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Rheumatoid arthritis

Joint-specific susceptibility to inflammation is determined in utero

In rheumatoid arthritis (RA), understanding why inflammation occurs in some joints but not others is a key area of research, particularly as joint-specific responses to therapy have been reported. Now, a study published in *Nature Immunology* indicates that the cellular composition and stromal architecture that develops in utero determines joint-specific inflammation in arthritis.

"We reasoned that if adult joints differ in their susceptibility to inflammation, some of those differences might be laid down much earlier, during development," explains Christopher Buckley, a co-corresponding author of the study. To obtain an overview of the developing finger joints, the authors performed single-cell RNA sequencing of human foetal proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints, the former of which is usually inflamed in RA and the latter of which is unaffected. This analysis indicated that at this stage of development, stromal cells predominate and distinct stromal compartments develop, which differ in PIP and DIP joints.

Specifically, PIP joints had a greater synovial volume and were more enriched for PI16$^+$ fibroblasts than DIP joints. Interestingly, these fibroblasts were localized to blood vessels and interstitial regions between developing tendons and ligaments, regions of the joint where inflammation typically occurs in arthritis.

Stimulating PI16$^+$ fibroblasts with pro-inflammatory cytokines (TNF and IL-1β) in vitro led to the upregulation of genes associated with chemotaxis and migration and the downregulation of genes associated with homeostasis (such as those encoding adhesion molecules). "This finding suggests that these cells might normally help organize tissue architecture and vascular or tendon–ligament integrity, but under inflammatory conditions they could help recruit immune cells and destabilize the local niche," comments Buckley.

Embryonic lining and sublining fibroblast subsets mapped to fibroblast populations from adults with RA and osteoarthritis (for example, PI16$^+$ fibroblasts mapped to adult CD34$^+$ sublining fibroblasts). Thus, the stromal joint niches that occur during development shape adult fibroblast compartments that are relevant to arthritis development.

"The next step is to determine how these developmental stromal niches are maintained, remodelled or reactivated in adult disease. In other words, how can we reset the synovium back to normal. Therapeutically, it raises the possibility of targeting stromal niches that licence inflammation or preserving the homeostatic tissue-organizing functions of fibroblasts, rather than treating fibroblasts only as generic inflammatory effector cells. Understanding those local stromal programmes could open new approaches to predicting, preventing and treating site-specific inflammatory disease," concludes Buckley.

Holly Webster

Original article: Davidson, S. et al. The embryonic origins of site-specific arthritis. *Nat. Immunol.* https://doi.org/10.1038/s41590-026-02542-2 (2026)

Clinical trials

Secukinumab shows diverging efficacy in PMR and GCA

Secukinumab, a monoclonal antibody that inhibits IL-17A, has been evaluated in two phase III trials in polymyalgia rheumatica (PMR) and giant cell arteritis (GCA), diseases that are closely related but differ in clinical course and treatment response.

Glucocorticoids remain the standard of care for both PMR and GCA, but long-term use is associated with substantial toxicity, and relapse is common. Targeting IL-17A is therefore a potential strategy to reduce glucocorticoid exposure and improve disease control in both conditions.

The phase III REPLENISH trial enrolled 381 patients with relapsed PMR who received secukinumab (150 or 300 mg) or placebo alongside a 24-week glucocorticoid taper. Secukinumab improved rates of sustained remission at 52 weeks, the primary end point, and reduced cumulative glucocorticoid use, consistent with a steroid-sparing effect. Sustained remission was achieved in 41.2% and 40.6% of patients receiving 300 and 150 mg of secukinumab, respectively, compared with 20.4% receiving placebo.

By contrast, the phase III GCAptAIN trial did not meet its primary endpoint. In this study, 353 patients with new-onset or relapsing GCA were randomly assigned to receive secukinumab (300 or 150 mg, following a protocol amendment) or placebo, alongside glucocorticoid tapering. In the 300-mg secukinumab treatment group, sustained remission at 52 weeks (the primary endpoint) occurred in 25.6% of patients compared with 16.9% in the placebo group, a difference that did not reach statistical significance.

Although secukinumab reduced cumulative glucocorticoid exposure in the higher-dose group, secondary outcomes (including sustained remission in the 150-mg secukinumab versus placebo group) were largely consistent with the primary result. Interpretation of these findings should take into account differences in glucocorticoid tapering between groups, with a longer taper in the placebo arm (52 weeks versus 26 weeks).

In both trials, secukinumab was generally well tolerated, with safety findings consistent with its established profile. Mild to moderate infections and hypersensitivity reactions were more frequent with secukinumab, but rates of serious adverse events were similar to placebo.

> **"IL-17A inhibition is effective in PMR but not in GCA"**

Overall, these findings suggest that IL-17A inhibition is effective in PMR but not in GCA under the conditions tested, highlighting differences across the PMR–GCA spectrum.

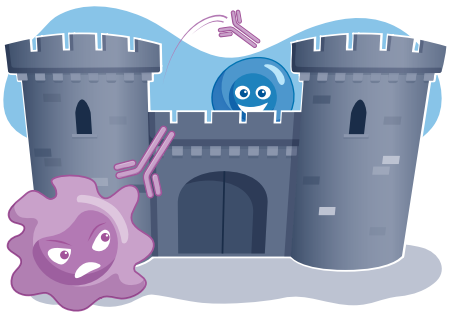
Jessica McHugh

Original articles: Stone, J. H. et al. Phase 3 trial of secukinumab in polymyalgia rheumatica. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2602567 (2026); Stone, J. H. et al. Secukinumab for giant cell arteritis. *N. Engl. J. Med. Evid.* https://doi.org/10.1056/EVIDoa2600112 (2026)

Related article: Muratore, F. et al. Treatment strategies in giant cell arteritis and polymyalgia rheumatica: beyond glucocorticoids. *Nat. Rev. Rheumatol.* **22**, 411–428 (2026)

Therapy

Lymph node 'hideouts' shield B cells from antibody therapy



B cell depletion using monoclonal antibodies (such as rituximab) is widely used to treat autoimmune diseases, as well as B cell malignancies. Despite strong clinical success, therapeutic responses are often incomplete and variable. New findings reveal that the lymph node architecture can function as a physical barrier, limiting the ability of antibody therapies to eliminate tissue-resident B cells.

Coming from a tumour immunology perspective, the researchers examined lymph node dynamics in a mouse model of lymphoma. Unlike healthy B cells, the malignant B cells exhibited a sessile phenotype, with limited recirculation into the blood, potentially reducing exposure of the cells to circulating therapeutic antibodies.

To explore the clinical relevance of this finding, the researchers used a sphingosine-1-phosphate inhibitor, fingolimod, to control the egress of healthy B cells from lymph nodes in mice. Notably, these trapped B cells, unlike B cells found in the bone marrow, were resistant to anti-CD20 antibody-mediated depletion. This resistance was not explained by restricted antibody diffusion as the antibodies could access and effectively opsonize B cells in the lymph nodes, which suggests that the local microenvironment limits therapeutic efficacy.

B cell depleting antibodies depend on Fc–Fc receptor (FcR) interactions to recruit effector immune cells and eliminate target cells. Multiplex imaging revealed that, in the lymph nodes, FcR-expressing effector cells, composed primarily of macrophages, were largely excluded from B cell zones. Reorganization of the lymph node microenvironment, using low-dose radiotherapy or vaccine-driven inflammation, brought FcγR$^+$ effector cells into closer proximity with B cell targets and improved antibody-mediated depletion. This effect was lost in FcγR-deficient mice and in mice depleted of macrophages, confirming the importance of these effector pathways.

> "Reorganization of the lymph node microenvironment ... improved antibody-mediated depletion"

"These findings suggest that anti-CD20 therapy alone may be insufficient, and that conditioning strategies such as radiotherapy could be important not only in oncology, but also in the context of autoimmune disorders," explains corresponding author Capucine Grandjean. "An important next step will be to identify immune modulators that could be combined with anti-CD20 monoclonal antibodies to enhance B cell depletion specifically within lymphoid tissues."

Jessica McHugh

Original article: Garcia, Z. et al. Lymph node microenvironment remodeling unlocks local antibody-mediated B cell depletion. *Sci. Adv.* **12**, eaed8962 (2026)

Autoinflammation

Dysfunctional *UBA1*-mutated myeloid cells promote inflammation in VEXAS syndrome

Somatic mutations in *UBA1* cause VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, but the mechanisms that link these mutations to systemic inflammation remain unclear. Now, findings published in *Blood* implicate myeloid dysfunction as a driver of inflammation in VEXAS syndrome.

Using a *UBA1*^{M41V} THP-1 monocytic model of VEXAS syndrome, Breillat et al. show that mutant myeloid cells have a higher sensitivity to TNF-induced cell death (specifically caspase-8-dependent apoptosis and MLKL-dependent necroptosis) than wild-type *UBA1* cells. Further analysis identified RIPK1 as a crucial mediator of this increased sensitivity to cell death; inhibition of RIPK1 reduced cell death and inflammation.

To validate these findings, the authors assessed CD14^{+} monocytes from individuals with VEXAS syndrome. Caspase-8-dependent apoptosis and MLKL-dependent necroptosis pathways were activated in these cells and RIPK1 autophosphorylation was essential for the activation of both pathways.

The NF-κB pathway is downstream of the TNF receptor, and the authors therefore assessed NF-κB activity in *UBA1*^{M41V} cells. Upon TNF stimulation, NF-κB signalling was diminished and expression of c-FLIP (a negative regulator of apoptosis) was reduced in *UBA1*-mutated compared with wild-type cells.

As VEXAS syndrome is characterized by susceptibility to infection, Toll-like receptor (TLR) responses (key mediators of innate immune recognition) were assessed in *UBA1*-mutant myeloid cells. Despite retaining TLR expression, mutant cells had impaired responses to TLR agonists, probably owing to diminished NF-κB signalling, potentially contributing to compromised host defence.

Analysis of biopsy-obtained skin samples from people with VEXAS syndrome revealed prominent cell death signatures. To further determine the role of mutant cells in the tissue, *UBA1*^{M41V} THP-1-derived macrophages were characterized.

Although mutant macrophages retained normal phagocytic function, they were unable to degrade engulfed debris. They also had a pro-inflammatory phenotype, characterized by high cytokine and chemokine production, which suggests that these cells might contribute to sustained inflammation by recruiting monocytes to inflamed tissues. Thus, *UBA1* mutations in myeloid cells promote inflammation and tissue damage via impaired resolution of inflammation, cell death and defective innate immune responses.

"Our next objective is to further analyse the molecular pathways connecting *UBA1* mutations to inflammatory cell death and myeloid dysfunction. Clinically, these findings may help identify disease activity and therapeutic response biomarkers and highlight new treatment strategies that target inflammatory cell death pathways and innate immune dysregulation," concludes Benjamin Terrier, corresponding author of the study.

Holly Webster

Original article: Breillat, P. et al. Inflammatory cell death and monocyte dysfunction in VEXAS syndrome. *Blood* **147**, 2944–2957 (2026)

Osteoporosis

Controlled release of magnesium ions shapes osteoporotic bone repair

Dysregulated inflammation, driven by pro-inflammatory macrophage and helper T (T_H) cell activity, can impair osteoporotic fracture repair. New research now suggests that controlled release of magnesium ions (Mg^{2+}) can attenuate these inflammatory responses to enable bone healing.

In the study, the researchers demonstrated in mice with surgically generated femoral defects that Mg^{2+} released from alginate hydrogels promoted T_H1 cell-associated inflammation in a dose-dependent manner. Mg^{2+} seemed to initially have anti-inflammatory effects but promoted a T_H1 cell-dominant immune response when present at excessive levels, with upregulation of inflammation-related genes and increased numbers of osteoclasts. Notably, Mg^{2+}-dependent changes in macrophage polarization were absent in T cell-deficient mice, which indicates that T cells are required for these effects.

Further ex vivo experiments revealed that the effects of Mg^{2+} can vary depending on the strength of T cell receptor stimulation. Strong calcium (Ca^{2+}) stimulation skewed CD4^{+} T cells towards a T_H1 cell phenotype, but extracellular Mg^{2+} suppressed this T_H1 cell differentiation and increased T_H2 cell differentiation by inhibiting TRPM7-mediated Ca^{2+} entry. Conversely, when Ca^{2+} stimulation of CD4^{+} T cells was moderate or weak, high levels of extracellular Mg^{2+} led to a modest increase in T_H1 cells and a decrease in T_H2 cells by inhibiting Ca^{2+} influx via Orai1 and voltage-gated calcium channels and activation of JAK–STAT1 signalling.

In isolated bone marrow monocytes, Mg^{2+} directly suppressed osteoclastogenesis in a dose-dependent manner by weakening RANKL-induced Ca^{2+} signalling. Mg^{2+} also suppressed macrophage polarization; however, in an environment rich in T_H1 cell-derived cytokines such as IFNγ, these suppressive effects of Mg^{2+} were overridden and macrophages shifted towards a pro-inflammatory state.

These findings led the researchers to develop a bioceramic intramedullary nail (IMN) able to deliver Mg^{2+} in a precise, time-phased manner. The IMN was engineered to deliver Mg^{2+} rapidly in the first few days after implantation into an osteoporotic fracture to curb early inflammation but then taper Mg^{2+} release thereafter to avoid the detrimental effects of continuous high levels of Mg^{2+} in the later stages of bone healing (when Ca^{2+} signalling subsides). In ovariectomized mice, the IMN suppressed T_H1 cells and pro-inflammatory macrophages in the early phase after fracture, and in later phases, it promoted T_H2 cell- and macrophage-mediated tissue repair and bone regeneration.

Together the findings suggest that fine-tuned delivery of Mg^{2+} offers a potential strategy for regulating the osteoimmune microenvironment during bone healing. Further studies are needed to elucidate how this immune regulation influences the quality of repaired bone.

Sarah Onuora

Original article: Kim, J. H. et al. Temporal immunomodulation of CD4^{+} T cells by magnesium regulates osteoimmune responses in osteoporotic fracture healing. *Sci. Adv.* **12**, eaeb2091 (2026)

Rheumatoid arthritis

PD-1 agonism puts the brakes on pathogenic T cell responses in RA

In rheumatoid arthritis (RA), synovial T cell subsets, including peripheral helper T (T_{PH}) cells, have high expression of the inhibitory receptor PD-1. Now, Higashioka et al. show that PD-1 regulates pathogenic T cell responses in RA.

Single-cell RNA sequencing (scRNA-seq) analysis of human synovial T cell subsets from people with RA revealed that the inhibitory receptors PD-1, BTLA and TIGIT were expressed on pathogenic T_{PH} cells and follicular helper T (T_{FH}) cells. Conversely, the ligands of these receptors (PD-L2 (PD-1), HVEM (BTLA) and CD155 (TIGIT)) were expressed on various stromal and immune cell populations.

In an in vitro co-culture, antigen-presenting cells (APCs) with high expression of these ligands activated inhibitory receptor signalling and subsequently reduced pro-inflammatory cytokine production by pathogenic T_{PH} cells and other $CD4^+$ T cells from RA synovial fluid. PD-L2-mediated PD-1 activation had the strongest inhibitory effects.

To assess if these effects were restricted to the RA synovium, scRNA-seq was performed on T cells from human tonsils. In this tissue, PD-L2 activation of PD-1 signalling in T_{FH} cells also had the strongest inhibitory effects on cytokine production. PD-L2-expressing APCs or a PD-1 agonist antibody also suppressed pro-inflammatory cytokine production in $CD4^+$ T cells from the blood (that is, circulating T cells) of healthy individuals. This inhibitory effect was lost when PD-1 was depleted from blood-derived $CD4^+$ T cells.

To more closely recapitulate stromal cell–T cell interactions in the tissue, the authors then created a 3D organoid model that contained cadherin-11^+ stromal cells with or without PD-L2 expression and $CD4^+$ T cells. Consistent with the previous results, pro-inflammatory cytokine production was reduced in cultures with PD-$L2^+$ cells, but not in those with PD-$L2^-$ cells.

To assess the effects of PD-L2 expression on T cell–B cell interactions, the authors co-cultured T cells and B cells in the 3D model system. In PD-$L2^-$ cultures, T cell activation led to the generation of T-bet^+ age-associated B cells (ABCs), whereas PD-L2 expression reduced T-bet expression and the induction of ABCs. Depletion of PD-1 in T cells attenuated this effect, which indicates that PD-L2 regulates pathogenic B cell responses indirectly through PD-1 signalling in T cells.

"Our study suggests that PD-1 agonism can suppress the function of multiple RA-relevant T cell populations, including T_{PH} cells. Future studies will further dissect out to what extent depletion versus activation of PD-1 on synovial T cells confers the clinical benefit seen with PD-1 agonists and PD-1-depleting antibodies in RA thus far," concludes Deepak Rao, corresponding author of the study.

Holly Webster

Original article: Higashioka, K. et al. PD-1 signalling restrains pathogenic T peripheral helper and effector $CD4^+$ T cell functions in rheumatoid arthritis. *Ann. Rheum. Dis.* https://doi.org/10.1016/j.ard.2026.06.007 (2026)

Related article: Kuchroo, J. R., Goldman, N. & Sharpe, A. H. PD-1, BTLA and TIGIT as therapeutic targets for rheumatic disease. *Nat. Rev. Rheumatol.* **22**, 89–104 (2026)

Psoriatic arthritis

https://doi.org/10.1038/s41584-026-01404-3

Going beyond cycling versus swapping for treatment sequencing in psoriatic arthritis

Jose Manuel Lema Martinez & Laura C. Coates

After treatment failure in psoriatic arthritis (PsA), choosing the next therapy involves more than simply cycling within a drug class or switching to another. Treatment sequencing is increasingly guided by dynamic, individualized strategies that account for a patient's long-term care pathway.

REFERS TO: Tomo, A. T. J. et al. Cycling versus swapping strategies for treatment of psoriatic arthritis after primary tumour necrosis factor inhibitors failure: a systematic review and meta-analysis. *Rheumatology* **65**, keag281 (2026).

The therapeutic landscape for psoriatic arthritis (PsA) has expanded dramatically over the past two decades. Alongside TNF inhibitors, clinicians can now choose from therapies targeting IL-17, IL-23, Janus kinases (JAKs) and other pathways, providing an increasingly diverse armamentarium for managing this heterogeneous disease[1]. Yet with greater therapeutic choice comes a new challenge: how do we select and sequence advanced therapies in PsA?

A 2026 meta-analysis has examined cycling versus swapping strategies after primary failure of a TNF inhibitor[2]. This study addresses one of the most clinically relevant questions encountered in routine practice, particularly as the increased use of targeted therapies leads to an expansion of the numbers of patients who will have been treated with more than one drug. The study synthesizes evidence from five observational studies, including 2,300 individuals with PsA, comparing outcomes in patients who receive a second TNF inhibitor ('cycling') with those who switch to a therapy with a different mechanism of action ('swapping'). The authors found that cycling and swapping strategies produce similar rates of response, 12-month retention and adverse effects, suggesting that either approach could be appropriate depending on patient characteristics.

For many years, cycling within the TNF inhibitor class was the default strategy after treatment failure[3]. The arrival of several targeted therapies has challenged this approach. Mechanistically, there are compelling reasons to believe that patients who fail to respond to treatment with one TNF inhibitor, particularly those who experience primary non-response, might benefit from a treatment that targets a different inflammatory pathway. The current meta-analysis[2] therefore addresses a question with immediate practical implications for clinicians, patients and guideline developers.

However, the authors also highlight the serious risk of bias in most of the studies that they included in their analysis owing to uncontrolled confounding in these observational studies. Treatment allocation is rarely random; decisions are influenced by disease manifestations, comorbidities, previous treatment experience, patient preferences and local prescribing practices. As a result, comparisons between cycling and swapping strategies are susceptible to confounding by indication. Patients who are switched to a drug with a different mechanism of action might differ systemically from those who receive another TNF inhibitor, making it difficult to determine whether observed differences in outcomes reflect treatment effects or underlying patient characteristics. The study therefore contributes to an evolving evidence base rather than providing a definitive answer.

Although the findings of the study provide valuable insight into treatment sequencing that is based on real-world evidence, they also highlight a broader issue: the field might be asking a question that is important but insufficient. In the setting of a lifelong condition, in which patients typically cycle through several medications over years of treatment, we need to think broadly about treatment sequencing from the time of diagnosis through to established disease.

Addressing this challenge will require a new generation of studies specifically designed to investigate treatment sequencing. Most trials evaluate therapies in isolation rather than as components of a long-term treatment pathway, yet treatment decisions in routine care are inherently sequential. One useful framework is the dynamic treatment strategy: a set of pre-specified decision rules that guide treatment adaptation over time according to patient characteristics and response, resulting in a set of possible dynamic treatment regimes. Sequential multiple assignment randomized trials (SMARTs)[4] are specifically designed to evaluate such strategies. Figure 1 shows an example of a two-stage SMART for treatment sequencing after failure of a TNF inhibitor, in which patients are randomized to either cycle to another anti-TNF or swap to a different drug class, and are then re-randomized according to their response. Because randomization occurs at each stage, SMARTs enable the comparison of several treatment strategies within a single trial free from confounding by indication, making it possible to determine not only whether cycling or swapping is preferable on average, but which sequencing rule performs best for which patients.

Throughout the treatment pathway in PsA, decisions are already individualized to a considerable extent. Clinicians routinely consider the relative importance of different disease domains when selecting therapy: psoriasis, axial involvement, enthesitis, dactylitis, related conditions and comorbidities all influence treatment selection[1]. The challenge is that this approach remains relatively crude. PsA encompasses a diverse collection of clinical phenotypes that probably arise from overlapping but distinct biological processes. Two patients who both experience primary failure of a TNF inhibitor could have fundamentally different drivers of disease and, consequently, different probabilities of responding to subsequent therapies. Current evidence offers only limited guidance on how to distinguish between them.

This observation points towards a more fundamental question. Rather than asking whether cycling or swapping is generally preferable, should we instead be asking which patients are most likely to benefit

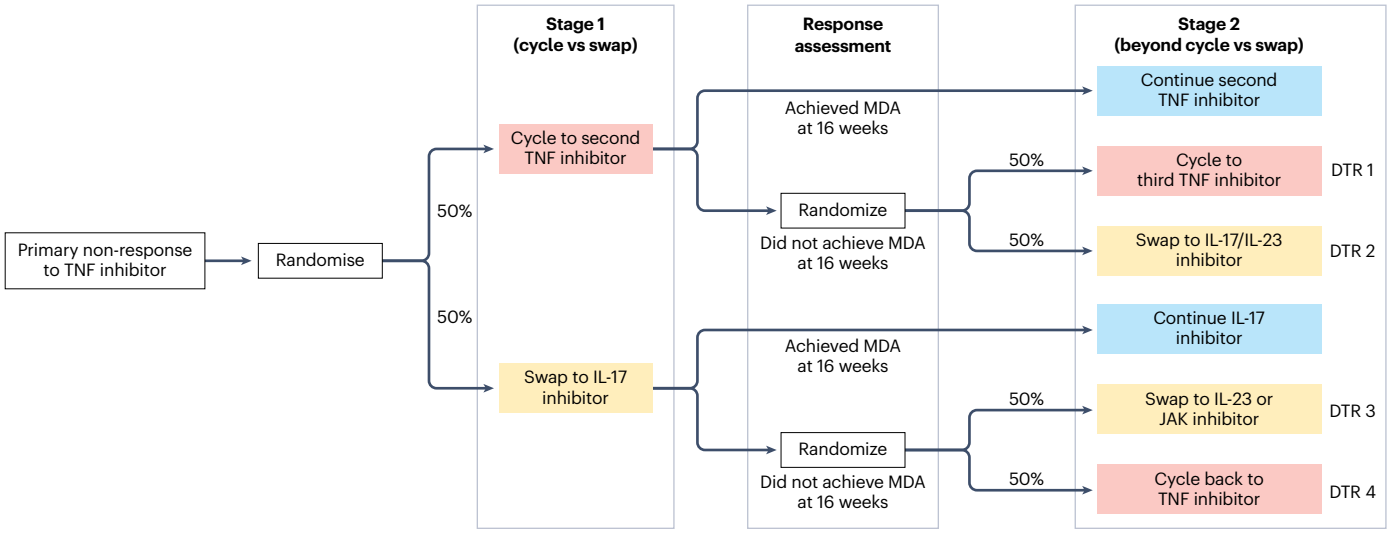


Fig. 1 | Example of a two-stage SMART design for treatment sequencing in PsA. After primary failure of TNF inhibition, patients with psoriatic arthritis (PsA) are randomized to cycle to a second TNF inhibitor or swap to an IL-17 inhibitor; non-responders (that is, those who do not achieve minimal disease activity (MDA)) are re-randomized to a tailored next-line strategy creating dynamic treatment regimes (DTRs). The four pathways (DTR 1–4) represent distinct embedded dynamic treatment strategies.

from each strategy? In diseases characterized by substantial clinical and biological heterogeneity, average treatment effects might obscure important differences between patient subgroups. This observation underpins the growing interest in the possibility of precision medicine[5]. The goal is not to determine the best next treatment in a treatment pathway at an average group level, but to identify the treatment most likely to benefit a specific patient before therapy begins. Advances in molecular profiling, imaging and biomarker discovery have generated optimism that such an approach could eventually be achievable[6]. Several avenues are being explored. Studies examining synovial tissue, skin pathology and molecular endotypes have already demonstrated substantial heterogeneity among patients with clinically similar disease. Blood-based biomarkers offer the advantages of accessibility and scalability, whereas tissue-based approaches can provide a more direct window into disease biology. Integrating these biological insights with clinical phenotyping could ultimately enable more rational treatment selection.

Nevertheless, important challenges remain. Few candidate biomarkers have demonstrated sufficient reproducibility or predictive performance for use in routine clinical practice. Synovial tissue sampling is not currently practical at scale, and translating complex molecular data into clinically actionable decisions remains difficult.

Against this backdrop, the current meta-analysis[2] serves as a timely reminder of both how far the field has progressed and how far it still needs to go. The question of cycling versus swapping matters because treatment failure is common and subsequent decisions have important consequences for patients. However, the debate over cycling versus swapping is not merely about choosing the next drug but about designing longitudinal care pathways to support sequential decision-making and ongoing efforts to personalize this approach for the individual patient. It is part of a larger transition from empirical treatment selection towards genuinely personalized care. The challenge now is to generate the evidence needed to make that transition a reality.

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Competing interests

L.C.C. declares that she has received grants and/or research support from AbbVie, Amgen, Janssen and UCB; has worked as a paid consultant for AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Enlivex, Janssen, Moonlake, Novartis, Pfizer, Proximi-T, Takeda and UCB; and has received speaker fees from AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer and UCB. J.M.L.M. declares no competing interests.

Autoinflammatory diseases

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When less is more: loss of IRAK2 signalling promotes inflammation

Adriana A. de Jesus

The identification of IRAK2 deficiency reveals how impaired Myddosome signalling can paradoxically promote interferon-driven inflammation, which expands the spectrum of monogenic immune dysregulation and underscores the importance of detecting structural variants in unsolved inborn errors of immunity.

Refers to Fei, Y. et al. IRAK2 deficiency causes immune dysregulation through defective Myddosome assembly and enhanced interferon responses. *Nat. Commun.* https://doi.org/10.1038/s41467-026-73383-8 (2026).

The expanding landscape of inborn errors of immunity (IEIs) continues to challenge traditional distinctions among immunodeficiency, autoimmunity and autoinflammation, demonstrating that the boundary between common rheumatological disease and rare monogenic immune dysregulation is less clearly defined than previously appreciated[1]. Reporting in *Nature Communications*, Fei et al. identify a biallelic copy-number variant (CNV) in *IRAK2* in 12 patients from 11 unrelated families and establish IRAK2 deficiency (termed DIRAK2) as a novel monogenic immune dysregulation disorder[2]. Beyond defining a new disease entity, the study provides mechanistic insights into innate immune signalling, highlights the importance of structural genomic variation as a cause of previously unsolved immune disorders, and offers clinical lessons that extend far outside rare disease.

IRAK2 is a key structural component of the Myddosome, a supramolecular signalling complex assembled downstream of Toll-like receptors (TLRs) and the IL-1 receptor. Comprising MyD88, IRAK4 and IRAK2, the Myddosome mainly activates the NF-κB and MAPK pathways to coordinate pro-inflammatory cytokine production and antimicrobial host defence[3,4]. Although it has been studied extensively in mouse models, human disease resulting specifically from DIRAK2 had not previously been described.

Fei et al. identified 12 patients from 11 unrelated Chinese families, all carrying the same homozygous in-frame deletion of exon 2 of *IRAK2* (*IRAK2*-Δex2)[2]. The breadth of clinical manifestations is striking. Four patients fulfilled classification criteria for systemic lupus erythematosus (SLE) accompanied by lupus nephritis; one was diagnosed with juvenile idiopathic arthritis (JIA); one was diagnosed with autoimmune encephalitis; and one was diagnosed with Hashimoto thyroiditis. Two patients developed gastrointestinal ulceration that resembled inflammatory bowel disease, whereas two others presented predominantly with recurrent infections. This phenotypic spectrum, which led the authors to classify affected patients into immunodeficiency-predominant, autoimmunity-predominant and autoinflammation-predominant subgroups, will resonate with rheumatologists who frequently encounter patients whose clinical features span these categories[2]. More broadly, DIRAK2 reinforces an emerging theme in human immunology: defects in innate immune pathways often manifest not only as susceptibility to infection but also as impairment of immunotolerance and immunoregulation.

The mechanistic investigation is comprehensive and particularly compelling because it reveals an unexpected signalling paradox. Structural analyses demonstrated that deletion of *IRAK2* exon 2 markedly disrupts the interaction between IRAK2 and IRAK4, preventing efficient Myddosome assembly. As anticipated, patient-derived cells showed impaired NF-κB activation and reduced production of pro-inflammatory cytokines following TLR stimulation. Likewise, knock-in mice carrying the same mutation were more resistant to high-dose lipopolysaccharide challenge but displayed impaired bacterial clearance. This duality mirrors the clinical phenotype, in which susceptibility to infection was generally milder than that reported for MyD88 or IRAK4 deficiency[5,6], probably reflective of the partially redundant functions of IRAK1 and IRAK2 in human TLR signalling.

The most important finding, however, lies beyond this expected signalling deficit. Despite defective Myddosome-dependent NF-κB activation, patients displayed elevated serum IFN-β, enhanced basal IRF3 phosphorylation and a prominent interferon-stimulated gene signature, most pronounced in those with SLE or lupus nephritis. Transcriptomic analyses of inflammatory monocytes confirmed activation of the type I interferon pathway, while principal component analysis clustered patients with DIRAK2 with interferonopathies rather than with classic Myddosome deficiencies, which has important implications for disease classification and treatment. The authors attribute this paradoxical response to a relative shift towards TRIF-dependent signalling when the Myddosome is disrupted, which results in excessive type I interferon production. Rather than simply dampening innate immunity, impaired Myddosome signalling rewires the balance between parallel signalling pathways, producing an interferonopathy-like state. DIRAK2 joins a growing group of monogenic disorders in which defective innate immune signalling drives autoimmunity and autoinflammation as readily as immunodeficiency (Fig. 1), which illustrates the fact that immune signalling pathways function as interconnected regulatory networks rather than as linear cascades[7].

The clinical spectrum of DIRAK2 also invites comparison with NASA (neuroinflammation, autoinflammation, splenomegaly and anaemia) syndrome caused by biallelic *IRAK4* variants, which similarly broadened the phenotypic consequences of defects within the Myddosome pathway beyond classic susceptibility to infection[8]. DIRAK2, however, extends this paradigm further: the prominent interferon signature

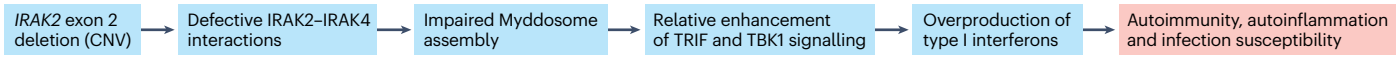

Fig. 1 | DIRAK2 links impaired Myddosome assembly to interferon-driven immune dysregulation. A biallelic exon 2 deletion in *IRAK2* disrupts IRAK2–IRAK4 interactions and Myddosome assembly, shifting signalling towards TRIF- and TBK1-mediated type I interferon responses and contributing to autoimmunity, autoinflammation and infection susceptibility. CNV, copy-number variant.

and autoimmune burden more closely resemble an interferonopathy than a conventional immunodeficiency, particularly in patients with SLE, lupus nephritis or JIA[2,9]. Together, these observations reinforce the view that defects that affect the Myddosome occupy a clinically and mechanistically heterogeneous spectrum that cannot be defined solely by susceptibility to infection.

Beyond mechanistic insights, the study also carries an important lesson for genomic diagnosis. The causal variant is not a single-nucleotide variant but is a recurrent homozygous CNV that occurs within a genomic region susceptible to Alu-mediated recombination that results in an in-frame truncated protein. Remarkably, all 11 unrelated families shared identical genomic breakpoints, and the variant is enriched in East Asian populations, with an allele frequency of approximately 1.4% in structural variant databases. These observations raise the strong possibility that DIRAK2 is substantially underdiagnosed.

This finding carries important implications for the diagnosis of IEIs. Although next-generation sequencing has transformed the assessment of patients with suspected monogenic immune disorders, many diagnostic pipelines remain optimized for the detection of single-nucleotide variants and small insertions or deletions. Exon-level deletions and duplications might therefore be overlooked unless dedicated CNV analyses are incorporated into routine workflows. Consequently, a substantial proportion of patients with compelling clinical phenotypes remain without a genetic diagnosis despite extensive sequencing[10]. DIRAK2 functions as a timely reminder that structural variation remains an important and underappreciated contributor to human immune disease. Routine incorporation of CNV detection into genomic diagnostic pipelines could therefore improve diagnostic yield, particularly in patients who present with unexplained immune dysregulation.

The study also raises intriguing therapeutic questions. Several patients exhibited elevated interferon signatures, and ex vivo treatment with the JAK inhibitor baricitinib attenuated activation of the interferon pathway. Although preliminary, these findings suggest that interferon-directed therapies might warrant investigation in selected patients with DIRAK2-associated autoimmunity. Future studies should determine whether interferon signatures correlate with disease activity, whether targeted inhibition translates into clinical benefit, and whether such therapies are safe and effective in this specific context.

By identifying DIRAK2 as a cause of immune dysregulation, Fei et al. reveal a previously unrecognized homeostatic role for IRAK2 and demonstrate how impaired Myddosome signalling can paradoxically promote interferon-mediated inflammation[2]. Equally importantly, their work highlights the contribution of structural genomic variation to the genetic architecture of IEIs. More broadly, the study conveys a lesson with growing resonance across immunology: within the highly interconnected networks of innate immunity, less signalling does not necessarily mean less inflammation.

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Competing interests

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Review article

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Advances in the treatment of eosinophilic granulomatosis with polyangiitis

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Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) is a small-vessel vasculitis associated with anti-neutrophil cytoplasmic antibodies and characterized by blood and tissue eosinophilia, severe respiratory manifestations, and multiorgan involvement. The management of newly diagnosed EGPA still relies on therapeutic strategies that were initially validated for other forms of anti-neutrophil cytoplasmic antibody-associated vasculitis, including microscopic polyangiitis and granulomatosis with polyangiitis. Whereas the long-term prognosis of microscopic polyangiitis and granulomatosis with polyangiitis depends primarily on controlling initial organ involvement and preventing relapses, EGPA is distinguished by chronic involvement of both upper and lower respiratory airways, which often necessitates prolonged glucocorticoid therapy. Data from clinical trials suggest that targeting the IL-5 pathway with mepolizumab or benralizumab can effectively control persistent respiratory symptoms and reduce the need for glucocorticoids, yet the role of these agents in the management of EGPA at the time of diagnosis and in the long term remains to be defined. Emerging retrospective data on therapies targeting other type 2 cytokines (such as IL-4, IL-13 and thymic stromal lymphopoietin) suggest potential benefits for relapsing respiratory symptoms; however, prospective evidence remains limited and safety has yet to be established. This Review discusses the role of these new targeted therapies in the management of EGPA, alongside historical treatments.

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Similarities and differences in management of EGPA and other AAVs

Conventional immunosuppressive therapies for EGPA

Targeting the IL-5 pathway

Targeting other T2 inflammation pathways and beyond

Additional considerations for optimizing EGPA management

Conclusions

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Key points

- Depending on disease severity, glucocorticoids and cyclophosphamide remain the cornerstone of remission-induction therapy in eosinophilic granulomatosis with polyangiitis.
- Despite the high efficacy of remission-induction therapies, more than half of patients with eosinophilic granulomatosis with polyangiitis experience persistent glucocorticoid-dependent, difficult-to-control lower and upper respiratory manifestations.
- In a randomized controlled trial, rituximab was not superior to conventional immunosuppressive strategies in terms of inducing and maintaining remission but demonstrated similar response rates.
- Therapies targeting the IL-5 pathway (mepolizumab and benralizumab) have proven to be effective in randomized controlled trials for inducing remission, controlling respiratory manifestations and preventing relapses while facilitating glucocorticoid withdrawal.
- IL-5 pathway-targeting therapies have an excellent safety profile, with only rare and generally mild adverse effects.
- Novel therapies, including ultra-long-acting anti-IL-5 agents (for example, depemokimab), therapies targeting other type 2 cytokines (thymic stromal lymphopoietin, IL-33 and IL-13) and Janus kinase inhibitors, are being evaluated in prospective trials.

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a syndrome that was first described in 1951 by Jacob Churg and Lotte Strauss. It is characterized by severe eosinophilic asthma and multiorgan involvement resulting from eosinophilic infiltration and necrotizing, granulomatous vasculitis of small vessels[1]. Since the 1994 Chapel Hill Consensus Conference nomenclature, which was revised in 2012, EGPA has been classified as a small-vessel vasculitis within the spectrum of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)[2,3]. It is distinguished from the other AAVs, namely microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), as well as from polyarteritis nodosa (PAN; a medium-vessel vasculitis), by the presence of asthma and circulating or infiltrating eosinophilia[2,3]. However, less than half of EGPA cases are ANCA-positive, predominantly with specificity for myeloperoxidase (MPO-ANCA), although ANCA directed at proteinase 3 (PR3) have been observed in a small subset[4].

EGPA is the rarest of all AAVs. Its incidence is estimated at 1–4 cases per million people per year, and its global prevalence at 15 cases per million people[5–8]. However, in patients with asthma, EGPA has a prevalence of up to 80 cases per million people[9,10]. Asthma is present in nearly all cases of EGPA and becomes apparent a mean of 3–12 years before EGPA diagnosis[4,11,12]. It is characteristically severe and worsens prior to the development of systemic and vasculitic manifestations[11,13]. Rhinosinusitis with or without nasal polyps is present in 50–80% of cases of EGPA and, unlike in GPA, is typically non-crusting and non-destructive[14,15]. Although not considered a severe disease manifestation, upper respiratory tract involvement can severely impair the quality of life of people with EGPA[4,16,17]. By contrast, systemic involvement can threaten organ function and be life-threatening[4,18]. For many patients, extra-pulmonary involvement differs in distribution according to ANCA status[4,19–22]. Patients with ANCA-positive EGPA tend to present with more vasculitic manifestations, such as glomerulonephritis, mononeuritis multiplex and purpura, whereas those with ANCA-negative disease tend to exhibit a predominance of eosinophilic manifestations, including eosinophilic cardiomyopathy and gastroenteritis. ANCA-negative EGPA can sometimes overlap with hypereosinophilic syndromes (HES), which can present with both upper and lower airway disease and systemic eosinophil-mediated complications[23,24]. The management of AAVs, including EGPA, is divided into remission-induction strategies, which aim to control systemic and airway manifestations, and remission-maintenance strategies, which aim to prevent relapses while enabling glucocorticoid tapering. Unlike in GPA and MPA, more than half of patients with EGPA continue to experience glucocorticoid-dependent and difficult-to-control respiratory manifestations even after the systemic disease is under control[5,11,18,25–27]. Chronic glucocorticoid dependency impairs quality of life and predisposes more than half of patients with EGPA to glucocorticoid-related complications, including osteoporosis, type 2 diabetes mellitus, cataract, glaucoma, hypertension and infections[18,26,28–31].

Growing insight into EGPA pathophysiology has highlighted the central role of type 2 inflammation (T2), particularly IL-5-driven eosinophil activation and survival, alongside ANCA-mediated neutrophil and complement activation, which are shared with other AAVs[32,33]. ANCAs are produced by autoreactive B lymphocytes, thereby identifying these cells as a key therapeutic target in AAVs[34]. These overlapping yet distinct mechanisms, supported by histopathological and genetic findings, help explain the heterogeneity of organ involvement and clinical phenotypes in EGPA[35,36]. As understanding of these pathways has expanded, treatment strategies have progressively moved beyond traditional glucocorticoid-based regimens towards biologic therapies targeting eosinophil activation pathways and B cells, reflecting a shift towards more mechanism-based and individualized management. Figure 1 summarizes these different pathogenic pathways and their respective therapeutic targets.

Although the diagnostic work-up and evaluation of EGPA have been thoroughly described in previous publications, it is important to recall the need to first exclude other eosinophilic disorders, such as drug hypersensitivity, malignancy (for example, lymphoma) or infection[37–40]. This Review explores the continued relevance of historic EGPA treatments in the remission-induction phase, the bearing of therapies targeting the IL-5 pathway on long-term EGPA management, and the potential application in EGPA of treatment strategies for AAV and eosinophilic disease.

Similarities and differences in management of EGPA and other AAVs

Over the past decade, the management of EGPA and other AAVs has evolved considerably, reflecting both advances in therapeutic options and a growing recognition of disease-specific features. Treatment strategies have progressively diverged from a unified approach to AAVs towards a more individualized management of EGPA, shaped by differences in pathophysiology, clinical presentation and prognosis.

Evolution of recommendations for the management of AAV

The first European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of small-vessel and medium-vessel vasculitis, published in 2009, covered all forms of AAV together, including MPA, GPA and PAN. High doses of glucocorticoids

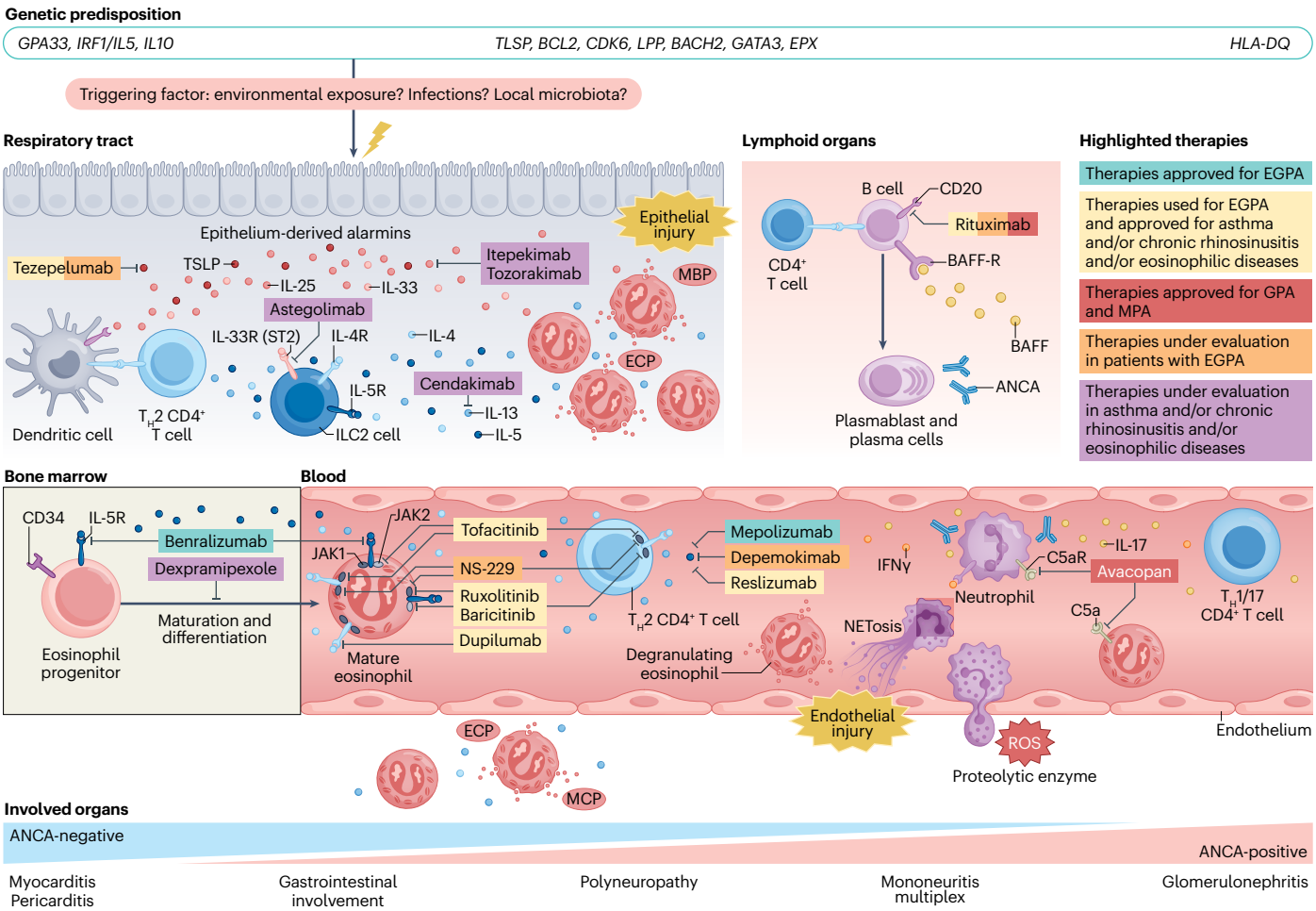

Fig. 1 | Pathophysiological pathways and targeted treatment in EGPA. The cytokine IL-5 is an essential contributor to the maturation, proliferation and differentiation of eosinophils and their precursors. It inhibits apoptosis, thereby promoting eosinophil survival, and facilitates tissue migration and degranulation[96–98,220]. Elevated IL-5 levels have been demonstrated in the serum and bronchoalveolar lavage fluid of patients with active eosinophilic granulomatosis with polyangiitis (EGPA). However, direct evidence that IL-5 contributes to EGPA pathogenesis remains limited[145,221]. IL-5 is antagonized by mepolizumab, depemokimab and reslizumab. Eosinophil progenitors and mature eosinophils express IL-5 receptor (IL-5R) and are depleted by benralizumab. The likely sources of IL-5 are type 2 innate lymphoid cells (ILC2s) and CD4$^+$ T2 cells present in the lungs, after activation by alarmins, such as thymic stromal lymphopoietin (TSLP) and IL-33, produced by the respiratory epithelium after aggression[221–224]. TSLP is inhibited by tezepelumab, and IL-33 by itepekimab and tozorakimab. The IL-33 receptor, ST2, is inhibited by astegolimab. Other T2 cytokines produced by ILC2s and T2 CD4$^+$ T cells include IL-4 and IL-13. The IL-4 receptor α-chain, which engages both IL-4 and IL-13, is inhibited by dupilumab. IL-13 is also inhibited by cendakimab. The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway has a central role in eosinophil, neutrophil, and T2-skewed T cell activation and in the production of key cytokines, such as IL-4, IL-5, IL-13 and IL-31 (ref. 225). The JAK–STAT pathway is inhibited by tofacitinib (JAK1/JAK3 inhibitor), ruxolitinib and baricitinib (JAK1/JAK2 inhibitors) and NS-229 (JAK1 inhibitor). EGPA and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis share the core feature of ANCA production by autoreactive B cells that bind to myeloperoxidase expressed on neutrophils, which triggers complement-dependent activation, degranulation and the release of neutrophil extracellular traps (NETs)[32]. Autoreactive B cells express CD20 and are depleted by rituximab. C5a, generated by the alternative complement pathway, is a key factor of neutrophil and eosinophil activation; its receptor C5aR is inhibited by avacopan. ECP, eosinophil cationic protein; GPA, granulomatosis with polyangiitis; MBP, major basic protein; MPA, microscopic polyangiitis; ROS, radical oxygen species; T$_H$, helper T.

combined with either cyclophosphamide or methotrexate were recommended as remission-induction therapies, depending on the presence of organ or life-threatening involvement, while azathioprine, methotrexate or leflunomide were recommended for remission maintenance[41]. The 2014 guidelines endorsed by the European Respiratory Society and Foundation for the Development of Internal Medicine in Europe, and subsequently the 2021 American College of Rheumatology–Vasculitis Foundation (ACR–VF) guidelines, the 2022 updated EULAR recommendations and the 2023 European EGPA Study Group guidelines, have individualized EGPA management and introduced several changes of paradigm[37,38,42,43]. For severe disease, induction of remission still relies on a combination of high-dose glucocorticoids and cyclophosphamide, with rituximab as an alternative, and maintenance of remission relies on conventional synthetic DMARDs

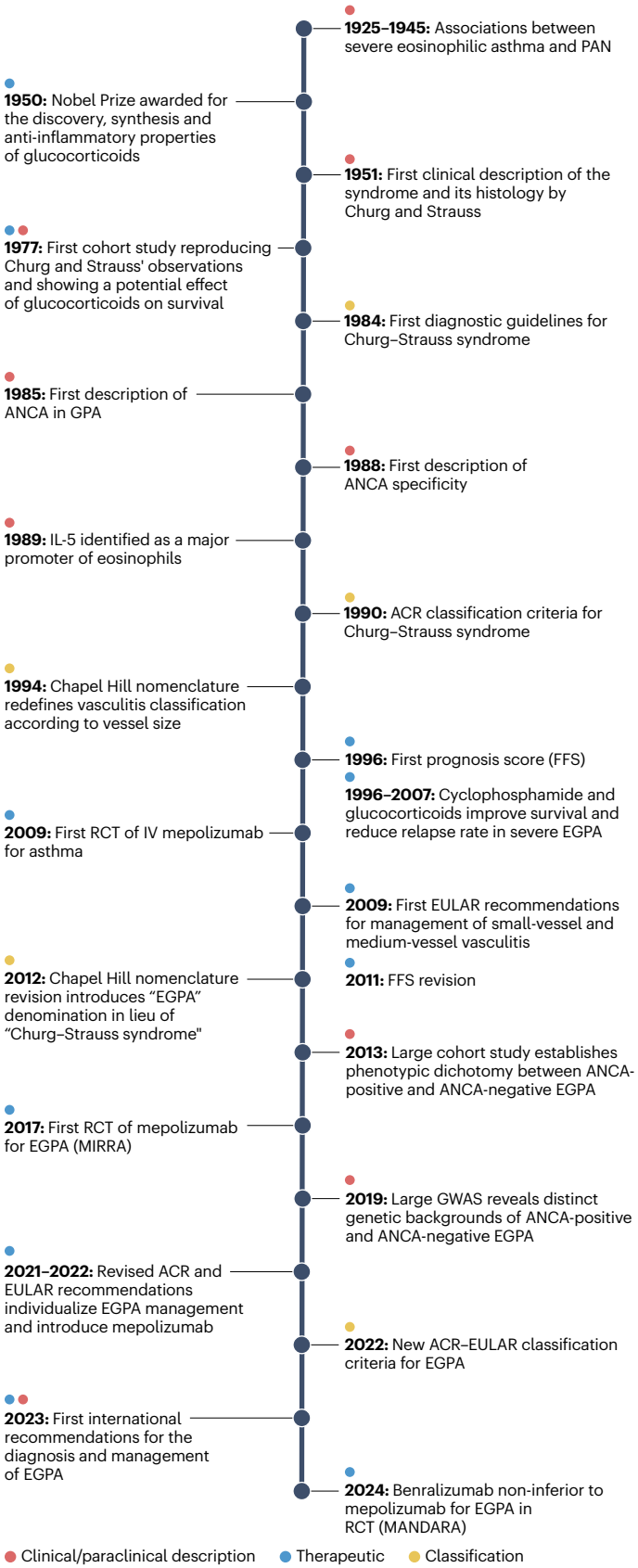

Fig. 2 | Main advances in diagnostic criteria and therapeutic strategies in EGPA. The understanding of eosinophilic granulomatosis with polyangiitis (EGPA) underwent a major turning point in the 1980s with the discovery of anti-neutrophil cytoplasmic antibodies (ANCAs) and the characterization of IL-5. The distinction of EGPA from other forms of ANCA-associated vasculitis and polyarteritis nodosa (PAN) was further refined in the 2000s. Advances in the comprehension of type 2 inflammation (T2)-driven pathways involved in eosinophilic diseases have provided growing evidence for the efficacy of anti-IL-5 targeted therapies, such as mepolizumab and benralizumab, in asthma and chronic rhinosinusitis. These findings were extended to EGPA, with the MIRRA trial published in 2017. Over the past 5 years, refined classification criteria have been developed, EGPA-specific management has been individualized in the latest American and European recommendations, and the efficacy of benralizumab has been demonstrated in the MANDARA trial. ACR, American College of Rheumatology; EULAR, European Alliance of Associations for Rheumatology; FFS, five-factor score; GPA, granulomatosis with polyangiitis; GWAS, genome-wide association study; IV, intravenous; RCT, randomized controlled trial.

(csDMARDs), including methotrexate, azathioprine and mycophenolate mofetil, with the introduction of mepolizumab or rituximab introduced as alternatives within the past 10 years. Recommendations for the induction of remission in non-severe disease diverge regarding the combination of immunosuppressants. The ACR–VF panel prefers mepolizumab in addition to glucocorticoids as initial treatment[43], whereas the EULAR and European EGPA Study Group panels recommend initially using glucocorticoids without additional immunosuppressants and adding mepolizumab in case of relapse or refractory manifestations[37,42].

Most of these recommendations were supported by low-quality or indirect evidence and expert opinion, with the exception of the randomized controlled trial (RCT) of mepolizumab (MIRRA trial), and were often based on treatment of vasculitis other than EGPA[44]. These factors limit the generalizability of the recommendations and underscore the importance of a personalized approach, tailored to each patient's specific manifestations and disease severity. Figure 2 summarizes the most notable developments in the classification and management of EGPA.

Prognosis stratification

Prognosis stratification guides the intensity of initial treatment. Given the rarity of EGPA, as well as the heterogeneity of its manifestations and their respective underlying mechanisms, their potential severity and chronic evolution, and the expanding choice of available treatments, diagnosis, evaluation of prognosis and tailored management of EGPA should be conducted in collaboration with, or within, centres with experience of vasculitis and/or eosinophilic diseases[38,41,45].

Historically, the severity of MPA, EGPA and PAN was assessed using the original five-factor score (FFS), which considered kidney involvement (defined by proteinuria >1 g per day or creatinine >139 µmol/l), cardiomyopathy, severe gastrointestinal involvement, and central nervous system involvement[46]. The FFS was revised in 2009 to also apply to GPA and to predict mortality on the basis of four factors associated with poor prognosis and one factor associated with a better outcome; scores of 1 and ≥2 are associated with a doubled and quadrupled risk of mortality at 5 years, respectively[47].

Currently, the FFS adequately captures the most common, severe and organ-threatening manifestations observed in AAVs and PAN. However, it might underestimate or overestimate the severity of some EGPA-specific manifestations. For example, the FFS does not consider

severe peripheral neuropathy because it is not associated with mortality but undertreatment of this manifestation could lead to persistent neurological sequelae[48,49]. Additionally, it does not include specific chest CT findings, such as ground-glass opacities, that have been linked to an elevated risk of glucocorticoid dependency[50]. Conversely, cardiac involvement might be overestimated due to the increasing use of cardiac MRI. Late gadolinium enhancement of the myocardium can be present in the absence of overt cardiomyopathy. This MRI finding has no effect on cardiac manifestations or outcomes and could fail to differentiate acute inflammatory and chronic fibrotic lesions[51–53]. ^{18}F-fluorodeoxyglucose-PET–CT could help detect active myocardial inflammation, but its validity and prognostic value have not been specifically or prospectively evaluated in EGPA[51]. Although poorly defined in the relevant studies, cardiac involvement has been independently associated with mortality in several studies[4,22,54,55]. Various prognostic scores for heart failure, such as MAGGIC, MECKI, HFSS and SHFM, are available but none were developed specifically for EGPA[56,57]. A retrospective study of patients with EGPA reported a higher risk of short-term mortality in those with acute eosinophilic myocarditis than in those with chronic inflammatory cardiomyopathy[55]. On the basis of these findings, the LATE-EAST score was proposed to help differentiate between these two forms of cardiac involvement. Nevertheless, optimal means for screening, diagnostic thresholds and risk stratification with respect to cardiac involvement remain to be established and require validation in prospective studies.

Current recommendations stratify remission-induction therapy according to a non-restrictive list of life-threatening or organ-threatening manifestations of EGPA. These manifestations include cardiac involvement, glomerulonephritis, mesenteric ischaemia, mononeuritis multiplex and central nervous system vasculitis[37,42,43]. The accurate identification and assessment of these manifestations in terms of both specificity and severity requires early diagnostic consideration and collaboration with experienced physicians[38,41].

Conventional immunosuppressive therapies for EGPA

Conventional immunosuppressive therapies have long formed the foundation of both induction and maintenance treatment in EGPA, with the use of glucocorticoids and cytotoxic agents to control disease activity and prevent organ damage. However, clinical trials in the 2010s began to challenge these traditional approaches, with the aim of treatment shifting to the achievement of effective disease control while minimizing long-term treatment-related toxicity. The main conventional therapies and their preferred regimen for induction and maintenance of remission in EGPA are summarized in Table 1.

The past, current and future place of glucocorticoids

Moderate to high doses of glucocorticoids are the cornerstone of EGPA treatment during the remission-induction phase, with the aim of quickly controlling systemic and respiratory manifestations of the disease. The use of glucocorticoids in EGPA was first documented by the Mayo Clinic in 1977 and was subsequently characterized in several pooled EGPA and PAN prospective studies between the 1980s and early 2000s[46,58–60]. The first 2009 EULAR recommendations for the management of small-vessel and medium-vessel vasculitis reflected this historical practice by recommending glucocorticoids at an initial daily dose of 1 mg/kg per day, followed by gradual tapering to 15 mg per day after 3 months and a maintenance dose of 10 mg per day[41].

The PEXIVAS and LOVAS trials, which included participants with GPA and MPA, demonstrated that reduced-dose glucocorticoid regimens for remission-induction therapy were non-inferior to standard-dose regimens while reducing the risk of serious infections[61,62]. These regimens aim to achieve a daily glucocorticoid dose of 5 mg within 5 months and complete withdrawal within 2 years. Glucocorticoid exposure could be shortened to as little as 4 weeks by combining glucocorticoids with the oral C5a receptor antagonist avacopan, as demonstrated in the ADVOCATE study in patients with GPA and MPA[63]. However, such reduced-dose regimens and early withdrawal of glucocorticoids might not be appropriate for the management of EGPA, as non-severe, glucocorticoid-dose-dependent respiratory relapses are common. In EGPA studies conducted before the widespread use of therapies targeting IL-5 or the IL-5 receptor (IL-5R), the median maintenance daily glucocorticoid dose remained ~10 mg per day after several years of follow-up[44,64–66].

Consequently, an initial daily glucocorticoid dose of 0.5 mg/kg to 1 mg/kg is still recommended in non-severe and severe EGPA cases, respectively, with pulse methylprednisolone therapy beforehand in severe cases, and concomitant immunosuppressants depending on disease severity[37,42,43]. In line with current clinical practice, glucocorticoids should be tapered slowly, targeting a maximum dose of 15–20 mg daily at 3 months and a maintenance dose of 5 mg daily after 6 months[17,27]. As an example, the tapering schedule used in the REOVAS trial[67] is shown in Supplementary Table 1. However, the long-standing paradigm of slow tapering and prolonged maintenance of glucocorticoid therapy in EGPA might now be reconsidered with the advent of T2-targeting therapies (Supplementary Table 2). Prospective evaluations of optimal tapering schedules and withdrawal strategies are still lacking.

Cyclophosphamide and rituximab

Cyclophosphamide. Cyclophosphamide is an alkylating agent originally used in oncology but its use was diverted to immunology owing to its immunosuppressive effects on B cells, T cells, neutrophils and eosinophils[68,69]. In EGPA, cyclophosphamide was first evaluated prospectively in the 1990s in pooled EGPA and PAN studies after its efficacy was demonstrated in GPA in the 1980s[58,60,70,71]. These uncontrolled studies suggested a pivotal role of cyclophosphamide in improving survival and preventing relapse in patients with poor prognosis (FFS ≥1), in whom a remission rate of nearly 90% was achieved. Since then, intravenous cyclophosphamide has remained the treatment of choice for remission induction in patients with severe EGPA manifestations[37,42,43]. However, these trials were not powered to evaluate the efficacy of cyclophosphamide among participants with EGPA specifically, making the generalization of their conclusions to patients with EGPA uncertain. Nonetheless, the historical efficacy of cyclophosphamide was corroborated in 2024 in two European target trial emulation studies[17,27], which included patients treated before the advent of therapies targeting the IL-5 pathway. The studies showed that, in patients with a poor prognosis according to the original 1996 FFS, treatment with intravenous cyclophosphamide is associated with a reduced risk of vasculitis relapse and glucocorticoid-dependent respiratory manifestations. This effect was not observed in patients without poor prognostic factors[17,27]. Adverse events associated with cyclophosphamide treatment include immediate toxic effects such as gastrointestinal symptoms, myelotoxicity and alopecia, as well as delayed complications, including infections, malignancies and bladder toxicity, with a risk of haemorrhagic cystitis and neoplasia. Gonadal toxicity can lead to amenorrhoea, infertility and teratogenesis[68]. The adverse effects of cyclophosphamide are severe and dose-dependent, with a recommendation that the cumulative dose

Table 1 | Main conventional and targeted therapies used for induction and maintenance of remission in EGPA

Therapy	Mechanism	Usual regimen	Indications	Adverse events	Key studies[a]	Comments
Glucocorticoids	Broad suppression of innate and adaptive immune cell activity via modulation of cytokine transcription and alteration of cellular signalling	Intravenous: 7.5–15 mg/kg for 1–3 days Oral: 0.5–1 mg per day, with tapering to a target of 15–20 mg at 3 months and 5 mg at 6 months	Induction and maintenance phase, with initial dose and formulation according to severity	Infections Weight gain Diabetes Dyslipidaemia Osteoporosis/necrosis Cataract Psychosis Cutaneous atrophy Amyotrophy	No prospective study has evaluated the best oral glucocorticoid regimen	A maintenance dose of 5–10 mg daily was used in most studies before the introduction of IL-5 pathway-targeting therapies[16,66] In the era of these therapies, glucocorticoid sparing should be a key therapeutic objective, with the ultimate aim of complete discontinuation
Cyclophosphamide	Inhibition of B cells, T cells, and neutrophils and eosinophil proliferation	Intravenous: 0.6 g/m^2 every 2 weeks for 1 month, then every 4 weeks thereafter for 6–12 doses	Induction phase in severe EGPA	Myelosuppression Infections Cystitis with haematuria Malignancies Infertility	Gayraud et al.[60b] Cohen et al.[25]	Although the 12-pulse regimen has shown superiority in preventing mild relapses, the 6-pulse regimen is generally preferred owing to the increased toxicity associated with higher cumulative exposure to cyclophosphamide
Rituximab	Depletion of CD20$^+$ B cells	Intravenous: 1 g on days 0 and 14 or 375 mg/m^2 weekly for 4 weeks	Induction phase in severe EGPA	Infections Hypogammaglobulinaemia Late-onset neutropenia Impaired humoral response to vaccines	REOVAS[67]	The superiority of rituximab to conventional therapy for remission induction has not been demonstrated Given its safety profile and well-established efficacy in GPA and MPA, rituximab could be an alternative option to conventional therapies for induction and maintenance phases
Azathioprine	Suppression of lymphocyte proliferation by a purine analogue	Oral: 2 mg/kg per day	Maintenance phase in severe EGPA or non-severe relapsing or refractory EGPA	Myelosuppression Infections Liver toxicity	Ribi et al.[85] CHUSPAN2 (ref. 16)[b]	Azathioprine is not recommended in the induction phase as it has failed to prove its superiority to glucocorticoids alone in non-severe EGPA[16]
Methotrexate	Inhibition of lymphocyte proliferation via inhibition of folate-dependent nucleotide synthesis, and promotion of extracellular adenosine accumulation, leading to reduced cytokine production	Oral or subcutaneous: 15–25 mg per week	Maintenance phase in severe EGPA or non-severe relapsing or refractory EGPA	Digestive intolerance Myelosuppression Infections Liver toxicity Pneumonia	Maritati et al.[87b]	Its use should be reserved for remission maintenance of non-severe vasculitis manifestations such as arthritis
Mepolizumab[c]	Inhibition of IL-5, leading to decreased proliferation, migration and activation of eosinophils	Subcutaneous: 300 mg every 4 weeks	Maintenance phase in severe EGPA or non-severe relapsing or refractory EGPA	Headaches Rare local reaction on site injection	MIRRA[44]	Prevents systemic and respiratory relapses while allowing glucocorticoid tapering, regardless of concomitant immunosuppressant administration
Benralizumab[c]	Binding to IL-5Rα leads to profound eosinophil depletion through antibody-dependent cell-mediated cytotoxicity	Subcutaneous: 30 mg every 4 weeks	Maintenance phase in severe EGPA or non-severe relapsing or refractory EGPA	Headaches Rare local reaction on site injection	MANDARA[66]	Similar remission rates to mepolizumab, yet complete glucocorticoid withdrawal achieved in a greater proportion of patients

EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis. [a]Only randomized controlled trials are cited. [b]Randomized controlled trials that include patients with EGPA, MPA, GPA or polyarteritis nodosa. [c]Mepolizumab and benralizumab are the only therapies that have received regulatory approval for the management of EGPA.

should not exceed 30 g. Therefore, continuation of cyclophosphamide is not recommended beyond 6 months when remission is achieved[37,42]. The ongoing E-MERGE trial, discussed below, will be pivotal in specifically assessing, within an EGPA population, the risk–benefit profile of cyclophosphamide compared with therapies targeting the IL-5 pathway.

Rituximab. Several RCTs in MPA and GPA have shown rituximab, an anti-CD20 monoclonal antibody that depletes autoreactive ANCA-producing B cells, to be non-inferior to cyclophosphamide for remission-induction therapy and superior to csDMARDs for remission-maintenance therapy[72–74]. Until the REOVAS trial, the use of rituximab in EGPA was supported only by small retrospective studies[75–80] (detailed in Supplementary Table 3). In these cohorts, most patients had refractory or relapsing EGPA with a baseline Birmingham Vasculitis Activity Score (BVAS) >10, reflecting highly active systemic disease. Remission, which was defined differently across studies, was achieved in 35–50% of cases within 6–12 months. On the basis of these data, rituximab was recommended as a viable alternative to cyclophosphamide for inducing remission in patients with severe EGPA[37,42,43]. The EULAR panel endorsed its use for remission-maintenance in patients with initially severe manifestations, whereas the ACR–VF panel did not, as there was no prospective evidence to support either recommendation[42,43].

The REOVAS trial, published in 2025, was the first prospective RCT to compare rituximab with the conventional treatment strategy for remission induction in patients with newly diagnosed or relapsing EGPA; the conventional strategy consisted of glucocorticoids, with or without cyclophosphamide, depending on the severity of disease[67]. The trial failed to demonstrate the superiority of rituximab over the conventional strategy: both treatments led to similar remission rates after 6 months (61–64%). Although the trial was not designed to evaluate the equivalence of rituximab to cyclophosphamide in patients with severe EGPA and specific organ involvement, such as glomerulonephritis or cardiomyopathy, it does not challenge existing recommendations. Compared with those treated with cyclophosphamide, patients with GPA or MPA treated with rituximab showed less leucopenia and pneumonia in the RAVE trial and a lower risk of malignancy in a long-term retrospective follow-up study[73,81,82]. Whereas rituximab might be preferred over cyclophosphamide for its more favourable safety profile, cyclophosphamide could remain the treatment of choice in patients with life-threatening disease.

The MAINRITSEG RCT (NCT03164473) is comparing rituximab and azathioprine for remission-maintenance in patients with severe and non-severe EGPA and has completed its follow-up phase. In the preliminary results, first presented at ACR Convergence 2025 (ref. 83), no significant difference in remission duration was observed between the rituximab and azathioprine treatment arms. There was also no clear evidence of differences in the following secondary outcomes: percentage of participants who remained in remission while treated with prednisone at a dose of ≤7.5 mg per day, with any prednisone dose, or with prednisone at a dose of ≤4 mg per day at months 3, 12 or 18; vasculitis relapse rate; rate of clinically significant asthma and/or rhinosinusitis exacerbations; glucocorticoid use; and quality of life[83]. In our clinical practice, we propose the use of rituximab for remission maintenance preferentially in patients with positivity for MPO-ANCA and/or severe vasculitic manifestations such as glomerulonephritis or peripheral neuropathy.

Although retrospective studies have suggested that remission rates following rituximab treatment are higher in ANCA-positive than in ANCA-negative EGPA, this finding was not confirmed in the REOVAS or MAINRITSEG trials, indicating that treatment decisions should not be based on ANCA status[67,75,77,78,84]. As these two trials were not designed to assess the non-inferiority of rituximab in people with ANCA-positive and/or severe disease, there remains a need for further studies in these populations. In the coming years, the use of rituximab, whether in combination, in a sequential regimen, or as an alternative to IL-5 pathway-targeting therapies, will need to be explored.

Other conventional therapies

Conventional synthetic DMARDS. In prospective and retrospective studies, >90% of patients without poor prognosis factors achieved remission with glucocorticoid therapy alone. However, up to half of these patients experienced systemic relapse within the first 2 years of follow-up[16,27,85]. The CHUSPAN2 RCT investigated the benefit of adding azathioprine to glucocorticoid therapy and demonstrated that, in patients without poor prognostic factors, rates of remission-induction failure and relapse, including specific vasculitic and respiratory relapses, were not different in those who received glucocorticoids alone compared with those treated with glucocorticoids and azathioprine[16]. As with early cyclophosphamide studies, this trial included a pooled population of patients with EGPA, MPA or PAN, rendering it underpowered to detect differences in outcomes and glucocorticoid tapering specifically in the EGPA subgroup.

Despite their widespread use in clinical practice, the efficacy of csDMARDs, including azathioprine, methotrexate, mycophenolate mofetil and leflunomide, stems from small-scale, uncontrolled studies only, with azathioprine and methotrexate most widely cited[4,18,22,86–90]. Furthermore, in the studies of IL-5 pathway-targeting therapies, only 24–52% of patients were being treated with csDMARDs at the time of enrolment, highlighting their limited efficacy in controlling persistent disease manifestations[44,64–66]. In addition, given their specific toxicities and the overall increased risk of infection associated with their use, the benefit–risk balance of csDMARDs remains uncertain. The use of csDMARDs to treat EGPA is expected to decline as the use of therapies targeting the IL-5 pathway expands, with the latter having demonstrated a more favourable and consistent efficacy and safety profile over the past few years. In our current practice, we favour IL-5 pathway-targeting therapies over csDMARDs, particularly for the management of persistent airway manifestations.

Intravenous immunoglobulins. There are limited data regarding the use of intravenous immunoglobulins (IVIg) in EGPA[91–93]. The results of a small prospective study suggested that IVIg might provide additional benefits over conventional treatment in controlling persistent peripheral neuropathy symptoms, although this study lacked a control group[94]. IVIg can be used for severe and refractory cases[37].

Plasma exchange. The addition of plasma exchange to cyclophosphamide for the treatment of severe EGPA failed to demonstrate superiority over standard therapy; therefore, its use is not recommended in routine practice[95]. Plasma exchange can be considered on a case-by-case basis for specific severe vasculitis manifestations such as alveolar haemorrhage or renal failure[42]. However, it should not be used routinely for the treatment of EGPA, which is consistent with the evidence established for GPA and MPA.

Targeting the IL-5 pathway

IL-5 is a key cytokine promoting the proliferation, maturation and survival of eosinophils[96–98]. Mepolizumab, the first anti-IL-5 monoclonal

antibody, has been shown to deplete both circulating and airway tissue eosinophils[99] and to significantly improve clinical and patient-reported outcomes in severe eosinophilic asthma[100,101]. Benralizumab, a monoclonal antibody targeting the α-subunit of IL-5R (IL-5Rα), showed comparable results[102–106]. Both agents have also demonstrated efficacy in the treatment of upper respiratory symptoms arising from chronic rhinosinusitis with nasal polyps (CRSwNP)[107,108]. In asthma studies, subcutaneous mepolizumab was administered at a dose of 100 mg every 4 weeks and subcutaneous benralizumab at a dose of 30 mg every 8 weeks, following three initial doses given 4 weeks apart. Both drugs are approved for the treatment of severe eosinophilic asthma in more than 80 countries, including the USA, Europe, Japan and China.

Compared with EGPA, both eosinophilic asthma and CRSwNP are characterized by a lower 'eosinophil burden', with 0.3% of people with asthma having blood eosinophil counts >1,500 cells per mm^3 and median levels of ~300–450 cells per mm^3 in clinical trials[101,102,107–109]. Patients with asthma have a lower exposure to glucocorticoids than do patients with EGPA or HES[110]. This difference limits the direct extrapolation of the dosing used in asthma trials and could justify the use of higher-dose mepolizumab and benralizumab regimens in EGPA[44,66,111,112].

Mepolizumab

The MIRRA trial, published in 2017, examined the effectiveness of mepolizumab, subcutaneously administered at a dose of 300 mg every 4 weeks, compared with placebo in 136 patients with non-severe, glucocorticoid-dependent (daily prednisone dose ≥7.5 mg) refractory or relapsing EGPA[44]. The mean prednisone dose at baseline was 12 mg per day, and 60% of patients in the trial were receiving an additional immunosuppressive agent. The results of the MIRRA trial demonstrated the superiority of mepolizumab over placebo in achieving remission (defined as a BVAS of 0 and a daily glucocorticoid dose of ≤4 mg) at weeks 36 and 48 (32% versus 3% of patients, respectively). When the response outcome was redefined as a composite end point (requiring remission, ≥50% reduction in glucocorticoid dose and absence of relapse), the response rate increased to 78% versus 32% in favour of mepolizumab[113]. Thus, approximately 80% of mepolizumab-treated participants experienced some clinical benefit. The trial also showed reduced relapse rates (defined as BVAS >0, worsening asthma or ear, nose, and throat (ENT) symptoms, treatment change, or hospitalization) at 1 year (hazard ratio (HR) 0.32), longer time to first major relapse within 1 year (HR 0.51), and lower glucocorticoid intake (mean daily dose 4.3 mg lower with mepolizumab; odds ratio 0.20). Headaches and infrequent systemic reactions to injections were reported more frequently in the mepolizumab group than in the placebo group but the overall tolerance of the drug was excellent and no severe infections were reported.

A total of 108 patients were included in the open-label extension study[114]. The follow-up period was extended by a mean of 3.2 years, with some patients receiving therapy for as long as 7 years. During this time, 66% of patients reduced their initial daily glucocorticoid dose by at least half, 38% achieved a daily glucocorticoid dose of ≤4 mg, and 20% stopped taking glucocorticoids altogether. One-third of the patients reported respiratory manifestations, and 27% discontinued treatment with the biologic, although less than half of these cases were attributed to treatment inefficacy or adverse events; 18% of patients reported serious infections, of which 4% were considered treatment-related[114].

Several retrospective studies and one prospective cohort following the MIRRA trial reported similar short-term and long-term efficacy and safety[30,64,79,80,115–118] (as detailed in Supplementary Table 4). Whereas many real-world studies used mepolizumab at a dose of 100 mg every 4 weeks in accordance with its license in severe eosinophilic asthma, it is recommended to use the higher dose of 300 mg monthly in patients with EGPA given the higher eosinophil burden associated with this disease[79]. In these studies, the proportion of patients with ANCA positivity at diagnosis ranged from 10% to 20%, and the baseline BVAS ranged from 0 to 4, reflecting a predominance of airway symptoms. The efficacy of mepolizumab for maintenance of remission is now well documented[119].

However, similar to cytotoxic and/or immunomodulatory agents, its efficacy and safety for remission induction remain to be established in placebo-controlled trials. A small retrospective study reported comparable efficacy of mepolizumab and cyclophosphamide in inducing remission in severe EGPA, with a similar improvement in BVAS, greater glucocorticoid tapering and fewer serious adverse events with mepolizumab after 6 months[120]. Several retrospective studies suggest mepolizumab to be more effective compared with rituximab for controlling respiratory symptoms but this finding remains to be confirmed in prospective trials[78–80]. The ongoing E-MERGE phase III RCT (NCT05030155) aims to demonstrate the superiority of mepolizumab against conventional strategies during the remission-induction phase of active systemic EGPA and has completed recruitment. The trial could redefine induction therapy of EGPA in favour of a less toxic and immunosuppressive treatment algorithm for patients.

Benralizumab

Benralizumab is a humanized, afucosylated IgG1 monoclonal antibody that targets IL-5Rα, which is highly expressed on eosinophils and their progenitors. Afucosylation increases the affinity of benralizumab for FcγRIIIα receptors on natural killer cells, macrophages and neutrophils, thereby enhancing its antibody-dependent cell-mediated cytotoxicity and inducing near-complete blood and tissue depletion of eosinophils and their progenitors[121–123]. In patients with eosinophilic asthma, benralizumab has been shown to induce more profound eosinophil depletion in blood and sputum compared with mepolizumab[124–128]. In patients with eosinophilic gastrointestinal diseases involving the lower digestive tract, treatment with benralizumab has led to complete tissue depletion of eosinophils in the initially affected areas[111,129]. Consequently, benralizumab is considered to achieve more complete eosinophil depletion than mepolizumab and might therefore be preferable to mepolizumab for the clinical management of these conditions.

The MANDARA trial, a RCT published in 2024, examined the efficacy of high-dose benralizumab versus mepolizumab in 140 patients with non-severe, relapsing or refractory EGPA[66]. The patients' characteristics were similar to those in the MIRRA trial. At the time of inclusion, study participants had a mean disease duration of 5.16 years, mean BVAS of 2.1, mean blood eosinophil count of 345 cells per mm^3, and a mean daily glucocorticoid dose of 11 mg. Use of concomitant immunosuppressants was reported in 36% of patients. The trial demonstrated the non-inferiority of benralizumab to mepolizumab in achieving remission at weeks 36 and 48 (58% and 56% of patients, respectively). After 1 year, relapses were reported in 30% of patients in both groups. Major relapses were reported only in four patients in the mepolizumab arm[66]. The initial daily glucocorticoid dose was reduced by ≥50% in 85% of patients in the benralizumab arm and 74% in the mepolizumab arm; of these patients, 68% and 70%, respectively, achieved a daily dose of ≤4 mg. Importantly, complete glucocorticoid withdrawal was observed more frequently in the benralizumab group, reaching 41% of patients, compared with 26% in the mepolizumab group. In the

first year of the open-label extension of this trial, in which all patients received benralizumab, those who switched from mepolizumab to benralizumab were equally able to taper off glucocorticoids compared with those who had received benralizumab for the entirety of the trial, with 44% of patients discontinuing glucocorticoid therapy; furthermore, two-thirds of patients achieved remission, establishing the durable effect of benralizumab treatment[130]. The safety profile was comparable to that of the MIRRA trial[44]. Persistent anti-drug antibodies were reported in three patients, all of whom achieved remission. These results were confirmed in a prospective Japanese cohort study published in 2025, which reported remission rates of 64%, with 36% of patients able to completely withdraw glucocorticoids after nearly 2 years of follow-up[30].

Several retrospective cohort studies have demonstrated similar rates of remission of EGPA and glucocorticoid-sparing capacity with benralizumab administered at the standard dosage for asthma. Patient characteristics were comparable across the studies[65,131–136], as detailed in Supplementary Table 5. Rates of remission and glucocorticoid withdrawal were higher in real-world studies than in the MANDARA trial. The difference could be explained in part by the increasing experience of physicians with therapies targeting the IL-5 pathway and their prioritization of glucocorticoid sparing.

Benralizumab could be a preferable choice for some patients not only for its superior glucocorticoid-sparing effect but also for its convenience of administration. Currently, mepolizumab treatment requires three 100-mg subcutaneous injections, whereas benralizumab is administered as a single 30-mg injection. Both treatments are given at 4-week intervals.

Prediction of response to therapies targeting the IL-5 pathway

In the MANDARA trial, more than 40% of patients did not achieve remission within 1 year of follow-up due to active manifestations, most often upper or lower airway, or due to glucocorticoid intake exceeding 4 mg per day[66]. Whether a response can be predicted before initiating therapies that target the IL-5 pathway remains an important question.

Several asthma studies have suggested greater efficacy of therapies targeting the IL-5 pathway in patients with adult-onset asthma and concomitant ENT involvement[137–140]. However, in both the MIRRA and MANDARA trials, as in most real-world studies, the majority of patients had both asthma and ENT involvement, which makes this observation difficult to reproduce. In fact, ENT involvement was not associated with a better response to mepolizumab or benralizumab[64,65,141] and both upper and lower respiratory manifestations improved with treatment[44,64,114]. Rates of relapse of asthma and ENT involvement were similar among mepolizumab-treated and benralizumab-treated patients; however, studies may have lacked the statistical power to detect differences between these two manifestations[44,64,114]. Systemic manifestations and ANCA status have been inadequately and/or under-represented in both prospective and retrospective studies, making it difficult to accurately assess the associated response rates. Therefore, it remains uncertain whether one type of involvement is more likely to respond to therapies targeting the IL-5 pathway.

Historical cohorts have shown that lower blood eosinophil counts at diagnosis are associated with increased risk of relapse[4,26]. In the MIRRA trial, a baseline blood eosinophil count <150 cells per mm^3 was associated with a limited response to mepolizumab[44]. The association between baseline blood eosinophil count and response to benralizumab was detected in a retrospective cohort but not confirmed in the MANDARA trial[65,66]. A marked reduction in blood eosinophil count is expected following initiation of IL-5 pathway-targeting therapy and is more pronounced in patients treated with benralizumab compared with mepolizumab[66,130]. Benralizumab treatment for asthma has also been shown to reduce sputum eosinophils, eosinophil progenitors and IL-5Rα-expressing type 2 innate lymphoid cells[125]. Whether the depth of these reductions correlates with the clinical response remains to be determined.

Fractional exhaled nitric oxide (FeNO) is a biomarker of T2 inflammation that is predominantly driven by IL-13; hence, it does not consistently fall following IL-5 pathway-targeting therapy[142,143]. FeNO correlates with blood and sputum eosinophilia and is a predictor of disease severity and risk in asthma[106,131,132,135,142–144]. Elevated FeNO in patients treated with agents targeting the IL-5 pathway could indicate a need for alternative asthma treatments, such as those that target thymic stromal lymphopoietin (TSLP). Although cytokine measurements in serum or sputum are not routinely performed, they could provide insight into optimal therapeutic targets and dosing strategy[145]. In HES, serum IL-5 levels have been associated with response to mepolizumab[146]. However, cytokine concentrations can fluctuate over time and only partially reflect the underlying inflammatory process in the tissue. The association of FeNO and cytokine profiles with treatment response remains to be established.

A post hoc pharmacogenetic analysis of the MIRRA study aimed to identify genetic variants associated with response to mepolizumab. Unfortunately, candidate gene analysis and genome-wide association approaches both failed to reveal any significant associations[147].

The association between relapse and ANCA positivity has been inconsistent across historical cohorts[4,18,26,148]. A post hoc analysis of the MIRRA trial found no association between remission status and ANCA positivity, baseline BVAS or vasculitis damage index score[141]. In MANDARA, complete withdrawal of glucocorticoids was not associated with ANCA status[149]. Interpreting vasculitic relapses in both prospective and retrospective studies is challenging because relapse definitions often overlap with vasculitic and respiratory components. One study reported an association between the risk of a vasculitis flare during benralizumab treatment and biopsy-proven vasculitis and/or ANCA positivity[65]. Interestingly, the rate of vasculitis relapse was similar between the mepolizumab and placebo groups in the MIRRA trial[141]. However, since vasculitic relapses occur mainly during the initial years of follow-up, it is likely that their frequency decreases over time, making it more difficult to detect differences. Nevertheless, tapering glucocorticoids and discontinuing conventional immunosuppressants following respiratory improvement during IL-5 pathway-targeting therapy could potentially promote systemic vasculitic relapses by unmasking the underlying disease, as has been reported in patients with asthma who developed systemic manifestations of EGPA after initiating IL-5 pathway-targeting therapy[150].

Therefore, patients with vasculitic and/or ANCA-positive features rather than predominantly eosinophilic disease could be more prone to systemic vasculitic relapses, which might be less responsive to therapies targeting the IL-5 pathway and might benefit from anti-CD20 therapies or cytotoxic agents. These observations are insufficient to support or discourage the use of IL-5 pathway-targeting therapies in this subgroup but they do encourage increased vigilance during tapering of glucocorticoids and conventional immunosuppressants.

Management of IL-5 pathway-targeting therapy

Therapies targeting the IL-5 pathway should be initiated with the higher-dose EGPA regimen (mepolizumab 300 mg every 4 weeks,

benralizumab 30 mg every 4 weeks). Improvements in respiratory function and quality of life are generally observed within the first few weeks of treatment. However, achievement of complete remission could require up to 6 months or several years of treatment in some cases[64,65,92,151,152]. When initiating an IL-5 pathway-targeting therapy, treatment success should include a reduction in vasculitic and respiratory relapses, as well as reduced exposure to glucocorticoids and conventional immunosuppressants. Consequently, decisions regarding treatment continuation or discontinuation should balance the benefits achieved across these objectives while considering patient preferences.

If there is no response to IL-5 pathway-targeting therapy, several options can be considered. Firstly, for patients treated with the dosing regimen that is standard for asthma treatment, dose escalation has been reported to benefit some patients with refractory EGPA and HES[64,79,153]. Before the MIRRA and MANDARA trials, IL-5 pathway-targeting therapies had mostly been administered using standard asthma regimens, yielding remission rates similar to those achieved with higher doses[64,65,79]. However, before concluding that a patient receiving a standard dose of an IL-5 pathway-targeting agent is a non-responder, the higher dosing regimen that has been approved for EGPA should be attempted. Secondly, switching from one IL-5 pathway-targeting biologic to the other may be beneficial. Contrary to the main result of the MANDARA trial, a 2025 retrospective real-world study suggested that benralizumab is more effective than mepolizumab administered through the standard asthma regimen[136]. This is in line with studies in asthma, in which switching from mepolizumab to benralizumab has been shown to reduce exacerbations and promote glucocorticoid withdrawal[154,155]. In the open-label extension of the MANDARA trial, switching from mepolizumab to benralizumab achieved comparable response rates but higher rates of glucocorticoid discontinuation were observed[130]. It should be noted, however, that a retrospective study reported that prior primary or secondary failure of mepolizumab was associated with a lesser response to benralizumab, probably reflecting the presence of a more severe form of disease or mechanisms involving non-T2-driven pathways[65].

For patients with refractory disease or who experience relapses despite therapy targeting the IL-5 pathway, inclusion in ongoing trials should be prioritized; alternatively, addition of an anti-T2 agent that acts further upstream (for example, tezepelumab) or a conventional immunosuppressant can be considered. Despite the lack of approval for use in EGPA, other T2-targeting therapies with established efficacy for asthma and CRSwNP could be promising therapeutic alternatives, as discussed below. In the event of a systemic relapse, the optimal approach to continuing or discontinuing IL-5 pathway-targeting therapy remains unclear and should be determined on a case-by-case basis according to the characteristics of the relapse. For example, a patient experiencing rapidly progressive glomerulonephritis or cardiomyopathy could receive IL-5 pathway-targeting therapy in conjunction with a new remission-induction regimen.

Once long-term goals, such as withdrawal of oral glucocorticoids and conventional immunosuppressants, have been achieved, several treatment optimizations can be considered. Since prolonged exposure to high-dose inhaled glucocorticoids is associated with glucocorticoid-related complications, a gradual dose reduction could be considered, as evidenced in asthma studies[156,157]. Further consideration might be given to increasing the dosing interval of IL-5 pathway-targeting therapies. A small retrospective study of 12 patients with EGPA found that a step-down of mepolizumab dosing successfully maintained remission and glucocorticoid-sparing over a median follow-up period of 27.5 months. Only half of the patients experienced recurrence of sinus symptoms[158]. However, in the COMET asthma trial, discontinuing mepolizumab after a median exposure of 44 months resulted in eosinophil recurrence, increased exacerbation rates and decreased asthma control[159]. The optimal duration and long-term continuation strategy of therapies targeting the IL-5 pathway in EGPA remain to be determined, with current evidence notably extrapolated from asthma studies and not tested in EGPA.

IL-5 pathway-targeting therapies under evaluation

Several drugs targeting the IL-5 pathway are being evaluated for the treatment of EGPA (Table 2).

Depemokimab is an ultra-long-acting monoclonal antibody with enhanced binding affinity for IL-5, subcutaneously administered every 6 months. In 2025, it was approved in the USA and Europe for the treatment of eosinophilic asthma at a dose of 100 mg twice per year[160]. In the SWIFT RCTs, depemokimab reduced asthma exacerbation rates with efficacy comparable to that seen in mepolizumab and benralizumab trials, and in the ANCHOR trials, it significantly improved CRSwNP symptoms[101,104,161,162]. The ongoing OCEAN RCT (NCT05263934) is evaluating high-dose depemokimab (200 mg every 6 months) versus mepolizumab in non-severe refractory or relapsing EGPA, using the same inclusion criteria as the MIRRA and MANDARA trials. The extended dosing interval of depemokimab could represent a convenient advance in EGPA management. SHR-1703 is an alternative long-acting monoclonal antibody that induces eosinophil depletion lasting up to 6 months[163]. It is administered subcutaneously and is currently being evaluated in EGPA in China (NCT05979051).

The anti-IL-5 antibody reslizumab has shown efficacy in asthma when administered intravenously but not subcutaneously[164,165]. Its intravenous formulation was evaluated in EGPA in the small, prospective RITE study[166]. Although reslizumab was effective in this open-label trial in terms of facilitating glucocorticoid withdrawal and reducing relapses, its intravenous formulation and the approval of other subcutaneously administered IL-5 pathway-targeting therapies have limited interest in further investigation in EGPA. Reslizumab remains an option in selected cases[167].

Targeting other T2 inflammation pathways and beyond

As biologic therapies for eosinophilic asthma expand to those that target T2-related pathways other than the IL-5 pathway, such as IL-4–IL-13, TSLP and IL-33, emerging retrospective data suggest their efficacy in EGPA. Similarly, novel therapies developed for AAVs could also be applicable to EGPA, especially for vasculitic manifestations. As these treatments have not been evaluated in EGPA, their safety in this setting remains to be determined.

T2-targeting therapies

Dupilumab, a monoclonal antibody that blocks both the IL-4 and IL-13 pathways, has demonstrated efficacy in the treatment of asthma, CRSwNP, atopic dermatitis and eosinophilic oesophagitis[168–171]. Compared with mepolizumab, it has been associated with greater improvements in CRSwNP-related outcomes and could thus be considered for patients with EGPA who have persistent upper respiratory manifestations[172,173]. However, dupilumab is frequently associated with an increase in blood eosinophil counts, which has been linked to both EGPA onset in people with asthma and with EGPA flares[174,175]. With use of dupilumab alone for the treatment of relapsing and/or refractory EGPA, EGPA flares occurred in one-third of patients and were

Table 2 | Drugs under evaluation for the treatment of EGPA

Agent	Target	Ongoing study	Countries involved	Inclusion criteria	Trial design and treatment arms	Main outcome	Follow-up
Rituximab	Anti-CD20 monoclonal antibody	NCT03164473 (MAINRITSEG) Phase III	France	EGPA in remission after induction therapy (maintenance phase)	Randomized, placebo-controlled, double-blind trial evaluating fixed-dose intravenous rituximab (500 mg every 6 months×4) versus azathioprine (2 mg/kg per day for 24 months)	BVAS = 0 and prednisone dose ≤7.5 mg per day	28 months
Mepolizumab	Anti-IL-5 monoclonal antibody	NCT05030155 (E-MERGE) Phase III Academic funding	France	Newly diagnosed or relapsing EGPA	Randomized, placebo-controlled, double-blind trial evaluating subcutaneous mepolizumab 300 mg every 4 weeks versus standard therapy according to FFS (placebo if FFS = 0; cyclophosphamide if FFS ≥1)	Prednisone dose ≤4 mg per day without experiencing a relapse	1 year
Depemokimab	Long-acting anti-IL-5 monoclonal antibody	NCT05263934 (OCEAN) Phase III Industry funding	USA, Europe, Asia	Non-severe relapsing or refractory EGPA	Randomized, placebo-controlled, double-blind trial comparing subcutaneous depemokimab 200 mg every 6 months×2 with mepolizumab	BVAS = 0 and prednisone dose ≤4 mg per day	1 year
SHR-1703	Anti-IL-5 monoclonal antibody	NCT05979051 Phase II–III Industry funding	China	Non-severe relapsing or refractory EGPA	Randomized, placebo-controlled trial	NA	48 weeks
Tezepelumab	Anti-TSLP monoclonal antibody	NCT06230354 (RACEMATE) Phase IIb Industry funding	UK	Non-severe relapsing and refractory EGPA	Randomized, placebo-controlled trial evaluating tezepelumab 210 mg every 4 weeks versus placebo	BVAS = 0 and prednisone dose ≤4 mg per day	24 weeks
NS-229	JAK1 inhibitor	NCT06046222 Phase II Industry funding	USA, Europe, Asia	Active EGPA	Randomized, placebo-controlled trial	BVAS = 0 and prednisone dose ≤4 mg per day	28 weeks

BVAS, Birmingham Vasculitis Activity Score; EGPA, eosinophilic granulomatosis with polyangiitis; FFS, five-factor score; JAK, Janus kinase; NA, not available; TSLP, thymic stromal lymphopoietin.

preceded by eosinophilia in 88%[175]. Reports of its combination with IL-5 pathway-targeting therapies are emerging and suggest a mitigated risk of EGPA flare[176]. The off-label use of dupilumab monotherapy in EGPA is therefore not recommended. Its safety and the potential need for combination with other EGPA treatments should be evaluated in prospective trials before use in clinical practice.

Omalizumab, an anti-IgE monoclonal antibody that has proven effective in treating allergic asthma and chronic urticaria, has shown limited efficacy in small, retrospective EGPA studies. This result is likely attributable to the low prevalence of atopic factors in these patients[79,177,178]. The use of omalizumab in EGPA is not advised.

Tezepelumab, an anti-TSLP monoclonal antibody, has proven efficacy in asthma and CRSwNP, independent of blood eosinophilia[179–181]. Its use in EGPA has only been reported in a few case reports and one small series[181–184]. After switching from therapies targeting the IL-5 pathway to tezepelumab, eosinophil counts could increase and lead to disease flares, as observed in one patient[181]. The ongoing phase IIb RACEMATE RCT (NCT06230354; Table 2) is evaluating the efficacy of tezepelumab (210 mg administered subcutaneously every 4 weeks) versus placebo in patients with non-severe, refractory or relapsing EGPA, using the same inclusion criteria as the MIRRA and MANDARA trials. Patients receiving therapy targeting the IL-5 pathway were allowed to participate in the study. Tezepelumab could therefore offer either an alternative or an add-on therapy for patients with refractory disease despite IL-5 pathway-targeting therapy. Caution is warranted after the switch.

Cendakimab, an anti-IL-13 monoclonal antibody, has demonstrated efficacy in treating atopic dermatitis and eosinophilic oesophagitis without raising safety concerns related to eosinophilia[185,186]. Monoclonal antibodies that target IL-33 (such as itepekimab and tozorakimab) and its receptor ST2 (such as astegolimab) are currently being evaluated for their potential use in the treatment of asthma, atopic dermatitis and chronic obstructive pulmonary disease[187–190]. Their use in EGPA has not yet been documented; however, these agents could be the focus of future clinical trials.

Targeting other inflammatory pathways

Complement pathway. C5a, an anaphylatoxin, is involved in the migration and activation of neutrophils in AAV. Targeting the C5a receptor with avacopan was reported to enable faster glucocorticoid tapering and improved renal outcomes in MPA and GPA in the ADVOCATE trial[63,191], with post hoc analyses suggesting a benefit for ENT, lung manifestations and alveolar haemorrhage[192,193]. However, in 2026, both the FDA and EMA proposed withdrawing avacopan's marketing approval after finding that unblinded sponsor personnel had manipulated ADVOCATE's primary endpoint data, rendering the trial's efficacy claims unreliable[194]. Hepatotoxicity, including fatal cases of vanishing bile duct syndrome, was also identified as a serious safety concern. Pending resolution of this regulatory review, the EULAR-based rationale for using avacopan in rapidly progressive MPO-ANCA glomerulonephritis or alveolar haemorrhage would probably be modified[42]. As the C5a receptor might contribute to IL-5-independent eosinophil activation, its targeted use in EGPA remains of theoretical interest only, as any clinical exploration would first require these efficacy and safety concerns to be addressed[195–197].

JAK–STAT pathway. Over the past few decades, the use of JAK inhibitors (such as tofacitinib, ruxolitinib and baricitinib) has expanded to

include the treatment of a wide range of inflammatory diseases[198]. Preliminary reports have suggested the potential efficacy of tofacitinib and ruxolitinib in AAV and lymphoid variant HES[199–201]. A small retrospective study reported that tofacitinib effectively controls systemic manifestations in EGPA; however, one patient developed a pulmonary cytomegalovirus infection during follow-up[202]. An ongoing phase II RCT (NCT06046222; Table 2) will be the first to evaluate the investigational selective JAK1 inhibitor NS-229 in patients with EGPA, with or without concomitant IL-5 pathway-targeting therapy. Owing to safety concerns associated with the use of JAK inhibitors (such as risks of venous and arterial thrombosis, infections and malignancies), this study is crucial for assessing the benefit–risk balance of JAK inhibitors in EGPA[203].

Additional considerations for optimizing EGPA management

Although the advent of new therapies has improved the treatment of EGPA, advances in trial design and other aspects of patient and disease assessment could also advance the field (Box 1). Current management of EGPA can also be optimized by considering the issues discussed in this section.

Owing to the heterogeneity of EGPA manifestations, collaboration between physicians specialized in the management of systemic inflammatory diseases (including rheumatologists, internists and clinical immunologists) and those dealing with organ-specific disorders is recommended. Inhaled therapy and chronic rhinosinusitis management should be optimized according to current guidelines alongside the consideration of biologic therapies[204,205]. For patients with persistent, symptomatic nasal polyps, therapies targeting the IL-5 pathway can be an option prior to surgery, as the need for surgery decreases during treatment[107,205–207].

Smoking negatively affects asthma and ENT symptom control, worsens lung function, and increases cardiovascular risk[208]. Occupational exposures, such as crystalline silica, organic solvents and chemical agents, as well as farming, have been associated with a predisposition to EGPA[209]. Therefore, patients should be advised to avoid exposure to respiratory irritants.

Prospective long-term studies with IL-5 pathway-targeting therapies have shown that serious infections occurred in 7–18% of patients, underscoring the importance of vaccinations and anti-infectious prophylaxis[30,114,130]. Vaccinations should be administered in accordance with guidelines relevant to patients receiving immunosuppressive therapy, considering disease severity and administered therapies[210]. Seasonal flu, SARS-CoV-2, pneumococcal, respiratory syncytial virus, herpes zoster and *Haemophilus influenzae* vaccines should be considered. Vaccines should be administered before the initiation of remission-induction therapy whenever possible, as immunosuppressive regimens can impair the immune response to vaccination[37,42]. Case reports have described the occurrence of new-onset or relapse of EGPA, including vasculitic manifestations, following SARS-CoV-2 and influenza vaccinations[211–213]. Although the causal relationship between vaccination and flare remains uncertain, both physicians and patients should be vigilant in the weeks after vaccination.

Box 1 | Trial designs and future directions

Classification and patient selection

Since the Chapel Hill Consensus Conference[2], inclusion criteria for eosinophilic granulomatosis with polyangiitis (EGPA) have become more consistent across studies. Nevertheless, residual variability persists, particularly in study design and patient selection. In the context of an inherently heterogeneous disease, such discrepancies could compromise both reproducibility and external validity. Future studies should therefore rely on validated classification criteria, such as the latest American College of Rheumatology–European Alliance of Associations for Rheumatology criteria[226]. Given the distinct pathophysiology and clinical trajectory of EGPA compared with other forms of anti-neutrophil cytoplasmic antibody-associated vasculitis, pooling of patients in trials should be avoided.

Defining relapse, refractoriness and remission

The definitions of relapse and refractoriness also remain insufficiently standardized. These entities can encompass both vasculitic and respiratory manifestations, which do not necessarily evolve in parallel. It is therefore essential to distinguish and systematically assess these components separately, both at baseline and throughout follow-up. The definition of remission has evolved in recent trials. Whereas earlier studies followed the European Alliance of Associations for Rheumatology definition (Birmingham Vasculitis Activity Score (BVAS) of 0 and a daily glucocorticoid dose of ≤7.5 mg), more recent trials, such as MIRRA and MANDARA, have adopted a more stringent threshold (BVAS of 0 and a daily glucocorticoid dose of ≤4 mg). This shift reflects the improved management of chronic and glucocorticoid-dependent manifestations of EGPA. In the era of IL-5-targeting therapies, complete withdrawal of glucocorticoids can now be considered a realistic objective for future clinical trials.

Disease activity assessment and biomarkers

BVAS, although widely used, was developed for heterogeneous vasculitis populations and does not adequately capture the distinction between vasculitic and respiratory disease activity[227]. This limitation highlights the need for a disease-specific activity index tailored to EGPA. Already validated scores for asthma and for ear, nose and throat manifestations should be assessed in trials.

There is a critical need for reliable biomarkers that could serve both as predictors of response to targeted therapies and as surrogate markers for vasculitic and/or respiratory remission. With anti-IL-5 therapies increasingly becoming the standard of care, such tools will be essential to refine disease monitoring and therapeutic strategies.

Patient-reported outcomes

Patient-reported outcomes have begun to be incorporated into clinical trials, using scores such as ACQ-6, SNOT-22, HAQ and SF-36. The AAV-PRO, a validated vasculitis-specific score, could provide additional value[228]. Although these tools capture either global functional status or specific respiratory symptoms, they do not fully reflect the multisystemic burden of EGPA. The development of an EGPA-specific patient-reported outcome score, encompassing the full spectrum of disease manifestations, represents an important unmet need and should be prioritized in future studies.

During the remission-induction phase of EGPA treatment, patients receiving additional immunosuppressants, such as cyclophosphamide or rituximab, should receive *Pneumocystis jirovecii* prophylaxis in accordance with the recommendations for MPA and GPA[37,42]. Screening for active hepatitis, tuberculosis and helminthiasis, namely *Strongyloides stercoralis*, is recommended in patients at risk of infection. Due to prolonged exposure to glucocorticoids, patients should receive osteoporosis prophylaxis according to current recommendations[214,215]. Cardiovascular risk should be assessed at diagnosis and periodically during follow-up, with the use of specific tools (for example, QRISK)[216]. This assessment includes screening for diabetes mellitus and dyslipidaemia and vascular imaging when clinically indicated. Prolonged exposure to cyclophosphamide should also prompt appropriate cancer screening.

Pregnancies should be planned during periods of remission whenever possible. Treatment should be optimized to minimize the risk of systemic or respiratory flares and glucocorticoid exposure, which can be associated with an increased risk of gestational diabetes[217,218]. From the time of conception and throughout pregnancy, the use of teratogenic immunosuppressants, such as cyclophosphamide, methotrexate and mycophenolate mofetil, is contraindicated, while other agents, such as rituximab or azathioprine, should be avoided whenever possible. No study has prospectively assessed the safety of IL-5 pathway-targeting therapies during pregnancy, either in asthma or EGPA. On the basis of current experience, no safety signal has been associated with IL-5 pathway-targeting therapies during pregnancy, and these agents might therefore be preferred over conventional immunosuppressants[219].

Conclusions

In the past 10 years, the results of several RCTs have reshaped therapeutic strategies for remission induction and maintenance in EGPA. Glucocorticoids and cyclophosphamide remain the cornerstones of remission-induction therapy, depending on the severity of disease. Rituximab, a well-established treatment for AAV, could be a safe alternative to cyclophosphamide, especially for vasculitic and/or MPO-ANCA-driven manifestations, even if its non-inferiority was not demonstrated.

Therapies targeting the IL-5 pathway have proven to be transformative. Patients with refractory, relapsing or glucocorticoid-dependent manifestations should be considered for the early introduction of IL-5 pathway-targeting therapies with the ambition to achieve complete glucocorticoid withdrawal.

Biomarkers to guide the use of IL-5 pathway-targeting and other T2-targeting therapies and those predicting relapses remain to be identified. Imminent future therapeutic directions include depemokimab (a long-acting anti-IL-5 monoclonal antibody) and tezepelumab (the anti-TSLP monoclonal antibody), with other agents targeting T2 and non-T2 pathways being on the horizon. Future studies will need to examine the role of ANCA status and whether hypereosinophilia and vasculitis require differential targeted strategies. Because BVAS poorly discriminates active EGPA manifestations, the use of organ-oriented scores should be encouraged for the accurate assessment of disease activity. Lastly, multidisciplinary management is fundamental for optimal patient-centred care, in combination with early diagnosis, timely access to services and expert review, access to targeted therapy, education, and guideline-supported treatment paradigms.

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Author contributions

A.C. researched data for article. A.C., B.T., F.R., A.N. and M.G. contributed substantially to discussion of the content. A.C. and B.T. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

F.R. declares speaker fees and consultancy fees for participation in advisory boards from AstraZeneca and GlaxoSmithKline. A.E. declares consulting and advisory board fees from AstraZeneca related to this topic. G.E. declares consulting, advisory board participation, and speaker's fees from GlaxoSmithKline and AstraZeneca related to this topic. M.G. declares personal fees from GlaxoSmithKline and AstraZeneca outside the submitted work. A.M.N. declares payment or honoraria for lectures and educational events from AstraZeneca, GlaxoSmithKline, Sanofi and Chiesi, and support for attending conferences from AstraZeneca and GlaxoSmithKline. U.S. declares receipt of consulting or advisory board honoraria from Amgen, Argenx, AstraZeneca, Boehringer-Ingelheim, ChemoCentryx, CSL Vifor and Novartis, and research grant support from Amgen, AstraZeneca, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, NorthStar Medical Radioisotopes, Novartis and NS-Pharma. M.E.W. declares receipt of consulting and/or advisory honoraria from Abbvie, Allakos, Apogee, Areteia Therapeutics, Arrowhead Pharmaceutical, Avalo Therapeutics, Belenos Bio, Celldex, Connect Biopharma, Eli Lilly, Enveda Therapeutics, Equillium, General Medicines, Gilead, Jasper Therapeutics, Kinaset, Kymera, Merck, MyBiometry, Pfizer, Pharming, Phylaxis, Pulmatrix, Rapt Therapeutics, Recludix Pharma, Roche/Genentech, Sentien, Sound Biologics, Tetherex Pharmaceuticals, Uniquity Bio, Verona Pharma and Zurabio; M.E.W. declares that he has received consulting, advising and/or speaking honoraria from AstraZeneca, Amgen, Regeneron, GlaxoSmithkline, Sanofi/Genzyme and is doing research sponsored by them; M.E.W. has received stock options from Cellergy Pharma Inc and has received consulting honoraria and stock options and is doing research sponsored by Upstream Bio. A.V. declares receipt of consulting fees from GlaxoSmithKline and AstraZeneca. B.T. declares consulting, advisory board participation, and speaker's fees from AstraZeneca and GlaxoSmithKline related to this topic. A.C. declares no competing interests.

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Review article

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Lung disease in rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is a prevalent chronic systemic autoimmune inflammatory disease that primarily targets synovial joints and periarticular tissues. In RA, systemic inflammation has been associated with extra-articular manifestations, including pulmonary involvement, which are leading causes of reduced survival. Tobacco smoking is a well-established risk factor for anti-citrullinated protein antibody (ACPA)-positive RA and is also associated with chronic obstructive pulmonary disease, interstitial lung disease (ILD) and lung cancer, the prevalence of which is elevated in people with RA. Pulmonary manifestations such as airway obstructive disease, ILD and bronchiolitis affect a substantial proportion of people with RA. Screening for pulmonary disease, particularly ILD, is gaining emphasis, with high-resolution CT recommended based on risk factors including age, sex, antibody status and smoking. Despite advances in therapies to effectively manage joint inflammation, evidence-based treatments for RA-associated ILD remain limited. Chronic obstructive pulmonary disease and bronchiectasis in RA warrant more recognition owing to their effect on morbidity and mortality, and should be managed in accordance with current international treatment guidelines for these conditions. This Review summarizes the pathophysiology of lung involvement in RA, diagnostic challenges and evolving management strategies aimed at optimizing patient outcomes.

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Key points

- Rheumatoid arthritis (RA) commonly involves the lungs, with interstitial lung disease (ILD), chronic obstructive pulmonary disease, bronchiectasis, bronchiolitis and lung cancer all contributing substantially to morbidity and mortality.
- Smoking, older age, male sex, high articular disease activity and anti-citrullinated protein antibody seropositivity are risk factors linked to RA-associated ILD (RA-ILD) and airway disease; screening should target patients with risk factors.
- High-resolution CT is the gold standard for detecting RA-related lung disease (including subclinical ILD) and for characterizing ILD patterns such as usual interstitial pneumonia, non-specific interstitial pneumonia, organizing pneumonia and alveolar macrophage pneumonia patterns.
- Management of RA-ILD requires a multidisciplinary, individualized approach that balances control of systemic RA with lung-directed therapies (such as immunomodulation with antifibrotics for progressive fibrosis) and supportive care (such as smoking cessation, vaccinations, pulmonary rehabilitation and airway clearance).
- RA-ILD (particularly usual interstitial pneumonia pattern) is associated with a worse prognosis, and antifibrotic therapy (for example, with nintedanib or pirfenidone) can be considered for progressive phenotypes.
- Bronchiectasis and airway disease in RA increase infection risk and mortality and require targeted infection control, physiotherapy and cautious use of immunosuppression.

Introduction

Rheumatoid arthritis (RA) is the most common chronic systemic autoimmune inflammatory joint (rheumatic) disease, with a prevalence of approximately 1% of the global population[1]. RA predominantly affects women in their fifth and sixth decades of life[1]. RA primarily targets synovial joints and periarticular soft tissues and is characterized by joint inflammation that leads to erosions and irreversible joint damage, substantially impairing daily function and profoundly impacting mobility, morbidity and mortality. The disease adversely affects patients' ability to work and their overall quality of life[1]. Furthermore, the systemic inflammation associated with RA frequently leads to extra-articular manifestations, especially pulmonary involvement and cardiac comorbidities, which currently represent the primary contributors to reduced survival in RA[2,3]. Respiratory diseases most commonly associated with RA are airway diseases, including chronic obstructive pulmonary disease (COPD) and bronchiectasis, as well as interstitial lung disease (ILD). Additionally, individuals with RA are at increased risks of developing lung cancer, rheumatoid nodules and pleural disease, which further complicate pulmonary management[3–5] Although distinct, these conditions often present with overlapping symptoms (Box 1) and all contribute to a reduced pulmonary function and decreased functional status (Table 1). Distinctions between these conditions are reflected in the choice of treatment strategies and follow-up protocols. In addition, COPD, bronchiectasis, bronchiolitis and even ILD and lung cancer often co-occur in a patient with RA[6,7].

Tobacco smoking is a well-established risk factor for anti-citrullinated protein antibody (ACPA)-positive RA[8]. This risk factor is shared with COPD, ILD and lung cancer, which have an increased prevalence among patients with RA compared with the general population; however, a direct causal relationship between tobacco smoking and these pulmonary conditions has not yet been definitively established[3].

The prevalence of pulmonary manifestations in RA is not well understood, probably as a result of heterogeneity in screening methods, diagnostic approaches, study populations and cohort characteristics across published studies. A 2025 multicentre prospective study evaluated 258 patients within 1–10 years of RA diagnosis with high-resolution CT (HRCT) and lung function for the presence of ILD, emphysema, bronchiolitis and nodules. The authors reported prevalences of ILD, emphysema and air trapping of 15%, 20% and 34%, respectively, in patients with RA[3].

To improve survival in patients with RA, current recommendations now include screening for cardiac disease as an integral part of RA management, and emerging evidence suggests that screening for ILD should be similarly integrated[9]. In the past 5–10 years, the topic of pulmonary disease screening has gained increasing attention, particularly with respect to the identification of ILD. The 2025 European Respiratory Society (ERS)–European Alliance of Associations for Rheumatology (EULAR) clinical practice guidelines for the management of ILD in rheumatic diseases suggested that the decision to screen patients with RA for ILD using HRCT should be based on the presence of ILD risk factors including age, male sex, elevated titres of RA-associated autoantibodies and smoking history[10]. By contrast, less emphasis has been placed on screening for COPD and bronchiectasis to date, although these conditions are also common in patients with RA and are associated with poor prognoses[11].

Patients with RA who develop COPD or bronchiectasis have historically received less clinical and research attention than those who develop ILD, although both patient groups could warrant equal attention in terms of diagnostic evaluation and disease-specific management. Both COPD and bronchiectasis are associated with considerable morbidity in patients with RA, contributing to increased symptom burden, reduced quality of life, and decreased survival[11]. Therefore, these pulmonary comorbidities must all be recognized and managed with the same rigour as RA-associated ILD (RA-ILD) to optimize patient outcomes. Other pulmonary manifestations of RA, such as pleural effusion and pulmonary nodules, and lung cancer have received even less attention in recent years, despite being relatively common in patients with RA[3,4].

This Review is aimed at summarizing emerging knowledge regarding the underlying pathophysiology of lung involvement in RA, to describe the most common forms of RA-associated pulmonary disease and to present current evidence on screening, diagnosis, treatment and prognosis in RA-related lung disease.

Obstructive airway disease in rheumatoid arthritis

Pathophysiology of chronic obstructive pulmonary disease in rheumatoid arthritis

Several factors contribute to obstructive airway disease in RA, including small-airway inflammation and remodelling, whereby lymphoid follicle formation in terminal bronchioles, mucus plugging and concentric fibrosis limit airflow and cause associated air-trapping[12]. Furthermore, the airway mucosa is a candidate site for loss of tolerance and citrullination, and local airway inflammation can predate joint disease[8]. Microbial colonization and infection, including infection with *Pseudomonas* spp., are common in RA and amplify neutrophilic inflammation, thereby accelerating airway damage. Susceptibility to infections is particularly

Box 1 | Respiratory evaluation in rheumatoid arthritis

Symptoms and clinical findings

- Rheumatoid arthritis (RA)-associated lung diseases present with insidious dyspnoea and cough, varying by subtype
- Chronic obstructive pulmonary disease (COPD) and bronchiectasis show slowly progressive exertional dyspnoea over years or decades
- Interstitial lung disease (ILD) is characterized by rapid onset, developing within months to a few years
- Cough in COPD and bronchiectasis is productive and strongest in the early morning and at night
- ILD cough is exertional and dry (non-productive) with rare night-time symptoms
- Asthma has variable symptoms, with asymptomatic periods and exacerbations often triggered by allergens, respiratory infections, exercise or other environmental exposures

Assessment tools

- Dyspnoea severity is graded simply via the Medical Research Council dyspnoea scale (0–5, activity-based), ideal for clinic use
- Patient-reported outcome measures such as the University of California San Diego Shortness of Breath Questionnaire offer detailed variability across tasks but are better suited to research than clinical use owing to their length

Physical examinations

- Auscultation reveals prolonged expiration and/or rhonchi in COPD and bronchiectasis, but bilateral inspiratory crackles in ILD
- Digital clubbing (nail-bed softening or enlargement) suggests ILD but its absence does not exclude ILD

Lung function patterns

- Obstructive lung function pattern (reduced airflow) in COPD, asthma and bronchiectasis; forced expiratory volume in 1 s (FEV1):forced vital capacity (FVC) ratio <70%
- Restrictive or normal spirometry with low volumes (FEV1, FVC, total lung capacity, residual volume and normal or increased FEV1/FVC ratio) in ILD
- Diffusing capacity for carbon monoxide declines early in ILD but also in advanced COPD with emphysema
- COPD shows hyperinflation (high total lung capacity and residual volume ratio)

relevant when immunosuppression is required for the control of RA disease activity[13]. Finally, smoking synergizes with ACPA seropositivity to drive both RA and COPD, and seropositive RA patients are also at an increased risk of COPD compared with seronegative patients[8,14]. Clinical phenotypes of obstruction in RA include small-airway disease, bronchiolitis, bronchiectasis, COPD and asthma[12].

Epidemiology of rheumatoid arthritis-associated chronic obstructive pulmonary disease

COPD is a heterogenous lung condition characterized by chronic respiratory symptoms including dyspnoea, cough and sputum production and associated with, often progressive, airflow limitation, mainly in smokers in high-income countries[15]. Risk factors other than smoking account for >50% of the global burden of COPD[15]. In people with COPD, HRCT can demonstrate features of chronic bronchitis, bronchiectasis and emphysema, depending on disease severity and phenotype. In patients with RA, an obstructive COPD phenotype, driven mainly by small-airway pathology, bronchiolitis and bronchiectasis and often related to current or previous smoking, is common yet under-recognized[16]. Prevalence estimates vary with disease definition; for instance, in a prospective cohort, obstructive lung functional limitation was detected by spirometry in 20.7% of patients with RA, whereas HRCT identified airway abnormalities including bronchial wall thickening, bronchiectasis and/or mosaic attenuation in 61% of these patients, underscoring that structural airway disease as detected by HRCT can exceed that detected by lung function testing[16]. In this study, small-airway limitations were common and associated with symptoms and impaired quality of life. A population-based analysis further showed that RA confers an increased risk of COPD, with a 5-year cumulative COPD probability of ~7.4% versus ~6.0% in matched individuals without RA[17].

Studies from the past 10–15 years have shown a significant and potentially bidirectional association between asthma, chronic rhinitis, nasal polyps and RA[18–20]. Multiple cohort, case–control and registry studies indicate that individuals with asthma are at an increased risk of developing RA and, conversely, that the prevalence of asthma is increased in patients with RA. A meta-analysis of six cohort and 14 case–control studies reported a pooled hazard ratio (HR) of 1.42 (95% CI 1.18–1.70) for RA among patients with asthma[19]. Mendelian randomization evidence further supports a causal link, suggesting that adult-onset asthma might increase the risk of RA (odds ratio (OR) 1.018)[20]. In a Korean population-wide study, RA was associated with asthma (OR 2.32; 95% CI 1.51–3.57), allergic rhinitis and sinusitis[21–23]. RA also correlated with higher chronic rhinosinusitis incidence and greater eosinophilic inflammation in nasal polyps[22,23]. Asthma can be more severe in people with RA, with higher in-hospital mortality and costs[24]. Overall, asthma seems to increase the risk of RA, whereas RA is linked to greater prevalence and severity of asthma.

Treatment considerations for obstructive lung disease in rheumatoid arthritis

Treatment approaches to obstructive lung disease in people with RA include control of the underlying disease and minimization of airway exposure to noxious particles, mainly tobacco smoke. Also, supportive and adjunctive interventions should be considered for any type of lung disease in RA (Box 2). This combination approach includes optimized control of RA-related systemic inflammation, and inhaled therapy. In symptomatic and asthma-like obstruction, inhaled bronchodilators (long-acting β-agonists or long-acting muscarinic antagonists) with or without inhaled corticosteroids are reasonable[25]. However, fixed, non-reversible obstruction in constrictive bronchiolitis might respond only modestly to inhalation therapy. As macrolides could reduce exacerbations and cough in bronchiolitis or bronchiectasis phenotypes, selected patients might benefit from macrolide treatment, in balance with antimicrobial stewardship. Important further treatment approaches include airway clearance techniques and vaccinations as well as smoking cessation and pulmonary rehabilitation.

Evidence-guided management of airway-predominant lung disease in RA with conventional synthetic DMARDs (csDMARDs) or biologic DMARDs (bDMARDs) is sparse. No specific treatment recommendations exist for RA-associated COPD beyond standard COPD guidelines; however, immunomodulatory agents used in RA management could confer an elevated risk of pulmonary infections[26]. The potential role of methotrexate in mitigating COPD-like patterns in RA warrants further study. In a nationwide Danish observational cohort study, the risk of hospitalized acute COPD exacerbation or death was reduced over a 6-month period in methotrexate users compared with matched non-methotrexate users[27].

Bronchiolitis in rheumatoid arthritis

Bronchiolitis in RA is a rare manifestation and can pathologically present as constrictive bronchiolitis obliterans, follicular (cellular) bronchiolitis or, less commonly, as diffuse panbronchiolitis[28]. Bronchiolitis obliterans often presents with severe irreversible airway obstruction and is clinically not different from COPD, being characterized by progressive breathlessness, a cough, sometimes productive, rarely wheezing and reduced exercise capacity. The symptom burden is often disproportionate to the radiological findings. The main feature distinguishing bronchiolitis obliterans from COPD is the lack of, or a very subtle, history of tobacco smoking, and often a protracted course of disease[28]. Differential diagnosis, such as occupational exposure, asthma, including childhood asthma, recurrent respiratory childhood infections and sequelae from premature birth, can be in the patient's history, but rarely results in bronchiolitis obliterans. Drug-induced bronchiolitis caused by penicillamine, sulfasalazine or gold salts has also been reported[29,30].

There seems to be a female preponderance and almost all patients, both women and men, develop bronchiolitis obliterans after a diagnosis of RA has been made[28,31]. Pulmonary function test reveals severe obstruction with a low FEV1/FVC ratio, typically with preserved (or only mildly reduced) diffusing capacity of the lungs for carbon monoxide (DLCO) and in body plethysmography increased residual volume due to air trapping. Inspiratory HRCT can show bronchial wall thickening, bronchiectasis, centrilobular emphysema and nodular opacities, with mosaic attenuation, especially in follicular bronchiolitis, whereas expiratory scans show pronounced air trapping (Fig. 1). Concomitant findings of ground-glass opacities, mild reticulation or even honeycombing in the lower lobes have been described[28,31]. Bronchoscopy with bronchoalveolar lavage can rule out lung infections and a differential white blood cell count most often shows a neutrophilic, non-specific inflammatory pattern. Transbronchial biopsies are rarely diagnostic[31] and surgical lung biopsy is rarely performed as the risk of complications most often outweigh the benefits of a highly confident diagnosis. Pathology can distinguish between chronic constrictive bronchiolitis, follicular bronchiolitis and mixed constrictive–follicular bronchiolitis, which can help to appreciate the potential reversibility of airflow obstruction. In most patients, the clinical, physiological and radiological presentations are sufficient for a diagnosis of bronchiolitis. In the largest case series of 41 patients with RA-associated bronchiolitis obliterans, all-cause mortality was 27% over 5 years[31]. There is limited literature on the treatment of bronchiolitis obliterans, but supportive treatment with bronchodilators and inhaled corticosteroids is often initiated[28,31]. Case-based and small-series data suggest that responses are variable to systemic glucocorticoids, cyclophosphamide, azathioprine and etanercept, which should be weighed against the risk of infection; in some case series, stabilization and even improvement upon treatment with macrolides was reported[29,32]. However, many patients do not respond to therapy and referral for lung transplantation evaluation should be considered[31].

Bronchiectasis in rheumatoid arthritis

The coexistence of RA and bronchiectasis, frequently conceptualized as bronchiectasis rheumatoid overlap syndrome (BROS), represents an important clinical association with complex biological pathways that remain to be fully elucidated[33]. HRCT is the diagnostic modality of choice for bronchiectasis, and typically reveals dilated bronchi with thickened bronchial walls (Fig. 2). On cross-sectional images, the bronchial diameter is usually greater than that of the accompanying pulmonary artery, a finding known as the 'signet ring' sign[34]. Bronchiectasis differs from traction bronchiectasis, which is selectively located in areas of fibrotic parenchyma. Additionally, bronchiectasis is often observed in the outer third of the lung, which distinguishes it from other conditions. Epidemiologically, RA confers an elevated risk of developing incident bronchiectasis compared with a control population (adjusted HR 2.12), with a higher prevalence in seropositive RA than in seronegative RA[35]. The prevalence of bronchiectasis in RA cohorts also varies widely owing

Table 1 | Evaluation and management of respiratory conditions in patients with rheumatoid arthritis

Investigation(s)	COPD	Bronchiectasis	ILD
Respiratory symptoms	Increased dyspnoea over years, morning cough, sputum	Dyspnoea, cough, sputum purulence, recurrent infections	Asymptomatic, or increased dyspnoea over a few months to years, dry cough
Lung auscultation	Prolonged expiration and/or rhonchi	Normal or rhonchi and/or crackles	Normal or Velcro crackles
Spirometry	Irreversible obstruction with low FEV1, normal or low FVC and FEV1/FVC ratio <70%	Obstruction with low FEV1, normal or low FVC and FEV1/FVC ratio <70%	Normal or equally decreased FEV1 and FVC
Body plethysmography and diffusion	High TLC and residual volume Decreased DLCO	Normal or high TLC and residual volume Normal or decreased DLCO	Normal or low TLC and residual volume Normal or decreased DLCO
HRCT patterns	Emphysema	Bronchiectasis	UIP, NSIP, organizing pneumonia, AMP, or indeterminate pattern
Treatment	LABA and/or LAMA and/or ICS	LABA and/or LAMA and/or antibiotics	Immunomodulation and/or antifibrotics
Follow-up	General practice or pulmonologist	General practice or pulmonologist	ILD centre, collaboration with pulmonologist and rheumatologist

AMP, alveolar macrophage pneumonia; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution CT; ICS, inhaled corticosteroids; ILD, interstitial lung disease; LABA, long-acting β2 agonist; LAMA, long-acting muscarinic antagonist; NSIP, non-specific interstitial pneumonia; TLC, total lung capacity; UIP, usual interstitial pneumonia.

Box 2 | Supportive and adjunctive interventions in rheumatoid arthritis-associated lung disease

Prophylaxis
- Smoking cessation programmes
- Minimize environmental and occupational inhalational exposure
- Vaccination
  - Influenza
  - COVID
  - Pneumococcus
  - Respiratory syncytial virus
- Pneumocystis prophylaxis[a]
  - Sulfamethoxazole with trimethoprim

Exercise training
- Pulmonary rehabilitation programmes
- Endurance and resistance training
- Aerobic exercise, yoga, tai chi etc.

Respiratory physiotherapy in patients with sputum production
- Airway clearance techniques[b]
  - Forced expiratory technique
  - Chest physical therapy
  - Positive expiratory pressure devices
  - Oscillating positive expiratory pressure devices

Oxygen therapy
- Long-term oxygen therapy (chronic hypoxaemia, used ≥15 h daily)
- Ambulatory oxygen therapy (exertional hypoxaemia, used during exercise and activities of daily living)
- Nocturnal oxygen therapy (night-time hypoxaemia, used during sleep hours)

Management of comorbidities
- Reflux, sleep apnoea, cardiac comorbidities, pulmonary hypertension[b]

Interventional therapies
- Lung volume reduction in patients with emphysema
- Early lung transplantation evaluation

Complementary interventions
- Dietary recommendations for weight gain or loss as relevant
- Mental health management (e.g., anxiety, depression[b])
- Management of glucocorticoid-induced adverse effects (e.g., myopathy, osteopenia[b])

Palliative care
- Symptom management
- Advance care planning
- End-of-life treatment

[a]Pneumocystis prophylaxis is recommended for patients with rheumatoid arthritis on high-dose glucocorticoid therapy[120]. [b]Some examples, not limited to those listed.

to the diagnostic approaches used: symptomatic bronchiectasis is found in approximately 2.7–3.1% of patients with RA, whereas systematic use of HRCT consistently reveals diffuse bronchiectasis in a substantially greater proportion (22.6–24.9%) of patients with RA[36]. Importantly, the BROS diagnosis is independently associated with severely impaired outcomes, including increased mortality, with a mortality risk nearly double that of idiopathic bronchiectasis (HR 1.88–2.03)[33].

Two prevailing conceptual models explain the pathogenesis linking RA and bronchiectasis. The 'airway-first' model suggests that an underlying genetic risk, such as heterozygosity for variants in the gene encoding cystic fibrosis transmembrane conductance regulator (*CFTR*), or innate immune defects, including undetectable circulating mannose binding lectin, cause chronic bronchial inflammation and subsequent infections[36–39]. The resulting antigenic stimulation, potentially involving the externalization of citrullinated peptides via neutrophil extracellular traps, triggers systemic autoimmunity and ACPA generation, leading to RA[37,40]. This model is historically supported by cohort studies in which bronchiectasis symptoms preceded RA onset in a high proportion of patients (83.3–93.8%)[41]. Conversely, the 'RA-first' model is strongly supported by more recent longitudinal data showing that RA antedates incident bronchiectasis, suggesting that systemic rheumatic inflammation might drive the pulmonary disease[13]. The risk of bronchiectasis is substantially more pronounced in seropositive RA (adjusted HR 2.34) than in seronegative RA (adjusted HR 1.56), illustrating the central role of high-grade rheumatic inflammation[35]. Risk factors for bronchiectasis also include older age, longer RA duration and specific HLA genetic variants[35].

The implications for treatment are complicated by the infectious nature of bronchiectasis. DMARDs (both conventional and biologic), along with glucocorticoids, constitute the backbone of RA treatment and increase a patient's susceptibility to recurrent lower respiratory tract infections, including susceptibility to mycobacteria[42]. This increased susceptibility often leads clinicians to avoid the use of bDMARDs in patients with RA known to have bronchiectasis. Consequently, the treatment must focus on targets that mitigate the underlying bronchiolar and articular inflammation without compromising antibacterial defenses. A promising anti-inflammatory strategy currently being explored in bronchiectasis is the inhibition of dipeptidyl peptidase 1 (DPP-1) by the neutrophil elastase inhibitor brensocatib, which reduces the frequency of pulmonary exacerbations[43]. This approach could represent a critical future avenue for the management of the chronic inflammatory component of BROS, while addressing the burden of recurrent lung infections.

Interstitial lung disease in rheumatoid arthritis

Pathophysiology of rheumatoid arthritis-associated interstitial lung disease

RA-ILD is a multifactorial disorder resulting from the interaction of genetic susceptibility, environmental factors and immune dysregulation. To date, the *MUC5B* promoter variant rs35705950 is the only

well-established genetic variant significantly associated with an increased risk of RA-ILD[44,45]. RA-ILD constitutes a heterogeneous entity encompassing multiple phenotypes, each characterized by distinct HRCT patterns and clinical courses, suggesting distinct underlying pathophysiological mechanisms. Indeed, the pathogenic effect of the *MUC5B* rs35705950 variant is restricted to patients exhibiting a usual interstitial pneumonia (UIP) pattern on HRCT, with an effect on the risk of RA-ILD comparable in magnitude and direction with that reported in idiopathic pulmonary fibrosis[44,46]. Beyond genetic factors, premature cellular senescence has emerged as a pivotal pathogenetic mechanism of RA-ILD[47,48].

Although it is not completely clear whether smoking contributes to the pathogenesis of RA-ILD, smoking has consistently been identified as a risk factor for the presence of ILD in RA[10,49], and it induces epithelial injury and impairs repair mechanisms in the lung parenchyma, facilitating fibrotic remodelling[50]. High RA disease activity is a risk factor for both incident[51] and prevalent ILD[52] in patients with RA, and can be associated with the prognosis of RA-ILD[53]; however, the precise role of RA-related systemic inflammation in the pathogenesis of ILD remains unclear.

The results of numerous studies emphasize the critical role of the lung in the pathogenesis of RA, consistent with the 'mucosal origins' hypothesis (reviewed by Holers et al.[54]). Two key lines of evidence support early pulmonary involvement in the development of RA. First, environmental exposures such as cigarette smoke and silica are important risk factors for ACPA-positive RA[55,56]. Second, elevated levels of ACPAs are detected in sputum samples from patients with RA, including those with early-stage disease,[57] suggesting that citrullination within the pulmonary mucosa could initiate local autoimmunity, thereby initiating RA pathogenesis. Additionally, temporal analyses show that ILD can precede or co-occur with RA diagnosis in 17–48% of cases[58–60]. Altogether, these findings highlight the lung as a potential primary site of the development of autoimmunity in RA. However, the specific contribution of locally produced ACPAs to the pathogenesis of RA-ILD remains to be fully elucidated.

Epidemiology of rheumatoid arthritis–associated interstitial lung disease

Among the various imaging phenotypes of RA-ILD, the UIP pattern predominates, with a pooled prevalence of approximately 46% in patients with RA-ILD[61]. This frequency of UIP contrasts markedly with ILD associated with other connective tissue diseases, in which other radiological patterns are more common[51]. Combined pulmonary fibrosis and emphysema, a condition in which emphysema is seen on HRCT in the apical parts of the lungs and fibrosis in the lower parts, has a prevalence of up to 48% in patients with RA-ILD[62]. Combined pulmonary fibrosis and emphysema is physiologically characterized by preserved lung volumes and significantly reduced DLCO and is associated with a high risk of pulmonary hypertension and lung cancer[62].

Short telomeres are a recognized risk factor for RA-ILD, with even more pronounced telomere shortening observed in patients exhibiting a UIP pattern. Short telomeres are strongly associated with increased

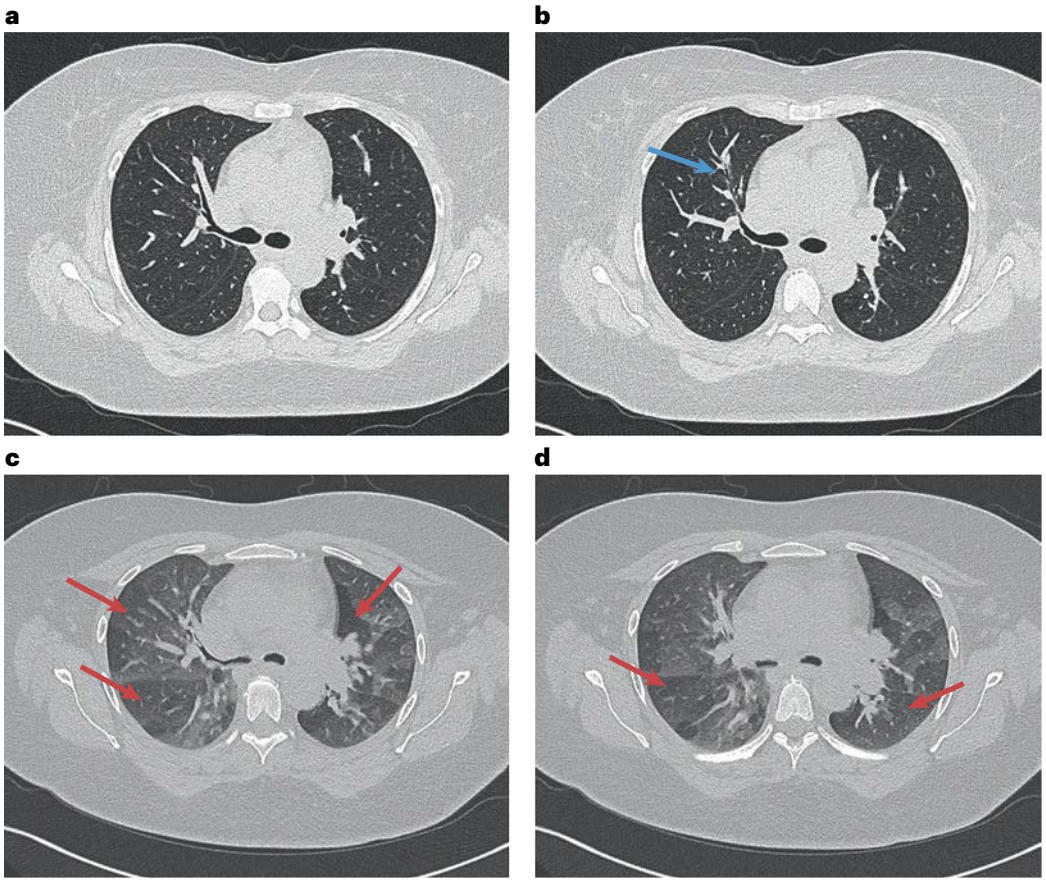

Fig. 1 | High-resolution chest CT of obstructive bronchiolitis. **a**, **b**, Inspiratory high-resolution CT (HRCT) images of obstructive bronchiolitis in a 72-year-old man with rheumatoid arthritis (RA) show discrete bronchiectasis (blue arrow). **c**, **d**, Expiratory HRCT images of the same patient show air trapping (red arrows).

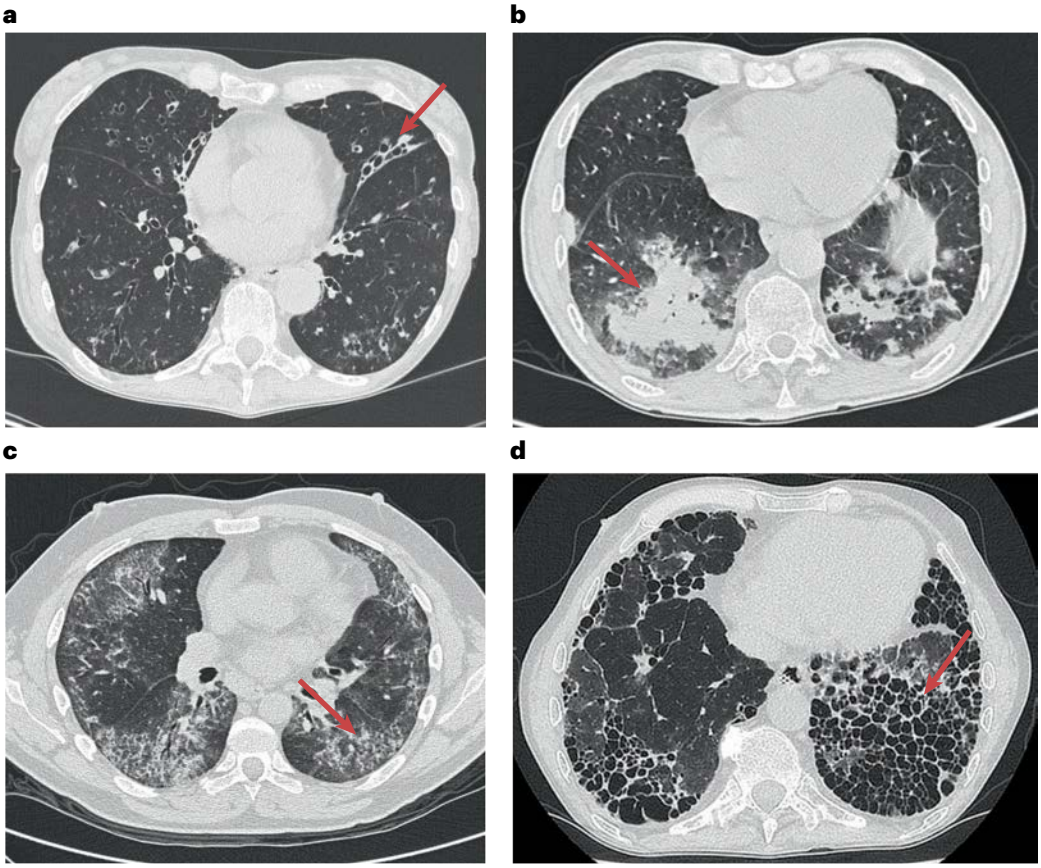

Fig. 2 | Characteristic high-resolution CT patterns of lung disease in rheumatoid arthritis. a, Bronchiectasis. The red arrow indicates dilated bronchi with thickened walls. **b**, Interstitial lung disease (ILD) with an organizing pneumonia pattern (red arrow) can appear as patchy, often peripheral or peribronchial, consolidations with a tendency to migrate over time. **c**, ILD with a non-specific interstitial pneumonia pattern (red arrow) is characterized by fine reticulation, ground glass opacity and traction bronchiectasis, often sparing the subpleural space, with less or no honeycombing compared with usual interstitial pneumonia. **d**, ILD with an usual interstitial pneumonia pattern is characterized by subpleural basal-predominant reticular abnormalities, honeycombing (red arrow) and traction bronchiectasis, reflecting fibrotic lung remodelling. The alveolar macrophage pneumonia pattern (not shown) is characterized by diffuse, bilateral ground-glass opacities predominantly in the lower lobes, often with a uniform distribution and minimal fibrosis or reticulation.

ILD prevalence, greater disease severity, accelerated lung function decline and worse outcomes in RA-ILD cohorts. Moreover, patients with short telomeres can experience reduced survival when exposed to immunosuppression[48,63–65].

Beyond genetic predisposition, several robust epidemiological and clinical risk factors for RA-ILD have been identified, including older age at RA onset, male sex, seropositivity (elevated ACPA titres), increased RA disease activity and prolonged disease duration[10,45,52,60,61,66]. Modifiable lifestyle factors such as smoking and obesity also contribute to the development of RA-ILD, highlighting potential avenues for risk reduction[49,67,68].

Despite these insights, epidemiological estimates of RA-ILD prevalence and incidence remain imprecise, largely because of heterogeneous definitions of ILD, variable diagnostic methodologies and differences in the timing of screening for ILD relative to the RA disease course. A 2023 systematic review and meta-analysis reported that symptomatic ILD has a prevalence of approximately 11% in patients with RA[61]. Similarly, three studies employing systematic HRCT screening of asymptomatic individuals with RA of mean durations ranging from <2 to 13.9 years revealed ILD prevalence rates of 11–21%[52,69]. Supporting these findings, a retrospective analysis of 293 patients with RA undergoing clinically indicated chest HRCT identified interstitial lung abnormalities (previously defined as subtle interstitial findings not meeting the diagnostic criteria for ILD but now considered preclinical ILD) in 44%, underscoring the considerable burden of subclinical lung involvement in this population[70].

Disease progression affects approximately half of patients with RA-ILD, whether symptomatic or asymptomatic, and is associated with a mortality risk exceeding that of both the general population and patients with RA without ILD[58,70–74]. Survival following diagnosis is variable, with median times ranging between 2.6 and 8 years and a 5-year mortality rate approaching 40%. The UIP pattern consistently correlated with worse outcomes across multiple cohorts[58,72,74–76]. Furthermore, a meta-analysis encompassing 1,256 patients highlighted pulmonary function metrics and the extent of lung involvement as potential prognostic indicators[77].

Screening for interstitial lung disease

Screening for RA-ILD involves the implementation of diagnostic evaluations in patients with RA who lack respiratory symptoms. This

approach differs from diagnostic assessment, initiated when patients have clinical manifestations of ILD, for which chest HRCT is the gold standard[78]. When screening for RA-ILD, HRCT, which provides detailed images of the lung parenchyma and offers superior sensitivity over chest radiography, should be performed without contrast enhancement but using a thin-slice technique (commonly <1 mm). Inspiratory and expiratory phases should be used to detect air trapping, a common finding in some RA-ILDs and bronchiolitis (Fig. 1). The most characteristic ILD patterns observed on HRCT are, with decreasing frequency, UIP, non-specific interstitial pneumonia, organizing pneumonia and alveolar macrophage pneumonia (formerly termed desquamative interstitial pneumonia)[61] (Fig. 2). Drug-induced ILD should always be considered in the differential diagnosis, particularly when organizing pneumonia is identified and when ILD develops within weeks to months following the initiation of a new medication[79].

Screening for RA-ILD can be conceptualized as a two-tiered process. The initial screening step involves systematic assessment of respiratory symptoms and focused clinical examination in all individuals with RA. Identification of relevant symptoms or signs at this stage warrants escalation from screening to definitive diagnostic evaluation, typically with chest HRCT. The subsequent, secondary screening step entails a more intensive surveillance strategy, applied selectively to patients at an elevated risk of ILD[68].

Both the 2025 ERS–EULAR and the 2023 American College of Rheumatology (ACR)–American College of Chest Physicians (CHEST) guidelines[10,80] favour a risk-based approach over universal screening for ILD in RA; however, they do not explicitly define the criteria identifying high-risk populations, and do not endorse the implementation of published risk-prediction models[52,81,82]. Importantly, a screening algorithm incorporating commonly assessed clinical variables, such as age at RA onset, sex and disease activity, has shown potential for early ILD detection in RA[82]. Both sets of guidelines discourage the use of chest radiography, invasive diagnostic procedures or chest ultrasonography for screening, designating chest HRCT as the preferred modality[10,80]. Notably, pulmonary function tests (FVC and DLCO) were excluded as screening tools by ERS–EULAR, whereas the ACR–CHEST panel advocated their use in conjunction with HRCT during screening[10,80].

Management of rheumatoid arthritis-associated interstitial lung disease

Current treatment recommendations for RA-ILD are largely extrapolated from randomized controlled trials (RCTs) focused on articular disease, as well as from retrospective, observational studies[10]. Recommendations for RA-ILD distinguish between immunomodulatory agents (primarily for control of articular disease with potential benefit for ILD) and antifibrotics (targeting fibrosis), often used alone or in combination with immunomodulation on the basis of individualized risk–benefit assessment. Methotrexate, a well-established evidence-based therapy for RA, has long been suspected of worsening pre-existing, chronic RA-ILD. Although methotrexate can rarely induce acute or subacute drug-induced pneumonitis[83], retrospective, registry-based and case–control studies have consistently demonstrated that methotrexate is not associated with an increased risk of worsening chronic ILD[84–86]. On the contrary, patients treated with methotrexate exhibit better survival, a longer time to ILD development, and fewer respiratory hospitalizations than patients with RA not receiving methotrexate, although some bias cannot be ruled out[86].

The management of RA-ILD is aimed at slowing the progression of lung disease, preventing acute exacerbations and improving survival. Controlling articular disease with a treat-to-target strategy using csDMARDs (such as methotrexate, sulfasalazine and leflunomide) and bDMARDs (including rituximab and abatacept) following the EULAR guidelines for the management of RA[87] remains essential, as these agents might also benefit ILD. Mycophenolate mofetil is often used in clinical practice for the treatment of RA-ILD, but does not treat articular disease and the evidence for its use in RA-ILD is very weak[10]. The addition of non-DMARD immunosuppressants requires careful consideration owing to the increased risks associated with immunosuppression.

Whereas the ACR–CHEST guidelines do not specify criteria for the initiation of ILD-targeted therapies[80], the ERS–EULAR guidelines recommend applying the inclusion criteria of RCTs to guide treatment in CTD–ILD[10]. Two scenarios warrant consideration for initiating ILD-targeted therapy: at the time of RA-ILD diagnosis in the case of advanced disease (moderate or severe ILD) and upon documentation of progression according to established criteria for progressive pulmonary fibrosis (PPF)[78].

Recommendations rely largely on expert consensus owing to limited data from trials. Both ACR–CHEST and ERS–EULAR endorse a multidisciplinary, individualized approach but note that little evidence is available, especially for immunosuppressants[10,80] (Fig. 3).

Over the past 25 years, numerous RCTs have established evidence-based treatments for RA, resulting in improved control of articular inflammation and a reduction in joint deformity. Both csDMARDs and bDMARDs have demonstrated efficacy in managing joint involvement in RA[87]. By contrast, no prospective RCTs have shown the efficacy of these treatments in RA-ILD. Only one phase II trial has been conducted specifically in RA-ILD: the TRAIL-1 trial, which compared pirfenidone to placebo in 123 patients[88]. Unfortunately, this trial was terminated early owing to slow recruitment during the COVID-19 pandemic; it did not reach its primary end point of reducing disease progression. However, the decline in FVC was attenuated in the total population and even more so in the subgroup of patients with a pattern of UIP on HRCT[88]. In the INBUILD study and the FIBRONEER-ILD study, treatment with nintedanib or nerandomilast, respectively, significantly slowed disease progression in patients with PPF (fibrotic ILD with a progressive phenotype). However, only 89 of the 663 patients enrolled

Glossary

Body plethysmography
Measures static lung volumes, including total lung capacity (the maximum volume of air the lungs can hold) and residual volume (the amount of air remaining after maximal exhalation), thereby capturing even air trapped in the lungs, which spirometry cannot assess.

Diffusing capacity of the lungs for carbon monoxide
(DLCO). Evaluates how effectively gases transfer from the lungs into the bloodstream, providing important information about lung gas exchange efficiency.

FEV1/FVC ratio
Compares the expiratory volume in the first 1s (FEV1) with the forced vital capacity (FVC) of the lungs, to distinguish obstructive (lower FEV1/FVC ratio) from restrictive (normal or increased FEV1/FVC ratio) lung disease patterns.

Spirometry
A key pulmonary function test that quantifies the amount of air a patient can forcibly exhale in the first 1s (forced expiratory volume in 1s (FEV1)) and the total volume of air exhaled forcefully after a deep breath (forced vital capacity (FVC)), as well as the FEV1/FVC ratio.

	ACR/CHEST 2023	ERS/EULAR 2025
First-line therapy		
Short-term low-dose glucocorticoids	■	□
Methotrexate	■	■
TNF inhibitors	■	■
Abatacept	■	■
Rituximab	■	■
JAK inhibitors	■	■
Mycophenolate mofetil	■	□
Azathioprine	■	□
Leflunomide	■	■
Cyclophosphamide	■	■
Tocilizumab	■	□
Progressive pulmonary fibrosis		
Nintedanib	■	■
Pirfenidone	■	■
Tocilizumab	■	■

■ Conditional recommendations for
■ Conditional recommendations against
■ Case-by-case discussion
■ Not specified
□ Usual clinical practice

Fig. 3 | Comparison of recommendations for the treatment of rheumatoid arthritis-interstitial lung disease. Recommendations for the treatment of interstitial lung disease (ILD) associated with rheumatoid arthritis (RA) were issued in 2023 by the American College of Rheumatology (ACR) and the American College of Chest Physicians (CHEST)[79] and in 2025 by the European Respiratory Society (ERS) and the European Alliance of Associations for Rheumatology (EULAR)[10]. Both sets of recommendations promote a multidisciplinary, individualized approach to the treatment of RA-ILD but differ in some respects.

in INBUILD, and 118 of the 1,176 patients enrolled in FIBRONEER-ILD, had RA-ILD[89,90]. ERS–EULAR recommend nintedanib for PPF and pirfenidone for patients with a UIP pattern, whereas ACR–CHEST consider both drugs as second-line options[10].

For patients with advanced progressive ILD despite maximal medical therapy, lung transplantation represents a viable option. Given the inherent medical complexities of this intervention, early referral for transplant evaluation is strongly recommended to weigh potential risks and benefits[91].

Overall, current guidance is based on low-certainty evidence, underscoring the urgent need for dedicated RCTs to optimize RA-ILD management.

Lung cancer in rheumatoid arthritis

RA confers a clinically meaningful excessive risk of lung cancer that extends beyond that conferred by shared risk factors such as smoking. Large contemporary cohorts show a 50–60% higher incidence of lung cancer in RA than in non-RA populations, with the highest risk concentrated in patients with RA-ILD[4,92]. In a 2024 US Veterans Health Administration cohort, RA was linked to a >50% increased risk of lung cancer overall and RA-ILD with an approximately threefold higher risk[4]. Parallel nationwide data from Asia and the USA support this association and suggest that elevated risk persists even among never-smokers, underscoring the contribution of RA-specific mechanisms[92]. These mechanisms might include chronic airway inflammation, citrullination, ectopic lymphoid structures within the lung and cumulative exposure to infections. The presence of RA-ILD, comparable with idiopathic pulmonary fibrosis[4], increases the risk of lung cancer, probably via fibrotic remodelling, altered immune microenvironments and diagnostic surveillance effects. It has been speculated that methotrexate, other csDMARDS and bDMARDs might contribute to the increased risk of lung cancer in RA or to an increased risk of cancer recurrence, but studies have produced conflicting results[93–96]. Whether the elevated risk of lung cancer in patients with RA, particularly those with RA-ILD, justifies dedicated lung cancer screening has not yet been established, but when screening for lung cancer, concomitant screening for ILD is also warranted. Lung cancer often presents clinically with worsening cough, dyspnoea, thoracic pain and systemic symptoms such as weight loss and fatigue, which should prompt timely referral for lung cancer diagnostics. Attention should be paid to the possibility of lung cancer whenever a chest CT is performed, and smoking cessation should be promoted among patients with RA.

Immune checkpoint inhibitors are increasingly used to treat advanced lung cancer. Pre-existing autoimmune rheumatic disease, including RA, does not preclude the benefit of immune checkpoint inhibitors, as it does not confer a greater risk of mortality or of severe immune-related adverse events in patients with these conditions compared with matched controls[96]. Although patients with RA and lung cancer were more likely to have immunotherapy-related adverse events in a retrospective cohort study, this finding was mostly restricted to mild RA flares or other mild adverse effects of immunotherapy[97]. Coordinated management across medical specialties (rheumatology, thoracic oncology, pulmonology) is key for optimizing lung health and oncological outcomes in patients with RA and lung cancer.

Rheumatoid nodules in rheumatoid arthritis

Pulmonary rheumatoid nodules are benign lesions, often found incidentally, and typically asymptomatic, even though some patients can present with cough, haemoptysis or pleuritic pain[98]. These lesions are more common in smokers and in those with severe, seropositive RA[5]. The primary clinical challenge lies in differentiating them from lung cancer, as a positive uptake might be seen on ^{18}F-FDG-PET in both conditions. Rheumatoid nodules are relatively rare, occurring in approximately 3.5% of patients with RA[3]. Their imaging characteristics on CT, including multiplicity, calcification, cavitation, smooth borders and peripheral subpleural location, help to distinguish them from malignant nodules[98] (Fig. 4). Accurate diagnosis of rheumatoid nodules is essential owing to overlap with infectious and malignant processes, and sometimes necessitates histopathological confirmation for definitive differentiation. Histopathology shows fibrinoid necrosis surrounded by a palisade of histiocytes and chronic inflammation[5]. Rheumatoid nodules in the lung generally do not require specific treatment unless symptomatic or complicated by infection or haemorrhage. Methotrexate and other DMARDs, such as anti-TNF agents, have been implicated in the development of rheumatoid nodules[99]. Therefore, it is important first to consider discontinuing these agents before assessing their impact. Subsequent treatment with selected conventional and biologic

DMARDs (such as hydroxychloroquine and rituximab) and targeted synthetic DMARDs (for example, Janus kinase inhibitors) can be associated with stabilization or regression of nodules, whereas surgical excision remains an option in refractory cases with diagnostic uncertainty[100–103].

Pleural diseases in rheumatoid arthritis

Common pleural manifestations of RA are pleurisy, pleural effusions and subpleural rheumatoid nodules[3]. Pleural involvement is often subclinical and primarily identified through imaging. Large pleural effusions can present with cough, dyspnoea, chest pain and fever[104]. The reported prevalence of pleural manifestations of RA varies widely. Symptomatic pleural disease occurs in <5% of cases, although some studies report frequencies as high as 20%[105,106], and post-mortem analyses show pleural effusions in about 50% of patients[107]. The frequency of pleural disease in people with RA is declining over time[108]. HRCT often demonstrates multiple pulmonary abnormalities, including parenchymal, airway and pleural involvement[109], and underscores the importance of imaging in detecting subclinical pleural disease. Effusions are more frequent in middle-aged men with high-titre seropositive disease, antinuclear antibodies and nodules[108,110]. Pleural complications are often late manifestations but can precede joint symptoms[106].

Pleural effusions in RA are usually unilateral exudates[111] and can co-occur with pericardial effusions[110]. Effusions rich in macrophages are non-specific and could suggest other causes, whereas lymphocytic predominance can suggest RA[111,112]. Neutrophil-predominant pleural effusions are usually infectious but can occasionally occur in RA[112]. Chronic or recurrent large effusions can result in pleural thickening and fibrosis[110].

Pleural thickening involves both parietal and visceral layers and can progress to fibrothorax, causing trapped lung and restrictive pathophysiology[113]. In rare instances, pleural thickening mimics malignancy, necessitating biopsy testing. Histology often shows non-specific pleural inflammation with epithelioid and multinucleated giant cells dominating over mesothelial cells[114]. Granulomatous features can be present in sampled nodules[115].

Subpleural nodules might cavitate and rupture into the pleural space, leading to pneumothorax, bronchopleural fistula, empyema and secondary infections[116]. Rarely, sterile emphysematous effusions or pseudochylothorax could follow the rupture of necrobiotic nodules[110]. Several reports suggest that drug toxicity can lead to accelerated nodulosis and recurrent pneumothoraces[110,116].

Management strategies are guided by symptom burden and underlying pathology[117]. Owing to the limited published data, evidence-based guidance for managing symptomatic cases remains lacking. Asymptomatic effusions can be observed, but symptomatic cases signal aggressive systemic disease and are treated with systemic glucocorticoids and DMARDs. Refractory or recurrent effusions might require repeated thoracentesis, pleurodesis or surgery[118]. Importantly, certain DMARDs have been implicated in drug-induced pleural disease, necessitating medication review.

Future perspectives

Future research priorities should focus on elucidating the mechanisms that link systemic rheumatic inflammation with distinct pulmonary phenotypes, including specifically ILD and airway disease. Large, longitudinal cohorts and deeply phenotyped registries are needed to define genetic, environmental and treatment-related risk factors, as well as trajectories of progression and treatment response across the spectrum of RA-associated lung disease. Emerging evidence also supports the use of lung ultrasonography as a promising, cost-effective, non-invasive screening tool for early detection of ILD in patients with RA[119] without respiratory symptoms. Therefore, lung ultrasonography could serve as an interesting tool for identifying patients eligible for further investigation through chest HRCT. Clinical trial design in RA-associated lung disease must account for disease heterogeneity, variable progression rates and competing risks such as infection and malignancy. Key priorities include standardized inclusion criteria, harmonized outcome measures (such as FVC decline, DLCO, imaging end points and patient-reported outcomes), and adequately powered trials that evaluate both antifibrotic and immunomodulatory strategies in well-characterized subgroups. Future studies should also explore the use of early antifibrotic therapy before patients fulfil the criteria for PPF; although supporting studies are currently lacking, this approach will probably represent the future standard for preventing irreversible lung damage. The management of RA-associated lung disease should be firmly anchored in multidisciplinary care, involving pulmonologists, rheumatologists, radiologists and, where available, specialized ILD centres. Given that the pattern and severity of lung

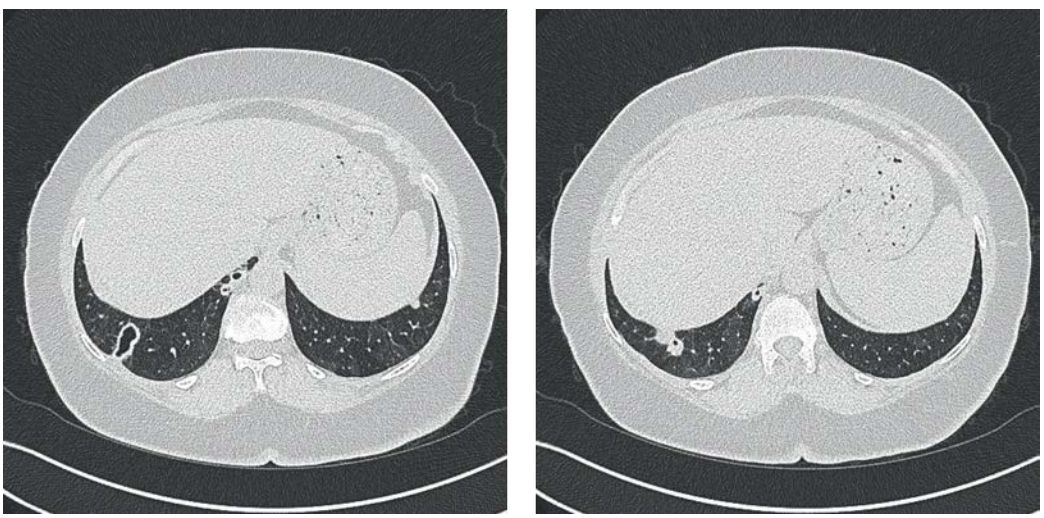

Fig. 4 | High-resolution CT of pulmonary rheumatoid nodules. High-resolution CT image showing cavitating nodules with irregular walls and central lucency representing cavitation in a patient with rheumatoid arthritis. Infection (including tuberculosis) and malignancy were ruled out. Histology revealed non-necrotizing granulomas compatible with rheumatic nodules.

involvement differ between patients, care pathways should be tailored to local health care structures while ensuring timely referral to expert centres for complex or progressive disease. Once a respiratory diagnosis is established, systematic and continuous collaboration with a rheumatologist is crucial to optimize control of the underlying RA and to align systemic therapy with pulmonary safety and efficacy considerations. Regular multidisciplinary discussions enable coordinated decisions on DMARDs (including biologic agents) and antifibrotic agents, balancing control of articular and pulmonary disease activity against treatment toxicity and comorbidities. Therapeutic strategies for RA-associated lung disease should be embedded within an integrated, multidisciplinary framework that also addresses smoking cessation, vaccination, pulmonary rehabilitation and comorbidity management to improve prognosis and quality of life. Continued expansion of clinical and translational research is essential to close current knowledge gaps, facilitate earlier and more accurate diagnosis and to establish robust, evidence-based management algorithms that ultimately reduce morbidity and mortality, particularly in RA-ILD.

Conclusions

RA-associated lung disease is a common and potentially severe extra-articular manifestation of RA. The prevalence varies widely, depending on the type of lung disease, but substantial numbers of patients with RA experience some form of lung involvement, ranging from mild interstitial changes to severe fibrotic disease. RA-ILD can lead to significant morbidity and is associated with increased mortality, thus reducing life expectancy.

In the past 5–10 years, research efforts in RA-ILD have intensified, garnering growing clinical and scientific interest. Advances in imaging and biomarker discovery have enriched understanding and offer promise for personalized approaches. Research into other RA-associated lung diseases, such as COPD and bronchiectasis, has been less prominent, although advances in treatment such as brensocatib for bronchiectasis have been reported.

However, despite these advances, high-quality evidence from RCTs remains limited, underscoring the ongoing need for rigorous studies. Novel treatments targeting not only fibrotic but also inflammatory pathways in the lungs should be aimed at modifying the burden conferred by ILD, COPD, bronchiectasis and other lung diseases in RA.

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Review article

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Metabolic exhaustion and immune ageing in rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) disproportionately affects adults over 50 years of age, highlighting how age-related immune remodelling undermines tolerance and promotes autoreactivity. In later adulthood, immune cells progressively lose metabolic resilience because of impaired nutrient sensing, reduced metabolic flexibility and disrupted anabolic–catabolic balance. In RA, these vulnerabilities are compounded by mitochondrial insufficiency across innate and adaptive immune lineages, creating a state of nutrient deprivation characterized by NAD^+ and ATP scarcity and diversion of carbon away from oxidative phosphorylation. Mechanistic studies identify this bioenergetic fragility as a core defect that limits cellular longevity and promotes inflammatory, non-apoptotic death pathways, including pyroptosis and PANoptosis. The hypoxic, nutrient-restricted synovial environment adds pressure that exceeds the diminished metabolic adaptability of aged immune cells. In RA T cells, accelerated mitochondrial injury initiates maladaptive stress responses, disrupts mitochondria–lysosome–endoplasmic reticulum communication and induces gasdermin D-dependent pore formation and inflammatory lysis. Synovial $MerTK^+$ reparative macrophages undergo a parallel metabolic crisis, whereby autocrine C1q sensing activates mitochondrial SARM1, causing NAD^+ degradation, ATP depletion and PANoptotic cell death. Together, these findings position ageing-associated metabolic exhaustion and organelle disintegration as unifying mechanisms that convert immune cells into tissue-damaging effectors and explain the heightened susceptibility to RA in older adults.

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Immune and bioenergetic ageing in autoimmunity

Mitochondrial dysfunction in RA

NAD^+ imbalance and metabolic stress in RA

Organelle stress response in T cells

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Misdirected cell death programmes in RA

Conclusion

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Key points

- Age-related immune remodelling predisposes individuals to autoimmune disease, including rheumatoid arthritis (RA), by weakening tolerance mechanisms and skewing innate and adaptive immune cells towards pro-inflammatory effector functions.
- Ageing immune cells lose metabolic resilience owing to impaired nutrient sensing, declining mitochondrial fitness and disrupted balance between anabolic and catabolic pathways, limiting energy supply and stress adaptation.
- In RA, mitochondrial insufficiency across immune lineages promotes the depletion of NAD^+ and ATP, and redirects carbon away from oxidative phosphorylation, creating a state of bioenergetic crisis and nutrient deprivation.
- This metabolic fragility restricts cellular longevity and promotes inflammatory, non-apoptotic death pathways, including pyroptosis and PANoptosis, linking defective bioenergetics directly to tissue-destructive immune activation.
- The hypoxic, nutrient-limited synovial environment creates a metabolic bottleneck that overwhelms aged immune cells, triggering maladaptive stress responses, disrupting organelle crosstalk and promoting gasdermin D-mediated inflammatory T cell death.
- Synovial $MerTK^+$ macrophages undergo a similar metabolic crisis: C1q–SARM1 signalling promotes NAD^+ loss, ATP depletion and PANoptotic death, highlighting metabolic exhaustion as an important pathogenic mechanism in RA.

Introduction

Rheumatoid arthritis (RA) is a prototypic autoimmune disease characterized by persistent synovial inflammation and progressive joint destruction. In more severe forms, RA becomes a systemic inflammatory syndrome that involves the lungs, heart, peripheral nerves, eyes and skin, and is associated with markedly increased cardiovascular morbidity. The disease arises from a multifactorial interplay of genetic, environmental, hormonal and lifestyle factors[1,2]. Although immunosuppressive therapies can dampen inflammation and slow structural damage, these therapies do not eliminate the fundamental drivers of autoimmunity[3].

Current paradigms propose that immune tolerance breaks down when post-translationally modified self-antigens, most prominently citrullinated proteins, function as neoantigens and elicit anti-citrullinated protein antibody responses[4]. These autoantibodies contribute to synovial inflammation and joint damage. However, citrullination is not the only modification of pathogenic relevance. Carbamylated and acetylated autoantigens are increasingly recognized as similarly important[5], pointing to defects in the clearance or processing of aberrantly modified proteins as a unifying pathogenic mechanism[6].

Additional insights challenge a model centred solely on immune complex-mediated pathology. RA shows a strong genetic association with elements of T cell biology, particularly polymorphisms in MHC class II molecules that govern antigen presentation to $CD4^+$ T cells[7,8]. These findings emphasize the central role of adaptive immunity and suggest that autoantigen formation, abnormal protein handling and T cell-driven responses jointly shape RA immunopathology.

Epidemiological evidence has renewed debate over whether autoreactivity to modified self-antigens represents a primary pathogenic trigger or a secondary consequence of broader immune dysfunction. In population-wide studies, age emerges as the strongest risk factor for RA (Fig. 1). Although RA can arise at any age, approximately 75% of patients are over 50 years of age at diagnosis, with a median age of 65 years[9]. From the standpoint of organismal ageing, tissue-specific proteomic clocks reveal an inflexion point around 50 years of age[10,11], with vascular and lymphoid tissues showing pronounced vulnerability to age-related molecular decline. Complementary multiomics analyses reveal that immune system ageing occurs in two distinct waves, with an initial 'breakpoint' occurring between 38 and 42 years of age and a second in the early 60s[12,13] (Fig. 1).

Thus, RA preferentially develops in individuals whose immune systems have already undergone substantial age-imposed remodelling, reflecting adaptations that maintain function despite cumulative system deterioration. A hallmark of ageing is extensive rewiring of metabolic pathways[14–16]. Declining metabolic efficiency forces compensatory changes in energy metabolism across cellular and tissue levels to sustain bioenergetic support despite progressive impairment of the metabolic machinery.

Consistent with this framework, molecular studies of immune cells from patients with RA, particularly $CD4^+$ T cells and macrophages, demonstrate convergent metabolic abnormalities that reprogramme these cells into highly pro-inflammatory effector populations that drive synovitis[17]. Notably, a consistent feature of these metabolically exhausted cells is an ageing phenotype, underscoring the close linkage between age-related losses in bioenergetic and biosynthetic capacity and altered immune function[18].

In this Review, we propose that age-related shifts in metabolic adaptability and resilience are key pathogenic mechanisms in autoimmune diseases that predominantly affect older adults, including RA. From this perspective, RA emerges not solely as a disease of immune hyperactivity, but as a state of immune insufficiency in which defective metabolic and regenerative capacities undermine immune homeostasis. We examine how metabolic ageing reshapes immune function, focusing on mitochondrial dysfunction and NAD^+ depletion and dysregulated organelle stress responses that permit persistent mTORC1 activation. We further consider how metabolic collapse redirects cell fate towards inflammatory, non-apoptotic cell death in T cells and synovial macrophages, and discuss the implications for therapeutic strategies aimed at restoring metabolic resilience and immune homeostasis. Such a framework raises the possibility that RA could, at least in part, be addressed through strategies aimed at immune reconstitution rather than solely through immunosuppression. Notably, several therapies currently used to treat RA already exert part of their efficacy through modulation of cellular metabolism, including effects on nucleotide synthesis, redox balance, lysosomal function and energy sensing (Table 1).

Immune and bioenergetic ageing in autoimmunity

The progressive increase in RA susceptibility with advancing age exposes a fundamental biological paradox: the decline of immune competence creates conditions that promote, rather than restrain, autoimmune pathology. Rather than conferring protection, age-associated immune deterioration predisposes the host to loss of self-tolerance and to chronic inflammation. This paradox emphasizes the need to

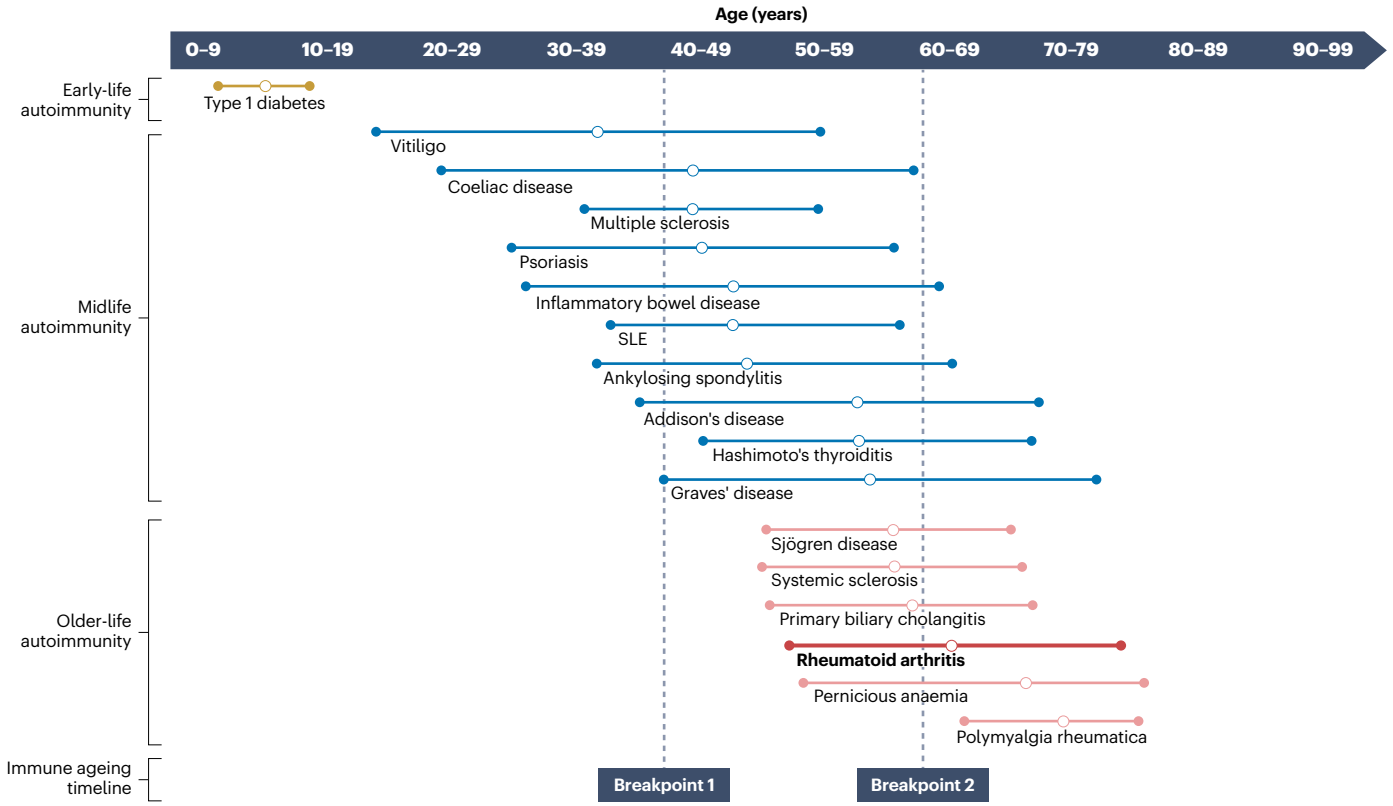

Fig. 1 | Immune ageing as a risk factor for rheumatoid arthritis. Autoimmune diseases can arise throughout life, but many cluster in later decades, coinciding with extensive age-associated remodelling of the immune system. Population-based data indicate that rheumatoid arthritis exemplifies this pattern, with a median age at diagnosis of approximately 65 years and an interquartile range of 53–77 years. Immune ageing is a nonlinear process, characterized by at least two major phases, with a first wave occurring around 38–42 years of age and a second in the early 60s. The peaks of these ageing transitions are indicated as breakpoints. SLE, systemic lupus erythematosus. Data taken from Conrad et al., Marquez et al. and Shen et al.[9,12,13].

reconsider immune ageing not simply as immunodeficiency, but as a state of dysregulated immunity. In this section, we examine how age-related declines in cellular bioenergetics, impaired stress buffering capacity and immune ageing interact to remodel immune function. We then explore how these alterations manifest in RA, ultimately enhancing susceptibility to persistent inflammatory disease.

Metabolic ageing and immune homeostasis

Ageing can be viewed as a coordinated breakdown of three organism-level homeostatic regulators — metabolic networks, immune surveillance and systemic stress-response pathways (including mitochondrial, proteostatic and redox control systems) — that normally function as an integrated control system (Fig. 2a). Metabolic ageing distorts nutrient sensing and energy allocation, reshaping immune cell differentiation, activation thresholds and inflammatory tone. These metabolic disturbances directly drive immune ageing by promoting 'inflammaging' and eroding T cell and B cell repertoire diversity[19]. In turn, immune ageing feeds back on organismal physiology: chronic innate immune activation and tissue-derived cytokines perturb systemic metabolism, including mitochondrial function and redox homeostasis.

Central features of metabolic ageing are the progressive loss of nutrient-sensing capacity, energetic efficiency and metabolic flexibility. Ageing disrupts key nutrient-sensing pathways, including IGF1, mTOR and AMPK signalling, leading to impaired control of glycolysis, the tricarboxylic acid (TCA) cycle, fatty-acid oxidation and amino acid and pentose-phosphate pathways[20–22]. Concomitantly, mitochondrial deficits accumulate: oxidative capacity falls, reactive oxygen species (ROS) production rises and mitochondrial dynamics are altered, collectively weakening cellular energy output and reinforcing low-grade inflammation[23]. Metabolic ageing is further characterized by impaired proteostasis, reduced autophagy and the accumulation of dysfunctional metabolites and organelles, destabilizing cellular homeostasis and amplifying inflammatory signalling[24].

Loss of metabolic flexibility across tissues and cell types is another hallmark of ageing. Single-cell analyses reveal heterogeneous vulnerabilities across immune, stromal and metabolic compartments[25]. This metabolic rigidity limits the ability of ageing cells to adapt to energetic stress, weakening immune function and promoting maladaptive trained-immunity programmes that sustain chronic inflammation[26]. Age-related shifts in lipid, glucose and amino acid homeostasis deepen systemic metabolic imbalance and heighten susceptibility to chronic disease[27]. Collectively, metabolic ageing is a multifaceted process marked by dysregulated nutrient sensing, mitochondrial decline, impaired cellular quality-control systems and immune metabolic dysfunction.

Table 1 | Metabolic targets of therapeutics currently used in rheumatoid arthritis

Drug class	Representative agents	Primary target	Metabolic pathways affected	Metabolic consequence in immune cells
Conventional synthetic DMARDs				
Folate antagonist	Methotrexate	Dihydrofolate reductase and adenosine pathway	Folate metabolism and purine and pyrimidine synthesis	Inhibits nucleotide synthesis, promotes adenosine-mediated anti-inflammatory signalling and limits lymphocyte proliferation[159]
Dihydroorotate dehydrogenase inhibitor	Leflunomide (teriflunomide)	Dihydroorotate dehydrogenase	De novo pyrimidine synthesis (mitochondria linked)	Restricts expansion of activated lymphocytes dependent on nucleotide synthesis[160]
Redox-modulating agent	Sulfasalazine	xCT cystine–glutamate antiporter	Glutathione metabolism and cellular redox balance	Alters oxidative stress handling and modulates inflammatory activation[161]
Lysosomal and/or autophagy inhibitor	Hydroxychloroquine	Lysosomal acidification	Autophagy and intracellular nutrient sensing	Interferes with antigen processing and metabolic adaptation, and impacts immune cell activation thresholds[162]
Glucocorticoids	Prednisone, methylprednisolone	Glucocorticoid receptor	Glucose, lipid and protein metabolism	Broad metabolic reprogramming, promotes catabolic state and suppresses immune activation[163]
Targeted and biologic therapies				
JAK inhibitors	Tofacitinib, baricitinib and upadacitinib	JAK–STAT signalling	Cytokine-driven metabolic pathways (such as glycolysis and mitochondrial function)	Reduces inflammation-associated metabolic activation and normalizes immune cell bioenergetics[164]
Tumour necrosis factor inhibitors	Etanercept, infliximab and adalimumab	Tumour necrosis factor	Inflammation-driven glycolysis and mitochondrial dysfunction	Reverses pro-inflammatory metabolic programming (known as the Warburg-like metabolic reprogramming)[165]
IL-6 pathway inhibitors	Tocilizumab and sarilumab	IL-6 receptor	Cytokine-regulated metabolic pathways	Reduces glycolytic bias and systemic metabolic dysregulation[166]
Costimulation blocker	Abatacept	Interaction between CD80 or CD86 and CD28	T cell activation-associated metabolic reprogramming	Prevents metabolic transition required for full T cell activation[167]

Immune ageing under metabolic constraint

Immune ageing proceeds in parallel with metabolic decline and is characterized by coordinated decline across innate and adaptive compartments. Hallmarks include thymic involution with reduced naive T cell output[28,29]; contraction of T cell and B cell receptor diversity[30,31]; and the accumulation of highly differentiated, often pro-inflammatory lymphocytes[32–36]. These changes coexist with bioenergetic dysfunction, most notably impaired mitochondrial performance and reduced metabolic flexibility, which limit effective immune activation while favouring stress-response and inflammatory programmes[37–40]. Ageing haematopoietic stem cells further acquire a myeloid bias, yielding dysregulated innate immunity characterized by diminished pathogen clearance alongside heightened baseline inflammatory signalling[41–43]. Additional features include telomere attrition, impaired autophagy and proteostasis, chronic low-grade inflammation and degradation of lymphoid stromal and vascular niches that sustain immune cell homeostasis[44,45]. Together, these alterations reduce immune competence, elevate inflammatory tone and create conditions conducive to chronic inflammatory and autoimmune disease.

Age-related remodelling of immune and metabolic networks is tightly integrated (Fig. 2b). Reduced mitochondrial fitness alters metabolite availability and redox cues, reshaping epigenetic and transcriptional programmes and accelerating immune senescence[37]. Conversely, chronically stimulated immune cells intensify metabolic stress within tissues, establishing a feedforward loop in which immune and metabolic ageing co-propagate and progressively diminish physiological adaptability[17]. Whereas self-tolerance is more often maintained earlier in life, the cumulative deficits that accrue with ageing increase susceptibility to autoimmunity; individuals who develop overt disease earlier in life probably harbour a greater burden of genetic or environmental factors that cause autoimmunity by unrelated mechanisms, while potentially also accelerating immune or metabolic ageing, relative to individuals who develop disease later in life.

Overall, ageing exposes latent vulnerabilities by eroding mitochondrial quality control and anabolic–catabolic balance, narrowing the adaptive range of immune metabolism such that tissue-specific stressors, particularly within the joint tissue microenvironment, can shift cellular programmes towards maladaptive response patterns that ultimately culminate in tissue-damaging inflammation.

T cell mitochondrial ageing

The close interface between immune ageing and metabolic ageing is particularly evident in T cells, providing a paradigmatic example of how mitochondrial decline constrains immune function. Emerging evidence identifies metabolic exhaustion and progressive mitochondrial dysfunction as core drivers of T cell ageing in healthy older individuals. Ageing T cells accumulate defective mitochondria, overproduce ROS and lose the capacity for efficient mitochondrial biogenesis, fission–fusion dynamics, mitophagy and metabolic flexibility[38,39,46–48]. These defects compromise ATP generation, disturb redox balance and undermine the formation and maintenance of long-lived memory subsets, key determinants of durable immunity. Metabolic signalling becomes increasingly dysregulated: aged T cells fail to dynamically transition between glycolysis and oxidative phosphorylation, remain trapped in hyperinflammatory, short-lived effector states and lose the ability to generate memory or T follicular helper cells, thereby

intensifying chronic low-grade inflammation and accelerating immune decline[33,49].

Multiple interconnected pathways drive mitochondrial insufficiency with age, including impaired mitochondrial quality control owing to defective mitophagy and altered fission–fusion dynamics, inadequate mitochondrial biogenesis linked to diminished PGC-1α activity, and an increased ROS burden that damages mitochondrial DNA (mtDNA) and respiratory chain components, reinforcing a self-perpetuating cycle of metabolic failure[38,39,46–48].

In chimeric antigen receptor (CAR) T cell biology, the idea that persistent proliferative stress exhausts mitochondrial capacity and undermines T cell longevity is now well established[50,51]. In cancer, CAR T cell persistence is pivotal for sustained antitumour immunity; however, immune and metabolic ageing progressively erode the cellular programmes needed for long-term survival. Senescent and exhausted states, marked by reduced mitochondrial biogenesis, diminished NAD^+ availability and chronic engagement of cellular stress pathways, limit the formation of long-lived, memory-like CAR T cell subsets[52,53]. Collectively, these pressures shorten CAR T cell longevity, blunt post-infusion expansion and impair persistence in hostile tumour microenvironments. Consequently, T cell products derived from aged or metabolically compromised immune systems display diminished durability, underscoring the need to enhance mitochondrial fitness, restore redox balance and reinforce memory-forming circuits to improve CAR T cell efficacy in older adults and in individuals with metabolically aged immune systems[54].

Importantly, T cell ageing reflects not only intrinsic mitochondrial dysfunction but also impaired interorganelle communication. Mitochondria–lysosome crosstalk is essential for metabolic reprogramming and the removal of damaged mitochondria; disruption of this process compromises mitochondrial fitness and downstream activation and differentiation[55]. Similarly, mitochondria–endoplasmic reticulum contacts regulate calcium homeostasis, lipid exchange and stress signalling, and deterioration of this communication impairs metabolic adaptability and increases susceptibility to exhaustion[56]. Stress-response pathways, including the mitochondrial unfolded protein response, normally buffer mitochondrial perturbations, particularly in regulatory T cells, but become inadequate with age, further destabilizing interorganelle communication[57].

Together, metabolic ageing limits T cell longevity, blunts adaptive immune responses and contributes to heightened susceptibility to autoimmunity, infection and chronic inflammation in older adults (Fig. 2).

Mitochondrial dysfunction in RA

Mitochondria occupy a central position in ageing biology by integrating metabolic and immune processes into a single, mutually reinforcing network[58,59]. In RA, mitochondrial integrity shapes the behaviour of $CD4^+$ T cells[60], synovial macrophages[61] and fibroblast-like synoviocytes[62–64] by governing bioenergetic capacity, stress-response signalling and cell-fate decisions[65–67]. At the molecular level, two recurring mitochondrial defects have emerged: genomic instability, including defective maintenance of the mitochondrial genome, and erosion of the intracellular NAD^+ pool. Both abnormalities are associated with impaired electron transport and ATP generation, reduced oxidative phosphorylation, inability to control ROS levels and maladaptive inflammatory signalling[18,40]. The direct causal relationships among these mitochondrial defects in RA remain incompletely defined.

Instability and defective repair of mtDNA

mtDNA is uniquely susceptible to oxidative injury owing to its proximity to sites of ROS generation and the absence of protective histones;

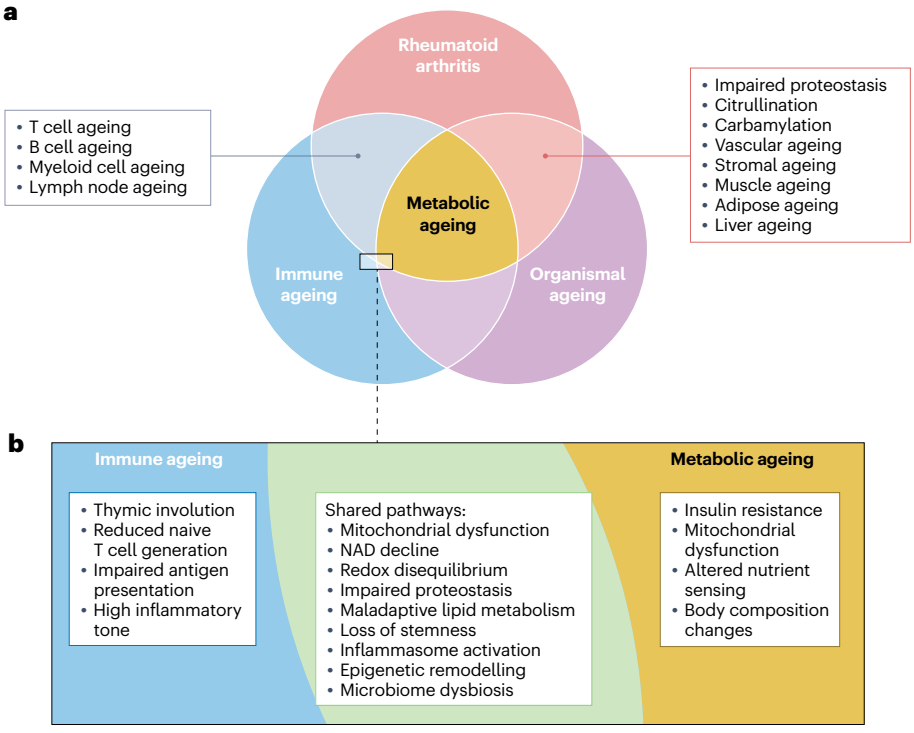

Fig. 2 | Metabolic ageing as a unifying feature of rheumatoid arthritis, immune ageing and organismal ageing. a, Organismal ageing is characterized by a progressive loss of metabolic resilience and flexibility, driven in part by the functional decline of metabolic endocrine organs. Metabolic ageing is similarly a hallmark of immune ageing, during which both innate and adaptive immune cells gradually lose metabolic fitness. Metabolic exhaustion has emerged as a central pathogenic feature in rheumatoid arthritis: T cells and synovial macrophages from patients with rheumatoid arthritis exhibit metabolic deficiencies, including mitochondrial dysfunction, that translate into disease-relevant inflammatory effector functions. **b**, At the intersection of immune ageing and metabolic ageing, multiple pathways drive the overlap between these two processes. Central to these shared pathways are key cellular organelles, including mitochondria, lysosomes and the endoplasmic reticulum, which undergo ageing-induced reductions in fitness.

maintenance of the mitochondrial genome therefore depends on nuclear-encoded repair factors that must be imported into mitochondria. In RA CD4$^+$ T cells, the nuclease MRE11A fails to localize to mitochondria, compromising the role of this factor as a guardian of mtDNA integrity. Reduced mitochondrial MRE11A availability compromises mtDNA repair, depresses oxygen consumption and ATP output, and precipitates caspase 1 activation and pyroptotic death[60,68]. Mechanistically, defective mtDNA maintenance produces two pathological outcomes (Fig. 3). First, inadequate synthesis of mtDNA-encoded respiratory subunits destabilizes the electron transport chain, curtailing oxidative phosphorylation and amplifying ROS production. Second, mtDNA escapes into the cytosol and extracellular space, where mtDNA functions as a mitochondrial damage-associated molecular pattern (DAMP) that activates AIM2 and NLRP3 inflammasomes. In humanized mouse models engrafted with synovial tissue, pharmacological or genetic inhibition of MRE11A in adoptively transferred human T cells increases synovial mtDNA deposition and triggers aggressive synovitis, whereas restoration of MRE11A rescues mitochondrial fitness and limits inflammation, directly linking T cell mtDNA leakage to joint pathology[60].

NAD$^+$ depletion and bioenergetic dysfunction

Loss of mitochondrial competence in RA is not limited to T cells and is increasingly linked to NAD$^+$ depletion across multiple cell types. A study published in 2026 demonstrates that MerTK$^+$CD206$^+$ macrophages (normally reparative, anti-inflammatory cells that support tissue homeostasis) isolated from the rheumatoid joint undergo metabolic exhaustion and PANoptotic death via a mitochondrial SARM1 NADase programme[61]. Autocrine C1q–C1QBP signalling activates SARM1, triggering NAD$^+$ cleavage to cyclic ADP-ribose (cADPR), depletion of ATP and execution of inflammatory lytic cell death; pharmacological inhibition of SARM1 attenuates synovitis in vivo (Fig. 4). More broadly, SARM1-mediated NAD$^+$ consumption rewires macrophage metabolism and cytokine programmes[69], supporting a model in which NAD$^+$ depletion functions as both a sensor and an effector of inflammatory stress. Notably, this metabolic vulnerability affects tissue-resident

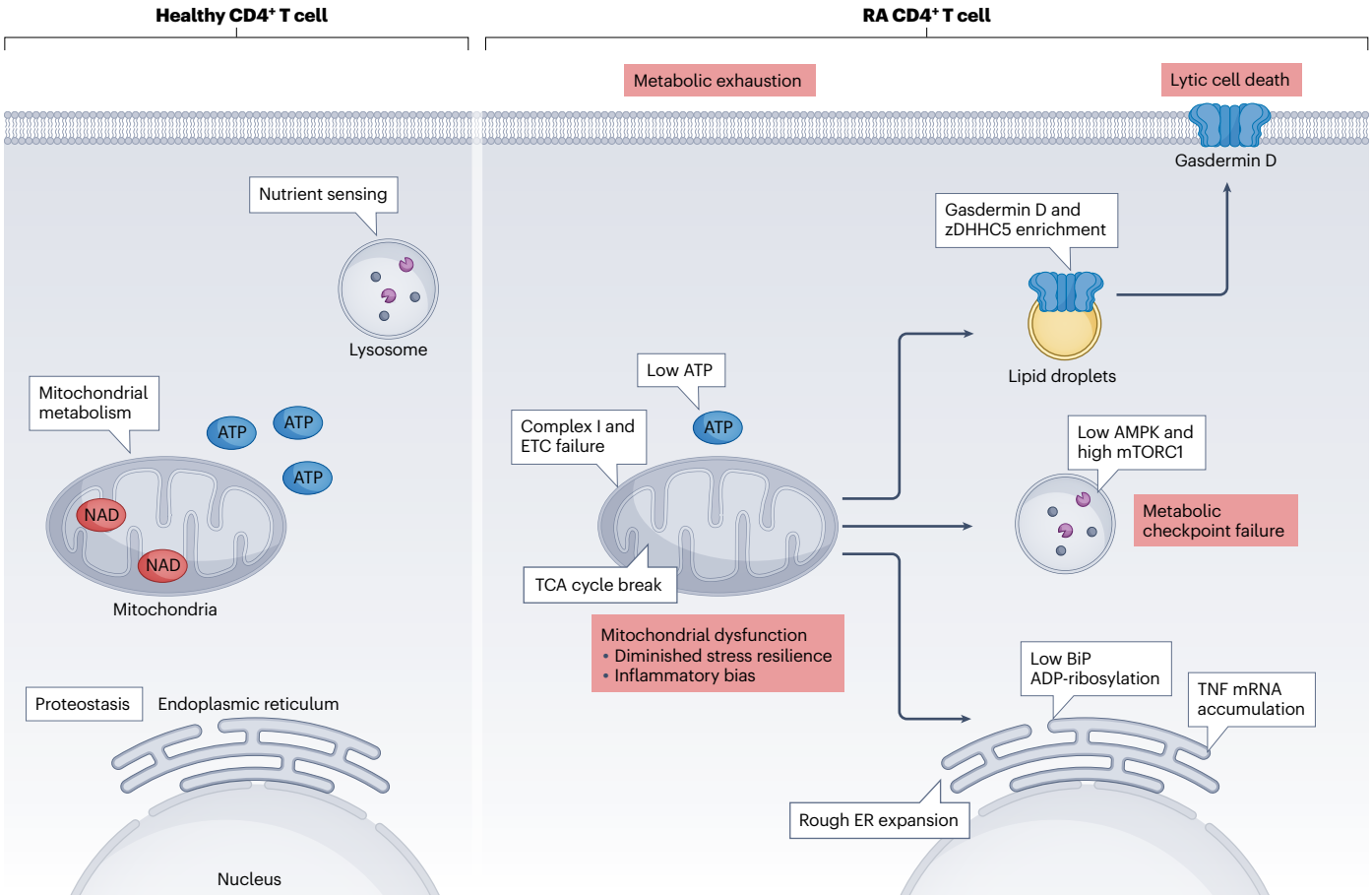

Fig. 3 | Organelle stress responses in pathogenic CD4$^+$ T cells. Healthy CD4$^+$ T cells maintain sufficient NAD$^+$ and ATP levels to support coordinated communication between mitochondria, the endoplasmic reticulum and lysosomes. By contrast, CD4$^+$ T cells from patients with rheumatoid arthritis (RA) exist in a state of profound metabolic exhaustion. Mitochondrial DNA damage-induced NAD$^+$ deficiency disrupts the electron transport chain (ETC) activity and tricarboxylic acid (TCA) cycle flux, initiating a broader mitochondrial crisis that secondarily impairs the function and integrity of lysosomal and endoplasmic reticulum (ER) functions. An important consequence of this bioenergetic crisis is the formation of lipid droplets enriched for the pore-forming effector gasdermin D and its activating enzyme zDHHC5. These lipid structures acquire membrane-damaging properties and drive pyroptotic T cell death. Processes associated with metabolic exhaustion include enhanced tissue invasiveness, increased tumour necrosis factor (TNF) production, lipid accumulation, mitochondrial DNA release and lytic cell death.

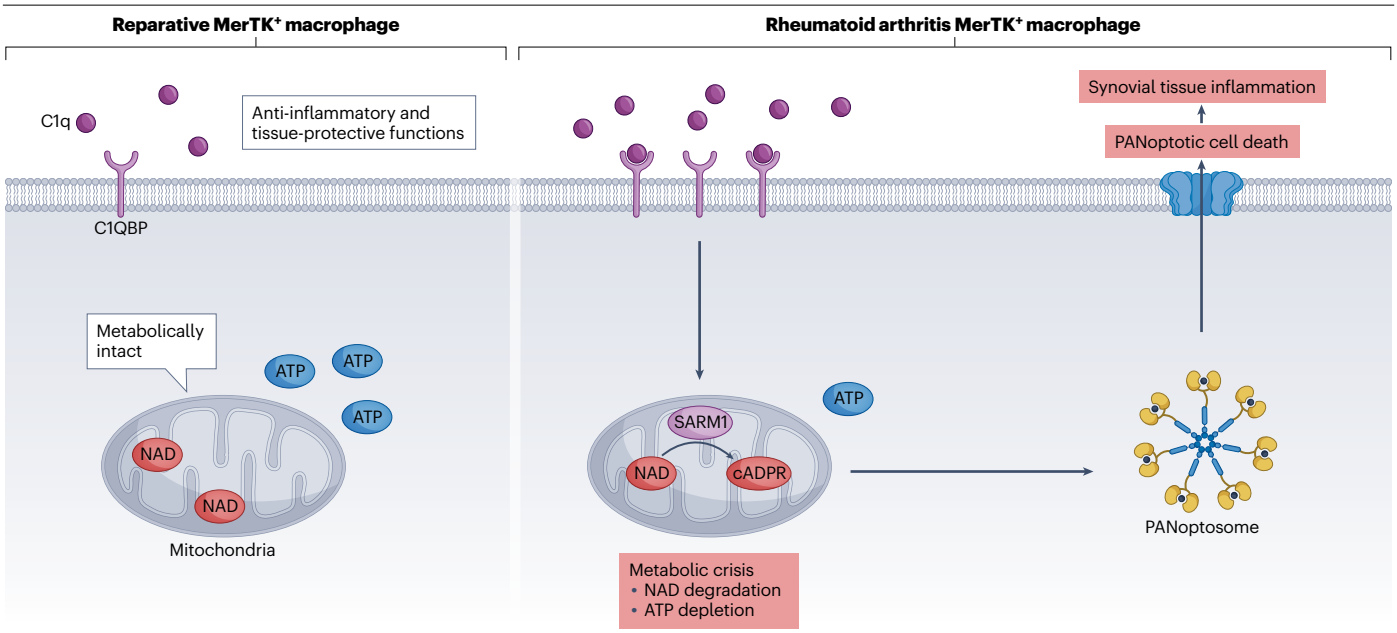

Fig. 4 | Metabolic control of lytic MerTK⁺ macrophage death in the rheumatoid joint. Rheumatoid synovitis is a macrophage-rich lesion composed of multiple distinct macrophage subsets. Under physiological conditions, CD206⁺ MerTK⁺ macrophages exert anti-inflammatory and tissue-protective functions (left). By contrast, MerTK⁺ macrophages within the rheumatoid joints are highly susceptible to lytic, pro-inflammatory cell death, converting these cells into potent drivers of synovial inflammation (right). Molecular profiling indicates that these death-prone macrophages exist in a state of metabolic crisis characterized by depletion of NAD^+ and ATP. Mechanistically, autocrine C1q–C1QBP signalling has emerged as an important regulator of mitochondrial function through activation of the mitochondrial NADase SARM1. After activation, SARM1 degrades NAD^+, triggering bioenergetic collapse and generating a surge of cyclic ADP-ribose (cADPR) that promotes PANoptosome assembly and execution of PANoptotic cell death.

macrophages that are normally reparative and anti-inflammatory, potentially compromising of synovial tissue integrity[70–73].

Defective organelle communication

Beyond intrinsic mitochondrial lesions, RA tissues exhibit pathway signatures consistent with disrupted communication between mitochondria and lysosomes or the endoplasmic reticulum, interfaces that govern mitophagy, lipid and Ca^{2+} exchange and metabolic signalling[1,74]. In T cells, mitochondria–lysosome crosstalk and contact-site dynamics modulate activation thresholds and cell fate; loss of this coordination links lysosomal dysfunction to mitochondrial decline[57,75]. Mechanistic work across multiple cell systems show that mitochondria–lysosome contacts, regulated by RAB7–TBC1D15 and DRP1, together with TFEB-controlled and TFE3-controlled lysosomal programmes, are essential for maintaining mitochondrial quality[76]; disruption of these pathways promotes ROS generation, defective mitophagy and inflammatory signalling[75,76]. In RA fibroblast-like synoviocytes, mitochondrial damage is accompanied by cGAS–STING activation, lysosomal impairment and autophagosome accumulation; experimental restoration of mitochondrial function normalizes lysosomal flux and dampens inflammatory cell death pathways, underscoring pathological organelle crosstalk in the joint niche[77,78].

Collectively, mitochondrial pathology in RA encompasses mtDNA repair failure owing to MRE11A insufficiency, inflammasome–gasdermin-mediated mitochondrial injury with DAMP release, and lineage-specific NAD^+ depletion (most prominently driven by SARM1 in synovial macrophages), all compounded by defective communication between mitochondria and lysosome or the endoplasmic reticulum. These convergent processes culminate in electron transport chain dysfunction, excess ROS production and inflammatory lytic cell death, converting immune and stromal cells into tissue-damaging effectors within the synovial microenvironment (Figs. 3 and 4).

A defining driver of metabolic stress and mitochondrial fragility in RA is the synovial microenvironment. Within the inflamed joint, immune cells are exposed to glucose depletion, glutamine abundance[79], fatty-acid accumulation[61,80] and reduced oxygen availability[81]. This combination of nutrient and oxygen imbalances creates a metabolically hostile niche that amplifies inflammatory effector programmes within the rheumatoid joint.

NAD^+ imbalance and metabolic stress in RA

$CD4^+$ T cells in RA show marked depletion of NAD^+ alongside accumulation of NADH, shifting the NAD^+ to NADH ratio from approximately 10 to 3 (ref. 82). This imbalance arises from impaired Complex I activity in the electron transport chain, which limits NADH oxidation and progressively reduces NAD^+ availability. By contrast, MerTK⁺ synovial macrophages lose NAD^+ through enzymatic degradation: excessive stimulation activates the mitochondrial NADase SARM1, triggering rapid NAD^+ cleavage, collapse of electron transport chain function and mitochondrial failure[61].

As a central redox cofactor, NAD^+ couples substrate oxidation in the TCA cycle to ATP production[83]. Multiple NAD^+-dependent dehydrogenases, such as isocitrate dehydrogenase, α-ketoglutarate dehydrogenase and malate dehydrogenase, catalyse oxidation of TCA intermediates while reducing NAD^+ to NADH[84]. The generated NADH then donates electrons to Complex I, driving proton pumping and

enabling oxidative phosphorylation. When NAD^+ becomes limiting, these reactions stall, leading to NADH accumulation and disruption of the redox balance. As a result, TCA cycle flux slows, reducing the production of citrate, α-ketoglutarate, malate and oxaloacetate, and restricting the flow of electrons into the electron transport chain. Diminished electron transport chain activity lowers ATP output and further restricts regeneration of NAD^+, producing a self-perpetuating cycle of mitochondrial energy deficit.

In RA, this metabolic bottleneck imposes a characteristic signature on T cells, characterized by reduced ATP production owing to impaired electron transport chain activity, depletion of oxaloacetate and aspartate resulting from reduced malate dehydrogenase activity, and accumulation of citrate and isocitrate as TCA cycle intermediates stall at NAD^+-dependent steps[85]. Consistent with this profile, $CD4^+$ T cells from patients with RA exhibit marked ATP deficiency, loss of oxaloacetate and aspartate and accumulation of citrate and acetyl-CoA, reflecting a broad impairment of oxidative metabolism[17,82,86,87] (Fig. 3).

Beyond the redox function of NAD^+, this cofactor serves as an essential substrate for enzymes that regulate mitochondrial gene expression and cellular stress responses. NAD^+-dependent sirtuins[88] (including SIRT1 and SIRT3) deacetylate metabolic regulators that support mitochondrial biogenesis, fatty-acid oxidation and respiratory efficiency. NAD^+ depletion reduces sirtuin activity, thereby compromising mitochondrial quality control and adaptive capacity. Consequently, cells enter a self-reinforcing metabolic decline, in which diminished energy production is coupled to impaired repair mechanism, and metabolism shifts away from oxidative phosphorylation towards glycolysis. This shift reduces metabolic flexibility, biosynthetic potential and resistance to oxidative stress.

NAD^+ availability also regulates the activity of NAD-consuming enzymes such as poly(ADP-ribose) polymerases (PARPs) and CD38, both of which are commonly upregulated in chronically activated immune cells[89,90]. Consumption of NAD^+ by these enzymes further depletes intracellular stores and exacerbates energetic insufficiency. DNA damage responses, including PARP1-mediated repair, depend heavily on adequate NAD^+ availability. PARP1 uses NAD^+ to synthesize ADP-ribose polymers; without sufficient NAD^+, DNA repair falters and PARP-dependent stress signalling is compromised[91].

ADP-ribosylation itself is a key regulatory modification in T cells, influencing activation, differentiation, transcriptional responsiveness and survival[92–94]. PARPs and mono-ADP-ribosyltransferases shape signalling networks by modifying transcription factors, chromatin proteins and metabolic enzymes. Appropriate PARP activity supports T cell receptor signalling, cytokine production and chromatin remodelling. Conversely, sustained PARP1 activation, often driven by DNA damage, exacerbates NAD^+ depletion and impairs mitochondrial metabolism[95–97]. ADP-ribosylation therefore functions as a metabolic stress-sensing rheostat that links NAD^+ availability to T cell functional competence.

NAD^+ deficiency in RA T cells ultimately triggers a state of metabolic crisis in which mitochondrial respiration can no longer be sustained and ATP generation becomes critically impaired. In healthy T cells, comparable metabolic stress activates the integrated stress response, a protective pathway that senses cellular injury and responds through phosphorylation of eIF2α[98–101]. This event suppresses global protein synthesis while selectively permitting translation of stress-adaptive transcripts such as ATF4, conserving energy and promoting restoration of homeostasis. Through these mechanisms, the integrated stress response orchestrates metabolic prioritization, damage-mitigation programmes and fate decisions, determining whether a stressed T cell adapts, recovers or dies.

Available data indicate that NAD^+-depleted RA T cells bypass or 'breakthrough' the integrated stress response, thereby escaping its protective constraints. Under normal circumstances, successful integrated stress response activation downregulates mTORC1 activity through downstream transcriptional programmes and reduced protein synthesis, culminating in the suppression of mTORC1-driven anabolic signalling. By contrast, RA $CD4^+$ T cells exhibit persistent mTORC1 activation despite profound metabolic stress[87], indicating failure to engage the integrated stress response-imposed brake[75]. This inability to downshift mTORC1 activity, under conditions that would normally enforce metabolic restraint, highlights a fundamental defect in the stress-adaptation machinery of RA T cells (Fig. 3).

Organelle stress response in T cells

Organelle stress responses are fundamental adaptive mechanisms that preserve cellular function in the face of fluctuating environmental and intrinsic challenges. Organelles such as the endoplasmic reticulum, mitochondria and lysosomes continuously monitor protein folding, metabolic flux and redox balance, activating specialized stress response pathways to restore homeostasis when perturbations arise. These responses are central to maintaining cellular resilience, enabling cells to repair damage, reprogramme metabolism and sustain viability under stress. However, with advancing age and cumulative injury, the capacity of these organelle-specific quality control systems becomes progressively compromised. As resilience declines, stressed organelles fail to adequately resolve damage, leading to the accumulation of dysfunctional proteins, metabolic imbalance and persistent intracellular stress signalling. In this section, we explore how this loss of adaptive capacity in RA shifts stress responses from protective to maladaptive responses, driving cellular dysfunction, inflammatory activation and, in severe cases, cell death.

Organelle stress signalling in healthy T cells

Healthy T cells respond to mitochondrial crisis, defined by impaired ATP production, redox balance or disruption of metabolite flux, through a conserved multilayered programme that prioritizes damage containment and organelle repair before committing the cell to survival or death. Initially, metabolic compensation increases glycolysis and activates AMPK to stabilize ATP levels. Stress-response modules, including the integrated stress response and the mitochondrial unfolded protein response, then suppress biosynthetic demand and induce cytoprotective gene expression[102–105]. Quality control systems such as mitophagy and proteostasis networks remove damaged components, whereas mitochondrial fission–fusion dynamics isolate dysfunctional segments. If these measures fail, the response transitions to apoptosis, characterized by cytochrome *c* release and caspase activation, or to necroptosis when bioenergetic collapse becomes irreversible[106,107].

Under persistent stress, the integrated stress response integrates signals from mitochondria, the endoplasmic reticulum, the Golgi apparatus and lysosomes into a unified programme that preserves proteostasis[108]. Its central regulatory axis consists of four eIF2α kinases[109–111]. The endoplasmic reticulum-resident kinase PERK couples the unfolded protein response to the integrated stress response at mitochondria–endoplasmic reticulum contact sites. PERK activation phosphorylates eIF2α, transiently attenuating global protein synthesis to reduce protein folding demand while influencing protein trafficking, organelle morphology and interorganelle signalling.

Mitochondrial dysfunction activates the integrated stress response through several routes. Defects in NADH oxidation or mitochondrial import disrupt TCA flux and deplete amino acids, particularly asparagine, thereby activating the amino acid sensor GCN2 (ref. 112). Mitochondria-derived reactive oxygen species amplify these signals, collectively suppressing global protein synthesis while promoting ATF4-dependent transcription of stress-adaptive genes[113]. Additional ISR kinases, including PKR and HRI, respond to viral stress, haem imbalance and redox perturbations, coordinating multi-organelle responses that stabilize proteostasis[109].

Stress signals from multiple organelles converge at contact sites, including mitochondria–endoplasmic reticulum contact sites, enabling rapid and coordinated cellular responses[58,114]. Ultimately, the endoplasmic reticulum unfolded protein response, mitochondrial unfolded protein response, lysosomal stress responses and Golgi surveillance systems converge on a common objective: restoration of proteostasis[115]. Through eIF2α phosphorylation and ATF4-driven transcription, the integrated stress response integrates these pathways to prevent global protein imbalance and re-establish cellular homeostasis[116].

Organelle stress responses in RA T cells

RA CD4$^+$ T cells exhibit a distinctive metabolic and molecular phenotype characterized by chronic multi-organelle stress, persistent metabolic insufficiency and maladaptive activation of organelle stress response pathways[17,117]. Despite adequate extracellular nutrients, these cells exist in a state of functional nutrient deprivation. RA CD4$^+$ T cells prioritize biosynthesis over ATP generation[87], exacerbating energy scarcity; shunt a disproportionate glucose flux into the pentose-phosphate pathway[118], thereby reducing the ROS levels needed for optimal TCR signalling; and rely on rerouted metabolic circuits that sustain hyperproliferation and tissue invasiveness[86,119]. Collectively, these abnormalities reprogramme RA CD4$^+$ T cells into highly inflammatory effector populations.

This 'starvation state' resembles tumour biology, in which pseudo-starved cancer cells activate stress-adaptive growth programmes despite nutrient availability[120]. Such programmes support the survival of metabolically compromised clones, facilitate expansion and are mechanistically linked to invasive behaviour, immune evasion and therapeutic resistance[120]. RA CD4$^+$ T cells recapitulate these features within an autoimmune context.

Mitochondrial–endoplasmic reticulum axis dysregulation. Mitochondrial dysfunction in RA CD4$^+$ T cells induces endoplasmic reticulum remodelling, including expansion of endoplasmic reticulum sheets, a phenotype that can be reproduced experimentally by inhibition of the electron transport chain[82]. Mechanistically, mitochondrial impairment restricts malate and oxaloacetate production, disrupting the malate–aspartate shuttle and creating a profound aspartate deficit. As cytosolic malate dehydrogenase requires oxaloacetate to oxidize NADH to NAD$^+$, aspartate scarcity stalls cytosolic NAD$^+$ regeneration. This cytosolic NAD$^+$ deficit is a defining metabolic abnormality in RA T cells[121] (Fig. 3).

Aspartate shortage triggers endoplasmic reticulum membrane biogenesis through phosphatidylcholine accumulation[82], leading to expansion of the rough endoplasmic reticulum. This state is sensed through ADP-ribosylation-regulated modulation of BiP, the endoplasmic reticulum-resident HSP70 chaperone. BiP binds nascent or misfolded polypeptides and sequesters the luminal domains of IRE1, PERK and ATF6, thereby maintaining these unfolded protein response sensors in an inactive state. During endoplasmic reticulum stress, unfolded proteins titrate BiP away, enabling activation of IRE1 and PERK through oligomerization and promoting ATF6 trafficking to the Golgi. Beyond serving as a binary switch, BiP modulates the threshold and dynamics of the unfolded protein response. In RA T cells, insufficient BiP ADP-ribosylation lowers this activation threshold, resulting in exaggerated endoplasmic reticulum stress responses[82].

Endoplasmic reticulum expansion has direct functional consequences for cytokine output. Enhanced co-translational translocation capacity and increased availability of TNF mRNA synergize to elevate TNF production[82], a central driver of RA pathology. Thus, endoplasmic reticulum remodelling amplifies inflammatory potential while reinforcing underlying metabolic dysfunction.

Lipid droplets as injury effectors. Lipid droplets, long viewed as inert storage depots, are now recognized as dynamic organelles that bud from the endoplasmic reticulum under conditions of lipid overload to buffer stress[122,123]. In physiological settings, lipid droplets protect against lipotoxicity and proteotoxicity by sequestering excess lipids[124]. In RA CD4$^+$ T cells, however, lipid droplets acquire a pathological role as 'killer organelles'[125]. Proteomic analyses show enrichment of gasdermin D and its palmitoyl-transferase zDHHC5 in lipid droplet fractions, and imaging studies reveal lipid droplets positioned beneath the plasma membrane[125]. Under lipid stress, lipid droplet–plasma membrane interactions facilitate gasdermin D pore formation and extrusion of lipid droplet contents. In addition, lipid droplets deliver caspase 1, enabling direct engagement of inflammasome and pyroptotic pathways[125].

Lipid droplet accumulation is a defining feature of RA CD4$^+$ T cells[119], with tissue-resident subsets exhibiting the highest burden. Cells with high lipid droplet content are especially susceptible to lipid-induced death, consistent with lipid droplet biogenesis as a compensatory stress response to mitochondrial dysfunction[126,127]. In this setting, damaged mitochondria fail to sustain ATP production, NAD$^+$ regeneration or β-oxidation; instead, mitochondria–endoplasmic reticulum contact sites amplify endoplasmic reticulum stress and promote further lipid droplet formation. Lipid droplet accumulation thus reflects both altered organelle organization and cellular vulnerability.

Sequestration of gasdermin D into lipid droplets places RA T cells in a precarious state. After inflammasome engagement, gasdermin D pores perforate the plasma membrane and permeabilize mitochondrial membranes[128,129] in a cardiolipin-dependent manner. This process triggers mitochondrial depolarization, increases ROS production and promotes the release of mtDNA into the cytosol, amplifying IL-1β secretion and pyroptosis. Gasdermin-mediated pore formation also facilitates extracellular mtDNA export[130], enhancing DAMP-driven inflammation in the rheumatoid joint.

In summary, mitochondrial dysfunction in RA CD4$^+$ T cells disrupts amino acid and redox homeostasis, impairs cytosolic NAD$^+$ regeneration and lowers the activation threshold of the unfolded protein response through BiP dysregulation. Concurrently, insufficient integrated stress response signalling fails to impose adequate translational restraint, whereas endoplasmic reticulum remodelling and lipid droplet reprogramming amplify inflammatory output and sensitize cells to gasdermin-mediated pyroptosis. Together, these interconnected defects establish a starved yet growth-permissive and injury-prone state that sustains chronic inflammation and drives joint pathology (Fig. 3).

Pathological growth mode of RA CD4⁺ T cells

Under physiological conditions, starvation signals, such as low ATP availability, NAD^+ depletion, amino acid scarcity and mitochondrial dysfunction, suppress mTORC1 via energy-sensing and nutrient-sensing checkpoints[131,132]. In healthy T cells, these stresses activate AMPK, restrain Rag GTPase-dependent and Rheb-dependent signalling, and shift the cell towards catabolic, survival-oriented programmes. By contrast, RA $CD4^+$ T cells exhibit the paradoxical coexistence of metabolic collapse and sustained mTORC1 activity, thereby supporting continued proliferation and effector differentiation[87]. This uncoupling reflects multiple coexisting defects and rewired signalling loops.

Disabled energy-sensing checkpoint

In healthy T cells, AMPK functions as an energy-sensing checkpoint that inhibits mTORC1 activity in response to reduced ATP availability[59]. In RA $CD4^+$ T cells, however, AMPK is mislocalized away from the lysosomal surface[87], the platform at which sensing of the AMP-to-ATP ratio is coupled to mTORC1 regulation, preventing AMPK activation even under conditions of a low-energy state. Loss of this gatekeeping function removes a primary brake on mTORC1 signalling during cellular starvation.

Dysfunctional lysosomal activation platform

mTORC1 assembly and activation occur on lysosomal membranes and depend on amino acid-sensing Rag GTPases, Rheb downstream of PI3K–AKT signalling and the lipid composition of the lysosomal membrane[133]. In RA $CD4^+$ T cells, increased phosphatidylcholine synthesis[82] and expansion of endoplasmic reticulum–lysosome–mitochondria contact sites generate a membrane environment that favours mTORC1 recruitment and activation despite low amino acid availability[17]. As a result, the lysosomal activation platform is functionally primed even when canonical nutrient inputs are insufficient.

Defective stress-to-translation coupling

In healthy cells, mitochondrial stress engages the integrated stress response, which restrains mTORC1 activity and global protein synthesis[111,134]. In RA $CD4^+$ T cells, however, engagement of the integrated stress response is impaired: GCN2-dependent and PERK-dependent signalling is insufficient or temporally misaligned, BiP is inadequately modified[82] and tuning of the unfolded protein response is dysregulated. Consequently, amino acid shortage and redox imbalance fail to suppress mTORC1.

Antigen receptor override

Chronic TCR stimulation in the presence of co-stimulatory signals (for example, CD28 signalling) can bypass metabolic checkpoints by activating PI3K–AKT signalling, inhibiting TSC2 and activating Rheb, thereby sustaining mTORC1 activity even under nutrient-poor conditions[135,136]. RA $CD4^+$ T cells exist in a self-reinforcing state of activation that keeps this 'growth-factor override' continuously engaged[137,138]. Several age-associated mechanisms have been identified that keep the AKT–mTORC1 pathway poised in naive $CD4^+$ T cells. For example, an age-associated increase in expression of miR-21 in naive $CD4^+$ T cells elevates PDK1 activity by targeting the phosphatase PTEN, thereby facilitating AKT phosphorylation at threonine 308 (ref. 139). Finally, persistent mTORC1 signalling is reinforced by its localization to an expanded late endosomal compartment, where amino acid delivery via the transporter SLC7A5 supports continued activation[140].

Stress signals misread as anabolic cues

Mitochondrial dysfunction in RA T cells impairs β-oxidation, promotes the release of mtDNA, expands mitochondria–endoplasmic reticulum contact sites and amplifies endoplasmic reticulum stress responses[141]. The resultant surge in stress-induced phospholipid synthesis (reflected by endoplasmic reticulum expansion, increased lipid droplet formation and enlarged membrane surfaces) is misinterpreted by the lysosomal mTORC1 machinery as a pro-anabolic signal rather than as starvation cue, thereby sustaining growth signalling[142].

Consequently, RA $CD4^+$ T cells adopt a pathological growth mode in which canonical coupling between metabolic sufficiency and anabolic signalling is lost: nutrient and energy limitation no longer restrain mTORC1 activity but instead coexist with, and even reinforce, mTORC1 activation (Fig. 3). This inverted logic parallels tumour pseudo-starvation, in which nutrient stress ceases to inhibit growth signalling and instead fuels cellular expansion. These findings suggest multiple points at which dysregulated metabolic signalling could be therapeutically intercepted, including pathways controlling nutrient sensing, mitochondrial fitness and cellular stress adaptation (Table 2).

Table 2 | Emerging metabolic targets

Target pathway	Example strategies	Rationale
mTOR signalling	Rapamycin and mTOR inhibitors	Regulates cellular growth, nutrient sensing and immune cell fate decisions[168]
AMPK activation	Metformin and AMPK agonists	Promotes energy homeostasis and counteracts pro-inflammatory metabolic programming[169,170]
Glycolysis inhibition	2-Deoxyglucose (experimental)	Targets heightened glycolytic flux in activated immune cells[171]
Mitochondrial function	Reactive oxygen species modulators and mitochondrial biogenesis enhancers	Restores mitochondrial fitness and prevents metabolic exhaustion[172]
NAD^+ metabolism	NAD^+ precursors (for example, nicotinamide riboside and NMN) and sirtuin activators	Supports cellular energy balance, redox homeostasis and longevity pathways[173]
Fatty acid metabolism	Fatty acid oxidation modulators	Influences immune cell differentiation and longevity
Renal and systemic glucose handling	SGLT2 inhibitors (for example, empagliflozin and dapagliflozin)	Reduces glucose availability, improves metabolic fitness and might dampen inflammation via systemic and immunometabolic effects
Incretin signalling	GLP1 receptor agonists (for example, semaglutide and liraglutide)	Modulates insulin sensitivity, reduces systemic inflammation and influences immune cell function and weight-related inflammatory burden

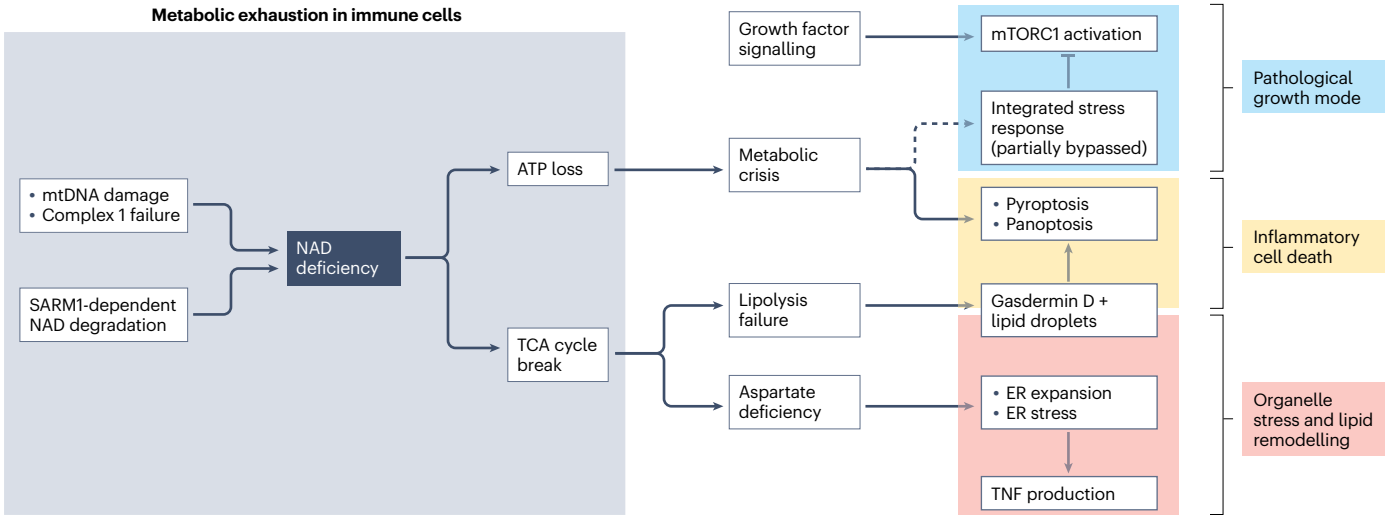

Fig. 5 | Molecular framework of metabolic exhaustion in rheumatoid arthritis. Ageing exposes and amplifies metabolic vulnerabilities in both innate and adaptive immune cells, predisposing the cells to pathogenic effector programmes that are directly shaped by metabolic fragility. Core molecular deficits converge on NAD^+ deficiency, arising from either excessive NAD^+ degradation or impaired NAD^+ regeneration. Declining NAD^+ concentrations disrupt ATP production and tricarboxylic acid (TCA) cycle flux, triggering compensatory stress pathways, including activation of the integrated stress response, that become maladaptive and host damaging rather than protective. As a result, stress-induced growth restraint fails to be engaged, and persistent mTORC1 signalling sustains protein translation and proliferative activity, despite metabolic insufficiency. When sufficiently advanced, metabolic exhaustion becomes irreversible and promotes non-apoptotic, lytic and highly inflammatory forms of cell death. ER, endoplasmic reticulum; mtDNA, mitochondrial DNA; TNF, tumour necrosis factor.

Misdirected cell death programmes in RA

When confronted with metabolic exhaustion, cells initially attempt to adapt and repair, with the integrated stress response serving as a central protective mechanism. If damage to the bioenergetic and biosynthetic machinery cannot be repaired and extracellular signals continue to drive activation, cells ultimately engage programmed death pathways[143–145]. Under physiological conditions, both innate and adaptive immune cells preferentially undergo apoptosis, a controlled, non-inflammatory and tolerogenic form of death that preserves tissue integrity and prevents chronic immune stimulation[146]. However, apoptosis is energetically demanding and tightly regulated by mitochondrial fitness[147]. When cells undergo metabolic collapse, they lose the capacity to execute apoptotic programmes[148] and instead default to lytic forms of cell death that release nuclear and cytosolic contents into the extracellular space, thereby provoking strong inflammatory responses[146].

In RA, emerging data support the concept that non-apoptotic, lytic cell death affects both T cells and macrophages[149–151] (Figs. 3 and 4) and contributes to the persistence of synovial inflammation[60,61]. RA $CD4^+$ T cells undergo pyroptosis through at least two upstream mechanisms. First, insufficient import of key mtDNA repair enzymes results in mtDNA damage, activation of inflammasome pathways and induction of pyroptosis[60]. Second, caspase 1 and gasdermin D become sequestered within lipid droplets, where they assemble into functional complexes that directly create membrane pores[125]. These findings identify caspase 1 activation as the pivotal event diverting RA $CD4^+$ T cells away from apoptosis and towards pyroptosis, with mitochondrial collapse positioned upstream of this shift. In humanized mouse models, either restoration of mtDNA repair or inhibition of lipid droplet formation was sufficient to protect synovial tissue from inflammatory injury[125].

More recent work has examined how macrophage death sustains rheumatoid synovitis. The inflamed RA synovium contains a heterogenous population of macrophages[72,152,153], including subsets typically associated with tissue repair and resolution[154,155]. Flow cytometric analyses reveal enrichment of $CD206^+CD163^+$ macrophages in inflamed synovium that express CD40, conferring T cell-stimulatory capacity[156]. Molecular profiling indicates that these macrophages not only fail to resolve inflammation but also adopt a pathogenic phenotype that actively sustains synovitis[61]. This functional switch is preceded by profound metabolic exhaustion[156,157] (Fig. 4). Analyses of macrophages isolated from patients with refractory RA have revealed that $MerTK^+CD206^+$ cells produce high levels of the complement component C1q while co-expressing its receptor, C1QBP[61], consistent with an autocrine or paracrine activation loop. C1q stimulation uncovered a striking metabolic vulnerability: engagement of the C1q–C1QBP axis reduced ATP production, triggered cleavage and depletion of mitochondrial NAD^+ and caused marked accumulation of cADPR[61]. Mechanistic studies identified SARM1 as the driver of this metabolic crisis. After activation, SARM1 rapidly hydrolyses NAD^+ to cADPR, precipitating energetic collapse and initiating PANoptotic cell death[61] (a composite, integrated cell death programme that encompasses pyroptotic, apoptotic and necroptotic features). The death of these metabolically compromised macrophages is accompanied by heightened inflammatory output, thereby amplifying synovitis. In vivo, administration of C1q exacerbated synovial inflammation, whereas pharmacological inhibition of SARM1 ameliorated disease severity. These findings establish SARM1 as both a biomarker of metabolically stressed synovial macrophages and a central executor of their pro-inflammatory demise. Targeting SARM1-dependent NAD^+ catabolism might therefore represent a promising therapeutic approach for

reprogramming macrophage behaviour and interrupting chronic inflammatory circuits in autoimmune disease.

Collectively, these observations illustrate how chronic metabolic stress, progressively encountered with ageing, can convert protective immune responses into tissue-damaging immunity[158], providing a mechanistic link between immune ageing, metabolic ageing and autoimmunity (Fig. 4). Together, these interconnected processes define a unified model of metabolic exhaustion and immune dysfunction in RA (Fig. 5).

Conclusion

RA is among the autoimmune diseases that preferentially emerge in later life. Even the initial loss of tolerance in clinically silent pre-RA mostly occurs into the second half of life, a period characterized by broad declines in immune competence. Organismal ageing does not reflect isolated functional failures, but rather a coordinated breakdown of three interconnected homeostatic systems: metabolic regulation, immune surveillance and systemic stress responses.

RA exemplifies how ageing disrupts the integrated metabolic–immune control system required to maintain self-tolerance (Fig. 5). Mitochondrial insufficiency, impaired nutrient sensing and utilization, and chronic deficits in NAD^+ and ATP reshape the bioenergetic and transcriptional programmes of both $CD4^+$ T cells and synovial macrophages, accelerating immune ageing systemically and within the joint. The nutrient-poor, lipotoxic synovial microenvironment further intensifies metabolic stress, promoting maladaptive integrated stress responses, persistent inflammatory transcription and dysregulated organelle homeostasis. In both lymphoid and myeloid lineages, metabolic collapse compromises the execution of apoptosis and diverts cells into lytic, pro-inflammatory death pathways that disseminate nuclear and cytosolic contents, promoting chronic synovial inflammation. Together, these processes position RA as a disease of coordinated failure across metabolic, immune and stress response networks, with ageing serving as the catalyst that exposes and amplifies these vulnerabilities.

This conceptual framework is increasingly reflected in therapeutic strategies. Several established RA treatments already derive part of their efficacy from modulation of cellular metabolism, including effects on mitochondrial function, energy-sensing pathways and inflammatory bioenergetics (Table 1). As understanding of disease-relevant metabolic circuits deepens, emerging therapies are being developed to directly target pathogenic metabolic programmes, such as dysregulated nutrient sensing, redox imbalance and defective bioenergetic resilience, in both adaptive and innate immune cells (Table 2). Thus, integrating metabolic intervention into RA treatment not only aligns with the underlying pathophysiology but also provides a rational avenue for developing next-generation therapies aimed at restoring immune homeostasis and tissue integrity.

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Review article

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Sex-dependent mechanisms in rheumatic diseases

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Abstract

Sex differences in the prevalence, clinical phenotypes and therapeutic responses of rheumatic diseases have been recognized for decades, but the underlying mechanisms remain largely unknown. Accumulating evidence highlights the critical roles of both immune and non-immune cells in disease pathogenesis and the influence of sex hormones on cellular function. In addition, factors such as sex chromosomes, hormonal regulation, antiviral immune response, the gut microbiome and genetic and epigenetic variation probably contribute to the divergent features of rheumatic diseases between women and men. A deeper understanding of these intersecting pathways might uncover novel therapeutic targets. Thus far, treatment strategies for rheumatic diseases largely focus on immunomodulation; however, elucidating the biological basis of sex differences could enable the development of preventative therapies that target hormonal pathways and the gut microbiome, with the potential to avert both the onset and progression of these debilitating diseases to improve health for all patients.

Sections

Introduction

Overview of sex differences in rheumatic diseases

Sex hormones in disease pathogenesis

X chromosome inactivation and dosage

Genetic and epigenetic regulation

Microbiome and host interactions

Viral infections and antiviral immunity

Implications for treatment

Conclusion

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Key points

- Sex differences in prevalence, clinical phenotypes and outcomes are a defining feature of major rheumatic diseases, yet the underlying mechanisms remain incompletely understood.
- Sex hormones modulate innate and adaptive immunity, as well as the function of non-immune cells involved in tissue repair and remodelling.
- Skewed X chromosome inactivation contributes to sex differences in the development and clinical manifestations of rheumatic diseases.
- Bidirectional interactions between the microbiome and sex hormones influence immune regulation and contribute to autoimmunity.
- Epigenetic mechanisms, including altered gene expression and microRNA regulation, contribute to sexual dimorphism in rheumatic diseases.
- Understanding the mechanisms underlying sexual dimorphism in rheumatic diseases will support the development of more effective individualized therapeutic strategies.

Introduction

Population-based studies estimate that approximately one in ten individuals live with an autoimmune disease[1]. Women are disproportionately affected, with a twofold higher likelihood of diagnosis than men[2,3], and autoimmune diseases represent the fourth leading cause of disability among women[4]. The female predominance is even more striking in autoimmune connective tissue diseases (Fig. 1), for which the female-to-male prevalence ratios can approach 15:1 in some conditions[5]. In addition to disease prevalence, biological sex (that is, sex assigned at birth; throughout this Review, 'sex' is used as a shorthand for biological sex) differences also exist in the clinical phenotype, severity and treatment response across several of these diseases.

Autoimmunity arises from a breakdown in self-tolerance within the innate and adaptive immune systems, leading to autoreactive immune responses that cause varying degrees of tissue injury, repair and pathological remodelling in target organs. However, the molecular mechanisms underlying sex differences in susceptibility remain incompletely understood. An increasing body of evidence implicates sex-specific biological factors, including hormonal regulation and genetic contributions such as X chromosome dosage and sex chromosome-encoded genes. In addition, gender-related factors, including behaviour and access to healthcare, might further shape autoimmune disease risk in women and men.

In this Review, we summarize emerging research on sex-biased autoimmune rheumatic diseases, focusing on the most prevalent connective tissue diseases, including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), rheumatoid arthritis (RA), primary Sjögren disease and idiopathic inflammatory myositis (IIM). We emphasize advances in understanding sex-specific biological mechanisms, alongside sex differences in clinical phenotypes, drawing on both notable studies published within the past 5 years and foundational historical work. Owing to rapidly evolving concepts and limited data related to gender, our discussion primarily focuses on biological sex. We highlight current paradigms, identify critical gaps in knowledge, and consider how mechanistic insights into sex differences might inform the development of therapeutic strategies to improve the health of all persons living with autoimmune diseases.

This article uses 'men' or 'male' and 'women' or 'female' to reflect the language used in specific cited studies, but recognizes that it is rarely clear how such information was collected or defined (for example, on the basis of endocrine or chromosomal analysis or assignment of sex at birth in medical records or health registry data). Moreover, even if data collection methods are specified, sex and gender information could still be inaccurate or incomplete; for example, when only binary categories such as 'male' and 'female' are available. *Nature Reviews Rheumatology* also acknowledges that sex and gender both exist on a spectrum, are not necessarily aligned and that a person with a rheumatic disease might not identify as either a woman or a man. Whereas sex-related differences are widely reported across rheumatology, gender-related determinants are far less consistently captured in clinical datasets, meaning that discussions within individual disease sections reflect the uneven availability of evidence.

Overview of sex differences in rheumatic diseases

A relationship between sex hormones and autoimmune rheumatic diseases is supported by both clinical observations (Fig. 1) and mechanistic studies. For example, SLE has a female-to-male ratio approaching 15:1, is most commonly diagnosed in premenopausal women and is associated with increased circulating oestrogen and reduced androgen levels[6]. SSc shows a similar female predominance, age at onset and association with oestrogen[7,8]. A potential role for androgen deficiency in SSc is further supported by reports of disease onset among cisgender (that is, individuals whose assigned sex at birth aligns with their gender identity) men undergoing orchiectomy and androgen deprivation therapy for prostate cancer[9,10], as well as transgender (that is, individuals whose gender identity differs from their assigned sex at birth) women receiving gender-affirming care involving orchiectomy and/or androgen suppression[11]. In RA, which has a female-to-male ratio of 3:1, epidemiological data link shorter reproductive span and early menopause with increased disease risk, suggesting a protective role for oestradiol[12]. However, increased oestrogen and reduced androgen levels within RA synovial fluid (probably driven by local aromatase activity[13]) highlight the complexity of hormonal effects in this disease. In primary Sjögren disease, although historical studies have shown a female-to-male ratio of up to 16:1 (ref. 14), more recent evidence suggests that this sex bias could vary across the lifespan[15]. In particular, the prevalence in both men and women seems to correlate with age-dependent trajectories of testosterone and oestradiol[15]. Consistently, patients with primary Sjögren disease demonstrate reduced circulating levels of dehydroepiandrosterone (DHEA), dihydrotestosterone (DHT), DHEA sulfate (DHEAS) and related androgens compared with healthy individuals[16], as well as impaired local androgen metabolism in salivary glands, including decreased conversion of testosterone to DHT[17]. Taken together, these findings support the concept that imbalance between oestrogen and androgen signalling might represent a shared mechanistic axis underlying sex-biased susceptibility across diverse rheumatic conditions.

Sex hormones in disease pathogenesis

Sex hormones differ between women and men, vary across the lifespan and are implicated in the pathogenesis of several rheumatic diseases. Oestrogens comprise oestrone (E1), the predominant form after menopause,

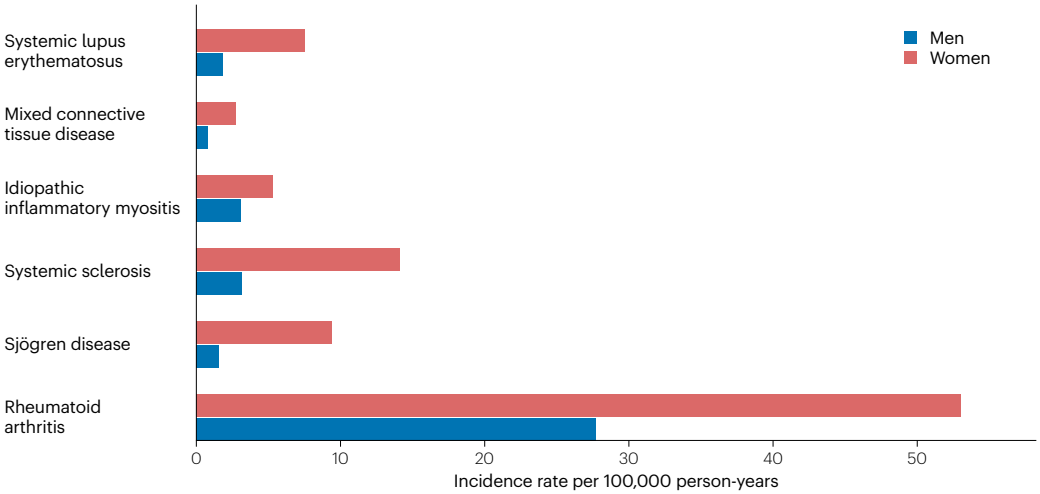

Fig. 1 | Incidence rates of autoimmune rheumatic diseases by sex. Incidence rates (per 100,000 person-years) in men and women are shown for the indicated rheumatic diseases (systemic lupus erythematosus, mixed connective tissue disease, idiopathic inflammatory myopathy, systemic sclerosis, Sjögren disease and rheumatoid arthritis)[114–118]. Data were derived from published studies conducted in different populations and time periods, with several estimates based on regional cohorts (for example, Olmsted County, Minnesota, Mayo Clinic cohort), and therefore might not be directly comparable or representative of global incidence.

oestradiol (E2; also known as 17β-oestradiol) the principal oestrogen during the reproductive years, and oestriol, the primary oestrogen during pregnancy. These hormones signal through nuclear oestrogen receptors (ERα) and membrane-associated ERs (ERβ), as well as G-protein-coupled receptors such as GPER. Androgens, including testosterone, are produced primarily in the gonads, whereas the adrenal glands produce precursors such as DHEA, DHEAS, androstenedione and androstenediol. Testosterone can be converted into the more potent androgen DHT or aromatized to oestrogens (E1 and E2) in many tissues[18]. Given the widespread expression of sex hormone receptors across immune cells and multiple tissues[19], these signalling pathways are well positioned to regulate the sexual dimorphism observed in rheumatic disease susceptibility and progression.

Effects on adaptive immunity

Receptors for sex hormones are expressed on B cells and T cells[18], and the immunological effects have been particularly well characterized in SLE. Given that many rheumatological diseases are defined by autoantibody production, the effects of oestrogens on B cell biology are especially relevant in mice, in which oestradiol promotes B cell survival, activation, class switching and somatic recombination[20,21]. Consistent with these findings, individuals with two X chromosomes show oestrogen-dependent expansion of $CD19^+CD27^+IgD^-$ class-switched memory B cells, which are highly efficient antibody producers, providing a potential explanation for the broader and more pronounced humoral responses observed in women[22]. In SLE, oestradiol further enhances B cell responses[23]. By contrast, evidence from primary Sjögren disease and RA suggests that the effects of oestrogen are context-dependent. In animal models of primary Sjögren disease, oestrogen deficiency promotes B cell accumulation[24], suggesting a protective role for oestrogen. Similarly, in RA, oestrogen might also confer some protection; postmenopausal oestrogen deficiency has been linked to reduced IgG sialylation in plasma cells, thereby increasing the risk of arthritis[25]. Thus, the relationship between oestrogen and B cells seems to be disease-specific, driving pathogenic responses in SLE while potentially exerting protective or modulatory effects in primary Sjögren disease and RA.

In terms of autoreactive T cells, oestrogen has a critical role in thymic T cell development[26] and exerts dose-dependent effects on $CD4^+$ T cell differentiation. In mouse models, low-dose exogenous oestrogen promotes T helper 1 cell differentiation via activating ERα signalling[27], whereas high-dose oestrogen favours the expansion of immunosuppressive regulatory T (T_{reg}) cells in both mice and humans[28]. Given that T_{reg} cells are central mediators of immune tolerance in RA[29,30], this pathway might contribute to the putative protective effects of oestrogen in this disease. In SLE, however, oestrogen seems to enhance T cell pathogenicity by increasing activation[31] and survival[32]. In addition, oestrogen has been shown to epigenetically downregulate the expression of the autoimmune regulator (*AIRE*) gene in human and mouse thymic cells, thereby impairing central tolerance. This effect promotes the survival and activation of autoreactive T cells, particularly $CD4^+$ helper subsets, and by extension disease susceptibility, in women with SLE[33].

In SSc, the role of oestrogen in disease pathogenesis is supported primarily by indirect evidence. For example, machine learning analyses of single-cell RNA sequencing (scRNA-seq) datasets have shown that, relative to sex-matched healthy individuals, skin biopsy samples from women with SSc, but not men with SSc, exhibit enrichment of memory B cells and plasma cells alongside reductions in $CD4^+$ memory T cells[34]; however, the relationship to oestrogen and other sex hormones was not directly assessed. Additional evidence of sex-biased lymphocyte responses has been reported in SSc-associated interstitial lung disease (ILD). Post-hoc analysis of bronchoalveolar lavage fluid (BALF) from the SLS1 and SLS II trials identified distinct, sex-biased molecular profiles that correlated with clinical phenotypes[35]. Specifically, BALF from the female participants, who exhibited greater responsiveness to lymphocyte-modulating therapies such as cyclophosphamide and mycophenolate, was enriched for inflammatory mediators such as IL-12, IL-7 and granulocyte colony-stimulating factor. By contrast, samples from the male participants were enriched in proteins associated with extracellular matrix (ECM) remodelling, including matrix metalloproteinase 13 (MMP13) and tissue inhibitor of metallopeptidase 1 (TIMP1)[35]. Although the source of these differences and their connection to sex hormones remain unclear, the established effects of oestrogen on lymphocyte activation suggests a model in which hormone availability and receptor signalling shapes SSc immunopathogenesis. Further mechanistic studies are needed to clarify these relationships.

Effects on innate immunity

Innate immune cells (including dendritic cells, monocytes, macrophages and neutrophils) contribute to autoimmune pathology through recognition of self-antigens and danger-associated molecular patterns released from injured cells and tissues, mediated by pattern recognition receptors (reviewed elsewhere[36]). Among these cell types, type I interferon-producing plasmacytoid dendritic cells (pDCs) have been consistently linked to sex-biased immune responses in SLE, primary Sjögren disease and, more recently, SSc[37,38]. In SLE and primary Sjögren disease, 17β-oestradiol markedly enhances Toll-like receptor 7 (TLR7)-dependent and TLR9-dependent production of IFNα by pDCs stimulated with synthetic ligands or nucleic acid-containing immune complexes, providing direct mechanistic evidence linking oestrogen signalling to type I interferon responses[39]. This effect might account for the higher production of IFNα observed in women than in men[40], highlighting a potential connection between oestrogen, pattern recognition receptors and disease phenotypes that warrants further study.

An additional role for TLR7 has been demonstrated in a spontaneous mouse model of SLE, in which dual knockout of *Def6* and *Swap70* results in a female-predominant SLE-like syndrome[41]. In these mice, a unique population of age-associated B cells (ABCs), characterized by expression of conventional B cell markers together with T-bet and CD11c, preferentially accumulates in aged female mice. These cells acquire an interferon-stimulated gene signature and effector phenotypes in a TLR7-dependent manner involving IRF5 and IRF8 (ref. 41). Notably, ABCs have also been identified in women with SLE[42]. Given the association of this cell population with ageing, declining oestrogen levels in older women might permit the expansion and/or functional activation of ABCs. Further work is needed to assess this emerging hypothesis.

scRNA-seq analyses of SSc skin biopsy samples have revealed sexually dimorphic innate immune activation[34]. Using machine learning approaches, the researchers identified discrete sex-specific immune signatures: compared with samples from sex-matched healthy individuals, samples from men with SSc showed enrichment of macrophages classified as M0 and M1, accompanied by reductions in dendritic cells and M2-like macrophages, whereas samples from women with SSc showed enrichment of M1-like macrophages[34]. These findings align with a recent scRNA-seq study, thus far only available in preprint form, in which machine learning analyses identified enhanced interferon-stimulated genes and expansion of type I interferon signature-expressing myeloid cell subsets in the zymosan model of RA[43]. Although neither study was designed to assess the role of sex hormones, the well-established capacity of oestrogens to promote inflammatory macrophage activation raises the possibility that sex hormones and/or their receptors contribute to sex-biased innate immune responses and tissue destruction in autoimmune rheumatic disease.

Effects on non-immune cells and tissue remodelling

The important role of sex hormones in non-immune mechanisms of tissue repair and remodelling has been extensively studied in individuals with SSc. A systematic review in 2020 highlighted substantial effects of sex hormones on fibroblast and endothelial cell functions[44]. In dermal fibroblasts, oestradiol stimulates fibronectin production in both primary cultures and human skin models, which are accompanied by increased dermal thickness[7], ECM deposition[45,46] and TGFβ production[47]. Mechanistically, dermal fibroblasts can generate oestradiol through IL-6-induced activation of aromatase, enabling subsequent conversion of androgens to oestrogens and suggesting a cell-autonomous immune-independent feedforward loop[45]. Consistent with a pathogenic role for oestrogen signalling, selective ER modulators (SERMs) have been identified as potential therapies in SSc using induced pluripotent stem cell-derived dermal fibroblasts and organoid models, as well as the commonly used repetitive bleomycin mouse model of SSc[48].

Experimental studies have also demonstrated opposing effects for the 17β-oestradiol metabolite 2-methoxyoestrogen (2-ME) on tissue remodelling. This metabolite reduces collagen deposition in mouse models of SSc-associated pulmonary complications[49,50], attenuates collagen I and connective tissue growth factor expression in SSc dermal fibroblasts[51] and mitigates joint destruction, neutrophil infiltration and reactive oxygen species production in a mouse model of postmenopausal RA[52], suggesting that 2-ME antagonizes the effects of oestradiol. Further evidence for the context-dependent effects of oestrogen comes from studies showing that 17β-oestradiol can stimulate the production of matrix-degrading enzymes[53] and IL-1α in human fibroblast-like synoviocytes, but suppresses TAK1 activation and apoptosis in these cells and in mice with collagen-induced arthritis[54–56]. These seemingly paradoxical results highlight this complexity of oestrogen signalling in tissue remodelling and support the need for further mechanistic investigation.

Agonistic anti-ERα antibodies have been detected in patients with SSc and correlate with disease activity and severity[57], supporting a pathogenic contribution of ER signalling. By contrast, short-term intravenous administration of conjugated oestrogen induces rapid arterial dilatation in patients with SSc and in healthy individuals, with effects observed within 15 min, and improves endothelium-dependent vascular reactivity without affecting vascular smooth muscle cells[58]. Similar vascular benefits have been reported for orally administered conjugated oestrogen[59]. Thus, oestradiol has dual roles in SSc, functioning as both a profibrotic mediator while also exerting macrovascular vasodilatory effects. This dichotomy complicates the use of oestrogen in hormone replacement therapy in patients with SSc. The available evidence suggests that supplemental oestrogen might confer benefit in patients with SSc who have severe vascular complications and are at high risk of pulmonary arterial hypertension, whereas caution is warranted in individuals with lung fibrosis.

Evidence suggests a largely protective role for oestrogen in primary Sjögren disease. Lacrimal glands from oestrogen-treated ovariectomized rabbits are protected from both lymphocyte infiltration and glandular apoptosis[60]. Furthermore, oestrogen deficiency induced by ovariectomy triggers lymphocytic inflammation followed by lacrimal acinar cell death in mouse models of Sjögren disease[24], supporting an immunologically mediated effect. A similar protective role has been described for the androgen DHT[61]. Consistent with these findings, patients with primary Sjögren disease have reduced circulating levels of DHEA, DHT and DHEA-S[16,62]. These observations indicate that sex hormones influence tissue pathology in primary organ involvement, adding further complexity to the disease mechanisms and underscoring the need for comparative studies across rheumatic diseases with divergent responses to sex hormone signalling.

Overall, the available data suggest that sex hormones exert context-dependent and disease-specific effects on immune cell function and tissue remodelling across rheumatological diseases. Oestradiol seems to have disease-driving functions in SLE while exerting protective or pathogenic effects in SSc, RA and primary Sjögren disease depending on hormone concentration, receptor engagement, target cell type and local milieu (Fig. 2). Further investigation of these

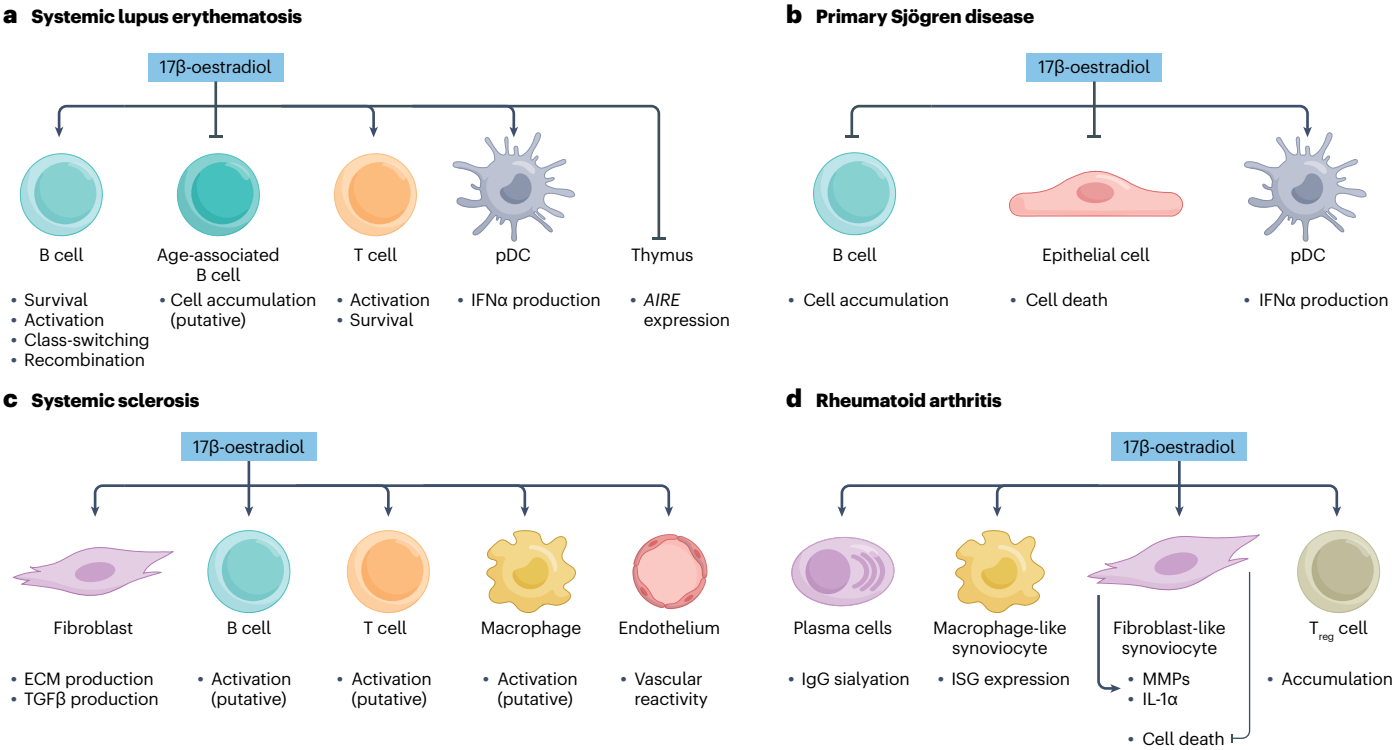

Fig. 2 | Proposed roles of oestradiol in rheumatic diseases. Oestrogen exerts pleiotropic and disease-dependent effects on immune and non-immune cell populations. **a**, In systemic lupus erythematosus, oestrogen signalling has been suggested to enhance humoral immune responses, T cell activation and plasmacytoid dendritic cell (pDC)-derived type I interferon production, while suppressing accumulation of age-associated B cells and thymic *AIRE* expression. **b**, In primary Sjögren disease, oestrogen promotes pDC-derived type I interferon production and reduces B cell accumulation and epithelial cell death in lacrimal glands. **c**, In systemic sclerosis, oestrogen is thought to promote B cell and T cell responses, macrophage activation, endothelium-mediated vascular reactivity and fibroblast activation. **d**, In rheumatoid arthritis, oestrogen exerts context-dependent effects, promoting immunosuppressive regulatory T (T_{reg}) cells while also enhancing pro-inflammatory remodelling properties in fibroblast-like synoviocytes and macrophage-like synoviocytes and reducing cell death in fibroblast-like synoviocytes. ECM, extracellular matrix; ISG, interferon-stimulated gene; MMP, matrix metalloproteinase.

mechanisms in human-relevant animal models, organotypic disease mimetics and primary patient specimens might inform ongoing and future clinical trials of SERMs and clarify the therapeutic potential of sex hormone pathways in rheumatic and connective tissue diseases.

X chromosome inactivation and dosage

Beyond sex hormone biology, the pronounced sex bias in rheumatic diseases has also prompted investigation of the X chromosome, which harbours many genes involved in immune regulation. X chromosome inactivation (XCI) refers to transcriptional inactivation of one of the female X chromosomes during embryonic development. However, some genes can escape XCI, resulting in increased expression of these genes in women (Fig. 3). Disruption of XCI has been linked to susceptibility to autoimmunity[63]. XIST, a long non-coding RNA essential for the establishment and maintenance of XCI, has a central role in enforcing X-linked gene silencing.

In SLE, abnormal maintenance of XCI and aberrant expression of X-linked immunity genes in B cells in both paediatric and adult patients are though to contribute to female disease predominance[64–66]. Consistent with these observations, B cells from the female-biased NZB/W F1 mouse model of SLE show upregulation of multiple genes, including X-linked genes associated with autoimmunity[67]. Furthermore, in a subset of pDCs over-represented in the blood of women with SSc, the X-linked genes *TLR7* and *TLR8* escape XCI at an increased frequency, accompanied by reduced expression of XIST, resulting in heightened type I interferon activity[38]. In female mice with conditional deletion of *Xist* in B cells, spontaneous lupus with glomerulonephritis develops in a subset of animals, alongside increased B cell expression of pro-inflammatory X-linked genes previously implicated in SLE (data currently available in preprint form)[68]. Impaired XCI has also been observed In T cells from two mouse models of spontaneous SLE, MRL/lpr and NZM2328 mice, with particularly pronounced defects in the strongly female-biased NZM2328 model, leading to altered expression of multiple genes involved in the immune response[69].

Increased X chromosome gene 'dosage' can also result from the presence of an additional X chromosome. This association is supported by the higher prevalence of triple X syndrome (47,XXX) among patients with primary Sjögren disease and SLE compared with the general population. Specifically, triple X syndrome occurs in approximately 1 in 344 patients with primary Sjögren disease and 1 in 404 patients with SLE compared with ~1 in 1,000 individuals in the general population[70]. Consistent with this association, among individuals with triple X syndrome, the prevalence of primary Sjögren disease is 2.9 times higher than in individuals with the 46,XX karyotype and 41-fold higher than in

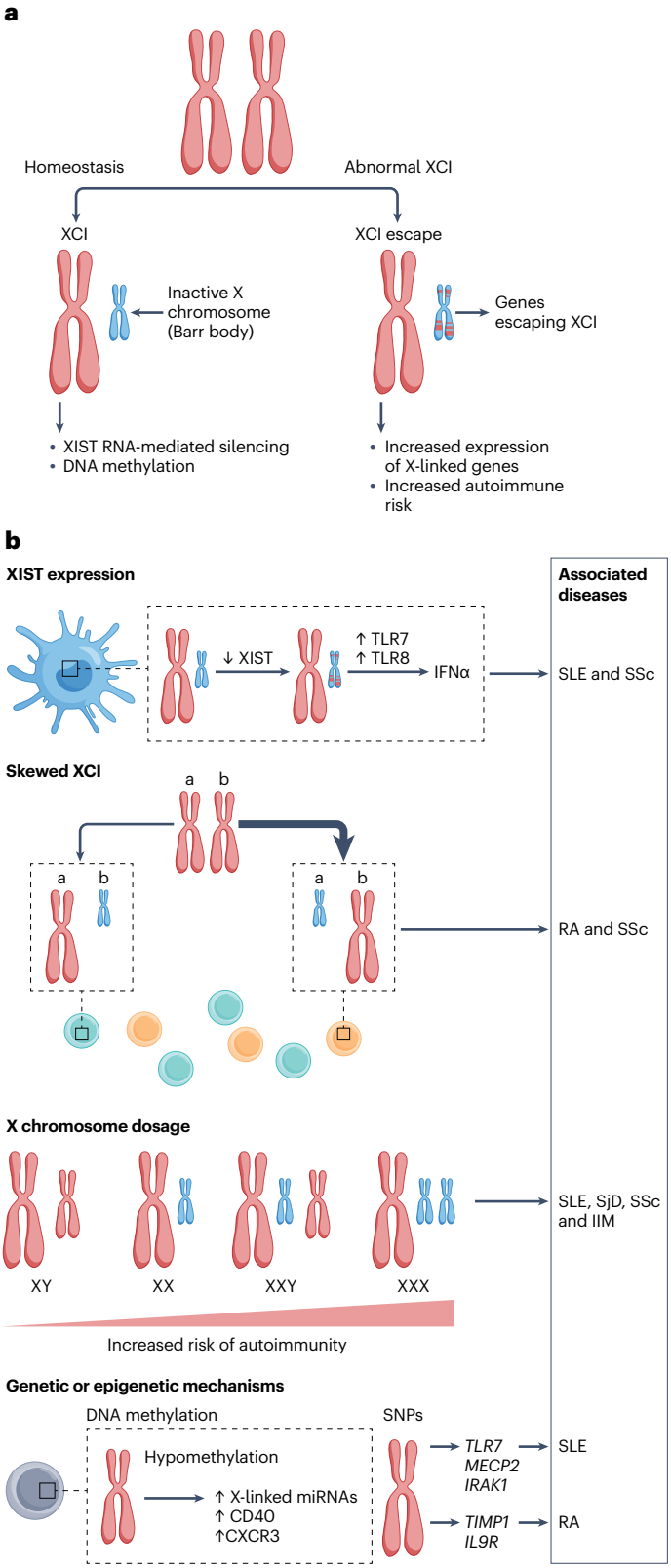

Fig. 3 | Role of X chromosome inactivation and gene dosage in autoimmune rheumatic diseases. X chromosome biology contributes to autoimmune susceptibility through multiple, interrelated mechanisms involving gene dosage and epigenetic regulation. **a**, Loss of X chromosome inactivation (XCI), normally mediated by XIST and DNA methylation, leads to increased expression of X-linked immune genes. **b**, In systemic lupus erythematosus (SLE) and systemic sclerosis (SSc), reduced expression of XIST in plasmacytoid dendritic cells is associated with increased type I interferon production. Additional evidence supporting a role for X chromosome gene 'dosage' in autoimmunity includes skewed XCI — where one X chromosome is preferentially inactivated across a majority of cells — observed in rheumatoid arthritis (RA) and SSc, as well as the increased risk of SLE, primary Sjögren disease (SjD), SSc and idiopathic inflammatory myopathy (IIM) in individuals with excess X chromosomes, such as Klinefelter syndrome (47,XXY) or triple X syndrome (47,XXX). Genetic studies further implicate X-linked variants in disease susceptibility, with single-nucleotide polymorphisms (SNPs) in *TIMP1* and *IL9R* associated with RA and variants in *TLR7*, *MECP2* and *IRAK1* associated with SLE. In $CD4^+$ T cells, oestrogen-induced DNA hypomethylation increases the expression of X-linked microRNAs (miRNAs) and immune-related genes, including *CD40L* and *CXCR3*. Collectively, these multifaceted influences converge to increase immune gene expression and contribute to increased susceptibility to autoimmune rheumatic diseases. TLR, Toll-like receptor.

individuals with the 46,XY karyotype[70]. Similarly, the prevalence of SLE in individuals with triple X syndrome is 2.5-fold higher than in 46,XX individuals and 25-fold higher than in 46,XY individuals[70]. By contrast, no enrichment of the 47,XXX karyotype has been observed among patients with RA, despite the female predominance of the disease[70]. Increased prevalence of IIM has also been observed in individuals with sex chromosome aneuploidies, including 47,XXY and 47,XXX, particularly inclusion-body myositis[71], further supporting a link between X chromosome dosage and susceptibility to inflammatory myopathy.

Increased X chromosome dosage has also been implicated in SLE and SSc in individuals with Klinefelter syndrome. Klinefelter syndrome (47,XXY) is characterized by congenital hypogonadism, and individuals with Klinefelter syndrome have a 14-fold increased risk of developing SLE compared with 46,XY individuals[72]. In addition, several cases of adult-onset SSc have been reported in individuals with Klinefelter syndrome over the past four decades[73]. Beyond aneuploidy, altered XCI patterns might further contribute to disease susceptibility. In a cohort of 44 patients with RA, skewed XCI was observed in 31.5% of women with the disease compared with 17.4% of healthy women[74], suggesting that preferential inactivation of one X chromosome, and consequent dysregulation of X-linked genes such as the androgen receptor, might contribute to disease susceptibility. Skewed XCI has also been reported in larger cohorts of women with RA ($n = 110$) and women with SSc ($n = 68$)[75], further implicating XCI in sex-biased susceptibility to rheumatic disease.

Emerging research that includes transgender and/or intersex individuals is beginning to enable the separation of sex chromosome and sex hormone effects in humans, although data remain limited. More extensive efforts to decouple these influences have been undertaken in model organisms. The most well-known system, the Four Core Genotypes model, manipulates the location of testis-determining gene (*Sry*) to generate mice with concordant or discordant combinations of sex chromosome complement and gonadal sex (including XX mice with ovaries, XX mice with testes, XY mice with ovaries and XY mice with testes)[76]. This useful tool facilitated the observation that the presence of two X chromosomes is sufficient to promote a spontaneous lupus-like phenotype through gonad-independent mechanisms including B cell

abnormalities such as enhanced expression of costimulatory markers. However, subsequent work identified an unrecognized chromosomal translocation affecting *Tlr7* gene dosage in some Four Core Genotypes mouse lines, indicating that certain earlier studies might have been confounded by this event[77]. Importantly, the availability of the original mouse line lacking the translocation preserves the validity of this model, while highlighting the need for careful interpretation of prior findings as well as for additional studies using this model and other modelling systems with relevance to human disease.

Another approach to studying sex chromosomes involves experimentally perturbing XCI. In mice, reduction of *Xist* leads to reactivation of X-linked genes, including *Tlr7*, across multiple immune cells such as monocytes, macrophages, dendritic cells and B cells[63]. This reactivation is associated with increased inflammatory responses and the production of anti-DNA autoantibodies[63]. In B cells, maintenance of XCI depends on continuous XIST expression, as many XIST-dependent genes lack promoter DNA methylation[42]. Consistent with this mechanism, escape of XIST-dependent genes has been observed in $CD11c^+$ atypical memory B cells from patients with SLE[42]. In addition, XIST RNA itself has been implicated in disease pathogenesis in humans: elevated XIST levels in leukocytes from patients with SLE can serve as a source of ligands for TLR7, stimulating IFNα production by pDCs in a TLR7-dependent manner[78]. Collectively, these findings indicate that skewed XCI and X chromosome dosage might represent an important initiating factor in predisposing individuals to the development of rheumatic diseases, and warrant further investigation (Fig. 3).

Genetic and epigenetic regulation

In addition to structural and dosage effects of the X chromosome, epigenetic and genetic regulatory mechanisms further modulate the expression of X-linked and autosomal immune genes. Genetic studies in SLE have identified autoimmune disease-associated single-nucleotide polymorphisms (SNPs) in genes involved in sex hormone signalling, immune pathways and epigenetic regulation, including DNA methylation and histone modification. Several of these variants occur in X-linked genes that might escape XCI, including *TLR7*, *TLR8*, *NR3C4*, *IRAK1* and *MECP2* (summarized elsewhere[79]). In RA, SNPs have been identified in the X-linked genes *TIMP1* and *IL9R*, with the *IL9R* association reported specifically in men, consistent with unbuffered (hemizygous) expression of X-linked risk alleles[80]. *TIMP1* encodes an inhibitor of MMPs, and the IL-9 receptor (encoded by *IL9R*) is involved in IL-9-mediated T cell development[80]; hence, these data support a role for X-linked SNPs in sex-based differences in joint degradation and T helper cell differentiation. To date, no associations with X-linked genetic variants have been noted in primary Sjögren disease, SSc or IIM.

Escape from XCI or skewed XCI also influences the expression of X-linked microRNAs (miRNAs). Several X-linked miRNAs show sex-biased and disease-associated differential expression in rheumatic diseases, and are regulated by oestrogen. In female lupus-prone NZB/W F1 mice, miR-31, miR-155, miR-127 and miR-379 are differentially expressed in splenocytes compared with male mice[81]. These miRNAs are also upregulated in immune cells from oestrogen-treated, orchiectomized male lupus-prone mice, reaching levels comparable to those observed in female NZB/W F1 mice[81]. Additional evidence links miRNA dysregulation to epigenetic abnormalities that might contribute to sex-biased immune responses in SLE. Increased expression of miR-21 and miR-148a in $CD4^+$ T cells from patients with SLE, as well as in female lupus-prone mice, is associated with reduced expression of DNA methyltransferase (DNMT), leading to DNA hypomethylation and increased expression of methylation-sensitive immune genes (including X-linked genes)[82]. Consistent with these observations, demethylation of genes on the inactive X chromosome contributes to increased expression of immune-related loci, including *CD40L*, *CXCR3*, *OGT*, miR-98, let-7f-2, miR-188-3p, miR-421 and miR-503 (ref. 83). These genes are overexpressed in $CD4^+$ T cells from women with SLE compared with those from men with the disease, and in $CD4^+$ T cells from healthy women following treatment with the DNMT inhibitor 5-azacytidine[83]. These findings suggest that drugs that modulate DNA methylation could potentially influence sex-biased immune responses in rheumatic diseases.

Microbiome and host interactions

Growing evidence implicates the microbiota (microorganisms) and microbiome (microorganisms, their genes and their environment) in autoimmune rheumatic disease. The composition of the gut microbiome differs between male and female mice, and early-life microbial colonization influences sex hormone levels, with downstream effects on immune development and autoimmune disease susceptibility[84]. Dysbiosis of the gut and oral microbiota has been documented in several rheumatic diseases. One potential mechanism linking the microbiome to sex-biased disease involves microbiota-derived enzymes such as β-glucuronidase, which converts inactive conjugated oestrogens into their active form, promoting reactivation and reabsorption of oestrogen into the blood[85]. Similarly, gut microorganisms can deconjugate glucuronidated androgens and modulate their metabolism[86]. These findings suggest that the microbiome might influence sex hormone availability and thereby contribute to sex-biased immune responses in rheumatic diseases (Fig. 4).

In lupus-prone mice, gut dysbiosis has been associated with disease progression, with distinct microbial compositions observed between female and male NZB×NZW F1 mice. Transfer of caecal contents from male to female mice reduces proteinuria, attenuates kidney disease and improves survival[87], suggesting that sex-specific microbial communities contribute to disease modulation. Specific microorganisms have been implicated in disease pathogenesis. For example, the translocation of *Enterococcus gallinarum* from the gut to other organs can trigger autoimmune features in lupus-prone mice, whereas administration of oral antibiotics, such as vancomycin or ampicillin, reduces anti-double stranded DNA and anti-RNA antibody production and improves overall survival[88]. However, whether these processes differ between sexes has not been assessed. In addition to microbial translocation, molecular mimicry provides another mechanism linking the microbiome to autoimmunity: bacterial surface proteins that have homology to eukaryotic proteins can induce antibody crossreactivity. As an example, several commensal bacteria encode orthologues of Ro60 and trigger production of anti-Ro60 autoantibodies as well as Ro60 autoreactive T cells in SLE[89], suggesting that the microbiota can trigger autoimmune disease in genetically predisposed individuals. As this study was conducted predominantly in samples from women, extending the findings to men with SLE requires further investigation, and whether such mechanisms contribute to sex differences in disease remains unclear.

In models of SSc-associated pulmonary fibrosis, low gut microbial diversity has been shown to amplify the profibrotic effects of oestrogen in female mice, suggesting that interactions between the gut microbiota and sex hormones contribute to lung fibrosis[90]. Consistent with a role for the microbiome in SSc, a cross-sectional international study in patients with SSc, with and without ILD, found that gut dysbiosis correlates with radiographic parameters of ILD severity

and inflammatory markers[91]. Although this study was not designed to assess sex differences, these findings highlight a potential intersection between microbiome composition, hormone signalling and disease progression that warrants future investigation.

Inflammation can, in turn, alter the composition of the gut microbiota through interactions between immune signalling and sex hormone metabolism. Inflammatory cytokines such as TNF, IL-1 and IL-6 can shift hormone levels, increasing oestrogen concentrations while decreasing androgen levels[92,93], and in turn these changes in sex hormones can alter the intestinal microbiota[93]. Consistent with this interplay, in a study in individuals with primary Sjögren disease (involving predominantly women), disease was associated with an enrichment in pro-inflammatory microbial taxa and depletion of anti-inflammatory species[94], supporting the possibility that inflammation-skewed and/or hormone-skewed environments, such as those shaped by increased oestrogen, might contribute to a pro-inflammatory microbial milieu.

The microbiota shapes the gastrointestinal metabolome, and intestinal-derived metabolites can spread to peripheral tissues, thereby influencing host physiology. Animal studies have demonstrated sex-specific differences in intestinal-derived metabolites in the peritoneal fluid, serum, liver, spleen and urine[95]. Consistent with the broader influence of microbiota-associated metabolites across tissues, a metabolomic analysis of muscle from patients with inclusion-body myositis identified alterations in central carbon metabolism, inflammasome activation and mitophagy, with stronger correlations between transcriptomic, metabolomic and clinical measures of muscle strength observed in men than in women[96], although these metabolites were not directly linked to microbiota.

The microbiome can also contribute to sex differences in immune responses through mechanisms that are independent of sex hormones, including those involving XCI and epigenetic regulation. In the Four Core Genotypes model described above, XX mice but not XY mice, exhibit increased numbers of IgM-secreting B cells and plasma cells following immunization with heat-killed *Streptococcus pneumoniae*[97]. This sex chromosome-dependent effect was abolished by antibiotic-mediated depletion of the gut microbiota and restored following reconstitution with short-chain fatty acid-producing bacteria[97]. These findings suggest that microbial factors are both sufficient and necessary to promote XX-dependent immune activation.

Overall, although the evidence remains preliminary, two X chromosomes and the immune-modulatory effects of sex hormones might interact with microbiome-specific factors to influence sex-biased susceptibility to rheumatic disease (Fig. 4). Further investigation is needed to determine whether differences in the gut microbiome contribute to sexual dimorphism in rheumatic diseases, and the importance of the skin and lung microbiome in this context.

Viral infections and antiviral immunity

In addition to microbiome-derived and endogenous factors, chronic exposure to viral antigens represents an important environmental axis through which sex differences in immune responses might arise. Associations between viral infections, particularly Epstein–Barr virus (EBV) infection, and autoimmune rheumatic diseases have been reported

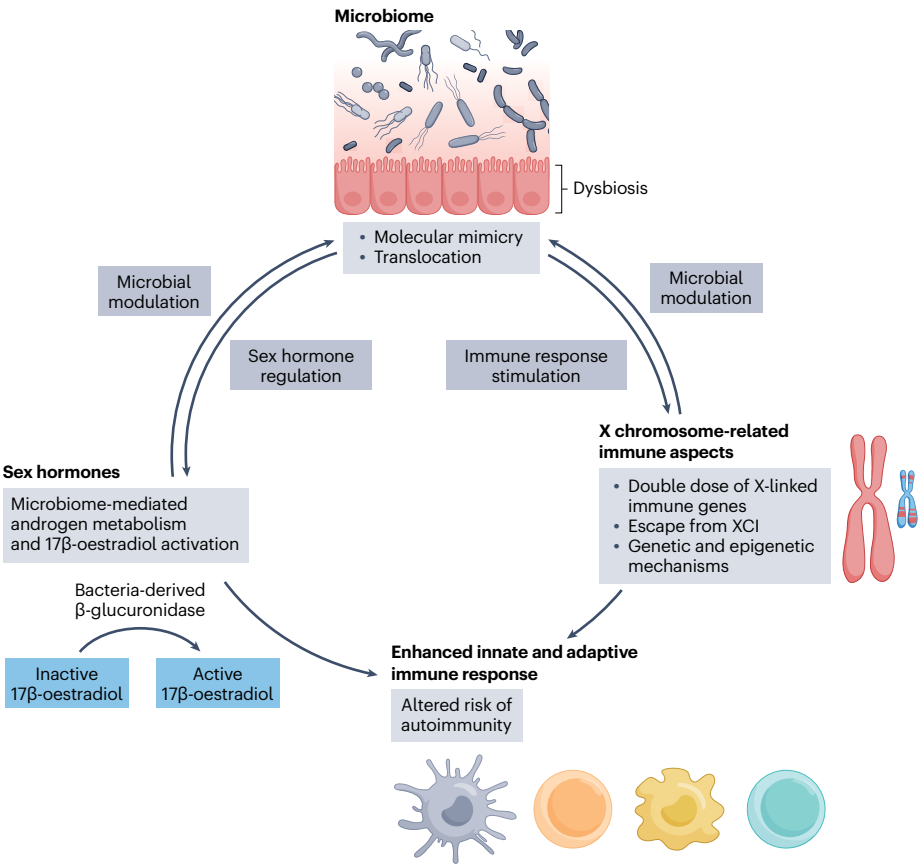

Fig. 4 | Interplay between sex hormones, X chromosome biology and the microbiome in autoimmune rheumatic diseases. Interactions among sex hormones, X chromosome-linked immune mechanisms and the microbiome form interconnected feedback loops that contribute to increased autoimmune susceptibility, particularly in women. Oestrogen exerts multiple effects on innate and adaptive immune responses that might promote microbial dysbiosis. Within the microbiome, bacterial enzymes such as β-glucuronidase convert conjugated (inactive) oestrogens into active forms. These reactivated oestrogens re-enter the circulation and are delivered to peripheral tissues, where they further enhance immune activation and contribute to disease development and/or progression. Increased immune activation resulting from biallelic expression of X-linked immune genes generates selective pressure on the microbiome, promoting dysbiosis. In turn, microbial antigens derived from a dysbiotic microbiota stimulate immune pathways, including those encoded on the X chromosome. Together, these bidirectional interactions alter the risk of autoimmune rheumatic diseases. XCI, X chromosome inactivation.

in SLE[98], SSc[99], RA[100] and primary Sjögren disease[101]. Evidence from both mouse[102] and human[103] studies indicates that women mount more robust antiviral immune responses than men, and EBV-infected women generate stronger IgG responses than men[104]. Investigation of EBV-induced immunological alterations might therefore provide important insights into mechanisms underlying sex-biased autoimmune conditions. Mechanistic insights into this relationship were provided by one study that applied single-cell sequencing, transposase-accessible chromatin sequencing (ATAC-seq) and chromatin immunoprecipitation followed by sequencing (ChIP–seq) analyses in patients with SLE[98]. This approach identified EBV-infected B cells in which EBV nuclear antigen 2 (EBNA2) binds to transcriptional start sites and regulatory regions of genes involved in immune regulation and antigen presentation. This transcriptional reprogramming drives the expansion of autoreactive B cells with antigen-presenting cell features, enabling activation of T cells and promoting the production of antibodies targeting neoantigens[98]. Although the predominance of women with SLE in this study precludes sex-based comparisons, these findings highlight the need for further studies in this area that address sex differences in antiviral immune responses and autoimmune pathogenesis.

Implications for treatment

Sexual dimorphism in treatment response is evident across rheumatic diseases. SLE[105], SSc[106] and primary Sjögren disease[107] tend to exhibit more severe and treatment-refractory disease in men, whereas RA[108] is often characterized by more severe clinical phenotypes in women. These disparities underscore the need for precision medicine approaches that incorporate sex-dependent mechanisms.

Given the growing evidence implicating sex hormones in various features of rheumatic and connective tissue diseases, hormone-based therapies have been explored as potential interventions to modify disease progression and/or activity. However, such treatments have not shown clear or consistent beneficial effects to date. For example, DHEA therapy in SLE demonstrated minor and variable effects on disease activity and progression across seven randomized controlled trials, although modest improvements in patient-reported quality of life were observed, alongside some adverse effects such as acne[109]. Similarly, hormone replacement therapy and testosterone-based interventions in RA have yielded mixed results (reviewed elsewhere[110]). These disappointing findings highlight the need for a more detailed understanding of the cell types and receptor pathways through which sex hormones influence disease activity.

Beyond hormone modulation, emerging therapeutic approaches targeting sex-dependent mechanisms are under investigation. Advances in genome editing raise the possibility of targeting sex chromosome-linked mechanisms directly; for example, CRISPR–Cas9-based approaches could, in principle, be adapted to correct skewed XCI or modulate expression of X-linked genes. Microbiome-targeted interventions, including dietary modification, selective microbial depletion, or even phage therapy, could provide novel ways to alter the disease course[111,112]. In parallel, computational approaches such as artificial intelligence-based drug repurposing and development could facilitate the identification of therapeutic targets related to sex-biased autoimmune consequences of antiviral immunity[113].

Realizing these goals will require collaborative multicentre efforts leveraging well-characterized patient cohorts and/or data or specimens from randomized clinical trials. In parallel, further research is needed to define how gender-affirming hormone therapies influence the risk of autoimmune disease onset, as well as disease progression and flares in individuals with existing autoimmune disease. As randomized controlled trials are not feasible in this setting, carefully designed observational studies will be essential to assess dose-dependent effects of hormone therapy on clinical outcomes. Similarly, the resurgence of hormone replacement therapy in postmenopausal women underscores the need to better understand how supplemental oestrogen affects autoimmune disease risk and progression. Looking forward, several important questions remain (Box 1), and addressing these gaps might identify additional targets for therapeutic intervention in autoimmune diseases.

Box 1 | Key questions on sex-dependent mechanisms

- What are the effects of sex hormones across all the cell types involved in rheumatic diseases?
- What are the effects of the various sex hormone metabolites?
- Do additional X chromosome inactivation-associated genes contribute to disease pathogenesis?
- Are distinct molecular or cellular pathways predominant by biological sex, and can these be selectively targeted therapeutically?
- Which components of the microbiome are beneficial or harmful, and how are these influenced by sex?

Conclusion

Currently, treatments for rheumatic diseases are not sex-specific, despite substantial evidence showing difference in therapeutic responses and sensitivities between women and men with rheumatic and inflammatory diseases. Variations in sex hormones, the microbiome, antiviral immunity, genetic architecture and epigenetic regulation probably contribute to differences in disease prevalence, clinical manifestations and treatment outcomes across sexes. Advances in emerging technologies are expected to improve understanding of these underlying mechanisms and support the development of precision medicine approaches that account for sex-dependent biology. Such strategies might enable more individualized treatment, reduce disease burden and ultimately improve care for all patients with rheumatic diseases.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

E.R.V. is a consultant for Boehringer Ingelheim, GlaxoSmithKline, AbbVie and Bristol Myers Squibb. E.L.H. is a consultant for Boehringer Ingelheim, Merck and Bristol Myers Squibb. C.F.-B declares no competing interests.

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