activation, whereas those who did not displayed fibroblast and matrix-remodelling gene signatures. B cell modules predicted a response to etanercept and rituximab, and myeloid and interferon modules predicted a response to tocilizumab. These signatures were distilled into a 524-gene NanoString nCounter panel for clinical patient stratification.

Within the STRAP cohort, the authors reproduced the classical Pathobiology of Early Arthritis Cohort (PEAC) pathotypes[2] — 'lympho-myeloid', 'diffuse-myeloid' and 'pauci-immune fibroid' — and linked them to the Accelerating Medicines Partnership cell-type abundance phenotype (CTAP) framework[3]. Shared cellular axes underpinned treatment-response signatures: enrichment for IL-1B$^+$ macrophages and B cell subsets predicted a response to etanercept, whereas NUPR1$^+$ and interferon-activated macrophages characterized a response tocilizumab. This bridge between bulk and single-cell frameworks shows how the PEAC and CTAP systems converge on shared cellular axes of inflammation that define molecular subtypes and therapeutic sensitivity.

At the clinical level, Maarseveen et al. applied multimodal deep learning to EHR data from 1,387 patients with early RA to identify latent patterns in joint involvement, serology and inflammation[4]. The model revealed four reproducible joint involvement patterns (JIPs) — 'foot-predominant', 'seropositive oligoarticular', 'hand-dominant' and 'polyarticular disease' — validated across several independent cohorts.

Whether patients belonged to one of the four JIPs was not explained by disease duration — the cluster with the longest duration had lower joint counts — which suggests that high-activity JIPs do not represent later disease stages. Instead, Maarseveen et al. describe distinct inflammatory configurations at presentation, defined by both activity and anatomical distribution[4].

JIPs showed distinct prognoses; the 'hand-dominant' subgroup (typically older adults who were seronegative) exhibited superior methotrexate retention and remission, whereas 'foot-predominant' and 'polyarticular disease' phenotypes had higher treatment failure rates. These associations were strongest among patients who were positive for anti-citrullinated protein antibodies. Histology from 194 biopsy-obtained synovial samples showed differences in inflammatory infiltrates and lining-layer hyperplasia: the 'seropositive oligoarticular' group showed low-grade synovitis; those with 'hand-dominant' JIPs had moderate inflammation but much higher stromal density; the 'foot-predominant' cluster displayed balanced moderate inflammation; and those with 'polyarticular disease' JIP exhibited the most severe inflammatory activity. These contrasts persisted after correction for disease activity.

A complementary commentary by Ospelt and Ciurea proposed that biomechanical load and joint-specific fibroblast programming influence the persistence of synovitis[5]. This perspective offers a plausible explanation for the poor prognosis of the 'foot-predominant' cluster, in which patients often experience treatment-resistant disease.

Key advances

- Molecular machine learning models trained on synovial RNA profiles predicted response to biologic therapies in rheumatoid arthritis (RA), enabling development of a streamlined 524-gene panel for clinical implementation[1].
- Deep learning in routine clinical data identified four reproducible RA phenotypes with distinct prognoses and histopathology, highlighting the importance of considering joint location for treatment decisions[4].
- Semi-supervised multi-organ modelling uncovered five hierarchical subtypes of systemic sclerosis, providing novel insights into patients with high-risk disease[6].

Table 1 | 2025 research on AI-based patient stratification in rheumatic diseases

Study	Study design	Patients (patient number)	Type of AI method	Primary findings
Lewis et al. (STRAP cohort)[1]	Prospective precision medicine trial with external validation using RNA-sequencing data from synovial samples	Patients with RA treated with etanercept, tocilizumab or rituximab (n = 208 for the STRAP cohort, and n = 100 for the R4RA validation cohort)	Supervised machine learning (predictive modelling and feature selection on transcriptomic data)	Machine-learning models predicted biologic therapy response (AUC 0.75–0.79). Those who responded to treatment showed B cell and T cell activation, and those who did not had fibroblast and ECM remodeling. A 524-gene NanoString panel reproduced the predictive signatures.
Maarseveen et al. (JIP framework)[4]	Multimodal deep learning analysis of EHRs	Early RA cohorts (n = 1,387 for discovery cohort, and $n \geq$ 2,000 validation cohort)	Unsupervised deep learning (representation learning and clustering)	Identified four reproducible JIPs (foot, hand, oligo and poly) with distinct prognoses and histopathology. Differences in lining hyperplasia and infiltrate persisted after correction for disease activity, defining stable clinical–histological subsets.
Trottet et al. (EUSTAR registry)[6]	Semi-supervised generative deep learning framework on longitudinal registry data	Patients with systemic sclerosis in the EUSTAR registry (n = 14,000)	Semi-supervised generative modelling (trajectory prediction across multi-organ features)	The model learned eight organ trajectories and defined five hierarchical multi-organ subtypes. The 'limited-skin but high-risk' subgroup was predictive of early lung and heart involvement (F1 = 0.77–0.83). Demonstrated robust multi-organ disease-trajectory modelling.

AI, artificial intelligence; AUC, area under the receiver operating curve; ECM, extracellular matrix; EHRs, electronic health records; EUSTAR, European Scleroderma Trials and Research; JIP, joint involvement patterns; RA, rheumatoid arthritis.

Taken together, these insights position the JIP framework as the clinical systems counterpart to molecular and cellular stratification efforts such as PEAC and Accelerating Medicines Partnership CTAP. By demonstrating that reproducible disease structure is detectable in routine EHR data, Maarseveen et al. extend precision rheumatology beyond tissue analysis[4].

Beyond RA and single-organ models, Trottet et al. applied a semi-supervised generative deep learning framework to 67,000 clinical visits from 14,000 patients in the European Scleroderma Trials and Research (EUSTAR) systemic sclerosis registry[6]. The model integrated longitudinal data across eight organ systems and expert severity scores to learn multi-organ disease trajectories.

The algorithm identified five hierarchical subtypes of systemic sclerosis spanning a mild-to-severe continuum. The 'limited-skin but high-risk' group showed elevated risk of lung and heart involvement despite minimal cutaneous disease. Other subtypes captured musculoskeletal or vascular trajectories. Modelling disease as a trajectory enabled prediction of organ involvement several visits in advance of the development of such involvement. Clinician-guided semi-supervision enhanced interpretability by aligning latent dimensions with recognizable organ systems. This work demonstrates how AI can synthesize incomplete, heterogeneous longitudinal data into coherent temporal phenotypes — an approach that parallels a trajectory-based approach using graph-based pseudotime clustering published in 2025 (ref. 7).

Although AI can reveal striking patterns, the value of this information depends on careful clinical and epidemiological interpretation. A central question in RA stratification is whether observed heterogeneity reflects fixed subsets or transient states[8]. Triaille et al. argued that correlations between molecular profiles and current disease activity favour a state-based interpretation[8]. However, the Maarseveen study shows that histological differences between RA clusters persist after adjustment for disease activity, and that clinical trajectories do not simply follow disease duration[4]. Longitudinal analyses — such as the trajectory modelling in systemic sclerosis by Trottet et al.[6], and similar trajectory work now emerging in RA[7] — provide further insight into whether differences are stable over time. Together, these findings suggest that activity-driven states alone cannot account for the diversity observed. A more coherent view is that RA heterogeneity arises from interactions between dynamic inflammatory states and more stable, anatomy or tissue-linked traits. This view reconciles the critique from Triaille et al.[8] with newer data; inflammation shapes much of the measurable variation, but it unfolds upon underlying predispositions that confer stability to specific disease patterns.

The three stratification studies highlighted here[1,4,6] collectively mark a transition from static classification to dynamic, data-driven stratification across rheumatic diseases. First, at the molecular level, transcriptomic models connect tissue biology with therapeutic response[1]. Second, at the clinical level, deep learning on routine data exposes structures that are invisible to standard scores[5]. Finally, at the systems level, generative modelling reconstructs multi-organ disease trajectories[6].

A unifying feature is the fusion of expert knowledge and AI, which enhances interpretability and provides important mechanistic context for AI discoveries. Rigorous replication[1,4] and expert-guided validation[6] reinforce confidence that these findings are biologically grounded. The next phase of disease stratification will probably adopt generative AI principles, including those seen in large language models exemplified by population-scale transformers such as DELPHI-2M, which learned long-term disease trajectories and could forecast risk decades ahead of time[9].

The advances in the three papers[1,4,6] emphasize that precision stratification depends on large, granular and diverse datasets. Future progress will rely on capturing all dimensions of rheumatic diseases, from detailed longitudinal EHRs and multi-omics tissue or blood data to imaging and, where feasible, routine biopsy-obtained synovial samples. Even at population scale, as illustrated by the DELPHI-2M model[9], the temporal sequence of diagnoses and clinical notes carries strong predictive power. For rheumatic diseases, richer data coupled with clinician-guided annotation can accelerate access to the correct therapy and inform strategies for early intervention or disease prevention.

Progress also requires inclusion of all patients. As emphasized in the 2025 *Nature Reviews Rheumatology* Editorial, "the optimal path forward is to ensure diversity in every aspect of clinical practice, so that the breakthrough of early diagnosis and equitable care can be celebrated at the journal's next notable anniversary."[10] Achieving true precision demands that data from each patient contribute to discovery. AI offers a route to this goal, as it enables stratification within heterogeneous populations rather than necessitating homogeneous cohorts, as in traditional trials. The studies highlighted here demonstrate that AI could enhance biological studies and clinical trials by defining biologically coherent, reproducible subsets of patients.

Rachel Knevel [1,2,3]

[1]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands. [2]Translational & Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK. [3]Delft Bioinformatics Lab, Delft University of Technology, Delft, the Netherlands.

e-mail: r.knevel@lumc.nl

Published online: 3 December 2025

References

1. Lewis, M. J. et al. STRAP collaborative group. Deep molecular profiling of synovial biopsies in the STRAP trial identifies signatures predictive of treatment response to biologic therapies in rheumatoid arthritis. *Nat. Commun.* **16**, 5374 (2025).
2. Lewis, M. J. et al. Molecular portraits of early rheumatoid arthritis identify clinical and treatment response phenotypes. *Cell Rep.* **28**, 2455–2470 (2019).
3. Zhang, F. et al. Deconstruction of rheumatoid arthritis synovium defines inflammatory subtypes. *Nature* **623**, 616–624 (2023).
4. Maarseveen, T. D. et al. Location and amount of joint involvement differentiates rheumatoid arthritis into different clinical subsets. *npj Digit. Med.* **8**, 623 (2025).
5. Ciurea, A. & Ospelt, C. Location-specific treatment of chronic inflammatory joint disease. *Nat. Rev. Rheumatol.* **21**, 507–508 (2025).
6. Trottet, C. et al. EUSTAR Collaborators. Deep hierarchical subtyping of multi-organ systemic sclerosis trajectories – a EUSTAR study. *npj Digit. Med.* **8**, 563 (2025).
7. Steinz, N. et al. Time-independent disease state identification defines distinct trajectories determined by localised vs systemic inflammation in patients with early rheumatoid arthritis. *Ann. Rheum. Dis.* https://doi.org/10.1016/j.ard.2025.04.011 (2025).
8. Triaille, C. et al. The relationship between clinical disease activity, synovial inflammatory profile, and treatment response in rheumatoid arthritis. *Lancet Rheumatol.* https://doi.org/10.1016/S2665-9913(25)00252-8 (2025).
9. Shmatko, A. et al. Learning the natural history of human disease with generative transformers. *Nature* **647**, 248–256 (2025).
10. The next breakthrough in rheumatology will require prioritizing diversity. *Nat. Rev. Rheumatol.* **21**, 641 (2025).

Competing interests

The author declare no competing interests.

Immunotherapies in 2025

https://doi.org/10.1038/s41584-025-01343-5

The dawn of 'off-the-shelf' B cell-depleting therapies for autoimmune diseases

Huji Xu

In 2025, a new wave of 'off-the-shelf' B cell-depleting modalities for the treatment of autoimmune diseases emerged, encompassing allogeneic cellular therapies, in vivo chimeric antigen receptor engineering, and bispecific antibodies.

By ablating pathogenic immune cells to re-establish durable homeostasis of the immune system, immune system reset offers a promising path towards durable, drug-free remission in severe, refractory autoimmune diseases. However, traditional approaches to immune system reset, such as bone marrow transplantation or autologous chimeric antigen receptor (CAR) T cell therapy, are limited by accessibility barriers and treatment-related toxicities. The year 2025 marked a pivotal shift toward 'off-the-shelf' B cell-depletion strategies, including universal allogeneic cellular products[1,2], in vivo engineering of host effector cells[3,4], and bispecific T cell engagers (TCEs)[5].

Although both CD19-directed and BCMA-directed autologous CAR T cell therapies have shown profound efficacy in the treatment of autoimmune diseases, including ulcerative colitis and systemic lupus erythematosus (SLE)[6,7], the heterogeneity in clinical responses to these therapies highlighted the need to delineate their effects on different B cell populations, which led to work suggesting that successful eradication of pathogenic clones could be achieved through combined CD19- and BCMA-targeted CAR T cell therapy[8,9] (Fig. 1a). Also, despite its potency, autologous CAR T cell therapy remains constrained by high cost and complex manufacturing logistics. The developments in B cell-depletion strategies in 2025 address these limitations of previous CAR T cell therapies.

Allogeneic cell products, which are manufactured ex vivo from cells from healthy donors or a 'master cell bank', can be produced at scale as ready-to-use, universal products, enabling timely intervention for critically ill patients. For instance, a genetically modified, hypoimmunogenic, donor-derived CD19-targeted T cell product demonstrated in vivo persistence and clinical efficacy comparable to that of autologous CAR T cells in patients with severe SLE complicated by lupus nephritis, with a desirable safety profile[1]. Beyond T cells, alternative effector cells, such as induced pluripotent stem cell-derived natural killer (NK) cells, were engineered to target both CD19 and BCMA for broad coverage of potentially pathological relevant B cell subsets (Fig. 1a). As proof of concept for this innovative approach, four consecutive infusions of induced pluripotent stem cell-derived CD19–BCMA-targeting CAR NK cells over 10 days achieved remarkable clinical efficacy in a patient with severe diffuse cutaneous systemic sclerosis, comparable to the responses seen after autologous and allogeneic CAR T cell therapy following a single infusion, with only minimal toxicities beyond lymphodepletion[2].

In vivo CAR engineering platforms have advanced rapidly, which has eliminated the need for ex vivo cell manufacturing. Targeted lipid nanoparticles, for instance, can deliver genes encoding B cell-targeting CARs directly to a patient's effector cells, enabling them to achieve depletion of B cells (Fig. 1b). Targeted lipid nanoparticles delivering anti-CD19 CAR mRNA specifically to $CD8^+$ T cells successfully generated functional CAR T cells in vivo, achieving depletion of peripheral B cells in humanized mice and cynomolgus monkeys, followed by reconstitution of naive B cells[3]. A first-in-human trial of this approach in five patients with SLE demonstrated transient in vivo CAR expression for approximately 1 day and significant B cell reduction or depletion that lasted for about 1 week[4]. All patients maintained the baseline level of glucocorticoids and hydroxychloroquine throughout the treatment and follow-up period, and a 5-mg dose of dexamethasone was given prior to each infusion of targeted lipid nanoparticles. Fever was observed in all patients, and transient cytokine-release syndrome and liver toxicity were observed in some patients[8]. Although further optimization is needed to match the safety and efficacy profile of adoptive cell transfer, these proof-of-concept studies establish a foundation for more-accessible immune system-resetting strategies.

Bispecific TCEs have also emerged as a potent 'off-the-shelf' B cell-depletion alternative. These TCEs bind simultaneously to a B cell surface marker, such as CD19 or BCMA, and the T cell co-receptor CD3, thereby directly engaging host T cells to mediate killing of B cells (Fig. 1c). Administration of the BCMA–CD3 TCE teclistamab as standard step-up dosing (three escalating doses over 5 days) followed by a one-time maintenance dose after 4 weeks induced a median B cell aplasia of 157 days among ten patients with refractory autoimmune disorders, and induced drug-free remission in six of the ten patients, with a median recorded response of 11 months (range, 8–15 months)[5]. Incidents of cytokine-zrelease syndrome, hypoglobulinemia and

Key advances

- Allogeneic induced pluripotent stem cell-derived CD19–BCMA-targeting chimeric antigen receptor (CAR) natural killer cell therapy showed safety and strong efficacy in refractory systemic sclerosis[2].
- A targeted lipid nanoparticle platform enables in vivo mRNA that generates functional CAR T cells, achieving effective tumour control and B cell depletion with immune system reset in pre-clinical models[3].
- A 1-month course of the bispecific T cell engager teclistamab successfully induced deep B cell depletion and lasting drug-free remission in six of ten patients with refractory autoimmune diseases[5].

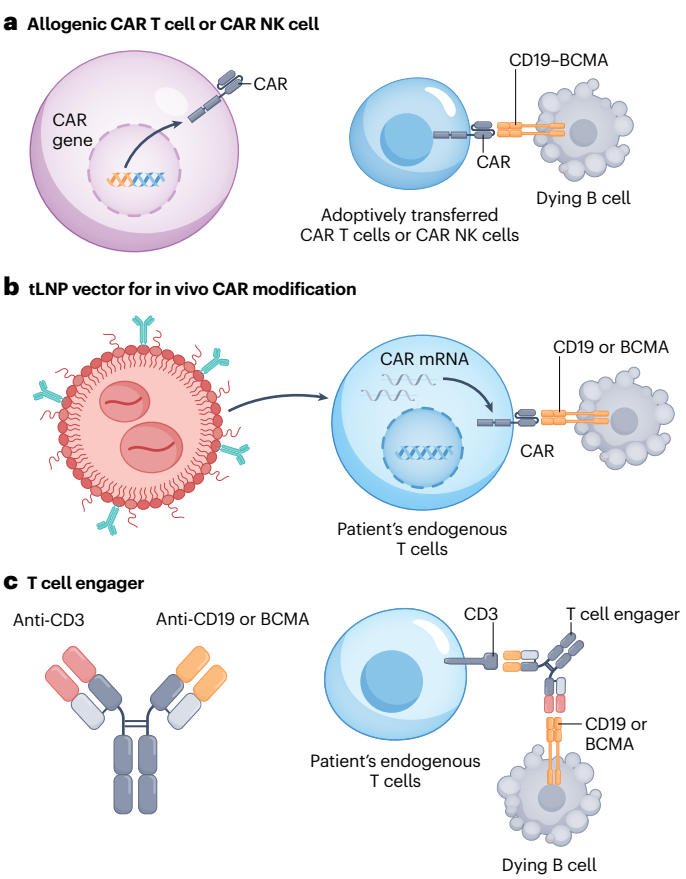


Fig. 1 | 'Off-the-shelf' B cell-deleting therapies for autoimmune diseases. **a**, Allogeneic chimeric antigen receptor (CAR) T cells or CAR natural killer (NK) cells engineered to target B cell markers (CD19 and BCMA). **b**, In vivo CAR modification to generate functional CAR T cells. tLNP, targeted lipid nanoparticle. **c**, T cell engager (TCE) activation of T cells (by targeting CD3) after recognition of a B cell surface marker (CD19 or BCMA).

infections were common but manageable. This on-demand, 'off-the-shelf' modality offers an appealing balance between potency and practicality.

In summary, 2025 solidified 'off-the-shelf' B cell depletion as a transformative therapeutic paradigm. Allogeneic cellular products and in vivo engineering platforms are addressing the manufacturing and accessibility challenges of CAR-engineered cellular products, while bispecific antibodies provide a highly practical complement. Future efforts will focus on optimizing efficacy, managing toxicity, and extending these strategies to a broader spectrum of autoimmune diseases.

Huji Xu [1,2]
[1]Department of Rheumatology and Immunology, National Key Laboratory for Immunity and Inflammation, Changzheng Hospital, Naval Medical University, Shanghai, China. [2]Peking-Tsinghua Center for Life Sciences, Tsinghua University, Beijing, China.
e-mail: xuhuji@smmu.edu.cn

Published online: 10 December 2025

References

1. Wang, X. et al. Allogeneic CD19-targeting T cells for treatment-refractory systemic lupus erythematosus: a phase 1 trial. *Nat. Med.* **31**, 3713–3724 (2025).
2. Wang, X. et al. An iPSC-derived CD19/BCMA CAR-NK therapy in a patient with systemic sclerosis. *Cell* **188**, 4225–4238 (2025).
3. Hunter, L. et al. In vivo CAR T cell generation to treat cancer and autoimmune disease. *Science* **388**, 1311–1317 (2025).
4. Wang, Q. et al. In vivo CD19 CAR T-cell therapy for refractory systemic lupus erythematosus. *N. Engl. J. Med.* **393**, 1542–1544 (2025).
5. Bucci, L. et al. BCMA T-cell engager therapy in patients with refractory autoimmune disease. *N. Engl. J. Med.* **393**, 1544–1547 (2025).
6. Müller, F. et al. CD19 CAR T-cell therapy in multidrug-resistant ulcerative colitis. *N. Engl. J. Med.* **393**, 1239–1241 (2025).
7. Hu, Z. et al. BCMA-targeted CAR T cell therapy can effectively induce disease remission in refractory lupus nephritis. *Ann. Rheum. Dis.* **84**, 1675–1683 (2025).
8. Feng, J. et al. Co-infusion of CD19-targeting and BCMA-targeting CAR-T cells for treatment-refractory systemic lupus erythematosus: a phase 1 trial. *Nat. Med.* **31**, 3725–3736 (2025).
9. Tur, C. et al. CD19-CAR T-cell therapy induces deep tissue depletion of B cells. *Ann. Rheum. Dis.* **84**, 106–114 (2025).

Competing interests

The author declares no competing interests.

Targeted therapies in 2025

https://doi.org/10.1038/s41584-025-01339-1

Advances in RNA-based nanotherapies for arthritis

Christine T. N. Pham & Farshid Guilak

Many of the current therapies for arthritis lack a targeted approach, limiting clinical benefits. Nanoparticle-based delivery systems have enabled more precise and efficient delivery of therapeutic agents, particularly nucleic acids. Studies in 2025 emphasize the promise of these strategies for the treatment of various forms of arthritis.

Arthritis encompasses autoimmune and degenerative conditions characterized by dysregulated inflammatory responses and the involvement of a variety of immune cells. Current therapies are thus focused on targeting pro-inflammatory cytokines or the underlying immune cell populations; however, these therapies have only shown partial clinical success, in part owing to challenges in achieving targeted delivery to specific cell types. The success of mRNA technology, most notable in COVID-19 vaccines, has opened new avenues for the direct modification of immune cell function in vivo[1]. Three studies published in 2025 demonstrate the potential of RNA-based nanotherapies for arthritis[2–4].

Autoimmune inflammatory arthritis includes rheumatoid arthritis (RA), psoriatic arthritis and systemic lupus erythematosus (SLE) and affects a considerable portion of the global population. These conditions are triggered by autoreactive T cells that evade immune tolerance, enabling them to attack self-tissues and indirectly assist B cells in producing autoantibodies, leading to chronic inflammation and tissue damage. Therefore, inducing immune tolerance represents a promising approach to treat autoimmune arthritis. One such strategy involves generating tolerogenic antigen-presenting cells (APCs) to reduce the activation of autoreactive T cells. Previous research has highlighted the role of tolerogenic APCs in maintaining immune tolerance by inducing T cell anergy, promoting the differentiation of regulatory T (T_{reg}) cells and eliminating autoreactive T cells[5]. Notably, the development of immunotherapeutic strategies using tolerogenic dendritic cells (DCs) has shown safety and efficacy in clinical trials for various autoimmune diseases. However, traditional methods for generating tolerogenic APCs involve the ex vivo manipulation of autologous cells, such as dendritic cells, which is costly and requires customization for each patient[6].

As an alternative approach, Liu et al.[2] present a new method for the in vivo generation of tolerogenic APCs through the delivery of mRNA that encodes PD-L1 (that is, *CD274*) within lipid nanoparticles (LNPs). In a mouse model of RA, subcutaneous administration of PD-L1-encoding LNPs induced high surface expression of PD-L1 on APCs, generating in situ tolerogenic APCs that effectively reduced activated T cell populations and promoted the expansion of T_{reg} cells. This therapy provides a method for immune modulation that could potentially be adapted for the generation of antigen-specific tolerogenic APCs. By optimizing LNP formulations, this approach serves to minimize immunogenicity, supporting the potential for improved safety and efficacy. This approach also circumvents the limitations of traditional tolerogenic APC therapies by enabling the generation of these cells without the need for ex vivo manipulation. However, the long-term durability of the induced immune tolerance and T_{reg} cell persistence remains to be evaluated. In addition, potential risks or adverse effects associated with the in vivo generation of tolerogenic APCs using mRNA technology still need to be determined.

Beyond T cells, the crucial role of B cells and plasma cells in the pathogenesis of RA and SLE is well established. Existing therapies, such as anti-CD20 and BAFF-targeting agents, have limitations in depleting long-lived plasma cells, leading to suboptimal clinical outcomes and emphasizing the need for more effective therapies that can specifically deplete these cells[7]. Emerging CD19-targeting therapies, including chimeric antigen receptor (CAR) T cell approaches, show promise in depleting autoreactive B cells, but these therapies often require previous lymphodepletion and carry risks of severe adverse effects such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome[8]. To address these challenges, investigators have begun to explore new approaches to more effectively target autoreactive B cells and plasma cells in autoimmune arthritis. This strategy builds on previous research that demonstrates the safety and efficacy of mRNA therapies, the need for targeted B cell depletion and the limitations of existing monoclonal antibody therapies in treating autoimmune arthritis.

Guo et al.[3] demonstrated that LNP-encapsulated mRNA-encoding antibodies that target CD19 can effectively induce robust and sustained production of anti-CD19 antibodies in vivo, leading to substantial

Key advances

- Subcutaneous delivery of *CD274* mRNA (encoding PD-L1) via lipid nanoparticles was used to generate tolerogenic antigen-presenting cells in vivo, which could prevent disease progression in mouse models of rheumatoid arthritis and ulcerative colitis[2].
- Lipid nanoparticle-encapsulated mRNA-encoding antibodies that targeted CD19 induced the production of anti-CD19 antibodies in vivo, and reduced disease severity in mouse models of rheumatoid arthritis and lupus[3].
- An injectable microenvironment-responsive hydrogel delivery system that encapsulated circular RNA for the NF-κB repressor srIκβα reduced disease severity and enhanced cartilage repair in a rodent model of OA[4].

depletion of $CD19^+$ B cells and $CD19^+CD138^+$ plasma cells in mouse models of lupus and RA. As CD19 is expressed on a broad range of B cells and plasma cells, targeting this marker might provide a more comprehensive approach to depleting autoreactive cells. Although the study demonstrates the efficacy of these LNPs in depleting $CD19^+$ B cells and plasma cells, it does not address the potential impact of $CD19^-$ autoreactive B cells or the long-term effects of such depletion on overall immune function. In addition, the authors use MRL/lpr lupus mice and collagen-induced arthritis models, which might not fully recapitulate the complexity of human SLE and RA, thus limiting the generalizability of the findings for humans. Nonetheless, these LNP-encapsulated mRNA-encoding antibodies that target CD19 represents a promising and relatively unexplored strategy that could be adapted for specific targets in future applications.

The application of RNA-based therapeutics has begun to extend to osteoarthritis (OA)[9], the most common form of arthritis characterized by cartilage degeneration and joint inflammation. Existing treatments primarily focus on symptom management rather than modifying the disease process and often have limited efficacy owing to rapid clearance of therapeutic agents from the joint space. The NF-κB signalling pathway has been identified as a mediator in the pathogenesis of OA that promotes inflammation and cartilage degradation. The super-repressor IκBα (srIκBα) can effectively inhibit NF-κB signalling and mitigate inflammatory responses in various contexts[10].

> "nanoparticle-based mRNA therapies might provide solutions to the unmet needs in arthritis treatment"

Li et al.[4] introduced a new approach using circular RNA encapsulated in LNPs to deliver the gene that encodes srIκBα (that is, *NFKBIA*), thereby enhancing stability and reducing immunogenicity. These LNPs were embedded in a silk fibroin composite hydrogel that is responsive to the OA joint microenvironment, and specifically targets areas of increased matrix metalloproteinase activity, which is associated with cartilage degradation. In a rodent model of papain-induced OA, this innovative delivery system showed improved drug retention and targeting of the joint, addressing the limitations of previous therapeutic strategies.

These studies contribute to the growing body of research exploring innovative therapeutic strategies that leverage the specificity and versatility of mRNA technology. Such approaches might address some of the limitations of traditional monoclonal antibody therapies and highlight the importance of developing more targeted and personalized therapies that modulate, rather than merely suppress, the immune system. Although further research is needed to assess the long-term safety and clinical applicability of these emerging treatments, nanoparticle-based mRNA therapies might provide solutions to the unmet needs in arthritis treatment.

Christine T. N. Pham [1] ✉ **& Farshid Guilak** [2,3] ✉
[1]Division of Rheumatology, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA. [2]Department of Orthopedic Surgery, Washington University School of Medicine, St. Louis, MO, USA. [3]Shriners Hospitals for Children, St. Louis, MO, USA.
✉e-mail: cpham@wustl.edu; guilak@wustl.edu

Published online: 1 December 2025

References

1. Sahin, U., Karikó, K. & Türeci, Ö. mRNA-based therapeutics — developing a new class of drugs. *Nat. Rev. Drug Discov.* **13**, 759–780 (2014).
2. Liu, Y. et al. Generation of tolerogenic antigen-presenting cells in vivo via the delivery of mRNA encoding PDL1 within lipid nanoparticles. *Nat. Biomed. Eng.* **9**, 1320–1334 (2025).
3. Guo, C. et al. Therapeutic potential of lipid nanoparticle-encapsulated CD19-targeting mRNAs in lupus and rheumatoid arthritis. *Adv. Sci.* **12**, e2501628 (2025).
4. Li, M. et al. Injectable microenvironment-responsive hydrogels encapsulating engineered NF-κB-targeting circular RNA for osteoarthritis therapy. *J. Control Release* **385**, 114039 (2025).
5. Kenison, J. E., Stevens, N. A. & Quintana, F. J. Therapeutic induction of antigen-specific immune tolerance. *Nat. Rev. Immunol.* **24**, 338–357 (2024).
6. Cifuentes-Rius, A., Desai, A., Yuen, D., Johnston, A. P. R. & Voelcker, N. H. Inducing immune tolerance with dendritic cell-targeting nanomedicines. *Nat. Nanotechnol.* **16**, 37–46 (2021).
7. Schett, G., Nagy, G., Kronke, G. & Mielenz, D. B-cell depletion in autoimmune diseases. *Ann. Rheum. Dis.* **83**, 1409–1420 (2024).
8. Mackensen, A. et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat. Med.* **28**, 2124–2132 (2022).
9. DeJulius, C. R. et al. Engineering approaches for RNA-based and cell-based osteoarthritis therapies. *Nat. Rev. Rheumatol.* **20**, 81–100 (2024).
10. Lee, H. I. et al. Exosome-mediated delivery of super-repressor IκBα alleviates inflammation and joint damages in rheumatoid arthritis. *Arthritis Res. Ther.* **26**, 2 (2024).

Competing interests

C.P. and F.G. are founders of SynGenix, Inc.

Rheumatoid arthritis in 2025

https://doi.org/10.1038/s41584-025-01342-6

Advances in understanding preclinical rheumatoid arthritis and prospects for prevention

Carol A. Hitchon & Hani S. El-Gabalawy

New research published in 2025 sheds light on the pre-clinical period that precedes the onset of classifiable rheumatoid arthritis, from risk factors to immunological events and opportunities to prevent the transition to clinical disease.

During the pre-clinical phase of rheumatoid arthritis (RA), environmental factors trigger immunological events in genetically susceptible people at risk of RA that lead to clinical synovitis. Several impactful publications from 2025 evaluated dietary environmental factors related to the risk of developing RA[1], provided insights into pre-disease immunological processes[2], described criteria for clinical risk stratification to inform potential intervention strategies in people at risk of RA[3] and evaluated preventive interventions[4].

While inhalational toxins are well-recognized triggers of immunological events associated with RA, studies in the past few years have also evaluated dietary factors, modification of which is easier than smoking cessation. Reduced incidence of RA was associated with diets high in vegetables and fruits but low in red meat (and seafood) in a Swedish population-based study[5], and with vitamin D plus omega-3 fatty acid supplementation in the VITAL trial[6]. In 2025, Deng et al. provide additional insights into dietary polyunsaturated fatty acids and RA risk in 1,640 participants with incident RA and 188,597 RA-free participants[1]. Incremental protective effects were seen with increasing intake of omega-3 fatty acids, but not with that of omega-6 fatty acids, especially for participants with high RA genetic risk scores. Proteomic analysis found biological pathways relevant to RA were associated with RA risk and intake of polyunsaturated fatty acids. Combined, these studies suggest that diet composition influences RA risk and that intake of omega-3 fatty acids mitigates RA risk in genetically susceptible people through effects on immunological pathways.

Thus far, the key indicator for the development of future RA has been the detection of circulating anti-citrullinated protein antibodies (ACPAs). It is well established that these autoantibodies are detectable months to years before the onset of classifiable disease in most people who develop seropositive RA. However, a substantial proportion of ACPA$^+$ people at risk of RA do not develop RA and can become seronegative with longitudinal follow-up. Thus, the immunological events underpinning the progression from asymptomatic ACPA positivity to clinically detectable synovitis and classifiable RA remain poorly understood. In 2025, He et al. published multi-omics analyses that have provided important information about this progression[2]. In this longitudinal study of 45 ACPA$^+$ people at risk of RA followed for a mean of 533 days, 16 (36%) developed RA. Compared with 38 ACPA$^-$ people, the at-risk group showed plasma proteomic and transcriptional changes in circulating immune cells indicative of an ongoing inflammatory state. Surprisingly, there was little at baseline to distinguish people at risk of RA who eventually developed RA from those who did not, although this study perhaps was underpowered to demonstrate such differences.

Importantly, the transcriptional changes demonstrated in naive T cell and B cell subsets suggested that these cells are in a functionally primed state prior to antigen exposure[2], increasing the risk of progressive autoimmunity that culminates in disease development. In the people at risk of RA who did progress to RA (progressors), transcriptional changes were most evident in activated CD4$^+$ memory T cells with a B cell helper gene signature, and in CD27$^-$ atypical or effector B cells. Interestingly, naive T cells seemed to be epigenetically biased towards a B cell helper phenotype in these progressors. Thus, T cell and B cell subsets could be providing bidirectional activating signals that support their mutual activation and expansion in the progression to clinical RA. Circulating ACPA levels were quite varied in the progressors and were similar to those in the non-progressors at baseline. In a longitudinal evaluation of the serological profile of the 16 progressors, perhaps surprisingly, there was no consistent increase in ACPA levels[2]; increasing ACPA levels have been associated in several multinational

Key advances

- Dietary polyunsaturated fatty acids, in particular omega-3 fatty acids, reduce the risk of rheumatoid arthritis (RA) development in genetically susceptible people at least in part through their effects on immune pathways[1].
- Naive T cell and B cell subsets are probably in a functionally primed state prior to antigen exposure, and transcriptional changes in activated CD4$^+$ memory T cells with a B cell helper gene signature are seen in people at risk of RA who progress to RA[2].
- Clinically relevant, data-driven guidelines for risk stratification in people at risk of RA with arthralgia, using clinically feasible measures, can effectively predict which groups will progress to clinical disease and thus are most likely to benefit from pre-disease interventions[3].
- Hydroxychloroquine taken for 1 year does not prevent anti-citrullinated protein antibody (ACPA)-positive people from developing RA[4].

cohorts with increasing IgG ACPA variable domain glycosylation, and with expansion of the autoantigens targeted[7].

In a complementary paper[8] by many of the same authors as in He et al.[2], although in a different population, 52 people at risk of RA who were ACPA$^+$ and/or were first-degree relatives of people with RA underwent extensive analysis by multimodal single-cell technologies, including mass cytometry and CITE-Seq (cellular indexing of transcriptomes and epitopes, with sequencing)[8]. Compared with the abundance of such cells in a group of healthy people, the people at risk of RA demonstrated expansion of CCR2$^+$CD4$^+$ T cells with high expression of signature transcripts related to the T_H17 and T_H22 helper T cell subsets, as well as of peripheral helper T cells, T_H1 cells and CXCR5$^+$CD8$^+$ T cells; expansion of an activated naive B cell population was also seen in ACPA$^+$ first-degree relatives. In contrast to the study by He et al.[2], no longitudinal or progression data were presented[8]. Moreover, another study that used mass spectrometry to evaluate the proteome across the evolution of RA revealed upregulation of multiple proteins in the pre-RA, at-risk period[9]. The upregulated proteins included those associated with neutrophil degranulation, cellular stress responses and cross-presentation of soluble exogenous antigens, although more-intense abnormalities in immune and acute-phase processes were seen from time points after the onset of clinical RA.

Together, these studies, including the work by He et al.[2], provide intriguing insights into the pre-clinical stages of ACPA$^+$ RA and demonstrate progressive inflammatory changes, along with expansion and activation of T cell and B cell subsets that provide mutual and reciprocal activation, resulting in amplification loops that ultimately lead to the development of classifiable RA. These studies suggest many potential intervention points that could modulate this progression.

To this end, a joint EULAR–ACR task force has developed a data-driven tool to identify people at risk of RA presenting with arthralgia who are most likely to progress to inflammatory arthritis within 1 year[3]. In pooled cohorts of people with DMARD-naive arthralgia at risk of developing future inflammatory arthritis or RA, six clinical and serological variables were associated with future inflammatory arthritis (or RA). These variables — morning stiffness, patient-reported joint swelling, difficulty making a fist, increased C-reactive protein level, ACPA positivity and rheumatoid factor positivity — were incorporated into a score to risk-stratify symptomatic people at risk of RA. The addition of MRI increased predictive ability but, surprisingly, the addition of ultrasonography did not. These pragmatic guidelines will assist clinicians counselling symptomatic people at risk of RA about interventions to prevent or ameliorate inflammatory arthritis. A parallel task force is currently developing additional guidelines for population-based risk stratification of people at risk of RA who have not yet presented to a clinic because of arthralgia.

Unfortunately, choosing an effective intervention to prevent RA in people at risk of RA remains challenging. In 2025, the phase II StopRA trial demonstrated that 1 year of hydroxychloroquine did not delay or prevent RA at 3 years in ACPA$^+$ people. In the broader landscape of RA-prevention trials involving people known to be at increased risk of developing RA[4], thus far no agent has effectively prevented RA, although abatacept substantially lowered rates of RA development while participants were on the study drug — an effect that waned, but was still present, about 12 months after the cessation of abatacept[10]. This finding might reflect the importance of T cells in pre-RA[2] but also could indicate that immune system abnormalities might not be easily reset, at least with the time-limited interventions that have been tested, once a certain level of autoimmunity has developed.

Preventing RA remains elusive. Identifying modifiable environmental influences, combined with insights into immunological progression before the development of inflammatory arthritis and tools for risk stratification, should inform feasible and effective strategies for disease prevention in people at risk of RA.

Carol A. Hitchon ✉ **& Hani S. El-Gabalawy**
Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada.
✉e-mail: carol.hitchon@umanitoba.ca

Published online: 15 December 2025

References

1. Chen, L. et al. Dietary polyunsaturated fatty acid and the risk of rheumatoid arthritis: insights from genetic predisposition and proteomics. *Arthritis Rheumatol.* **77**, 1475–1487 (2025).
2. He, Z. et al. Progression to rheumatoid arthritis in at-risk individuals is defined by systemic inflammation and by T and B cell dysregulation. *Sci. Transl. Med.* **17**, eadt7214 (2025).
3. van Steenbergen, H. W. et al. EULAR/American College of Rheumatology risk stratification criteria for development of rheumatoid arthritis in the risk stage of arthralgia. *Arthritis Rheumatol.* https://doi.org/10.1002/art.43218 (2025).
4. Deane, K. D. et al. A phase 2 trial of hydroxychloroquine in individuals at risk for rheumatoid arthritis. *Arthritis Rheumatol.* https://doi.org/10.1002/art.43366 (2025).
5. Bäcklund, R. et al. Quantified intakes of key diet components and the risk of developing rheumatoid arthritis: results from a nested case-control study. *Ann. Rheum. Dis.* **84**, 1791–1800 (2025).
6. Hahn, J. et al. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. *BMJ* **376**, e066452 (2022).
7. Kissel, T. et al. IgG anti-citrullinated protein antibody variable domain glycosylation increases before the onset of rheumatoid arthritis and stabilizes thereafter: a cross-sectional study encompassing ~1,500 samples. *Arthritis Rheumatol.* **74**, 1147–1158 (2022).
8. Inamo, J. et al. Deep immunophenotyping reveals circulating activated lymphocytes in individuals at risk for rheumatoid arthritis. *J. Clin. Invest.* **135**, e185217 (2025).
9. He, S. et al. A longitudinal cohort study uncovers plasma protein biomarkers predating clinical onset and treatment response of rheumatoid arthritis. *Nat. Commun.* **16**, 6692 (2025).
10. Cope, A. P. et al. Abatacept in individuals at high risk of rheumatoid arthritis (APIPPRA): a randomised, double-blind, multicentre, parallel, placebo-controlled, phase 2b clinical trial. *Lancet* **403**, 838–849 (2024).

Acknowledgements

We thank K. Deane for thoughtful review of the work.

Competing interests

The authors declare no competing interests.

Fibromyalgia in 2025

https://doi.org/10.1038/s41584-025-01344-4

Progress in mechanisms and therapy for fibromyalgia

Hance Clarke & Mary-Ann Fitzcharles

Fibromyalgia remains a challenge for researchers and clinicians. Three studies published in 2025 shed light on mechanisms and management by implicating gut microbiota in symptom perpetuation, demonstrating the potential of home-based neuromodulation, and examining the uncertain role of low-dose naltrexone.

Fibromyalgia remains one of the most challenging chronic pain conditions to understand and treat, characterized by widespread pain, fatigue and cognitive symptoms without structural pathology. Although central sensitization is widely accepted as a key mechanism, the initiating and perpetuating factors remain elusive. Research has explored the role of antibodies, cytokine profiles, glial-mediated inflammatory responses and alterations in brain metabolism, structure and connectivity, yielding findings across multiple biological levels but without pinpointing the definitive trigger[1,2]. In 2025, research continued to probe these complexities, with notable studies exploring the gut–immune–brain axis[3], neuromodulation strategies[4] and pharmacological interventions aimed at nociplastic pain[5]. These investigations offer fresh insights into pathogenesis and therapeutic possibilities, while underscoring the heterogeneity of fibromyalgia and the need for individualized approaches.

One striking finding from 2025 came from a study reporting the transference of fibromyalgia pain to germ-free mice through faecal microbiota transplantation from patients with fibromyalgia[3]. This work builds on earlier evidence of altered microbiome profiles in fibromyalgia, including variable changes in the abundance of certain gut species[6]. Transplantation of faecal microbiota from patients with fibromyalgia, but not from healthy individuals, into germ-free mice induced spontaneous pain and pain hypersensitivity, along with immune activation and metabolomic changes[3]. This pain condition was reversed when healthy microbiota replaced the fibromyalgia microbiota in the mice. These findings highlight the gut–immune–brain axis as a potential therapeutic target.

Although the microbiome profile remains remarkably stable after childhood, factors such as genotype, environment, diet, physical activity and antibiotic use can influence its composition and function. These latest findings raise important questions regarding what factors alter the microbiome profile in patients with fibromyalgia and, if transplantation is considered, how long the new profile would remain stable (Box 1). Equally compelling is whether dietary changes — particularly a shift towards a healthier plant-based diet with reduced fats and sugars — could sufficiently alter the gut microbiome and alleviate pain. Given the broad health benefits of a healthy diet, we advocate that simple dietary advice should be an integral component of routine care for all patients, especially those with fibromyalgia. The microbiome story represents a substantial step forwards in understanding the pathogenesis and potential for shaping future treatment strategies for fibromyalgia.

Beyond microbiome research, neuromodulation has emerged as another promising avenue. In line with the concept of neuroplasticity in fibromyalgia, the second notable 2025 paper examined treatment interventions using neuromodulation[4]. Transcranial direct current stimulation (tDCS) aims to modulate neuroplasticity by delivering low-intensity electrical stimulation to the central nervous system. Two previous 2025 systematic reviews reported that tDCS could reduce pain compared with sham stimulation in patients with fibromyalgia[7,8]. However, questions remained regarding optimal stimulation sites, treatment frequency and duration, persistence of treatment response and the role of concomitant therapy. Practical barriers — including cost and the need for 'in clinic' treatment — continue to limit widespread adoption of this procedure.

Caumo et al.[4] addressed some of these questions in a home-based, sham-controlled randomized clinical trial. In this study, bifrontal tDCS was applied to the dorsolateral prefrontal cortex, combined with exercise and pain neuroscience education. Over a 4-week period, active treatment resulted in reduced pain and pain-related disability and an improvement in endogenous pain modulation, particularly in individuals prone to a placebo response[4], with effects persisting for 4 months. Interestingly, the study integrated placebo responsiveness into its mechanistic framework, noting that tDCS influences connectivity patterns linked to placebo analgesia. tDCS modulates brain regions involved in pain and emotion, including the insula, thalamus and pathways connecting the prefrontal cortex to deeper pain-control centres. These findings highlight the potential of neuromodulation as a non-invasive, mechanism-focused intervention for fibromyalgia and underscore the promise of home-based delivery for reaching a wide patient population at a considerably reduced cost.

Key advances

- Faecal microbiota transplantation from patients with fibromyalgia induced pain and immune activation in germ-free mice, highlighting the gut–immune–brain axis as a potential therapeutic target[3].
- Home-based transcranial direct current stimulation combined with exercise improved pain and disability in fibromyalgia, with effects persisting for 4 months, supporting neuromodulation as a non-invasive treatment option[4].
- Low-dose naltrexone showed limited efficacy and no clear mechanistic correlation in fibromyalgia, emphasizing the need for rigorous trials to define its role in nociplastic pain management[5].

Box 1 | Key unanswered questions

- **Microbiota transplantation:** How durable are the microbiome changes? Can dietary interventions replicate the transplantation effects?
- **Neuromodulation:** What is the optimal stimulation protocol? Do the benefits persist long term?
- **Low-dose naltrexone:** Which patient phenotypes respond best? What is the most effective dose?

The third noteworthy publication of 2025 — examining low-dose naltrexone — might seem curious as it reported largely negative findings[5]. Naltrexone is an opioid antagonist, but when administered in doses of about one-tenth of usual dosing, has a paradoxical analgesic effect. Low-dose naltrexone has long held promise for nociplastic pain conditions such as fibromyalgia. Nociplastic pain refers to pain that cannot be fully explained by tissue damage, is associated with sensitization of the nervous system, and often presents with salient central symptoms such as fatigue and cognitive changes. Low-dose naltrexone is postulated to attenuate neuroinflammation by antagonizing Toll-like receptor 4 (TLR4), and possibly other targets, on activated microglial cells, making it a plausible candidate for modulating nervous system sensitization. An earlier study comparing low-dose naltrexone (6 mg/day) with placebo in 99 women with fibromyalgia found no overall superiority for pain relief, although almost half of the participants receiving low-dose naltrexone achieved a 30% pain reduction compared with one-quarter in the placebo group, suggesting potential benefit for certain patient subgroups[9]. In the 2025 study[5], the same authors followed up these findings to explore whether improvements in pain correlated with measures of central pain mechanisms and functional capacity, including conditioned pain modulation, pain tolerance, temporal summation and muscular endurance. Although conditioned pain modulation improved in the low-dose naltrexone group, this change did not normalize the measure, and could perhaps even reflect a decrease in conditioned pain modulation in the placebo group. Other indicators of central pain mechanisms were not associated with pain relief among responders. These mostly negative findings could possibly be explained as a dosing issue, as most prior studies used ≤4.5 mg/day, with some preclinical studies even suggesting that 'ultra-low' doses could have analgesic effects. These findings highlight the notion that preclinical evidence for an effect cannot immediately be translated into the clinical context without rigorous evaluation.

These results are disappointing as low-dose naltrexone has long held promise for the treatment of many chronic pain conditions, including more recently the treatment of long COVID, a condition with considerable overlap with fibromyalgia. Both disorders share similarities in symptom profiles, neuroimmune mechanisms, brain–gut axis involvement and treatment strategies, as highlighted in a recent narrative review[10]. Although no single pathophysiological mechanism has been identified for either condition, evidence points to nervous system dysfunction, including glial cell activation and central sensitization. Interest in low-dose naltrexone is reflected in the plethora of publications over the past 5 years and increasing reports of its off-label use for long COVID, with many suggesting symptom improvement and better functional status with minimal adverse effects. Given the heterogeneity of both conditions, low-dose naltrexone might benefit a selection of patients, although the phenotype predicting response remains elusive. In the absence of effective treatments for these conditions and with patients continuing to be affected, a cautious off-label trial of low-dose naltrexone for at least 12 weeks could be considered in selected patients. We argue that low-dose naltrexone should not be discarded and call for well-designed clinical trials to clarify its role in the challenging world of nociplastic pain management.

No drug treatment currently provides consistent or substantial benefit in fibromyalgia, prompting a search for new non-pharmacological interventions. Modulating the microbiome to influence the gut–immune–brain axis represents a promising therapeutic strategy. Similarly, neuromodulation using tDCS, particularly in home-based programmes, is emerging as a non-invasive treatment option. Finally, drugs that target neuroinflammation, such as low-dose naltrexone, provide a mechanistic explanation for alleviating nociplastic pain in fibromyalgia.

Hance Clarke[1,2] & Mary-Ann Fitzcharles[3,4]
[1]Department of Anesthesia and Pain Management, Pain Research Unit, Toronto General Hospital, Toronto, Ontario, Canada. [2]Transitional Pain Service, University of Toronto, Toronto, Ontario, Canada. [3]Department of Rheumatology, McGill University, Montreal, Quebec, Canada. [4]Alan Edwards Pain Management Unit, McGill University, Montreal, Quebec, Canada.
e-mail: mfitzcharles@sympatico.ca

Published online: 19 December 2025

References

1. Findeisen, K., Guymer, E. & Littlejohn, G. Neuroinflammatory and Immunological Aspects of Fibromyalgia. *Brain Sci.* **15**, 206 (2025).
2. Kelleher, E. M. et al. Brain signatures of nociplastic pain: Fibromyalgia Index and descending modulation at population level. *Brain* https://doi.org/10.1093/brain/awaf307 (2025).
3. Cai, W. et al. The gut microbiota promotes pain in fibromyalgia. *Neuron* **113**, 2161–2175.e2113 (2025).
4. Caumo, W. et al. Home-based transcranial direct current stimulation vs placebo for fibromyalgia: a randomized clinical trial. *JAMA Netw. Open* **8**, e2514262 (2025).
5. Bruun, K. D. et al. Effect of naltrexone on spinal and supraspinal pain mechanisms and functional capacity in women with fibromyalgia: exploratory outcomes from the randomized placebo-controlled FINAL trial. *CNS Drugs* **39**, 685–692 (2025).
6. Minerbi, A. et al. Altered microbiome composition in individuals with fibromyalgia. *Pain* **160**, 2589–2602 (2019).
7. Moshfeghinia, R. et al. The effects of transcranial direct-current stimulation (tDCS) on pain intensity of patients with fibromyalgia: a systematic review and meta-analysis. *BMC Neurol.* **23**, 395 (2023).
8. Teixeira, P. E. P. et al. The analgesic effect of transcranial direct current stimulation in fibromyalgia: a systematic review, meta-analysis, and meta-regression of potential influencers of clinical effect. *Neuromodulation* **26**, 715–727 (2023).
9. Due Bruun, K. et al. Naltrexone 6 mg once daily versus placebo in women with fibromyalgia: a randomised, double-blind, placebo-controlled trial. *Lancet Rheumatol.* **6**, e31–e39 (2024).
10. Goldenberg, D. L. The pivotal role of central sensitization in long COVID, fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome. *Expert Rev. Neurother.* **25**, 973–989 (2025).

Competing interests

H.C. is the president of the Canadian Pain Society. M.-A.F. declares no competing interests.

Precision medicine in 2025

https://doi.org/10.1038/s41584-025-01345-3

Fibroblast heterogeneity in 2025

Adam P. Croft & Annie Hackland

Advances in cellular and spatial profiling technologies have rapidly expanded the understanding of fibroblast heterogeneity within the target tissues of disease. In 2025, there has been a shift towards a consensus definition of shared cross-tissue fibroblast states and a greater understanding of their molecular drivers and disease-relevant effector functions.

Fibroblasts have a crucial role in healthy tissue homeostasis; these tissue-resident cells form the 'scaffold' upon which the inflammatory response is conducted[1]. During chronic inflammation, fibroblasts orchestrate immune cell responses. They can acquire specific effector phenotypes that directly contribute to inflammatory tissue pathology and damage[2,3], but they can also regulate immune cells to promote the resolution of inflammation[4]. Despite advances in the treatment of immune-mediated inflammatory diseases (IMIDs), the current therapeutic emphasis on targeting pro-inflammatory pathways has not led to a cure. IMIDs are characterized by the persistence of inflammation at distinct anatomical sites[5]. The tissue microenvironment in which inflammation occurs is a key determinant of disease outcome and treatment response[2]. Fibroblasts are promising therapeutic targets owing to their capacity to modulate the inflamed tissue microenvironment without the need for direct immunosuppression; however, they have yet to be therapeutically targeted. A major barrier to targeting these cells is the lack of understanding of the molecular drivers underpinning their heterogeneity and the functional role of specific fibroblast subtypes in health and disease.

In 2025, three studies provided new insights into fibroblast heterogeneity, contributing to a new taxonomy of the fibroblast lineage[6–8] (Fig. 1).

The ability to perform minimally invasive biopsies of IMID target tissues combined with advances in single-cell and spatial profiling technologies has revolutionized the understanding of fibroblast heterogeneity. This understanding has led to the emergence of a large number of cell atlas studies across IMID target tissues, providing a timely opportunity to perform integrated cross-tissue comparative studies designed to identify shared and unique fibroblast states.

In 2025, Steele et al.[6] constructed an integrated spatially resolved atlas of fibroblasts from healthy adult skin, with reference mapping to 23 inflammatory and fibrotic skin diseases. The atlas comprised 2.1 million skin cells, within which 357,276 fibroblasts were profiled from 251 individual donors. Downstream analysis of this comprehensive dataset led to the identification of six healthy skin fibroblast states and three uniquely disease-associated states. Two of these fibroblast states were found to be conserved across tissues and were predicted to be immune-interacting.

Firstly, a fibroblastic reticular cell (FRC)-like state (expressing the genes *CCL19*, *CD74* and *HLA-DRA*; *CCL19*$^{+}$*CD74*$^{+}$*HLA-DRA*$^{+}$) was identified and localized to superficial perivascular immune niches within the dermis. FRCs are known to display immunomodulatory properties and are responsible for the organization of specific immune cell niches within lymphoid tissues[9]. Steele et al.[6] describe FRC-like skin fibroblasts that are thought to similarly facilitate T cell–dendritic cell interactions. Fibroblasts with an FRC-like phenotype have been identified in other organs, including the inflamed lung, bowel and salivary gland[10]. The enrichment of FRC-like skin fibroblasts in human skin probably underpins the prominent perivascular immune infiltrates and ectopic lymphoid structures that are pathological hallmarks of chronic inflammatory skin disease. This pathogenic fibroblast state might represent a credible cross-tissue therapeutic target to disrupt fibroblast-driven pathology in IMIDs.

Secondly, the authors describe an inflammatory myofibroblast population (*IL11*$^{+}$*MMP1*$^{+}$*CXCL5*$^{+}$*IL7R*$^{+}$) that is similar in phenotype to myofibroblast states described in cancer and other IMIDs. Importantly, uniquely high prevalence of this fibroblast population characterized skin conditions with high scarring risk, and these fibroblasts had a predicted role in neutrophil and monocyte recruitment across tissues. These findings highlight how the composition of tissue fibroblast states dictates immune cell dynamics and the outcome of tissue-specific pathology, such as scarring versus non-scarring resolution.

Cell atlas studies have repeatedly identified similar sets of fibroblast transcriptional states across tissues; however, the molecular mechanisms underpinning the differentiation of these states are poorly understood. Identification of the molecular regulators that govern specific fibroblasts states could be therapeutically exploited to suppress pathogenic programs and augment homeostatic and reparative functions through cellular reprogramming.

Southard et al.[7] used high-throughput CRISPR-based gene activation combined with single-cell RNA-sequencing (Perturb-seq) to upregulate the expression of 1,836 candidate transcription factors

Key points

- Construction and analysis of a single-cell and spatial tissue atlas of human skin fibroblasts revealed shared disease-related fibroblast states, including two cross-tissue immune-interacting fibroblast states implicated in distinct inflammatory tissue pathologies in immune-mediated inflammatory diseases[6].
- A CRISPR-based gene activation platform combined with single-cell RNA sequencing revealed key transcription factors that regulate disease-relevant fibroblast gene programs, including a 'universal' program that innately antagonizes the 'inflammatory' program, highlighting the therapeutic potential of fibroblast reprogramming[7].
- Rheumatoid arthritis synovial fibroblasts that express MHC class II molecules demonstrate immunosuppressive functions via antigen presentation to T cells without co-stimulation, which limits T cell activation in the joint, adding to the emerging body of evidence of the regulatory roles of fibroblasts in inflammatory diseases[8].

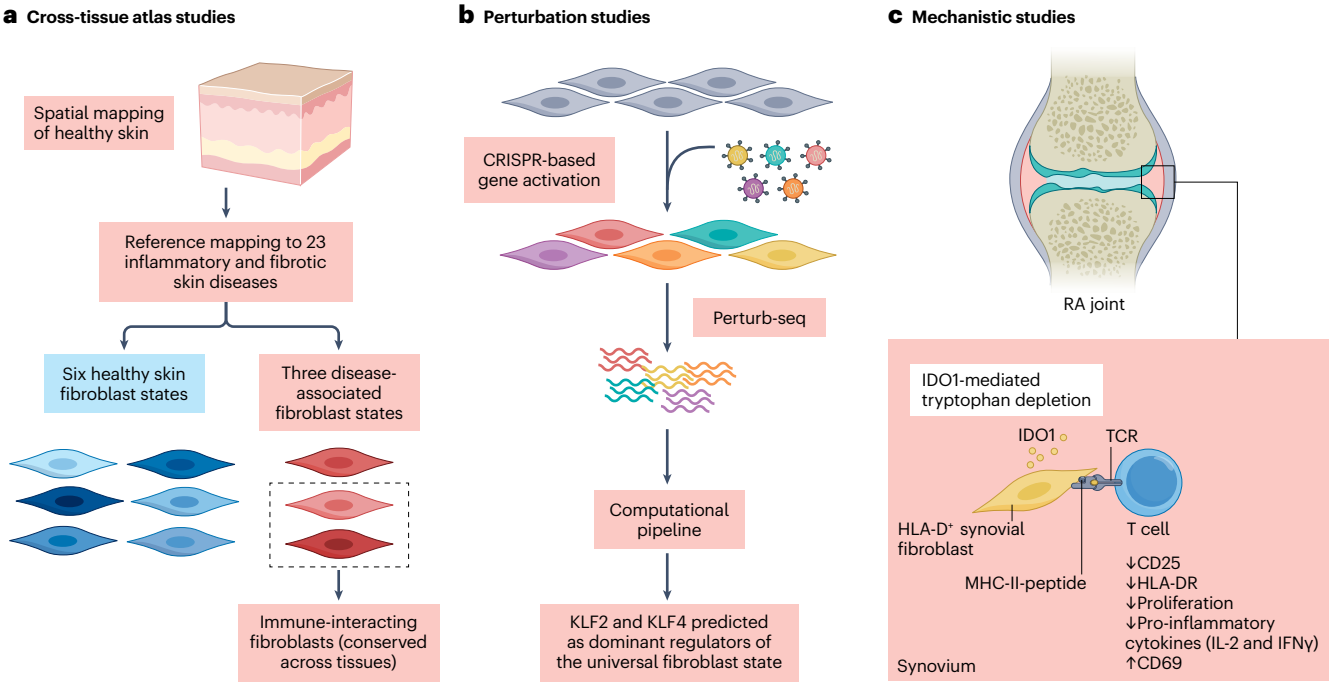


Fig. 1 | Advances in fibroblast heterogeneity. Three 2025 studies[6–8] used distinct approaches to investigate fibroblast heterogeneity, providing important insights for the future development of fibroblast-targeting therapies. **a**, The development of a fibroblast atlas of the human skin to identify shared and common fibroblast states. **b**, Investigation of molecular regulators of fibroblast state using Perturb-seq (CRISPR-based gene activation of transcription factors combined with single-cell RNA-sequencing). **c**, Mechanistic study investigating disease-relevant regulatory functions of synovial tissue fibroblasts. MHC-II, MHC class II molecule; RA, rheumatoid arthritis; TCR, T cell receptor.

in dermal fibroblasts, enabling faithful recapitulation of in vivo gene expression programs. The authors identified the transcription factors KLF2 and KLF4, which are known to be enriched in healthy tissues, as dominant regulators of the universal fibroblast state; these findings are consistent with prior links between fibrotic diseases and KLF transcription factor deficiency in fibroblasts. Notably, inducing the universal fibroblast state suppressed the inflammatory program, suggesting a potential therapeutic strategy that could be used across multiple tissues to reprogram pathogenic fibroblasts towards a universal state, rather than targeting disease-specific fibroblasts.

Targeting fibroblasts therapeutically requires the translation of computational predictions of function into mechanistic roles in disease. Fibroblasts have diverse roles in homeostasis and disease, and strategies for therapeutic targeting of fibroblasts must consider their emerging immunoregulatory roles in the tissue microenvironment. Although computational predictions provide key insights into fibroblast diversity, mechanistic studies are essential to establish their effector functions. The importance of this approach has been highlighted in studies of T cell activation in the inflamed synovium.

Fibroblasts that express MHC class II molecules are present across multiple human tissues, where they can present antigens to $CD4^+$ T cells with context-dependent effects. Romoff et al.[8] demonstrated that tissue-resident fibroblasts in the inflamed rheumatoid arthritis synovium express MHC class II molecules (HLA-D) but lack the co-stimulatory signals typically required for T cell activation. Compared with professional antigen-presenting cells, such as macrophages, these fibroblasts produced high levels of IDO1 and induced low CD25 and HLA-DR expression, reduced IL-2 and IFNγ production and suppressed proliferation in T cells. Upon interaction with these fibroblasts, T cells instead upregulate CD69, which limits cytokine production, restrains T helper 17 cell differentiation, promotes a regulatory T cell phenotype and inhibits tissue egress. Thus, fibroblast HLA-D expression stabilizes synovial fibroblast–T cell contact, helping to retain T cells within a tryptophan-depleted immunosuppressive niche. These findings contribute to the growing body of evidence regarding the immunoregulatory capacity of fibroblasts, highlighting the importance of using precision-targeting approaches in the future.

The next decade will see research focus on maximizing the potential of the data generated as part of the Human Cell Atlas. The fibroblast studies reviewed here highlight the power of large-scale integrated cell atlas studies in the identification and definition of cellular states across tissues using a common nomenclature, revealing that the composition of fibroblasts within the tissue is a fundamental determinant of the subsequent response to injury and inflammation. Combined with insights into the molecular circuitry responsible for specific fibroblast states and their functional roles in diseased tissue, these findings could offer therapeutic avenues to modulate fibroblast pathogenicity and permit precision approaches that preserve their regulatory and protective functions while suppressing their pathogenic role in disease.

Adam P. Croft ✉ **& Annie Hackland**
Rheumatology Research Group, Department of Inflammation and Ageing, University of Birmingham, Birmingham, UK.
✉e-mail: a.p.croft@bham.ac.uk

Published online: 19 December 2025

References

1. Plikus, M. V. et al. Fibroblasts: origins, definitions, and functions in health and disease. *Cell* **184**, 3852–3872 (2021).
2. Davidson, S. et al. Fibroblasts as immune regulators in infection, inflammation and cancer. *Nat. Rev. Immunol.* **21**, 704–717 (2021).
3. Croft, A. P. et al. Distinct fibroblast subsets drive inflammation and damage in arthritis. *Nature* **570**, 246–251 (2019).
4. Rauber, S. et al. $CD200^+$ fibroblasts form a pro-resolving mesenchymal network in arthritis. *Nat. Immunol.* **25**, 682–692 (2024).

5. Netea, M. G. et al. A guiding map for inflammation. *Nat. Immunol.* **18**, 826–831 (2017).
6. Steele, L. et al. A single-cell and spatial genomics atlas of human skin fibroblasts reveals shared disease-related fibroblast subtypes across tissues. *Nat. Immunol.* **26**, 1807–1820 (2025).
7. Southard, K. M. et al. Comprehensive transcription factor perturbations recapitulate fibroblast transcriptional states. *Nat. Genet.* **57**, 2323–2334 (2025).
8. Romoff, M. R. et al. Rheumatoid arthritis synovial fibroblasts modulate T cell activation. *JCI Insight* **10**, e193054 (2025).
9. De Martin, A., Stanossek, Y., Pikor, N. B. & Ludewig, B. Protective fibroblastic niches in secondary lymphoid organs. *J. Exp. Med.* **221**, e20221220 (2023).
10. Barone, F. et al. Stromal fibroblasts in tertiary lymphoid structures: a novel target in chronic inflammation. *Front. Immunol.* **7**, 477 (2016).

Competing interests

The authors declare no competing interests.

nature reviews rheumatology

https://doi.org/10.1038/s41584-025-01296-9

Review article

Check for updates

PD-1, BTLA and TIGIT as therapeutic targets for rheumatic disease

Juhi R. Kuchroo[1,2,3], Naomi Goldman[1,2,3] & Arlene H. Sharpe[1,2]

Abstract

Immune-checkpoint molecules have essential roles in regulating immune responses, which maintain the delicate balance between physiological immune reactions and autoimmunity. The clinical success of immune checkpoint blockade for cancer therapy, and the occurrence of immune-related adverse events during cancer immunotherapy, highlight the profound effect of modulating these receptors on both tumour-specific and 'self'-specific responses. As a result, interest in exploring how these molecules can be targeted to treat autoimmune and rheumatological diseases is expanding. Targeting of the immune-checkpoint molecules PD-1, B and T lymphocyte attenuator (BTLA) and T cell immunoreceptor with Ig and ITIM domains (TIGIT) to induce immune tolerance has shown therapeutic promise in pre-clinical models and, in some instances, clinical trials. A comprehensive understanding of how these receptors function in various immune cell populations, particularly T cells, and across different diseases is crucial for the successful translation of these findings to clinical applications.

Sections

[1]Department of Immunology, Blavatnik Institute, Harvard Medical School, Boston, MA, USA. [2]Gene Lay Institute of Immunology and Inflammation, Brigham and Women's Hospital, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA. [3]These authors contributed equally: Juhi R. Kuchroo, Naomi Goldman.
e-mail: arlene_sharpe@hms.harvard.edu

Key points

- Inhibitory immune-checkpoint receptors maintain immune tolerance. Blocking these receptors during cancer treatment can disrupt tolerance and result in new or worsening autoimmune manifestations known as immune-related adverse events.
- Agonism of inhibitory immune-checkpoint receptors improves rheumatic diseases in animal models and is under investigation in clinical settings to treat autoimmunity.
- Strategies that activate PD-1 signalling, which could inhibit both effector and regulatory T cell responses, have been translated to clinical trials and have been well tolerated in patients.
- BTLA signalling has diverse roles in T cells and other immune cells. Approaches to agonizing BTLA have moved to clinical trials but have not yet demonstrated efficacy.
- TIGIT mediates inhibition of T cell responses through multiple cell-intrinsic and -extrinsic mechanisms to maintain tolerance, making it an attractive therapeutic target; it has yet to be developed clinically for autoimmune diseases.
- Multiple other inhibitory receptors are being assessed as therapeutic targets alone and in combination for rheumatic diseases.

Introduction

T cell activation is a finely regulated process. Initial activation of naive T cells requires two signals: engagement of the T cell receptor (TCR) with peptide-MHC complexes and co-stimulatory signalling. Interaction of the CD28 receptor on T cells with its ligands CD80 (B7-1) and CD86 (B7-2) delivers the primary co-stimulatory signal needed for initial activation of T cells[1] (Fig. 1). In addition, during early T cell activation, inhibitory second signals are induced to counterbalance the activation process[1–3]. Co-inhibitory receptors, often termed 'immune checkpoints', serve as brakes that regulate the strength and duration of immune responses. Key co-inhibitory receptors include PD-1, T cell immunoreceptor with Ig and ITIM domains (TIGIT), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte-activation gene 3 (LAG-3) and B and T lymphocyte attenuator (BTLA)[4]. The inhibitory functions of these receptors are vital for maintaining the balance between effective protective immune responses and preventing immune-mediated tissue damage and autoimmune disease. Furthermore, during chronic viral infection or cancer, persistent antigen exposure leads to T cell exhaustion, a state of reduced effector function[4–9] and an increased, sustained expression of immune-checkpoint receptors (Fig. 2). These receptors are often simultaneously upregulated on exhausted T cells and have important roles in limiting the functions of exhausted T cells[3,4,10].

Anti-CTLA-4 and anti-PD-1 therapies highlight the therapeutic potential of blocking immune-checkpoint receptors in cancer and have become mainstay treatments for multiple cancer types since their initial FDA approvals in 2011 and 2014, respectively. However, approximately 7–12% of patients experience severe autoimmune-like multi-organ tissue inflammation termed immune-related adverse events (irAEs) that can limit cancer treatment[9,11–16]. These irAEs are hypothesized to occur, in part, owing to the activation of autoreactive T cells that are normally restrained by co-inhibitory molecules. These irAEs can affect many organs, including the endocrine glands, skin, intestine and liver[13,17,18]. Some patients who develop diabetes-like irAEs or thyroiditis have evidence of autoantibody production analogous to patients with autoimmune disease[14,19–22]. Similarly, HLA alleles that confer risk in certain autoimmune diseases such as colitis and pruritus are also associated with patients who are predisposed to developing corresponding organ-specific irAEs[23].

Although further work is required to better understand the pathogenesis of irAEs versus traditional autoimmunity, interest in targeting co-inhibitory receptors as a strategy for treating autoimmune diseases is increasing. CTLA-4, the first co-inhibitory receptor both discovered and targeted for therapy, binds to CD80 and CD86 with higher affinity than the CD28 co-stimulatory receptor thereby attenuating T cell responses[24]. CTLA-4 Ig, a soluble fusion protein composed of the extracellular domain of CTLA-4, antagonizes CD28 co-stimulation, thus inhibiting T cell responses in a variety of settings including rheumatoid arthritis (RA) and notably for treatment of irAE-associated myocarditis[24,25]. The FDA approval and wide use of CTLA-4 Ig therapies, such as abatacept and belatacept, highlight the promise of targeting other immune checkpoints for treating autoimmune and inflammatory disease[24].

Interestingly, an 'exhaustion transcriptional signature' in $CD8^+$ T cells, which includes several immune checkpoint receptors, correlates with poor viral clearance but indicates a better prognosis for autoimmune disease[26]. These findings support the idea that T cell exhaustion limits immunopathology during chronic antigen stimulation, which can occur during chronic viral infection and autoimmunity. Consequently, manipulating signals that regulate T cell exhaustion has therapeutic promise for treating chronic autoimmune conditions. Specifically, this approach would agonize, rather than inhibit, immune-checkpoint receptors.

In this Review, we focus on the three immune checkpoint receptors PD-1, BTLA and TIGIT because they have had preclinical and, in some cases, clinical successes in treating rheumatic diseases. We describe their functions in different immune-cell types, focusing on their effects on T cells and T cell-mediated inflammation (Table 1), and highlight evidence of their involvement in rheumatic diseases (Table 2). We review both preclinical and clinical studies (Table 3) of PD-1, BTLA and TIGIT antibody agonists, considering their potential for treating rheumatic diseases. Finally, we discuss other promising targets and the evolution of the field as it moves towards more nuanced biologic therapies for rheumatic disease aimed at enhancing treatment efficacy, limiting off-target effects and promoting induction of tolerance or exhaustion.

PD-1

The pivotal role of PD-1 in regulating T cell responses and maintaining immune tolerance provides a foundation for modulating T cell function in a variety of disease contexts. In cancer immunotherapy, blockade of PD-1 has revolutionized cancer treatment by enhancing antitumour T cell responses. Conversely, therapeutic approaches for treating autoimmunity focus on activating PD-1 signalling to reduce immune activation and promote tissue tolerance. Preclinical models of autoimmunity have informed therapeutic strategy development, leveraging the PD-1–PD-L1 axis to re-establish immune balance and restore immune homeostasis. These strategies underscore the dual potential of PD-1 modulation to enhance or inhibit immune responses, depending on the disease setting.

PD-1 ligands

The PD-1 receptor (CD279) is upregulated on T cells in response to TCR activation and CD28-mediated T cell co-stimulation[27,28]. This upregulation counterbalances T cell activation and controls the resolution of inflammation, preventing overactive T cell responses. When antigen is not acutely cleared, such as during chronic infections and cancer, PD-1 expression persists (Fig. 2) and is associated with impaired T cell function[6,29–31]. In addition to T cells, PD-1 is expressed on natural killer (NK) cells, NK T cells, activated B cells, innate lymphoid cells (ILCs), macrophages and neurons[3,32–34]. The PD-1 ligands, PD-L1 (CD274) and PD-L2 (CD273), are expressed on a variety of cell types[32,33,35]. Although PD-L1 is widely expressed on both haematopoietic and non-haematopoietic cells, PD-L2 expression is mainly restricted to haematopoietic cells, including dendritic cells (DCs), B cells and macrophages, but PD-L2 can also be expressed on some non-haematopoietic cells, including lung epithelial cells[32,33]. Notably, both ligands can be expressed by cancer cells, often in response to IFNγ[3,36]. PD-1 ligands each have an additional unique binding partner (Fig. 1). PD-L1 interacts with CD80 in *cis* (that is, when both molecules are expressed on the surface of the same cell) on antigen-presenting cells (APCs), but not in *trans* (that is, when the molecules are expressed on different cells), which sequesters PD-L1 and prevents interactions with PD-1 on T cells[37]. The affinity of PD-L1 interactions with PD-1 (K_d 0.77 mM) in *trans* is similar to that of PD-L1 with CD80 in *cis* (K_d 1.4 mM), suggesting the possibility of competition, which might be influenced by the local levels of PD-L1 and CD80 on the cell surface. PD-L2 also binds repulsive guidance molecule b (RGMb), which is expressed on immune cells, including T cells and alveolar and interstitial macrophages, as well as on non-haematopoietic cells[38]. Studies from the past decade indicate that PD-L2–RGMb interactions promote immune tolerance[39] and limit antitumour immunity[40].

PD-1 function

PD-1 interactions with its ligands limit T cell activation by recruiting Src homology region 2 domain-containing phosphatase-1 and 2 (SHP-1 and SHP-2). This recruitment results in dephosphorylation of key molecules downstream of the TCR, including Lck and Zap70 (refs. 41–44). In addition, PD-1 engagement by PD-L1 can cause dephosphorylation of CD28, resulting in loss of co-stimulatory signalling[45]. PD-1 signals also antagonize the downstream PI3K–AKT (phosphoinositide 3 kinase–protein kinase B) and RAS–MEK–ERK (RAS/RAF–mitogen-activated protein kinase–extracellular signal related kinase) pathways, which are crucial for the survival and expansion of effector T cells[42,46]. This signalling limits glucose uptake and glycolysis, which are essential for the expansion and differentiation of T cells following activation[43]. Consequently, PD-1 signals lead to reduced T cell proliferation[32,33,47] and cytokine production, including IL-2, IFNγ and TNF[48,49].

The role of PD-1 in autoimmune disease

As PD-1 regulates T cell survival, growth, expansion and activation, it has a crucial role in maintaining immune tolerance and, consequently, influences the onset and severity of autoimmune disease. Studies in mouse models of T cell-mediated autoimmune diseases show that loss of PD-1 expression results in increased tissue inflammation and, in some cases, accelerated disease progression. Similarly, human studies have revealed correlations not only between PD-1 gene polymorphisms and the incidence of autoimmune diseases but also between PD-1 tissue expression and the severity of disease. Collectively, both preclinical evidence and clinical evidence support the potential of

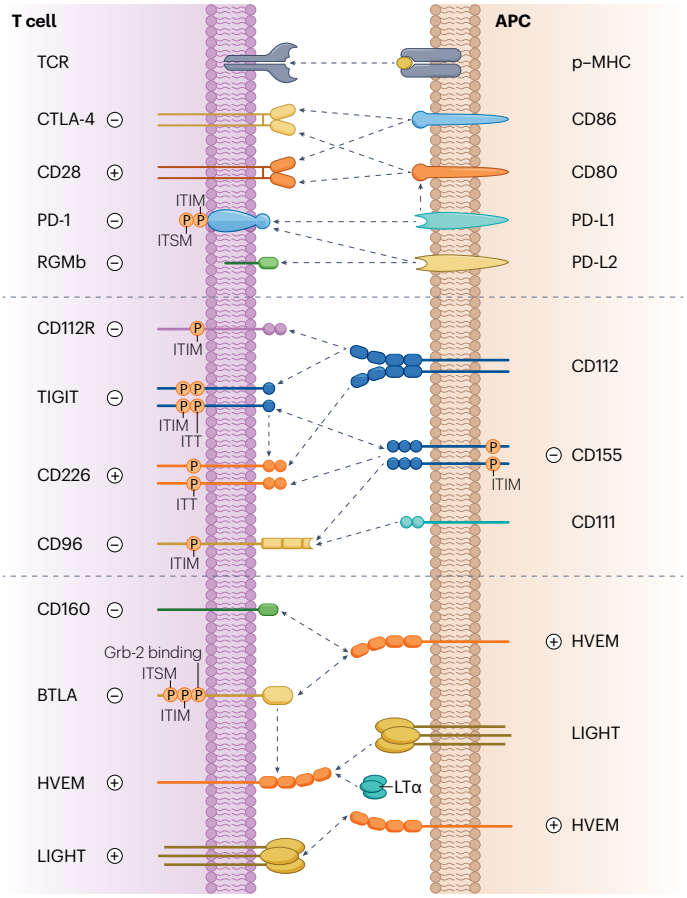


Fig. 1 | Immune-checkpoint receptors and their ligands. Activation of naive T cells integrates interactions of the T cell receptor (TCR) and peptide–MHC (p–MHC) complexes with a second co-stimulatory signal provided through CD28–CD80 or CD86 interactions. Additional select co-stimulatory and co-inhibitory receptors are depicted. Dotted lines indicate ligand–receptor interactions. Select intracellular domains (including immunoreceptor tyrosine-based inhibitory motif (ITIM), immunoreceptor tyrosine-based switch motif (ITSM) and immunoglobulin tyrosine tail (ITT)) that mediate downstream receptor signalling after phosphorylation are depicted. CD28 and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) share CD80 and CD86 as ligands. Although CD28 interactions with these ligands provide a T cell co-stimulatory signal, binding of CTLA-4 to CD80 and CD86 opposes CD28 co-stimulation, thereby inhibiting T cell responses. PD-1 binding to its ligands PD-L1 and PD-L2 opposes signals through the TCR and CD28, resulting in inhibition of T cell responses. PD-L1 can also interact with CD80 in *cis* (on the same cell) and PD-L2 can also bind to repulsive guidance molecule b (RGMb). T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) and CD226 share the ligands CD112 and CD155. CD226 binding these ligands provides a co-stimulatory signal, whereas TIGIT binding to these ligands results in a co-inhibitory signal in T cells. Binding of TIGIT to CD155 delivers an inhibitory signal into antigen-presenting cells (APCs). TIGIT can also interact with CD226 in *cis*. Additional binding partners for TIGIT ligands are depicted; CD155 binds CD96 and CD112 binds CD112R. CD96 can bind to CD111. B and T lymphocyte attenuator (BTLA) can bind its ligand herpesvirus entry mediator (HVEM) in *cis* or *trans* (on another cell). HVEM also binds to CD160, LIGHT, and lymphotoxin-α (LTα). HVEM or LIGHT engagement results in a T cell co-stimulatory signal, whereas BTLA or CD160 engagement leads to a T cell co-inhibitory signal. HVEM engagement on APCs can also lead to a stimulatory signal. Stimulatory signals are indicated by '+' signs, and '–' signs indicate inhibitory signals.

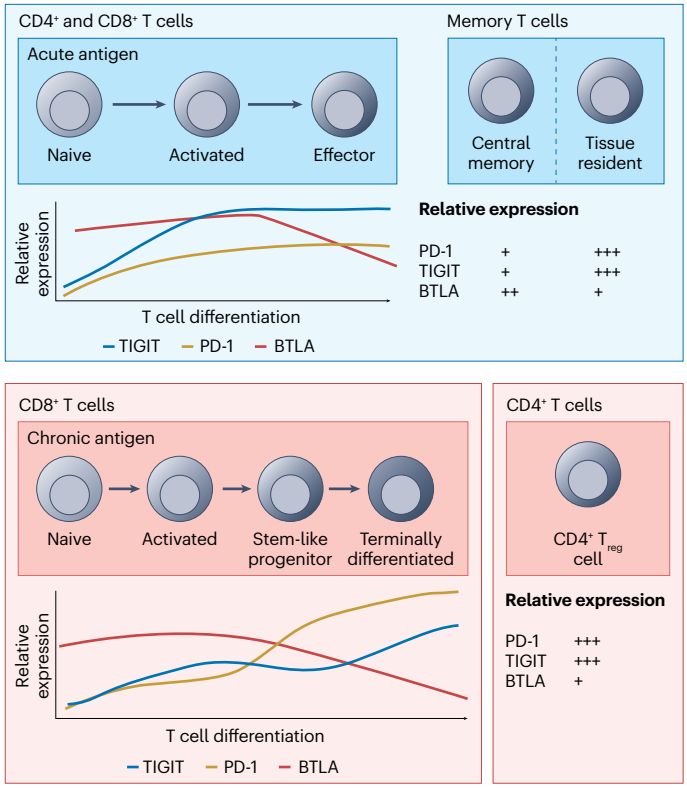


Fig. 2 | Immune-checkpoint receptor expression during T cell differentiation. Relative expression profiles are depicted with '+' symbols for PD-1, B and T lymphocyte attenuator (BTLA) and T cell immunoreceptor with Ig and ITIM domains (TIGIT) during phases of $CD4^+$ T cell and $CD8^+$ T cell differentiation in response to acute and chronic antigen. Relative expression is shown between memory T cell subsets (central memory versus tissue resident memory) as well as regulatory T (T_{reg}) cells.

PD-1 as a promising therapeutic target for the treatment of rheumatic diseases (Table 2).

Preclinical studies. Early studies in the non-obese diabetic (NOD) mouse model (an autoimmune model of human type 1 diabetes mellitus (T1DM)), and the experimental autoimmune encephalomyelitis (EAE) mouse model (a model for human multiple sclerosis), highlight the function of PD-1 in tolerance. Constitutive loss of PD-1 in NOD mice, or antibody-mediated PD-1 blockade administered at any time between 1 and 10 weeks of age, accelerates the onset of disease[50]. T1DM-like disease elicited by PD-1 blockade is characterized by the expansion of activated $CD8^+$ T cells in the pancreas and severe insulitis[51]. Similarly, in EAE, PD-1 blockade or loss leads to earlier onset and more severe disease, with an increased infiltration of immune cells in the central nervous system (CNS) and a high frequency of pro-inflammatory IFNγ and IL-17-producing T cells in the CNS[52,53].

Models of rheumatic disease have shown similar findings. In NOD/ShiLtJ mice, a model of Sjögren disease (SjD), PD-L1 blockade leads to an increased infiltration of T cells and B cells and an upregulation of IFNγ in the submandibular glands[54]. Similarly, in the collagen-induced arthritis (CIA) mouse model, loss of PD-1 leads to an increased frequency and severity of disease with concomitant increases in T cell proliferation and pro-inflammatory cytokine production (IFNγ and IL-17)[55,56]. This increased disease severity can be reversed by inhibiting the PI3K–AKT–mTOR (the mechanistic target of rapamycin) pathway, suggesting a mechanism by which PD-1 restrains CIA.

Clinical evidence. Findings from patients with rheumatic disease parallel studies in mouse models of autoimmunity. Considerable evidence exists on the role of PD-1 in human autoimmune and rheumatic diseases. Associations between polymorphisms in the *PDCD1* gene and rheumatic diseases have been reported. Specifically, the PDCD1 promoter SNP PD1.1 is associated with increased susceptibility to RA and juvenile-onset systemic lupus erythematosus (SLE)[57–59]. PD-1.3 A, located within a putative enhancer in intron 4, is associated with an increased risk of SLE, lupus nephritis and RA[60–63]. This variant correlates with reduced basal and induced PD-1 expression on $CD4^+$ T cells in homozygous but not heterozygous patients with SLE[64]. Within exon 5, PD-1.5 C/C and PD-1.5 T are associated with increased susceptibility to SLE[65] and RA[66] respectively, whereas SNP PD-1.9 T is associated with an increased risk of ankylosing spondylitis[67,68]. Notably, these genetic polymorphisms are only associated with rheumatic diseases in certain ethnic groups.

Serum levels of autoantibodies against PD-1 are higher in patients with new-onset SLE compared with healthy individuals, providing further evidence of the role of PD-1 regulation in rheumatic disease; anti-PD-1 IgG levels correlate positively with both the SLE disease activity index score and erythrocyte sedimentation rate (ESR)[69]. In addition, APCs from patients with SLE do not upregulate PD-L1 but instead express co-stimulatory markers, a trend associated with an increase in disease activity[70]. By contrast, patients with SjD have elevated expression of both PD-1 and PD-L1 on tissue-infiltrating T cells and increased PD-L1 expression on ductal and acinar epithelial cells[71]. It remains unclear if this increased expression is because of increased inflammatory responses.

In patients with RA, PD-1 and PD-L1 expression are increased in the synovium[55,72,73]. A population of $PD\text{-}1^{hi}CXCR5^-CD4^+$ T cells (a subset of T peripheral helper cells) is expanded in the synovium and promotes B cell antibody production in the tissue[74]. Similarly, the proportion of $PD\text{-}1^+CD4^+$ T cells increases in the peripheral blood and synovium of patients with RA[75]. These findings suggest that increased levels of PD-1 and PD-L1 might reflect highly activated effector cells in the tissue (Fig. 2). However, other studies report reduced PD-1 expression on peripheral blood $CD4^+$ and $CD8^+$ T cells from patients with RA that is associated with positive C-reactive protein (CRP) and higher disease activity scores, consistent with a role for PD-1 in regulating disease course[76]. In addition, soluble PD-1 and PD-L1 are found in the plasma of patients with RA. Soluble PD-1 is a result of alternative splicing, which produces an isoform of PD-1 that lacks the transmembrane domain in exon 3; soluble PD-L1 can result from alternative splicing or proteolytic cleavage from the cell membrane[77]. Soluble forms of both PD-1 and PD-L1 have been profiled mostly in the setting of antitumour immunity, but their potential use as biomarkers for responsiveness to immunotherapy remains unclear[78,79]. Patients with RA have high serum and synovial fluid levels of soluble PD-1, which correlate positively with disease activity[76,80,81]. Further studies are needed to determine whether high levels of soluble PD-1 and PD-L1 affect strategies to target PD-1 in autoimmunity. Across several rheumatic diseases, consistent differences in PD-1 expression between patients and healthy individuals suggest that differential PD-1 expression and signalling might be causal or

responsive to inflammation, indicating that PD-1 could be a promising target for treating rheumatic diseases.

Perhaps the strongest evidence of the role of PD-1 in regulating tissue inflammation and autoimmune responses is the emergence of irAEs in patients treated with anti-PD-1 and anti-PD-L1 for cancer. Between 7% and 12% of patients can present with severe (grade three or higher) irAEs following treatment with anti-PD-1 therapy[16,82,83]. In patients treated with anti-PD-1 or PD-L1 cancer therapies there is evidence of exacerbated SLE, new-onset lupus nephritis-like disease and checkpoint inhibitor-induced subacute cutaneous lupus erythematosus-like symptoms[84–88]. Inflammatory arthritis has also emerged as a common irAE following anti-PD-1 therapy and there is evidence of the worsening of new-onset arthritis that resembles RA[89–92]. In one retrospective study, 50% of patients with pre-existing RA treated with immune-checkpoint inhibitors (ICIs), mostly anti-PD-1 therapy, experienced RA flare[93]. Notably, patients can be negative for rheumatoid factor and cyclic citrullinated peptide antibodies, which suggests that mechanisms of disease pathogenesis might differ when comparing RA and anti-PD-1-induced inflammatory arthritis[92,94–99]. Polymyalgia rheumatica is also associated with anti-PD-1 and PD-L1 therapies[100–102]. In addition, myositis and exacerbation of pre-existing SjD and sicca syndrome are associated with these therapies, although, as with inflammatory arthritis, the mechanism of ICI-induced sicca syndrome probably differs from that of SjD[103–107]. Finally, mucosal inflammation with flares of pre-existing or new-onset psoriatic lesions and psoriatic arthritis-like disease are associated with anti-PD-1 therapy[108–112]. Although the incidence and prevalence of ICI-induced connective tissue disorders and their mechanistic differences from classically defined diseases are still debated, clear evidence indicates worsening or new-onset tissue inflammation following PD-1 blockade. These data highlight the role of PD-1 in maintaining tissue tolerance and the therapeutic promise of targeting PD-1.

The role of PD-1 in T_{reg} cells. Although extensive research has focused on the role of PD-1 in effector T cells, studies over the past 10 years have shed light on the function of PD-1 in regulatory T (T_{reg}) cells. PD-1 can restrain T_{reg} cell activity; in the peripheral blood of healthy individuals, PD-1 expression is associated with diminished T_{reg} cell suppressive capacity, increased IFNγ expression, increased phosphorylation of FOXO1 (and subsequent nuclear exclusion) and decreased demethylation of the T_{reg} cell-specific demethylated region locus, which suggests decreased stability and expression of FOXP3. In addition, these dysfunctional T_{reg} cells are enriched for components of the PI3K–AKT and mTOR pathways[113]. The PI3K–AKT pathway is known to restrain T_{reg} cell function, owing, in part, to the phosphorylation and nuclear exclusion of FOXO1 by PI3K–AKT[114–118].

Blockade or loss of PD-1 on T_{reg} cells enhances their suppressive capacity[119–121]. In the lupus mouse model NZB/W F1, treatment with anti-PD-1 reduces the number of $CD4^+$ T cells in the kidneys, promotes T_{reg} cell-mediated suppression of B cells and T helper (T_H) cells and ameliorates nephritis[122,123]. In both the NOD and EAE mouse models, selective genetic deletion of PD-1 specifically in T_{reg} cells increases their suppressive capacity both in vitro and in vivo, which is mediated, in part, through reduced PI3K–AKT pathway signalling in PD-1-deficient T_{reg} cells[124]. The role of PD-1 in regulating the PI3K–AKT pathway highlights a mechanism by which PD-1 directly inhibits T_{reg} cell function.

Parallel observations in people with cancer indicate that PD-1 blockade can enhance the suppressive capacity of T_{reg} cells within tumours, which limits the effectiveness of therapy. Studies in patients with gastric cancer, non-small-cell lung cancer and glioblastoma reveal that expression of PD-1 on T_{reg} cells is associated with T_{reg} cell dysfunction, including expression of the pro-inflammatory cytokine IFNγ[113,119,120]. In a subset of patients with cancer, hyperprogression of disease can occur after PD-1 blockade[119]. It has been hypothesized that the balance between PD-1-expressing $CD8^+$ effector T cells and PD-1-expressing T_{reg} cells might predict the response to PD-1 blockade. Indeed, in one study, an increase in PD-1-expressing T_{reg} cells was associated with a lack of clinical benefit from anti-PD-1 monotherapy in patients with metastatic clear-cell renal cell carcinoma[125]. In this study patients with a high ratio of PD-1^+ T_{reg} cells to PD-1^+Tim-3^-Lag-3^-CD8^+ T cells had shorter survival and a lower response rate, suggesting that this ratio might have predictive value and can serve as a biomarker for response to treatment[125]. The role of PD-1 in effector T cells versus T_{reg} cells makes PD-1 a unique immune-checkpoint target, as a PD-1 agonist would inhibit both effector and regulatory T cell responses. Whether these divergent cell-type-specific effects could dampen the success of a PD-1 agonist in treating rheumatic disease needs to be critically assessed.

Strategies to target PD-1 for autoimmune disease

Therapeutic strategies to target PD-1 for treatment of autoimmunity are being investigated in vitro and in in vivo mouse models. In one study, mice were treated with engineered DCs that expressed both PD-L1 and peptide–MHC complexes, which substantially ameliorated EAE[126]. Agonist antibodies that specifically activate, rather than block, PD-1 receptor signalling are being explored as a potential therapeutic approach to autoimmune disease. The generation of agonist antibodies is complex and often requires empirical validation of antibody function in vitro and in vivo. Despite these challenges, agonist antibody design can be informed by analytical approaches that consider factors such as antibody binding affinity, epitope specificity and Fc receptor engagement[127–129].

To this end, a bispecific molecule, known as ImmTAII (immune modulating monoclonal TCR against autoimmunity) has been developed with the aim of providing tissue-specific protection by fusing a PD-1 agonist antibody with a high-affinity recombinant TCR that

Table 1 | Downstream effects of immune-checkpoint receptor signalling in T cells

Immune checkpoint receptor	Conventional T cell ($CD4^+$ $FOXP3^-$)	Regulatory T cell ($CD4^+$ $FOXP3^+$)
PD-1	Decreased activation, proliferation, cytokine production, survival, glucose uptake and glycolysis[32,41–43,47,48,261]	Increase in IFNγ production and the PI3K–AKT–mTOR pathway[113]; decreased suppressive capactiy[121,123,124]
BTLA	Decreased activation, proliferation and cytokine production[140,144,174]	No direct effect of BTLA on T_{reg} cell suppressive function[146]; HVEM$^+$ T_{reg} cells inhibit BTLA$^+$ effector T cells[146]
TIGIT	Decreased activation, proliferation[202,230] and cytokine production[202]	Increased suppressive function, FOXP3 expression, IL-10 and FGL2 production[203,210]; decreased PI3K–AKT pathway[19]

AKT, protein kinase B; BTLA, B and T lymphocyte attenuator; FGL2, fibrinogen-like protein 2; HVEM, herpesvirus entry mediator; mTOR, mechanistic target of rapamycin; PI3K, phosphoinositide 3 kinase; TIGIT, T cell immunoreceptor with Ig and ITIM domains; T_{reg} cells, regulatory T cells.

Table 2 | Summary of preclinical studies of immune-checkpoint receptors in models of autoimmune and inflammatory diseases

Immune checkpoint receptor	Agonism or activation	Antagonism or genetic deletion
PD-1	Inhibits NFAT activation, IL-2 production and $CD8^+$ T cell cytotoxicity in vitro[130] Ameliorates GVHD and adoptive transfer colitis[129] Reduces disease severity in the BM12 transfer model of lupus[132] Disruption of CD80–PD-L1 interactions with antibodies reduces disease severity and cytokine-producing cells in mouse models of arthritis and SjD[133]	More severe insulitis and accelerated diabetes development in the NOD mouse model[50,51] Increases EAE disease severity[52,53] Increases tissue infiltration of T cells and B cells in a mouse model of SjD[54] Increases severity and frequency of CIA[55] T_{reg} cell-specific deletion ameliorates disease in EAE and NOD mouse models[124]
BTLA	Delays NOD diabetes[171,172] Ameliorates disease in a mouse model of psoriasis[196]	Increases EAE disease severity[140] Accelerates diabetes in RIP-OVA model[169] Loss of $CD4^+$ T cell-mediated oral tolerance[169] Increases autoantibodies and lymphocyte infiltration into tissue in the MRL/lpr mouse model of lupus[170]
TIGIT	Reduces anti-collagen antibodies and disease severity in CIA[219] Ameliorates bone marrow failure in aplastic anaemia[227] Reduces autoantibodies and increases survival in lupus-prone NSB/NZW mice[229] Reduces EAE disease severity[218,231] Reduces autoantibody production in imiquimod-induced lupus[231]	Increases EAE disease severity[201,202]

BTLA, B and T lymphocyte attenuator; CIA, collagen-induced arthritis; EAE, experimental autoimmune encephalomyelitis; GVHD, graft-versus-host disease; NOD, non-obese diabetic; SjD, Sjögren disease; SLE; systemic lupus erythematosus; TIGIT, T cell immunoreceptor with Ig and ITIM domains.

is specific for pancreatic-restricted peptide–HLA complexes. These bispecific antibodies use the TCR to direct PD-1 agonist antibodies to cells presenting preproinsulin peptide, thereby locally inhibiting autoreactive T cells, with potential application as a treatment for T1DM[130]. Data from studies of cell lines and primary human T cells indicate that ImmTAII successfully activates PD-1 signalling, inhibits nuclear factor of activated T cells (NFAT) activity, suppresses IL-2 production and reduces $CD8^+$ T cell cytotoxicity in vitro[130]. In another study, a computational approach was used to engineer novel proteins to agonize PD-1 using a binding motif identified in both human and mouse PD-L1, resulting in a soluble miniprotein called PD-MP1. This 40-amino acid protein binds PD-1 in monomeric and trimeric forms. Co-culture of the miniprotein trimer with T cells from mice reduced T cell activation, as measured by CD69 expression[131]. Researchers have also screened anti-PD-1 antibodies for agonistic function and found that agonist activity correlates with binding to the membrane-proximal extracellular region of PD-1, which is distinct from binding epitopes of most PD-1 blocking antibodies and requires Fc receptor-dependent cross-linking. In mouse models of graft-versus-host disease and adoptive transfer colitis models, preventative administration of this agonistic antibody ameliorates disease severity and reduces cytokine-producing effector T cells[129]. Another PD-1 agonist that ameliorates disease severity when delivered before disease onset has been studied in the BM12 transfer model of lupus[132]. This PD-1 agonist functions by excluding large receptor-type protein tyrosine phosphatases, such as CD45, from the receptor complex and enables recruitment of SHP-2. Additionally, human and mouse antibodies that target CD80 have been developed to disrupt the *cis* interaction between CD80 and PD-L1, thereby enabling uninterrupted interactions between PD-L1 and PD-1 (ref. 133). In several mouse models of rheumatic disease, including arthritis and SjD, treatment with these anti-CD80 antibodies prior to disease onset (but after disease induction) reduces disease severity and cytokine-producing T cells[133]. These approaches illustrate the translational potential of harnessing PD-1 agonism for the treatment of autoimmune diseases.

PD-1 agonists in clinical trials

Given the success in preclinical studies, several PD-1 agonists are now being explored in clinical trials (Table 3). Rosnilimab is a humanized IgG1-k antibody that targets PD-1. This therapy probably functions by both depleting PD-1 and acting as an agonist that binds a membrane proximal epitope and has optimized Fc receptor binding affinity[134]. This drug is reported to specifically deplete activated $PD\text{-}1^{hi}$ T cells, including effector T cells, T follicular helper (T_{FH}) cells and peripheral T helper cells, and agonize any remaining $PD\text{-}1^+$ T cells. This mechanism is anticipated to lead to reduced T cell migration, proliferation and cytokine secretion and also decreased plasma-cell generation and autoantibody levels[134]. In the $CD4^+$ T cell transfer mouse model of colitis, rosnilimab-treated mice did not lose weight, had reduced colon pathology and showed lower expression of pro-inflammatory genes in colonic tissue than isotype-treated animals[134]. Rosnilimab was well tolerated in a phase I trial; administration resulted in reduced PD-1-expressing $CD4^+$ and $CD8^+$ T cells (without altering T_{reg} cell numbers) and reduced effector T cell functions when restimulated ex vivo[135]. Rosnilimab is now being studied in phase II trials (NCT06041269 and NCT06127043) in moderate-to-severe RA and ulcerative colitis. In a phase IIb trial (NCT06041269) evaluation of placebo versus rosnilimab in patients with moderate-to-severe RA, who were also being treated with other anti-rheumatic drugs such as methotrexate, rosnilimab showed a statistically significant reduction in disease activity after 12 weeks of treatment. Patients who received 100 mg every 4 weeks and 600 mg every 2 weeks had a mean reduction of 2.06 in the disease

activity score in 28 joints using C-reactive protein concentrations (DAS28-CRP) and patients who received 400 mg every 4 weeks had a mean reduction of 2.12 in the DAS28-CRP score[136]. By contrast, rosnilimab failed in a phase II trial (NCT05205070) for alopecia areata[137]; the reasons for these differences remain unclear.

Peresolimab is a humanized IgG1 monoclonal antibody designed to activate PD-1 signalling. Peresolimab showed efficacy in a placebo-controlled phase II trial (NCT04634253) of 98 patients with mild-to-severe RA who had a poor response to conventional therapies[138]. Patients who received 700 mg of peresolimab had a statistically significant reduction in the DAS28-CRP score after 12 weeks, which was the primary end point of the study, compared with the placebo group[138,139]. A phase IIb trial (NCT05516758) of peresolimab in RA was terminated owing to evaluations of the risk:benefit ratio in this setting. The future direction for the development of peresolimab is currently unclear.

PD-1 is a promising therapeutic target because its expression is induced specifically upon T cell activation, meaning that strategies to enhance its function will probably only affect antigen-specific T cell responses rather than causing global immune suppression. However, given the role of PD-1 in controlling initial T cell activation, the balance and activation of T effector cells versus T_{reg} cells and T cell exhaustion, PD-1 agonist approaches require careful evaluation. Expanding patient cohorts and extending clinical trials to assess long-term efficacy and potential adverse effects, especially increased susceptibility to infections or cancer, will be essential.

BTLA

BTLA was first identified in a microarray screen as a T_H1 cell-specific transcript with predicted inhibitory function[140]. BTLA has emerged as a key receptor in a network of interactions that modulate immune activation, with considerable implications for antitumour responses and autoimmunity. Although ongoing research is beginning to unravel the mechanisms underlying the role of BTLA in rheumatic disease, this research is complex as herpesvirus entry mediator (HVEM, also known as CD270), the ligand for BTLA, has multiple other binding partners that are broadly expressed across immune-cell populations. Efforts are underway to translate research findings into clinical applications.

BTLA–HVEM interactions

BTLA is expressed by many immune cells, including B cells, T cells, NK cells, monocytes and DCs[141–145]. BTLA is constitutively expressed at high levels on naive B cells, with lower expression on naive $CD4^+$ and $CD8^+$ T cells but can be induced upon activation[142,146]. In addition, BTLA is highly expressed on T_{FH} cells in germinal centres[147]. In contrast to other inhibitory receptors, such as PD-1, BTLA is not highly expressed on $CD4^+FOXP3^+$ T_{reg} cells[146].

HVEM is a member of the TNF family of receptors. HVEM is expressed on several immune-cell types, including B cells, T cells (including $CD4^+FOXP3^+$ T_{reg} cells), NK cells, DCs and other myeloid cells[148]. HVEM binding to BTLA induces phosphorylation of two tyrosine-containing motifs in the cytoplasmic tail of BTLA (ITIM and ITSM), which leads to the recruitment of SHP-1 and SHP-2 (ref. 140).

Table 3 | Clinical trials of immune checkpoint agonists in autoimmune and inflammatory diseases

Agent	NCT number	Trial overview	Status	Results
PD-1				
Rosnilimab	NCT06127043	Phase II efficacy and safety study in people with moderate-to-severe ulcerative colitis (ROSETTA)	Recruiting	Not applicable
Rosnilimab	NCT06041269	Phase IIb efficacy and safety study in people with moderate-to-severe RA (RENOIR)	Active (not recruiting)	Met primary end point with statistically significant change from baseline disease at 12 weeks[262]
Rosnilimab	NCT05205070	Phase II efficacy and safety study in people with moderate-to-severe alopecia areata (AZURE)	Terminated	No results posted
Peresolimab	NCT05959109	Phase I relative bioavailability study in healthy people	Completed	No results posted
Peresolimab	NCT05516758	Phase IIb study in people with moderately-to-severely active RA (RESOLUTION-1)	Completed	No results posted
Peresolimab	NCT04634253	Phase IIa study in people with RA	Completed	Reduced DAS28-CRP[138]
BTLA				
LY3361237	NCT03695198	Phase I study in people with SLE	Completed	No results posted
LY3361237	NCT04975295	Phase I study in people with psoriasis	Completed	No results posted
LY3361237	NCT05123586	Phase II study in people with at least moderately active SLE	Terminated	Lack of efficacy
LY3361237	NCT03933943	Phase I study in people with SLE	Completed	No results posted
LY3361237	NCT05781451	Phase II study in people with SjD	Withdrawn	No results posted
ANB032	NCT05935085	Phase II study to evaluate the safety, tolerability and efficacy in people with moderate-to-severe atopic dermatitis	Terminated	Did not meet primary or secondary end points[197]

BTLA, B and T lymphocyte attenuator; DAS28-CRP, disease activity score in 28 joints using C-reactive protein concentrations; RA, rheumatoid arthritis; SjD, Sjögren disease; SLE, systemic lupus erythematosus.

BTLA also contains a third tyrosine motif in its cytoplasmic domain that binds Grb-2 and is thought to mediate interactions with PI3K[149].

HVEM has several ligands in addition to BTLA, including CD160, lymphotoxin α, LIGHT (also known as TNFSF14), synaptic adhesion-like molecule 5 and herpesvirus glycoprotein D[146,150–156]. HVEM binding to its other ligands induces effects that counteract BTLA inhibitory signalling, such as lymphocyte activation, proliferation and pro-inflammatory cytokine production[148,150,157–159].

BTLA function

BTLA–HVEM interactions transmit signals bidirectionally. BTLA binding to HVEM transmits an inhibitory signal into the BTLA-expressing cell. This inhibitory signalling downregulates immune-cell function and maintains tolerance[142]. This BTLA–HVEM interaction can also send a co-stimulatory signal into HVEM-expressing cells that results in the activation of NF-κB signalling and increased cell survival[142].

HVEM binding to BTLA on both mouse and human T effector cells results in dephosphorylation of CD3ζ and CD28 (refs. 160,161). Downstream effects include reduced proliferation, activation and cytokine production (IFNγ and IL-10)[140,144]. HVEM–BTLA interactions between T effector cells and T_{reg} cells serve as one mechanism of inhibition. Effector T cells downregulate HVEM upon activation, whereas T_{reg} cells upregulate HVEM expression upon activation; elevated HVEM expression on T_{reg} cells enables these cells to interact with BTLA-expressing effector T cells and induce suppression of these effector T cells[146]. In an MHC mismatched cardiac allograft mouse model, HVEM$^{-/-}$ T_{reg} cells were less suppressive than those from wild type animals in vitro and in vivo, which suggests a crucial role for HVEM in T_{reg} suppressive function[146].

B cells in both mice and humans express higher levels of BTLA than T cells, and the interaction of BTLA on B cells with HVEM leads to similar inhibitory effects, including reduced B cell proliferation and cytokine production (IL-6, IL-10 and TNF)[145,152,162,163]. BTLA can also be expressed on DCs, and studies in mice indicate that it can suppress their proliferation, maturation and pro-inflammatory cytokine production[142,164,165]. Thus, BTLA not only inhibits T cell and B cell responses but also suppresses APCs.

BTLA can bind to HVEM in *cis* or *trans*[154,166]; BTLA–HVEM *cis* interactions prevent HVEM from binding to its activating ligands on other cells[154,157], thereby serving as a mechanism by which BTLA limits T cell activation.

Role of BTLA in autoimmune disease

Similar to PD-1, BTLA has a key role in the maintenance of tolerance and controlling the onset and severity of autoimmune disease. Mouse models of NOD diabetes and EAE have shown that loss of BTLA leads to accelerated disease, whereas the presence or agonism of BTLA inhibits T cell responses and delays disease onset. Studies in humans have found differential expression of BTLA in patients and healthy individuals, and potential defects in the BTLA axis that could contribute to disease. Thus, BTLA represents a therapeutic target that has been studied in both preclinical and clinical settings (Table 2).

Preclinical studies. In mouse models, BTLA has an essential role in maintaining tolerance. BTLA-deficient 129/SvEV mice develop spontaneous autoimmune hepatitis-like disease with features of SjD, a common complication of autoimmune hepatitis, including pro-inflammatory cell infiltrates in the salivary glands[167]. Loss of BTLA in mice leads to increased severity of EAE and reduced IL-10 production from BTLA$^{-/-}$ T_{reg} cells and B cells[140,168]. BTLA deficiency prevents the induction of ovalbumin (OVA) peptide-induced oral tolerance in CD4$^+$ T cells[169]. In the RIP-OVA mouse model of T1DM, transfer of BTLA$^{-/-}$ OT-1 CD8$^+$ T cells accelerates the development of disease compared with control mice, which demonstrates a role for BTLA in CD8$^+$ T cell tolerance[169]. Loss of BTLA in the MRL/lpr mouse model of lupus accelerates disease, with elevated levels of autoantibodies and increased lymphocytic infiltrates in the salivary glands, kidneys and knee joints compared with BTLA-sufficient MRL/lpr mice[170].

Administering a BTLA-targeting antibody (clone 6F7), which can both agonize BTLA and deplete BTLA-expressing cells, to NOD mice increases the proportion of T_{reg} cells, reduces B cell and effector T cell populations and delays onset of disease. In addition, this anti-BTLA antibody delays the onset of anti-PD-1-induced diabetes in NOD mice when co-administered[171]. Transfer of bone-marrow-derived, BTLA-transfected DCs into NOD mice inhibits CD8$^+$ T cell responses and also delays disease onset and incidence[172]. In a mouse model of islet transplantation, a non-depleting BTLA antibody (clone PJ196) improved graft survival[173]. The PJ196 antibody downregulated the expression of cell-surface BTLA without depleting BTLA-expressing cells[173]; however, PJ196 did not decrease T cell proliferation in vitro[174], which suggests that it lacks agonistic activity. Further work is needed to elucidate the mechanism of action of PJ196 in vivo. Despite these uncertainties, these findings show the therapeutic potential of targeting BTLA in autoimmunity.

Clinical evidence. Human studies parallel findings in mouse models of disease and suggest a role for BTLA in maintaining immune tolerance. Genetic polymorphisms in the *BTLA* gene are associated with susceptibility to autoimmune disease in specific ethnic populations. The C + 800 T SNP in exon 5 and 590 C SNP in exon 4 of BTLA are associated with increased susceptibility to RA[175,176]. In stimulated Jurkat cells (an immortalized human T cell line), expression of BTLA with the 590 C SNP results in increased IL-2 expression compared with BTLA 590A-expressing control cells, suggesting that the 590 C SNP impairs the inhibitory function of BTLA[176]. The SNP 1p36 in HVEM is also associated with increased susceptibility to RA[177–182].

Beyond genetic associations, a number of research groups have reported differential BTLA protein expression in patients with rheumatic diseases[183–185]. In individuals with active SLE, the percentage of peripheral blood BTLA$^+$CD4$^+$ T cells is reduced compared with healthy individuals, despite no statistically significant difference in BTLA expression levels on T_{reg} cells[183]. Similarly, naive B cells from people with SLE express lower levels of BTLA compared with those from healthy individuals[184]. Further research is needed to determine whether patients who are predisposed to autoimmune diseases have a genetic tendency towards lower BTLA expression or if these alterations in expression are a response to dysregulated tissue inflammation. However, some evidence suggests that BTLA regulation and function in patients with rheumatic disease is defective; for example, CD4$^+$ T cells from people with SLE have impaired BTLA upregulation following ex vivo activation, are less sensitive to BTLA-mediated inhibition, as indicated by altered proliferation and CD25 expression, and have reduced recruitment of the BTLA receptor to the TCR synapse upon activation[185]. The potential effects of such inherent BTLA defects on BTLA-targeting therapies remain to be evaluated.

By contrast, studies in RA indicate elevated BTLA expression in immune cells; in people with RA the percentages of CD3$^+$, CD4$^+$ and CD8$^+$ T cells that express BTLA are increased in peripheral blood,

whereas the percentages of $CD3^+$, $CD4^+$ and $CD8^+$ T cells that express HVEM are decreased[186]. The frequency of $BTLA^+CD8^+$ T cells correlates negatively with swollen joint count[186]. Additionally, in people with RA, BTLA expression is higher on synovial $CD11c^+$ DCs than those at the periphery; HVEM is also increased in the synovial tissue of patients with RA[187–191]. Differences in SLE and RA might stem from differences in cell activation status and differences in tissue inflammation (synovium inflammation in RA versus multi-organ inflammation in SLE). Further studies are needed to better understand these differences and their implications for disease pathogenesis.

There has been considerable interest in characterizing BTLA expression on T_{reg} cells in people with autoimmune disease, as T_{reg} cells are essential for maintaining tolerance and T_{reg} cell dysfunction is implicated in several autoimmune diseases, including SLE and RA[192–194]. Activated T_{reg} cells isolated from peripheral mononuclear blood cells (PBMCs) from patients with SLE express higher levels of BTLA than those from healthy individuals, whereas no differences in BTLA expression are observed in resting T_{reg} cells[195]. BTLA expression on activated T_{reg} cells is particularly high in patients with mild-to-severe SLE and is associated with circulating anti-double-stranded DNA autoantibodies[195]. The increased expression of BTLA on activated T_{reg} cells in patients with SLE[195] could prolong BTLA interactions with HVEM in *cis* on T_{reg} cells and reduce the interactions of HVEM on T_{reg} cells with BTLA on effector T cells. Prolonged BTLA–HVEM *cis* interactions could also dampen *trans* engagement of HVEM with other ligands.

BTLA dysregulation in autoimmune disease, coupled with its established role in T cell inhibition, has positioned BTLA as an attractive therapeutic target. A potential agonistic antibody, BTLA monoclonal antibody PK18, can reduce T cell proliferation, IL-2 secretion and antigen-specific T cell activation in mouse $CD4^+$ and $CD8^+$ T cells in vitro[174]. Similarly, in studies using human PBMCs, crosslinking BTLA on naive and pre-activated $CD4^+$ T cells in vitro inhibits proliferation and reduces IFNγ and IL-10 production. In $CD8^+$ T cells, however, these inhibitory effects are only observed when pre-activated $CD8^+$ T cells are cultured with anti-BTLA, probably owing to differences in BTLA expression level; $CD4^+$ T cells express higher BTLA at baseline than $CD8^+$ T cells[144]. The ability of anti-BTLA to inhibit pre-activated T cells is particularly relevant for treating autoimmunity and inflammatory diseases as effector T cells are typically in an activated state during autoimmune reactions.

In summary, studies in patients with autoimmune disease have highlighted multiple mechanisms by which the BTLA–HVEM axis may regulate tolerance, supporting its continued investigation as a therapeutic target. Further work is needed to dissect these possible interactions and determine how BTLA–HVEM *cis* interactions on T_{reg} cells contribute to the severity of inflammation observed in patients with SLE and other autoimmune diseases. The differing responses of $CD4^+$ T cells and $CD8^+$ T cells to BTLA agonists suggest that therapeutic agonism strategies might be more effective against $CD4^+$ T cell-mediated tissue inflammation than $CD8^+$ T cell-mediated tissue inflammation, and more studies are needed to address this issue.

BTLA agonists in clinical trials

Successes in preclinical studies have translated to the clinic with several agonists currently undergoing clinical trials (Table 3). Three humanized BTLA agonistic antibodies have been developed that have unique and non-overlapping epitope specificities and agonistic activity both in vitro and in a mouse model of psoriasis[196]. One such antibody is the monoclonal antibody 22B3, which not only binds BTLA and promotes BTLA inhibitory signals but also antagonizes stimulatory HVEM signalling when bound to BTLA engaged with HVEM in *cis*[196]; however, a phase II trial of 22B3 (LY3361237) in SLE was terminated owing to a lack of efficacy (NCT03933943). In a phase IIb trial, another BTLA agonist, ANB032, did not meet primary or secondary endpoints for moderate-to-severe atopic dermatitis[197]; ANB032 development has now been halted. Evaluating clinical outcomes and the extent of potential adverse effects or safety concerns will be essential for identifying promising BTLA agonist agents that can effectively inhibit effector T cells and B cells and activated APCs to treat ongoing tissue inflammation.

TIGIT

TIGIT (also known as Vstm3), was first identified as a novel co-inhibitory receptor in 2009 by several research groups[198–200]. Since that time, TIGIT has gained considerable interest in the field of cancer immunotherapy, with many clinical trials underway to antagonize its inhibitory functions[10]. Concurrently, TIGIT signalling is being studied extensively as a regulator of tolerance in autoimmunity and could have potential as a therapeutic target for multiple rheumatic diseases.

TIGIT ligands

TIGIT is expressed on a range of immune cell types, including $CD4^+$ T cells, $CD8^+$ T cells, T_{reg} cells, T_{FH} cells, B cells, NK cells, ILCs and macrophages[198–203]. Similar to other immune-checkpoint receptors, TIGIT is upregulated upon T cell activation[202]. TIGIT and the costimulatory receptor CD226 share two ligands: CD155 (also known as poliovirus receptor, PVR) and CD112 (also known as PVRL2 or nectin-2)[198,204]. Both ligands are expressed on APCs, non-haematopoietic cells and tumour cells[198,199,201,204,205]. Each of these ligands has additional binding partners; CD112 binds to CD112R (also known as PVRIG), whereas CD155 binds to CD96 (CD96 can also bind to CD111 (ref. 206)) (Fig. 1).

TIGIT function

Studies in both mice and humans demonstrate that TIGIT inhibits T cell responses by both cell-intrinsic (signalling into TIGIT-expressing cells) and cell-extrinsic mechanisms (interactions with other cells). The high binding affinity of TIGIT enables it to outcompete CD226 for their shared ligands[198,199,201,204,205,207,208] (Fig. 1). TIGIT also interacts with CD226 in *cis*, preventing CD226 dimerization, a requisite step for CD226 co-stimulatory signalling[209]. TIGIT binding to CD155 on APCs triggers 'back-signalling', which results in a decrease in IL-12 production and increased IL-10 production, leading to the generation of tolerogenic DCs[198]. TIGIT–ligand interactions on $CD4^+FOXP3^-$ T cells, $CD8^+$ T cells and NK cells inhibit their effector functions[10,202]. By contrast, TIGIT–ligand interactions on T_{reg} cells enhance their effector functions[203,210]. Thus, TIGIT can induce bi-directional inhibition; TIGIT signalling within T cells can promote T_{reg} cell activity and suppress effector T cell function, whereas 'back-signalling' via its ligand CD155 sends a negative signal into APCs (such as DCs), which limits their ability to promote the generation of effector T cells[198]. In addition, TIGIT might directly inhibit TCR components and signalling, although this mechanism is not fully understood[202].

In both mice and humans, TIGIT is constitutively expressed on T_{reg} cells, unlike effector T cells[198,203,210,211], and has a role in the maintenance and suppressive function of natural T_{reg} cells as well as in the induction of induced T_{reg} cells[203]. $TIGIT^+$ T_{reg} cells are more suppressive in vitro, produce more IL-10 and express higher levels of FOXP3 than $TIGIT^-$ T_{reg} cells[203,210]. TIGIT induces expression of the

immunoregulatory molecule FGL2 in mouse T_{reg} cells. FGL2 enhances T_{reg} cell suppressive function and selectively inhibits T_H1 and T_H17 cells rather than T_H2 cells, thereby adjusting the balance of $CD4^+$ T cell subsets[203]. A potential molecular mechanism by which TIGIT signalling enhances T_{reg} cell function is by inhibiting the PI3K–Akt pathway. This inhibition prevents PI3K–Akt pathway-mediated restraint of T_{reg} cell function and thereby increases T_{reg} cell suppressive activity[114–117,212,213].

TIGIT expression is also induced following B cell activation and can enhance the regulatory functions of these cells[214]. Selective deletion of TIGIT in B cells leads to the development of spontaneous CNS neuroinflammation, which results in a paralytic disease in mice[215]. In vitro co-culture assays demonstrate that $TIGIT^{hi}$ memory B cells from human PBMCs express more IL-10 and granzyme B, inhibit $CD4^+$ T cell proliferation and suppress both DC maturation and pro-inflammatory cytokine production more efficiently than $TIGIT^-$ B cells[214]. Similarly, TIGIT expression on B cells in both mice and humans is associated with optimal IL-10 production[215,216], and analysis of $TIGIT^+$ B cells from PBMCs obtained from healthy donors shows that these cells suppress T_{FH} cell proliferation and IL-17 production in vitro[217]. Patients with multiple sclerosis who respond to B cell depletion therapy show an increased frequency of $TIM\text{-}1^+TIGIT^+$ B cells[216], which suggests that response to therapy in these patients might depend on promoting $TIM\text{-}1^+$ $TIGIT^+$ regulatory B cell reconstitution after depletion.

Role of TIGIT in autoimmune disease

Both preclinical and clinical studies demonstrate that TIGIT has a regulatory role in autoimmune disease (Table 2); however, there are currently no clinical trials underway to evaluate targeting TIGIT therapeutically for rheumatic disease.

Preclinical studies. Preclinical models of autoimmune disease highlight a crucial role for TIGIT in protecting against aberrant effector T cell responses and tissue inflammation. Blockade or genetic deletion of TIGIT exacerbates disease in mice with EAE, and the frequency of antigen-specific $CD4^+$ T cells and pro-inflammatory cytokines are increased upon restimulation with myelin peptide in vitro[201,202,218]. In addition, when 2D2 mice, TcR transgenic mice with a T cell receptor recognizing myelin oligodendrocyte glycoprotein (MOG), are crossed with $TIGIT^{-/-}$ mice, the resulting 2D2x$TIGIT^{-/-}$ mice develop spontaneous neurological dysfunction as early as 28 weeks. Compared with 2D2 transgenic mice, 2D2x$TIGIT^{-/-}$ mice develop spontaneous clinical signs of EAE that are more severe, which suggests a role for TIGIT in maintaining tolerance in CNS autoimmune models[202]. Overexpression of TIGIT in the CIA mouse model of RA ameliorates disease severity, with a concomitant reduction in the levels of anti-collagen type II antibodies[219]. These findings support the therapeutic potential of TIGIT agonism in RA.

Clinical evidence. TIGIT expression on T cells is altered in people with rheumatic diseases. TIGIT expression correlates inversely with disease activity[219]. In patients with RA, the frequency of $TIGIT^+CD4^+$ T cells in the synovial fluid is lower during active disease than in inactive disease. TIGIT expression is also lower on NK cells in patients with RA or SLE, and TIGIT expression correlates negatively with NK-cell IFNγ production[220]. Patients with active SLE have lower frequencies of $TIGIT^+$ NK cells in PBMCs than patients with inactive disease. Blockade of TIGIT on these NK cells enhances IFNγ production, which indicates that even low cell-surface expression of TIGIT can still restrain NK-cell function[221]. Similarly, the frequencies of $TIGIT^+CD4^+$ T cells and $TIGIT^+CD8^+$ T cells are lower in the periphery of patients with SLE and renal involvement than in healthy individuals[222]. In patients with psoriasis, TIGIT expression is also reduced on $CD4^+$ T cells from PBMCs compared with healthy individuals[223,224]. Treatment with the anti-TNF therapy infliximab increases the expression of TIGIT on $CD4^+$ T cells from people with psoriasis. Patients with lower baseline TIGIT expression on $CD4^+$ T cells have a greater reduction in psoriasis area and severity index score than people with higher baseline expression. This finding suggests that assessing TIGIT expression on circulating T cells prior to treatment might predict responsiveness to infliximab[224].

Other studies, however, report elevated TIGIT expression on T cells in rheumatic diseases, which probably reflects their activation status, as TIGIT expression is increased upon T cell activation (Fig. 2). In SLE, elevated TIGIT expression on $CD4^+$ T cells, particularly in patients with high antibody titres, correlates positively with SLE disease activity index, CRP and ESR scores. $TIGIT^+CD4^+$ T cells also exhibit higher levels of CD69 expression than $TIGIT^-$ counterparts, which suggests that TIGIT expression might mark a subset of activated $CD4^+$ T cells in patients with SLE[225]. It remains unclear if a connection exists between high autoantibody production in patients with SLE and the role of TIGIT in T_{FH} cells or T follicular regulatory cells, which might regulate autoreactive B cells and autoantibody production. Similarly, analysis of PBMCs from patients with active SjD reveals higher frequencies of $CD4^+$ and $CD8^+$ T cells that express CD226 and TIGIT compared with those with inactive disease, and $TIGIT^+CD4^+$ T cells correlate positively with ESR[226]. To reconcile these findings, further functional analyses of $CD4^+$ and $CD8^+$ T cell subsets that express TIGIT in highly inflammatory autoimmune microenvironments across various diseases and tissues are needed to distinguish correlation from causality.

Strategies to agonize TIGIT in autoimmune disease

Several approaches are being developed to activate TIGIT signalling. These approaches, which include TIGIT overexpression, a recombinant CD155 protein, TIGIT-Ig fusion proteins and agonist antibodies, have shown success in modulating T cell responses and disease in preclinical models. Overexpression of TIGIT in $CD4^+$ T cells can ameliorate disease in the CIA mouse model of RA and mouse models of aplastic anaemia[219,227]. Overexpression of TIGIT (via transfection) in $CD4^+$ T cells isolated from the synovial fluid of patients with RA inhibits proliferation and pro-inflammatory cytokine production[219].

Recombinant human CD155–Fc protein binds to TIGIT and agonizes receptor signalling; however, given that TIGIT ligands have several binding partners, recombinant CD155 could engage TIGIT, CD226 and CD96. Isolating $CD4^+$ T cells from psoriatic lesions from patients and culturing these cells with soluble CD155–Fc protein reduces their proliferation and pro-inflammatory cytokine production, with a concomitant increase in IL-10 production[223]. Multiple autoimmune diseases are associated with an increased frequency of 'T_H1 T_{reg} cells', which are characterized by reduced suppressive capacity and increased pro-inflammatory cytokine production[212]. Pre-treatment of $IFNγ^+$ T_H1 T_{reg} cells isolated from patients with multiple sclerosis with the CD155–Fc protein reduces IFNγ production and increases the suppressive capacity of these cells[212]. Administration of recombinant CD155–Fc protein also delays disease onset in vivo in the MRL/lpr model of lupus[228].

Administering a recombinant TIGIT–Ig fusion protein to lupus-prone NSB/NZW mice prior to disease onset reduces autoantibody production, and increases survival compared with mice treated with a control IgG[229]. In the CIA model, treatment with a TIGIT tetramer or TIGIT–Ig fusion protein causes statistically significant reductions

in disease, decreases serum levels of IL-6 and IL-10 and reduces $CD4^+$ T cell production of IL-17A, TNF, IFNγ and IL-10 (ref. 201). The observed reduction in anti-inflammatory cytokines (such as IL-10) probably results from an overall inhibition of $CD4^+$ effector T cell responses, although T_{reg} cells might also be affected.

TIGIT agonist antibodies show inhibitory effects in mouse models of autoimmunity and in human cells in vitro. Both the low-affinity 1G9 and high-affinity 4D4 agonist antibodies ameliorate disease severity in mice with EAE and reduce the frequency of IL-17-producing T cells in the CNS[218]. Human $CD4^+$ and $CD8^+$ T cells cultured with TIGIT-agonizing antibodies exhibit reduced proliferation, activation (lower CD25 and CD69 expression) and cytokine production (IL-2 and IFNγ)[201,230]. In human TIGIT knock-in mice, administration of human TIGIT-agonizing antibodies reduces EAE severity and increases suppression of T cell-dependent autoantibody production in the imiquimod-induced lupus disease model[231]. Possible mechanisms include reduced activation of T_{FH} cells and peripheral helper T cells and increased suppressive capacity of T_{reg} cells. These studies underscore how TIGIT agonism can inhibit effector responses and ameliorate disease.

The dual functions of TIGIT on T_{reg} cells and effector T cells makes it an attractive checkpoint molecule. TIGIT signalling not only suppresses effector cells but also enhances T_{reg} cell function. TIGIT agonism would, therefore, suppress tissue inflammation by inhibiting effector T cells and increasing T_{reg} cell functions. For this reason, TIGIT agonists could offer greater promise in targeting tissue inflammation than PD-1 agonists. Although no clinical trials are currently underway, the success observed in preclinical studies suggests that TIGIT would be a promising target to pursue.

The future of immune-checkpoint modulation for autoimmunity and inflammation

Checkpoint agonists hold considerable promise for treating rheumatic diseases by providing a more specific strategy to inhibit effector responses, compared with current therapies, such as glucocorticoids or cytokine inhibitors, which broadly inhibit immune responses[232,233]. Although checkpoint agonists for PD-1, BTLA and TIGIT have demonstrated success in preclinical models of autoimmune disease, the effectiveness of PD-1 and BTLA agonists in clinical trials remains limited. Considering the multiple mechanisms by which co-inhibitory receptors exert their inhibitory functions is important; for example, both TIGIT and BTLA can participate in *cis* interactions with their ligands CD226 and HVEM respectively, which limits T cell activation by sequestering these activating receptors and simultaneously transmitting inhibitory signals in *trans* into $TIGIT^+$ or $BTLA^+$ cells. Therapeutic agonist design should be aimed at preserving these interactions to supplement overall inhibitory signalling. Intriguingly, rosnilimab, which has shown efficacy in phase IIb clinical trials for RA, has both depleting and agonistic properties. This finding raises the question of whether it is advantageous to design agonists with these dual properties to deplete activated T cells and agonize remaining T cells to restore immune balance.

The co-expression of co-inhibitory receptors on T cells suggests that there might be potential efficacy of dual agonism, such as PD-1 and TIGIT or TIGIT and BTLA. Combined agonism of both PD-1 and TIGIT with recombinant PD-L1 and CD155 in $CD4^+$ T cells from MRL/lpr mice synergistically inhibits $CD4^+$ T cell production of IFNγ and proliferation compared with single-agent agonism[234]. These findings support the potential of multi-receptor agonism as a promising therapeutic strategy, particularly for patients who do not respond to first-line treatments.

Although checkpoint agonism offers promise for treating autoimmune diseases, critically evaluating this approach for potential adverse effects is essential. Phase I clinical trials of BTLA and PD-1 agonists indicate good tolerability; however, because checkpoint agonist therapy results in prolonged inhibition of immune activation, monitoring the increased risk of infection is crucial. The most concerning adverse effect, which might require a much longer timeline to assess, is the potential for an increased risk of cancer. Adverse effects in the phase II trial of peresolimab include infections, such as skin bacterial infections and candidiasis, over the 24 weeks of the trial[138]. This time frame is insufficient to evaluate a heightened cancer risk, highlighting the importance of monitoring this factor over a longer period of time.

Other immune-checkpoint receptors are emerging as promising targets for modulating rheumatic disease. Among them is T cell immunoglobulin mucin receptor 3 (TIM-3), a member of the TIM family of proteins. TIM-3 can bind to multiple ligands, including Galectin-9, phosphatidylserine and high-mobility group box 1 (HMGB1), and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1)[10]. TIM-3 is expressed on many cell types including $CD4^+$ T cells, $CD8^+$ T cells, $CD4^+FOXP3^+$ T_{reg} cells, NK cells, myeloid cells, mast cells and B cells[235–239]. In mouse models, blockade of TIM-3 exacerbates autoimmune and inflammatory diseases, including EAE, NOD diabetes and inflammatory bowel disease[240–242]. Similar to TIGIT, TIM-3 enhances T_{reg} cell suppressive function and inhibits effector T cell responses[243–245]. Polymorphisms in TIM-3 are associated with an increased risk of autoimmune diseases[246]. Interestingly, although cellular TIM-3 expression is low in patients with psoriasis, cellular and soluble TIM-3 expression are elevated in RA[247–250].

Another promising target, lymphocyte activation gene 3 protein (LAG-3), is expressed on activated $CD4^+$ T cells, $CD8^+$ T cells and T_{reg} cells, a subset of NK cells and plasmacytoid DCs[10,251]. LAG-3 binds MHCII with higher affinity than CD4 (ref. 252). LAG-3 also has several other ligands, including liver and lymph node sinusoidal endothelial cell C-type lectin (LSECtin), FGL1, Galectin-3, α-synuclein and amyloid β precursor-like protein 1[253–256]. Loss or blockade of LAG-3 in mouse models of autoimmune disease, including NOD diabetes and EAE in B6.SJL mice, results in increased disease severity[257,258]. Findings suggest that the function of LAG-3 on T_{reg} cells might be dependent on the disease context[257,259]. Elevated levels of soluble LAG-3 are observed in patients with RA both at the periphery and in synovial fluid and are associated with disease progression[260]. Further research is needed to elucidate how LAG-3 affects disease outcomes in distinct mouse models of autoimmunity and in patients with rheumatic diseases, and to determine if LAG-3 ligands have context-dependent effects.

As several immune-checkpoint receptors including podoplanin, protein C receptor and peptidoglycan recognition protein 1 (PGLYRP1) are upregulated simultaneously, or as a module, in response to inflammation and activation[4], these inhibitory receptors also have the potential to serve as promising targets for treating autoimmune disease. A better understanding of how other checkpoint molecules influence effector T cell and T_{reg} cell function and signalling could help to identify the most promising targets for therapeutic agonism.

Conclusions

Dysregulation of PD-1, BTLA and TIGIT in patients with rheumatic disease highlights their potential as therapeutic targets for autoimmunity and inflammation. Preclinical studies demonstrate that PD-1, BTLA and TIGIT agonists can modulate T effector cells and ameliorate rheumatic disease in mouse models. Clinical trials with PD-1 agonists

show promise, as these therapeutics are well tolerated. TIGIT is particularly appealing as it supports the maintenance of and suppressive function of T_{reg} cells and also inhibits T effector cells[202,211,218]. By contrast, PD-1 agonism inhibits both effector and T_{reg} cells. These agonists can directly inhibit effector T cells, thereby reducing T effector cell-mediated inflammation and pro-inflammatory cytokine production. Some agonists can enhance regulatory functions of both T cells and B cells, further inhibiting effector responses. In addition, some agonists can prevent the differentiation of pro-inflammatory $CD4^+$ and $CD8^+$ T cell subsets and alter DC function to decrease pro-inflammatory cytokine production and DC-mediated induction of effector responses. Although further evaluation is needed to address potential adverse effects, including increased risks of infection or tumour development, checkpoint agonism represents a promising new therapeutic approach to rheumatic diseases.

Published online: 2 December 2025

References

1. Schildberg, F. A., Klein, S. R., Freeman, G. J. & Sharpe, A. H. Coinhibitory pathways in the B7-CD28 ligand-receptor family. *Immunity* **44**, 955–972 (2016).
2. Joller, N., Peters, A., Anderson, A. C. & Kuchroo, V. K. Immune checkpoints in central nervous system autoimmunity. *Immunol. Rev.* **248**, 122–139 (2012).
3. Burke, K. P., Chaudhri, A., Freeman, G. J. & Sharpe, A. H. The B7:CD28 family and friends: unraveling coinhibitory interactions. *Immunity* **57**, 223–244 (2024).
4. Chihara, N. et al. Induction and transcriptional regulation of the co-inhibitory gene module in T cells. *Nature* **558**, 454–459 (2018).
5. Odorizzi, P. M. & Wherry, E. J. Inhibitory receptors on lymphocytes: insights from infections. *J. Immunol.* **188**, 2957–2965 (2012).
6. Bengsch, B. et al. Bioenergetic insufficiencies due to metabolic alterations regulated by the inhibitory receptor PD-1 are an early driver of $CD8^+$ T cell exhaustion. *Immunity* **45**, 358–373 (2016).
7. Wherry, E. J. T cell exhaustion. *Nat. Immunol.* **12**, 492–499 (2011).
8. Wherry, E. J. & Kurachi, M. Molecular and cellular insights into T cell exhaustion. *Nat. Rev. Immunol.* **15**, 486–499 (2015).
9. Sharma, P. & Allison, J. P. The future of immune checkpoint therapy. *Science* **348**, 56–61 (2015).
10. Joller, N., Anderson, A. C. & Kuchroo, V. K. LAG-3, TIM-3, and TIGIT: distinct functions in immune regulation. *Immunity* **57**, 206–222 (2024).
11. Baumeister, S. H., Freeman, G. J., Dranoff, G. & Sharpe, A. H. Coinhibitory pathways in immunotherapy for cancer. *Annu. Rev. Immunol.* **34**, 539–573 (2016).
12. June, C. H., Warshauer, J. T. & Bluestone, J. A. Is autoimmunity the Achilles' heel of cancer immunotherapy? *Nat. Med.* **23**, 540–547 (2017).
13. Boutros, C. et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat. Rev. Clin. Oncol.* **13**, 473–486 (2016).
14. Osorio, J. C. et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Ann. Oncol.* **28**, 583–589 (2017).
15. Dillard, T., Yedinak, C. G., Alumkal, J. & Fleseriu, M. Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes. *Pituitary* **13**, 29–38 (2010).
16. Marrone, K. A., Ying, W. & Naidoo, J. Immune-related adverse events from immune checkpoint inhibitors. *Clin. Pharmacol. Ther.* **100**, 242–251 (2016).
17. Pauken, K. E., Dougan, M., Rose, N. R., Lichtman, A. H. & Sharpe, A. H. Adverse events following cancer immunotherapy: obstacles and opportunities. *Trends Immunol.* **40**, 511–523 (2019).
18. Burke, K. P., Grebinoski, S., Sharpe, A. H. & Vignali, D. A. A. Understanding adverse events of immunotherapy: a mechanistic perspective. *J. Exp. Med.* **218**, e20192179 (2021).
19. Dougan, M. & Pietropaolo, M. Time to dissect the autoimmune etiology of cancer antibody immunotherapy. *J. Clin. Invest.* **130**, 51–61 (2020).
20. Stamatouli, A. M. et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. *Diabetes* **67**, 1471–1480 (2018).
21. Iwama, S. et al. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. *Sci. Transl. Med.* **6**, 230ra245 (2014).
22. Oyarbide-Valencia, K. et al. Therapeutic implications of autoimmune vitiligo T cells. *Autoimmun. Rev.* **5**, 486–492 (2006).
23. Hasan Ali, O. et al. Human leukocyte antigen variation is associated with adverse events of checkpoint inhibitors. *Eur. J. Cancer* **107**, 8–14 (2019).
24. Bluestone, J. A., St Clair, E. W. & Turka, L. A. CTLA4Ig: bridging the basic immunology with clinical application. *Immunity* **24**, 233–238 (2006).
25. Salem, J. E. et al. Abatacept for severe immune checkpoint inhibitor-associated myocarditis. *N. Engl. J. Med.* **380**, 2377–2379 (2019).
26. McKinney, E. F., Lee, J. C., Jayne, D. R., Lyons, P. A. & Smith, K. G. T-cell exhaustion, co-stimulation and clinical outcome in autoimmunity and infection. *Nature* **523**, 612–616 (2015).
27. Keir, M. E., Butte, M. J., Freeman, G. J. & Sharpe, A. H. PD-1 and its ligands in tolerance and immunity. *Annu. Rev. Immunol.* **26**, 677–704 (2008).
28. Ahn, E. et al. Role of PD-1 during effector CD8 T cell differentiation. *Proc. Natl Acad. Sci. USA* **115**, 4749–4754 (2018).
29. Hakim, M. S., Rahmadika, N. & Jariah, R. O. A. Expressions of inhibitory checkpoint molecules in acute and chronic HBV and HCV infections: Implications for therapeutic monitoring and personalized therapy. *Rev. Med. Virol.* **30**, e2094 (2020).
30. Urbani, S. et al. PD-1 expression in acute hepatitis C virus (HCV) infection is associated with HCV-specific CD8 exhaustion. *J. Virol.* **80**, 11398–11403 (2006).
31. Schietinger, A. & Greenberg, P. D. Tolerance and exhaustion: defining mechanisms of T cell dysfunction. *Trends Immunol.* **35**, 51–60 (2014).
32. Freeman, G. J. et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J. Exp. Med.* **192**, 1027–1034 (2000).
33. Sharpe, A. H. & Freeman, G. J. The B7-CD28 superfamily. *Nat. Rev. Immunol.* **2**, 116–126 (2002).
34. Zhao, J. et al. PD-L1/PD-1 checkpoint pathway regulates hippocampal neuronal excitability and learning and memory behavior. *Neuron* **111**, 2709–2726.e2709 (2023).
35. Latchman, Y. et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat. Immunol.* **2**, 261–268 (2001).
36. Eppihimer, M. J. et al. Expression and regulation of the PD-L1 immunoinhibitory molecule on microvascular endothelial cells. *Microcirculation* **9**, 133–145 (2002).
37. Sugiura, D. et al. Restriction of PD-1 function by cis-PD-L1/CD80 interactions is required for optimal T cell responses. *Science* **364**, 558–566 (2019).
38. Siebold, C., Yamashita, T., Monnier, P. P., Mueller, B. K. & Pasterkamp, R. J. RGMs: structural insights, molecular regulation, and downstream signaling. *Trends Cell Biol.* **27**, 365–378 (2017).
39. Xiao, Y. et al. RGMb is a novel binding partner for PD-L2 and its engagement with PD-L2 promotes respiratory tolerance. *J. Exp. Med.* **211**, 943–959 (2014).
40. Park, J. S. et al. Targeting PD-L2-RGMb overcomes microbiome-related immunotherapy resistance. *Nature* **617**, 377–385 (2023).
41. Sheppard, K. A. et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett.* **574**, 37–41 (2004).
42. Patsoukis, N. et al. Selective effects of PD-1 on Akt and Ras pathways regulate molecular components of the cell cycle and inhibit T cell proliferation. *Sci. Signal.* **5**, ra46 (2012).
43. Parry, R. V. et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol. Cell Biol.* **25**, 9543–9553 (2005).
44. Okazaki, T., Maeda, A., Nishimura, H., Kurosaki, T. & Honjo, T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *Proc. Natl Acad. Sci. USA* **98**, 13866–13871 (2001).
45. Hui, E. et al. T cell costimulatory receptor CD28 is a primary target for PD-1-mediated inhibition. *Science* **355**, 1428–1433 (2017).
46. Kortum, R. L., Rouquette-Jazdanian, A. K. & Samelson, L. E. Ras and extracellular signal-regulated kinase signaling in thymocytes and T cells. *Trends Immunol.* **34**, 259–268 (2013).
47. Carter, L. et al. PD-1:PD-L inhibitory pathway affects both $CD4^+$ and $CD8^+$ T cells and is overcome by IL-2. *Eur. J. Immunol.* **32**, 634–643 (2002).
48. Chemnitz, J. M., Parry, R. V., Nichols, K. E., June, C. H. & Riley, J. L. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J. Immunol.* **173**, 945–954 (2004).
49. Boussiotis, V. A. Molecular and biochemical aspects of the PD-1 checkpoint pathway. *N. Engl. J. Med.* **375**, 1767–1778 (2016).
50. Ansari, M. J. et al. The programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese diabetic (NOD) mice. *J. Exp. Med.* **198**, 63–69 (2003).
51. Collier, J. L. et al. Single-cell profiling reveals unique features of diabetogenic T cells in anti-PD-1-induced type 1 diabetes mice. *J. Exp. Med.* **220**, e20221920 (2023).
52. Salama, A. D. et al. Critical role of the programmed death-1 (PD-1) pathway in regulation of experimental autoimmune encephalomyelitis. *J. Exp. Med.* **198**, 71–78 (2003).
53. Carter, L. L. et al. PD-1/PD-L1, but not PD-1/PD-L2, interactions regulate the severity of experimental autoimmune encephalomyelitis. *J. Neuroimmunol.* **182**, 124–134 (2007).
54. Zhou, J., Jin, J. O., Kawai, T. & Yu, Q. Endogenous programmed death ligand-1 restrains the development and onset of Sjögren's syndrome in non-obese diabetic mice. *Sci. Rep.* **6**, 39105 (2016).
55. Raptopoulou, A. P. et al. The programmed death 1/programmed death ligand 1 inhibitory pathway is up-regulated in rheumatoid synovium and regulates peripheral T cell responses in human and murine arthritis. *Arthritis Rheum.* **62**, 1870–1880 (2010).
56. Yang, L. et al. Program death-1 suppresses autoimmune arthritis by inhibiting Th17 response. *Arch. Immunol. Ther. Exp.* **64**, 417–423 (2016).
57. Mahmoudi, M. et al. PDCD1 single nucleotide genes polymorphisms confer susceptibility to juvenile-onset systemic lupus erythematosus. *Autoimmunity* **48**, 488–493 (2015).
58. Tahoori, M. T. et al. Association of programmed cell death-1 (PDCD-1) gene polymorphisms with rheumatoid arthritis in Iranian patients. *Clin. Exp. Rheumatol.* **29**, 763–767 (2011).

59. Liu, C. et al. A promoter region polymorphism in PDCD-1 gene is associated with risk of rheumatoid arthritis in the Han Chinese population of Southeastern China. *Int. J. Genomics* **2014**, 247637 (2014).
60. Ferreiros-Vidal, I. et al. Association of PDCD1 with susceptibility to systemic lupus erythematosus: evidence of population-specific effects. *Arthritis Rheum.* **50**, 2590–2597 (2004).
61. Prokunina, L. et al. A regulatory polymorphism in PDCD1 is associated with susceptibility to systemic lupus erythematosus in humans. *Nat. Genet.* **32**, 666–669 (2002).
62. Kong, E. K. et al. A new haplotype of PDCD1 is associated with rheumatoid arthritis in Hong Kong Chinese. *Arthritis Rheum.* **52**, 1058–1062 (2005).
63. Zou, Y., Zhang, Z., Liu, Y., Liu, D. & Xu, W. Are programmed cell death 1 gene polymorphisms correlated with susceptibility to rheumatoid arthritis?: a meta-analysis. *Medicine* **96**, e7805 (2017).
64. Bertsias, G. K. et al. Genetic, immunologic, and immunohistochemical analysis of the programmed death 1/programmed death ligand 1 pathway in human systemic lupus erythematosus. *Arthritis Rheum.* **60**, 207–218 (2009).
65. Chua, K. H., Lian, L. H., Sim, X. J., Cheah, T. E. & Lau, T. P. Association between PDCD1 gene polymorphisms and risk of systemic lupus erythematosus in three main ethnic groups of the Malaysian population. *Int. J. Mol. Sci.* **16**, 9794–9803 (2015).
66. Lin, S. C. et al. Association of a programmed death 1 gene polymorphism with the development of rheumatoid arthritis, but not systemic lupus erythematosus. *Arthritis Rheum.* **50**, 770–775 (2004).
67. Lee, S. H. et al. Association of the programmed cell death 1 (PDCD1) gene polymorphism with ankylosing spondylitis in the Korean population. *Arthritis Res. Ther.* **8**, R163 (2006).
68. Liu, X. et al. Programmed cell death 1 gene polymorphisms is associated with ankylosing spondylitis in Chinese Han population. *Rheumatol. Int.* **31**, 209–213 (2011).
69. Shi, H. et al. Elevated serum autoantibodies against co-inhibitory PD-1 facilitate T cell proliferation and correlate with disease activity in new-onset systemic lupus erythematosus patients. *Arthritis Res. Ther.* **19**, 52 (2017).
70. Mozaffarian, N., Wiedeman, A. E. & Stevens, A. M. Active systemic lupus erythematosus is associated with failure of antigen-presenting cells to express programmed death ligand-1. *Rheumatology* **47**, 1335–1341 (2008).
71. Kobayashi, M. et al. Enhanced expression of programmed death-1 (PD-1)/PD-L1 in salivary glands of patients with Sjogren's syndrome. *J. Rheumatol.* **32**, 2156–2163 (2005).
72. Moret, F. M., van der Wurff-Jacobs, K. M., Bijlsma, J. W., Lafeber, F. P. & van Roon, J. A. Synovial T cell hyporesponsiveness to myeloid dendritic cells is reversed by preventing PD-1/PD-L1 interactions. *Arthritis Res. Ther.* **16**, 497 (2014).
73. Hatachi, S. et al. CD4+ PD-1+ T cells accumulate as unique anergic cells in rheumatoid arthritis synovial fluid. *J. Rheumatol.* **30**, 1410–1419 (2003).
74. Rao, D. A. et al. Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis. *Nature* **542**, 110–114 (2017).
75. Chen, Y. J. et al. Characteristics of PD-1^{+}CD4^{+} T cells in peripheral blood and synovium of rheumatoid arthritis patients. *Clin. Transl. Immunol.* **13**, e70006 (2024).
76. Li, S. et al. Expression of programmed death-1 (PD-1) on CD4+ and CD8+ T cells in rheumatoid arthritis. *Inflammation* **37**, 116–121 (2014).
77. Hayashi, H. et al. Soluble immune checkpoint factors reflect exhaustion of antitumor immunity and response to PD-1 blockade. *J. Clin. Invest.* **134**, e168318 (2024).
78. Costantini, A. et al. Predictive role of plasmatic biomarkers in advanced non-small cell lung cancer treated by nivolumab. *Oncoimmunology* **7**, e1452581 (2018).
79. Liao, G. et al. Prognostic role of soluble programmed death ligand 1 in non-small cell lung cancer: a systematic review and meta-analysis. *Front. Oncol.* **11**, 774131 (2021).
80. Wan, B. et al. Aberrant regulation of synovial T cell activation by soluble costimulatory molecules in rheumatoid arthritis. *J. Immunol.* **177**, 8844–8850 (2006).
81. Greisen, S. R. et al. Increased soluble programmed death-1 (sPD-1) is associated with disease activity and radiographic progression in early rheumatoid arthritis. *Scand. J. Rheumatol.* **43**, 101–108 (2014).
82. Naidoo, J. et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann. Oncol.* **26**, 2375–2391 (2015).
83. Topalian, S. L. et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med.* **366**, 2443–2454 (2012).
84. Khorasanchi, A., Korman, A. M., Manne, A. & Meara, A. Immune checkpoint inhibitor-induced subacute cutaneous lupus erythematosus: a case report and review of the literature. *Front. Med.* **11**, 1334718 (2024).
85. Diago, A., Hueso, L., Ara-Martin, M. & Abadias-Granado, I. Subacute cutaneous lupus erythematosus induced by PD-1 Inhibitor therapy: two case reports and literature review. *Australas. J. Dermatol.* **62**, e347–e349 (2021).
86. Blakeway, E. A. et al. Cutaneous lupus associated with pembrolizumab therapy for advanced melanoma: a report of three cases. *Melanoma Res.* **29**, 338–341 (2019).
87. Michot, J. M. et al. Drug-induced lupus erythematosus following immunotherapy with anti-programmed death-(ligand) 1. *Ann. Rheum. Dis.* **78**, e67 (2019).
88. Zitouni, N. B. et al. Subacute cutaneous lupus erythematosus induced by nivolumab: two case reports and a literature review. *Melanoma Res.* **29**, 212–215 (2019).
89. Leonardi, G. C. et al. Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders. *J. Clin. Oncol.* **36**, 1905–1912 (2018).
90. Hassel, J. C. et al. Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4): evaluation and management of adverse drug reactions. *Cancer Treat. Rev.* **57**, 36–49 (2017).
91. Calabrese, C., Kirchner, E., Kontzias, A., Velcheti, V. & Calabrese, L. H. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. *RMD Open.* **3**, e000412 (2017).
92. Belkhir, R. et al. Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. *Ann. Rheum. Dis.* **76**, 1747–1750 (2017).
93. McCarter, K. R. et al. Immunomodulator use, risk factors and management of flares, and mortality for patients with pre-existing rheumatoid arthritis after immune checkpoint inhibitors for cancer. *Semin. Arthritis Rheum.* **64**, 152335 (2024).
94. Kostine, M. et al. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer-clinical aspects and relationship with tumour response: a single-centre prospective cohort study. *Ann. Rheum. Dis.* **77**, 393–398 (2018).
95. Liu, Y. et al. Immune checkpoint inhibitor-induced inflammatory arthritis: a novel clinical entity with striking similarities to seronegative rheumatoid arthritis. *Clin. Rheumatol.* **39**, 3631–3637 (2020).
96. Nobashi, T. & Mittra, E. PD-1 blockade-induced inflammatory arthritis. *Radiology* **289**, 616 (2018).
97. Ponce, A. et al. Imaging findings in patients with immune checkpoint inhibitor-induced arthritis. *Diagnostics* **12**, 1961 (2022).
98. Pundole, X., Abdel-Wahab, N. & Suarez-Almazor, M. E. Arthritis risk with immune checkpoint inhibitor therapy for cancer. *Curr. Opin. Rheumatol.* **31**, 293–299 (2019).
99. Richter, M. D. et al. Rheumatic syndromes associated with immune checkpoint inhibitors: a single-center cohort of sixty-one patients. *Arthritis Rheumatol.* **71**, 468–475 (2019).
100. Lundberg, I. E., Sharma, A., Turesson, C. & Mohammad, A. J. An update on polymyalgia rheumatica. *J. Intern. Med.* **292**, 717–732 (2022).
101. Martin de Fremont, G. et al. Features of polymyalgia rheumatica-like syndrome after immune checkpoint inhibitor therapy. *Ann. Rheum. Dis.* **81**, e52 (2022).
102. Calabrese, C. et al. Polymyalgia rheumatica-like syndrome from checkpoint inhibitor therapy: case series and systematic review of the literature. *RMD Open.* **5**, e000906 (2019).
103. Cappelli, L. C. et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. *Ann. Rheum. Dis.* **76**, 43–50 (2017).
104. Ramos-Casals, M. et al. Sicca/Sjogren's syndrome triggered by PD-1/PD-L1 checkpoint inhibitors. Data from the international ImmunoCancer registry (ICIR). *Clin. Exp. Rheumatol.* **37**, 114–122 (2019).
105. Mavragani, C. P. & Moutsopoulos, H. M. Sicca syndrome following immune checkpoint inhibition. *Clin. Immunol.* **217**, 108497 (2020).
106. Jayan, A., Mammen, A. L. & Suarez-Almazor, M. E. Immune checkpoint inhibitor-induced myositis. *Rheum. Dis. Clin. North. Am.* **50**, 281–290 (2024).
107. Pinal-Fernandez, I. et al. Transcriptomic profiling reveals distinct subsets of immune checkpoint inhibitor induced myositis. *Ann. Rheum. Dis.* **82**, 829–836 (2023).
108. Suzuki, M., Matsumoto, S., Takeda, Y. & Sugiyama, H. Systemic psoriasiform dermatitis appeared after the administration of pembrolizumab. *Intern. Med.* **59**, 871–872 (2020).
109. Yu, Y. et al. Immune checkpoint inhibitors in the treatment of patients with cancer and preexisting psoriasis: a systematic review and meta-analysis of observational studies. *Front. Oncol.* **12**, 934093 (2022).
110. Halle, B. R. et al. Immune checkpoint inhibitors in patients with pre-existing psoriasis: safety and efficacy. *J. Immunother Cancer* **9**, e003066 (2021).
111. Johnson, D. et al. IL17A blockade successfully treated psoriasiform dermatologic toxicity from immunotherapy. *Cancer Immunol. Res.* **7**, 860–865 (2019).
112. Nigro, O. et al. Psoriatic arthritis induced by anti-PD1 and treated with apremilast: a case report and review of the literature. *Immunotherapy* **12**, 549–554 (2020).
113. Lowther, D. E. et al. PD-1 marks dysfunctional regulatory T cells in malignant gliomas. *JCI Insight* **1**, e85935 (2016).
114. Walsh, P. T. et al. PTEN inhibits IL-2 receptor-mediated expansion of CD4^{+} CD25^{+} Tregs. *J. Clin. Invest.* **116**, 2521–2531 (2006).
115. Bensinger, S. J. et al. Distinct IL-2 receptor signaling pattern in CD4^{+}CD25^{+} regulatory T cells. *J. Immunol.* **172**, 5287–5296 (2004).
116. Crellin, N. K., Garcia, R. V. & Levings, M. K. Altered activation of AKT is required for the suppressive function of human CD4^{+}CD25^{+} T regulatory cells. *Blood* **109**, 2014–2022 (2007).
117. Huynh, A. et al. Control of PI(3) kinase in T_{reg} cells maintains homeostasis and lineage stability. *Nat. Immunol.* **16**, 188–196 (2015).
118. Gerriets, V. A. et al. Foxp3 and Toll-like receptor signaling balance T_{reg} cell anabolic metabolism for suppression. *Nat. Immunol.* **17**, 1459–1466 (2016).
119. Kamada, T. et al. PD-1^{+} regulatory T cells amplified by PD-1 blockade promote hyperprogression of cancer. *Proc. Natl Acad. Sci. USA* **116**, 9999–10008 (2019).
120. Kumagai, S. et al. The PD-1 expression balance between effector and regulatory T cells predicts the clinical efficacy of PD-1 blockade therapies. *Nat. Immunol.* **21**, 1346–1358 (2020).
121. Perry, J. A. et al. PD-L1–PD-1 interactions limit effector regulatory T cell populations at homeostasis and during infection. *Nat. Immunol.* **23**, 743–756 (2022).
122. Kasagi, S. et al. Anti-programmed cell death 1 antibody reduces CD4^{+}PD-1^{+} T cells and relieves the lupus-like nephritis of NZB/W F1 mice. *J. Immunol.* **184**, 2337–2347 (2010).
123. Wong, M., La Cava, A. & Hahn, B. H. Blockade of programmed death-1 in young (New Zealand Black x New Zealand White) F_1 mice promotes the suppressive capacity of CD4^{+} regulatory T cells protecting from lupus-like disease. *J. Immunol.* **190**, 5402–5410 (2013).
124. Tan, C. L. et al. PD-1 restraint of regulatory T cell suppressive activity is critical for immune tolerance. *J. Exp. Med.* **218**, e20182232 (2021).

125. Denize, T. et al. PD-1 expression on intratumoral regulatory T cells is associated with lack of benefit from anti-PD-1 therapy in metastatic clear-cell renal cell carcinoma patients. *Clin. Cancer Res.* **30**, 803–813 (2024).
126. Hirata, S. et al. Prevention of experimental autoimmune encephalomyelitis by transfer of embryonic stem cell-derived dendritic cells expressing myelin oligodendrocyte glycoprotein peptide along with TRAIL or programmed death-1 ligand. *J. Immunol.* **174**, 1888–1897 (2005).
127. Feng, Y. et al. PD-1 antibody interactions with Fc gamma receptors enable PD-1 agonism to inhibit T cell activation — therapeutic implications for autoimmunity. *J. Autoimmun.* **149**, 103339 (2024).
128. Yu, X. et al. Reducing affinity as a strategy to boost immunomodulatory antibody agonism. *Nature* **614**, 539–547 (2023).
129. Suzuki, K. et al. Anti-PD-1 antibodies recognizing the membrane-proximal region are PD-1 agonists that can down-regulate inflammatory diseases. *Sci. Immunol.* **8**, eadd4947 (2023).
130. Curnock, A. P. et al. Cell-targeted PD-1 agonists that mimic PD-L1 are potent T cell inhibitors. *JCI Insight* **6**, e152468 (2021).
131. Bryan, C. M. et al. Computational design of a synthetic PD-1 agonist. *Proc Natl. Acad Sci USA* **118**, e2102164118 (2021).
132. Lippert, A. H. et al. Antibody agonists trigger immune receptor signaling through local exclusion of receptor-type protein tyrosine phosphatases. *Immunity* **57**, 256–270.e10 (2024).
133. Sugiura, D. et al. PD-1 agonism by anti-CD80 inhibits T cell activation and alleviates autoimmunity. *Nat. Immunol.* **23**, 399–410 (2022).
134. AnaptysBio. Rosnilimab — rheumatoid arthritis. https://www.anaptysbio.com/pipeline/rosnilimab/rheumatoid-arthritis/ (2024).
135. Luu, K. et al. DOP81 rosnilimab, a novel PD-1 agonist monoclonal antibody, reduces T cell proliferation, inflammatory cytokine secretion, and PD-1high expressing CD4 and CD8 T cells: results from a Phase 1 healthy volunteer clinical trial. *J. Crohns Colitis* **18**, i226–i226 (2024).
136. AnaptysBio. AnaptysBio announces rosnilimab achieved positive results in RA Phase 2b trial and highest ever reported CDAI LDA response over 6 months. https://ir.anaptysbio.com/news-releases/news-release-details/anaptys-announces-rosnilimab-achieved-positive-results-ra-phase (2025).
137. AnaptysBio. AnaptysBio announces portfolio update across best-in-class immune cell modulating antibodies. https://ir.anaptysbio.com/news-releases/news-release-details/anaptysbio-announces-portfolio-update-across-best-class-immune (2023).
138. Tuttle, J. et al. A phase 2 trial of peresolimab for adults with rheumatoid arthritis. *N. Engl. J. Med.* **388**, 1853–1862 (2023).
139. Mullard, A. PD1 agonist antibody passes first phase II trial for autoimmune disease. *Nat. Rev. Drug. Discov.* **22**, 526 (2023).
140. Watanabe, N. et al. BTLA is a lymphocyte inhibitory receptor with similarities to CTLA-4 and PD-1. *Nat. Immunol.* **4**, 670–679 (2003).
141. del Rio, M. L., Kaye, J. & Rodriguez-Barbosa, J. I. Detection of protein on BTLA^{low} cells and in vivo antibody-mediated down-modulation of BTLA on lymphoid and myeloid cells of C57BL/6 and BALB/c BTLA allelic variants. *Immunobiology* **215**, 570–578 (2010).
142. Murphy, K. M., Nelson, C. A. & Sedy, J. R. Balancing co-stimulation and inhibition with BTLA and HVEM. *Nat. Rev. Immunol.* **6**, 671–681 (2006).
143. De Sousa Linhares, A., Leitner, J., Grabmeier-Pfistershammer, K. & Steinberger, P. Not all immune checkpoints are created equal. *Front. Immunol.* **9**, 1909 (2018).
144. Otsuki, N., Kamimura, Y., Hashiguchi, M. & Azuma, M. Expression and function of the B and T lymphocyte attenuator (BTLA/CD272) on human T cells. *Biochem. Biophys. Res. Commun.* **344**, 1121–1127 (2006).
145. Han, P., Goularte, O. D., Rufner, K., Wilkinson, B. & Kaye, J. An inhibitory Ig superfamily protein expressed by lymphocytes and APCs is also an early marker of thymocyte positive selection. *J. Immunol.* **172**, 5931–5939 (2004).
146. Tao, R., Wang, L., Murphy, K. M., Fraser, C. C. & Hancock, W. W. Regulatory T cell expression of herpesvirus entry mediator suppresses the function of B and T lymphocyte attenuator-positive effector T cells. *J. Immunol.* **180**, 6649–6655 (2008).
147. Nurieva, R. I. et al. Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages. *Immunity* **29**, 138–149 (2008).
148. Cai, G. & Freeman, G. J. The CD160, BTLA, LIGHT/HVEM pathway: a bidirectional switch regulating T-cell activation. *Immunol. Rev.* **229**, 244–258 (2009).
149. Gavrieli, M. & Murphy, K. M. Association of Grb-2 and PI3K p85 with phosphotyrosile peptides derived from BTLA. *Biochem. Biophys. Res. Commun.* **345**, 1440–1445 (2006).
150. Sedy, J. R. et al. B and T lymphocyte attenuator regulates T cell activation through interaction with herpesvirus entry mediator. *Nat. Immunol.* **6**, 90–98 (2005).
151. Gonzalez, L. C. et al. A coreceptor interaction between the CD28 and TNF receptor family members B and T lymphocyte attenuator and herpesvirus entry mediator. *Proc. Natl Acad. Sci. USA* **102**, 1116–1121 (2005).
152. Vendel, A. C. et al. B and T lymphocyte attenuator regulates B cell receptor signaling by targeting Syk and BLNK. *J. Immunol.* **182**, 1509–1517 (2009).
153. Shui, J. W., Steinberg, M. W. & Kronenberg, M. Regulation of inflammation, autoimmunity, and infection immunity by HVEM-BTLA signaling. *J. Leukoc. Biol.* **89**, 517–523 (2011).
154. Cheung, T. C. et al. T cell intrinsic heterodimeric complexes between HVEM and BTLA determine receptivity to the surrounding microenvironment. *J. Immunol.* **183**, 7286–7296 (2009).
155. Cai, G. et al. CD160 inhibits activation of human CD4+ T cells through interaction with herpesvirus entry mediator. *Nat. Immunol.* **9**, 176–185 (2008).
156. Zhu, Y. et al. Neuron-specific SALM5 limits inflammation in the CNS via its interaction with HVEM. *Sci. Adv.* **2**, e1500637 (2016).
157. Rodriguez-Barbosa, J. I. et al. HVEM, a cosignaling molecular switch, and its interactions with BTLA, CD160 and LIGHT. *Cell Mol. Immunol.* **16**, 679–682 (2019).
158. Cheung, T. C. Modulation of T cell proliferation through the LIGHT-HVEM-BTLA cosignaling pathway. *Recent Pat. DNA Gene Seq.* **3**, 177–182 (2009).
159. Marsters, S. A. et al. Herpesvirus entry mediator, a member of the tumor necrosis factor receptor (TNFR) family, interacts with members of the TNFR-associated factor family and activates the transcription factors NF-κB and AP-1. *J. Biol. Chem.* **272**, 14029–14032 (1997).
160. Xu, X. et al. PD-1 and BTLA regulate T cell signaling differentially and only partially through SHP1 and SHP2. *J. Cell Biol.* **219**, e201905085 (2020).
161. Gavrieli, M., Watanabe, N., Loftin, S. K., Murphy, T. L. & Murphy, K. M. Characterization of phosphotyrosine binding motifs in the cytoplasmic domain of B and T lymphocyte attenuator required for association with protein tyrosine phosphatases SHP-1 and SHP-2. *Biochem. Biophys. Res. Commun.* **312**, 1236–1243 (2003).
162. Hurchla, M. A. et al. B and T lymphocyte attenuator exhibits structural and expression polymorphisms and is highly induced in anergic CD4+ T cells. *J. Immunol.* **174**, 3377–3385 (2005).
163. Thibult, M. L. et al. CpG-ODN-induced sustained expression of BTLA mediating selective inhibition of human B cells. *J. Mol. Med.* **91**, 195–205 (2013).
164. Xin, H. et al. Adenovirus-mediated CCR7 and BTLA overexpression enhances immune tolerance and migration in immature dendritic cells. *Biomed. Res. Int.* **2017**, 3519745 (2017).
165. Kobayashi, Y. et al. B and T lymphocyte attenuator inhibits LPS-induced endotoxic shock by suppressing Toll-like receptor 4 signaling in innate immune cells. *Proc. Natl Acad. Sci. USA* **110**, 5121–5126 (2013).
166. Cheung, T. C. et al. Evolutionarily divergent herpesviruses modulate T cell activation by targeting the herpesvirus entry mediator cosignaling pathway. *Proc. Natl Acad. Sci. USA* **102**, 13218–13223 (2005).
167. Oya, Y. et al. Development of autoimmune hepatitis-like disease and production of autoantibodies to nuclear antigens in mice lacking B and T lymphocyte attenuator. *Arthritis Rheum.* **58**, 2498–2510 (2008).
168. Huarte, E. et al. Regulatory T cell dysfunction acquiesces to BTLA+ regulatory B cells subsequent to oral intervention in experimental autoimmune encephalomyelitis. *J. Immunol.* **196**, 5036–5046 (2016).
169. Liu, X. et al. Cutting edge: a critical role of B and T lymphocyte attenuator in peripheral T cell tolerance induction. *J. Immunol.* **182**, 4516–4520 (2009).
170. Oya, Y. et al. Lack of B and T lymphocyte attenuator exacerbates autoimmune disorders and induces Fas-independent liver injury in MRL-lpr/lpr mice. *Int. Immunol.* **23**, 335–344 (2011).
171. Truong, W. et al. BTLA targeting modulates lymphocyte phenotype, function, and numbers and attenuates disease in nonobese diabetic mice. *J. Leukoc. Biol.* **86**, 41–51 (2009).
172. Li, S. et al. Dendritic cells expressing BTLA induces CD8+ T cell tolerance and attenuates the severity of diabetes. *Vaccine* **29**, 7747–7751 (2011).
173. Truong, W. et al. Negative and positive co-signaling with anti-BTLA (PJ196) and CTLA4Ig prolongs islet allograft survival. *Transplantation* **84**, 1368–1372 (2007).
174. Krieg, C., Han, P., Stone, R., Goularte, O. D. & Kaye, J. Functional analysis of B and T lymphocyte attenuator engagement on CD4$^+$ and CD8$^+$ T cells. *J. Immunol.* **175**, 6420–6427 (2005).
175. Lin, S. C., Kuo, C. C. & Chan, C. H. Association of a BTLA gene polymorphism with the risk of rheumatoid arthritis. *J. Biomed. Sci.* **13**, 853–860 (2006).
176. Oki, M. et al. A functional polymorphism in B and T lymphocyte attenuator is associated with susceptibility to rheumatoid arthritis. *Clin. Dev. Immunol.* **2011**, 305656 (2011).
177. Raychaudhuri, S. et al. Common variants at CD40 and other loci confer risk of rheumatoid arthritis. *Nat. Genet.* **40**, 1216–1223 (2008).
178. Huang, H. et al. Interaction analysis between BLK rs13277113 polymorphism and BANK1 rs3733197 polymorphism, MMEL1/TNFRSF14 rs3890745 polymorphism in determining susceptibility to rheumatoid arthritis. *Autoimmunity* **50**, 403–408 (2017).
179. Kurreeman, F. A. et al. Use of a multiethnic approach to identify rheumatoid-arthritis-susceptibility loci, 1p36 and 17q12. *Am. J. Hum. Genet.* **90**, 524–532 (2012).
180. El-Gabalawy, H. S. et al. Non-HLA genes modulate the risk of rheumatoid arthritis associated with HLA-DRB1 in a susceptible North American Native population. *Genes. Immun.* **12**, 568–574 (2011).
181. Coenen, M. J. et al. Common and different genetic background for rheumatoid arthritis and coeliac disease. *Hum. Mol. Genet.* **18**, 4195–4203 (2009).
182. van der Linden, M. P. et al. Association of a single-nucleotide polymorphism in CD40 with the rate of joint destruction in rheumatoid arthritis. *Arthritis Rheum.* **60**, 2242–2247 (2009).
183. Oster, C. et al. BTLA expression on Th1, Th2 and Th17 effector T-cells of patients with systemic lupus erythematosus is associated with active disease. *Int. J. Mol. Sci.* **20**, 4505 (2019).
184. Wiedemann, A. et al. BTLA expression and function are impaired on SLE B cells. *Front. Immunol.* **12**, 667991 (2021).
185. Sawaf, M. et al. Defective BTLA functionality is rescued by restoring lipid metabolism in lupus CD4+ T cells. *JCI Insight* **3**, e99711 (2018).

186. Yang, B. et al. The expression of BTLA was increased and the expression of HVEM and LIGHT were decreased in the T cells of patients with rheumatoid arthritis [corrected]. *PLoS ONE* **11**, e0155345 (2016).
187. Canavan, M. et al. Functionally mature CD1c$^+$ dendritic cells preferentially accumulate in the inflammatory arthritis synovium. *Front. Immunol.* **12**, 745226 (2021).
188. Kim, W. J. et al. LIGHT is involved in the pathogenesis of rheumatoid arthritis by inducing the expression of pro-inflammatory cytokines and MMP-9 in macrophages. *Immunology* **114**, 272–279 (2005).
189. Pierer, M. et al. The TNF superfamily member LIGHT contributes to survival and activation of synovial fibroblasts in rheumatoid arthritis. *Rheumatology* **46**, 1063–1070 (2007).
190. Ishida, S. et al. LIGHT induces cell proliferation and inflammatory responses of rheumatoid arthritis synovial fibroblasts via lymphotoxin β receptor. *J. Rheumatol.* **35**, 960–968 (2008).
191. Shang, Y. et al. The expression and anatomical distribution of BTLA and its ligand HVEM in rheumatoid synovium. *Inflammation* **35**, 1102–1112 (2012).
192. Dominguez-Villar, M. & Hafler, D. A. Regulatory T cells in autoimmune disease. *Nat. Immunol.* **19**, 665–673 (2018).
193. Bonelli, M., von Dalwigk, K., Savitskaya, A., Smolen, J. S. & Scheinecker, C. Foxp3 expression in CD4+ T cells of patients with systemic lupus erythematosus: a comparative phenotypic analysis. *Ann. Rheum. Dis.* **67**, 664–671 (2008).
194. van Roon, J. A., Hartgring, S. A., van der Wurff-Jacobs, K. M., Bijlsma, J. W. & Lafeber, F. P. Numbers of CD25$^+$Foxp3$^+$ T cells that lack the IL-7 receptor are increased intra-articularly and have impaired suppressive function in RA patients. *Rheumatology* **49**, 2084–2089 (2010).
195. Aubergeon, L. et al. High BTLA expression likely contributes to contraction of the regulatory T cell subset in lupus disease. *Front. Immunol.* **12**, 767099 (2021).
196. Cheung, T. C. et al. Epitope topography of agonist antibodies to the checkpoint inhibitory receptor BTLA. *Structure* **31**, 958–967.e3 (2023).
197. AnaptysBio. AnaptysBio announces phase 2b trial of ANB032, a BTLA agonist, did not meet primary or secondary endpoints in atopic dermatitis. https://ir.anaptysbio.com/news-releases/news-release-details/anaptys-announces-phase-2b-trial-anb032-btla-agonist-did-not (2024).
198. Yu, X. et al. The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. *Nat. Immunol.* **10**, 48–57 (2009).
199. Stanietsky, N. et al. The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. *Proc. Natl Acad. Sci. USA* **106**, 17858–17863 (2009).
200. Boles, K. S. et al. A novel molecular interaction for the adhesion of follicular CD4 T cells to follicular DC. *Eur. J. Immunol.* **39**, 695–703 (2009).
201. Levin, S. D. et al. Vstm3 is a member of the CD28 family and an important modulator of T-cell function. *Eur. J. Immunol.* **41**, 902–915 (2011).
202. Joller, N. et al. Cutting edge: TIGIT has T cell-intrinsic inhibitory functions. *J. Immunol.* **186**, 1338–1342 (2011).
203. Joller, N. et al. Treg cells expressing the coinhibitory molecule TIGIT selectively inhibit proinflammatory Th1 and Th17 cell responses. *Immunity* **40**, 569–581 (2014).
204. Bottino, C. et al. Identification of PVR (CD155) and Nectin-2 (CD112) as cell surface ligands for the human DNAM-1 (CD226) activating molecule. *J. Exp. Med.* **198**, 557–567 (2003).
205. Casado, J. G. et al. Expression of adhesion molecules and ligands for activating and costimulatory receptors involved in cell-mediated cytotoxicity in a large panel of human melanoma cell lines. *Cancer Immunol. Immunother.* **58**, 1517–1526 (2009).
206. Chiang, E. Y. & Mellman, I. TIGIT-CD226-PVR axis: advancing immune checkpoint blockade for cancer immunotherapy. *J. Immunother Cancer* **10**, e004711 (2022).
207. Mendelsohn, C. L., Wimmer, E. & Racaniello, V. R. Cellular receptor for poliovirus: molecular cloning, nucleotide sequence, and expression of a new member of the immunoglobulin superfamily. *Cell* **56**, 855–865 (1989).
208. Chan, C. J. et al. The receptors CD96 and CD226 oppose each other in the regulation of natural killer cell functions. *Nat. Immunol.* **15**, 431–438 (2014).
209. Johnston, R. J. et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8$^+$ T cell effector function. *Cancer Cell* **26**, 923–937 (2014).
210. Fuhrman, C. A. et al. Divergent phenotypes of human regulatory T cells expressing the receptors TIGIT and CD226. *J. Immunol.* **195**, 145–155 (2015).
211. Zhang, Y. et al. Genome-wide DNA methylation analysis identifies hypomethylated genes regulated by FOXP3 in human regulatory T cells. *Blood* **122**, 2823–2836 (2013).
212. Lucca, L. E. et al. TIGIT signaling restores suppressor function of Th1 Tregs. *JCI Insight* **4**, e124427 (2019).
213. Soond, D. R. et al. Pten loss in CD4 T cells enhances their helper function but does not lead to autoimmunity or lymphoma. *J. Immunol.* **188**, 5935–5943 (2012).
214. Hasan, M. M. et al. Implication of TIGIT$^+$ human memory B cells in immune regulation. *Nat. Commun.* **12**, 1534 (2021).
215. Xiao, S. et al. Checkpoint receptor TIGIT expressed on Tim-1$^+$ B cells regulates tissue inflammation. *Cell Rep.* **32**, 107892 (2020).
216. Varghese, J. F. et al. Human regulatory memory B cells defined by expression of TIM-1 and TIGIT are dysfunctional in multiple sclerosis. *Front. Immunol.* **15**, 1360219 (2024).
217. Asashima, H. et al. Impaired TIGIT expression on B cells drives circulating follicular helper T cell expansion in multiple sclerosis. *J. Clin. Invest.* **132**, e156254 (2022).
218. Dixon, K. O. et al. Functional anti-TIGIT antibodies regulate development of autoimmunity and antitumor immunity. *J. Immunol.* **200**, 3000–3007 (2018).
219. Zhao, W. et al. TIGIT overexpression diminishes the function of CD4 T cells and ameliorates the severity of rheumatoid arthritis in mouse models. *Exp. Cell Res.* **340**, 132–138 (2016).
220. Wang, F. et al. TIGIT expression levels on human NK cells correlate with functional heterogeneity among healthy individuals. *Eur. J. Immunol.* **45**, 2886–2897 (2015).
221. Luo, Q. et al. Decreased expression of TIGIT in NK cells correlates negatively with disease activity in systemic lupus erythematosus. *Int. J. Clin. Exp. Pathol.* **11**, 2408–2418 (2018).
222. Zhou, H. et al. Dysregulated T cell activation and aberrant cytokine expression profile in systemic lupus erythematosus. *Mediators Inflamm.* **2019**, 8450947 (2019).
223. Wang, F. F., Wang, Y., Wang, L., Wang, T. S. & Bai, Y. P. TIGIT expression levels on CD4+ T cells are correlated with disease severity in patients with psoriasis. *Clin. Exp. Dermatol.* **43**, 675–682 (2018).
224. Yu, Y. et al. Infliximab modifies regulatory T cells and co-inhibitory receptor expression on circulating T cells in psoriasis. *Int. Immunopharmacol.* **96**, 107722 (2021).
225. Luo, Q. et al. Elevated expression of TIGIT on CD3$^+$CD4$^+$ T cells correlates with disease activity in systemic lupus erythematosus. *Allergy Asthma Clin. Immunol.* **13**, 15 (2017).
226. Deng, C. et al. Alteration of CD226/TIGIT immune checkpoint on T cells in the pathogenesis of primary Sjogren's syndrome. *J. Autoimmun.* **113**, 102485 (2020).
227. Zhang, T. et al. Increased expression of TIGIT on CD4+ T cells ameliorates immune-mediated bone marrow failure of aplastic anemia. *J. Cell Biochem.* **115**, 1918–1927 (2014).
228. Mao, L. et al. TIGIT signalling pathway negatively regulates CD4$^+$ T-cell responses in systemic lupus erythematosus. *Immunology* **151**, 280–290 (2017).
229. Liu, S. et al. Treatment of murine lupus with TIGIT-Ig. *Clin. Immunol.* **203**, 72–80 (2019).
230. Lozano, E., Dominguez-Villar, M., Kuchroo, V. & Hafler, D. A. The TIGIT/CD226 axis regulates human T cell function. *J. Immunol.* **188**, 3869–3875 (2012).
231. Kojima, M. et al. Anti-human-TIGIT agonistic antibody ameliorates autoimmune diseases by inhibiting Tfh and Tph cells and enhancing Treg cells. *Commun. Biol.* **6**, 500 (2023).
232. Mysler, E., Caubet, M. & Lizarraga, A. Current and emerging DMARDs for the treatment of rheumatoid arthritis. *Open Access Rheumatol.* **13**, 139–152 (2021).
233. Katarzyna, P. B., Wiktor, S., Ewa, D. & Piotr, L. Current treatment of systemic lupus erythematosus: a clinician's perspective. *Rheumatol. Int.* **43**, 1395–1407 (2023).
234. Guo, Q. et al. Engineered PD-1/TIGIT dual-activating cell-membrane nanoparticles with dexamethasone act synergistically to shape the effector T cell/Treg balance and alleviate systemic lupus erythematosus. *Biomaterials* **285**, 121517 (2022).
235. Monney, L. et al. Th1-specific cell surface protein Tim-3 regulates macrophage activation and severity of an autoimmune disease. *Nature* **415**, 536–541 (2002).
236. Gao, X. et al. TIM-3 expression characterizes regulatory T cells in tumor tissues and is associated with lung cancer progression. *PLoS ONE* **7**, e30676 (2012).
237. Anderson, A. C. et al. Promotion of tissue inflammation by the immune receptor Tim-3 expressed on innate immune cells. *Science* **318**, 1141–1143 (2007).
238. Ndhlovu, L. C. et al. Tim-3 marks human natural killer cell maturation and suppresses cell-mediated cytotoxicity. *Blood* **119**, 3734–3743 (2012).
239. Phong, B. L. et al. Tim-3 enhances FcεRI-proximal signaling to modulate mast cell activation. *J. Exp. Med.* **212**, 2289–2304 (2015).
240. Lee, S. Y. & Goverman, J. M. The influence of T cell Ig mucin-3 signaling on central nervous system autoimmune disease is determined by the effector function of the pathogenic T cells. *J. Immunol.* **190**, 4991–4999 (2013).
241. Li, X. et al. Involvement of T cell Ig Mucin-3 (Tim-3) in the negative regulation of inflammatory bowel disease. *Clin. Immunol.* **134**, 169–177 (2010).
242. Sanchez-Fueyo, A. et al. Tim-3 inhibits T helper type 1-mediated auto- and alloimmune responses and promotes immunological tolerance. *Nat. Immunol.* **4**, 1093–1101 (2003).
243. Ju, Y. et al. The Tim-3/galectin-9 pathway involves in the homeostasis of hepatic Tregs in a mouse model of concanavalin A-induced hepatitis. *Mol. Immunol.* **58**, 85–91 (2014).
244. Sakuishi, K. et al. TIM3$^+$FOXP3$^+$ regulatory T cells are tissue-specific promoters of T-cell dysfunction in cancer. *Oncoimmunology* **2**, e23849 (2013).
245. Gupta, S. et al. Allograft rejection is restrained by short-lived TIM-3+PD-1+Foxp3+ Tregs. *J. Clin. Invest.* **122**, 2395–2404 (2012).
246. Liu, R., Wang, X., Chen, X., Wang, S. & Zhang, H. TIM-3 rs1036199 polymorphism increases susceptibility to autoimmune diseases: evidence based on 4200 subjects. *Biosci Rep.* **38**, BSR20181235 (2018).
247. Matsumoto, H. et al. T cell immunoglobulin and mucin domain-3 is associated with disease activity and progressive joint damage in rheumatoid arthritis patients. *Medicine* **99**, e22892 (2020).
248. Skejoe, C. et al. T-cell immunoglobulin and mucin domain 3 is upregulated in rheumatoid arthritis, but insufficient in controlling inflammation. *Am. J. Clin. Exp. Immunol.* **11**, 34–44 (2022).
249. Liu, Y. et al. Increased Tim-3 expression on peripheral lymphocytes from patients with rheumatoid arthritis negatively correlates with disease activity. *Clin. Immunol.* **137**, 288–295 (2010).
250. Kanai, Y., Satoh, T., Igawa, K. & Yokozeki, H. Impaired expression of Tim-3 on Th17 and Th1 cells in psoriasis. *Acta Derm. Venereol.* **92**, 367–371 (2012).
251. Triebel, F. et al. LAG-3, a novel lymphocyte activation gene closely related to CD4. *J. Exp. Med.* **171**, 1393–1405 (1990).
252. Huard, B., Prigent, P., Tournier, M., Bruniquel, D. & Triebel, F. CD4/major histocompatibility complex class II interaction analyzed with CD4- and lymphocyte activation gene-3 (LAG-3)-Ig fusion proteins. *Eur. J. Immunol.* **25**, 2718–2721 (1995).
253. Xu, F. et al. LSECtin expressed on melanoma cells promotes tumor progression by inhibiting antitumor T-cell responses. *Cancer Res.* **74**, 3418–3428 (2014).

254. Wang, J. et al. Fibrinogen-like protein 1 is a major immune inhibitory ligand of LAG-3. *Cell* **176**, 334–347.e12 (2019).
255. Kouo, T. et al. Galectin-3 shapes antitumor immune responses by suppressing CD8$^+$ T cells via LAG-3 and inhibiting expansion of plasmacytoid dendritic cells. *Cancer Immunol. Res.* **3**, 412–423 (2015).
256. Mao, X. et al. Aplp1 interacts with Lag3 to facilitate transmission of pathologic α-synuclein. *Nat. Commun.* **15**, 4663 (2024).
257. Zhang, Q. et al. LAG3 limits regulatory T cell proliferation and function in autoimmune diabetes. *Sci. Immunol.* **2**, eaah4569 (2017).
258. Jha, V. et al. Lymphocyte activation gene-3 (LAG-3) negatively regulates environmentally-induced autoimmunity. *PLoS ONE* **9**, e104484 (2014).
259. Kim, D. et al. Inhibitory co-receptor Lag3 supports Foxp3$^+$ regulatory T cell function by restraining Myc-dependent metabolic programming. *Immunity* **57**, 2634–2650.e5 (2024).
260. Pedersen, J. M. et al. Lymphocyte activation gene 3 is increased and affects cytokine production in rheumatoid arthritis. *Arthritis Res. Ther.* **25**, 97 (2023).
261. Nurieva, R. et al. T-cell tolerance or function is determined by combinatorial costimulatory signals. *EMBO J.* **25**, 2623–2633 (2006).
262. AnaptysBio. Rosnilimab — overview. https://www.anaptysbio.com/pipeline/rosnilimab/overview/ (2024).

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
A.H.S. has patents on B7-1 and B7-2 (US-6218510, US-6294660, US-6608180, US-7153934 and US-7619078) and patents on the PD-1 pathway (US-7432059, US-7722868; US-8652465, US-9457080, US-9683048, US-9815898, US-9845356, US-9988452, US-10202454, US-10370446, US-10457733, US-9580684, US-10752687, US-10851165, US-0934353, US-11124569, US-11207393, US-10577586, US-9885016, US-11359013, US-11359020, US-11413340, US-11492403, US-11827704). A.H.S. is on advisory boards for Elpiscience, Monopteros, Alixia, Corner Therapeutics, BioEntre, GlaxoSmithKline, Amgen, Janssen, ImmVue, AltruBio and MabQuest. A.H.S. has research funding from TaiwanBio, Calico and Yosemite unrelated to this Review. J.R.K. and N.G. declare no competing interests.

Additional information
Peer review information *Nature Reviews Rheumatology* thanks Mihir Wechalekar, who co-reviewed with Annabelle Small, Anne Bass, Laura Cappelli and Linde Meyaard, for their contribution to the peer review of this work.

nature reviews rheumatology

https://doi.org/10.1038/s41584-025-01332-8

Review article

Check for updates

Osteoarthritis as a systemic disease

Kelsey H. Collins[1,2] ✉, Ida K. Haugen[3,4], Tuhina Neogi[5] & Farshid Guilak[6,7,8]

Abstract

Osteoarthritis (OA) is a painful disorder of the synovial joints characterized by dysfunctional cellular metabolism and extracellular matrix degradation that activates maladaptive repair responses, including pro-inflammatory pathways of innate immunity. OA has historically been viewed as an unavoidable consequence of ageing owing to wear-and-tear of the joint. Most strategies to mitigate OA have primarily focused on the articular cartilage and, more recently, other specific joint tissues, which limits understanding of OA as a systemic disease beyond the joint. Preclinical and clinical data support a paradigm shift in understanding OA as a disease of the whole person, focusing on changes throughout the body that both promote and are caused by OA. This shift provides novel insights into why preclinical research findings have not been successfully translated into clinical therapies. Moreover, a viable strategy for OA drug development could be to treat pain separately from OA structural damage. Challenging classically held views that lack evidence or have been disproven is required for progress. We explore some key emerging questions that should be carefully considered in future OA studies. Adapting and integrating new technologies, techniques, and tools into the rapidly evolving understanding of OA could lead to the development of drugs that might not only treat OA but also provide mechanistic insight into other conditions that result from the dysregulation of systemic factors or from the communication breakdown in inter-organ crosstalk. Such developments would reposition OA researchers from adapting approaches from other fields of science and medicine to leaders in the fight against chronic disease.

Sections

[1]Department of Orthopaedic Surgery, University of California, San Francisco, San Francisco, CA, USA. [2]Department of Anatomy, University of California, San Francisco, San Francisco, CA, USA. [3]Center for Treatment of Rheumatic and Musculoskeletal Diseases, Diakonhjemmet Hospital, Oslo, Norway. [4]Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [5]Division of Rheumatology, Boston University Chobanian & Avedisian School of Medicine Medicine, Boston, MA, USA. [6]Department of Orthopaedic Surgery, Washington University in St. Louis, St. Louis, MO, USA. [7]Shriners Hospitals for Children St. Louis, St. Louis, MO, USA. [8]Center of Regenerative Medicine, Washington University in St. Louis, St. Louis, MO, USA. ✉e-mail: kelsey.collins@ucsf.edu

Key points

- Osteoarthritis (OA) has been viewed historically as an inevitable part of ageing owing to the gradual wear-and-tear of articular joints. Consequently, research and treatment strategies have focused primarily on cartilage or joint tissues.
- Preclinical and clinical evidence indicate that OA is a systemic, whole-body disease, revealing biological changes that both drive and result from OA and clarifying why preclinical discoveries rarely translate clinically.
- OA research progress can occur by challenging outdated assumptions to explore emerging ideas on how OA influences systemic ageing, metabolic dysfunction and cardiovascular health, fostering a deeper understanding of its broader impacts.
- Integrating emerging technologies and analytical tools into OA research will enable the development of therapies that treat OA while uncovering mechanisms underlying systemic dysfunction and impaired inter-organ communication in related chronic diseases.
- This forward-looking approach positions OA researchers to shift from adapting strategies across disciplines to pioneering new methods that could redefine how chronic diseases are studied and treated.

Introduction

Osteoarthritis (OA), a disorder that involves the synovial joints, is a leading cause of pain and disability worldwide. Despite this burden, existing pain management strategies are inadequate[1], which has, in turn, led to musculoskeletal disorders becoming the leading indication for opioid prescription[2]. Furthermore, although OA is the most common form of arthritis, affecting over 600 million people worldwide[3], there are no approved disease-modifying osteoarthritis drugs (DMOADs) that alter the course of joint pathology[1]. Despite musculoskeletal conditions directly leading to morbidity and reduced healthspan, the understanding of OA remains limited. Moreover, the age at which patients are receiving total joint replacement is becoming increasingly younger, further increasing the societal cost of OA[4].

Historically, OA has been narrowly understood as an unavoidable, cartilage-centric, wear-and-tear disease that is inevitable with ageing[5,6]. This narrow perspective has limited the mechanistic understanding of changes beyond the articular cartilage and fails to consider prevalent risk factors, such as injury, obesity or genetics[7], which affect other tissues and organs of the body and co-occur with OA. Approaches to study this painful disease have often focused on evaluating single tissues in isolation (such as cartilage, subchondral bone, bone marrow lesions or synovitis) and assume that OA pathology is focused solely within the joint, or the organ system, which is made up of several joint tissues[6]; however, articular joints do not function in isolation, they are part of a complex organism. Clinical data illustrate that most individuals with OA (59–87%) are managing at least one other chronic condition[8]; for example, people with obesity are far more likely to develop OA[9]. Several studies also indicate that OA disproportionally affects women[10] and individuals from minority groups[11], which contributes to the widening health disparities for OA care, consistent with many other chronic diseases.

In the rheumatology field, the approach to OA is rather unique, as it has historically been studied on an individual anatomic basis, such as a focus on the knee joint or the hand joints in isolation from other joint involvement. This anatomically focused categorization is likely attributed to the focused end-stage treatment of OA, specifically total joint replacement, and the notion that the pathomechanisms of OA may be joint or site-specific. Other rheumatic diseases also have variable joint involvement; however, studies of those diseases do not typically focus only on the most commonly involved joints.

The need for both phenotyping and endotyping in OA is becoming increasingly apparent. Clinical phenotypes might help to identify individuals with OA who are at risk of more severe structural damage, pain or developing comorbidities. Understanding the pathological mechanisms of different endotypes of OA to develop first-in-class therapeutic targets is urgent owing to the exponential increase in disease burden[12] and to facilitate healthy ageing[13].

In this Review, we aim to summarize the current literature to fuel an ongoing strategic shift in the field to consider OA as a systemic, whole-person (or organism) disease, rather than focusing myopically on studying a single joint (such as the knee, hand or hip) or tissue (such as cartilage, bone or synovium) in isolation. First, we state the clinical problem and urgency and summarize the historical view of OA. We share insights from the literature on why preclinical findings have yet to successfully translate to approved clinical therapeutics or improve clinical outcomes. We highlight the ongoing work in the field, such as the 2024 call for a name change to 'systemic OA', which provides evidence of systemic drivers of OA and musculoskeletal pain, and we propose key research questions that the OA and rheumatology research communities might consider in future studies and trials.

Clinical problem and urgency

One of the primary and most recognized risk factors for OA is ageing. Among people with symptomatic OA, the median age at diagnosis is estimated to be 55 years, with 73% of individuals being diagnosed by the age of 65 (ref. 14). However, it is important to note that there are individuals who do not demonstrate knee pain or structural damage with age, indicating that ageing and OA can be distinct processes.

Moreover, other factors also demonstrate strong positive relationships with OA prevalence, including biological sex (that is, sex assigned at birth, throughout the article, 'sex' is used as a shorthand for biological sex). In addition to higher OA prevalence, women also have worse clinical scores than men[10]. In addition, lifetime OA risk is highest in women with obesity and lowest in men without obesity[14], which demonstrates a complex interaction between sex as a biological variable, comorbidities, ageing and OA. Neglecting to account for sex as a biological variable might broaden health disparities, as observed by data on sex differences in anatomy, injury responses and metabolic signatures, which are not simply explained by sex hormones[15,16].

Clinically, a discordance exists between pain and radiographic evidence of structural damage in OA owing to the numerous other factors that contribute to the pain experience[17], and this discordance could be more pronounced in women[10,18]. When people with one painful and one non-painful knee are evaluated, a clear association between structure and pain is observed[19]. When individual joints are considered in hand OA, the joints with structural damage are far more likely to be painful than normal joints[20]; however, when pain severity in the hand is considered with the severity of OA, the association is weak[20]. In the MOST cohort, a pain susceptibility phenotype was identified that increased the risk of developing persistent knee pain over a 2-year period.

This group was characterized primarily by pain sensitization, and these findings suggest that factors beyond pathology in the joint predispose to chronic pain[21]. Together, these data support a complicated relationship between OA pathology and pain but underline the importance of also assessing other factors (such as systemic factors and comorbidities) that contribute to the pain experience.

We and others[22] have proposed an alternative hypothesis to the historical view of OA that obesity-associated systemic metabolic changes are a causal pathogenic factor driving OA[23–27]. Acknowledging that OA is not simply a consequence of increased loading owing to body mass is essential, and we and others have demonstrated that signals from adipose tissue are necessary and sufficient to drive OA in a reversible manner[24,27]. Moreover, loss of muscle[28] and a suboptimal ratio of lean mass to adipose tissue are also associated with increased risk of OA[29]. Muscle loss in an individual with obesity, defined as sarcopenic obesity[30], can increase the risk of OA and worse outcomes[31]. The POMELO study demonstrated that personalized nutrition, resistance exercise and self-management support for people with sarcopenic obesity and OA improved muscle, mobility and quality of life when compared with usual care, focusing on a primary outcome of weight reduction in people with OA[30]. These data suggest that systemic factors can drive OA and, in turn, OA can have systemic consequences (Fig. 1). OA is a serious disease; it increases the prevalence of other chronic diseases that directly reduce healthspan, and contributes to walking disability, which is associated with mortality[26,32,33]. Although evidence suggests that OA might not always directly lead to mortality, the influence of OA on lifespan or healthspan remains to be directly tested. However, these data cannot be obtained if studies are not designed to assess for these parameters; we advocate for a comprehensive view of OA, which incorporates the contribution of multimorbidity and systemic factors, as doing so could provide an important opportunity for meaningful intervention for this increasingly prevalent, painful disease. The compartmentalized, site-specific approach of many OA studies compounded by the historically cartilage-centric focus in OA research, has potentially hindered the opportunity to understand OA as a systemic disease and a systemic driver of disease, or at least the identification of an endotype related to systemic mechanisms.

Endotypes are mechanistically defined as distinct pathways that lead to disease end points[34], which could mean that individuals advance to a similar clinical pain or structural end point through different mechanisms. In the APPROACH trial, investigators demonstrated that longitudinally stable structural disease endotypes might be leveraged to generate biomarker-based endotyping in a clinical trial setting[35]. These data pave the way to both illustrate relationships between systemic factors and OA, and to identify patients who might respond to a particular therapy or intervention. However, treatments that target a particular molecular pathway can only be successful in trials if people with OA who have disease that is driven by that specific pathway are identified for

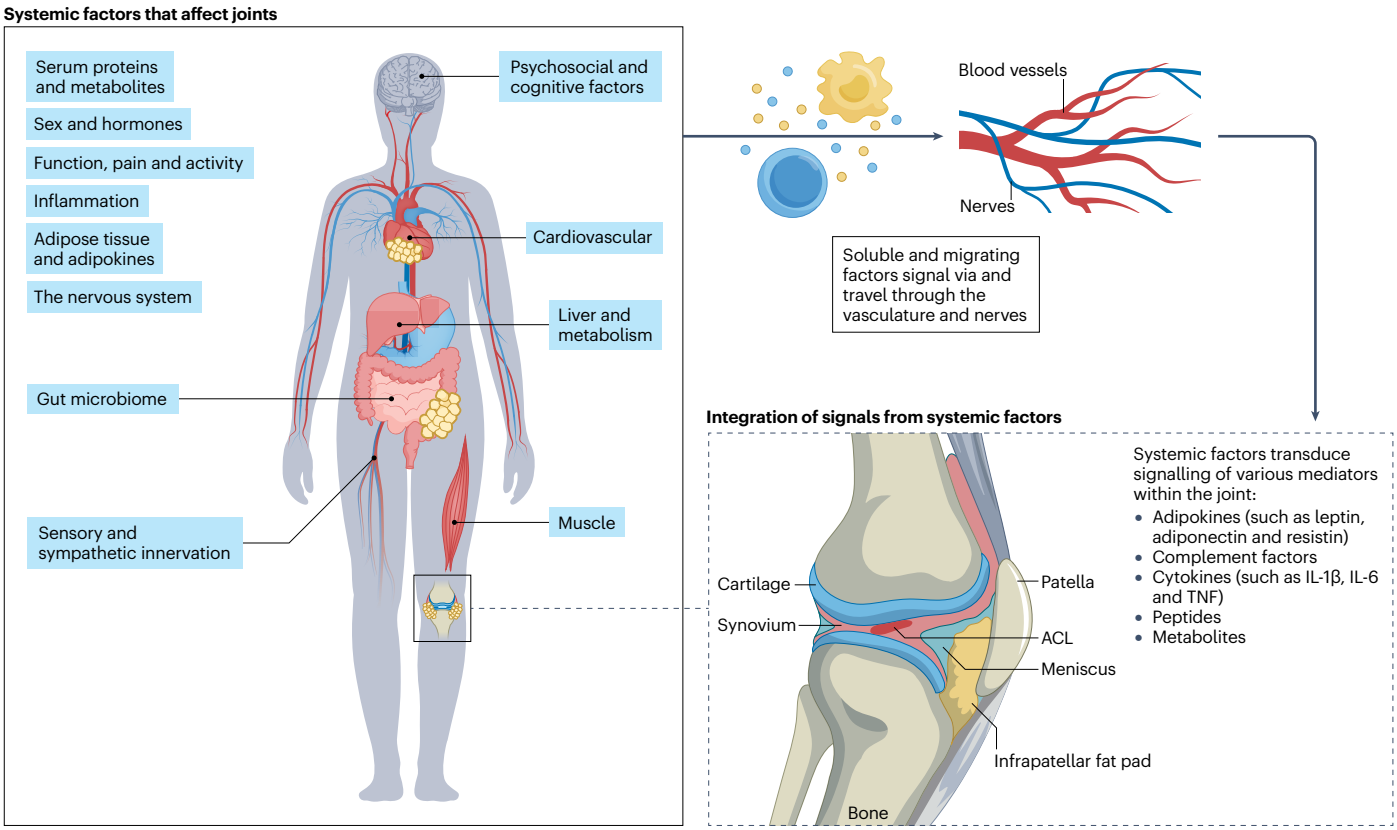


Fig. 1 | Effects of systemic factors on joint health. The precise signals and secreted factors involved in systemic osteoarthritis are unclear. In addition, the tissues and/or cell types in the joint that transduce these systemic signals remain unknown. However, preliminary data indicate that the synovium, blood vessels or bone marrow might be the key transducers of these signals. We posit that a tissue or cell type receives and integrates the signal and subsequently signals to recipient cells, which remain to be determined. Ultimately, these signals drive cartilage loss, bone remodelling, synovitis and other hallmark factors of osteoarthritis. ACL, anterior cruciate ligament.

enrolment into those trials, which demonstrates the need for patient endotyping to maximize treatment efficacy.

Although several biologic drugs have been evaluated in OA, the development of DMOADs has failed in a variety of contexts; for example, in hand and knee OA[36], studies of pharmacological inhibitors of TNF[37–40], IL-6[41], IL-1, matrix metalloproteinases or senolytics have all failed to meet their primary end point[42]. There are many reasons why these drugs have failed (reviewed elsewhere[43–45]), including short duration of treatment and follow-up, enrolling individuals who are too far along in their disease pathology trajectory, and not necessarily including the right patients for the treatment targets being tested[37–42]. Another reason for treatment failure might be because OA is treated as one disease rather than as an umbrella term for a common end pathology that occurs through and is modified by many different pathways, including injury, genetics, sex, obesity, ageing, malalignment, altered biomechanics, inactivity or other reasons[46]. Moreover, renewed excitement and more data to support the hypothesis that OA is a systemic disease are evident in the drugs that are currently pursued for secondary indications for OA, including systemic administration of semaglutide, liraglutide, metformin and other drugs that aim to target systemic hormone or metabolic dysfunction in patients[47].

Historical view of OA

Converging evidence implicates crosstalk among joint tissues, immune pathways and systemic factors such as ageing, obesity and sex-specific biology in driving OA onset and progression. Despite advances in molecular and imaging technologies, translational progress remains hindered by preclinical models that inadequately capture the temporal, cellular and systemic complexity of OA. Innovative approaches (including organoid and 'joint-on-a-chip' platforms, context-relevant models, integrative omics, pain assessments and multi-joint phenotyping) are poised to bridge these gaps and advance a holistic framework that defines OA as a disease of the whole organism rather than of a single joint.

Moving beyond a focus on cartilage damage

OA has been classically viewed as an inevitable condition of ageing, caused purely by mechanical wear-and-tear of the articular cartilage, with little attribution to the role of systemic biological processes in maintaining the overall health of various joint tissues. Early analyses of cartilage were focused on its mechanical function in transmitting joint loads and providing a bearing surface for movement, albeit with a recognition of its lack of intrinsic repair properties[48]. Through the increasing understanding of the role of chondrocytes in the maintenance of cartilage homeostasis, the field has gained an improved understanding of the biological processes that govern the maintenance and health of the joint[49]. Nonetheless, despite the recognition that both biomechanical factors and biological signals (such as inflammation) have a role in OA, the field experienced substantial debate as to the 'tissue of origin' of the disease (that is, bone versus cartilage)[50] and whether joint inflammation was involved in the disease process[51]. Even with the mounting evidence that indicates the involvement of multiple tissue types and both biological and biomechanical processes, 20–30 years ago, investigators were still questioning whether OA was a disease of cartilage or whether it should be termed 'osteoarthrosis' instead of 'osteoarthritis' owing to a lack of classical characteristics of inflammation[52,53].

A role for inflammation in OA

Although historically considered vastly different with independent pathophysiology, there is an increasing appreciation that similar clinical phenotypes occur in OA and rheumatoid arthritis[54], including similar pain and disability scores and involvement of synovial inflammation (albeit synovial inflammation is more florid in rheumatoid arthritis than in OA). Moreover, in many studies, OA serum is used as a control for rheumatoid arthritis serum, which might have skewed the understanding of the relative involvement and pathways of inflammation present in both diseases. Inflammation in OA is readily recognized clinically as joint effusions, but the degree of inflammation differs from other rheumatic diseases[55,56]. Ultrasonography and MRI demonstrate a high prevalence of inflammatory features (such as synovitis)[57], and sustained synovitis is related to considerably higher rates of OA progression[58] and pain[59,60]. Furthermore, changes in the infrapatellar fat pad, consistent with inflammation, are related to patient-reported pain and function in OA, and these relationships differ in women and individuals with obesity[61]. Notably, these signs of inflammation can be observed in patients who have no known history of knee injury[62]. These data are corroborated by single-cell and 'omic atlassing' efforts that aim to use untargeted profiling approaches to demonstrate synovial fluid and infrapatellar fat pad transcriptomic changes consistent with inflammation in OA[63,64].

Owing to this oversimplified understanding and approach to the OA disease process, much of the process of drug discovery for DMOADs has focused on single tissues (cartilage or bone) or single pathways (biomechanical or biological). Historically, drug discovery that targeted single processes, such as cartilage degradation (for example, aggrecanase)[65,66] or bone loss (such as bisphosphonates)[67], showed beneficial effects for bone and cartilage but generally failed in clinical trials. Bisphosphonates, calcitonin or MIV-711 (cathepsin K inhibitor) also showed beneficial effects for cartilage in addition to bone[68] but these drugs also failed.

Although mechanical factors can lead to cartilage loss and bone remodelling, a role for mechanisms beyond tissue wear-and-tear is clear, such as the involvement of important 'mechanobiological' components[69]. Similarly, the biological processes involved in cartilage maintenance are not represented simply by the balance of anabolic and catabolic activities of chondrocytes. Numerous complex pathways of local and systemic inflammation, cell metabolism, ageing, senescence, and innate immune activation interact with both genetic and epigenetic factors in multiple tissues of the joint. This complexity has been shown in other diseases, such as type 2 diabetes mellitus (T2DM) and cardiovascular disease, and is now suggested in the pathophysiology of OA[70]. Taken together, evidence shows that cells and tissues of the joint do not function in isolation but, rather, the joint functions as an organ within the integrated organism; these inter-organ crosstalk interactions are essential in the physiology and pathology of the synovial joint[6]. Another inherent limitation of prior work in OA is that most research is focused on the knee, which does not necessarily translate to other joints (such as the hand and hip).

A vulnerable joint: local and systemic factors drive OA

We posit here the concept that a vulnerable joint might arise from additional systemic predispositions or external driving factors that function in concert to accelerate disease onset and progression. This concept remains to be directly tested. There are several key questions to address; for example, from a clinical perspective, what can be learned about OA as a systemic disease from studying multi-joint pathophysiology? Efforts underscore the value of comprehensive phenotyping of multi-joint OA versus studying OA in single anatomic locations[71]. Another important factor to address is whether unilateral knee OA is

the same as bilateral hand OA that involves all proximal interphalangeal joints. The use of animal models with comorbidities, such as obesity and ageing, should be evaluated to determine if they can help to address some of these knowledge gaps. Increasing evidence suggests that the whole-body burden of OA could potentially be sexually dimorphic[15]. A deeper understanding of the pathophysiology of sex differences will be fundamental in advancing patient-relevant outcomes such as functional limitations and quality of life; however, a definition of multi-joint OA is lacking, which limits progress in clinical studies that aim to understand OA as a systemic disease.

The gap between preclinical findings and translation

There are several fundamental mechanistic aspects of preclinical models of OA that require investigation: innervation patterns[72,73]; how the outcomes of interest of the trajectory of OA disease pathogenesis change over time; how obesity, ageing and sex differences alter disease; the influence of genetic and epigenetic risk factors; clear consensus on how to study early signs of disease in mice; and studies that focus on structural damage at predefined study end points. The latter might reflect a lack of time-course studies and the use of models that do not recapitulate key components of OA phenotypes in preclinical models. These gaps require preclinical investigations as well as reverse translation of clinical findings and discovery biology in human tissues. Addressing clinically or translationally meaningful outcomes in these studies is also important.

Although the concept of the joint as an organ is broadly accepted, it remains difficult to address such questions using in vitro models or even in most preclinical models of OA (such as rodents). In vitro models are often limited to the use of a single-cell or tissue type, in which control of the genetic background is limited, and a focused use of either animal or human cells. Many of these limitations are just beginning to be addressed; development of organoids[74,75] and 'joint-on-a-chip' models[76–79] are improving, which combine multiple tissue types and potentially allow for control of signalling, directionality and genetically defined human cell types (such as induced pluripotent stem cells) that can be edited to include specific genetic risk factors for OA[80].

Designing preclinical models to interrogate clinically relevant gaps in knowledge

Both in vitro and in vivo models can provide systems whereby genetic risk factors can be defined together with other OA risks (such as obesity, joint injury and ageing). Thus far, such preclinical in vivo models have often been limited by a focus on a single sex (typically, male) with limited outcome measures that integrate all aspects of OA across the body (that is, they focus on a single joint), including measures of pain. Many studies are generally joint-specific without considering multi-joint OA, which is difficult to model preclinically. However, with diet-induced obesity, we demonstrated the presence of multi-joint OA in the knee and shoulder, but not the hip, in Sprague–Dawley rats[81]. A holistic approach in both preclinical and human studies is needed to study all the joints in the body, particularly in preclinical models in which the effect of an inciting agent can be extensively studied, and clinical insights and phenotypes can be reverse translated to probe mechanisms and evaluate treatments. Furthermore, Cre-Lox and transgenic mouse systems that enable several key tissues or cell types to be targeted in the mouse joint (such as the synovium, infrapatellar fat pad and bone marrow) are lacking. Such approaches could be used, to separate the roles of these effector tissues in transducing systemic signals to various joint tissues.

A barrier to gaining foundational understanding regarding endotypes is that it has been common practice to test the mechanisms, safety and efficacy of drugs in young male mice, which contrasts with the clinical OA population that largely comprises women or people from minority backgrounds in the middle-to-late stages of life. The lack of testing in more relevant preclinical models could be because of perceived limitations of animal models; for example, the assertion that female mice do not get OA. Although this statement might be true for histology, in that female mice might demonstrate more modest cartilage damage, data from a recent study showed that, in the destabilization of the medial meniscus (DMM) mouse model, female mice have a similar severity of hyperalgesia to male mice, but the structural changes observed, despite being substantial, were less severe in female mice[82].

Shifting the focus from established OA to early OA in mice

Typically, clinical trials use radiographic assessments of disease, which are relatively insensitive measures. Additionally, many clinical studies focus on studying individuals with established disease and, as such, preclinical assessments have also focused on modelling established or end-stage disease. From the perspective of understanding disease mechanisms, a challenge with studying organisms or people with established disease is that key (and potentially intervenable) risk factors that contribute to the early disease processes are missed. From the perspective of clinical trials, the expectation that targeting a single molecular pathway might be successful is probably unrealistic when the disease is well established, as numerous downstream pathways or factors that influence the outcomes beyond the single molecular pathway being targeted are activated — akin to trying to close the stable door after the horse has already bolted. Disease-related changes will probably occur in people or in model systems a long time before they are studied, and those individuals who have these risk factors but do not develop overt disease could provide important insights into how their tissues, biomarkers or endotypes might differ from those of individuals who do develop disease. In particular, risk factors that lead to disease might persist for many years prior to the development of the established disease. Efforts are under way to develop classification criteria to validate the identification of individuals with early-stage symptomatic knee OA prior to the development of established disease to facilitate epidemiological studies and trials at a stage when both studying risk factors and intervening might be more fruitful[83].

A limitation in the study of early OA is a lack of widely accepted assays or outcomes to identify early signs of disease in preclinical models. Thus far, only histology, which requires a terminal end point, is widely accepted for this purpose but pain hyperalgesia can be detected as early as 2–4 weeks after injury[82,84]. Many single-cell transcriptomic studies of joint tissues in well-established OA have been published. However, the opportunity exists to use a variety of techniques (including measuring proteins and metabolites, using spectral flow cytometry and other untargeted techniques) to profile secreted and circulating factors to define the serum or systemic changes that occur earlier in the disease process since it is well known that animal models of OA generally demonstrate measurable joint damage after 8–12 weeks[85]. Depending on the research question, it could also be valid to use pain outcomes to detect early changes owing to post-traumatic OA independent of structural damage. This focus on uncovering early OA in animal models is important in addressing clinically or translationally meaningful early changes in OA at both the local and systemic levels

and in beginning to define acceptable outcomes or disease trajectory benchmarks in well-controlled preclinical model systems.

Systemic metabolic factors in driving early OA

To understand the risk of early OA, younger patients (that is, those individuals who are younger than the typical age of OA diagnosis) should be monitored for risk of OA and pain (that is, earlier than middle age). Although most people aged 30–40 years might not demonstrate overt metabolic distress, the relationship between metabolic changes and OA risk or progression has not been studied systemically to date. A 2025 proteomic atlas of ageing revealed that adipose tissue is among the first tissues to show measurable signs of ageing in the fourth decade of life[86], which can lead to metabolic disturbance that might or might not be monitored clinically as standard of care. These findings emphasize the need to understand the metabolic or systemic comorbidity status of individuals aged 30–40 years to create a deeper understanding of the pathophysiology of early OA, a group that could potentially benefit from interventions to mitigate or prevent OA progression.

Although obesity is defined by body mass index (BMI), lower BMI is not always indicative of a healthy metabolic status and, furthermore, individuals can have an unfavourable ratio of adipose tissue to lean muscle mass despite having a lower BMI. Moreover, measuring body composition and metabolic status, even in people with a BMI of 25–29 kg/m^2, will provide insights into the underlying metabolic risk in younger people[29,87]. Even among those with obesity, there are differential metabolic consequences; for example, sarcopenic obesity or low muscle mass coincident with obesity occur in approximately 10% of individuals with OA, and can influence walking speed, endurance, strength and other patient-reported outcomes[88,89]. The mechanisms of the interactions with obesity, ageing and sex differences that drive OA, genetics and epigenetics, among other key comorbidities with systemic manifestations, remain to be clarified. Indeed, physical function is a better prognostic marker for premature mortality than almost any laboratory test among those with or without a form of arthritis, obesity or comorbidities[90–96].

Interrogating pain and behaviour in animal models

Pain is by definition a complicated construct involving both sensation and emotion, articulated by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[97]. There are strong associations and a probable bidirectional relationship between emotional and cognitive factors (such as depression, anxiety, pain catastrophizing and self-efficacy), sleep and comorbidities; for example, people with a high burden of psychological factors, comorbidities and sensitization but a low degree of OA report the highest level of pain[24]. In these people, targeting cartilage may not improve their pain, yet the outcomes of interest in preclinical studies are almost exclusively focused on mitigating, reversing or preventing joint damage, and clinical trials do not differentiate inclusion criteria based upon those factors that contribute to the pain experience of an individual. Although some studies describe factors that might have separable, and even paradoxical, roles in driving pain and structural damage[24], historically, factors do not seem to be pursued or reported if an element of structural damage was not involved; the outcome of this is that several relevant or interesting targets have not been pursued. This lack of reporting might be because pain has only been considered in preclinical models in the past few years[98].

Notably, there are largely three categories of pain that are present in rheumatic diseases: nociceptive pain, neuropathic pain and nociplastic pain, which are reviewed elsewhere[99]. In addition to nociceptive pain (caused by nociceptive input from pathological peripheral tissues), nociplastic pain, which is characterized by altered nociceptive processing and central sensitization in the absence of tissue pathology, is also present in some people with OA, and is probably more prevalent in people with OA and comorbidities[100]. The identification of factors involved in different pain mechanisms can improve understanding of the separable and overlapping contributors to pain and structural damage in OA and of how these might be driven or affected by systemic factors[24,82] to identify new promising therapeutic targets in preclinical and clinical studies. As studies do not often consider the whole joint or the whole organism, many preclinical models do not capture potential key aspects of relevant OA pain mechanisms that can be affected by systemic factors (such as diet, sex, environment, genetics, epigenetics and the microbiome)[25] and the interactions of these relevant factors. Notably, knee pain is not relieved by joint replacement in ~20–30% of individuals, probably owing to persistent pain sensitization and other systemic contributors to pain beyond joint pathology. More data are needed to better understand this relationship.

Factors beyond the joint

Genetic, metabolic and systemic factors outside the joint converge to drive OA structural damage and symptoms. Preclinical and clinical data highlight roles for adipokines, inter-organ crosstalk and sex-specific mechanisms that might be affected by age and comorbidity status. Targeting metabolic dysfunction, inflammation and systemic pathways offers promising avenues for disease-modifying therapies.

Genetic risk

In the past three decades, data from large-scale genome-wide association studies (GWAS) have revealed genetic variants of relevant functional consequences in hand OA. These variants have testable treatment targets, such as Matrix Gla protein (MGP; a vitamin K-dependent protein) and aldehyde dehydrogenase 1 family A2 (ALDH1A2; a key enzyme for the synthesis of all-trans retinoic acid), both of which can be targeted with available inhibitors[101]. Such insights further support the concept of OA as a systemic disease; for example, even post-traumatic knee OA, which is typically considered to be isolated to the affected joint, could potentially have an underlying genetic predisposition or systemic driver to explain why some people go on to develop OA but others do not despite the same mechanism of injury (such as severity of an anterior cruciate ligament tear). Indeed, there is some evidence of a genetic contribution to the severity of post-traumatic OA[102,103]. At the same time, these studies highlight the multifactorial nature of OA since not all individuals with these genetic variants develop OA. The Genetics of Osteoarthritis consortium is undertaking work on GWAS of OA endophenotypes[104] that will provide foundational mechanistic understanding of the role of genetic drivers of OA, which have been demonstrated, in part, to be associated with systemic metabolic diseases[105]. The roles of epigenetics and gene regulatory mechanisms in driving OA are also being explored in addition to genetic drivers, which have been reviewed elsewhere[106–108]. Some of these GWAS studies have been functionalized in preclinical models to assess mechanistic gene regulatory interactions; for example, the *R2de* region of the mouse *Gdf5* gene, which is among the most cited OA risk variants[109]. Genetic testing services demonstrate how single-nucleotide polymorphism analysis could become a more accessible tool that could be used to

gain a deeper mechanistic understanding of the causal role of genetics in OA and thus provide potential treatment targets.

Reverse translation of clinical phenotypes and endotypes

One opportunity to bridge the gap between preclinical models and clinical data is the use of preclinical models that can demonstrate the necessity and sufficiency of factors of interest such as leptin[110–113] (Box 1). Mice or other preclinical models enable more comprehensive profiling that can help to establish cause and effect, which could enable better translation if the models were more fit for purpose. The association between obesity and symptomatic OA is stronger than between obesity and radiographic OA[114], and adipose tissue exerts effects on OA-related pain independent of body mass[24,25,27]. Quantifying adipose mass, body mass and obesity is challenging, and clinical data on the role of adipokines are conflicting. However, the systemic effects of obesity might be explained by leptin, which has been shown to have promising links to pain, radiographic changes and American College of Rheumatology diagnostic criteria. Leptin, a satiety hormone, is the most consistently increased adipose tissue-derived mediator reported in obesity-induced OA[115,116]. Leptin-knockout mice are protected from OA, despite being morbidly obese[117,118], and leptin is sufficient to induce OA in the absence of adipose tissue in mice[24]. However, the precise mechanistic role of leptin, its target tissues in the joint and elsewhere, remains unknown. In a cohort of people with hand OA, individuals with overweight and obesity reported more severe pain not only in the knees and hips but also in their hands[114,119]. The association with hand pain was mediated through leptin, supporting the systemic effects of obesity on pain, which have also been recapitulated in mouse models of knee OA[24].

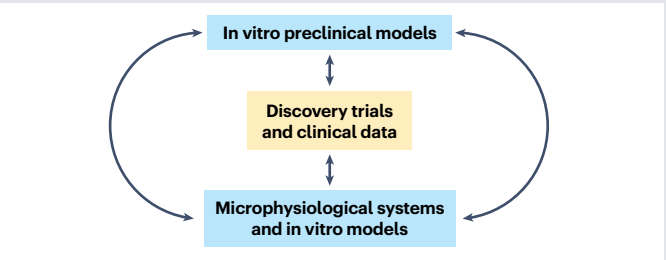
Similarly, visceral adiposity, but not subcutaneous adipose tissue, has been associated with knee pain severity[120], highlighting the importance of differentiating metabolically active adipose tissue from overall body mass. The effects of obesity on hand pain and painful total body joint count in this study were partially mediated by leptin and high-sensitivity C-reactive protein (CRP)[120]. Furthermore, bariatric surgery not only reduces lower extremity joint pain but also hand pain and reduces sensitization[121,122]. Coincidentally, decreases in leptin and increases in glucagon-like peptide 1 (GLP1) are observed almost immediately post-operatively, even before weight loss[123], which suggests that altering systemic factors and mitigating pain can be separate from overt weight loss. There are also new spatial tools to consider for OA research (including spatial profiling tools such as spatial transcriptomics, spatial metabolomics and spatial proteomics) that we and others have begun to develop for mouse models and human studies[63,64,120], which will provide important missing spatial context on how the joint responds to systemic factors in both human and preclinical discovery studies. These spatial tools help to overcome the limitations of the current strategies used to target tissue-specific changes or observe them in situ or in a whole-joint preparation (that is, for samples obtained from mice, human cells or organoids).

Inter-organ crosstalk between adipose tissue and OA

Research has demonstrated a causal relationship between adipose tissue and knee joint damage in mice[27,124], which is corroborated by

Box 1 | Forward and reverse translation in OA research

To advance the understanding of osteoarthritis (OA) as a systemic disease, in vitro, preclinical and clinical samples can be used in a forward and reverse translational capacity. All of these approaches bring opportunities to OA research:



Microphysiological systems and in vitro models

- Holistic phenotyping (tissues, fluids (such as serum and synovial fluid), whole joints and multi-joints)
- Controlled systems for early OA assay development
- Measuring pain and structural changes in vitro
- Drug repurposing
- Inclusion of clinically relevant factors such as sex, obesity, ageing and comorbidities
- Time-course studies
- Studies that test the directionality of signalling

In vivo preclincial models

- Use of human materials with known risk factors
- Assessing inter-organ crosstalk
- The ability to establish cause and effect
- Inclusion of clinically relevant factors such as sex, obesity, ageing and comorbidities
- Time-course studies
- Assessment of pain factors
- Development of early diagnostic tools in mice to better study early OA

Discovery trials and clinical samples

- Holistic phenotyping (tissues, fluids (such as serum and synovial fluid), whole joints and multi-joints
- Measuring pain and structural changes to probe both aspects together and separately
- Determine the timing and type of rare OA signs and symptoms
- Inclusion of clinically relevant factors such as sex, obesity, ageing and comorbidities
- Time-course and prospective cohort studies
- Investigating early OA in people at risk
- Determining factors that drive persistent pain after treatment

Glossary

Deep learning
A subset of machine learning that uses multilayered artificial neural networks to model complex data patterns.

Elastic net
A regularization method used in machine learning that combines Ridge and Lasso regression models.

Healthspan
The number of years lived in good health, free from chronic disease or disability.

Lifespan
The total number of years that a person lives (from birth to death).

Neuropathic pain
Pain caused by lesions, injury or disease that affects the somatosensory nervous system.

Nociceptive pain
Pain that occurs owing to the activation of nociceptors due to tissue injury, inflammation or disease.

Nociplastic pain
Pain originating from altered nociception without clear evidence of tissue damage or nerve injury.

Pain catastrophizing
A pain-specific response that involves magnified negative thoughts and feelings of helplessness.

clinical evidence[100,125,126]. Moreover, adipose tissue has been suggested to be essential to organismal ageing. Thus, monitoring individuals with metabolic risk factors for OA-related pain might be important to better understand, separate and triangulate the individual and the combined impact of multimorbidity, adipose tissue, and metabolic disturbance on ageing and age-related musculoskeletal disease[100,127]. For example, the role of fat in OA has been shown using a mouse model of lipodystrophy[24,27]. Global unsupervised multiomics of conditioned media from adipose tissue implants revealed that leptin exerts a regulatory effect on adipsin (also known as complement factor D), which is part of the alternative complement pathway[16]. Interestingly, the loss of adipsin protected OA joints but resulted in pronounced sensitivity to pressure-pain hyperalgesia, which was detectable as soon as 2 weeks after injury in both male and female mice[82]. Evaluating and understanding the role of the innate immune system and other factors that might be activated or upregulated by adipokines, such as leptin and adipsin, and have a unique role in pain and/or structural damage, might be foundational data from which new drugs could be developed[24,27,82].

Repurposing anti-obesity and metabolic dysfunction drugs for OA

Much excitement has come from the findings of the STEP 9 trial of semaglutide, a GLP1 receptor agonist, which demonstrated greater pain improvement and weight loss in the intervention arm than in the placebo arm in patients with OA[26]. Similarly, GLP1 receptor expression has been reported in joint tissues in rodents, and treatment with systemic liraglutide in rodents alleviates pain, independent of weight loss[128]. Although the GLP1 family of drugs has been proposed to slow down the ageing processes and improve healthspan[129], the mechanism by which this occurs and how it potentially improves OA specifically is unknown. Some studies report negative outcomes of GLP1 drugs, for example, worsening of OA[130,131] and bone loss[132]. Another prominent concern is loss of lean muscle mass[131,133] in concert with adipose tissue to achieve overall weight loss, resulting in a potential risk of sarcopenia and detriment to strength and function. These findings indicate that understanding the systemic mechanisms of OA is essential to better use these incretin-targeting drugs and identify patients who will benefit most from their administration. This point is especially concerning as an increased risk of OA has been reported in individuals with muscle loss or weakness[31,88,134].

Other potential therapeutic targets to treat metabolic dysfunction could be identified through new insights gained from studies of the gut microbiome. Although initial studies aimed to understand the role of the gut microbiome as a link between diet and OA[135–138], data now indicate that the gut microbiota–GLP1 axis could be a highly attractive drug target for OA[47]. Several association studies have linked gut microbiome dysbiosis to OA[139,140], and DMM-induced OA is reduced in mice that lack a gut microbiome[141]. Faecal microbiota transplantation can confer resilience in mouse models of OA, which suggests that microbiome manipulation or transplantation might be a viable therapy for OA[142]. It remains unclear if the microbiome-mediated influences on the joint occur in a manner dependent or independent of lipopolysaccharide signalling[135,143], but research is ongoing[144]. Data from the Lifelines-DEEP study demonstrate that this association is driven by local inflammation in the knee joint[145]. Further details about the pathophysiological role of the microbiome in OA, the role of the microbiome in systemic OA and the therapeutic potential of targeting the gut microbiome have been reviewed elsewhere[146].

Another promising therapeutic approach is targeting insulin resistance systemically. Treating the metabolic effects that might drive OA using metformin, a T2DM drug, has been shown to mitigate structural OA pathogenesis, pain and immune changes in mouse models and people with OA[147]. A high number of individuals with OA are at risk of or diagnosed with T2DM or metabolic syndrome. In a 2025 trial of people with painful knee OA and a BMI of ≥25 kg/m^2, metformin was superior to placebo for pain reduction[148]. Metformin is also currently being interrogated as a candidate anti-ageing drug, as it was shown to slow the effects of ageing in the TAME trial[149,150], and is being evaluated in OA in a clinical trial aiming to prevent post-anterior cruciate ligament injury OA (that is, post-traumatic knee OA; NCT06096259). These trials provide further support for the notion that a complex interaction between metabolism and ageing promotes OA pathogenesis.

Sex hormones and sexual dimorphism in OA

Another key factor at the interface of systemic factors in OA, ageing and adipose tissue is menopause. A sizable proportion of individuals with OA are women in post-menopause with obesity, and the female sex is one of the strongest predictors of OA development[151]. This observation underscores the need to better understand the role of sex, hormones, pain and metabolic dysregulation in OA. Data on the effects of hormone replacement therapy (HRT) on OA and knee pain are mixed. In a post hoc analysis of a large trial of HRT in women with cardiovascular disease[152], there was no difference in knee pain compared with placebo. More trials are needed to better understand the potential role of HRT in OA pain[153,154].

Xist (X-inactive specific transcript) is a non-coding RNA that has a key role in the X-inactivation process. In 2024, Xist ribonucleoproteins were shown to drive innate immunity in women[155], which is highly relevant to OA pathogenesis and might be another mechanism by which sexually dimorphic systemic phenotypes are driven in OA. Novel models to study sexual dimorphisms can be used to understand the role of cell-intrinsic and systemic effects of chromosomal and gonadal sex on OA and pain but more work is needed[16,156].

Although much interest has been focused on hormonal differences as an explanation for the high prevalence of OA in women, studies thus far have not yielded actionable insights. For example, sexual dimorphism is evident in cartilage before menopause and can be affected by chromosomal sex. Dimorphic phenotypes are not reversed with ovariectomy, and ovariectomy does not fully replicate the natural progression of OA in women in post-menopause. Future studies could consider investigating dimorphic factors that are not driven by sex hormones or cell-intrinsic effects of sex. For example, measuring dimorphic circulating factors, such as proteins, gene transcripts and metabolites, in the serum and designing studies to determine how these dimorphic factors are affected by obesity, age, and other known risk factors for OA could contribute to the understanding of the complex role of sex as a biological variable in systemic OA.

Repurposing DMARDs as DMOADs

DMARDs are successful treatments for many rheumatic diseases, and given some shared potential pro-inflammatory drivers of rheumatic diseases with OA, there is potential to repurpose approved drugs for OA indications with appropriate data and trials. Inflammation is another key link between OA and systemic drivers. Several phase II trials of inhibitors of IL-1β (a key cytokine in OA) have either shown negative results or demonstrated a small effect that might not be clinically relevant or translationally meaningful. Similarly, several trials of colchicine, a drug with anti-inflammatory properties, in knee and hand OA have been negative. A commonality across these trials is that they have been small in size and of short duration (for example, of 6 months). The CANTOS trial, a large placebo-controlled trial of canakinumab, an IL-1β inhibitor, was conducted in ~10,000 people with cardiovascular disease and an increased level of high-sensitivity CRP, followed for a median of 3.7 years. In a post hoc analysis, those on canakinumab had a ~40% lower risk of joint replacement compared with placebo[157]. Similarly, the LoDoCo2 trial of colchicine in ~5,500 people with coronary artery disease (followed for a median of 2.4 years), demonstrated a ~30% lower risk of joint replacement compared with placebo[158]. Since knee replacement surgery is predominantly performed for knee OA, it necessarily implies that the lower rates of joint replacement in the anti-inflammatory treatment arms were related to lower knee OA structural progression, symptoms, or both, and highlights the relevance of considering a systemically acting drug capable of inhibiting inflammation in the whole body or organism. These cardiovascular trials also highlight the challenges with OA trials thus far, which have probably been too small in size, of too short a duration and too heterogeneous to identify an efficacy signal. Efforts must now be made to understand which patients are most likely to benefit from such treatments, again reiterating the importance of systemic patient phenotyping.

Future research opportunities

The paradigm shift towards regarding OA as a potential whole-body disease that leads to pain and loss of physical function, at least in a subset of patients, is a useful lens through which new insights into OA can be gained. However, identifying those factors that limit more representative clinical and/or translational studies is an important step. Some factors include sample size, heterogeneity of study samples

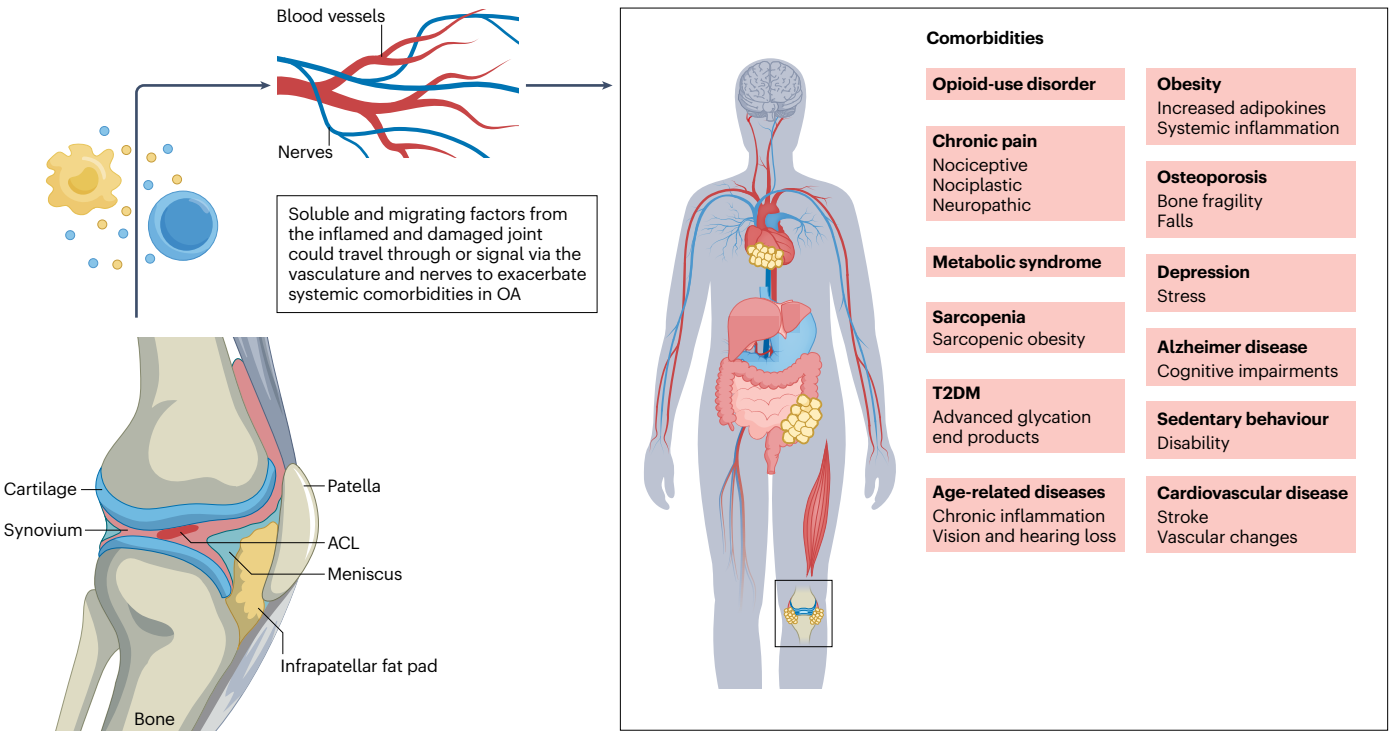


Fig. 2 | Effects of joint health on systemic factors and comorbidities. Although data that establish cause and effect remain to be generated, changes to the local joint environment are coincident, if not drivers, of systemic pathology. Several studies indicate associations with the onset and progression of several diseases and disorders that are systemic in nature (shown in red boxes). It remains unknown if the driving factors (genetics, epigenetics, environment, comorbidities, sex and age) for these systemic diseases also promote osteoarthritis (OA), or if OA promotes these factors independently. ACL, anterior cruciate ligament; T2DM, type 2 diabetes mellitus.

Box 2 | Questions and directions for future OA research

1. Is osteoarthritis (OA) a systemic disease that generates symptoms and pathologies in the joint?
2. Which joint cell populations are vulnerable to systemic or adipose tissue-derived signals, and which populations might drive systemic changes?
3. What is the relationship between pain and structure, and what is lost by focusing on one or the other and not both?
4. How does the whole organism communicate with the joint, and how can clinical observations be reverse translated to better model whole-organism disease using preclinical or in vitro approaches?
5. Can failed trials or interventions be leveraged to better understand potential systemic mechanisms of OA?
6. What can be learned through the integration of existing datasets and cohorts to mine for meaningful clues about the clinical problem of OA?
7. Can OA be used as a model to better understand other diseases of multi-organ ageing?
8. Why do some people get OA with specific risk factors (such as knee injury) and others do not, and how can the 'multi-hit hypothesis' be best evaluated given that joint injury often but not always causes OA, and odds increase with systemic effects such as obesity?

and sample bias, and the fact that discovery research is not typically conducted on systemic factors, largely owing to the limitations of available profiling tools in past efforts. Objective, untargeted profiling of a variety of circulating factors (such as proteins, metabolites[159], cells and immune populations) and multiomic changes in an unbiased manner in blood (that is, serum or plasma) and synovial fluid[160] in early OA is an exciting opportunity for future studies[161]. These data can be objectively integrated, assessed and analysed using machine learning methods such as deep learning[162] and elastic net[163].

OA as a driver of systemic disease

In addition to the concept that systemic factors can influence OA, there is growing evidence that shows the effects of knee pain and damage on the rest of the organism, illustrating a bidirectional relationship. This concept has also been demonstrated in a study that showed that knee injury and pain might cause changes to the cardiovascular system[164], brain[165,166], adipose tissue[24] and other organ systems (Fig. 2). However, observational data from systemic metabolic diseases have not demonstrated consistent associations or shown the same findings as in preclinical models. The potential reasons for this include preclinical models not being fit for purpose (many animal models have limitations in recapitulating human OA); the timing of studying people with well-established disease being too late to understand mechanisms that probably started decades earlier; and the fact that available tools to study systemic effects in humans, typically blood biomarkers, which are often studied in isolation of one another at a single time-point in people with well-established disease, are inadequate to gain insights regarding relevant exposures in the joint environment (and local microenvironment within the joint) at the time of disease initiation. Spatial high-resolution tools[24,108,161,162], such as spatial transcriptomics[64], spatial proteomics[167] and spatial metabolomics[168] and whole-joint anatomical mapping efforts (REJOIN study)[73], will help to triangulate how cells in joint tissues respond to external signals and how cell-intrinsic responses might dictate protection or vulnerability in different tissues. This tissue-specific response might also manifest as an endotype.

A need for unbiased discovery

Reimagining discovery approaches to integrate basic and clinical studies will improve the understanding of mechanisms and targets for systemic OA. To this end, future studies should consider using high-dimensional multimodal assays to analyse human samples for discovery and validate them in preclinical models with the appropriate controls, which could provide new insights. This approach contrasts with performing discovery studies in rodents and designing translational and clinical studies from preclinical mechanistic data, although both approaches are important. The use of an integrated, untargeted multiomics approach to analyse serum and synovial fluid samples might begin to provide much-needed, meaningful insights into systemic OA pathophysiology. Future work should continue to examine the roles of systemic factors on the joint by comprehensively investigating risk factors, the role of tissues outside the joint (tendons, muscle, adipose, cardiovascular system and the nervous system), and the effects of inter-organ crosstalk and systemic mediators (Box 2).

Conclusion

Collectively, these findings underscore the complex and intertwined relationship between systemic factors that drive OA and pain. A shift towards considering systemic drivers of OA will enable the identification of other druggable targets that can be used to treat, manage or prevent OA as well as a myriad of devastating interrelated diseases that co-occur with ageing and obesity. This approach would position the OA community as leading the way for the development of novel treatment strategies for metabolic disease and ageing. Such profiling, for example, of blood, synovial fluid or other systemic factors, might also improve clinical triaging of patients and better identify patients at risk owing to multimorbidity. There remains a key role for preclinical models and in vitro studies to pave the way towards a mechanistic understanding of systemic factors that drive OA, and how OA might promote changes in systemic factors that lead to multimorbidity. Pain assessments, earlier evaluation, reverse translation of clinical paradigms and systemic profiling will provide a deeper, much-needed understanding of the systemic OA phenotype. This ongoing paradigm shift highlights the opportunity to consider the whole patient and pain when evaluating potential individuals with OA or those at high risk of disease in the future.

Published online: 3 December 2025

References

1. Malfait, A. M. Why we should study pain in animal models of rheumatic diseases. *Clin. Exp. Rheumatol.* **35** (Suppl. 107), 37–39 (2017).
2. Stokes, A., Berry, K. M., Hempstead, K., Lundberg, D. J. & Neogi, T. Trends in prescription analgesic use among adults with musculoskeletal conditions in the United States, 1999-2016. *JAMA Netw. Open* **2**, e1917228 (2019).
3. GBD 2021 Forecasting Collaborators. Burden of disease scenarios for 204 countries and territories, 2022-2050: a forecasting analysis for the global burden of disease study 2021. *Lancet* **403**, 2204–2256 (2024).
4. Losina, E. & Katz, J. N. Total knee arthroplasty on the rise in younger patients: are we sure that past performance will guarantee future success? *Arthritis Rheum.* **64**, 339–341 (2012).
5. Griffin, T. M., Huebner, J. L., Kraus, V. B., Yan, Z. & Guilak, F. Induction of osteoarthritis and metabolic inflammation by a very high-fat diet in mice: effects of short-term exercise. *Arthritis Rheum.* **64**, 443–453 (2012).

6. Loeser, R. F., Goldring, S. R., Scanzello, C. R. & Goldring, M. B. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum.* **64**, 1697–1707 (2012).
7. Hatzikotoulas, K. et al. Translational genomics of osteoarthritis in 1,962,069 individuals. *Nature* **641**, 1217–1224 (2025).
8. Hawker, G. A. Osteoarthritis is a serious disease. *Clin. Exp. Rheumatol.* **37** (Suppl. 120), 3–6 (2019).
9. Berenbaum, F., Wallace, I. J., Lieberman, D. E. & Felson, D. T. Modern-day environmental factors in the pathogenesis of osteoarthritis. *Nat. Rev. Rheumatol.* **14**, 674–681 (2018).
10. Segal, N. A., Nilges, J. M. & Oo, W. M. Sex differences in osteoarthritis prevalence, pain perception, physical function and therapeutics. *Osteoarthr. Cartil.* **32**, 1045–1053 (2024).
11. Abdullah, Y., Olubowale, O. O. & Hackshaw, K. V. Racial disparities in osteoarthritis: Prevalence, presentation, and management in the United States. *J. Natl Med. Assoc.* **117**, 55–60 (2025).
12. GBD 2021 Osteoarthritis Collaborators. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the global burden of disease study 2021. *Lancet Rheumatol.* **5**, e508–e522 (2023).
13. Sebbag, E. et al. The world-wide burden of musculoskeletal diseases: a systematic analysis of the World Health Organization burden of diseases database. *Ann. Rheum. Dis.* **78**, 844–848 (2019).
14. Losina, E. et al. Lifetime risk and age at diagnosis of symptomatic knee osteoarthritis in the US. *Arthritis Care Res.* **65**, 703–711 (2013).
15. Hernandez, P. A. et al. Unraveling sex-specific risks of knee osteoarthritis before menopause: do sex differences start early in life? *Osteoarthr. Cartil.* **32**, 1032–1044 (2024).
16. Betancourt-Torres, A. et al. A role for chromosomal sex in dimorphic control of osteocyte signaling, osteoarthritis, and joint function. *Transactions of the Orthopaedic Research Society*, 260 (2025).
17. Carlesso, L. C. & Neogi, T. Identifying pain susceptibility phenotypes in knee osteoarthritis. *Clin. Exp. Rheumatol.* **37** (Suppl. 120), 96–99 (2019).
18. Li, J. X. L. et al. Sex differences in pain expressed by patients across diverse disease states: individual patient data meta-analysis of 33,957 participants in 10 randomized controlled trials. *Pain* **164**, 1666–1676 (2023).
19. Neogi, T. et al. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. *BMJ* **339**, b2844 (2009).
20. Haugen, I. K., Slatkowsky-Christensen, B., Boyesen, P., van der Heijde, D. & Kvien, T. K. Cross-sectional and longitudinal associations between radiographic features and measures of pain and physical function in hand osteoarthritis. *Osteoarthr. Cartil.* **21**, 1191–1198 (2013).
21. Carlesso, L. C. et al. Pain susceptibility phenotypes in those free of knee pain with or at risk of knee osteoarthritis: the multicenter osteoarthritis study. *Arthritis Rheumatol.* **71**, 542–549 (2019).
22. Herrero-Beaumont, G. et al. Systemic osteoarthritis: the difficulty of categorically naming a continuous condition. *Aging Clin. Exp. Res.* **36**, 45 (2024).
23. Ratneswaran, A. et al. Investigating molecular signatures underlying trapeziometacarpal osteoarthritis through the evaluation of systemic cytokine expression. *Front. Immunol.* **12**, 794792 (2021).
24. Collins, K. H. et al. Adipose-derived leptin and complement factor D mediate osteoarthritis severity and pain. *Sci. Adv.* **11**, eadt5915 (2025).
25. Binvignat, M., Sellam, J., Berenbaum, F. & Felson, D. T. The role of obesity and adipose tissue dysfunction in osteoarthritis pain. *Nat. Rev. Rheumatol.* **20**, 565–584 (2024).
26. Bliddal, H. et al. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. *N. Engl. J. Med.* **391**, 1573–1583 (2024).
27. Collins, K. H. et al. Adipose tissue is a critical regulator of osteoarthritis. *Proc. Natl Acad. Sci. USA* **118**, e2021096118 (2021).
28. Bennell, K. L., Wrigley, T. V., Hunt, M. A., Lim, B. W. & Hinman, R. S. Update on the role of muscle in the genesis and management of knee osteoarthritis. *Rheum. Dis. Clin. North Am.* **39**, 145–176 (2013).
29. Collins, K. H. et al. Association of body mass index (BMI) and percent body fat among BMI-defined non-obese middle-aged individuals: Insights from a population-based Canadian sample. *Can. J. Public Health* **107**, e520–e525 (2017).
30. Godziuk, K. et al. Improving muscle function through a multimodal behavioural intervention for knee osteoarthritis and obesity: the POMELO trial. *J. Cachexia Sarcopenia Muscle* **16**, e70025 (2025).
31. Godziuk, K., Prado, C. M., Woodhouse, L. J. & Forhan, M. Associations between self-reported weight history and sarcopenic obesity in adults with knee osteoarthritis. *Obesity* **29**, 302–307 (2021).
32. Hawker, G. A. et al. All-cause mortality and serious cardiovascular events in people with hip and knee osteoarthritis: a population based cohort study. *PLoS One* **9**, e91286 (2014).
33. Nuesch, E. et al. All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study. *BMJ* **342**, d1165 (2011).
34. Mobasheri, A. & Loeser, R. Clinical phenotypes, molecular endotypes and theratypes in OA therapeutic development. *Nat. Rev. Rheumatol.* **20**, 525–526 (2024).
35. Hannani, M. T. et al. Longitudinal stability of molecular endotypes of knee osteoarthritis patients. *Osteoarthr. Cartil.* **33**, 166–175 (2025).
36. Neogi, T. & Colloca, L. Placebo effects in osteoarthritis: implications for treatment and drug development. *Nat. Rev. Rheumatol.* **19**, 613–626 (2023).
37. Kloppenburg, M. et al. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **77**, 1757–1764 (2018).
38. Chevalier, X. et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **74**, 1697–1705 (2015).
39. Aitken, D. et al. A randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand osteoarthritis — the HUMOR trial. *Osteoarthr. Cartil.* **26**, 880–887 (2018).
40. Verbruggen, G., Wittoek, R., Vander Cruyssen, B. & Elewaut, D. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. *Ann. Rheum. Dis.* **71**, 891–898 (2012).
41. Richette, P. et al. Efficacy of tocilizumab in patients with hand osteoarthritis: double blind, randomised, placebo-controlled, multicentre trial. *Ann. Rheum. Dis.* **80**, 349–355 (2021).
42. Kloppenburg, M. et al. Phase IIa, placebo-controlled, randomised study of lutikizumab, an anti-interleukin-1α and anti-interleukin-1β dual variable domain immunoglobulin, in patients with erosive hand osteoarthritis. *Ann. Rheum. Dis.* **78**, 413–420 (2019).
43. Felson, D. T. & Neogi, T. Emerging treatment models in rheumatology: challenges for osteoarthritis trials. *Arthritis Rheumatol.* **70**, 1175–1181 (2018).
44. Kaptchuk, T. J. The double-blind, randomized, placebo-controlled trial: gold standard or golden calf? *J. Clin. Epidemiol.* **54**, 541–549 (2001).
45. Feinstein, A. R. An additional basic science for clinical medicine: II. The limitations of randomized trials. *Ann. Intern. Med.* **99**, 544–550 (1983).
46. van der Esch, M. et al. Clinical phenotypes in patients with knee osteoarthritis: a study in the Amsterdam osteoarthritis cohort. *Osteoarthr. Cartil.* **23**, 544–549 (2015).
47. Yang, Y. et al. Osteoarthritis treatment via the GLP-1-mediated gut-joint axis targets intestinal FXR signaling. *Science* **388**, eadt0548 (2025).
48. Hunter, W. Of the structure and disease of articulating cartilages. *Trans. R. Soc.* **42**, 514–521 (1743).
49. Alexopoulos, L. G., Setton, L. A. & Guilak, F. The biomechanical role of the chondrocyte pericellular matrix in articular cartilage. *Acta Biomater.* **1**, 317–325 (2005).
50. Radin, E. L. & Rose, R. M. Role of subchondral bone in the initiation and progression of cartilage damage. *Clin. Orthop. Relat. Res.* **213**, 34–40 (1986).
51. Pelletier, J. P., Roughley, P. J., DiBattista, J. A., McCollum, R. & Martel-Pelletier, J. Are cytokines involved in osteoarthritic pathophysiology? *Semin. Arthritis Rheum.* **20**, 12–25 (1991).
52. Radin, E. L. Protest the continuing common usage of the term osteoarthritis. *Clin. Orthop. Relat. Res.* **254**, 311 (1990).
53. Brandt, K. D., Radin, E. L., Dieppe, P. A. & van de Putte, L. Yet more evidence that osteoarthritis is not a cartilage disease. *Ann. Rheum. Dis.* **65**, 1261–1264 (2006).
54. Koyama, K., Ohba, T., Odate, T., Wako, M. & Haro, H. Pathological features of established osteoarthritis with hydrathrosis are similar to rheumatoid arthritis. *Clin. Rheumatol.* **40**, 2007–2012 (2021).
55. Dequeker, J. & Luyten, F. P. The history of osteoarthritis-osteoarthrosis. *Ann. Rheum. Dis.* **67**, 5–10 (2008).
56. Buckwalter, J. A. & Martin, J. A. Osteoarthritis. *Adv. Drug Deliv. Rev.* **58**, 150–167 (2006).
57. Hayashi, D., Roemer, F. W., Jarraya, M. & Guermazi, A. Update on recent developments in imaging of inflammation in osteoarthritis: a narrative review. *Skelet. Radiol.* **52**, 2057–2067 (2023).
58. Ramezanpour, S. et al. Impact of sustained synovitis on knee joint structural degeneration: 4-year MRI data from the osteoarthritis initiative. *J. Magn. Reson. Imaging* **57**, 153–164 (2023).
59. Maglaviceanu, A., Wu, B. & Kapoor, M. Fibroblast-like synoviocytes: role in synovial fibrosis associated with osteoarthritis. *Wound Repair Regen.* **29**, 642–649 (2021).
60. Mehta, B. et al. Machine learning identification of thresholds to discriminate osteoarthritis and rheumatoid arthritis synovial inflammation. *Arthritis Res. Ther.* **25**, 31 (2023).
61. Wagner, J. G. et al. Relationships between the infrapatellar fat pad and patellofemoral joint osteoarthritis differ with body mass index and sex. *J. Orthop. Res.* **43**, 770–779 (2025).
62. Atukorala, I. et al. Synovitis in knee osteoarthritis: a precursor of disease? *Ann. Rheum. Dis.* **75**, 390–395 (2016).
63. Philpott, H. T. et al. Association of synovial innate immune exhaustion with worse pain in knee osteoarthritis. *Arthritis Rheumatol.* **77**, 664–676 (2024).
64. Peters, H. et al. Cell and transcriptomic diversity of infrapatellar fat pad during knee osteoarthritis. *Ann. Rheum. Dis.* **84**, 351–367 (2025).
65. Tortorella, M. D. & Malfait, A. M. Will the real aggrecanase(s) step up: evaluating the criteria that define aggrecanase activity in osteoarthritis. *Curr. Pharm. Biotechnol.* **9**, 16–23 (2008).
66. Lohmander, L. S., Neame, P. J. & Sandy, J. D. The structure of aggrecan fragments in human synovial fluid. Evidence that aggrecanase mediates cartilage degradation in inflammatory joint disease, joint injury, and osteoarthritis. *Arthritis Rheum.* **36**, 1214–1222 (1993).
67. Saag, K. G. Bisphosphonates for osteoarthritis prevention: "Holy Grail" or not? *Ann. Rheum. Dis.* **67**, 1358–1359 (2008).
68. Conaghan, P. G. et al. Disease-modifying effects of a novel cathepsin K inhibitor in osteoarthritis: a randomized controlled trial. *Ann. Intern. Med.* **172**, 86–95 (2020).
69. Guilak, F. Biomechanical factors in osteoarthritis. *Best Pract. Res. Clin. Rheumatol.* **25**, 815–823 (2011).

70. McDonnell, E. et al. Epigenetic mechanisms of osteoarthritis risk in human skeletal development. Preprint at *medRxiv* https://doi.org/10.1101/2024.05.05.24306832 (2024).
71. Nelson, A. E. Multiple joint osteoarthritis (MJOA): What's in a name? *Osteoarthr. Cartil.* **32**, 234–240 (2024).
72. Newton, M. D. et al. Cross-platform transcriptomic data integration identifies an overactive neuro-immune signature in human osteoarthritis synovium. *Osteoarthr. Cartil.* https://doi.org/10.1016/j.joca.2025.08.013 (2025).
73. Cruz-Almeida, Y. et al. Clinical and biobehavioral phenotypic assessments and data harmonization for the RE-JOIN research consortium: Recommendations for common data element selection. *Neurobiol. Pain* **16**, 100163 (2024).
74. O'Connor, S. K., Katz, D. B., Oswald, S. J., Groneck, L. & Guilak, F. Formation of osteochondral organoids from murine induced pluripotent stem cells. *Tissue Eng. Part A* **27**, 1099–1109 (2021).
75. Bloks, N. G. et al. A damaging COL6A3 variant alters the MIR31HG-regulated response of chondrocytes in neocartilage organoids to hyperphysiologic mechanical loading. *Adv. Sci.* **11**, e2400720 (2024).
76. Li, Z. A. et al. Synovial joint-on-a-chip for modeling arthritis: progress, pitfalls, and potential. *Trends Biotechnol.* **41**, 511–527 (2023).
77. Makarczyk, M. J. et al. Current models for development of disease-modifying osteoarthritis drugs. *Tissue Eng. Part C Methods* **27**, 124–138 (2021).
78. Makarcyzk, M. J. et al. Creation of a knee joint-on-a-chip for modeling joint diseases and testing drugs. *J. Vis. Exp.* https://doi.org/10.3791/64186 (2023).
79. Lutolf, M. P. et al. In vitro human cell-based models: what can they do and what are their limitations? *Cell* **187**, 4439–4443 (2024).
80. Adkar, S. S. et al. Genome engineering for personalized arthritis therapeutics. *Trends Mol. Med.* **23**, 917–931 (2017).
81. Collins, K. H., Hart, D. A., Seerattan, R. A., Reimer, R. A. & Herzog, W. High-fat/high-sucrose diet-induced obesity results in joint-specific development of osteoarthritis-like degeneration in a rat model. *Bone Jt Res.* **7**, 274–281 (2018).
82. Tjandra, P. M. et al. Complement factor D (adipsin) mediates pressure-pain hypersensitivity post destabilization of medial meniscus injury. *Arthritis Res. Ther.* **27**, 221 (2025).
83. Mahmoudian, A. et al. Timing is everything: Towards classification criteria for early-stage symptomatic knee osteoarthritis. *Osteoarthr. Cartil.* **32**, 649–653 (2024).
84. Obeidat, A. M. et al. Piezo2 expressing nociceptors mediate mechanical sensitization in experimental osteoarthritis. *Nat. Commun.* **14**, 2479 (2023).
85. Ma, H. L. et al. Osteoarthritis severity is sex dependent in a surgical mouse model. *Osteoarthr. Cartil.* **15**, 695–700 (2007).
86. Ding, Y. et al. Comprehensive human proteome profiles across a 50-year lifespan reveal aging trajectories and signatures. *Cell* https://doi.org/10.1016/j.cell.2025.06.047 (2025).
87. Collins, K. H. et al. Association of metabolic markers with self-reported osteoarthritis among middle-aged BMI-defined non-obese individuals: a cross-sectional study. *BMC Obes.* **5**, 23 (2018).
88. Godziuk, K. & Hawker, G. A. Obesity and body mass index: past and future considerations in osteoarthritis research. *Osteoarthr. Cartil.* **32**, 452–459 (2024).
89. Godziuk, K., Prado, C. M., Woodhouse, L. J. & Forhan, M. The impact of sarcopenic obesity on knee and hip osteoarthritis: a scoping review. *BMC Musculoskelet. Disord.* **19**, 271 (2018).
90. Pavasini, R. et al. Short physical performance battery and all-cause mortality: systematic review and meta-analysis. *BMC Med.* **14**, 215 (2016).
91. Studenski, S. et al. Gait speed and survival in older adults. *JAMA* **305**, 50–58 (2011).
92. Barbour, K. E. et al. Hip osteoarthritis and the risk of all-cause and disease-specific mortality in older women: a population-based cohort study. *Arthritis Rheumatol.* **67**, 1798–1805 (2015).
93. Covinsky, K. E., Justice, A. C., Rosenthal, G. E., Palmer, R. M. & Landefeld, C. S. Measuring prognosis and case mix in hospitalized elders. The importance of functional status. *J. Gen. Intern. Med.* **12**, 203–208 (1997).
94. Pincus, T. & Castrejon, I. Low socioeconomic status and patient questionnaires in osteoarthritis: challenges to a "biomedical model" and value of a complementary "biopsychosocial model". *Clin. Exp. Rheumatol.* **37** (Suppl. 120), 18–23 (2019).
95. Rumsfeld, J. S. et al. Health-related quality of life as a predictor of mortality following coronary artery bypass graft surgery. participants of the department of veterans affairs cooperative study group on processes, structures, and outcomes of care in cardiac surgery. *JAMA* **281**, 1298–1303 (1999).
96. Sokka, T. & Hakkinen, A. Poor physical fitness and performance as predictors of mortality in normal populations and patients with rheumatic and other diseases. *Clin. Exp. Rheumatol.* **26**, S14–S20 (2008).
97. Raja, S. N. et al. The revised international association for the study of pain definition of pain: concepts, challenges, and compromises. *Pain* **161**, 1976–1982 (2020).
98. Wood, M. J., Miller, R. E. & Malfait, A. M. The genesis of pain in osteoarthritis: inflammation as a mediator of osteoarthritis pain. *Clin. Geriatr. Med.* **38**, 221–238 (2022).
99. Murphy, A. E., Minhas, D., Clauw, D. J. & Lee, Y. C. Identifying and managing nociplastic pain in individuals with rheumatic diseases: a narrative review. *Arthritis Care Res.* **75**, 2215–2222 (2023).
100. Mulrooney, E. et al. Comorbidities in people with hand OA and their associations with pain severity and sensitization: data from the longitudinal nor-hand study. *Osteoarthr. Cartil. Open* **5**, 100367 (2023).
101. den Hollander, W. et al. Genome-wide association and functional studies identify a role for matrix Gla protein in osteoarthritis of the hand. *Ann. Rheum. Dis.* **76**, 2046–2053 (2017).
102. Valdes, A. M. et al. The genetic contribution to severe post-traumatic osteoarthritis. *Ann. Rheum. Dis.* **72**, 1687–1690 (2013).
103. Kerkhof, H. J. et al. Large-scale meta-analysis of interleukin-1 beta and interleukin-1 receptor antagonist polymorphisms on risk of radiographic hip and knee osteoarthritis and severity of knee osteoarthritis. *Osteoarthr. Cartil.* **19**, 265–271 (2011).
104. Loeser, R. F., Berenbaum, F. & Kloppenburg, M. Vitamin K and osteoarthritis: is there a link? *Ann. Rheum. Dis.* **80**, 547–549 (2021).
105. Boer, C. G. et al. Deciphering osteoarthritis genetics across 826,690 individuals from 9 populations. *Cell* **184**, 4784–4818.e17 (2021).
106. Roberts, J. B. & Rice, S. J. Osteoarthritis as an enhanceropathy: gene regulation in complex musculoskeletal disease. *Curr. Rheumatol. Rep.* **26**, 222–234 (2024).
107. Rice, S. J., Beier, F., Young, D. A. & Loughlin, J. Interplay between genetics and epigenetics in osteoarthritis. *Nat. Rev. Rheumatol.* **16**, 268–281 (2020).
108. Ramos, Y. F. M. et al. Evolution and advancements in genomics and epigenomics in OA research: how far we have come. *Osteoarthr. Cartil.* **32**, 858–868 (2024).
109. Coveney, C. R. et al. Complex regulatory interactions at *GDF5* shape joint morphology and osteoarthritis disease risk. *Arthritis Rheumatol.* **77**, 1488–1502 (2025).
110. Conde, J. et al. E74-like factor (ELF3) and leptin, a novel loop between obesity and inflammation perpetuating a pro-catabolic state in cartilage. *Cell Physiol. Biochem.* **45**, 2401–2410 (2018).
111. Otero, M. et al. Phosphatidylinositol 3-kinase, MEK-1 and p38 mediate leptin/interferon-gamma synergistic NOS type II induction in chondrocytes. *Life Sci.* **81**, 1452–1460 (2007).
112. Otero, M. et al. Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* **65**, 1198–1201 (2006).
113. Otero, M., Lago, R., Lago, F., Reino, J. J. & Gualillo, O. Signalling pathway involved in nitric oxide synthase type II activation in chondrocytes: synergistic effect of leptin with interleukin-1. *Arthritis Res. Ther.* **7**, R581–R591 (2005).
114. Yusuf, E. et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. *Ann. Rheum. Dis.* **69**, 761–765 (2010).
115. Gao, Y. H. et al. An update on the association between metabolic syndrome and osteoarthritis and on the potential role of leptin in osteoarthritis. *Cytokine* **129**, 155043 (2020).
116. Berenbaum, F., Griffin, T. M. & Liu-Bryan, R. Review: metabolic regulation of inflammation in osteoarthritis. *Arthritis Rheumatol.* **69**, 9–21 (2017).
117. Griffin, T. M. et al. Diet-induced obesity differentially regulates behavioral, biomechanical, and molecular risk factors for osteoarthritis in mice. *Arthritis Res. Ther.* **12**, R130 (2010).
118. Griffin, T. M., Huebner, J. L., Kraus, V. B. & Guilak, F. Extreme obesity due to impaired leptin signaling in mice does not cause knee osteoarthritis. *Arthritis Rheum.* **60**, 2935–2944 (2009).
119. Gloersen, M. et al. Associations of body mass index with pain and the mediating role of inflammatory biomarkers in people with hand osteoarthritis. *Arthritis Rheumatol.* **74**, 810–817 (2022).
120. Li, S. et al. Association of visceral adiposity with pain but not structural osteoarthritis. *Arthritis Rheumatol.* **72**, 1103–1110 (2020).
121. Stefanik, J. J. et al. Changes in pain sensitization after bariatric surgery. *Arthritis Care Res.* **70**, 1525–1528 (2018).
122. Jafarzadeh, S. R. et al. Mediating role of bone marrow lesions, synovitis, pain sensitization, and depressive symptoms on knee pain improvement following substantial weight loss. *Arthritis Rheumatol.* **72**, 420–427 (2020).
123. Beckman, L. M., Beckman, T. R. & Earthman, C. P. Changes in gastrointestinal hormones and leptin after Roux-en-Y gastric bypass procedure: a review. *J. Am. Diet. Assoc.* **110**, 571–584 (2010).
124. Kong, H. et al. The crosstalk among macrophages, chondrocytes and mesenchymal stem cells in osteoarthritis: the role of extracellular vesicles. *Stem Cell Res. Ther.* **16**, 553 (2025).
125. Francisco, V. et al. Adipokines and inflammation: is it a question of weight? *Br. J. Pharmacol.* **175**, 1569–1579 (2018).
126. Ait Eldjoudi, D. et al. Leptin in osteoarthritis and rheumatoid arthritis: player or bystander? *Int. J. Mol. Sci.* **23**, 2859 (2022).
127. Nguyen, T. T. & Corvera, S. Adipose tissue as a linchpin of organismal ageing. *Nat. Metab.* **6**, 793–807 (2024).
128. Meurot, C. et al. Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis. *Sci. Rep.* **12**, 1567 (2022).
129. Kreiner, F. F., von Scholten, B. J., Kurtzhals, P. & Gough, S. C. L. Glucagon-like peptide-1 receptor agonists to expand the healthy lifespan: current and future potentials. *Aging Cell* **22**, e13818 (2023).
130. Lavu, M. S. et al. The five-year incidence of progression to osteoarthritis and total joint arthroplasty in patients prescribed glucagon-like peptide 1 receptor agonists. *J. Arthroplast.* **39**, 2433–2439.e1 (2024).
131. Xie, Y., Choi, T. & Al-Aly, Z. Mapping the effectiveness and risks of GLP-1 receptor agonists. *Nat. Med.* **31**, 951–962 (2025).
132. Jensen, S. B. K. et al. Bone health after exercise alone, GLP-1 receptor agonist treatment, or combination treatment: a secondary analysis of a randomized clinical trial. *JAMA Netw. Open* **7**, e2416775 (2024).
133. Prado, C. M., Phillips, S. M., Gonzalez, M. C. & Heymsfield, S. B. Muscle matters: the effects of medically induced weight loss on skeletal muscle. *Lancet Diabetes Endocrinol.* **12**, 785–787 (2024).

134. Zhu, H. et al. Glucagon-like peptide-1 receptor agonists as a disease-modifying therapy for knee osteoarthritis mediated by weight loss: findings from the Shanghai Osteoarthritis Cohort. *Ann. Rheum. Dis.* **82**, 1218–1226 (2023).
135. Loeser, R. F. et al. Association of increased serum lipopolysaccharide, but not microbial dysbiosis, with obesity-related osteoarthritis. *Arthritis Rheumatol.* **74**, 227–236 (2022).
136. Schott, E. M. et al. Targeting the gut microbiome to treat the osteoarthritis of obesity. *JCI Insight* **3**, e95997 (2018).
137. Guss, J. D. et al. The effects of metabolic syndrome, obesity, and the gut microbiome on load-induced osteoarthritis. *Osteoarthr. Cartil.* **27**, 129–139 (2019).
138. Collins, K. H. et al. A high-fat high-sucrose diet rapidly alters muscle integrity, inflammation and gut microbiota in male rats. *Sci. Rep.* **6**, 37278 (2016).
139. Collins, K. H., Schwartz, D. J., Lenz, K. L., Harris, C. A. & Guilak, F. Taxonomic changes in the gut microbiota are associated with cartilage damage independent of adiposity, high fat diet, and joint injury. *Sci. Rep.* **11**, 14560 (2021).
140. Hahn, A. K. et al. The microbiome mediates epiphyseal bone loss and metabolomic changes after acute joint trauma in mice. *Osteoarthr. Cartil.* **29**, 882–893 (2021).
141. Ulici, V. et al. Osteoarthritis induced by destabilization of the medial meniscus is reduced in germ-free mice. *Osteoarthr. Cartil.* **26**, 1098–1109 (2018).
142. Velasco, C. et al. Ear wound healing in MRL/MpJ mice is associated with gut microbiome composition and is transferable to non-healer mice via microbiome transplantation. *PLoS One* **16**, e0248322 (2021).
143. Huang, Z. Y., Stabler, T., Pei, F. X. & Kraus, V. B. Both systemic and local lipopolysaccharide (LPS) burden are associated with knee OA severity and inflammation. *Osteoarthr. Cartil.* **24**, 1769–1775 (2016).
144. Collins, K. H. & Guilak, F. Trimming the fat - is leptin crosstalk the link between obesity and osteoarthritis? *Osteoarthr. Cartil.* **31**, 23–25 (2023).
145. Boer, C. G. et al. Intestinal microbiome composition and its relation to joint pain and inflammation. *Nat. Commun.* **10**, 4881 (2019).
146. Hendesi, H. et al. Gut and joint microbiomes: implications in osteoarthritis. *Rheum. Dis. Clin. North Am.* **51**, 295–324 (2025).
147. Lim, Y. Z. et al. Metformin as a potential disease-modifying drug in osteoarthritis: a systematic review of pre-clinical and human studies. *Osteoarthr. Cartil.* **30**, 1434–1442 (2022).
148. Pan, F. et al. Metformin for knee osteoarthritis in patients with overweight or obesity: a randomized clinical trial. *JAMA* **333**, 1804–1812 (2025).
149. Barzilai, N., Crandall, J. P., Kritchevsky, S. B. & Espeland, M. A. Metformin as a tool to target aging. *Cell Metab.* **23**, 1060–1065 (2016).
150. Justice, J. N. et al. Development of clinical trials to extend healthy lifespan. *Cardiovasc. Endocrinol. Metab.* **7**, 80–83 (2018).
151. Szilagyi, I. A., Waarsing, J. H., van Meurs, J. B. J., Bierma-Zeinstra, S. M. A. & Schiphof, D. A systematic review of the sex differences in risk factors for knee osteoarthritis. *Rheumatology* **62**, 2037–2047 (2023).
152. Nevitt, M. C., Felson, D. T., Williams, E. N. & Grady, D. The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: the heart and estrogen/progestin replacement study, a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* **44**, 811–818 (2001).
153. Gilmer, G. et al. Uncovering the "riddle of femininity" in osteoarthritis: a systematic review and meta-analysis of menopausal animal models and mathematical modeling of estrogen treatment. *Osteoarthr. Cartil.* **31**, 447–457 (2023).
154. Gilmer, G. et al. Menopause-induced 17β-estradiol and progesterone loss increases senescence markers, matrix disassembly and degeneration in mouse cartilage. *Nat. Aging* **5**, 65–86 (2025).
155. Dou, D. R. et al. Xist ribonucleoproteins promote female sex-biased autoimmunity. *Cell* **187**, 733–749.e16 (2024).
156. Hernandez, P. A. et al. Sexual dimorphism in the extracellular and pericellular matrix of articular cartilage. *Cartilage* **13**, 19476035221121792 (2022).
157. Schieker, M. et al. Effects of interleukin-1β inhibition on incident hip and knee replacement: exploratory analyses from a randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* **173**, 509–515 (2020).
158. Heijman, M. W. J. et al. Association of low-dose colchicine with incidence of knee and hip replacements: exploratory analyses from a randomized, controlled, double-blind trial. *Ann. Intern. Med.* **176**, 737–742 (2023).
159. Rockel, J. S. et al. Identification of a differential metabolite-based signature in patients with late-stage knee osteoarthritis. *Osteoarthr. Cartil. Open* **4**, 100258 (2022).
160. Welhaven, H. D. et al. Metabolic phenotypes reflect patient sex and injury status: a cross-sectional analysis of human synovial fluid. *Osteoarthr. Cartil.* **32**, 1074–1083 (2024).
161. Rai, M. F. et al. Three decades of advancements in osteoarthritis research: insights from transcriptomic, proteomic, and metabolomic studies. *Osteoarthr. Cartil.* **32**, 385–397 (2024).
162. Rockel, J. S. et al. Deep learning-based clustering for endotyping and post-arthroplasty response classification using knee osteoarthritis multiomic data. *Ann. Rheum. Dis.* **84**, 844–855 (2025).
163. Zou, H. & Hastie, T. Regularization and variable selection via the elastic net. *J. R. Statist. Soc. B* **67**, 301–320 (2005).
164. Shu, C., Mihailidou, A., Ashton, A., Bryant, A. & Little, C. B. Bad knees & broken hearts: mirs released from osteoarthritic (OA) joints increase cardiovascular disease (CVD) risk. *Osteoarthr. Cartil.* **32** (Suppl. 1), 7 (2024).
165. Gupta, D. P. et al. Knee osteoarthritis accelerates amyloid beta deposition and neurodegeneration in a mouse model of Alzheimer's disease. *Mol. Brain* **16**, 1 (2023).
166. Vassilaki, M. et al. Long-term cognitive trajectory after total joint arthroplasty. *JAMA Netw. Open* **5**, e2241807 (2022).
167. Schurman, C. A. et al. Tissue and extracellular matrix remodeling of the subchondral bone during osteoarthritis of knee joints as revealed by spatial mass spectrometry imaging. Preprint at *bioRxiv* https://doi.org/10.1101/2024.08.03.606482 (2025).
168. Welhaven, H. D. et al. Tissue-specific and spatially dependent metabolic signatures perturbed by injury in skeletally mature male and female mice. Preprint at *bioRxiv* https://doi.org/10.1101/2024.09.30.615873 (2025).

Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

K.H.C. declares no competing interests. I.K.H. has received personal fees (consultancies and speaker honorarium) from Argenx, Pacira, Grünenthal, Abbvie and GSK for work unrelated to this manuscript. F.G. is a founder, shareholder and employee of Cytex Therapeutics, unrelated to this manuscript. T.N. has served as a consultant for Novartis and Merck for work unrelated to this manuscript.

Additional information

Peer review information *Nature Reviews Rheumatology* thanks Gabriel Herrero-Beaumont, Ali Mobasheri and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

nature reviews rheumatology

https://doi.org/10.1038/s41584-025-01333-7

Review article

Check for updates

Emerging and underrecognized viral triggers of autoimmune inflammatory rheumatic disease flares

Ivonne Melano[1], M. Elaine Husni[2], Nicolas S. Piuzzi[3], Suan-Sin Foo[1,4] & Weiqiang Chen[1,4]

Abstract

Autoimmune rheumatic diseases (AIRDs), such as rheumatoid arthritis and systemic lupus erythematosus, substantially affect quality of life, with viral infections increasingly recognized as potential but underappreciated triggers of worsening preexisting AIRD symptoms. Despite growing evidence that post-viral infections are associated with heightened autoimmune activity and disease flares, the precise mechanisms underlying the complex virus–autoimmune response remain poorly understood. As AIRD is most prevalent in women, hormonal factors might have a role in AIRD pathogenesis. Hormones can influence immune regulation, potentially affecting the risk and severity of viral-induced AIRD flares. Given the global rise of viral disease outbreaks with increasing evidence of viral persistence in AIRD pathology, this Review addresses a critical knowledge gap in understanding the immune crosstalk during viral-induced AIRD flares. We place an emphasis on emerging viruses and their potential role in AIRD flares, exploring mechanisms of immune dysregulation, chronic inflammation, molecular mimicry, viral persistence and emerging therapeutic strategies to mitigate virus-induced AIRD exacerbations. This Review is aimed at shedding light on the mechanisms by which emerging viruses promote AIRD flares, serving as a practical guide to improve clinical management and therapeutic innovations.

Sections

[1]Department of Infection Biology, Global Center for Pathogen Research and Human Health, Cleveland Clinic, Cleveland, OH, USA. [2]Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, OH, USA. [3]Department of Orthopaedic Surgery, Cleveland Clinic, Cleveland, OH, USA. [4]Cleveland Clinic Lerner College of Medicine CWRU, Cleveland, OH, USA. e-mail: chenw3@ccf.org

Introduction

The pathogenesis of autoimmune rheumatic diseases (AIRDs) remains incompletely understood, with no single causative factor identified. Current evidence suggests that AIRD onset is governed by a combination of genetic susceptibility, environmental exposures and dysregulated immune responses. Among the proposed environmental triggers, viral pathogens have long been suspected to contribute to the initiation and progression of certain AIRDs, including rheumatoid arthritis and systemic lupus erythematosus (SLE)[1–3]. Although a causal relationship has not been firmly established, mounting data suggest that viral infections can modulate disease risk in genetically susceptible individuals. Prior to 2020, studies focused on the role of viruses in autoimmune disease initiation[2,3]. However, the COVID-19 pandemic has illuminated a dynamic interplay between viral infections and AIRD activity, revealing that viral exposures might trigger disease flares or exacerbate subclinical autoimmunity to the point of overt manifestations[4,5]. Patients with AIRD have a heightened risk of severe COVID-19 and associated AIRD flares[6,7]. Even prior to the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), other viruses such as dengue virus (DENV) and influenza were implicated in worsening AIRD clinical manifestations[8,9]. Mechanistic studies suggest that immune complex dysregulation, molecular mimicry and viral persistence might underlie these flares[8–40].

Several well-characterized viruses such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), hepatitis B virus (HBV) and human T cell leukaemia virus type 1 (HTLV-1) have long been associated with AIRD[3,41] (Box 1). However, there is a lack of appreciation of the role of emerging viruses, such as flaviviruses and coronaviruses, in AIRD. Moreover, the emerging interplay between hormonal states and viral pathogenesis, including potential modulation by sex hormones and stress, presents a complex area of study in viral-induced AIRD flares, although the precise mechanisms are not yet fully understood. In this Review, we examine key viral pathogens implicated in AIRD flares selected based on documented clinical associations, epidemiological relevance and experimental evidence of immune dysregulation. We discuss the potential underlying mechanisms by which these viruses might worsen AIRD symptoms and shed light on emerging therapeutic strategies aimed at mitigating flares. This integrated perspective contributes to a deeper understanding of the multifactorial processes driving AIRD pathogenesis and flare recurrence.

Viruses linked to autoimmune rheumatic disease flares

Several viral infections have been associated with AIRD flares. Observational studies, case reports and retrospective analyses have documented increased disease activity or new-onset symptoms following viral exposure in patients with established AIRD. Notably, SARS-CoV-2 infection has been linked to flares across multiple AIRD conditions. Similarly, other respiratory and arboviral infections, such as influenza, DENV, Zika virus (ZIKV) and chikungunya virus (CHIKV), have been associated with worsening AIRD symptoms or prolonged post-viral inflammatory syndromes. This section highlights key viral pathogens implicated in AIRD flares and summarizes the clinical evidence supporting their role in exacerbating AIRD activity.

Coronaviruses

Coronaviruses are enveloped, positive-sense singe-stranded RNA viruses responsible for several notable outbreaks[42]. SARS-CoV-2, the causative agent of the COVID-19 pandemic, has emerged as a potent immunological stressor, capable of inducing systemic inflammation and disrupting immune tolerance. Although patients with mild COVID-19 typically present with fever, cough and fatigue, severe cases can progress to acute respiratory distress syndrome and multiorgan failure[43,44]. Patients with AIRDs are particularly vulnerable to SARS-CoV-2 infection owing to immunosuppressive therapies and underlying immune dysregulation. AIRD flares following COVID-19 infection are well documented, including exacerbations of rheumatoid arthritis and SLE[6,7,45–49]. For example, a cohort study in Wuhan, China, reported that 19% of hospitalized patients (4 out of 21) with pre-existing AIRD (rheumatoid arthritis, SLE, ankylosing spondylitis, or polymyalgia rheumatica) experienced disease flares during COVID-19 illness[50]. Furthermore, a case report described a patient with stable SLE developing neuropsychiatric lupus (lupus cerebritis) shortly after SARS-CoV-2 infection[47].

SARS-CoV-2 infection has been linked to an increase in the production of autoantibodies, including anti-cyclic citrullinated peptide (anti-CCP) antibodies (that is, anti-CCP2 and anti-CCP3 antibodies), which are hallmark serological markers of rheumatoid arthritis. Notably, elevated levels of anti-CCP2 and anti-CCP3 antibodies were detected in a patient with COVID-19 who experienced persistent finger pain 2 months after her initial COVID-19 diagnosis, compared with the levels observed on the day of diagnosis[51]. The patient was ultimately diagnosed with rheumatoid arthritis, potentially reflecting a pathogenic link between COVID-19 and AIRD. Relapses of juvenile idiopathic arthritis have also been reported during the pandemic, suggesting that SARS-CoV-2 might affect immune homeostasis in paediatric AIRD[52,53]. Additionally, human coronavirus OC43 (HCoV-OC43), which typically causes the common cold, has been associated with post-acute COVID-19 syndrome (long COVID) in patients with pre-existing rheumatoid arthritis and psoriatic arthritis (PsA). In these vulnerable populations, altered humoral immunity and stronger binding of the Fcγ receptor to the

Box 1 | Well-characterized viruses and autoimmune rheumatic disease activity

In addition to emerging viruses, several well-characterized viruses, including Epstein–Barr virus (EBV), cytomegalovirus (CMV), hepatitis B virus (HBV) and human T cell leukaemia virus type 1 (HTLV-1), have been implicated in exacerbating autoimmune rheumatic disease activity. Reactivation of the lymphotropic herpesvirus EBV is associated with increased systemic lupus erythematosus (SLE) disease flare, with positivity for EBV-viral capsid antigen IgA and a higher frequency of EBV-infected B cells correlating with a greater prevalence of SLE flares[183–185]. Similarly, positivity for the beta-herpesvirus CMV has been significantly associated with progression to SLE flares and poorer clinical outcomes[158,186]. CMV antigenaemia has also been reported to aggravate juvenile SLE that presents with cardiac tamponade, which improved following antiviral therapy using ganciclovir and valganciclovir[187]. Moreover, HBV reactivation has been observed in patients with SLE receiving immunosuppressive therapy, often accompanied by increased mortality following reactivation[188,189]. In rheumatoid arthritis, infection with the human retrovirus HTLV-1 has been linked to elevated inflammatory marker C-reactive protein levels and a diminished response to anti-TNF biologics, suggesting heightened systemic inflammation and altered immune regulation in HTLV-1-positive patients with rheumatoid arthritis[190–192].

HCoV-OC43 spike protein are potential mechanisms underpinning post-viral autoimmunity[19].

Flaviviruses

DENV is part of the *Flaviviridae* family, comprising single-stranded positive-sense RNA viruses that are primarily transmitted through bites of infected mosquitoes[54]. Although approximately 60–80% of DENV infections are asymptomatic, symptomatic dengue can be classified according to the World Health Organization into dengue without warning signs, dengue with warning signs, or severe dengue. Although most patients recover without difficulty, progression to severe disease, as indicated for example by thrombocytopenia[55], requires close monitoring[56]. Beyond the acute phase, a longitudinal follow-up study reported that up to one-third of DENV-infected individuals experienced persistent musculoskeletal symptoms, such as muscle pain, arthralgia and arthropathy, lasting up to 2 years following hospital discharge, providing epidemiological evidence that DENV can contribute to AIRD-like sequelae[8]. These symptoms are often accompanied by alterations in AIRD markers, including elevated anti-nuclear antibodies (ANA), C3 and C4 complement factors, immune complexes, rheumatoid factor, and C-reactive protein (CRP)[8], suggesting potential DENV-related autoimmune dysregulation.

ZIKV, another member of the flavivirus family, is primarily transmitted via mosquitoes, although additional transmission routes include sexual contact, vertical transmission from mother to fetus and blood transfusion[54]. In adults, ZIKV infections are typically mild or asymptomatic, but have been associated with immune-mediated complications such as Guillain–Barré syndrome[57]. Although evidence linking ZIKV to AIRD flares is limited, a case study documented the exacerbation of immune thrombocytopenia and the emergence of ANA positivity following ZIKV infection[58], suggesting that ZIKV might act as a trigger for the onset of autoimmune disease.

West Nile virus (WNV), another major flavivirus, is the leading cause of arboviral disease in North America and is an emerging public health concern in Europe[59,60]. Although the majority of WNV infections are asymptomatic, symptomatic cases typically manifest as an acute systemic febrile illness known as 'West Nile fever'. Despite being rare, WNV infection can progress to severe neuroinvasive diseases such as aseptic meningitis, encephalitis, or an acute poliomyelitis-like syndrome. Notably, in a patient with active SLE who presented with altered mental status and worsening proteinuria, cerebrospinal fluid tested positive for WNV, suggesting that WNV might have triggered SLE activity[61]. Another case involved a woman with longstanding SLE and lupus nephritis on immunosuppressive therapy who developed progressive neurological deterioration and was subsequently diagnosed with WNV by PCR testing of blood and urine[62]. Despite receiving supportive care, the patient died within days of intensive care admission[62]. These cases highlight the potential for WNV infection to exacerbate SLE activity and illustrate the complexity in distinguishing viral neuroinvasion from neuropsychiatric lupus in immunocompromised patients.

Alphaviruses

Alphaviruses, members of the *Togaviridae* family, are positive-sense single-stranded RNA viruses typically classified as Old World or New World alphaviruses. Infection with Old World alphaviruses, such as CHIKV and Ross River virus (RRV), typically results in severe arthritic joint manifestations[63,64]. Although acute alphavirus infection often causes febrile illness accompanied by myalgia, polyarthralgia or rash, most patients progress to the chronic phase of the disease, experiencing persistent joint pain, swelling and stiffness that last for months or even years[65]. Approximately 25% of individuals infected with CHIKV progress to chronic inflammatory rheumatism, and 14% develop chronic arthritis[66]. Notably, CHIKV and rheumatoid arthritis share overlapping clinical and immunological features, including elevated activated T killer cells[67,68]. In individuals with pre-existing spondyloarthritis (SpA), CHIKV infection can trigger disease flares, with symptoms worsening, despite treatment with NSAIDs[69].

Orthomyxoviruses

Influenza viruses, members of the *Orthomyxoviridae* family, are segmented, negative-stranded RNA viruses that cause annual epidemics of respiratory illness. Clinical manifestations include high fever, rhinitis, severe muscle and joint aches, and, in some cases, severe pneumonia[70]. Although influenza-infected patients with pre-existing rheumatic conditions such as rheumatoid arthritis often achieve full recovery[71], a risk of serious or fatal outcomes remains in immunocompromised individuals. A case report described severe septic shock from influenza A virus subtype H1N1 infection in a patient with pre-existing SLE[72]. Moreover, an autopsy of a patient with pre-existing psoriasis and obesity revealed a positive test for H1N1 prior to death[73]. Importantly, beyond case reports, a nationwide Korean cohort study identified a significant association between influenza infection and hospitalization for SLE flares, using oseltamivir prescription as a surrogate marker for confirmed influenza cases, emphasizing the population-level effect of viral respiratory infections on AIRD activity[74]. Collectively, these observations highlight the potential of influenza viruses to exacerbate underlying immune alterations in patients with AIRD.

Parvoviruses

Human parvovirus B19 (B19V) is a small single-stranded non-enveloped DNA virus belonging to the *Parvoviridae* family. B19 infection typically begins in childhood and can persist throughout life. Transmission commonly occurs through inhalation of respiratory droplets, transfusion of blood products and vertical transmission from mother to fetus. The clinical manifestations of B19 infection vary widely, including fifth disease (also known as erythema infectiosum) in children, fetal hydrops, transient aplastic crisis in individuals with haemolytic anaemia or lymphoproliferative disorders, and chronic red cell aplasia in immunocompromised hosts[75,76].

In adults, B19V infection has been associated with symptoms that mimic rheumatoid arthritis and SLE, such as arthralgia, rash, myalgia and the presence of positive autoantibodies (such as rheumatoid factors, ANA and anti-DNA)[77–82]. Furthermore, B19V infection has been implicated in triggering severe flares of pre-existing AIRDs. For example, B19V DNA was detected in the synovial tissue of 30 out of 39 patients with rheumatoid arthritis[38]. Additionally, the presence of anti-B19V IgM was identified in patients with SLE who developed necrotizing lymphadenitis, commonly referred to as Kikuchi's disease[83]. These findings highlight the association between B19 and flare-ups in AIRDs[84].

Mechanisms linking viral infections to autoimmune rheumatic disease flares

Viruses implicated in triggering AIRD flares share immunopathogenic mechanisms. These include dysregulated cytokine signalling, breakdown of regulatory T cell function, molecular mimicry, immune-complex deposition and the persistence of viral antigens in immune-privileged or inflamed tissues (Table 1). Below, we outline the

mechanistic insights derived from viral infections and discuss their relevance to AIRDs.

Immune dysregulation and chronic inflammation

Chronic inflammation is a hallmark of AIRD flares and is driven by numerous cytokines that are central to disease immunopathology[85,86]. Hyperactivation and accumulation of T helper 1 (T_H1) cells and T_H17 cells promote tissue inflammation in AIRDs[87,88]. Advances in multi-omics technologies, such as transcriptomics, proteomics and single-cell profiling, have enabled the discovery of immune signatures that can inform prognosis and guide individualized AIRD therapy[13,89]. Single-cell analyses reveal that rheumatoid arthritis flares, even during drug-free remission, are marked by shifts in immune-cell composition, including an expansion of circulating pro-inflammatory T cell subsets. These shifts highlight dysregulated immune function that predisposes individuals to recurrent flares[89]. Sequential activation of B cells and pre-inflammatory mesenchymal cells in the peripheral blood prior to symptom onset further suggests systemic immune dysregulation that is responsive to environmental triggers, such as viral infections[90].

T_H1 cells and T_H17 cells are key mediators of inflammatory tissue damage in AIRDs[91]. T_H1 cell-derived interferon-γ (IFNγ) activates macrophages and amplifies inflammatory cytokine cascades, whereas T_H17 cell-derived IL-17 and IL-22 promote neutrophil recruitment and contribute to inflammation and disruption of synovial and mucosal barriers. IL-17A, a central T_H17 cell-derived cytokine, in particular, has been implicated in rheumatoid arthritis pathogenesis[92]. Other cytokines, such as IL-1, IL-6, IL-1β, TNF and IL-10, also contribute to synovial inflammation and joint degradation[86]. Clinical evidence supports the pro-inflammatory role of T_H17 cells in AIRDs. In patients with rheumatoid arthritis, synovial T_H17 cells are associated with elevated CRP levels, fibrinogen in the blood, and increased count of neutrophils and total leukocytes in synovial fluid[93]. In seropositive rheumatoid arthritis, the abundance of peripheral blood T_H17 cells also correlates with higher CRP levels and increased total leukocyte counts in the synovial fluid[93]. Similarly, in patients with SpA, synovial T_H17 cells are associated with erythrocyte sedimentation rate (ESR) and increased neutrophil counts in the synovial fluid[93]. These correlational data suggest a pivotal role of T_H17 cells in driving inflammatory processes within AIRDs.

Viral infections share several gene-expression profiles and immunopathological features with AIRDs, potentially exacerbating the pro-inflammatory milieu by mimicking or amplifying cytokine-driven immune pathways seen in AIRDs[67,94] (Fig. 1). For example, patients with chronic CHIKV infection exhibit elevated serum levels of IL-17A, IL-21, IL-22 and IL-23. In *Il17a*$^{-/-}$ knockout mice, CHIKV infection results in significantly reduced neutrophil infiltration in joint tissues compared with wild-type mice, highlighting the pathogenic role of IL-17 (ref. 29). Similarly, RRV-infected mice show IL-17$^+$ CD4$^+$ and CD8$^+$ T cell infiltration in inflamed joints, and IL-17 blockade reduces virus-induced arthritic disease severity[30,31]. Severe influenza infection in humans is characterized by T_H1 cell and T_H17 cell hypercytokinaemia, with upregulated IL-6, IL-8, IL-9 and IL-17 contributing to a flare-prone inflammatory state[35]. In COVID-19, elevated IL-1β and IFNγ levels reflect heightened T_H1 cell activation[10]. In addition, B19V VP1 antigen enhances IL-6 and TNF production in human monocytic cell lines (U937 and THP-1) co-cultured with synovial cells derived from B19V-positive patients with rheumatoid arthritis[38]. Furthermore, expression of B19V NS1 protein in human haematopoietic cells (K562, Raji and THP-1) and primary endothelial cells induces IL-6 production through activation of the NF-κB binding site in the IL-6 promoter region[39]. These convergences between viral and autoimmune cytokine networks suggest that viral infections might trigger or amplify AIRD flares by promoting a pro-inflammatory cytokine milieu.

Table 1 | Viral mechanisms altering autoimmune rheumatic diseases

Virus	Mechanisms	Associated AIRDs
SARS-CoV-2	Viral persistence (such as ORF8 in plasma, macrophage reservoirs)[13,14] Molecular mimicry (Spike protein as CCDC63, ORF8 as IL-17A mimic)[11,12] Cytokine dysregulation (increased expression of T_H17 cells, IFN-I)[10] Reduced circulating or functionally competent T_{reg} cells[15,16]	RA, SLE, PsA, JIA, PMR, SpA[6,7,45–50]
HCoV-OC43	Molecular mimicry (myelin basic protein)[17,18] Altered Fcγ receptor responses[19]	RA and PsA[17,19]
Dengue virus	Persistent symptoms and immune complexes[8,20] IgM anti-platelet autoantibodies[20] FcγRIIa polymorphism-linked joint symptoms[8] Thrombocytopenia possibly contributing to immune-mediated joint symptoms[20,55]	RA-like symptoms[8]
Zika virus	Molecular mimicry (E protein and C1q)[9] Induction of anti-C1q antibodies[9]	SLE[9,58,122]
Chikungunya virus	Persistent IFN signalling[21,22] Viral persistence in synovium[21] Molecular mimicry (E1 glycoprotein with HLA-B27, complement and fibronectin)[23–28] T_H17 cell and IL-17-driven inflammation[29]	RA, SLE, PsA, SpA[23–28,69]
Ross River virus	T_H17 cell-driven inflammation[30,31] Viral persistence in macrophages[32–34]	RA[30,31]
Influenza A virus	T_H1 cell and T_H17 cell cytokine surge[35] Modulation of T_{reg} cell and B cell responses[36,37]	SLE, RA[72–74]
Parvovirus B19	Increased IL-6 and TNF production[38,39] Persistent activation of macrophages and lymphocytes[40]	RA, PsA[38,40]

AIRD, autoimmune rheumatic disease; FcγRIIa, Fcγ receptor IIa; HCoV-OC43, human coronavirus OC43; INF, interferon; JIA, juvenile idiopathic arthritis; PMR, polymyalgia rheumatica; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; T_H1 cell, T helper 1 cell; T_{reg} cell, regulatory T cell.

Persistent IFN signalling, especially type I IFN (IFNα and IFNβ), represents another key axis linking viral infection to autoimmunity. Although acute IFN responses are critical for antiviral defence, prolonged IFN signalling is deleterious, leading to sustained antigen presentation through MHC class I upregulation and priming antigen-presenting cells to activate autoreactive T cells. Notably, elevated IFNα expression has been detected in both acute and chronic CHIKV infection, and can persist up to a year post-infection[21,22]. Chronic IFN signalling might therefore establish a pro-autoimmune environment, blurring the line between host defence and immune dysregulation.

Sustained type I IFN signalling and systemic inflammation also inhibits regulatory T (T_{reg}) cell differentiation and function, thereby

disrupting regulatory immune-cell mechanisms[95]. During the onset of rheumatoid arthritis flare, regulatory CD4$^+$ T_{reg} cells are functionally impaired, marked by elevated expression of *IKZF2* (encoding the zinc finger protein Helios) and *PRDM1* (encoding BLIMP1), and reduced CD39 (ref. 89). Viral infections can further disturb peripheral immune-tolerance mechanisms that rely on T_{reg} cells. During influenza virus infection, accumulation of FOXP3$^+$Helios$^+$ T_{reg} cells has been observed in the lungs and lung-draining mediastinal lymph nodes of infected mice[36], accompanied by heightened IL-17A expression that drives plasmacytic B-1a cell differentiation through NF-κB and BLIMP1 upregulation[37]. Similarly, SARS-CoV-2 infection has been associated with a reduction in circulating T_{reg} cells and their functional exhaustion, coinciding with hyperactivation of effector T cells and cytokine-mediated tissue inflammation[15,16]. These alterations suggest that acute viral infections reduce circulating or functionally competent T_{reg} cells and skew immune regulation towards a flare-prone profile by modulating both T_{reg} cell and B cell responses. In genetically predisposed individuals with AIRD, such T_{reg} cell dysfunction weakens immune tolerance, enabling autoreactive lymphocytes to expand, thereby disrupting immune homeostasis and aggravating AIRD inflammation[96].

In the synovium of people with AIRD, activated CD4$^+$ T cells and cytokines such as IL-1 and TNF stimulate chondrocytes and fibroblasts to secrete matrix metalloproteinases (MMP)[97,98], especially MMP3, which drive extracellular matrix degradation and joint destruction. Indeed, MMP3 levels correlate with disease activity in patients with rheumatoid arthritis and ankylosing spondylitis[99–101]. In the context of virus infection, MMP3 has an antiviral effect against influenza virus and DENV. Upon virus infection, MMP3 translocates to the nucleus, where it modulates NF-κB signalling and promotes production of

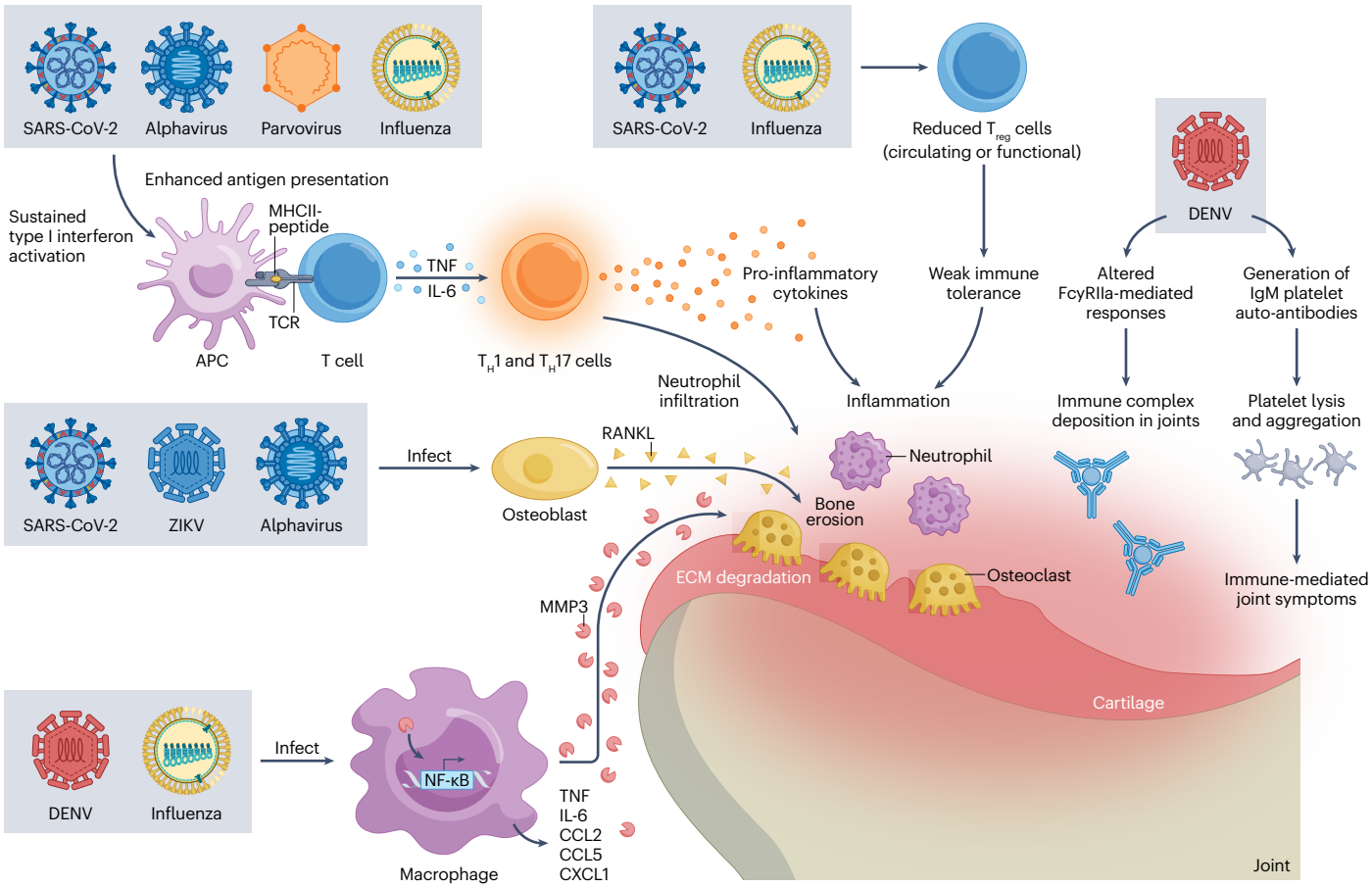


Fig. 1 | Virus-induced immune dysregulation and joint inflammation. Chronic inflammation in autoimmune rheumatic diseases (AIRDs) is driven by T helper 1 (T_H1) cell- and T_H17 cell-mediated cytokine cascades that contribute to synovial inflammation and joint degradation. Viral infections such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), alphaviruses (such as chikungunya virus and Ross River virus), parvovirus B19V, influenza, dengue virus (DENV) and Zika virus (ZIKV) recapitulate these inflammatory pathways by inducing similar cytokine and chemokine signatures, promoting immune-cell recruitment and tissue infiltration. Viral infections initiate innate immune sensing through pattern-recognition receptors, resulting in production of type I interferon (IFNα and IFNβ) and pro-inflammatory cytokines. Persistent IFN activation sustains antigen presentation and primes autoreactive lymphocytes. Virus-induced inflammation amplifies T_H1 cell and T_H17 cell responses, reduces regulatory T (T_{reg}) cells and suppresses T_{reg} cell function, disrupting immune tolerance. DENV infection can alter Fcγ receptor IIa (FcγRIIa)-mediated responses, impairing clearance of immune complexes, thus increasing immune-complex deposition in joints. DENV infection also results in the generation of IgM platelet autoantibodies that mediate platelet lysis and aggregation, contributing to worsening immune-mediated joint symptoms. In the synovium, viral infection also amplifies pathogenic processes such as RANKL-driven osteoclastogenesis and matrix metalloproteinase 3 (MMP3)-mediated extracellular matrix degradation, which contribute to joint erosion and autoimmune amplification. APC, antigen-presenting cell; ECM, extracellular matrix; MHCII, major histocompatibility complex class II.

pro-inflammatory mediators, including TNF, IL-6 and chemokines such as CCL2, CCL5, and CXCL1 (refs. 102,103). The nuclear translocation of MMP3 and its modulation of NF-κB signalling amplify a feedforward loop of inflammation, linking viral infection to the progression to joint pathology.

Bone erosion, a key determinant of disease severity in rheumatoid arthritis, is driven by excessive osteoclast activation[104]. Osteoclast-mediated bone resorption is facilitated through the action of receptor activator of NF-κB ligand (RANKL), produced by osteoblasts in response to pro-inflammatory cytokines IL-1, IL-6, IL-17 and TNF[105–107]. Notably, viruses such as RRV, CHIKV, ZIKV and SARS-CoV-2 have been documented to infect osteoblasts, disrupting their function and leading to increased secretion of RANKL[108–112], which binds to receptor activator of NF-κB (RANK) on osteoclast precursor cells, inducing osteoclastogenesis[113]. Collectively, these findings suggest that viral infection of osteoblasts can disrupt bone remodeling and potentially exacerbate bone erosion in AIRDs.

Chemokine dysregulation also contributes to the initiation and amplification of AIRD flares[114]. Critically ill patients with COVID-19 exhibit elevated circulating levels of granulocyte–macrophage colony-stimulating factor (GM-CSF), IFNγ-induced protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1α (MIP1A) and TNF[10]. Similar chemokine expression patterns are observed in a viral arthritis model, where synovial fibroblasts infected with RRV in culture upregulate MCP1, IL-8 and GM-CSF, whereas infected macrophages exhibit elevated levels of MCP1, IL-18, MIP2 and IP10 (ref. 115). These findings demonstrate how viral-induced chemokine storm mirrors the leukocyte-driven inflammation observed in AIRD, highlighting how viral perturbations of chemokine networks might tip the immune balance towards the exacerbation of synovitis and joint inflammation that is characteristic of AIRD.

Beyond chemokines, viral infections can provoke autoimmunity through the induction of autoreactive antibodies. In DENV infection, one such mechanism involves the generation of IgM anti-platelet autoantibodies[20]. These autoantibodies are significantly elevated not only in the acute phase of infection (3–7 days post-fever onset) but they also persist into the convalescent (1–3 weeks) and late (8–9 months) infection phases when compared with control sera from healthy individuals[20]. Functionally, IgM anti-platelet autoantibodies mediate platelet lysis and inhibit platelet aggregation, contributing to thrombocytopenia and potentially initiating or worsening immune-mediated joint symptoms[20,55].

Host factors further influence susceptibility to viral-triggered autoimmunity. One well-characterized example is a polymorphism in the gene encoding the low-affinity IgG Fcγ receptor IIa (FcγRIIa), specifically the histidine/histidine (HH) genotype, which has been associated with joint, muscle and bone pain during viral infections[8]. Fcγ receptors are crucial for immune homeostasis because they mediate the recognition, internalization and clearance of immune complexes by phagocytes. When this system is compromised, such as in individuals with altered Fcγ receptor functions, immune complexes can persist in tissues and trigger chronic activation of the innate and adaptive immune system[116]. Fcγ receptors regulate the internalization and subsequent degradation of immune complexes; however, inefficient clearance of immune complexes can result in sustained immune stimulation, contributing to the onset or exacerbation of AIRD such as SLE[117]. Importantly, Fc receptor signalling is not only involved in systemic autoimmune diseases but is also upregulated in diseases that are tissue specific. For example, transcriptomic analyses have shown upregulation of Fc receptor-related genes in the synovium during rheumatoid arthritis flares[90]. These observations suggest that local immune complex signalling might contribute directly to disease exacerbation. In the case of DENV infection, altered FcγRIIa-mediated responses have been implicated in the persistence of musculoskeletal symptoms even after viral clearance. These responses might reflect prolonged immune-complex deposition in joints and tissues, representing a potential mechanism by which DENV infection can trigger or worsen AIRD pathology[8].

Together, these findings show that although antiviral immunity is vital for clearing infection, its sustained or dysregulated activation can promote or exacerbate AIRD. Chemokine-driven immune-cell recruitment, autoantibody production, impaired immune complex clearance and host genetic susceptibility can collectively amplify inflammation and tissue damage. In immunocompromised individuals or those predisposed to autoimmunity, viral infections may serve not only as initial triggers but also as drivers of recurrent flares through prolonged immune activation and breakdown of tolerance.

Molecular mimicry of viral proteins

Molecular mimicry, the process in which viral proteins resemble host antigens in structure or sequence, is a well-established mechanism contributing to the pathogenesis of AIRD[118]. During viral infections, the host immune system mounts responses against viral epitopes that can inadvertently cross-react with self-antigens, leading to the production of autoantibodies and immune dysregulation, ultimately worsening AIRDs. From an evolutionary perspective, molecular mimicry reflects a finely balanced trade-off between viral immune evasion and host autoimmunity[119]. For viruses, it confers a selective advantage by enabling immune evasion, thereby reducing recognition by neutralizing antibodies or cytotoxic T cells and facilitating persistence within the host. However, excessive overlap between viral and host epitopes increases the risk of host immune activation and autoimmune pathology, imposing evolutionary constraints on both virus and host. In Table 2, we outline several viruses known to exploit molecular mimicry, illustrating their roles in triggering or exacerbating AIRDs.

Severe acute respiratory syndrome coronavirus 2. The SARS-CoV-2 genome comprises 11 genes encoding multiple open reading frames (ORFs). Among these, ORF8, a secreted protein, has been found at elevated levels in the blood of patients with COVID-19 who have pre-existing AIRDs, such as rheumatoid arthritis, SLE and polymyalgia rheumatica[13]. Notably, ORF8 structurally and functionally mimics IL-17A, a potent pro-inflammatory cytokine with a well-documented role in the pathogenesis of rheumatoid arthritis[12,92]. Mechanistically, the Y42 and E106 residues of ORF8 can bind to IL-17RA, and residues I71 and I76 can bind to IL-17RC, promoting heterodimerization and downstream activation of the NF-κB pathway, as evidenced by increased phosphorylation of p65 and IκBα. NF-κB signalling, in turn, leads to robust expression of pro-inflammatory genes, including *CCL20*, *CXCL1*, *CXCL2* and *IL6*. Notably, ORF8 induces a more potent and broader inflammatory response than IL-17A itself[12]. Moreover, in osteoblasts derived from patients with rheumatoid arthritis, ORF8 enhances RANKL production, stimulating osteoclastogenesis and contributing directly to joint inflammation and destruction in patients with pre-existing AIRDs[13].

The SARS-CoV-2 Spike protein is a key structural protein that facilitates viral entry through the angiotensin-converting enzyme 2 (ACE2) receptor on host cells[120]. In patients with COVID-19, several new-onset autoantibodies have been identified, targeting a broad

range of proteins that include CALU, CCDC63, SNURF, TRIM63, IFNA6, ANO2, TPO and NPC1 (ref. 11). Of note, sequence homology has been observed between the Spike protein and epitopes of TRIM63, CCDC63 and NPC1. For example, the fusion peptide region of spike (residues 816–825, SFIEDLLFNK) aligns well with TRIM63 (residues 240–245, SFIEAL) and CCDC63 (residues 182–189, IEDLRFEK), whereas a segment of the Spike S1 C-terminal domain (residues 656–660, VNNSY) shows similarity to NPC1 (residues 567–571, VNNYY). Among these, anti-CCDC63 autoantibodies have been linked to persistent musculoskeletal symptoms following COVID-19, suggesting that molecular mimicry between Spike and CCDC63 might contribute to post-infection muscular and joint complications in patients with AIRD[11].

Human coronavirus OC43. HCoV-OC43 has been implicated in molecular mimicry linked to rheumatoid arthritis. The HCoV-OC43 p65-like protein (residues 656–668) shows homology with myelin basic protein (MBP, residues 84–104), a proposed autoantigen in rheumatoid arthritis[17,18]. Genetic studies have revealed an association between elevated MBP expression and rheumatoid arthritis pathology, particularly in the synovial lining[18]. Furthermore, MBP autoantibodies were significantly elevated in patients with rheumatoid arthritis compared with healthy controls, and often recognized citrullinated MBP[18], consistent with the broader role of post-translational modifications in enhancing autoantigenicity. The strong sequence alignment between MBP and HCoV-OC43 supports the hypothesis that viral mimicry of MBP promotes autoantibody generation and drives rheumatoid arthritis progression. In support of this notion, administration of HCoV-OC43 mimic peptide to rats induces persistent pain hypersensitivity, highlighting its potential role in mediating rheumatoid arthritis-associated pain and inflammation[17].

Table 2 | Viral proteins and their molecular mimicry with self-antigens, triggering autoimmune responses

Virus	Viral protein	Mimic	Mechanism
SARS-CoV-2	ORF8	IL-17A	ORF8 binds to IL-17R (ORF8 Y42 and E106 residues bind to IL-17RA, and I71 and I76 residues bind to IL-17RC), which induces pro-inflammatory cytokine expression in monocytes and promotes osteoclastogenesis[12,13]
SARS-CoV-2	Spike fusion proteins	CCDC63	The development of anti-CCDC63 autoantibodies might contribute to post-infection muscle and joint complications[11]
ZIKV	E proteins	C1q	C1q initiates the classical complement pathway; the development of anti-C1q autoantibodies drives flares of lupus nephritis[9,122]
CHIKV	E1 proteins	HLA-B27, C3 and C5, fibronectin, β-arrestin	E1 shares sequence and structural homology with HLA-B27 and host proteins (C3, C5, fibronectin, β-arrestin), potentially triggering cross-reactive immune responses and chronic arthritis in predisposed hosts[23–27]
HCoV-OC43	Peptides	MBP	Anti-MBP autoantibodies and their citrullination contribute to pain and inflammation[17,18]

CHIKV, chikungunya virus; HCoV-OC43, human coronavirus OC43; MBP, myelin basic protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ZIKV, Zika virus.

Zika virus. ZIKV encodes three structural proteins: capsid (C), premembrance (prM) and envelope (E), as well as seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5)[121]. Among these, the E protein shares functional similarity with complement protein C1q, an autoantigen involved in SLE pathogenesis. In murine models, ZIKV infection elicits anti-C1q autoantibody production[9]. In patients with SLE, elevated levels of anti-C1q antibodies are associated with increased flare risk of lupus nephritis and greater renal disease activity[122]. These findings suggest that ZIKV-induced anti-C1q mimicry might contribute to complement dysregulation, immune-complex accumulation and tissue inflammation, thereby exacerbating SLE pathogenesis.

Chikungunya virus. CHIKV possesses a ~11.8-kb genome that encodes four non-structural proteins (nsP1–4) responsible for viral replication and five structural proteins (capsid, E3, E2, E1 and 6 K)[123]. The E1 glycoprotein, in particular, has garnered attention for its potential role in autoimmune pathogenesis. E1 contains a four-amino acid sequence (TQLV or TELV) that is homologous to HLA-B27, a major histocompatibility complex (MHC) class I allele strongly associated with SpA and other autoimmune conditions. Additionally, the CHIKV E1 protein shares structural homology with host proteins implicated in rheumatoid arthritis, PsA and SpA, including complement components C3 and C5, fibronectin and β-arrestin 1 (refs. 23–27). Moreover, in silico analyses of conserved regions within the structural polyproteins of arthritogenic alphaviruses, including CHIKV, RRV, Mayaro virus, O'nyong'nyong virus and Barmah Forest virus, have identified immunogenic regions harbouring predicted B cell epitopes and MHC class II binding sites[28]. Among these are autoantigens implicated in rheumatoid arthritis and SLE, such as alpha-1B-glycoprotein, LRP2 and CILP[28,124–126].

Together, these findings underscore a multifaceted role for CHIKV in the induction of autoimmunity, particularly in individuals with a genetic predisposition. The ability of CHIKV to mimic self-antigens at both the sequence and structural level might prime autoreactive immune responses that persist beyond acute infection, contributing to chronic inflammatory arthritis and AIRD flares. Future work is needed to elucidate the precise immunological pathways linking CHIKV infection to the onset or exacerbation of AIRD pathogenesis.

Persistent viral reservoirs

Several viruses establish long-term reservoirs in immune-privileged or inflamed tissues, enabling prolonged antigen presentation and sustained immune activation. In AIRDs, such reservoirs might serve as continuous sources of local cytokine production, immune-cell recruitment and tissue injury, ultimately driving disease flares (Fig. 2).

In patients with chronic CHIKV-associated arthralgia, viral RNA and proteins have been detected in synovial macrophages up to 18 months after infection, despite a robust systemic immune response[21]. Notably, $CD14^+$ infiltrating monocytes and $CD56^+$ natural killer (NK) cells were detected in the synovial fluid. In addition, elevated levels of CCL2, IL-6 and IL-8 were detected in the synovial fluid compared with serum[21], suggesting that CHIKV establishes a localized inflammatory niche within joint tissues, maintained by persistent activation of monocytes and NK cells. Histological analyses have revealed perivascular accumulation of $CD18^+$ macrophages and the presence of $CD4^+$ and $CD56^+$ cells, including both quiescent and activated NK cells. Immunostaining for

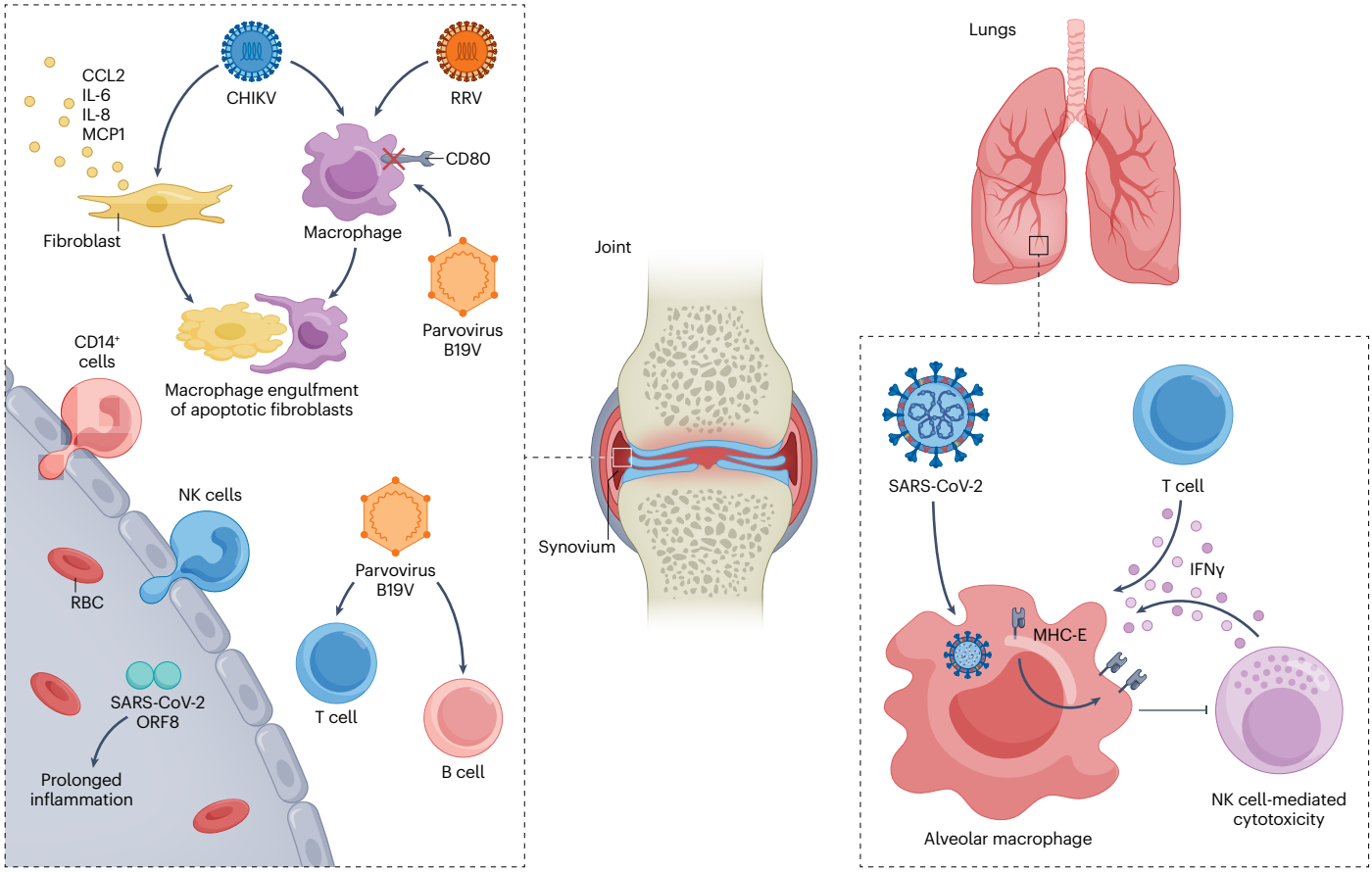


Fig. 2 | Persistent viral reservoirs and their role in autoimmune rheumatic disease inflammation. Chikungunya virus (CHIKV), Ross River virus (RRV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and parvovirus B19V can persist in macrophages, fibroblasts and lymphocytes within the synovium or mucosal tissues. In chronic CHIKV arthritis, viral RNA and proteins can be detected in synovial macrophages and fibroblasts, circulating levels of CCL2, IL-6, IL-8 and monocyte chemoattractant protein 1 (MCP1) are elevated, stromal cells undergo apoptosis, and $CD14^+$ infiltrating monocytes and $CD56^+$ natural killer cells are detected in the synovial fluid. RRV persists in macrophages and dysregulates immunoregulatory molecules such as CD80, with stress-induced reactivation modulating phagocytic and immunoregulatory functions. Parvovirus B19V infects macrophages and lymphocytes in the rheumatoid arthritis and psoriatic arthritis synovium, maintaining inflammatory cytokine production and immune infiltration. SARS-CoV-2 ORF8 protein is detectable in the plasma of patients with autoimmune rheumatic disease (AIRD) post-infection, whereas replication-competent virus can persist in bronchoalveolar macrophages, supported by interferon-γ (IFNγ)-induced major histocompatibility complex E (MHC-E) expression that impairs natural killer (NK) cell clearance. These viral reservoirs provide continuous antigenic stimulation, disrupt immune homeostasis and potentially contribute to recurrent flares and progressive tissue injury in AIRDs. RBC, red blood cell.

cleaved PARP in fibroblasts demonstrated high levels of apoptosis[21], suggesting that inefficient clearance of infected apoptotic cells might support long-term viral persistence in joint tissues.

RRV, like CHIKV, has been shown to persist in macrophages for months, with virus levels fluctuating between detectable and undetectable states[32–34]. RRV relapse, a key clinical feature of RRV disease, can be induced in vitro by altering cell-culture conditions, such as serum concentration or temperature, suggesting that stress or other environmental factors might trigger reactivation of the virus[32]. RRV infection also enhances macrophage phagocytic activity and dysregulates the immunoregulatory molecules CD80, IFNγ and TNF, a mechanism that is thought to promote evasion of immune clearance and persistence in the host[32]. Together, these findings suggest that enhanced phagocytic activity in macrophages might facilitate antigen transfer and contribute to the establishment and maintenance of viral reservoirs.

Persistent expression of SARS-CoV-2 proteins, particularly ORF8, has been reported in the plasma of individuals with pre-existing AIRDs, including rheumatoid arthritis, PsA and Sjögren's syndrome, even months after COVID-19 diagnosis[13]. This prolonged protein persistence could conceivably contribute to sustained inflammatory signalling and post-viral disease flares[13]. Additionally, replication-competent SARS-CoV-2 has also been detected in bronchoalveolar fluid macrophages from infected cynomolgus macaques up to 18 months post-infection[14]. Notably, IFNγ upregulates MHC-E expression on these bronchoalveolar macrophages, which in turn inhibits NK cell-mediated cytotoxicity, potentially enabling viral immune evasion and long-term tissue residence[14].

In the case of B19V, co-culture of macrophage cell lines with synovial cells from $B19V^+$ patients with rheumatoid arthritis resulted in macrophages that were positive for the viral protein VP1, indicating that B19V

infects macrophages[38]. Immunohistochemical analysis of rheumatoid arthritis and PsA synovial tissues confirmed the presence of B19V VP1 and VP2 capsid proteins in B lymphocytes and T lymphocytes within the synovial stroma[40]. Persistent activation of macrophages and lymphocytes by B19V might drive excessive production of pro-inflammatory cytokines, promoting immune-cell infiltration and joint damage. Taken together, these findings suggest that viruses exploit immune cells such as macrophages as long-term reservoirs. The sustained presence of viral antigens in inflamed joint and mucosal tissues may perpetuate immune activation, exacerbate autoimmunity and contribute to AIRD flares.

Hormonal modulation and virus-induced autoimmune rheumatic disease exacerbations

Hormonal signalling is a crucial yet often underappreciated modifier of both antiviral immunity and AIRD flares[127–129]. Sex hormones (such as oestrogen, progesterone and testosterone), glucocorticoids (such as cortisol) and the thyroid hormones all interact with immune pathways, thereby potentially shaping infection outcomes and autoimmunity risk. In Table 3, we summarize how specific hormones influence viral pathogenesis and AIRD through modulation of inflammation, viral persistence and immune tolerance.

Sex hormones in viral and autoimmune pathways

Oestrogen and progesterone. Certain AIRDs, such as rheumatoid arthritis and SLE, disproportionately affect women of reproductive age, who account for nearly 80% of patients, suggesting the involvement of female sex hormones in driving immune dysregulation and autoimmunity[130,131]. A randomized trial of hormone replacement therapy (HRT) in menopausal patients with pre-existing SLE reported a higher incidence of mild to moderate flares in the HRT group than with placebo[132], suggesting that exogenous oestrogen and progesterone might amplify AIRD activity. Oestrogen, particularly oestradiol (E_2), has been shown to promote survival of autoreactive B cells by disrupting B cell receptor-mediated apoptosis and increasing the expression of anti-apoptotic proteins such as CD22, SHP1, BCL2 and VCAM1 (ref. 133). Activation of oestrogen receptor-α (ERα) has a key role in regulating B cell maturation[134]. Moreover, stimulation of peripheral blood mononuclear cells derived from women with phytohaemagglutinin, PMA and ionomycin led to overexpression of inflammatory and cytotoxic effector molecules that contain oestrogen response element binding sites, such as *GNLY*, *IL1F5*, *LTB*, *OAS1* and *OAS3* (ref. 135). Together, these findings support the pro-inflammatory influence of female sex hormones in AIRDs.

In parallel, progesterone and oestrogen also influence antiviral immune responses. Serum progesterone levels were elevated in SARS-CoV-2-infected individuals and correlated negatively with disease severity[127]. Notably, progesterone induces type I IFN signalling through SRC-mediated phosphorylation of IRF3, promoting IFNβ production[127]. E_2 also has antiviral effects, reducing influenza viral titres in pretreated cells[136]. Computational modelling suggests that oestrogens suppress inflammation in SARS-CoV-2 infection by interacting with ESR1 and ESR2 (ref. 137). Moreover, retrospective studies linked HRT use to lower mortality in patients with COVID-19 (refs. 138,139). Altogether, these findings suggest that, although progesterone and oestrogen enhance antiviral immunity, they might also disrupt immune tolerance and trigger flares in patients with pre-existing AIRD.

Testosterone. Testosterone, the primary male sex hormone, exerts anti-inflammatory effects that modulate immune responses. Epidemiological data indicate that male sex is associated with a lower risk of AIRDs and is a strong predictor of remission in rheumatoid arthritis[140]. Levels of total and free testosterone are negatively associated with rheumatoid arthritis development in men[141]. In an experimental autoimmune orchitis (EAO) model — a rodent model of testicular inflammation and autoimmunity — testosterone replacement reduced disease severity by decreasing $CD4^+$ T cell and macrophage infiltration, while increasing

Table 3 | Hormonal modulation of immune responses, viral infection and autoimmune rheumatic disease flare

Hormone	Effects on immune system	Effects on virus infection	Influence on AIRD flare severity
Oestrogen	Enhances B cell survival and autoantibody production[133] ERα regulates B cell maturation[134]	Might reduce influenza virus replication[136] Suppresses inflammation in COVID-19 (refs. 138,139) HRT lowers COVID-19 mortality[138,139]	Might influence flare frequency in postmenopausal women with SLE undergoing HRT[132]
Progesterone	Induces type I IFN signalling[127]	Elevated levels correlate negatively with COVID-19 severity[127] HRT use lowers COVID-19 mortality[138,139]	Might influence flare frequency in postmenopausal women with SLE undergoing HRT[132]
Testosterone	Decreases $CD4^+$ T cell and macrophage infiltration[128] Enhances immunosuppressive T_{reg} cell activity[128] Suppresses pro-inflammatory cytokines[128]	SARS-CoV-2 and ZIKV infections decrease testosterone levels[143,144]	Low levels linked to increased flare risk[141] Androgen therapy reduces RA disease activity in men[142]
Cortisol	Chronic or dysregulated secretion can contribute to immune dysfunction and progression of inflammatory disease[145]	Elevated levels correlated with increased cytokines and chemokines in influenza-infected patients[129] Adrenal infarction reported in patients with COVID-19 who have high cortisol levels[148]	Elevated stress and cortisol linked to AIRD flare risk[146]
Thyroid hormones	Regulate T cell and macrophage activation and polarization[149,153] Alter fibroblast function in joints[149,153]	ZIKV infection reduces thyroid hormones, possibly by disrupting the HPT axis[154] WNV and B19V have been detected in thyroid tissues[155,156]	Hypothyroidism is associated with lupus nephritis[150,151] Thyroid imbalances can worsen synovial inflammation[149,153]

AIRD, autoimmune rheumatic diseases; ERα, oestrogen receptor-α; HPT, hypothalamic–pituitary–thyroid axis; HRT, hormone replacement therapy; IFN, interferon; RA, rheumatoid arthritis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; T_{reg} cell, regulatory T cell; WNV, West Nile virus; ZIKV, Zika virus.

immunosuppressive $CD4^+CD25^+FOXP3^+$ T_{reg} cells[128]. In that same model, testosterone supplementation downregulated *MCP1* expression and pro-inflammatory T_H1 cell cytokines IL-2 and IFNγ[128]. These animal findings appear to translate to humans, as androgen replacement therapy in male patients with rheumatoid arthritis reduced inflammation and improved symptoms[142]. These results suggest that the immunosuppressive effects of testosterone might protect against AIRD flares.

Importantly, viral infections can reduce testosterone levels. In a cohort of 121 men recovering from COVID-19, a total of 12 patients (10%) exhibited reduced testosterone levels over a 7-month period[143]. Similarly, ZIKV infection in immunocompromised (A129) mice significantly decreased testosterone concentrations in serum and in the testis[144]. Taken with the above, it is possible that virus-induced reductions in testosterone levels might increase susceptibility to AIRD flares.

Cortisol

Cortisol, the primary stress hormone, mediates the stress response and regulates inflammation and infection[145]. Although cortisol typically has anti-inflammatory effects, chronic or dysregulated secretion, as observed during prolonged psychological stress, systemic inflammation or infection, can paradoxically contribute to immune dysfunction and the progression of inflammatory diseases[145]. Dysregulated cortisol dynamics have been implicated in AIRD activity. Patients with rheumatoid arthritis have higher cortisol levels than healthy controls, with levels correlating with disease severity[146]. Mechanistically, these patients show diminished hypothalamic–pituitary–adrenal axis responsiveness, potentially impairing cortisol regulation and limiting immune control[147].

Viral infections can further disrupt cortisol homeostasis. Cortisol levels are elevated in patients infected with influenza and correlate with increased levels of circulating chemokine and cytokines such as CCL20, IL-10, IL-6, IL-17F, IL-17E and IL-23 (ref. 129). Adrenal gland infarction has been observed in patients with COVID-19 who exhibit high cortisol levels[148]. Although the causal relationship remains unclear, these findings suggest that viral infections may perturb adrenal function through direct viral tropism, endothelial injury or cytokine-mediated vascular damage. Hence, viral infections might increase AIRD severity by exacerbating cortisol imbalances and immune activation.

Thyroid hormones

Thyroid hormones regulate cellular metabolism and influence immune function[149]. Altered thyroid function is common in autoimmune diseases and is linked to disease severity. Hypothyroidism is prevalent among patients with SLE and is associated with lupus nephritis[150,151]. Similarly, patients with rheumatoid arthritis are at an increased risk of thyroid dysfunction, especially hypothyroidism[152]. Thyroid imbalances affect synovial fibroblast function and modulate the activation and polarization of macrophages and T cells[149,153], suggesting that its dysregulation might exacerbate autoimmune inflammation.

Viral infections can disrupt thyroid hormone balance through direct or indirect mechanisms. For example, ZIKV infection in neonatal mice reduced serum levels of thyroid-stimulating hormone, triiodothyronine and thyroxine levels, which normalized following viral clearance[154]. Although no histopathological abnormalities were observed in the thyroid, ZIKV was detected in the hypothalamus, suggesting that disruption of the hypothalamic–pituitary–thyroid axis might underlie the hormonal imbalance[154].

The thyroid gland can also be directly targeted by viruses, in turn potentially altering systemic thyroid hormone levels and immune responses. In fatal cases of neuroinvasive WNV disease, WNV antigens were detected in thyroid tissues[155]. In addition, B19V DNA has been identified in thyroid tissue by PCR amplification[156]. Although the effect of viral presence in the thyroid gland requires further investigation, these observations raise the possibility that viral persistence might contribute to thyroiditis or subclinical alterations in thyroid function. Taken together, these findings suggest that viral infections might influence AIRD severity by disrupting thyroid hormone signalling, either through impairment of the hypothalamic–pituitary–thyroid axis or by directly infecting thyroid tissue.

Current challenges and emerging therapeutic strategies

Despite advances in biologics and DMARDs, the management of AIRD remains challenging. Current therapies are largely immunosuppressive and non-selective, providing symptomatic relief but rarely achieving durable immune tolerance[157]. Many patients experience incomplete remission or relapse after treatment withdrawal. Moreover, chronic immunosuppression increases susceptibility to infections, which is a particularly crucial concern given the role of viral triggers in AIRD flares[48]. Distinguishing between viral infection and autoimmune reactivation can also be diagnostically complex, often leading to therapeutic delays or overtreatment[61,67]. Thus, in patients with AIRD flares, screening for virus exposure should be considered before initiating immunosuppressive therapy, as viral infections can mimic AIRD flares[67,158]. Integrating insights from virology, endocrinology and immunology offers an opportunity to tailor treatment to the underlying triggers for a given patient[159]. Treatment strategies might include combination therapies that pair antivirals with hormone-based or immunoregulatory agents, advancing towards precision care in AIRDs. In this section, we discuss emerging approaches that target latent viral reservoirs, leverage hormonal pathways and ultimately enable precision medicine to prevent or mitigate AIRD flare-ups in the setting of viral infection.

Targeting viral reservoirs

Viral reservoirs in tissues can serve as persistent sources of immune activation[13,21,32–34]. Hence, antiviral strategies that target residual viruses in immunocompromised individuals or patients with AIRD might reduce flare recurrence. One promising approach is the repurposing of small-molecule inhibitors that disrupt viral replication, for flare-prone AIRD patients with signs of ongoing viral activity. Promisingly, remdesivir, an FDA-approved antiviral for COVID-19 that inhibits viral RNA-dependent RNA polymerase[160], was found to reduce T_H17 cells in rheumatoid arthritis peripheral blood mononuclear cells and suppress pro-inflammatory cytokines in the synovium, such as IFNγ, IL-17, IL-6, CCL2, IL-1β and TNF[161].

Immunomodulatory drugs, including certain DMARDs, can offer dual benefits in suppressing both viral persistence and inflammation[162]. Notably, the Janus kinase (JAK) inhibitor baricitinib, approved for treating rheumatoid arthritis, showed therapeutic synergy when combined with remdesivir in patients with COVID-19, shortening recovery time and improving clinical outcomes. This combination attenuated the production of pro-inflammatory cytokines and chemokines, reduced neutrophil and macrophage infiltration, and dampened T cell activation and proliferation[163,164]. These findings underscore the therapeutic potential of combining antiviral and immunomodulatory strategies to manage virus-triggered AIRD flares.

Hormonal modulation in autoimmune rheumatic disease therapy

Hormonal modulation represents another promising strategy for regulating immune responses in AIRD. Androgens such as testosterone have demonstrated anti-inflammatory effects[120,136]. Both animal and clinical studies suggest that testosterone not only modulates immune signalling but also suppresses cytokine production, leading to reduced pro-inflammatory responses that characterize AIRD flares[128,142,144,165]. Testosterone replacement therapy (TRT) has also been explored in the context of viral infection, given its potential to mitigate hypercytokinaemia. Although a 2-month course of TRT improved signs of hypogonadism (indicated by a reduction of gynecomastia) in a patient with long COVID, it did not significantly alleviate systemic symptoms such as joint or muscle pain[166]. Furthermore, a clinical trial reported that COVID-19 could blunt the efficacy of TRT[167]. Thus, although androgens might hold therapeutic value, their clinical utility in AIRD warrants further investigation.

Cortisol, as described above, has been linked to heightened inflammation during viral infection. Elevated cortisol levels correlate with increased pro-inflammatory markers during influenza infection[129] and are a well-documented feature of depression[168]. Moreover, depression itself is associated with elevated levels of CRP, IL-1 and IL-6 (ref. 169). Psychological interventions, including cognitive-behavioural therapy, stress management and relaxation training, have been shown to reduce depressive symptoms and systemic inflammation[170]. Systematic reviews and meta-analyses further support their efficacy in improving physical activity, reducing joint tenderness and alleviating depressive symptoms in patients with rheumatoid arthritis[171–173]. Collectively, these findings highlight the potential benefit of integrating psychological support into standard AIRD treatment regimens.

Antigen-specific immunotherapies and cellular therapies

Emerging therapeutic approaches are aimed at restoring self-tolerance without global immunosuppression. Antigen-specific immunotherapies, including tolerogenic peptide vaccines, are under investigation to selectively silence autoreactive T cell responses[174]. Tolerogenic peptide vaccines, which deliver disease-relevant epitopes in a non-inflammatory context, can induce T cell anergy or deletion and promote T_{reg} cell expansion[174]. Peptide-based therapies targeting citrullinated peptides in rheumatoid arthritis have shown the potential to reduce autoreactive T cell activity and cytokine production in a phase I clinical trial[175]. Cellular therapies, such as tolerogenic dendritic cells and engineered chimeric antigen receptor regulatory T (CAR-T_{reg}) cells, offer additional avenues to re-establish immune homeostasis[176,177]. Although early in development, these interventions represent promising steps towards precision therapy for virus-triggered AIRD flares.

Precision biomarkers and translational discovery

The diagnosis and monitoring of AIRDs remain challenging owing to the limited sensitivity and specificity of routine tests[178]. Promisingly, however, high-throughput discovery platforms such as phage immunoprecipitation sequencing, molecular indexing of proteins by self-assembly and protein microarrays now enable comprehensive mapping of virus–autoantibody repertoires and therapeutic targets, bridging the gap between discovery and translational application[178–180]. Phage immunoprecipitation sequencing screening of synovial fluid and sera from patients with rheumatoid arthritis has identified rare anti-peptide antibodies, such as BCOR, LOC645453 and ATAD5, independent of seropositivity status, which could serve as biomarkers in seronegative patients[179]. Molecular indexing of proteins by self-assembly profiling of plasma from patients with severe COVID-19 revealed the presence of neutralizing IFNλ3 autoantibodies, possibly contributing to the severity of COVID-19 symptoms[180]. Protein microarrays have likewise proven effective in delineating autoantibody signatures in AIRDs such as SLE and rheumatoid arthritis[181,182]. These technologies not only help to refine disease classification but also lay the foundation for precision-medicine approaches, with the goal of earlier diagnosis, individualized therapeutic selection and real-time monitoring of virus-triggered AIRD flares.

Conclusion

Viral pathogens can disrupt immune regulation and induce flares through several mechanisms, including molecular mimicry, persistent antigen presentation and cytokine imbalance. Concurrently, hormonal factors, including oestrogen, progesterone, testosterone, cortisol and thyroid hormones, modulate immune function with both protective and pathogenic effects. These insights highlight the importance of a multidisciplinary approach to AIRD management, one that bridges rheumatology, virology, endocrinology and immunology. Future research should prioritize identifying biomarkers that can predict virus-induced flares, elucidating mechanisms of hormone–virus–immune crosstalk, and developing personalized therapies that preserve immune competence while minimizing flare risk. Such integrative strategies hold promise for improving outcomes and quality of life for patients living with AIRDs.

Published online: 8 December 2025

References

1. Hileman, C. O., Malakooti, S. K., Patil, N., Singer, N. G. & McComsey, G. A. New-onset autoimmune disease after COVID-19. *Front. Immunol.* **15**, 1337406 (2024).
2. Korzeniowska, A. & Bryl, E. Infectious agents in the pathogenesis of autoimmune rheumatic diseases. *Transl. Res.* **276**, 39–45 (2025).
3. Sundaresan, B., Shirafkan, F., Ripperger, K. & Rattay, K. The role of viral infections in the onset of autoimmune diseases. *Viruses* **15**, 782 (2023).
4. El Hadiyen, F., Tsang, A. S. M. W. P., Lissenberg-Witte, B. I., Voskuyl, A. E. & Bultink, I. E. M. Intercurrent infection as a risk factor for disease flares in patients with systemic lupus erythematosus. *Lupus Sci. Med.* **11**, e001131 (2024).
5. Ramirez, G. A. et al. Infection-associated flares in systemic lupus erythematosus. *Pathogens* **13**, 934 (2024).
6. Li, R. et al. Analysis of related factors for RA flares after SARS-CoV-2 infection: a retrospective study from patient survey. *Sci. Rep.* **14**, 4243 (2024).
7. Mok, C. C., Cheung, C. C. L., Chan, K. L., Tse, S. M. & To, C. H. Effect of SARS-CoV2 infection on disease flares in patients with systemic lupus erythematosus: a case-control study. *Rheumatology* **63**, 3390–3396 (2024).
8. García, G. et al. Long-term persistence of clinical symptoms in dengue-infected persons and its association with immunological disorders. *Int. J. Infect. Dis.* **15**, e38–e43 (2011).
9. Koma, T. et al. Zika virus infection elicits auto-antibodies to C1q. *Sci. Rep.* **8**, 1882 (2018).
10. Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **395**, 497–506 (2020).
11. Jernbom, A. F. et al. Prevalent and persistent new-onset autoantibodies in mild to severe COVID-19. *Nat. Commun.* **15**, 8941 (2024).
12. Wu, X. et al. Viral mimicry of interleukin-17A by SARS-CoV-2 ORF8. *mBio* **13**, e0040222 (2022).
13. Melano, I. et al. SARS-CoV-2 ORF8 drives osteoclastogenesis in preexisting immune-mediated inflammatory diseases. *JCI Insight* **9**, e178820 (2024).
14. Huot, N. et al. SARS-CoV-2 viral persistence in lung alveolar macrophages is controlled by IFN-γ and NK cells. *Nat. Immunol.* **24**, 2068–2079 (2023).
15. Kalfaoglu, B., Almeida-Santos, J., Tye, C. A., Satou, Y. & Ono, M. T-cell hyperactivation and paralysis in severe COVID-19 infection revealed by single-cell analysis. *Front. Immunol.* **11**, 589380 (2020).
16. Wang, H. et al. Regulatory T cells in COVID-19. *Aging Dis.* **12**, 1545–1553 (2021).
17. Shubayev, V. I., Dolkas, J., Catroli, G. F. & Chernov, A. V. A human coronavirus OC43-derived polypeptide causes neuropathic pain. *EMBO Rep.* **23**, e54069 (2022).
18. Terao, C. et al. Myelin basic protein as a novel genetic risk factor in rheumatoid arthritis-a genome-wide study combined with immunological analyses. *PLoS ONE* **6**, e20457 (2011).
19. Herman, J. D. et al. Humoral immunity to an endemic coronavirus is associated with postacute sequelae of COVID-19 in individuals with rheumatic diseases. *Sci. Transl. Med.* **15**, eadf6598 (2023).

20. Lin, C.-F. et al. Generation of IgM anti-platelet autoantibody in dengue patients. *J. Med. Virol.* **63**, 143–149 (2001).
21. Hoarau, J.-J. et al. Persistent chronic inflammation and infection by Chikungunya arthritogenic alphavirus in spite of a robust host immune response. *J. Immunol.* **184**, 5914–5927 (2010).
22. Ng, L. F. P. et al. IL-1β, IL-6, and RANTES as biomarkers of Chikungunya severity. *PLoS ONE* **4**, e4261 (2009).
23. Reddy, V., Desai, A., Krishna, S. S. & Vasanthapuram, R. Molecular mimicry between Chikungunya virus and host components: a possible mechanism for the arthritic manifestations. *PLOS Negl. Trop. Dis.* **11**, e0005238 (2017).
24. Chang, X. et al. Citrullination of fibronectin in rheumatoid arthritis synovial tissue. *Rheumatology* **44**, 1374–1382 (2005).
25. Li, P. et al. Increased expression of beta-arrestin 1 and 2 in murine models of rheumatoid arthritis: isoform specific regulation of inflammation. *Mol. Immunol.* **49**, 64–74 (2011).
26. Markiewski, M. M. & Lambris, J. D. The role of complement in inflammatory diseases from behind the scenes into the spotlight. *Am. J. Pathol.* **171**, 715–727 (2007).
27. Arias de la Rosa, I. et al. Complement component 3 as biomarker of disease activity and cardiometabolic risk factor in rheumatoid arthritis and spondyloarthritis. *Ther. Adv. Chronic Dis.* **11**, 2040622320965067 (2020).
28. Venigalla, S. S. K., Premakumar, S. & Janakiraman, V. A possible role for autoimmunity through molecular mimicry in alphavirus mediated arthritis. *Sci. Rep.* **10**, 938 (2020).
29. Liu, X. et al. Interleukin-17 contributes to chikungunya virus-induced disease. *mBio* **13**, e00289–00222 (2022).
30. Mostafavi, H. et al. Interleukin-17 contributes to Ross River virus-induced arthritis and myositis. *PLoS Pathog.* **18**, e1010185 (2022).
31. Colin de Verdière, N. & Molina, J.-M. Rheumatic manifestations caused by tropical viruses. *Jt Bone Spine* **74**, 410–413 (2007).
32. Way, S. J. R., Lidbury, B. A. & Banyer, J. L. Persistent Ross River virus infection of murine macrophages: an in vitro model for the study of viral relapse and immune modulation during long-term infection. *Virology* **301**, 281–292 (2002).
33. Suhrbier, A. & La Linn, M. Clinical and pathologic aspects of arthritis due to ross river virus and other alphaviruses. *Curr. Opin. Rheumatol.* **16**, 374–379 (2004).
34. Linn, M. L., Aaskov, J. G. & Suhrbier, A. Antibody-dependent enhancement and persistence in macrophages of an arbovirus associated with arthritis. *J. Gen. Virol.* **77**, 407–411 (1996).
35. Bermejo-Martin, J. F. et al. Th1 and Th17 hypercytokinemia as early host response signature in severe pandemic influenza. *Crit. Care* **13**, R201 (2009).
36. Lu, C. & Chen, W. Influenza virus infection selectively triggers the accumulation and persistence of more potent Helios-expressing Foxp3$^+$ regulatory T cells in the lungs. *Immunol. Cell Biol.* **99**, 1011–1025 (2021).
37. Wang, X. et al. IL-17A promotes pulmonary B-1a cell differentiation via induction of Blimp-1 expression during influenza virus infection. *PLOS Pathog.* **12**, e1005367 (2016).
38. Takahashi, Y. et al. Human parvovirus B19 as a causative agent for rheumatoid arthritis. *Proc. Natl Acad. Sci.* **95**, 8227–8232 (1998).
39. Moffatt, S. et al. A cytotoxic nonstructural protein, NS1, of human parvovirus B19 induces activation of interleukin-6 gene expression. *J. Virol.* **70**, 8485–8491 (1996).
40. Mehraein, Y. et al. Detection of parvovirus B19 capsid proteins in lymphocytic cells in synovial tissue of autoimmune chronic arthritis. *Mod. Pathol.* **16**, 811–817 (2003).
41. Maslinska, M. & Kostyra-Grabczak, K. The role of virus infections in Sjögren's syndrome. *Front. Immunol.* **13**, 823659 (2022).
42. Petrosillo, N., Viceconte, G., Ergonul, O., Ippolito, G. & Petersen, E. COVID-19, SARS and MERS: are they closely related? *Clin. Microbiol. Infect.* **26**, 729–734 (2020).
43. da Rosa Mesquita, R. et al. Clinical manifestations of COVID-19 in the general population: systematic review. *Wien. Klin. Wochenschr.* **133**, 377–382 (2021).
44. Hernandez Acosta, R. A., Esquer Garrigos, Z., Marcelin, J. R. & Vijayvargiya, P. COVID-19 pathogenesis and clinical manifestations. *Infect. Dis. Clin. North. Am.* **36**, 231–249 (2022).
45. Mageau, A. et al. Risk of systemic lupus erythematosus flare after COVID-19 hospitalization: a matched cohort study. *PLoS ONE* **19**, e0309316 (2024).
46. Naranjo-Millán, J. A., Bedoya-Joaqui, V. & Cañas, C. A. Systemic lupus erythematosus flare during SARS-CoV-2 infection: Report of 3 cases presented during the fourth wave of the pandemic in Colombia. *Int. J. Rheum. Dis.* **26**, 1807–1810 (2023).
47. Khalid, M. Z., Rogers, S., Fatima, A., Dawe, M. & Singh, R. A flare of systemic lupus erythematosus disease after COVID-19 infection: a case of lupus cerebritis. *Cureus* **13**, e16104 (2021).
48. Di Iorio, M. et al. DMARD disruption, rheumatic disease flare, and prolonged COVID-19 symptom duration after acute COVID-19 among patients with rheumatic disease: a prospective study. *Semin. Arthritis Rheumatism* **55**, 152025 (2022).
49. van Dam, K. P. J. et al. Primary SARS-CoV-2 infection in patients with immune-mediated inflammatory diseases: long-term humoral immune responses and effects on disease activity. *BMC Infect. Dis.* **23**, 332 (2023).
50. Ye, C. et al. Clinical features of rheumatic patients infected with COVID-19 in Wuhan, China. *Ann. Rheum. Dis.* **79**, 1007–1013 (2020).
51. Perrot, L. et al. First flare of ACPA-positive rheumatoid arthritis after SARS-CoV-2 infection. *Lancet Rheumatol.* **3**, e6–e8 (2021).
52. Hügle, B., Krumrey-Langkammerer, M. & Haas, J.-P. Infection with SARS-CoV-2 causes flares in patients with juvenile idiopathic arthritis in remission or inactive disease on medication. *Pediatr. Rheumatol.* **19**, 163 (2021).
53. Naddei, R. et al. Increased relapse rate during COVID-19 lockdown in an Italian cohort of children with juvenile idiopathic arthritis. *Arthritis Care Res.* **75**, 326–331 (2023).
54. van Leur, S. W., Tiaan, H., Deeksha, M. & Sanyal, S. Pathogenesis and virulence of flavivirus infections. *Virulence* **12**, 2814–2838 (2021).
55. Khazali, A. S., Hadrawi, W. H., Ibrahim, F., Othman, S. & Nor Rashid, N. Thrombocytopenia in dengue infection: mechanisms and a potential application. *Expert. Rev. Mol. Med.* **26**, e26 (2024).
56. Paz-Bailey, G., Adams, L. E., Deen, J., Anderson, K. B. & Katzelnick, L. C. Dengue. *Lancet* **403**, 667–682 (2024).
57. Davies, A. J. et al. Guillain-Barré syndrome following Zika virus infection is associated with a diverse spectrum of peripheral nerve reactive antibodies. *Neurol. Neuroimmunol. Neuroinflamm* **10**, e200047 (2023).
58. Zea-Vera, A. F. & Parra, B. Zika virus (ZIKV) infection related with immune thrombocytopenic purpura (ITP) exacerbation and antinuclear antibody positivity. *Lupus* **26**, 890–892 (2017).
59. Farooq, Z. et al. European projections of West Nile virus transmission under climate change scenarios. *One Health* **16**, 100509 (2023).
60. McDonald, E. et al. Surveillance for West Nile virus disease — United States, 2009–2018. *Am. J. Transplant.* **21**, 1959–1974 (2021).
61. Iyer, N. R., McCune, W. J. & Wallace, B. I. West Nile encephalitis mimicking neuropsychiatric lupus in a patient with systemic lupus erythematosus. *BMJ Case Rep.* **12**, e229537 (2019).
62. Schiuma, M. et al. Case report: a fatal case of West Nile virus meningoencephalomyelitis in a woman with systemic lupus erythematosus initially misdiagnosed as SARS-CoV-2 infection. *Am. J. Trop. Med. Hyg.* **104**, 1716–1718 (2021).
63. Powers, A. M. et al. Evolutionary relationships and systematics of the alphaviruses. *J. Virol.* **75**, 10118–10131 (2001).
64. Marks, M. & Marks, J. L. Viral arthritis. *Clin. Med.* **16**, 129–134 (2016).
65. Freppel, W. et al. Pathogenicity and virulence of chikungunya virus. *Virulence* **15**, 2396484 (2024).
66. Rodríguez-Morales, A. J., Cardona-Ospina, J. A., Fernanda Urbano-Garzón, S. & Sebastian Hurtado-Zapata, J. Prevalence of post-chikungunya infection chronic inflammatory arthritis: a systematic review and meta-analysis. *Arthritis Care Res.* **68**, 1849–1858 (2016).
67. Miner, J. J. et al. Brief report: Chikungunya viral arthritis in the United States: a mimic of seronegative rheumatoid arthritis. *Arthritis Rheumatol.* **67**, 1214–1220 (2015).
68. Amaral, J. K., Bilsborrow, J. B. & Schoen, R. T. Chronic chikungunya arthritis and rheumatoid arthritis: what they have in common. *Am. J. Med.* **133**, e91–e97 (2020).
69. Blettery, M. et al. Brief report: management of chronic post-chikungunya rheumatic disease: the Martinican experience. *Arthritis Rheumatol.* **68**, 2817–2824 (2016).
70. Javanian, M. et al. A brief review of influenza virus infection. *J. Med. Virol.* **93**, 4638–4646 (2021).
71. Bournia, V. K., Sfontouris, C., Konsta, M. & Iliopoulos, A. H1N1 influenza outcome in rheumatic patients under biological therapy. *Clin. Exp. Rheumatol.* **30**, 311–312 (2012).
72. Tselios, K., Tsioka, R., Sarantopoulos, A., Mouloudi, E. & Boura, P. Influenza A/H1N1 septic shock in a patient with systemic lupus erythematosus. A case report. *BMC Infect. Dis.* **11**, 358 (2011).
73. Kling, M. C., Larian, A. A., Scordi-Bello, I., Emer, J. & Lebwohl, M. G. Fatal influenza A(H1N1) respiratory tract infection in a patient having psoriasis treated with infliximab. *Arch. Dermatol.* **146**, 651–654 (2010).
74. Joo, Y. B., Kim, K. J., Park, K. S. & Park, Y. J. Influenza infection as a trigger for systemic lupus erythematosus flares resulting in hospitalization. *Sci. Rep.* **11**, 4630 (2021).
75. Landry, M. L. Parvovirus B19. *Microbiol. Spectr.* https://doi.org/10.1128/microbiolspec.dmih2-0008-2015 (2016).
76. Rogo, L. D., Mokhtari-Azad, T., Kabir, M. H. & Rezaei, F. Human parvovirus B19: a review. *Acta Virol.* **58**, 199–213 (2014).
77. Cohen, B. J. et al. Human parvovirus infection in early rheumatoid and inflammatory arthritis. *Ann. Rheum. Dis.* **45**, 832–838 (1986).
78. Alexander, V., Das, S., Mangan, A. S. & Iyadurai, R. Acute parvovirus B19 infection presenting as rheumatoid arthritis mimic. *J. Fam. Med. Prim. Care* **8**, 1257–1259 (2019).
79. Sève, P. et al. Lupus-like presentation of parvovirus B19 infection. *Semin. Arthritis Rheum.* **34**, 642–648 (2005).
80. Hemauer, A., Beckenlehner, K., Wolf, H., Lang, B. & Modrow, S. Acute parvovirus B19 infection in connection with a flare of systemic lupus erythematodes in a female patient. *J. Clin. Virol.* **14**, 73–77 (1999).
81. Nesher, G., Osborn, T. G. & Moore, T. L. Parvovirus infection mimicking systemic lupus erythematosus. *Semin. Arthritis Rheum.* **24**, 297–303 (1995).
82. Hassan, F. et al. Rheumatic manifestations and sequela of acute parvovirus B19 infection in hospitalized adult population. *Int. J. Rheum. Dis.* **27**, e15409 (2024).
83. Meyer, O. et al. Parvovirus B19 infection can induce histiocytic necrotizing lymphadenitis (Kikuchi's disease) associated with systemic lupus erythematosus. *Lupus* **1**, 37–41 (1991).
84. Tzang, C.-C. et al. Clinical implications of human Parvovirus B19 infection on autoimmunity and autoimmune diseases. *Int. Immunopharmacol.* **147**, 113960 (2025).
85. Taams, L. S. Interleukin-17 in rheumatoid arthritis: trials and tribulations. *J. Exp. Med.* **217**, e20192048 (2020).
86. Kirkham, B. W. et al. Synovial membrane cytokine expression is predictive of joint damage progression in rheumatoid arthritis: a two-year prospective study (the DAMAGE study cohort). *Arthritis Rheum.* **54**, 1122–1131 (2006).
87. YAMADA, H. et al. Preferential accumulation of activated th1 cells not only in rheumatoid arthritis but also in osteoarthritis joints. *J. Rheumatol.* **38**, 1569–1575 (2011).
88. Hirota, K. et al. Preferential recruitment of CCR6-expressing Th17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model. *J. Exp. Med.* **204**, 2803–2812 (2007).

89. Baker, K. F. et al. Single-cell insights into immune dysregulation in rheumatoid arthritis flare versus drug-free remission. *Nat. Commun.* **15**, 1063 (2024).
90. Orange, D. E. et al. RNA Identification of PRIME cells predicting rheumatoid arthritis flares. *N. Engl. J. Med.* **383**, 218–228 (2020).
91. Luo, P. et al. Immunomodulatory role of T helper cells in rheumatoid arthritis : a comprehensive research review. *Bone Jt Res.* **11**, 426–438 (2022).
92. Zhao, R. et al. Genetic association between interleukin-17 and susceptibility to rheumatoid arthritis. *BMC Med. Genomics* **16**, 277 (2023).
93. Zizzo, G. et al. Synovial fluid-derived T helper 17 cells correlate with inflammatory activity in arthritis, irrespectively of diagnosis. *Clin. Immunol.* **138**, 107–116 (2011).
94. Nakaya, H. I. et al. Gene profiling of Chikungunya virus arthritis in a mouse model reveals significant overlap with rheumatoid arthritis. *Arthritis Rheumatism* **64**, 3553–3563 (2012).
95. Gangaplara, A. et al. Type I interferon signaling attenuates regulatory T cell function in viral infection and in the tumor microenvironment. *PLoS Pathog.* **14**, e1006985 (2018).
96. Sakaguchi, S., Yamaguchi, T., Nomura, T. & Ono, M. Regulatory T cells and immune tolerance. *Cell* **133**, 775–787 (2008).
97. SHINGU, M. et al. The effects of cytokines on metalloproteinase inhibitors (TIMP) and collagenase production by human chondrocytes and TIMP production by synovial cells and endothelial cells. *Clin. Exp. Immunol.* **94**, 145–149 (2008).
98. Choy, E. H. S. & Panayi, G. S. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N. Engl. J. Med.* **344**, 907–916 (2001).
99. Sun, S. et al. The active form of MMP-3 is a marker of synovial inflammation and cartilage turnover in inflammatory joint diseases. *BMC Musculoskelet. Disord.* **15**, 93 (2014).
100. Chen, C.-H. et al. Serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in ankylosing spondylitis: MMP-3 is a reproducibly sensitive and specific biomarker of disease activity. *Rheumatology* **45**, 414–420 (2005).
101. Yang, C. et al. Serum levels of matrix metalloproteinase 3 and macrophage colony-stimulating factor 1 correlate with disease activity in ankylosing spondylitis. *Arthritis Care Res.* **51**, 691–699 (2004).
102. Feng, T. et al. Matrix metalloproteinase 3 restricts viral infection by enhancing host antiviral immunity. *Antivir. Res.* **206**, 105388 (2022).
103. Zuo, X., Pan, W., Feng, T., Shi, X. & Dai, J. Matrix Metalloproteinase 3 promotes cellular anti-dengue virus response via interaction with transcription factor NFκB in cell nucleus. *PLOS ONE* **9**, e84748 (2014).
104. Schett, G. & Gravallese, E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. *Nat. Rev. Rheumatol.* **8**, 656–664 (2012).
105. Geusens, P. The role of RANK ligand/osteoprotegerin in rheumatoid arthritis. *Ther. Adv. Musculoskelet. Dis.* **4**, 225–233 (2012).
106. Liu, X.-H., Kirschenbaum, A., Yao, S. & Levine, A. C. Cross-talk between the interleukin-6 and prostaglandin E2 signaling systems results in enhancement of osteoclastogenesis through effects on the osteoprotegerin/receptor activator of nuclear factor-κB (RANK) ligand/RANK system. *Endocrinology* **146**, 1991–1998 (2005).
107. Lam, J. et al. TNF-α induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. *J. Clin. Investig.* **106**, 1481–1488 (2000).
108. Chen, W. et al. Arthritogenic alphaviral infection perturbs osteoblast function and triggers pathologic bone loss. *Proc. Natl Acad. Sci.* **111**, 6040–6045 (2014).
109. Noret, M. et al. Interleukin 6, RANKL, and osteoprotegerin expression by chikungunya virus-infected human osteoblasts. *J. Infect. Dis.* **206**, 455–457 (2012).
110. Mumtaz, N. et al. Zika virus infection perturbs osteoblast function. *Sci. Rep.* **8**, 16975 (2018).
111. Freiberger, R. N. et al. SARS-CoV-2 impairs osteoblast differentiation through spike glycoprotein and cytokine dysregulation. *Viruses* **17**, 143 (2025).
112. Camargos, V. N. et al. In-depth characterization of congenital Zika syndrome in immunocompetent mice: antibody-dependent enhancement and an antiviral peptide therapy. *eBioMedicine* **44**, 516–529 (2019).
113. Nakagawa, N. et al. RANK Is the essential signaling receptor for osteoclast differentiation factor in osteoclastogenesis. *Biochem. Biophys. Res. Commun.* **253**, 395–400 (1998).
114. Chang, M. H. et al. Arthritis flares mediated by tissue-resident memory T cells in the joint. *Cell Rep.* **37**, 109902 (2021).
115. Mateo, L. et al. An arthrogenic alphavirus induces monocyte chemoattractant protein-1 and interleukin-8. *Intervirology* **43**, 55–60 (2000).
116. Sepúlveda-Delgado, J., Llorente, L. & Hernández-Doño, S. A comprehensive review of Fc gamma receptors and their role in systemic lupus erythematosus. *Int. J. Mol. Sci.* **26**, 1851 (2025).
117. Takai, T. Roles of Fc receptors in autoimmunity. *Nat. Rev. Immunol.* **2**, 580–592 (2002).
118. Fehringer, M. & Vogl, T. Molecular mimicry in the pathogenesis of autoimmune rheumatic diseases. *J. Transl. Autoimmun.* **10**, 100269 (2025).
119. Maguire, C. et al. Molecular mimicry as a mechanism of viral immune evasion and autoimmunity. *Nat. Commun.* **15**, 9403 (2024).
120. Yoshimoto, F. K. The proteins of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2 or n-COV19), the cause of COVID-19. *Protein J.* **39**, 198–216 (2020).
121. Bhat, E. A., Ali, T., Sajjad, N., Kumar, R. & Bron, P. Insights into the structure, functional perspective, and pathogenesis of ZIKV: an updated review. *Biomed. Pharmacother.* **165**, 115175 (2023).
122. Stojan, G. & Petri, M. Anti-C1q in systemic lupus erythematosus. *Lupus* **25**, 873–877 (2016).
123. Singh, A., Kumar, A., Uversky, V. N. & Giri, R. Understanding the interactability of chikungunya virus proteins via molecular recognition feature analysis. *RSC Adv.* **8**, 27293–27303 (2018).
124. Biswas, S. et al. Identification of novel autoantigen in the synovial fluid of rheumatoid arthritis patients using an immunoproteomics approach. *PLoS ONE* **8**, e56246 (2013).
125. Ooka, S., Matsui, T., Nishioka, K. & Kato, T. Autoantibodies to low-density-lipoprotein-receptor-related protein 2 (LRP2) in systemic autoimmune diseases. *Arthritis Res. Ther.* **5**, R174 (2003).
126. Tsuruha, J. et al. Implication of cartilage intermediate layer protein in cartilage destruction in subsets of patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum.* **44**, 838–845 (2001).
127. Su, S. et al. Modulation of innate immune response to viruses including SARS-CoV-2 by progesterone. *Signal. Transduct. Target. Ther.* **7**, 137 (2022).
128. Fijak, M. et al. Testosterone replacement effectively inhibits the development of experimental autoimmune orchitis in rats: evidence for a direct role of testosterone on regulatory T cell expansion. *J. Immunol.* **186**, 5162–5172 (2011).
129. Lopez-Acevo, C. A. et al. Cortisol and perceived stress are associated with cytokines levels in patients infected with influenza B virus. *Cytokine* **138**, 155400 (2021).
130. Kvien, T. K., Uhlig, T., Ødegård, S. & Heiberg, M. S. Epidemiological aspects of rheumatoid arthritis. *Ann. N. Y. Acad. Sci.* **1069**, 212–222 (2006).
131. Lisnevskaia, L., Murphy, G. & Isenberg, D. Systemic lupus erythematosus. *Lancet* **384**, 1878–1888 (2014).
132. Buyon, J. P. et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. *Ann. Intern. Med.* **142**, 953–962 (2005).
133. Grimaldi, C. M., Cleary, J., Dagtas, A. S., Moussai, D. & Diamond, B. Estrogen alters thresholds for B cell apoptosis and activation. *J. Clin. Invest.* **109**, 1625–1633 (2002).
134. Hill, L., Jeganathan, V., Chinnasamy, P., Grimaldi, C. & Diamond, B. Differential roles of estrogen receptors α and β in control of B-cell maturation and selection. *Mol. Med.* **17**, 211–220 (2011).
135. Hewagama, A., Patel, D., Yarlagadda, S., Strickland, F. M. & Richardson, B. C. Stronger inflammatory/cytotoxic T-cell response in women identified by microarray analysis. *Genes. Immun.* **10**, 509–516 (2009).
136. Peretz, J., Pekosz, A., Lane, A. P. & Klein, S. L. Estrogenic compounds reduce influenza A virus replication in primary human nasal epithelial cells derived from female, but not male, donors. *Am. J. Physiol. Lung Cell Mol. Physiol.* **310**, L415–L425 (2016).
137. Li, F. et al. Estrogen hormone is an essential sex factor inhibiting inflammation and immune response in COVID-19. *Sci. Rep.* **12**, 9462 (2022).
138. Dambha-Miller, H. et al. Mortality in COVID-19 among women on hormone replacement therapy: a retrospective cohort study. *Fam. Pract.* **39**, 1049–1055 (2022).
139. Seeland, U. et al. Evidence for treatment with estradiol for women with SARS-CoV-2 infection. *BMC Med.* **18**, 1–9 (2020).
140. Forslind, K., Hafström, I., Ahlmén, M. & Svensson, B. Sex: a major predictor of remission in early rheumatoid arthritis? *Ann. Rheum. Dis.* **66**, 46–52 (2007).
141. Pikwer, M. et al. Association between testosterone levels and risk of future rheumatoid arthritis in men: a population-based case–control study. *Ann. Rheum. Dis.* **73**, 573–579 (2014).
142. Cutolo, M., Balleari, E., Giusti, M., Intra, E. & Accardo, S. Androgen replacement therapy in male patients with rheumatoid arthritis. *Arthritis Rheum.* **34**, 1–5 (1991).
143. Salonia, A. et al. Testosterone in males with COVID-19: a 7-month cohort study. *Andrology* **10**, 34–41 (2022).
144. Zheng, B. et al. Testosterone protects mice against Zika virus infection and suppresses the inflammatory response in the brain. *iScience* **25**, 105300 (2022).
145. Dhabhar, F. S. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection versus immunopathology. *Allergy Asthma Clin. Immunol.* **4**, 2–11 (2008).
146. Wróbel, A., Szklarczyk, J., Barańska, I., Majda, A. & Jaworek, J. Association between levels of serotonin, melatonin, cortisol and the clinical condition of patients with rheumatoid arthritis. *Rheumatol. Int.* **43**, 859–866 (2023).
147. Straub, R. H., Dhabhar, F. S., Bijlsma, J. W. J. & Cutolo, M. How psychological stress via hormones and nerve fibers may exacerbate rheumatoid arthritis. *Arthritis Rheum.* **52**, 16–26 (2005).
148. Popescu, M. et al. COVID-19 infection: from stress-related cortisol levels to adrenal glands infarction. *Rom. J. Morphol. Embryol.* **63**, 39–48 (2022).
149. Wenzek, C. et al. The interplay of thyroid hormones and the immune system — where we stand and why we need to know about it. *Eur. J. Endocrinol.* **186**, R65–R77 (2022).
150. Gao, H. et al. Subclinical hypothyroidism and its association with lupus nephritis: a case control study in a large cohort of Chinese systemic lupus erythematosus patients. *Lupus* **20**, 1035–1041 (2011).
151. Miller, F. W., Moore, G. F., Weintraub, B. D. & Steinberg, A. D. Prevalence of thyroid disease and abnormal thyroid function test results in patients with systemic lupus erythematosus. *Arthritis Rheum.* **30**, 1124–1130 (1987).
152. Liu, Y. J., Miao, H. B., Lin, S. & Chen, Z. Association between rheumatoid arthritis and thyroid dysfunction: a meta-analysis and systematic review. *Front. Endocrinol.* **13**, 1015516 (2022).
153. Pörings, A.-S., Lowin, T., Dufner, B., Grifka, J. & Straub, R. H. A thyroid hormone network exists in synovial fibroblasts of rheumatoid arthritis and osteoarthritis patients. *Sci. Rep.* **9**, 13235 (2019).
154. Wu, Y. H. et al. Zika virus infection in hypothalamus causes hormone deficiencies and leads to irreversible growth delay and memory impairment in mice. *Cell Rep.* **25**, 1537–1547.e1534 (2018).
155. Armah, H. B. et al. Systemic distribution of West Nile virus infection: postmortem immunohistochemical study of six cases. *Brain Pathol.* **17**, 354–362 (2007).
156. Weider, T. et al. High prevalence of common human viruses in thyroid tissue. *Front. Endocrinol.* **13**, 938633 (2022).

157. Soriano, E. R. Current status and future challenges in the treatment of rheumatic diseases. *Front. Drug Saf. Regul.* https://doi.org/10.3389/fdsfr.2022.881556 (2022).
158. Rozenblyum, E. V., Allen, U. D., Silverman, E. D. & Levy, D. M. Cytomegalovirus infection in childhood-onset systemic lupus erythematosus. *Int. J. Clin. Rheumatol.* **8**, 137–146 (2013).
159. Miner, J. J. & Fitzgerald, K. A. A path towards personalized medicine for autoinflammatory and related diseases. *Nat. Rev. Rheumatol.* **19**, 182–189 (2023).
160. Beigel, J. H. et al. Remdesivir for the treatment of covid-19 — final report. *N. Engl. J. Med.* **383**, 1813–1826 (2020).
161. Lee, A. R. et al. Remdesivir alleviates joint damage in collagen-induced arthritis and inhibits inflammatory cell death of RA synovial fibroblasts. *Immunol. Lett.* **275**, 107009 (2025).
162. Perricone, C. et al. The anti-viral facet of anti-rheumatic drugs: lessons from COVID-19. *J. Autoimmun.* **111**, 102468 (2020).
163. Kalil, A. C. et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N. Engl. J. Med.* **384**, 795–807 (2021).
164. Hoang, T. N. et al. Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques. *Cell* **184**, 460–475.e421 (2021).
165. Traish, A., Bolanos, J., Nair, S., Saad, F. & Morgentaler, A. Do androgens modulate the pathophysiological pathways of inflammation? Appraising the contemporary evidence. *J. Clin. Med.* **7**, 549 (2018).
166. Amodeo, A., Persani, L., Bonomi, M. & Cangiano, B. Use of testosterone replacement therapy to treat long-COVID-related hypogonadism. *Endocrinol. Diabetes Metab. Case Rep.* **2024**, 23–0097 (2024).
167. Pencina, K. M. et al. Testosterone replacement therapy and risk of COVID-19 and effect of COVID-19 on testosterone's treatment effect. *J. Endocr. Soc.* **9**, bvaf002 (2025).
168. Qin, D. -d et al. Prolonged secretion of cortisol as a possible mechanism underlying stress and depressive behaviour. *Sci. Rep.* **6**, 30187 (2016).
169. Howren, M. B., Lamkin, D. M. & Suls, J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Biopsychosoc. Sci. Med.* **71**, 171–186 (2009).
170. Thornton, L. M., Andersen, B. L., Schuler, T. A. & Carson, W. E. I. A psychological intervention reduces inflammatory markers by alleviating depressive symptoms: secondary analysis of a randomized controlled trial. *Biopsychosoc. Sci. Med.* **71**, 715–724 (2009).
171. Astin, J. A., Beckner, W., Soeken, K., Hochberg, M. C. & Berman, B. Psychological interventions for rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Arthritis Rheum.* **47**, 291–302 (2002).
172. Knittle, K., Maes, S. & de Gucht, V. Psychological interventions for rheumatoid arthritis: examining the role of self-regulation with a systematic review and meta-analysis of randomized controlled trials. *Arthritis Care Res.* **62**, 1460–1472 (2010).
173. Prothero, L., Barley, E., Galloway, J., Georgopoulou, S. & Sturt, J. The evidence base for psychological interventions for rheumatoid arthritis: a systematic review of reviews. *Int. J. Nurs. Stud.* **82**, 20–29 (2018).
174. Peakman, M. & Dayan, C. M. Antigen-specific immunotherapy for autoimmune disease: fighting fire with fire? *Immunology* **104**, 361–366 (2001).
175. Benham, H. et al. Citrullinated peptide dendritic cell immunotherapy in HLA risk genotype-positive rheumatoid arthritis patients. *Sci. Transl. Med.* **7**, 290ra287 (2015).
176. Phillips, B. E., Garciafigueroa, Y., Engman, C., Trucco, M. & Giannoukakis, N. Tolerogenic dendritic cells and T-regulatory cells at the clinical trials crossroad for the treatment of autoimmune disease; emphasis on type 1 diabetes therapy. *Front. Immunol.* **10**, 148 (2019).
177. Selck, C. & Dominguez-Villar, M. Antigen-specific regulatory t cell therapy in autoimmune diseases and transplantation. *Front. Immunol.* **12**, 661875 (2021).
178. Li, S. et al. Applications of protein microarrays in biomarker discovery for autoimmune diseases. *Front. Immunol.* **12**, 645632 (2021).
179. Larman, H. B. et al. PhIP-Seq characterization of autoantibodies from patients with multiple sclerosis, type 1 diabetes and rheumatoid arthritis. *J. Autoimmun.* **43**, 1–9 (2013).
180. Credle, J. J. et al. Unbiased discovery of autoantibodies associated with severe COVID-19 via genome-scale self-assembled DNA-barcoded protein libraries. *Nat. Biomed. Eng.* **6**, 992–1003 (2022).
181. Carlsson, A. et al. Serum protein profiling of systemic lupus erythematosus and systemic sclerosis using recombinant antibody microarrays. *Mol. Cell. Proteom.* **10**, M110.005033 (2011).
182. Auger, I. et al. New autoantigens in rheumatoid arthritis (RA): screening 8268 protein arrays with sera from patients with RA. *Ann. Rheum. Dis.* **68**, 591–594 (2009).
183. Gross, A. J., Hochberg, D., Rand, W. M. & Thorley-Lawson, D. A. EBV and systemic lupus erythematosus: a new perspective. *J. Immunol.* **174**, 6599–6607 (2005).
184. Chen, C.-J. Epstein-Barr virus reactivation and disease flare of systemic lupus erythematosus. *Taiwan. J. Obstet. Gynecol.* **63**, 161–164 (2024).
185. Chen, C.-J. et al. High prevalence of immunoglobulin A antibody against Epstein-Barr virus capsid antigen in adult patients with lupus with disease flare: case control studies. *J. Rheumatol.* **32**, 44–47 (2005).
186. Zhang, T. et al. Clinical phenotypes and prognosis of cytomegalovirus infection in the pediatric systemic lupus erythematosus: a longitudinal analysis. *Pediatr. Rheumatol.* **21**, 25 (2023).
187. Barros, L. C. M., Lima, M. E. S., Pereira, R. M. M., Vasconcelos, L. A. A. & Rabelo, W. C. Juvenile lupus, cytomegalovirus infection and cardiac tamponade: case report. *Rev. Paul. Pediatr.* **40**, e2020291 (2021).
188. Lin, W. T. et al. Increased risk of hepatitis B virus reactivation in systemic lupus erythematosus patients receiving immunosuppressants: a retrospective cohort study. *Lupus* **27**, 66–75 (2018).
189. Chen, M. H. et al. High risk of viral reactivation in hepatitis B patients with systemic lupus erythematosus. *Int. J. Mol. Sci.* **22**, 9116 (2021).
190. Umekita, K. et al. Treatment with anti-tumor necrosis factor biologic agents in human t lymphotropic virus type I-positive patients with rheumatoid arthritis. *Arthritis Care Res.* **66**, 788–792 (2014).
191. Suzuki, T. et al. Brief report: attenuated effectiveness of tumor necrosis factor inhibitors for anti-human T lymphotropic virus type I antibody-positive rheumatoid arthritis. *Arthritis Rheumatol.* **70**, 1014–1021 (2018).
192. Umekita, K. & Okayama, A. HTLV-1 infection and rheumatic diseases. *Front. Microbiol.* **11**, 152 (2020).

Acknowledgements
W.C. is supported by the Cleveland Clinic Catalyst Award (CCG0336).

Author contributions
W.C. and S.-S.F. contributed to the conceptualization of the manuscript. All authors researched, compiled data and wrote the manuscript. All authors contributed substantially to the discussion of the content and reviewed the final manuscript before submission.

Competing interests
The authors declare no competing interests.

Additional information
Peer review information *Nature Reviews Rheumatology* thanks Siew-Wai Fong, Jean Roudier and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

nature reviews rheumatology

https://doi.org/10.1038/s41584-025-01329-3

Consensus statement

Check for updates

Consensus definitions of complex-to-manage and treatment-refractory psoriatic arthritis: a GRAPPA initiative

Fabian Proft[1,23] ✉, Andre L. Ribeiro[2,3,23], Shikha Singla[4], Vinod Chandran[5,6,7], Wilson Liao[8], Christine Lindsay[9], Enrique R. Soriano[10], Tina Bhutani[8], Atul Deodhar[11], Kurt de Vlam[12,13], Lihi Eder[6,14], Mitsumasa Kishimoto[15], Ying Ying Leung[16], Ennio Lubrano[17], Dennis McGonagle[18], Denis Poddubnyy[1,5,6], Laura Savage[19], Filip Van den Bosch[20,21] & Philip Mease[22]

Abstract

Despite advances in the treatment of psoriatic arthritis (PsA), a substantial proportion of patients continue to report persistent symptoms and impaired quality of life. However, terminology remains inconsistent for patients who fail to achieve disease control despite treatment, which limits research comparability and contributes to therapeutic inertia. To address this gap, a Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) task force developed consensus definitions for two distinct states: complex-to-manage PsA (C2M-PsA) and treatment-refractory PsA (TR-PsA). C2M-PsA is defined as a state of persistent symptoms despite treatment with at least one biologic or targeted synthetic DMARD (b/tsDMARD), extending beyond biological non-response to include factors such as comorbidities, overlapping conditions, psychosocial burden and treatment-related challenges (for example, non-adherence). TR-PsA, a more specific subset of C2M-PsA, is characterized by failure of at least three therapies with distinct mechanisms of action (including at least two biologic/targeted synthetic DMARDs), persistent symptoms considered problematic by both patient and clinician, and objective evidence of ongoing inflammation — after ruling out alternative explanations for treatment refractoriness. These consensus-derived GRAPPA definitions provide a shared framework to standardize terminology, support individualized care, and improve patient stratification in research and practice. Prospective validation across diverse settings and phenotypes is needed to confirm their reliability, responsiveness and clinical utility.

Sections

A full list of affiliations appears at the end of the paper. ✉e-mail: Fabian.Proft@charite.de

Introduction

Psoriatic arthritis (PsA) is a chronic, immune-mediated disease characterized by musculoskeletal and extra-musculoskeletal manifestations, including peripheral arthritis, enthesitis, dactylitis, axial involvement, and skin and nail psoriasis, as well as associated conditions such as uveitis and inflammatory bowel disease[1,2]. Management of PsA is further complicated by frequent comorbidities, such as metabolic syndrome, cardiovascular diseases, anxiety, depression and fibromyalgia, all of which contribute to an increased disease burden and therapeutic challenges[3–5]. This heterogeneity hinders accurate disease monitoring, individualized care and treat-to-target strategies in routine practice.

Over the past two decades, the PsA treatment landscape has evolved substantially with the approval of numerous biologic and targeted synthetic DMARDs (b/tsDMARDs), which inhibit different molecular targets and inflammatory pathways[6]. These include inhibitors of tumor necrosis factor (TNF), interleukin-12 (IL-12)–IL-23, IL-17, IL-23, phosphodiesterase-4 (PDE4), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and Janus kinases (JAKs)[6]. In response to these developments, treatment recommendations from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and European Alliance of Associations for Rheumatology (EULAR) have evolved accordingly, adopting a domain-based, patient-centred approach[7,8].

These recommendations generally support the use of conventional synthetic DMARDs (csDMARDs) as initial therapy in selected domains, such as peripheral arthritis, with escalation to b/tsDMARDs in cases of inadequate response. In cases of axial involvement or severe enthesitis, early initiation of b/tsDMARDs is often warranted when available. Importantly, the GRAPPA recommendations avoid rigid treatment hierarchies and a one-size-fits-all approach, instead emphasizing clinical flexibility, shared decision-making, regular assessment of treatment response and domain-specific treatment adjustments. Nonetheless, they do not define how many prior treatment failures constitute therapeutic refractoriness, underscoring the need for standardized criteria.

Despite these therapeutic advancements, a 2020 systematic review and meta-analysis reported that fewer than 30% of people with PsA achieve remission when assessed by composite measures, and up to 50% report residual symptoms despite treatment[9]. These findings highlight the unmet needs in PsA care and have prompted increasing attention to the concept of patients who are 'difficult to treat' (D2T). In the absence of standardized terminology, these patients are variably referred to as 'refractory', 'treatment-resistant', 'D2T' or 'complex', depending on context and clinical perception. This lack of uniformity limits the comparability of studies and impairs the design of clinical trials, ultimately contributing to therapeutic inertia.

Estimates of the prevalence of treatment-refractory (TR) PsA vary considerably, depending on the specific criteria used. When applying the EULAR definition of D2T rheumatoid arthritis (D2T-RA) — which requires failure of at least two b/tsDMARDs with distinct mechanisms of action (MoAs), evidence of active and/or progressive disease, and problematic management as perceived by the clinician and/or patient[10] — prevalence in PsA cohorts is ~16–30%[11–13]. However, the transferability of these criteria to PsA is questionable. Unlike RA, PsA is a multidomain disease with substantial clinical and pathophysiological heterogeneity, distinct treatment pathways, and a complex interplay of skin and joint involvement, mechanical stress, obesity and metabolic syndrome, mental health, and lifestyle factors[14]. The application of RA-derived criteria can overlook or misclassify important subgroups within the PsA spectrum — for example, patients with a predominant enthesitis phenotype — thereby reinforcing the need for disease-specific definitions that better reflect disease complexity and patient experience[15]. Thus, the heterogeneity of PsA mandates a framework that captures both biologic treatment failure and the broader contextual complexity of disease management.

Recognizing these unmet needs[16,17], the GRAPPA D2T-PsA task force initiated a structured, multi-phase initiative to define more precisely the spectrum of patients whose disease is particularly complex-to-manage (C2M-PsA) or TR-PsA[18]. This project integrates perspectives from clinicians, health care professionals (HCPs), and — critically — patients, reflecting a shared-decision model of care that is central to GRAPPA's philosophy.

The primary aim of this project was to develop consensus-based definitions for C2M-PsA and TR-PsA. To ensure that these definitions were grounded in empirical evidence and informed by diverse stakeholder perspectives, the project incorporated three key components to guide the consensus process: a review of existing terminology and conceptual frameworks related to TR-PsA and difficult-to-treat-PsA; a survey of HCPs to identify real-world challenges in PsA management; and an analysis of international patient-reported data to capture emotional, psychosocial and contextual factors contributing to treatment complexity or failure. This Consensus Statement presents the resulting consensus definitions for C2M-PsA and TR-PsA, which are intended to support shared clinical decision making and to enable more effective patient stratification in both observational studies and clinical trials.

Methods

Steering committee and working group

The development of these definitions began in March 2023 with the approval of the project from the GRAPPA Research Committee and the subsequent establishment of a dedicated steering committee and working group, together forming the GRAPPA D2T-PsA task force. The steering committee included two project co-leads (F.P. and P.M.), two Young-GRAPPiAns (A.L.R. and S.S.), a rheumatologist (V.C.), a dermatologist (W.L.) and a patient research partner (PRP; C.L.). The broader working group consisted of an additional 12 individuals, including 10 rheumatologists and 2 dermatologists (Supplementary Fig. 1).

The project started with a scoping literature review to explore existing definitions and terminologies related to refractory PsA[19]. This review was followed by two complementary surveys, one capturing the perspectives of HCPs[20] and the other focusing on insights from patients[21]. These findings informed the steering committee in the development of preliminary definitions and proposed terminology for C2M-PsA and TR-PsA. These initial drafts were presented at the first task-force meeting, where discussions centred on refining the definitions around three core components: treatment failure history, characterization of active and/or symptomatic disease, and disease perception.

Scoping literature review

A scoping literature review was conducted in July 2023 to identify existing terminologies, definitions and criteria applied to the concept of D2T-PsA and TR-PsA. The search was carried out in the PubMed, Embase, and Web of Science databases for articles published between January 2000 and September 2022, using combinations of terms including "psoriatic arthritis", "difficult to treat", "refractory", "resistant" and related descriptors. To broaden the scope, both investigators (A.L.R. and S.S.) independently screened all titles and abstracts from

the most recent major international conferences: ACR Convergence 2022 and EULAR Congress 2023. Discrepancies were resolved by a third investigator (F.P.). The full findings of this review have been published separately[19].

Group for Research and Assessment of Psoriasis and Psoriatic Arthritis health care professionals survey

An international, web-based survey was developed by the working group and disseminated to all GRAPPA members between June and September 2023. Eligible participants were HCPs involved in PsA care. The survey included demographic questions, structured multiple-choice items on proposed criteria, and open-ended questions to capture qualitative insights. Survey development involved iterative rounds of review and input from both clinician-investigators and PRPs. Responses were analysed using descriptive statistics and thematic qualitative analysis. A detailed account of the methodology and results has been published separately[20].

Group for Research and Assessment of Psoriasis and Psoriatic Arthritis patient survey

A parallel international survey targeting people with lived experience of PsA was conducted between October 2023 and January 2024, with the aim of identifying patient-perceived features related to treatment ineffectiveness. The questionnaire was developed in English and translated into nine languages (Chinese, Dutch, French, German, Italian, Japanese, Portuguese, Spanish and Turkish). It included both structured items and free-text responses. The survey was distributed electronically with support from patient organizations and GRAPPA PRPs. A medical anthropologist contributed to the analysis, which employed a mixed-methods approach combining quantitative summaries with qualitative content analysis. The full dataset and analysis were published in a separate manuscript[21].

Task force meetings and Delphi consensus round

Between March 2023 and December 2024, the GRAPPA D2T task force conducted a structured, multi-phase consensus process to develop and refine definitions for C2M-PsA and TR-PsA. The process began with a dedicated kick-off meeting in March 2023, followed by feedback discussions at the GRAPPA Annual Meeting (July 2023) and a roundtable dialogue at ACR Convergence (November 2023). Findings from the scoping literature review, expert survey and patient survey were synthesized and discussed within the task force. Between March and November 2024, a series of structured virtual task force meetings took place, complemented by broader stakeholder engagement during the EULAR 2024 Congress, where the draft framework was discussed. Additional input was obtained during the GRAPPA Collaborative Research Network (CRN) meeting with industry representatives and during a dedicated GRAPPA Membership session at the 2024 Annual Meeting. From August to November 2024, the Steering Committee convened several virtual meetings to further refine the definitions and incorporate multidisciplinary feedback. Two formal Delphi rounds were conducted between August and November 2024 to evaluate the proposed definitions, overarching statements and clarifying statements. These items were initially drafted by the steering committee based on evidence from the literature review and survey findings, and were subsequently refined through structured discussions with the full task force. In each Delphi round, task force members were asked to indicate their agreement with each item using a binary response format ("agree" or "not agree"). Items that did not reach the predefined consensus threshold of ≥ 75% agreement in round 1 were revised by the steering committee, drawing on qualitative feedback from free-text comments submitted during the online voting and follow-up virtual task force discussions. The revised items were then redistributed for a second round of voting using the same response format. The final task force proposals were subsequently presented and discussed at the GRAPPA-Adjacent-to-ACR meeting (November 2024) and submitted for full GRAPPA membership voting in December 2024.

The final endorsed definitions were presented at the EULAR 2025 Congress[22], concluding the consensus process and establishing a framework co-developed with patients, clinicians, researchers and industry stakeholders. Supplementary Fig. 2 summarizes the process.

Development of the definitions of complex-to-manage and treatment-refractory psoriatic arthritis

Scoping literature review

The scoping review[19] identified 565 articles, including 15 publications that directly or indirectly addressed the concept of refractory PsA. Most studies did not apply standardized definitions; instead, terminology varied substantially across publications. Commonly used descriptors included "refractory", "multi-resistant", "complex" and "non-responding", often applied without predefined criteria. Key features reported in these studies included exposure to multiple b/tsDMARDs, persistent disease activity across domains, presence of comorbidities and low treatment satisfaction. The review underscored the conceptual heterogeneity and the absence of disease-specific criteria, emphasizing the need for standardized, PsA-specific definitions.

Health care professionals survey

A total of 223 responses from 47 countries were included in the HCP survey[20]. Respondents were mostly rheumatologists (80.2%) and dermatologists (17.9%) from Europe (45.7%), Latin America (18.8%) and North America (18.3%). Most respondents supported distinguishing between TR-PsA (or D2T-PsA) and C2M-PsA (82.9%), associating the former with ongoing inflammation and treatment failure and the latter with contextual challenges despite controlled inflammation. A large majority (90.6%) also emphasized the need for objective markers of inflammation in defining TR-PsA. However, there was no consensus on the number of treatment failures required, with suggestions ranging from one to four or more b/tsDMARDs.

Importantly, the shift towards the terminology 'complex-to-manage' was driven by early and meaningful involvement of PRPs. During preparatory meetings for the survey design, the initial term 'difficult-to-manage' was initially selected. However, particularly when discussing the project with the PRPs, they expressed concern that the label 'difficult-to-manage' carried unintended negative connotations. They felt that this phrasing risked assigning blame or stigma to patients, potentially reinforcing perceptions of non-adherence or psychological resistance. In response, the steering committee formally adopted the alternative term 'complex-to-manage', which was viewed as more respectful, neutral and aligned with a biopsychosocial understanding of the disease.

Patient survey

A total of 570 patients with PsA completed the multilingual survey[21]. Fatigue, pain and functional limitation were among the most commonly cited reasons for treatment dissatisfaction. Ranking analysis also showed the negative impact of peripheral arthritis, axial disease,

chronic pain, comorbidities and fatigue. Thematic analysis of open responses confirmed a high emotional burden and frequent reference to frustration with ineffective treatment changes, poor communication and lack of individualized care. These insights emphasized the patient-perceived mismatch between clinical assessment and real-world disease experience. Additionally, there were meaningful language-specific differences in patient narratives, emphasizing the need for culturally sensitive communication and definitions. The prominence of these findings aligns with the multidimensional burden captured in the C2M-PsA definition.

Task-force meetings

Findings from the literature review and surveys were presented and discussed during task-force meetings. Members reached initial agreement on key conceptual elements, including the need for a multidimensional, domain-inclusive definition that balances treatment history, persistent disease activity and contextual factors. Feedback from breakout groups revealed tensions regarding how to weigh subjective symptoms versus objective findings and the relevance of comorbidities. As a result, an initial framework was proposed that grouped the construct into three core domains: objective inflammation, patient-reported disease impact and complicating contextual features.

Drafting and endorsement of the definitions and overarching statements

To capture the broader challenges encountered in clinical management beyond objective inflammation, and in acceptance of feedback from PRPs, the steering committee adopted the term 'complex-to-manage psoriatic arthritis' (C2M-PsA). This terminology aligns conceptually with similar initiatives, such as the Assessment of SpondyloArthritis International Society (ASAS) definition of D2T axial spondyloarthritis, and reflects the multifactorial nature of disease burden in spondyloarthritis and in PsA[23,24]. C2M-PsA includes patients with persistent symptoms that are not solely attributable to active inflammation, but also to other contributing mechanisms such as comorbidities, psychosocial factors and high subjective symptom burden. To specifically address the subgroup of patients with true biological non-response and ongoing objective inflammation, the term 'treatment-refractory PsA' (TR-PsA) was endorsed to characterize those with persistent disease activity despite multiple therapeutic interventions.

The final terminology, definitions, conceptual framework and overarching statements were voted on by 184 GRAPPA members, including 140 full members, 37 early-career members, 6 PRPs and 1 advanced practice provider. In this final phase, 95.1% of participants (n = 175) endorsed the proposal, confirming strong community support and leading to the formal adoption of the C2M-PsA and TR-PsA definitions along with the overarching principles (Table 1).

Overarching statements, definitions and clarifying statements

Overarching principles

The five overarching statements provide a conceptual framework to distinguish between complex contextual challenges and true therapeutic resistance in PsA (Fig. 1), serving as a clinical guide for applying the C2M-PsA and TR-PsA definitions in practice (Fig. 2).

Overarching statement 1: Psoriatic arthritis is a heterogeneous disease that requires multidisciplinary care; treatment decisions should involve shared decision making, addressing the individual patient holistically. PsA is a clinically heterogeneous condition that affects multiple domains — including skin and nails, musculoskeletal system, eyes, gastrointestinal tract and mental health. Optimal management of PsA requires a multidisciplinary team approach and treatment decisions guided by shared decision-making. Care should be individualized, addressing both the physical and psychological dimensions of disease burden. Socioeconomic and systemic barriers – such as limited access to care, insurance coverage, diagnostic delays and misinformation regarding the disease and/or its treatment – further complicate management and underscore the need for patient-centred and equitable models of care[25].

Overarching statement 2: Management of psoriatic arthritis should consider all potentially affected disease domains and be guided by shared decision-making and predefined treatment targets; composite disease activity scores may serve as supportive tools, but it is essential to recognize that some psoriatic arthritis manifestations may not be fully captured by these scores. Effective management of PsA requires systematic assessment of all potentially affected domains. Although treatment should follow predefined targets, there is no universally accepted end point, and treatment goals should be established collaboratively with the patient[26].

Composite disease activity scores can aid clinical decision-making, but none fully capture the multidimensional nature of PsA or encompass the entire GRAPPA core domain set[27,28]. They should therefore complement, rather than replace, individualized assessment of each domain. Moreover, these scores can occasionally reflect factors unrelated to PsA activity, potentially leading to misinterpretation. Selection and interpretation of these assessment tools should be guided by the patient's specific clinical features and priorities.

Overarching statement 3: A lack of, or inadequate response to, recommended psoriatic arthritis treatments at adequate dosing and over an appropriate length of time, should prompt a re-evaluation of the diagnosis and consideration of the presence of comorbidities or other factors contributing to treatment non-response. For this statement, 'recommended PsA treatments' are according to the current GRAPPA management recommendations. This statement underscores the importance of reassessing both PsA diagnosis and potential treatment barriers in cases of inadequate response (examples are described in Supplementary Table 1). When patients do not improve despite appropriate therapy, clinicians should investigate other contributors such as comorbidities, overlapping conditions, poor adherence or alternative diagnoses[29,30]. This structured re-evaluation aligns with the GRAPPA guidelines and supports a more personalized approach to treatment-resistant cases[7].

Overarching statement 4: Reasons for inadequate treatment responses can be classified into complex-to-manage psoriatic arthritis, a broader and more heterogenous group that includes factors such as comorbid conditions, persistent symptoms despite effective control of inflammation, and significant impacts on the quality of life; within this larger group, treatment-refractory psoriatic arthritis constitutes a smaller, specific subgroup characterized by inadequate treatment response and objective evidence of ongoing inflammation despite multiple attempted therapeutic strategies. For this statement, the factors related to C2M-PsA (Supplementary Table 1) include, but are not limited to, mal-adherence, chronic pain, comorbidities and fibromyalgia.

Table 1 | Overarching principles and definitions for complex-to-manage and treatment-refractory psoriatic arthritis

Principle or definition	Content	Level of agreement by the task force
Overarching principles		
Overarching statement 1	PsA is a heterogeneous disease that requires multidisciplinary care; treatment decisions should involve shared decision making, addressing the individual patient holistically	100%
Overarching statement 2	Management of PsA should consider all potentially affected disease domains and be guided by shared decision making and predefined treatment targets; composite disease activity scores may serve as supportive tools, but it is essential to recognize that some PsA manifestations may not be fully captured by these scores	100%
Overarching statement 3	A lack of, or inadequate response to, recommended PsA treatments[a] at adequate dosing and over an appropriate length of time, should prompt a re-evaluation of the diagnosis and consideration of the presence of comorbidities or other factors contributing to treatment non-response	100%
Overarching statement 4	Reasons for inadequate treatment response can be classified into C2M-PsA, a broader and more heterogenous group that includes factors[b] such as comorbid conditions, persistent symptoms despite effective control of inflammation and significant impacts on the quality of life; within this larger group, TR-PsA constitutes a smaller, specific subgroup characterized by objective evidence of ongoing inflammation despite multiple attempted therapeutic strategies	94%
Overarching statement 5	For the definition of TR-PsA, the presence of objective evidence of ongoing inflammation in affected domains is required: arthritis[c], dactylitis[c], enthesitis[c,d], or skin/nail disease (by inflammation-sensitive imaging modalities for axial disease, or through laboratory assessments[e] such as acute-phase reactants or synovial-fluid analysis) must be present in patients with persistent symptoms and inadequate response to treatment	89%
Definitions of C2M-PsA and TR-PsA		
Definition of C2M-PsA	C2M-PsA is a disease state[f] characterized by persistent symptoms despite at least one adequate trial of a bDMARD or tsDMARD recommended[a] for PsA treatment; this category extends beyond pure biological non-response to also include factors[g] such as comorbidities, overlapping conditions and treatment-related challenges	89%
Definition of TR-PsA	TR-PsA is a state[h] defined as the failure to respond to ≥ 3 previous treatments for PsA[i] with different modes of action (including ≥ 2 b/tsDMARDs), AND persistent symptoms perceived as problematic by both the treating clinician and the patients, AND the presence of objective evidence of ongoing inflammation	100%

bDMARD, biologic DMARD; C2M, complex-to-manage; csDMARD, conventional synthetic DMARD; D2T, difficult-to-treat; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; MSUS, musculoskeletal ultrasonography; PsA, psoriatic arthritis; TR, treatment refractory; tsDMARD, targeted synthetic DMARD. [a]According to the current GRAPPA management recommendations. [b]Factors including, but not limited to, mal-adherence, chronic pain, comorbidities and fibromyalgia. [c]If clinical evaluation is inconclusive, confirmation with inflammation-sensitive imaging (MSUS or MRI) is recommended. [d]If enthesitis is the only sign of active disease, confirmation with inflammation-sensitive imaging is recommended. [e]Other causes of elevated acute-phase reactants or a high cell-count in synovial fluid must be excluded. [f]That a PsA patient is in a C2M state can be acknowledged by the treating clinician and/or the patient in the case of treatment inefficacy and signs/symptoms regarded as problematic. [g]Comorbidities, overlapping conditions, chronic pain, non-adherence, treatment side effects, socioeconomic or psychological barriers, etc. [h]That a PsA patient is in a TR state must be recognized by both the clinician and the patient in the case of treatment inefficacy and signs/symptoms regarded as problematic. [i]csDMARDs, tsDMARDs or bDMARDs according to the current GRAPPA management recommendations.

This statement introduces a critical differentiation within the spectrum of challenging PsA cases (Fig. 1). Inadequate treatment response can be used to categorize patients into the broader and more heterogeneous group of C2M-PsA, which includes factors such as comorbid conditions, persistent symptoms despite effective control of inflammation and substantial impacts on quality of life. Within this broader group, a more specific subset, TR-PsA, is characterized by objective evidence of ongoing inflammation despite multiple attempted therapeutic strategies. This framework enables clinicians to better stratify patients and tailor interventions to both biological and contextual complexities.

Overarching statement 5: For the definition of treatment-refractory psoriatic arthritis, the presence of objective evidence of ongoing inflammation in affected domains is required: arthritis, dactylitis, enthesitis, or skin/nail disease (by inflammation-sensitive imaging modalities for axial disease, or through laboratory assessmentse such as acute-phase reactants or synovial-fluid analysis) must be present in patients with persistent symptoms and inadequate response to treatment. For the definition of TR-PsA, if clinical evaluation of arthritis, dactylitis, enthesitis or skin and/or nail disease is inconclusive, confirmation with inflammation-sensitive imaging (musculoskeletal ultrasonography (MSUS) or MRI) is recommended. If enthesitis is the only sign of active disease, confirmation with inflammation-sensitive imaging is recommended. With regard to laboratory assessments, other causes of elevated acute phase reactants or a high cell-count in synovial fluid must be excluded.

The final overarching statement establishes objective criteria for defining TR-PsA. It reinforces that confirmation of TR-PsA must go beyond symptoms and include verifiable signs of inflammation in at least one domain. Because both peripheral and axial PsA manifestations can be difficult to assess clinically[31,32], inflammation-sensitive imaging modalities, such as MSUS or MRI, have a key role in evaluating disease activity. Laboratory parameters such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can also support the TR-PsA definition, although they are elevated in only about half of PsA cases[33,34]. The task force emphasizes the importance of a comprehensive assessment, accounting for the limitations of isolated biomarkers and ensuring the exclusion of non-inflammatory causes of elevated inflammation (for example, infection or adiposity) or abnormal MSUS[35–37].

Definitions of complex-to-manage and treatment-refractory psoriatic arthritis

Definition of complex-to-manage refractory psoriatic arthritis: 'Complex-to-manage psoriatic arthritis' is a disease state characterized by persistent symptoms despite at least one adequate trial

of a biologic DMARD or targeted synthetic DMARD recommended for psoriatic arthritis treatment; this category extends beyond pure biological non-response to also include factors such as comorbidities, overlapping conditions and treatment-related challenges. That a patient with PsA is in a C2M state can be acknowledged by the treating clinician and/or the patient in the case of treatment inefficacy and signs and/or symptoms regarded as problematic.

For this definition, 'recommended PsA treatments' are treatments that are recommended according to the current GRAPPA management recommendations. The C2M-PsA category includes factors including, but not limited to, comorbidities, overlapping conditions, chronic pain, non-adherence, treatment side effects, socioeconomic or psychological barriers (Supplementary Table 1).

The task force acknowledges that C2M-PsA is a dynamic state that can improve with appropriate interventions. Many factors could lead to this complex presentation, including mental-health issues, chronic-pain syndromes, or logistical barriers to accessing care (see Supplementary Table 1). Recognizing this variability, the inclusion criterion of failure of at least one approved treatment is aimed at capturing both ends of the spectrum: from patients with longstanding complexity to those who might surprise clinicians with an unexpectedly positive response to initial therapy.

This category underscores the multifactorial nature of PsA management challenges and the need for flexible, adaptive care strategies[38,39]. C2M-PsA can be identified from either the clinician's or the patient's perspective, supporting a holistic approach that maximizes the potential for meaningful improvement (Supplementary Fig. 3).

Definition of treatment-refractory psoriatic arthritis: 'Treatment-refractory psoriatic arthritis' is a disease state defined as the failure to respond to ≥3 previous treatments for PsA with different modes of action (including ≥2 biologic/targeted synthetic DMARDs), AND persistent symptoms perceived as problematic by both the treating clinician and the patient, AND the presence of objective evidence of ongoing inflammation. That a PsA patient is in a TR state must be recognized by both the clinician and the patient in the case of treatment inefficacy and signs and/or symptoms regarded as problematic. 'Previous treatments for PsA' refers to csDMARDs or b/tsDMARDs according to the current GRAPPA management recommendations.

TR-PsA represents a more stringent subset within the broader construct of C2M-PsA, and specifically identifies patients with therapeutic resistance due to persistent active inflammation (Fig. 2, Supplementary Fig. 4). The first criterion addresses persistent PsA-related symptoms. The second criterion refers to treatment failure across multiple agents with different MoAs. The third criterion emphasizes a high symptom burden acknowledged by both clinician and patient. The fourth criterion requires objective confirmation of active inflammation, which can be done via clinical examination (for example, swollen joints or active skin disease), imaging (by MSUS or MRI, especially for isolated axial disease or enthesitis), or by laboratory markers (for example, increased CRP or synovial-fluid analysis). This confirmation is necessary to distinguish inflammatory disease from mimickers such as fibromyalgia, hypermobility syndrome or mechanical pain[40,41]. Finally, alternative explanations for the four criteria must be carefully evaluated and excluded before fulfilling the definition of TR-PsA.

The requirement of inadequate response to at least three therapies, with at least two being b/tsDMARDs, was strongly supported during the Delphi consensus. Although clinicians usually initiate treatment with a csDMARD, often leading to a good response, in other situations a b/tsDMARD might be started directly, particularly for those presenting to dermatologists with severe skin disease, or for those with axial involvement or associated conditions, which typically do not respond well to treatment with csDMARDs. Therefore, prior exposure to csDMARDs is not mandatory for meeting the definition of TR-PsA. Instead, the emphasis is on an inadequate response to treatments with different MoAs, ensuring that the classification captures true therapeutic resistance regardless of treatment sequence (see the clinical vignettes provided in Supplementary Box 1).

Importantly, treatment intolerance or discontinuation due to adverse events should not be counted towards the definition of TR-PsA, as these scenarios do not reflect resistance to therapy. This distinction reinforces the notion that TR-PsA is defined by biological non-response with active inflammation despite adequate therapeutic trials. Moreover, given the expanding landscape of therapeutics targeting distinct immunopathogenic pathways across PsA domains, a threshold of at least three targeted treatments was considered both clinically appropriate, to enhance specificity, and sensitive, to identify patients in whom multiple treatment options have failed without achieving adequate disease control.

Finally, recognizing the importance of defining a specific time frame to ascertain TR-PsA status, the task force concluded that additional evidence is needed to support a consensus owing to the complexity of evaluating treatment responses across diverse therapies. This gap highlights an important area for future research, as well as the need to differentiate between primary and secondary treatment failure (Table 2).

Clarifying statements

Following the formal endorsement of the terminology and proposed framework, a series of clarifying statements were drafted and voted upon by the task force to further delineate the boundaries and operationalization of the C2M-PsA and TR-PsA definitions. These statements were designed to resolve areas of ambiguity and guide their consistent application in clinical and research settings.

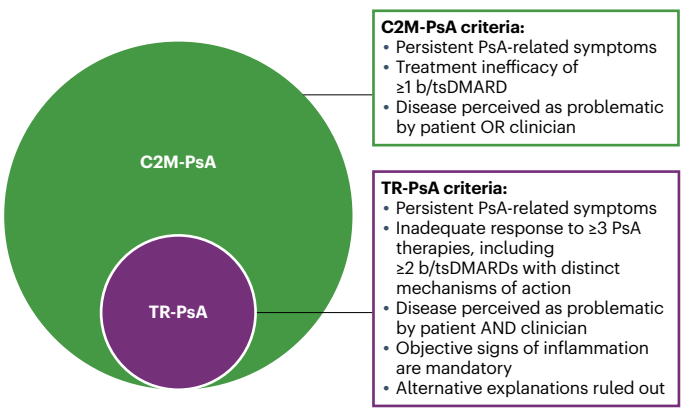


Fig. 1 | Interplay between complex-to-manage and treatment-refractory psoriatic arthritis. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) consensus definitions define two distinct states of psoriatic arthritis (PsA) in the context of inadequate response to treatment: complex-to-manage PsA (C2M-PsA) and treatment-refractory PsA (TR-PsA). b/tsDMARD), biologic or targeted synthetic DMARD.

Clarifying statement 1: complex-to-manage psoriatic arthritis. That a patient with PsA is in a C2M state can be acknowledged by the treating clinician and/or the patient in the case of treatment inefficacy and signs and/or symptoms regarded as problematic. This statement reached 89% agreement within the task force.

Clarifying statement 2: treatment-refractory psoriatic arthritis. That a patient with PsA is in a TR state must be recognized by both the clinician and the patient in the case of treatment inefficacy and signs and/or symptoms regarded as problematic. This statement reached 94% agreement within the task force.

Clarifying statement 3: comorbid conditions. Active disease of associated conditions (such as acute anterior uveitis or inflammatory bowel disease) will also contribute to TR-PsA and should ideally be assessed by the appropriate specialist (e.g. ophthalmologist, gastroenterologist) as part of a multidisciplinary approach that includes the rheumatologist. This statement reached 89% agreement within the task force.

Clarifying statement 4: minimum duration of therapy. The minimal treatment duration of treatment with a b/tsDMARD before assessing treatment failure should be 12–24 weeks according to the MoA. This statement reached 94% agreement within the task force. For C2M-PsA only, this minimum treatment duration does not apply when therapy is discontinued owing to intolerance or adverse effects.

Clarifying statement 5: exclusion criteria for treatment-refractory psoriatic arthritis. Reasons such as contraindications, intolerance, lack of access to treatment, and non-adherence will be incorporated only into the C2M-PsA definition, in order to ensure that the TR-PsA group is as pure as possible and that the TR-PsA definition truly reflects 'treatment-refractory' disease with persistent inflammation. This statement reached 100% agreement within the task force.

Discussion

This project represents the first formal effort to develop consensus definitions for C2M-PsA and TR-PsA. These definitions are aimed at standardizing terminology, improving patient stratification and

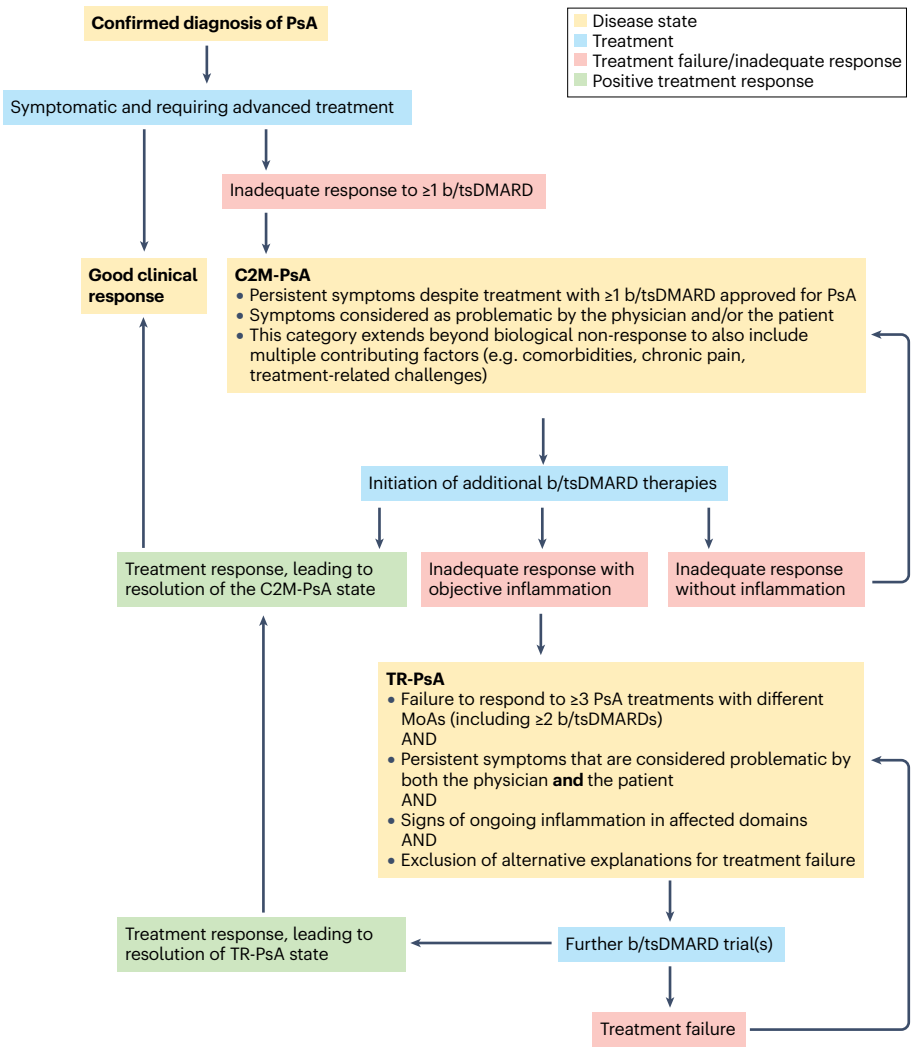


Fig. 2 | Classification of treatment failure in psoriatic arthritis and definitions of complex-to-manage and treatment-refractory psoriatic arthritis. This algorithm illustrates the classification of treatment failure in psoriatic arthritis (PsA), with emphasis on the definitions of complex-to-manage PsA (C2M-PsA) and treatment-refractory PsA (TR-PsA). Patients with a confirmed diagnosis of PsA who remain symptomatic despite advanced therapy are assessed for treatment response. C2M-PsA is defined as a state involving persistent symptoms, considered problematic by the rheumatologist and/or the patient, following inadequate response to at least one biologic or targeted synthetic DMARD (b/tsDMARD), and can be driven by multiple contributing factors. TR-PsA is a more specific subset of C2M-PsA, characterized by failure of three or more therapies with different mechanisms of action (MoAs) (including at least two b/tsDMARDs), persistent symptoms acknowledged by both clinician and patient as problematic, and objective evidence of ongoing inflammation with exclusion of alternative explanations.

Table 2 | Research agenda for complex-to-manage refractory psoriatic arthritis and treatment-refractory psoriatic arthritis

Agenda item	Research priority	Rationale
1. Definitions and timeframes		
1.1	Define optimal treatment duration thresholds by specific mechanism of action	Determine the minimal exposure time needed to assess treatment effect or failure for csDMARDs, bDMARDs and tsDMARDs based on pharmacodynamics and expected onset of action
1.2	Establish time frame criteria for classifying C2M-PsA and TR-PsA	Define the required duration of persistent symptoms, treatment resistance and the allowable window for treatment failures to accumulate
1.3	Differentiate between primary and secondary treatment failure	Clarify whether early (primary) versus delayed (secondary) non-response indicates different underlying mechanisms or requires different management
1.4	Define 'rapid radiographic progression' in PsA	Identify meaningful structural changes and optimal imaging intervals for monitoring radiographic damage
1.5	Use real-world data to define C2M-PsA duration thresholds	Empirically assess the time needed for symptoms or complexity to persist before confirming a C2M-PsA classification
2. Epidemiology and predictors		
2.1	Assess the frequency and distribution of C2M-PsA and TR-PsA	Use registry and cohort data to quantify prevalence and trends across care settings
2.2	Identify predictive factors for C2M-PsA and TR-PsA at treatment initiation	Assess clinical, demographic and biomarker variables associated with increased risk
2.3	Develop and validate a C2M-PsA and TR-PsA risk stratification tool	Build practical tools to help clinicians to identify high-risk patients early in the disease course
2.4	Examine sex and gender differences in C2M-PsA and TR-PsA	Explore differences in presentation, response and outcomes between male and female patients
2.5	Investigate ethnic, socioeconomic, and geographic disparities	Address inequalities in access, outcomes and disease burden across populations
3. Mechanistical understanding		
3.1	Study the role of chronic-pain mechanisms and central sensitization in C2M-PsA	Differentiate non-inflammatory contributors such as fibromyalgia or nociplastic pain
3.2	Elucidate domain-specific pathophysiological mechanisms in TR-PsA	Investigate how different domains (e.g. axial, entheseal, skin) contribute to treatment resistance
3.3	Identify immunological and molecular signatures of TR-PsA	Use transcriptomic, cytokine or cell profiling to define biological endotypes
3.4	Explore microbiome and metabolomic signatures in C2M-PsA and TR-PsA	Investigate the role of the gut–skin–joint axis and metabolic dysregulation as potential contributors to treatment failure and persistent symptoms
3.5	Investigate genetic susceptibility markers associated with C2M-PsA and TR-PsA	Identify genetic polymorphisms or HLA associations that may predispose patients to a more complex or refractory disease course
4. Assessment and outcomes		
4.1	Validate the C2M-PsA and TR-PsA definitions in independent cohorts	Test reproducibility and clinical utility in registries, observational cohorts and trials
4.2	Optimize outcome measures for C2M-PsA and TR-PsA	Determine how composite scores (e.g. PASDAS, DAPSA) and domain-specific tools can be integrated to assess complex disease
4.3	Explore patient–clinician discordance in disease perception	Assess how differences in perceived disease burden affect classification, satisfaction and outcomes
4.4	Develop digital and wearable-based outcome tracking for complex disease	Assess the feasibility of integrating continuous monitoring tools (e.g. mobile apps, wearables) to capture fluctuations in symptoms and function in real-world settings
4.5	Characterize long-term outcomes and disease trajectories in C2M-PsA and TR-PsA	Use longitudinal cohort data to define prognosis, flares and functional decline in patients with persistent complexity or refractory inflammation
5. Management and implementation		
5.1	Define optimal therapeutic strategies for C2M-PsA and TR-PsA	Assess whether treatment escalation, switching, or combination therapies are most effective for each subgroup
5.2	Study the impact of adherence and drug survival patterns on progression to C2M-PsA and TR-PsA	Understand how adherence behaviour influences disease trajectory and classification
5.3	Evaluate the feasibility and impact of multidisciplinary care models	Test whether integrated care involving rheumatologists, dermatologists, psychologists, physiotherapists etc. improves outcomes

Table 2 (continued) | Research agenda for complex-to-manage refractory psoriatic arthritis and treatment-refractory psoriatic arthritis

Agenda item	Research priority	Rationale
5. Management and implementation (continued)		
5.4	Assess the economic and health care system burden of C2M-PsA and TR-PsA	Quantify direct and indirect costs, resource utilization and work disability
5.5	Conduct strategy trials specifically targeting C2M-PsA and TR-PsA populations	Design trials comparing treatment sequences, treat-to-target protocols, or response-guided approaches to optimize care pathways in complex or refractory PsA
5.6	Evaluate the safety and efficacy of dual- or combination-therapy regimens	Investigate whether combining bDMARDs and/or tsDMARDs is effective in patients with persistent inflammation unresponsive to sequential monotherapy

To improve the understanding, classification and care of patients with C2M-PsA and TR-PsA, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis Task Force proposes research priorities across five key domains, as presented in this table. bDMARDs, biologic DMARDs; C2M-PsA, complex-to-manage psoriatic arthritis; DAPSA, disease activity in psoriatic arthritis; PASDAS, psoriatic arthritis disease activity score; PsA, psoriatic arthritis; TR-PsA, treatment refractory psoriatic arthritis; tsDMARDs, targeted synthetic DMARDs.

providing a foundation for research and clinical care in PsA cases marked by therapeutic complexity or resistance.

The need for this initiative reflects the fact that, despite therapeutic advances, a substantial proportion of patients continue to report suboptimal outcomes, including residual pain, functional limitations and impaired quality of life[42,43]. Until now, the absence of standardized criteria to characterize such patients has hindered research comparability and may have contributed to therapeutic inertia in clinical practice. At the same time, growing recognition of disease heterogeneity and variable treatment responses in PsA underscores the importance of a more nuanced classification that takes into consideration all patient characteristics[44–46].

Emerging conceptual frameworks have further underscored the importance of differentiating between non-inflammatory persistent symptomatic PsA (NIPsA) and persistent inflammatory PsA (PIPsA)[47]. NIPsA refers to cases in which patients have persistent symptoms despite well-controlled inflammation, often driven by factors such as structural damage, fibromyalgia, central sensitization or hypermobility syndrome, akin to C2M-PsA. By contrast, PIPsA encompasses cases in which active inflammation persists despite multiple therapies, similar to TR-PsA. Recognizing this distinction is essential, as NIPsA could benefit more from multidisciplinary care and non-pharmacological strategies, whereas PIPsA might require optimization of immunomodulatory therapy[29,48].

Informed by a scoping literature review[19], international HCP and patient surveys[20,21], and structured deliberations by the task force, the GRAPPA definitions adopt a multidimensional, patient-centred perspective. C2M-PsA is a broader category that extends beyond pure biological non-response to include persistent symptomatic burden despite the use of at least one b/tsDMARD, including factors such as comorbidities, overlapping conditions, or psychosocial and cultural barriers[49–51] (Supplementary Table 1). Importantly, with this category the fluctuating nature of disease complexity is acknowledged and the potential for clinical improvement through targeted, multidisciplinary interventions is highlighted[38,39].

TR-PsA is a narrower, more stringent subset within C2M-PsA, requiring the presence of four elements: persistent PsA-related symptoms; failure of at least three treatments with different MoAs (including at least two b/tsDMARDs); symptoms being considered problematic by both clinician and patient; and objective evidence of persistent inflammation. Thus, all patients with TR-PsA also fulfil the criteria for C2M-PsA, but not necessarily vice versa (Table 3 and Supplementary Box 2). These criteria are aimed at identifying patients with refractory inflammatory disease who might benefit from novel therapeutic approaches or enrolment in clinical trials and translational research focused on elucidating underlying disease mechanisms[52,53]. The inclusion of at least three different PsA treatments, rather than a narrower range, accounts for the diversity of therapeutic strategies across PsA domains. The potential inclusion of one csDMARD among the three prior treatments acknowledges regional differences, as cost constraints or reimbursement policies might mandate the use of a csDMARD prior to initiation of advanced therapies[54].

In contrast to the definition of TR-PsA, that of C2M-PsA is intentionally more inclusive, requiring failure of only one b/tsDMARD. Many cases of PsA, such as those involving obesity, multimorbidity or psychosocial barriers, are perceived as complex even before starting advanced treatments. However, as clinical experience shows, some of these patients can respond well to the first b/tsDMARD. Thus, requiring failure of one b/tsDMARD treatment trial allows for identification of complex cases without prematurely categorizing them as such. This layered framework (Fig. 2) provides conceptual granularity and practical thresholds for both clinical and research use.

The thresholds of at least one b/tsDMARD failure for C2M-PsA and at least prior therapies with different MoAs (including at least two b/tsDMARDs) for TR-PsA are consensus-based choices intended to balance inclusivity (early identification of clinically complex presentations) with specificity (delineating true biological non-response). These thresholds were selected to remain applicable across health care systems in which access and costs influence treatment sequencing and to avoid mandating csDMARD failure. Although developed with broad international input, we recognize that access to targeted therapies, imaging and laboratory infrastructure, and socioeconomic factors vary across regions and might influence classification of C2M-PsA and TR-PsA; in low- and middle-resource settings, constrained access to bDMARDs and JAK inhibitors could limit treatment sequencing, yet the treatment exposure requirement within the TR-PsA definition — namely, failure of at least three treatments with different MoAs, including at least two b/tsDMARDs — remains universal. We acknowledge that these thresholds are pragmatic and somewhat arbitrary and that their performance might differ by disease stage and treatment-access context. We propose prospective validation stratified by disease duration and resource context, which might, in time, support alternative exposure thresholds and region-sensitive adaptations while preserving the core consensus definitions.

To enhance practical implementation of the definitions and strengthen reproducibility by reducing interobserver variability,

we also provide explicit operational guidance. The structure for this implementation involves five specific pillars: treatment exposure; persistent symptoms; symptoms perceived as problematic; objective inflammation; and exclusion of alternative explanations for ongoing inflammation. For the 'persistent symptoms' pillar, we specify composite thresholds (for example, failure to achieve minimal disease activity and domain-specific criteria[55]. For the subjective component, 'perceived as problematic', we prefer anchoring to the patient-acceptable symptom state[56] and introduce a parallel physician item, the physician-acceptable state screen, with numeric fallbacks when patient-acceptable symptom state and/or physician-acceptable state screen are unavailable. For TR-PsA, 'objective inflammation' is standardized across clinical, laboratory, imaging, synovial fluid, and active associated conditions, with prespecified thresholds. Full details are provided in Supplementary Box 2.

Several aspects of this work deserve emphasis. First, the development process was grounded in stakeholder engagement, including early and sustained involvement of PRPs, who played a critical role in shaping terminology, especially the replacement of 'difficult-to-manage' with 'complex-to-manage'. Unlike other initiatives that rely solely on input from a small number of patients, we aimed to capture a wider range of patient perspectives by developing a multilingual patient survey that yielded nearly 600 responses from people with PsA worldwide. Furthermore, the framework builds on established principles from prior consensus efforts, including ASAS and EULAR definitions of D2T disease[10,23], while adapting them to the specific pathophysiology and clinical features of PsA.

The requirement of objective evidence of inflammation in the TR-PsA definition was widely supported by GRAPPA membership, aligning with the need to differentiate inflammatory disease from chronic pain, which can be difficult with physical examination alone[57,58]. However, the limitations of currently available biomarkers and imaging modalities were acknowledged, underscoring the importance of expert clinical judgment. In practice, whichever imaging modality is available should be used; MSUS is particularly valuable in peripheral disease, as it can detect synovitis, erosions, tenosynovitis, paratenonitis and dactylitis, whereas MRI is especially relevant for axial disease, enabling assessment of bone-marrow oedema, sacroiliitis and deep soft-tissue inflammation. The modalities are complementary, and feasibility and availability should guide prioritization[59]. Regarding the timing of therapeutic-failure adjudication, we considered a minimum exposure of 12–24 weeks before determining failure, reflecting the heterogeneous onset kinetics of PsA therapies. This window mirrors pharmacodynamic response profiles and aligns with treat-to-target guidance that recommends reassessment at approximately 12 weeks and attainment of the treatment target by ~6 months[60]. Consistent with this approach, the 2023 EULAR recommendations for PsA management advises reassessing csDMARD efficacy at ~12 weeks, aiming for ≥ 50% improvement by 3 months, and achievement of the treatment target by 6 months[8], and the GRAPPA 2021 recommendations support reassessment and potential escalation every 12–24 weeks[7]. We acknowledge that optimal timing might vary by MoA and disease domain, underscoring the need for prospective validation (Table 2).

A key limitation of this initiative lies in the fact that the proposed definitions were developed through a structured consensus process rather than being derived from prospective cohort data. As such, their predictive value remains to be established. However, the definitions were grounded in extensive international stakeholder input and explicitly designed to generate hypotheses and guide future studies. The diverse views within the task force also reflect ongoing uncertainties in the field — such as optimal thresholds for treatment failure or the precise role of contextual factors — but these uncertainties were addressed through transparent voting and discussion. Importantly, a major strength of this effort is its emphasis on inclusivity and clinical applicability, which was achieved by integrating the views of HCPs and patients across multiple continents and specialties. This patient-informed approach ensured that the definitions account for both biological resistance and the broader realities of PsA management.

Another limitation of our drug exposure criterion for TR-PsA is that it counts MoAs, but prior therapies are not weighted by relative efficacy or domain coverage. Therefore, prospective validations should stratify outcomes according to the therapeutic target of the treatment class (for example, TNF, IL-17, IL-23, JAK or PDE4) and also evaluate potency- and domain-weighted exposure metrics.

Despite the achievement of a strong consensus on the definitions, further validation in clinical and research settings is essential. Future studies should evaluate the performance of the definitions in prospective cohorts, registries and pragmatic trials, assess their prognostic utility and explore their role in guiding treatment decisions. To facilitate structured uptake and ensure scientific rigour, five quality

Table 3 | Comparison of complex-to-manage psoriatic arthritis and treatment-refractory psoriatic arthritis

Aspect	C2M-PsA	TR-PsA
Treatment exposure	Failure of ≥1 b/tsDMARD (≥12 weeks or earlier if the patient has adverse events or intolerance)	Failure to respond to ≥3 MoAs including ≥2 b/tsDMARDs; adverse events or intolerance not counted; adequate dose, interval and duration
Persistent symptoms	Composite or domain-specific activity present	Composite or domain-specific activity present
Perceived as problematic	Either patient or clinician threshold positive	Both patient and clinician thresholds positive at the same visit
Objective inflammation	Not required, although can be present[a]	Required: (a) clinical, (b) laboratory, (c) imaging, (d) synovial fluid or (e) active associated conditions
Alternative explanations evaluated	Not mandatory	TR-PsA classification if PsA activity is the primary driver of disease manifestations Exclusion should only occur when another condition better explains the clinical picture[b]
Pillars[c] required	Pillars 1–3	Pillars 1–5

bDMARDs; biologic DMARDs; C2M-PsA, complex-to-manage psoriatic arthritis; MoAs, mechanisms of action; TR-PsA, treatment-refractory psoriatic arthritis; tsDMARDs, targeted synthetic DMARDs. [a]Document contextual drivers if absent. [b]Exclusions refer only to cases where another condition better explains the clinical picture (e.g., pure mechanical OA, infections, gout flare with monosodium urate crystals). Coexisting conditions do not preclude classification of TR-PsA if PsA activity is present. [c]Pillar 1: treatment exposure; pillar 2: persistent symptoms; pillar 3: perceived as problematic; pillar 4: objective inflammation; pillar 5: exclusion of an alternative explanation as the main driver of systemic inflammation.

indicators have been proposed: external validation in independent cohorts; inclusion in clinical recommendations; citation frequency; use in clinical trials; and application in translational research (Supplementary Table 2). These efforts will ensure that the definitions are both clinically meaningful and methodologically robust, ultimately strengthening their role in real-world application and policy development. Finally, to ensure their continued relevance over time, a formal re-evaluation by the GRAPPA task force is planned 3 years post-publication (Supplementary Fig. 2), allowing for incorporation of new data and clinical experience to determine whether refinement is warranted.

Conclusions

These consensus-derived GRAPPA definitions provide a shared framework for standardizing terminology, supporting individualized care and improving patient stratification in both research and practice. They offer practical tools for clinicians and researchers, serving as a foundation for future observational studies and clinical trials, and supporting the earlier recognition of patients with C2M or TR disease. Prospective validation across diverse settings and phenotypes is needed to establish their reliability, responsiveness and clinical utility.

Published online: 27 November 2025

References

1. Ritchlin, C. T., Colbert, R. A. & Gladman, D. D. Psoriatic arthritis. *N. Engl. J. Med.* **376**, 957–970 (2017).
2. FitzGerald, O. et al. Psoriatic arthritis. *Nat. Rev. Dis. Prim.* **7**, 59 (2021).
3. Perez-Chada, L. M. & Merola, J. F. Comorbidities associated with psoriatic arthritis: review and update. *Clin. Immunol.* **214**, 108397 (2020).
4. Husted, J. A., Thavaneswaran, A., Chandran, V. & Gladman, D. D. Incremental effects of comorbidity on quality of life in patients with psoriatic arthritis. *J. Rheumatol.* **40**, 1349–1356 (2013).
5. Gupta, S., Syrimi, Z., Hughes, D. M. & Zhao, S. S. Comorbidities in psoriatic arthritis: a systematic review and meta-analysis. *Rheumatol. Int.* **41**, 275–284 (2021).
6. Ayan, G., Ribeiro, A., Macit, B. & Proft, F. Pharmacologic treatment strategies in psoriatic arthritis. *Clin. Ther.* **45**, 826–840 (2023).
7. Coates, L. C. et al. Group for research and assessment of psoriasis and psoriatic arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat. Rev. Rheumatol.* **18**, 465–479 (2022).
   These most recent GRAPPA recommendations underpin the domain-based, individualized treatment approach that informed the structure of the C2M/TR-PsA definitions.
8. Gossec, L. et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update. *Ann. Rheum. Dis.* **83**, 706–719 (2024).
9. Hagège, B. et al. Remission and low disease activity in psoriatic arthritis publications: a systematic literature review with meta-analysis. *Rheumatology* **59**, 1818–1825 (2020).
10. Nagy, G. et al. EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann. Rheum. Dis.* **80**, 31–35 (2021).
    The EULAR definition of difficult-to-treat RA provided a conceptual and methodological benchmark for structuring the TR-PsA definition.
11. Philippoteaux, C. et al. Characteristics of difficult-to-treat psoriatic arthritis: a comparative analysis. *Semin. Arthritis Rheum.* **63**, 152275 (2023).
12. Perrotta, F. M., Scriffignano, S., Ciccia, F. & Lubrano, E. Clinical characteristics of potential "Difficult-to-treat" patients with psoriatic arthritis: a retrospective analysis of a longitudinal cohort. *Rheumatol. Ther.* **9**, 1193–1201 (2022).
13. Vassilakis, K. D. et al. Identification and characteristics of patients with potential difficult-to-treat psoriatic arthritis: exploratory analyses of the Greek PsA registry. *Rheumatology* **63**, 2427–2432 (2024).
14. Schett, G. et al. Psoriatic arthritis from a mechanistic perspective. *Nat. Rev. Rheumatol.* **18**, 311–325 (2022).
15. Siebert, S. & Marzo-Ortega, H. Difficult-to-treat psoriatic arthritis: moving out of the rheumatoid arthritis shadow. *Nat. Rev. Rheumatol.* **20**, 135–136 (2024).
16. Winthrop, K. L. et al. Unmet need in rheumatology: reports from the advances in targeted therapies meeting, 2023. *Ann. Rheum. Dis.* **83**, 409–416 (2024).
    This expert summary highlighted unmet needs in PsA management and emphasized the importance of treatment-resistant phenotypes.
17. Hailey, L. et al. The top 10 research priorities in psoriatic arthritis: a James Lind Alliance priority setting partnership. *Rheumatology* **62**, 2716–2723 (2023).
18. Ayan, G. et al. GRAPPA 2023: major projects, key advances, and milestones. *J. Rheumatol.* **51** (Suppl 2), 65–69 (2024).
19. Singla, S., Ribeiro, A., Torgutalp, M., Mease, P. J. & Proft, F. Difficult-to-treat psoriatic arthritis (D2T PsA): a scoping literature review informing a GRAPPA research project. *RMD Open.* **10**, e003809 (2024).
    This scoping review mapped the heterogeneous terminology and conceptual gaps around D2T PsA, providing a foundational rationale for this consensus initiative.
20. Ribeiro, A. L. et al. Deciphering difficult-to-treat psoriatic arthritis (D2T-PsA): a GRAPPA perspective from an international survey of healthcare professionals. *Rheumatol. Adv. Pract.* **8**, rkae074 (2024).
    This GRAPPA HCP survey identified real-world challenges in PsA treatment and informed the operational separation of C2M-PsA and TR-PsA.
21. Ribeiro, A. L. et al. Deciphering difficult-to-treat psoriatic arthritis (D2T-PsA): insights from an international survey of patients with psoriatic arthritis. *Rheumatology* **64**, keaf207 (2025).
    This large international, multi-lingual patient survey highlighted the psychosocial, contextual and cultural factors contributing to treatment complexity in PsA.
22. Proft, F. et al. Op0175 establishing definitions for difficult-to-treat psoriatic arthritis (D2T-PSA) and complex-to-manage psoriatic arthritis (C2M-PSA): insights from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) initiative. *Ann. Rheum. Dis.* **84**, 143–145 (2025).
23. Poddubnyy, D. et al. The Assessment of Spondyloarthritis International Society (ASAS) consensus-based expert definition of difficult-to-manage, including treatment-refractory, axial spondyloarthritis. *Ann. Rheum. Dis.* **84**, 538–546 (2025).
    This ASAS definition of D2M- and TR-axial SpA guided the development of C2M-PsA and TR-PsA definitions with respect to inflammation-based criteria and stakeholder consensus.
24. Ribeiro, A. L. & Proft, F. Navigating the complexities of difficult-to-treat axial spondyloarthritis. *Jt Bone Spine* **91**, 105770 (2024).
25. Lucas Ribeiro, A. et al. Development of a questionnaire to assess the patient perspective regarding challenges in psoriatic arthritis treatment-a mixed-methods study. *Adv. Rheumatol.* **64**, 72 (2024).
26. Zhang, A. D. & Kavanaugh, A. Treat to target in psoriatic arthritis. *Rheum. Dis. Clin. North. Am.* **45**, 505–517 (2019).
27. Leung, Y. Y. et al. Initiating evaluation of composite outcome measures for psoriatic arthritis: 2022 updates from the GRAPPA-OMERACT working group. *J. Rheumatol.* **50**, 53–57 (2023).
28. Orbai, A. M. et al. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. *Ann. Rheum. Dis.* **76**, 673–680 (2017).
29. Kumthekar, A., Ashrafi, M. & Deodhar, A. Difficult to treat psoriatic arthritis — how should we manage? *Clin. Rheumatol.* **42**, 2251–2265 (2023).
30. Lubrano, E., Scriffignano, S. & Perrotta, F. M. Difficult to treat and refractory to treatment in psoriatic arthritis. *Rheumatol. Ther.* **10**, 1119–1125 (2023).
31. Felbo, S. K. et al. Do tender joints in active psoriatic arthritis reflect inflammation assessed by ultrasound and magnetic resonance imaging? *Rheumatology* **61**, 723–733 (2022).
32. Diaz, P., Feld, J., Eshed, I. & Eder, L. Characterising axial psoriatic arthritis: correlation between whole spine MRI abnormalities and clinical, laboratory and radiographic findings. *RMD Open.* **8**, e002011 (2022).
33. Elmamoun, M. et al. Using acute-phase reactants to inform the development of instruments for the updated psoriatic arthritis core outcome measurement set. *J. Rheumatol.* **46**, 266–273 (2019).
34. Haroon, M., Gallaghar, P., Ahmad, M. & FitzGerald, O. Elevated CRP even at the first visit to a rheumatologist is associated with long-term poor outcomes in patients with psoriatic arthritis. *Clin. Rheumatol.* **39**, 2951–2961 (2020).
35. Ribeiro, A. L. & Eder, L. From psoriasis to psoriatic arthritis: ultrasound insights connecting psoriasis with subclinical musculoskeletal inflammation and the path to psoriatic arthritis. *Curr. Rheumatol. Rep.* **26**, 235–247 (2024).
36. Moshrif, A., Abdel Noor, R., Aly, H., Mortada, M. & Hafez, A. Aging and entheses: an ultrasonographic probing of degenerative enthesopathy in a cohort of 147 healthy subjects. *Int. J. Rheum. Dis.* **25**, 481–488 (2023).
37. Falsetti, P. et al. Diffuse peripheral enthesitis in metabolic syndrome: a retrospective clinical and power doppler ultrasound study. *Reumatol. Clin.* **18**, 273–278 (2022).
38. Hailey, L. H. et al. Lifestyle modifications and nonpharmacologic interventions to improve outcomes in psoriatic arthritis: a systematic review. *Clin. Ther.* **45**, 841–851 (2023).
39. Lubrano, E., Ambrosino, P. & Perrotta, F. M. Psychological health in the management of patients with psoriatic arthritis: an intricate relationship. *Rheumatol. Ther.* **12**, 407–419 (2025).
40. Mease, P., Reed, G., Ogdie, A., Pappas, D. A. & Kremer, J. M. Prevalence of fibromyalgia and widespread pain in psoriatic arthritis: association with disease severity assessment in a large US registry. *Arthritis Care Res.* **76**, 1313–1321 (2024).
41. Currado, D. et al. From pain catastrophising to multidimensional psychological distress: unravelling the complexity of difficult-to-treat psoriatic arthritis. *Clin. Exp. Rheumatol.* **43**, 1871–1878 (2025).
42. Coates, L. C. et al. Residual disease associated with suboptimal treatment response in patients with psoriatic arthritis: a systematic review of real-world evidence. *Rheumatol. Ther.* **9**, 803–821 (2022).
43. Zardin-Moraes, M. et al. Prevalence of psoriatic arthritis patients achieving minimal disease activity in real-world studies and randomized clinical trials: systematic review with metaanalysis. *J. Rheumatol.* **47**, 839–846 (2020).

44. Proft, F. et al. Treatment strategies for spondyloarthritis: implementation of precision medicine — or "one size fits all" concept? *Autoimmun. Rev.* **23**, 103638 (2024).
45. Jin, J. Q. et al. Sociodemographic and clinical characteristics associated with multiple biologic failure in psoriasis: a 2015-2022 prospective cohort analysis of the CorEvitas psoriasis registry. *J. Am. Acad. Dermatol.* **89**, 974–983 (2023).
46. Eder, L. et al. Sex-related differences in patient characteristics, and efficacy and safety of advanced therapies in randomised clinical trials in psoriatic arthritis: a systematic literature review and meta-analysis. *Lancet Rheumatol.* **5**, e716–e727 (2025).
47. Zabotti, A., Aydin, S. Z., David, P., Di Matteo, A. & McGonagle, D. Delineating inflammatory from non-inflammatory mechanisms for therapy optimization in psoriatic arthritis. *Nat. Rev. Rheumatol.* **21**, 237–248 (2025).
This Perspective article highlights the clinical relevance of separating inflammatory from non-inflammatory mechanisms in PsA management and research.
48. Fagni, F., Motta, F., Schett, G. & Selmi, C. Difficult-to-treat psoriatic arthritis: a conceptual approach. *Arthritis Rheumatol.* **76**, 670–674 (2024).
This conceptual framework reinforced the importance of distinguishing therapeutic refractoriness from broader contextual disease complexity in PsA.
49. Ribeiro, A. L. et al. Challenges in the management of psoriatic arthritis in Latin America: a systematic review. *Clin. Ther.* **45**, 860–867 (2023).
50. Gialouri, C. G. et al. Depression and anxiety in a real-world psoriatic arthritis longitudinal study: should we focus more on patients' perception? *Clin. Exp. Rheumatol.* **41**, 159–165 (2023).
51. Kancharla, H. et al. Fibromyalgia influences health-related quality of life and disease activity in psoriatic arthritis. *Rheumatol. Int.* **42**, 511–517 (2022).
52. Chakraborty, D. & Raychaudhuri, S. P. Concept of dual immune inhibitors for the treatment of drug-resistant psoriatic disease. *Curr. Opin. Immunol.* **95**, 102602 (2025).
53. Scher, J. U., Ogdie, A., Merola, J. F. & Ritchlin, C. Moving the goalpost toward remission: the case for combination immunomodulatory therapies in psoriatic arthritis. *Arthritis Rheumatol.* **73**, 1574–1578 (2021).
54. Fernández-Ávila, D. G. et al. Pan American league of associations for rheumatology recommendations for the treatment of psoriatic arthritis. *J. Rheumatol.* **51**, 563–576 (2024).
55. Helliwell, P. S. et al. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). *Ann. Rheum. Dis.* **72**, 986–991 (2013).
56. Lubrano, E. et al. Assessment of the patient acceptable symptom state (PASS) in psoriatic arthritis: association with disease activity and quality of life indices. *RMD Open.* **6**, e001170 (2020).
57. Macchioni, P. et al. Ultrasonographic and clinical assessment of peripheral enthesitis in patients with psoriatic arthritis, psoriasis, and fibromyalgia syndrome: the ULISSE study. *J. Rheumatol.* **46**, 904–911 (2019).
58. Meridor, K. et al. Association of clinical and sonographic factors with discrepancy between patients' and evaluators' global assessments in psoriatic arthritis. *Rheumatology* **64**, 5058–5064 (2025).
59. Mandl, P. et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. *Ann. Rheum. Dis.* **74**, 1327–1339 (2015).
60. Smolen, J. S. et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann. Rheum. Dis.* **77**, 3–17 (2018).

Acknowledgements

We extend our deepest gratitude to all the patients who participated in this study, lending invaluable insights and experiences. We are thankful for the collaborative support from our colleagues and contributors, including N. Chronis, C. Hay-Rollins, M. Torgutalp, and the translators who facilitated communication across languages. Our appreciation also goes to the entire Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) membership, the GRAPPA Research Committee and the GRAPPA Administration for their continuous support and commitment to this project. A special tribute is owed to D. Jadon, whose foundational contributions were vital to our endeavours until his untimely departure; his legacy continues to inspire and drive our work forward. This project was conducted on behalf of GRAPPA. No funding has been received for this project. Logistical support from the GRAPPA Administration was provided.

Author contributions

F.P., A.L.R., S.S. and P.M. researched data for the article. F.P., A.L.R. and P.M. wrote the manuscript. All authors made a substantial contribution to discussion of the content and reviewed/edited the manuscript before submission.

Competing interests

F.P. has received grants and personal fees from Novartis, Eli Lilly and UCB and personal fees from AbbVie, AMGEN, BMS, Celgene, Janssen, Hexal, Medscape, Moonlake, MSD, Pfizer and Roche outside the presented work. A.L.R. has received honoraria and support for attending conferences from Novartis, Eli Lilly, UCB, AbbVie and Janssen, all outside the presented work. S.S. has received consulting fees from AbbVie, Johnson & Johnson and UCB, speaker fees from Johnson & Johnson, and research grants from AbbVie, Eli Lilly and Prometheus Biosciences. V.C. has received grants from AbbVie, Amgen and Eli Lilly and honoraria for advisory board member roles from AbbVie, BMS, Eli Lilly, Fresenius Kabi, Janssen, Novartis and UCB; V.C.'s spouse is an employee of AstraZeneca; and V.C. is supported by the Dr. Dafna D. Gladman Chair in Psoriatic Arthritis Research, a joint Hospital-University Named Chair between the University of Toronto, the University Health Network, and the UHN Foundation. W.L. has received research funding from Amgen, Janssen, Leo and Regeneron. C.L. has acted as a consultant for Tonix Pharmaceuticals, and owns stock with Amgen and Arcutis. E.R.S. has participated in advisory boards for, given conferences for and/or received grants from AbbVie, Amgen, Bristol-Myers Squibb, Elea, Glaxo, Janssen, Lilly, Montpellier, Novartis, Pfizer, Raffo, Roche, Sandoz and UCB. T.B. has received research funding from Amgen, Castle, CorEvitas, Novartis, Pfizer and Regeneron; she has served as an adviser for AbbVie, Arcutis, Aslan, Boehringer-Ingelheim, Bristol Myers Squibb, Dermavant, Galderma, Incyte, Janssen, Leo, Lilly, Pfizer, Novartis, Sanofi, Sun, Takeda and UCB; and she is a speaker for AbbVie, Amgen, Arcutis, BMS, Dermavant, Galderma, Janssen, Lilly, Leo, Ortho, Sanofi and UCB. A.D. has participated in consulting and advisory boards for Bristol Myers Squibb, Eli Lilly, J&J, Novartis, Pfizer, UCB, and has received research grants from Bristol Myers Squibb, Eli Lilly, J&J, MoonLake, Novartis, Pfizer and UCB. K.d.V. has participated in consulting and advisory boards for Bristol Myers Squibb, Eli Lilly, J&J, Novartis, Pfizer, UCB, AlfaSigma, Moonlake & Allegro, and has received research grants from Pfizer and UCB. L.E. has received grants from AbbVie, UCB, Novartis, J&J, Eli Lilly, Pfizer, Novo Nordisk, Fresenius Kabi and Amgen, and has participated in consulting for BMS, AbbVie, UCB, Novartis, J&J and Eli Lilly. M.K. has received speakers bureau fees from AbbVie, Amgen, Asahi-Kasei Pharma, Ayumi Pharma, BMS, Chugai, Daiichi Sankyo, Eisai, Janssen, Lilly, Novartis, Tanabe-Mitsubishi and UCB, and has acted as a consultant for AbbVie, Amgen, Asahi-Kasei Pharma, Ayumi Pharma, BMS, Chugai, Gilead, Janssen, Lilly, Novartis, Takeda, Tanabe-Mitsubishi and UCB. Y.Y.L. has received speaking fees from AbbVie, DKSH, Jassen, Novartis and Pfizer, outside of the present work. E.L. has received speaker´s fees from AbbVie, Lilly, Janssen, Novartis and UCB. D.M. has received grants and speaker fees from AbbVie, BMS, Novartis, Eli Lilly, UCB, Celgene, Janssen, Moonlake and Pfizer. D.P. has received research grants from AbbVie, Eli Lilly, Janssen, Novartis, Pfizer and UCB, consulting fees from AbbVie, Eli Lilly, Greywolf Therapeutics, Janssen, Merk, Moonlake, Novartis, Pfizer and UCB, and speaker fees from AbbVie, Canon, Eli Lilly, Janssen, Medscape, Novartis, Peervoice, Pfizer and UCB; he serves as a member of the executive committee of ASAS, a member of the steering committee of GRAPPA, and editor of *Therapeutic Advances in Musculoskeletal Disease*. L.S. has received honoraria from AbbVie, Almirall, Novartis, Janssen, Lilly, UCB, Pfizer, Bristol-Myers-Squibb, Boehringer Ingelheim, Amgen, Medac, Moonlake, Leo Pharma, Takeda, Galderma, Biogen, Celgene, Celltrion, Sanofi and Fresenius Kabi for consulting and speaker roles, and has received support for travel from AbbVie, Janssen, Lilly, Novartis, UCB, Bristol-Myers-Squibb, Boehringer Ingelheim and Leo Pharma. F.V.d.B. has received consulting fees from AbbVie, Alfasigma, Celltrion, Eli Lilly, Fresenius Kabi, GreyWolf Therapeutics, Janssen, Novartis, UCB and Xencor. P.M. has received research grants, consulting fees and speaker fees from AbbVie, Acelyrin, Amgen, Bristol Meyers Squibb, Century, Eli Lilly, Inmagene, Johnson & Johnson, Moonlake, Novartis, Pfizer, Takeda and UCB, and is a data safety board member of Genascence.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41584-025-01329-3.

Peer review information *Nature Reviews Rheumatology* thanks Wilson Bautista-Molano and Roberta Ramonda for their contribution to the peer review of this work.

[1]Department of Gastroenterology, Infectiology and Rheumatology (including Nutrition Medicine), Charité – Universitätsmedizin Berlin, Berlin, Germany. [2]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. [3]Hospital Moinhos de Vento, Porto Alegre, Brazil. [4]Department of Rheumatology, Medical College of Wisconsin, Milwaukee, WI, USA. [5]Gladman Krembil Psoriatic Arthritis Program, Schroeder Arthritis Institute, University Health Network and Division of Rheumatology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada. [6]Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada. [7]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada. [8]Department of Dermatology, University of California San Francisco, San Francisco, CA, USA. [9]GRAPPA Patient Research Partner, Prosper, TX, USA.

[10]Rheumatology Section, Internal Medicine Service, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina. [11]Division of Arthritis and Rheumatic Diseases, Oregon Health & Science University, Portland, OR, USA. [12]Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium. [13]Department of Development and Regeneration, Skeletal Biology and Engineering Research Center (SBE), KULeuven, Leuven, Belgium. [14]Division of Rheumatology, Women's College Hospital, University of Toronto, Toronto, Ontario, Canada. [15]Department of Nephrology and Rheumatology, Kyorin University School of Medicine, Tokyo, Japan. [16]Department of Rheumatology and Immunology, Duke-NUS Medical School, Singapore General Hospital, Singapore, Singapore. [17]Academic Rheumatology Unit, University of Molise, Molise, Italy. [18]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK. [19]Department of Dermatology, University of Leeds, Leeds, UK. [20]Department of Internal Medicine and Pediatrics, VIB-UGent Center for Inflammation Research, Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium. [21]Department of Rheumatology, University Hospital Ghent, Ghent, Belgium. [22]Providence Swedish Medical Center and University of Washington School of Medicine, Seattle, WA, USA. [23]These authors contributed equally: Fabian Proft, Andre L. Ribeiro.