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Rheumatoid arthritis

Targeting P2X7R on synovial fibroblasts to treat refractory RA

P2X7 receptor (P2X7R) has been explored as a therapeutic target in rheumatoid arthritis (RA), but early clinical trials were unsuccessful, and the precise role of this purinergic receptor in RA pathogenesis remained unclear. New research suggests that overexpression of P2X7R in synovial fibroblasts contributes to synovial inflammation in refractory RA and that its inhibition with an antagonist highly selective for human P2X7R could have therapeutic potential in this setting.

The researchers first demonstrated that P2X7R was overexpressed in inflamed synovial tissue from patients with RA and that its expression was associated with the severity of synovitis. *P2X7R* was expressed predominantly by the synovial lining subset of synovial fibroblasts. Moreover, in an evaluation of *P2X7R* expression across different cell-type abundance phenotypes (CTAPs), *P2X7R* expression was highest in the fibroblast-rich subtype of synovial inflammation (CTAP-F), which is associated with multidrug-resistant RA. Thus, the researchers linked expression levels of P2X7R to both local synovitis and systemic inflammation. "This finding reframes P2X7R not merely as an immune receptor, but as a marker of disease-associated stromal activation," says Zhanguo Li, a corresponding author of the study published in *Science Advances*.

Treatment of human synovial fibroblasts with EVT-401, a potent and highly selective antagonist of human P2X7R, suppressed their proliferation by inducing cell-cycle arrest and apoptosis. EVT-401 treatment also suppressed the secretion of pro-inflammatory IL-6 and tissue-destructive mediators such as MMP-3 and DKK-1 by RA synovial fibroblasts and inhibited their migration and invasive potential. Transcriptomic analysis revealed that EVT-401 downregulates the expression of genes involved in Notch signalling and extracellular matrix organization — pathways that are enriched in synovial fibroblast subsets associated with refractory RA.

Noting the potential translational limitations of rodent models, including that P2X7R antagonists can have differential selectivity for rat versus human P2X7R, the researchers assessed the effects of EVT-401 in a non-human primate (NHP) model of arthritis and in a humanized cartilage–RA synovial fibroblast co-implantation model in SCID mice, as well as in a rat model of collagen-induced arthritis. "Critically, EVT-401 showed robust efficacy in the NHP arthritis model and in the co-implantation model, whereas it lacked efficacy in rats, directly validating the species-selectivity problem that likely contributed to earlier clinical failures," Li notes.

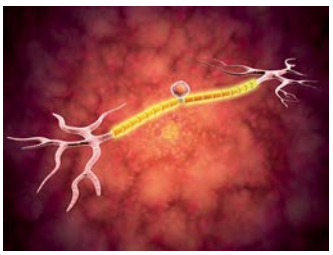
Collectively, these findings highlight P2X7R on synovial fibroblasts as a potential therapeutic target associated with refractory RA. A phase II clinical trial of EVT-401 involving participants with methotrexate-resistant RA is underway, and the researchers plan to further investigate the mechanisms underlying the drug's effects.

Sarah Onuora

Original article: Rao, P. et al. P2X7R of synovial fibroblasts is a potential therapeutic target associated with refractory rheumatoid arthritis. *Sci. Adv.* **12**, eadw9543 (2026)

Connective tissue disease

Sensory nerves protect against tendon degeneration



Pain is a hallmark of chronic tendinopathy, but the role of sensory neurons seems to extend beyond pain signalling. Now, findings build on this concept by indicating that sensory neurons have a protective role in tendon repair.

"We have previously shown that peripheral sensory neurons enhance tendon repair after an acute injury, by promoting tendon sheath progenitor cell proliferation and differentiation," explains corresponding author of the study Aaron James.

In the current study, tendon degeneration was associated with an increase in sensory nerve innervation and vascularity in two mouse models of chronic Achilles tendinopathy. To further assess the role of peripheral nerves in tendon repair, the authors used the Ngf^{Csf1r} transgenic mouse model, in which mice lack *Ngf* (the gene that encodes nerve growth factor) specifically in macrophages. These mice had reduced tendon innervation that resulted in tendon degeneration. In addition, tendon repair was diminished in $TrkA^{F592A}$ mice, which lack the nerve growth factor receptor.

The use of retrograde labelling enabled the identification and characterization of sensory neurons that innervate the Achilles tendon. Denervation of the sural nerve (a sensory nerve in the Achilles tendon) accelerated tendon degeneration. Single-cell RNA sequencing of tendon samples obtained after denervation indicated a functional shift in mesenchymal cells from a regenerative phenotype to a pro-inflammatory, degenerative phenotype. In addition, denervation increased macrophage infiltration and also skewed these cells towards a pro-inflammatory phenotype.

To better understand the protective effects of sensory neurons, the authors mapped the interactions between neurons and innervated tendon cells. These analyses identified fibroblast growth factor 1 (FGF1), derived from neurons, as a key mediator of tendon repair.

Ex vivo validation using mouse tendon cultures showed that FGF1 treatment increased tendon cell proliferation and reduced apoptosis. In a mouse model of tendinopathy, FGF1 injections reduced tendon inflammation and degeneration. Finally, analysis of human tendinopathy samples showed co-localization of FGF1 with innervating nerve fibres, in further support of the crucial role of this protein in tendon repair.

"This work lays the foundation for multiple next steps. One concept is to boost local sensory innervation as a method to combat or prevent tendon degeneration. Another is to use one or more neural-derived regulatory molecules, such as FGF1, as potential local therapeutic targets. Ultimately the goal is to harness the regenerative properties of sensory neurons," concludes James.

Holly Webster

Original article: Zhu, M. et al. Sensory nerves protect against preclinical tendinopathic changes through FGF1 signaling. *Sci. Transl. Med.* **18**, eaec1380 (2026)

Systemic lupus erythematosus

Dapirolizumab pegol improves SLE disease activity in phase III trial

Results of the phase III PHOENYCS GO study support the continued evaluation of dapirolizumab pegol as a potential treatment option for people with systemic lupus erythematosus (SLE). In the 48-week trial, the addition of dapirolizumab pegol to standard-of-care medication improved disease activity compared with placebo.

Dapirolizumab pegol is a pegylated Fab′ fragment that binds CD40 ligand (CD40L). By interfering with CD40–CD40L signalling, the drug affects various immune processes involved in SLE immunopathology, including B cell and T cell activation, as well as production of type I interferon and other cytokines.

In PHOENYCS GO, which was conducted at 177 centres across 25 countries, 321 people with moderate-to-severe, active SLE were randomly assigned to receive standard-of-care medication plus either dapirolizumab pegol or placebo. Glucocorticoid tapering, with the aim of reaching a daily dose of ≤7.5mg, was required and had to be initiated no later than week 8.

The primary outcome of the trial was met, as significantly more patients in the dapirolizumab pegol group than in the placebo group achieved BICLA response at week 48 (50% versus 35%), reflective of clinically relevant improvement in disease activity. Although the key secondary outcome of BICLA response at week 24 was not met, results in favour of dapirolizumab pegol were observed across other secondary outcomes, including prevention of severe BILAG flares, improvement from baseline in SLEDAI-2K score, and achievement of Lupus Low Disease Activity State and glucocorticoid tapering.

Treatment-emergent adverse events, most commonly COVID-19 and urinary tract or upper respiratory tract infections, were observed in 83% of the dapirolizumab pegol group, compared with 75% of the group that received placebo, with serious treatment-emergent adverse events occurring in 10% and 15% of the participants in each group, respectively.

> “the addition of dapirolizumab pegol to standard-of-care medication improved disease activity”

An open-label extension of PHOENYCS GO and a second confirmatory phase III study, PHOENYCS FLY, are now underway to further assess the safety and efficacy of dapirolizumab pegol for the treatment of SLE.

Sarah Onuora

Original article: Clowse, M. E. B. et al. Efficacy and safety of the CD40 ligand inhibitor dapirolizumab pegol in systemic lupus erythematosus (PHOENYCS GO): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **407**, 2291–2304 (2026)

Fibroinflammatory disorders

Obexelimab reduces the risk of IgG4-RD flare

Treatment with the bifunctional antibody obexelimab lowers the risk of disease flare and reduces exposure to glucocorticoids in people with active IgG4-related disease (IgG4-RD), according to the results of the phase III INDIGO trial. These latest findings build on those of a previous phase II open-label trial and indicate that obexelimab could be a promising new treatment option for IgG4-RD.

Glucocorticoids are the standard first-line therapy for IgG4-RD, but evidence implicating B cells in the pathogenesis of IgG4-RD has led to the development of new drugs that target these cells. Unlike the B cell-depleting therapies rituximab and inebilizumab, which can be associated with an increased risk of infection, obexelimab inhibits B cells, without inducing their depletion, by binding to both CD19 and the inhibitory FcγRIIb receptor.

In the INDIGO study, 194 participants with active IgG4-RD were randomly assigned to receive treatment with obexelimab administered subcutaneously at a dose of 250 mg once weekly or matched placebo, for 52 weeks. Glucocorticoids were tapered in both treatment groups, with discontinuation by week 8.

Time to the first adjudicated flare of IgG4-RD that required rescue therapy was significantly longer in the obexelimab group than in the placebo group (hazard ratio 0.44). Overall, flares were reported in 26.8% of obexelimab-treated participants, compared with 54.6% of those who received placebo. A greater proportion of participants in the obexelimab group achieved complete remission at week 52 (37.1% versus 19.6%).

Notably, the cumulative dose of glucocorticoid rescue therapy for IgG4-RD through week 52 was 329.5 mg in the obexelimab group, compared with 929.8 mg in the placebo group. The incidence of adverse events during the double-blind treatment period was similar across the two treatment groups, although the percentage of participants who experienced serious adverse events was lower in the obexelimab group (10.3% versus 18.6%).

> “obexelimab could be an effective treatment for IgG4-RD”

Overall, the 52-week results of the INDIGO trial suggest that obexelimab could be an effective treatment for IgG4-RD. Additional efficacy and safety data will be collected in an ongoing open-label extension of this study.

Sarah Onuora

Original article: Della-Torre, E. et al. Obexelimab for the treatment of IgG4-related disease. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2601337 (2026)

Related article: Peyronel, F. et al. IgG4-related disease and other fibro-inflammatory conditions. *Nat. Rev. Rheumatol.* **21**, 275–290 (2025)

Myositis

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Progress made and the road ahead for cancer screening in myositis

Thomas V. Guy & Matthew J. S. Parker

Since the publication of an international cancer-screening guideline for patients with idiopathic inflammatory myopathy, multiple validation studies have described its performance in various cohorts and regions. Taken collectively, the studies support the sensitivity of risk stratification but raise concerns about low specificity and possible increased costs.

REFERS TO: Pellico, M. R. et al. Real-world application of the international myositis assessment and clinical studies group guidelines on cancer risk stratification. *Rheumatology (Oxford)* **65**, keag171 (2026).

It has been over 35 years since the first methodologically sufficient study helped to establish the long-suspected association between idiopathic inflammatory myopathy (IIM) and an increased risk of malignancy[1]. Reliably identifying patients with IIM who also have cancer has since become a major clinical priority. Subsequent enquiry in areas of oncology, autoimmunity and immunogenetics has revealed numerous, often fascinating, discoveries relevant to this patient population, including the establishment of anti-TIF1γ dermatomyositis as a prototypic paraneoplastic rheumatic autoimmune disease.

In 2023, the International Myositis Assessment and Clinical Studies Group (IMACS) published a guideline on cancer screening in IIM informed by a well-conducted meta-analysis and subsequent systematic review[2]. This international guideline evolved by way of a modified Delphi approach that collated 75 individual multispecialty expert opinions and resulted in 18 strong or conditional recommendations. Despite the complexity of the clinical scenario, the guideline was refreshingly simple to follow. Essentially, cancer risk should be considered for all patients with IIM, but only those with intermediate- or high-risk factors should undergo investigations beyond the age- and sex-appropriate local cancer-screening programmes. The guideline suggested the investigations to perform in each stratified group, although it recommended an individualized approach influenced by local cancer epidemiology, as well as by the availability of and required expertise for various investigations. The authors suggested that further work to review the performance of the guideline in a broad range of clinical settings would be required and anticipated the likelihood that the guideline would benefit from further iterations informed by this feedback, integrated with the rapidly evolving research in cancer-associated myositis (CAM).

Pellico et al. have now published a multicentre study evaluating the performance of this guideline in 411 participants with IIM[3]. This is now, to our knowledge, the seventh publication to specifically evaluate the guideline since its development. It provides an opportunity to consider how the guideline seems to work in practice and to what degree it might address the unmet need for cancer screening in clinical practice. Taken collectively, the seven publications included 1,764 patients with IIM across myositis cohorts from Italy (two cohorts), USA (two cohorts), Japan, Hong Kong and Australia[3–9]. These studies all apply the guideline retrospectively, and some expand the patient population beyond the specific scope of the guideline to capture a longer period before and after IIM diagnosis.

> "studies have helped to reinforce the value of personalized cancer risk assessment in patients with IIM"

It is interesting that despite the differences between the studies, the authors consistently arrived at similar conclusions. Where reported on, the studies all replicated the same risk factor associations identified in the IMACS guideline, with no novel associations. The guideline performed well in stratifying all participants with cancer into intermediate- or high-risk groups, and the suggested screening investigations recommended in the guideline would have detected the cancer in almost all participants. However, all studies have helped to highlight that only a small proportion (0–18%) of adults with IIM fall within the 'standard-risk' group. Somewhat related to this finding, the two studies that projected financial costs predicted substantially increased direct healthcare costs as a consequence of implementing the IMACS guideline[6,9]. It has been long appreciated that the underlying cancers identified differ across various cohorts, and this phenomenon again was highlighted in the studies, with the most common malignancy being nasopharyngeal carcinoma in the Japanese and Hong Kong cohorts[7,9] and breast cancer in the US, Italian and Australian cohorts[3–6,8].

In subsequent refinements to the IMACS guideline, it is likely that the influence of age at IIM onset will be considered carefully — at present, any patient with IIM onset at or after the age of 40 years is assigned to at least the 'intermediate-risk' group, but numerous authors have postulated or modelled in their data that increasing this age cut-off should improve specificity while maintaining sensitivity and probably reducing costs. Our opinion is that it seems likely that handling risk-assessment and screening decisions in patients with TIF1γ dermatomyositis (who make up the great majority of cases of CAM) differently from handling this in those with other types of IIM would improve guideline performance. There would be value in an ideally prospective multicentre international implementation-validation study that incorporates an estimate of its costs and benefits.

Ultimately, it is our opinion that the aforementioned guideline-implementation studies have helped to reinforce the value of personalized cancer risk assessment in patients with IIM. In turn, this risk

assessment can inform the extent, choice and interval repetition of screening investigations. The IMACS guideline represents a seminal publication in IIM research and provides an excellent reference resource for clinicians involved in these determinations. It does not perform perfectly when applied rigidly in its current format, and clinicians will still feel that there remains a substantial, albeit hopefully diminished, unmet need. Even with refinements to the current guideline, we believe it is unrealistic to expect the highly complex bidirectional deterministic and stochastic interactions in an individual that result in CAM to lend themselves to a universal protocolized approach to cancer screening. For the foreseeable future, we suggest that the IMACS guideline be considered a trusted companion on the journey towards better outcomes for patients with IIM with and without cancer. The current situation brings to mind the anthropomorphized reply to a boy demoralized by his perception of the road ahead when he sighed "We have such a long way to go"; a horse responded "Yes, but look how far we've come" [10].

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Competing interests

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Rheumatoid arthritis

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Targeting ferroptosis resistance in RA fibroblast-like synoviocytes

Burkhard Möller & Jennifer Amsler

Therapeutic targeting of ferroptosis, particularly in pathogenic fibroblast-like synoviocytes, could hold promise for rheumatoid arthritis. However, ferroptosis research in health and disease is still in its infancy, and further research is needed to identify specific therapeutic targets, inform drug development and assess the possible effects of targeting ferroptosis in other cell types and tissues.

Refers to Liu, J. et al. IRE1/p-JNK/NRF2 axis-mediated GPX4 upregulation underlies ferroptosis resistance in rheumatoid arthritis fibroblast-like synoviocytes. *Arthritis Res. Ther.* https://doi.org/10.1186/s13075-026-03827-5 (2026).

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease with several features of autoimmunity, in which fibroblast-like synoviocytes (FLSs) have a crucial role in disease pathogenesis[1]. Despite considerable efforts over the past three decades, FLSs remain characterized largely by their functional properties rather than by distinct molecular markers. FLSs from patients with RA can survive for months following transfer into immunodeficient SCID mice. They can infiltrate cartilage tissue and migrate via the bloodstream into other, distant cartilage transplants[1]. Furthermore, in people with RA, the migration of FLS cells into cartilage precedes disease flare[2]. Thus far, FLSs have remained difficult to target in a cell-specific manner. Emerging evidence has shown that targeting ferroptosis in FLSs could be a promising therapeutic approach for RA. A study published by Liu et al.[3] now provides further insights into ferroptosis resistance in FLSs.

The term ferroptosis, an iron-dependent form of regulated cell death driven by the accumulation of lipid peroxides, was coined in 2012 (ref. 4). However, the pathways and molecules involved in ferroptosis were discovered much earlier. For example, glutathione (GSH), which is the substrate of GSH peroxidase 4 (GPX4) and is involved in the redox mechanism after lipid peroxidation, was discovered in 1888. In the past decade, the intracellular signalling of ferroptosis has attracted considerable attention. Among its mediators, NRF2 modulates ferroptosis through several pathways, including the regulation of GSH biosynthesis[5]. Furthermore, IRE1α (an isoform of IRE1) directly regulates ferroptosis upon stimuli of the stressed endoplasmic reticulum[6]. In RA synovitis, FLSs are exposed to oxidative stress, which is one of many factors that can induce ferroptosis, but FLSs in RA show resistance to ferroptosis and other types of programmed cell death.

In the study by Liu et al., in vitro-cultured FLSs from patients with longstanding RA exhibited features of endoplasmic reticulum dysfunction and stress[3]. Specifically, expression of IRE1, NRF2 and GPX4 and phosphorylation of c-Jun N-terminal kinase (p-JNK) were increased. Notably, these FLSs were protected from ferroptosis-mediated cell death.

To further study the function of IRE1, the authors knocked down *ERN1* (the gene that encodes IRE1) in RA FLSs in vitro. Loss of *ERN1* reduced protein levels of NRF2 and GPX4, decreased cell proliferation and impaired the migratory capacity of FLSs. Furthermore, electron microscopy revealed a substantial increase in mitochondrial morphological alterations characteristic of ferroptosis. Interestingly, the effects of *ERN1* silencing on morphology and function were largely antagonized by the administration of an NRF2 activator. Thus, NRF2 in RA FLSs seems to function downstream of IRE1 located on the endoplasmic reticulum. In addition, the resistance of RA FLSs to ferroptosis was overcome by inhibition of NRF2: this treatment induced morphological and biochemical features of ferroptosis and reduced the expression of GPX4, IRE1 and p-JNK. On the basis of these findings, it can be hypothesized that the anti-ferroptotic stress-response proteins IRE1 and NRF2 reciprocally activate each other.

These extensive in vitro experiments support the preliminary conclusion that several distinctive properties of FLSs in RA — including their resistance to regulated cell death, migratory behaviour and invasive potential — might be explained, at least in part, by resistance to ferroptosis. The authors treated collagen-induced arthritis in rats with a small-molecule IRE1 inhibitor (4μ8C) for 7 days. They found that intraperitoneal injection of 4μ8c decreased the expression of pro-inflammatory mediators and GPX4 and substantially attenuated the severity of arthritic joint destruction, including considerable preservation of cartilage.

Although it is still at a very early preclinical stage, this work hints at the possibility that inducing ferroptosis in FLSs by targeting IRE1 and, subsequently, NRF2 might reveal a novel therapeutic target for RA. However, in our opinion, the simultaneous reduction in expression of GPX4 and concentrations of GSH — the co-substrate required for GPX4 activity — after activation of NRF2 observed in a control experiment raises methodological questions that warrant further investigation. It might be informative to compare the levels of GSH to those of its oxidized form, GSH disulfide. Furthermore, it would be interesting to observe the effects of *ERN1* silencing on the NRF2-binding protein KEAP1, to understand in greater detail the interplay between IRE1 and NRF2.

To further complicate the interpretation of these key findings, different FLS phenotypes have been described that do not all positively correlate with disease activity[7]. As further evidence of the heterogeneity of this cell type, some mouse synovial fibroblast subsets found in models of RA were resistant to ferroptosis-inducing agents, whereas others were not[8]. Thus, the method of inducing ferroptosis might

differ depending on the synovial fibroblast subset, so evaluating the effects of ferroptosis-inducing agents, beyond in vitro studies, on certain FLS subtypes in different animal models of arthritis will be important.

Organ-specific and cell type-specific effects are also important considerations for the neutralization of IRE1. Inhibition of IRE1 with 4μ8c, the same inhibitor used in the study by Liu et al.[3], increased cellular GSH levels and blocked ferroptosis in wild-type MDA-MB-231 cancer cells in vitro, suggestive of an opposite effect of ferroptosis in different cell types[6]. This consideration is of particular importance when considering the safety of using small-molecule inhibitors of IRE1 systemically (as these agents target both IRE1α and IRE1β, and IRE1α is expressed in numerous hematopoietic cells and in other cell types). Furthermore, although no negative effects of ferroptosis induction on cartilage were reported in the 7-day in vivo experiment in the study by Liu et al.[3], particular focus should be given to chondrocytes, in which ferroptosis could have long-term detrimental effects[9]. Notably, although the work of Liu et al.[3] is elegant and comprehensive, it focuses intensely on the biology of isolated RA FLSs, which might have a much less aggressive phenotype than that of in situ FLSs in RA that are exposed to the entire pro-inflammatory environment of the RA joint[10].

In summary, despite these promising preclinical effects, many questions remain concerning the safety and feasibility of inducing any form of regulated cell death, including ferroptosis, whether in specific cell types or systemically, owing to concerns that it could jeopardize the integrity of healthy tissues.

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Competing interests

The authors declare no competing interest.

Therapy

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Time to rethink the treatment of palindromic rheumatism

Kulveer Mankia

Guidance on how to manage palindromic rheumatism is lacking, but new clinical trial data support the use of abatacept to reduce the risk of progression to rheumatoid arthritis and to improve symptoms in patients with this difficult-to-manage condition.

REFERS TO Sanmarti, R. et al. Abatacept versus hydroxychloroquine for prevention of rheumatoid arthritis in individuals with palindromic rheumatism: a randomized open-label trial. *Nat. Med.* https://doi.org/10.1038/s41591-026-04395-6 (2026).

Palindromic rheumatism presents a conundrum for rheumatologists. Most encounter it in clinical practice, yet the pathobiology and clinical management remain poorly defined. Acute, transient articular and periarticular flares, with complete resolution, are the hallmark of the condition. The presence of rheumatoid arthritis (RA)-related autoantibodies (especially anti-citrullinated protein antibodies (ACPA)) in most patients imply a rheumatoid-like aberrant adaptive immune response, yet the acute, transient periarticular flares, which are more akin to crystal and autoinflammatory diseases, suggest the innate immune system is also critically implicated. Rates of progression to RA are high, particularly in those with high levels of ACPA[1]. As such, people with palindromic rheumatism are considered 'at risk of RA'. When compared with other at-risk populations, for example people with clinically suspect arthralgia, the severe, unpredictable inflammatory flares mark out palindromic rheumatism as a prodromal phase of RA with a particularly debilitating effect on quality of life. It is therefore important to find treatments that will reduce both the effect of flares as well as the progression to RA. The PALABA trial, by Sanmarti and colleagues[2], suggests abatacept is capable of both, and as such represents an exciting advance to the treatment landscape for palindromic rheumatism.

Trials over the past three years in individuals at risk of RA have given cause for optimism. In ACPA-positive individuals with arthralgia, abatacept produced encouraging results in two separate European randomized-controlled trials[3,4]. In both the APIPPRA and ARIAA trials, ACPA-positive individuals with arthralgia were clearly prevented from developing clinical arthritis when taking abatacept[3,4]. In APIPPRA, the largest RA prevention trial to date, active treatment was stopped after 1 year; although the protection from abatacept waned after the drug was stopped, there remained a significant benefit at 2 years (from start of treatment)[3]. Results of a long-term extension study of APIPPRA, the ALTO study[5], suggest that patients with very high ACPA levels could remain protected from developing clinical arthritis even 3 years after stopping treatment with abatacept.

In the absence of guidance on how to manage palindromic rheumatism, clinicians often lump people with this condition in with others in the early, prodromal phase of RA (for example, those with ACPA-positive arthralgia). Indeed, one could speculate that a proportion of the participants included in the above trials might have actually had palindromic rheumatism, although this possibility was not explicitly addressed. The PALABA trial by Sanmarti and colleagues[2] is therefore a logical and timely advance. PALABA was a randomized, open-label trial conducted in 14 rheumatology centres in Spain. Only 73 participants were included, but this small population size was mitigated by careful case selection, mandating fulfilment of Guerne and Weisman criteria[6] and positivity for ACPA and/or rheumatoid factor. Participants were randomly allocated to receive treatment with either 125 mg of abatacept subcutaneously weekly or 5 mg kg^{-1} of hydroxychloroquine orally daily for 2 years. Importantly, the abatacept dose was reduced to 125 mg every other week in the second year, whereas the hydroxychloroquine dose remained unaltered throughout the study period. Given that most rheumatologists routinely use hydroxychloroquine to treat their patients with palindromic rheumatism, albeit in the absence of robust trial data, this drug was a sensible choice of comparator. The primary outcome was the development of persistent arthritis fulfilling the 2010 American College of Rheumatology (ACR)–EULAR classification criteria for RA[7]. Overall, 7 (20.6%) of the 34 patients treated with abatacept and 18 (50%) of the 36 patients treated with hydroxychloroquine developed RA at 2 years, with a risk difference of almost 30%. In a time-to-event analysis, those treated with abatacept experienced a significantly longer time to progression to RA than those treated with hydroxychloroquine[2].

As well as stopping progression to RA, the ability of a medicine to reduce the severity and frequency of flares is without doubt a key priority for patients with palindromic rheumatism. Importantly, over half (55%) of the patients who received abatacept achieved remission (that is, they were flare-free for at least 12 months during the 2-year study period), compared with only 23% of those who received hydroxychloroquine. That said, median flare frequency was not significantly different between the two groups. Flare intensity, recorded using a visual analogue scale, improved in those treated with abatacept (median intensity of 7.0 before the start of treatment reduced to 4.0 during months 0–24 of the study), whereas no improvement in flare intensity was seen in those who received hydroxychloroquine. Reported flare duration also improved more markedly in those treated with abatacept, with almost a third of flares lasting <24 h in the abatacept group compared with only 17% of flares in the hydroxychloroquine group.

Although the apparent beneficial effects of abatacept on palindromic rheumatism symptoms in this trial are undoubtedly encouraging, there are some important caveats. Treatment allocation in PALABA was open and unblinded and therefore the trial was susceptible to reporting bias, especially for subjective outcomes such as patient-reported flare characteristics. Furthermore, palindromic rheumatism flares are complex, multifaceted events that involve varying degrees of pain, swelling, erythema and joint restriction. It is not clear which aspects are most important to patients, nor which aspects were most sensitive

to therapy in the trial. Also, without the use of a mandated app or flare diary, it is likely that flare details reported at trial visits were subject to at least some recall bias.

In PALABA, abatacept was continued for the full 2-year trial period rather than being stopped for a drug-free observation period[2]. This decision was perhaps a fortuitous one as the results of APIPPRA and ARIAA have taught us that 1 year of abatacept therapy seems to be insufficient for achieving durable arthritis prevention[3,4]. However, rather than taper the dose to alternate weeks, it might have been more informative to continue at the full licensed dose for the full 2 years for proof of concept of abatacept's ability to treat palindromic rheumatism and prevent RA, with the ability to taper reserved for a follow-on study.

Previous treatment studies in patients with palindromic rheumatism have been limited to case series and retrospective cohort studies[8]. As such, PALABA, as the first randomized controlled trial in palindromic rheumatism, undoubtedly provides a much-anticipated major advance for the field. Abatacept certainly seems to be an efficacious treatment option, with the ability to prevent progression to RA and improve flares in this hard-to-manage patient group.

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Competing interests

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Review article

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TLR7 in systemic lupus erythematosus: genetics and emerging therapies

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Abstract

Systemic lupus erythematosus (SLE) is a disease with considerable unmet treatment needs. Endosomal nucleic acid sensing by Toll-like receptor 7 (TLR7) is emerging as a key pathogenic pathway. Gain-of-function mutations in the genes encoding TLR7 and its chaperone UNC93B1 can cause monogenic childhood-onset SLE; rare variants in proteins that regulate ligand availability or downstream signalling proteins also contribute to disease. *TLR7* variants can increase the affinity of this receptor for its ligands and can alter binding to endogenous antagonists. Both self RNA–protein complexes and viruses have been implicated in TLR7 activation. Key pathogenic mechanisms include breakdown in B cell tolerance and autoantibody production and type I interferon secretion. Although current therapies such as B cell-depleting chimeric antigen receptor (CAR) T cells and anifrolumab (anti-type I interferon receptor) offer benefit, they are limited by high costs and lack of oral options. In this context, TLR7 has emerged as a promising therapeutic target. Phase II trials of an oral dual TLR7–TLR8 antagonist show durable suppression of the interferon signature in all patients, indicating that TLR7 and TLR8 drive this signature in SLE. This treatment has shown clinical benefit for SLE and cutaneous lupus erythematosus, although the primary endpoint (a dose–response effect) was only met in cutaneous lupus erythematosus. Thus, TLR7–TLR8 antagonists might reshape SLE treatment, alone or in combination with other drugs.

Sections

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Key points

- Genetic variants in *TLR7* and its chaperone *UNC93B1* that increase TLR7 signalling are increasingly being reported as monogenic causes of systemic lupus erythematosus.
- Several pathogenic *TLR7* variants identified thus far localize to site 1 (which enhances guanosine binding) or to site 3 (which reduces the binding or inhibitory activity of endogenous *TLR7* antagonists).
- Individuals with *TLR7* gain-of-function variants often present with immune thrombocytopenia and develop clinical manifestations that span the clinical spectrum and heterogeneity typical of systemic lupus erythematosus, often with prominent central nervous system involvement.
- Pharmacological inhibition of *TLR7* using oral antagonists results in suppression of the type I interferon signature and show encouraging results in early-phase clinical trials.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease with a prevalence of 97 per 100,000 people in the UK[1]. SLE is much more common in women than in men (90% of patients are women, and prevalence is higher in some ethnic groups, notably individuals of African and Caribbean descent[2]). Disease often presents in young people but can occur at any age. People who develop SLE in childhood or adolescence often have more severe disease manifestations, particularly the rare monogenic forms of the disease[3]. SLE can affect any organ or tissue of the body. The most common symptoms are rash, hair loss, mouth ulcers, fatigue and joint pain. Although these manifestations are not life threatening, they have major effects on quality of life. Severe manifestations include renal disease, neuropsychiatric lupus and profound anaemia or thrombocytopaenia[2].

The pathogenesis of SLE is complex and involves dysfunction of both the innate and adaptive immune system, characterized by autoantibodies to self-nucleic acids[4]. Anti-nuclear antibodies (ANAs) are present in 90% of patients but are not specific to SLE[2]. Anti-double-stranded DNA (anti-dsDNA) and anti-nucleosome antibodies are highly specific to SLE and substantial evidence indicates that their deposition in tissues causes inflammation and clinical effects[5].

Despite advances, the high cost of therapies, the need for systemic administration and the associated adverse effects highlight the ongoing need for alternative approaches to treating SLE. Evidence supporting novel therapeutic targets has emerged from studies of monogenic childhood-onset SLE, which is driven by genetic variants that disrupt nucleic acid sensing pathways[3]. Among these, Toll-like receptor 7 (TLR7) signalling is emerging as a key pathway in SLE, this receptor has a role in the breach of B cell tolerance, myeloid cell activation and production of type I interferon[6,7]. A *TLR7* gain-of-function (GOF) variant identified in a child who developed severe SLE was reproduced in a mouse model, proving a causal role for overactive TLR7 signalling in SLE[8]. In the past few years, multiple rare GOF variants in *TLR7* and *UNC93B1* (a crucial chaperone for TLR7 and TLR8 trafficking and endosomal localization) that cause SLE have been identified[8–20]. TLR7 and TLR8 are endosomal pattern recognition receptors that have a crucial role in the detection of single-stranded RNA (ssRNA) fragments[21,22]. Detection of RNA fragments is essential to mount immune responses to viruses such as SARS-CoV-2, in which TLR7 deficiencies are life threatening[23].

Key advances in the past 4 years underscore the need to revisit this pathway in SLE. First, phenotypic analysis of patients with juvenile SLE who carry pathogenic variants in *TLR7* and *UNC93B1* suggests that overactive TLR7 signalling can cause almost the entire spectrum of SLE-related autoimmune clinical manifestations and laboratory findings[8–20]. Second, the delineation of a crucial signalling axis downstream of TLR7 that involves SLC15A4, TASL, IRF5 and IRF7 and is largely independent of NF-κB is reshaping understanding of disease pathogenesis[24–27]. Third, the discovery of endogenous natural RNA inhibitors of TLR7 and TLR8, which bind to a pocket that is frequently mutated in patients with SLE, suggests that blocking binding of small RNA fragments might be crucial to prevent autoimmunity[28]. Fourth, promising early clinical trial results from at least three oral TLR7 antagonists show favourable safety profiles, robust suppression of the type I interferon signature and encouraging early efficacy signals[29–31]. Collectively, these findings support selective TLR7 inhibition as a rational, targeted and potentially oral therapeutic approach that might complement or replace existing immunosuppressive regimens.

This Review synthesizes mechanistic insights from human genetics, animal models and the identification of physiological ligands and regulators, all of which build a compelling case for targeting TLR7 in SLE. We also highlight emerging clinical data from several early-phase trials of oral TLR7–TLR8 antagonists, a potentially promising new treatment for SLE. Although we briefly address how TLR7 dysregulation influences various immune-cell types, we do not explore its broader roles in antiviral immunity or immune tolerance, which have been comprehensively reviewed elsewhere[3,6,21,22].

TLR7 as an endosomal receptor for single-stranded RNA

TLR7 is a highly conserved innate sensor for ssRNA fragments expressed in many immune cells with phagocytic function, and most abundantly in plasmacytoid dendritic cells (pDCs) and some B cell subsets (Fig. 1a,b). Notably, TLR7 and its closely related homologue TLR8 (Fig. 1c,d) are both located in close proximity on chromosome X (Xp22.2)[32]. Structurally, TLR7 comprises an endosomal N-terminal ectodomain, a transmembrane helix and a cytosolic TIR domain[33] (Fig. 1a). The ectodomain is a curved structure, consisting of 26 leucine-rich repeat motifs, which are separated by a Z-loop between repeats 14 and 15. Upon activation, the Z-loop undergoes proteolytic cleavage enabling the formation of a homodimer that engages RNA degradation products via two structurally and functionally distinct ligand-binding sites[34,35].

Activating ligands

Two sites within TLR7 and TLR8 recognize different terminal degradation products of RNA[34–37] (Fig. 1a,c). Site 1 is a highly conserved region between TLR7 and TLR8. At this site, TLR7 accommodates purine nucleosides such as guanosine (a cofactor signal of viral RNA breakdown) and 2′,3′-cGMP via a larger, more permissive pocket, with hydrogen bonding tailored to guanine[34,35,38]. TLR8 has a more constrained pocket optimized for pyrimidines, particularly uridines from actively degraded pathogen RNA[36,37]. Site 1 thus provides a molecular determinant for achieving drug selectivity: purine-mimetic compounds can preferentially target TLR7, whereas uridine-like scaffolds favour TLR8. In addition to natural ligands, site 1 also accommodates base

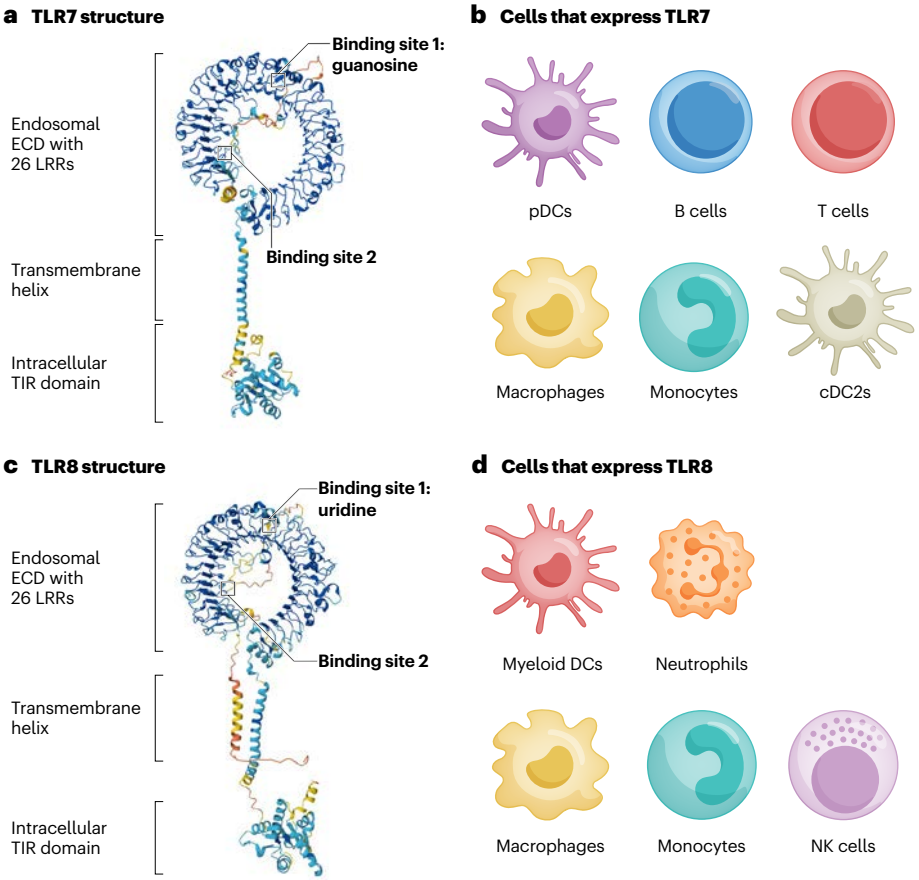


Fig. 1 | Structure and cellular expression of human TLR7 and TLR8. a, Predicted structure of human TLR7 (refs. 175,176) with key domains and ligand-binding sites[34,35]. **b**, Immune cells that express TLR7. **c**, Predicted structure of human TLR8 (refs. 175,176) with key domains and ligand binding sites. **d**, Immune cells that express TLR8. DCs, dendritic cells; cDC2, type 2 conventional dendritic cells; ECD, ectodomain; LRRs, leucine-rich repeats; NK, natural killer; pDCs, plasmacytoid dendritic cells; TIR, toll/interleukin-1 receptor.

analogues and imidazoquinolinone derivatives such as imiquimod (TLR7-specific) and resiquimod (TLR7 and TLR8), which are sufficient to induce receptor activation[34–37].

Site 2 supports the recognition of short uridine-rich motifs, as short as 2 or 3 bases[34], which facilitates synergistic enhancement of receptor activation through cooperative engagement with site 1 for both TLR7 and TLR8. Potent RNA ligands for TLR7 include motifs found in ssRNA40 derived from the exogenous retrovirus HIV[39], motifs from ssRNA9.2 synthetic RNA[40] and a similar GUUGUGU motif present within the *env* gene in a subset of human endogenous retroviruses (HERV-K)[41]. Notably, envelope-coding HERV-K loci are increased in the blood of individuals with SLE[42]. Multiple small self-RNAs such as those bound to Ro60 (ref. 43) and Xist (a female sex-specific long non-coding RNA that mediates X-chromosome inactivation) RNA fragments[44] can also function as TLR7 agonists at site 2.

The coordinated interaction of site 1 and site 2 amplifies the sensitivity of TLR7 and TLR8 to small RNA degradation fragments. The cleavage of ssRNA into these activating fragments is essential for receptor activation and is dependent on the activity of endonucleases RNase T2 and RNase 2 and the 5′–3′ phospholipase D (PLD) exonucleases 3 (PLD3) and 4 (PLD4)[45–50]. RNase T2 and PLD4 can produce endogenous 2′3′ cGMP and PLD4 also generates RNA fragments for pocket 2 (ref. 46). Loss of RNase T2 severely impairs TLR7- and TLR8-mediated immune activation[45,46]. The role of PLD4 seems more nuanced than initially thought, as described in the following sections.

Besides being activated by viral RNA, TLR7 and TLR8 can also bind self-RNAs taken up by phagocytosis or during the process of efferocytosis. These self-RNAs might originate from a variety of sources, including reactivated endogenous retroelements, mitochondrial stress, apoptotic cells, neutrophil extracellular traps (NETs) and cellular debris resulting from genomic instability or antimitotic drug exposure[3]. Self-RNAs were not thought to be immunostimulatory owing to nucleoside modifications in mammalian RNA[51]; however, research from the past decade indicates that TLR7 and TLR8 only bind to very short RNA fragments such as UUU and UG[34,36], which are unlikely to contain silencing RNA modifications. This finding suggests that self-derived nucleic acids represent a substantial risk for the development of autoimmune responses, particularly under conditions of impaired debris clearance.

Inhibitory ligands

To mitigate the potential for aberrant activation, endogenous inhibitory ligands compartmentalize and antagonize TLR7 and TLR8. Localization to late endosomes restricts their exposure to self-ligands under homeostatic conditions[52]. Endogenous natural antagonists are only beginning to be understood. Among these are short 2′-*O*-methylated (2′-OMe) guanosine RNA fragments that bind to a previously uncharacterized ‘site 3’ on TLR7 (Fig. 2) and TLR8[28]. These modified RNA fragments, which are presumably mostly derived from ribosomal RNA, function as endogenous antagonists, selectively dampening TLR7 and TLR8 signalling and preserving immune tolerance. Mutations

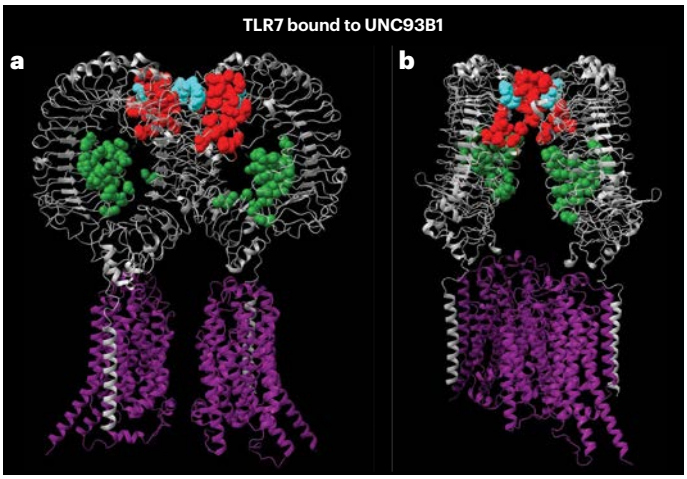


Fig. 2 | Crystal structure of UNC93B1 in complex with TLR7 homodimer. **a**,**b**, Two plane views of the crystal structure of UNC93B1 (purple) in complex with the TLR7 homodimer embedded in the late endosomal membrane; residues corresponding to binding site 1 are shown in red, site 2 in green and antagonistic sites in cyan. Generated using Protein Database (pdb_00007cyn) based on cryo-EM data from Ishida et al.[33].

that affect residues within inhibitory site 3 in TLR7 reduce the suppressive capacity of 2′-OMe guanosine fragments and have been identified in patients with SLE[28]. These findings underscore the importance of 2′-OMe guanosine motifs in maintaining immune homeostasis. Synthetic 2′-OMe guanosine-modified oligonucleotides with defined sequence specificity can suppress TLR7 and TLR8 activation in a sequence-specific manner[28], revealing a promising therapeutic avenue for the management of TLR7–TLR8-driven inflammatory and autoimmune conditions[53].

Thus, the dual-site recognition of TLR7 and TLR8 enables highly sensitive detection of RNA degradation products; however, this same sensitivity renders them vulnerable to misrecognition of self-RNA degradation products. A multilayered regulatory network (comprising enzymatic processing, endosomal sequestration and inhibitory RNA ligands that target this third site) has evolved to safeguard against inappropriate activation of TLR7 and TLR8. Disruption of this balance, be that through genetic mutation or excessive RNA degradation, contributes to SLE pathogenesis.

TLR7 overactivity and systemic lupus erythematosus

Twenty years ago, RNA-associated autoantigens were shown to activate self-reactive B cells through co-ligation of the B cell receptor and TLR7 (ref. 54) and gene duplication of the *Tlr7* locus was found to accelerate lupus-like disease in susceptible mice[55,56]. In these mice, the segment of the X chromosome containing the *Tlr7* locus is translocated to the Y chromosome (referred to as the Y-linked autoimmune accelerator (*Yaa*) allele), which doubles TLR7 expression[55,56]. This discovery was followed by the identification of distinct, antagonistic roles for TLR7 and TLR9 in lupus-prone mouse models, in which TLR7 promoted disease and TLR9 was protective[54].

Several studies report associations between human *TLR7* genetic variation and SLE. Increased *TLR7* copy number was associated with childhood-onset SLE in a case–control study conducted in Mexico, particularly among male patients[57]. Using a candidate gene approach, the SNP rs3853839 in the *TLR7* 3′ untranslated region was associated with SLE in East Asian populations, with a stronger effect observed in male patients[58]. In a case–control study in Japanese women, additional associations between SLE and *TLR7* SNPs located in both the 3′ untranslated region and intron 2 were reported[59]. In 2018, enhanced TLR7 signalling was observed in B cells from individuals with SLE, suggesting that TLR7 has a role in driving the formation of pathogenic B cells[6].

TLR7 overactivity as a direct cause of human SLE was first reported in 2022, upon the identification of individuals with SLE carrying GOF variants in *TLR7* (ref. 8). Pathogenicity was confirmed by introducing the de novo orthologue variant (Y264H) in *TLR7* identified in a patient with SLE into mice. These mice (termed *kika* mice) subsequently developed lupus-like disease[8]. Since then, multiple individuals with systemic autoimmunity and pathogenic variants in *TLR7* and *UNC93B1* have been reported[8–20].

Besides genetic variation per se, *TLR7* X chromosome dosage is emerging as an important contributor to SLE and is thought to underpin much of the biological sex bias that occurs in SLE[60,61]. Total or partial escape from X-inactivation enables biallelic *TLR7* expression in immune cells of women and individuals with an extra X chromosome[60]. Furthermore, Xist can act as a TLR7 ligand[44] and, when part of a large ribonucleoprotein (RNP) complex, functions as an autoantigen that promotes SLE and other female sex-biased autoimmunity[44,62].

As well as being a key driver of type I interferon production, *TLR7* is an interferon-stimulated gene[63,64]. Therefore, TLR7 expression can be increased within an inflammatory milieu, functioning as a positive feedback loop that enables breach of B cell tolerance during other inflammatory insults such as viral infections.

TLR7-expressing cells in systemic lupus erythematosus

In systemic autoimmunity, multiple immune cells are involved in disease pathogenesis: B cells, T cells and innate cells. TLR7 is expressed by all these cells, and has several roles in immune dysregulation.

TLR7 and TLR8 dysregulation of innate immunity

TLR7 can alter key innate immune cells, most prominently pDCs (which are potent producers of type I interferon[65]), monocytes and macrophages[66,67]. Release of NETs and oxidized mitochondria by neutrophils, and excess or exposed nucleic acids derived from apoptotic cells, are thought to provide ligands for TLR7, TLR8 and TLR9 in B cells, pDCs and myeloid cells[3,68].

RNP-containing immune complexes, which form as a result of TLR7-mediated breach of B cell tolerance, can be taken up by pDCs and myeloid cells that express Fc gamma receptors. Within the endocytic compartment, digested RNA fragments from RNP complexes can further activate TLR7, promoting the production of type I interferon and triggering the feedforward loop that fuels autoimmunity[69–73]. Unlike TLR7, TLR8 is expressed in neither B cells nor pDCs, but is expressed highly in neutrophils, myeloid DCs and natural killer cells (Fig. 1b,d). Both receptors are expressed in monocytes and macrophages where they initiate production of pro-inflammatory cytokines including TNF, IL-6, IL-12p70 and IFNγ. TLR8 can promote NETosis and reactive oxygen species production[73–75]. The differential expression of TLR7 and TLR8 directly impacts their respective inflammatory programmes, with IFNα and TNF often used as canonical markers for TLR7 and TLR8, respectively[32].

TLR7 dysregulation of adaptive immunity

TLR7 is also expressed by B cells, effector T cells and regulatory T cells. B cells are key to disease development, as demonstrated by the elimination of autoimmunity when B cells are depleted using anti-CD19 chimeric antigen receptor (CAR) T cells[76]. TLR7 activation begins in immature B cell stages, wherein it promotes the survival of autoreactive transitional B cells that have bound self-antigen and would otherwise undergo deletion[8,77]. This signalling is also essential for the differentiation of B cells into pathogenic, self-reactive CD11c$^+$ age-associated B cells (ABCs), which function as precursors to autoantibody-producing cells[69,78,79]. In humans, ABCs are referred to as double negative 2 (DN2) B cells, owing to the absence of IgD and CD27 expression[6,7]. Notably, in mixed (50:50) bone marrow chimeric mice, only ABCs and plasma cells that carry the *Tlr7* GOF variant accumulate[8], indicating that TLR7 overactivity in B cells is required for the breach in tolerance.

The accumulation of effector T cells in SLE is primarily driven by extrinsic factors, including antigen presentation by ABCs[80]. Evidence from mixed bone marrow chimeric mice suggests that T cell-intrinsic factors might contribute to the accumulation of extrafollicular T cells (CD4$^+$ PD-1^{hi}, CXCR5^{lo} and CXCR3^{hi})[8]. CD4$^+$ T cells do express TLR7, albeit at lower levels than B cells and pDCs. Notably, TLR7 ligands can induce IFNγ production by mouse CD4$^+$ T cells during infection, even in the absence of TCR stimulation[81,82]. In humans, TLR7 (but not TLR8) engagement in CD4$^+$ T cells triggers a considerable increase in intracellular calcium but prevents cell-cycle entry, and decreases production of IL-2 and IFNγ upon subsequent CD3 and CD28 costimulation[82]. Direct stimulation of memory CD4$^+$ T cells with the TLR7 and TLR8 ligand R848 promotes proliferation and also enhances IFNγ production[83].

The possible opposing role of TLR9

Evidence indicates that TLR9 deficiency enhances disease in mouse models of lupus[54,84,85], possibly partly owing to competition for trafficking by UNC93B1 (ref. 86). One exception is in the TLR9-dependent lupus-like disease in BALB/c mice, which have a loss-of-function (LOF) mutation in *Pld4*[87]. Experimental data suggest qualitative differences in signalling downstream of the TIR domains of TLR7 and TLR9 and a 'scaffold' role of TLR9 in TLR7 regulation[84,88,89]. Human data validating the role of TLR9 in SLE are still lacking.

Systemic lupus erythematosus-causing genetic defects in the TLR7 pathway

Most spontaneous and genetically engineered mouse models of lupus are dependent on TLR7 signalling, underscoring its essential role in disease pathogenesis[90]. Dysregulated TLR7 signalling is also probably important in polygenic human SLE, as many common genetic drivers, including most of the strongest SLE genome-wide association study loci, occur in genes that regulate TLR7 and/or MyD88 signalling, including *SLC15A4*, *IRAK1*, *TNFAIP3*, *IRF5*, *IRF7*, *IRF8*, *IKZF1*, *PLD4*, *STAT4*, *DNASE1L3*, *BANK1*, *BLK*, *TYK2* and *TNIP1* (refs. 25,91–96). Furthermore, the best validated causes of monogenic SLE also seem to converge on enhanced TLR7 pathway activation and are summarized in this section.

Upstream of TLR7

Defects in the clearance of apoptotic cells and the consequent exposure to self-nucleic acids can lead to increased activation of TLR7, triggering a breakdown in adaptive immune tolerance against self-antigens, as seen in SLE (Fig. 3).

Complement. LOF variants in early classical complement components (C1q, C1r, C1s and C4) prevent efficient opsonization of nucleic acid-decorated apoptotic cell debris[97] and immune complexes[98,99] (Fig. 3). Indeed, complete deficiencies in these proteins have long been noted to be a cause of monogenic SLE and other complement components have also been implicated in SLE[98,99].

PLD4 exonuclease. Biallelic genetic variants in the 5′ exonuclease, *PLD4*, caused SLE in five probands[95]. PLD4 localizes to endolysosomes and can cleave ssRNA and ssDNA[46,50]. Although PLD4 is reportedly essential for generation of site 2 TLR7 ligands in cell lines[46], mice that lack PLD3 and PLD4 show accumulation of small ssRNAs, which in turn lead to heightened TLR7 activation and inflammation that can be rescued by *Unc93b1* deficiency[49]. A possible explanation for this paradox is that PLD4, as an exonuclease, might be directly involved in the production of 5′ end 2′-OMe guanosine RNA fragments that effectively inhibit TLR7 basal function. Loss of PLD4 could result in loss of 5′ end 2′-OMe guanosine residues, increasing receptor activation by self-RNA fragments[28].

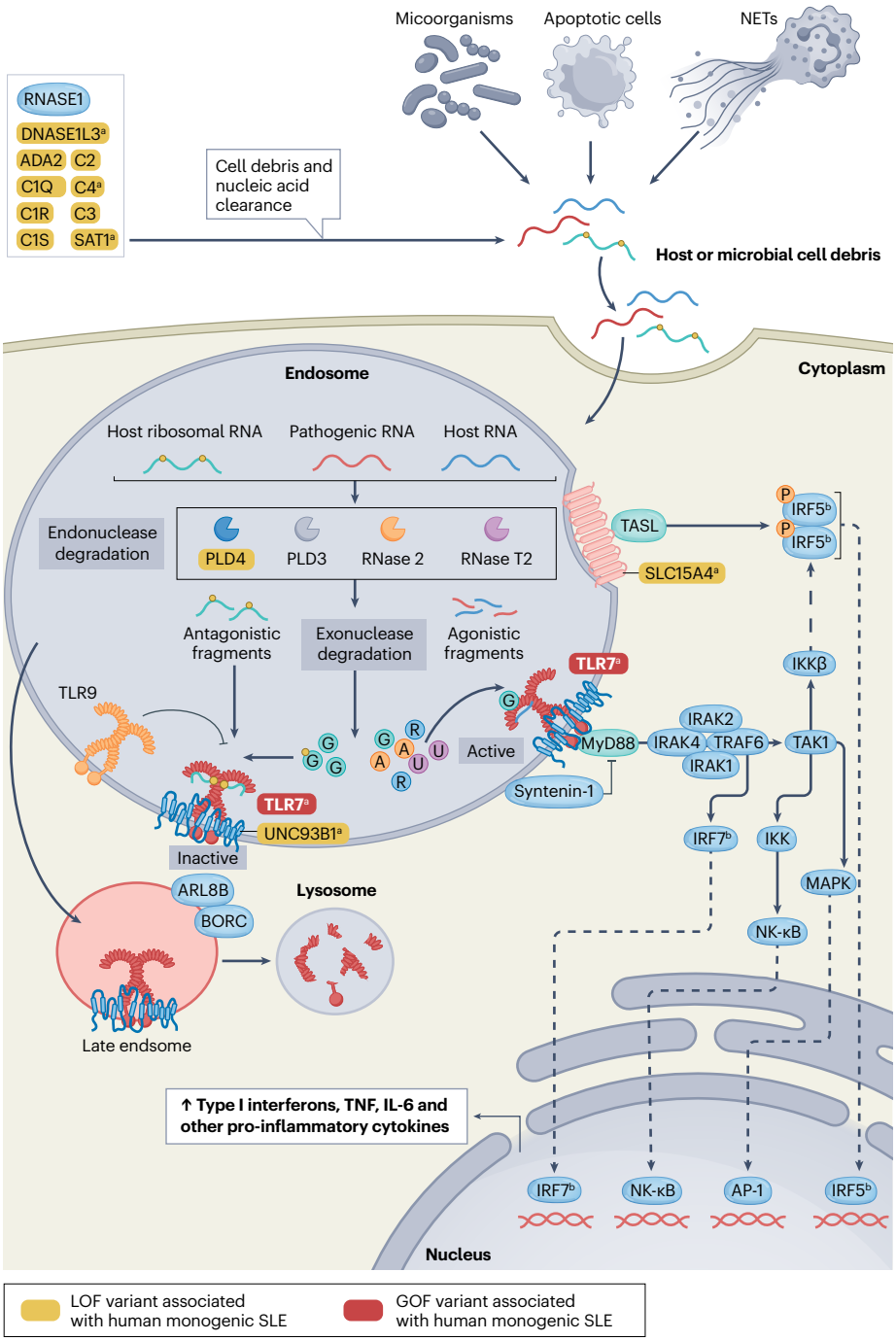
DNases. Defects of extracellular and endosomal exonucleases are also clearly linked to autoimmunity. DNASE1L3 degrades chromatin and dsDNA in apoptotic microparticles, and DNase1 is involved in clearance of DNA from NETs[100] (Fig. 3). Evidence indicates that autosomal-recessive *DNASE1L3* deficiency causes monogenic SLE and neutralizing autoantibodies against DNASE1L3 are found in patients with SLE[101–103]. Autoimmunity in *Dnase1l3*-deficient mice is, at least in part, TLR7 dependent[104]. Notably, beyond 2′-OMe guanosine RNAs, TLR7 can also be antagonized by short thymine-rich DNA fragments[105,106], which is directly dependent on inhibitory site 3 (ref. 28). Thus, similar to PLD4, loss of DNASE1L3 might reduce the relative abundance of TLR7 antagonistic DNA fragments, resulting in enhanced signalling. The evidence for *DNASE1* deficiency contributing to SLE is weaker, with only one report thus far[107].

Variants in *TLR7* and *UNC93B1* that cause systemic lupus erythematosus

GOF variants in *TLR7* and *UNC93B1* are increasingly being reported as key drivers of monogenic SLE (Table 1 and Fig. 4). Although SLE is typically polygenic (a vast number of associated genes have been identified in genome-wide association studies), monogenic SLE provides insights into common mechanisms and key biological pathways that underpin the spectrum of disease, which can lead to the discovery of novel drug targets.

Despite sharing many common features with TLR7, TLR8 has a divergent role in innate immunity, mainly because these receptors are expressed on different cell types. Reported *TLR8* GOF variants are associated with a distinct phenotype that includes prominent immunodeficiency mainly owing to neutropenia, autoinflammation and lymphoproliferative components not typically observed in *TLR7* GOF variants (Table 1). However, when interpreting clinical data it is important to consider that most reported variants are identified in people with severe childhood-onset autoimmune and inflammatory disorders, which causes an inherent selection bias against alternative disease phenotypes caused by rare variants of these proteins.

TLR7 gain-of-function mutations. Several novel *TLR7* GOF variants (*R28G*, *Y264H*, *P267L*, *P435S*, *F506S*, *F507L*, *F507S*, *L528I*, *G818V* and *L840R*) have been identified as causes of severe, childhood-onset



monogenic SLE and/or immune thrombocytopenia (Table 1 and Fig. 4). All observed variants are monoallelic, five are confirmed de novo and one is mosaic, underscoring the pathogenicity of these variants. All arise from single nucleotide substitutions and all but one are located within the endosomal ectodomain of TLR7, which is involved in ligand binding and dimerization (Table 1 and Fig. 4).

Two variants, *Y264H* and *P267L*, change residues within site 1 that interact with the guanosine ligand (Fig. 4d). The *Y264H* variant increases the affinity for this ligand and causes TLR7 activation, lowering the requirement for uridines binding to site 2 (ref. 8).

Four variants identified in people with SLE (*P435S*, *F506S*, *F507L* and *F507S*) are localized on site 3 (which binds to 2′-OMe guanosine), close to the Z-loop (Fig. 4d) and exert an inhibitory effect on guanosine binding on site 1, and thus on TLR7 activation[28]. Notably, recombinant TLR7 mutant proteins F506L, F507L, F507S and P435S have a decreased affinity for 2′-OMe guanosine RNAs in vitro, without influencing binding of R848 to site 1 (ref. 28). *F507S* had the most impaired affinity for 2′-OMe guanosine RNAs and also decreases the inhibitory activity of endogenous 2′-OMe guanosine RNA fragments in cell-based assays[28] (Fig. 3). Thus, limiting the activity of endogenous

Fig. 3 | Human TLR7 signalling in endosomes. Upstream of Toll-like receptor 7 (TLR7), single-stranded RNA (ssRNA) ligands are produced by microorganisms, or through cellular apoptosis and formation of neutrophil extracellular traps (NETs). Extracellular enzymes and complement have an important role in the clearance of cell debris to minimize exposure to endogenous ligands; monogenic defects in these mechanisms have been shown to cause systemic lupus erythematosus (SLE) and other forms of systemic autoimmunity. Microbial ligands and excess endogenous ligands are endocytosed by pDCs and B cells. TLR7 is usually confined to late endosomes and is activated by binding to exogenous or endogenous ssRNA. TLR7 activation is homeostatically regulated by its endoplasmic reticulum-to-endosome chaperone protein UNC93B1 via multiple mechanisms, including recruitment of syntenin-1, to dampen signalling or interaction with the BORC complex to enable degradative sorting within lysosomes. TLR9 also has a key role in the regulation of both TLR7 activation and signalling; however, the mechanisms are not yet well defined. Downstream of TLR7, two distinct pathways are activated upon ligand binding and homodimerization. First, TLR7 interacts with TIRAP to recruit MyD88, leading to formation of the 'myddosome' through recruitment of IRAK4, then IRAK1 and IRAK2. This recruitment results in activation of the ubiquitin ligase TRAF6, which activates TAK1 as well as IRF7. TAK1 binds with TAB1–3 as part of the TAK1 complex, which initiates the activation of both the MAPK pathway, leading to AP-1 activation, and the IKK pathway, leading to NF-κB activation. Second, SLC15A4 recruits the adaptor protein TASL, which facilitates activation of IRF5. Together, the transcription factors IRF5, IRF7, AP-1 and NF-κβ initiate a strongly pro-inflammatory cytokine programme that is crucial to antiviral immunity and is also implicated in autoinflammatory and autoimmune disorders including SLE. Loss-of-function (LOF) variants associated with human monogenic SLE (orange); gain-of-function (GOF) variants associated with human monogenic SLE (red). Variants in *UNC93B1* effectively cause a gain of TLR7 function, even though mechanistically they may impair the ability of UNC93B1 to degrade TLR7 (and thus coloured orange). [a]Causes of monogenic SLE confirmed in humans or mouse models. [b]Associated with human SLE in two or more genome-wide association studies[7]. The short-dashed lines indicate translocation to the nucleus and the long-dashed line indicates that this process is currently supported by limited evidence. BORC, BLOC1-related complex; PLD, phospholipase D.

TLR7 antagonists has emerged as a plausible mechanism by which these four variants in site 3 might lead to autoimmunity[28].

Regarding the clinical presentation of TLR7 GOF variants, immune thrombocytopenia — which is often refractory — is frequently the first clinical manifestation; neuroinflammation is also present in the majority of patients. Renal pathology and cardiovascular disease are also common features, and arthralgia, thyroid disease, and mucocutaneous manifestations have also been reported (Table 1 and Fig. 5). Hypocomplementaemia, anaemia and autoantibodies characteristic of SLE (ANA and anti-dsDNA) occur in most patients. Evidence of increased type I interferon activity is common, and central nervous system calcifications reminiscent of the interferonopathy seen in Aicardi–Goutières syndrome have been reported in one proband[18]. Notably, a girl who developed disease at 1 month of age and had a de novo *TLR7*^{F507S} allele is the only individual with reported hypertriglyceridaemia[19]. A 9-year-old female patient with a maternally inherited variant allele, *TLR7*^{F507S}, has a predominant neuromyelitis optica phenotype with antibodies against AQP-4, whereas her mother has SLE[8]. An 8-month-old female patient with a de novo variant, *TLR7*^{G818V}, had immune thrombocytopenia and anti-GPIIB and anti-GBIIIA autoantibodies; the patient had a bone marrow transplantation[9]. Thus, collectively, those individuals with reported monogenic SLE associated with *TLR7* GOF variants present with almost every clinical manifestation associated with SLE. These findings support the idea that a single dysregulated molecular pathway — increased TLR7 signalling — might underlie the full spectrum of SLE, whereby modifier genes, *HLA* alleles or specific autoantibody profiles underlie clinical heterogeneity, rather than multiple distinct pathways driving variation between patients.

***TLR8* gain-of-function variants.** Despite similarities between TLR7 and TLR8 in terms of structure and ligand binding, differences in cellular expression[108,109] (Fig. 1b,d) lead to some key distinctions in the phenotypic spectrum of *TLR8* GOF variants reported thus far (*P432L*, *P432Q*, *P432R*, *V434L*, *F494L*, *G572D* and *G572V*) (Table 1 and Fig. 4b). Notably, the *P432* and *F494* variants in *TLR8* correspond to residues P435 and F506 in human TLR7 and therefore influence the inhibitory function of site 3 (ref. 28). Accordingly, functional analyses of the *F494L* variant in vitro showed decreased inhibitory activity of 2′-OMe guanosine RNAs on TLR8 (ref. 28) and cells that express the *P432L* variant could not be inhibited by the small molecule inhibitor Cu-CPT9a, which binds to site 3 (ref. 110). The striking similarities between the functional effects of site 3 variants in TLR7 and TLR8 probably underline the emerging essential role that the natural antagonism of these receptors has in preventing their aberrant engagement.

Notably, the patients that have these variants come from a small number of published reports, therefore a high risk of ascertainment bias exists in this evidence base. Nevertheless, it is becoming clear that patients with *TLR8* GOF variants generally do not present with SLE. For most people with these variants, immunodeficiency with recurrent or invasive bacterial and fungal infections secondary to neutropenia is the primary presenting feature[110–113] (Table 1). Lymphoproliferation that results in hepatosplenomegaly, lymphadenopathy, hypogammaglobulinaemia and multiple cytopenias in the context of bone marrow failure are usually detected after the initial presentation.

Interestingly, most probands are hemizygous males, with five showing monoallelic mosaicism (8–26%) and two with de novo germline mutations[110,112], suggesting strong selection against homozygosity and germline transmission owing to phenotypic severity. Notably, in one of the published reports, the two probands are monozygotic twins with a maternally inherited variant (*G572V*) whose presentation is more SLE-like, with severe autoimmune haemolysis, fever, arthritis and neuroinflammation, and whose mother has a diagnosis of antiphospholipid syndrome[111], this inheritance pattern represents a clinical outlier. Functional assessment of this variant suggests impaired TLR8 stability and cross-reactivity to TLR7 ligands, resulting in activation of pro-inflammatory pathways usually associated with TLR7. Potential mechanisms of TLR8 and TLR7 cross-regulation warrant further exploration.

***UNC93B1* variants.** Multiple *UNC93B1* missense variants associated with SLE have been identified that function by enhancing TLR7 and TLR8 activity; occasionally variant-specific bias towards one receptor over the other can occur[114] (Table 1). UNC93B1 is a 12-pass transmembrane chaperone that is crucial for the endosomal trafficking and stability of TLR3, TLR7, TLR8 and TLR9 (ref. 33) (Fig. 2). The selective effects of UNC93B1 on enhancing TLR7 and TLR8 signalling in SLE but not TLR9 might be caused by the fact that TLR9 is released from UNC93B1 in endosomes, whereas TLR7 and TLR8 remain associated[115]. In addition to its role in endoplasmic reticulum-to-endosome transport, UNC93B1 also contributes to homeostatic regulation of TLR7 activation through

Table 1 | Autoimmunity-causing gene variants in *TLR7*, *TLR8* (immunodeficiency with or without autoimmunity) and *UNC93B1*

Variant details			Patient information and clinical features					Laboratory findings			Refs.
Variant	Type of variant	Inheritance	Asympto-matic carriers	Sex	Age of onset	Principal diagnoses	Key clinical features	Autoantibodies	Type I interferon activity	C3, C4	
TLR7 Xp22.2											
R28G	GOF	Heterozygous, unknown	No	Female	18 years	SLE	Fever, photosensitive rash, mucocutaneous ulcers, arthralgia	ANA, anti-dsDNA, anti-RNP, anti-SSA/Ro	Unknown	Unknown	8
Y264H	GOF	Heterozygous de novo	Unknown	Female	7 years	SLE	ITP, arthralgia, neuroinflammation, hemichorea, CNS microbleeds, renal hypertension, lupus nephritis, mitral valve disease	ANA, anti-dsDNA	High	Low	8
P267L	GOF	Heterozygous de novo	Unknown	Female	13 months	Anti-NMDAR encephalitis, SLE	AIHA, neuroinflammation serositis	ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-β2GP1	High	Low	15
P435S	GOF	Heterozygous de novo	Unknown	Female	2 years	SLE	ITP, anaemia, neuroinflammation, pyramidal syndrome, lupus nephritis, chilblain rash, cryoglobulinaemia	ANA, anti-interferon, anti-C1q	High	Low	16
F506S	GOF	Hemizygous mosaic (36%)	Unknown	Male	15 days	SLE	ITP, anaemia, rashes, proteinuria, intestinal vasculitis, myocardial damage, thyroid dysfunction, neuroinflammation, intracranial calcifications	ANA, ANCA, anti-lupus anticoagulant, anti-cardiolipin	High	Low	18
F507L	GOF	Maternal heterozygous, unknown	No	2 female	9 years; 25 years	NMO, SLE	Optic neuritis, transverse myelitis, hemiplegic cerebral palsy	ANA, anti-AQP4	Unknown	Unknown	8
F507S	GOF	Maternal heterozygous, unknown	No	2 female	4 years; 12 years	SLE, APS	ITP, neuroinflammation, arterial thrombosis, lupus nephritis	ANA, anti-dsDNA	High	Low	11
	GOF	Maternal hemizygous	No	Male	1 day	Unspecified	Neuroinflammation	None	High	Low	11
	GOF	Heterozygous de novo	No	Female	1 month	SLE	ITP, anaemia, neuroinflammation, hypertriglyceridaemia	ANA	Unknown	Low	19
L528I	GOF	Heterozygous de novo	Unknown	Female	1 year	Evans-like and SLE-like syndrome	ITP, AIHA, neuroinflammation	Anti-SSA/Ro	Unknown	Unknown	11
G818V	GOF	Heterozygous de novo	Unknown	Female	8 months	ITP[a]	ITP	Anti-GPIIb, anti-GPIIIa	High	Normal	9
L840R	GOF	Maternal hemizygous	Mother (heterozygous)	Male	3 years	SLE	ITP, anaemia, proteinuria, thyroid dysfunction	ANA, Anti-dsDNA, Anti-platelet, anti-lupus anticoagulant, anti-TPO	Unknown	Low	20
TLR8 Xp22.2											
P432L	GOF	Hemizygous mosaic (12–26%)	Unknown	5 male	0–16 years	Immunodeficiency, autoinflammation, ITP T1DM	Neutropenia, hypogamma-globulinaemia, anaemia, thrombocytopenia, lymphoproliferation, mucocutaneous ulcers, colitis	ANCA, (1 of 5 patients) and anti-La (1 of 5 patients)A	Normal or moderately high	Unknown	110,112
	GOF	Hemizygous de novo	Unknown	Female	5 months	Pure red-cell aplasia, immunodeficiency	Neutropenia, hypogamma-globulinaemia, anaemia, thrombocytopenia, lymphoproliferation	None	Unknown	Unknown	110

Table 1 (continued) | Autoimmunity-causing gene variants in *TLR7*, *TLR8* (immunodeficiency with or without autoimmunity) and *UNC93B1*

Variant details			Patient information and clinical features					Laboratory findings			Refs.
Variant	Type of variant	Inheritance	Asympto-matic carriers	Sex	Age of onset	Principal diagnoses	Key clinical features	Autoantibodies	Type I interferon activity	C3, C4	
TLR8 Xp22.2 (continued)											
P432Q	GOF	Hemizygous mosaic (7%)	Unknown	Male	9 years	Immunodeficiency, autoinflammation	Neutropenia, anaemia, thrombocytopenia, lymphoproliferation, arthritis, mucocutaneous ulcers	None	Unknown	Unknown	110
P432R	GOF	Hemizygous mosaic (15%)	Unknown	Male	28 years	Immunodeficiency, autoinflammation	Neutropenia, anaemia, thrombocytopenia, lymphoproliferation	None	Unknown	Unknown	110
V434L	Mild GOF	Maternal hemizygous	Mother (heterozygous)	1 male; 1 female	4–45 years	Non-haemolytic anaemia, West syndrome, pure red-cell aplasia	Anaemia	Unknown	Unknown	Unknown	113
F494L	GOF	Hemizygous mosaic (8%)	Unknown	Male	7 years	Immunodeficiency	Neutropenia, hypogamma-globulinaemia, bone marrow failure, lymphoproliferation	Unknown	High	Unknown	112
G572D	GOF	Hemizygous de novo	Unknown	Male	9 months	Immunodeficiency	Neutropenia, hypogamma-globulinaemia, bone marrow failure, lymphoproliferation	Unknown	High	Unknown	112
G572V	Dysregu-lation of TLR7 and TLR8	Maternal hemizygous	No	2 male	7 months; 1.5 years	AIHA, immuno-deficiency, autoinflammation	AIHA, neuroinflammation, fever, arthritis, enteritis, hypogammaglobulinaemia, lymphoproliferation	Unknown	High	Unknown	111
	Dysregu-lation of TLR7 and TLR8	Heterozygous, unknown	No	Female	Unknown	APS	Thrombosis, arthritis	Unknown	High	Unknown	111
UNC93B1 11q13.2											
E49dup (6xE)	GOF (TLR7 and TLR8)	Paternal heterozygous	Father (heterozygous)	Female	7 years	SLE	Dermatitis, thyroiditis, lymphoproliferation	ANA	High	Low	12
E92G	GOF (TLR7 and TLR8)	Maternal or paternal homozygous	Parents (heterozygous)	1 male; 1 female	4 months; 2 years	SLE	AIHA, ITP, multiple rashes, panniculitis, lymphoproliferation, nephritis PRES and hypertensive crisis, multi-organ inflammation	ANA, anti-dsDNA, anti-SSA/Ro, anti-RNP, anti-GPIIb/GPIIIa, anti-cardiolipin, anti-β2GP1	High	Low	12
T93I	GOF (TLR7 and TLR8)	Paternal heterozygous, unknown	No	3 female; 1 male	3–12 months	Tumid lupus	Photosensitive rash, chronic cutaneous lupus	ANA	Unknown	Low or normal	117
R95L	GOF (TLR7 and TLR8)	Maternal or paternal homozygous	Parents (heterozygous)	Female	Unknown	SLE	Fever, photosensitive rash, cutaneous lupus	ANA, anti-dsDNA, anti-Sm, anti-RNP	High	Low	14

Table 1 (continued) | Autoimmunity-causing gene variants in *TLR7*, *TLR8* (immunodeficiency with or without autoimmunity) and *UNC93B1*

Variant details			Patient information and clinical features					Laboratory findings			Refs.
Variant	Type of variant	Inheritance	Asympto-matic carriers	Sex	Age of onset	Principal diagnoses	Key clinical features	Autoantibodies	Type I interferon activity	C3, C4	
UNC93B1 11q13.2											
V117L	GOF (TLR7 and TLR8)	Maternal or paternal heterozygous, unknown	No	7 female	8–26 years	SLE	Rash and alopecia, mucocutaneous ulcers, arthritis, multi-organ inflammation	ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-SSA/Ro	High	Low	13
T314A	GOF (TLR7 more than TLR8)	Heterozygous, unknown	No	Female	8 years	SLE	Fever, mucocutaneous ulcers, multi-organ inflammation	ANA, anti-dsDNA, anti-SSA/Ro	Unknown	Low	13
I317M	GOF (TLR7 more than TLR8)	Homozygous, unknown	No	Female	1 year	SLE	AIHA	ANA, anti-dsDNA	Unknown	Unknown	10
G325C	GOF (TLR7 more than TLR8)	Maternal heterozygous	Mother (heterozygous)	Female	5 years	SLE	AIHA, pulmonary involvement, cutaneous lupus	ANA, anti-RNP	High	Unknown	10
wL330R	GOF TLR8	Heterozygous, unknown	No	Male	< 1 year	Chilblain lupus	Chilblain rash	None	High	Unknown	10
R336L	GOF (TLR7 and TLR8)	Maternal or paternal heterozygous, unknown	No	2 male	18 months; 5 years	SLE, APS	Multiple rashes, lymphoproliferation, nephritis, arthralgia	ANA, anti-dsDNA, anti-β2GP1, anti-cardiolipin	High	Low	17
R336C	GOF TLR7 and TLR8	Heterozygous de novo	Unknown	Female	11 months	JIA, cutaneous lupus	Photosensitive rash, tumid and chilblain rashes, polyarthritis, neuroinflammation	None	High	Unknown	117
R336H	Unknown	Maternal or paternal heterozygous, unknown	No	2 female, 2 male	1–7 years	JIA, RA, ITP	Polyarthritis, ITP, interstitial pneumonia	ANA, RF, anti-CCP	High	Low	118
R466S	GOF TLR8	Heterozygous, unknown	No	Female	<1 year	Chilblain lupus	Chilblain rash, mucocutaneous ulcers	None	High	Unknown	10
D551N	GOF TLR7 and TLR8	Heterozygous, unknown	No	Female	16 years	SLE	Cutaneous lupus, polyarthritis, ITP	ANA, anti- dsDNA	Unknown	Unknown	118
R525P	GOF TLR8	Maternal or paternal heterozygous, unknown	No	2 female, 2 male	6–59 years	Chilblain lupus	Chilblain rash, acrocyanosis, sclerodactyly, polyarthralgia	ANA, RF, anti-SSA/Ro	High	Normal	10,174

[a]These children underwent 10/10 HLA-matched unrelated donor haematopoietic stem-cell transplant owing to refractory ITP. AIHA, autoimmune haemolytic anaemia; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; APS, antiphospholipid syndrome; CNS, central nervous system; dsDNA, double-stranded DNA; ITP, immune thrombocytopenic purpura; JIA, juvenile idiopathic arthritis; NMDAR, NMDA receptor; NMO, neuromyelitis optica; PRES, posterior reversible encephalopathy syndrome; RA, rheumatoid arthritis; RF, rheumatoid factor; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; SSA, Sjögren's-syndrome-related antigen A; T1DM, type 1 diabetes mellitus; TPO, thyroid peroxidase.

at least two mechanisms: first, the recruitment of syntenin-1, which dampens TLR7 signalling following activation[116] and second, interaction with the small GTPase ARL8B[12]. BLOC1-related complex (BORC), a key regulator of lysosomes, recruits ARL8B as an adaptor protein and then engages downstream effectors to enable lysosomal transport and fusion. UNC93B1 engagement with ARL8B facilitates BORC-dependent recruitment and fusion of lysosomes with TLR7-containing endosomes to enable degradative sorting of TLR7 (ref. 12). Additionally, a strong association between the ectodomain of TLR7 and UNC93B1 has been proposed that might limit the conformational flexibility of the TLR7 ectodomain and thus its capacity for ligand binding and dimerization[117].

Fifteen reported *UNC93B1* variants have been implicated in monogenic systemic autoimmunity[10,12–14,17,117,118] (Table 1 and Fig. 4c). Seven of the observed variants arise from amino acid substitutions within the large cytosolic loop between the 6th and 7th transmembrane helices, of which three are variants of *R336* alone[17,117,118]. One variant arises from a duplication (E49dup, causing 6xE)[12] positioned in the cytosolic N-terminal portion. Most of the identified *UNC93B1* variants are associated with enhanced TLR7 signalling in response to stimulation with synthetic ligands. This enhanced signalling is probably a result of structural changes to key binding sites on UNC93B1 that destabilize its complex with TLR7 and reduce its ability to regulate activation (which seems to be independent of the syntenin-1 regulatory mechanism)[20]. For example, the *E49dup* variant can disrupt UNC93B1 interaction with the BORC complex via ARL8B, a process that is crucial for degradative sorting of TLR7. This mutation was paternally inherited from a clinically unaffected man, suggesting that the autoimmune phenotype manifests only in the context of higher TLR7 gene dosage[12]. Indeed, three variants (*E92G*, *R95L* and *I317M*)[10,12,14] have been observed in homozygotes and only one variant (*R336C*)[117] is confirmed to be de novo, suggesting a lower penetrance and/or pathogenicity of this set of variants in comparison with direct *TLR7* GOF (Table 1).

Many of the identified *UNC93B1* variants also result in enhanced TLR8 signalling and consequently produce more mixed phenotypes than isolated *TLR7* or *TLR8* GOF variants[10]. The *UNC93B1* variants that have been tested for effects across different TLRs have shown very limited effect on TLR3 or TLR9 signalling, which demonstrates the diversity of function across the different structural domains of UNC93B1; for example, the *T93I* variant reduces the stability of the UNC93B1–TLR7 interaction without affecting UNC93B1–TLR3 interactions[117].

Autoimmune phenotypes associated with *UNC93B1* variants include SLE, and rare chronic cutaneous forms such as tumid and chilblain lupus, but almost all individuals show some form of skin involvement (such as rashes or alopecia) (Table 1). Many variants also cause joint involvement, including two variants occurring at the same position (*R336C* and *R336H*) that are linked with juvenile idiopathic arthritis

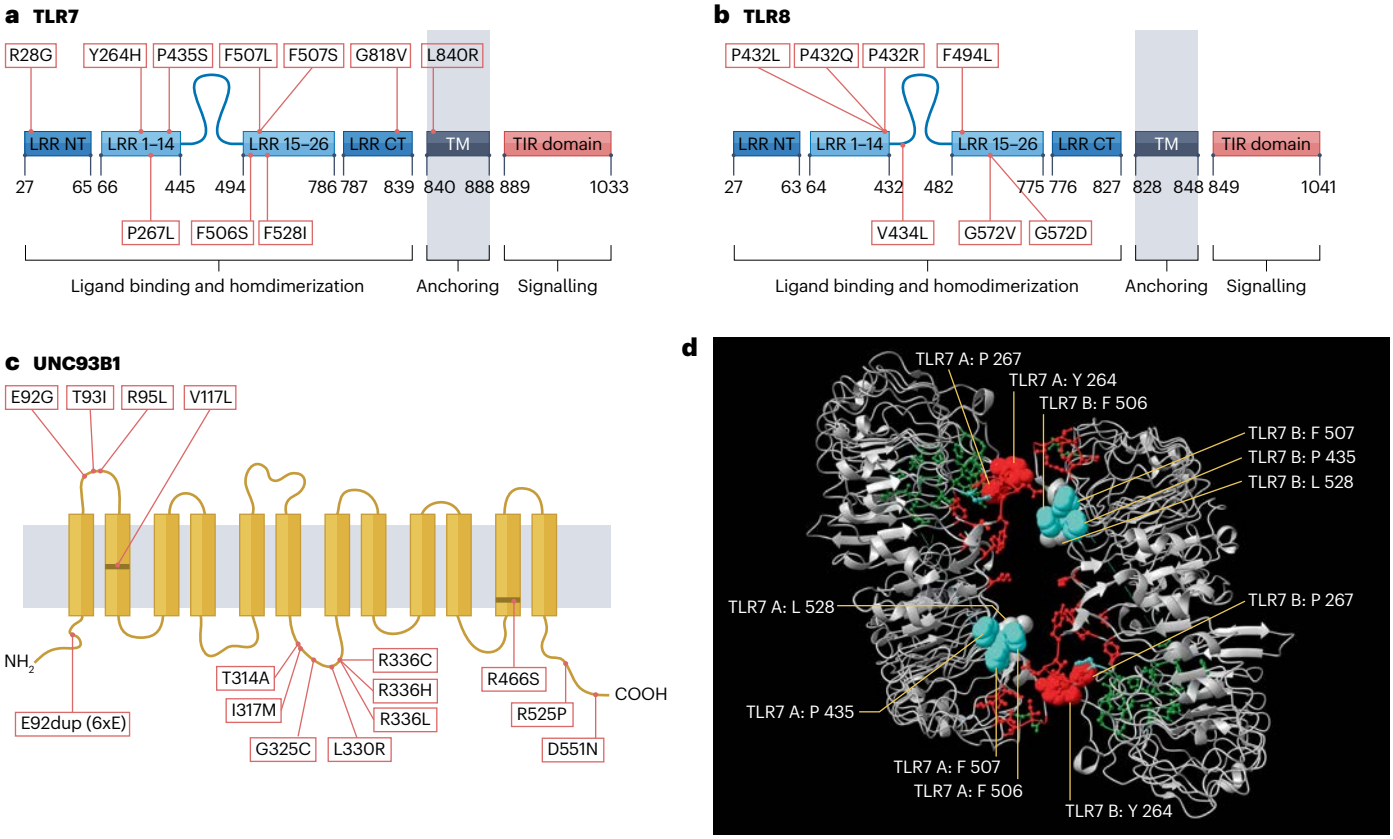


Fig. 4 | Reported pathogenic variants in *TLR7*, *TLR8* and *UNC93B1*. **a**–**c**, Reported gain-of-function variants in human *TLR7* (**a**), human *TLR8* (**b**) and *UNC93B1* (**c**) resulting in Toll-like receptor 7 (TLR7) and TLR8 gain-of-function. The resulting amino acid changes from these variants are marked as spheres on linearized protein domain structures (full details of each variant are provided in Table 1). **d**, Localization of site 1 and site 3 *TLR7* variants within the dimeric structure (PDB accession number for this crystal is 7CYN). Residues in site 1 are shown in red, residues in site 2 are shown in green and residues in the antagonistic site 3 are coloured in cyan. The spheres are the reported TLR7 mutations at sites 1 (red) and 3 (cyan).

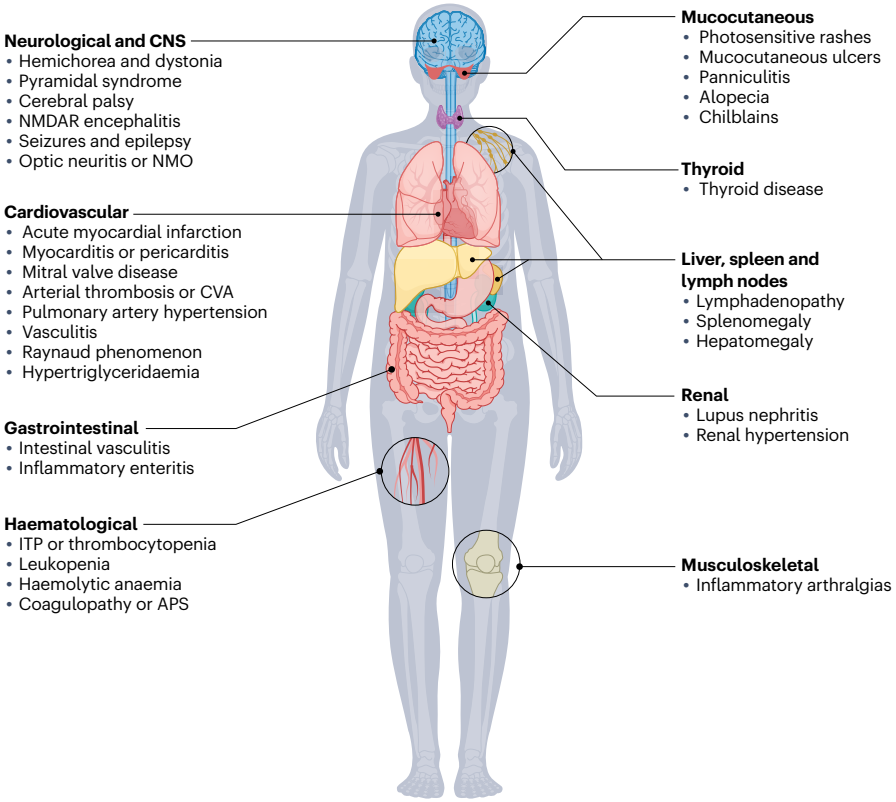


Fig. 5 | Clinical manifestations in patients with *TLR7* gain-of-function variants. Combined clinical manifestations of 14 patients carrying ten *TLR7* gain-of-function variants. Full details of variants and clinical manifestations are described in Table 1. APS, antiphospholipid syndrome; CNS, central nervous system; CVA, cerebrovascular accident; HTN, hypertension; ITP, immune thrombocytopenic purpura; NMDAR, NMDA receptor; NMO, neuromyelitis optica; TP, immune thrombocytopenic purpura.

and rheumatoid arthritis (RA) phenotypes[117,118]. Lymphoproliferation is prominent for at least three variants[12,17]. Strong lupus-associated autoantibody signatures and hypocomplementaemia occur in most variants; those without these features still show increased type I interferon activity, although quantification and reporting vary considerably across studies.

Downstream of TLR7

Upon activation and homodimerization, the cytosolic domain of TLR7 recruits the TIR adaptor protein (TIRAP), which facilitates recruitment and interaction with MyD88 (refs. 119,120). This signalling cascade is the primary downstream pathway of TLR7 and involves multiple adaptor proteins, protein kinases and transcription factors, which culminates in the expression of pro-inflammatory cytokines. MyD88 recruits IRAK proteins to form the 'myddosome': IRAK4 activation enables IRAK1 and IRAK2 auto-phosphorylation and recruitment of TRAF6 (an E3 ubiquitin ligase). TRAF6 facilitates the downstream non-degradative poly-ubiquitination of TGF-β-activated protein kinase 1 (TAK1), which forms a complex with its binding proteins TAB1–3, and also has a key role in activating IRF7 downstream of TLR7 and cytosolic nucleic acid sensors[121,122].

Signalling pathways then diverge. A pathway increasingly recognized as central to SLE downstream of TLR7 links MyD88–TAK1 signalling to the solute carrier SLC15A4–TASL adaptor complex that relays TLR7 signalling to activate IRF5 (ref. 123). SLC15A4 is found in the endolysosomal membrane of immune cells, particularly B cells and pDCs, and has crucial roles in the proper co-localization of endosomal TLRs and their ligands[124] and also recruitment of the adaptor protein TASL to endolysosomes[25,27]. TASL recruits IRF5 into the signalling complex so that it can be phosphorylated by downstream kinases, driving autoimmunity in mouse models of lupus independently of the MAPK and NF-κB activation pathways[24,26]. Both SLC15A4 and TASL are required for the development of TLR-driven autoimmunity in mouse models[125] and have also been genetically linked with human SLE[126–130]. Among the transcription factors activated downstream of TLR7, IRF7 seems to be the dominant determinant of high type I interferon gene induction in pDCs that have constitutive IRF7 expression[131]. IRF5 is activated downstream of TLR7–SLC15A4–TASL in myeloid cells[27] and has an important role in the pathogenic B cell response in mouse models of lupus[132]. The MAPK pathway leads to the activation and nuclear translocation of the transcription factor AP-1. The IκB kinase (IKK) pathway promotes the nuclear translocation of NF-κB (Fig. 3).

LOF variants of negative regulators of TLR7 and MyD88 signalling and downstream type I interferon production have been linked with monogenic SLE, including tartrate-resistant acid phosphatase (TRAP; encoded by *ACP5*)[133], the haematopoietic transcription factor IKAROS (encoded by *IKZF1*)[134–136] and the ubiquitin-modifying enzyme A20 (encoded by *TNFAIP3*)[137–140].

Together, these pathways position TLR7 signalling, particularly via the SLC15A4–TASL–IRF5 axis, as a central driver of B cell activation and type I interferon-mediated inflammation in SLE.

The unmet need in systemic lupus erythematosus therapeutics

Before effective therapy was available, the natural history of SLE was devastating. In the 1950s, the 5-year life expectancy was about

50%[141]. In the latter half of the twentieth century, drugs such as prednisolone, hydroxychloroquine, cyclophosphamide, azathioprine and mycophenolate were introduced for the management of SLE and both life expectancy and the prevalence of end-stage renal failure improved. Thus, by the mid-1990s, the 10-year life expectancy was 85%[142]. Despite this undoubted improvement, individuals with SLE still have a three-fold increase in all-cause mortality compared with the general population[143]. In addition to this increased risk of mortality, individuals with SLE also have an increased incidence of cancer and cardiovascular disease[2,144]. Thus, the treatment of SLE represents an unmet need that is compounded by standard therapy either being glucocorticoids or broad-spectrum immunosuppressant agents that have major adverse effects. Infection represents a major challenge and increasing evidence indicates that long-term use of glucocorticoids maintenance therapy has major disadvantages[145].

Irreversible damage accrual in SLE can be caused by disease and/or treatment and is used as a method of quantifying long-term disease burden. Damage can be measured using the Systemic Lupus International Collaborative Clinics (SLICC) Damage Index and increased damage is associated with increased mortality[146,147]. Thus, researchers have sought to develop new biologic drugs that target specific cells or soluble mediators of the immune system to reduce clinical symptoms, long-term damage and mortality in individuals with SLE and minimize adverse effects. Here, we briefly discuss biologic drugs that have previously been studied and then focus on a promising new approach for targeting TLR7. The primacy of autoantibodies has led to B cell-targeting therapies being the main category of biologic drugs proposed for SLE.

Rituximab is a monoclonal anti-CD20 antibody that depletes B cells and was the first B cell agent assessed for SLE after promising results in B cell lymphoma and RA. Early studies indicated good efficacy, but two large randomized controlled trials (RCTs) failed to reach the primary end point[148–150]. Despite these results, rituximab is still used widely for the management of SLE. In two lupus nephritis trials, obinutuzumab (a newer anti-CD20 agent with more powerful B cell-depleting effects) has shown efficacy[151,152]. Belimumab reduces the survival of naive and transitional B cells[153] — a high proportion of which can be self-reactive — by targeting B lymphocyte stimulator (BlyS). In large clinical trials, belimumab out-performed standard-of-care in both renal and non-renal SLE[154–156].

A case series from Erlangen in Germany described eight patients with refractory SLE treated with CAR T cell therapy who had sustained drug-free remission for up to 2 years[76]. CAR T therapy is expensive and invasive, requiring hospital admission and immune system depletion before infusion of autologous CAR T cells. Several adverse effects have been noted and larger controlled studies across multiple centres are required before considering incorporating this therapy into the management of SLE. Even then, this approach will probably remain limited to the subset of patients who have the most severe or treatment-resistant forms of SLE. Rituximab, belimumab and obinutuzumab are not effective for all patients, so the development of alternative biologic drugs is important.

Anti-TNF agents have been very successful in RA and spondyloarthropathy, but are not used widely in SLE as they can promote the development of ANA and several patients with SLE treated with anti-TNF therapy developed serious adverse effects[157].

Anifrolumab is a monoclonal antibody that targets the type I interferon receptor. Increased interferon signalling has long been associated with active SLE. An 'interferon gene signature' that could function as a biomarker of response to treatment for anti-interferon drugs has been described in SLE[158]. In an RCT comparing monthly intravenous anifrolumab plus standard-of-care therapy with standard-of-care therapy alone, the anifrolumab group had statistically significantly better outcomes than the standard-of-care alone group, particularly in patients positive for the interferon gene signature at baseline[159].

All the biologic therapies mentioned above are administered via injection or infusion, which increases both the cost and complexity of treatment. Moreover, these agents often exert broad immunosuppressive effects, a major limitation that leaves patients more vulnerable to infections. Therefore, there remains a clear need for alternative therapeutic approaches.

Development of TLR7 and TLR8 antagonists

Several different potential therapeutic agents aimed at inhibiting TLR7 and/or TLR8 have been developed[160]. As natural 2′-OMe oligonucleotides can bind the inhibitory site of TLR7 and TLR8 to limit signalling, interest in developing synthetic 2′-OMe oligonucleotides as potential therapeutic agents has increased. The initial basis of the design was to incorporate a 7-deaza-dG or arabino-G modification into the immune stimulatory motif of the oligonucleotide with 2′*O*-methylribonucleotides as the immune regulatory motif[161]. Antagonist compounds that inhibit the action of TLR7, TLR8 and TLR9 have been identified using cell-based assays and mouse models[161], resulting in the lead candidate IMO-8400 (also known as bazlitoran) reaching phase IIa trials in plaque psoriasis and dermatomyositis[162,163]. For psoriasis, weekly subcutaneous injections of IMO-8400 at various doses for 12 weeks was safe but showed no statistically significant clinical efficacy compared with placebo[162]; however, this study was primarily to assess safety and only included 46 patients, which could have influenced the results. A study of weekly subcutaneous injections of IMO-8400 in 30 patients with dermatomyositis also failed to show clinical efficacy over placebo in either skin or muscle manifestations over 24 weeks of follow-up[163]. An analogue of IMO-8400, IMO-8503, has shown potential for the treatment of cancer cachexia based on preclinical studies in which it inhibited myoblast cell death induced by extracellular vesicles of pancreatic or lung tumour cells[164].

Immunoregulatory DNA sequences, including four contiguous guanosines that are potent inhibitors of TLR9 activation in vitro and in vivo, have been described[165]. These sequences were shown to inhibit TLR7 activation (IRS661) or both TLR7 and TLR9 (IRS954)[166]. These immunoregulatory DNA sequences can inhibit the immune complex-induced interferon responses in pDCs and prevent the development of lupus-like disease in some mouse models[167]; however, this approach has not led to any clinical trials thus far. Notably, the oligonucleotide agents described (except for IRS661) inhibit both TLR7 and TLR9 responses and might therefore not be effective in SLE, in which these TLRs appear to have opposing effects.

An alternative approach to the use of oligonucleotides is to inhibit TLR7 and TLR8 with small molecules such as imidazole or imidazoquinolinone derivatives. The chemistry of these compounds is beyond the scope of this Review but has been described extensively elsewhere[160,168]. However, the indole-based ligand afimetoran and the quinoline-based ligand enpatoran are relevant to this Review, as they have been used in SLE trials.

TLR7 and TLR8 antagonists in cutaneous lupus erythematosus and systemic lupus erythematosus

Three oral TLR7 and TLR8 antagonists are in clinical development: afimetoran[29], E6742[169] and enpatoran[31]. An anti-TLR7 antagonistic

monoclonal antibody, DS-7011a[170], which has not yet been assessed in SLE, has shown to be safe and well tolerated in healthy individuals[30]. Although TLR7 is predominantly localized to endosomes, it can also be expressed on the surface of immune cells, which may explain how monoclonal antibodies can access and target it[171].

Afimetoran and E6742. In a phase Ib randomized double-blind placebo-controlled study, eight patients with cutaneous lupus erythematosus (CLE) received afimetoran and five received placebo with 16 weeks of follow-up[29]. Safety data were reassuring, with only mild or moderate adverse effects (although one patient discontinued afimetoran owing to COVID-19 infection). From week 1 onwards, afimetoran treatment inhibited the interferon gene signature compared with placebo. Some patients did show improvement in skin manifestations, but the trial size was too small to draw any clear conclusions about efficacy[29].

Similar results were obtained in a phase I–II study of patients with SLE, in which two doses of E6742 (100 mg twice daily and 200 mg twice daily) were compared with placebo over a follow-up period of 12 weeks. There were treatment-emergent adverse events in 6 of the 9 patients in the placebo group, 3 of the 8 patients in the 100-mg group and 7 of the 9 patients in the 200-mg group, but all were mild. As for afimetoran, suppression of the interferon gene signature by this drug has been observed[169].

Enpatoran. Prior to studies in SLE, the safety of enpatoran was evaluated in 96 healthy individuals who were given escalating doses of the drug up to 200 mg per day for 14 days and compared with placebo[31]. The main finding being that all treatment-emergent adverse effects were mild-to-moderate and resolved without sequelae[31].

In May 2026, the results of the WILLOW two-arm, double-blind placebo-controlled phase II RCT of enpatoran were published, showing encouraging results[172,173]. The first part of this trial (termed cohort A), focused on cutaneous manifestations, recruiting 100 patients with CLE or SLE with predominant cutaneous manifestations[172]. All patients had active disease at baseline with a Cutaneous Lupus Erythematosus Disease Activity and Severity Index (CLASI-A) of ≥8. Patients were randomly assigned to receive either placebo, enpatoran 25 mg twice daily, enpatoran 50 mg twice daily or enpatoran 100 mg twice daily, in addition to continuing prior oral or topical glucocorticoids and/or immunosuppressants. The trial met its primary end point of a dose–response effect on adjusted mean CLASI-A score improvement from baseline to week 16 ($P = 0.0002$), and all three enpatoran groups showed greater improvements in CLASI-A score than placebo. At week 16, adjusted mean CLASI-A had improved by 44% in the placebo group versus 64% in the 25 mg enpatoran group ($P < 0.0001$), 68% ($P = 0.0241$) in the 50-mg group and 68.572% in the 100-mg group ($P = 0.0006$)[172]. In all three enpatoran groups, interferon gene signature suppression occurred within 2 weeks and persisted over the 24-week study period. No major adverse effects were reported.

In WILLOW cohort B, 354 patients with active SLE were enrolled[173]. Active disease was defined using the British Isles Lupus Assessment Group (BILAG)-2004 index. Patients were randomized to receive twice daily doses of placebo ($n = 94$), enpatoran 25 mg ($n = 71$), 50 mg ($n = 74$) or 100 mg ($n = 114$), as well as continuing background oral or topical glucocorticoids and/or immunosuppressants. All three enpatoran groups had greater improvements in the BILAG-based Composite Lupus Assessment (BICLA) at 24 weeks than the placebo group, but the primary outcome of a dose–response effect was not met: BICLA response was 39.4% in the placebo group, 57.7% in the 25-mg group, 48.6% in the 50-mg group and 49.1% in the 100-mg group. Larger effects were observed in those patients taking ≥10 mg of glucocorticoids per day at baseline and those with active cutaneous disease or high interferon gene score. As in cohort A, all three enpatoran groups showed a suppression of the interferon gene signature within 2 weeks over 24 weeks, with no major adverse effects observed.

Notably, all enpatoran treatment groups in the WILLOW cohort A and cohort B studies showed statistically better outcomes than the placebo group. The different results regarding the primary outcome of a dose–response effect were probably caused by the very different outcome measures used in the two arms of the study. The CLASI-A used in WILLOW cohort A evaluates the skin only, whereas BICLA, which was used in WILLOW cohort B, examines all organs affected by the disease.

An intriguing finding in both studies was that 100% of patients had interferon signature suppression, indicating that TLR7 and TLR8 are the drivers of this signature in SLE. The suppression of the interferon signature was reversed within 2 weeks of drug cessation, again suggesting that the underlying driver of TLR7 and TLR8 activation is intrinsic to patients with SLE and CLE.

Future directions

Emerging evidence that supports a central role of TLR7 signalling in SLE pathogenesis opens up several promising avenues for future research, although important questions remain. Key issues with therapeutic implications include understanding the relative contribution of TLR7 signalling to disease initiation versus disease maintenance and progression; whether TLR7 inhibition can ameliorate disease after B cell tolerance has been breached and long-lived autoreactive B cell populations (which sustain autoantibody production) are established; and the contribution of TLR8 signalling to SLE pathogenesis. Ongoing and future clinical trials of oral TLR7–TLR8 antagonists such as afimetoran, E6742 and enpatoran, might help to refine patient stratification and identify biomarkers that predict response to treatment.

Further elucidation of the mechanisms that regulate TLR7 activity, including the role of endogenous inhibitory RNAs and how these molecules are generated by distinct nucleic acid-processing enzymes, could inform the development of more selective and potent therapeutic agents. In addition, a deeper understanding of biological sex-based differences in TLR7 expression and X chromosome inactivation escape could reveal additional therapeutic opportunities. Integration of genetic screening for variants in *TLR7*, *TLR8* and *UNC93B1* will also remain important for identifying patients with monogenic forms of disease, with implications for diagnosis, management and reproductive counselling. Finally, combination strategies, such as pairing TLR7 antagonists with B cell-depleting therapies or using TLR7 inhibitors following anti-CD19 CAR T cell therapy, might enhance efficacy while minimizing the need for prolonged B cell depletion and associated immunosuppression.

Conclusions

SLE remains a challenging autoimmune condition with complex pathogenesis and substantial unmet therapeutic needs. Advances in genetics and immunology have firmly established TLR7 as a pivotal driver of disease. The identification of GOF variants in *TLR7* and its associated signalling components, along with validation in animal models, underscores the causal role of this pathway in autoimmunity. Although current biologic therapies have improved outcomes for many patients, limitations in efficacy, safety and delivery methods persist.

Oral TLR7–TLR8 antagonists represent a novel and rational therapeutic strategy with the potential to provide targeted immunomodulation. Larger, controlled studies will determine whether selective inhibition of this pathway can offer a safer, more effective and accessible option for a broader population of individuals living with SLE.

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Review article

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Diagnostic, prognostic and therapeutic biomarkers in rheumatoid arthritis

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Abstract

Outcomes in rheumatoid arthritis (RA) have improved considerably with the advent of new therapeutic modalities, improved therapeutic strategies and greater recognition of the need to manage comorbidities. Nevertheless, unmet needs remain. Sustained remission is achieved by only a minority of patients, in part owing to delays in diagnosis, imprecise risk stratification and suboptimal treatment selection. A pressing need therefore exists for robust diagnostic and prognostic tools to support clinical decision making. Advances in genetic, protein, imaging and multi-omics biomarkers offer opportunities to refine RA diagnosis, predict disease course and guide therapeutic choices. Parallel progress in biomarker discovery is also shaping understanding of major RA-associated comorbidities, including cardiovascular disease, interstitial lung disease, osteoporosis and malignancy. Together, clinical introduction of such biomarkers could enable earlier intervention, more precise therapy and improved outcomes for patients with RA.

Sections

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Key points

- Laboratory and imaging biomarkers have diagnostic, therapeutic and prognostic value in rheumatoid arthritis (RA), and can also inform assessment and monitoring of RA-associated comorbidities.
- Some biomarkers are already used in routine clinical practice; however, numerous laboratory and imaging markers remain under investigation for potential clinical application.
- Laboratory biomarkers include genetic and proteomic markers, the latter encompassing inflammatory mediators, acute-phase proteins, autoantibodies, matrix-degrading proteases and other markers.
- Some biomarkers can characterize RA-associated comorbidities, primarily cardiovascular, pulmonary, osteoporotic and malignant conditions.
- Multi-biomarker platforms might provide greater clinical value than reliance on single biomarkers alone.
- Ultimately, clinical implementation of validated biomarkers has the potential to improve disease management and patient outcomes in RA.

Introduction

Rheumatoid arthritis (RA) is a clinically heterogeneous disease with substantial variability in presentation, disease course and long-term outcomes[1–3] (Fig. 1). Although some patients achieve rapid and sustained disease control, others experience persistent pain and/or inflammation, progressive joint damage and the accumulation of multiple comorbidities. Even in early RA cohorts managed with treat-to-target approaches, remission or low disease activity was achieved in only 35–58% of patients, and rarely exceeded 74%[4,5].

From a clinical perspective, a reliable biomarker set that could assist in diagnosis and predict disease course and comorbid outcomes would be highly valuable. Such a 'clinical use set' could comprise individual or more likely multiple components. Prognostic biomarkers provide information about the expected outcomes of the disease. Predictive biomarkers are aimed at identifying patients who could benefit from a certain course of treatment. Therapeutic or monitoring biomarkers reflect treatment effectiveness and inform subsequent management decisions[1–3] (Figs. 1 and 2). A variety of clinical, laboratory and imaging biomarkers have been explored in RA and across RA-associated comorbidities[6–10].

In this Review, we summarize the most relevant biomarkers used for the diagnosis, prognosis and therapeutic follow-up of patients with RA. We provide a comprehensive and critical appraisal that integrates biomarkers of RA-associated comorbidities within a clinically relevant temporal framework and incorporates insights from multi-omics approaches. We highlight the advantages of multi-biomarker platforms over single-marker approaches and assess biomarkers according to their clinical utility and stage of translational maturity.

Diagnostic biomarkers

The 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria[11] illustrate that autoantibodies and acute-phase reactants remain the most informative diagnostic tools currently available for RA. Importantly, the diagnostic performance of any biomarker is highly dependent on the disease stage and clinical context of assessment. Large differences in pre-test probability exist between populations, ranging from healthy individuals to those with arthralgia or early arthritis. For example, one study estimated the pre-test risk at 0.00025% in the general population compared with 17% among individuals with clinically suspected arthralgia (CSA)[12]. As a consequence, most available diagnostic tests exhibit a very low positive predictive value when applied to the general population. Reliable detection or prediction of RA in the general population would require biomarkers with performance characteristics that substantially exceed those of currently available tests. To maximize clinical validity, we therefore mainly focus on the performance of diagnostic biomarkers in patients with early RA, defined by a symptom duration of ≤6 months[5].

Genetic risk factors and risk scores

The substantial genetic contribution to RA, reflected in heritability estimates of approximately 50% for anti-citrullinated protein antibody (ACPA)-positive RA compared with 20% for ACPA-negative disease, has prompted interest in the potential diagnostic value of genetic profiling[13] (Table 1).

Large multi-ancestry genome-wide association studies (GWAS) have identified more than 120 loci associated with RA, and contemporary polygenic risk scores typically integrate ~80–100 variants, often including HLA loci[14]. These polygenic risk scores show graded associations across the RA continuum. In a study on individuals with CSA, both polygenic risk scores (based on 85 RA-associated variants) and HLA shared epitope (HLA-SE) frequencies increased stepwise from healthy individuals to individuals with CSA, to individuals with CSA who subsequently developed RA, and finally to individuals with early RA, with the most pronounced separation observed among ACPA-positive individuals[15]. Notably, HLA-SE prevalence increased from ~45% in ACPA-positive CSA to ~79% in ACPA-positive RA.

Beyond risk stratification, genetic information could also support diagnostic classification in patients with early arthritis. Evaluation of a genetic probability tool (G-PROB), which relies on polygenic risk scores, in ~1,700 individuals with new-onset inflammatory arthritis demonstrated an area under the receiver operating characteristic curve of up to 0.84 and correct prioritization of the eventual diagnosis in ~45% of cases, while enabling reliable exclusion of at least one alternative diagnosis in most individuals[16]. An independent validation study in 972 patients with early arthritis further indicated that G-PROB produces meaningful and easily interpretable outputs, but is mainly helpful for ruling out unlikely diagnoses[17].

Genetic biomarkers are therefore promising, but diagnostic utility remains limited when these markers are used in isolation and without appropriate clinical context. Furthermore, the diagnostic relevance of these markers in ACPA-negative disease remains uncertain.

Epigenetic biomarkers

Epigenetic modifications influence gene expression without altering the underlying DNA sequences. MicroRNAs, which function as epigenetic regulators of gene expression, are short non-coding RNAs that can circulate in blood[18]. The stability of circulating microRNAs and the availability of sensitive detection methods have stimulated interest in their potential as diagnostic biomarkers for RA. Plasma levels of several circulating microRNAs, including miR-24-3p and miR-155, have shown diagnostic promise, but most studies have involved small cohorts and

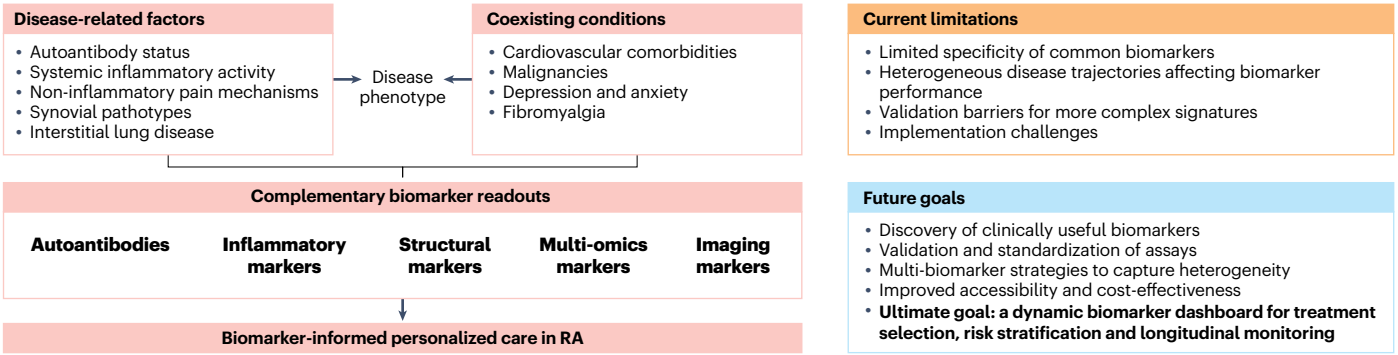


Fig. 1 | Biomarkers in rheumatoid arthritis. Rheumatoid arthritis (RA) is a clinically heterogeneous disease shaped by both disease-related factors and coexisting conditions. Different types of biomarkers capture complementary aspects of RA. Inflammatory markers reflect systemic inflammatory activity and can aid disease monitoring. Structural biomarkers mirror the extent of joint damage and the long-term impact of disease. Imaging modalities provide anatomical and functional information on joint inflammation and structural change. Multi-omics approaches integrate signals across multiple biological pathways and thus better reflect disease heterogeneity than single biomarkers. Current biomarker use is limited by issues including restricted specificity of commonly used markers (such as C-reactive protein and erythrocyte sedimentation rate), variable performance across heterogeneous disease trajectories, barriers to validation and standardization of complex signatures and challenges to wide-scale implementation related to cost and accessibility. Future goals should therefore include identifying and validating novel biomarkers, harmonizing measurement protocols and developing multi-biomarker combinations to support biomarker-informed personalized care in RA. Original figure created using BioRender.

remain unreplicated[19–21] (Table 1). Other regulatory RNAs, such as long non-coding RNAs and circular RNAs, are under active investigation as potential biomarkers in RA, but require further exploration[21].

Protein biomarkers

Protein biomarkers underpin most current diagnostic approaches in RA, capturing immune dysregulation, inflammatory activity and RA-associated tissue responses. In this section, we summarize the diagnostic performance and limitations of established and emerging protein-based markers.

Autoantibodies. Autoantibodies remain the cornerstone of diagnostic biomarker use in RA. Among these autoantibodies, ACPAs, most commonly measured using anti-cyclic citrullinated peptide (anti-CCP) antibody assays, provide the greatest diagnostic utility, followed by IgM rheumatoid factor[11,22,23]. Meta-analyses highlight an important distinction between these assays: anti-CCP antibody assays achieve substantially higher specificity than rheumatoid factor (around 95% versus 85%), whereas sensitivities are broadly comparable — approximately 67% in established RA and closer to 50% in early disease[24,25]. Given its high specificity and acceptable sensitivity, anti-CCP antibody testing is an appropriate first-line test in early arthritis. One could argue that adding IgM rheumatoid factor offers only limited incremental value, as requiring positivity for both markers increases specificity at the expense of sensitivity, whereas accepting either marker as sufficient reduces specificity. These trade-offs should be carefully considered when incorporating rheumatoid factor into diagnostic decision making[11] (Table 1). Although several smaller studies have reported that specific ACPA and rheumatoid factor isotypes (especially IgA) might have better diagnostic or prognostic characteristics than ACPA IgG and rheumatoid factor IgM, these findings have not been proven conclusively in larger, well-replicated studies or meta-analyses[24]. Notably, ACPAs and rheumatoid factor can be detected several years before the onset of clinical symptoms, defining an at-risk phase with increased likelihood of progression compared with seronegative individuals[26,27].

Although ACPAs show high specificity in secondary-care rheumatology settings, diagnostic performance deteriorates markedly when testing is applied to healthy individuals or primary care populations[28]. Because RA prevalence is low in these settings, the positive predictive value of ACPA testing declines sharply. In a cohort of more than 12,000 asymptomatic adults, approximately 2% were ACPA positive, yet fewer than 1 in 10 developed RA within 3 years[29]. Thus, routine ACPA testing, as well as testing for any other RA-associated autoantibody, is unsuitable for unselected primary care populations, as such strategies generate substantial numbers of false-positive results and lead to unnecessary investigation and follow-up.

Diagnostic performance is broadly similar across commercially available ACPA assays. Anti-CCP2, anti-CCP3, anti-CCP3.1 and anti-mutated citrullinated vimentin (MCV) antibody assays show comparable sensitivity and specificity, and no assay has demonstrated a clear advantage in routine practice[30]. Autoantibodies targeting a distinct citrullinated protein, scavenger receptor-A (SRA), might provide additional diagnostic value, as anti-SRA antibodies have been reported in anti-CCP antibody-negative patients[31]. Separately, studies evaluating serum SRA autoantigen found that the addition of serum SRA testing to anti-CCP antibody testing increased diagnostic sensitivity in RA from 74% to 87% (and from 72% to 79% in early RA)[32]; however, these findings await confirmation in non-Asian cohorts.

Other post-translational modifications also serve as targets of autoantibodies. Anti-carbamylated protein (anti-CarP) antibodies recognize proteins in which lysine residues have been converted to homocitrulline[33]. Despite substantial cross-reactivity between citrullinated and homocitrullinated (that is, carbamylated) epitopes, anti-CarP antibodies are detected in 8–14% of ACPA-negative patients[34–36]. Across early arthritis cohorts and meta-analyses, anti-CarP antibodies show reasonably high specificity (≈89–96%) but low sensitivity (≈40–45%), resulting in weaker diagnostic performance than ACPAs or rheumatoid factor[34,36] (Table 2). Thus, anti-CarP testing provides only modest incremental diagnostic value, largely restricted to patients who otherwise lack serological markers.

Autoantibodies targeting other post-translationally modified proteins have also been described in RA. Such antibody responses include antibodies directed against acetylated residues (anti-acetylated peptide antibodies) and antibodies recognizing oxidative or glycation-derived modifications, such as malondialdehyde-acetaldehyde (MAA) adducts or advanced glycation end-products[37–39]. Studies consistently show that these antibody specificities lack disease specificity: anti-MAA IgG antibodies are present in 80% of patients with RA but also in 74% of patients with osteoarthritis or spondyloarthritis, whereas anti-advanced glycation end-product antibodies are found in 45% of patients with RA compared with 33% of patients with non-RA inflammatory arthritis[40]. Some studies have linked anti-MAA antibody levels to systemic inflammation[40] and to extra-articular complications (including lung and vascular disease)[41,42], raising intriguing questions about underlying pathophysiological mechanisms.

Antibodies targeting citrullinating enzymes, particularly peptidylarginine deiminase 4 (PAD4), could also potentially have diagnostic value in RA. Anti-PAD4 antibodies are found in approximately 22–45% of patients with established RA, with reported specificities ranging from 77% to 100%[43]. Similar to anti-CarP antibodies, anti-PAD4 antibodies have also been detected in 2–19% of ACPA-negative RA, suggesting a potential role for closing the so-called 'serological gap'[43].

Although studies have described many additional autoantibody specificities — too numerous to cover here — the diagnostic relevance of most remains uncertain. None currently matches the diagnostic performance of antibodies targeting CCP, which continue to represent the most informative serological markers for RA.

Acute-phase reactants. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) serve as valuable markers of systemic inflammation in RA, but neither marker provides diagnostic specificity. Notably, normal values do not exclude RA, as approximately 33–42% of patients present with normal ESR and CRP levels at diagnosis[44]. Among the two markers, CRP is generally considered a more direct and reliable marker of acute inflammation because CRP levels respond rapidly to IL-6-driven inflammatory signalling. ESR, by contrast, is sensitive but less specific, influenced not only by inflammatory activity but also by other factors, including age, sex (with women having mean ESR levels approximately 1.22-fold higher than men), anaemia and circulating immunoglobulin concentrations[45,46]. Another acute-phase reactant, serum amyloid A (SAA), is often elevated in RA and might detect inflammatory activity with greater sensitivity than ESR or CRP[47]. However, SAA lacks specificity for RA, as a range of inflammatory and infectious conditions also elevate SAA levels[47]. Similar limitations apply to additional markers

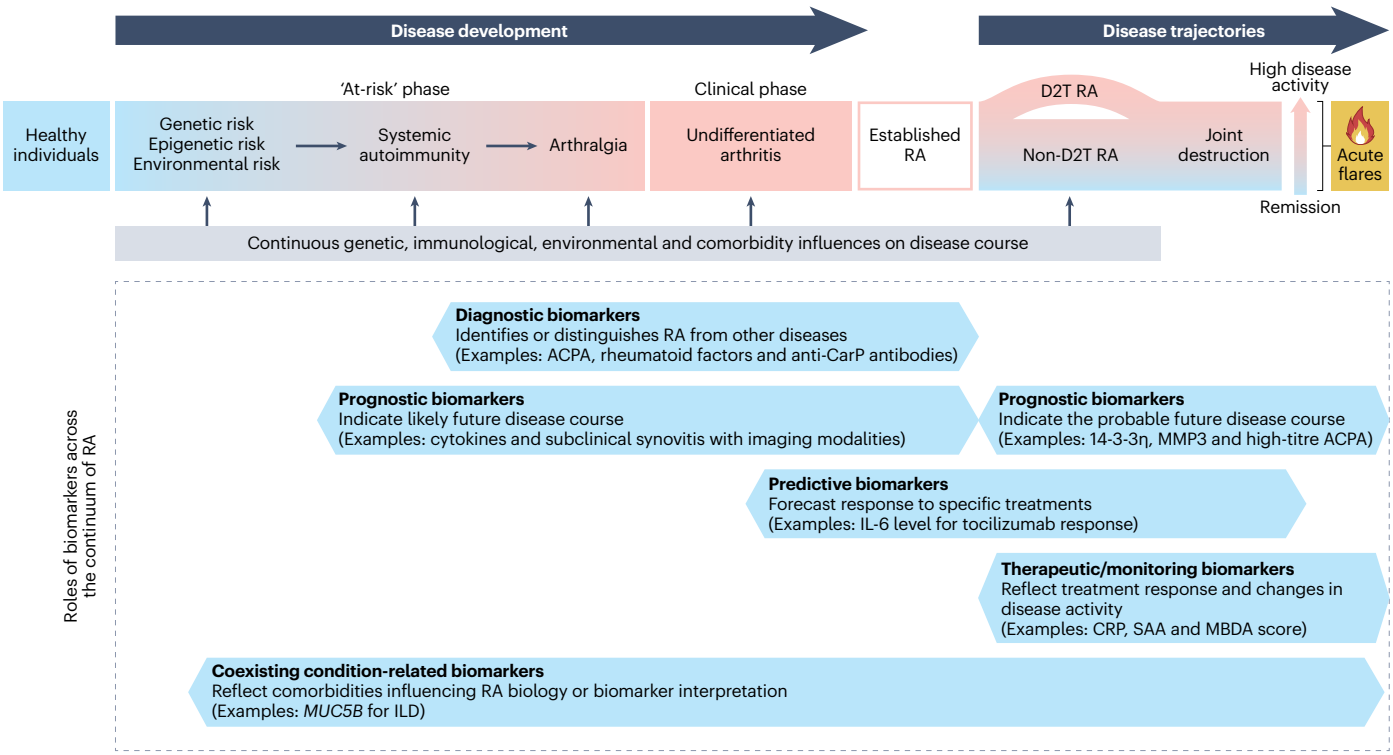


Fig. 2 | The role of different biomarkers across the disease continuum of rheumatoid arthritis. Rheumatoid arthritis (RA) evolves from genetic and environmental susceptibility through systemic autoimmunity, arthralgia and undifferentiated arthritis to established disease, followed by divergent disease trajectories. Horizontal bars indicate the disease phases in which different biomarker categories are most informative. Diagnostic biomarkers are most relevant during preclinical and early clinical stages to support disease classification. Prognostic biomarkers provide insight into progression from at-risk states to clinical RA or into long-term disease trajectories. Predictive biomarkers guide treatment selection at therapy initiation, whereas therapeutic and monitoring biomarkers reflect treatment response and dynamic changes in disease activity during follow-up. Biomarkers related to coexisting conditions could influence disease biology or modify interpretation of other biomarkers across all disease stages. Original figure created using BioRender. ACPA, anti-citrullinated protein antibody; CarP, carbamylated protein; CRP, C-reactive protein; D2T, difficult-to-treat; ILD, interstitial lung disease; MBDA, multi-biomarker disease activity; MMP3, matrix metalloproteinase-3; SAA serum amyloid A.

Table 1 | Diagnostic, prognostic and therapeutic biomarkers in rheumatoid arthritis

Type of biomarker		Biomarker	Diagnostic	Prognostic	Therapeutic
Genetic and genomic biomarkers		*HLA-DRB1* (*HLA-DRB1*01* and *HLA-DRB1*04*)	Not recommended	Promising (investigational)	Not recommended
		Major non-HLA genetic risk variants (*PTPN22* and rs2833522)	Not recommended	Promising (investigational)	Not recommended
Transcriptomic biomarkers		*NLRP3*, *CARD8*, *CD26*, *SOCS1*	Not recommended	Promising (investigational)	Not recommended
Epigenetic biomarkers		MicroRNAs (miR-24, miR-155, miR-23, miR-16, miR-146a, miR-223, miR-27a and miR-125a)	Promising (investigational)	Promising (investigational)	Not recommended
Proteins	Autoantibodies	ACPA (anti-CCP and anti-MCV)	Routinely used	Routinely used	Promising (investigational)
		IgM rheumatoid factor	Routinely used	Routinely used	Promising (investigational)
		Anti-CarP antibodies	Promising (investigational)	Promising (investigational)	Promising (investigational)
		Anti-PAD4 antibodies	Promising (investigational)	Promising (investigational)	Not recommended
		Others (AAPA, anti-MAA and anti-AGE)	Promising (investigational)	Promising (investigational)	Not recommended
	Acute-phase reactants	CRP and ESR	Not recommended	Routinely used	Promising (investigational)
		SAA	Not recommended	Promising (investigational)	Promising (investigational)
		Calprotectin	Not recommended	Promising (investigational)	Promising (investigational)
	Cytokines	IL-6	Not recommended	Promising (investigational)	Promising (investigational)
	Proteolytic enzymes	MMP3	Not recommended	Promising (investigational)	Not recommended
	Others	14-3-3η	Promising (investigational)	Promising (investigational)	Promising (investigational)
		COMP	Not recommended	Promising (investigational)	Promising (investigational)
		CTX-I and CTX-II	Not recommended	Promising (investigational)	Not recommended
		Matrix components (hyaluronic acid and aggrecan)	Not recommended	Promising (investigational)	Not recommended
	Multi-biomarker platforms	MBDA score	Promising (investigational)	Promising (investigational)	Promising (investigational)
		Synovial fluid or tissue multi-omics	Not recommended	Promising (investigational)	Promising (investigational)
Imaging	Conventional radiography	N/A	Not recommended	Routinely used	Not recommended
	Ultrasonography	N/A	Not recommended	Routinely used	Promising (investigational)
	MRI	N/A	Not recommended	Routinely used	Promising (investigational)

See further details and references in the text. AAPA, anti-acetylated peptide antibody; ACPA, anti-citrullinated protein antibody; AGE, advanced glycation end-product; CarP, carbamylated protein; CCP, cyclic citrullinated peptide; COMP, cartilage oligomeric protein; CRP, C-reactive protein; CTX, C-terminal crosslinking telopeptide; ESR, erythrocyte sedimentation rate; MAA, malondialdehyde-acetaldehyde; MBDA, multi-biomarker disease activity; MCV, modified citrullinated vimentin; MMP, matrix metalloproteinase; N/A, not available; PAD4, peptidylarginine deiminase 4; SAA, serum amyloid A.

of systemic inflammation, including serum calprotectin (S100A8 and S100A9)[48].

14-3-3η. The 14-3-3η regulatory protein is involved in several signalling pathways implicated in RA, including MAPK signalling mediated by ERK, SAPK–JNK signalling and the JAK–STAT pathway[49,50]. Circulating 14-3-3η can be detected in the blood of patients with RA and shows moderate diagnostic performance, with reported sensitivities of 58–77% and specificities of 88–93%[49,50]. Diagnostic utility seems greatest when 14-3-3η testing is combined with ACPA and rheumatoid factor testing, increasing sensitivity for early RA from approximately 64% to 78%[49]. Thus, 14-3-3η testing might aid in identifying seronegative patients with RA. An important feature of this marker is the absence of a non-specific inflammatory response, enabling discrimination between RA and other inflammatory rheumatic conditions, such as systemic lupus erythematosus and ankylosing spondylitis[50]. The extent to which 14-3-3η can accurately distinguish early RA from phenotypically similar diseases, such as psoriatic arthritis or reactive arthritis, remains insufficiently investigated in large cohorts. Nevertheless, 14-3-3η represents a promising diagnostic biomarker for inclusion in future classification criteria for RA[50] (Table 1).

Other diagnostic biomarkers

Several other proteomic biomarkers, including cytokines and matrix metalloproteinases (MMP) such as MMP1 and MMP3 have attracted interest as potential diagnostic biomarkers, but current evidence does not yet support diagnostic application[51]. Similar constraints limit the diagnostic use of cellular biomarkers, including dysregulated T cell subsets, antigen-specific B cells and emerging tissue-based phenotypes[3,8]. Although these markers are not (yet) suited to diagnostic use, they provide valuable biological insights (Table 1).

Prognostic biomarkers

Several biomarkers used for diagnosis in RA might also serve as prognostic markers. To avoid redundancy, this section focuses exclusively on prognostic implications. Across disease stages, biomarker signatures can inform long-term outcomes, structural damage and therapeutic response. Their prognostic value is most apparent during prodromal and early clinical phases. In the following section, we summarize prognostic insights derived from blood-based biomarkers, synovial tissue and fluid analyses, imaging biomarkers and omics-based approaches.

Blood-based prognostic biomarkers

Beyond disease classification and diagnosis, autoantibodies, particularly ACPAs, can inform long-term outcomes and therapeutic responses. Prognostic value is particularly evident during prodromal disease phases. Once disease becomes clinically apparent, higher levels of rheumatoid factor and/or ACPA are associated with a more aggressive disease course characterized by sustained disease activity, inflammation and more severe structural joint damage[3,52–56] (Table 1). Furthermore, bone erosions can already be present before the development of overt clinical symptoms in seropositive RA[3,52–56].

Acute-phase reactants are widely used for monitoring treatment responses in RA, despite limitations related to low disease specificity and inter-patient variability[3,57] (Table 1). Elevated concentrations of CRP and increased ESR are associated with inflammatory burden, radiographic damage and functional disability, partially reflecting synovial inflammatory activity. However, these markers show weaker correlations with patient-reported outcomes (PROs), such as pain and fatigue, consistent with the multi-factorial aetiology of PROs[3,57,58]. Serum calprotectin (S100A8 and S100A9) correlates with disease activity, and elevated levels are linked to a more erosive phenotype[3,57,58]. By contrast, studies investigating the prognostic role of SAA indicate limited capacity to predict long-term outcomes[3,57,59].

Levels of 14-3-3η are increased in both serum and synovial fluid in early and established RA and correlate with autoantibody positivity. Higher baseline concentrations are associated with increased disease activity and radiographic progression, especially in early, untreated RA[3,57]. In a cohort of 98 patients with untreated early RA, baseline serum concentrations of MMP1 and MMP3 correlated with inflammatory activity and predicted radiographic and functional outcomes over 12 months. Among these markers, MMP3 was the strongest predictor of future erosive disease in patients with non-erosive disease at presentation[3,57,60]. Notably, baseline MMP3 levels predicted radiographic damage in the feet but not in the hands[61].

Additional biomarkers reflecting cartilage and bone remodelling also show prognostic associations. Cartilage oligomeric matrix protein (COMP), a marker of cartilage turnover, is associated with progression of structural joint damage[53]. Serum hyaluronic acid levels are 10–20 times higher in RA than in healthy individuals, correlating with disease activity and radiographic damage[62]. In addition, high levels of C-terminal cross-linking telopeptide of type I and type II collagen (CTX-I and CTX-II), measured in serum or urine, predict joint destruction[62–64].

In current clinical practice, the only broadly established blood-based biomarkers in RA are rheumatoid factor and ACPA for prognostic stratification, and CRP and ESR for monitoring inflammatory disease activity, whereas MMP3 and calprotectin remain promising but not yet standardized for routine use. Other biomarkers, including 14-3-3η, SAA, COMP, hyaluronic acid, CTX-I and CTX-II, remain investigational.

Synovial tissue and fluid biomarkers

Synovial fluid components and specific inflammatory cell subsets within the synovial tissue could function as tissue-level biomarkers in RA. Although synovial fluid sampling is not performed routinely in practice, access to synovial fluid and tissue has increased and can support both pathogenetic investigation and therapeutic prediction[62]. Soluble moieties in synovial fluid are readily measurable; however, most lack sufficient added value to justify routine clinical use. Indeed, many biomarkers described elsewhere in this Review are detectable in both the blood and synovial fluid compartments[3,57,62,65] (Table 1). Regarding

Table 2 | Performance of diagnostic biomarkers

Test	Disease stage	Sensitivity (95% CI)	Specificity (95% CI)	PLR	NLR	PPV	NPV	Ref.
Anti-CCP antibodies	Early RA	54%	96%	NR	NR	NR	NR	34
		72%	98%	NR	NR	88%	94%	32
	Established RA	67% (65–68%)	95% (95–96%)	12.32	0.40	NR	NR	24
		74%	98%	NR	NR	95%	86%	32
Rheumatoid factor	Early RA	59%	91%	NR	NR	NR	NR	34
		63%	96%	NR	NR	79%	92%	32
	Established RA	69% (68–70%)	85% (84–86%)	3.86	0.41	NR	NR	24
		71%	89%	NR	NR	81%	83%	32
Anti-CarP antibodies	Early RA	44%	89%	NR	NR	NR	NR	34
	Established RA	44% (39–49%)	96% (94–97%)	9.27	0.62	NR	NR	36
Anti-PAD4 antibodies	Established RA	22–45%	86–99%	NR	NR	NR	NR	43
14-3-3η	Early RA	64% (53–73%)	93% (88–96%)	8.60	NR	NR	NR	49
	Established RA	77% (69–84%)	93% (88–96%)	10.40	NR	NR	NR	49
SRA autoantigen	Early RA	59%	97%	NR	NR	80%	91%	32
	Established RA	67%	92%	NR	NR	85%	82%	32

CarP, carbamylated protein; CCP, cyclic citrullinated peptide; NLR, negative likelihood ratio; NPV, negative predictive value; NR, not reported; PAD, peptidylarginine deiminase; PLR, positive likelihood ratio; PPV, positive predictive value; RA, rheumatoid arthritis; SRA, scavenger receptor A.

synovial fluid, fragments of aggrecan, a structural component of cartilage, are increased in RA and are associated with disease severity and rapid joint destruction; however, these markers, along with other markers measured in synovial fluid, are not used in routine clinical practice[62].

Minimally invasive synovial tissue biopsy offers a unique and compelling alternative to blood-based or synovial fluid-based biomarker approaches. Studies from the Pathobiology of Early Arthritis Cohort have identified distinct synovial tissue pathotypes, including a lympho-myeloid subtype enriched in lymphocytes and plasma cells, a diffuse-myeloid subtype dominated by myeloid infiltration with few B-lineage cells, and a pauci-immune subtype characterized by expanded fibroblast populations and minimal immune infiltrates[66,67]. These pathotypes show characteristic differences in cellular composition and corresponding gene-expression profiles, which are associated with disease severity and subsequent radiographic progression[66,67].

B cell-related features, in particular, link to a more erosive disease course. Levels of synovial CXCL13 (a key chemokine governing B cell recruitment and organization) are typically higher in patients with erosions and align with bone-remodelling signals that extend beyond conventional inflammatory markers[68]. Among the numerous pro-inflammatory chemokines implicated in the pathogenesis of RA[69], CXCL13 has emerged as a potential 'master chemokine', with roles in RA-associated cell adhesion, B cell activation and angiogenesis, and could hold promise as a future routine biomarker[70].

Synovial tissue macrophages also comprise functionally distinct subpopulations with divergent roles in disease progression and remission. $MerTK^{+}CD206^{+}$ and $MerTK^{+}LYVE1^{+}$ macrophages are associated with disease remission and produce anti-inflammatory mediators, whereas $MerTK^{-}CD206^{-}$ macrophages are associated with a pro-inflammatory phenotype[71]. Notably, a low proportion of $MerTK^{+}$ synovial tissue macrophages during remission predicts an increased risk of disease flare following treatment withdrawal[71]. Overall, these findings deepen understanding of disease processes taking place within the joint and, beyond providing prognostic information and enabling patient stratification, might eventually help to guide treatment decisions.

Prognostic imaging biomarkers

Imaging biomarkers provide direct structural information and therefore complement molecular markers in prognostic assessment. Conventional radiography remains the reference standard for detecting joint damage (including erosions and joint-space narrowing), and the presence of erosions at diagnosis predicts an increased risk of subsequent radiographic progression and a reduced likelihood of long-term remission[3,72]. Musculoskeletal ultrasonography extends radiography by enabling more sensitive detection of synovitis, tenosynovitis and early erosion changes[73]. Power Doppler ultrasonography, in particular, can detect active synovial vascularity that can persist despite clinical remission[74]. Furthermore, ultrasonography can detect subclinical inflammation in individuals with clinically suspected arthralgia, and power Doppler ultrasonography-detected tenosynovitis represents an independent predictor of progression to RA[75].

MRI provides the most comprehensive assessment of both inflammatory and structural lesions (including synovitis, tenosynovitis, erosions and bone-marrow oedema (osteitis)), supported by standardized scoring systems such as the Outcome Measures in Rheumatology RA MRI scoring system[76]. MRI-detected bone marrow oedema represents one of the strongest imaging predictors of future erosions[77]. In addition, MRI-detected synovitis and tenosynovitis might improve prediction of RA development in at-risk populations beyond clinical and serological markers[71].

Practical considerations nonetheless limit widespread implementation of imaging-based strategies. Ultrasonography is operator dependent and protocol dependent, MRI is resource intensive, and not all imaging-guided strategies improve outcomes in treat-to-target settings[72,73,76,77]. Taken together, these limitations reinforce the role of imaging biomarkers as complements to, rather than replacements for, clinical assessment and molecular biomarkers[72,73,76,77].

Omics-based prognostic insights

Genetic variations also probably contribute to disease prognosis in RA (Table 1). *HLA-DRB1* shared epitope alleles are associated with a more severe, ACPA-positive disease trajectory[3,21]. In addition, GWAS have identified SNPs, including rs2833522, that correlate with more aggressive joint destruction in ACPA-negative patients[78].

Epigenetic factors, including circulating microRNAs such as miR-16, miR-146a, miR-155 and miR-223, have been linked to inflammatory burden in early disease[19]. Notably, one study in early RA identified miR-223 as a potential marker of disease activity and suggested that combined miR-16 and miR-223 expression could predict clinical outcomes[19]. However, most microRNA signals remain heterogeneous across cohorts, and thresholds for clinical decision making are not yet established[3,21].

Transcriptomic markers derived from blood or synovial tissue might capture inflammatory gene signatures with prognostic relevance. Several mRNA transcripts, including *NLRP3*, *CARD8*, *CD26* and *SOCS1*, show promising prognostic value[79–82], and have been reported to be associated with disease activity, joint damage or radiographic progression. However, these findings remain exploratory and primarily hypothesis generating, requiring further validation[79–82].

Proteomic approaches have extended and refined the prognostic utility of previously established protein biomarkers. The multi-biomarker disease activity (MBDA) blood test is a validated, clinically available tool for assessing disease activity. In the BeSt trial, the 12-protein MBDA score predicted radiographic progression: baseline MBDA discriminated progressors more effectively than the disease activity score (DAS; area under the curve 0.767 versus 0.521), and high baseline MBDA was associated with markedly increased progression risk[83]. A subsequent meta-analysis of 32 studies further supported the value of MBDA as a reliable prognostic marker of radiographic progression[84]. By contrast, broad-spectrum profiling of other proteomic signatures, including pathway-agnostic approaches enabled by platforms such as Olink or SomaLogic, remains an active area of development.

Metabolomic approaches similarly provide insights into the pathogenetic properties of RA. In DMARD-naive early RA, baseline metabolic profiles, characterized predominantly by alterations in histidine, sphingolipid, arachidonic acid, proline and arginine metabolism, have been associated with the achievement of sustained drug-free remission[85]. However, the lack of validation and generalizability requires further research to strengthen the role of metabolomics in predicting prognosis[85].

Multi-omics technologies have redefined biomarker research by enabling simultaneous analysis of genetic, epigenetic, transcript, proteomic and metabolomic data. Across these diverse platforms, a clear pattern emerges: RA signatures consistently point to a convergence of chronic immune dysregulation and stromal activation, primarily driven by cytokine signalling[85]. Nevertheless, most candidate markers emerging from omics-based studies remain at the discovery or early validation stages and have yet to translate into clinically validated prognostic biomarkers.

In summary, although some biomarkers, such as rheumatoid factor, ACPAs, CRP, ESR and, to some extent, imaging measures, have already been integrated into clinical practice, many others remain investigational, despite promising associations with disease progression, radiographic damage or treatment outcomes. Collectively, these observations suggest that future prognostic approaches will rely less on single markers and more on integrated, multi-domain stratification approaches that capture the biological and clinical heterogeneity of RA[84], including the risk of progression to difficult-to-treat (D2T) disease[86,87].

Therapeutic biomarkers

Therapeutic biomarkers hold promise for guiding treatment selection and predicting response to DMARDs in RA. In this section, we examine blood-based, tissue, imaging and multi-omics biomarkers proposed to support therapeutic decision making, highlighting both current limitations and future potential.

Blood-based biomarkers of treatment response

The impact of serostatus on treatment response varies across classes of DMARDs. A pooled analysis of 16 registries showed that associations between rheumatoid factor and/or ACPA positivity and treatment outcomes differ by DMARD type[88]. Seropositivity was not associated with discontinuation of TNF inhibitors (adjusted HR 1.01; 95% CI 0.95–1.07) and showed only a modest, non-significant trend towards lower discontinuation with tocilizumab (HR 0.89; 95% CI 0.78–1.02). By contrast, seropositivity was associated with lower discontinuation rates for abatacept (HR 0.80; 95% CI 0.72–0.88) and rituximab (HR 0.70; 95% CI 0.59–0.84)[88]. In comparison, a meta-analysis of 28 randomized controlled trials reported broadly comparable efficacy of biological DMARDs in both autoantibody-positive and autoantibody-negative patients, and pooled data from phase III trials suggested a similar pattern for tofacitinib[3,53,54,88–90]. Findings from different cohorts suggest an association between clinical improvement with abatacept and anti-CarP antibody positivity, with more consistent association observed when anti-CarP antibody status is evaluated in combination with ACPAs and/or anti-PAD4 antibody status[3,57,91,92]. For rituximab, anti-MCV antibody isotype profiling might further refine response characterization; an IgG-dominant pattern was associated with more favourable outcomes, whereas concomitant IgA positivity predicts poorer response[53,93]. Overall, serostatus alone provides limited prognostic information and remains insufficient to guide treatment selection. Notably, emerging evidence suggests that combinations and interaction profiles might improve predictive performance, although further validation is required before clinical implementation[94].

Both CRP and ESR are routinely used to monitor the inflammatory component of disease activity, but these markers reflect different aspects of systemic inflammation. Higher baseline ESR is associated with poorer response to conventional synthetic and biology DMARD therapy[3,95]. By contrast, higher CRP at baseline aligns with improved response to TNF inhibition, consistent with CRP more reliably tracking inflammatory burden. However, for IL-6 receptor blockade, results are conflicting. IL-6 receptor inhibitors directly suppress hepatic CRP production, making CRP a pharmacodynamic marker in this setting, limiting prognostic utility and confounding interpretation within some composite disease activity measures[3,53,57,58].

Cytokines and other proteins in the blood might also serve as therapeutic markers. Measurement of serum IL-6 levels might predict a more favourable response to tocilizumab[96], and low levels of serum IL-6 after discontinuation of tocilizumab have been linked to reduced relapse rates[3,97]. In a Japanese cohort, low pre-treatment concentrations of 14-3-3η (≤ 0.40 ng/ml) in patients receiving tocilizumab independently predicted remission[98]. In additional, lower pre-treatment levels of COMP (< 10 U/l) have been associated with improved response to adalimumab[99]. However, routine clinical use of circulating cytokines remains limited, owing to substantial inter-individual variability in peripheral levels and a lack of disease specificity[3].

Joint microenvironment mapping

Several biopsy-driven studies have demonstrated associations between synovial molecular signatures and differential responses to DMARDs[66,100–103]. In the R4RA trial, response to rituximab was associated with synovia enriched for B cells, T cells and humoral immune-response genes, whereas response to tocilizumab was linked to myeloid cell-rich synovial tissue[101,102]. By contrast, non-response to both drugs was associated with the pauci-immune synovial phenotype, accompanied by downregulation of immune-cell-related gene modules and upregulation of extracellular matrix gene expression[101,102].

Although the STRAP trial showed that a simple binary classification of synovial tissue as B cell-poor versus B cell-rich did not distinguish 16-week American College of Rheumatology 20 responses, subsequent analyses demonstrated that combining baseline synovial tissue volume with single-cell RNA sequencing stratifies myeloid, lymphoid and fibroid pathotypes and identifies gene signatures and cell signatures linked to response to rituximab, tocilizumab or etanercept, as well as signatures of treatment resistance[103,104]. Building on these findings, investigators developed a machine-learning algorithm to predict DMARD response, validated predictive performance in the R4RA cohort, and are currently testing the model prospectively[103,104].

Collectively, these findings demonstrate that tissue-based stratification could serve as a cornerstone for personalized medicine; the imperative now is to bridge the gap between clinical research and routine care. However, wider use is limited by practical requirements, including the need for ultrasound-guided sampling, trained operators, standardized tissue processing and access to transcriptomic analyses, as well as limitations related to cost and turnaround time. If these approaches can be standardized and simplified for broader implementation, and if ongoing validation studies confirm existing observations, synovial biopsy-based stratification might facilitate earlier identification of patients with persistent inflammatory disease, inform more appropriate therapeutic selection and reduce exposure to ineffective immunosuppression[105].

Imaging biomarkers of response

Detection of subclinical inflammation by ultrasonography can support assessment of therapeutic response, and power Doppler signal and tenosynovitis scores have shown potential value for predicting response to JAK inhibitors[3,57,74,106,107]. Ultrasonography might uncover residual inflammatory activity in patients with D2T disease, particularly when clinical assessment is confounded by comorbidities such as obesity or fibromyalgia[87,108]. Beyond peripheral imaging, emerging evidence suggests that functional MRI of the brain might also provide prognostic information on clinical response to TNF inhibitors[109,110]. In the PreCePRA trial, patients with RA were stratified according to pain-related brain activation patterns measured by functional MRI and were randomly assigned to be treated with certolizumab pegol or placebo; patients with high baseline brain activation were more likely to respond to the treatment (57%) than those with low brain

activation (44%) or receiving placebo (26%)[109]. The response to treatment was particularly driven by improvements in PROs, such as pain and global disease activity, highlighting the contribution of central nervous system processes in modulating the patient's experience of pain and symptoms and response to treatment[109]. At present, however, functional MRI-based stratification remains exploratory and unsuitable for routine clinical use.

Multi-omics predictors of DMARD response

Genetic factors can also influence treatment response in RA, although robust predictive markers remain limited. Pharmacogenomic analyses based on genome-wide genotyping data from 457 patients with RA identified variants in *TYMS*, *DHFR*, *FPGS* and *ENOSF1* as potential predictors of a poor response to methotrexate[111]; however, these associations have not been consistently replicated. For example, one study using multivariate regression analysis identified *TYMS* genetic variation as a risk factor for non-response to methotrexate[112]. However, evidence from a systematic review indicated that although *TYMS* and *DHFR* variants might be associated with methotrexate efficacy, these associations have not been consistently confirmed across independent studies[113]. Evidence links the rs6427528 variant of *CD84* to a favourable response to etanercept[113]; however, replication analyses have not convincingly validated this association, revealing only a non-significant trend in a Portuguese cohort and no association in a Japanese cohort[114]. Moreover, the *PTPRC* rs10919563 variant has been linked to improved responses to TNF inhibitors[115], a finding further supported by results from a large UK cohort[116].

Among the various epigenetic mechanisms, DNA methylation patterns show particular potential for predicting progression from undifferentiated arthritis to RA[117]. DNA methylation and other epigenetic factors can also distinguish responders from non-responders to TNF inhibitors[118]. Furthermore, several microRNAs (including miR-23, miR-223, miR-27a-3p and miR-125a-5p) have been associated with differential responses to TNF inhibition or rituximab[3,21] (Table 1). Studies integrating multiple omics layers have further enabled monitoring and prediction of treatment response. One multi-omics study showed that response to DMARDs in RA reflected a shift towards a 'healthy' molecular profile, with biologic DMARDs exerting stronger effects than methotrexate, particularly at the proteome and transcriptome levels[119]. Achievement of 'molecular remission' at 24 weeks strongly predicted long-term, stable disease inactivity, with patients exhibiting lower disease activity and improved quality of life over 90 weeks[119]. Another study profiled peripheral blood mononuclear cells, monocytes and $CD4^+$ T cells to identify transcriptomic and DNA-methylation signatures distinguishing response to etanercept versus adalimumab; this analysis revealed divergent expression patterns between responders, etanercept-related DNA hypermethylation patterns, and demonstrated that machine-learning models based on these molecular signatures accurately predicted response to TNF inhibitors[120]. Finally, a blood-based molecular signature response classifier integrating gene expression and clinical data successfully stratified patients by risk of inadequate response to TNF inhibitors in both treatment-naive and TNF-inhibitor-exposed patients[121].

Although multi-omics approaches provide valuable insights into disease mechanisms and might improve the prediction of treatment response, implementation in routine clinical practice remains premature. Most available evidence derives from heterogeneous cohorts with relatively small sample sizes and is subject to platform-dependent variability and limited standardization in sample collection, preparation and analytics. At present, the main value of multi-omics approaches lies in biomarker discovery and patient stratification in research settings. Broader clinical adoption requires robust standardization, external validation and demonstration of clear added value over conventional clinical and serological parameters. Furthermore, given the cost and complexity of these methods, future work must clarify whether multi-omics approaches provide incremental benefit across all patients compared with using simpler clinical and serological markers, or whether these methods are best reserved for selected settings such as D2T disease or the identification of biologically distinct yet clinically similar patient subgroups.

Biomarkers guiding DMARD tapering

In patients in sustained remission, an important clinical consideration is identifying which individuals can safely undergo tapering or discontinuation of DMARD therapy without triggering a flare. Predicting successful DMARD tapering at the individual level remains challenging, and although several biomarker candidates have been proposed to help stratify relapse risk during tapering, evidence supporting routine clinical use remains insufficient[122–125]. In this context, distinguishing baseline flare risk modifiers, which reflect relatively stable patient characteristics such as ACPA or rheumatoid factor status, from markers of residual inflammation — best captured by imaging and supported by laboratory markers — is informative. Drug-exposure measures might support selected de-escalation strategies but do not, in isolation, reliably predict flare risk.

Successful DMARD tapering seems more likely in patients who are negative for autoantibodies (including ACPAs and rheumatoid factor) than in autoantibody-positive individuals[126]. In the prospective BIO-FLARE study, investigating potential factors of relapse, baseline ACPA and rheumatoid factor levels contributed to flare risk during treatment tapering[127]. Markers of residual inflammatory activity might further inform tapering decisions. In a real-world cohort of patients with RA undergoing conventional synthetic DMARD tapering, inflammatory parameters (including CRP concentrations and inflammation-associated T cell profiles), together with tender joint count and PROs, were associated with subsequent flare[125]. In addition, serum calprotectin (S100A8 and S100A9) concentrations were higher in patients who relapsed within 12 months of DMARD tapering[123], and the MBDA, especially when combined with ACPA status, improved prediction of relapse during tapering[124].

Residual subclinical inflammation tested by imaging has been hypothesized to precede relapse during DMARD tapering. Ultrasonography, especially power Doppler ultrasonography, has emerged as a useful tool in this setting owing to its ability to detect subclinical synovitis, as demonstrated in several studies[74,87,125,128–130]. In a cohort of patients in remission, the presence of power Doppler ultrasonography activity was the most accurate determinant of flare[129]. Consistently, another study reported that ultrasonography could help to identify patients in clinical remission who are suitable for biologic DMARD tapering[131]. These findings align with meta-analytic evidence showing that ultrasonography-detected subclinical synovitis predicts both flare and progressively erosive damage[130]. The STARTER study further extended this concept by showing that power Doppler ultrasonography positivity in both joints and tendons independently increases the risk of flares in patients with RA in clinical remission[128]. However, evidence supporting MRI remains controversial. In the PREDICTRA study, baseline MRI measures of inflammation were not associated with flare occurrence, underscoring current limitations of

imaging as a standalone predictor for tapering decisions[132]. Furthermore, MRI-detected inflammatory features do not seem to predict achievement of sustained DMARD-free remission[133]. By contrast, in the AVERT study in early RA, MRI-detected erosion predicted disease flare after treatment withdrawal[134]. Thus, even if some controversy exists, sensitive imaging techniques might be useful for predicting flare, even in the absence of clinical symptoms.

Consideration has also been given to whether measurement of circulating drug concentrations could support selected de-escalation decisions. Therapeutic drug monitoring, together with assessment of anti-drug antibodies, has been investigated in RA in this context. A EULAR task force issued points to consider on the clinical utility of therapeutic drug monitoring for biopharmaceuticals in inflammatory rheumatic diseases, concluding that proactive use of therapeutic drug monitoring is not recommended, whereas reactive therapeutic drug monitoring could be considered in certain clinical situations, such as clarifying clinical non-response or helping to guide dose tapering[135]. Although TNF inhibitor drug levels have generally not predicted successful tapering in RA, higher adalimumab concentrations have been associated with successful dose reduction in some studies[136,137]. Anti-drug antibodies occur in a clinically relevant subset of patients and have been linked to non-response to biologic DMARD therapy[135,137,138].

In summary, tapering in clinical practice is best considered in patients with sustained clinical remission who show no evidence of residual inflammation on imaging or inflammatory markers and who have a low baseline risk of relapse, as indicated by serostatus. At present, biomarker-informed tapering should be viewed as complementary to careful clinical monitoring rather than as a stand-alone basis for definitive decision making[122].

Biomarkers of rheumatoid arthritis-related comorbidities

RA is associated with a range of clinically impactful comorbidities, particularly cardiovascular and metabolic disease, interstitial lung disease (ILD), psychological disorders, bone loss and malignancy[6–10]. Biomarkers already have established clinically utility across several of these areas. In this section, we briefly review current biomarkers with potential value for the diagnosis, risk stratification and prognostics of major RA-associated comorbidities. We also consider markers that can inform clinical decision making in this context (Table 3). Each comorbidity is characterized by a distinct biomarker milieu (Fig. 3), underscoring the need for a holistic approach to diagnosis and longitudinal monitoring.

Cardiovascular biomarkers

Most cardiovascular risk scores used in the general population (such as SCORE) underestimate cardiovascular risk in patients with RA; accordingly, EULAR recommends application of a 1.5-fold multiplication factor[139]. Laboratory and imaging biomarkers could provide additional value for cardiovascular risk assessment in RA[9,139–141]. Informative biomarkers span several domains, including genetic, autoimmune and inflammatory, endothelial and angiogenic, metabolic and other pathways[140–146]. In the future, incorporation of such biomarkers could support risk stratification, monitoring of therapeutic effects or predictive screening of subclinical cardiovascular disease (CVD)[141–145] (Table 2).

Genetic biomarkers. Both RA and atherosclerotic CVD share a substantial genetic component, as highlighted by GWAS[145,147,148]. Carriage of *HLA-DRB1* risk alleles confers a markedly increased risk of cardiovascular mortality, with patients carrying two risk alleles exhibiting a threefold higher risk than those carrying one or none[140]. In addition, numerous non-HLA genetic variants, including those in *MTHFR*, *TNFA*, *IL6*, *SMAD3* and *PON1*, have been linked to increased cardiovascular risk in RA[140]. By contrast, variants in genes such as *IRF5, IL33* and *OPG* might exert protective cardiovascular effects[140]. Although these genetic variants have been linked to cardiovascular risk in RA, they have not been incorporated into routine clinical recommendations.

Inflammation-related biomarkers. Among the pro-inflammatory biomarkers discussed above, rheumatoid factor and ACPA have also been associated with inflammatory atherosclerosis and increased cardiovascular risk in RA[145,146]. Citrullinated proteins have been detected within atherosclerotic plaques[149], providing a plausible mechanistic link for ACPA-dependent promotion of atherogenesis. Consistent with this association, ACPA-seropositive patients with RA exhibit higher mortality than ACPA-seronegative patients[150]. Anti-CarP antibodies similarly correlate with subclinical atherosclerosis[151] and all-cause mortality in RA[150]. In addition, antibodies to oxidized LDL (oxLDL), β2 glycoprotein I (β2GPI), oxLDL–β2GPI complexes, apolipoprotein A1 and heat shock proteins (HSP60 and HSP65) have been implicated in the pathogenesis of atherosclerosis in RA[141,145,146,152]. However, these antibody specificities are not part of routine laboratory diagnostics.

CRP, particularly high-sensitivity CRP, is an important and pragmatic marker of inflammation[140,146,153,154]. In RA, large observational cohort studies have confirmed associations between elevated CRP concentrations and increased risk of major adverse cardiovascular events, heart failure, stroke and cardiovascular death[153–155]. Notably, each 20-mg/l increase in CRP is linked to a ~1% increase in 10-year cardiovascular risk[154]. Pathogenetically, CRP is directly implicated in the development and progression of atherosclerosis and thrombosis via complement activation, platelet and endothelial activation, enhanced leukocyte–endothelial adhesion and induction of MMP expression[153]. Thus, CRP is an important biomarker that links inflammation with atherosclerosis and cardiovascular risk[153]. Similarly, ESR and SAA have been associated with increased cardiovascular risk in RA[144,156].

Regarding cytokines, TNF, IL-6, IL-1, type I and type II interferons, IL-32 and soluble TNF receptor 1 (sTNFR1) have all been implicated in RA-related cardiovascular risk[140,144,146,154–158]. However, with the notable exception of IL-6, the assessment of circulating cytokines in the blood is not useful for this purpose. In RA, serum IL-6 levels correlate positively with cardiovascular risk, as estimated by SCORE[154], and increased serum IL-6 levels have been reported to predict long-term cardiovascular outcomes[159]. Thus, similar to infectious and autoinflammatory conditions, circulating IL-6 levels might hold some clinical relevance in cardiovascular assessment[154,159]. Supporting this notion, a serum IL-6 concentration of >1.0 pg/ml has been reported to be highly predictive of coronary atherosclerosis[159].

Cardiometabolic syndrome is associated with both RA and CVD[160–162]. Biomarkers related to cardiometabolic syndrome, including atherogenic lipids, insulin resistance and various adipokines, contribute to RA-related atherogenesis[140,160–164]. Alterations in lipid, lipoproteins and carbohydrate metabolism are well-described in RA, and are likely to increase cardiovascular risk; however, these metabolic biomarkers have been extensively reviewed elsewhere and are therefore not discussed further here[160–162].

By contrast, adipokines – primarily leptin, resistin and chemerin – exert both metabolic and pro-inflammatory effects in RA[84,140,160,161].

Table 3 | Laboratory biomarkers of the most relevant rheumatoid arthritis-associated comorbidities

Type of biomarker		Biomarker	Cardiovascular	ILD	Bone
Genetic		*HLA-DRB1*, *MTHFR*, *TNFA*, *IL6*, *SMAD3*, *PON1* and others	Promising (investigational)	Not recommended	Not recommended
		MUC5B	Not recommended	Promising (investigational)	Not recommended
Cellular		Neutrophil-to-lymphocyte ratio	Not recommended	Promising (investigational)	Not recommended
Protein	Autoantibodies	ACPA, rheumatoid factor and anti-CarP antibodies	Routinely used	Promising (investigational)	Not recommended
		Anti-oxLDL, anti-β2GPI, anti-oxLDL–β2GPI complexes, anti-ApoA1, anti-HSP60 and anti-HSP65 antibodies	Promising (investigational)	Not recommended	Not recommended
	Acute-phase reactants	CRP (or hsCRP) and ESR	Routinely used	Routinely used	Not recommended
		SAA	Promising (investigational)	Not recommended	Not recommended
	Cytokines	IL-6	Promising (investigational)	Not recommended	Not recommended
		Others (TNF, IL-1, IL-17, type I and type II interferons, IL-32 and sTNFR1)	Not recommended	Not recommended	Not recommended
	Chemokines	Angiogenic chemokines	Promising (investigational)	Not recommended	Not recommended
		CXCL10	Not recommended	Promising (investigational)	Not recommended
	Growth factors	VEGF and EGF	Promising (investigational)	Not recommended	Not recommended
	Cell adhesion molecules	VCAM1 and E-selectin	Not recommended	Not recommended	Not recommended
	MMPs	MMP3 and MMP1	Promising (investigational)	Not recommended	Promising (investigational)
		MMP7	Not recommended	Promising (investigational)	Not recommended
	Lipids and related mediators	Total cholesterol and LDL-C	Routinely used	Not recommended	Not recommended
		Atherogenic indices (total cholesterol-to-HDL-C, LDL-C-to-HDL-C and ApoB-to-ApoA1 ratios)	Routinely used	Not recommended	Not recommended
		Others (lipoprotein a, sdLDL, oxLDL, and PON1)	Promising (investigational)	Not recommended	Not recommended
	Adipokines	Leptin, resistin, chemerin and adiponectin-to-leptin ratio	Promising (investigational)	Not recommended	Not recommended
	Bone markers	OPG and DKK1	Promising (investigational)	Not recommended	Promising (investigational)
		RANK, RANKL, osteocalcin, P1NP, CTX, cathepsin K, OPG-to-RANKL ratio and P1NP-to-CTX ratio	Not recommended	Not recommended	Routinely used
	TAAs	CA19-9	Not recommended	Not recommended	Not recommended
		KL-6	Not recommended	Promising (investigational)	Not recommended
	Others	NT-proBNP	Routinely used	Not recommended	Not recommended
		Troponins	Routinely used	Not recommended	Not recommended
		SP-D	Not recommended	Promising (investigational)	Not recommended
		Galectin 3	Promising (investigational)	Not recommended	Not recommended
		YKL-40	Promising (investigational)	Not recommended	Not recommended
	Multi-biomarker assays	MBDA score and multi-biomarker platforms	Promising (investigational)	Promising (investigational)	Promising (investigational)
Imaging	Ultrasound-based techniques	Carotid plaque, CAC score, carotid IMT and arterial stiffness	Routinely used	Not recommended	Promising (investigational)
	HRCT	N/A	Not recommended	Routinely used	Not recommended
	PET-CT	N/A	Promising (investigational)	Promising (investigational)	Not recommended
	DXA	N/A	Not recommended	Not recommended	Routinely used

See further details and references in the text. ACPA, anti-citrullinated protein antibody; ADMA, asymmetric dimethylarginine; Apo, apolipoprotein; β2GPI, β2 glycoprotein I; CA 19-9, cancer antigen 19-9; CAC, coronary artery calcium; CarP, carbamylated protein; CEA, carcinoembryonic antigen; CRP, C-reactive protein; DKK, Dickkopf; DXA, dual-energy X-ray absorptiometry; EGF, epidermal growth factor; ESR, erythrocyte sedimentation rate; Gal-3, galectin 3; HDL, high-density lipoprotein; HE4, human epididymis protein 4; HRCT, high-resolution CT; hs, high sensitivity; HSP, heat shock protein; ILD, interstitial lung disease; IMT, intima-media thickness; MBDA, multi-biomarker disease activity; MMP, matrix metalloproteinase; MTHFR, methylenetetrahydrofolate reductase; MUC5B, mucin 5B; N/A, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; oxLDL, oxidized low-density lipoprotein; OPG, osteoprotegerin; P1NP, procollagen type I N-propeptide; PON, paraoxonase; RANK, receptor activator of nuclear factor-κB; RANKL, RANK ligand; SAA, serum amyloid A; sdLDL, small dense low-density lipoprotein; SMAD, small mothers against decapentaplegic; SP-D, surfactant protein D; sTNFR, soluble TNF receptor; TAA, tumour-associated antigen; VCAM, vascular cell adhesion molecule; VDR, vitamin D receptor; VEGF, vascular endothelial growth factory; YKL-40, chitinase-3-like protein 1 (CHI3L1).

Therefore, these adipokines might serve as useful biomarkers linking RA, cardiometabolic syndrome and CVD[84,140,160,161]. Specifically, the adiponectin-to-leptin ratio might be a strong indicator of cardiovascular risk in RA[161,164,165], whereas chemerin and resistin are promising biomarkers of early carotid atherosclerosis[166,167]. Standard thresholds associated with higher cardiovascular risk include serum leptin concentrations >10.3 ng/ml and resistin concentrations >15 ng/ml[167]. An adiponectin-to-leptin ratio between 0.5 and 1 has been associated with a medium risk, whereas values <0.5 indicate a high cardiovascular risk[168]. Associations between chemerin and carotid plaque formation in RA remain highly variable[166,167]. Thus, although adiponectin levels might be associated with cardiovascular risk in RA, their application remains confined to research settings rather than routine clinical practice.

Imaging biomarkers. Several imaging modalities have been applied to detect subclinical and clinical vascular pathology in RA[154,169]. These include coronary artery calcium scoring by CT, as well as ultrasonography-based methods such as carotid plaque assessment, brachial artery flow-mediated vasodilation, common carotid intima-media thickness (IMT) measurement, pulse-wave velocity assessment and various echocardiography approaches[139,140,154,169]. Collectively, these techniques capture various stages of endothelial and vascular pathology. Certainly, carotid plaque imaging and coronary artery calcium scoring are the most reliable in determining overt atherosclerosis, whereas flow-mediated vasodilation and pulse-wave velocity might provide additional information on early endothelial dysfunction and arterial stiffness, respectively[139,140,154,169]. Reflecting their complementary value, the EULAR task force has conditionally recommended the use of selected vascular imaging techniques for the assessment of cardiovascular risk in RA[139].

Beyond structural and functional vascular imaging, ^{18}F-FDG-PET-CT enables simultaneous assessment of synovial and vascular inflammation in RA[144,154,170]. In the TARGET trial, arterial inflammation determined by PET-CT was associated with multiple laboratory biomarkers of inflammation and tissue damage[144,171]. PET-CT, where available, is also suitable for monitoring the effects of various targeted therapies on both joint and arterial inflammation in RA[170]. However, future studies are required to establish the role of imaging-based approaches in quantifying and predicting cardiovascular risk.

Emerging cardiovascular biomarkers. A broad range of emerging biomarkers have been investigated for their descriptive and predictive roles in RA (Table 3). Levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) are increased in RA and predict subsequent major adverse cardiovascular events[141,154]. Patients with RA and NT-proBNP concentrations >100 pg/ml show an approximately 3.4-fold increased risk of cardiovascular mortality compared with individuals with normal NT-proBNP levels[154]. By comparison, studies in the general population show that NT-proBNP levels >100 pg/ml confer a 1.5–3.8-fold increased risk of cardiovascular mortality[172]. Together, these findings suggest a somewhat greater prognostic impact of NT-proBNP in RA. Cardiac troponins, including hsTnT and cTn-I, are also increased in RA and are associated with subclinical myocardial injury[141,154]. Detection of elevated troponin concentrations in asymptomatic patients with RA should prompt cardiology referral[154].

Elevated serum levels of osteoprotegerin (OPG) and Dickkopf-1 (DKK1), biomarkers more commonly linked to bone remodelling, have also been associated with carotid plaque burden and cardiovascular events in RA[140,143,154]. Galectin-3, a mediator of myocardial dysfunction and vascular fibrosis, has emerged as a viable biomarker of subclinical CVD[143,154]. Finally, YKL-40, a 40-kDa glycoprotein produced by inflammatory cancer cells, contributes to cell proliferation, inflammation, angiogenesis and matrix remodelling, and thus could be associated with cardiovascular risk in RA[144,154]. Collectively, these biomarkers hold promise for future cardiovascular risk assessment, but evidence does not yet support routine clinical testing.

Biomarkers of rheumatoid arthritis-associated interstitial lung disease

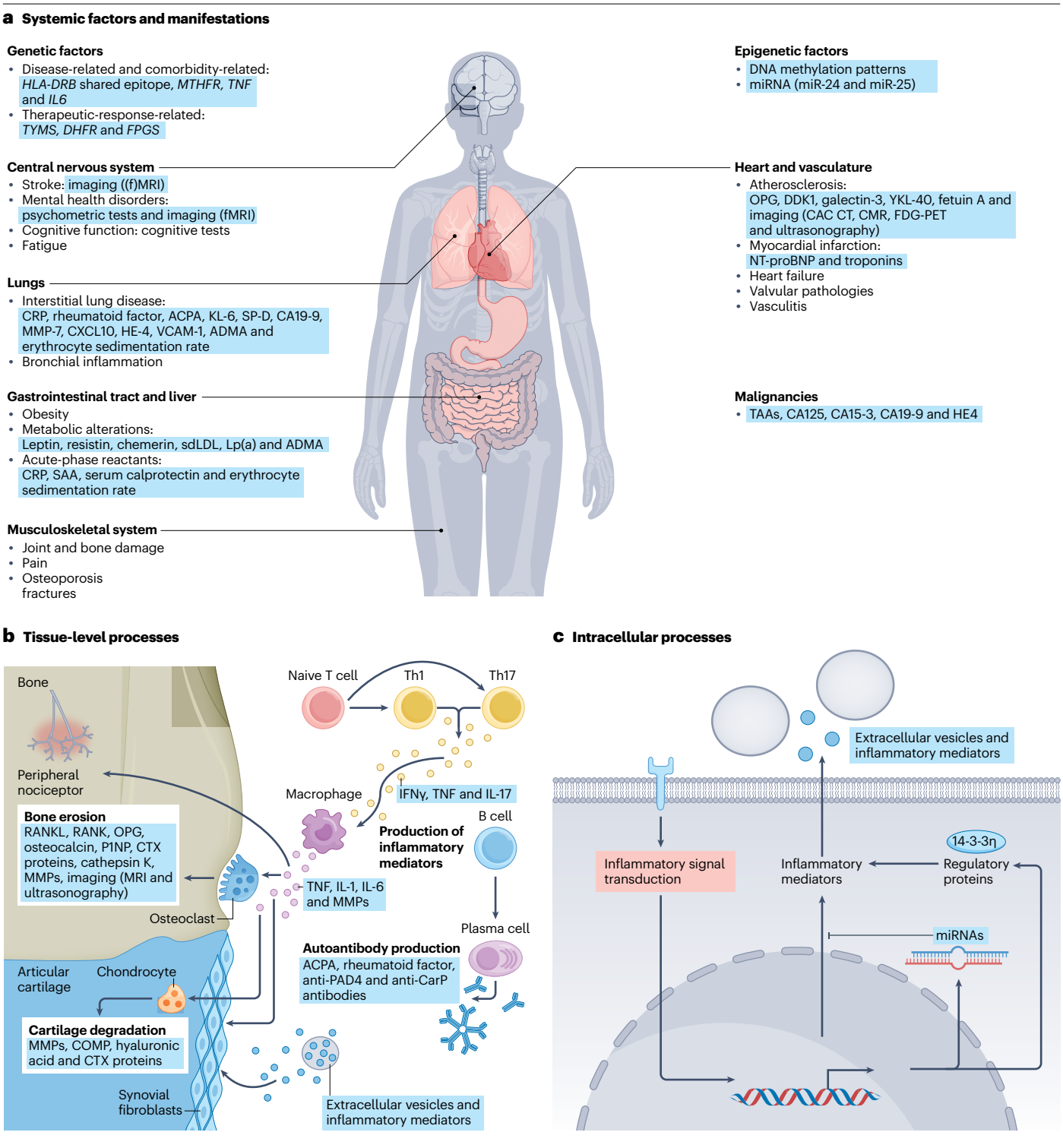
Pulmonary involvement, especially ILD, might be the most common extra-articular manifestation of RA and is a leading cause of RA-related death[6,9,42,173]. Current diagnosis of RA-associated ILD relies on clinical assessment, imaging and pulmonary function testing[173]. Biomarkers hold promise for assessing disease activity, progression and treatment responses in RA-associated ILD[9,42,173–175] (Table 3). A range of biomarkers have been implicated in ILD, albeit with variable specificity. For example, anti-CarP and anti-MCV antibodies have been linked to RA-associated ILD, as well as broader extra-articular manifestations[3,53,54,56,176,177]. Among other routinely used biomarkers, CRP, ESR, rheumatoid factor and ACPAs, as well as surfactant protein D (SP-D), KL-6, MMP7, CXCL10 chemokine ligand, the neutrophil-to-lymphocyte ratio and variants in *MUC5B* have been reported to differentiate patients with RA and ILD from patients with RA without ILD[9,173,178].

SP-D, a mucin-like glycoprotein expressed by type II alveolar epithelial cells, is considered the best marker for detecting and monitoring ILD in RA and other autoimmune diseases[173,178]. KL-6 demonstrates high sensitivity (76–94%) for RA-associated ILD, correlates with lung fibrosis and pulmonary function tests, and rising serum levels predict disease progression[173,178]. MMP7 concentrations increase early in RA-associated ILD and are associated with subsequent progression[173,178]. CXCL10, a chemokine linked to T cell activation, reflects active pulmonary inflammation in RA but is less well-established than KL-6 or SP-D[173,178]. The neutrophil-to-lymphocyte ratio is a readily available, low-cost laboratory marker and is increased in RA-associated ILD. A ratio above 3.15 might raise concern[173,178], but low specificity necessitates interpretation of the neutrophil-to-lymphocyte ratio in combination with more specific biomarkers. Finally, the *MUC5B* rs35705950 promoter polymorphism is a major risk factor for the development of the usual interstitial pneumonia pattern of RA-associated ILD. This genetic variant can identify high-risk patients who warrant frequent pulmonary screening[173,178].

Beyond individual biomarkers, integrated biomarker signatures might improve identification of RA-associated ILD. In a registry study, composite blood biomarker signatures encompassing autoantibodies, cytokines, chemokines, adipokines and MMPs were measured[42]. Eight out of 15 blood-based signatures were associated with RA-associated ILD and showed superior discriminatory performance compared with clinical risk factors alone[42]. Nevertheless, more work is required to establish the clinical utility of these and other biomarker panels in RA-associated ILD.

Biomarkers of inflammatory bone turnover

Inflammatory bone loss, generalized osteoporosis and increased bone turnover, together with increased fracture risk, are characteristic features of RA[179–181] (Table 3). The receptor activator of nuclear factor-κB (RANK), its ligand (RANKL) and OPG are key mediators of bone turnover in RA[179,180]. In addition, components of the canonical Wnt–β catenin signalling pathway, primarily DKK-1, are important regulators of bone formation during inflammation[179,180]. Other biomarkers of bone formation, namely osteocalcin and procollagen



type I N-propeptide (P1NP), as well as markers of bone resorption, such as CTX, cathepsin K and MMPs, might be used to assess and monitor inflammatory bone turnover in RA[179,180]. Treatment with various bDMARDs and tsDMARDs suppresses bone resorption and promotes bone formation, reflected by increases in the OPG-to-RANKL or P1NP-to-CTX ratios[179] (Table 3). Thus, any of the mentioned bone biomarkers might provide useful tools for assessing and monitoring inflammatory bone turnover in RA.

Biomarkers of secondary malignancies

Onco-rheumatology represents an emerging area within the RA biomarker field, reflecting the increased baseline risk of malignancies,

Fig. 3 | Biomarker layers across systemic and molecular levels in rheumatoid arthritis. Overview of systemic (**a**), organ-level (**b**) and molecular (**c**) processes underlying rheumatoid arthritis (RA), together with representative biomarker types. These biomarkers include genetic and epigenetic markers, blood-based molecular biomarkers (such as autoantibodies and soluble inflammatory proteins, including acute-phase reactants and cytokines), imaging biomarkers and functional measures. Text highlighted in blue denotes example biomarkers and measurement approaches. Original figure created using BioRender. ACPA, anti-citrullinated protein antibody; ADMA, asymmetric dimethylarginine; CAC, coronary artery calcium; CarP, carbamylated protein; CMR, cardiac magnetic resonance; COMP, cartilage oligomeric protein; CRP, C-reactive protein; CTX, C-terminal crosslinking telopeptide; FDG, fluorodeoxyglucose; fMRI, functional MRI; miRNA, microRNA; MMP, matrix metalloproteinases; OPG, osteoprotegerin; SAA, serum amyloid A; sdLDL, small dense low-density lipoprotein; TAA, tumour-associated antigen; VCAM, vascular cell adhesion molecule.

the production of tumour-associated antigens and concerns regarding malignancy risk following certain bDMARD and tsDMARD therapies[182–184]. Several tumour-associated antigens contribute to cancer cell adhesion and metastasis processes; however, inflammatory leukocytes can also express these antigens[182,183]. Moreover, increased production of CA125, CA15-3 and CA19-9 has been reported in RA in the absence of malignancy[182,183]. Therefore, measurements of tumour-associated antigens, which might be increased in RA as a result of systemic inflammation, lack specificity and are not suitable for the routine cancer screening or monitoring in patients with RA[182,183].

Some bDMARD and tsDMARDs possibly increase the risk of malignancy in patients with RA, especially in those with various risk factors[184]. Post hoc analyses from the ORAL Surveillance studies identified biomarker patterns associated with higher malignancy risk[184]. As with other comorbidities, sustained inflammation and persistent disease activity, reflected by consistently increased DAS28 scores and circulating CRP concentrations, seem to represent major contributing factors[184]. Thus, effective disease control aimed at remission, with monitoring that includes CRP assessment, is likely to be important for minimizing malignancy risk in RA[182,184].

Biomarkers at comorbidity intersections

In RA, comorbidities often cluster and interact, reflecting shared pathogenic mechanisms[6,10]. Accordingly, assessment of common biomarkers might support integrated multi-morbidity management[6,10] (Table 3).

Cardiovascular risk and bone loss are closely linked to each other, in part through the cumulative inflammatory burden over time[181]. In one study, vascular and bone imaging together with laboratory biomarkers were simultaneously assessed in patients with RA receiving anti-TNF therapy[185]. Osteoporosis correlated with carotid IMT, and changes in DAS28 and CRP correlated with multiple bone and vascular biomarkers. These findings support a link between bone loss and cardiovascular pathologies in RA, mostly mediated by inflammation and RA disease activity[185]. In this context, rheumatoid factor, ACPAs, CRP, as well as OPG and DKK-1 (bone-remodelling mediators that connect bone loss and atherosclerosis), might support simultaneous assessment of cardiovascular and osteoporosis risk in RA.

Similarly, increased cardiovascular risk, either directly or indirectly through shared inflammatory pathways, might contribute to malignancy risk in RA[182,186]. For example, in the ORAL Surveillance trial, longer disease duration, older age and higher cardiovascular risk were associated with increased malignancy incidence among patients treated with JAK inhibitors compared with those treated with TNF inhibitors[184].

Multi-biomarker assessment and artificial intelligence

No single biomarker currently serves as a gold standard for diagnostic, prognostic, therapeutic stratification or comprehensive assessment of multi-morbidity risk in RA[3,84,154]. In this context, multi-biomarker integrated panels that incorporate inflammatory, metabolic, bone-related, fibrotic and other biomarkers have shown promise[84,154]. One such example is the Vectra MBDA test, which comprises 12 laboratory biomarkers (CRP, SAA, IL-6, sTNFR1, VCAM1, EGF, VEGF-A, YKL-40, MMP1, MMP3, leptin and resistin). MBDA scores correlate with conventional measures of disease activity, and higher scores predict radiographic progression[84,187] (Table 1). Beyond joint outcomes, MBDA score has also been linked to cardiovascular risk. In the TARGET trial, MBDA scores correlated with arterial inflammation detected by ^{18}F-FDG-PET-CT, whereas changes in DAS28 or CRP did not predict changes in arterial inflammation, following 24 weeks of DMARD therapy[171] (Table 3). Thus, these findings suggest that the MBDA score might provide additional value in capturing arterial inflammation relevant to inflammatory-driven CVD in RA. More broadly, application of multi-biomarker platforms increasingly relies on advanced analytical approaches, including artificial intelligence[188]. In one study, artificial intelligence-based models identified strong associations between disease duration, carotid IMT and plaque burden, as well as rheumatoid factor and ACPA levels. Such approaches could outperform conventional methods in comorbidity risk assessment and management in RA[188].

Conclusions

In summary, this Review highlights the expanding landscape of biomarkers in RA and the variable readiness of different markers for routine clinical utility. A major challenge lies in translating increasingly complex signatures into cost-effective, accessible and standardized tools for widespread clinical practice. Although the development and clinical application of these biomarkers continues to dynamically change (Table 1), some biomarkers (such as ACPAs, rheumatoid factor, CRP and MMP3) are well established in clinical practice, whereas others (including calprotectin, IL-6 and SAA) show promise but need further validation. Many additional biomarkers remain confined to research settings or are unlikely to enter routine practice soon. Although numerous potential biomarkers remain at the research stage, several discussed in this Review have already entered clinical use, with the potential to support earlier intervention, more precise therapy and improved outcomes for patients with RA.

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Author contributions

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Review article

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Advances in targeting IL-1 family cytokines for the treatment of inflammatory diseases

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Abstract

The IL-1 family comprises key pro-inflammatory cytokines that are central to host defence against noxious stimuli, as evidenced by their prominent expression at barrier tissues and their shared myeloid differentiation primary response 88 (MyD88)-dependent signalling pathways with Toll-like receptors. The generation of biologically active IL-1 agonists is tightly controlled by proteolytic processing (including inflammasome-dependent and independent mechanisms), which converts inactive precursors into mature cytokines or substantially amplifies the activity of selected family members. IL-1 signalling is further regulated at multiple levels by endogenous inhibitors, decoy receptors and receptor antagonists, ensuring a finely tuned balance between pro-inflammatory and anti-inflammatory responses; this balance is essential for effective antimicrobial immunity while limiting immunopathology. Converging evidence from human studies and experimental disease models demonstrates that disruption of this regulatory balance underlies a broad spectrum of inflammatory diseases. Numerous therapies that target IL-1 cytokines have been approved for the treatment of inflammatory diseases or are in development, and the clinical efficacy of these therapies provides compelling validation of their pathogenic role in numerous disease contexts.

Sections

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Key points

- The IL-1 family comprises a set of 11 cytokines, including pro-inflammatory agonists and inhibitors that are involved in the control of host responses against various exogenous and endogenous danger signals.
- The biological activity of pro-inflammatory agonists is tightly regulated at different levels, including via protein synthesis, post-translational activation, receptor antagonists and decoy molecules.
- The role of dysregulated IL-1 cytokine signalling is exemplified by monogenic inflammatory diseases associated with excessive IL-1 production or inhibitor deficiency.
- The successful use of targeted therapies has led to their approval for the management of several monogenic and non-genetically associated inflammatory diseases.
- Clinical development of targeted therapies will further improve understanding of the role of IL-1 cytokines in rheumatic and inflammatory diseases.

Introduction

The IL-1 family of cytokines comprises 11 members, including several well characterized pro-inflammatory agonists (such as IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β and IL-36γ); two receptor antagonists (the IL-1 receptor antagonist (IL-1Ra) and IL-36Ra) and two cytokines (IL-37 and IL-38), all of which are generally regarded as anti-inflammatory mediators, although their mechanisms of action remain incompletely defined[1]. Apart from IL-18 and IL-33, the genes encoding these cytokines are clustered on chromosome 2 in both humans and mice and probably originated from duplication events of the *IL1B* gene[2]. Except for the secreted isoform of IL-1Ra, IL-1 family cytokines lack a classical hydrophobic signal peptide and are therefore released via unconventional secretory pathways (Fig. 1). In addition, amino-terminal proteolytic processing of full-length proteins is required to generate mature bioactive cytokines or to enhance their biological activity[3–5].

The cytosolic domains of IL-1 cytokine receptors share considerable amino acid homology with Toll-like receptors (TLRs), and contain a conserved TIR domain that mediates MyD88-dependent signalling (Fig. 2). Pro-inflammatory IL-1 family agonists signal through heterodimeric receptor complexes. For instance, IL-1, IL-33 and IL-36 bind to specific receptor α chains in combination with a common β chain, known as the IL-1 receptor accessory protein (IL-1RAcP). By contrast, IL-18 signals through a distinct receptor complex composed of IL-18Rα and IL-18Rβ. Receptor engagement results in recruitment of MyD88 and IL-1-receptor-associated kinases (IRAKs), leading to the activation of NF-κB and MAPK pathways[1].

IL-1 family cytokines are produced by multiple cell types; however, many of them are constitutively expressed in epithelial cells and keratinocytes. Consequently, they can be rapidly released following mucosal or skin injury, thereby initiating inflammatory responses[6]. The shared structural and functional features of IL-1 receptors and TLRs, and their activation of overlapping signalling pathways, underscore the pivotal role of IL-1 cytokines in early inflammatory responses to a wide range of danger signals. These cytokines can therefore be considered key upstream mediators of inflammation induced by pathogens and other noxious stimuli. Another distinctive feature of the IL-1 family is the existence of multiple endogenous inhibitory mechanisms[7], including receptor antagonists, decoy receptors and soluble receptors that limit excessive signalling.

Recognition of the pathogenic role of IL-1 cytokines in various monogenic autoinflammatory diseases has provided crucial insights into the clinical manifestations associated with excessive IL-1 signalling. Consistent with the expression of these cytokines in barrier tissues, most of these genetic conditions are characterized by signs of skin and/or mucosal inflammation. The clinical success of IL-1-targeting therapies in these rare disorders has subsequently led to clinical trials and/or off-label use in other inflammatory conditions, thereby expanding interest in the field. These positive results have been accompanied by the development of novel IL-1 antagonists, including monoclonal antibodies and small-molecule inhibitors. In this Review we discuss advances in our understanding of how IL-1 family cytokines contribute to the pathogenesis of rheumatic and inflammatory diseases. We also examine the results of clinical trials evaluating IL-1-targeted therapies in the past decade.

IL-1α, IL-1β and IL-1Ra

IL-1α, IL-1β and IL-1Ra were the first recognized members of the IL-1 family more than 40 years ago. These cytokines have a major role in innate immunity and stimulate potent inflammatory responses. IL-1α and IL-1β are both agonists, whereas IL-1Ra functions as a competitive inhibitor by preventing the interaction of IL-1α and IL-1β with their cell surface receptor[8].

IL-1 biology

IL-1α and IL-1β are produced as 31-kilodalton propeptides but their cellular localization, mechanisms of maturation and secretion differ substantially[8]. Pro-IL-1 is constitutively present in epithelial cells and its expression is induced in myeloid cells. The pro-IL-1α amino-terminal moiety contains a nuclear localization sequence that enables its translocation to the nucleus, where it can exert intracellular activities independent of IL-1 receptor binding. The N-terminal region of pro-IL-1α can be cleaved by various proteases, leading to marked enhancement of extracellular IL-1α biological activity[9]. By contrast, pro-IL-1β is a cytosolic, biologically inert protein that requires N-terminal processing to become active. The production of mature IL-1β is regulated by two signals: first, pro-IL-1β is synthesized in response to the activation of innate immune receptors such as TLRs; second, pro-IL-1β processing is regulated by a multimeric cytosolic protein complex called the inflammasome[1,3] (Box 1).

The IL-1 receptors include three members: the type 1 IL-1 receptor (IL-1R1), the type 2 IL-1 receptor (IL-1R2) and IL-1RAcP. Binding of IL-1 to IL-1R1 leads to recruitment of IL-1RAcP and intracellular signalling. IL-1R2 has a short cytoplasmic domain, is unable to transduce intracellular signals and thus functions as a decoy receptor. IL-1Ra binds avidly to IL-1R1 but fails to activate signalling and therefore functions as a specific IL-1 inhibitor[8] (Fig. 3).

IL-1 in rheumatic and inflammatory diseases

Circulating IL-1 levels are frequently unmeasurable or barely detectable, which has been a considerable limitation in deciphering the role of IL-1 in disease. Thus, monogenic mutations that lead to excessive IL-1 agonist production or impaired IL-1 inhibition have been particularly

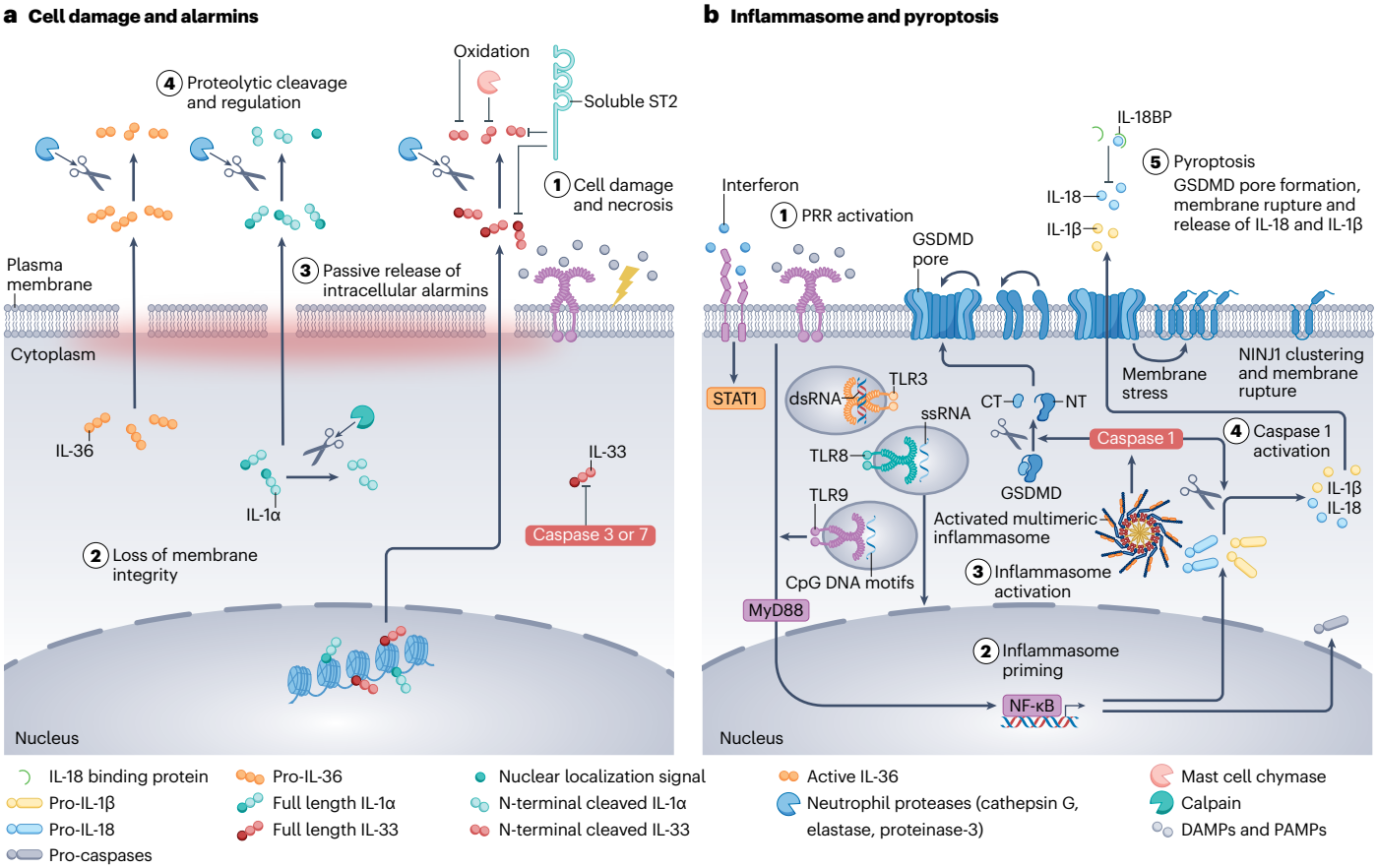


Fig. 1 | Mechanisms of release and activation of IL-1 family cytokines. Schematic representation of the mechanisms that control the release, activation and regulation of IL-1 family cytokines through two major pathways. **a**, Cell damage and alarmins: cell injury leads to passive release of the alarmin cytokines IL-1α and IL-33, which are constitutively expressed in the nucleus of epithelial cells (or induced in immune cells). Their activity can be enhanced by proteolytic cleavage (for example, by calpains or neutrophil proteases) and is regulated by natural inhibitors, decoy receptors (such as soluble ST2) or post-translational modifications. Similarly, cytosolic pro-IL-36 (mainly expressed in keratinocytes) is released upon cell damage and activated extracellularly by proteolytic cleavage. **b**, Inflammasome and pyroptosis: TLR-mediated NF-κB signalling primes the inflammasome by upregulating pro-IL-1β, pro-IL-18 and pro-caspase 1. Upon inflammasome activation, caspase 1 cleaves pro-IL-1β and pro-IL-18 to their active forms. Gasdermin D-dependent pore formation and subsequent pyroptosis facilitate cytokine release. CpG, cytosine–phosphorothioate–guanine oligodeoxynucleotides; CT, carboxy terminal; DAMPs, damage-associated molecular patterns; dsRNA, double-stranded RNA; GSDMD, gasdermin D; IL-18BP, IL-18 binding protein; IL-36Ra, IL-36 receptor antagonist; NF-κB, nuclear factor-κB; NINJ1, ninjurin-1; NT, amino-terminal; PAMPs, pathogen-associated molecular patterns; PRR, pattern recognition receptors; ssRNA, single-stranded RNA; sST2, soluble ST2; STAT1, signal transducer and activator of transcription 1; TLR, Toll-like receptor. The original version of this figure was created with BioRender.com.

informative in illustrating the role of IL-1 in inflammatory diseases, which has been reviewed elsewhere[10].

Gain-of-function mutations in inflammasome sensors such as NLRP3, NLRP1, NLRC4 or MEFV are associated with excessive production of mature IL-1β and autoinflammatory manifestations. In addition to those in inflammasome sensors, mutations in other proteins involved in regulating inflammasome activation are also linked to autoinflammatory syndromes. Mutations in *PSTPIP1* (which encodes proline–serine–threonine phosphatase-interacting protein 1, PSTPIP1) promote binding to pyrin and inflammasome activation[11]. Conditions associated with *PSTPIP1* mutations include pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome and PSTPIP1-associated myeloid proteinaemia inflammatory syndrome (PAMI) syndrome. Pyrin-associated autoinflammation with neutrophilic dermatosis is a syndrome associated with *MEFV* mutations (p.S242R and p.E244K) that are distinct from those reported in people with familial Mediterranean fever (FMF). These mutations lead to impaired binding of the regulatory 14-3-3 proteins, increased inflammasome activation and release of IL-1β and IL-18 (refs. 12,13). Mutations in the *MVK* gene cause enzymatic defects with reduced geranylgeranyl pyrophosphate, leading to a lower threshold of pyrin activation[14]. Loss-of-function in dipeptidyl peptidase 9 leads to NLRP1 activation[15] (Table 1).

Genetic deficiency of IL-1Ra (DIRA) is a disease that causes severe neonatal-onset systemic inflammation with sterile multifocal osteitis and skin manifestations. However, in 2023, an individual with an *IL1R1* mutation that was associated with impaired IL-1Ra binding, excessive IL-1 signalling and multifocal osteitis, did not present with skin manifestations[16]. Treatment with anti-IL-1β was sufficient to control

the disease, suggesting that IL-1α did not contribute substantially to the clinical phenotype, consistent with the absence of skin involvement (Table 1).

The role of IL-1 in experimental models of arthritis has been demonstrated using IL-1 blockers and genetically deficient mice[8]. IL-1 blockade was also beneficial in experimental models of osteoarthritis[17]. Monosodium urate, calcium pyrophosphate dihydrate deposition disease and basic calcium crystals can activate the NLRP3 inflammasome, leading to release of mature IL-1β[18,19]. In vitro stimulation of monocytes with serum from people with Still disease led to increased IL-1β release in cell supernatants[20] (Box 2).

Targeting IL-1 in rheumatic and inflammatory diseases

A wide array of drugs that target IL-1 have been developed (Fig. 3 and Table 2). Inhibitors of the inflammasome pathway are also in clinical development and have been reviewed elsewhere[21,22].

Monogenic mutations of inflammasome sensors, in particular *NLRP3* mutations, which cause cryopyrin-associated periodic

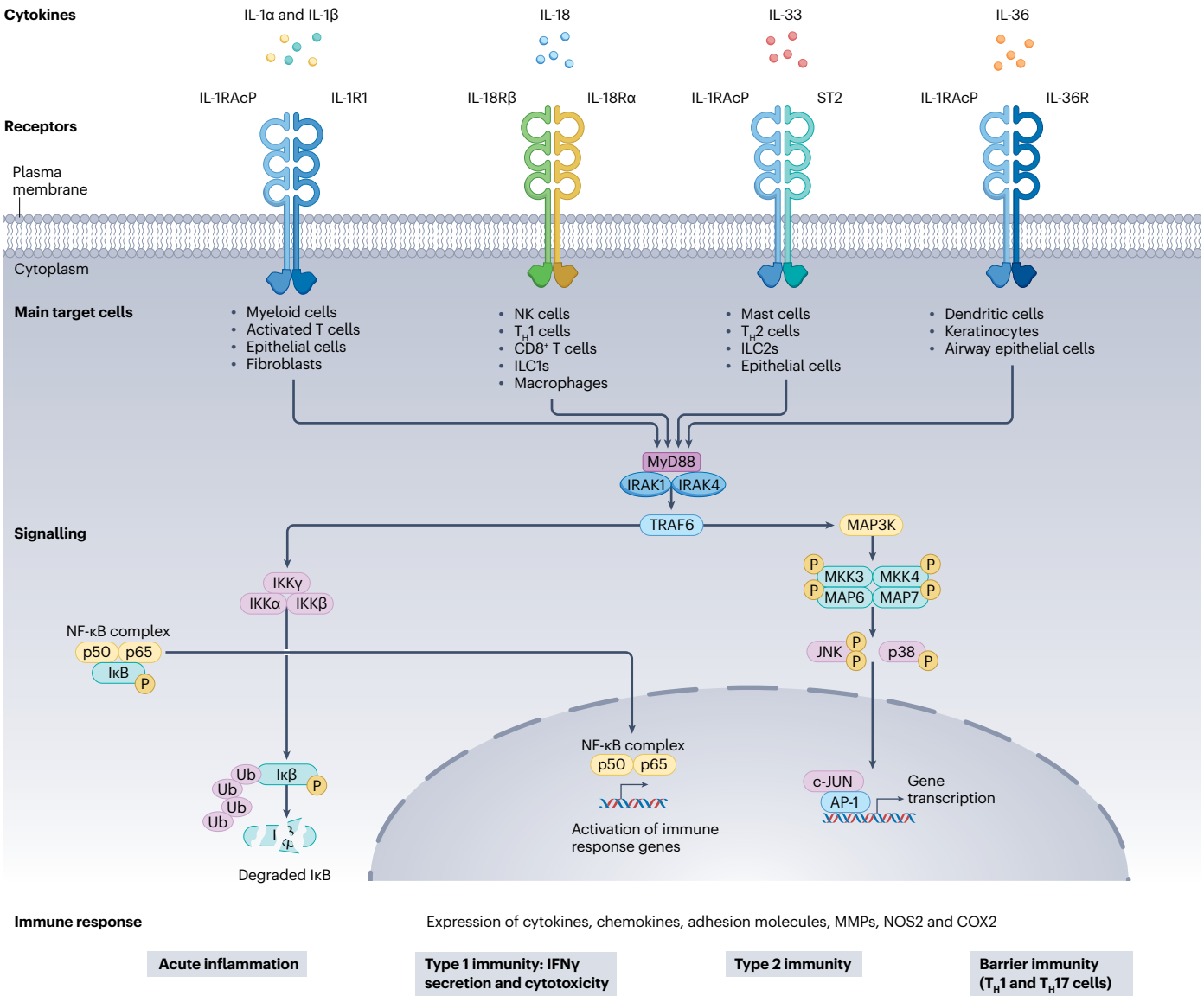


Fig. 2 | Cell-type-specific immune responses driven by IL-1 family cytokines. IL-1 family cytokines, including IL-1, IL-18, IL-33 and IL-36, signal through heterodimeric receptor complexes comprising a ligand-binding chain (IL-1R1, IL-18Rα, ST2 and IL-36R) and the shared co-receptor IL-1 receptor accessory protein (IL-1RAcP) or IL-18Rβ. Despite shared intracellular signalling, each cytokine induces distinct, cell-type-specific responses to orchestrate a range of immune responses from acute inflammation to type 1, type 2 and barrier immunity. AP-1, activator protein 1; cJUN, a transcription factor; COX2, cyclooxygenase-2; IKK, IκB kinase; IκB, inhibitor of κB; ILC, innate lymphoid cell; IRAK, IL-1-receptor-associated kinase; JNK, cJUN N-terminal kinases; MAP3K, mitogen-activated protein kinase kinase kinases; MKK, mitogen-activated protein kinase kinase; MMP, matrix metalloproteinase; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor-κB; NK, natural killer; NOS2, inducible nitric oxide synthase; p38, p38 mitogen-activated protein kinase; T_H cell, T helper cell; TRAF6, TNF-receptor-associated factor 6; Ub, ubiquitin. The original version of this figure was created with BioRender.com.

Box 1 | Inflammasome pathways

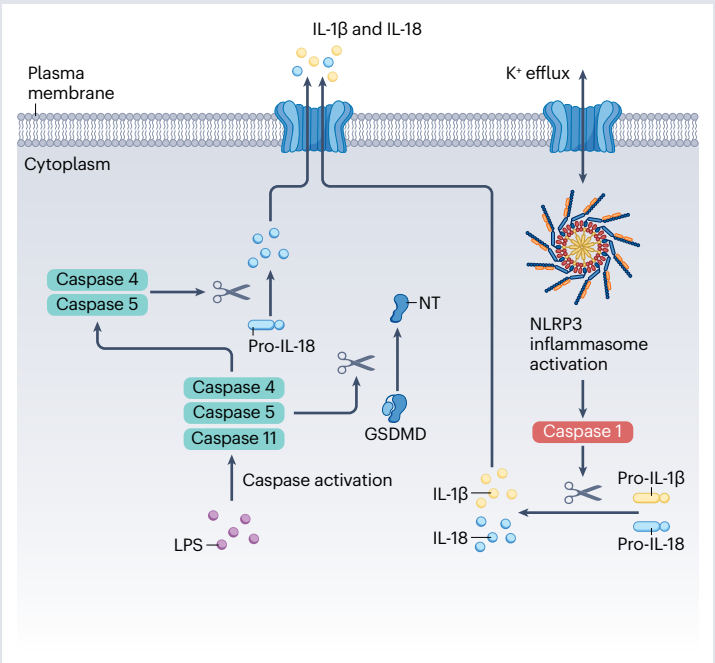
The canonical inflammasome

The canonical inflammasome is made up of a set of cytosolic proteins consisting of sensor molecules (or receptors), the adaptor molecule ASC (apoptosis-associated speck-like protein containing a caspase activation and recruitment domain) and caspase 1. The sensor molecules comprise a NOD-like receptor (NLR). An NLR containing a pyrin domain is referred to as NLRP, whereas an NLR containing a CARD domain is referred to as NLRC. Other inflammasome receptors include AIM2 (absent in melanoma 2) and pyrin. The activation of sensors by exogenous and endogenous molecules typically leads to the recruitment of ASC and pro-caspase 1, followed by protein multimerization, cleavage and activation of caspase 1, followed by pro-IL-1β and pro-IL-18 processing. Gasdermin D (GSDMD) is also a cleavage substrate of caspase 1. Amino-terminal (NT) fragments of GSDMD oligomerize and create cell membrane pores that enable the extracellular release of mature IL-1β and IL-18.

The non-canonical inflammasome

The inflammasome can be activated via an alternative pathway, termed the non-canonical inflammasome (see figure). In this case, cytosolic lipopolysaccharides (LPS) activate caspase 4 and caspase 5 (caspase 11 in mice) leading to gasdermin D cleavage, cell membrane pore formation, K^+ efflux with subsequent NLRP3 inflammasome complex formation. Caspases 4 and caspase 5 (but not caspase 11) can process pro-IL-18 into mature IL-18 (ref. 184).

Pyroptosis is a form of inflammatory cell death[3] that occurs when cell membrane pore formation enables the release of mature IL-1β and IL-18. In addition, nerve-injury-induced protein 1, a cell membrane protein, is also activated during pyroptosis, leading to plasma membrane rupture and the release of various larger danger-associated molecular patterns, including alarmins, with further propagation of the inflammatory responses[185] (Fig. 1).



syndromes (CAPS), lead to excessive IL-1 signalling and have shown remarkable responses to IL-1 antagonists[10]. However, up-dosing of canakinumab (a monoclonal antibody that targets IL-1β) was frequently required to control inflammatory manifestations, particularly in children with CAPS[23]. In another CAPS study, persistent central nervous system inflammation was observed despite canakinumab treatment[24]. In a 7-day proof-of-concept phase II clinical trial in people with CAPS, the NLRP3 inhibitor usnoflast (also known as ZY-IL1) decreased disease activity and inflammatory markers[25]. Other NLRP3 inhibitors are currently being tested for CAPS[21]. Improved tissue penetration might be possible with small-molecule inhibitors, which could lead to better results than those observed with monoclonal antibodies, such as canakinumab, for central nervous system inflammation.

In a randomized, placebo-controlled clinical trial of canakinumab in people with FMF, mevalonate kinase deficiency (MKD) or TNF-receptor-associated periodic syndrome (TRAPS), canakinumab demonstrated efficacy[26]. Regression of symptoms after anakinra treatment (recombinant IL-1Ra) was observed in people with PAPA syndrome[27]. Consistent with the role of urate crystals in IL-1β production, the effects of canakinumab or rilonacept have been examined for the management and prevention of gouty flares. In two multicentre, randomized controlled trials, a single dose of canakinumab was superior to a single dose of triamcinolone acetonide in reducing gout attacks and the risk of new flare-ups in people whose treatment options were limited owing to comorbidities[28]. In another randomized, multicentre clinical trial that included people with gout receiving urate-lowering therapy, canakinumab after a single dose or after four 4-weekly doses provided superior prophylaxis against flare-ups compared with daily colchicine[29]. In a pilot, placebo-controlled, crossover, single-blind clinical trial, rilonacept reduced pain and levels of C-reactive protein in people with chronic gouty arthritis[30]. In a randomized, multicentre, placebo-controlled clinical trial, rilonacept reduced the number of flare-ups following the initiation of urate-lowering therapy[31].

In an open-label, phase IIa, multidose, proof-of-concept clinical trial, the NLRP3 inhibitor dapansutrile (OLT1177) showed a marked reduction of joint inflammation and pain after 3 days and after 7 days of therapy with a good safety profile[32]. Anakinra is efficacious in the treatment of acute calcium pyrophosphate dihydrate deposition disease (often referred to as 'pseudogout')[33] and in people with acute calcific periarthritis[34].

In two phase III randomized controlled trials of canakinumab (one parallel-arm study and one withdrawal study) in paediatric-onset Still disease, treatment was beneficial compared with placebo[35]. In adult-onset Still disease, anakinra has shown efficacy in observational studies and in one randomized controlled trial[36]. In a phase II, randomized, placebo-controlled clinical trial, canakinumab failed to meet its primary outcome (DAS28 > 1.2), but did show improved ACR response rates compared with placebo[37].

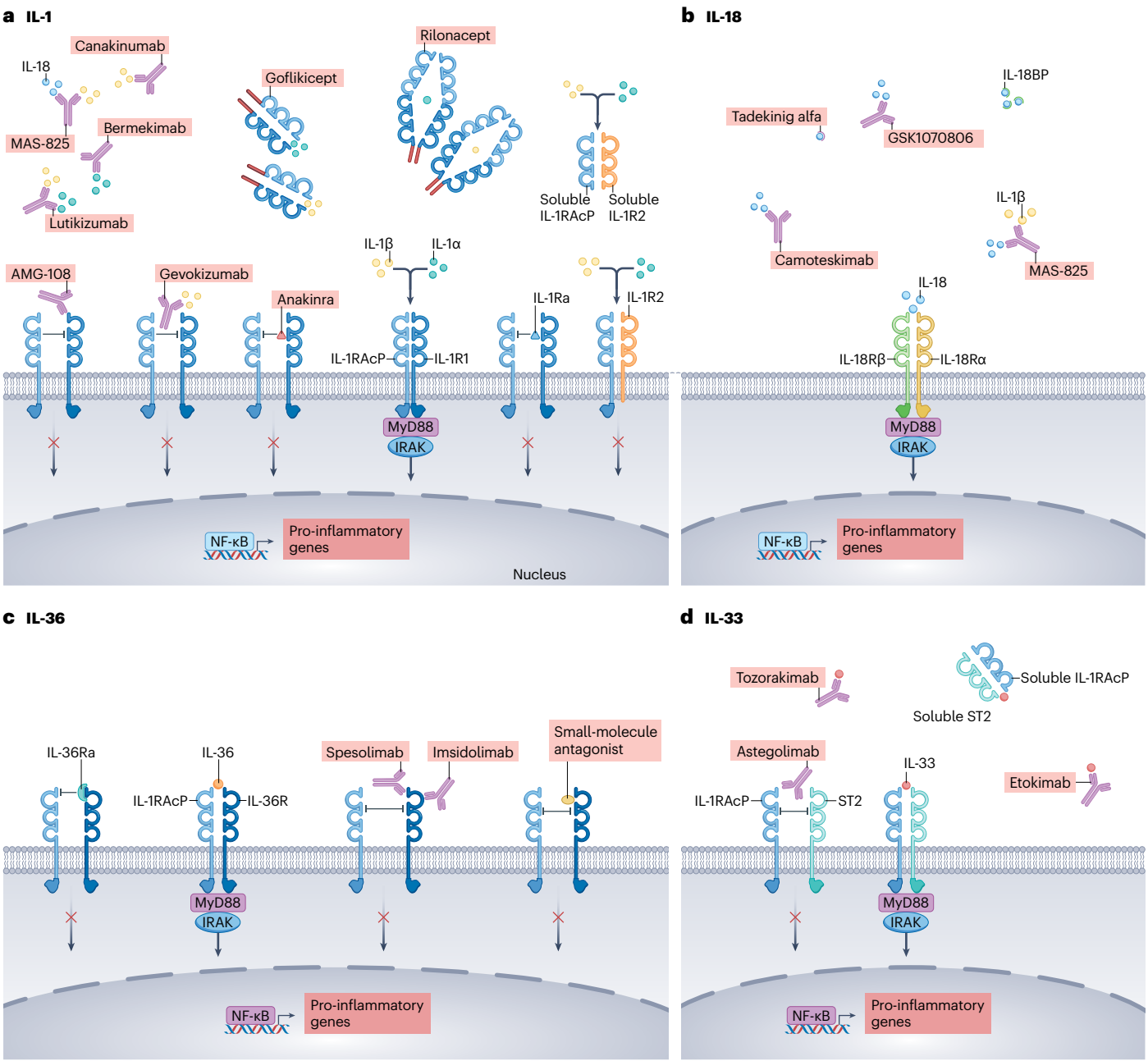


Fig. 3 | Targeting IL-1 cytokine signalling therapeutically. Schematic representation of the signalling of IL-1 cytokines and current therapeutic strategies that target IL-1α, IL-1β, IL-18, IL-36 and IL-33. The binding of cytokines to their respective receptors — IL-1R, IL-18Rα, IL-36R and ST2 — induces recruitment of the accessory protein IL-1RAcP (or IL-18Rβ), triggering myeloid differentiation primary response 88 (MyD88)-dependent signalling cascades that involve IRAK activation and NF-κB-mediated transcription of pro-inflammatory genes. **a**, IL-1α and IL-1β signalling can be inhibited using monoclonal antibodies (canakinumab, gevokizumab, bermekimab, lutikizumab and AMG-108), the recombinant receptor antagonist anakinra and the decoy receptor fusion proteins rilonacept and goflikicept. Soluble IL-1R2 and IL-1RAcP, the antagonist IL-1Ra and the decoy receptor IL-1R2 are also depicted as endogenous regulatory mechanisms. Soluble IL-1R2 forms a high-affinity trimeric complex with IL-1 and soluble IL-1RAcP. **b**, IL-18 signalling via IL-18Rα and IL-18Rβ can be neutralized by recombinant IL-18 binding protein (IL-18BP, tadekinig alfa) and monoclonal antibodies that target IL-18 (camoteskimab and GSK1070806) and the bispecific antibody MAS-825 (which targets IL-18 and IL-1β). IL-18BP is shown as a natural IL-18-binding inhibitor. **c**, IL-36α, IL-36β and IL-36γ engagement of IL-36R can be inhibited by IL-36R-targeting monoclonal antibodies (spesolimab and imsidolimab) and small-molecule antagonists. IL-36Ra is shown as a natural receptor antagonist. **d**, IL-33 binding to ST2 can be blocked therapeutically using anti-IL-33 antibodies (tozorakimab, etokimab) or anti-ST2 antibodies (astegolimab). Soluble ST2 is represented as a physiological decoy receptor. Soluble ST2 forms a high-affinity trimeric complex with IL-33 and soluble Il-1RAcP. IL-1RAcP, IL-1 receptor accessory protein; IL-1R1, IL-1 receptor type 1; IL-36R, IL-36 receptor; IL-18Rα, IL-18 receptor α; IL-18Rβ, IL-18 receptor β; IL-36Ra, IL-36 receptor antagonist; IRAK, IL-1-receptor-associated kinase; NF-κB, nuclear factor-κB. The original version of this figure was created with BioRender.com.

Table 1 | Monogenic autoinflammatory diseases driven by IL-1 family cytokines

Mutated gene	Disease	Main symptoms	Cytokine(s)	Refs.
Inflammasome sensor-associated diseases				
NLRP3 (cryopyrin-associated periodic syndromes)	Familial cold autoinflammatory syndrome	Chills, conjunctivitis, myalgia, arthralgia and fever	IL-1β	Reviewed in ref. 10
	Muckle–Wells syndrome	Urticarial rash, conjunctivitis, myalgia, arthralgia and fever		
	Neonatal-onset multisystem inflammatory disease	Chronic meningitis (hearing and vision loss), impaired mental and physical growth, knee arthropathy and bony overgrowth, urticarial rash and fever		
NLRP1	Syndromic form of juvenile-onset recurrent respiratory papillomatosis	Respiratory papillomatosis and various mild skin lesions	IL-1β	162
	NLRP1-associated autoinflammation with arthritis and dyskeratosis (NAIAD)	Fever, diffuse skin dyskeratosis and arthritis	IL-1β, IL-18	163
NLRC4 (NLRC4-associated auto-inflammatory diseases)	Familial cold autoinflammatory syndrome 4 (FCAS4)	Urticaria and fever	IL-1β, IL-18	164
	Autoinflammation with infantile enterocolitis (AIFEC)	MAS, severe enterocolitis, skin rash and fever		82
MEFV	Familial Mediterranean fever (FMF)	Fever, serositis, arthralgia or arthritis and erysipelas-like erythema	IL-1β	Reviewed in ref. 10
	Pyrin-associated autoinflammation with neutrophilic dermatosis	Fever, neutrophilic dermatosis, arthralgia and myalgia		12,13
Other inflammasome-related disorders				
PTSPIP1	Pyogenic arthritis with pyoderma gangrenosum and acne	Arthritis and skin lesions	IL-1β, IL-18	Reviewed in ref. 51
	PSTPIP1-associated myeloid proteinaemia inflammatory syndrome	Fever, cytopenia, splenomegaly and colitis		
MVK	Mevalonate kinase deficiency (also known as hyper-IgD syndrome)	Fever, skin rash, mouth ulcers, cervical lymphadenopathies, abdominal pain, diarrhoea, joint pain and muscle pain	IL-1β, IL-18	14,72
WDR1	WDR1 deficiency	Fever, skin rash, mouth and perianal ulcers, thrombocytopenia and immunodeficiency	IL-1β, IL-18	165
CDC42 (C-terminus)	Neonatal onset cytopenia, autoinflammation and recurrent HLH	Fever, skin rash and MAS	IL-1β, IL-18	Reviewed in ref. 51
DPP9	DPP9 deficiency	MAS, skin pigmentation abnormalities and poor growth	IL-1β, IL-18	15
Loss-of-inhibition-related diseases				
IL1RN	Deficiency of IL-1 receptor antagonist (DIRA)	Fever, multifocal osteomyelitis and pustulosis	IL-1	Reviewed in ref. 10
IL36RN	Deficiency of IL-36 receptor antagonist (DITRA)	Fever and generalized pustular psoriasis	IL-36	141
IL1R1	*IL1R1* mutation	Multifocal osteomyelitis	IL-1β, IL-18	16
IL18BP	IL-18BP deficiency	Fulminant viral hepatitis	IL-18	166
Others				
XIAP	XIAP deficiency (including type 2 X-linked lymphoproliferative syndrome)	Colitis, hepatitis, uveitis and MAS	IL-18	Reviewed in ref. 51
PNP	Purine nucleoside phosphorylase deficiency	Combined immunodeficiency and MAS	IL-18	Reviewed in ref. 51
PEPD	Prolidase deficiency	Chronic skin ulcers and immunodeficiency	IL-18	Reviewed in ref. 51

DPP9, dipeptidyl peptidase 9; IgD, immunoglobulin D; IL-18BP, IL-18 binding protein; MAS, macrophage activation syndrome; PSTPIP1, proline–serine–threonine phosphatase-interacting protein 1; WDR1, WD repeat domain 1; XIAP, X-linked inhibitor of apoptosis.

The efficacy and safety of IL-1 inhibitors have been extensively evaluated in rheumatoid arthritis (RA). Evidence from clinical trials show acceptable safety profiles but only modest efficacy. Indeed, a meta-analysis of clinical trials showed that people with RA treated with anakinra were less likely to achieve ACR20, ACR50 or ACR70 responses than those receiving TNF antagonists[38]. Clinical trials of anakinra in

ankylosing spondylitis and psoriatic arthritis also had disappointing outcomes[39,40].

In addition, clinical trials of IL-1 antagonists in knee and hand osteoarthritis were mostly negative[41–43]. However, an exploratory post hoc analysis of the CANTOS trial showed that the hazard ratio for total hip or knee replacement owing to osteoarthritis was substantially reduced in people treated with canakinumab[44]. NLRP3 inhibitors are currently being tested in people with knee osteoarthritis[21].

The striking efficacy of IL-1 blockade in CAPS inspired additional clinical trials and off-label use in other autoinflammatory syndromes[45]. Clinical manifestations of Schnitzler syndrome (a rare autoinflammatory syndrome characterized by the occurrence of hives, fever and bone lesions and IgM gammopathy) responded to either anakinra or canakinumab[46,47]. Randomized controlled trials of bermekimab (an anti-IL-1α antibody) in people with hidradenitis suppurativa who were either naive to anti-TNF therapy or who did not respond to TNF inhibitors, showed positive results[48]; however, these positive results were not confirmed in a 2025 study[49]. Bermekimab is currently under investigation in pyoderma gangrenosum (NCT01965613). In a phase II clinical trial, lutikizumab, a humanized bispecific antibody that neutralizes both IL-1α and IL-1β, showed positive results in hidradenitis suppurativa[50].

IL-1 inhibitors have been approved in several indications and are also being tested in many other inflammatory diseases. In addition to antibodies that target either of the IL-1 agonists, other drugs blocking inflammasome components are in clinical development, further increasing the therapeutic armamentarium against these cytokines.

IL-18

IL-18 was recognized as a member of the IL-1 family in 1995, six years after its initial description as an IFNγ-inducing factor. The implication of IL-18 in the pathogenesis of some autoinflammatory diseases was established a decade ago, leading to the development of several inhibitors.

IL-18 biology

IL-18 has a maturation and release process similar to that of IL-1β, which occurs when the inflammasome–caspase 1 pathway is activated. Unlike IL-1β, IL-18 is constitutively expressed in various cell types, especially myeloid cells, but also in epithelial cells, and can be further upregulated in response to TLR agonists, IFNα and IFNγ (reviewed in ref. 51). Once secreted, IL-18 activity is tightly controlled by IL-18 binding protein (IL-18BP), which functions as a decoy receptor (Figs. 1 and 3b). IL-18BP circulates in the blood at high concentrations and binds mature IL-18 with high affinity (dissociation constant of approximately 50 picomolar)[52]. In this Review, we use the term 'total' IL-18 to describe IL-18 whether it is complexed to IL-18BP or not, whereas 'free IL-18' refers to IL-18 unbound to IL-18BP. IL-18Rα is constitutively expressed on the surface of various cell types, whereas IL-18Rβ is constitutively expressed on natural killer (NK) cells, NK-like innate lymphoid cells (ILCs) and on activated $CD4^+$ and $CD8^+$ T cells. The expression of IL-18Rβ is dependent on IL-2, IL-12 or IL-15 (reviewed in ref. 51). IL-18 activates intracellular signalling pathways similar to those of IL-1R. Additional signalling pathways have also been described including signal transducer and activator of transcription 3 (STAT3), tyrosine kinase 2 (TYK2), nuclear factor of activated T cells, cytoplasmic 4 (NFATc4) and PI3K–AK–mTOR (phosphoinositide 3 kinase–protein kinase B–mechanistic target of rapamycin)[53]. IL-18 mainly promotes type 1 immunity, especially by inducing IFNγ secretion and cytotoxicity, but can also exert alternative functions (activation of the T helper cells T_H2 and T_H17) depending on the cytokine microenvironment (reviewed in ref. 51). IL-18BP is constitutively produced by a wide array of haematopoietic and non-haematopoietic cells and is further induced by IFNγ, thereby creating a negative feedback loop[54].

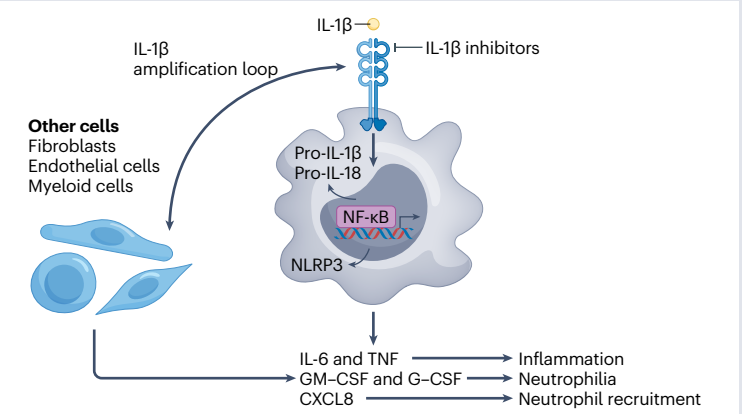
IL-18 in rheumatic and inflammatory diseases

IL-18 expression has been explored in many rheumatic and inflammatory diseases. Compared with healthy individuals, serum levels of IL-18 are elevated in RA, systemic lupus erythematosus and other connective tissue diseases, Crohn disease and anti-neutrophil cytoplasmic antibody-associated vasculitis; serum levels of IL-18 often

Box 2 | IL-1 signalling in Still disease

Evidence suggests that IL-18 is involved in the pathogenesis of Still disease. However, IL-1β blocking agents are widely and successfully used in clinical practice to treat these conditions. These treatments do not directly interfere with inflammasome activation and mature IL-18 production but inhibit the stimulatory effect of IL-1β on macrophages (and other cell types; see figure), thus dampening the inflammatory manifestations of Still disease, which include:

- NLRP3 expression
- IL-1β and IL-18 gene expression
- Production of pro-inflammatory cytokines, colony-stimulating factors and chemokines (such as IL-6, TNF, GM–CSF, G-CSF and CXCL8)
- Phagocytosis



CXCL8, C-X-C motif chemokine ligand 8; GM–CSF, granulocyte-macrophage colony-stimulating factor; G–CSF, granulocyte-colony-stimulating factor; NF-κB, nuclear factor-κB.

Table 2 | Biologic therapies in clinical development that target IL-1 family members

Drug	Conditions	Development stage
Targeting IL-1		
Anakinra (recombinant receptor antagonist)	Rheumatoid arthritis, CAPS, FMF and severe COVID-19 pneumonia	Approved
	Prevention of knee osteoarthritis after anterior cruciate ligament injury	Phase I clinical trial, recruiting (NCT03968913)
	Refractory haemochromatosis	Phase II clinical trial, terminated (NCT02263638)
	Coronary artery disease in rheumatoid arthritis	Completed trial (NCT01566201), improved coronary artery and left ventricular function[167]
Canakinumab (human anti-IL-1β mAb)	CAPS, TRAPS, MVK, FMF, Still disease, gout flares and Schnitzler syndrome	Approved for Schnitzler syndrome in Japan. Ongoing observational clinical trial for CAPS, FMF, MVK and juvenile-onset Still disease in Korea (NCT06838143)
	Polymyalgia rheumatica	Phase III, three-armed, clinical trial comparing secukinumab, canakinumab or prednisone (NCT01364389), terminated and failed[168]
Gevokizumab (humanized anti-IL-1β mAb)	Pyoderma gangrenosum	Several trials completed but results are unpublished: phase II, completed (NCT01882504); phase III terminated (NCT02315417, NCT02326740, NCT02318914). No current active clinical trials in rheumatic diseases
Bermekimab (human anti-IL-1α mAb)	Systemic sclerosis	Phase II, randomized placebo-controlled, proof-of-concept clinical trial, completed (NCT04045743); lung function improved and the number of inflamed joints decreased[169]
	Atopic dermatitis	Several phase II clinical trials completed (NCT04021862, NCT03496974, NCT03953196, NCT04544813) or terminated (NCT04990440, NCT04791319). Efficacy has been observed in small trials, but not confirmed in larger clinical trials[170]
	Hidradenitis suppurativa	Several phase II clinical trials completed (NCT04019041, NCT03512275) or terminated (NCT04988308). Positive results in participants naive to or who did not respond to anti-TNF therapy. Results were not confirmed in another study, leading to early termination for inefficacy[49]
	Moderate-to-severe acne vulgaris	Phase II clinical trial, completed (NCT01474798), unpublished results
	Moderate-to-severe psoriasis	Phase II clinical trial completed (NCT01384630). Good tolerability and mild effects shown in eight participants[171]
	Pyoderma gangrenosum	Phase II clinical trial, completed (NCT01965613), unpublished results
Lutikizumab (humanized mAb that neutralizes IL-1α and IL-1β)	Crohn disease and ulcerative colitis	Phase II clinical trial, recruiting (NCT06548542); phase II trial active, recruitment complete (NCT06257875)
	Rheumatoid arthritis and psoriatic arthritis	Phase II clinical trials, evaluating multiple therapies (NCT06972446, NCT06865105) are recruiting
	Atopic dermatitis	Phase II clinical trial, recruiting (NCT06718101)
	Hidradenitis suppurativa	Phase III clinical trial, recruiting (NCT06468228)
Rilonacept (fusion protein)	CAPS and recurrent pericarditis	Approved
	DIRA	Phase II clinical trial completed (NCT01801449). Anakinra-induced remission was maintained with rilonacept[172]
	Cardiac sarcoidosis	Phase II clinical trial, recruiting (NCT06660732)
	Subacromial bursitis	Randomized clinical trial comparing local injections of rilonacept versus triamcinolone (glucocorticoid), completed (NCT01830699). Rilonacept was less efficacious than triamcinolone[173]
Goflikicept (fusion protein)	Recurrent pericarditis	Phase III clinical trial, active, recruitment complete (NCT05673902)
Targeting IL-18		
Tadekinig alfa	Adult-onset Still disease	Phase II clinical trial, completed (NCT02398435). Clinical and biological markers improved, glucocorticoid tapering effect shown[81]
	NLRC4-MAS and XIAP deficiency	Phase III clinical trial, completed (NCT03113760), with open label extension, completed (NCT03512314), unpublished results
	CAR-T-cell-related cytokine release syndrome and HLH-like syndrome	Early phase I clinical trial, recruiting (NCT05306080)
MAS825	NLRC4-associated autoinflammatory diseases, AIFEC, XIAP deficiency and CDC42 mutations	Phase II clinical trial, active, recruitment complete (NCT04641442)
	Adult and paediatric Still disease	Phase II clinical trial, recruiting (NCT07203001)

Table 2 (continued) | Biologic therapies in clinical development that target IL-1 family members

Drug	Conditions	Development stage
Targeting IL-18 (continued)		
MAS825 (continued)	Coronary heart disease and CHIP	Phase II clinical trial, completed (NCT06097663), unpublished results
	COVID-19 pneumonia and impaired respiratory function	Phase II clinical trial, completed (NCT04382651). Failed to improve primary outcome (Apache II score)[88]
	Hidradenitis suppurativa	Phase II clinical trial, active, recruitment complete (NCT03827798)
GSK1070806	Atopic dermatitis	Phase II clinical trial, terminated (NCT05999799), with long-term extension study, terminated (NCT06447506), unpublished results
	Crohn disease	Phase I–II clinical trial, completed (NCT03681067), unpublished results
	Behçet syndrome	Phase II clinical trial, unknown status (NCT03522662)
	Prevention of delayed graft function after renal transplantation	Phase II clinical trial, terminated (NCT02723786), failed[174]
	Type 2 diabetes mellitus	Phase II clinical trial, terminated (NCT01648153), failed to improve glucose plasma levels[175]
Camoteskimab	Still disease	Phase I clinical trial, terminated (NCT04752371), unpublished results
	Atopic dermatitis	Phase II clinical trial, completed (NCT06436183), primary endpoint met
Targeting IL-33		
Tozorakimab (anti-IL-33 mAb)	COPD	Phase I and II clinical trials completed (NCT03096795). Positive effect in a subgroup of participants with COPD with a high risk of exacerbations[121,122]; several phase III clinical trials ongoing (NCT05742802, NCT06040086)
Itepekimab (anti-IL-33 mAb)	COPD and bronchiectasis	Phase I clinical trial completed (NCT06280391)[176]; phase II trial, ongoing (NCT06208306)
	Chronic rhinosinusitis	Phase III clinical trial, ongoing (NCT06834347)
Etokimab (anti-IL-33 mAb)	Atopic dermatitis	Phase II clinical trial completed (NCT03533751), primary endpoint not reached
	Peanut allergy	Phase II clinical trial, completed (NCT02920021), safe with potential to desensitize people with peanut allergy[177]
	Severe eosinophilic asthma	Phase II clinical trial, completed (NCT03469934), unpublished results
	Rhinosinusitis	Phase II clinical trial, completed (NCT03614923), failed to reach primary endpoint in interim analysis
Melrilimab (anti-ST2 mAb)	Asthma	Phase I clinical trial (NCT04366349), completed[178]; phase II (NCT03207243), completed. Encouraging safety, pharmacology and efficacy results[179]
Astegolimab (anti-ST2 mAb)	COPD and severe asthma	Phase I clinical trial, completed without safety concerns[180]; phase II clinical trials completed (NCT06462118, NCT05037929) with results in preparation; phase III clinical trial in COPD, recruiting (NCT05595642)
	Severe atopic dermatitis	Phase II clinical trial completed (NCT03747575), failed primary and secondary endpoints[181]
Targeting IL-36		
Spesolimab (BI-655130)	Generalized pustular psoriasis flare	FDA approved (2022)[154,182]. Phase IV clinical trial, active, recruitment complete (NCT06013969)
	Hidradenitis suppurativa	Phase II clinical trial, completed (NCT04762277, NCT04876391)[183] Phase IIb–III clinical trials, completed (NCT05819398, NCT06241573); no definitive results published yet
	Pyoderma gangrenosum	Phase II clinical trial, terminated (NCT06092216), unpublished results; phase III clinical trial, ongoing (NCT06624670)
	Palmoplantar pustulosis	Phase II clinical trial, terminated (NCT04493424), failed, unpublished results
	Ulcerative colitis and inflammatory bowel disease	Phase II clinical trials, completed (NCT03648541, NCT03123120); unpublished results Phase II–III clinical trial, completed (NCT03482635); failed to meet its primary endpoint, unpublished results
	Netherton syndrome	Phase II–III clinical trial, terminated (NCT05856526), unpublished results
	Crohn disease	Phase II clinical trial, terminated (NCT05013385); failed, unpublished results Phase II clinical trial, completed (NCT03752970); failed, unpublished results
Imsidolimab (ANB019)	Generalized pustular psoriasis	Phase II clinical trial completed (NCT03619902)[155]; results showed rapid resolution of symptoms and pustular eruptions Phase III clinical trial, completed (NCT05352893) and terminated (NCT05366855); treatment reduced the occurrence of disease flares. Awaiting FDA approval (2026)
	Palmoplantar pustulosis	Phase II clinical trial, completed (NCT03633396); failed, unpublished results
	Acne vulgaris	Phase II clinical trial, completed (NCT04856917); failed, unpublished results

Table 2 (continued) | Biologic therapies in clinical development that target IL-1 family members

Drug	Conditions	Development stage
Targeting IL-36 (continued)		
Imsidolimab (ANB019) (continued)	Hidradenitis suppurativa	Phase II clinical trial, completed (NCT04856930); failed, unpublished results
	Ichthyosis	Phase II clinical trial, terminated (NCT04697056); failed, unpublished results
	Acneiform rash	Phase IIa clinical trial in people with cancer receiving EGFR inhibitors or MEK inhibitors (NCT04697069); terminated probably owing to low recruitment (4 participants)
IL-36 small-molecule antagonists	Inflammatory diseases	Preclinical stage

AIFEC, autoinflammation with infantile enterocolitis; CAPS, cryopyrin-associated periodic syndrome; CDC42, cell division control protein 42; CAR, chimeric antigen receptor; CHIP, clonal haematopoiesis of indeterminate potential; COPD, chronic obstructive pulmonary disease; DIRA, deficiency of IL-1 receptor antagonist; EGFR, epidermal growth factor receptor; FMF, familial Mediterranean fever; HLH, haemophagocytic lymphohistiocytosis; mAb, monoclonal antibody; MEK, MAP kinase kinases; MVK, mevalonate kinase deficiency; TRAPS, TNF-receptor-associated periodic fever syndrome; XIAP, X-linked inhibitor of apoptosis.

correlate with disease activity (reviewed in ref. 55). Moreover, IL-18 overexpression has been described in the synovium of people with RA[56] and in people with lupus nephritis[57], in the salivary glands of people with Sjögren disease[58] and in the colonic tissue of people with Crohn disease[59]. Preclinical studies in animal models and ex vivo experiments support a pathogenic role of IL-18 in several rheumatic diseases and have paved the way for IL-18-targeted therapies (reviewed in ref. 60).

Tadekinig alfa, a recombinant human IL-18BP, was administered to people with RA or psoriasis in clinical trials but failed to demonstrate efficacy for these indications[61]. One explanation for these disappointing results lies in the unique mechanisms that regulate IL-18 biology. Indeed, elevated total IL-18 levels do not necessarily result in any biological effect unless IL-18 production exceeds the binding capacity of IL-18BP (reviewed in ref. 62).

During the past decade, a distinct group of hyperinflammatory conditions have been described, which are characterized by substantial release of mature IL-18 and detectable free IL-18 (refs. 52,63). These diseases belong to the group of autoinflammatory diseases termed 'IL-18opathies'[51]. In addition, markedly high levels of IL-18 are a hallmark of macrophage activation syndrome (MAS), a life-threatening complication shared by several IL-18opathies[51].

IL-18 in autoinflammatory diseases

The established EULAR–PReS (Paediatric Rheumatology European Society) recommendations for the management of Still disease recognized systemic-onset juvenile idiopathic arthritis and adult-onset Still disease as a single clinical entity[64]. These recommendations also support the inclusion of measuring IL-18 levels for the diagnosis of Still disease.

In a European collaborative study, serum levels of total IL-18 in Still disease could discriminate it from other monogenic or genetically undiagnosed autoinflammatory diseases with a higher accuracy than other tested biomarkers, including ferritin[65]. Free IL-18 was detected in only a minority of the tested diseases, and the highest levels were found in Still disease. Elevated IL-18 levels in Still disease were associated with a higher risk of MAS and a protracted disease course[66]. Among hyperinflammatory syndromes, circulating IL-18 levels are particularly high in people with MAS that occurs in the context of Still disease, NLRC4-associated autoinflammatory disorder or X-linked inhibitor of apoptosis (XIAP) deficiency as compared with other conditions such as Kawasaki disease-like hyperinflammatory syndrome, virus-associated or malignant haemophagocytic lymphohistiocytosis[67,68].

Lung disease is another severe complication of Still disease, which is associated with elevated total and free IL-18 levels. Drugs that block IL-18 have shown promise for this complication[69,70].

Notably, circulating IL-18 levels are not elevated in other autoinflammatory diseases associated with excessive inflammasome activity. For example, IL-18 levels are not increased in people with cryopyrinopathies[65]. Some people with FMF exhibit elevated total IL-18 levels that are comparable to those observed in people with Still disease; however, free IL-18 is barely detectable in these people[65]. This discrepancy is not related to higher levels of IL-18BP in FMF. Instead, the differences between FMF and Still disease might relate to the kinetics of inflammatory flares, which are substantially longer in Still disease, resulting in higher and more sustained IL-18 production.

Findings also suggest that MKD might also be driven by IL-18, given that elevated total IL-18 levels have been reported in people with MKD[65,71,72]. Other autoinflammatory disorders such as PSTPIP1-associated PAPA and PAMI syndromes also exhibit elevated levels of IL-18 (refs. 11,73).

IL-18 in connective tissue diseases

Systemic lupus erythematosus was the first connective tissue disease in which IL-18 expression was investigated. Findings have been inconclusive thus far; however, IL-18 might have a specific role in lupus nephritis and neuropsychiatric lupus, especially in seizures[74,75]. Elevated serum levels of IL-18 have been reported in idiopathic inflammatory myopathies in adults and in juvenile dermatomyositis, but typically they are far below those observed in IL-18opathies[76,77]. IL-18 levels are particularly elevated in people with interstitial lung disease[77,78]. These people also have increased ferritin levels, although not to the extent seen in Still disease and MAS. More broadly, serum levels of IL-18 are considerably higher in those people with connective tissue diseases that are complicated with interstitial lung diseases[79,80]. The therapeutic benefit of targeting IL-18 in this subset of patients remains to be determined.

IL-18 targeting for the management of rheumatic and inflammatory diseases

Thus far, no IL-18 inhibitor has been licensed but four IL-18 blocking agents are currently being evaluated in clinical trials (Fig. 3 and Table 2). Tadekinig alfa is the recombinant form of human IL-18BP, the

administration of which resulted in a substantial and rapid response in adults with Still disease in a phase II clinical trial[81]. This drug also successfully treated a critically ill infant with an NLRC4 gain-of-function mutation complicated by severe enterocolitis and MAS[82]. Clear efficacy was also demonstrated in a child with Still disease complicated by recurrent MAS[83]. Two adults with Still disease who received prolonged tadekinig alfa treatment demonstrated excellent response and good tolerance[84]. In a patient with a refractory form of XIAP deficiency, treatment with tadekinig alfa led to fast and sustained disease management[85]. These reports emphasize the quick and remarkable decrease in free IL-18 levels following the first dose of tadekinig alfa.

Notably, in one patient, relapse following discontinuation of tadekinig alfa coincided with a rise in free IL-18 levels[84]. A phase III clinical trial of tadekinig alfa in NLRC4-associated autoinflammatory disease and XIAP deficiency has been conducted but the results are not yet published (NCT03512314). MAS825 is a bispecific anti-IL-1β and anti-IL-18 antibody. Its efficacy, safety and tolerability are currently under evaluation in two phase II clinical trials in people with monogenic IL-18opathies, including NLRC4-associated autoinflammatory disease, XIAP deficiency and CDC42 mutations (NCT04641442) and in both children and adults with Still disease (NCT07203001). Several case reports have described promising clinical responses with acceptable safety profiles in children with Still disease complicated with recurrent MAS[70,86,87], and in two children with severe Still disease-associated lung disease[69,70]. Notably, MAS825 failed to improve the APACHE II score in a phase II clinical trial assessing its efficacy in individuals with COVID-19 pneumonia and impaired respiratory function[88]. MAS825 is also being tested in severe hidradenitis suppurativa (NCT03827798). GSK1070806 and camoteskimab are both anti-IL-18 IgG1 monoclonal antibodies. Camoteskimab is a fully human antibody, whereas GSK1070806 is a humanized antibody. A clinical trial that intended to evaluate camoteskimab in Still disease was prematurely terminated because of insufficient recruitment (NCT04752371). Camoteskimab has been tested for atopic dermatitis, but the results have not yet been reported (NCT06436183). Atopic dermatitis is also the first indication that GSK1070806 has been assessed for in clinical trials, although no results are currently available. A clinical trial of GSK1070806 in Behçet disease is planned but its status has not been reported. Results from a clinical trial evaluating GSK1070806 in moderate to severe Crohn disease are also pending.

The only evidence supporting an effect of GSK1070806 in a chronic inflammatory disease comes from the successful treatment of an individual with very early onset inflammatory bowel disease who had elevated serum IL-18 levels and no identified pathogenic mutation[89].

The effect of IL-18 inhibitors in a variety of inflammatory diseases is an area of active investigation. Promising results reported from case series of people with genetic and non-genetic autoinflammatory diseases, a phase II clinical study in adults with Still disease and ongoing clinical trials might lead to future licensing of some of these drugs.

IL-33

The IL-33 receptor ST2 was identified approximately 15 years prior to the discovery of its ligand and was initially considered to be an orphan receptor. The identification of IL-33 was a crucial step in defining the role of the IL-33–ST2 pathway under different inflammatory conditions, prompting the subsequent development of drugs that target this pathway for the management of human diseases.

IL-33 biology

IL-33 is encoded by a gene located on chromosome 9 in humans (chromosome 19 in mice) and was originally identified as a nuclear factor in endothelial cells[90,91]. IL-33 localizes to the nucleus, where its N-terminal domain, a conserved homeodomain-like helix-turn-helix motif, binds to DNA chromatin[92]. This nuclear protein is passively released upon cell damage or necrosis and is therefore classified as an alarmin. Primarily recognized for its extracellular bioactivity, but evidence suggests that IL-33 might also have intracellular functions[93]. IL-33 is biologically active in its full-length form (30–32 kilodaltons); however, during acute inflammation, its extracellular activity is further enhanced by the cleavage of its N-terminal domain by various proteases[94]. Conversely, this activity can be counteracted when the C-terminal IL-1 family core structure is disrupted, such as following chymase processing[95]. Furthermore, IL-33 proteolysis by caspase 3 or caspase 7 during apoptosis results in functional inactivation [96] (Fig. 1).

IL-33 is constitutively expressed by various barrier cell types and can also be induced in activated innate immune cells and fibroblasts. Once released extracellularly, IL-33 interacts with its cognate heterodimeric receptor complex, composed of the ST2 receptor (also named IL-33Rα) and IL-1RAcP (Fig. 2). This interaction activates the classical IL-1R–TLR signalling pathway, leading to T_H2-cell-dominated inflammatory responses[97]. The IL-33 receptor is expressed on fibroblasts, mast cells, T_H2 cells (regulated by GATA3) and can be induced on T_H1 cells, regulatory T (T_{reg}) cells and ILC2s. Beyond T_H2 cells, IL-33 enhances the production of type I cytokines, such as IFNγ[98] and can promote T_H17 cell responses[99], depending on the target cell. IL-33 also has a role in tissue repair and epithelial regeneration[100].

IL-33 activity is tightly regulated by several endogenous mechanisms. Soluble ST2 binds IL-33 and forms a trimeric high-affinity complex with soluble IL-1RAcP, thereby neutralizing its activity (Figs. 2 and 3d). Additionally, IL-33 oxidation and disulfide bond formation prevent it from binding to ST2, providing another layer of regulation[101]. A regulatory role of IL-33 has also been described, whereby IL-33 signalling induces $ST2^+$ T_{reg} cells to produce IL-1Ra, thereby limiting innate inflammatory responses[102].

IL-33 in rheumatic and inflammatory diseases

In addition to its well established role in T_H2-cell-mediated diseases, such as asthma, atopic dermatitis and allergic rhinitis, the IL-33–ST2 axis has been implicated in a variety of rheumatic and inflammatory disorders, including osteoarthritis[103]. Both circulating and synovial fluid levels of IL-33, and its decoy receptor soluble ST2, are elevated in RA as compared with osteoarthritis and psoriatic arthritis[104]. The extracellular matrix of the inflamed synovium has been described as an important source of IL-33, further supporting its involvement in RA pathophysiology[105]. Elevated IL-33 levels in RA correlate with increased disease activity[106] and with markers of disease severity, including the presence of autoantibodies and bony erosions[107,108].

IL-33 has also been implicated in extra-articular manifestations of RA, notably interstitial lung disease, in which it mediates inflammatory responses through the ERK signalling pathway[109]. In spondyloarthritis, IL-33 has a key role in regulating new bone formation, potentially contributing to disease progression[110]. In systemic sclerosis, IL-33 is associated with fibrosis and endothelial dysfunction, highlighting its role in tissue remodelling and vasculopathy[111–113].

Experimental models have further demonstrated the pro-arthritogenic effects of ST2 signalling. In the mouse collagen-induced arthritis model, administration of a neutralizing anti-ST2 antibody

alleviated arthritis severity and bony erosions[105]. Similarly, ST2-deficient (*St2*$^{-/-}$) mice were protected in the collagen-induced arthritis model, whereas IL-33 administration exacerbated arthritis severity in *St2*$^{-/-}$ mice engrafted with wild-type mast cells, underscoring the contribution of mast cells in IL-33-driven arthritis[114]. In the methylated bovine serum albumin-induced arthritis model, IL-33 promotes joint inflammation by activating ST2^{+} macrophages, which in turn enhances neutrophil recruitment through the production of chemokines (CXCL1 and CCL3) and cytokines (TNF and IL-1β)[115]. *St2*$^{-/-}$ mice were also protected in the serum-transfer-induced arthritis model[116].

The role of IL-33 in bone turnover is still not fully understood, with conflicting data reported[117]. Chronic IL-33 overexpression in CMV–IL-33 transgenic mice led to a severe pro-inflammatory phenotype characterized by dysregulated myelopoiesis, increased tissue neutrophils, paw swelling and growth retardation, indicating that sustained IL-33 expression promotes strong systemic inflammation[118].

In mice, repeated IL-33 injections during the induction phase of arthritis conferred protection, probably by promoting T_H2 cell and T_{reg} cell responses[119]. Moreover, IL-33-deficient mice did not exhibit reduced arthritis severity in several arthritis models, including albumin-induced arthritis, collagen-induced arthritis and K/BxN serum-transfer-induced arthritis. These findings suggest that endogenous IL-33 is not essential for the development of immune-mediated arthritis[116,120] and indicate a differential role for IL-33 and its receptor ST2 in the pathogenesis of arthritis.

Collectively, these findings highlight the complex and context-dependent role of IL-33 in the initiation and amplification of inflammatory responses in arthritis. Although IL-33 can enhance inflammation under certain conditions, endogenous IL-33–ST2 signalling does not seem to be strictly required for disease development.

Targeting IL-33 in rheumatic and inflammatory diseases

Despite promising preclinical findings, there are currently no clinical trials of drugs that specifically target the IL-33–ST2 axis in rheumatic diseases. By contrast, several clinical trials have investigated IL-33 neutralization in T_H2-cell-driven inflammatory conditions (Fig. 3 and Table 2). Tozorakimab, a human monoclonal antibody that neutralizes IL-33, was evaluated in a phase I study in healthy individuals and people with atopic dermatitis or chronic obstructive pulmonary disease (COPD). The results demonstrated a favourable safety profile with a reduction of IL-5 and IL-12 levels in people with COPD[121]. In a subsequent phase IIa clinical trial, tozorakimab improved the pre-bronchodilator forced expiratory volume per second in a subgroup of participants who had a high risk of exacerbation, compared with placebo[122]. Similarly, astegolimab, a monoclonal antibody that targets ST2, demonstrated positive results in moderate-to-very-severe COPD[123] and in adults with severe asthma[124]. Etokimab, a monoclonal anti-IL-33 antibody, showed fast and sustained clinical benefits in a small clinical trial that involved 12 adults with atopic dermatitis[125]. Collectively, these findings suggest a potential therapeutic role for IL-33 inhibition in the management of T_H2-cell-mediated inflammatory diseases. Conflicting preclinical findings, especially in arthritis models, might account for the lack of investigation of IL-33 blockers in rheumatic diseases.

IL-36α, IL-36β, IL-36γ and IL-36Ra

IL-36α, IL-36β, IL-36γ and IL-36Ra are predominantly expressed in keratinocytes and other epithelial cells. The identification of people with *IL36RN* (encoding IL-36Ra) deficiency, which causes severe generalized pustular psoriasis, and the results from experimental studies using genetically modified mice led to the development and approval of IL-36 inhibitors for the treatment of generalized pustular psoriasis and these inhibitors are being investigated for other inflammatory skin and intestinal diseases.

IL-36 biology

The IL-36 cytokines include three agonists (IL-36α, IL-36β and IL-36γ) and one antagonist (IL-36Ra) — formerly named IL-1F6, IL-1F8, IL-1F9 and IL-1F5, respectively — which are encoded by genes located within the *IL1* gene cluster on chromosome 2 (ref. 126). IL-36 agonists signal through the IL-36 receptor (IL-36R, also known as IL-1Rrp2) together with IL-1RAcP, whereas IL-36Ra functions as a competitive antagonist of IL-36R, similar to IL-1Ra and IL-1R1. IL-36 cytokines are enriched in barrier tissues, particularly in keratinocytes[127], but are also produced by monocytes, macrophages, dendritic cells and T cells[128,129].

IL-36 agonist cytokines are produced as poorly active cytosolic precursors (full-length IL-36). Upon tissue stress or inflammation, IL-36 is passively released into the extracellular space. Extracellular N-terminal truncation increases the biological activity of IL-36 by several hundred-fold[130]. Neutrophil-derived cathepsin G, elastase and proteinase-3 are the major activating proteases[131]; in some tissues cathepsin S can also contribute (Fig. 1). This protease-dependent mechanism creates a feedforward circuit whereby IL-36 maturation promotes neutrophil recruitment, and neutrophil-released enzymes further generate bioactive IL-36.

IL-36 agonists activate classical IL-1R–TLR intracellular signalling pathways[132]. In epithelial cells, STAT3 can also be activated; it supports inflammatory responses through enhanced transcription of *IL36* genes[133]. Transcription of IL-36 is induced by TLR agonists, microbial stimuli, epithelial stress and pro-inflammatory cytokines, including IL-1β, TNF, IL-22 and IL-17A; IL-36γ is the most robustly produced isoform, particularly in epithelial cells[134]. Downstream transcriptional programmes include a wide variety of cytokines, chemokines, growth factors and antimicrobial peptides[128,132].

IL-36Ra is mainly produced in the skin by keratinocytes and binds to IL-36R with higher affinity than IL-36 agonists[135], thus restraining excessive immune activation (Fig. 3). IL-36Ra has been identified as a key regulatory molecule, especially in psoriasis[136].

IL-38 is presumed to provide an additional layer of negative regulation. Structurally related to IL-36Ra, IL-38 has been reported to be a partial IL-36R antagonist[137]. However, the exact mechanisms underlying the anti-inflammatory effects of IL-38 remain incompletely defined, results vary across experimental systems[138] and emerging data show conflicting information regarding the antagonist function that IL-38 has on IL-36R[139]. Notably, a truncated form of IL-37, which mimics cathepsin C cleavage, stimulated pro-inflammatory responses in vitro and in vivo via IL-36R signalling[140]

IL-36 in rheumatic and inflammatory diseases

IL-36 cytokines have emerged as important mediators of innate immune-driven inflammation across a spectrum of monogenic and complex inflammatory diseases. The most compelling evidence for their pathogenic role comes from the DITRA (deficiency of the IL-36 receptor antagonist) syndrome. Loss-of-function mutations in *IL36RN* result in uncontrolled IL-36 signalling, leading to excessive neutrophilic inflammation and severe systemic and cutaneous flare-ups, thereby firmly establishing IL-36 as a central driver of sterile autoinflammation[141].

Beyond monogenic conditions, IL-36 also contributes to the pathogenesis of complex inflammatory diseases. In psoriasis, particularly generalized pustular psoriasis, IL-36α, IL-36β and IL-36γ are highly expressed in lesional skin, predominantly by keratinocytes and their expression correlates with neutrophil infiltration and disease severity[127]. IL-36 also has a role in inflammatory bowel disease, whereby epithelial- and myeloid-cell-derived IL-36 promotes mucosal inflammation, barrier dysfunction and T_H17-cell-skewed immune responses[142].

In rheumatic diseases such as RA and psoriatic arthritis, IL-36 expression has been detected in inflamed synovial tissues and circulating immune cells, leading to amplified cytokine production and innate immune activation[143]. However, studies in mice indicate that IL-36 signalling is not required for the development or severity of inflammatory arthritis[144]. These findings suggest that, despite its expression in arthritic joints, IL-36 does not represent a central pathogenic driver in arthritis. Elevated serum levels of IL-36 have been reported in systemic lupus erythematosus[145]; however, direct experimental evidence supporting a causal role for IL-36R signalling in the pathogenesis of systemic lupus erythematosus remains limited.

Across inflammatory diseases, dysregulated control of IL-36 signalling nonetheless emerges as a recurrent feature. Excessive IL-36 activity can result from sustained exposure to pro-inflammatory cytokines (IL-1β, TNF and IL-17A), persistent neutrophil infiltration and increased availability of the neutrophil-derived proteases that generate bioactive IL-36 (refs. 131,146). In mouse models of mucosal inflammation, including dextran-sulphate-sodium-induced colitis, IL-36γ expression is markedly increased and IL-36R signalling contributes to the amplification of epithelial and myeloid inflammatory responses, illustrating how insufficient control of IL-36 can exacerbate tissue inflammation[128,147]. Moreover, impaired counter-regulatory mechanisms, including reduced activity of endogenous antagonists such as IL-36Ra or IL-38, further prolong IL-36-driven signalling and enhance inflammatory outputs[148].

Together, these observations support a context-dependent model in which IL-36 functions as a potent inflammatory amplifier in barrier-driven autoinflammatory diseases, while remaining largely dispensable in the inflammatory rheumatic diseases explored thus far.

Targeting IL-36 in rheumatic and inflammatory diseases

Beyond monogenic autoinflammatory disorders, IL-36 blockade is being actively explored in a range of complex inflammatory diseases, including psoriasis[149] and inflammatory bowel disease[150]. Importantly, abrogation of IL-36R signalling is well tolerated in humans. Experimental data suggest that, as opposed to TNF and IL-1, IL-36R signalling is dispensable for host responses against *Mycobacterium tuberculosis*[151]. Consequently, IL-36 inhibition offers the advantage of simultaneously dampening multiple downstream inflammatory pathways while maintaining an acceptable safety profile. The most advanced therapeutic strategies rely on IL-36R antagonists (Fig. 3 and Table 2).

Spesolimab, a humanized monoclonal antibody that targets IL-36R, approved by the United States Food and Drug Administration, has demonstrated fast and robust clinical efficacy in people with generalized pustular psoriasis, including individuals with *IL36RN* mutations, thereby confirming IL-36 signalling as a key pathogenic driver of neutrophil-dominated skin inflammation[152–154].

In parallel, imsidolimab, a humanized IgG4 monoclonal antibody that targets IL-36R, has shown encouraging clinical activity in pustular and inflammatory skin diseases[155], further supporting the translational relevance and therapeutic potential of IL-36 pathway inhibition.

Beyond monoclonal antibodies, low-molecular-weight antagonists of IL-36 have been developed; however, their efficacy has so far been limited, largely owing to their ability to bind selectively to only one IL-36 agonist[156]. Several low-molecular-weight compounds directly targeting IL-36R have been successfully developed, resulting in improved efficacy[157,158]. A key advantage of these low-molecular-weight compounds is their improved tissue penetration and oral administration[159].

Another emerging concept is the combination of IL-36 blockade with inhibitors of the IL-23–IL-17 pathway. Given the strong bidirectional crosstalk between IL-36 and the IL-23–IL-17 axis[127,160], dual-targeting strategies might provide deeper and more sustained disease control[161], particularly in people with refractory disease.

Future perspectives

The biological activity of IL-1 family cytokines is controlled by an unusually complex, multilayered regulatory network encompassing transcriptional and post-translational mechanisms, endogenous receptor antagonists, soluble receptors and decoy molecules. Such tight regulation is essential to achieve effective host defence against noxious stimuli while preventing pathological inflammation. Disruption of these regulatory mechanisms can lead to excessive cytokine signalling and inflammatory responses, particularly in barrier tissues where IL-1 family members shape inflammation. Despite shared structural features, receptors and intracellular signalling pathways, individual IL-1 cytokines are associated with distinct clinical and tissue-specific phenotypes, reflecting the differential expression patterns of both ligands and receptors. The integration of mechanistic biomarkers (including inflammasome gene mutations, *IL36RN* variants, free IL-18 levels and cytokine-induced transcriptional signatures) with emerging upstream and combination-targeting strategies, should further advance precision therapeutic approaches in inflammatory diseases.

Conclusion

Since the discovery of the first IL-1 family members more than four decades ago, it has become increasingly clear that these cytokines occupy a position at the apex of inflammatory responses. Aberrant IL-1 family signalling has now been implicated in a wide spectrum of rheumatic and inflammatory diseases. Evidence supporting a causal role for these cytokines derives from converging lines of investigation and, most decisively, observations from human monogenic disorders. Moreover, the clinical success of cytokine-targeted therapies has provided compelling proof-of-concept for the pathogenic relevance of IL-1 family members. Therapeutic targeting of the IL-1 family has not only transformed the management of some inflammatory diseases but has also become a powerful experimental tool with which to dissect cytokine function in humans. The rapid translation of IL-1 biology into clinical practice followed the identification of IL-1Ra and the development of recombinant anakinra. Subsequent studies have revealed pronounced clinical benefit for systemic inflammatory disorders characterized by excessive IL-1β activity, driving the development of multiple agents that are now approved or in advanced stages of clinical testing. Extending this paradigm, blockade of IL-36 receptor signalling has now been approved for the treatment of generalized pustular psoriasis, while inhibitors of IL-18 and IL-33 are progressing through clinical development. Thus, targeting IL-1 cytokines has drastically changed the management and outcomes of many severe inflammatory diseases and the continued development of IL-1-targeted therapies holds promise for the future treatment of these diseases.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

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In the version of the article initially published, the label "L840R" was incorrectly included in Fig. 4b and has now been removed in the HTML and PDF versions of the article, as seen in Fig. 1.

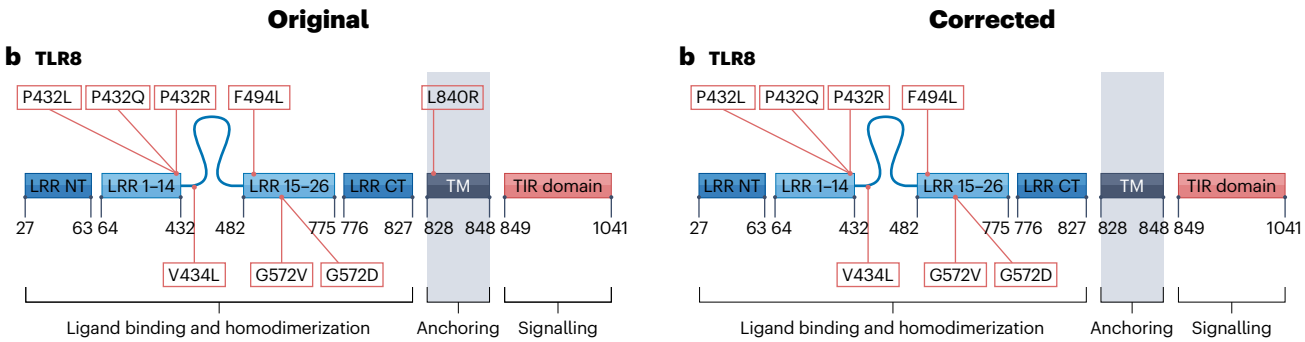

Fig. 1 | Original and corrected Fig. 4b.