

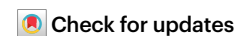
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Advancing rheumatic disease care through generative artificial intelligence

Arjun Mahajan, David W. Bates, Katherine P. Liao & Jeffrey A. Sparks



Generative artificial intelligence promises to reshape clinical care in rheumatology by supporting diagnostic reasoning, treatment planning and patient communication. Yet its potential rests on careful validation, transparent integration and thoughtful collaboration that strengthens, rather than substitutes, the human expertise central to patient care.

Generative artificial intelligence (GenAI) is increasingly gaining attention in healthcare¹, but its potential influence on clinical reasoning and decision-making in rheumatology remains relatively unexplored. Moving beyond the often narrow, task-specific functions of early medical AI tools in rheumatology, generative models offer capabilities in contextual insight, iterative dialogue, generating explanatory narratives, and cross-domain knowledge synthesis that position them as potential partners in clinical thought. Such partnerships could fundamentally reshape how rheumatologists approach clinical decision-making, though realizing this promise will depend on cautious, thoughtful implementation.

Traditional AI tools often generate static outputs with limited adaptability¹. Generative models, by contrast, have the potential to achieve increased diagnostic and therapeutic accuracy through fine-tuning outputs based on clinician feedback, seeking clarifications when additional information is required, exploring alternative diagnoses or decisions, correcting misunderstandings in real time, and adapting recommendations to emerging clinical context or changing guidelines¹. Use of iterative dialogue is particularly valuable in rheumatology, wherein evolving or heterogeneous clinical presentations like those seen in systemic autoimmune rheumatic diseases, nuanced treatment algorithms like those for systemic lupus erythematosus (SLE), and individualized risk–benefit assessments often require iterative questioning and clarification to achieve accurate diagnosis and tailored treatment.

A recent study introduced AMIE, a large language model (LLM)-based system that used self-play with critic feedback and a chain-of-reasoning framework to improve simulated doctor–patient conversations on dimensions such as history taking, diagnostic accuracy, management and empathy². In a randomized, blinded evaluation using real-world clinical transcripts and simulated diagnostic conversations across multiple specialties (including rheumatology), AMIE outperformed clinicians, showing that iterative dialogue, wherein feedback is incorporated at each step to refine differentials and communication, can enhance the quality of medical consultations.

Unlike traditional AI tools often trained for specific tasks, generative models also have the potential to leverage their training on broad medical datasets to synthesize knowledge across specialties and identify clinically relevant connections between seemingly disparate findings. This proves valuable in rheumatology, wherein multisystemic conditions such as antiphospholipid syndrome are likely to involve thrombotic, obstetric and neurological features that require integrated rather than siloed assessment. For instance, a recent pilot study demonstrated how LLMs with generative adversarial networks can evaluate medical record data across dermatological, cardiac and neuropsychiatric specialty domains to support automated SLE classification³.

Importantly, generative models can externalize reasoning steps, potentially changing how clinicians approach problem-solving. Although AI-generated reasoning explanations might not completely or faithfully reflect actual internal model processes⁴, inconsistencies or logical gaps in these narratives are likely to correlate with and signal potential errors and provide clinicians with useful oversight mechanisms. This ‘transparency’ is especially relevant in rheumatology, wherein complex and overlapping clinical presentations, high-risk therapeutic decisions and medicolegal considerations require clear reasoning pathways for optimal patient care. Collectively, the advanced properties of GenAI listed above underscore its potential to transform rheumatological clinical practice. In particular, GenAI tools can assist diagnosis, treatment decisions and communication with patients.

First, in rheumatology, multimodal LLMs have demonstrated unique capabilities in synthesizing heterogeneous data streams – such as medical notes, laboratory results, imaging and pathology findings and genomic profiles – into actionable diagnostic insights. Although evaluation has often been limited to structured clinical vignettes, LLMs have demonstrated comparable or superior diagnostic accuracy to rheumatologists in disease diagnosis and shown emerging capabilities to integrate multimodal data^{5,6}. Such systems could potentially integrate imaging, dermatological findings and serologies to support earlier recognition of conditions such as psoriatic arthritis than isolated specialty assessments allow. Emerging evidence shows that top-10 differentials produced by clinicians who used LLMs were more accurate, comprehensive and clinically appropriate than differentials produced by clinicians who did not use GenAI, suggesting these systems might actively shape and strengthen diagnostic reasoning rather than simply provide answers⁷. As such, a deep uncertainty lies less in whether generative models can produce appropriate differentials than in whether rheumatologists can learn to trust and challenge them in ways that reliably improve patient care.

Second, generative models have the potential to support personalized treatment planning for rheumatic disease, effectively incorporate efficacy and safety trade-offs given comorbidities and patient preferences, adapt to evolving clinical guidelines and evidence, and help structure shared deliberation⁸. A study benchmarking GPT-4 against rheumatologists showed that LLMs can generate clinically

appropriate treatment plans. Although expert rheumatologists still preferred specialist-generated treatment recommendations over AI-generated plans in a majority of cases, GPT-4 demonstrated comparable safety in first-line treatment recommendations⁸. Such evidence points towards a future in which human clinical reasoning is extended through contextualized, evidence-based support, shifting clinical roles as decision-making increasingly spans physicians, allied health professionals and AI systems.

Third, GenAI systems might also reshape how clinical reasoning and content is shared with patients, enhancing engagement and outcomes through personalized educational materials that adapt to individual preferences, health literacy, and disease and treatment-specific considerations. In SLE, GPT-4 produced patient-facing answers to commonly asked questions that rheumatologists rated as comparable or superior to expert-curated materials in terms of quality and empathy, illustrating how GenAI might help translate complex clinical content into language patients can understand and act upon⁹. Thus, GenAI might further shift patient education from passive receipt of information to more active participation in the reasoning process, fostering greater shared decision-making and trust.

The integration of GenAI in clinical practice faces numerous challenges, and several key areas merit careful attention for effective clinical decision-making partnerships. Future work must ensure GenAI reasoning partners undergo rigorous testing for harmful or clinically inappropriate recommendations, bias and failure modes before deployment in clinical settings to prevent GenAI use creating errors or exacerbating disparities¹⁰. A systematic review of LLM evaluations in clinical medicine found that only 5% of studies used real patient care data for evaluation, with most relying on medical examination questions or hypothetical vignettes – highlighting the need for real-world testing before deployment¹⁰. Model transparency, explainability and confidence estimation will be especially important in rheumatology given the field's inherent diagnostic uncertainty and reliance on clinical judgment in ambiguous presentations.

Successful adoption of GenAI will also depend on integration that fits practically into clinical workflows, avoiding excessive training, failure to meaningfully reduce documentation burden, increased alert fatigue, and, ultimately, consumption of clinician time on technology rather than patient care. Data integration challenges might be particularly pronounced in rheumatology, wherein patient care involves multiple subspecialists, fragmented electronic health records, longitudinal disease monitoring spanning decades, and multimodal data, which require technical infrastructure and standardized data formats – both features that many healthcare systems currently lack³.

As GenAI becomes embedded in clinical reasoning, an open question is how reliance on these systems may subtly reshape clinicians' own cognitive processes over time. There is a pressing need to study not only the immediate accuracy of AI-assisted decisions, but also the long-term effects on diagnostic reasoning and therapeutic judgment. This is particularly relevant in rheumatology, wherein many conditions lack definitive biomarkers, and expert clinicians must develop comfort with uncertainty and presentations that resist algorithmic classification. Understanding optimal models of collaboration between

human and AI reasoning will be essential to ensure that such tools strengthen, rather than erode, patient care and safety. Importantly, whereas GenAI has the potential to support cognitive reasoning, the human work of compassion, trust building and respect for autonomy remains with clinicians.

Together, current advances position GenAI to potentially transform rheumatological practice towards greater accuracy, efficiency and patient-centred care. To achieve this, GenAI integration in clinical practice must occur with rigorous validation, attention to equity and appropriate safeguards.

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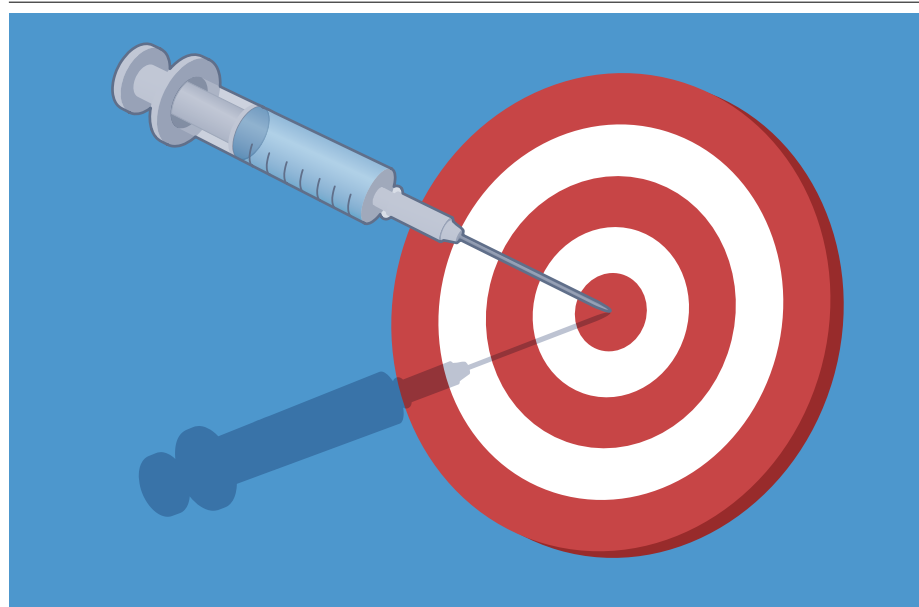
Competing interests

J.A.S. has received research support from Boehringer Ingelheim, Bristol Myers Squibb, Janssen, and Sonoma Biotherapeutics unrelated to this work. He has performed consultancy for AbbVie, Amgen, Anaptys, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, Inova Diagnostics, Johnson & Johnson, Merck, MustangBio, Optum, Pfizer, ReCor, Sana, Sobi, and UCB, none of which are relevant to the present work. D.W.B. reports grants and personal fees from EarlySense, personal fees from CDI Negev, equity from ValeraHealth, equity from Clew, equity from MDCClone, personal fees and equity from AESOP, personal fees and equity from Feelbetter, equity from Guided Clinical Solutions, and grants from IBM Watson Health, none of which are relevant to the present work. D.W.B. has a patent pending (PHC-028564 US PCT), on intraoperative clinical decision support. A.M. and K.P.L. declare no competing interests.

Research highlights

Inflammation

cPLA2 as a therapeutic target in chondrocytes for OA and IVDD



Cytosolic phospholipase A₂ (cPLA2) is an enzyme involved in the release of the pro-inflammatory mediator, arachidonic acid, which has a well-established role in inflammation. In degenerative joint diseases such as osteoarthritis (OA) and intervertebral disc degeneration (IVDD), inflammation has a key role in disease pathogenesis, but research on the role of cPLA2 in this context is limited. Now, findings in *Bone Research* provide mechanistic evidence that cPLA2 is involved in the pathogenesis of these joint diseases.

When discussing the motivation for this study, corresponding author Chuan-ju Liu notes “given that cPLA2 links inflammation and lipid metabolism, two key processes in OA and IVDD, we sought to define its role in these conditions and assess whether pharmacological inhibition could be protective”. Single-cell RNA sequencing of cartilage from healthy individuals and individuals with OA showed that *PLA2G4A* (which encodes cPLA2) is expressed in prehypertrophic chondrocytes and fibrochondrocytes. This expression correlated with OA-related and SASP (senescence-associated secretory phenotype)-related gene profiles in individuals with OA.

Depletion of cPLA2 from human chondrocytes in vitro (either by genetic deletion

or pharmacological inhibition using fexofenadine, a type of antihistamine that targets cPLA2) regulated gene expression profiles relating to both senescence and metabolism.

To assess these effects in vivo, the authors used surgically induced and age-induced mouse models of OA and IVDD. In all the models tested, fexofenadine reduced cartilage loss, pain and inflammation. Liu notes “we reveal fexofenadine, an FDA-approved, widely used, and over-the-counter drug, as a promising disease-modifying candidate, beyond its traditional anti-allergic use”.

Overall, these data provide insights into the role of cPLA2 in the pathogenesis of OA and IVDD and show that inhibiting this pro-inflammatory mediator could target both senescence and inflammation in chondrocytes. “The long-term goal is to develop a safe and affordable therapy that can not only alleviate symptoms but also slow or prevent structural damage, ultimately addressing a major unmet need in current clinical management of degenerative joint disorders”, concludes Liu.

Holly Webster

Original article: Huang, G. et al. Cytosolic phospholipase A₂ as a therapeutic target for degenerative joint diseases. *Bone Research* **13**, 86 (2025)

Research highlights

Sjögren disease

Nipocalimab reduces Sjögren disease activity in phase II trial

Nipocalimab, a human monoclonal antibody that binds the neonatal Fc receptor (FcRn), decreased clinical disease activity in adults with Sjögren disease (SjD) in the phase II DAHLIAS trial. These improvements seemed to be related to reductions in circulating titres of IgG antibodies – including titres of autoantibodies – consistent with the proposed mechanism of action of nipocalimab.

No disease-modifying therapies are available for SjD but drugs that deplete autoantibodies have shown promise. By specifically blocking FcRn from binding to IgG, nipocalimab prevents FcRn-induced recycling of IgG and thereby decreases circulating IgG.

The double-blind, multicentre DAHLIAS trial involved 163 adults with moderate-to-severe active primary SjD who were seropositive for anti-Ro IgG antibodies. Participants received treatment with intravenous nipocalimab (5 mg/kg or 15 mg/kg) or placebo every 2 weeks for 22 weeks plus concomitant standard-of-care. The reduction in ClinESDAI score from baseline to week 24 (the trial primary end point) was significantly greater in the 15 mg/kg nipocalimab group than in the placebo group. The primary end point

was not met in the 5 mg/kg nipocalimab group. Both doses of nipocalimab were safe and well-tolerated, with similar rates of adverse events in the nipocalimab groups and the placebo group.

Post-hoc analysis revealed that the greatest change from baseline in ClinESDAI score occurred in participants with the highest baselines levels of anti-Ro60, anti-La and anti-Ro52 autoantibodies. Nipocalimab was also associated with dose-dependent reductions in levels of anti-Ro60, anti-La and anti-Ro52 autoantibodies, as well as total IgG, from weeks 2 to 24.

Overall, the findings of the phase II DAHLIAS trial support the further development of nipocalimab for the treatment of SjD. A multicentre phase III trial to assess the efficacy and safety of this FcRn blocker in adults with moderate-to-severe SjD is now underway (NCT06741969).

Sarah Onuora

Original article: Noaiseh, G. et al. Efficacy and safety of nipocalimab in patients with moderate-to-severe Sjögren's disease (DAHLIAS): a randomised, phase 2, placebo-controlled, double-blind trial. *Lancet* [https://doi.org/10.1016/S0140-6736\(25\)01430-8](https://doi.org/10.1016/S0140-6736(25)01430-8) (2025)

Related article: Baldini, C. et al. Update on the pathophysiology and treatment of primary Sjögren syndrome. *Nat. Rev. Rheumatol.* **20**, 473–491 (2024)

Therapy

Positive phase II trial of IL-17A–IL-17F-targeting nanobody sonelokimab for PsA

Dual inhibition of IL-17A and IL-17F with monoclonal antibodies has shown promise for psoriatic arthritis (PsA). Nanobodies present an attractive therapeutic option owing to their smaller size and ability to accumulate in tissues. A phase II trial published in *Nature Medicine* describes sonelokimab, a nanobody that binds to both IL-17A and IL-17F with high affinity, and evaluates the efficacy and safety of this therapy for active PsA.

The phase II ARGO trial enrolled 207 patients with active PsA who were randomly assigned to receive 60 mg or 120 mg of sonelokimab (both with induction dosing at weeks 0, 2, 4 and 6 and then every 4 weeks from week 8 until the end of the study (week 24)), 60 mg sonelokimab given every 4 weeks with no induction, 40 mg adalimumab (a TNF inhibitor that is the current standard of care) every 2 weeks, or placebo. Ennio Lubrano, who researches therapies for PsA but was not involved in the study, notes that “While including adalimumab is a strength, it’s important to remember that it was not powered for statistical comparison. Therefore, any conclusions about the superiority or non-inferiority of sonelokimab to adalimumab should be made cautiously.”

Overall, as with other IL-17-targeted therapies, sonelokimab was safe and well tolerated. After 12 weeks, the primary endpoint, the proportion of patients achieving ACR50 response was met for the 60 mg and 120 mg doses with induction (46.3% and 46.5%, respectively), compared with placebo (20%).

The key secondary endpoints of ACR20 and PASI90 at week 12 were also met, and robust responses were observed for ACR70 and PASI100 at week 24. The most common adverse events reported were nasopharyngitis, upper respiratory tract infection, injection-site erythema and headache.

Iain McInnes, the corresponding author of this study, comments that “these findings help to reinforce the efficacy of dual IL-17A and IL-17F inhibition in PsA and highlight the potential of nanobodies for achieving multidomain responses.” Lubrano notes that “The study is innovative and paves the way to a phase III trial in PsA and, potentially, offers a new treatment scenario for this complex syndrome.”

On the basis of the results of this trial, two phase III trials are underway that aim to further evaluate the efficacy of sonelokimab for PsA: IZAR-1 (NCT06641076) in patients with PsA who are naive to biologic agents, and IZAR-2 (NCT06641089) in patients with PsA who have shown an inadequate response to or intolerance to TNF inhibitors. “These studies aim to confirm the efficacy and safety of sonelokimab in PsA and provide broader insights on the potential of nanobody-based therapies in the management of complex inflammatory diseases,” explains McInnes.

Holly Webster

Original article: McInnes, I. B. et al. Sonelokimab, an IL-17A/IL-17F-inhibiting nanobody for active psoriatic arthritis: a randomized, placebo-controlled phase 2 trial. *Nat. Med.* <https://doi.org/10.1038/s41591-025-03971-6> (2025)

Autoinflammation

Unravelling the cellular mechanisms of VEXAS syndrome

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, caused by somatic mutations in *UBAI*, is characterized by severe autoinflammation and bone marrow failure. Yet, how a single genetic lesion promotes such diverse pathology has remained elusive. Findings published in *Nature* reveal that VEXAS-associated mutations disrupt early ubiquitin-dependent signalling at inflammatory receptors, predisposing myeloid cells to inflammatory cell death while simultaneously biasing haematopoietic stem cells towards a myeloid lineage.

Using precise base-editing to introduce patient-specific *UBAI* mutations into human and mouse cells, the researchers show that macrophages carrying the mutation undergo highly inflammatory forms of lytic cell death that is mediated by the RIPK1–RIPK3–caspase 8 axis.

“At a molecular level, we found that these aberrant inflammatory cell death programs were associated with impaired Lys63/Met1-linked polyubiquitin chain formation on inflammatory signalling complexes, thereby linking the pathogenesis of VEXAS with that of rarer disorders [such as] those affecting components of the linear ubiquitin chain assembly complex

(LUBAC),” explains Alexander Gitlin, corresponding author on the study. This disruption in ubiquitylation compromises early nuclear factor- κ B activation and promotes the release of pro-inflammatory molecules, which in turn might promote myeloid-biased haematopoiesis.

In haematopoietic stem and progenitor cells, *UBAI* mutations trigger an unfolded protein response and promote spontaneous myeloid-biased differentiation while reducing viability and preventing engraftment – recapitulating the myeloid bias and bone marrow failure seen in patients. Notably, these effects occur independently of cell death pathways.

Together, these findings clarify how *UBAI* mutations simultaneously disrupt inflammatory signalling and blood cell development, pointing to new therapeutic opportunities. “It will be intriguing to test whether therapeutics targeting this cell death axis can ameliorate the autoinflammatory features of VEXAS,” remarks Gitlin.

Jessica McHugh

Original article: Narendra, V. K. et al. Independent mechanisms of inflammation and myeloid bias in VEXAS syndrome. *Nature* <https://doi.org/10.1038/s41586-025-09815-0> (2025)

Cell-free DNA fragmentation signatures link cancer and autoimmunity

Lam C. Tsoi & John Varga



Circulating cell-free DNA (cfDNA) and cfDNA fragmentation signatures are emerging as promising non-invasive biomarkers for various indications, most notably cancer. New analysis of cfDNA fragmentation in autoimmunity highlights potential links to cancer, as well as the promise of these tools for improved understanding and clinical care of autoimmune disease.

REFERS TO Curtis, S. D. et al. Fragmentation signatures in cancer patients resemble those of patients with vascular or autoimmune diseases. *Proc. Natl Acad. Sci. USA* **122**, e2426890122 (2025).

Circulating cell-free DNA (cfDNA) has emerged as a powerful biomarker for cancer diagnosis over the past decade, and recent work has revealed the potential use of cfDNA as a biomarker for systemic lupus erythematosus and other autoimmune disorders¹. Historically, the diagnosis and monitoring of these conditions have relied on circulating markers such as C-reactive protein, autoantibodies or complement levels, which lack tissue specificity. A new study by Curtis et al.² represents a technical milestone in the development of cfDNA-based metrics for screening in cancer and autoimmunity. The findings highlight limitations on the specificity of cfDNA analysis in cancer diagnosis, but they also provide evidence linking cancer to autoimmune conditions, an association that has been long recognized but for which the mechanistic basis has remained elusive^{3,4}.

Circulating cfDNA was first described decades ago in cancer⁵ and has subsequently also been described in pregnancy, myocardial infarction, organ transplantation, autoimmunity and many other conditions⁶. Analysis of cfDNA in the blood, often referred to as liquid biopsy, is now used in prenatal testing, early detection of cancer and monitoring after organ transplantation. cfDNA is released by many different cell types after physiological or pathological cell death (including death by NETosis) or by active secretion, and cfDNA could have roles in physiological and immune system regulation⁷.

cfDNA breaks down in the circulation via a process known as cfDNA fragmentation. This process is not random and is influenced by various factors, including the mechanism of cell death and the cell type and/or tissue of origin, as well as possibly other external factors, such as disease. Analysis of cfDNA fragmentation signatures has shown promise in improving the sensitivity of cfDNA-based cancer screening, but its relevance in other diseases has been unclear. A key advance in the study by Curtis et al.² is the use of different orthogonal fragmentation-based

metrics to define signatures in different disease groups, including cancer and other autoimmune diseases. These fragmentation metrics include information-weighted fraction of aberrant fragments, which captures fragment end positions and quantifies abundance; fragment length ratio, which indicates the length pattern; and motif diversity score, which characterizes the fragment end-motif pattern. These orthogonal features capture distinct patterns of cfDNA that surpass the information gleaned from total cfDNA levels alone.

The researchers systematically analyzed the fragmentation signatures of circulating cfDNA in 882 individuals, including healthy individuals and patients with cancer, autoimmunity or vascular diseases². A notable finding in the study is the similarity in cfDNA fragmentation signatures observed in patients with autoimmune conditions (including systemic lupus erythematosus, dermatomyositis and systemic sclerosis) and those with cancer². This convergence suggests that cfDNA fragmentation might reflect fundamental aspects of cell death and chromatin organization that cut across pathologies. The mechanisms underlying rheumatologic diseases often involve dysregulated cell death pathways and aberrant nuclease activity⁸.

Hence, cfDNA fragmentation-based metrics might elucidate molecular processes not captured by conventional clinical assays. The results of Curtis et al.² thus highlight the shared biology of immune-mediated tissue injury and point towards opportunities to repurpose cfDNA tools developed for oncology into autoimmune disease contexts. The inclusion of diverse disease cohorts also highlights the generalizability of the approach, addressing a common limitation of biomarker studies restricted to single disease settings.

The authors employed a supervised learning algorithm that integrates cfDNA fragmentation signatures as well as plasma protein markers of inflammation to distinguish samples from patients with cancer versus those from patients with autoimmune disease. A key innovation of the study is the extension of binary classification to multi-class inference, which enables the model to learn distinct fragment signatures to classify autoimmune and vascular disease (Fig. 1). Unlike conventional plasma biomarkers, which provide a broad signal of systemic inflammation, incorporating cfDNA as a biomarker can offer a route to resolving which tissues are actively injured in real time⁹, a central challenge in monitoring autoimmune disease. The ability to track whether cfDNA signals originate from the kidneys, skin or vasculature could fundamentally reshape how clinicians assess disease flares and tailor treatment strategies; hence, this area warrants further investigation. Specifically, cfDNA fragmentation signatures can provide information complementary to that obtained with conventional biomarkers and thus can add an orthogonal layer of resolution for diagnosis, disease activity and, potentially, prognosis. For example, although levels of C-reactive protein rise in both infectious inflammation and autoimmune inflammation, the cfDNA fragmentation signature could distinguish whether concurrent kidney injury reflects lupus nephritis or another process, a distinction critical for therapeutic decisions.

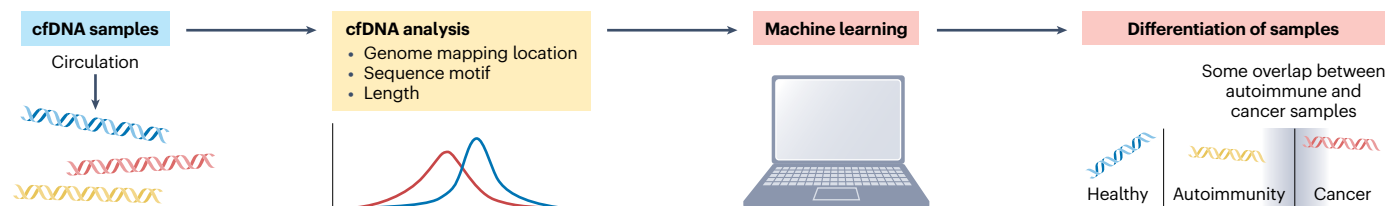


Fig. 1 | cfDNA fragmentation-based analysis for disease classification. Cell-free DNA (cfDNA) fragments are released into circulation from apoptotic or necrotic cells, reflective of underlying tissue and disease processes. Multiple metrics can be derived from the cfDNA fragments, including genomic mapping location, sequence motif preferences at fragment ends, and fragment length

distribution. These features are integrated through the use of machine learning approaches to capture complex fragmentation signatures that enable the classification of cfDNA profiles to distinguish among cancer, autoimmune, vascular and healthy states, providing a non-invasive tool (liquid biopsy) for systemic disease assessment.

However, several challenges remain for the translation of cfDNA analysis into rheumatology. First, these approaches require careful preprocessing, including correction for technical noise and batch effects, which might limit scalability across diverse cohorts. Second, autoimmune diseases are heterogeneous, and the cfDNA patterns can also vary within control and disease groups, as illustrated in this study². Thus, cfDNA fragmentation patterns will need to be examined and validated in patient cohorts of larger size and in longitudinal studies that capture disease flare and remission over time. Finally, integration with other data modalities – such as transcriptomics, proteomics or even spatial information, measured at single-cell resolution – could enhance the clinical impact of cfDNA analysis and might further contextualize cfDNA signatures to the broader immune network. Future studies will be needed to harmonize such multi-omics information.

In summary, the work by Curtis et al.² uncovers unexpected similarities between patients with cancer and patients with autoimmune diseases in their cfDNA fragmentation signatures and provides a technical framework that holds promise for rheumatology. By leveraging plasma cfDNA characteristics beyond simply cfDNA levels to capture multidimensional fragmentation features, this study opens a new analytic frontier for capturing the complexity of autoimmune diseases and exploring their links to cancer. Precise and accurate tissue-of-origin inference will be necessary to understand the pathophysiology and status of the disease, especially for diseases for which direct access to inflamed tissue is often impractical. The study of cfDNA fragmentation might represent a minimally invasive window into disease biology in autoimmune conditions, with the potential to transform both the mechanistic understanding and clinical care of these diseases.

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Competing interests

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Monogenic disorders of the TNF signalling pathway

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Abstract

TNF is a central regulator of immune responses, inflammation and programmed cell death, and has an essential role in maintaining tissue and immune homeostasis. Abnormal TNF signalling is implicated in a broad spectrum of physiological and pathological processes, as exemplified by monogenic disorders arising from dysregulation of core components of the TNF pathway. These rare conditions encompass various autoinflammatory syndromes, immunodeficiencies, autoimmune diseases and neurodegenerative conditions, and offer unique insights into the molecular mechanisms driving pathology via TNF-mediated inflammation and cell death. Collectively, these diseases underscore the importance of tightly regulated TNF signalling for immune balance and illustrate how distinct molecular defects can produce overlapping clinical phenotypes. Variability in pathway integration and tissue-specific gene expression further shapes disease presentation, whereas disruption of post-translational modifications and cell-death regulators have emerged as central pathogenic mechanisms. Together, these insights highlight the need for precise genetic and mechanistic understanding to inform diagnosis and therapeutic strategies.

Sections

Introduction

The TNF signalling pathway

Autoinflammatory syndromes

Immunodeficiencies and autoimmune syndromes

Mixed autoinflammation, immunodeficiency and autoimmune syndromes

Future directions

Conclusions

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Key points

- Gain-in-function and loss-of-function mutations in key components of the TNF pathway disrupt inflammatory and cell-death signalling, causing autoinflammatory, immunodeficiency, autoimmune and neurodegenerative disorders.
- Anti-TNF therapies are widely used in chronic inflammatory diseases but do not address all aspects of TNF-related monogenic diseases.
- The role of TNFR2 in TNF-mediated pathology is frequently underappreciated and warrants more attention.
- Murine models have provided valuable insights into disease mechanisms; however, the influence of genetic background and environmental context — often absent in controlled settings — must not be overlooked.
- TNF signalling interconnects apoptosis, necroptosis and pyroptosis and dysregulation of this network can exacerbate inflammatory responses.
- RIPK1 is an important regulatory node linking cell death and inflammation, representing a promising target for therapeutic intervention.

Introduction

TNF is produced in response to infection or tissue damage and initiates a wide range of cellular responses through complex signalling pathways. TNF is a potent pro-inflammatory cytokine with central roles in both the innate and adaptive immune systems, as well as in physiological processes such as tissue repair, regeneration, remodelling and central nervous system homeostasis^{1,2}. TNF exerts its effects through two receptors, TNF receptor 1 (TNFR1) and TNFR2, activating downstream signalling cascades that mediate cell survival, gene expression, proliferation and cell death. To coordinate such diverse and sometimes opposing outcomes, TNF signalling is tightly regulated at multiple levels.

Given the critical role of TNF in inflammation and immune regulation, this cytokine is implicated in the pathogenesis of numerous inflammatory diseases. Anti-TNF therapies are now among the top-selling drugs globally and have proven highly effective in the treatment of chronic inflammatory and autoimmune conditions (Table 1). The success of these drugs was initially attributed to direct inhibition of TNF-induced inflammatory pathways. However, subsequent evidence has highlighted that TNF also contributes to inflammation by promoting cell death, some forms of which are inherently pro-inflammatory and amplify inflammation. Consequently, inhibiting cell-death pathways has emerged as a promising therapeutic approach for TNF-driven diseases.

Advances in human genetics have facilitated the rapid identification of genes that underlie rare monogenic disorders. Monogenic disorders caused by mutations in genes involved in the TNF signalling pathway have traditionally been classified within the broader categories of nuclear factor- κ B (NF- κ B)-related or ubiquitin-related diseases. Yet, emerging evidence reveals a more intricate network of TNF signalling, characterized by extensive crosstalk with other inflammatory

and cell-death pathways. These insights underscore the need for a unified and comprehensive review of genetic defects that affect core components of TNF signalling.

In this Review, we aim not only to catalogue monogenic disorders involving the TNF pathway but also to integrate findings from human cases and murine models to illuminate the molecular mechanisms driving disease. Emphasis is placed on the pathogenic role of TNF and the functional interplay between dysregulated cell death and aberrant TNF signalling, offering a refined perspective on the pathophysiology of these conditions.

The TNF signalling pathway

TNF is a master regulator of immune responses, inflammation and cell fate decisions. Understanding the molecular architecture and regulatory checkpoints of TNF signalling is essential for deciphering its dual roles in maintaining homeostasis and driving pathology.

TNF-induced survival and contained inflammation

TNF exerts its effects through two receptors, TNFR1 and TNFR2, which cooperatively promote cell survival under homeostatic conditions. Engagement of these receptors triggers the assembly of membrane-bound signalling complexes that activate the canonical NF- κ B and mitogen-activated protein kinase (MAPK) pathways, thereby inducing the transcription of genes involved in inflammation, proliferation and survival. The key distinction between TNFR1 and TNFR2 lies in the presence of a cytoplasmic death domain in TNFR1, which enables the recruitment of death domain-containing proteins³. Despite this capacity to trigger cytotoxic signals, multiple molecular checkpoints prevent TNFR1-mediated cell death. Apoptosis, necroptosis or pyroptosis typically occur only when these checkpoints are disrupted.

Upon TNF binding, TNFR1 initiates the assembly of complex I at the plasma membrane through the recruitment of TNFR1-associated death domain (TRADD) and receptor-interacting serine/threonine protein kinase (RIPK1), via their respective death domains^{4,5}. Subsequently, TNF receptor-associated factor 2 (TRAF2) and the E3 ubiquitin ligases cIAP1 and cIAP2, followed by the linear ubiquitin chain assembly complex (LUBAC), are recruited to the complex and polyubiquitylate RIPK1 and other components^{6–15}. The K63 ubiquitin chains assembled via cIAP1 and cIAP2 function as scaffolds for the recruitment of the TGF β activating kinase 1 (TAK1)-binding proteins TAB2 and TAB3, and TAK1 (ref. 16). The linear ubiquitin chains generated via LUBAC recruit the I κ B kinase (IKK) regulatory subunit NEMO (NF- κ B essential modulator, also known as IKK γ), which facilitates the assembly of the IKK complex (comprising IKK α and IKK β), as well as TANK binding kinase 1 (TBK1) and IKK ϵ ^{14,17,18}. The proximity of TAK1 to the IKK complex facilitates the phosphorylation of IKK β , which in turn phosphorylates I κ B α . This modification leads to the degradation of I κ B, thereby releasing the NF- κ B subunit p65. Together with other NF- κ B subunits, p65 translocates to the nucleus and activates gene transcription, promoting cell survival and inflammatory responses. In parallel, TAK1 also phosphorylates MAP kinases, further contributing to the regulation of survival and inflammation (Fig. 1a).

To prevent persistent activation of inflammatory signalling pathways, polyubiquitin chains are removed by deubiquitylating enzymes such as A20, ubiquitin carboxyl-terminal hydrolase (CYLD) and ubiquitin thioesterase otulin (OTULIN)^{19–21}. Concurrently, complex I is internalized and converted into complex II in the cytosol, where it recruits Fas-associated death domain (FADD) via its death domain, as well as caspase 8 and c-FLIP, an NF- κ B-inducible caspase 8 inhibitor²².

Table 1 | TNF inhibitors in clinical practice: approved and off-label applications

TNF inhibitors	Approved by the FDA?									Additional information	
	RA	PsA	AS	PsO	JIA	CD	UC	HS	Uveitis	Common off-label uses	Structure
Etanercept	Yes	Yes	Yes	Yes	Yes	No	No	No	No	N/A	Two copies of the extracellular domain of TNFR2 linked to human Fc
Infliximab	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	N/A	Chimeric mouse–human IgG1 anti-TNF monoclonal antibody
Adalimumab	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Behçet disease, sarcoidosis and pyoderma gangrenosum	Fully human IgG1 anti-TNF monoclonal antibody
Certolizumab pegol	Yes	Yes	Yes	No	No	Yes	No	No	No	Sarcoidosis and Behçet disease	PEGylated Fab' fragment that lacks an Fc region
Golimumab	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Vasculitis and sarcoidosis	Fully human IgG1 anti-TNF monoclonal antibody

AS, ankylosing spondylitis; CD, Crohn's disease; HS, hidradenitis suppurativa; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; PsO, plaque psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis.

To ensure cell survival, complex II-mediated cell death is blocked by several molecular checkpoints. First, RIPK1 is phosphorylated at multiple sites by kinases including TAK1, IKK β , TBK1, IKK ϵ , ULK1, JAK1 and SRC, suppressing the death-promoting activity of RIPK1 (refs. 17,23–28). Within complex II, the FLIP–caspase 8 heterodimer cleaves RIPK1, prompting RIPK1 dissociation and preventing cell death^{29–32}. In addition, lysosomal degradation of complex II contributes to signal resolution and provides further safeguarding against cell death³³. When cIAP1 and cIAP2 are depleted by other receptors such as TNFR2, Fn14 or LT β receptor, secondary checkpoints are in place to restrain cell death.

In contrast to the ubiquitous expression of TNFR1, TNFR2 expression is limited to lymphocytes, myeloid cells, endothelial cells and neurons (reviewed elsewhere³⁴). Unlike TNFR1, TNFR2 lacks a death domain and instead contains TRAF2-binding motifs, enabling the recruitment of TRAF2, TRAF1, cIAP1 and cIAP2 (refs. 35–38). The TNFR2–TRAF–cIAP complex is subsequently targeted for proteasomal degradation, thereby limiting the availability of these signalling mediators for other pathways^{38–40}. Notably, TRAF2, cIAP1 and cIAP2 have an important role in suppressing the non-canonical NF- κ B pathway by promoting the degradation of NIK. Depletion of these signalling mediators stabilizes the expression of NIK, leading to the phosphorylation and processing of p100 into p52, and subsequent activation of p52–RelB NF- κ B dimers, providing long-term and tissue-specific inflammatory responses^{41,42} (Fig. 1b).

It might be expected that TNFR2-mediated depletion of cIAP1 and cIAP2 would sensitize cells to TNFR1-induced cell death. However, cells typically remain viable when TNF engages both TNFR1 and TNFR2 simultaneously, despite the reduced availability of cIAP1 and cIAP2. This survival is partly attributed to the activities of X-linked inhibitor of apoptosis (XIAP), which suppresses the cytotoxic activity of complex II through mechanisms that remain incompletely understood^{43–45}. Moreover, MK2-mediated phosphorylation of RIPK1, MIB2-mediated ubiquitylation of RIPK1 and TNKS-mediated PARylation of complex II probably serve as additional safeguards against cell death in the context of cIAP1 and cIAP2 depletion^{46–50}. Although TNFR2 recruits LUBAC and the IKK complex less efficiently than TNFR1, TNFR2 can nonetheless contribute to activation of the canonical NF- κ B pathway, further promoting cell survival⁵¹ (Fig. 1b). Collectively, these redundant layers of control likely evolved to protect host cells from microbial effectors targeting transcriptional and post-translational regulatory nodes of the TNF pathway.

TNF-induced cell death and uncontrolled inflammation

When molecular checkpoints are compromised, TNF signalling rapidly shifts from promoting survival to activating programmed cell death. In these scenarios, complex I rapidly transitions to complex II, which can execute apoptosis, necroptosis or pyroptosis depending on the context and molecular availability. In the absence of c-FLIP, owing to transcriptional repression or pathogen interference, caspase 8 forms homodimers, leading to activation of caspase 3 and apoptosis²² (Fig. 2a). Similarly, genetic deletion or pharmacological inhibition of cIAP1 and cIAP2 or LUBAC impair RIPK1 ubiquitylation, favouring complex II assembly and RIPK1-dependent cell death (apoptosis or necroptosis)^{9,52–54}. The defect in RIPK1 ubiquitylation might reflect defective recruitment of RIPK1-inhibitory kinases, because loss of phosphorylation by TAK1, IKKs, TBK1, JAK1 or SRC unleashes the catalytic and oligomerization potential of RIPK1 within complex II^{17,23–28} (Fig. 2b).

When caspase 8 is absent or inactive, because of either genetic or pathogenic factors, RIPK1 and RIPK3 form oligomers and autophosphorylate⁵⁵. RIPK3 then phosphorylates MLKL, which oligomerizes and translocates to the plasma membrane to form pores, triggering necroptosis^{56–58}. The resulting release of intracellular content initiates potent inflammatory responses (Fig. 2c).

A third inflammatory death pathway, pyroptosis, was traditionally attributed to pattern recognition receptor engagement. However, TNF signalling can also initiate pyroptosis through crosstalk with the apoptotic machinery^{59,60}. Pyroptosis is mediated by inflammasomes, which activate caspase 1 to cleave IL-1 β and GSDMD. Cleaved GSDMD forms membrane pores, facilitating the release of pro-inflammatory cytokines such as IL-1 β (reviewed elsewhere⁶¹). Intriguingly, XIAP restricts TNFR2-induced pyroptosis, and XIAP deficiency promotes RIPK3-dependent IL-1 β secretion and pyroptotic death^{43–45} (Fig. 2b). Furthermore, caspase 8 can directly cleave GSDMD, whereas caspase 3 can cleave GSDME, another pore-forming family member^{59,60,62–64}. Conversely, inhibition of caspase 8 enzymatic activity or inhibition of RIPK3 cleavage augments caspase 1-driven pyroptosis^{65–67}. This extensive crosstalk between apoptosis, necroptosis and pyroptosis is thought to represent an evolutionary countermeasure against microbial strategies that selectively block individual death pathways to enhance microbial replication (Fig. 2).

Although TNF-induced cell death has critical antimicrobial effects that support human health, much of our understanding of

the homeostatic roles of this pathway has come from the study of monogenic diseases, which present with a large spectrum of clinical manifestations (Box 1).

Autoinflammatory syndromes

Monogenic autoinflammatory syndromes linked to TNF pathway dysregulation arise from aberrant innate immune signalling, resulting in excessive cytokine production and recurrent systemic inflammation in the absence of autoantibodies or antigen-specific T cells. These disorders illustrate how defective control of TNF-mediated cell death and NF- κ B activation can precipitate unrestrained inflammation.

TNF receptor-associated periodic fever syndrome

TNF receptor-associated periodic fever syndrome (TRAPS) is an autosomal-dominant autoinflammatory disorder caused by heterozygous mutations in the gene encoding TNFR1 (*TNFRSF1A*)^{68–74}. Onset typically occurs in childhood and is characterized by recurrent, prolonged episodes of fever accompanied by severe abdominal pain, myalgia, arthralgia, migratory erythematous rash and ocular inflammation^{68–74}. Persistent inflammation also increases the risk of systemic amyloidosis^{68,69,72,74,75}. The initial description

of this condition, together with that of familial Mediterranean fever, another monogenic disorder affecting innate immune pathways, led to the introduction of the term ‘autoinflammatory’ diseases to define an expanding group of conditions driven by dysregulation of innate immunity⁶⁸.

The extracellular domain of TNFR1 contains four cysteine-rich domains critical for disulfide bonding, homotrimerization and ligand binding^{76–78}. TNFR1 can be cleaved to produce soluble TNFR1, which sequesters TNF⁷⁹. Most pathogenic TRAPS mutations reside in the first two cysteine-rich domains or the transmembrane domain and not in the intracellular signalling regions of the protein⁸⁰. The initial findings of reduced levels of soluble TNFR1 in patients with TRAPS led to the shedding hypothesis, positing that impaired receptor cleavage contributes to disease⁶⁸. However, this view has been challenged by inconsistent findings across mutations and cell types, as not all variants or cellular contexts show receptor shedding dysregulation^{69,81,82}. Alternative models suggest that mutant TNFR1 is retained within cells, facilitating self-association of TNFR1, aberrant activation of NF- κ B and MAPK signalling and reduced apoptosis^{83–87}. Yet, conflicting data suggest that reactive oxygen species-driven MAPK activation might be more relevant than NF- κ B hyperactivation^{88–91} (Table 2). Studies with murine models carrying TRAPS mutations have shown that mutant

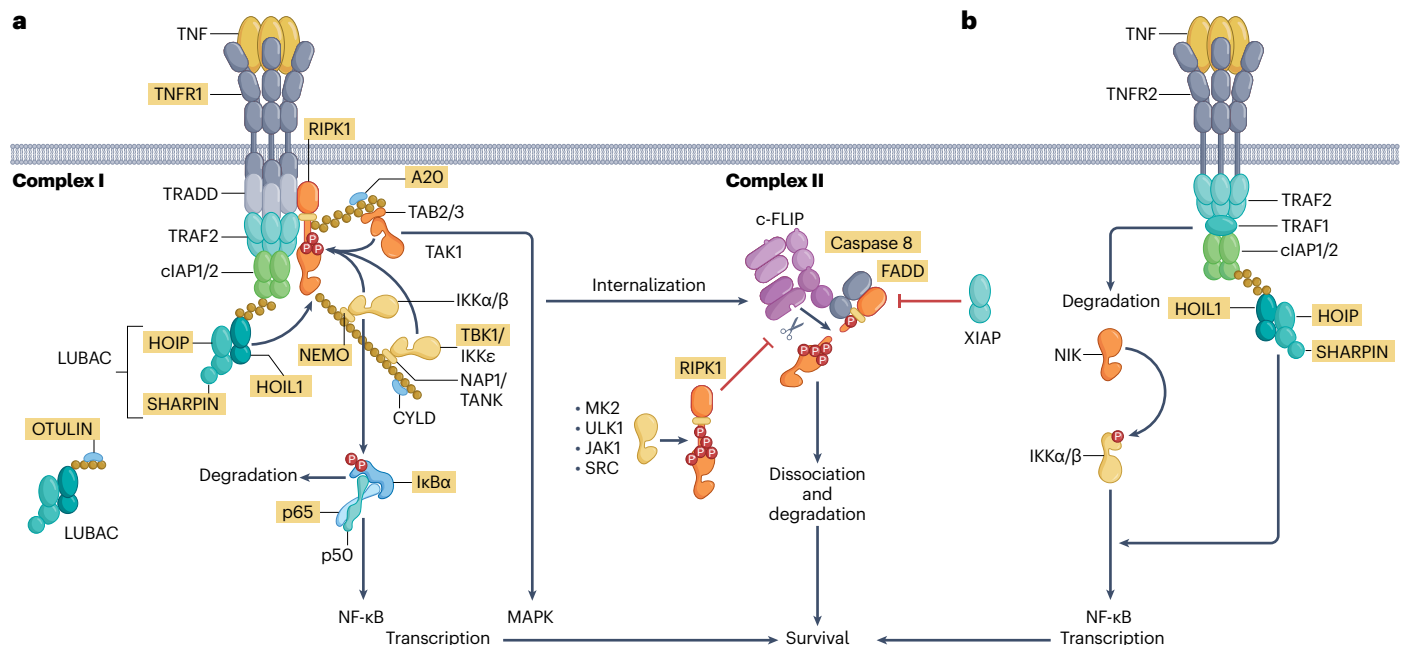


Fig. 1 | TNF-induced cell survival. TNF promotes cell survival under homeostatic conditions. Pathogenic mutations in genes encoding components of the TNF signalling pathway are linked to a large spectrum of disorders and are highlighted in yellow. **a**, Upon TNF binding to TNFR1, complex I forms at the membrane, where cIAP1 and cIAP2 catalyse ubiquitylation of themselves and RIPK1. This ubiquitylation recruits TAB2, TAB3, NEMO and the kinases TAK1, IKK α and IKK β . TAK1 phosphorylates IKK β , promoting activation of the canonical nuclear factor- κ B (NF- κ B) pathway. Simultaneously, the linear ubiquitin chain assembly complex (LUBAC; composed of HOIL1, HOIP and SHARPIN) is recruited to cIAP-linked ubiquitin chains and catalyses linear-linked ubiquitylation of RIPK1, facilitating further recruitment of NEMO, IKK α and IKK β . The adaptors NAP1 and TANK, together with kinases IKK ϵ and TBK1, are also recruited to linear ubiquitin chains. RIPK1 within complex I is phosphorylated by IKKs, TBK1 and TAK1. TAK1 also activates the MAPK signalling cascade, whereas IKK α and IKK β

phosphorylate I κ B α , leading to its degradation and release of the NF- κ B p65–p50 heterodimer. In the cytosol, RIPK1 is further phosphorylated by MK2, ULK1, JAK1 and SRC, inhibiting its autophosphorylation and preventing its incorporation into complex II. Deubiquitylating enzymes A20 and CYLD hydrolyse ubiquitin chains, thus terminating the transcriptional response. Upon internalization of complex I, complex II forms in the cytosol, comprising FADD, caspase 8, RIPK1 and c-FLIP. Within this complex, c-FLIP–caspase 8 heterodimers cleave RIPK1, leading to disassembly of complex II. Lysosomal degradation of complex II is another molecular brake to inhibit cell death. **b**, TNF binding to TNFR2 recruits TRAF1, TRAF2, cIAP1 and cIAP2. Degradation of TRAF2, cIAP1 and cIAP2 stabilizes NIK, leading to activation of the non-canonical NF- κ B pathway. LUBAC is also recruited to promote canonical NF- κ B activation. XIAP limits the cytotoxic potential of complex II that could occur through TNFR2-mediated degradation of cIAP1 and cIAP2.

TNFR1 is retained in the cytoplasm and mediates ligand-independent signalling, validating this hypothesis. Nonetheless, the cooperation between mutant and wild-type TNFR1 in disease pathogenesis remains a matter of debate^{88,92,93}.

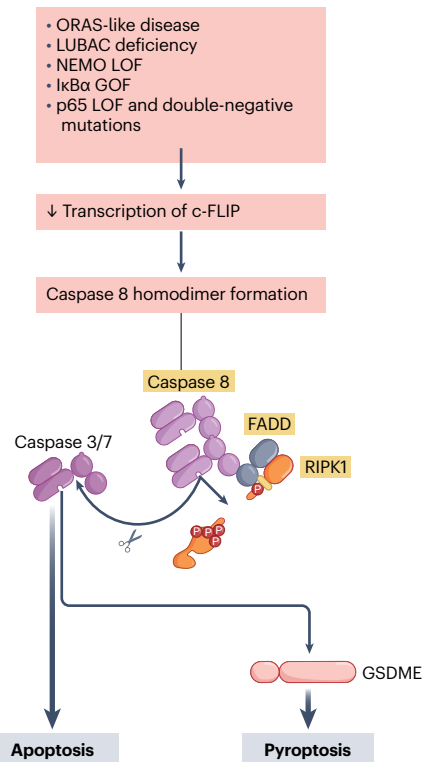
Therapeutically, corticosteroids alleviate acute flares but fail to prevent long-term complications or amyloidosis in patients with TRAPS⁹⁴. Despite the rationale of using TNF inhibitors in a disease driven by constitutive TNF signalling, the efficacy of these drugs in TRAPS remains limited. Etanercept achieves a complete response in only 30% of patients⁹⁴. Conversely, treatment with adalimumab or infliximab worsens the disease during flares, potentially owing to the ability of these drugs to activate the complement system^{86,95,96}. Interestingly, IL-1 β inhibitors elicit beneficial clinical responses and are now used as first-line treatments^{97,98}. These findings raise the question of why anti-IL-1 β therapies are more effective than anti-TNF therapies. Given the role of TNFR2 in inflammasome priming under conditions of low XIAP expression^{43–45}, a potential hypothesis is that impaired TNFR1 surface expression leads to TNFR2-mediated IL-1 β production. However, the contribution of the TNFR2–XIAP axis to TRAPS pathogenesis remains underexplored, warranting further investigation.

Gain-of-function mutations in RIPK1

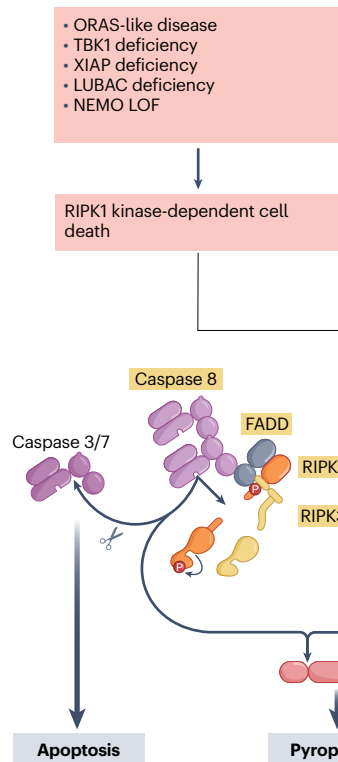
RIPK1 functions as a molecular switch that regulates apoptosis, necroptosis and inflammatory pathways downstream of TNFR1 and other innate immune receptors such as pattern recognition receptors (reviewed elsewhere⁹⁹). The ability of RIPK1 to shift from a pro-survival to a pro-death mediator depends on its ubiquitination, phosphorylation and cleavage status (reviewed elsewhere⁹⁹). Various studies have shown that mutations at the caspase 8 cleavage site (D324 or L321) of RIPK1 result in an autoinflammatory disease termed cleavage-resistant RIPK1-induced autoinflammatory (CRIA) syndrome^{32,100,101}. Patients with CRIA syndrome are heterozygous for these mutations and exhibit classic autoinflammatory symptoms, including recurrent fevers, lymphadenopathy and elevated systemic levels of pro-inflammatory cytokines such as TNF, IL-6 and IL-1 β ^{32,100,101} (Table 2).

Mice harbouring a heterozygous mutation at D325 (the murine orthologue of D324) seem phenotypically normal under specific pathogen-free conditions^{32,102,103}. However, similar to peripheral blood mononuclear cells from patients harbouring the equivalent mutation, the immune cells from the mice produce increased amounts of cytokines upon stimulation with TNF, LPS or poly(I:C)^{32,102,104}. Remarkably, although RIPK1-null mice die shortly after birth^{105–108},

a Inhibition of NF- κ B



b Inhibition of RIPK1 ubiquitylation or phosphorylation



c Inhibition of caspase 8

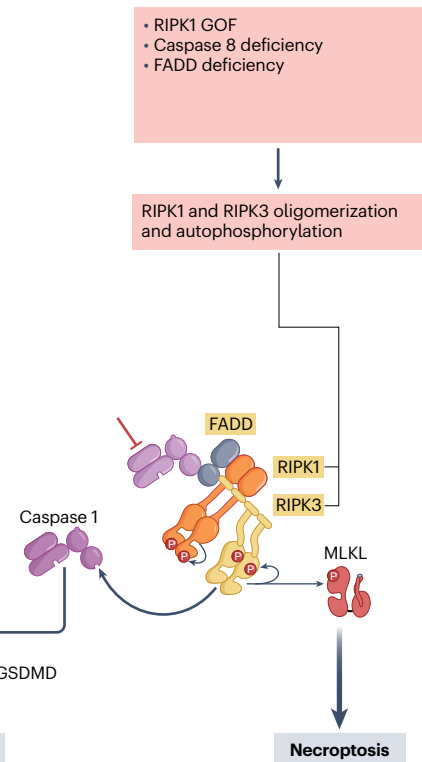


Fig. 2 | TNF-induced cell death in monogenic diseases. Pathogenic mutations in TNF signalling pathway components that cause monogenic diseases (highlighted in yellow) can also trigger, or are predicted to trigger, various modes of cell death. **a**, When nuclear factor- κ B (NF- κ B)-mediated transcription is inhibited and the levels of c-FLIP drop, caspase 8 forms homodimers that activate caspase 3 and caspase 7 to induce apoptosis. In certain contexts, caspase 3 can cleave GSDME, triggering pyroptosis. **b**, Inhibition of RIPK1 ubiquitylation or phosphorylation allows RIPK1 autophosphorylation, inducing a conformational shift that

promotes RIPK3 recruitment. In this context, caspase 8 cleaves caspase 3 and caspase 7 to drive apoptosis, GSDMD to trigger pyroptosis, and both RIPK1 and RIPK3 to prevent necroptosis and pyroptosis, respectively. **c**, When caspase 8 is inactive or absent, RIPK1 and RIPK3 oligomerize and autophosphorylate; RIPK3 then phosphorylates MLKL to induce necroptosis and can also activate caspase 1 to promote pyroptosis. GOF, gain of function; LOF, loss of function; LUBAC, linear ubiquitin chain assembly complex; ORAS, OTULIN-related autoinflammatory syndrome.

Box 1 | Non-rheumatological monogenic disorders of the TNF pathway

TBK1 haploinsufficiency

Heterozygous loss-of-function mutations in *TBK1* co-segregate with amyotrophic lateral sclerosis (ALS) and frontotemporal dementia^{292–294}. These mutations often lead to decreased expression of TBK1 or disruption of its interaction with optineurin, an adaptor protein implicated in ALS pathogenesis. Additionally, TAK1, another kinase known to phosphorylate RIPK1 to limit its cytotoxic activity, shows reduced expression in the brains of older individuals (>60 years old) and patients with ALS²⁵. A mouse model study revealed that combined heterozygosity of TAK1 in myeloid cells and TBK1 results in ALS and frontotemporal dementia-like pathology mediated by RIPK1 kinase activity²⁵. This finding suggests that TBK1 haploinsufficiency, in combination with an age-related decline of TAK1, triggers a RIPK1-dependent neuroinflammatory response. These findings, along with work from other studies (reviewed elsewhere²⁹⁵), have provided the rationale for targeting RIPK1 to treat ALS. However, despite, promising preclinical data, the only blood–brain-barrier-penetrant RIPK1 inhibitor, DNL747, was discontinued owing to compound-specific toxicity identified during safety studies²⁹⁶.

RIPK3 deficiency

The kinase activity of RIPK3 is essential for mediating necroptosis downstream of TNF receptors, pattern recognition receptors and IFN

receptors (reviewed elsewhere²⁹⁷). Under specific conformational conditions, RIPK3 also employs its scaffolding function to recruit RIPK1 and FADD, thereby promoting caspase 8-dependent apoptosis^{298,299}. A recent report described a paediatric case of herpes simplex encephalitis (HSE) associated with compound heterozygous loss-of-function mutations in RIPK3 (ref. 300). These variants impair TNFR1-mediated, TLR3-mediated, and ZBP1-mediated apoptosis and necroptosis³⁰⁰. HSE is primarily caused by herpes simplex virus type 1 (HSV-1) and consistent with this aetiology, RIPK3-deficient human pluripotent stem cell-derived cortical neurons were resistant to HSV-1-induced cell death, resulting in excessive viral replication³⁰⁰. Similarly, *RIPK3*-deficient mice exhibit impaired HSV-1-induced necroptosis and uncontrolled HSV-1 replication³⁰¹. The patient also showed impaired TLR3-mediated CCL3 production, further supporting the role of RIPK3 in regulating cytokine and chemokine responses during infection^{302,303}. In murine models, both cell-death-dependent and cell-death-independent functions of RIPK3 have been implicated in restricting viral infections, including those caused by West Nile and Zika viruses^{301,304,305}. Despite these defects, the RIPK3-deficient patient has not experienced severe infectious diseases other than HSV-1 (ref. 300). This case highlights the non-redundant and virus-specific role of RIPK3 in human antiviral immunity, particularly in the control of HSV-1 replication and neuroinvasion.

homozygous RIPK1 cleavage-resistant mice (*Ripk1*^{D325A/D325A}) die at mid-gestation, underscoring the gain-of-function (GOF) nature of D325 mutations^{32,102,104}. Although RIPK1 cleavage by caspase 8–FLIP heterodimers suppresses necroptosis³⁰, deletion of either RIPK3 or MLKL alone fails to rescue *Ripk1*^{D325A/D325A} embryonic lethality^{32,102,104}. Instead, lethality is driven by TNFR1-dependent and RIPK1 kinase-dependent activation of both apoptotic and necroptotic pathways^{32,102,104}. Mechanistically, resistance to cleavage leads to stabilization of the TNFR1 complex II, which simultaneously promotes both forms of cell death³².

Looking beyond CRIA syndrome, a preprint has described two patients carrying compound heterozygous *RIPK1* variants (K377E and R390G) who presented with recurrent fevers, lymphadenopathy, skin rashes and very early onset inflammatory bowel disease (VEO-IBD)¹⁰⁹. Although the function of R390 remains unclear, K377 is a known site of K63-linked ubiquitination^{110–112}. In line with the mutation of D325 in mice, homozygous mutation of K376 (the murine orthologue of K377) also resulted in embryonic lethality owing to TNFR1-dependent and RIPK1 kinase-dependent cell death¹¹². Unlike the human D324 variants^{32,100,101}, the K377E/R390G variant suppresses NF- κ B activation, suggesting that the autoinflammation is driven by transcriptional dysregulation in these patients¹⁰⁹. However, both mutations share a common phenotype of heightened sensitivity to TNF-induced cell death, highlighting RIPK1-mediated cell death as an important driver of autoinflammation^{32,109}.

Despite elevated TNF levels and the hypersensitivity of patient cells to TNF, anti-TNF therapy has had limited efficacy in patients carrying D324, L321 or K377E/R390G variants³². By contrast, anti-IL-6 treatment has resulted in substantial clinical improvements^{32,100,101,109}. Whether RIPK1 directly influences IL-6 signalling or whether IL-6 elevation is a secondary effect of inflammation and cell death remains an open

question. Given that the genetic ablation of RIPK1 kinase activity rescued the lethality of *Ripk1*^{D325A/D325A} mice^{32,102}, pharmacological inhibition of RIPK1, currently under clinical evaluation for several polygenic inflammatory diseases, could be another therapeutic option for patients carrying pathogenic D324 variants.

OTULIN-related autoinflammatory syndrome and OTULIN haploinsufficiency

OTULIN is a deubiquitinase that hydrolyses linear ubiquitin chains generated by LUBAC, suppressing TNF-dependent cell death and inflammatory signalling (reviewed elsewhere¹¹³). Homozygous loss-of-function (LOF) mutations in *OTULIN* cause OTULIN-related autoinflammatory syndrome (ORAS), also known as otulipenia, a potentially fatal disease characterized by neonatal-onset recurrent fevers, panniculitis, diarrhoea and arthritis^{114–118}. In addition, some reports have also described patients with ORAS-like symptoms who either have heterozygous dominant-negative mutations or compound heterozygous mutations^{119–121}. These patients show overlapping features with ORAS, such as sterile abscesses, skin lesions, oedema and systemic inflammation, although with variable onset and severity^{119–121}. All known pathogenic mutations, except for one intronic variant¹¹⁸, occur within the catalytic OTU domain of OTULIN, impairing ubiquitin binding, enzyme activity or protein stability^{114–118,120,121} (Table 2).

A unifying molecular hallmark of ORAS and ORAS-like cases is increased global linear ubiquitination in patient cells^{114–118,120,121}. This feature is accompanied by loss of LUBAC expression in B cells, T cells and fibroblasts, but not myeloid cells, and enhanced activation of NF- κ B and MAPK signalling pathways in monocytes^{114–118,120,121}. Consistent with these findings in monocytes, mice lacking OTULIN in myeloid cells, but not lymphoid cells, develop a strong inflammatory phenotype,

Table 2 | Monogenic disorders of the TNF signalling pathway

Gene (protein)	Mutations	Clinical features	Contribution of TNF	Treatment	Refs.
Autoinflammatory					
<i>TNFRSF1A</i> (TNFR1)	Heterozygous in CRD and TM domains	Recurrent fever, abdominal pain, myalgia, arthralgia, migratory erythematous rash and ocular inflammation	In patients: cells have aberrant activation of TNF-induced NF- κ B and MAPK signalling pathway and reduced apoptosis	Anti-IL-1 β therapy	68–75, 80–91
<i>RIPK1</i> (RIPK1)	Heterozygous GOF at the cleavage site	Recurrent fevers, lymphadenopathy, abdominal pain, arthralgia and oral ulcers	In mice: cells with heterozygous GOF D325A mutation have increased susceptibility to TNF-induced cell death; homozygote GOF D325A mutation is lethal owing to aberrant TNFR1-dependent and RIPK1 kinase-dependent cell death	Anti-IL-6 therapy	32,100,101
	Heterozygous GOF at the ubiquitin site	Recurrent fevers, lymphadenopathy, skin rashes and VEO-IBD	In mice: homozygous GOF K377R mutation is lethal owing to aberrant TNFR1-dependent and RIPK1 kinase-dependent cell death	Anti-IL-6 therapy	109
<i>OTULIN</i> (OTULIN)	Homozygous LOF	Recurrent fevers, panniculitis, diarrhoea and arthritis	In mice: embryonic lethality caused by homozygous OTULIN deficiency is delayed by loss of TNFR1; in adult mice, inactivation of OTULIN triggers lethal multi-organ inflammation, which can be prevented by TNFR1 blockade	Anti-TNF therapy	114–118
	Heterozygous DN, Compound heterozygous	Sterile abscesses, skin lesions and oedema	In mice: embryonic lethality caused by the C129A mutation is delayed by genetic ablation of TNFR1	Anti-TNF therapy	119–121
	Heterozygous LOF	Fasciitis and skin necrosis in response to staphylococcal α -toxin	No information available	Anti-TNF therapy	126,127
<i>TBK1</i> (TBK1)	Homozygous LOF	Recurrent fever, arthritis, vasculitis and epileptic episodes with neurocognitive developmental delay	In patients: cells have increased susceptibility to TNF-induced cell death and tissue-biopsy samples express markers of apoptosis In mice: loss of TBK1 is lethal owing to the resulting TNF-induced and RIPK1 kinase-induced cell death	Anti-TNF therapy	129
Immunodeficiency and autoimmunity					
<i>RIPK1</i> (RIPK1)	Homozygous LOF	Primary immunodeficiency, VEO-IBD and recurrent infections	In patients: cells have impaired TNF-induced NF- κ B and MAPK signalling	HSCT	136–142
<i>CASP8</i> (caspase 8)	Homozygous LOF	Early onset: ALPS-like symptoms and VEO-IBD Late onset: neurological symptoms and organ lymphocytic infiltration	In mice: embryonic lethality of caspase 8-deficient mice is delayed by the loss of TNFR1	No information available	147–152, 166–168
<i>FADD</i> (FADD)	Homozygous LOF Compound heterozygous	Recurrent bacterial infections owing to hyposplenism, developmental delay, recurrent febrile episodes, encephalopathy, seizures and liver dysfunction, often triggered by viral infections	In mice: embryonic lethality of FADD-deficient mice is delayed by loss of TNFR1	No information available	172–175
<i>XIAP</i> (XIAP)	Hemizygous LOF (males)	Primary immunodeficiency, HLH triggered by EBV, IBD, splenomegaly, liver disease, recurrent fever and skin involvement	In mice: XIAP-deficient mice have an increased susceptibility to murine EBV (MHV-68), driven by TNF-dependent and RIPK3-dependent cell-death pathways	Anti-TNF therapy, anti-IL-1 β therapy and HSCT	187–196
Mixed autoinflammatory, immunodeficiency and autoimmunity					
<i>TNFAIP3</i> (A20)	Heterozygous LOF	Recurrent fever, joint and gastrointestinal manifestations, autoimmune symptoms, mucosal ulcers and skin lesions	In mice: A20 ZnF7 mutant mice present with TNF-dependent arthritis	Anti-TNF therapy, JAK inhibitors and HSCT	202–209, 229–237
<i>RBCK1</i> and <i>RNF31</i> (HOIL1 and HOIP)	Homozygous LOF compound, heterozygous LOF	Primary immunodeficiency, autoinflammation and abnormal glycogen storage in the heart, skeletal muscle and liver	In patients: fibroblasts and B cells have impaired TNF-induced NF- κ B activation and increased susceptibility to TNF-induced apoptosis; tissue samples express markers of apoptosis and pyroptosis	HSCT in one patient with HOIL1 deficiency	193–195, 237–239
<i>SHARPIN</i> (SHARPIN)	Homozygous LOF	Mild immunodeficiency, autoinflammation and abnormal glycogen storage in the heart, skeletal muscle and liver	In patients: cells present with impaired TNF-induced NF- κ B activation and have an increased susceptibility to TNF-induced apoptosis; tissue samples express markers of apoptosis and pyroptosis	Anti-TNF therapy	243

Table 2 (continued) | Monogenic disorders of the TNF signalling pathway

Gene (protein)	Mutations	Clinical features	Contribution of TNF	Treatment	Refs.
Mixed autoinflammatory, immunodeficiency and autoimmunity (continued)					
<i>IKBK</i> (NEMO)	Heterozygous complete LOF (females and XXY males)	Incontinentia pigmenti (abnormal skin, teeth, hair, eyes and central nervous system) and miscarriages of male foetuses	In patients: cells have increased susceptibility to TNF-induced cell death In mice: <i>Ikbkg</i> ^{-/-} female mice develop a TNF-dependent skin phenotype	Anti-TNF therapy after HSCT	252–258
	Hemizygous LOF (males XY)	Embryonically lethal	N/A	N/A	252–258
	Heterozygous and hemizygous partial LOF (females and males XY)	Ectodermal dysplasia (sparse hair, conical teeth and absence of sweat glands) with immunodeficiency and IBD; immunologically, patients present with impaired antibody production and recurrent infections	In patients: cells have impaired NF-κB activation downstream of TNF In mice: mice with intestinal epithelial-specific NEMO deficiency develop TNFR1-dependent and RIPK1 kinase-dependent intestinal inflammation	Anti-TNF therapy after HSCT	262–274
	Deletion of exon 5	Ectodermal dysplasia, panniculitis, lipoatrophy, hyperpigmentation, fever, rash, periorbital oedema, liver disease and failure to thrive	In patients: TNF stimulation induces the expression of IKKε, leading to hyperresponsiveness of the virus-sensing pathways	Anti-TNF therapy	278–283
<i>NFKB1A</i> (κBα)	Heterozygous GOF	Ectodermal dysplasia (sparse hair, conical teeth and absence of sweat glands) with immunodeficiency; immunologically, patients present with impaired antibody production and recurrent infections	No information available	HSCT	265–268, 270,271
<i>RELA</i> (p65)	Heterozygous LOF	Recurrent fever, gastrointestinal and skin inflammation, arthritis, systemic lupus erythematosus, lymphadenopathy and conjunctivitis	In patients: cells have impaired NF-κB signalling and increased susceptibility to TNF-induced apoptosis	Anti-TNF therapy	284–289

ALPS, autoimmune lymphoproliferative syndrome; CRD, cysteine-rich domain; DN, dominant negative; EBV, Epstein–Barr virus; GOF, gain of function; HLH, haemophagocytic lymphohistiocytosis; HSCT, haematopoietic stem-cell transplantation; IBD, inflammatory bowel disease; LOF, loss of function; NF-κB, nuclear factor-κB; TM, transmembrane; VEO-IBD, very early onset inflammatory bowel disease.

involving spontaneous activation of NF-κB and secretion of TNF^{114,122}. Moreover, although OTULIN-deficient mice and mice with mutations in the OTU domain of OTULIN that disrupt its catalytic activity and/or its binding to ubiquitin (W96R, D336E, C129S and L272P) die during mid-gestation, inactivation of OTULIN in adult mice caused lethal multi-organ inflammation that is prevented by TNFR1 blockade^{115,123–125}. Accordingly, although anti-IL1β is ineffective, anti-TNF therapy has proven beneficial in managing ORAS symptoms^{114–118,120,121}.

Beyond ORAS, individuals carrying heterozygous LOF variants in OTULIN are susceptible to fasciitis and skin or pulmonary necrosis in response to *Staphylococcus aureus* infection¹²⁶. In contrast to ORAS, OTULIN haploinsufficiency does not result in loss of LUBAC expression or impaired TNF signalling¹²⁶. Instead, haploinsufficiency leads to the accumulation of caveolin 1 complexes, causing retention of ADAM10, the receptor for the virulent staphylococcal α-toxin. These effects enhance α-toxin-mediated cytotoxicity specifically in fibroblasts, but not in leukocytes¹²⁶. Notably, OTULIN haploinsufficiency exhibits incomplete penetrance, which could be due to monoallelic expression as well as the presence of pre-existing α-toxin-neutralizing antibodies in many individuals¹²⁷. OTULIN haploinsufficiency in mice results in exaggerated inflammatory responses to TLR ligands, confirming the role of OTULIN in microbial-driven inflammation¹²⁸. Interestingly, in these mice, inflammation was predominantly driven by the haematopoietic compartment¹²⁸, contrasting with the non-haematopoietic tissue involvement observed in patients with haploinsufficiency of OTULIN¹²⁶. This discrepancy suggests that additional mechanisms might underlie the human pathology or that species-specific differences shape OTULIN-dependent immune regulation. Despite preserved

TNF receptor signalling in patients with OTULIN haploinsufficiency, TNF blockade, rather than IL-1 inhibition, has proven a highly effective treatment, leading to the resolution of necrosis and hyperinflammation in at least one reported case¹²⁷.

TBK1 deficiency

In the TNF signalling pathway, TBK1 phosphorylates RIPK1 to prevent RIPK1-mediated cytotoxicity^{17,25}. Biallelic LOF mutations in *TBK1* cause an early-onset autoinflammatory syndrome¹²⁹. Affected individuals present with arthritis, vasculitis, recurrent fever and neuronal involvement, including epileptic episodes and neurocognitive developmental delay¹²⁹. Some identified that *TBK1* mutations result in a complete loss of protein expression, whereas others are speculated to produce a catalytically inactive form of TBK1 (ref. 129). Consistent with findings in *Tbk1*-mutant mice^{130,131}, the T cell compartment of these patients is also dysfunctional¹²⁹. Despite the well-established role of TBK1 in type I interferon signalling, patients with TBK1 deficiency do not exhibit increased susceptibility to viral infections because IKKε seems to compensate for the loss of TBK1 to preserve RIG-I-induced type I IFN responses¹²⁹ (Table 2).

Tbk1-knockout is embryonically lethal in mice owing to TNF-dependent and RIPK1 kinase-dependent cell death^{25,132–135}. Consistently, cells derived from patients with TBK1 deficiency have an increased susceptibility to TNF-induced necroptosis; furthermore, histological analysis of tissue samples from these patients has confirmed the presence of apoptotic cells, suggesting that the autoinflammation is driven primarily by excessive RIPK1-dependent cell death¹²⁹. Mechanistically, TBK1 normally restrains RIPK1-driven cell death, not

only by phosphorylating RIPK1 at Thr190 but also by phosphorylating CYLD^{17,25}. Therapeutically, these findings are of immediate relevance. Although anti-IL-6 therapy has proven ineffective in patients with TBK1 deficiency, patients have responded well to anti-TNF treatment¹²⁹. Furthermore, given the central role of RIPK1 kinase activity in driving cell death in the absence of TBK1, RIPK1 inhibitors represent a promising, yet unexplored, therapeutic avenue for these patients.

Immunodeficiencies and autoimmune syndromes

Certain mutations that impair TNF signalling pathways can compromise immune-cell survival and function, resulting in primary immunodeficiencies. In certain contexts, defective immune regulation promotes loss of tolerance and autoimmunity. These disorders highlight the essential role of TNF and its regulators in maintaining balanced immune responses, where insufficient signalling can predispose to infection and aberrant activation can trigger self-reactivity.

RIPK1 deficiency

RIPK1 deficiency results from LOF homozygous or compound heterozygous missense mutations in RIPK1 that lead to partial or complete loss of the protein. The patients present with primary immunodeficiency and VEO-IBD^{136–142}. Fibroblasts from patients with *RIPK1* deficiency have impaired NF- κ B and MAPK signalling downstream of stimulation with TNF or TLR ligands, and diminished cytokine production^{136–138}. Patient-derived monocytes exhibit necroptosis-dependent IL-1 β release, consistent with findings in murine *RIPK1*-deficient macrophages^{136,138,143} (Table 2).

Furthermore, the clinical manifestations observed in RIPK1-deficient individuals closely resemble the systemic inflammatory phenotype reported in RIPK1-deficient mice^{105,106,144,145}. However, the murine phenotype is more severe than in humans, as *Ripk1*-deficient mice do not survive the perinatal period^{105–108,144–146}.

Differences between human and mouse phenotypes might be attributed to interspecies differences or residual expression of RIPK1 in patients. Notably, although patients carrying the A195T variant have been classified as *RIPK1* deficient¹³⁷, unpublished data indicate that the antibody used in that study does not detect the A195T mutant protein and that these patients retain partial protein expression of RIPK1 (N.L., unpublished). Consistent with this finding, individuals carrying A195T develop VEO-IBD but do not present with recurrent infections, unlike those individuals with more profound RIPK1 deficiency (N.L., unpublished). Whether the residual function of A195T contributes to disease through a potential GOF mechanism remains unclear.

Standard immunosuppressants have provided limited therapeutic benefit in patients with RIPK1 deficiency. Anti-TNF therapy resulted in only modest improvement^{136,141} and anti-IL-1 β therapy exacerbated intestinal ulceration in one patient but ameliorated colitis in another¹⁴¹. Mouse models have implicated RIPK1 in promoting inflammation in non-haematopoietic compartments, a mechanism that might underlie gastrointestinal pathology in humans. Nevertheless, haematopoietic stem-cell transplantation (HSCT) resolved or improved intestinal symptoms in 6 of the 9 patients treated^{138,141}. However, transplant-related mortality was higher for these patients than that observed in patients with classical primary immunodeficiencies, potentially owing to the lack of RIPK1 expression in non-haematopoietic cells^{138,141}. Given the role of RIPK1 in regulating inflammasome activation, pre-transplant or peri-transplant blockade of IL-1 β and/or IL-18 signalling could hypothetically reduce systemic inflammation and improve transplant outcomes.

Caspase 8 deficiency

Caspase 8 deficiency presents with a heterogeneous clinical spectrum, with recurrent infections being the most consistent feature across all reported cases^{147–152}. Autoimmune lymphoproliferative syndrome (ALPS)-like symptoms and VEO-IBD can also occur, sometimes appearing in isolation^{147,149,152} and sometimes co-occurring in the same patient^{150,151}. Neurological symptoms and organ lymphocytic infiltration can also occur in individuals with late-onset disease¹⁴⁸. Interestingly, individuals harbouring the same mutation, such as R248T, can have different clinical features, from early-onset lymphadenopathy and recurrent infections¹⁴⁷ to late-onset neurological symptoms and immune infiltration¹⁴⁸. To date, reported *CASP8* mutations localize within either the p18 or the p10 subunit of caspase 8 and result in reduced expression or impaired processing of caspase 8 (refs. 147,149–151). These molecular defects give rise to several shared functional consequences, including impaired Fas-mediated apoptosis^{147,151,152}, defective lymphocyte activation and proliferation^{147,149}, altered T cell subset distribution^{148,149,151}, reduced T cell receptor-induced NF- κ B signalling^{147,151} and, in some cases, increased inflammasome activity¹⁴⁹.

The clinical variability observed in caspase 8 deficiency might be attributed to differences in residual caspase 8 expression, auto-processing and/or enzymatic activity^{147,149}. Supporting this idea, murine studies have demonstrated that inhibition of caspase 8 autoproteolysis selectively impairs apoptosis, whereas complete loss of caspase 8 or inhibition of its catalytic activity leads to inflammation^{66,67,153–162}. Specifically, caspase 8 deficiency induces a necroptotic inflammatory response, whereas catalytic inactivation of caspase 8 results in a pyroptotic inflammatory phenotype^{66,67,153–162}. Furthermore, N4BP1, a caspase 8 substrate that normally suppresses MYD88-dependent TLR signalling¹⁶³, might contribute to immune dysregulation in these patients. Impaired cleavage of N4BP1 could enhance inflammatory cytokine production, potentially exacerbating susceptibility to IBD and infections.

The viability of patients with caspase 8 deficiency contrasts sharply with the embryonic lethality observed in caspase 8-deficient mice, which die in utero because of uncontrolled necroptosis^{30,164,165}. Notably, loss of TNFR1 only delayed, but did not fully prevent, the embryonic lethality of caspase 8-deficient mice¹⁰⁶. This discrepancy might arise from the functional redundancy between caspase 8 and its paralogs, caspase 10, in humans. In mice, inhibition of necroptosis (for example, by RIPK3 or MLKL deletion) rescues viability but leads to a lymphoproliferative phenotype characterized by accumulation of double-negative T cells, a hallmark of ALPS. Whether human caspase 8 deficiency should be classified as an ALPS disorder is a subject of ongoing debate, given that lymphadenopathy is absent in some patients and, when present, is associated with apoptosis-resistant T cells rather than double-negative T cells^{151,166–168}. A failure to cleave RIPK1, another caspase 8 substrate, might contribute to lymphadenopathy in these patients because diseases caused by heterozygous RIPK1 mutations that prevent caspase 8 cleavage (for example, CRIA) also feature lymphadenopathy as a core clinical sign^{32,100,101}. Given the rarity of this condition, no clinical treatment protocols exist, and patients receive symptomatic treatment such as intravenous immunoglobulin and prophylactic acyclovir to decrease the risk of infections. Anti-TNF therapy has been attempted in one patient, with limited success¹⁴⁹ (Table 2).

FADD deficiency

FADD deficiency shares several biological hallmarks with ALPS, including the expansion of circulating double-negative T cells,

increased serum levels of IL-10 and FasL, and defective Fas-mediated apoptosis^{169–171}. However, unlike ALPS, patients with FADD deficiency do not develop autoimmunity or overt lymphoproliferation^{169–171}. Instead, the clinical phenotype is dominated by immunodeficiency with recurrent bacterial infections, largely attributable to functional hyposplenism, as well as developmental delay, recurrent febrile episodes accompanied by encephalopathy, seizures and liver dysfunction, often triggered by systemic viral infections^{169–171}. To date, nearly all reported patients have carried homozygous mutations that affect the residue C105 within the first α -helix of the death domain, which reduces FADD expression and disrupts its interaction with Fas and potentially other death-domain-containing proteins^{169,170,172}. One additional patient was described as having compound heterozygous mutations, including one allele bearing the C105 variant¹⁷¹. Variable expressivity has also been noted, as illustrated by a patient with homozygous C105 mutations who presented primarily with neurological manifestations and hepatic disease¹⁷².

FADD deficiency is associated with high mortality in early childhood. Nevertheless, affected infants are born alive, in sharp contrast to *Fadd*-deficient mice, which die during embryogenesis because of unrestrained necroptosis^{165,173–176}. In mice, FADD restrains necroptosis to permit normal T cell proliferation. By contrast, T cell proliferation is preserved in patients with FADD deficiency, further emphasizing differences between species^{169,170,173,176–182}. Interestingly, *Fadd*-deficient mice develop lethal cardiac defects, a feature observed in some, but not all, patients, suggesting that some of the developmental roles of FADD are partially conserved across species^{170,174,175,183}. The recurrent viral infections observed in patients might reflect an additional function of FADD in regulating NF- κ B and type I interferon signalling downstream of the viral sensor RIG-I, a mechanism supported by murine studies^{184,185}. FADD deficiency is rare and treatment approaches remain unstandardized. Reported patients have so far mainly received supportive care, including antimicrobial prophylaxis or immunoglobulin replacement^{169–172} (Table 2).

XIAP deficiency

Beyond its conventional role in caspase inhibition, XIAP restricts TNF-mediated, RIPK3-dependent cell death^{43–45}. XIAP also modulates pro-inflammatory signalling downstream of nucleotide-binding oligomerization domain-containing protein 2 (NOD2) by promoting the ubiquitination of RIPK2 (reviewed elsewhere¹⁸⁶). XIAP deficiency, also known as X-linked lymphoproliferative disease type 2 (XLP-2), is a primary immunodeficiency that typically manifests in men within the first few years of life and might also occur in women owing to skewed X chromosome inactivation^{187–189}. The most common clinical features include haemophagocytic lymphohistiocytosis, which can be triggered by Epstein–Barr virus (EBV) infection and IBD. Less common manifestations include haemophagocytic lymphohistiocytosis-independent splenomegaly, liver disease, recurrent fever, hypogammaglobulinaemia and dermatological involvement^{187,188,190–196} (Table 2).

Mutations in XIAP are distributed throughout the gene and include nonsense and missense mutations, deletions, insertions and intronic variants^{187,188,190–196}. These mutations lead to complete loss of XIAP or the expression of a truncated, non-functional, or dysfunctional protein. Missense mutations often cluster within the BIR2 and RING domains, underscoring the functional importance of these domains¹⁹⁷. Despite this clustering, no clear genotype–phenotype correlation has emerged, as affected siblings often have highly variable clinical presentations^{187,188,190–196}. Cells from patients with deficiency of XIAP

have impaired responses to MDP stimulation, consistent with the role of XIAP in NOD2 signalling (reviewed elsewhere¹⁸⁶).

Loss of XIAP compromises the immune responses and survival of mice following infection with certain pathogens. Notably, infection of mice with murine herpesvirus 68 (MHV-68), the murine homologue of EBV, leads to splenomegaly within days, accompanied by increased lymphoid and myeloid cellularity^{45,198}. This phenotype is driven by TNF-dependent and RIPK3-dependent cell death, consistent with the role of XIAP in suppressing TNFR2-mediated RIPK3-dependent inflammasome activation^{43–45}. Studies in mice also indicate that XIAP deficiency promotes intestinal inflammation through mechanisms beyond NOD2 signalling. Loss of XIAP renders Paneth cells susceptible to microbiota, TNFR1-dependent, RIPK1-dependent and RIPK3-dependent cell death^{199,200}. This microbiota sensitivity might underlie the incomplete penetrance of IBD among patients with deficiency of XIAP.

Altogether, these findings suggest a pathological role for TNF signalling in human XIAP deficiency. However, anti-TNF therapy is not considered a first-line treatment. Anti-TNF therapy has been used in patients with IBD, but this approach often only yielded incomplete clinical responses (reviewed elsewhere¹⁹³). Instead, HSCT is regarded as the primary curative option for patients with severe disease, although only a subset of patients undergo transplantation. Transplant-related mortalities were initially high with this approach, owing to the exaggerated inflammation, but better outcomes can now be achieved using reduced myeloablative regimens (reviewed elsewhere¹⁹³). In addition, other therapeutic approaches are being explored, including anti-IL-1 β therapy, which has shown success in one patient and is consistent with the role of XIAP in regulating inflammasome activity^{43–45,201}.

Mixed autoinflammation, immunodeficiency and autoimmune syndromes

Certain monogenic defects within the TNF pathway blur the classical boundaries between autoinflammation, immunodeficiency and autoimmunity. These ‘mixed’ syndromes exemplify how a single molecular lesion can simultaneously activate inflammatory cascades, disrupt lymphocyte function and impair tissue homeostasis. Understanding the mechanistic overlap among these entities provides key insights into the shared molecular architecture of inflammatory and immune dysregulation disorders.

HA20

A20 is a ubiquitin-editing enzyme that functions as both a deubiquitinase and a ubiquitin ligase, and has a crucial function in regulating inflammation and cell death. Haploinsufficiency of A20 (HA20) results from heterozygous LOF mutations in *TNFAIP3* (the gene encoding A20). Initially, HA20 was classified as a genetic form of Behçet disease owing to the prevalence of mucosal ulcers and skin lesions in affected patients^{202–204}. However, further studies have revealed that HA20 encompasses a full and complex range of multisystemic manifestations^{205–208} (Table 2).

Approximately half of patients with HA20 experience recurrent fever episodes, gastrointestinal involvement and skin involvement, whereas a third of the patients present with autoimmune and joint manifestations^{205,209}. The link to autoimmunity is unsurprising, given that *TNFAIP3* polymorphisms are associated with conditions such as systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and type 1 diabetes²¹⁰. Less common but notable clinical features include humoral deficiencies and lymphadenopathy^{205,209}.

Structurally, A20 comprises an OTU domain responsible for deubiquitinase activity and seven ZnF domains. ZnF4 supports E3 ligase activity and K63-ubiquitin binding, whereas ZnF7 binds to linear ubiquitin chains. A20 suppresses NF- κ B signalling by integrating its deubiquitinase, E3 ubiquitin ligase and ubiquitin-binding activities to mediate proteasomal degradation of key signalling intermediates downstream of TNFR1, TLR, IL-17R and IL-1R signalling pathways. Additionally, A20 targets IL-1 β , RIPK3 and caspase 8 to restrict inflammasome activation, apoptosis and necroptosis (reviewed elsewhere²¹¹).

To date, researchers have identified over 80 disease-causing *TNFAIP3* variants, with most variants predicted to result in a LOF or reduced expression of A20 (ref. 205). These mutations are evenly distributed between the OTU domain and the carboxy-terminal ZnF domains. Whether mutation type or location influence the clinical phenotype is a subject of ongoing debate. Emerging genotype–phenotype correlations have been suggested; two studies reported that OTU-domain mutations correlate with an increased incidence of genital ulcers, whereas predicted LOF variants show a strong association with autoimmunity^{205,209} (Table 2).

Mouse studies of homozygous A20 mutants have shown that loss of either the deubiquitinase or E3 ligase activity alone (as in OTU-mutant or ZnF4-mutant mice) was insufficient to trigger overt inflammation^{212–215}. By contrast, disrupting the ability of A20 to bind linear ubiquitin (as with ZnF7 mutant mice) results in spontaneous arthritis, splenomegaly, lymphadenopathy and liver inflammation^{213,216,217}. This phenotype is further exacerbated in mice with mutations in both ZnF4 and ZnF7 motifs; in these mice, simultaneous impairment of the binding of A20 to both K63-linked and linear ubiquitin leads to perinatal lethal systemic inflammation, closely resembling the phenotype observed in A20-deficient mice^{213,217–222}. These findings are consistent with clinical data showing that predicted LOF variants in A20 are frequently associated with severe disease and autoimmune manifestations^{205,209}. Mechanistically, studies of mice with tissue-specific A20 deficiency have demonstrated that myeloid cells are the main drivers of autoimmunity, primarily through activation of the NLRP3 inflammasome and necroptosis^{216,217,223,224}. Interestingly, deletion of *Tnf*, but not *Nlrp3*, rescued the arthritis phenotype observed in A20 ZnF7 mutant mice. Altogether, the findings suggest that complete loss of A20 might drive NLRP3-dependent pathology, whereas mutations affecting only the ZF7 domain could promote disease through TNF-driven mechanisms²¹³.

Although most studies have focused on homozygous A20 mutant mice, some evidence indicates that under specific pathogen-free conditions, A20 haploinsufficiency causes only subclinical immune dysregulation. However, upon immune challenges, these mice display increased susceptibility to TNF, experimental psoriasis and atherosclerosis^{217,225,226}. Moreover, B cell–restricted haploinsufficiency of A20 in mice results in moderately hyperreactive B cells and female-biased autoimmunity^{227,228}, consistent with the TNF-dependent skewing of B cell and T cell repertoires towards polyreactive ‘permissive’ receptors observed in patients with HA20 (ref. 229). Together, these findings indicate that A20 haploinsufficiency alone is often insufficient to trigger overt disease but lowers the threshold for inflammation and autoimmunity, particularly under immunological or environmental stress.

To date, treatment strategies for HA20 have remained unstandardized and primarily symptom driven. Colchicine is effective in over one-third of patients with HA20, particularly in milder cases, consistent with the frequent presence of Behçet disease-like features^{205,209,230}.

TNF inhibitors, commonly used in Behçet disease, are the most frequently prescribed and effective biologic agents in HA20, probably because of the role of A20 in the TNF signalling pathway^{205,209,230}. Although A20 also regulates the inflammasome, only a small number of patients have received treatment with IL-1 β ^{205,209,230}. HSCT has been performed in 6 patients with severe and refractory manifestations, resulting in clinical improvement in four of the patients. However, some autoimmune sequelae persisted despite transplantation^{208,231–233}. Finally, JAK inhibitors have shown promising efficacy in patients expressing a type I interferon signature^{234,237}.

LUBAC deficiencies

LUBAC is a trimeric complex composed of HOIL1, HOIP and SHARPIN. LUBAC catalyses the addition of linear ubiquitin chains to key components of the NF- κ B signalling pathway and other immune-related complexes. HOIP serves as the E3 ubiquitin ligase, whereas HOIL1 and SHARPIN function primarily as scaffolding proteins. However, emerging evidence indicates that HOIL1 also possesses E3 ligase activity, particularly for monoubiquitylation of carbohydrates²³⁶.

Homozygous and compound heterozygous LOF mutations in HOIL1 and HOIP genes cause early-onset, potentially life-threatening immunodeficiency, autoinflammation and abnormal glycogen storage in the heart, skeletal muscle and liver^{237–239}. As seen in LUBAC knockout mice^{15,54,240,241}, these mutations lead to markedly reduced levels of all three components of LUBAC^{237–239}. Patient-derived fibroblasts and B cells show impaired NF- κ B activation in response to TNF, IL-1 or CD40L, providing a mechanistic basis for the observed immunodeficiency^{237–239}. The autoinflammatory phenotype has been attributed to monocyte hyperresponsiveness to inflammatory stimuli^{237–239} (Table 2).

Patients with a deficiency of HOIL1 or HOIP also present with non-immune manifestations such as glycogenosis, with HOIL1 deficiency typically presenting with more severe pathology than HOIP deficiency^{237–239}. This observation correlates with findings in HOIL1 E3 ligase-inactive mice (Cys458Ser), which spontaneously develop glycogen accumulation in the heart and brain, attributed to defective ubiquitylation of glucosaccharides²⁴².

Similarly, patients with SHARPIN deficiency have features of autoinflammation such as recurrent fevers and arthritis, reduced levels of HOIL1 and HOIP and impaired NF- κ B signalling²⁴³. However, unlike patients with HOIL1 or HOIP deficiencies, the immunodeficiency is milder and does not involve monocyte hyperactivation²⁴³. Mouse models have shown that LUBAC is essential for restraining TNF-induced cell death, both by promoting NF- κ B-mediated prosurvival signalling via complex I and by preventing cell death signalling through complex II^{13,15,54,240,241,244,245}. Accordingly, human LUBAC-deficient cells are more prone to TNF-induced apoptosis than cells from healthy individuals, and tissue samples from affected patients contain markers of apoptosis and pyroptosis²⁴³. The exact mechanism of pyroptosis remains unclear; whether pyroptosis results from caspase 8-mediated GSDMD cleavage or is modulated through the involvement of LUBAC in inflammasome regulation remains under investigation^{63,64,246,247}.

A striking interspecies difference in SHARPIN deficiency is that SHARPIN-deficient mice develop severe dermatitis, whereas this phenotype is absent in humans. Despite SHARPIN being expressed in human keratinocytes and T cells, affected individuals show no signs of skin inflammation or T cell abnormalities^{248–250}. Mouse studies have demonstrated that keratinocyte-specific deletion of SHARPIN

leads to severe skin inflammation, whereas fibroblast-specific deletion causes milder dermatitis but pronounced arthritis, pointing to cell-type-specific functions of SHARPIN²⁵¹.

TNF and IL-1R blockade therapies show limited efficacy in individuals with a deficiency of HOIL1 (refs. 237–239). However, HSCT successfully reversed autoinflammation in one patient with a deficiency of HOIL1 (ref. 238). By contrast, consistent with murine models in which *Tnfr1* deletion rescues SHARPIN-driven inflammation^{244,245}, anti-TNF therapy markedly improved arthritis and colitis in one patient with SHARPIN deficiency, highlighting the central role of TNF signalling in SHARPIN-related disease²⁴³. Notably, the detection of active RIPK1 in tissue samples from patients with LUBAC deficiency suggests that RIPK1 inhibitors could represent a promising therapeutic approach²⁴³.

Loss-of-function and gain-of-function mutations in NEMO and IκBα

As a scaffolding protein, NEMO binds to ubiquitin chains and orchestrates the recruitment of IKK kinases, thereby ensuring proper activation of the NF-κB signalling pathway. In unstimulated cells, IκBα sequesters NF-κB subunits in the cytosol. Upon stimulation, IκBα is phosphorylated by the IKK complex, leading to its proteasomal degradation and the release of NF-κB subunits. These subunits then translocate to the nucleus, where they activate the transcription of NF-κB target genes. NEMO is encoded by the X-linked gene *IKBKG*, whereas IκBα is encoded by *NFKBIA*. Mutations in *IKBKG* or *NFKBIA* are associated with a spectrum of genetic disorders characterized by immune dysfunction and ectodermal abnormalities.

Complete LOF mutations in *IKBKG* (NEMO) cause incontinentia pigmenti, an X-linked dominant disorder that primarily affects females and is typically lethal in male foetuses^{252–255}. Affected females survive because of X chromosome disomy and preferential inactivation of the mutant X chromosome²⁵³. In the rare instances of incontinentia pigmenti in male patients it is typically associated with either a 47,XXY karyotype (Klinefelter syndrome) or postzygotic mosaicism²⁵⁶. However, most male cases lack a confirmed molecular diagnosis, most likely because testing is performed on peripheral blood rather than affected tissues. This observation suggests that mutations restricted to non-haematopoietic lineages might underlie the phenotype²⁵⁷. Patients with incontinentia pigmenti present with congenital neuroectodermal defects, resulting in abnormalities of the skin, teeth, hair, eyes and central nervous system; additionally, female patients experience recurrent miscarriages of male foetuses.

A recurrent deletion of exons 4–10 in *IKBKG* accounts for over 80% of incontinentia pigmenti cases²⁵⁸. In addition, nonsense mutations, missense mutations and small insertions or deletions can also cause the disease. These genetic alterations impair NF-κB activation in response to several cytokines, including the TNF superfamily member ectodysplasin A, which is critical for ectodermal development. NF-κB pathway disruption also renders mutant cells highly sensitive to TNF-induced cell death²⁵², likely explaining the embryonic lethality observed in males with complete LOF mutations and the skewed X inactivation observed in females (Table 2). Interestingly, female mice heterozygous for NEMO deficiency and mice with keratinocyte-specific NEMO deficiency develop a skin phenotype that closely resembles incontinentia pigmenti and that is dependent on TNF^{259–261}.

By contrast, hypomorphic or partial LOF mutations in *IKBKG* are compatible with male survival. These mutations, as well as heterozygous GOF mutations in *NFKBIA* (encoding IκBα), typically result in ectodermal dysplasia with immunodeficiency (EDA-ID) in both males and females,

although one exception has been reported in a patient presenting with immunodeficiency in the absence of ectodermal dysplasia^{262–272}. EDA-ID is characterized by sparse hair, conical teeth and the absence of sweat glands. Immunologically, the disease involves impaired antibody production and defective NF-κB activation in lymphocytes, leading to severe, recurrent infections early in life^{262–267}. Hypomorphic *IKBKG* mutations are typically missense variants, in-frame indels or intronic mutations, whereas the GOF mutations in *NFKBIA* result in degradation-resistant forms of IκBα. Collectively, these mutations impair NF-κB activation downstream of TNF, IL-1 and TLR signalling^{262–272}.

In addition to immunodeficiency, patients with EDA-ID frequently develop autoinflammatory manifestations, such as IBD, which has been shown to respond to TNF blockade following successful HSCT^{273,274}. This observation is consistent with findings in mice lacking NEMO specifically in intestinal epithelial cells, which develop TNFR1-dependent intestinal inflammation²⁷⁵. Notably, this inflammation is dependent on RIPK1 kinase activity, supporting the hypothesis that RIPK1 inhibitors are a potential therapeutic option for patients with EDA-ID and IBD^{276,277} (Table 2).

More recently, researchers have described a distinct clinical entity termed NEMO-Deleted Exon 5 Autoinflammatory Syndrome (NDAS). NDAS shares the ectodermal dysplasia observed in incontinentia pigmenti and EDA-ID but does not involve severe infections^{278–281}. Patients with NDAS predominantly present with panniculitis, lipoatrophy, hyperpigmentation, fever, rash, periorbital oedema, liver disease and failure to thrive^{278,279,281–283}. Pathogenic NDAS mutations are typically heterozygous splice site variants that result in skipping of exon 5. The condition occurs more frequently in females, in whom pathogenic variants typically arise as germline mutations with or without skewed X chromosome inactivation. By contrast, affected males usually present with a 47,XXY karyotypes or exhibit mosaic mutations^{278,279,281–283}.

Overexpression of the mutant allele is thought to be critical for pathogenesis^{278,279,281}. The pathogenic effect of the mutant allele is tissue specific and depends on the relative expression levels of wild-type and mutant NEMO, as well as its counterpart, IKKε. Immune cells from patients with NDAS exhibit type I IFN and NF-κB gene signatures, driven by high levels of IKKε, which bind to mutant NEMO. By contrast, fibroblasts show defective virus-sensing signalling pathways owing to low expression of both mutant NEMO and IKKε. Interestingly, TNF stimulation in these cells induces IKKε expression, leading to hyperresponsiveness of the virus-sensing pathways. In line with this mechanism, symptoms in patients with NDAS have been shown to improve with anti-TNF therapy²⁸⁰ (Table 2).

p65 haploinsufficiency and dominant negative mutations

RELA encodes the NF-κB transcription factor p65 (also known as RelA), a critical regulator of genes involved in inflammation, cell proliferation and cell death. Pathogenic heterozygous mutations in *RELA* lead to a spectrum of autoinflammatory and autoimmune manifestations^{284–289}. Initially, p65 haploinsufficiency was considered a monogenic form of Behçet disease due to the frequent occurrence of chronic mucocutaneous ulceration, a hallmark feature also observed in HA2O. However, subsequent findings have expanded the clinical phenotype to include recurrent fever, gastrointestinal and cutaneous inflammation, arthritis, systemic lupus erythematosus, lymphadenopathy, ALPS-like conditions and conjunctivitis^{284–289} (Table 2).

Pathogenic variants either result in reduced expression of p65 (~50% decrease) or produce truncated proteins that lack transcriptional activity. Consequently, patient-derived cells exhibit impaired NF-κB

Box 2 | Limitations of mouse models in studying human TNF signalling

Mechanistic insights from monogenic disorders have greatly enhanced our understanding of the TNF signalling pathway. Although several murine models have elucidated various pathogenic mechanisms and guided therapeutic development, other models fail to replicate key aspects of the human phenotype. These discrepancies arise from species-specific differences in immune architecture and signalling. Notably, mice lack caspase 10 and the long isoform of c-FLIP, and exhibit distinct necroptosis responses compared with humans^{306–308}. Experimental context further limits translational relevance. Most studies rely on inbred strains maintained in ultraclean facilities, reducing genetic and microbial diversity. This controlled environment narrows the scope for identifying gene–environment interactions and disease modifiers. For example, RIPK1-deficient and SHARPIN-deficient mice exhibit variable phenotypes depending on the genetic background^{105–107,146,245,249,309}. Similarly, immune dysfunction in XIAP-deficient or A20-deficient mice becomes apparent only under environmental challenge, such as exposure to *Helicobacter* species or co-housing with pet-shop mice^{199,310}. To improve translational value, future studies should integrate outbred and environmentally enriched ('dirty') mouse models, which better reflect the complexity of human immune responses. Complementary use of humanized models and organoid systems could further bridge interspecies differences in TNF biology.

signalling and increased susceptibility to TNF-induced apoptosis²⁸⁴. Although the reported cases remain limited, two research groups have attempted to classify the *RELA* mutation types and their associated phenotypic features^{287,289}. Their findings indicate that truncating mutations might function in a dominant-negative fashion, by forming non-functional dimers with wild-type p65, thereby further impairing NF- κ B signalling. These mutations seem to skew the balance between NF- κ B and type I interferon pathways, leading to aberrant IFN signalling. These dominant-negative variants are associated with an increased expression of type I IFN signatures and a higher likelihood of developing systemic lupus erythematosus^{287,289}.

Unlike complete p65 deficiency, which severely compromises lymphocyte function, p65 haploinsufficiency seems to have a minimal impact on adaptive immune-cell function in mice. In line with this observation, the T cell and B cell function of most patients is normal, except for in two reported cases^{285,286}. Collectively, human and murine studies suggest that p65 haploinsufficiency sensitizes epithelial and stromal cells to TNF-mediated cytotoxicity, which might drive tissue-specific inflammation. In mouse models, *Rela* haploinsufficient mice develop cutaneous ulcerations following TNF exposure. This phenotype is not rescued by bone marrow transplantation from wild-type donors, indicating that the underlying pathology is driven by defects intrinsic to epithelial or stromal cells rather than haematopoietic cells²⁸⁴. Consistent with these observations, anti-TNF therapy has proven effective in managing mucocutaneous ulcerations in patients with p65 haploinsufficiency^{284–289}.

Future directions

Important questions remain that will shape the future of this field. The extent to which disease manifestations are driven by

RIPK1-mediated cell death versus its non-death signalling roles remains unclear. Addressing this distinction will be vital for the development and safe deployment of targeted therapies, including small-molecule RIPK1 inhibitors, which are now entering clinical development. Because RIPK1 functions as a central regulator of multiple forms of cell death and inflammatory signalling pathways, pharmacological inhibition of RIPK1 could be relevant across a spectrum of TNF-driven monogenic disorders. The use of these drugs in monogenic conditions holds promise, but safety and efficacy will require careful validation, particularly in children and immunocompromised patients. Importantly, translational efforts must also consider that TNF blockade, although effective in certain disorders such as in OTULIN-related and TBK1-related diseases, shows limited benefit in other disease (for example, TRAPS, CRIA, HA20 and deficiencies in HOIL or HOIP), underscoring the need for pathway-specific interventions. In this context, RIPK1 inhibitors might provide therapeutic benefit where TNF inhibition fails, and their rational implementation will depend on a clearer mechanistic understanding of disease pathogenesis. Finally, emerging RIPK1 degraders have therapeutic potential^{290,291}, but the safety and efficacy of this approach remain uncertain given the immunodeficiency associated with RIPK1 deficiency and the unknown scaffolding function of RIPK1 in TNF-driven monogenic diseases.

Beyond RIPK1, the discovery of new regulators of the TNF signalling cascade would offer additional therapeutic targets. Advances in single-cell technologies, human organoids and physiologically relevant in vivo models – such as laboratory mice exposed to natural environmental microbes (known as 'dirty mice') – will be critical to understanding disease mechanisms and therapeutic responses (Box 2). Ongoing gene discovery efforts are expected to expand the classification of TNF-associated monogenic diseases, whereas investigations into genetic modifiers and compensatory pathways could help to clarify the variable penetrance and clinical severity observed across affected individuals. Importantly, a clear mechanistic distinction between autoinflammation and immunodeficiency remains essential, as clinical management and therapeutic strategies differ substantially between these disease categories. Together, these approaches will enable a more precise understanding of TNF biology in human disease and support the development of personalized therapeutic interventions.

Conclusions

Since the identification of the first TNF-related monogenic disease in 1999 (TRAPS)⁶⁸ the number of recognized disorders has expanded considerably, driven by remarkable advances in genetic screening. Monogenic diseases that affect core components of the TNF pathway now represent a complex and evolving spectrum that includes not only autoinflammatory conditions but also immunodeficiency, autoimmune and neurodegenerative disorders. Collectively, these diseases highlight the critical importance of finely tuned TNF signalling in maintaining immune homeostasis, regulating inflammation and preserving neural integrity. These conditions demonstrate how precise molecular defects can result in distinct yet overlapping clinical syndromes, reinforcing the value of accurate, mechanism-informed genetic diagnosis. Because many TNF pathway regulators interact with other signalling cascades, differences in pathway integration and tissue-specific expression are also likely to influence disease severity and tissue-specific pathology, adding an additional layer of complexity to our understanding of these conditions. Central regulators of the TNF

pathway are extensively post-translationally modified, and disruption of specific events, such as RIPK1 ubiquitylation, phosphorylation or proteolytic cleavage, is also directly implicated in pathogenesis. Increasingly, these syndromes reveal the pathological consequences of dysregulated cell death, particularly through the interconnected pathways of apoptosis, necroptosis and pyroptosis. RIPK1 frequently sits at the crossroads of these pathways and has emerged as a central disease mediator in several monogenic disorders. Together, the study of these rare disorders continues to illuminate fundamental principles of TNF biology and immune regulation. Insights from monogenic diseases will not only refine therapeutic strategies for affected patients but also inform our understanding and treatment of common inflammatory and degenerative conditions.

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Insights into the pathogenesis of childhood-onset SLE in the past decade

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Abstract

Childhood-onset systemic lupus erythematosus (SLE) is associated with more active disease trajectories, increased cardiovascular risk, earlier development of organ damage (which commonly affects the kidney, central nervous and musculoskeletal systems) and increased use of glucocorticoids and immunosuppressive treatments than adult-onset SLE. However, the understanding of immunopathogenic mechanisms in childhood-onset SLE is far less established than in adult-onset disease. Technological advances over the past decade have accelerated progress in understanding the immune, genetic, epigenetic, metabolic and proteomic profiles of childhood-onset SLE, and have also established the mechanistic roles of immune dysregulation, interferon signalling, biological sex, gender and ethnicity in shaping disease heterogeneity. These insights have led to the elucidation of the mechanisms that drive the increased severity of childhood-onset SLE and point towards new pathways for personalized therapeutic approaches aimed at improving long-term outcomes and quality of life for patients.

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Key points

- Childhood-onset systemic lupus erythematosus (SLE) is more severe than adult-onset SLE, with earlier disease onset, more organ involvement, and higher morbidity and mortality.
- Genetic and epigenetic studies in childhood-onset SLE have revealed age-enriched mechanisms, including monogenic and polygenic contributions, with heightened type I interferon signalling and impaired apoptotic body clearance having central roles.
- Immune profiling technologies have enabled unique immune cell signatures and organ-specific inflammation patterns to be uncovered in childhood-onset SLE, advancing understanding of disease mechanisms and heterogeneity to guide future precision medicine strategies.
- Novel biomarkers, notably urinary, lipid and neuroinflammatory markers, have shown promise for early detection and monitoring of lupus nephritis, cardiovascular disease and central nervous system involvement in childhood-onset SLE.
- Treatments for childhood-onset SLE increasingly include biologic drugs and targeted therapies, although access remains limited; ongoing trials and approval of paediatric-specific treatments and guidelines are essential for therapeutic equity.
- Future research must prioritize inclusive, multi-ethnic studies, age-specific diagnostic consideration and expanded paediatric clinical trial infrastructure to enable personalized, equitable care for children with childhood-onset SLE.

Introduction

Childhood-onset systemic lupus erythematosus (defined as onset at <18 years of age) accounts for 15–20% of all patients with SLE^{1,2}. Global prevalence estimates range from 1.1 to 25.7 per 100,000 children, with a predominance in women and girls, and ethnic disparities have also been reported^{1–3}. Children and adolescents with childhood-onset SLE have higher disease activity at presentation, increased prevalence of severe organ involvement and consequently greater treatment and damage burden compared with people with adult-onset SLE (Table 1). Specifically, renal involvement (lupus nephritis) and neurological and/or neuropsychiatric symptoms are more frequent^{4–8}, and cardiovascular risk is also increased in childhood-onset SLE compared with adult-onset SLE^{9,10}. As a result, childhood-onset SLE has higher morbidity and mortality rates, with up to six times the standardized mortality ratio^{5,11}, and higher hospitalization rates^{4,5}.

Despite differences in clinical severity, both childhood-onset SLE and adult-onset SLE are classified similarly. Both the American College of Rheumatology (ACR) and the Systemic Lupus International Collaborating Clinics (SLICC) criteria are used to support SLE classification, both of which are validated for use in adult and paediatric populations. The 2019 ACR–European League Against Rheumatism (EULAR) classification criteria have also demonstrated satisfactory performance in childhood-onset SLE¹².

Consistent with the clinical phenotype, cumulative exposure to treatment is also higher in childhood-onset SLE than in adult-onset

SLE^{6,13}; however, individuals with childhood-onset SLE demonstrate higher rates of remission on treatment and achieve low disease activity states more frequently¹⁴. This finding probably reflects the shorter disease duration and lower cumulative organ damage at earlier stages, rather than fundamental differences in response to treatment. Drug-free remission remains less common in childhood-onset SLE than in adult-onset SLE^{15–18}.

Despite the severity of disease and the impact that it has on affected individuals, the immunopathology of childhood-onset SLE remains under-studied compared with adult-onset SLE and other, more prevalent, paediatric autoimmune conditions. Challenges in studying childhood-onset SLE include limited availability of samples from paediatric patients, small cohort sizes with inadequate ethnic representation, disease heterogeneity in presentation and treatment approaches, loss of follow-up during transfer to adult care (often owing to system-level gaps in continuity of care and/or patient disengagement) and reduced funding opportunities, all of which contribute to a limited understanding of the underlying mechanisms of the disease.

Understanding the pathogenesis of childhood-onset SLE has previously been approached from two directions: by identifying the genetic abnormalities that promote early disease presentation (typically pre-puberty), which defines the monogenic SLE phenotype, and by molecular investigation of polygenic childhood-onset SLE, which is linked to onset later in childhood or adolescence. Advances in molecular, cellular and tissue characterization in the past decade, including high-throughput sequencing, single-cell analyses, spatial omics, mass cytometry and systems immunology, have enabled substantial insights into the molecular origins of rare diseases, even from small datasets¹⁹. However, high-quality research in childhood-onset SLE has been limited by strict regulatory constraints, the disease rarity and a historical reliance on adult studies to guide management strategies and explain disease pathogenesis²⁰.

This Review focuses on advances in childhood-onset SLE pathogenesis in the past 10 years, emphasizing key discoveries that have reshaped understanding of the disease. We highlight genetic, epigenetic, molecular and immunological mechanisms that contribute to the development of childhood-onset SLE, discuss their implications for molecular diagnosis and targeted therapy and identify gaps in knowledge. We also briefly discuss clinical management and treatment outcomes. Throughout this Review we aim to adopt a life-course, spectrum-based perspective. Childhood-onset SLE and adult-onset SLE share similar core immunopathogenic pathways but differ in enrichment and timing of these processes; for example, monogenic or high-polygenic burden are more common in children and adolescents. This framing balances two priorities: first, identifying age-specific mechanisms that merit paediatric-tailored care, and second, enabling reasoned extrapolation from adult evidence for overlapping mechanisms, an approach currently essential for paediatric regulatory approval.

Disease susceptibility

Genetic influence is a major factor in SLE susceptibility and pathogenesis, and contributes to the differences observed in clinical phenotype between childhood-onset SLE and adult-onset SLE. Likewise, biological sex (that is, sex assigned at birth; throughout the article, ‘sex’ is used as a shorthand for biological sex) and ethnicity also influence the prevalence, clinical presentation and outcomes of both adult-onset SLE and childhood-onset SLE.

Table 1 | Clinical and demographic differences between childhood-onset SLE and adult-onset SLE

Clinical feature or outcome	Childhood-onset SLE	Adult-onset SLE	Refs.
Proportion of people with SLE (%)	15–20	80–85	1,2
Global prevalence	1.1–25.7 per 100,000 children	30–150 per 100,000 adults	1–3
Sex ratio (female to male)	4.5:1	9:1	1–3
Disease activity at presentation	Higher	Lower	4,5
Renal involvement (lupus nephritis) (%)	44–60	33–37	4–6
Neuropsychiatric manifestations (%)	25–29	19.6–20	4,5,7
Cardiovascular disease risk	100–300-fold increase versus healthy population	50-fold increase in women aged 35–44 years	9,10
Standardized mortality ratio	18.3	3.1	5,11
Hospitalization rates	Higher	Lower	4,5
High-dose glucocorticoid exposure (%)	97	80	6,13
Immunosuppressive therapy exposure (%)	66–68	37–43	6,13
Remission on treatment (%)	42–61	~29	14
Low disease activity state (%)	32–82	37–44	14
Sustained remission off therapy (%)	10.8–31	14.5	15–18

SLE, systemic lupus erythematosus. Adapted from ref. 158, CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

Polygenic defects

Advances in genetics over the past decade have led to major progress in analysing susceptibility genes for childhood-onset SLE. Most discoveries stem from genome-wide association studies (GWAS), which have enabled the identification of many single nucleotide polymorphisms (SNPs) associated with adult-onset SLE^{21,22}, including SNPs known to be functional non-coding adult-onset SLE risk variants²³. Usually, a combination of risk alleles (defined as polygenic risk) and/or environmental factors explain the disease risk. Variants linked to both childhood-onset SLE and adult-onset SLE can be broadly grouped into those that affect type I interferon (IFN) signalling, antigen processing and/or presentation, and lymphocyte activity²¹. Most individual genes cannot explain SLE risk, prompting the development of polygenic risk scores to estimate heritability. Global limitations, including missed rare variants in GWAS, epigenetic and environmental factors that cannot be quantified easily, and under-representation of certain ethnicities, mean that polygenic risk scores only explain 30–73% of SLE heritability²⁴.

The more severe phenotype observed in childhood-onset SLE has been suggested to result from a higher genetic burden, with more risk alleles identified in individuals diagnosed at a younger age, particularly in childhood and early adolescence^{24–26}. An HLA genetic risk score applied to 665 individuals with adult-onset SLE (30% of whom had lupus nephritis) and 572 individuals with childhood-onset SLE (41% of whom had lupus nephritis) found a stronger association between genetic risk score and lupus nephritis risk in individuals of European ancestry with

childhood-onset SLE than in those with adult-onset SLE²⁷. An analysis of 112 individuals with childhood-onset SLE, 280 with adult-onset SLE and 14,869 relatives, revealed higher SLE rates among first-degree or second-degree relatives of individuals with childhood-onset SLE, whereas for adult-onset SLE, higher SLE rates were more often observed among third-degree relatives, consistent with a stronger and more proximal genetic contribution in childhood-onset disease²⁸. In a UK study, genotyping 319 children and adolescents with childhood-onset SLE using panel sequencing and quantitative trait loci analysis identified gene–gene interactions that affect endoplasmic and cytosolic type I IFN, and were associated with age at onset, disease activity and mucocutaneous involvement²⁹. In this cohort, common *TLR7* variants were linked to ancestry-specific childhood-onset SLE risk and organ involvement³⁰. Genetic variability (both general and gene-specific) correlated with ancestry, age at onset, organ involvement and disease severity in the UK JSLE cohort³¹. In the first childhood-onset specific SLE multi-ancestral GWAS study, a novel locus intronic to *CCDC113* was identified and was associated with earlier age at diagnosis³². Thus, larger cohorts, and modern tools can identify novel SNPs and map them onto clinical phenotypes, a major step forward in molecular diagnosis.

Monogenic defects

In clinical terms, monogenic SLE refers to SLE-like disease caused by a single-gene mutation that affects immune regulation. Although monogenic SLE is rare, research on this form of disease has provided key mechanistic insights into how self-tolerance is lost in all forms of SLE. Specifically, studies of monogenic disorders of immune dysregulation in children have revealed rare and extremely rare variants that are associated with childhood-onset SLE-like clinical phenotypes. The generalized application of high-throughput technologies has substantially advanced understanding of early-onset SLE. Candidate gene approaches and next-generation sequencing indicate that approximately 7% of childhood-onset SLE cases can be attributed to monogenic causes, encompassing over 30 distinct genotypes³³. This concept of monogenic SLE has reshaped understanding of SLE pathogenesis³⁴. Among autoimmune diseases, SLE stands out as most strongly associated with inherited defects, particularly those affecting nucleic acid sensing, type I IFN regulation and/or B cell defects. Although these rare variants often affect the same immunological pathways as the common SLE-associated polymorphisms, they typically have larger effect sizes, can confer disease risk independently and are frequently associated with distinct clinical features^{33,35} (Table 2). The most studied monogenic causes of SLE are the complement deficiencies³⁶. These highlight the dual role of complement in clearing both apoptotic debris and immune complexes. The complement component C1q also has a direct regulatory effect on IFN α production.

In 2022, a novel Toll-like receptor 7 (TLR7) gain-of-function mutation was identified in a girl with childhood-onset SLE. Knocking this specific mutation into mice recapitulated the systemic autoimmunity³⁷. This mouse model indicated that cell-intrinsic expansion of CD11c⁺Tbet⁺ age-associated B cells might drive disease. Thus far, ten individuals with TLR7 gain-of-function mutations with systemic autoimmunity and frequent neuroinflammatory symptoms have been reported. Rare variants in *UNC93BI*, a gene encoding a TLR trafficking protein, have also been identified in patients with childhood-onset SLE, which reinforces the role of endosomal TLR7 and TLR8 signalling in disease pathogenesis^{38,39}. Defects in *PACSL1*, a gene encoding a protein that is also involved in TLR7 function, have also been reported, which further highlights the importance of TLR7 signalling⁴⁰.

Table 2 | Monogenic defects associated with childhood-onset SLE-like clinical and pathogenic phenotypes

Gene(s)	Protein(s)	Inheritance	Primary features	Secondary features
Complement deficiency and other defects in extracellular nucleic acid sensing				
<i>C1QA, C1QB, C1QC, C1R, C1S</i>	C1QA, C1QB, C1QC, C1R, C1S	Autosomal recessive	CNS involvement and lupus nephritis	Recurrent infections ANA positivity dsDNA antibodies Low complement (as measured by CH50 levels) even in remission
<i>C4A, C4B</i>	C4A, C4B	C4A and C4B are duplicated, rare complete deficiency, autosomal recessive	More common in childhood-onset SLE than in adult-onset SLE	Low complement activity (as measured by CH50 and C4 levels) even in remission
<i>C2</i>	C2	Autosomal recessive	Adult-onset Skin rash	Low complement (as measured by CH50 levels) even in remission
<i>MBL2</i>	MBL	Autosomal recessive	Incomplete penetrance Adult-onset	
<i>DNASE1L3</i>	DNASE1L3	Autosomal recessive	SLE Lupus nephritis	Lupus nephritis ANCA antibody positivity
<i>TLR7</i>	TLR7	X-linked dominant	SLE Antiphospholipid syndrome	Neuroinflammation
<i>PACSIN1</i>	PACSIN1	Autosomal dominant	SLE	Unknown
<i>UNC93B1</i>	UNC93B1	Autosomal dominant	SLE	Neuroinflammation
Type I interferonopathies and other defects in intracytosolic nucleic acid sensing				
<i>TREX1</i>	TREX1	Autosomal recessive and/or autosomal dominant	Chilblain lupus SLE	Early-onset Familial autoimmunity High IFN signature Chilblain lupus Spasticity
<i>SAMHD1</i>	SAMHD1	Autosomal recessive	Chilblain lupus SLE	Spasticity Moyamoya Vasculitis High IFN signature
<i>RNASEH2A, RNASEH2B, RNASEH2C</i>	RNASEH2A, RNASEH2B, RNASEH2C	Autosomal recessive and/or autosomal dominant	SLE	Chilblain lupus Brain calcification Neurological involvement High IFN signature
<i>IFIH1</i>	MDA5	Autosomal dominant	SLE	Chilblain lupus Brain calcification Neurological involvement High IFN signature
<i>STING1</i>	STING	Autosomal dominant	SLE ILD	High IFN signature
<i>COPA</i>	COPA	Autosomal dominant	Alveolar haemorrhage Lupus glomerulonephritis	Lung disease High IFN signature
<i>ACP5</i>	TRAP	Autosomal recessive	SLE Renal and haematological involvement Bone dysplasia	Growth retardation High IFN signature
<i>DNASE2</i>	DNASE2	Autosomal recessive	SLE Extra-membranous glomerulonephritis	ANA positivity
B cell apoptosis deficiency				
<i>PRKCD</i>	PKCδ	Autosomal recessive	SLE Immunodeficiency	Lymphoproliferation Recurrent infection Defect in ROS production

Table 2 (continued) | Monogenic defects associated with childhood-onset SLE-like clinical and pathogenic phenotypes

Gene(s)	Protein(s)	Inheritance	Primary features	Secondary features
Other mutations associated with SLE development				
<i>STAT1</i>	STAT1	Autosomal dominant	SLE Bacterial and mycobacterial infections Chronic mucocutaneous candidiasis	Recurrent infection Candidiasis
<i>SOCS1</i>	SOCS1	Autosomal dominant	SLE Evan syndrome Allergies	Familial autoimmunity
<i>PTPN2</i>	PTPN2	Autosomal dominant	Hepatitis SLE Evan syndrome	Familial autoimmunity
<i>IKZF1</i>	IKAROS	Autosomal dominant	SLE Lymphoproliferation Recurrent infections	CVID Low IgG levels Low numbers of lymphocytes
<i>PIK3CD</i>	PIK3	Autosomal dominant	SLE Lymphoproliferation Recurrent infections	Lymphoproliferation
<i>SAT1</i>	SSAT1	X-linked	SLE	Occurs in boys
<i>DOCK11</i>	DOCK11	X-linked	Evan syndrome SLE Autoimmune hepatitis	Occurs in boys
<i>TNFAIP3</i>	A20	Autosomal dominant	Recurrent aphthous Features of Behçet disease	ANA positivity
<i>PTPN11, SOS1, RAF1, KRAS NRAS, SHOC2</i>	PTPN11, SOS1, RAF1, KRAS NRAS, SHOC2	Autosomal dominant	Facial dysmorphism Growth delay Cardiac malformations Skeletal anomalies Delayed developmental skills	Constitutional anomalies Lymphoproliferation

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; CH50, total haemolytic complement activity; CNS, central nervous system; CVID, common variable immunodeficiency; dsDNA, double-stranded DNA; IFN, interferon; ILD, interstitial lung disease; ROS, reactive oxygen species; SLE, systemic lupus erythematosus.

A subset of rare genetic disorders known as type I interferonopathies cause overactivation of the same IFN pathways that drive SLE owing to single-gene defects. These inherited conditions blur the line between classic SLE and primary immune dysregulation, as antiviral mechanisms become permanently switched on, which mimics chronic infection. These monogenic disorders involve genes implicated in nucleic acid sensing (such as *IFIH1* and *DDX58* (also known as *RIGI*)), signalling (such as *STING1* and *COPA*) and metabolism (such as *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *TREX1*, *ACP5* and *DNASE2*). Loss-of-function mutations in *TREX1*, an exonuclease responsible for degrading damaged or antigenic DNA in the cytosol, leads to cytoplasmic accumulation of nucleic acids and constitutive activation of the cyclic GMP–AMP synthase (cGAS)–stimulator of IFN genes (STING) pathway, which results in sustained type I IFN production⁴¹.

There are over 50 reports of deoxyribonuclease I-like 3 (DNASE1L3) deficiency in childhood-onset SLE⁴², which are linked to the lupus nephritis phenotype and a distinct IFN profile from those identified in type I interferonopathies. DNASE1L3 is an extracellular enzyme involved in the degradation of immunogenic forms of cell-free DNA in apoptotic bodies. Mice that lack *Dnase1l3* develop autoimmunity, rescued by the deletion of *MyD88*, which indicates the prominent role of TLR signalling in disease pathogenesis⁴³. Notably, CIq autoantibodies have

already been reported to be predictive of lupus nephritis⁴⁴, and ~30% of individuals with SLE have autoantibodies against DNASE1L3 (ref. 45). These findings illustrate that autoantibody-mediated interference with these pathways can mimic the effects of underlying genetic defects (referred to as ‘phenocopies’), as observed in other inborn errors of immunity.

Defects in downstream cytokine signalling pathways, such as Janus kinase (JAK)–signal transducers and activators of transcription (STAT) pathways, have also been implicated in the SLE phenotype²⁴. Haploinsufficiency of *PTPN2* or *SOCS1*, both negative regulators of cytokine signalling, results in cytokine hypersensitivity and immune dysregulation^{46,47}. These defects can benefit from JAK inhibition, which has been shown to rescue the cellular phenotype in vitro.

In the context of immune tolerance and lymphocyte regulation, rare variants in *PIK3CD*, which encodes the phosphoinositide 3-kinase (PI3K) catalytic subunit, have been linked to activated PI3K δ syndrome. This condition can present with features of childhood-onset, although the SLE phenotype is not fully penetrant^{48,49}. By contrast, biallelic mutations in *PRKCD*, which encodes PKC δ , results in a fully penetrant childhood-onset SLE phenotype characterized by lymphoproliferation, lupus nephritis and moderate-to-severe immunodeficiency⁵⁰. These findings highlight the essential role of PKC δ in maintaining B cell tolerance and preventing autoimmunity.

To explore shared mechanisms using genome-wide sequencing, 71 individuals suspected to have monogenic childhood-onset SLE were screened for variants across 36 genes that had previously been implicated in monogenic or SLE-like disease. Damaging variants were identified in 13% of patients; patients with these variants tended to be considerably younger at disease onset (mean 6.8 ± 3.7 years) than those without such variants (mean 9.2 ± 3.8 years)⁵¹. Next-generation sequencing of 83 children with childhood-onset SLE and 109 unaffected parents also highlighted enrichment of common SLE risk variants, in addition to a substantial number of individuals (11%) carrying rare variants in known monogenic SLE genes associated with earlier disease onset⁵².

Thus, at least some instances of childhood-onset SLE arises from monogenic causes with variable penetrance, and oligogenic and environmental factors probably add complexity. These findings indicate that childhood-onset SLE is a useful model for studying autoimmune genetics and immune tolerance⁵³.

Epigenetic defects

Epigenetics has a key role in gene regulation without altering DNA sequences, mainly through DNA methylation at CpG sites, histone modifications that affect chromatin structure and non-coding RNAs, such as long non-coding RNAs or micro-RNAs²⁴. These heritable (yet reversible) mechanisms can be tissue-specific, and can be influenced by the environment, early life trauma, hormones, infections, diet and treatment.

Epigenetic changes can also be age-specific; for example, in adult-onset SLE, *CD70* promoter hypomethylation in CD4⁺ T cells enhances B cell activation, a change not observed in childhood-onset SLE, which supports age-related divergence⁵⁴. Conversely, hypomethylation of the *LCK* gene in CD4⁺ T cells might promote excessive T cell activation in childhood-onset SLE⁵⁵. *FOXP3* promoter hypermethylation can impair regulatory T (T_{reg}) cell function and, together, tip the balance towards loss of immune tolerance⁵⁶. In childhood-onset SLE, *JAK2* hypomethylation or *SOCS3* hypermethylation enhances JAK–STAT signalling and type I IFN production⁵⁷, whereas type I IFN-linked genes such as *MXI*, *PARP9* and *DTX3L* undergo hypomethylation⁵⁵. Hypomethylation and upregulation of *OAS1* and *OAS2* in CD8⁺ T cells and neutrophils, and hypomethylation of long interspersed nuclear element 1 (LINE1) elements also seem more prominent in childhood-onset SLE. *IFI44L* methylation is under investigation as a potential childhood-onset SLE biomarker⁵⁸. Finally, epigenetic attenuation of type I IFN signalling through methylation is associated with milder disease manifestations in older patients with SLE, which suggests a potential mechanism that contributes to more severe disease in childhood-onset SLE⁵⁹. Beyond methylation, micro-RNA dysregulation in childhood-onset SLE has been linked to an imbalance between T_{reg} cells and effector T cells, altered innate immune sensing and heightened damage-associated molecular patterns responses, which correlates with disease activity, organ involvement and long-term damage²⁴.

Overall, an exciting new era of genetic and epigenetic studies, enabled by cutting-edge technologies, has arrived, shining a light on key pathogenic pathways, such as TLR and type I IFN hyper-signalling, complement deficiency, apoptotic body clearance and nucleic acid sensing, which underlie the breakdown in immune tolerance observed in childhood-onset SLE. Importantly, the field is now focused on translating these discoveries into therapeutic targets⁴⁹.

Sex, gender and ethnicity as risk and severity factors

Ethnic disparities are well-established in SLE; Black people and people of Asian ancestry have a higher prevalence, earlier disease onset

and more severe manifestations (including lupus nephritis) compared with white people⁶⁰. These disparities are more pronounced in childhood-onset SLE^{61–63}, in which genetic susceptibility, environmental exposures and variable access to health care are amplified early in life⁶⁴. Increased IFN signatures have been reported in Black people (83.3%) and people of Asian ancestry (86.5%) compared with white individuals (63.5%), which might contribute to increased disease activity⁶⁵, although larger and more diverse studies are needed to clarify the genetic and environmental contributions.

Biological sex and gender (gender is not necessarily binary and exists as a spectrum) differences are a striking feature of SLE. In adult-onset SLE, the female to male sex ratio is 9:1 and in childhood-onset SLE is 4.5:1 (refs. 4,66). The less pronounced female sex bias in childhood-onset SLE is thought to reflect a reduced influence of sex hormones on disease pathogenesis in childhood, which is potentially confounded by the greater contribution of monogenic forms of SLE to early-onset compared with adult-onset disease⁶⁷. Childhood-onset SLE also includes the adolescent population, in which puberty and sex hormone dynamics substantially shape immune responses⁶⁸. For example, young post-pubertal cisgender (that is, individuals whose assigned sex at birth aligns with their gender identity) men have an increased number of anti-inflammatory T_{reg} cells with enhanced function than cisgender women, which is linked to testosterone-driven PI3K–AKT signalling. This finding is supported by results from cohorts of young transgender (that is, individuals whose gender identity differs from their assigned sex at birth) people who are receiving gender-affirming sex hormone treatment (for example, exogenous testosterone); this sex-dimorphic immune mechanism seems to be dysregulated in childhood-onset SLE⁶⁹. Conversely, oestrogen in matched gender-diverse cohorts promotes CD19⁺CD27⁺IgD⁺ class-switched memory B cell development, which is central to the pathogenesis of childhood-onset SLE⁷⁰. These B cells are reduced in young transgender men who are receiving testosterone and increased in cisgender postmenopausal women in who are receiving hormone replacement therapy, which highlights the immune-activating role of oestrogen. In girls and women, plasmacytoid dendritic cells (pDCs) produce more type I IFN in response to TLR7 signalling, a process that is influenced by both low testosterone and higher X chromosome dosage⁷¹. IFN production increases at puberty in young women, which mirrors the rise in female-biased SLE onset during reproductive years. Young transgender men who are receiving testosterone have reduced IFN responses, further supporting the role of sex hormones in immune modulation and sex-bias of childhood-onset SLE risk⁷². Sex-specific childhood-onset SLE pathogenic mechanisms have been proposed⁶⁹, but sex bias in the presentation and severity of childhood-onset SLE remains controversial, as reports vary⁷³.

Sex chromosome dosage also has a crucial role in immune modulation as several key genes, including *TLR7*, *IRAK1*, *CXCR3*, *SAT1*, *CD40L* and *FOXP3*, are located on the X chromosome⁷⁴. Alterations in X chromosome dosage, as seen in Klinefelter (XXY) and Triple X (XXX) syndromes, are associated with increased risk of childhood-onset SLE, whereas Turner syndrome (XO) is associated with reduced risk^{75,76}. X chromosome inactivation variability via Xist (X-inactive specific transcript) expression might also contribute to immune dysregulation, and elevated expression of Xist RNA in leukocytes from women with adult-onset SLE has been shown to function as a TLR7 ligand, enhancing IFN production and contributing to the female bias⁷⁷. Although similar studies in childhood-onset SLE are lacking, early-onset monogenic disease presentations that are associated with TLR7 gain-of-function

mutations (*TLR7* is an X-linked gene, the overactivity of which is probably more common in women and girls) illustrate the genetic basis of sexual dimorphism observed in SLE³⁷.

Considerable limitations of current SLE cohorts include a lack of ethnic diversity, and the under-representation of children and male patients, which limits the relevance of novel pathogenic discoveries. Socioeconomic, cultural and genetic factors interact to shape disease course, care engagement and response to treatment. These overlapping influences highlight the urgent need for inclusive and representative research in both adult-onset SLE and childhood-onset SLE.

Immune profiles in childhood-onset SLE

Advances in high-dimensional immune profiling have identified both shared and phenotype-specific immune dysregulation in SLE (Fig. 1). The evolution of this technology across both blood and tissue has provided insights into how immune cells behave during disease flares and around organ involvement.

Blood immunology

The circulating immune landscape of childhood-onset SLE was first characterized using conventional flow cytometry^{19,78}. Combining classical analyses with machine learning approaches, eight top-ranked immune features of childhood-onset SLE have been identified: elevated

total CD8⁺ T cells, naive CD8⁺ T cells and monocytes, and reduced CD4⁺ T cells, CD8⁺ effector memory T cells, invariant natural killer T cells and specific B cell subsets (Bm1 cells and unswitched memory B cells)⁷⁸. An increased CD8⁺ effector memory T cell signature has been characterized in a subgroup of patients with persistently active disease over a mean follow-up of 4.9 years.

In the first single-cell RNA sequencing (scRNA-seq) study in cohorts of both paediatric and adult patients with SLE, samples from 33 individuals with childhood-onset SLE and 11 matched healthy individuals were analysed⁷⁹, and 20 transcriptionally distinct immune subsets were identified. These subsets included expansion of CD14⁺ monocytes, granzyme K (GZMK)⁺CD8⁺ T cells and CD4⁺ T cells in patients childhood-onset SLE compared with healthy individuals, with concurrent reductions in pDCs, CD16⁺ natural killer (NK) cells and various T cell subsets. Importantly, this study was the first direct transcriptomic comparison between childhood-onset SLE and adult-onset SLE, and found that monocytes, plasma cells, T cell subsets and NK cells were expanded in both groups, with hierarchical clustering revealing overlapping immune phenotypes, especially in individuals with high disease activity. IFN-driven immune signatures were also conserved in childhood-onset SLE and adult-onset SLE. Multiplexed scRNA-seq (specifically, multiplexed droplet single-cell sequencing) profiling revealed ancestry-linked immune variation in adult-onset SLE,

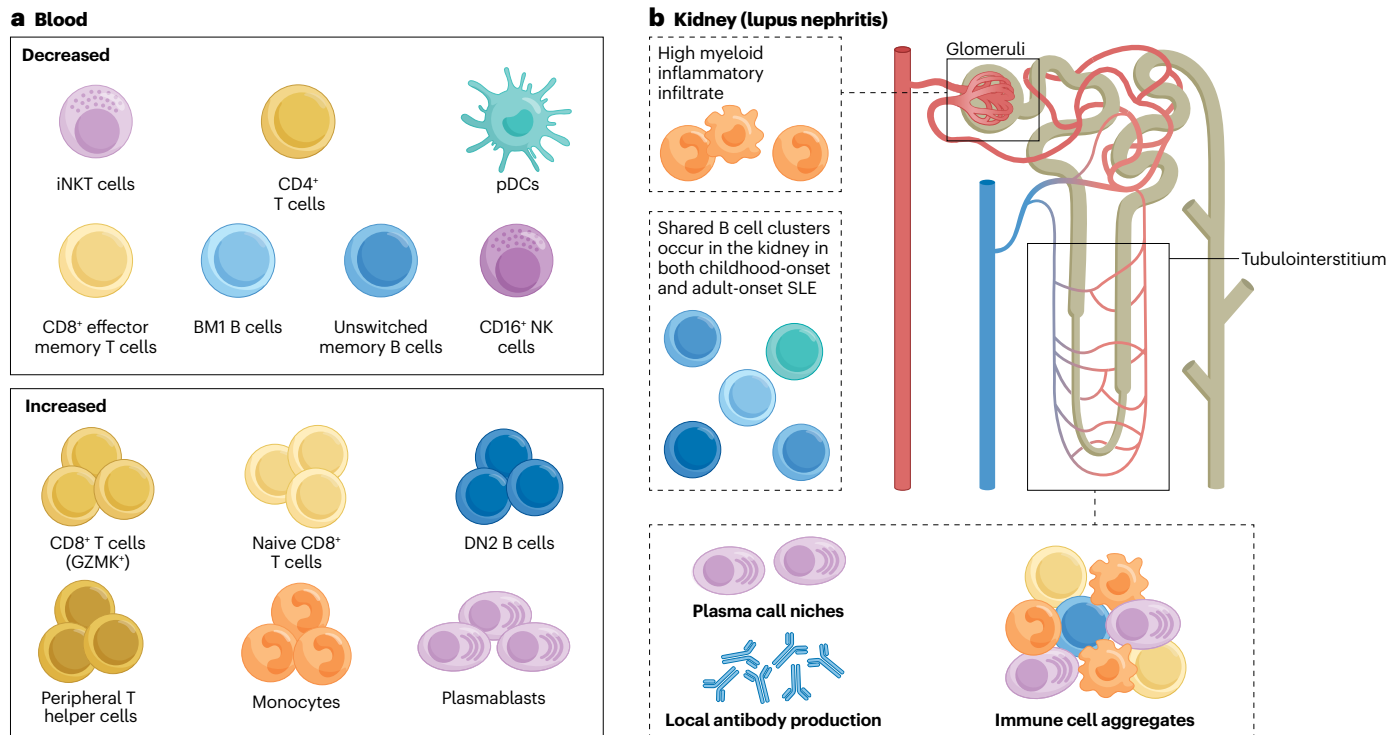


Fig. 1 | Blood and tissue immune phenotypes in childhood-onset SLE.

Advances in technology over the past decade have greatly expanded understanding of immunopathogenic mechanisms in rare diseases such as childhood-onset systemic lupus erythematosus (SLE). **a**, High-dimensional flow cytometry has helped to delineate the circulating immune landscape, revealing clinically relevant shifts in both innate and adaptive immune cell subsets. Among these, effector memory CD8⁺ T cells have emerged as a notable population of cells that, while reduced overall in childhood-onset SLE, are associated with increased disease severity and lower cytotoxic potential through mitochondrial

dysfunction, although a small subgroup of patients who have increased levels of these cells (relative to other patients) present with worse disease outcomes. **b**, Immune phenotyping has extended to tissue-level analyses, whereby multiplexed imaging and sequencing technologies have enabled insights into SLE-specific organ manifestations, such as lupus nephritis. These approaches reveal distinct inflammatory profiles across renal compartments that might inform organ-targeted therapies. GZMK, granzyme K; iNKT cell, invariant natural killer T cell; NK cell, natural killer cell; pDCs, plasmacytoid dendritic cells.

associated with expansion of GZMH⁺ cytotoxic CD8⁺ T cells⁸⁰, which are distinct from the GZMK⁺ population described in childhood-onset SLE⁷⁹. In another study in patients with childhood-onset SLE, CD8⁺ T cell cytotoxic function was reduced, independent of treatment or disease activity, and was accompanied by a decreased abundance of effector memory CD8⁺ T cells, which suggests both numerical and functional deficits in the cytotoxic T cell compartment⁸¹.

Using alternative immune phenotyping technologies, such as high-dimensional mass cytometry (for example, cytometry by time of flight (CyTOF)), combined with transcriptomics in treatment-naïve patients with childhood-onset SLE at the time of diagnosis revealed a prominent extrafollicular B cell signature, including expanded DN2 B cells, Bnd2 cells and plasmablasts, and also increased peripheral T helper cells and heightened type I IFN signalling⁸². These features were strongly associated with disease activity and the presence of lupus nephritis, which implicates this B cell–T cell axis in renal involvement in childhood-onset SLE. This work adds important depth to the understanding of childhood-onset SLE immunopathology by linking peripheral immune signatures to organ-specific involvement.

Tissue immunology

Parallel advances in tissue-based immune profiling can facilitate the interrogation of in situ cellular interactions, particularly relevant for lupus nephritis in the context of childhood-onset SLE. Spatial transcriptomic analysis has been applied to kidney biopsies from children with lupus nephritis, with single-cell gene activity evaluated across distinct cellular compartments⁸³. The analysis identified 30 immune and resident kidney cell types from eight patients with childhood-onset SLE and four healthy individuals. Myeloid cells were enriched in inflamed glomeruli, and T cells and B cells formed clusters in tubulointerstitial regions, potentially supporting local plasma cell generation. Interestingly, even morphologically normal glomeruli in these patients had transcriptional evidence of inflammation. Integration of childhood-onset SLE analyses with an existing adult-onset SLE lupus nephritis scRNA-seq dataset⁸⁴ revealed strong concordance in B cell subset composition, highlighting an activated B cell cluster as having central importance to immune cell interaction networks. Spatial mapping showed B cells, plasma cells, T cells and myeloid cells forming structured immune aggregates in the tubulointerstitium, implicating these cells in chronic inflammation and tissue damage in childhood-onset SLE.

Stratification of patients with childhood-onset SLE

An arguably ‘ahead-of-its-time’ longitudinal ‘immunomonitoring’ study was published in 2016 (ref. 85). The study applied integrated whole-blood bulk transcriptomic analysis and clinical profiling to a large cohort of patients with childhood-onset SLE, revealing stable type I IFN and plasmablast-driven molecular modules that tracked disease activity and predicted flares. Linking longitudinal immune signatures with clinical trajectories demonstrated that childhood-onset SLE could be clustered into reproducible molecular endotypes, some of which were dominated by type I IFN signalling and others by plasmablast or neutrophil activity. These modular patterns proved consistent across time and therapy exposure, providing one of the first systems-level frameworks for stratifying patients according to underlying immune networks, rather than clinical manifestations alone. This work laid essential groundwork for later single-cell and multiomic efforts.

Since the 2016 study, multiomics studies have further showcased the power of integrating transcriptomic, proteomic and immune

phenotyping data to unravel biologically and clinically meaningful disease heterogeneity in childhood-onset SLE. A bulk blood transcriptome analysis of 952 patients with childhood-onset SLE and 94 healthy individuals used unsupervised clustering on microarray data to define three molecular subgroups⁸⁶. One subgroup was marked by high disease activity and lupus nephritis, another was associated with low disease activity and vasculitis, and the third was enriched for central nervous system (CNS) manifestations and was more common in boys. Distinct underlying pathogenic pathways are thus evident, highlighting the potential for personalized therapy and novel therapeutic targets⁸⁶. In parallel, a targeted multiomics study that involved whole-blood transcriptomics, serum cytokines and 40-colour flow cytometry enabled the stratification of a cohort of patients with childhood-onset SLE (17-patient discovery cohort and 12-patient validation cohort) into three immune phenotypes linked to disease activity, but notably not to organ involvement, revealing differential key cell subsets that shifted over time⁸⁷. Together, these multiomic approaches demonstrate robust capacity to define biologically coherent, clinically relevant disease subsets, moving beyond traditional phenotyping to tools that might inform precision medicine strategies and tailored treatment decisions.

The role of type I IFN

Type I IFN has a clear and important role in driving many of the immunopathogenic changes observed in childhood-onset SLE through enhanced pro-inflammatory signalling. Type I IFNs are antiviral cytokines that are normally produced in response to infections, but in SLE they become chronically elevated, driving inflammation even in the absence of pathogens⁸⁸. This persistent IFN signalling amplifies immune activation, which leads to continuous stimulation of T cells, B cells and innate immune sensors. Genetic variants that contribute to elevated type I IFN production in childhood-onset SLE have been investigated extensively²⁴. Many of these variants affect signalling pathways that activate downstream IFN-stimulated genes (ISGs), thus driving inflammation.

The abnormal activation of antiviral sensors is considered the defining feature of inborn errors of autoimmunity associated with enhanced type I IFN signalling, such as the prototypical Aicardi–Goutières syndrome, which shares features with SLE. In one study in 823 patients with SLE, individuals with elevated IFN signatures (including *IFI27*, *IFI44*, *IFI44L* and *RSAD2*) were younger at first SLE manifestation and diagnosis, and had more frequent haematological, immunological and cutaneous involvement, with similar rates of lupus nephritis⁶⁵. These findings support an age-biased role of type I IFN in childhood-onset SLE pathogenesis. A scRNA-seq study found that the ISG expression profile of childhood-onset SLE originates from eight transcriptionally distinct subpopulations within key immune lineages, such as CD16⁺ monocytes (which co-express IL-1 β), naïve-like CD4⁺ T cells, cytotoxic CD8⁺ T cells, NK cells, conventional dendritic cells, pDCs, B cells, and most notably, plasma cells⁷⁹. Both individuals with childhood-onset SLE and individuals with adult-onset SLE with high disease activity showed an expansion of unique immune cell subsets enriched in ISGs and/or expression of genes associated with monogenic SLE. However, ISG-high subclusters were still observed in individuals with childhood-onset SLE (both high-activity disease and low-activity disease) compared with healthy individuals, supporting the underlying role of type I IFN signalling in childhood-onset SLE pathogenesis. Elevated ISG15 has been reported in CD16⁺ monocytes and CD8⁺ T cells in childhood-onset SLE versus adult-onset SLE⁵⁸. In addition, reduced

cytotoxic capacity of CD8⁺ T cells in childhood-onset SLE has been linked to enhanced type I IFN signalling, mitochondrial dysfunction and selective loss of effector memory CD8⁺ T cells, independent of treatment or disease activity⁸¹.

Upstream of ISG activity, IFN α protein expression can be measured directly, although the low levels of this cytokine necessitate ultra-sensitive detection methods such as the single-molecule array immunoassay. In a study quantifying serum IFN α 2 in childhood-onset SLE, baseline IFN α 2 levels were modestly, but statistically significantly, higher in individuals with high or moderate disease activity than in those with low disease activity or remission, and higher levels predicted shorter time to flare⁸⁹. A European childhood-onset SLE inception cohort study ($n = 48$) tracked serum IFN α 2 protein and whole-blood ISG expression over 3 years⁹⁰. Both markers declined over time, indicating treatment-induced modulation of the IFN pathway. Although ISG signatures were more effective in distinguishing individuals with childhood-onset SLE from healthy people, IFN α 2 protein levels were superior in predicting disease flares. Similarly, in another study, ISG levels did not consistently correlate with changes in disease activity over time⁹¹. These studies focused solely on the IFN α 2 subtype, raising the possibility that persistent ISG activation might be driven by other IFN α subtypes or crosstalk with type II IFN signalling⁹². Anti-IFN α autoantibodies, reported in 14% of people with adult-onset SLE, have been associated with reduced ISG signatures and lower disease activity⁹³, but their prevalence and neutralizing capacity in childhood-onset SLE remain unclear. However, a 2025 study in individuals with childhood-onset SLE found increased levels of anti-mitochondrial autoantibodies that

correlated with elevated serum IFN α 2 and disease activity⁹⁴, consistent with the role of mitochondria-derived signals in type I IFN production in childhood-onset SLE⁹⁵. Although type I ISG signatures seem more prevalent in childhood-onset SLE (Fig. 2), larger validation studies are needed, particularly studies that incorporate diverse disease states and multilevel analysis of the IFN pathway and simpler, more reliable, cost-effective ways of quantifying IFN-based biomarkers are required to facilitate clinical applications⁹⁶.

Biomarkers of childhood-onset SLE comorbidities

Individuals with childhood-onset SLE are at an elevated risk of severe organ manifestations, including lupus nephritis and CNS involvement, and other comorbidities such as cardiovascular disease (CVD). Identifying reliable and age-appropriate biomarkers for these disease manifestations is essential to enable earlier detection, risk stratification and personalized interventions beyond conventional serological markers.

Lupus nephritis

Lupus nephritis is a key organ manifestation in childhood-onset SLE. Although conventional serological markers such as anti-double-stranded DNA (anti-dsDNA) antibodies and low C3 and C4 levels are widely used as biomarkers of disease activity, their reliability remains inconclusive⁹⁷. Additional urinary biomarkers that reflect active renal pathology are still required.

Validated urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemoattractant protein 1 (MCP1), α_1 -acid glycoprotein, ceruloplasmin, lipocalin-type

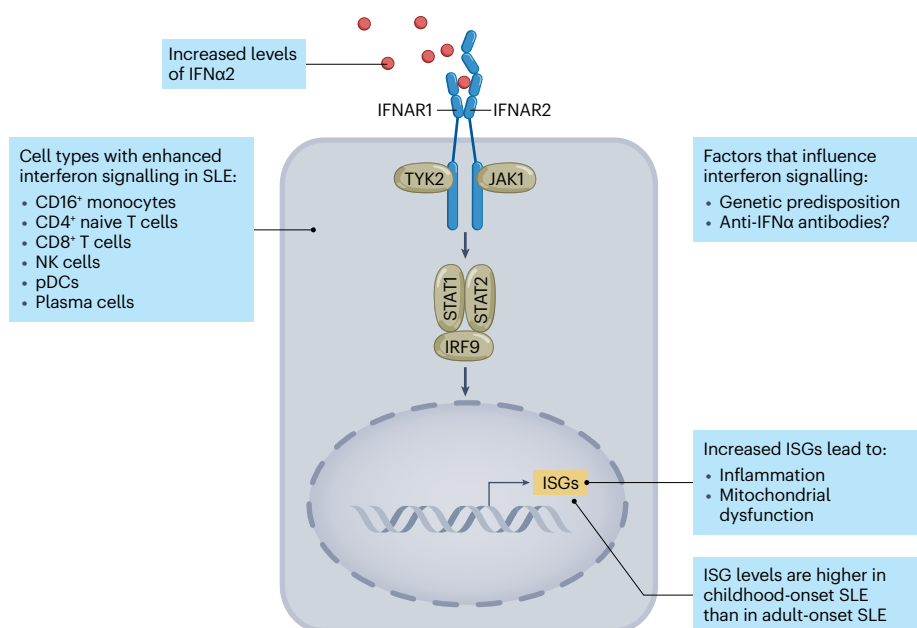


Fig. 2 | Mechanisms of exacerbated type I IFN signalling in childhood-onset SLE pathogenesis.

A central feature of systemic lupus erythematosus (SLE) pathology is heightened type I interferon (IFN) signalling, which both drives and reflects the autoimmune state. The more severe phenotypes observed in childhood-onset SLE have been linked to increased type I IFN activity, supported by findings of stronger IFN-stimulated gene (ISG) signatures, greater genetic predisposition and elevated IFN α levels, some of which predict disease flares. Ongoing validation in diverse cohorts is essential, particularly in clarifying links between type I IFN signalling and disease activity. Key immune subsets

and mitochondrial dysfunction have been implicated in this axis. A disconnect exists between IFN signalling measures in the laboratory setting and disease activity measures in the clinic, which suggests that IFN influences underlying pathology, but is not a direct readout of disease activity. IFNAR1, IFN α receptor 1; IFNAR2, IFN α receptor 2; IRF9, IFN regulatory factor 9; JAK1, Janus kinase 1; NK cell, natural killer cell; pDC, plasmacytoid dendritic cell; STAT1, signal transducer and activator of transcription 1; STAT2, signal transducer and activator of transcription 2; TYK2, tyrosine kinase 2.

prostaglandin D synthetase and transferrin have demonstrated strong predictive value for lupus nephritis activity and progression in childhood-onset SLE⁹⁸. These biomarkers often arise months before clinical flares and can predict proliferative lupus nephritis and refractory disease. Furthermore, urinary proteomic profiling has identified additional biomarkers, with activated leukocyte cell adhesion molecule, vascular cell adhesion molecule and platelet factor 4 emerging as the most discriminatory urinary biomarkers for childhood-onset SLE renal disease activity, outperforming conventional biomarkers including proteinuria⁹⁹. By contrast, a proteomic study in adult-onset SLE identified novel urinary biomarkers such as intercellular adhesion molecule 2, fatty acid-binding protein 4, Fas ligand, insulin-like growth factor-binding protein 2, E-selectin and B cell activating factor (BAFF; also known as TNFSF13B), with high diagnostic accuracy for active lupus nephritis¹⁰⁰; however, these markers were evaluated in established renal disease, emphasizing their diagnostic, rather than predictive, use.

Of particular relevance to childhood-onset SLE, these findings suggest that patients with lupus nephritis might benefit from urinary biomarker-driven disease monitoring, potentially enabling early intervention and tailored immunosuppressive strategies to improve long-term outcomes. Continued validation of the above suggested urine biomarker targets in larger multi-ethnic cohorts remains necessary to confirm their global applicability in childhood-onset SLE.

Cardiovascular disease

Individuals with SLE are at increased risk of cardiometabolic comorbidities, particularly atherosclerosis-driven CVD and myocardial infarction. This risk is more pronounced in childhood-onset SLE than in adult-onset SLE¹⁰¹. Growing evidence implicates chronic inflammation, dyslipidaemia and broader lipid metabolic disturbances as key contributors^{101,102}. In childhood-onset SLE, lipid abnormalities emerge early, including persistently reduced small LDL particles and transient flare-associated elevations in the levels of VLDL¹⁰³. In the largest metabolomics cohort study of SLE to date (164 patients with SLE (14–76 years old) and 123 healthy individuals (13–72 years old)), decreased levels of apolipoprotein A1, which is a surrogate marker of HDL particles, was observed in patients with SLE across all ages¹⁰⁴, highlighting a need for early CVD risk management interventions¹⁰⁵.

Despite these lipid disturbances, no beneficial effects of statins (cholesterol-lowering drugs) have been reported for adult-onset SLE or childhood-onset SLE, as neither the Lupus Atherosclerosis Prevention Study (LAPS) nor the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) trial met its primary end point of reduced atherosclerosis progression with statin treatment^{106,107}. However, re-analysis of the APPLE trial revealed two distinct trajectories of carotid intima-media thickness progression in the placebo arm over 3 years¹⁰⁸. A six-metabolite lipid signature, including various LDL and cholesterol fractions, predicted high carotid intima-media thickness progression in the placebo but not in the statin arm, suggesting that disease-related mechanisms, in addition to dyslipidaemia, probably contribute to atherosclerosis. This hypothesis is also supported by the expansion of CD8⁺ T cells in adolescents with childhood-onset SLE and pro-atherogenic lipid profiles, characterized by elevated type I IFN signalling and T cell activation pathways¹⁰⁹.

Patients with childhood-onset SLE also have increased CVD risk as demonstrated by the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) score (a tool validated for use in individuals ≥ 14 years of age). In a comparative analysis of two independent childhood-onset SLE cohorts of different ages, PDAY scores were higher in young adults with

a longer history of childhood-onset SLE, suggesting that disease duration and age are key contributors to cumulative CVD risk¹¹⁰. This study also highlights current limitations and the need for age-appropriate or pan-age SLE risk stratification tools. Thus, an atherosclerosis risk signature comprising 35 serum metabolites and five clinical traits predictive of atherosclerosis plaque has been validated in two independent cohorts of individuals with adult-onset SLE and in the APPLE trial childhood-onset SLE cohort, supporting its potential for clinical applications across all ages in SLE¹¹¹.

The cardiometabolic dysregulation observed in SLE across the lifespan includes a combination of lipid dysregulation, immune-mediated inflammation and treatment-related metabolic effects. These abnormalities emphasize the need for improved CVD-risk monitoring, early identification of individuals at elevated risk and prompt management interventions to address both metabolic and immune-mediated inflammation to mitigate long-term CVD complications in childhood-onset SLE.

CNS involvement

CNS involvement in childhood-onset SLE is both more prevalent and often more severe than in adult-onset SLE, contributing substantially to morbidity and mortality⁴. CNS manifestations in childhood-onset SLE are often overlapping, heterogeneous and poorly predicted by traditional biomarkers such as raised anti-dsDNA antibodies or low C3 levels¹¹². Brain immaturity could also contribute to increased vulnerability to CNS manifestations¹¹³.

Anti-phospholipid antibodies are associated with neuropsychiatric SLE in both adults and children¹¹². Anti-ribosomal P and anti-ganglioside M1 antibodies are more frequently detected in childhood-onset SLE, but their associations with psychiatric symptoms remain inconsistent, which has also been observed in some adult cohorts. However, antibodies against aquaporin 4 and myelin oligodendrocyte glycoprotein are associated with demyelinating phenotypes in childhood-onset SLE^{98,114}. Results from longitudinal studies show combinations of brain-reactive proteins, including S100A8, S100A9, S100B, NGAL, anti-NR2 and anti-ribosomal P antibodies, as potential blood-based biomarkers for neurocognitive dysfunction in childhood-onset SLE¹¹⁵. Serum neurofilament light chain, which can be used as a blood-based marker of brain injury, was elevated in people with neuropsychiatric SLE in a cohort of patients that included children¹¹⁶.

Although neuroimaging, particularly MRI, is a key diagnostic tool, conventional brain MRI lacks specificity, as abnormal findings can be present even in asymptomatic patients¹¹⁷. Promising, yet underused advanced modalities include structural MRI and MR spectroscopy, which have demonstrated abnormalities associated with cognitive impairment in childhood-onset SLE^{118,119}. Furthermore, functional MRI has shown altered activation patterns, which suggests an early compensatory mechanism prior to overt impairment¹²⁰. Screening tools such as the Pediatric Automated Neuropsychological Assessment Metrics¹²¹, alongside emerging blood and neuroimaging markers, might facilitate early detection of cognitive impairment.

Overall, among organs and systems, childhood-onset SLE might present with more severe organ manifestations than adult-onset SLE, which highlights the need for age-specific, non-invasive biomarkers and monitoring strategies to enable earlier diagnosis and targeted interventions. From a clinical perspective, only a limited number of the biomarkers discussed are currently accessible for routine testing. Conventional serological markers such as anti-dsDNA antibodies,

complement levels and basic lipid panels remain standard in clinical practice, whereas newer urinary biomarkers, detailed serum lipoprotein measures and IFN α assays are available mainly in research or specialized reference laboratories. Emerging technologies such as multiplex proteomic panels and transcriptomics for IFN signatures are under active validation but are not yet cost-effective for widespread clinical use. Similarly, although next-generation sequencing for suspected monogenic SLE is increasingly available in tertiary centres, the cost-effectiveness of this technology depends on targeted use guided by clinical features and family history, rather than as a screening tool for all patients with childhood-onset SLE.

Treatment

Advances in understanding SLE pathogenesis have transformed the potential therapeutic landscape for childhood-onset SLE. The identification of pathogenic genes associated with early disease onset, increased availability of genetic screening and expanded access to paediatric clinical trials suggest a more nuanced and targeted treatment approach in children. As a result, therapeutic options now extend beyond conventional glucocorticoids and DMARDs to include biologic drugs, targeted synthetic DMARDs and cell-based therapies.

Children with SLE are especially disadvantaged in their access to new and effective treatments compared with patients with adult-onset SLE. Many of the therapies used in childhood-onset SLE are only available off-licence, under national commissioning policies, within clinical trials or through compassionate access from pharmaceutical companies¹²². Health inequalities in access to treatment persist globally¹²³. Further investment in therapeutic development, particularly for severe and refractory childhood-onset SLE is urgently needed. Although the focus of this Review is on the pathogenesis of childhood-onset SLE rather than therapy, an overview of current treatment principles is included to provide clinical context. The discussion

below highlights how mechanistic insights have begun to shape therapeutic strategies and how precision approaches might evolve from these discoveries.

Treatment of monogenic forms of childhood-onset SLE

Monogenic SLE is increasingly identified in younger children who present with childhood-onset SLE and represents a distinct subset with unique treatment challenges and opportunities. An updated classification of genetic defects associated with childhood-onset SLE has informed emerging targeted therapies⁴⁹. For example, complement and NETosis pathway deficiencies can be managed with regular fresh frozen plasma infusions¹²⁴, whereas BAFF inhibition using belimumab is beneficial for CIq deficiency¹²⁵. Patients with more severe disease manifestations might respond to allogeneic haematopoietic stem cell transplantation¹²⁶, whereas those with DNase1L3 deficiency might benefit from a range of therapies, including rituximab, belimumab and newer agents such as NTR-441 (a DNase1L3 enzyme analogue) or MyD88 inhibitors¹²⁷. Similarly, defects in extracellular nucleic acid sensing, such as TLR7 pathway dysregulation, respond to hydroxychloroquine or targeted TLR7 and/or MyD88 inhibitors^{37,128}. Intracellular nucleic acid degradation defects, such as DNase II or TREX1 deficiency (the latter of which can cause Aicardi–Goutières syndrome) might be amenable to IFN1R1 blockade with anifrolumab or JAK inhibitors¹²⁹.

TLRopathies, which involve TLR7 or TLR9 gain-of-function mutations associated with the childhood-onset SLE phenotype, might be managed with TLR7 or TLR9 blockade¹³⁰. Abnormalities in cytoplasmic sensors (such as RIG-I, MDA5 and cGAS–STING), have been shown to respond to JAK or cGAS–STING inhibitors^{131,132}. SLE manifestations associated with Noonan syndrome or protein kinase C δ deficiency can be treated with CD20 inhibitors such as ofatumumab^{133,134} and mTOR–AKT activation in PKC δ deficiency can be targeted by mTOR inhibitors¹³⁵.

Table 3 | Current clinical trials in childhood-onset SLE

Therapeutic intervention	Mechanism of action	NCT number	Phase	Indication	Paediatric population	Dose regimens
Voclosporin (VOCAL trial)	Calcineurin inhibitor	NCT05288855	Phase III	Lupus nephritis	12–18 years of age	Multiple doses tested (15.8 mg, 23.7 mg and 31.6 mg, all twice per day) in addition to standard of care with mycophenolate mofetil and glucocorticoids
Voclosporin (VOCAL-EXT trial)	Calcineurin inhibitor	NCT05962788	Phase III extension study	Lupus nephritis	12–18 years of age	Dose determined in the VOCAL study (23.7 mg, twice daily)
Anifrolumab	Type 1 interferon receptor antagonist	NCT05835310	Phase III	Moderate-to-severe active SLE	5 to <18 years of age	Dosing regimen needs to be determined for paediatric populations
Ianalumab (SIRIUS-SLE 2 trial)	Dual mechanism of action: direct ADCC-mediated B cell depletion and BAFF-R blockade	NCT05624749	Phase III	Moderate-to-severe active SLE	12 to <18 years of age	Dosing regimen needs to be determined for paediatric populations
CAR T cells	CD19 CAR T cell therapy	NCT06839976 NCT06904729	Single-centre, single-arm, open-label phase I–II studies open in various centres	Refractory, childhood-onset SLE (including both lupus nephritis and non-renal childhood-onset SLE)	12–18 years of age	Low-dose ($\sim 5 \times 10^5$ cells per kg) or high-dose ($\sim 1 \times 10^6$ cells per kg)

ADCC, antibody-dependent cellular cytotoxicity; BAFF-R, B cell activating factor receptor; CAR, chimeric antigen receptor; SLE, systemic lupus erythematosus.

Overactivation of immune signalling pathways, such as JAK–STAT (for example, SOCS1 or PTPN2 haplodeficiency) or NF- κ B (such as TNFAIP3 haploinsufficiency), has also been identified in monogenic childhood-onset SLE. For which, JAK inhibitors, methotrexate, calcineurin inhibitors and cytokine-targeted agents have demonstrated efficacy^{46,47,136,137}.

Treatment of polygenic childhood-onset SLE

Individuals with polygenic childhood-onset SLE, especially those who present during adolescence, typically receive therapies that are used in adult-onset SLE, as paediatric-specific drug approvals remain scarce and are often delayed owing to limited trial data. These approaches continue to rely on appropriate evidence extrapolated from adult data, given the shared pathophysiological mechanisms and similar pharmacodynamic responses. Belimumab is the first biologic drug licensed for use in active childhood-onset SLE in children over 5 years of age¹³⁸. Trials of obinutuzumab (a fully humanized anti-CD20 antibody), anifrolumab (anti-IFN1R1 antibody), voclosporin (calcineurin inhibitor) and CD19 chimeric antigen receptor (CAR) T cells are ongoing, which might lead to further licensed therapies in childhood-onset SLE (Table 3).

Guideline development continues to outpace paediatric evidence. Although the British Society for Rheumatology adopted a life-course approach in 2023 (ref. 139) and the ACR updated their guidelines for lupus nephritis in 2025 (ref. 140), the EULAR and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines remain adult-focused¹⁴¹, and the SHARE recommendations for childhood-onset SLE have not been revised since 2016 (ref. 7). In routine practice, paediatric rheumatologists often extrapolate treatment recommendations from adult protocols.

Rituximab has become an important therapeutic option in childhood-onset SLE, particularly for refractory or organ-threatening disease such as lupus nephritis, neuropsychiatric SLE and autoimmune cytopenias. Although randomized trials are scarce, retrospective studies provide strong supportive evidence¹⁴². The largest multicentre analysis, the JIR cohort study, found rituximab to be well tolerated and clinically effective, improving disease activity and enabling glucocorticoid tapering, across European centres¹⁴³. A single-centre study from the Children's Hospital of Alabama similarly found reduced glucocorticoid use, improved outcomes and a good safety profile¹⁴⁴. Together, these findings support rituximab as a viable and accessible option for treatment-refractory childhood-onset SLE, although prospective studies are still needed to define long-term efficacy and safety.

Belimumab has shown efficacy in lupus nephritis in children, enabling glucocorticoid tapering¹⁴⁵, and ofatumumab also seems safe and effective¹⁴⁶. However, these medications are not universally available for use in childhood-onset SLE. Combination regimens, such as multitarget therapy with glucocorticoids, mycophenolate and cyclosporine, or tacrolimus-based strategies, have demonstrated benefit in small studies¹⁴⁷. Emerging molecular targets, such as mTOR (targeted by sirolimus), PI3K and JAK2 inhibitors, offer additional promise¹⁴⁸. Notably, CD19 CAR T therapy has led to remission in two people with treatment-refractory childhood-onset SLE and is now being tested in clinical trials^{149,150}.

Holistic management and glucocorticoid-sparing

All current treatment guidelines for children with SLE stress the importance of a holistic approach to care, including comorbidity prevention and risk stratification for CVD, infection, bone health, reproductive issues and attention to psychosocial well-being^{102,139}. Regular

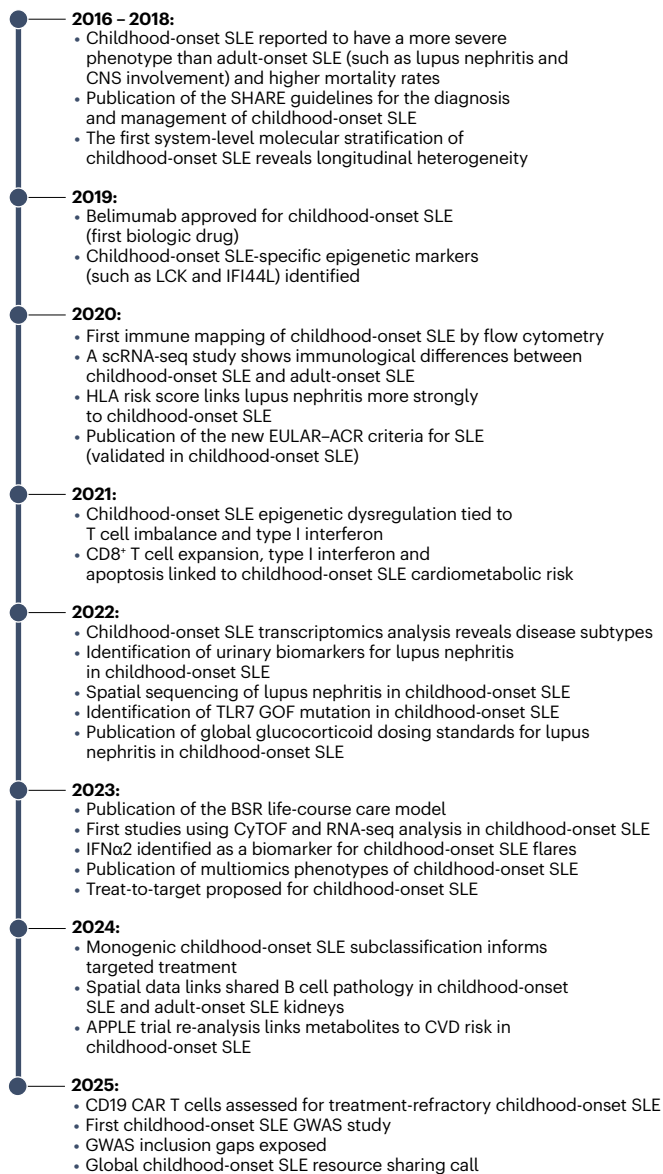


Fig. 3 | Major advances in childhood-onset SLE in the past decade. This timeline highlights major developments in the understanding and management of childhood-onset systemic lupus erythematosus (SLE) over the past decade. Substantial progress has been made in characterizing the clinical phenotype, refining disease classification and elucidating immunopathogenic mechanisms. These advances have led to updated treatment strategies, age-appropriate clinical trial designs and revised classification criteria, reinforcing the recognition of childhood-onset SLE as a distinct entity from adult-onset SLE. Despite these improvements, research and clinical infrastructure in childhood-onset SLE continue to lag behind those in adult-onset SLE, with notable gaps in disease-specific biomarkers, long-term outcome data and tailored therapeutic options. Ongoing efforts are critical to bridge these gaps and ensure that children with SLE receive evidence-based, individualized care. ACR, American College of Rheumatology; BSR, British Society for Rheumatology; CAR T cells, chimeric antigen receptor T cells; CNS, central nervous system; CVD, cardiovascular disease; CyTOF, cytometry by time of flight; EULAR, European League Against Rheumatism; GOF, gain-of-function; GWAS, genome-wide association study; IFI44L, interferon-induced protein 44-like; IFN α 2, interferon- α 2; LCK, lymphocyte-specific protein tyrosine kinase; RNA-seq, RNA sequencing; scRNA-seq, single-cell RNA sequencing; TLR7, Toll-like receptor 7.

monitoring of growth, puberty, metabolic markers and adherence is crucial, alongside lifestyle and fertility counselling.

In parallel, glucocorticoid minimization remains a shared goal across adult-onset SLE and childhood-onset SLE. Prolonged glucocorticoid use exacerbates many of the comorbidities that clinicians strive to prevent, including obesity, metabolic syndrome, osteoporosis, mood disorders and impaired growth and fertility¹⁰⁵. Thus, glucocorticoid-sparing is not only a therapeutic goal, but also supports the broader objectives of holistic management. Although KDIGO recommends tapering glucocorticoids within 3 months and ACR–EULAR within 6 months, achieving 10–20 mg per day prednisone by week 24 of induction therapy in lupus nephritis is recommended by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus¹⁵¹. However, this target remains relatively high, highlighting the ongoing need for earlier and more effective glucocorticoid-sparing strategies in childhood-onset SLE.

A ‘treat-to-target’ approach tailored for childhood-onset SLE is also increasingly being advocated, which emphasizes defined disease activity states and early glucocorticoid reduction¹⁵². Current consensus definitions include the Lupus Low Disease Activity State, a validated target associated with reduced flare and damage accrual, and DORIS remission criteria, which define sustained clinical and serological quiescence either on-therapy or off-therapy^{153–155}. Biologic drugs and targeted therapies are used not only to achieve remission, but also to sustain it, ideally with no glucocorticoid use. Together, the integration of holistic management and glucocorticoid-sparing strategies has been one of the most important paradigm shifts in the past decade of childhood-onset SLE research and clinical practice.

Future perspectives

Insights from studies over the past 10 years have enhanced understanding of the pathogenesis of childhood-onset SLE (Fig. 3). Guided by these groundbreaking studies, the next decade holds great promise for transforming childhood-onset SLE care through precision medicine. A key future direction is the integration of validated biomarkers, particularly non-invasive options such as ‘liquid biopsy’, to enable early diagnosis, guide personalized treatment decisions, monitor organ-specific involvement and reduce reliance on invasive procedures such as kidney biopsies. Multiomics approaches and machine learning offer powerful tools to develop composite molecular signatures, combining transcriptomic, metabolomic, proteomic and epigenetic data to stratify patients and predict outcomes. In paediatric populations, these technologies have also been instrumental in uncovering monogenic causes of disease, highlighting the unique genetic architecture of childhood-onset autoimmunity and informing precision medicine strategies.

Equally crucial is the expansion of paediatric clinical trials, including adaptive and basket trial designs to overcome recruitment barriers in this rare disease. Direct comparisons between childhood-onset SLE and adult-onset SLE, alongside longitudinal studies that follow individuals across developmental stages, are essential to capture age-specific disease dynamics, such as those related to type I IFN activity. Reporting age, sex, ethnicity and disease onset in SLE studies is essential, as many existing datasets overlook these key distinctions.

Future studies must also enhance inclusion of diverse ethnicities in pan-genomic analyses and epigenetic research to address known disparities in disease burden and heritability¹⁵⁶. This inclusion will require international collaborations, harmonization of reporting standards and pooling of core datasets and biobanked samples across biorepositories, as already proposed¹⁵⁷. Better integration of sex and

gender variables, amid ongoing global political constraints, is also necessary to fully understand sex-dimorphic pathways and improve therapeutic equity. Together, these efforts can unlock the full potential of translational research to deliver truly individualized, equitable care in childhood-onset SLE.

Our aim is not to separate childhood-onset SLE and adult-onset SLE as entirely different diseases, but to highlight their age-salient biology and pathology (such as IFN signalling, monogenic subsets and hormonal effects) that might influence personalized therapy, dosing, end points or safety. This balanced approach promotes precision care whilst preserving practical drug access routes for young patients. Running adult-onset SLE and childhood-onset SLE clinical trials in parallel will be important in preventing delays in treatment advances for younger patients.

Conclusion

Childhood-onset SLE remains a unique and more severe entity within the SLE spectrum, marked by earlier disease onset, increased organ damage and age-enriched immunopathogenic mechanisms. Over the past decade, major strides have been made in understanding the genetic, epigenetic and immune landscape of this disease, especially in relation to IFN signalling and disease heterogeneity. Despite these advances, gaps persist in the representation of children and adolescents in clinical research, in validated biomarkers for organ-specific manifestations and in paediatric-focused treatment guidelines. Bridging these gaps through interdisciplinary, inclusive and translational research will be essential to improving outcomes for young people living with this challenging disease.

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The authors declare no competing interests.

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Mechanisms of osteoclast activation in inflammatory bone loss in rheumatoid arthritis

Martina Rauner ¹ & Aline Bozec ^{2,3} 

Abstract

Rheumatoid arthritis is an autoimmune disease that affects ~1% of the global population and leads to joint inflammation, local bone erosions and systemic bone loss. The disability and immobility caused by inflammatory bone loss, joint destruction and fractures in rheumatoid arthritis present a clinical challenge and impose a considerable socioeconomical burden. Osteoclasts have the unique ability to resorb bone and cause bone loss. A comprehensive understanding of the regulatory mechanisms of osteoclasts and their crosstalk with stromal cells, such as osteoblasts, or immune cells during inflammation is essential for the development of targeted therapies to prevent and treat bone loss. The objective of this Review is to present a comprehensive overview of the current knowledge of osteoclast regulation at different levels: from systemic pathways to changes in the bone microenvironment, including the involvement of local cells, to osteoclast-intrinsic regulation such as metabolic adaptations. We also discuss some of the current and emerging therapies that can counteract inflammatory bone loss.

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Introduction

Osteoclast generation and differentiation pathways

Regulation of osteoclasts by cytokines and pro-inflammatory mediators

The effect of immune cells on osteoclastogenesis

Metabolic regulation of osteoclast function in inflammatory conditions

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Skeletal effects of current RA therapies

Anti-osteoporosis therapies that prevent inflammation-induced bone loss

Future emerging strategies

Conclusions

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Key points

- Pro-inflammatory cytokines and immune cell crosstalk drive pathological osteoclastogenesis in rheumatoid arthritis.
- Osteoclast differentiation and activation are regulated by classical and pro-inflammatory pathways.
- Osteoclast differentiation and activity are tightly coupled to metabolic changes, including increased glycolysis, oxidative phosphorylation and fatty acid oxidation. Key metabolic regulatory pathways modulate osteoclast function and survival.
- Conventional and biological DMARDs reduce inflammation and slow down joint erosion. Anti-resorptive therapies and bone-anabolic therapies preserve bone mass. A combination of these treatments is essential for effective treatment of skeletal complications of rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that primarily affects the joints. Synovitis is one of the main characteristics of RA, whereby inflammation of the synovial membrane leads to the destruction of the adjacent articular cartilage and subchondral bone. In addition to local bone erosions, systemic bone loss is another important skeletal feature of the disease, which ultimately leads to an increased rate of fractures, further decreasing the quality of life of affected individuals¹.

Bone remodelling is a dynamic process that assures the maintenance of skeletal integrity and mineral homeostasis. The remodelling of the bone starts with the activation of osteoclast differentiation and then resorption, which is then followed by a long period of bone formation from the osteoblasts that produce the bone matrix². The bone-resorbing cells, termed osteoclasts, are multinucleated cells derived from the myeloid lineage. The differentiation and function of osteoclasts are regulated by a range of systemic (such as hormones) and local (such as cytokines) factors derived from surrounding cells, which include osteoblasts, other stromal cell populations and immune cells present within the bone marrow³.

In RA, stromal cell–osteoclast and immune cell–osteoclast crosstalk is disrupted⁴. Systemic inflammation in RA has a profound influence on osteoclastogenesis and osteoclast function, which is mediated by cytokines, hormones and other factors. Pro-inflammatory cytokines, including TNF, IL-1 β , IL-6 and IL-17, which are markedly elevated in patients with RA, can promote osteoclastogenesis⁵. These cytokines are also the primary target of biologic DMARDs (bDMARDs), which are used when conventional DMARDs (cDMARDs), such as methotrexate, fail to obtain a good response⁶. Pannus formation in the RA synovium occurs owing to infiltration of immune cells, including T cells, macrophages, granulocytes and fibroblast-like synoviocytes (FLS). These immune cells disturb the microenvironment, which leads to a local inflammatory milieu characterized by elevated local production of receptor activator of NF- κ B ligand (RANKL), TNF and other cytokines that amplify osteoclastogenesis and suppress osteoblast function⁷ (Fig. 1). Furthermore, the accumulation of reactive oxygen species (ROS) and metabolic byproducts within the inflamed tissue contributes to the dysregulation of bone metabolism in RA⁸. Emerging research has

highlighted the importance of intrinsic metabolic alterations in osteoclast differentiation and function in RA. Therein, the rates of glycolysis, oxidative phosphorylation and fatty acid oxidation (FAO) are augmented, providing the necessary substrates for osteoclastogenesis⁹. These intrinsic metabolic adaptations are now recognized as potential therapeutic targets for the mitigation of inflammatory bone loss.

A thorough understanding of the complex mechanisms underlying osteoclast-mediated bone loss in RA is essential for the development of targeted therapeutic interventions. This Review provides a comprehensive overview of factors that regulate osteoclasts in the context of inflammatory bone loss, with particular emphasis on the unique features of RA and insights into potential therapeutic strategies.

Osteoclast generation and differentiation pathways

Osteoclasts are the major bone-resorbing cells, which are particularly active during RA. The differentiation of osteoclasts is driven by two key factors: macrophage colony-stimulating factor (M-CSF) and RANKL. The transition of osteoclast precursor cells (OCPs) into multinucleated osteoclasts is mediated by RANKL-induced activation of downstream pathways and transcription factors, including nuclear factor of activated T cells 1 (NFATc1), c-Fos and Myc¹⁰. Mature osteoclasts are characterized by their unique multinucleated morphology and a distinct sealing zone and ruffled border, which enables them to attach tightly to the bone surface and seal the resorption pit (which are shallow depressions, pits or grooves on the bone surface where osteoclasts actively break down and remove bone tissue during bone remodelling). To avoid damage to neighbouring structures, osteoclasts generate a highly acidic environment to dissolve the bone mineral and to degrade the collagenous matrix using enzymes that are active in acidic environments such as cathepsin K. Osteoclasts are then thought to undergo apoptosis, although emerging evidence suggests a recycling pathway of osteoclasts, whereby mature osteoclasts can produce daughter cells, so called ‘osteomorphs’, which can fuse with other osteoclast syncytia to generate new mature osteoclasts. These osteomorphs are transient in nature and express several non-canonical osteoclast genes that are associated with bone loss¹¹ but their role in arthritis remains unclear. This section provides fundamental insights into osteoclast origin, OCPs and classical osteoclast signalling pathways.

The origin of osteoclasts

Pioneering work from the 1970s provided compelling evidence that osteoclasts derive from a haematopoietic origin¹². These findings were supported by studies showing that osteopetrosis in mice could be mitigated by bone marrow or splenic transplantation^{12,13} (which gave rise to mature, bone-resorbing osteoclasts a few weeks post-treatment) or by parabiosis experiments via transfer of circulating mononuclear haematopoietic cells¹⁴. Moreover, mouse and human osteoclasts can be generated in vitro from highly purified haematopoietic stem cells (HSCs), splenic macrophages and monocytes from peripheral blood, which indicates that osteoclasts are of myeloid origin^{15–17}. The use of more refined fate-mapping and lineage tracing approaches has provided clarity about the origin of osteoclasts. During fetal development, osteoclasts derive from erythroid–myeloid progenitor cells (EMPs), which emerge around embryonic day 7 in the yolk sac and can differentiate into macrophages positive for colony-stimulating factor 1 receptor (Csf1r; also known as CD115) that give rise to tissue-resident macrophages¹⁴. These cells are long-lived and serve as progenitors for osteoclasts. Tracing experiments in mice show that Csf1r⁺

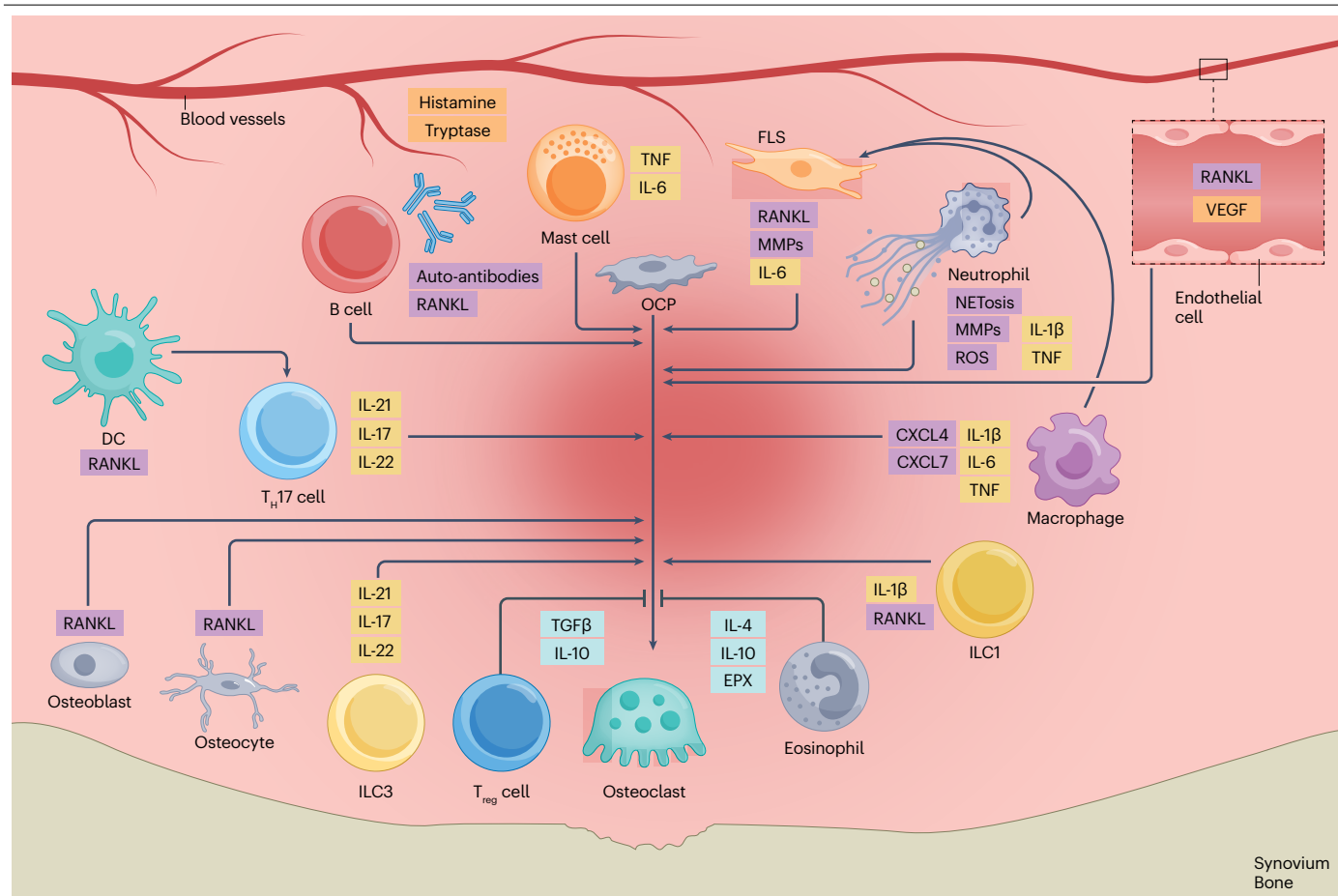


Fig. 1 | The cellular and molecular landscape of the inflamed synovium in inflammatory arthritis. The immune, stromal and bone-resorbing cells that cause joint inflammation and destruction are interconnected in the inflamed synovium. In the inflamed synovial membrane, macrophages, neutrophils and type 1 innate lymphoid cells (ILCs) contribute to inflammation and osteoclast activation by producing IL-1 β , IL-6 and TNF. Macrophages activate fibroblast-like synoviocytes (FLS) to secrete pro-inflammatory mediators, such as IL-6, the osteoclast-promoting cytokine receptor activator of NF- κ B ligand (RANKL) and matrix-degrading matrix metalloproteinases (MMPs). Neutrophils also produce neutrophil extracellular traps (NETs) and reactive oxygen species (ROS), which enhance osteoclastogenesis. Mast cells further amplify inflammation and vascular permeability via histamine and tryptase. Eosinophils, highlighted as immunomodulatory players, can produce IL-4 and IL-10 and modulate local

immune responses by communicating with macrophages and osteoclasts. Dendritic cells (DCs) bridge innate and adaptive immunity by activating T cells and promoting the differentiation of T helper 17 (T_H17) cells. These cells and ILC3s secrete IL-17, IL-21 and IL-22, which sustain chronic inflammation. B cells can produce auto-antibodies and interact with T cells and osteoclast precursor cells (OCPs), thereby exacerbating bone erosion. RANKL signalling from multiple cellular sources, including FLS, B cells and DCs, further drives osteoclastogenesis. Endothelial cells express vascular endothelial growth factor (VEGF) and RANKL, which support angiogenesis and the migration of OCPs. Mediators that promote inflammation and osteoclastogenesis are shown in purple, mediators that promote inflammation are shown in yellow, immunomodulatory mediators are shown in blue, and mediators that promote angiogenesis are shown in orange. EPX, eosinophil peroxidase; T_{reg}, regulatory T.

macrophages are present at bone surfaces at least 6 months after birth, thus providing evidence that these cells not only contribute to osteoclasts during fetal development but also in adulthood^{14,18}. Interestingly, parabiosis studies revealed that these EMP-derived osteoclasts continuously fuse with HSC-derived monocytes, one-by-one, generating osteoclasts of mixed EMP origin and HSC origin¹⁴. The fact that osteopetrosis can be rescued by transfusion of neonatal monocytic cells underscores that osteoclasts can be generated by iterative fusion of monocytic precursor cells. Overall, these fusion events are rather scarce during bone homeostasis in adults, but they can be accelerated after treatment with RANKL or in states of injury or inflammation in mice^{11,14,18,19}. EMP-derived and HSC-derived osteoclasts

can contribute to bone repair at a fracture site, which highlights that these cells can migrate to distant sites¹⁹. Finally, analysis of the phenotypes of mice lacking *Csflr* (the M-CSF receptor) or *Tnfrsf11a* (the RANKL receptor), either in EMPs or HSCs, demonstrated that osteoclasts of both origins are necessary to maintain properly functioning osteoclasts throughout life¹⁸. An early osteopetrosis phenotype was detected in mice lacking *Csflr* or *Tnfrsf11a* in EMPs, which resolved over time, whereas deficiency in HSCs led to osteopetrosis only later in life; thus, these data suggest a shift in the origin of osteoclasts from EMPs to HSCs during adulthood.

Another long-standing area of interest is whether osteoclasts can derive not only from monocytes and macrophages but also from

dendritic cells. Several studies have convincingly shown that osteoclasts can be generated from immature CD11c⁺ dendritic cells, which express a similar set of osteoclast-specific genes as those generated from monocytes and macrophages, and demonstrate bone-resorbing potential in vitro^{20–24}. These transdifferentiation processes were particularly evident under inflammatory conditions²⁵. Moreover, adoptive transfer of CD11c⁺ dendritic cells into mice with osteopetrosis rescued the bone excess, showing that these cells can produce functionally competent, bone-resorbing osteoclasts^{20,21,26}. In addition, depleting CD11c⁺ cells in vivo or knocking out *Tnfrsf11a* in CD11c⁺ cells led to a lack of osteoclasts in long bones²⁷. Overall, there seems to be a high degree of plasticity in the immature myeloid precursor populations of osteoclasts, which might also depend on environmental cues (such as homeostasis versus pathological conditions).

Osteoclast precursors in inflammation

An unresolved issue building on ontogeny and precursor plasticity is whether osteoclasts that are involved in normal bone remodelling are distinct from those induced by inflammation. Conceptually, homeostatic remodelling osteoclasts function within low-inflammation bone-remodelling units. They are sustained by local CSF1R⁺ macrophage and EMP lineages with limited input from HSC-derived monocytes. Additionally, they couple resorption to formation via RANKL and M-CSF from osteocytes and osteoblasts²⁸. Markers used to identify myeloid cells, such as CD14, CD11b, CD117 (also known as c-Kit), CX3CR1 and RANK, can be used in combination to identify OCPs²⁹.

Under chronic inflammation, however, the precursor pool and differentiation programme shift; the synovial milieu causes expansion of osteoclastogenic precursors. Specific subsets of OCPs emerge and assume crucial roles in the process of bone erosion (Box 1). The term ‘arthritis-associated osteoclastogenic macrophages’ refers to a specific type of immune cell that arises from inflammatory monocytes in mouse models of arthritis³⁰. These cells exhibit a high degree of osteoclastogenic potential when stimulated by RANKL and TNF, with FOXM1 functioning as an essential transcriptional regulator. Chronic inflammation gives rise to inflammatory OCPs, which are distinguished from homeostatic OCPs by their adaptation to inflammatory environments, high resorptive activity and regulation by TNF, S100A8 and S100A9. Both CX3CR1⁺ and CX3CR1⁻ subsets of these cells have been described³¹. In humans, the expansion of CD14⁺CD16⁺ pro-inflammatory monocytes during inflammation contributes to osteoclastogenesis, which is amplified by the production of TNF and IL-1 β ³². Furthermore, under inflammatory conditions, immature CD11c⁺ dendritic cells can transdifferentiate into osteoclasts²⁰. Collectively, these findings underscore the contribution of distinct inflammatory myeloid subsets to pathological bone remodelling and highlight the necessity for targeted therapeutic strategies.

The RANKL–RANK axis in osteoclast differentiation

The key cytokine that induces osteoclastogenesis is RANKL. This cytokine is mainly produced by osteoblasts and osteocytes under physiological conditions³³. In RA, activated T cells can produce RANKL, which increases the interactions between T cells and dendritic cells³⁴. Furthermore, FLS triggered by T helper 17 (T_H17) cells can produce RANKL³⁵; however, using cell-type-specific RANKL-knockout mice, FLS have also been identified as a source for RANKL that contributes to inflammatory bone loss³⁶.

RANKL binds to its cognate receptor RANK on OCPs, which activates several downstream pathways that result in the induction of NFATc1, the

master transcription factor for osteoclasts³⁷. Similar to RANKL, RANK expression is also induced on OCPs in response to inflammatory stimuli, including TNF, IL-1 β and IL-6 (ref. 38). In addition to RANK signalling, costimulatory signalling through immunoreceptor tyrosine-based activation motif (ITAM)-carrying receptors, such as DAPI2 and Fc γ R, is necessary to induce NFATc1 expression via calcium-dependent signalling pathways and to sustain the activation of osteoclastogenesis^{39,40}. Although the activation of DAPI2 and Fc γ R is not sufficient to induce osteoclastogenesis in the absence of RANKL, they synergistically contribute to NFATc1 activation together with RANK signalling, and thus lead to a robust activation of osteoclastogenesis³⁷. In this section, we focus on RANKL–RANK signalling pathways given that NFATc1-dependent osteoclastogenic signalling pathways have been reviewed elsewhere^{41,42}.

Upon RANKL–RANK binding, the adaptor protein TNF receptor-associated factor 6 (TRAF6) is recruited, which in turn activates the NF- κ B signalling pathway and mitogen-activated protein kinase (MAPK) pathways. The trimeric complex that is formed when RANK interacts with TRAF6 is essential for osteoclastogenesis^{42,43}. Transgenic mice and human studies highlight the crucial role of classical NF- κ B during osteoclastogenesis. Mice lacking the NF- κ B proteins p50 or p52 develop osteopetrosis, similar to humans who carry a point mutation in IKK β , an upstream subunit that activates NF- κ B^{44,45}. In addition, several MAPK pathways are essential for osteoclast development, although many

Box 1 | Niche-specific osteoclast precursors in inflammatory bone loss

In addition to classical monocyte-derived precursors, inflammation-specific osteoclastogenic populations emerge in the synovium and bone marrow under pathological conditions. These subsets possess distinct surface markers, transcriptional programmes and metabolic profiles that are adapted to inflammatory environments.

Arthritis-associated osteoclastogenic macrophages

Arthritis-associated osteoclastogenic macrophages are derived from CX3CR1^{lo}Ly6C^{hi} inflammatory monocytes, they are highly enriched in arthritic joints, and express MHC class II, CD80, CD86 and CD11c. These cells promote osteoclastogenesis in response to TNF and receptor activator of NF- κ B ligand (RANKL), and their transcriptional profile is regulated by FOXM1 (ref. 291).

Inflammatory osteoclast precursors

Inflammatory osteoclast precursors arise under chronic inflammation from Ly6C^{hi}CD11b^{hi} cells and exhibit enhanced expression of metabolic and resorptive enzymes. In contrast to homeostatic osteoclast precursor cells, inflammatory osteoclast precursors are highly dependent on S100A8 and S100A9 signalling and demonstrate CX3CR1-defined heterogeneity³¹.

Dendritic cell-derived osteoclasts

Immature CD11c⁺ dendritic cells have the capacity to transdifferentiate into functional osteoclasts, particularly in the context of rheumatoid arthritis and other inflammatory conditions. This finding underscores the plasticity of myeloid precursors in chronic inflammation²⁰.

in vivo studies are hampered by embryonic lethality of *MAPK* gene knockouts and/or compensatory activation of isoforms⁴⁶. Various members of the activator protein 1 family, such as c-Fos, c-Jun, JunB and Fra1, are activated by the JNK–MAPK pathway during osteoclastogenesis; however, only c-Fos and c-Jun are required for osteoclastogenesis in vitro and in vivo during homeostatic conditions⁴⁷. The c-Fos–c-Jun protein complex binds to the promoter region of NFATc1 and induces its transcription⁴⁸. Besides activating NF-κB and MAPK signalling, RANK–TRAF6 signalling also leads to the activation of c-Src downstream signalling, which results in the activation of phosphatidylinositol 3-kinase (PI3K) and, further downstream, of the AKT (also known as protein kinase B) survival pathway⁷. Mice lacking *c-Src* develop osteopetrosis as, despite developing, osteoclasts cannot attach to the bone matrix and form a sealing zone, which highlights the crucial role of c-Src in the actin organization of the cytoskeleton⁴⁹. Furthermore, *c-Src*-deficient osteoclasts show reduced levels of AKT and reduced survival rates compared with wild-type cells, which indicates that the c-Src–PI3K–AKT pathway is important for osteoclast function via cytoskeletal rearrangement and survival⁵⁰.

RANKL-induced activation of TRAF6 and costimulatory signals via Tec kinases (a family of non-receptor tyrosine kinases) and phospholipase C γ further mobilize intracellular calcium, which activates the Ca²⁺–calcineurin pathway. Indeed, RANKL stimulation induces calcineurin-dependent auto-amplification of NFATc1 expression. Together with c-Fos and c-Jun, NFATc1 binds to its own promoter and induces its transcription, which leads to a powerful auto-amplification loop. Blocking calcium signalling with BAPTA-AM (a highly selective calcium chelator) or calcineurin activity using FK506 or cyclosporin A both potentially inhibit osteoclastogenesis, indicating that these pathways are required for osteoclastogenesis³⁷.

To protect against bone loss, there are multiple negative feedback loops that control for excessive osteoclast maturation and function, including feedback mechanisms through NF-κB signalling and negative regulators of NFATc1 signalling, which are reviewed elsewhere^{41,42}. One of the most important negative regulators of osteoclastogenesis is osteoprotegerin (OPG), which is a decoy receptor for RANKL and can thus prevent the binding of RANKL to RANK and inhibit subsequent osteoclastogenesis⁵¹. Although OPG is produced by several cell types, including osteoblasts, osteocytes, smooth muscle cells and B cells, only OPG production by osteoblasts seems to be physiologically relevant for regulating bone mass⁵². During states of inflammation, OPG expression is downregulated in several cell types in the synovial tissue, whereas the expression of RANKL is induced, particularly by synovial fibroblasts, which leads to enhanced osteoclastogenesis^{53,54}. Thus, targeting the RANKL–RANK pathway is a promising strategy to prevent inflammation-induced bone loss. Preclinical and clinical studies have shown the efficacy of blocking RANKL to halt inflammation-induced bone loss and bone erosions, without affecting the course of inflammation, which we discuss later in this Review^{34,55–57}.

Novel factors that regulate osteoclast maturation

Besides classical RANKL–RANK signalling, single-cell RNA sequencing (scRNA-seq) analyses have uncovered several new regulators of specific stages of osteoclast differentiation. In addition to the verification of RANKL-expressing CD11c cells as an important transient cell population during mouse in vitro osteoclastogenesis, Cited2 was identified as a novel factor that regulates the terminal differentiation of osteoclasts²⁷. Depleting this factor in OCPs results in a failure to commit to the transition to mature osteoclasts, leading to an osteopetrotic phenotype.

A study using human CD14⁺ monocytes from peripheral blood identified several distinct subpopulations with specific transcriptomic profiles during osteoclastogenesis⁵⁸. Although genes associated with metabolic reprogramming and mitochondrial activation were among the earliest genes to be upregulated during osteoclast differentiation, typical markers of osteoclast function, such as *CTSK*, *ACP5*, *DCSTAMP* and *CA2*, were among the genes upregulated later in osteoclast differentiation. At the mature stages, two specific populations were identified, both of which were characterized by the transcription factors NFATc1 and JUN; however, they differed in their expression of other transcription factors: one population had a high expression of CEBPB, FOS and BCL6, which correlated with an enrichment in the biological processes of lipid metabolism, cytokine production and cell migration, whereas the other population was characterized by high expression of ATF1, NRF1 and SIX5, which correlated with mitochondrial processes, ATP transport and translation. Currently, it remains unclear if these two populations have different resorptive activity or represent fused versus non-fused mature osteoclasts. The exact nature of these cell populations requires further investigation. This study also identified other factors, such as complement 5A receptor 1, somatostatin receptor 2 and free fatty acid receptor 4, as important regulators of human osteoclast maturation⁵⁸.

Integration of scRNA-seq data sets from in vitro mouse and human osteoclastogenesis showed that OCPs in a mitotic phase do not differentiate into osteoclasts⁵⁹. Moreover, using ligand–receptor analysis, CSF1–CSF1R, TGFβ1–TGF receptor, CCL2–CCR1 and CCL3–CCR1 were identified as high-affinity interactions within osteoclast subpopulations. RAB38 was among the highest induced factors after RANKL stimulation in both human and mouse osteoclasts. Depletion of RAB38 impaired osteoclast maturation and actin-ring formation, which also impaired osteoclast function⁵⁹.

Taken together, scRNA-seq analyses have resulted in the definition of novel osteoclast subsets and factors that regulate osteoclastogenesis; however, how these subsets and factors are regulated during inflammatory conditions requires further investigation.

Regulation of osteoclasts by cytokines and pro-inflammatory mediators

The following section will cover the role and function of pro-inflammatory and anti-inflammatory cytokines in the differentiation and function of osteoclasts (Table 1).

Pro-osteoclastic cytokines

Cytokines and pro-inflammatory mediators continually regulate bone remodelling by modulating the balance between osteoclast and osteoblast activity, particularly during inflammatory processes. In addition to the RANKL signalling pathway, TNF, IL-1β and IL-6 have been shown to effectively induce osteoclastogenesis, while simultaneously inhibiting bone formation⁶⁰. During an inflammatory response, macrophages are activated into a classically activated phenotype and release a cascade of pro-inflammatory cytokines⁶¹. For instance, TNF is found in the synovial and bone microenvironment and the levels of TNF are enhanced under inflammatory conditions; in this context, TNF can promote the production of RANKL by stromal cells such as osteoblasts and osteocytes⁶². Furthermore, stimulating bone marrow-derived monocytes with TNF and RANKL increases NF-κB and MAPK pathway-dependent osteoclast differentiation compared with RANKL alone⁶³. Similarly, stimulating bone marrow-derived macrophage cells with IL-6, or a combination of IL-6 and TNF, also increases the differentiation of osteoclasts⁶⁴. Finally, another synergistic cytokine response was observed with IL-1β,

Table 1 | Cytokines that influence osteoclastogenesis

Cytokine	Effect on osteoclastogenesis	Source cells	Effects on osteoclasts
RANKL	Increases	Osteoblasts Stromal cells	Binds to the RANK receptor on OCPs, which activates NF-κB and NFATc1 pathways
TNF	Increases	Macrophages T cells	Activates NF-κB and MAPK pathways, which enhance osteoclast differentiation
IL-1	Increases	Macrophages Monocytes	Promotes RANKL expression by surrounding cells and enhances NF-κB activation
IL-6	Increases	T cells Macrophages Fibroblasts	Stimulates RANKL by surrounding cells via JAK–STAT signalling
IL-17	Increases	T _H 17 cells	Induces RANKL production and amplifies osteoclastogenesis via STAT3
IL-10	Inhibits	T _{reg} cells Macrophages	Suppresses NF-κB signalling and promotes anti-inflammatory responses by surrounding cells
TGFβ	Inhibits	T _{reg} cells Osteoblasts	Inhibits RANK signalling and promotes osteoclast apoptosis
IFNγ	Inhibits	T cells NK cells	Interferes with NF-κB activation and inhibits osteoclast formation
IL-4	Inhibits	T cells Mast cells	Inhibits osteoclastogenesis by reducing RANKL expression
IL-12	Inhibits	Dendritic cells Macrophages	Downregulates RANK expression on osteoclasts and inhibits their differentiation
IL-33	Inhibits	Mast cells T cells	Modulates TGFβ signalling, which suppresses osteoclast activity
GM-CSF	Inhibits	Macrophages Dendritic cells	Alters OCP survival and RANK signalling
IL-23	Increases	Dendritic cells T cells	Enhances osteoclastogenesis via STAT3 and IL-23 receptor pathways
M-CSF	Increases	Osteoblasts Stromal cells	Supports survival and differentiation of OCPs via CSF1R (also known as c-FMS) activation
IL-18	Inhibits	Macrophages Dendritic cells	Reduces RANKL-induced NF-κB activation, which inhibits osteoclastogenesis
IL-11	Increases	Fibroblasts T cells	Promotes osteoclast differentiation by modulating RANKL expression
IL-21	Increases	T cells NK cells	Enhances the effects of RANKL and osteoclast survival through STAT3 signalling

CSF1R, colony-stimulating factor 1 receptor; GM-CSF, granulocyte–macrophage colony-stimulating factor; JAK, Janus kinase; M-CSF, macrophage colony-stimulating factor; NFATc1, nuclear factor of activated T cells, cytoplasmic 1; NK, natural killer; OCPs, osteoclast precursor cells; MAPK, mitogen-activated protein kinase; RANK, receptor activator of NF-κB; RANKL, RANK ligand; STAT, signal transducer and activator of transcription; T_H17, T helper 17; T_{reg}, regulatory T.

which directly targets OPCs and promotes osteoclast differentiation in the presence of TNF and RANKL^{65,66}. IL-1β binds to IL-1R1 and IL-1R2; signalling via these receptors activates the protein kinase IRAK4, which then phosphorylates IRAK1, IRAK2 and TRAF6. IL-1β can also reduce osteoclast death, which is dependent on the PI3K–Akt or MEK–ERK pathways⁶⁷, the latter also being an important factor for osteoclastogenesis⁶⁸.

IL-6 exerts its effects through activation of the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling pathway. This cytokine is elevated in RA and is produced by many different cell types in the inflamed synovium⁶⁹ (Fig. 1). IL-6 has an important role in joint damage and periarticular bone erosion⁷⁰, especially as it can stimulate the production of RANKL from fibroblastic

stromal cells and osteoblasts⁷¹. The JAK–STAT pathway is downstream of IL-6 and has a pivotal role in inflammatory bone loss in RA^{72,73}. For example, phosphorylated STAT proteins function as transcription factors by passing into the nucleus and regulating the expression of genes involved in osteoclastogenesis such as RANKL. In mouse models of RA, JAK inhibition increased osteoblast function via WNT signalling, which indirectly regulates osteoclasts via osteogenic RANKL production⁷².

Anti-osteoclastic cytokines

Evidence indicates that anti-inflammatory cytokines, such as IL-4, IL-13, IL-10 and TGFβ, can preserve the bone from inflammatory bone loss. T_H2 cells are the main producers of IL-4 and IL-13 and these cells can promote the resolution of inflammation and inflammatory bone loss.

IL-13 and IL-4 inhibit osteoclast differentiation by binding to their receptor complex, comprising IL-4 receptor- α and the common γ -chain. This binding activates downstream signalling via JAK and STAT6 (refs. 74,75). This activation suppresses the expression of RANK on OCPs, thereby reducing their response to RANKL. Furthermore, IL-4 can inhibit downstream RANKL signalling pathways, such as c-Fos and NFATc1, thereby impairing the transcriptional programme of osteoclastogenesis⁷⁶. IL-4 also regulates PPAR γ activation in OCPs, which seems to be essential for IL-4-mediated inhibition of osteoclast differentiation⁷⁷. Furthermore, IL-4 can induce an alternatively activated phenotype in macrophages via STAT3, which increases the secretion of anti-inflammatory cytokines and regulates osteoclast function⁷⁸.

IL-10 is an anti-inflammatory cytokine that can inhibit the expression of TNF, IL-1 β and IL-6 (ref. 79). IL-10 can directly inhibit osteoclast differentiation by binding to its receptor complex (IL-10R1 and IL-10R2), which activates JAK1 and tyrosine kinase 2. Upon phosphorylation, STAT3 translocates to the nucleus and induces the expression of SOCS proteins. SOCS proteins, in particular SOCS1 and SOCS3, can inhibit key osteoclastogenic signalling pathways, including the RANK–RANK–NFATc1 pathway by blocking TRAF6 (ref. 80). IL-10 is produced by many cell types, including macrophages and regulatory B cells, has a crucial role in suppressing T_H17 and T_H1 cells, and induces the differentiation of T regulatory type 1 cells (which also secrete IL-10), favouring the resolution of collagen-induced arthritis^{81–83}.

TGF β can either inhibit or activate osteoclast differentiation, depending on the time of activation and the co-stimulation signals. Downstream of TGF β , SMAD1 and SMAD3 can regulate RANK and matrix metalloproteinase 9 (MMP9) expression⁸⁴. TGF β can reprogramme macrophages into the non-canonical TGF β pathways by inducing IRF8 degradation and BMyb induction, which facilitates the recruitment of OCPs⁸⁵. During prolonged inflammation, the regulatory function of TGF β shifts to an anti-osteoclastogenic role by promoting OPG expression and inhibiting RANKL signalling⁸⁵.

The effect of immune cells on osteoclastogenesis

Osteoclasts can interact directly and indirectly with innate and adaptive immune cells under inflammatory conditions.

Innate immune cells

Macrophages. Macrophages maintain tissue homeostasis, respond to the pathological mechanisms during disease and can contribute to both chronicity and resolution pathways during inflammation⁶¹. One of the examples that links macrophages to osteoclasts is the secretion of the pro-inflammatory cytokine TNF through the activation of LPS–TLR4 signalling⁸⁶. However, the secretion of this TNF by macrophages in arthritis is manifold, as they also secrete IL-1 β , IL-6, CXCL4 and CXCL7 (which promote osteoclastogenesis and bone resorption) and cytokines such as IFN γ and IL-12 (which positively influence bone homeostasis)⁸⁷. When macrophages undergo polarization into alternative activated macrophages during the resolution phase of arthritis, they secrete anti-inflammatory cytokines, which protect the bone against degradation.

Throughout the progression of RA, synovial macrophages transition from a homeostatic state to a pathogenic state prior to the onset of symptoms and subsequently control structural damage once RA is established. Prior to clinical onset, CD206⁺CD163⁺CD40^{hi} synovial macrophage populations and IL1B⁺CCL20⁺ and SPPI⁺MT2A⁺ macrophage clusters, which influence fibroblast responses, are expanded in 'at-risk' joints⁸⁸. In established RA, quantitative histology of synovial

tissues shows that sub-lining CD68⁺ synovial macrophage infiltration is higher in patients with severe bone erosion than in patients with low bone erosion. This infiltration independently predicts destructive progression in the joint, which underscores synovial macrophage function as a driver of erosive disease beyond standard clinical and serological factors^{88,89}.

Another type of myeloid cells are the osteomacs. These cells are located along the bone surface near the remodelling site in mice and humans and are in contact with osteoblast lining cells^{90,91}. CD166⁺ osteomacs are a distinct population of myeloid cells that can differentiate into osteoclasts; however, their role in inflammatory bone loss remains to be determined^{90,91}.

Neutrophils. Neutrophils respond to infectious or inflammatory challenges and have a multitude of functions within the immune system; for example, in conjunction with other innate immune cells, neutrophils have an important role in peripheral trained immunity. Neutrophils present in the bone marrow milieu can regulate osteoclast differentiation through both direct and indirect mechanisms^{92–94}. Neutrophils can release a range of pro-inflammatory mediators, including ROS, MMPs and cytokines such as TNF and IL-1 β ⁹⁵. These factors promote the recruitment and activation of OCPs and lead to the accelerated degradation of the bone matrix.

A subset of TGF β 1⁺CCR5⁺ neutrophils can also regulate the mesenchymal pool, especially in aged mice⁹⁶. Moreover, neutrophil extracellular traps (NETs), which are structures comprising chromatin and antimicrobial proteins, have been linked to the modulation of bone resorption in inflammatory contexts⁹⁷. In one study, NETs induced by the calcium ionophore A23187 were shown to inhibit RANKL-induced bone resorption⁹⁸ but, in another study, NETs stimulated osteoclastogenesis in a TLR4-dependent manner as well as via NET-associated proteins such as histones and neutrophil elastase⁹³. In patients with RA, NET formation is increased in circulating and synovial fluid neutrophils, and TNF and IL-17 can promote NETosis⁹⁹. As NETs externalize citrullinated auto-antigens and immunomodulatory factors, these structures might perpetuate the inflammatory response and thereby indirectly stimulate bone resorption⁹⁹. Thus, the role of neutrophils and NETosis in the regulation of osteoclasts and bone homeostasis in inflammatory conditions remains unclear.

Eosinophils. Eosinophils, which have historically been associated with allergic responses and parasitic infections¹⁰⁰, can also regulate bone homeostasis and modulate inflammatory arthritis. Eosinophils inhibit excessive osteoclast formation and activity through the release of eosinophil peroxidase, which impairs ROS production and MAPK signalling in OCPs¹⁰¹. This suppression of osteoclast activity helps to preserve bone mass in experimental models of arthritis¹⁰². Moreover, different subsets of eosinophils have distinct functions; for instance, regulatory eosinophils exert their effects by releasing anti-inflammatory mediators and cytokines, such as IL-4 and IL-10, which promote the resolution of inflammation and foster a tissue environment conducive to healing¹⁰³. In experimental models of arthritis, regulatory eosinophils actively suppress the progression of disease by inhibiting pro-inflammatory pathways and reducing the recruitment of pathogenic immune cells to the affected joints^{103,104}. The interconnection between eosinophilic asthma and inflammatory bone loss remains a field of investigation since the effect of EETosis, that is, the degranulation of eosinophils, has so far been poorly studied.

Dendritic cells. Dendritic cells are primarily recognized for their role in antigen presentation but have also been shown to contribute to osteoclastogenesis¹⁰⁵. As mentioned previously, dendritic cells can function as OCPs²¹. In specific microenvironmental conditions, such as those present in inflammatory diseases, dendritic cells can undergo a transdifferentiation process towards osteoclasts, thereby contributing to bone resorption²⁵. This process is particularly evident in conditions such as RA, in which the inflammatory milieu is rich in cytokines such as TNF and IL-1 β . These cytokines can promote the differentiation of dendritic cells into osteoclast-like cells upon exposure to RANKL and M-CSF²⁰. Dendritic cell-derived osteoclasts display functional resorptive activity and therefore have a role in pathological bone loss²⁵. In inflammatory conditions, a specific subset of dendritic cells expresses RANKL, which directly promotes osteoclast differentiation from monocyte precursors. Among dendritic cell subsets in the mouse spleen, conventional dendritic cells (cDCs) exhibit the highest osteoclastogenic potential *in vitro*²⁰. In the oc/oc mouse model of osteoporosis, where osteoclasts lack an effective osteoclast resorptive function, cDCs injected into these mice can differentiate into functional osteoclasts²⁶. This differentiation process is mediated by the presence of activated CD4⁺ T cells, which induce RANKL expression in bone marrow stromal cells²⁶. A subset of CD1a⁺ dendritic cells (RANK⁺, CD14⁻, HLA-A^{int}, HLA-B^{int}, HLA-C^{int}, HLA-DR^{int}, CD80^{lo}, CD83^{lo} and CD86^{lo}), which correspond to osteoclasts that differentiate from immature dendritic cells in mice, have been described in the synovium of patients with RA and are located in close proximity to osteoclasts²¹.

Other innate immune cells. Mast cells are another type of innate immune cell that have a role in bone remodelling via the release of histamine, tryptase and cytokines such as IL-6 and TNF. These mediators not only stimulate osteoclast activity but also inhibit osteoblast function. Co-culturing human mast cells with OCPs for 1 week (without the addition of RANKL) led to the development of mature osteoclasts that exhibited bone resorptive activity¹⁰⁶.

The family of innate lymphoid cells (ILCs) includes cytotoxic natural killer cells and cytokine-producing ILCs. Cytokine-producing ILCs are classified into three groups (ILC1, ILC2 and ILC3) based on their effector cytokines and developmental requirements. Natural killer cells, which are part of the ILC1 family, contribute to the inflammatory milieu. The activation of natural killer cells results in the production of IFN γ and TNF, which in turn modulate osteoclastogenesis¹⁰⁷. Although IFN γ can inhibit RANKL signalling¹⁰⁸, chronic IFN γ production, in combination with TNF, is associated with an increased level of bone resorption¹⁰⁷. Moreover, IL-15-activated natural killer cells, but not resting natural killer cells, can kill osteoclasts via a process that is dependent on leukocyte function-related antigen 1 (ref. 109). Evidence from *in vitro* and *in vivo* studies shows that ILC2s can resolve inflammation¹¹⁰ and potentially inhibit the generation of bone-resorbing osteoclasts^{111,112}. ILC2-mediated osteoclast inhibition is associated with the expression of IL-4 and IL-13 and STAT6 activation in myeloid target cells¹¹². In response to IL-1 β and IL-23, ILC3s can produce IL-17 and IL-22, which positions them as the innate counterpart of T_H17 cells. Notably, the expansion of ILC3s in ankylosing spondylitis is driven by pro-inflammatory CX3CR1⁺ mononuclear phagocytes, which can be a pathway of local bone alteration¹¹³. In the context of RA, CCR6⁺ ILC3s are enriched in inflamed joints and produce high levels of IL-17A and IL-22, which increase osteoclast differentiation and function and contribute to inflammation and bone erosion¹¹⁴.

Adaptive immune cells

The adaptive immune system has a considerable role in modulating osteoclastogenesis, particularly T cells and B cells, which can either promote or inhibit the differentiation and function of osteoclasts.

T cells. CD4⁺ T cells, especially the T_H1 and T_H17 cell subsets, are central to this process in inflammatory conditions such as RA. T cells can regulate osteoclastogenesis by upregulating RANKL and IFN γ expression, in LPS-induced bone loss¹¹⁵. A subset of T cells, referred to as osteoclastogenic T cells, has been identified as a rare yet important subset of cells that are involved in aberrant bone resorption. For example, IL-1 β -driven osteoclastogenic regulatory T (T_{reg}) cells accelerate bone erosion in arthritic mice compared with conventional T_{reg} cells. Moreover, T_{reg} cells with a similar phenotype (RANKL^{hi}FOXP3⁺ T cells) have been identified in humans¹¹⁶. In contrast to other T helper cells, osteoclastogenic T helper cells produce minimal IFN γ ; however, they promote local inflammation and stimulate pro-inflammatory cytokines that upregulate RANKL expression on synovial fibroblasts¹¹⁷. T_H17 cells, which produce IL-17, IL-17F, IL-21 and IL-22, can have osteoclastogenic properties and are important in the immune response to extracellular pathogens but they also have a pivotal role in the pathogenesis of RA^{118,119}. IL-17 can induce the expression of RANKL in mesenchymal cells, including osteoblasts and synovial fibroblasts¹²⁰. In addition, T_H17 cells can recruit other immune cells, such as neutrophils and macrophages, to inflamed tissues, which exacerbates local inflammation and enhances the release of ROS, all of which promote bone resorption. Targeting IL-17A with a neutralization antibody in human TNF transgenic mice led to a reduction of local and systemic bone loss, which was dependent on IL-1 β ¹²¹. CX3CR1⁺ inflammatory osteoclasts induce immunogenic CD4 T cell responses by controlling their IL-17 secretion, thus forming a pro-inflammatory feedback loop¹²².

By contrast, conventional T_{reg} cells are important inhibitors of osteoclastogenesis; these cells maintain bone homeostasis and suppress T_H17 cells. Pro-inflammatory mediators, such as TNF, can inhibit the function of CD25^{hi} T_{reg} cells in humans¹²³. T_{reg} cells exert their anti-osteoclastogenic effects via the secretion of anti-inflammatory cytokines such as IL-10 and TGF β . IL-10 inhibits the production of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF, which are key drivers of RANKL expression and osteoclast activation¹²⁴. Co-culturing osteoclasts with CD25⁺ T_{reg} cells from mice resulted in partial inhibition of osteoclasts (this was not observed with CD25⁻ T_{reg} cells), which was achieved via the production of IL-4 and IL-10 (ref. 125). Moreover, T_{reg} cells can affect osteoclasts directly through cell-to-cell contact, which is facilitated by cytotoxic T lymphocyte antigen 4 (CTLA4) on T_{reg} cells binding to CD80 or CD86 on osteoclasts. Indeed, osteoclasts that lack CD80 and CD86 are not inhibited by CTLA4 or T_{reg} cells¹²⁶. Mechanistically, CD80 or CD86 interactions with CTLA4 result in the activation of the enzyme indoleamine 2,3-dioxygenase in OCPs, which leads to the degradation of tryptophan and promotes apoptosis¹²⁶. Osteoclasts can activate FOXP3⁺ CD8 T cells, which in turn inhibit osteoclastogenesis¹²⁷. Through the production of TGF β and other regulatory mediators, T_{reg} cells can inhibit T_H17 cell differentiation and IL-17 production, which reduces the pro-osteoclastogenic signals in the local microenvironment¹²⁸. This antagonistic relationship between T_{reg} cells and T_H17 cells is crucial for maintaining the delicate balance between bone formation and resorption.

B cells. B cells influence osteoclastogenesis not only through the production of RANKL and OPG but also via antibody-mediated

mechanisms that substantially affect osteoclast activity in inflammatory conditions¹²⁹. In RA, auto-antibodies, such as rheumatoid factor and anti-citrullinated protein antibodies (ACPAs), are highly prevalent and have a direct role in modulating the disease pathophysiology and bone erosions via regulating osteoclast activity¹³⁰. ACPAs can bind to citrullinated proteins in the bone and joint microenvironment, forming immune complexes that activate Fc receptors on OCPs and mature osteoclasts. Auto-antibodies against citrullinated vimentin bind to cells of the osteoclast lineage, foster their differentiation into bone-resorbing cells and promote bone loss¹³¹. ACPA auto-antibodies can stimulate FLS migration and joint inflammation, which requires pre-exposure to IL-8. This treatment also led to increased expression of peptidylarginine deiminases, protein citrullination and the activation of PI3K, which contributes to bone erosion¹³². Additionally, ACPA-stimulated immune complexes can amplify local inflammation by recruiting and activating other immune cells, such as macrophages, which release pro-inflammatory cytokines (such as TNF, IL-6 and IL-1 β)³⁸. ACPA regulates TNF production by macrophages via Fc γ receptors in vitro, and this effect is amplified by the presence of IgM rheumatoid factor binding to IgG¹³³.

Beyond ACPAs, rheumatoid factor targeting the Fc portion of IgG contributes to osteoclast-mediated bone erosion by forming immune complexes that stimulate OCPs¹³⁴. The engagement of Fc receptors by these immune complexes triggers osteoclastogenic signalling, including the upregulation of RANKL and pro-inflammatory mediators. Fc γ RI is expressed on osteoclasts and can bind IgG2a antibodies but is not required for osteoclastogenesis. Osteoclast activation via Fc γ RI-IV engagement altered bone homeostasis; notably, Fc γ RIV-deficient mice with an osteoclast-specific deletion had a considerable reduction in the generation of osteoclasts¹³⁴. Intravenous immunoglobulins can trigger resolution of inflammation and inflammatory bone loss by binding to Fc γ RIIb in a C-type lectin and Dectin 1-dependent manner. The binding of intravenous immunoglobulins to inhibitory Fc γ RIIb leads to the reprogramming of osteoclasts in arthritis¹³⁵.

Interestingly, B cells also function as a source of RANKL and cytokines, further promoting osteoclastogenesis in inflammatory environments. RANKL expression is increased on activated CD80⁺CD86⁺ B cells, a subset that is more abundant in patients with RA than in healthy individuals^{136,137}. Bone marrow B cells, which highly express HIF1 α , also show high levels of RANKL production^{138,139}. Similarly, RANKL deletion in B cells leads to increased bone density. A subset of FCRL4⁺ B cells expresses a distinct pattern of cytokines and surface proteins, specifically RANKL and TNF^{140,141}. In aged mice, B cells fail to produce sufficient levels of OPG, which exacerbates the imbalance between bone formation and resorption¹⁴² and could also be of high importance for RA. The actions of B cells through RANKL, as well as their cytokine-mediated or antibody-mediated actions, highlight their multifaceted role in osteoclastogenesis (Table 1).

Effects of non-immune cells on osteoclasts

Non-immune cells, including osteoblasts, fibroblasts and mesenchymal cells, influence osteoclast activity by regulating the production of key osteoclastogenic factors.

Fibroblast-like synoviocytes. In addition to the immune cells that invade the synovium in RA, synovial fibroblasts are also key drivers of inflammatory bone loss. In the joint, FLS are found in the lining and sub-lining layer of the synovial membrane and are essential for the maintenance of tissue integrity by producing extracellular matrix.

During inflammation, invading immune cells, including macrophages and neutrophils, activate FLS to adopt a pro-inflammatory, proliferative and tissue-destructive phenotype^{143,144}. FLS produce high levels of RANKL in the synovial tissue, thereby stimulating osteoclastogenesis and osteoclast activity. RANKL expression in FLS is stimulated by TNF and IL-1 β produced by macrophages, by IL-17 produced by T_H17 cells, and by IL-6, which is mainly produced by FLS themselves¹⁴⁵⁻¹⁴⁷. In addition, activated FLS produce MMPs and aggrecanases that promote cartilage destruction. MMP1, MMP3, MMP9, MMP13 and MMP14 are overexpressed in FLS from patients with RA; MMP3 can function as a relevant biomarker to predict RA disease activity¹⁴⁸. Moreover, blocking MMPs using the synthetic inhibitor FR217840 in a model of arthritis in rats prevented inflammation-induced bone and joint destruction but did not modulate the inflammatory response¹⁴⁹, which highlights the essential role of MMP activation in the pathogenesis of joint destruction in RA. Finally, the inflammatory and hypoxic environment metabolically reprogrammes FLS to use glycolysis as the main pathway for energy production. Blocking glycolysis using itaconate inhibits FLS activation and decreases joint inflammation in a rat model of arthritis¹⁵⁰.

Notably, the advent of single-cell sequencing techniques has yielded important insights into the heterogeneity of FLS. Fibroblast activation protein- α (FAP α)-expressing FLS are crucial for the development of arthritis and inflammation-induced bone loss. Further analyses revealed two distinct populations within this subset of cells, distinguished by high or low expression of THY1. Although FAP α ⁺THY1⁺ 'immune effector' FLS, which are located in the synovial sub-lining, direct the invasion of immune cells and actively participate in the inflammatory process, FAP α ⁺THY1⁺ 'destructive' FLS, located in the synovial lining layer, contribute to bone destruction¹⁴³. Single-cell sequencing analysis of samples from 51 patients with RA identified that THY1⁺HLA-DRA^{hi} sub-lining FLS are expanded over 15-fold in RA and confirmed that they are the main producers of IL-6 (ref. 145). Furthermore, another single-cell sequencing study of synovial samples from patients with RA identified a population of FLS that express podoplanin, THY1, and cadherin 11 and lack CD34 that localizes at the perivascular zone of the inflamed synovium. These cells show all the characteristics of activated, destructive FLS, including a proliferative and invasive phenotype and a high secretion of pro-inflammatory cytokines¹⁴⁴.

Chondrocytes, osteoblasts and osteocytes. Chondrocytes are important for the maintenance of cartilage homeostasis, whereas osteoblasts and osteocytes contribute to bone homeostasis. All three cell types are affected by inflammation and have an impaired matrix-producing function and/or a paucity in their abundance. Increased cell death of osteoblasts, osteoclasts and chondrocytes has been observed upon TNF and IL-1 β stimulation. Although chondrocytes have not been described as an important producer of RANKL, osteoblasts and osteocytes can both increase their expression of RANKL in response to inflammatory stimuli, thereby contributing to osteoclast-mediated bone loss¹⁵¹. Conversely, pro-inflammatory signals, including TNF and IL-6, are potent inhibitors of Wnt signalling, one of the most important bone-anabolic signalling pathways. The expression of several Wnt ligands is modulated in the synovium by inflammation¹⁵². The expression of Wnt inhibitors, such as Dickkopf 1 and sclerostin, is increased in arthritis¹⁵³. Wnt signalling, in turn, regulates the expression of OPG¹⁵⁴. Thus, in states of inflammation, by reducing Wnt signalling, the reduction of OPG further enhances osteoclastogenesis. Finally, the increased expression

of Dickkopf1 in FLS can mediate inflammation-induced angiogenesis. Thus, targeting Dickkopf1 might alleviate several RA-relevant pathologies, including inflammation, bone destruction and angiogenesis¹⁵⁵. In contrast to canonical Wnt signals that are reduced by inflammation, the expression of Wnt5a, a member of the non-canonical pathway, is increased in osteoblasts and FLS in RA. Wnt5a promotes the production of cytokines and chemokines and thus perpetuates the inflammatory response^{156,157}.

Endothelial cells. Similar to FLS, endothelial cells, which form the inner lining of blood vessels, become activated during states of inflammation. Thus, endothelial cells upregulate the expression of adhesion molecules, such as vascular cell adhesion molecule 1 and intercellular adhesion molecule 1, to facilitate the recruitment and adhesion of immune cells into the inflamed synovium^{158,159}. The activation of endothelial cells leads to increased vascular permeability, which enables further immune cell invasion. One of the key angiogenic mediators during inflammation is vascular endothelial growth factor (VEGF), which is induced by hypoxia and cytokines produced by synovial macrophages and fibroblasts¹⁶⁰. Increased levels of VEGF have consistently been found in the synovial tissue of patients with RA and correlate with disease activity^{161,162}. Even though endothelial cells have never been shown to directly target osteoclasts, VEGF induces the expression of RANKL in FLS, thereby indirectly promoting osteoclastogenesis¹⁶³. Targeting the activation of the endothelium has shown promise in controlling disease activity in animal models^{164–166} but has so far not been translated to humans.

Interestingly, mass cytometry of human synovial tissue from patients with RA showed that leukocyte-poor RA samples had a high abundance of endothelial cells, whereas leukocyte-rich RA tissues were characterized by a low abundance of endothelial cells but high abundance of CD4 T cells, CD8 T cells and B cells, suggesting that, at later stages of synovial infiltration, the vasculature might be disrupted¹⁴⁵.

Metabolic regulation of osteoclast function in inflammatory conditions

Cellular metabolism regulates the complex use of fuels for both catabolic and anabolic processes, supporting the production of cellular energy and structural elements. The growing field of immunometabolism demonstrates the crucial role of cellular metabolism in the function and activity of immune cells¹⁶⁷. Metabolic regulation in osteoclasts controls their differentiation and function, particularly under inflammatory conditions in which energy demands are higher than in homeostatic conditions.

OCPs undergo considerable metabolic reprogramming during differentiation to support the energy-intensive processes of bone resorption and matrix degradation, and differentiated osteoclasts rely on increased aerobic glycolysis and glycolysis-derived lactate production¹⁶⁸. The metabolic shift that occurs during osteoclast differentiation is characterized by increased reliance on glycolysis, oxidative phosphorylation and FAO pathways, collectively fuelling the cells to maintain their function, which is interestingly different in male and female mice, depending on the expression of carnitine palmitoyltransferase 1a¹⁶⁹.

Pro-inflammatory cytokines such as TNF, IL-1 and IL-6, which are abundant in inflammatory diseases such as RA, further exacerbate osteoclast metabolic changes. For instance, TNF can enhance glycolytic activity in OCPs by upregulating glucose transporter expression and activating key glycolytic enzymes, which provides the energy required

for differentiation and resorption activity¹⁷⁰. Additionally, inflammatory conditions stimulate mitochondrial biogenesis and oxidative phosphorylation to meet the ATP demands of bone resorption¹⁷¹. This metabolic adaptation is accompanied by an activation of NRF2, which mitigates oxidative stress that is elevated during differentiation and resorption owing to increased ROS production¹⁷². ROS is a known promoter of osteoclastogenesis through the activation of RANKL–RANK signalling pathways¹⁷³. By counteracting ROS, NRF2 not only inhibits excessive osteoclast differentiation but also protects bone tissue from resorptive damage. In RA, systemic and local oxidative stress is pronounced, and the dysfunction or suppression of NRF2 exacerbates osteoclast activity and bone erosions.

Itaconate, a metabolite derived from the tricarboxylic acid cycle intermediate cis-aconitate, also exerts substantial effects on osteoclasts and inflammatory bone loss. Itaconate is synthesized in immune cells by the enzyme immune-responsive gene 1, which is upregulated during inflammation¹⁷⁴. In macrophages, itaconate modulates cellular metabolism and redox balance by inhibiting succinate dehydrogenase, reducing ROS production and activating NRF2 via electrophilic modification of its repressor, KEAP1. Furthermore, itaconate has anti-inflammatory effects that indirectly influence osteoclastogenesis by reducing the production of pro-osteoclastogenic cytokines, such as TNF, IL-1 and IL-6, by macrophages and other immune cells. FAO further complements energy production, with evidence suggesting that FAO supports prolonged osteoclast survival and resorptive capacity under inflammatory conditions. Key metabolic regulators, such as AMP-activated protein kinase, HIF1 α and mammalian target of rapamycin (mTOR), orchestrate these pathways, integrating signals from pro-inflammatory cytokines and growth factors¹⁷⁵. In osteoclasts, Acod1 inhibits osteoclast differentiation by decreasing succinate dehydrogenase-dependent production of ROS and Hif1 α -mediated induction of aerobic glycolysis¹⁷⁶.

Serine metabolism is crucial for osteoclast differentiation and activity owing to its role in biosynthetic and redox homeostasis. Serine serves as a substrate for one-carbon metabolism via the folate cycle, which is essential for the synthesis of nucleotides, amino acids and lipids. Additionally, serine metabolism supports the generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH), a critical cofactor for maintaining redox balance and fuelling lipid synthesis that is required for membrane expansion in OCPs¹⁷⁷. In inflammatory conditions, increased demand for serine metabolism is observed, as pro-inflammatory cytokines, such as TNF and IL-6, stimulate the metabolic pathways that rely on serine. These metabolic shifts not only support the differentiation of osteoclasts but also sustain their high resorptive activity¹⁷⁸. The serine synthesis pathway-derived α -ketoglutarate controls histone demethylases, which eliminate the repressive marks in the NFATc1 locus, thereby regulating osteoclastogenesis¹⁷⁹.

L-arginine is a semi-essential amino acid that has anti-inflammatory effects on macrophages, particularly through its involvement in nitric oxide production and polyamine synthesis. L-arginine inhibits osteoclast function. Arginine restriction enhances outcomes in various mouse models of arthritis by inducing metabolic quiescence in pre-osteoclasts. This state is linked to disrupted tricarboxylic acid cycle activity and altered metabolite production. Notably, the effects of arginine deprivation on osteoclastogenesis occur independently of mTORC1 activity or broad transcriptional and translational suppression¹⁸⁰. L-arginine effectively suppressed arthritis and bone loss across three different arthritis models, directly inhibiting TNF-induced

osteoclastogenesis in both mouse and human cells. RNA sequencing and mass spectrometry analyses revealed that L-arginine shifted metabolic pathways from glycolysis to oxidative phosphorylation in inflammatory osteoclasts, resulting in enhanced ATP production, increased purine metabolism, and elevated levels of inosine and hypoxanthine. The conversion of L-arginine into nitric oxide by inducible nitric oxide synthase in OCPs could regulate osteoclasts. Nitric oxide is known to function as a signalling molecule in osteoclastogenesis, with dual effects depending on its concentration and context¹⁸¹, but the link with L-arginine remains unclear in osteoclasts, especially under inflammatory stress.

Box 2 | Targeting metabolic changes in osteoclasts in inflammatory arthritis

Osteoclasts undergo substantial metabolic reprogramming during the process of differentiation and activation, particularly within the inflammatory environment that is characteristic of rheumatoid arthritis. This metabolic rewiring gives rise to selective dependencies that can be therapeutically exploited.

Glycolytic shift

Osteoclasts increase glucose uptake and glycolysis during differentiation. Inflammation further enhances this shift via TNF-induced glucose transporter expression. Pharmacological glycolysis inhibitors (such as 2-deoxy-D-glucose) and itaconate can impair osteoclast function and reduce joint damage in preclinical models of inflammatory arthritis.

Oxidative stress and the NRF2 pathway

Bone resorption generates high levels of reactive oxygen species (ROS). Although ROS promote osteoclastogenesis, excessive oxidative stress is counterbalanced by the nuclear factor erythroid-related factor 2 (NRF2) antioxidant pathway. The efficacy of activators of NRF2, such as dimethyl fumarate, in mitigating inflammatory bone loss has demonstrated substantial promise²⁹².

Serine metabolism

Serine is a crucial fuel for the biosynthesis of both nucleotides and nicotinamide adenine dinucleotide phosphate (NADPH), which are vital for maintaining redox balance and facilitating membrane expansion within osteoclasts. Inhibiting serine synthesis enzymes disrupts osteoclast formation and epigenetic activation of nuclear factor of activated T cells, cytoplasmic 1 (NFATc1). Disrupting serine metabolism through inhibition of enzymes, such as phosphoglycerate dehydrogenase, which catalyses the first step in serine biosynthesis, has been shown to impair osteoclast function and reduce bone resorption¹⁸⁰.

L-arginine and purine pathways

A reduction in the availability of arginine can impede the process of osteoclastogenesis by shifting metabolic flux towards oxidative phosphorylation and altering purine metabolism. Inhibition of inosine and hypoxanthine can reverse this suppressive effect, thereby identifying purine salvage as a metabolic checkpoint in osteoclast regulation²⁹³.

These metabolic adaptations not only sustain osteoclast activity but also present potential therapeutic targets for mitigating inflammatory bone loss (Box 2). Modulating glycolysis, oxidative phosphorylation or FAO pathways could disrupt the metabolic support of osteoclastogenesis, thereby reducing bone resorption in conditions such as RA.

Periarticular bone loss in RA

Periarticular bone loss is a distinct skeletal phenotype of RA and is a gradient of demineralization that occurs adjacent to but not necessarily contiguous with synovitis. This gradient is most conspicuous around the metacarpophalangeal and proximal interphalangeal joints. Periarticular bone loss can be detected very early in RA with hand dual-energy X-ray absorptiometry (DXA) and high-resolution peripheral quantitative computed tomography^{182,183}. Although focal osteopenia at these small joint sites rarely results in fragility fractures, it is highly characteristic of RA and helpful in distinguishing it from psoriatic arthritis. This periarticular loss mechanistically reflects an osteoclast-driven process, which can be amplified by RA-related autoimmunity. ACPA-induced bone loss can occur before the onset of clinical arthritis and can directly enhance osteoclast differentiation and activity¹⁸⁴. From a prognostic standpoint, early hand DXA-detected bone mineral density (BMD) loss predicts subsequent radiographic progression independently of conventional disease measures¹⁸⁵. The central role of osteoclasts is further underscored clinically by the reduction in erosion progression with RANKL inhibition by denosumab without a commensurate anti-inflammatory effect. Together, these data suggest that periarticular bone loss and the associated osteoclast biology should be defined targets for early RA trials and disease monitoring.

Skeletal effects of current RA therapies

Current therapies for RA, including DMARDs (such as methotrexate, sulfasalazine, hydroxychloroquine and leflunomide), glucocorticoids and biologic drugs, have a crucial role in reducing inflammation and joint damage, thereby helping to preserve bone health. Biologic drugs have revolutionized RA therapy by directly targeting cytokines that are involved in the pathogenesis of RA. However, despite the potent control of inflammation, bone erosions and systemic osteoporosis might still progress, which highlights the need for more specific anti-osteoporosis drugs, including anti-resorptive drugs (bisphosphonates and denosumab) or bone-anabolic drugs (teriparatide and romosozumab). In the following section, we discuss the effects of current therapies for RA on inflammatory bone loss.

Glucocorticoids

Glucocorticoids are commonly used to treat the acute phase of RA as even small doses alleviate joint swelling and achieve pain relief; however, even the use of small doses of prednisone (5 mg per day or equivalent) for more than 3 months is associated with bone loss¹⁸⁶. Bone loss after glucocorticoid treatment mainly affects trabecular bone sites, and thus substantially increases the risk of vertebral fractures. Even though there is a large heterogeneity of intra-individual glucocorticoid sensitivity, one study showed that prolonged treatment with 10 mg prednisone per day increased the risk of vertebral fractures (17-fold) and hip fractures (sevenfold), which highlights the importance of tapering off glucocorticoids as soon as possible^{187,188}. Glucocorticoid-induced bone loss is characterized by a rapid activation of bone resorption, mainly due to the stimulation of RANKL and inhibition of OPG production by stromal cells and the subsequent activation of osteoclasts^{189,190}. This phase

is followed by a persistent phase of suppressed bone formation that is caused by impaired osteoblast function and an induction of osteoblast and osteocyte apoptosis^{191,192}. The suppression of the anabolic Wnt signalling pathway is one of the key mechanisms of inhibited bone formation by glucocorticoids, which also contributes to the stimulation of osteoclastogenesis via suppressed Wnt-mediated OPG production^{193,194}.

Conventional DMARDs

Among cDMARDs, methotrexate is considered the gold standard drug used in the initial therapy of RA owing to its potent anti-inflammatory actions, low cost and the extensive experience of practitioners with this drug. Methotrexate reduces tissue inflammation and slows down the progression of cartilage and bone erosions. In vitro, methotrexate reduces the expression of RANKL and inhibits osteoclastogenesis by reducing calcium fluxes in OCPs¹⁹⁵. Moreover, treating synovial tissue from patients with RA with methotrexate showed reduced expression of RANK and a lower RANKL-to-OPG ratio at the mRNA and protein level¹⁹⁶. The differentiation of osteoclasts generated from the peripheral blood of patients with RA was inhibited upon methotrexate treatment, which highlights that methotrexate can reduce osteoclastogenesis by modulating RANKL–RANK interactions. Finally, serum RANKL concentrations were reduced after 3 months of methotrexate treatment in patients with RA and correlated with the levels of ACPA and bone erosions¹⁹⁷. In contrast to these studies showing anti-osteoclastogenic effects of methotrexate, a study in young rats treated with methotrexate showed that it reduced trabecular bone mass, bone formation, osteoblast viability and longitudinal bone growth with no effects on biomechanical properties of bone^{198–201}. Another study conducted in young rats showed that the methotrexate-induced inhibition of bone growth and reduction of bone mass is transient, indicating a recovery of growth plate cartilage and trabecular bone mass after 3 weeks of treatment²⁰². Overall, in a clinical setting, methotrexate has minor effects on the bone in patients with RA^{199,203}. Although some studies report lower BMD in patients with RA treated with methotrexate compared with untreated patients, multivariate analyses show that these reductions were due to confounders such as disease activity²⁰⁴. Nonetheless, an increasing number of reports have highlighted that methotrexate can cause osteopathy, characterized by bone pain and stress fractures of the lower extremities, often in close proximity to the knee or ankle joints^{205,206}. Even though these instances are rare, discontinuing methotrexate treatment and initiating bone-anabolic therapies seems to be useful to mitigate methotrexate-induced osteopathy²⁰⁷.

The effects of the cDMARDs sulfasalazine, hydroxychloroquine and leflunomide were also tested on osteoclastogenesis in vitro. Although sulfasalazine and leflunomide inhibited osteoclastogenesis and reduced the expression of RANKL, IL-6 and MMPs on RA FLS, hydroxychloroquine did not alter osteoclast formation or RANKL expression^{208–210}. In a cohort of 30 patients with RA at pre-menopause, sulfasalazine (and methotrexate) did not alter BMD after 12 months of treatment²¹¹. Additionally, leflunomide was not associated with adverse effects on BMD in a study of 40 patients with RA²¹².

Biologic DMARDs

Biologic drugs, such as TNF inhibitors and IL-6 blockers, are important pillars in the treatment of RA and have shown promise in reducing bone erosion and systemic bone loss by suppressing pro-inflammatory cytokines that drive osteoclast activation²¹³. In the following section, the various biologic agents and their effects on bone are discussed.

TNF inhibitors. Anti-TNF antibodies were the first biologic agents used in the treatment of RA and remain the most used in clinical practice. Besides their potent effect in reducing inflammation and controlling disease activity, TNF blockers also slow down bone erosions and loss of BMD. A study of infliximab has shown that, after a 1-year treatment period, both people who responded to treatment and those who did not were protected from inflammation-induced loss of BMD at the spine and femoral neck²¹⁴. A similar prevention of systemic bone loss by TNF inhibitors has been observed in other studies^{215–218}. In the majority of studies, but not all, reduced levels of serum bone resorption markers were detected in patients with RA who received anti-TNF antibodies²¹⁹. In some studies, increases in bone formation markers were also observed, which suggests a positive effect of TNF inhibition on bone turnover in RA²¹⁶. This observation is in line with studies in mice showing that TNF is a key inducer of Dickkopf 1, a potent inhibitor of the bone-anabolic Wnt signalling pathway¹⁵³. Although initial studies suggested that blocking TNF might not improve metacarpal cortical bone loss^{215,220}, refined imaging techniques highlighted that TNF inhibition using various agents does halt the progression of bone erosions compared with methotrexate treatment alone, with or without clinical response^{221–223}. Moreover, in various experimental models of arthritis, TNF blockade prevented inflammation-induced bone loss^{79,224}. Interestingly, when investigating fractures, two studies that used either population-based health registries in Denmark or a retrospective analyses of four large administrative databases showed no benefit of using bDMARDs (infliximab, adalimumab, etanercept, certolizumab, golimumab, abatacept, tocilizumab, rituximab and anakinra) versus cDMARDs (methotrexate, sulfasalazine, hydroxychloroquine and leflunomide) or anti-TNF antibodies versus cDMARDs in reducing the risk of fragility fractures in patients with RA^{225–227}. However, two other large observational studies with over 11,000 and 8,000 patients with RA, respectively, showed a reduction in vertebral fractures or overall fracture risk in those using TNF blockers^{228,229}. However, pooling nine studies together in a meta-analysis again highlighted no protective effect of bDMARDs on fracture risk in patients with RA²³⁰. Taken together, despite the amelioration of generalized bone loss through treatment with anti-TNF antibodies in patients with RA, this observation does not fully translate into a protection from fragility fractures. Thus, other factors, such as bone quality, might have a role in inflammation-induced loss of bone strength that is not prevented by blocking TNF signalling.

IL-6 inhibitors. IL-6 inhibitors are commonly used in the treatment of RA and are highly effective in reducing disease burden and bone erosions^{231,232}. Owing to its pro-osteoclastogenic effects, blocking IL-6 should be a promising strategy to halt inflammatory bone loss. In fact, serum IL-6 levels negatively correlate with the T-score of the hip and spine in patients with RA²³³. Blocking the IL-6 receptor (IL-6R) using tocilizumab was more effective than cDMARDs in reducing disease activity and structural joint damage and achieved higher rates of remission^{234,235}. In a comparative study with TNF inhibitors, tocilizumab was more effective in reducing bone erosions than the TNF blocker adalimumab in combination with methotrexate, as assessed by high-resolution imaging^{234,236}. In a study with 416 patients with RA, those treated with tocilizumab and methotrexate had a marked reduction in serum markers of cartilage turnover and bone resorption and an increase in bone formation markers, indicating a positive effect on bone metabolism when compared with patients treated only with tocilizumab or methotrexate²³⁷. The inhibitory effect of tocilizumab on bone resorption markers was further validated in a study

Table 2 | The effects of rheumatoid arthritis therapies on bone

DMARD	Bone resorption	Bone formation	Bone erosions	BMD	Fractures ^a
Methotrexate	Decreased	Decreased	Unaltered	Unaltered	Not known
Sulfasalazine	Decreased	Unaltered	Not known	Unaltered	Not known
Hydroxychloroquine	Unaltered	Decreased	Not known	Not known	Not known
Leflunomide	Decreased	Decreased	Not known	Unaltered	Not known
TNF inhibitor	Decreased	Increased	Fewer	Stabilized	Reduced
IL-6 receptor inhibitor	Decreased	Increased	Fewer	Stabilized or increased	Reduced
Abatacept	Decreased	Increased	Fewer	Increased at femoral neck	Not known
Rituximab	Decreased	Unaltered	Fewer	Improved at lumbar spine	Not known
JAK inhibitor	Decreased	Increased	Fewer	Stabilized	Down

BMD, bone mineral density; JAK, Janus kinase. ^aCompared with placebo.

with almost 300 patients²³⁸. Blocking IL-6R in mice that overexpress TNF ameliorated bone degradation without improving joint inflammation, which suggests that blocking IL-6 signalling is beneficial for bone independently of inflammation²³⁹. The anti-osteoclastogenic effects and pro-osteogenic effects of IL-6R inhibition were verified in a primate model of arthritis²⁴⁰. These positive effects of tocilizumab on bone metabolism also result in a stabilization of BMD over the course of treatment. Patients with RA treated with tocilizumab and methotrexate showed no change in lumbar spine or hip BMD over 48 weeks or 1 year of treatment^{241–243}. Patients who had osteopenia at baseline even benefited from the tocilizumab treatment and showed an increase in BMD²⁴².

Abatacept. Abatacept, which blocks T cell co-stimulation via CTLA4 blocking, can inhibit osteoclasts *in vitro* and *in vivo* in a dose-dependent manner and prevents bone destruction in a rat model of arthritis²⁴⁴. Pre-clinical studies showed that CTLA4 or abatacept induced the activation of indoleamine 2,3-dioxygenase in OCPs, which promoted osteoclast apoptosis¹²⁶. In patients with RA, abatacept increased the femoral neck BMD (but not BMD at the lumbar spine) after 1 year of treatment compared with patients receiving either TNF or IL-6 blockers²⁴⁵. Moreover, abatacept ameliorated the progression of bone erosions in RA²⁴⁶. This finding has been validated using high-resolution peripheral quantitative CT; 1 year of abatacept treatment slowed down the progression of bone erosions and prevented the formation of new erosions compared with cDMARDs²⁴⁷.

Rituximab. Rituximab, a CD20 monoclonal antibody therapy that targets B cells, was associated with a decrease in osteoclasts in synovial tissue and a decrease in RANKL in the serum of patients with RA^{248,249}. In a small group of patients, rituximab was shown to ameliorate the progression of joint destruction²⁴⁹. Furthermore, patients with RA who were treated with rituximab for 18 months had improved lumbar spine BMD with no change in femoral BMD reported in people who were classified as responding to treatment²⁵⁰. However, as rituximab is often co-administered with steroids and/or methotrexate, larger-scale studies to document the effect of rituximab on systemic bone metabolism are needed.

Targeted DMARDs

JAK inhibitors, such as tofacitinib, have proven to be effective in the treatment of RA²⁵¹. Phase III clinical trials with tofacitinib unequivocally

show that it reduces inflammation and inhibits progression of cartilage and bone damage, either alone or in combination with methotrexate²⁵¹. In a preclinical model of RA, tofacitinib also ameliorated signs of inflammation and osteoclast-mediated bone destruction^{252–254}. However, this anti-osteoclastogenic effect was not a direct effect on osteoclasts but was rather caused by reduced RANKL production by lymphocytes²⁵⁵. This indirect effect of JAK inhibitors on osteoclastogenesis via the modulation of RANKL production was confirmed in another study using healthy and arthritic mice⁷². The bone mass of healthy mice increased when osteoblast differentiation was stimulated via the Wnt signalling pathway. A small study with 30 patients with RA showed that a 1-year treatment period with tofacitinib stabilized BMD and positively influenced bone turnover markers²⁵⁶. A post hoc analysis of pooled clinical trial data in patients with RA showed reduced fracture rates in patients treated with tofacitinib compared with placebo, while the fracture rates were higher compared with TNF inhibitors²⁵⁷ (Table 2).

Anti-osteoporosis therapies that prevent inflammation-induced bone loss

Despite receiving potent pharmacological treatment, patients with RA still have a twofold higher risk for fractures than the general population, which might depend on disease activity, disability, age, previous fracture, BMD and the cumulative dose of glucocorticoids²⁵⁸. Thus, a specific therapy to improve bone mass and reduce fracture risk is essential. Besides encouraging typical lifestyle changes, including (weight-bearing) exercise, a protein-rich diet, and supplementation with calcium and vitamin D, specific drugs are used to either block bone resorption (bisphosphonates and denosumab) or promote bone formation (teriparatide and abaloparatide).

Bisphosphonates

Bisphosphonates are among the most commonly used drugs to treat osteoporosis owing to their potent suppression of osteoclast activity and their cost-effectiveness. As bisphosphonates bind to the hydroxyapatite mineral, they are incorporated into the bone and have long-lasting effects. Oral and intravenous bisphosphonates have been used in the treatment of osteoporosis in patients with RA. Most studies using bisphosphonates, including pamidronate, risedronate, alendronate, neridronate and minodronate, have shown a positive effect on maintaining BMD^{259–262}. Applying finite element modelling on CT scans of patients with RA showed that alendronate can prevent the inflammation-induced loss of bone strength²⁶³. Alendronate is more

effective in protecting against fractures compared with risedronate, probably owing to a more sustained suppression of bone resorption²⁶⁴. Two studies suggest that the use of bisphosphonates with a monthly administration interval (neridronate or minodronate) might result in more pronounced increases in BMD as compared with weekly administration (alendronate or risedronate)²⁶⁰. Zoledronic acid, one of the most potent bisphosphonates, is also effective for the maintenance of BMD in patients with RA and can reduce structural damage and bone erosions^{265,266}. Overall, despite some preclinical studies showing anti-inflammatory effects of bisphosphonates, such as reducing the production of pro-inflammatory cytokines by macrophages, these findings do not translate into improved disease control in patients with RA²⁶⁷. Thus, bisphosphonates need to be used in combination with DMARDs.

Ex vivo peripheral blood mononuclear cell (PBMC) studies demonstrate treatment-specific effects of bisphosphonates. Risedronate reduces circulating OCPs and PBMC-derived osteoclastogenesis after 3 months (with lower RANKL and TNF), whereas alendronate lowers resorption markers earlier (such as C-terminal telopeptide of type I collagen), but OCP numbers only begin to decline after 9–12 months, which implies that initial suppression of mature osteoclasts occurs before OCP suppression. A separate cohort study comparing ibandronate, alendronate and risedronate reports similar patterns. Although these data are not specific to RA, they demonstrate differential effects on human osteoclastogenesis that could be relevant to RA anti-resorptive therapies²⁶⁸.

Denosumab

Denosumab is a neutralizing antibody that targets RANKL. Denosumab is approved for the treatment of post-menopausal osteoporosis, glucocorticoid-induced osteoporosis, and bone metastases in patients with breast and prostate cancer. In patients with RA, denosumab treatment reduced the extent of bone erosions in the hands and metacarpal shaft cortical bone loss as assessed using MRI and radiographic radiogrammetry^{55,269,270}. Furthermore, BMD and bone turnover markers were assessed in a randomized, double-blind, placebo-controlled phase II study of denosumab in patients with RA receiving concurrent glucocorticoids or bisphosphonates. Denosumab reduced bone turnover and increased BMD at the lumbar spine and total hip compared with placebo after 6 and 12 months of treatment²⁷¹. BMD improvement was independent of glucocorticoid use or previous therapy with bisphosphonates. As expected, blocking RANKL did not affect the extent of inflammation or cartilage degradation and did not lead to the development of additional infections when combined with anti-TNF therapies^{272,273}. Although denosumab effectively halted joint damage in patients with RA treated with cDMARDs, the combined use of denosumab and bDMARDs to block bone erosions has not been investigated thus far²⁷⁴.

Teriparatide and abaloparatide

Teriparatide is a recombinant parathyroid hormone (PTH) analogue comprised of the 1–34 N-terminal amino acids of human PTH. Teriparatide is used for the treatment of osteoporosis and is one of the few bone-anabolic drugs available thus far²⁷⁵. For teriparatide to be effective in this context, it must be given intermittently (daily), in contrast to continuous exposure (such as in hyperparathyroidism), which is associated with increased bone resorption and bone loss. In the intermittent application scheme, teriparatide increases bone formation by stimulating the Wnt signalling pathway. The reduction of clinical fractures (vertebral and non-vertebral fractures) with teriparatide was

as effective in patients with RA as in those without RA²⁷⁶. Another study showed that switching from bisphosphonate treatment to teriparatide in patients with RA during an 18-month follow-up period led to better fracture reduction than continuing bisphosphonate treatment²⁷⁷. Bone erosions are not affected by teriparatide treatment, suggesting that the inflammatory microenvironment might negate some of its anabolic actions²⁷⁸. Abaloparatide is a PTH-related peptide analogue used in the treatment of post-menopausal osteoporosis and generates a faster and more substantial increase in BMD than teriparatide²⁷⁹. Thus far, no studies have been published that assess abaloparatide for the treatment of RA.

Romosozumab

Romosozumab is an antibody that targets sclerostin, a potent inhibitor of Wnt signalling. As such, romosozumab increases bone formation and suppresses bone resorption via increasing OPG production, thus leading to a large anabolic window²⁸⁰. During the initial phase of treatment, patients receiving romosozumab show considerable increases in BMD²⁸¹. However, these effects wane, and therefore follow-up therapies are required to maintain this rise in BMD. Currently, romosozumab is used for severe osteoporosis, and some limitations have arisen owing to concerns about its potential to increase cardiovascular events. Nonetheless, romosozumab has been tested in a few studies for the treatment of RA. The use of romosozumab in women in post-menopause with and without RA showed that elevated BMD was reduced in patients with RA compared with those without, which suggests that factors involved in the pathogenesis of RA limit the bone-anabolic effects observed in RA²⁸². However, another study comparing romosozumab to denosumab indicated that the increase in BMD at the lumbar spine was similar after 6 months and even higher after 12 months of treatment in the romosozumab-treated group^{283,284}. Despite initial concerns stemming from preclinical arthritis models showing an exacerbated disease course after inhibition of sclerostin, romosozumab had no effect on disease activity status in patients with RA^{285–287}. Furthermore, this drug effectively increased BMD in patients with RA who also received glucocorticoids^{285,286}.

Future emerging strategies

The treatment of inflammatory bone loss is evolving beyond traditional therapies, with emerging strategies focusing on precision and targeted approaches. Small molecules, gene therapy and nanomedicine are at the forefront of novel interventions aimed at mitigating excessive osteoclast activity and restoring bone homeostasis in conditions such as RA.

Small molecules

Targeted small-molecule inhibitors represent a promising therapeutic approach owing to their ability to modulate key signalling pathways involved in osteoclastogenesis and inflammation²⁸⁸. Molecules are being developed to target metabolic pathways and oxidative stress or prostaglandin synthesis in osteoclasts. For example, inhibitors of glycolysis, FAO and serine biosynthesis can disrupt the metabolic support needed for osteoclast differentiation⁹. Additionally, activators of NRF2, such as dimethyl fumarate and novel electrophilic compounds, hold promise for reducing oxidative stress and inflammatory bone destruction²⁸⁹.

Gene therapy

Gene-editing technologies, such as CRISPR–Cas9, offer the potential to modulate genes that are crucial to osteoclast function and

inflammatory responses. For instance, targeting genes that encode RANK, RANKL or key cytokines (such as TNF and IL-17) in OCPs or immune cells could provide long-lasting relief from inflammatory bone loss. Viral and non-viral vectors are being optimized to deliver these therapeutic genes specifically to inflamed joints or bone tissue, minimizing off-target effects. RNA interference and antisense oligonucleotides²⁹⁰ are also being explored to silence pro-inflammatory or pro-osteoclastogenic genes such as those involved in ROS production or cytokine signalling.

Nanomedicine

Nanotechnology-based therapies offer highly targeted delivery of drugs, genes or therapeutic agents directly to affected bone or joint tissues, enhancing efficacy while minimizing systemic adverse effects. Nanoparticles can be engineered to deliver anti-resorptive agents, such as RANKL inhibitors or cytokine-neutralizing antibodies, specifically to osteoclasts or inflamed tissues. Moreover, nanoparticles loaded with anti-inflammatory agents, such as itaconate derivatives or NRF2 activators, can provide localized suppression of inflammation and oxidative stress. Nanocarriers are also being designed to deliver RNA-based therapeutics or CRISPR constructs, offering precise genetic modulation in inflammatory environments.

Clinical implications and future directions

The integration of these advanced therapies into clinical practice will require addressing challenges such as optimizing delivery systems, ensuring safety and specificity, and managing costs. Combination approaches that integrate small molecules, gene therapy and nanomedicine might offer synergistic benefits, addressing both the local and systemic aspects of inflammatory bone loss. Additionally, personalized medicine, driven by biomarkers that predict disease activity and response to therapy, will be crucial in selecting the most appropriate treatment for individual patients. As these novel strategies progress through preclinical and clinical trials, they hold the potential to revolutionize the management of inflammatory arthritis, offering more effective and targeted treatments with fewer adverse effects to more successfully treat both inflammation and bone loss simultaneously.

Conclusions

Local and systemic inflammatory bone loss is the result of a complex interplay of various immune cells, resident cells, cytokines, chemokines and metabolites. Initial inflammatory responses and the production of auto-antibodies lead to a vicious cycle of immune cell activation, which eventually leads to the activation of osteoclasts and, thus, to bone resorption; bone repair processes are also inhibited. Various pathways that are crucial for the pathophysiology of RA, such as TNF, IL-6 and JAK signalling, have been therapeutically targeted and show powerful effects on reducing disease burden. Owing to the amelioration of inflammation, many of these drugs have indirect bone-sparing effects; however, in most cases, these are not potent enough to protect patients with RA from systemic bone loss and the increased rate of fractures. Thus, bone-specific treatments that directly and potently target osteoclasts to reduce bone loss and fracture risk are needed. Future research is required to better understand the inflammatory mechanisms that lead to osteoclast activation. A deeper knowledge of the processes within the osteoclast that lead to prolonged activation and survival will give rise to useful targets for future therapies. Moreover, emerging therapies, including gene therapy and nanomedicine, might result in more refined treatment strategies to suppress

inflammation and reduce bone loss and to minimize adverse effects. Finally, optimization of treatment regimens and evaluation of long-term outcomes are necessary to prevent or slow down inflammation-induced bone loss.

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WHO benchmarks for equitable hip-fracture care and osteoporosis treatment in older people

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Abstract

Hip fractures cause major morbidity, mortality and long-term disability among older persons worldwide. The World Health Organization has defined two key indicators within the framework of the UN Decade of Healthy Ageing to measure health system performance in providing care for older adults with hip fractures: the proportion who receive surgery within 48 h of fracture; and the proportion who receive pharmacological treatment for osteoporosis post-fracture. This Perspective article, which describes the clinical importance of these indicators, their amenability for adoption and implications for health equity, is based on findings from audits, guidelines and key literature. Numerous evidence-based solutions – for example, fracture liaison services, orthogeriatric care models and digital tools support hip-fracture management, yet major barriers remain, such as data gaps, system preparedness and pathway variability. New or modified policies developed by national governments, ministries of health and other relevant authorities and tailored to specific geopolitical contexts are urgently needed to enable the implementation of timely surgical care and secondary fracture prevention strategies aligned with the WHO indicators. Improved health information systems to measure performance and to ensure translation to real-world changes in the lives of older people worldwide are of paramount importance.

Sections

Introduction

What gets measured gets done

Indicator 1: timely hip fracture surgery

Indicator 2: pharmacological treatment post-fracture

Moving towards equitable, integrated care for older persons

Conclusions

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Introduction

At the 73rd World Health Assembly in 2020, WHO member states endorsed the Decade of Healthy Ageing (2021–2030), marking an important advance in global efforts to promote longer and healthier lives for people aged 60 years and older, the age group defined by the WHO and United Nations (UN) as ‘older people’. The initiative was subsequently declared the United Nations (UN) Decade of Healthy Ageing (2021–2030) at the 75th session of the UN General Assembly in 2021 (ref. 1). This global initiative reflects an unprecedented political and strategic commitment to reorient health systems to meet the needs of an ageing population. The resolution mandates the WHO to monitor progress across three key milestone years, 2023, 2026 and 2029, by assessing how well countries are advancing across four interconnected action areas: changing how we think, feel, and act towards age and ageing; ensuring that communities foster the abilities of older people; delivering person-centred, integrated care and primary health services that are responsive to older people; and providing access to long-term care for those who need it. To support this mandate, in May 2025 the WHO developed a core set of measurable indicators that enable member states to benchmark their performance, identify equity gaps, and track improvements in the responsiveness of health systems to older people. Progress reporting at each of the three milestone years is intended not only to assess accountability but also to catalyse policy reforms and encourage cross-country learning.

This emphasis on measurable progress is especially critical given the rising burden of age-related conditions, chief among them being osteoporotic fractures, a major threat to the health and independence of older adults worldwide. As the global population of older persons continues to grow, the health economic burden of osteoporotic fractures, particularly hip fractures, is rising exponentially^{2–6}. A hip fracture in an older adult is more than just a broken bone; it is often the tipping point that sets off a cascade of decline, from loss of independence to long stays in care facilities, and even early death⁷. This vulnerability arises in part from the biological relationship between ageing and skeletal fragility: as people age, bone mass and quality deteriorate owing to cumulative imbalances in bone remodelling and hormonal changes, leading to osteoporosis and an increased risk of fragility fractures⁸. Unfortunately, less than one in three older persons with a hip fracture return to their pre-morbid level of function. For many, a hip fracture will be the point of permanent loss of independence⁹. The mortality rate 1 year after hip fracture remains unacceptably high among older persons, with reported rates varying substantially even across high-income settings, ranging from 10.8% in Singapore to 23.8% in New Zealand¹⁰. In settings with fewer resources, the chances of surviving a year after a hip fracture are even lower¹¹. Behind these numbers are real people facing delays in surgery, limited access to rehabilitation and little support to avoid future fractures. Standard management of hip fractures in older adults includes prompt surgical repair, post-operative rehabilitation and pharmacological treatment to prevent future fractures¹². Yet in many settings, these essential components of care remain fragmented or inconsistently delivered, resulting in missed opportunities to restore function, extend life and prevent avoidable suffering.

Fragility fractures are an interesting litmus test for how well (or poorly) the care needs of older people are being addressed. These disparities underscore the need to examine not only clinical care pathways but also broader systemic responses to ageing and fracture prevention. It is in this context that the WHO has included two important indicators in its framework for measuring the progress and impact of the UN Decade of Healthy Ageing¹: the proportion of older persons receiving surgical

treatment for hip fracture within 48 h, and the proportion of older persons receiving pharmacological treatment for osteoporosis after a hip fracture. These indicators effectively capture two important processes in fracture care, namely the acute management phase and the secondary prevention phase, and they provide implementable and measurable metrics for health systems to use as a benchmark for their own performance. The purpose of this Perspective article is to reflect upon the rationale for the selection of these indicators, summarize the evidence that supports the utilization of these measures, assess the operational feasibility of the indicators in an international context, and briefly discuss how implementation at local, national and global levels can be accelerated through coordinated policy, models of care and data systems.

What gets measured gets done

The adage ‘what gets measured gets done’ underpins the WHO’s emphasis on defining clear, meaningful indicators within the UN Decade of Healthy Ageing framework. Selecting the right metrics is critical, not only to track progress but also to drive policy change and accountability. The indicators were formulated through a rigorous consultative process involving global experts, and are grounded in principles of measurability, relevance and equity¹. Although the two indicators discussed here, namely timely hip fracture surgery and post-fracture pharmacological treatment, primarily capture process elements, their real-world utility lies in their ability to reflect outcomes such as survival, recovery and long-term independence. Both are classified as ‘Tier II’ indicators in the WHO framework¹, meaning that they are considered high-priority measures for which data may not yet be consistently available across all countries but are crucial for benchmarking and system transformation.

It is important to note that although these indicators focus specifically on hip-fracture management and secondary prevention, they do not address the equally important area of primary prevention that includes population-based screening, assessment, and pre-fracture treatment of osteoporosis. This area lies beyond the scope of the current article; however, it is worth emphasizing that primary prevention remains an essential pillar in reducing the global burden of osteoporotic fractures⁸.

Indicator 1: timely hip fracture surgery

The WHO Healthy Ageing Framework includes the indicator “Percentage of older people who received surgical treatment for hip fractures within 48 h after admission to the hospital, over the past year”¹. This indicator reflects not only timely access to emergency orthopaedic care but also serves as a tracer for health-system responsiveness, coordination and overall quality of acute care for older persons. The WHO does not specify whether “admission” refers to the time of presentation to hospital (including emergency-department arrival) or to formal inpatient admission to an acute-care ward. Internationally, both definitions are in use: for example, the Australian Institute of Health and Welfare¹³ and the Australian and New Zealand Hip Fracture Registry¹⁴ define the 48-h window from presentation to hospital, whereas the Canadian Institute for Health Information¹⁵ defines it from inpatient admission. Although the WHO does not specify which definition should be applied, this distinction is noted here to acknowledge differing national conventions in interpreting the indicator.

Rationale for inclusion of this indicator

Large population-based and randomized controlled studies have found no significant difference in outcomes when surgery is performed

within 6 h as compared with 24 h after fracture^{16–18}, and mortality and complications do not typically emerge until at least 24 h after fracture. However, there is strong and consistent evidence that surgery delayed beyond 48 h is associated with significantly worse outcomes. Surgical fixation of an osteoporotic fracture within 48 h is associated with decreased mortality at 30 days and 1 year, fewer complications and quicker functional recovery¹⁹. A 2018 systematic review and meta-analysis found that people who underwent surgery within 48 h of a hip fracture had a 20% lower risk of 12-month mortality (risk ratio (RR) 0.80, 95% CI 0.66–0.97)¹⁹. This review incorporated 28 prospective observational studies, encompassing a total of 31,242 people with hip fracture, a robust sample size that enhances confidence in the findings. Although most of the included studies originated from North America and Europe, the review also encompassed data from Asia and Australia, providing broad regional coverage and suggesting that the findings have global relevance across diverse health care systems. A retrospective cohort analysis of data from the American College of Surgery (ACS) National Surgical Quality Improvement Program (NSQIP) database that included 43,071 severely ill people with hip fracture reinforces the evidence that surgery delayed beyond 48 h carries significantly higher complication and mortality rates, particularly among the frailest people²⁰. In this population, hip-fracture surgery performed after 48 h was associated with not only higher complication rates and mortality, but also with higher rates of cerebrovascular accidents (odds ratio (OR) 1.542; CI 1.048–2.269), pneumonia (OR 1.886; CI 1.611–2.209), urinary tract infections (OR 1.546; CI 1.283–1.861), readmission (OR 1.212, CI 1.074–1.366), postoperative length of stay beyond 6 days (OR 1.829, CI 1.670–2.003) and mortality (OR 1.475, CI 1.286–1.693) compared with immediate surgery²⁰. These converging data clearly support the 48-h window as a critical cut-off for timely surgical care, allowing for clinical stabilization while avoiding further avoidable harm.

Delays beyond 48 h have been related to both patient-related characteristics such as the presence of comorbidities as well as to modifiable factors at the health care system level, including limited surgical slots, limited perioperative optimization pathways and inefficient triage to surgery in the emergency department²¹. It is important to note, however, that in the old-old and the oldest-old, terms often used to describe individuals 85–94 years and ≥95 years old, respectively²², comorbidities might require stabilization before surgery, potentially justifying short, medically warranted delays. It is in this setting that orthogeriatric co-management becomes particularly valuable, offering a coordinated approach to balancing timely surgery with necessary medical stabilization. Orthogeriatric co-management entails the collaborative care of people with hip fracture by orthopaedic surgeons and geriatricians throughout the perioperative and early-recovery phases. This integrated approach facilitates medical optimization, delirium prevention, early mobilization and discharge planning and has been shown to enhance perioperative optimization, shorten time to surgery, and improve both functional recovery and survival²³. A 2022 systematic review reported a 28% reduction in-hospital mortality and a 14% reduction in 1-year mortality with early orthogeriatric involvement²⁴. Although several models of orthogeriatric care such as geriatric consultation services, where geriatricians act in an advisory role to the orthopaedic team; geriatric wards, where orthopaedic teams provide input; and integrated care models, where both specialties co-manage patients from admission to discharge exist, and were reviewed in the study, none of them was shown to be superior to the others. However, the consistency of improved outcomes across these

models highlights the critical importance of timely, coordinated medical input during the perioperative period²⁴.

Current national standards and benchmarks for time to hip-fracture surgery

Although the importance of timely surgical intervention in hip fracture care is widely acknowledged, the performance indicators used across health systems continue to vary substantially. A 2025 mixed-methods review identified 241 performance indicators for hip-fracture care²⁵. ‘Time to surgery’ was the most frequently reported indicator, appearing in 83% of the studies included in the review. However, definitions of this indicator varied not only with respect to time thresholds, but also in operational parameters, for example, whether time was counted from the moment of injury, hospital presentation or admission, whether medically unfit patients were excluded and whether the clock stopped for delays due to health optimization. This heterogeneity made it impossible to make meaningful comparisons of the quality of care across institutions and countries²⁵. Several countries have made time to surgery an official indicator in their national standards, and existing national indicators align closely with the WHO’s 48-h benchmark. In the UK, the National Institute for Health and Care Excellence guideline²⁶ and National Hip Fracture Database (NHFD; <https://www.nhfd.co.uk/>) performance indicators define prompt surgery as occurring on the day of or the day after hospital admission (thus prescribing surgery within a time frame of ≤36 h), and Australia’s Hip Fracture Clinical Care Standard²⁷ document states that patients must receive surgery in a timely manner within 36 h. Similar standards exist in Canada¹⁵, New Zealand (<https://anzhfr.org/registry-reports>), Israel²⁸ and Scotland²⁹ and are reported via mandated registries or performance programmes at a national level. These pre-existing benchmarks demonstrate widespread early adoption of timely surgery targets, even before the WHO-endorsed 48-h benchmark was introduced in May 2025. Although these countries are aligned in intent, actual measurement infrastructure and reporting consistency still vary and no country has formally updated its system to explicitly label the indicator as the ‘WHO-endorsed’ measure. Formal integration of the WHO indicator into national monitoring systems across all member states remains a key next step in global harmonization. Alignment efforts are therefore still at a nascent stage, and the WHO Technical Advisory Group encourages member states to consider incorporating these globally standardized indicators to support harmonized tracking, benchmarking, and accountability over the course of the UN Decade of Healthy Ageing¹.

Strategies to improve the timeliness of hip-fracture care

Several system-level strategies have been shown to enhance the timeliness and quality of hip-fracture surgery. These strategies include the use of standardized perioperative care pathways, early involvement of orthogeriatric care, the use of clinical checklists and care bundles, and structured documentation and audit systems. Countries such as the UK and Australia have successfully implemented these strategies through national programmes. For instance, the UK NHFD and the Australia and New Zealand Hip Fracture Registry (ANZHFR; <https://anzhfr.org/>) have supported initiatives such as the Best Practice Tariff³⁰ and the Hip Fracture Clinical Care Standard²⁷, respectively. These efforts have helped to improve time to surgery and reduce variation in care through audit, benchmarking and system-level feedback.

In the USA, although there is no national hip fracture registry equivalent to the NHFD or ANZHFR, individual institutions and health

care systems have adopted similar interventions. These interventions include multidisciplinary co-management protocols, enhanced recovery pathways and clinical documentation tools, often tracked through the ACS NSQIP Geriatric Surgery Program³¹ or institutional quality-improvement dashboards³². However, implementation in the USA remains decentralized and variable, lacking the unified national standards seen in the UK or Australia.

It must be noted that, although the WHO's recommendation that hip-fracture surgery be performed within 48 h provides a relevant benchmark for the global community, achieving this standard understandably remains a challenge in many low- and middle-income countries (LMICs). In these settings, delays are quite often compounded by systemic issues: direct out-of-pocket costs for implants, limited availability of surgical theatres, delayed admissions and poor perioperative capacity. A 2025 systematic review of evidence from LMICs reflects this reality, with some studies reporting delays of over 2 weeks between injury and surgery³³.

Transitioning from such 2-week delays to a 2-day window requires a multipronged strategy. Key enablers of this strategy include the development of fracture-care pathways, the formation of multidisciplinary teams that include trauma surgeons, anaesthesiologists, geriatricians, physiotherapists and other relevant professionals to oversee the pathways, implementing protocols that facilitate immediate admission of all older hip-fracture patients at the time of diagnosis, fast-tracking of patients from the emergency department to orthopaedic wards, dedicated orthopaedic trauma lists, perioperative protocols to expedite medical clearance and securing supply chains for timely implant availability. Certain interventions, such as education of care providers, prioritization of people with hip fractures in triage and standardized preoperative assessment forms and so on can be implemented at a relatively low cost and might yield early gains. Education of patients and caregivers on the need for early surgery and system-level audits to identify avoidable delays also contribute to addressing institutional bottlenecks that contribute to treatment delays, such as delayed surgical clearance, limited access to operating theatres, or a lack of clarity about clinical responsibility. Importantly, such efforts will signal a shift in institutional culture – one that recognizes hip-fracture surgery in older adults as a true time-sensitive emergency rather than an elective orthopaedic event.

Thus, although the 48-h threshold might not yet be feasible in all LMIC settings, it remains a critical aspirational benchmark, and one that is achievable with targeted reforms. Efforts should focus on context-specific strategies that will incrementally reduce surgical delays while maintaining safety and equity in care delivery. For instance, at a tertiary teaching hospital in Punjab, India, the implementation of geriatric hip-fracture care protocols led to positive outcomes: 60.5% of older people with femoral-neck fractures had surgery within 24 h of admission, and 99% underwent surgery within 1 week³⁴.

Indicator 2: pharmacological treatment post-fracture

The WHO Healthy Ageing Framework includes the indicator: “Percentage of older people who have experienced a fragility fracture of the hip or the spine, or more than one fracture, treated with anti-osteoporosis medication over the past year”¹. This indicator captures the effectiveness of secondary fracture prevention efforts and reflects the capacity of health systems to deliver continuity of care, evidence-based chronic-disease management, and long-term risk reduction for older adults following a major sentinel event. Although

the WHO document does not clarify whether this term encompasses calcium and vitamin D supplementation, it is generally interpreted in the context of currently available pharmacological treatments for osteoporosis.

Rationale for including this indicator

A prior hip fracture is a powerful predictor of subsequent fragility fractures, with patients at an extremely high and imminent risk of a second fracture if pharmacological treatment for osteoporosis is not initiated to address the underlying skeletal fragility³⁵. Conversely, approximately 50% of individuals presenting with a hip fracture have already had a prior fracture, underscoring missed opportunities for earlier intervention^{36,37}. In the USA, health care costs associated with a second fracture have been shown to be up to three times higher than those incurred for the initial fracture³⁸. Therefore, the first fragility fracture is the prototypical ‘low-hanging fruit’ that represents both a clear, early warning sign and an important opportunity for intervention that can prevent both clinical decline and escalating costs³⁹.

Randomized controlled trials and meta-analyses have shown that anti-osteoporosis therapies significantly reduce the risk of subsequent fractures in individuals with a prior fragility fracture^{40,41}. The results of the HORIZON Recurrent Fracture Trial demonstrated that annual infusion of zoledronic acid, initiated within 90 days of a hip fracture, reduced the risk of new clinical fractures by 35% and lowered all-cause mortality by 28% over a median follow-up of 1.9 years⁴². These results were subsequently supported by a 2017 meta-analysis, which confirmed a 26% reduction in non-vertebral fractures (RR 0.74; 95% CI 0.56–0.98) with zoledronic-acid administration in people with a recent low-trauma fracture⁴¹. Oral bisphosphonates, denosumab and anabolic agents such as teriparatide have all demonstrated efficacy in secondary fracture prevention, with RR reductions ranging from 20% to 50% depending on the agent, fracture site and compliance with therapy^{40,41}.

Current standards and benchmarks for post-fracture pharmacological treatment

Treatment rates after hip fracture vary widely across countries. A 2023 international study that included health care data at the patient level from 19 countries and regions, and that included people aged 50 years and older hospitalized with a hip fracture from 2005 to 2018, revealed that the proportion who received post-fracture pharmacological treatment ranged from as low as 11.5% (95% CI 11.1–11.9%) in Germany to 50.3% (95% CI 50.0–50.7%) in the UK⁴³. These figures highlight the substantial gap between evidence and real-world practice, even in high-income health systems. Currently, very few countries have formally adopted this WHO indicator into national quality frameworks. Nonetheless, uptake of pharmacological treatment is now tracked in several national registries and audits. In England and Wales, the NHFD reported that 50.8% of people presenting with a hip fracture were discharged on anti-osteoporosis medication between 2016 and 2020 (ref. 44). In Canada, publicly accessible data from the Ontario Osteoporosis Strategy indicate that fewer than 20% of patients with a fracture undergo diagnosis or adequate treatment for osteoporosis⁴⁵. Similarly, in Japan, 80% of people with a hip fracture initially go untreated, and medication continuation rates after 1 year are just 20%⁴⁶. These national-level measures underscore both progress and persistent gaps and provide a foundation to benchmark and improve care via secondary-fracture prevention initiatives.

Barriers to post-fracture pharmacological treatment

Despite the strong evidence supporting secondary fracture prevention, multiple barriers continue to impede the initiation of treatment for osteoporosis after hip fracture. Several authoritative international guidelines, including those from the International Osteoporosis Foundation (IOF) and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis¹², the American Association of Clinical Endocrinologists and American College of Endocrinology⁴⁷, the Endocrine Society⁴⁸ and national guidance documents such as those from the UK National Osteoporosis Guidance Group⁴⁹ recommend prompt initiation of pharmacological therapy in people with fragility fractures, particularly hip fractures. These guidelines consistently emphasize the need to treat underlying osteoporosis to reduce the risk of future fractures. However, patients and physicians alike often lack awareness of existing guidelines, and they often underestimate the proven benefits of pharmacological therapy. There may be apprehension regarding adverse effects associated with long-term use of some osteoporosis medicines (such as atypical femur fractures and osteonecrosis of the jaw), cost of medications and confusion about who should initiate treatment, whether it be orthopaedics, rheumatology, endocrinology, geriatrics or primary care⁵⁰. Poor communication between health care providers, limited patient education and fragmented systems of care only add to the inertia⁵¹. Although focused primarily on primary and not secondary prevention of fractures, a systematic review of qualitative studies examining health care providers' views on osteoporosis, falls and fracture risk revealed deeper issues beneath the surface⁵². In addition to the barriers mentioned above, clinicians, particularly general practitioners, expressed frustration with the ambiguity and impracticality of current guidelines. Many found the recommendations ill-suited to the complex reality of managing older people with multiple co-morbidities and long lists of medications. In addition, scepticism existed amongst the providers about whether guidelines reflect real-world practice. The health care providers also expressed that there was a growing disconnect between research findings and the realities of everyday patient care⁵². In LMICs, these issues are compounded by structural limitations to health systems. Barriers such as poor access to specialized care, lack of surgical and rehabilitation services, high out-of-pocket medication costs, and irregular availability of drugs make it even more difficult to deliver consistent, guideline-based osteoporosis management after a fragility fracture⁵³. These multi-level barriers highlight the urgent need for system-wide reforms, improved education for providers, and structured care coordination to close the evidence–practice gap in post-fracture treatment of osteoporosis.

Strategies to improve rates of post-fracture pharmacological treatment

Transitioning from delayed to timely post-fracture treatment is feasible when health systems prioritize strengthening perioperative and rehabilitation infrastructure, public-insurance coverage for essential medications, training of non-specialist providers in osteoporosis care, institutional dashboard tracking and audit feedback as well as patient and caregiver education initiatives.

One evidence-based solution to overcoming the barriers to medical therapy and follow-up post-fracture is through the implementation of fracture liaison services (FLS), that ensure that all eligible patients are identified, assessed and started on appropriate osteoporosis therapy. FLS reduce ambiguity, improve interdisciplinary communication (for example, between emergency, orthopaedic and endocrinology departments), help to tailor decisions to individual patient contexts, and

to embed pharmacological treatment into routine post-fracture workflows, thus reducing the risk that treatment becomes an afterthought (or is simply forgotten). FLS are designed to address specifically the types of organizational and behavioural barriers that have historically impeded the implementation of secondary-fracture prevention. They have repeatedly been shown to improve rates of treatment initiation^{54–56}, to reduce rates of refracture⁵⁷ and refracture costs^{58–61}. FLS assign responsibility for initiating osteoporosis care to a dedicated coordinator or team; in doing so, the ambiguity about who initiates treatment is removed. Concerns about adverse effects and medication costs can be addressed early through structured counselling and coordinated follow-up. Notably, by automating the identification, assessment and initiation of therapy, FLS can help alleviate the burden on individual clinicians and potentially reduce the risk of patients falling through the cracks. In addition, FLS enable treatment decisions to be made through patient-specific assessments, often with input from multiple disciplines, and to apply guidelines in an individualized manner that considers comorbidities, life expectancy and patient preferences^{62,63}. In doing so, they help to close the evidence-to-practice gap and facilitate the feasibility and scalability of secondary-fracture prevention.

FLS can offer a pragmatic approach to strengthening secondary-fracture prevention in LMICs, too. By streamlining care pathways, identifying cost-effective treatment strategies and prioritizing limited resources (such as surgical access and medications) for people at highest risk, FLS can facilitate more sustainable and targeted service delivery. A qualitative study from Malaysia that examined the perspectives of health care professionals on FLS implementation reported widespread support for the model, while also highlighting critical challenges such as limited staff awareness about FLS and their importance, inconsistent coordination and the absence of dedicated coordinator roles and multidisciplinary training⁶⁴. Similarly, a commentary from India described a structured, low-cost, multidisciplinary FLS model, but underscored systemic barriers including fragmented follow-up mechanisms and low adherence to medications⁶⁵. A prospective study in rural Taiwan that evaluated the clinical impact of FLS implementation observed meaningful improvements in length of stay in hospital and in the proportion of people with hip fracture who underwent surgery within 48 h of admission⁶⁶. Subgroup analysis of the FLS cohort in this study further revealed that those who received anti-osteoporotic treatment had significantly decreased mortality and 30-day readmission rates compared with those who did not⁶⁶, reinforcing the feasibility and value of FLS implementation even in resource-constrained environments.

Global initiatives to reduce secondary fracture

Capture the Fracture (CtF; <https://www.capturethefracture.org/>), a global initiative developed by the IOF, the world's largest non-governmental organization dedicated to musculoskeletal health, seeks to prevent secondary fractures through the integration of FLS into health care systems. As of June 2025, >1,180 FLS from 62 countries have been registered with CtF and evaluated against its internationally endorsed Best Practice Framework for quality of care. The CtF programme is supported by a global network of clinical experts and national societies and thus is uniquely positioned to standardize the identification, investigation and initiation of pharmacological treatment for people with fragility fractures. With its globally endorsed benchmarking framework, practical implementation tools and widespread adoption, the CtF programme is expected to help

transform often fragmented responses to osteoporotic fractures into a coordinated, preventive care pathway.

The CtF programme supports providers seeking to establish and scale up the implementation of FLS by offering a suite of practical tools, including the Best Practice Framework for benchmarking, structured implementation toolkits and clinical pathways that are adaptable to local contexts. It facilitates mentorship through a global network of experienced FLS practitioners, enables service improvement via self-assessment audits and feedback mechanisms, and amplifies advocacy efforts by recognizing high-performing sites and promoting national and regional policy engagement. Its benchmarking and quality indicators align closely with the WHO indicator for the percentage of people receiving pharmacological treatment after a hip fracture¹. By translating this global target into clear, auditable actions, such as ensuring timely osteoporosis assessment, initiation of therapy and structured follow-up, the CtF framework functions not only as an implementation guide but also as a practical enforcement mechanism. It helps health systems to move from aspirational commitments to concrete, trackable performance, thereby accelerating real-world adoption of the WHO indicator within national and local service-delivery models.

Regional efforts have further supported the scale-up of secondary fracture prevention, particularly in the Asia–Pacific region. The Asia Pacific Consortium on Osteoporosis⁶⁷ has actively leveraged the CtF framework to harmonize clinical standards and promote the broader uptake of FLS across the region. Although this consortium does not directly implement services, its regional efforts have included the development of tailored educational materials, cross-disciplinary training and an ongoing collaboration with the South Asian Federation of Endocrine Societies to evaluate the cost-effectiveness of FLS models in LMICs in the Asia–Pacific region. In parallel, several providers across the region have adapted the FLS model to local realities, for instance, by embedding FLS coordination into orthopaedic wards, using telehealth to support follow-up and engaging non-physician staff to deliver osteoporosis education and adherence counselling. These adaptations reflect the importance of flexibility in applying the CtF Best Practice Framework within diverse health-system contexts. Complementing these regional efforts, the Fragility Fracture Network, in collaboration with other global and regional organizations such as the IOF, International Geriatric Fracture Society, European Federation of National Associations of Orthopaedics and Traumatology, and European Geriatric Medicine Society, launched a global call to action outlining multidisciplinary strategies to improve acute care, rehabilitation and secondary prevention for people presenting with fragility fractures⁶⁸. Collectively, these initiatives reflect a growing international consensus namely that coordinated, system-wide responses are essential to closing the care gap and reducing the incidence of secondary fractures, even in resource-constrained settings.

Moving towards equitable, integrated care for older persons

Tracking the progress of 194 WHO member countries through clear indicators such as timely hip-fracture surgery and post-fracture treatment of osteoporosis, turns aspiration into accountability, showing where health systems are succeeding, where they are stalling and what must change so that every older person can benefit from the promise of the UN Decade of Healthy Ageing.

Although these indicators were only formally endorsed by WHO in May 2025, as previously mentioned, analogous measures have already

been in use across several countries, particularly those with national fracture registries or post-fracture care programmes. This suggests that the infrastructure for implementation exists in many contexts, even if not yet uniformly aligned with the definitions used in the WHO indicators. Beyond their immediate public-health relevance, the two WHO-recommended indicators, namely timely surgery following a hip fracture and initiation of post-fracture pharmacological treatment, offer valuable insights into how health systems are performing in the delivery of equitable, integrated care to older persons. For instance, these indicators can function as proxies for structural equity: evidence from national hip-fracture registries shows that men, individuals living with dementia and those from rural or socio-economically disadvantaged backgrounds are consistently less likely to receive timely surgical intervention or appropriate secondary-fracture prevention therapy⁶⁹. In this sense, tracking such indicators not only supports clinical benchmarking but also helps to expose the inequalities embedded in many care systems. Moreover, these measures reflect the degree of system integration, that is, the link between emergency triage and surgical scheduling, how effectively multidisciplinary teams coordinate perioperative care and whether discharge planning transitions smoothly into long-term follow-up. They serve as signals of whether a health system is evolving beyond episodic, disease-based responses towards more person-centred, functional, continuous care models. Both indicators provide countries with a way of monitoring how their health systems are adapting to the challenges of population ageing, specifically whether innovations in service delivery promote greater system integration, continuity of care, and person-centred approaches aligned with the ‘healthy ageing’ agenda. Over time, these measures enable jurisdictions to benchmark progress, compare performance across regions and identify outliers or best-practice examples. This capability is especially relevant as many health systems still operate using a disease- or episode-based care model as opposed to a continuity-care- or function-based approach.

Looking ahead, countries can leverage the WHO indicators to transition from aspirational targets to measurable improvements by embedding them into national monitoring systems, aligning care models accordingly and ensuring routine data collection and feedback. Support from global and regional stakeholders including technical assistance, harmonized reporting tools and shared learning platforms will be essential to accelerate progress and close persistent care gaps throughout the UN Decade of Healthy Ageing.

Operationalizing these indicators at scale will probably require national policies that are informed by, and aligned where appropriate, with the WHO-recommended definitions of timely hip-fracture surgery and post-fracture treatment of osteoporosis, alongside coordinated investment in data systems, workforce capacity and service delivery infrastructure. Essential targeted system-level investments include linking hospital performance metrics to national surgical standards, allocating dedicated theatre slots for emergency orthopaedic procedures, strengthening perioperative capacity (for example, anaesthesiology and diagnostics) and improving triage and transfer systems, particularly in facilities where delays are driven by resource constraints and expanding orthogeriatric models of care.

Likewise, national funding is needed to scale up FLS across both tertiary and secondary hospitals. Community-based providers, general practitioners and trained health workers must also be empowered to ensure continuity of treatment after discharge. Addressing affordability through the inclusion of osteoporosis medications that are included on national essential medicines lists would help to ensure

Table 1 | Optimizing timely hip-fracture care barriers and actionable strategies

Event	Potential barriers	Solutions and strategic implementations
ED assessment and triage	Inefficient triage due to lack of clear protocols Inability of ED staff to recognize fragility fractures due to insufficient knowledge Lack of timely access to imaging	Clearly defined protocols for hip fracture triage in ED Fragility fracture recognition training for ED staff Standing orders for imaging if fracture suspected in older fallers Implementation of geriatric triage screening tools Pre-hospital notification systems to trigger hip-fracture care pathways
Surgical team consultation and planning; medical assessment and optimization	Presence of comorbidities that require assessment and stabilization Delays in acquisition of imaging tests Delays in obtaining laboratory results, ECGs or risk clearance Anticoagulation or polypharmacy concerns not addressed Delay in referrals to medical teams for management of comorbidities Delays in orthopaedic consultation No 24/7 orthopaedic team coverage (especially on weekends)	Standardized pre-operative care pathways Automated ED-to-orthopaedics alerts Hip fracture 'fast-track' protocol Multidisciplinary checklists for pre-surgical readiness Standing orders for labs and/or ECGs for suspected hip fractures Early orthogeriatric co-management
Hip-fracture surgery	Limited access to surgical scheduling systems and limited surgical slots Out-of-pocket expenses (especially in LMICs) Lack of theatre prioritization for hip fractures No target time for surgery set as standard (such as ≤48 h)	Dedicated surgical slots and/or teams Clinical checklists and care bundles Time-to-surgery audit benchmarks (e.g. national registry standards) Financial subsidies or bundled payment models Care Coordinator to ensure surgery readiness by 36–48 h
Post-operative care; in-hospital rehabilitative care; osteoporosis assessment and medication initiation	Insufficient inpatient physiotherapy and rehabilitative resources No delirium prevention protocols Osteoporosis not linked as the cause of the fracture Delays or inaccessibility to DXA and specialized labs to check for secondary osteoporosis Concern about starting osteoporosis medications too early after fracture and adverse effects of medicines No clear referral pathway to endocrinology and/or rheumatology No inpatient and/or bedside counselling of patients	Interdisciplinary rounds (physiotherapy, occupational therapy, nursing) Hip Fracture Care pathways with early mobilization targets Delirium screening and prevention protocols Referral to FLS for medication counselling, for treatment recommendations and to facilitate referrals to appropriate departments Standing orders for BMD testing post-fracture (as baseline for therapy monitoring once initiated) Digital health tools with embedded decision support for osteoporosis diagnosis and treatment and tracking of medication initiation
Discharge and outpatient follow-up	No post-discharge continuity of care No communication with primary care provider and no documentation of treatment plan Non-adherence to medications Inconsistent follow-up scheduling	FLS co-ordinator follow-up Discharge summaries with a clear osteoporosis treatment plan Integration with primary-care electronic medical record Telehealth follow-up with pharmacist and/or nurse National patient registries to track medication adherence

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; ED, emergency department; FLS, fracture liaison services; LMICs, low- and middle-income countries.

equitable access. Robust health information and data systems are essential for turning measurement into meaningful action. Linking inpatient and outpatient records enables tracking of treatment initiation after fractures, whereas tools such as digital FLS dashboards, automated alerts and integrated risk assessments can support timely bone mineral density testing and therapy uptake. Strengthening these systems to support real-time tracking of timing of surgery, treatment initiation and follow-up across care settings is critical to transforming indicators from mere reports into drivers of tangible improvements. National registries such as the ANZHF in Australia and New Zealand⁶ and the NHFD in the UK⁷⁰ provide scalable models for integrating such data streams and enabling continuous quality improvement. Ultimately, however, the value of measurement lies not in the data themselves but in their ability to inform action and improve care delivery. Well-designed systems help clinicians to identify care gaps, support hospitals in refining care pathways, and give policymakers an insight into directing resources where they are most needed. In this way, indicators become not just tools for accountability but catalysts for real and lasting change.

A consolidated overview of key system-level barriers and the corresponding strategies across the hip-fracture care continuum is presented in Table 1.

Conclusions

The world is now halfway through the UN Decade of Healthy Ageing (2021–2030). The WHO indicators for hip-fracture surgery within 48 h and initiation of pharmacological treatment of osteoporosis after fracture are more than clinical metrics; they are sentinel measures of a health system's readiness for rapidly ageing populations. Systematic tracking of these indicators allows countries to gauge their transition from reactive, fragmented services to proactive, integrated care models. But measurement alone is insufficient. Achieving meaningful change will require sustained political commitment, investment in workforce and digital infrastructure, and a shift in mindset that treats a fracture not as the end of care but as the starting point for lifelong bone-health management.

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Author contributions

M.C. researched data for the article. M.C., J.A.T., O.B., N.H., R.R. and J.-Y.R. substantially contributed to discussion of the content. M.C. wrote the article. All authors edited/reviewed the manuscript before submission.

Competing interests

The authors declare no competing interests.

Additional information

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 Check for updates

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& **Alan Silman**

In the version of this article initially published, there were mistakes in some confidence intervals listed. In the second paragraph of the “Systemic sclerosis” subsection, in the text now reading “CERR 1.01 (95% CI 0.94–1.08),” CI 0.94–1.08 replaces the original “CI 0.9–41.08.” In the first row of Table 1, “Meta-analysis of 16 studies,” the text now reading “By sex: women CERR 1.03 (95% CI 0.74–1.44)” has been updated from the original “(95% CI 4.54–52.87).” In the second row of Table 1, “Meta-analysis of 19 studies,” the text now reading “By sex: women (OR 2.10; 95% CI 1.24–3.55); men (OR 3.06; 95% CI 1.90–4.91)” replaces the original “By sex: women (CERR 1.03; 95% CI 4.54–52.87; I² 26%); men (CERR 3.02; 95% CI 1.24–7.35; I² 55.3%).” At the end of the “Asbestos” subsection, the sentence now reading “This increased risk of RA was also shown in people exposed to asbestos in a Swedish register-based cohort study (RR 1.1, 95% CI 0.9–1.3)” replaces the original “This increased risk of RA in those exposed to vermiculite mining was also shown in a Swedish register-based cohort study (RR 1.8, 95% CI 0.9–1.3).” The text and table are amended in the HTML and PDF versions of the article.

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