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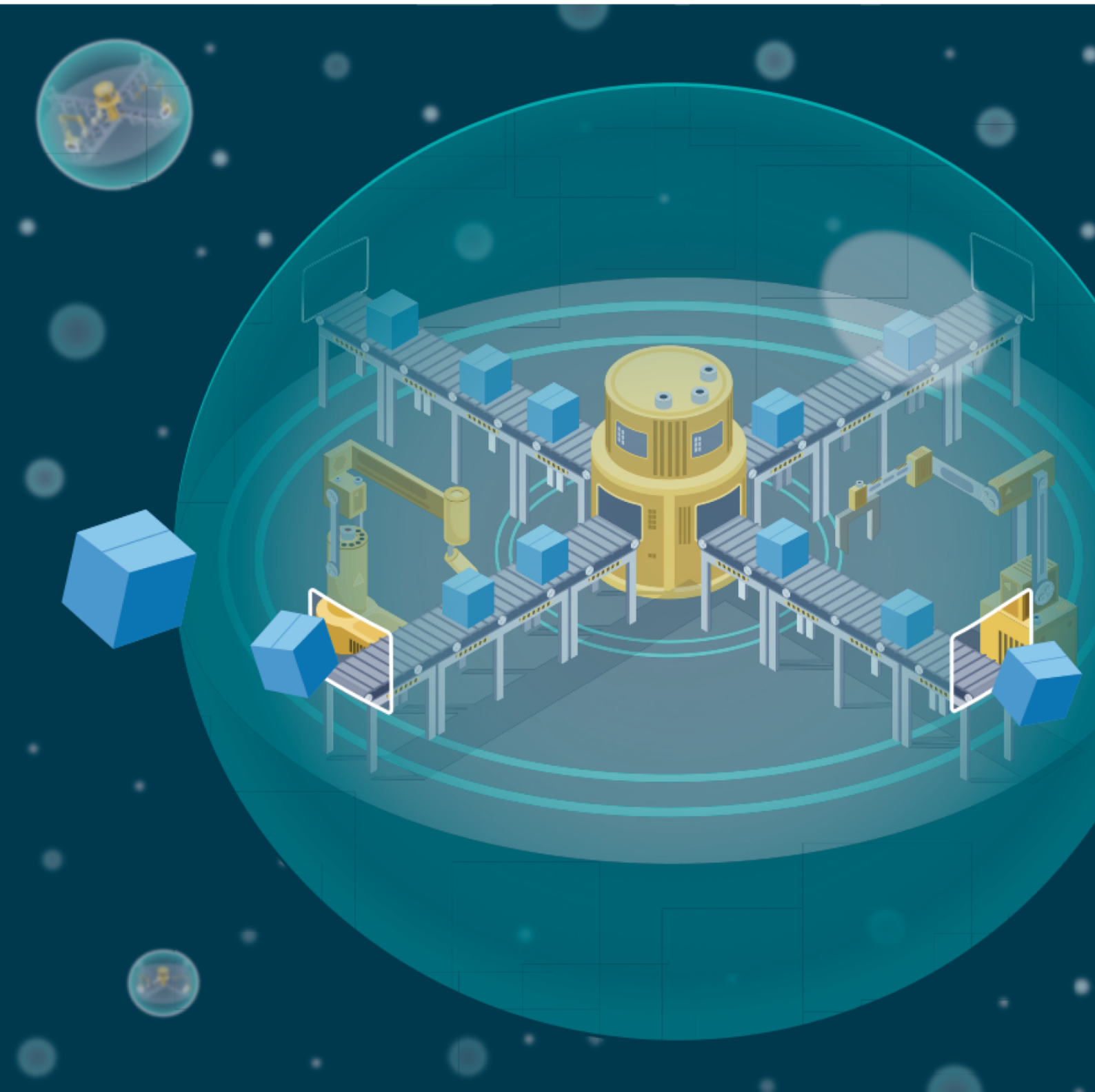

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The future of autologous stem cell transplantation in systemic sclerosis

Charlotte Schimmel & Julia Spierings

Autologous haematopoietic stem cell transplantation revolutionized the treatment of severe systemic sclerosis as the first therapy able to induce long-term remission in this relentlessly fibrosing disease. Nevertheless, questions remain about patient selection, conditioning, and how this treatment fits into the evolving immune-modifying therapeutic landscape. The field should move beyond standardization towards precision therapy.

Systemic sclerosis (SSc) is a heterogeneous autoimmune disorder driven by vascular injury, immune system activation and progressive fibrosis of the skin and internal organs. Over the past two decades, autologous haematopoietic stem cell transplantation (AHSCT) has emerged as the most effective therapy for diffuse cutaneous SSc. Landmark trials, such as the ASTIS and SCOT trials, demonstrated that AHSCT confers substantial survival and quality-of-life benefits over cyclophosphamide-based regimens[1]. Both meta-analyses and real-world data from large cohorts, such as the European Society for Blood and Marrow Transplantation, have confirmed these findings[1,2].

AHSCT enables immune system 'reset' through high-dose immunoablation followed by infusion of autologous haematopoietic progenitor cells, which leads to the reconstitution of a naive, self-tolerant immune repertoire. However, the risk of infection and treatment toxicity is considerably higher in AHSCT than in other immunosuppressive therapies, and treatment-related mortality occurs in up to 10% of patients, owing mainly to cardiopulmonary toxicity and infection[1].

With optimized protocols and careful patient selection, progression-free survival now exceeds 85% at 2 years after treatment. Cardiac screening has substantially improved safety outcomes[3]. As a result, the role of AHSCT has evolved from a last-resort intervention to a strategic therapy for select patients. The challenge has shifted from proving efficacy to refining who, when and how to treat. Considerable efforts have been made towards standardizing patient selection, conditioning and post-transplantation care. Pre-transplantation assessments routinely include 24-hour Holter monitoring, cardiac MRI, right-heart catheterization and pulmonary evaluation to mitigate risk[3]. Patients with advanced interstitial lung disease or considerable cardiac dysfunction are typically excluded, although debate continues about the inclusion of those with cardiac involvement — patients who might be both at higher risk and in greatest need of intervention.

Conditioning regimens strive to balance toxicity with the depth of immunodepletion. Cyclophosphamide combined with anti-thymocyte globulin (ATG), with or without $CD34^+$ cell selection, is most commonly used. Comparative analyses suggest that enrichment for $CD34^+$ cells improves engraftment and immune system reset but might slightly delay reconstitution and incurs greater cost. Reduced-intensity regimens show promising short-term effectiveness, but confirmation of long-term benefits is needed, as relapse rates might be high[3].

Management after transplantation, however, remains heterogeneous. Despite relapse rates being below 15%, some centres administer low-dose mycophenolate or methotrexate as maintenance therapy. From our perspective, the routine use of post-transplantation immunosuppression risks overtreatment and should be avoided. Although the use of such therapies might be warranted in patients with a high risk of relapse, reliable markers for identifying these patients are currently lacking. Efforts in 2025 have aimed to harmonize criteria for response and relapse, which represents an important step towards consistency, but the optimal role of post-transplantation immunosuppression remains undefined[4,5].

Research priorities in optimizing immune reset in AHSCT

Mechanistic studies have increasingly elucidated how AHSCT resets the immune system[6]. Transplantation eradicates autoreactive lymphocytes and regenerates a tolerant immune network, but the innate immune system, the dynamics of immune system reconstitution and the relationship with fibrosis and angiogenesis remain incompletely understood. Furthermore, the occurrence of severe cytokine-release syndrome and infections during and after AHSCT is rather unpredictable. Further research into the immunological repertoire and immune system dynamics will enhance understanding of these processes, guide patient selection and management, and help prevent these complications.

Emerging single-cell and immune repertoire analyses reveal heterogeneous recovery trajectories —some marked by skewed T cell receptor repertoires or functionality and levels of autoantibodies that are predictive of early relapse or poor outcome[6,7]. Comparable progress in biomarker discovery, including transcriptomic signatures and serum cytokine profiles, might further enhance the evaluation of immune system reset quality[6]. Integrating such immunological metrics into clinical monitoring could enable risk-adapted conditioning and post-transplantation management.

In addition, integrated multidimensional data (clinical, genetic and immunological) is needed for the development of predictive models that guide treatment intensity and timing. Adaptive conditioning could tailor chemotherapy and ATG dosing to patient-specific factors such as comorbidities, immune kinetics and pharmacogenomic profiles[8]; for example, ATG dosing based on lymphocyte counts, or testing cytochrome P450 variants that influence cyclophosphamide metabolism and cardiac toxicity risk, offer opportunities for individualizing regimens and reducing complications.

Another research priority is the timing of interventions in SSc. Analyses from the European Society for Blood and Marrow Transplantation

and the Cochrane Library consistently show better outcomes with earlier transplantation[1,2]. Once fixed-organ fibrosis develops, reversibility decreases and transplantation risk rises sharply. Hence, consensus is growing to perform AHSCT within the 'window of reversibility', which is typically within 5 years of disease onset and prior to irreversible cardiopulmonary damage. Prospective validation of timing thresholds remains an urgent knowledge gap and is currently being investigated in the randomized UPSIDE trial[9].

Although AHSCT is increasingly used in severe SSc, the landscape of immunomodulation is rapidly evolving. Conceptually, AHSCT achieves a broad immune system reset, whereas emerging cellular therapies aim for selective immune deletion and modification. Among these, B cell-directed chimeric antigen receptor (CAR) T cell therapy has demonstrated efficacy in the treatment of refractory autoimmune diseases. Given the important role of B cells in SSc and the potential of rituximab, CAR T cell therapy could offer a precision-based strategy for achieving thorough and long-term B cell depletion[10]. Early data from patients with SSc suggest the potential for treating inflammatory manifestations, possibly for those with advanced disease or those who are not eligible for AHSCT. CAR T cell therapy might also be better tolerated than high-dose chemotherapy followed by AHSCT in this population, but more safety data are needed to confirm this observation. Furthermore, cytokine-release syndrome seems to be a frequent adverse event in CAR T cell therapy that requires more investigation. Moreover, the high cost and logistical complexity of manufacturing CAR T cells limits widespread implementation of this therapy.

'Off-the-shelf' therapies, including allogeneic CAR T cells, CAR natural killer cells and induced pluripotent stem cell-derived CAR T cells or generating CAR T cells in vivo, aim to reduce some of these barriers. Other innovations, such as bispecific antibodies (including bispecific T cell engagers), allogeneic mesenchymal stromal cells, CAR regulatory T cells and chimeric autoantibody receptor T cells, are still in the early stages of clinical development but might ultimately expand the therapeutic landscape by offering antifibrotic, immunomodulatory and tolerance-restoring effects in SSc.

Further research needs to be done on the (long-term) efficacy and safety of these emerging cellular therapies in patients with SSc. The most promising path forward will probably combine insights from AHSCT and novel therapies, using immunological profiling and clinical characteristics to identify the patients who will benefit from systemic immune system reboot versus targeted immune cell ablation.

A new vision for AHSCT in SSc

AHSCT remains the benchmark treatment for re-establishing immunotolerance in severe diffuse cutaneous SSc, a uniquely effective therapy proven to halt disease progression and induce sustained remission. Among the available interventions, it stands as the most successful strategy for reversing aggressive autoimmunity and preventing irreversible organ damage.

However, the field now faces a pivotal transition. Although AHSCT has matured into a standardized procedure, the next phase must focus on precision, prediction and personalization. The challenge is to determine which patients will benefit most; those for whom AHSCT should be prioritized early, and those who might instead respond to less intensive approaches such as targeted DMARDs or biologic drugs.

Emerging immunological treatments, including CAR T cells, bispecific T cell engagers and related strategies, are highly promising but remain supported by limited evidence in SSc. Their cost, complexity and early-stage data underscore the need for rigorous comparative studies before their integration into standard care. Determining the right therapeutic sequence — whether AHSCT followed by maintenance or stepwise escalation from biologic to cellular therapy — will shape the next generation of immunological intervention.

Future priorities include refining timing thresholds for transplantation, validating biomarkers that predict immune reset success and rigorously evaluating how novel immunotherapies fit within the evolving therapeutic landscape. By taking these steps forward, AHSCT can evolve from a general intensive therapy into a precisely targeted recalibration of immune system homeostasis.

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Competing interests

The authors declare no competing interests.

Gout

Novel approach mitigates immunogenicity of uricase treatment

Although uricase (urate oxidase) is a potent urate-lowering therapy, its use for the treatment of gout is limited by the formation of anti-drug antibodies (ADAs). Combination therapy with pegloticase and an immunosuppressant can reduce immunogenicity but typically requires frequent dosing and does not reliably prevent ADA formation. Research now published in *Science Advances* shows that in animal models, coadministration of erythrocyte-conjugated uricase with a single dose of cyclophosphamide can effectively treat gout by inducing durable immunotolerance.

"Conjugating uricase to erythrocytes ensures efficient, physiological targeting to the spleen, where splenic myeloid cells capture and process the antigen within a naturally tolerogenic clearance pathway," explains corresponding author Xiaofei Gao.

In the study, coadministration of erythrocyte-conjugated uricase and a single dose of cyclophosphamide was able to prevent ADA formation in mice, even after repeated challenge with mouse erythrocyte–uricase conjugates or free uricase. This effect was not replicated by combination treatment with free uricase plus cyclophosphamide or by treatment with cyclophosphamide alone.

The researchers also showed that the induction of immunotolerance by erythrocyte-conjugated uricase enhances the bioavailability and urate-lowering efficacy of uricase-based therapy in rodent models. Mechanistically, this tolerance induction required splenic uptake of erythrocyte-conjugated uricase, particularly by macrophages, and was associated with the expansion of splenic effector regulatory T cells.

Together, the findings suggest that erythrocyte-conjugated uricase could address a long-standing barrier to the use of uricase for the treatment of uncontrolled gout. The authors also suggest the findings highlight the broader potential of this approach. "Looking ahead, we anticipate that combining erythrocyte-mediated spleen targeting with transient immunosuppression could serve as the basis of a versatile tolerance-induction platform, with potential applications not only in gout but also in autoimmune diseases and immune-related toxicities where durable and selective immune tolerance is urgently needed," Gao notes.

Sarah Onuora

Original article: Nie, X. et al. Single coadministration of erythrocyte-uricase conjugate and immunosuppressant induces durable immune tolerance for gout therapy. *Sci. Adv.* https://doi.org/10.1126/sciadv.aea5196 (2025)

Related article: Schlesinger, N. et al. Mechanisms and rationale for uricase use in patients with gout. *Nat. Rev. Rheumatol.* **19**, 640–649 (2023)

Myositis

Monocyte-driven vasculopathy distinguishes dermatomyositis from CLE

Dermatomyositis is an autoimmune disease in which cutaneous inflammation can be difficult to distinguish from that observed in cutaneous lupus erythematosus (CLE). Although type I interferons contribute to pathology in both diseases, the mechanisms linking skin inflammation to the prominent vascular abnormalities characteristic of dermatomyositis (including nailfold capillary changes) have remained unclear. In a new study, single-cell RNA sequencing provides a cross-disease comparison that offers fresh insight into shared and disease-specific pathways.

The researchers profiled paired lesional and non-lesional skin, alongside matched peripheral blood, and compared these datasets with CLE and healthy skin. The analysis revealed an interferon-rich environment in dermatomyositis marked by enrichment for IL-18 and vascular endothelial growth factor pathways.

Several cell populations were expanded in dermatomyositis relative to their abundance in CLE, including Langerhans cells in non-lesional skin and peripheral helper T cells in lesional skin. Most striking, however, were the endothelial cells, which expressed markers of activation and a pronounced senescence signature in dermatomyositis. The study also uncovered a dermatomyositis-enriched subset of hyperinflammatory $CD14^{+}$ monocytes in both the blood and skin. Ligand–receptor analysis and functional assays indicated that these monocytes promote endothelial cell apoptosis and dysfunction.

Notably, the JAK1 inhibitor upadacitinib reduced monocyte-induced endothelial apoptosis in vitro and decreased endothelial senescence signatures and inflammatory pathway activation in ex vivo-treated dermatomyositis skin samples. These effects were not fully reproduced by inhibition of TWEAK alone, which suggests that broader suppression of JAK1-dependent cytokine signalling is needed to disrupt the pathogenic interactions between monocytes and endothelial cells.

> "the JAK1 inhibitor upadacitinib reduced monocyte-induced endothelial apoptosis"

"Clinically, we have known that JAK inhibition might be helpful for dermatomyositis overall, but now we are tying some specific mechanisms to this improvement," explains J. Michelle Kahlenberg, corresponding author on the study. "We now need to better understand this pro-inflammatory monocyte population and whether it is associated with any particular disease phenotype. Better understanding of vascular–monocyte interactions in dermatomyositis will also be important."

Jessica McHugh

Original article: Osborne, G. A. et al. Dermatomyositis is characterized by JAK1-mediated monocyte-driven vasculopathy and inflammation. *Sci. Transl. Med.* **17**, eaea9007 (2025)

Osteoarthritis

Denosumab targets synovial inflammation to attenuate knee OA

RANKL is a crucial regulator of abnormal bone remodelling in osteoarthritis (OA). In a phase IIa trial, targeting the RANK–RANKL pathway using denosumab was shown to improve erosive hand OA. However, the exact mechanisms through which this drug attenuates OA are unclear. Now, a study in *Nature Communications* provides insight into these mechanisms in the context of knee OA.

The authors first showed that high expression of RANK and RANKL in the synovium, particularly in fibroblast-like synoviocytes (FLSs), is associated with OA in mice and humans. Across three rodent models of OA (post-traumatic, inflammatory and age-related models) denosumab treatment reduced immune cell infiltration and abnormal bone remodelling and improved synovitis and pain. Similar results were also observed when using denosumab to treat knee OA in beagle dogs.

RNA sequencing analysis of whole joints from mice with OA indicated that FLSs were the primary target of denosumab. FLSs produce numerous pro-inflammatory molecules that perpetuate synovial inflammation and denosumab treatment inhibited these responses.

In vitro analyses validated these results: FLSs stimulated with RANKL secreted pro-inflammatory cytokines and extracellular matrix degrading enzymes. Treating chondrocytes and macrophages with media from these FLSs promoted inflammatory phenotypes in both cell types. Treatment with denosumab reversed these effects.

The RNA sequencing data revealed *Fstl1* as the most highly expressed gene in FLSs from mice with OA, and that denosumab downregulated the expression of this gene.

Further research demonstrated that denosumab prevents RANKL from activating the RANK–TRAF6–NF-κB pathway, thereby preventing the expression of FSTL1. Knocking down the expression of TRAF6 or FSTL1 in FLSs in vitro prevented RANK-induced pro-inflammatory effects.

Corresponding author Wei Tong notes that "this research highlights a previously underappreciated, inflammation-targeted action of denosumab in OA, extending its therapeutic rationale beyond bone protection to include direct modulation of the synovial microenvironment."

The authors also conducted a small single-arm clinical trial of denosumab in 9 individuals with knee OA. After 6 months, a single treatment with denosumab improved synovitis, joint function and pain compared with baseline.

"Moving forward, we aim to address the limitations of systemic denosumab administration, such as low joint exposure and systemic adverse effects, while overcoming the challenges of intra-articular injections (such as infection risk, repetitive procedures and poor patient compliance)," comments Tong.

Holly Webster

Original article: Hu, Y. et al. Denosumab attenuates knee osteoarthritis progression by inhibiting synovial inflammation via the RANK/TRAF6/FSTL1 signalling. *Nat. Commun.* **16**, 11394 (2025)

Related article: Wittoek, R. et al. RANKL blockade for erosive hand osteoarthritis: a randomized placebo-controlled phase 2a trial. *Nat. Med.* **30**, 829–836 (2024)

Rheumatoid arthritis

Vagus nerve stimulation shows clinical benefits for RA in pivotal trial

The results of the pivotal RESET-RA trial demonstrate that active stimulation of the vagus nerve using an implantable device offers a safe and effective non-pharmacological option for the treatment of rheumatoid arthritis (RA).

In the trial, a vagus nerve-targeted neuroimmune modulation device was implanted into 242 people with moderately to severely active RA who had an inadequate response or intolerance to treatment with one or more biologic or targeted synthetic DMARD. Participants were randomly assigned to receive active or sham stimulation during a 3-month controlled phase; all patients were then eligible to receive open-label active stimulation through 12 months.

The primary end point of the study was met, as rates of ACR20 response were higher in the active stimulation arm than in the sham arm at 3 months (35.2% versus 24.2%). In the open-label stimulation period, the proportion of responders further increased to 50.0% of all participants at 6 months and 52.8% at 12 months. Moreover, 44.8% of participants achieved a state of low disease activity or remission by DAS28-CRP criteria at 12 months.

As well as decreasing joint inflammation, the vagus nerve-stimulation treatment reduced progression of bone erosions in a subgroup of participants determined to be at high risk for structural damage at baseline. The active stimulation treatment, which was delivered for 1 minute daily, was generally well tolerated, and 78.1% of all participants reported being 'somewhat to very satisfied' with the therapy at 6 months.

Sarah Onuora

Original article: Tesser, J. R. P. et al. Vagus nerve-mediated neuroimmune modulation for rheumatoid arthritis: a pivotal randomized controlled trial. *Nat. Med.* **32**, 369–378 (2026)

Therapy

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Engineered sialylated IgG1 Fc as a dose-sparing alternative to IVIG

Sruthi Vijaya Retnakumar & Jagadeesh Bayry

Intravenous immunoglobulin (IVIG) is a cornerstone of autoimmune disease therapy, but its use is constrained by high costs and limited supply. A sialylated IgG1 Fc variant with enhanced affinity for the inhibitory Fcγ receptor FcγRIIB could offer an effective dose-sparing alternative to IVIG, potentially transforming treatments for autoimmune diseases.

Refers to Jones, A. T. et al. The anti-inflammatory activity of IgG is enhanced by co-engagement of type I and II Fc receptors. *Science* **390**, eadv2927 (2025).

Intravenous immunoglobulin (IVIG) is a preparation of pooled normal IgG derived from the plasma of thousands of healthy donors. IVIG has been a mainstay in clinical practice for several decades, initially introduced as a replacement therapy for people with immunodeficiencies and later widely used — at high doses (1–2 g kg^{-1} body weight) — to treat an array of autoimmune and inflammatory disorders owing to its immunomodulatory and anti-inflammatory effects. Despite its established efficacy, the clinical use of IVIG is challenged by limited supply, high dosing requirements and high costs, prompting efforts to develop effective, affordable and sustainable alternatives to this complex biologic therapy[1,2]. Research now demonstrates that a recombinant sialylated IgG1 Fc variant with enhanced affinity for inhibitory Fcγ receptor IIB (FcγRIIB) effectively treats autoimmune disease models at substantially lower doses than conventional IVIG therapy, while uncovering new mechanisms that drive the anti-inflammatory activity of sialylated Fc[3].

The immunomodulatory activity of IVIG is explained by several mutually non-exclusive mechanisms, targeting many components of the immune system and mediated by its $F(ab')_2$ and Fc fragments[1,2]. Mechanisms proposed to underlie the Fc-mediated action of IVIG include the competitive blockade of activating type I Fc receptors (the canonical FcγRs), which reduces immune complex-driven inflammation; saturation of the neonatal Fc receptor, leading to accelerated clearance of pathogenic autoantibodies; and upregulation of the inhibitory receptor FcγRIIB, which serves to restrain pro-inflammatory responses. Furthermore, experimental studies have demonstrated that terminal sialic acid residues in the IgG Fc domain are crucial[4]. Whereas non-sialylated Fc adopts an open conformation, which makes it accessible to canonical type I FcRs, sialic acid glycans confer a closed Fc conformation that occludes type I FcR binding and instead enables binding to type II FcRs, which are represented by a family of C-type lectin receptors that includes dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) and CD23 (ref. 5). However, the precise contribution of sialylation and the requirement for DC-SIGN in IVIG binding and activity have been debated, and cross-species differences in FcγR expression and affinity for human IgG complicate extrapolation from animal models to human disease[6].

To address these issues, Jones et al.[3] used recombinant sialylated IgG1 Fc fragments (sFc) in FcγR-humanized mice to confirm the role of Fc sialylation and type I FcγR engagement in the anti-inflammatory effects of IVIG. The sFc showed anti-inflammatory activity prophylactically in a serum transfer-induced arthritis model at a 25-fold lower dose than IVIG, whereas non-sialylated Fc or a mutant IgG1 Fc that cannot engage type I FcγRs did not protect mice from arthritis[3] (Fig. 1).

Blockade of activating FcγRs was one of the first theories proposed to explain the therapeutic mechanism of IVIG, especially because high doses of IVIG are required. However, there has not been formal proof-of-concept for this mechanism, and it has subsequently been shown that the inhibitory receptor FcγRIIB is essential for the therapeutic effect of IVIG in several models of autoimmune diseases, which shifted researchers' focus to the modulation of inhibitory signalling as a prevailing mechanism of IVIG therapy[7]. To further explore these ideas, Jones et al.[3] engineered different sFc variants with altered affinity to the inhibitory receptor FcγRIIB or the activating receptor FcγRIIA and investigated whether these variants can protect against inflammation at a lower dose than wild-type sFc. In the serum transfer-induced arthritis model, the V11 sFc variant, which has a higher affinity (~37-fold) than wild-type sFc for FcγRIIB, showed protective efficacy comparable to that of wild-type sFc even at one-tenth the dose, whereas the GA sFc variant, which has a higher affinity (~10-fold) than wild-type sFc for FcγRIIA, was ineffective at this lower dose, indicating that blockade of the activating receptor FcγRIIA was not implicated in the anti-inflammatory actions of sFc. Although removal of sialylated glycans by neuraminidase treatment reduced the efficacy of V11 sFc, mice treated with this variant were nonetheless significantly protected from inflammation, indicating that sFc has sialylation-independent effects. In addition, the researchers demonstrated the protective effect of V11 sFc in a FcγR-humanized mouse model of multiple sclerosis, supporting the broad translational potential of this strategy across multiple autoimmune diseases.

Another key finding from the study is the synergistic cooperation between type I and type II Fc receptors in mediating the anti-inflammatory effects of sFc. The findings demonstrate that DC-SIGN directly interacts with the ectodomains of type I FcRs through a glycan-dependent mechanism, thereby enhancing the binding of sFc to FcγRIIB. This coordinated engagement of FcγRIIB and DC-SIGN underpins the anti-inflammatory activity of sFc and can be further augmented by engineering sFc variants with increased affinity for FcγRIIB[3].

The engineered sFc developed by Jones et al.[3] is an elegant therapeutic approach with the potential for broader application in various autoimmune diseases. In terms of clinical outcomes, the engineered sFc recapitulates the anti-inflammatory effects of IVIG at markedly lower

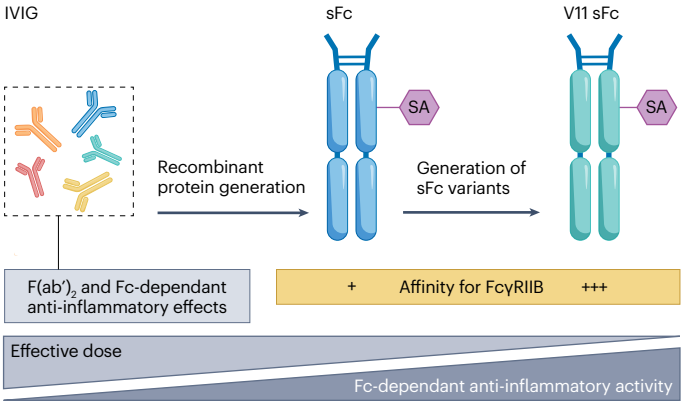

Fig. 1 | Engineered sialylated IgG1 Fc as a dose-sparing alternative to IVIG. Recombinant sialylated IgG1 Fc fragments (sFc), engineered by mutagenesis to have increased affinity for the inhibitory receptor FcγRIIB, reproduce the anti-inflammatory effects of intravenous immunoglobulin (IVIG) at substantially lower doses in FcγR-humanized mouse models of autoimmune diseases. SA, sialic acid.

doses, thus reducing the dependence on large numbers of healthy donors and intricate fractionation procedures and unlocking prospects for scalable and reliable therapeutic production. It is important to note that other Fc-derived molecules, such as an IgG1 Fc hexamer that mimics the action of IVIG, are also in the clinical development[8]. Furthermore, the engineering of monoclonal antibodies to enhance the interaction of Fc with FcγRs or complement proteins is a rapidly evolving area that has already led to several approved treatments for cancer and other diseases, further reinforcing the clinical safety and translational potential of these molecular modifications[9].

Dissection of the mechanisms of action of IVIG in humans and experimental models has revealed several important features. Some mechanisms are mediated by the Fc region, whereas others depend on the $F(ab')_2$ fragments. Notably, certain effects require the presence of intact IgG molecules[1,2]. For example, activation of the autophagy pathway in innate immune cells depends primarily on the $F(ab')_2$ fragments[1]. By contrast, regulation of immune metabolism is mediated by both Fc and $F(ab')_2$ fragments but is dependent on the sialylated glycans of IgG[10]. Together, the evidence indicates that the therapeutic benefits of IVIG do not arise from a single pathway but instead from a set of mutually non-exclusive mechanisms acting together. In this context, it remains uncertain whether recombinant sFc alone can fully reproduce the cellular and molecular actions of IVIG, or how any differences in the molecular mechanisms, regulatory pathways, or target cells might influence long-term clinical outcomes. Addressing these issues will require detailed mechanistic studies, carefully designed clinical trials, and systematic head-to-head comparisons with conventional IVIG across several indications.

In summary, the work by Jones et al.[3] provides strong preclinical evidence that enhancing the affinity of sFc for the inhibitory receptor FcγRIIB substantially enhances its anti-inflammatory effects and offers a potential candidate for clinical development for the treatment of autoimmune diseases. Furthermore, by leveraging the use of FcγR-humanized mouse models, the study sheds clear light on disputed theories regarding the role of various FcγRs and sialylation in the anti-inflammatory effects of IVIG.

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Competing interests

The authors declare no competing interests.

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Review article

Check for updates

The obesity–inflammation axis in psoriatic disease: mechanisms and therapeutic strategies

Rebecca H. Haberman[1], Alexis Ogdie[2], Joseph F. Merola[3,4], Jose U. Scher[1,5] & Lihi Eder[6]

Abstract

Obesity constitutes a substantial burden in psoriatic disease that affects approximately half of patients. Importantly, increased adiposity and psoriatic disease are strongly linked, with obesity functioning as both a possible trigger and a disease modifier. Obesity predisposes individuals to develop psoriasis and is likely to drive, at least partially, the progression from psoriasis to psoriatic arthritis. For people with psoriasis or psoriatic arthritis, obesity is associated with lower rates of remission and poorer responses to treatment. Several mechanisms probably underlie this relationship, including systemic and local pro-inflammatory properties of adipose tissue, increased biomechanical stress on joints and entheses, gut dysbiosis and synergistic effects of osteoarthritis. Notably, weight loss can improve both psoriatic disease course and response to therapy; however, current approaches (such as dietary interventions or bariatric surgery) are difficult to implement. Glucagon-like peptide-1-based therapies are an effective strategy for weight loss in psoriatic disease and might even have additive disease-modifying effects to conventional immunomodulators. Although often overlooked, weight loss intervention and obesity management should be included as an integral part of psoriatic disease treatment algorithms.

Sections

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Key points

- Obesity is a chronic, relapsing disease characterized by excess adipose tissue, which affects up to 50% of individuals with psoriatic disease.
- Obesity and psoriatic disease are probably causally linked. Clinical evidence demonstrates that increased adiposity is associated with higher risk of psoriatic disease development, worse disease severity and decreased therapeutic response.
- Several mechanisms might underlie this relationship, including adipose dysfunction, metaflammation, biomechanical stress, gut dysbiosis, pain amplification and exacerbation of obesity-related comorbidities.
- Weight loss can improve psoriatic disease outcomes. Glucagon-like peptide-1 receptor agonists might have additional anti-inflammatory functions, providing a synergistic effect to existing immunomodulatory therapies.
- Addressing obesity is crucial in the care of individuals with psoriatic disease and weight loss should be systematically integrated into psoriatic disease treatment algorithms.

Introduction

Psoriasis is an inflammatory skin condition that affects 2–3% of people worldwide[1]. Up to one-third of individuals with psoriasis ultimately develop psoriatic arthritis (PsA), a chronic immune-mediated disease characterized by joint and entheseal pain, stiffness and swelling[2]. Together, psoriasis and PsA are often termed psoriatic disease, to acknowledge their overlapping features and shared pathophysiology. Although key cytokines, such as IL-23, IL-17 and TNF, cause the characteristic inflammatory symptoms of psoriatic disease, the underlying drivers of this immune system dysfunction remain largely unknown and are probably multifactorial. Metabolic, genetic, mechanical and microbial factors have all been implicated in the pathogenesis of psoriatic disease[3].

Obesity is a chronic, relapsing, progressive disease, characterized by excess adipose tissue that impairs health[4]. Overweight and obesity are defined as a BMI of 25–30 mg/m^2 and ≥30 mg/m^2, respectively[5]; additional anthropometric measurements, such as waist circumference, might also be considered. Although it cannot explain all of psoriatic disease susceptibility, the association of obesity with psoriatic disease is particularly intriguing. Advances in the understanding of the pathophysiology of adipose tissue dysfunction have identified obesity as a chronic low-grade inflammatory state, with immune system alterations similar to those observed in psoriatic disease. Additionally, unlike other contributors to psoriatic disease susceptibility and outcomes, obesity might be modifiable, particularly with the emergence of effective therapies such as glucagon-like peptide1 (GLP-1)-based therapies.

In this Review, we examine the influence of obesity on the risk of psoriatic disease development and on disease outcomes. We briefly discuss the possible mechanisms underlying the obesity–inflammation axis in psoriatic disease, including metaflammation, biomechanical stress, gut dysbiosis, pain amplification and adipose-related comorbidities. Finally, we explore the effect of weight loss strategies in psoriatic disease, propose a framework for the management of obesity in people with psoriatic disease and highlight existing gaps in knowledge.

Clinical link between psoriatic disease and obesity

Overweight and obesity are among the most common comorbidities in psoriatic disease, reported in up to 70% of individuals with psoriatic disease[6–16]. Individuals with psoriasis are almost two times more likely to have obesity compared with the general population[17,18]. Furthermore, visceral adipose tissue, which is a predictor of cardiovascular adverse events, can be increased in individuals with psoriatic disease compared with those with equivalent BMIs[19]. Importantly, increased adipose tissue functions as both a possible trigger for psoriatic disease development and modifier of disease severity and response to treatment.

Risk of psoriatic disease development

Adiposity increases the likelihood of developing psoriatic disease. In a population-based study, the risk of developing skin psoriasis in people with obesity is nearly double that in people with a normal body weight[20]. Furthermore, the risk of psoriasis increases with BMI in a dose-dependent manner. In the Nurses' Health Study, compared with individuals with normal weight, individuals with overweight had a relative risk of 1.21 for developing psoriasis, which increased to 1.63 and 2.03 in those with a BMI of 30–34.9 mg/m^2 and ≥35 mg/m^2, respectively[21]. Measures of central adiposity and weight gain have also been identified as risk factors for psoriasis, independent of baseline BMI[20–23].

The same pattern is observed in PsA. In a Norwegian population-based study, the relative risk of PsA in individuals with overweight and obesity were 1.4 and 2.5, respectively[24], whereas a US population-based study showed that individuals with a BMI of ≥35 mg/m^2 have a risk of developing PsA more than six times that of individuals with a normal BMI[25]. In individuals with psoriasis, the relative risk of progressing to PsA in individuals with obesity ranges from 1.2 to 2.7 (refs. 26–28). Although weight loss can be associated with reduced risk of progression to PsA[28], higher BMI at 18 years of age was predictive of PsA in a prospective psoriasis cohort[29], indicating that early adiposity might have long-term effects on the risk of psoriatic disease.

Obesity and psoriatic disease severity

Obesity is associated with worse skin psoriasis[30,31]. Individuals with obesity have a 47% higher risk of severe skin involvement than those without obesity[6]. In a Taiwanese study, compared with those with a normal weight, the likelihood (odds ratio) of individuals with obesity having severe psoriasis was 2.7 (ref. 32). A dose-dependent relationship is observed between BMI and the degree of skin involvement; an increase of 0.25 units in Psoriasis Area and Severity Index (PASI) has been reported for each unit increase in BMI[33].

Adiposity is also associated with worse measures of PsA; individuals with obesity are almost 50% less likely than those with a normal BMI to achieve sustained minimal disease activity (MDA)[14]. These individuals are also more likely to have sonographic entheseal abnormalities[34] and, in those with axial spondyloarthritis (axSpA), increased BMI is linked to new bone formation (that is, syndesmophytes and enthesophytes)[35–38]. In addition, individuals with obesity have higher tender joint and enthesitis counts and worse pain, physical function and quality of life compared with those without obesity[39,40].

Obesity and poor response to treatment

The presence of obesity impedes treatment of skin psoriasis[41–44]. In two large cohort studies, a BMI of ≥30 mg/m^2 reduced the likelihood of

achieving a ≥75% improvement in PASI score (PASI75) by 25% compared with a normal BMI[45,46]. This effect, however, might be specific to the therapeutic mechanism of action, as BMI affects response to treatment with TNF and IL-17 inhibitors in psoriasis[46]. Meanwhile, several small, real-world studies have shown that obesity has a minimal effect on psoriasis response to IL-23p19 inhibitors or phosphodiesterase-4 inhibitors[47–51]. Obesity also decreases treatment persistence[41,52,53]. An assessment of drug survival rates of first-course biologic or targeted synthetic DMARDs (bDMARDs or tsDMARDs) in the treatment of patients with psoriasis showed that individuals with a BMI of ≥35 mg/m^2 are more likely to discontinue their medication owing to ineffectiveness, rather than adverse effects, compared with individuals with a normal BMI[54]. In a meta-analysis of 16 cohorts of people with psoriasis, obesity predicted treatment discontinuation with a hazard ratio of 1.2 (ref. 55).

Obesity also reduces the chance of achieving remission after initiation of bDMARDs or tsDMARDs in patients with PsA[56,57]. Across several disease states (inflammatory bowel disease, rheumatoid arthritis, psoriasis, PsA or axSpA), obesity is associated with 60% higher odds of non-response to TNF inhibitors compared with those without obesity[58]. A one unit increase in BMI was associated with a 6.5% increase in the odds of non-response to treatment, further demonstrating a dose–response relationship with BMI[58]. Most, but not all, studies of TNF inhibitors in PsA have shown similar results; obesity reduces the chance of achieving remission by 50%[56,59–61]. It remains unclear if obesity affects all classes of medication. In a large cohort study, individuals with obesity had a ~50% reduction in remission regardless of the mechanism of action of the drug; however, over 90% of the patients were receiving TNF inhibitors, which limits generalizability[57]. Additionally, except for phosphodiesterase-4 inhibitors, which can lead to weight loss, bDMARDs or tsDMARDs do not ameliorate obesity[62,63]. Although treatment with TNF inhibitors might be linked with decreased cardiovascular events, use of these drugs is also associated with mild weight gain[63–65]. Studies assessing the effect of obesity on treatment persistence in PsA have shown mixed results[59,66–68]. This attenuated efficacy of advanced therapies in psoriatic disease might result from immunological and/or pharmacological factors.

Pharmacokinetic factors. Independent of immune effects, obesity alters drug pharmacokinetics. Increased adiposity expands the volume of distribution and might accelerate clearance of monoclonal antibodies, particularly when administered at fixed doses. This change can result in lower serum drug levels and subtherapeutic tissue exposure in individuals with high body mass[69]. Although weight-based dosing of infliximab and dose escalation of ustekinumab in individuals with a body weight of >100 kg offers partial compensation, these strategies might be insufficient. Notably, studies have indicated that BMI is inversely correlated with ustekinumab efficacy, suggesting that adiposity-related factors beyond volume of distribution, such as immune dysregulation, also have a role[70]. Fixed-dose IL-23p19 inhibitors might be similarly affected[71]; pharmacokinetic studies have shown reduced drug levels in individuals with a body weight of >100 kg[72].

Similar to TNF and IL-23 inhibitors, clinical pharmacology data for secukinumab, an IL-17A inhibitor, show lower serum drug levels and diminished response in individuals with a body weight of ≥90 kg, leading to recommendations for increased dosing in this subgroup[73]. Indeed, drug administration every 2 weeks (rather than every 4 weeks) improves outcomes in individuals with obesity. Although dose optimization might mitigate pharmacological challenges, an adjunctive and potentially synergistic strategy is weight reduction. Dietary interventions leading to moderate weight loss enhance response to TNF inhibitors in individuals with obesity and PsA, which offers dual benefits for inflammatory disease control and cardiometabolic health[74].

Immune mechanisms. Several biologic therapies for PsA target key pro-inflammatory cytokines, such as TNF and IL-17, which are elevated in obesity. The 'sink effect' is a pharmacological hypothesis proposed to explain reduced TNF inhibitor efficacy in obesity, whereby increased adipose-derived TNF functions as a reservoir that binds and sequesters therapeutic monoclonal antibodies and thus diminishes their bioavailability at sites of inflammation (such as the synovium and skin)[75]. Additionally, obesity is associated with upregulation of the IL-23–T helper 17 (T_H17) cell pathway, which has a central role in psoriasis and PsA, resulting in worsening of the skin and musculoskeletal inflammation in people with PsA and obesity[76,77]. Adipokine imbalances, including increased leels of leptin and IL-6, can enhance T_H17 cell differentiation and IL-17 production, potentially overwhelming the suppressive capacity of IL-17 inhibitors in individuals with obesity and a heightened baseline pro-inflammatory milieu[76,77].

Mechanisms that link obesity to inflammation in psoriatic disease

Obesity is increasingly recognized as both a causal contributor and a disease modifier in psoriatic disease (Fig. 1). Chronic metabolic inflammation (that is, inflammation that results from metabolically active organs such as adipose tissue, the liver, brain and pancreas) which is termed 'metaflammation'[78,79] and is associated with obesity, creates a systemic, low-grade pro-inflammatory milieu that might lower the threshold for PsA development in genetically or immunologically primed individuals. This state might exacerbate pre-existing synovio-entheseal inflammation through shared immune pathways or trigger musculoskeletal inflammation through biomechanical stress or other mechanisms. Nonetheless, it remains unclear if obesity initiates musculoskeletal inflammation in PsA or instead amplifies pre-existing inflammation that originates at the skin, gut or joint level, thereby promoting chronicity and worsening clinical manifestations. Clarifying this distinction is important, as it might inform the development of preventative strategies aimed at halting the progression of psoriasis to PsA and worsening of PsA phenotype (Fig. 2). Obesity could also influence disease outcomes through other mechanisms. In this section, we review several potential pathways by which obesity modulates psoriatic disease.

Adipose dysfunction and metaflammation in obesity

Obesity is now recognized as a complex, chronic, progressive and relapsing disease, characterized by an excessive accumulation of adipose tissue that adversely impacts health[80]. Although environmental influences, such as dietary habits and physical inactivity have an important role, increasing evidence suggests that genetic and epigenetic factors contribute substantially to the pathogenesis of obesity[81,82]. A defining feature of obesity is the phenotypic remodelling and altered distribution of white adipose tissue (WAT), which underlies many of the associated metabolic alterations, including insulin resistance, systemic inflammation and dyslipidaemia[83].

WAT is a metabolically active endocrine and lipid storage organ that has a pivotal role in energy homeostasis and immune regulation[84]. Obesity arises from sustained energy imbalance, excessive energy intake relative to energy expenditure, leading to triglyceride accumulation

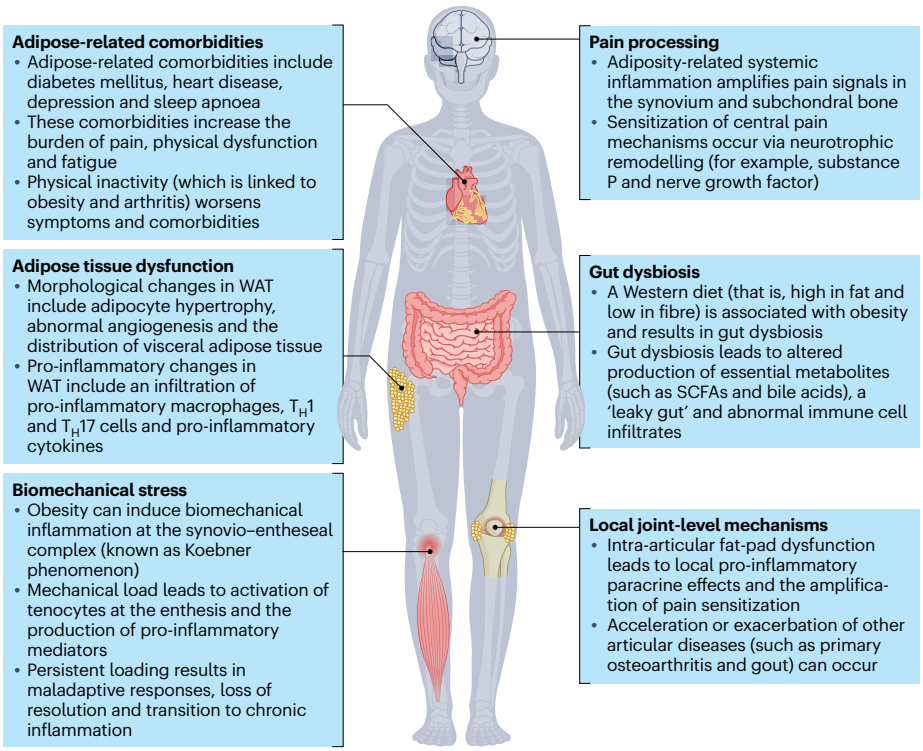

Fig. 1 | Potential mechanistic links between obesity and psoriatic disease. There are several mechanisms by which obesity might affect the onset, severity and symptoms of psoriatic disease, including via adipose-related comorbidities, adipose tissue dysfunction, metaflammation, biomechanical stress, pain processing, gut dysbiosis and local joint-level mechanisms. SCFA, short-chain fatty acids; T_H, T helper; WAT, white adipose tissue.

within adipocytes. With chronic energy surplus, adipose tissue expands beyond its physiological storage capacity, resulting in phenotypic changes in adipose tissue distribution, morphology and function[85].

Adipose tissue dysfunction exerts systemic effects through both metabolic and immunological pathways (Fig. 3). Metabolic consequences include insulin resistance and altered lipid handling. Concurrently, a shift towards metaflammation occurs. This shift is characterized by an infiltration of immune cells, particularly macrophages, which form pro-inflammatory niches that sustain systemic inflammation and contribute to obesity-related comorbidities, including type 2 diabetes mellitus (T2DM), cardiovascular disease and potentially psoriatic disease[83].

Obesity profoundly alters immune system dynamics by promoting the activation of immune pathways relevant to PsA, particularly those involving T_H1 and T_H17 cells and innate immune components[86,87]. In obesity, macrophages become the predominant innate immune cell population in the dysfunctional WAT, comprising up to 50% of this population[88]. These macrophages shift towards a pro-inflammatory phenotype and secrete pro-inflammatory cytokines, such as TNF[89]. Adipocyte death, a hallmark of WAT dysfunction, promotes macrophage recruitment and the formation of crown-like structures[90]. In parallel, adaptive immune cells within the dysfunctional adipose tissue exhibit skewed profiles, with increased T_H1 and T_H17 cell polarization and diminished regulatory T (T_{reg}) cell responses, promoting sustained inflammation[86,87,91]. Adipokines are bioactive molecules secreted by adipocytes that mediate several of these pro-inflammatory effects; for example, leptin, which is elevated in obesity and psoriatic disease, activates the JAK–STAT3 pathway, promotes pro-inflammatory macrophage polarization and drives the differentiation and activation of T_H1 and T_H17 cells, thereby amplifying TNF, IL-1β and IL-6 production[92,93].

Metaflammation in PsA

Clinical and translational studies support the role of metaflammation in modulating PsA risk and severity[27,94]. Individuals with PsA have increased visceral and abdominal adiposity and this adiposity correlates with reduced muscle mass, which correlates with heightened production of pro-inflammatory cytokines and adipokines[95–97]. Mendelian randomization studies have suggested that metabolic disturbances, such as insulin resistance and hypertriglyceridaemia, confer an increased risk of psoriasis and PsA independent of BMI, reinforcing a causal link[98–100]. Moreover, Mendelian randomization analyses support a bidirectional relationship; psoriasis (and possibly PsA) might contribute to increased adiposity and metabolic dysfunction, potentially via inflammation-induced behaviours, such as poor diet quality and reduced exercise, or systemic metabolic changes, such as inflammation-induced glucose intolerance and atherogenic lipid profile, thus establishing a feedforward loop between psoriatic disease and obesity, termed the 'psoriatic march'[101,102].

Findings from animal models of psoriasis underscore the contribution of high-fat diet and metabolic factors to the altered immune state observed in psoriasis. In a high-fat diet mouse model of psoriasis, obese mice exposed to imiquimod developed more severe cutaneous disease and have increased IL-17 responses compared with lean mice[103–105]. Obese mice also show an increase in NLRP3 inflammasome activation, resulting in IL-1β and IL-18 production, which promotes IL-17-producing γδ T cells and worsened skin inflammation[105]. These findings highlight a potential mechanistic link between diet quality, innate immune activation and T_H17 cell-driven pathology in psoriatic disease.

As described previously, adipokines secreted by dysfunctional adipose tissue modulate both immune and metabolic pathways. In psoriatic disease, adipokine profiles shift towards a pro-inflammatory phenotype;

elevated levels of leptin, resistin, and visfatin contribute to T_H1 and T_H17 cell polarization and T_{reg} cell dysfunction[106–109]. An immunohistochemistry study further showed that leptin and its receptor are overexpressed in psoriatic skin, with expression levels correlating with disease severity and duration[110]. Increased leptin levels in PsA, particularly in women, are associated with increased pain and osteoclast precursor activity[111,112], which highlights the potential contribution of this increase to musculoskeletal pathology. Animal models offer additional insights into adipokine function. Leptin-deficient mice, despite being profoundly obese, are protected from developing psoriasis and osteoarthritis, underscoring the pro-inflammatory role of leptin[113,114]. Conversely, the role of adiponectin, an adipokine that is typically anti-inflammatory, remains ambiguous. Despite an inverse association with adiposity, adiponectin levels are paradoxically elevated in PsA and are linked with greater disease activity, suggesting a complex, context-dependent role[107,115].

Intra-articular fat pads, such as the infrapatellar fat pad in the knee, have dual mechanical and immunological roles. In addition to functioning as shock absorbers in joints, they secrete adipokines and cytokines that modulate local inflammation. In osteoarthritis, the infrapatellar fat pad, characterized by immune cell infiltration and activation of nuclear factor-κB (NF-κB) signalling, has been implicated in knee joint inflammation and pain[116,117]. Although analogous data are lacking in PsA, intra-articular adipose tissue depots might also contribute to disease pathogenesis through local paracrine immune–metabolic crosstalk.

Obesity and biomechanical stress in PsA

A compelling mechanistic link between obesity and PsA involves mechano-inflammation at the synovio-entheseal complex. Enthesitis, a hallmark lesion in PsA, is considered the primary site of inflammation[118]. Epidemiological evidence supports the contribution of biomechanical stress to the onset of PsA[119,120]. The term 'deep Koebner phenomenon' was introduced to describe how repetitive microtrauma in the joints and entheses (from, for example, occupational strain) can trigger PsA, highlighting the role of biomechanical stress in disease initiation[121].

Data from both animal and human studies support the role of mechanical strain in entheseal inflammation. Under mechanical load, tenocytes and local mononuclear cells release pro-inflammatory mediators, including IL-1β, CCL2 and CXCL1, and also matrix metalloproteinases. Although these responses are essential for tissue repair, persistent or excessive loading, as observed in obesity, might result in maladaptive responses, loss of resolution and transition to chronic inflammation, which are key features of PsA[122,123].

Importantly, obesity is associated with both increased mechanical load and systemic pro-inflammatory effects, confounding the distinction between mechanical, metabolic and immune-mediated enthesopathies. This overlap presents a diagnostic challenge, as mechanical and inflammatory enthesitis can appear similar on clinical and imaging assessments. Nonetheless, studies consistently show that obesity is associated with entheseal pathology both in individuals with PsA and in those without PsA[34,124,125]. For instance, in a rat model of diet-induced obesity, excessive adiposity impaired enthesis healing after surgery and increased tendon inflammation[126]. In humans, individuals with obesity exhibited a greater burden of sonographic entheseal abnormalities, underscoring the mechanical contribution[124]. Among patients with PsA, BMI correlates with higher ultrasound scores for both active enthesitis and structural changes such as new bone formation[34].

Reducing biomechanical stress, or 'off-loading', might represent a therapeutic strategy for entheseal inflammation. In mouse models, limb suspension to reduce mechanical load attenuated entheseal inflammation and structural damage[127]. These findings, alongside

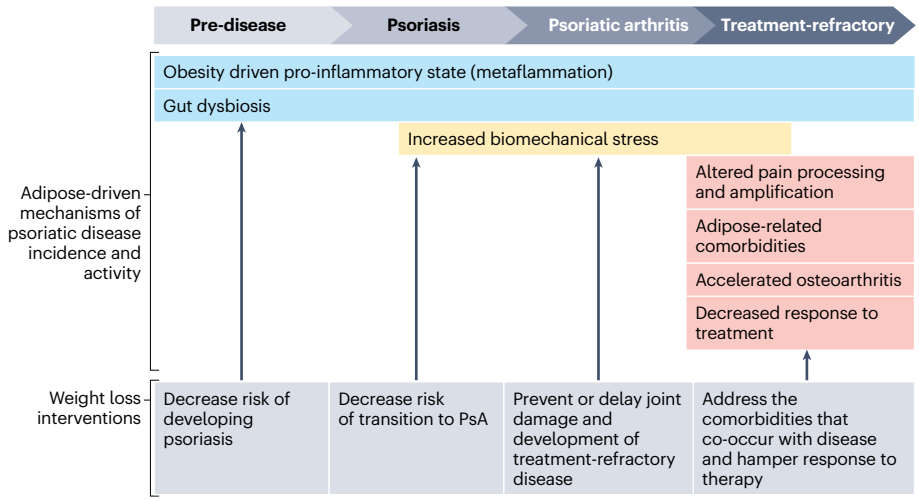

Fig. 2 | Obesity-driven mechanisms across stages of psoriatic disease. Obesity-driven mechanisms probably have a role throughout the continuum of psoriatic disease. The overall pro-inflammatory state, gut dysbiosis and increased biomechanical stress are probably both drivers and modifiers of disease. Obesity-driven changes in pain perceptions, comorbidity burden and response to treatment also function as amplifiers of disease. Given the effect of obesity throughout the disease course, weight loss interventions might be integral in altering the trajectory for patients with psoriatic disease. Prior to disease onset, weight loss can decrease the risk of developing psoriasis and psoriatic arthritis (PsA). Basic and clinical data support a causal relationship between obesity and PsA, which is exemplified by the ability of bariatric surgery to reduce psoriatic disease risk. Early PsA might also present a 'window of opportunity' during which aggressive intervention, including weight loss, might substantially alter long-term outcomes. Lastly, after the development of PsA, weight loss is still vital as it can address and/or reverse altered pain processing and amplification, adipose-related comorbidities (such as fibromyalgia and sleep apnoea), accelerated osteoarthritis and decreased response to therapy. Glucagon-like peptide-1 (GLP-1)-based therapies might be of particular interest as a method for weight loss, along with lifestyle modifications, as preliminary data indicate direct anti-inflammatory and pain-modulating effects.

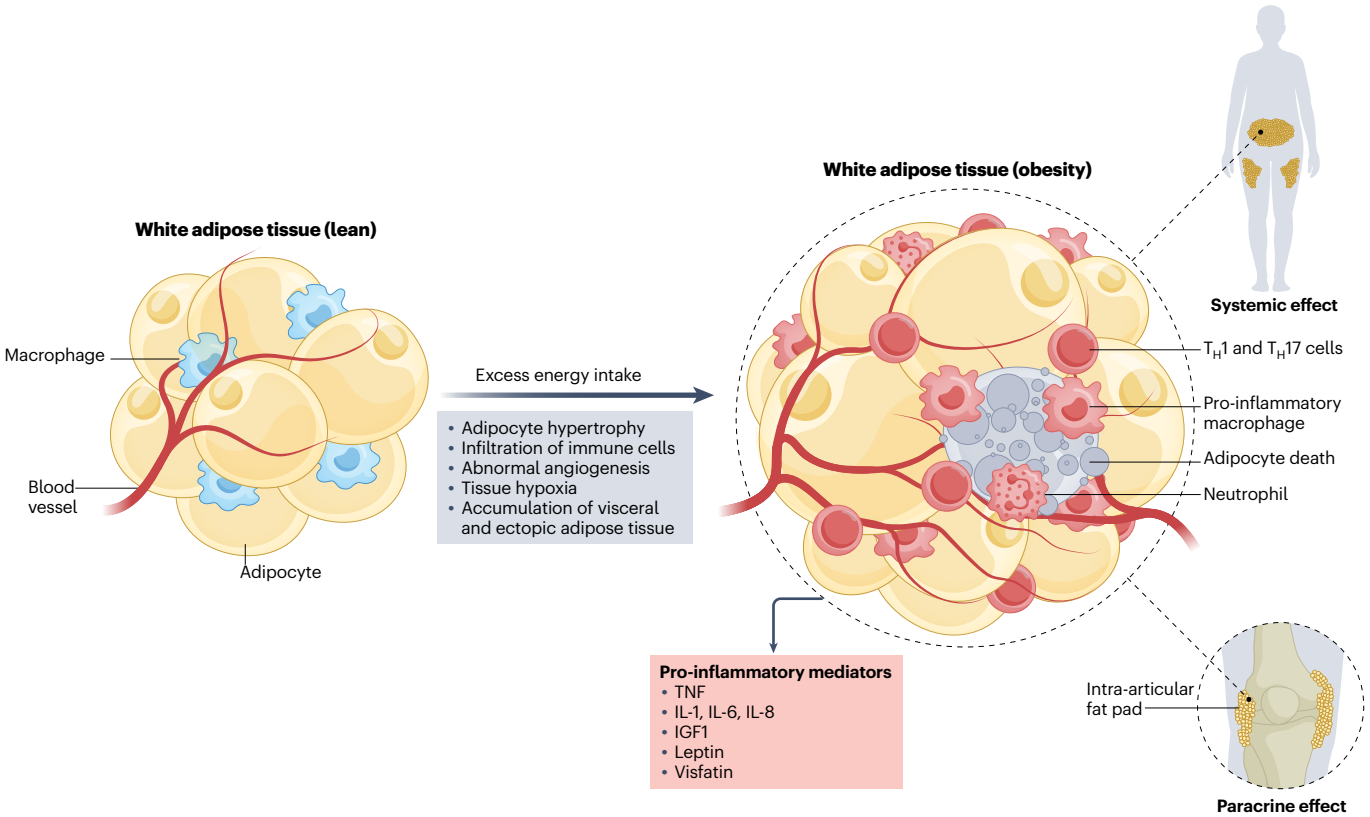

Fig. 3 | Obesity-induced modification of white adipose tissue. Excess energy intake results in the modification of white adipose tissue through adipocyte hypertrophy, infiltration of immune cells, abnormal angiogenesis, tissue hypoxia and the accumulation of visceral and ectopic adipose tissue. These changes promote the activation of T helper 1 (T_H1) and T_H17 cells, skew macrophages towards a pro-inflammatory phenotype and the secretion of pro-inflammatory mediators such as TNF, IL-6, IL-1, IL-8, leptin, visfatin and insulin-like growth factor 1 (IGF1). These effects are exerted both systemically and locally in the joints via paracrine signalling from the intra-articular fat pad.

clinical data that link weight reduction to improvements in PsA outcomes, highlight weight loss as a promising intervention that targets biomechanical drivers of disease.

Gut dysbiosis in obesity and PsA

The gut microbiota has a crucial role in regulating host metabolism, immune homeostasis and barrier function. Abnormal gut microbial composition, termed gut dysbiosis, has been implicated in the pathogenesis of both obesity and PsA[128,129] (Fig. 4).

The key role of the gut microbiota in obesity is shown in germ-free mice that are resistant to diet-induced weight gain, which indicates that specific gut microbial communities promote energy harvest and lipid storage[130]. Similarly, the immunological relevance of gut microbial signals is demonstrated using HLA-B27 transgenic rats, which develop spondyloarthritis only in the presence of intestinal microbiota[131]. Gut dysbiosis is observed in patients with PsA, suggesting a potential role in triggering or perpetuating disease[128,132].

Gut dysbiosis disrupts the production of microbial metabolites and impairs regulatory host–microorganism interactions, which contributes to both metabolic imbalance and immune dysregulation[133]. A central mechanism by which gut dysbiosis might contribute to both obesity and PsA is intestinal barrier dysfunction, commonly referred to as a 'leaky gut'[128,129]. Diets that are high in fat and low in fibre, typically associated with obesity, favour microbial taxa that downregulate epithelial tight junction proteins, thereby increasing intestinal permeability[134,135]. This increased permeability enables translocation of bacteria and microbial components, such as lipopolysaccharide (LPS), into the systemic circulation, a phenomenon termed 'metabolic endotoxaemia'. In obesity, increased levels of circulating LPS activates Toll-like receptor 4 (TLR4) on immune cells, which promotes pro-inflammatory cytokine production and contributes to systemic inflammation and insulin resistance[136,137].

In PsA, microbial translocation might also drive inflammation via activation of pattern recognition receptors and inflammasomes in gut-associated antigen-presenting cells, leading to increased IL-23 production and T_H17 cell expansion[138]. Specific microbial peptides might be presented by disease-associated HLA alleles (such as HLA-B27 or HLA-C06) potentially activating autoreactive T cells[132,139]. Although it remains unclear if systemic T_H17 cell activation in PsA is microbiota-dependent, these mechanisms suggest overlapping pathways with obesity-related metaflammation.

Microbial metabolites might also link gut dysbiosis with PsA and obesity. These metabolites, particularly short-chain fatty acids (SCFAs) and bile acids, function as key mediators of gut–host communication[140]. Diets that are high in fat might alter the gut microbiome by reducing SCFA-producing bacterial taxa; this depletion is also observed in people with PsA[133]. SCFAs, especially butyrate and propionate, have

immunoregulatory effects; they promote T_{reg} cell differentiation and suppress NF-κB-driven inflammation[141]. Thus, reduction of these SCFAs might contribute to loss of immune tolerance in both conditions.

Bile acid metabolites might also mediate the effect of microbial composition on systemic immune–metabolic status. Gut bacteria convert primary bile acids into secondary bile acids, which signal through host receptors (such as farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5)) to regulate lipid metabolism, glucose homeostasis and immune responses[129,138]. Gut dysbiosis alters the bile acid pool in obesity, shifting the profile towards pro-inflammatory species[142,143]. Altered bile acid signatures have been reported in patients with psoriasis and PsA, which were associated with both cutaneous and musculoskeletal disease severity[142,144]. Together, these data suggest that gut microbiota-driven metabolite imbalances that involve SCFAs and bile acids modulate inflammation and metabolism in PsA and obesity.

Although therapeutic strategies that target the microbiome, such as probiotics, prebiotics, dietary interventions and faecal microbiota transplantation, have shown promise in obesity[145,146], results in psoriatic disease remain limited and inconsistent. Trials in psoriasis and PsA using microbiota-modifying approaches have not yet demonstrated robust or durable clinical benefit, probably owing to the complexity and individual variability of host–microbiome interactions[147,148].

In summary, gut dysbiosis constitutes a shared pathophysiological mechanism that links obesity and PsA. By impairing barrier function, altering metabolite profiles (such as SCFAs and bile acids) and promoting IL-23–T_H17 cell immune activation, gut dysbiosis contributes to systemic inflammation and metabolic dysfunction common to both conditions.

Obesity and pain amplification

Individuals with obesity frequently report higher pain sensitivity than those with normal weight[149]. People with PsA who also live with obesity often experience disproportional levels of pain and physical disability, which might not be fully explained by objective inflammation or joint damage[14,150]. Similar observations in osteoarthritis led to extensive research that highlighted the role of obesity and adipose tissue dysfunction in amplifying pain independently of structural joint changes. Although specific data in PsA are limited, following studies in knee osteoarthritis, several mechanisms through which obesity can exacerbate pain have been proposed, including increased biomechanical stress, adipose-derived inflammatory mediators and neurotrophic modulation of peripheral and central sensitization pathways[151].

Dysfunctional adipose tissue promotes a state of chronic low-grade inflammation that activates Toll-like receptor pathways in the synovium and subchondral bone and sensitizes local nociceptors. Leptin has also been implicated in pain modulation[152]. In osteoarthritis, both serum and synovial leptin levels correlate with pain severity independently of BMI[152]. Local adipose tissue depots also contribute to pain severity. The infrapatellar fat pad, which is richly innervated by substance P-positive fibres, exhibits inflammation, fibrosis and increased leptin expression[116,153]. In humans, MRI-detected alterations in the infrapatellar fat pad have been associated with greater knee pain, underscoring the paracrine effects of peri-synovial adipose tissue on nociception[154].

Obesity also affects neurosensory circuits, promoting increased pain sensitivity through neurotrophic remodelling. Circulating levels of neuropeptides, including substance P, neuropeptide Y, nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are increased in obesity[155–157]. These molecules lower pressure pain thresholds and enhance temporal summation via activation of receptors (such as transient receptor potential vanilloid 1 (TRPV1) and tyrosine kinase A) on peripheral nociceptors and dorsal root ganglia[156,157]. Psychophysical testing in individuals with obesity reveals widespread hyperalgesia and features of central sensitization. Importantly, substantial weight loss, either through bariatric surgery, pharmacological therapy or calorie restriction, can reduce pain levels and reduce spinal nociceptive facilitation, suggesting a direct link between excess adiposity and neural amplification of pain[158–160].

Obesity-related comorbidities and PsA outcomes

Obesity is a well-established risk factor for a range of comorbid conditions that might exacerbate symptom burden in patients with PsA, independently of underlying musculoskeletal inflammation. These comorbidities include T2DM, congestive heart failure, depression, obstructive sleep apnoea and osteoarthritis, each of which can contribute to chronic pain, stiffness and fatigue[161,162]. Such overlapping symptomatology might confound the clinical assessment of PsA disease activity and artificially inflate composite outcome measures, even in the absence of active musculoskeletal inflammation. Moreover, obesity and obesity-associated comorbidities are often accompanied by adverse alterations in body composition, including sarcopenia and an increased adipose tissue-to-muscle ratio, which further impair physical function and limit mobility[163]. These non-inflammatory drivers of symptomatology underscore the need for comprehensive assessment strategies in individuals with PsA and obesity.

Weight loss interventions in psoriatic disease

Although weight loss is an effective strategy in the treatment of psoriatic disease, the most common means of weight loss (dietary interventions or bariatric surgery) present challenges. Diet and lifestyle

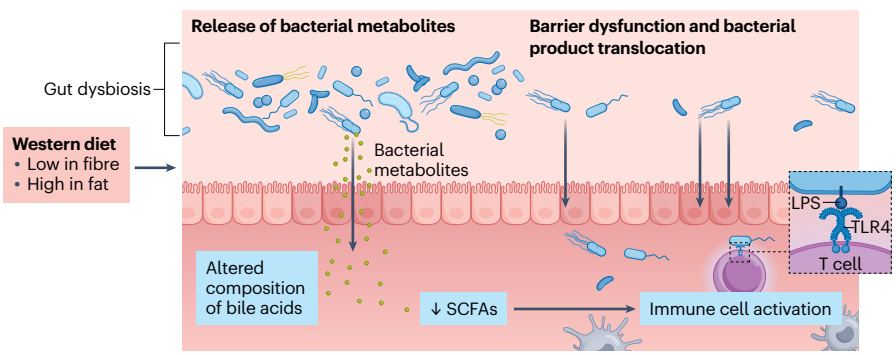

Fig. 4 | Gut dysbiosis in obesity and psoriatic arthritis. Gut dysbiosis has been implicated in both psoriatic arthritis and obesity. A Western diet could affect the gut microbiome composition in turn resulting in abnormal production of metabolites (such as short-chain fatty acids (SCFAs) and bile acids) and subsequent immune cell activation. This diet also contributes to gut barrier dysfunction and interaction of bacterial components with immune cells. LPS, lipopolysaccharide; TLR4, Toll-like receptor 4.

changes can be successful, but often require frequent, intensive interventions, with only around 50–60% of patients achieving their goal weight[164,165]. Bariatric surgery, including gastric bypass and banding, is very effective, with over 60% of patients maintaining weight loss for over 10 years[166]; however, both early complications (bowel obstruction, thromboembolism, gastrointestinal bleed, wound infection and hernia) and late complications (bowel strictures, ulcerations, nutritional deficiencies and malabsorption) can occur, limiting the widespread use of these interventions[167].

Effect of diet-induced weight loss in psoriatic disease

Diet-induced weight loss improves skin psoriasis in individuals with obesity[168–171]. Although not uniformly observed across all studies, a meta-analysis of seven randomized control trials (RCTs) found that individuals receiving a weight loss intervention had lower PASI scores than those receiving usual care or not receiving a weight loss intervention (−2.5; 95% confidence interval, −3.90 to −1.08) and were almost three times more likely to achieve a PASI75 response[168,172,173]. Even a limited weight loss might be beneficial for psoriasis outcomes. Individuals with psoriasis who are on a diet and exercise plan, compared with informative counselling alone, had higher reductions in PASI score (48% versus 26%) even though only 30% of the group reached the weight loss goal (≥5% body weight loss)[174].

Evidence also supports the efficacy of diet-induced weight loss in the treatment of PsA[175]. In a non-randomized study in 46 individuals with obesity and PsA, a hypocaloric diet for 12–16 weeks resulted in a 19% median body weight loss. MDA increased from 29% to 54% with improvements in active entheseal and joint counts, inflammatory markers, skin psoriasis, physical function, perception of health, pain and fatigue[176]. Sustained improvements were reported up to 24 months[177]. In another study, 138 individuals with PsA and overweight or obesity on TNF inhibitors were randomized to a hypocaloric diet or a free self-managed diet. Weight loss, regardless of diet type, was associated with MDA in a dose-dependent manner. Compared with individuals who had a <5% body weight loss, individuals with 5–10% and >10% body weight loss were 3.8 times and 6.7 times more likely to achieve MDA, respectively. The DIPSA (Diet Interventions in Psoriatic Arthritis) study randomized 92 individuals with PsA and overweight or obesity who experienced residual musculoskeletal symptoms (Disease Activity in Psoriatic Arthritis (DAPSA) score of >10) to a Mediterranean diet, a low-calorie diet, or control with general dietary recommendations. Modest weight loss was noted across all three groups as well as a considerable improvement in DAPSA score, tender joint count, pain and fatigue; however, no statistically significant differences were found for change in weight and PsA parameters across the groups[178]. Weight loss magnitude was associated with improvement in PsA outcomes regardless of dietary intervention[178].

Other smaller studies have also investigated the effect of specific diets for PsA. In one study, 20 participants on a very-low-calorie ketogenic diet showed improvement in DAPSA score that correlated with BMI reduction[179]. In another study in 22 participants, a ketogenic diet was compared with a Mediterranean diet. Although the ketogenic diet was associated with greater improvement in PsA disease measures, the ketogenic diet also resulted in increased (although not statistically significant) weight loss compared with the Mediterranean diet[180]. A study in 37 participants who practised intermittent fasting in the context of Ramadan for 1 month showed improvement in PsA outcomes despite limited or no weight loss[181]. However, in addition to their small size, these studies lack clarity regarding intervention implementation and adherence. Overall, evidence supports the view that weight loss, rather than the type of diet itself, probably contributes to improvement of disease.

Importantly, given the overall increased risk of cardiovascular events in psoriatic disease[182], dietary weight loss interventions have also been shown to improve cardiovascular outcomes in psoriatic disease. In an RCT including 60 individuals with psoriasis and obesity, participants were given either a low-energy diet or a normal diet. In addition to losing more weight, the intervention group had reduced blood pressure, resting heart rate, cholesterol and plasma glucose[183]. Improvement in lipids, glucose and need for antihypertensive treatment was maintained after a 2-year follow-up of individuals with PsA who had achieved weight loss[177].

Effects of bariatric surgery in psoriatic disease

Bariatric surgery is another weight loss option that improves psoriatic disease outcomes. Case reports document complete resolution of psoriasis after Roux-en-Y gastric bypass surgery[184–186]. A case series of 33 individuals with psoriasis and a BMI of ≥40 mg/m^2 undergoing bariatric procedures found that, after the procedure, 30% of patients were able to reduce their psoriasis medication and 25% had improvement in psoriasis severity, for which gastric bypass conferred more improvement than non-bypass procedures[187]. In a small monocentre study in 86 participants with psoriatic disease, self-reported outcomes for both skin and joint activity improved 1 year after bariatric surgery, and this effect was most pronounced among those with severe disease at baseline[188].

Bariatric surgery might decrease the incidence of psoriatic disease, as shown in two large European population-based studies. Data from a Swedish registry showed that bariatric surgery (compared with usual care) was associated with a reduced incidence of psoriasis in individuals with obesity (hazard ratio 0.65) but did not affect the risk of PsA[189]. In a Danish cohort, the risk of incident psoriasis was reduced with gastric bypass (hazard ratio 0.44), but not with gastric banding (hazard ratio 1.23), whereas the incidence of PsA was decreased by both procedures (hazard ratios 0.29 and 0.53)[190]. These differential impacts of gastric bypass and banding might be because of effects beyond changes in adiposity. Although both procedures lead to similar levels of weight loss, gastric bypass also elicits endocrine changes. Specifically, gastric bypass increases postprandial secretion of the gut-derived hormone GLP-1, which is not affected by gastric banding[191,192]. Therefore, the use of GLP-1-based therapies might mimic the effect of gastric bypass without the need to undergo surgery and could thus provide a new strategy for treating obesity in psoriatic disease.

Effect of GLP-1 based therapies

Case reports, case series and small cohort studies have shown the efficacy of GLP-1-based therapies in the treatment of skin psoriasis in individuals with concomitant T2DM[193–197]. Small interventional studies have also generally shown positive results. In one study, 25 individuals with active plaque psoriasis and T2DM were randomized to acitretin alone or acitretin plus the GLP-1 receptor agonist (RA) liraglutide. Treatment with acitretin and liraglutide led to greater improvements in both PASI and Dermatology Life Quality Index (DLQI), more weight loss and improvement in cholesterol measures than treatment with acitretin alone. Although both groups showed decreases in levels of IL-17, IL-23, and TNF in psoriatic lesions after treatment, the liraglutide group had lower expression of IL-17 and IL-23 than the acitretin-alone group[198]. Similarly, in an RCT in 31 individuals with psoriasis and T2DM

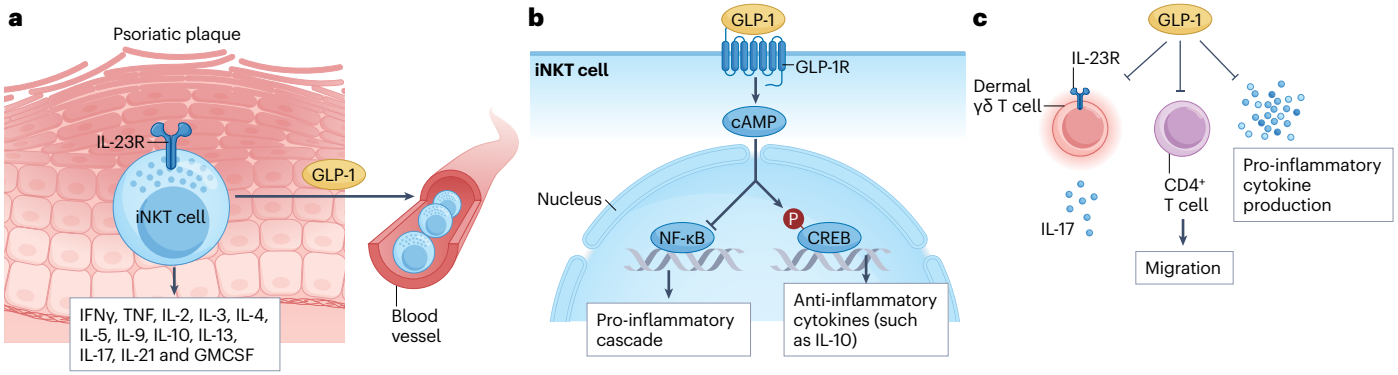

Fig. 5 | Direct anti-inflammatory and immunological effects of GLP-1-based therapies in psoriatic disease. Glucagon-like peptide-1 (GLP-1) receptor agonists might have direct anti-inflammatory effects through multiple mechanisms. **a**, Invariant natural killer T (iNKT) cells are implicated in the pathogenesis of psoriasis and have several immunoregulatory effector functions, including the rapid production of cytokines. In response to GLP-1-based therapies, iNKT cells move from psoriatic plaques to the periphery, thereby reducing the severity of psoriasis. **b**, GLP-1 receptors (GLP-1Rs) are located on iNKTs. Stimulation of GLP-1R upregulates cAMP, leading to the inhibition of nuclear factor-κB (NF-κB) and its subsequent pro-inflammatory cascade and the phosphorylation of cAMP response element-binding protein (CREB), which in turn upregulates anti-inflammatory pathways. **c**, IL-23-responsive, IL-17-producing dermal γδ T cells are implicated in psoriasis pathogenesis and are found in high numbers in psoriatic plaques. GLP-1 therapies decrease the percentage of dermal γδ T cells and reduce IL-17 expression. In addition, GLP-1 therapies inhibit $CD4^+$ T cell migration via effects on phosphoinositide 3-kinase and stromal cell-derived factor 1, and decrease overall production of pro-inflammatory cytokines including TNF. GMCSF, granulocyte–macrophage colony-stimulating factor; IL-23R, IL-23 receptor.

that compared the GLP-1RA semaglutide with usual care, those receiving semaglutide had improved PASI scores and reduced DLQI, serum IL-6 and C-reactive protein (CRP)[199]. Conversely, in a study in individuals with obesity, but not T2DM, no differences in PASI, DLQI or CRP were found in patients taking liraglutide compared with the placebo group, despite weight loss[200]. Clinical data regarding PsA outcomes are limited, but a case series from North America demonstrated an association between GLP-1-based therapies and clinically meaningful weight loss and improvement in CRP and pain[201].

Importantly, improvement in skin involvement can precede weight loss with the use of GLP-1-based therapies[194,202]. Individuals with psoriasis on liraglutide show improvements in PASI, CRP and quality of life independent of weight loss[203]. This improvement is probably a consequence of direct anti-inflammatory and immunoregulatory effects of GLP-1RA on key psoriatic disease pathways, including invariant natural killer T cells, dermal γδ T cells, lymphocyte migration and pro-inflammatory cytokines[193,204–210] (Fig. 5).

GLP-1-based therapies have already shown efficacy in osteoarthritis, which can occur concomitantly with psoriasis and PsA. In the STEP 9 trial, once-weekly treatment with semaglutide was associated with considerable reduction in body weight and pain related to knee osteoarthritis[211]. Although the pain reduction might have been solely owing to the observed weight loss, mechanistic studies have shown the presence of GLP-1 receptors in the synovial membrane in individuals with osteoarthritis, and GLP-1-based therapies might therefore suppress degradation of the joint[212–214]. Given the effects of both weight loss and possible direct anti-inflammatory and immunomodulating effects of GLP-1-based therapies, they might represent a unique adjuvant therapy for psoriatic disease, but evidence remains preliminary.

GLP-1-based therapies lead to consistent improvement of cardiovascular outcomes in the general population[215,216]. Furthermore, a 2025 study using the TriNetX database showed that GLP-1RA use in individuals with psoriasis is associated with a statistically significant decrease in all-cause mortality and risk of major adverse cardiac events[217]. Interestingly, the risk reduction is higher in individuals with psoriasis than in those without psoriasis[217], which possibly indicates an added benefit in inflammatory disease. Decreased rates of mortality and major adverse cardiac events have similarly been shown in individuals with PsA treated with GLP-1RAs[218].

Other FDA-approved weight loss medications include orlistat (a lipase inhibitor), phentermine–topiramate (a combination sympathomimetic and anticonvulsant that works by blocking voltage-gated sodium channels) and naltrexone–bupropion (a combination opioid antagonist and antidepressant), but are generally less effective than GLP-1-based therapies[219]. Thus far, no studies have assessed these drugs for psoriatic disease or inflammation, but small case series and case reports provide limited insights. In a case series of seven individuals with psoriasis and concomitant mood disorders, treatment with topiramate monotherapy resulted in improved psoriatic skin activity and weight loss[220]. Conversely, case reports have revealed that naltrexone–bupropion might even flare psoriatic skin disease[221,222]. Furthermore, the extensive cardiovascular benefits reported with GLP-1-based therapies are not observed with the other approved weight loss drugs[223]; however, orlistat has shown mild cardiovascular benefits[224], and phentermine–topiramate and naltrexone–bupropion have shown mixed results regarding their effect on cardiovascular risk and disease[225–228].

Unmet needs and future research

The relationship between obesity and the development, severity and therapeutic responsiveness of PsA is now well established. Obesity is not merely a comorbidity but exerts a pathogenic influence on disease phenotype. The emergence of GLP-1-based therapies has introduced a promising pharmacological strategy to address both obesity and the associated state of metabolic inflammation in PsA[229]. Although traditional interventions, such as hypocaloric diets and bariatric surgery, remain viable options, the former often yields only modest and usually

Box 1 | Proposed approach to obesity management in psoriatic disease

Addressing overweight and obesity needs to be part of a systematic approach to psoriatic disease management and should start with the rheumatologist. From there, an interdisciplinary team should be formed to help patients achieve their weight loss goals, including nutritionists, primary health-care providers, advanced practice providers, cardiologists, endocrinologists and/or bariatric surgeons. All individuals with overweight and obesity with a BMI of >25 mg/m^2 should be referred to a nutritionist for diet counselling. In addition, if an individual with obesity has a BMI of >27 mg/m^2 plus comorbidities or a BMI of >30 mg/m^2, pharmaceutical intervention should be considered. We propose that GLP-1-based therapies should be considered first if using pharmaceutical interventions, along with lifestyle changes such as diet and exercise. Bariatric surgery should be considered for individuals with a BMI of ≥35 mg/m^2 plus comorbidities or a BMI of >40 mg/m^2 with or without pharmacological interventions.

unsustainable weight loss, whereas the latter, though more effective, is invasive and not without procedural risk.

By contrast, GLP-1-based therapies offer a non-invasive, pharmacologically effective and safe approach to achieving meaningful weight reduction in individuals with a broad spectrum of body mass indices. These agents might confer additional benefits beyond weight loss, including anti-inflammatory effects, pain reduction and cardiometabolic protection, making them particularly attractive for use in individuals with PsA[230,231]. Although clinical evidence is limited, small studies have suggested that targeting obesity through GLP-1-based therapies in adiposity-driven conditions such as Ps, might function not only as a symptomatic intervention, but also as a disease-modifying adjunct that potentially influences disease progression and enhances therapeutic response. Additional high-quality evidence is needed to address this hypothesis. The TOGETHER-PsO (NCT06588283) and TOGETHER-PsA (NCT06588296) trials are investigating treatment with ixekizumab and tirzepatide compared with ixekizumab alone in psoriasis and PsA, respectively. The TOGETHER-AMPLIFY-PsO (NCT06857942) and TOGETHER-AMPLIFY-PsA (NCT06864026) trials are currently evaluating the efficacy of adding tirzepatide for individuals with psoriasis or PsA who are already on ixekizumab. Registries and observational cohorts are also underway.

Although the general health benefits of weight loss in obesity are well substantiated, the high cost of GLP-1-based therapies and limited access to comprehensive obesity care programmes raise important questions about the optimal timing and patient selection for weight-loss interventions within PsA management paradigms. Most individuals with overweight or obesity would probably benefit from GLP-1-based therapies, but three populations might be of particular interest: individuals with psoriasis who are at high risk of progression to synovio-entheseal disease; patients who are early in their disease course; and patients who meet the definition of treatment-refractory or difficult-to-manage PsA[232] (Fig. 2).

Despite their potential, GLP-1-based therapies are not without limitations. Gastrointestinal adverse effects, especially nausea and vomiting, are common and might affect adherence[233]. These symptoms overlap with known adverse effect profiles of commonly prescribed DMARDs, such as methotrexate, apremilast and leflunomide, potentially complicating attribution and management[234–236]. Concerns also exist regarding unintended loss of lean muscle mass, which might be particularly relevant in the context of pre-existing sarcopenia (a common, under-recognized issue in PsA[163]). Thus, real-world data on tolerability, safety and outcomes in individuals with psoriatic disease are essential. In addition, interdisciplinary care models, including allied health professional and obesity specialists are required to optimize the implementation of GLP-1-based therapy. Close monitoring, individualized dose titration and comprehensive patient education are key to mitigating risks and enhancing outcomes.

The mechanistic basis by which weight loss improves PsA outcomes remains incompletely understood. Interventional studies offer a unique opportunity to investigate candidate pathways, including changes in adipokine signalling, metabolic inflammation, immune cell function, pain sensitization and more. Integration of translational research methodologies, such as advanced imaging, tissue biomarker profiling and multi-omics, will be necessary to delineate the relative contributions of these mechanisms.

Proposed strategies to address obesity in psoriatic disease

Despite robust data indicating the potential of weight loss to enhance therapeutic efficacy and expert panel consensus that it should be an essential part of psoriatic disease management[237,238], weight loss is not currently systematically incorporated into PsA treatment algorithms. Although weight is often a sensitive topic, the introduction of obesity as part of psoriatic disease management must begin with dermatologists and rheumatologists (Box 1). Primary rheumatological and/or dermatological intervention should be followed by the involvement of interdisciplinary health-care providers including family physicians, cardiologists, endocrinologists, and even bariatric surgeons and medical nutritionists, to help patients achieve optimal weight goals. For individuals considering pharmacological interventions, we propose that GLP-1 therapeutic agents should be considered before other weight loss therapies, given their proven efficacy and safety and potentially synergistic effects.

Conclusions

Obesity is a chronic, inflammatory condition that interacts inextricably with psoriatic disease. Incorporating structured obesity interventions, especially for selected high-risk individuals, represents a promising frontier in PsA management. Strategic, pragmatic trials are needed to inform the development of future clinical practice guidelines that incorporate weight management not simply as a lifestyle recommendation, but as a disease-modifying adjunctive therapy in psoriatic disease. Real-world evidence on the short-term and long-term effectiveness of these therapies, predictors of optimal treatment outcomes and cost-effective therapies are urgently needed for individuals with psoriatic disease. Finally, future research that incorporates underlying molecular and immune features is needed to understand the in-depth mechanisms of the obesity–psoriatic disease axis.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

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Review article

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Endosome traffic in rheumatic diseases: mechanistic insights and therapeutic opportunities

Andras Perl

Abstract

Endosomal traffic governs various core processes that maintain immune homeostasis and self-tolerance, including receptor signalling, antigen processing, cytokine secretion and cellular metabolism. Traffic-regulated receptors — both intracellular and on the cell surface — modulate immune sensing of infection, nutrient availability and endogenous stress signals arising from cellular or tissue injury. In rheumatic diseases, such as systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, systemic sclerosis, Sjögren syndrome and osteoarthritis, mounting evidence implicates disruptions in endosomal pathways as important drivers of disease onset and progression. Dysregulated endosomal trafficking contributes to type I interferon activation via signalling through Toll-like receptors, aberrant autoantigen presentation, and altered expression of metabolite transporters in immune cells and target organs. Endosome trafficking mediates autophagosome formation, the production of exosomes and the turnover of organelles, such as mitochondria that generate oxidative stress, thereby controlling chronic inflammation and connective tissue remodelling. Therefore, understanding the molecular architecture of endosomal recycling pathways and their integration with immune cell function can provide important insight into rheumatic diseases. Restoring trafficking fidelity — through modulation of RAB GTPases, endosomal Toll-like receptor signalling, metabolic reprogramming, autophagic flux and extracellular vesicle biology — represents a promising therapeutic strategy.

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Sections

Key points

- Endosomes are sorting stations that receive proteins from the Golgi or plasma membrane via endocytosis and recycle them to the cell surface, trans-Golgi network, or lysosomes for degradation.
- Disrupted endosomal traffic contributes to rheumatic diseases, including systemic lupus erythematosus, rheumatoid arthritis and systemic sclerosis, by impairing immune regulation and tissue homeostasis.
- Endosomes regulate immune homeostasis through receptor traffic and signal transduction, antigen processing, cytokine secretion, and cellular metabolism.
- Endosomal pathways initiate autophagosomes and exosome formation and remove damaged organelles, including oxidative stress-generating mitochondria that promote inflammation and connective tissue remodelling.
- Dysregulated endosomal traffic activates type I interferon via Toll-like receptors, disrupts antigen presentation and alters metabolite transporter expression in immune cells.
- Key checkpoints of endosomal traffic, including RAB GTPases, endosomal Toll-like receptors, recycled receptors, metabolite cargos, autophagy flux and exosome formation, represent promising therapeutic targets in endosomal dysfunction.

Introduction

The immune system depends on tightly coordinated membrane trafficking to regulate surface receptor expression, signal transduction, and degradation or recycling of internalized cargo[1]. These trafficking decisions, primarily orchestrated through endosomes, influence critical immune processes such as antigen processing[2], T cell and B cell activation[3], cytokine release[4], and resolution of inflammation[5]. Defects in endosomal trafficking are increasingly recognized not merely as downstream consequences of inflammation but as causal contributors in the pathogenesis of autoimmune and inflammatory disorders.

Endosomal trafficking senses and regulates virtually every aspect of cellular function[6]. In rheumatic diseases, where sustained activation of innate and adaptive immune responses drives chronic tissue injury, endosome dysfunction can amplify immunogenicity and perturb immune tolerance[3]. Endosomal traffic has a central role in regulating the recycling and expression of nutrient-sensing surface receptors, the activity of nucleic acid-sensing intracellular receptors, and the biogenesis and degradation of organelles through lysosomal pathways. Endosome traffic is guided by RAB GTPases along a network of microtubules sustained by the actin cytoskeleton[7]. In humans, over 60 RAB GTPases function as master regulators of intracellular membrane traffic[8,9]. Distinct RAB GTPases control different phases of endosome traffic to ensure that membrane-bound cargoes are transported to their correct destinations within the cell[10].

In this Review, we examine recent advances in the biogenesis and trafficking of endosomes, with an emphasis on Toll-like receptor (TLR)-dependent interferon signalling in the innate immune system, the recycling of metabolite-sensing receptors in adaptive immune responses and the regulation of end-organ resistance. These insights reveal broader implications for the pathogenesis and treatment of rheumatic diseases, including in the development and progression of degenerative joint disorders.

Endosomal function

Endosomes are dynamic cellular compartments that function as sorting stations for proteins and lipids, orchestrating membrane-enclosed traffic and intracellular communication. Endocytic recycling pathways regulate the trafficking of receptors and organelles, shaping cell membrane composition and cellular responsiveness[11]. Endosomes receive cargo from both the extracellular environment and biosynthetic pathways, directing this cargo to various destinations such as the plasma membrane, Golgi or lysosomes for degradation. Essentially, endosomes are responsible for regulating the flow of cellular components, influencing cell signalling and maintaining cellular homeostasis. Defects in endosome function can lead to various diseases[12], including metabolic disorders, neurodegenerative diseases, cancer and rheumatic diseases, the latter of which is the focus of this Review.

Endosomal biogenesis and maturation

Like all cell membranes within the endomembrane system, endosome membranes are composed of a phospholipid bilayer[7]. This bilayer features hydrophilic head groups that are oriented outwards, facing the aqueous environment, and hydrophobic tails that point inwards, forming the core of the membrane. Endosomal biogenesis is a highly coordinated process essential for controlling membrane protein turnover, receptor signalling and antigen presentation. Endosomes are formed by endocytosis, where the cell membrane invaginates and pinches off to form a vesicle. During biogenesis, the endosome membrane is structurally similar to other cellular membranes; however, endosomes also contain unique proteins and lipids that define their specific functions and maturation stages.

Endosome maturation begins with the formation of early endosomes at the cell periphery, following the internalization of cargo via endocytosis[13]. These early endosomes serve as dynamic sorting hubs, directing internalized material towards recycling or degradation pathways (Fig. 1). Endocytosis proceeds through two main pathways: clathrin-mediated endocytosis and clathrin-independent endocytosis[14,15]. Clathrin-mediated endocytosis involves the assembly of clathrin and adaptor proteins, such as AP2, at the plasma membrane, forming a clathrin-coated pit. This pit invaginates and pinches off to form a clathrin-coated vesicle[16]. Clathrin-mediated endocytosis accounts for 95% of endocytic vesicles[17].

Early endosomes undergo maturation processes that involve morphological changes, spatial movement and acidification. The mature late endosome fuses with a lysosome, forming a transient organelle known as an endolysosome, which subsequently becomes a classical dense lysosome[13]. RAB GTPases, functioning as molecular switches, orchestrate each stage of this process[18] (Fig. 1). RAB5, enriched on early endosomes, regulates internalization and homotypic fusion as well as cargo sorting via effectors such as early endosomal antigen 1 (EEA1) and the class III phosphoinositide 3-kinase (PI3K) complex[19]. Cargo destined for rapid recycling to the plasma membrane engages RAB4A, which mediates fast recycling via direct sorting tubules. This pathway is critical for rapid restoration of immune receptors such as CD98 (also known as SLC3A2) and CD71 during lymphocyte activation[3]. These receptors are internalized following phosphorylation by protein kinase C (PKC). By contrast, RAB11 regulates slower recycling from perinuclear recycling endosomes[20], maintaining surface expression of immune receptors, such as CD4

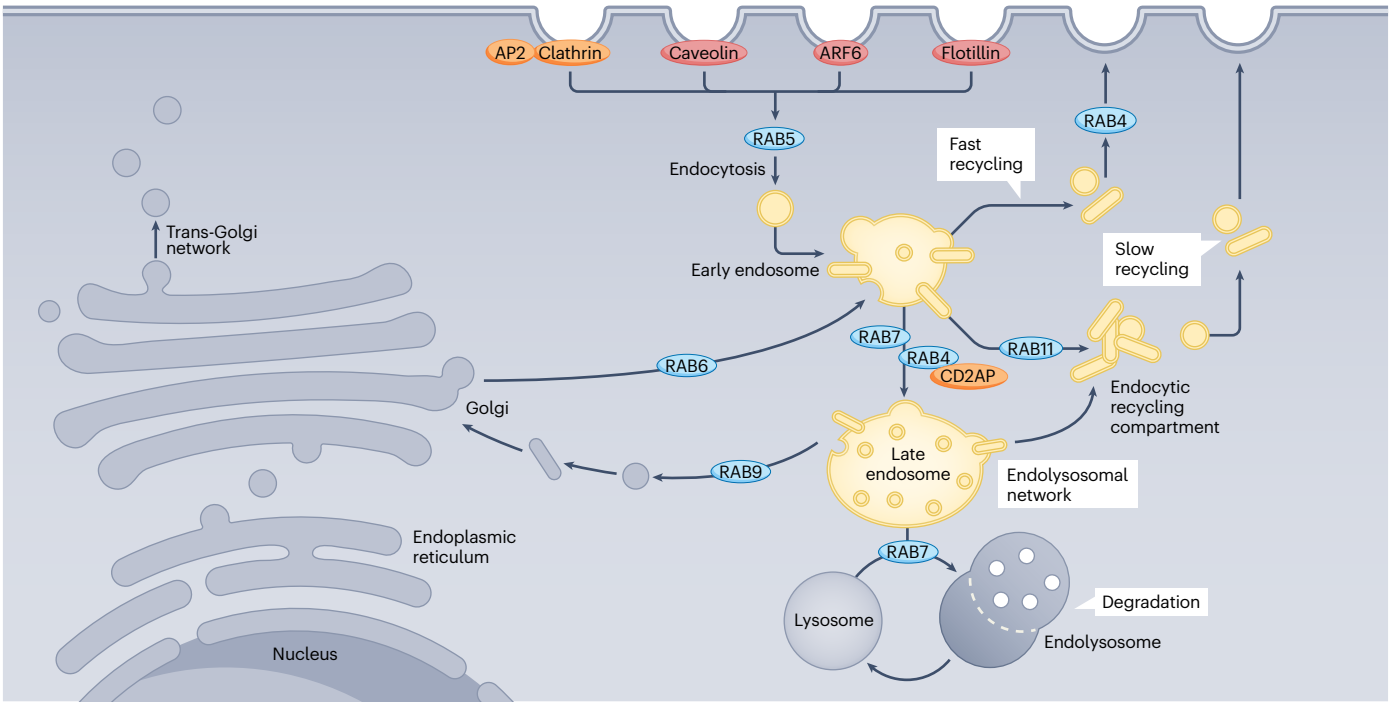


Fig. 1 | Endosomal pathways: biogenesis, recycling, exosome formation and lysosomal delivery. Endosome biogenesis relies on clathrin[274], caveolin[227], ARF6 (ref. 275) or flotillin[149] for vesicle formation. Clathrin is associated with AP2. RAB5A is a key regulator of the formation and internalization of early endosomes, which are the initial sorting stations for internalized cargo. RAB4 collaborates with RAB11 in recycling processes: RAB4 controls the fast-recycling pathway, directly returning cargo from early endosomes to the plasma membrane or to the lysosome; whereas RAB11 is located in perinuclear recycling endosomes and regulates the slow-recycling pathway, which involves the transport of cargo from the recycling endosomes to the cell surface. RAB7 has a role in the maturation of early endosomes to late endosomes (facilitating the RAB5 to RAB7 switch) and in the subsequent fusion of late endosomes with lysosomes, essential for lysosomal degradation. RAB9 isoforms mediate the traffic from late endosomes to the trans-Golgi network[24], whereas RAB6 oppositely regulates transport between the Golgi and endosomes[25]. CD2-associated protein (CD2AP) interacts with RAB4 and helps to regulate the sorting and recycling of cargo between early and late endosomes[28]. CD2AP also promotes the transition from RAB5$^+$ early endosomes to RAB7$^+$ late endosomes, targeting cargo for lysosomal degradation[29].

(ref. 21), and integrins during sustained responses[22]. Maturation towards degradation involves RAB conversion, whereby RAB5 is replaced by RAB7 (ref. 23) through the action of the MON1–CCZ1 exchange complex, promoting cargo transport to late endosomes and lysosomes[11].

RAB9A and RAB9B are primarily involved in the traffic from late endosomes to the trans-Golgi network[24] (Fig. 1). RAB6 regulates bidirectional transport between the Golgi and endosomes[25]. RAB7-mediated trafficking controls antigen processing in lysosome-related compartments for major histocompatibility complex (MHC) antigen loading. The spatiotemporal regulation of RAB activation by guanine nucleotide exchange factors and GTPase-activating proteins ensures precise coordination of endosomal dynamics[26], linking receptor fate decisions to innate and adaptive immune function[27]. CD2-associated protein (CD2AP) interacts with RAB4A to regulate cargo sorting and recycling between early and late endosomes[28]. CD2AP also promotes the transition from RAB5$^+$ early endosomes to RAB7$^+$ late endosomes, targeting cargo for lysosomal degradation[29]. Dysregulation of these pathways has been implicated in aberrant immune activation and impaired tolerance, contributing to the pathogenesis of autoimmune rheumatic disease[3,30,31].

Endosomal trafficking pathways

After internalization, endosomes travel through an interconnected tubular network that controls the transfer of cargoes between organelles. As already discussed, early endosomes (marked by RAB5) initiate sorting, directing cargo either for recycling via RAB4A$^+$ or RAB11$^+$ compartments or for degradation through late endosomes and lysosomes[1]. Endosomes can also be returned to the cell surface and become exosomes[32,33]. Thus, upon fusion with the plasma membrane, endosomes can become exosomes that allow sharing of intracellular materials between cells in close proximity and throughout the body[34].

The acidic environment of the early endosome forces ligands to be released from the receptors such as transferrin and iron from CD71 (Fig. 2a). Most ligands are sorted into recycling endosomes and directed to lysosomes for degradation. The receptors themselves can also be degraded within lysosomes or recycled back to the cell surface for reuse[10]. As an example of endosomal trafficking, the transferrin receptor CD71 is internalized via clathrin-mediated endocytosis[35], a process regulated by RAB5, which also facilitates the uptake of its cargo, transferrin and iron[15]. Once internalized, CD71 is recycled to the plasma membrane via RAB4A[36–38] or RAB11 (ref. 39). In turn, RAB7$^+$ vesicles transport newly synthesized CD71 from the Golgi to the plasma membrane[40]. The intracellular protein dynamin-related protein 1 (DRP1) also traffics via clathrin-coated vesicles[41]. DRP1 is critical for the initiation of mitochondrial fission, a process required for mitochondrial turnover through mitochondrial autophagy, known as mitophagy[42]. When DRP1 is depleted via lysosomal trafficking,

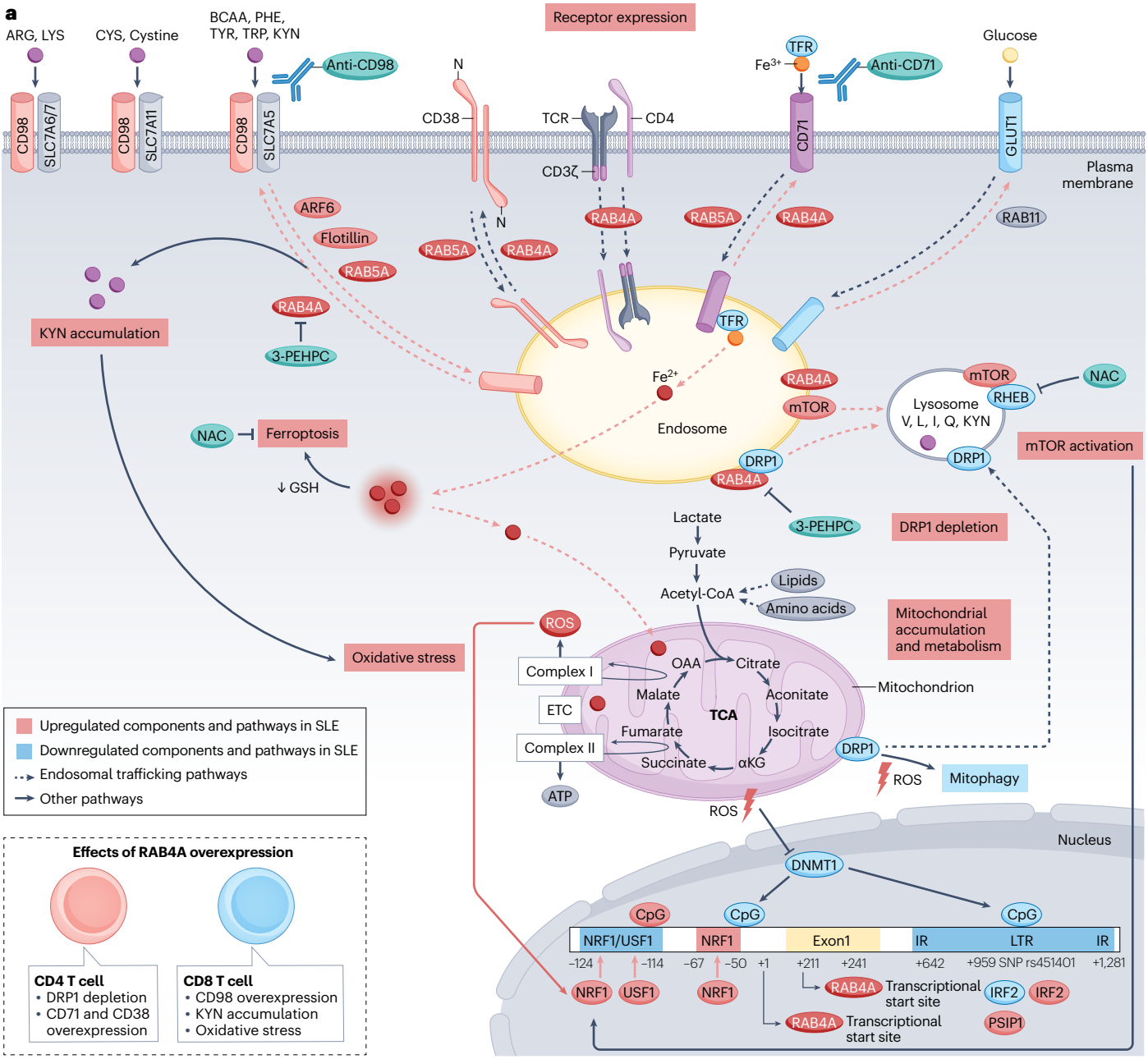

a
ARG, LYS
CYS, Cystine
BCAA, PHE, TYR, TRP, KYN
Anti-CD98
CD98
SLC7A6/7
SLC7A11
SLC7A5
Receptor expression
CD38
N
TCR
CD4
CD3ζ
TFR
Fe3+
Anti-CD71
CD71
Glucose
GLUT1
Plasma membrane
ARF6
Flotillin
RAB5A
RAB4A
RAB11
KYN accumulation
3-PEHPC
Fe2+
Endosome
mTOR
RHEB
NAC
Lysosome
V, L, I, Q, KYN
mTOR activation
Ferroptosis
↓GSH
DRP1
DRP1 depletion
Lactate
Pyruvate
Acetyl-CoA
Lipids
Amino acids
Mitochondrial accumulation and metabolism
ROS
Oxidative stress
Complex I
ETC
Complex II
ATP
OAA
Citrate
Aconitate
Isocitrate
αKG
Succinate
Fumarate
Malate
TCA
Mitochondrion
Mitophagy
Upregulated components and pathways in SLE
Downregulated components and pathways in SLE
Endosomal trafficking pathways
Other pathways
Effects of RAB4A overexpression
CD4 T cell
• DRP1 depletion
• CD71 and CD38 overexpression
CD8 T cell
• CD98 overexpression
• KYN accumulation
• Oxidative stress
Nucleus
DNMT1
CpG
NRF1/USF1
NRF1
Exon1
IR
LTR
IR
−124
−114
−67
−50
+1
+211
+241
+642
+959 SNP rs451401
+1,281
USF1
RAB4A
Transcriptional start site
IRF2
PSIP1
b
FKBP12
Rapamycin
Raptor
mTOR
mTORC1
Rictor
mTORC2
CD4 T cell
↑ Glycolysis
↑ TCA
↑ PPP
CD8 T cell
↑ KYN
↓ TCA
↓ αKG
↑ CREMα
↑ MDA
mTORC1
mTORC2
TH17 cell
TPH cell
TFH cell
DN T cell
TEMRA cell
CD8 EM T cell
CD4 Treg cell
Upregulated
Downregulated

Fig. 2 | Complexity of endosome traffic-mediated T cell lineage skewing in SLE. Endosomal trafficking has an important role in the pathogenesis of systemic lupus erythematosus (SLE). Multiple mechanistically interconnected checkpoints that regulate endosomal trafficking and mechanistic target of rapamycin complex (mTOR) signalling, including CREMα, Raptor, Rictor, RAB4A, RAB5A and CD98, are dysregulated in SLE. These components can lead to the upregulation and downregulation of various processes (depicted in red and blue boxes, respectively), in a T cell-specific fashion, leading to skewed T cell lineage commitment. **a**, RAB4A engages in cell-type-specific positive feedback loops with mTOR signalling, driving metabolic and immunological reprogramming. In $CD4^+$ T cells, RAB4A promotes dynamin-related protein 1 (DRP1) depletion, upregulates CD71 and CD38, and enhances mitochondrial activity and pentose phosphate pathway (PPP) activity. In $CD8^+$ T cells, increased CD98 recycling leads to kynurenine (KYN) accumulation, oxidative stress and cell loss. RAB4A also facilitates lysosomal degradation of CD4 and CD3ζ and impaired T cell receptor (TCR) signalling. Increased iron uptake via CD71, combined with glutathione (GSH) depletion, elicits ferroptosis[276]. RAB4A expression is regulated via its 5′ promoter by redox-sensitive transcription factors NRF1 and USF1 and its polymorphic LTR-enhancer by interferon-regulated IRF2 (ref. 25), linking oxidative stress to RAB4A induction. Reactive oxygen species (ROS) further inhibit DNA methyltransferase 1 (DNMT1), causing demethylation of the RAB4A promoter and its overexpression. Additionally, mTOR amplifies this axis by upregulating NRF1 and RAB4A expression. **b**, RAB4A overexpression enhances mTORC1 activity while suppressing mTORC2 activity in human primary $CD4^+$ T cells[168]. Consistent with this pattern, T cells from patients with SLE exhibit increased mTORC1 and reduced mTORC2 signalling[277]; however, the degree of dysregulation is lineage specific across SLE T cell subsets[181,278,279]. Stimulatory (red), inhibitory (blue) or undefined (grey) roles of mTORC1 and mTORC2 are shown for T cell development (bottom right box). For both panels, molecules shown in red are upregulated in SLE, and those shown in blue are downregulated in SLE. Red arrows indicate molecular pathways that are accelerated in SLE, and grey arrows indicate molecular pathways that have no defined directional abnormality in SLE; dashed arrows indicate endosome trafficking, and solid arrows represent other pathways. For RAB molecules, those shown in red are upregulated in SLE, and those shown in grey are involved in the trafficking of indicated proteins without evidence of altered expression in SLE. In both figure parts, pharmacological interventions with 3-PEHPC, N-acetylcysteine (NAC) and rapamycin as well as with CD71 and CD98 blocking antibodies are shown in green. αKG, α-ketoglutarate; BCAA, branched-chain amino acids; DN, double negative; EM, effector memory; ETC, electron transport chain; GLUT1, glucose transporter 1; MDA, malondialdehyde; OAA, oxaloacetate; TCA, tricarboxylic acid; TEMRA, terminally differentiated effector memory T cells re-expressing CD45RA; TFH, T follicular helper; TFR, transferrin; T_H17, T helper 17; T_{PH}, T peripheral helper; T_{reg}, regulatory T.

mitophagy is disrupted, resulting in the accumulation of mitochondria. These mitochondria can contribute membrane components for accelerated autophagosome formation[43,44].

Clathrin-independent endocytosis encompasses various pathways that do not rely on clathrin for vesicle formation[45]. These pathways include caveolin-mediated endocytosis, which involves the caveolin proteins 1, 2 and 3, and the formation of caveolae (flask-shaped invaginations of the plasma membrane)[46]; ARF6-dependent endocytosis, which relies on the small GTPase ARF6 and its associated proteins; and flotillin-dependent endocytosis, which utilizes flotillin proteins and lipid rafts[45] (Fig. 1). As an example, the amino acid transporter CD98 might be internalized via clathrin-independent endocytosis[15] involving flotillin[47], ARF6 (ref. 48), or RAB5A[47] and recycled back to the plasma membrane via RAB4A-regulated endosomes[3] (Fig. 2a).

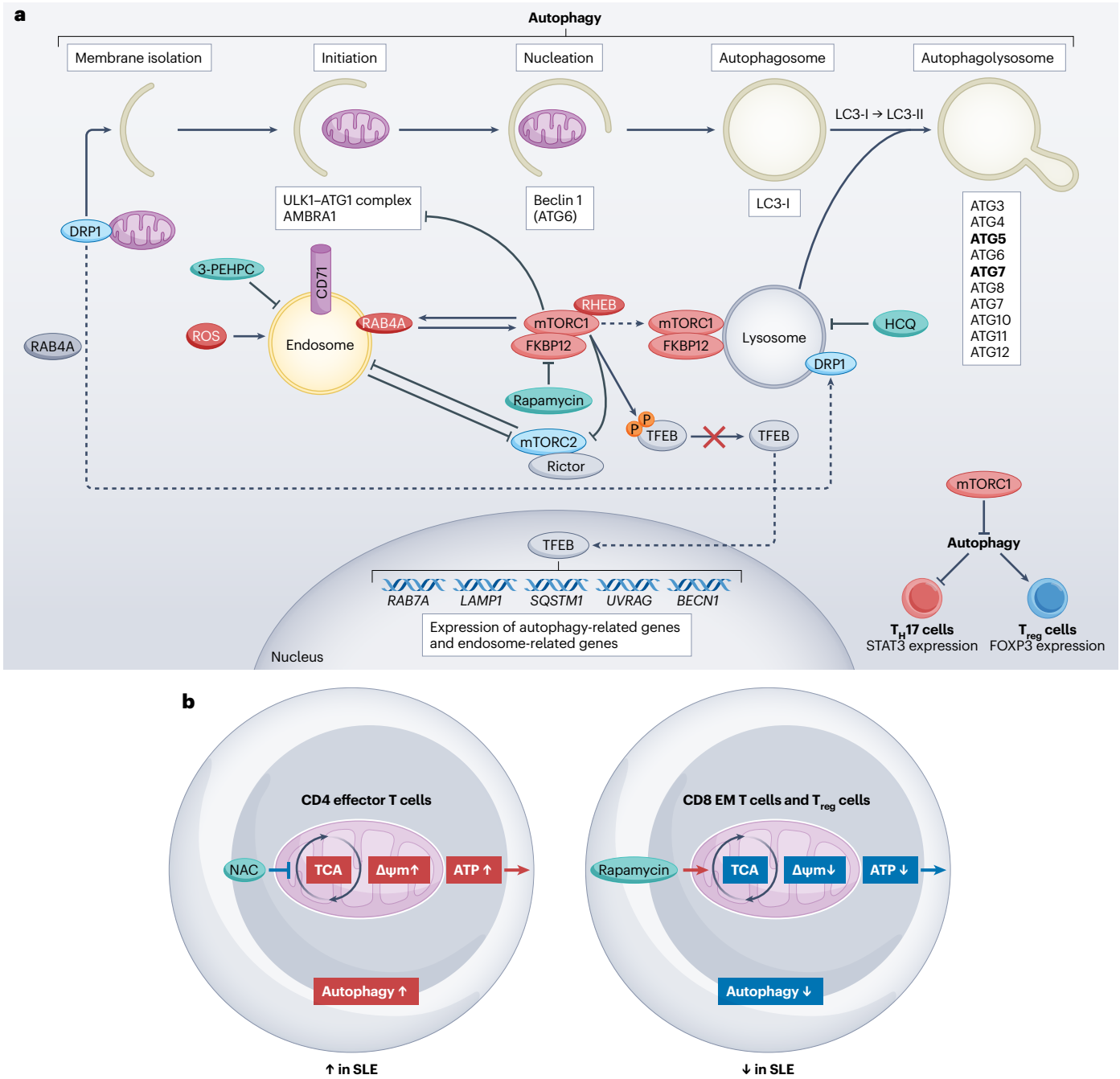
Exosome formation

Extracellular vesicles constitute a broad array of cell-derived, lipid-bound particles[49]. Exosomes represent a subset of extracellular vesicles that originate from endosomes and are released when multivesicular bodies fuse with the plasma membrane, whereas other extracellular vesicles, such as microvesicles, are formed by direct budding from the plasma membrane. Exosomes are generally smaller in size (30–150 nm) than microvesicles (100–1,000 nm) and are characterized by specific markers, including tetraspanins such as lysosome-associated membrane protein 3 (LAMP3; also known as CD63)[49]. The accumulation of endosomes stimulates the formation and secretion of exosomes[50], facilitating the intercellular spread of inflammatory signals and autoantigens[51,52]. Among the RAB GTPases, RAB4A has emerged as a prominent regulator of exosome biogenesis[32,33,53] and colocalizes with LAMP3 (refs. 54,55). The LAMP3 interactome also includes several other endosomal GTPases such as RAB5A, RAB11A, RAB7A, RAB27A, RAB27B and ARL8B[56]. Notably, exosome production is enhanced[57,58], along with the expression of RAB4A, in both patients and mice with systemic lupus erythematosus (SLE)-like disease[31,59,60]. Extracellular vesicles are also implicated in other rheumatic diseases, including rheumatoid arthritis (discussed in a later section).

Endosomal control of autophagy

Endocytosis and autophagy are both cellular processes that deliver materials to lysosomes for degradation, yet these processes differ fundamentally in their origin, cargo and mechanism. Endocytosis mediates the internalization of extracellular substances and the redistribution of membrane-bound components. By contrast, autophagy is a catabolic process that begins within the cell with the formation of an autophagosome, and involves the removal and recycling of damaged or unnecessary intracellular components, macromolecules and organelles. The two pathways exhibit extensive 'crosstalk' and can influence each other[61]. Transcription factor EB (TFEB) is a central regulator of endosomal and lysosomal biogenesis, essential for the recycling of organelles and intracellular debris during autophagy[62] (Fig. 3a). For example, under nutrient-rich conditions, mechanistic target of rapamycin complex 1 (mTORC1) phosphorylates TFEB on serine residues 142 and 211, retaining TFEB in the cytoplasm in an inactive state[63,64]. Upon dephosphorylation, when nutrient levels are low, TFEB translocates to the nucleus and regulates the expression of autophagy-related genes within the CLEAR (coordinated lysosomal expression and regulation) network, including genes encoding ATG5 and ATG8 (also known as LC3), and of RAB7 (ref. 65). In addition to controlling autophagy-related genes, TFEB regulates genes involved in endosomal trafficking and maturation, such as genes encoding RAB5A, RAB7A and caveolin 2, and an overall large subset of 623 endocytosis-related genes, thereby linking autophagy with endocytic pathways[62]. mTORC1 directly inhibits autophagy by blocking the function of the activating molecule in Beclin1-regulated autophagy (AMBRA1, Fig. 3).

RAB4A has a pivotal role in autophagosome formation[44] and endosomal trafficking[31,60]. RAB4A directs cargo, such as CD3ζ[60] and DRP1 (ref. 31), to lysosomes for degradation, and facilitates the recycling of CD71 and CD98 to the plasma membrane in a cell-type-specific manner[3]. Functional studies have shown that increased RAB4A expression contributes to these trafficking outcomes, as small interfering RNA-mediated knockdown in primary human T cells[60] or CD4Cre-driven deletion in mouse T cells reverses these effects[3]. RAB4A-mediated downregulation of the autophagy regulator DRP1



has been implicated as a pathogenic mechanism in SLE, as discussed in a later section.

Genetic and epigenetic drivers of endosomal dysfunction

Various genetic and epigenetic factors are linked to the disruption of endosomal pathways, contributing to the pathogenesis of rheumatic diseases. For example, the UNC93B1 protein facilitates the trafficking of nucleotide-sensing TLRs from the endoplasmic reticulum to endolysosomes[66], where they initiate immune responses. Genome-wide association studies in patients with SLE have identified risk variants in *UNC93B1* (refs. 67–69), highlighting the role of intracellular trafficking in autoimmune pathogenesis. Epigenetic regulation also intersects with trafficking pathways: DNA methylation-dependent associations involving DNA methyltransferase 1 (DNMT1)[70] (Fig. 2a) and DNMT3 have been reported between RAB4A and SLE[21], and between RAB4B and chronic obstructive pulmonary disease[71], implicating RAB GTPases in immune dysfunction. Notably, the retroviral features of the HRES1/RAB4 locus[38] and the high level of sequence homology between RAB4A and RAB4B (Supplementary Fig. 1) suggest a gene duplication event via retroposition[72]. Regulatory non-coding RNAs further modulate trafficking pathways: microRNA-155 controls exosome secretion[73],

Fig. 3 | Endosome–autophagy interactions shape T cell metabolic reprogramming in SLE. Multiple regulatory nodes integrate endosomal trafficking, autophagy and mitochondrial metabolism to shape T cell dysfunction in systemic lupus erythematosus (SLE). **a**, Autophagy occurs through a series of steps under the regulation of various molecules (shown in white boxes). Autophagosome membrane formation might be initiated by sourcing membranes from mitochondria[280], a process that is accelerated by RAB4A[44]. Endosome biogenesis is regulated by transcription factor EB (TFEB)-induced gene expression and post-translational modifications mediated by mechanistic target of rapamycin complex 1 (mTORC1). TFEB also regulates the expression of various autophagy-related genes (including Beclin 1, encoded by *BECN1*). Phosphorylation of serine residues on TFEB by mTORC1 retains TFEB in the cytosol in an inactive form[63]. mTORC1 also promotes the activity of RAB4A and inhibits the activity of activating molecule in Beclin1-regulated autophagy (AMBRA1), a key regulator of autophagy. RAB4A targets dynamin-related protein 1 (DRP1) for lysosomal degradation and supports the accumulation of oxidative stress-generating mitochondria, particularly in T helper 17 (T_H17) cells. Under physiological conditions, autophagy supports FOXP3 expression and regulatory T (T_{reg}) cell development and restrains STAT3 expression and T_H17 cell development. In SLE, various components of these pathways are upregulated (shown in red) or downregulated (shown in blue). Notably, in this setting, crosstalk between RAB4A$^+$CD71$^+$ recycling endosomes and lysosomes activates mTOR, establishing a positive feedback loop that sustains mTOR activation and RAB4A overexpression. **b**, In SLE, mitochondrial metabolic flux, ATP production and autophagy are enhanced in CD4$^+$ T cells but reduced in CD8$^+$ effector memory (EM) and T_{reg} cells[278]. mTOR activation blocks autophagy in T_{reg} cells (not shown). For both panels, pharmacological interventions with 3-PEHPC, N-acetylcysteine (NAC), hydroxychloroquine (HCQ) and rapamycin are shown in green. ΔΨm, mitochondrial transmembrane potential; ROS, reactive oxygen species; TCA, tricarboxylic acid.

whereas microRNA-574 is transferred intracellularly between cells via exosomes and activates TLR7, promoting type I interferon production by plasmacytoid dendritic cells (pDCs)[57]. Together, these findings point to a convergence of genetic susceptibility and epigenetic mechanisms in endosome-regulated and exosome-regulated immune signalling.

Nucleotide-binding domain (NOD)-like receptors (NLRs) are intracellular proteins that detect pathogens and activate the inflammasome. The subcellular localization and interaction of these receptors with endosomal compartments vary by receptor subtype. Although NOD1 and NOD2 sense cytosolic bacterial products, NLRP3 is also recruited to endosomes in response to the build-up of lipid phosphatidylinositol 4-phosphate (PI4P), a process driven by endocytic disruption[74,75]. Notably, genetic polymorphisms of *NLRP3* have been linked to rheumatoid arthritis and Sjögren syndrome[76].

C-type lectin receptors (CLRs) are endocytic receptors that internalize bound ligands, including both microbial components and host-derived molecules, through pathways such as clathrin-mediated endocytosis[77]. Following internalization, these CLRs and their ligands are delivered to early and late endosomes, where their fate — either recycling to the cell surface or degradation in lysosomes or phagolysosomes — depends on the specific CLR and its ligand. CLRs are crucial for innate immunity and antigen presentation. One CLR of particular interest in this context is C-type lectin-like domain family 16 member A (CLEC16A). Variants in the gene encoding CLEC16A have been linked to a wide spectrum of autoimmune disorders, including juvenile idiopathic arthritis[78], anti-cyclic citrullinated peptide-negative rheumatoid arthritis[78], type 1 diabetes[79], Crohn disease[80] and multiple sclerosis[81]. Although the precise functional relevance of this link is not yet fully understood, CLEC16A is expressed in multiple immune cell types, where it regulates both autophagic processes and receptor expression. Notably, the autoimmune risk genotype is associated with higher expression of CLEC16A in CD4$^+$ T cells[82]. In B cell lines in vitro, CLEC16A expression and its disease-associated locus, rs17673553, promote starvation-induced autophagy by inhibiting mTOR[83]. However, in primary human lymphocytes, increased CLEC16A expression instead activates mTOR and confers resistance to autophagy, suggesting a cell lineage-specific effect[84].

Functionally, CLEC16A encodes an endosomal membrane protein that supports mitophagy[85] and localizes to RAB4A$^+$ recycling endosomes in CD4$^+$ T cells[81]. In CLEC16A-deficient mice, mitophagy is disrupted in both T cells and B cells, but this defect can be reversed by pharmacological inhibition of PI3K and mitogen-activated protein kinase kinase (MEK)[86]. These findings further implicate CLEC16A as a key mediator linking endosome trafficking to the pathogenesis of autoimmune diseases.

The cGAS–STING pathway also engages endosomal compartments at multiple stages of its activation and resolution[71]. Both cGAS and STING translocate to endosomes as part of their activation pathway, and the presence of STING in endosomal membranes is essential for interferon induction (Supplementary Fig. 2). Binding of cGAS to the endosomal membrane activates the enzyme to synthesize cGAMP, which in turn helps STING translocate from the endoplasmic reticulum to endosomes. Subsequently, RAB7-driven endosomal traffic moves STING to lysosomes for degradation, which counters excessive inflammation[71,87]. Activating genetic mutations in STING predispose to STING-associated vasculopathy with onset in infancy[88] and SLE[89].

Endosomal pathways in immune processes

Endosomal pathways have a central role in shaping immune responses by regulating receptor signalling, antigen processing, cellular metabolism and lineage specification. Their roles are particularly evident in TLR signalling and in the pathogenesis of autoimmune diseases such as SLE and rheumatoid arthritis.

Endosomal pathways in TLR signalling

Endosomal TLRs, including TLR3, TLR7, TLR8, TLR9 and TLR13, recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), initiating innate immune responses[90]. Although TLR13 is restricted to mice[91], the remaining TLRs are critical sensors in human immunity. PAMPs and DAMPs trigger immune system activation through binding to the leucine-rich repeat segment of TLRs[92]. PAMPs, such as bacterial CpG DNA and single-stranded RNA, are derived from pathogens such as bacteria and viruses[93], whereas DAMPs, such as double-stranded RNA, are released from damaged or dying host cells[94]. Endosome-trafficked TLR3 senses double-stranded RNA and induces the production of pro-inflammatory cytokines, including type I interferons[95], which are implicated in the pathogenesis of several rheumatic diseases[96,97] (Fig. 4).

Systemic lupus erythematosus. In SLE, altered endosomal trafficking has a central role in dysregulated nucleic acid sensing by B cells and the innate immune system. The transmembrane protein UNC93B1 regulates the localization of TLR7 to endosomes[98] (Fig. 4). TLR7 and TLR9, normally restricted to endolysosomal compartments, become

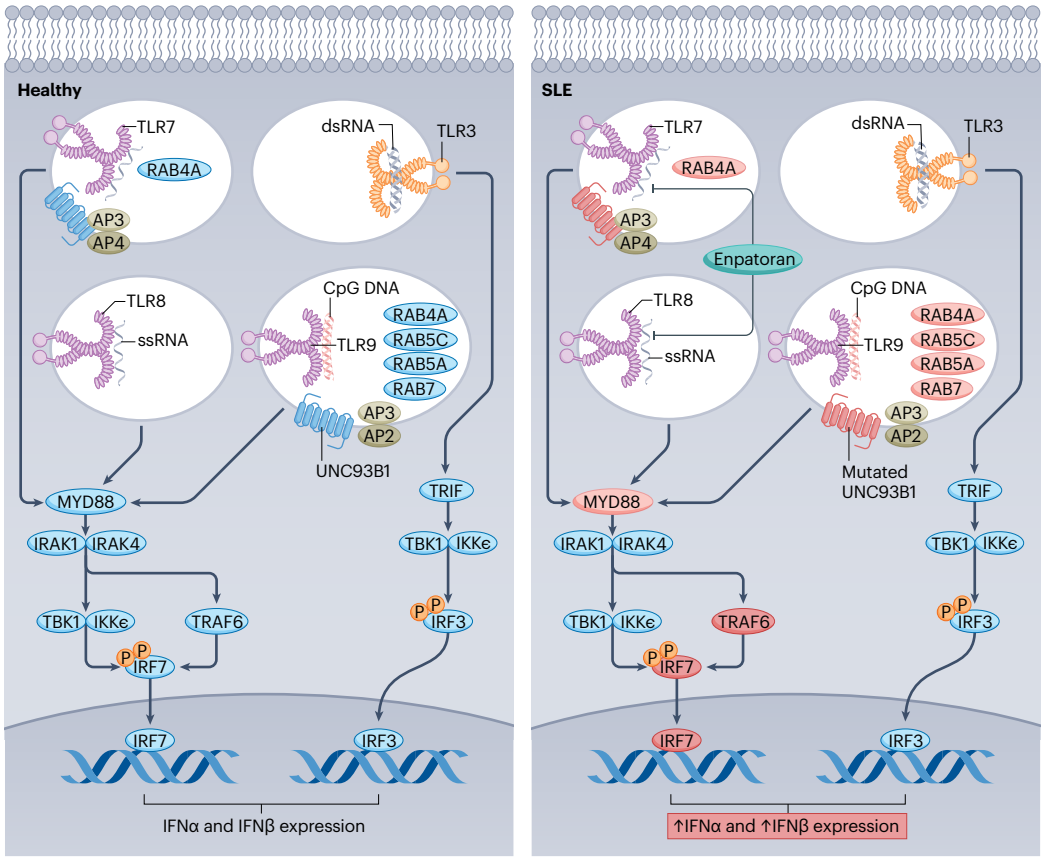


Fig. 4 | Regulation of TLR-mediated interferon production via endosome traffic. Toll-like receptor (TLR)-mediated interferon production is altered in systemic lupus erythematosus (SLE) (right). In healthy conditions (left), single-stranded RNA (ssRNA), double-stranded RNA (dsRNA) and CpG DNA from viruses and bacteria activate TLR3, TLR7, TLR8 and TLR9, initiating MYD88-dependent and TRIF-dependent signalling. TLR7 and TLR9 require endosomal trafficking through RAB5A$^+$, RAB4A$^+$ and RAB7$^+$ endosomes[108]. RAB4A directly binds CD2-associated protein (CD2AP)[60,204] and interacts with AP1 (ref. 26), AP2 (ref. 281) and AP3 adaptor proteins[26] (not shown). Deletion of CD2AP abrogates dendritic cell migration[282]. Both TLR7 and TLR9 signalling depend on AP3 (ref. 283). UNC93B1 (shown in blue, left) regulates TLR7 and TLR9 endosomal trafficking, using adaptor proteins AP2 and AP4 for TLR9 and TLR7 transport, respectively[66]. In SLE (right), mutated forms of UNC93B1 (shown in red, right) skew trafficking towards TLR7, amplifying MYD88-mediated and TRAF6-mediated expression of IFNα and IFNβ[103]. Enpatoran, a dual TLR7 and TLR8 inhibitor (shown in green), has shown preliminary evidence for safety and efficacy in SLE[104]. AP, accessory protein; dsDNA, double-stranded DNA.

hyperactivated in SLE owing to overexpression, defective trafficking (for example, via UNC93B1), and/or persistent engagement with self-RNA or DNA[99,100]. UNC93B1 controls homeostatic TLR7 activation by balancing TLR9 to TLR7 trafficking; pro-inflammatory mutations, such as D34A, skew this balance, promoting TLR7-mediated B cell-dependent CD4 T cell activation in mouse models[101].

UNC93B1 mutations can cause monogenic SLE or chilblain lupus owing to differentially enhanced TLR7 and TLR8 signalling over TLR9 signalling[67,68]. Similarly, missense mutations in *UNC93B1* have been associated with either autosomal dominant or autosomal recessive forms of SLE in multiple families[67]. G325C and I317M amino acid substitutions in UNC93B1 enhance TLR7 signalling and type I interferon production in patients with SLE and chilblain lupus[67]. These mutations activate TLR7 signalling both in monocytes and pDCs and elicit excessive type I interferon (IFNα and IFNβ) production, hallmarks of SLE[67,68,102]. Mechanistically, SLE-associated *UNC93B1* mutations promote MyD88-mediated and TRAF6-mediated expression of IFNα and IFNβ via preferential TLR7 signalling[103]. Enpatoran, a dual TLR7 and TLR8 inhibitor, has shown preliminary evidence of safety and efficacy in SLE[104].

Viral infections are well-established triggers of disease flares in patients with SLE and other rheumatic diseases[105,106]. Viral proteins can directly interact with Rab GTPases[107]. Additionally, viral RNA can activate TLR7 and TLR9, a process that is tightly regulated by endosomal trafficking involving RAB4A$^+$ and RAB7A$^+$ endosomes[108] (Fig. 4).

Endosomal TLR signalling is also critical for xenobiotic-induced autoimmunity, as demonstrated by the requirement of TLR trafficking from the endoplasmic reticulum to endolysosomal and phagosomal compartments for $HgCl_2$-induced hypergammaglobulinaemia and autoantibody production, independent of type I interferon signalling[100]. In SLE, patients carrying E92G and R336L variants in *UNC93B1* exhibit hypergammaglobulinaemia and expansion of memory-switched B cells, consistent with enhanced B cell hyperresponsiveness driven by TLR7 hyperactivity[102]. These findings indicate that type I interferon production by pDCs and autoantibody generation by B cells could be independently triggered through TLR signalling in SLE.

Rheumatoid arthritis. In rheumatoid arthritis, synovial fibroblasts exhibit increased endocytic recycling involving RAB44 (ref. 109) and TLRs that enhance invasiveness and cytokine responsiveness[110]. These processes involve the overexpression of endosome-bound TLRs (such as TLR7, TLR8 and TLR9) on rheumatoid arthritis synoviocytes[111]. TLR7 expression is also upregulated on CD8 T cells in rheumatoid arthritis[112]. Endogenous ligands, such as U111snRNA[113], miR-let-7b[114] and extracellular miR-574-5p, activate TLR7 and TLR8 signalling, driving osteoclast differentiation and contributing to joint destruction[115,116]. Neutrophil extracellular traps, which release nucleic acids into the extracellular space, serve as additional sources of TLR ligands in rheumatoid arthritis[111,117]. Neutrophil extracellular traps are internalized by macrophages in rheumatoid arthritis via RAB5A-trafficked endosomes, triggering the production of pro-inflammatory cytokines such as IL-6 and TNF[118]. Similarly, TLR4 activation by lipopolysaccharides (LPS) in macrophages depends on RAB5A-mediated endocytosis in rheumatoid arthritis[119]. Given the involvement of endosome traffic in rheumatoid arthritis pathogenesis, pro-inflammatory RAB5A alone or in combination with TLRs might serve as novel targets for therapeutic interventions.

Antigen processing

Endosomes serve as primary compartments for the internalization and processing of exogenous antigens, such as bacteria or viruses, by antigen-presenting cells (APCs) through processes such as phagocytosis and endocytosis[120,121]. Endosomes guide phagocytosed cargo for presentation via MHC class I and class II pathways[122]. The type of receptor used for internalization can determine the initial routing and subsequent processing of the antigen. Specific sorting signals on the cytoplasmic tails of receptors guide them, along with their internalized cargo, into various endosomal pathways[123]. For instance, some receptors target antigens to non-degradative endosomes for cross-presentation, whereas others lead to rapid degradation in lysosomes[124]. In particular, RAB4-directed[125,126] and endophilin A2-directed endosome traffic promotes antigen presentation by B cells[127].

HLA-B27, a MHC class I molecule, is strongly associated with susceptibility to spondyloarthropathies, particularly ankylosing spondylitis[128]. Within APCs, endosome-derived vesicular traffick facilitates HLA-B27-mediated antigen presentation at the immunological synapse, promoting activation of CD8 T cells in ankylosing spondylitis[129]. Notably, β2-microglobulin-free HLA-B27 heavy chains, including disulfide-linked homodimers ($B27_2$), can be expressed at the cell surface in ankylosing spondylitis following endosomal recycling of conventional β2-microglobulin-associated HLA-B27 heterotrimers. These free heavy-chain forms, including $B27_2$, engage innate immune receptors on T cells, natural killer cells and myeloid cells, thereby promoting pro-inflammatory signalling[130]. Although direct mechanistic evidence is lacking, genes involved in endosomal trafficking, such as *RAB5C*, *SYNJ1* and *RNF19B*, are overexpressed in synovial tissue-infiltrating T cells and monocytes from patients with ankylosing spondylitis[131]. *SYNJ1* encodes synaptojanin 1, a phosphoinositide phosphatase critical for synaptic vesicle recycling and membrane trafficking[132], whereas *RNF19B* encodes a ubiquitin ligase involved in autophagy[133]. Thus, endosome trafficking pathways might contribute to enhanced MHC class I-dependent antigen presentation in ankylosing spondylitis[134].

Immune cell metabolism

Endosome traffic influences immune cell metabolism by regulating the cell-surface expression of receptors that mediate nutrient uptake. These receptors include glucose transporters (glucose transporter 1 (GLUT1) and GLUT4)[135], CD71 (the transferring receptor that mediates iron uptake)[136] and the CD98–SLC7A5 heterodimer, which mediates the transport of branched-chain amino acids (including leucine, isoleucine and valine) and aromatic amino acids (including tryptophan, kynurenine, tyrosine and phenylalanine)[3] (Fig. 2a). Beyond SLC7A5, CD98 also forms heterodimers with SLC7A6 or SLC7A7, which transports arginine and lysine, and SLC7A11, which transports cysteine and cystine.

Endosomal pathways are also involved in mitochondrial metabolic pathways. RAB4A controls endosomal trafficking of DRP1 to the lysosome, and RAB4A-driven DRP1 depletion promotes the accumulation of oxidative stress-generating mitochondria[31]. In parallel, nutrient uptake supports distinct metabolic programmes across immune cell subsets. Glucose fuels glycolytic flux[137], which predominates in CD4 effector T cells[137], whereas iron supports mitochondrial biogenesis[136]. By contrast, CD8 T cells and regulatory T (T_{reg}) cells rely on mitochondrial respiration for survival[138]. Overexpression of phosphoenolpyruvate carboxykinase 1 (PCK1) can enhance glycolytic activity and the effector functions of tumour-infiltrating CD4 and CD8 T cells[139]. Additionally, effector memory CD8 T cells might shift towards glycolysis upon viral infection[140].

During enhanced metabolic activity, the integrity of a cell depends on the maintenance of a reducing environment, the availability of reduced glutathione and the production of NADPH by the pentose phosphate pathway[141]. Notably, glutathione depletion activates mTORC1 in T cells from patients with SLE, an effect that can be reversed by treating patients with its amino acid precursor N-acetylcysteine[142]. Diminished expression of SLC7A11 and the depletion of glutathione predispose renal tubular epithelial cells to ferroptosis in lupus nephritis[143] (Fig. 2a). mTOR has an important role in sensing amino acid sufficiency[144], a process that depends on dynamin-mediated endocytosis, which delivers amino acids to the lysosome and facilitates the recruitment and activation of mTORC1 and mTORC2 onto the lysosomal surface[3,145]. Distortions of these endosomal pathways lead to metabolic dysregulation and contribute to autoimmune rheumatic disorders, such as SLE, as reviewed elsewhere[146].

T cell lineage specification

Endosomal trafficking regulates the surface expression of receptors that are critical for signal transduction in adaptive immune cells, including both T cells[3,38,60] and B cells[30,125,147]. In T cells, recycling endosomes deliver T cell receptors (TCRs) to the plasma membrane, supporting immunological synapse formation and sustained signalling[148]. TCR internalization occurs via distinct endocytic pathways depending on ligand engagement: ligand-bound TCRs are internalized together with trogocytosed MHC from APCs through a clathrin-independent process[149], whereas non-engaged TCRs are internalized by RAB5 via clathrin-dependent endocytosis and recycled to the plasma membrane through $RAB4^+$ recycling endosomes[150,151].

TCR signalling also depends on the formation of supramolecular activation clusters at the T cell side of the immunological synapse[152]. RAB4A regulates the recycling of CD71 (ref. 153), which is also recruited to the supramolecular activation cluster in CD4 T cells[154]. RAB4A promotes surface expression of CD71 in CD4 but not in CD8 T cells, whereas RAB4A selectively promotes the recycling and expression of CD98 in CD8 T cells[3]. Thus, RAB4A-mediated endosome traffic initiates distinct, cell-type-specific metabolic reprogramming via these nutrient-sensing transporters in CD4 and CD8 T cells[3] (Fig. 2b). In T_{reg} cells, CTLA4 surface expression and recycling are also regulated by endosomal trafficking pathways. The expression of FOXP3 and the immunosuppressive

function of T_{reg} cells critically depend on CTLA4, the deficiency of which results in fatal autoimmunity[155]. Endosomal trafficking of CTLA4 is controlled by the LPS-responsive beige-like anchor protein (LRBA) and RAB11 (ref. 156). RAB4B has also been associated with T cell dysfunction and is implicated in disrupting the balance between T helper 17 cells and T_{reg} cells, a dysregulation linked to the development of insulin resistance[157].

Finally, endosomal trafficking facilitates mTOR activation, glycolysis and mitochondrial metabolism via GLUT1-mediated glucose transport[137] and CD71-mediated iron uptake, as discussed in the previous section. These metabolic processes support the development of effector memory T cells re-expressing CD45RA and contribute to the metabolic regulation of T helper 17 cell expansion relative to T_{reg} cells[136].

Endosomal trafficking in rheumatic diseases

Disruptions in endosome trafficking can lead to both immune dysregulation and end-organ vulnerability in rheumatic diseases (such as the compromised resilience of renal podocytes observed in SLE[158,159]), increasing susceptibility to inflammatory and tissue damage. Within the immune system, endosome traffic affects the surface expression of antigen receptors, such as the TCR, signal transduction via the TCR and other receptors, immune synapse formation, phagocytosis, and cytokine and antibody production. Beyond immune cells, aberrant endosomal trafficking affects cellular metabolism, autophagy and apoptotic signalling, contributing to end-organ injury. For example, pathological changes can occur in chondrocytes[160], fibroblasts[161] and renal podocytes[162], which are central to the progression of joint, connective tissue and kidney involvement in rheumatic diseases.

Systemic lupus erythematosus

RAB4A has emerged as a key molecular link between genetic susceptibility and immune dysregulation in SLE. Polymorphic alleles of *RAB4A* have been associated with susceptibility to SLE[163,164] and multiple sclerosis[165–167]. Overexpression and hyperactivation of RAB4A disrupt T cell development and contribute to SLE pathogenesis[3,31]. RAB4A expression is transcriptionally regulated via its 5′ promoter by redox-sensitive transcription factors NRF1 and USF1, and through its polymorphic LTR-enhancer by interferon-regulated IRF2 (ref. 168) (Fig. 2a). Thus, oxidative stress and activation of the interferon pathway contribute to RAB4A overexpression[168].

The gene encoding RAB4A originates from the *HRES1/RAB4* human endogenous retroviral element[38], which might function as a sensor of viral infection and potential mediator of autoimmunity[169,170]. Polymorphic alleles of *HRES1/RAB4* have been linked to autoantibody production and susceptibility to autoimmune diseases, including SLE[163,164] and multiple sclerosis[165,166]. Specific *HRES1* haplotypes influence autoantibody profiles and organ involvement, such as glomerulonephritis, in patients with SLE[163]. *HRES1* polymorphisms impact the expression RAB4A. Importantly, RAB4A is overexpressed in patients with SLE carrying rs451401CC alleles in the retroviral long terminal repeat of *HRES1*, which elicits mTORC1 activation[25].

In SLE, RAB4A-mediated downregulation of the autophagy regulator DRP1 impairs mitochondrial clearance, leading to the accumulation of damaged mitochondria and elevated oxidative stress[31,171]. Autophagy is generally diminished in SLE owing to cell-type-specific mTOR activation and underlying genetic defects[172,173]. Diminished autophagic flux leads to the accumulation of immunogenic debris and enhancement of TLR-dependent inflammation[174]. Lysosomal acidification is also impaired in lupus-prone models, altering endosomal maturation and antigen degradation[175,176]. Although RAB4A activates mTOR[168], the underlying molecular mechanisms are incompletely understood[3].

RAB4A directly facilitates mTOR trafficking to lysosomes, where mTOR senses amino acid sufficiency, including branched-chain amino acids, tryptophan and kynurenine, which are accumulated in lupus-prone mice[177,178] and patients with SLE[179]. The two mTOR protein complexes (mTORC1 and mTORC2) have crucial roles in lineage development both within the innate and adaptive immune systems[180,181]. Notably, mTOR enhances the expression of redox-sensitive transcription factor NRF1 (ref. 182) that binds to the *RAB4A* promoter[168]. Thus, RAB4A and mTOR form a positive feedback loop (Fig. 2a). mTOR itself localizes to endosomes[183] alongside small GTPases such as RAB4A[60], RAB7 (ref. 183) and RAB5 (ref. 184). Both RAB4A and RAB5 are overexpressed in T cells from patients with SLE[60] and lupus-prone mice[31]. However, only RAB4A overexpression, and not RAB5 overexpression, precedes mTOR activation, anti-nuclear antibody (ANA) production and the onset of nephritis in lupus-prone mice[31].

RAB4A promotes pro-inflammatory T cell lineage specification via mTOR activation at multiple levels, as demonstrated in lupus-prone B6 SLE1.2.3 triple-congenic (B6.TC) mice. In this model, constitutively active $RAB4^{AQ72L}$ drives mTOR activation and reveals cell-type-specific roles for RAB4A in promoting inflammatory T cell lineage development[3]. In CD4 T cells, RAB4A enhances iron uptake via CD71, supporting mitochondrial metabolism by increasing mitochondrial accumulation, facilitating recycling and expression of CD71 (which provides iron for electron transport[136]), and increasing mitochondrial ATP production[3]. This metabolic reprogramming supports elevated flux through the tricarboxylic acid cycle and pentose phosphate pathway, thereby sustaining cell proliferation. In CD8 T cells, RAB4A accelerates the recycling and surface expression of CD98 (Fig. 2a), which serves as a receptor for branched-chain amino acids, phenylalanine, tyrosine and tryptophan metabolites such as kynurenine. Kynurenine accumulates in serum and CD8 T cells via CD98 uptake in SLE[19,31], contributing to oxidative stress and CD8 T cell depletion. This imbalance amplifies inflammation by favouring CD4 T cell expansion over CD8 T cells. Activation of RAB4A-mediated mTOR pathways augments ANA and antiphospholipid autoantibody production and promotes glomerulonephritis in mice[3]. By contrast, targeted inactivation of RAB4A in T cells, or pharmacological blockade of mTOR, abrogates mTOR hyperactivation, prevents lineage skewing and attenuates autoimmune pathology[3]. Notably, elevated CD98 expression by T cells predicts the therapeutic response to mTOR blockade in patients with SLE[3,185].

RAB4A also promotes the endocytic recycling and surface expression of CD38 (ref. 186), a transmembrane glycoprotein expressed by multiple immune cell types that has an important role in NAD^+ metabolism. Elevated expression of CD38 in SLE consequently drives NAD^+ depletion, activates mTORC1 and suppresses IL-2 production in CD4 T cells. Mechanistically, CD38 activity depletes NAD^+ and leads to the build-up of nicotinamide and ADP-ribose and a secondary reduction in cyclic ADP-ribose levels. CD38 is internalized by RAB5A[187] and is recycled by RAB4A[186]. Notably, RAB4A-dependent upregulation of CD38 and associated IL-2 suppression occur independently of mTOR signalling. Instead, enhanced activity of CD38 elevates STAT3 expression and acetylation as well as FOXO1 expression, collectively contributing to IL-2 repression in CD4 T cells[186]. Together, these findings identify a previously unrecognized RAB4A–CD38 signalling axis that links receptor trafficking to pro-inflammatory metabolic reprogramming, highlighting potential therapeutic targets in SLE[188] (Fig. 5).

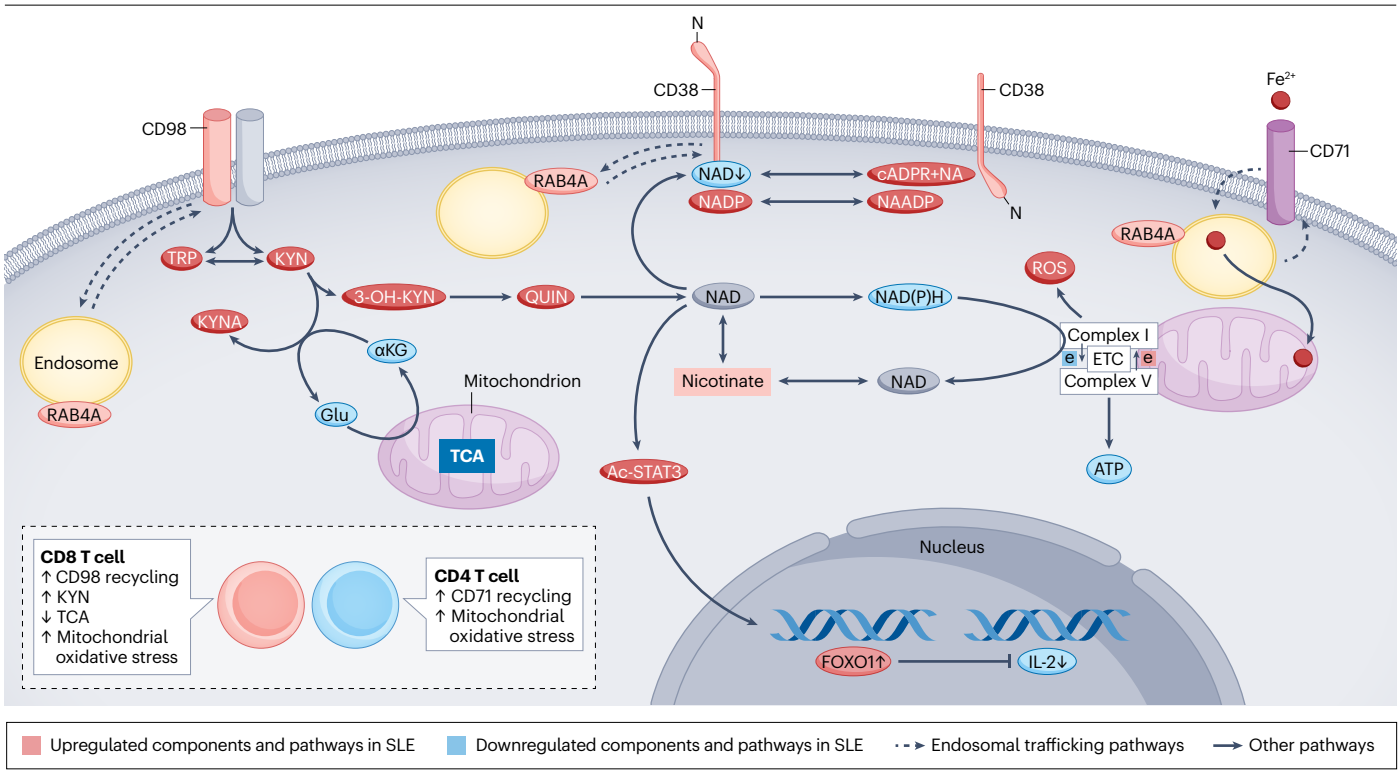


Fig. 5 | RAB4A-recycled receptors synergistically promote mitochondrial oxidative stress in T cells in SLE. RAB4A promotes the recycling of CD71 and CD98 in $CD4^+$ and $CD8^+$ T cells, respectively[3], as well as CD38. CD98 facilitates the transport of kynurenine (KYN), a precursor for de novo NAD biosynthesis, yet KYN metabolism depletes α-ketoglutarate (αKG), a key tricarboxylic acid (TCA) cycle intermediate. Notably, immune cells can make NAD from KYN[284]. Concurrently, CD38 — a bidirectional ectoenzyme — reduces NAD levels both intracellularly and extracellularly[285], impairing electron transport chain (ETC) activity and triggering reactive oxygen species (ROS) generation at complex I[286]. Increased activity of CD38 also promotes STAT3 expression and acetylation, and subsequent FOXO1 expression, and suppresses IL-2 expression in CD4 T cells. In parallel, CD71-mediated iron uptake exacerbates mitochondrial oxidative stress and promotes ferroptosis[287]. Together, these processes converge to amplify metabolic stress in systemic lupus erythematosus (SLE) T cells, with molecules shown in blue downregulated and those in red upregulated in SLE. 3-OH-KYN, 3-hydroxykynurenine; Ac-STAT3, acetylated STAT3; cADRP, cyclic ADP-ribose; NA, nicotinic acid; NAADP, nicotinic acid adenine dinucleotide phosphate; QUIN, quinolinic acid.

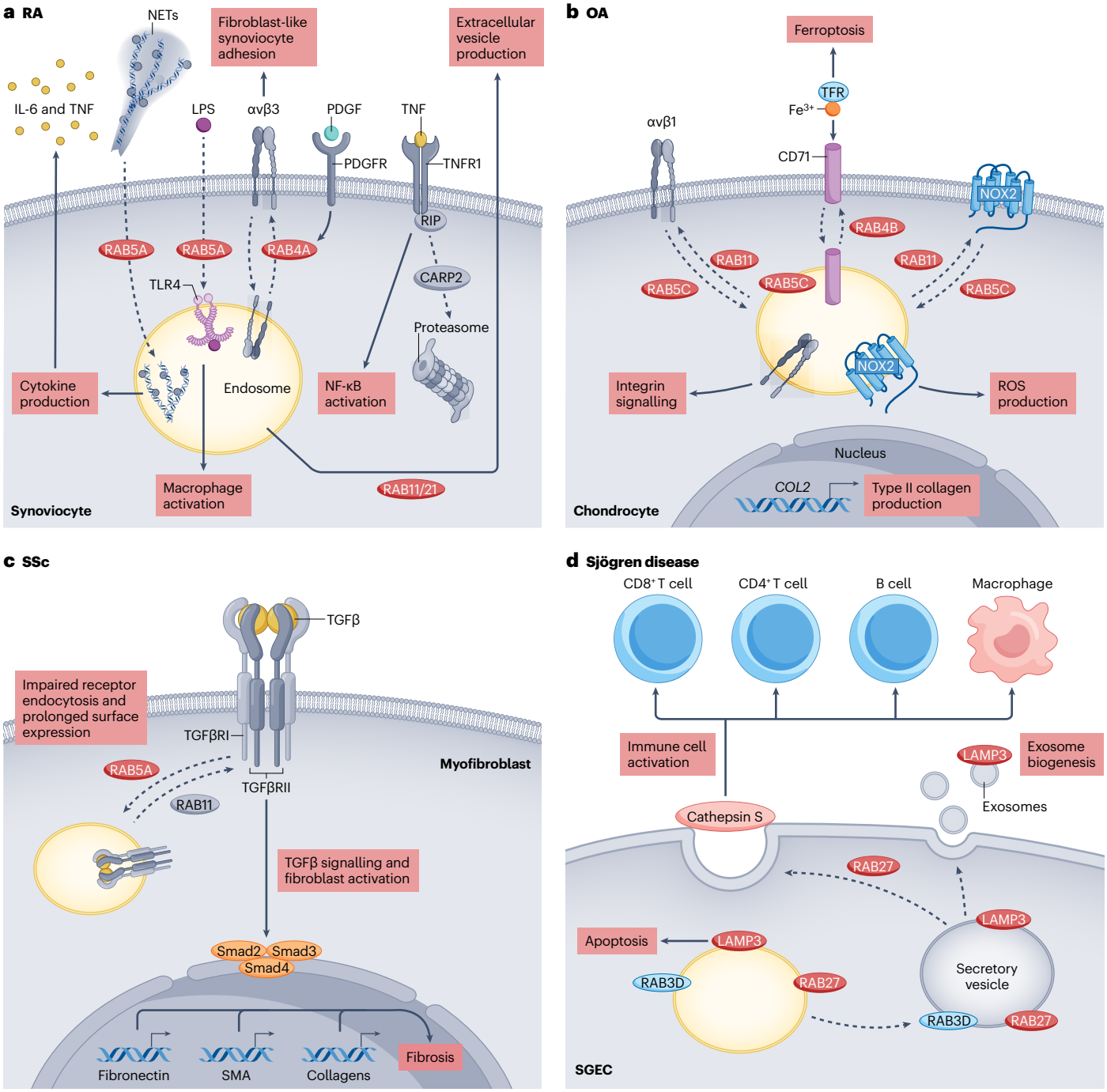
Although RAB4A interacts with CD4, CD71 and CD2AP, it does not interact with the CD8 antigen[60]. Intracellular CD8 expression has been observed in monocytes[189]; however, the potential association of CD8 with endosomal compartments, its recycling dynamics or targeting for lysosomal degradation remain undefined. In terms of other RAB GTPases[31], palmitoylated CD8 associates with lck in lipid rafts[190], a configuration that might facilitate interaction with $RAB11^+$ endosomes[191]. Within CD8 T cells, RAB27A regulates the release of cytotoxic granules[192] and is notably overexpressed in lymphocytes from patients with SLE[193]. Finally, in the B cell compartment, RAB7 controls immunoglobulin class switching and plasma cell survival via CD40 trafficking and NF-κB signalling in murine models of SLE, directly linking endosomal dynamics to humoral autoimmunity[30].

Lupus nephritis

Lupus nephritis, a severe manifestation of SLE, arises from infiltration of the kidney by cells of the innate and adaptive immune system[194], deposition of immune complexes[195] and intrinsic defects in renal cell homeostasis, potentially involving dysregulated endosomal traffic[196]. Disruption of endosomal protein sorting impairs podocyte integrity and contributes to glomerular injury in humans and mouse models of nephritis[162,197]. Deletion of key endocytic traffic regulators, including class III phosphatidylinositol 3-kinase vacuolar protein sorting 34 (Vps34), dynamin and synaptojanin, results in aberrant endosomal membrane morphology in podocytes, accompanied by foot process effacement and proteinuria in mouse models[198,199]. Endosomal uptake of IgG via the natural Fc receptor (FcRn) is required for immune complex-induced autoimmunity[200] and glomerulonephritis[201]. Deletion of CD2AP, an endosomal protein that is critical for stabilizing contacts between T cells and APCs, leads to congenital nephritis syndrome[202]. Notably, both FcRn[203] and CD2AP interact with RAB4A in T cells[7] and podocytes[204]. Whether activation of RAB4A directly affects podocyte function in SLE remains to be determined[3].

Rheumatoid arthritis

In rheumatoid arthritis, endosomal trafficking regulates integrin recycling, which contributes to persistent fibroblast migration and cartilage destruction. The αvβ3 integrin, expressed on activated macrophages, osteoclasts and endothelial cells[205], mediates adhesion of fibroblast-like synoviocytes (FLSs) in rheumatoid arthritis joints[206]. Platelet-derived growth factor (PDGF) activates FLSs in rheumatoid arthritis joints[207,208], and is involved in RAB4-dependent recycling of αvβ3 integrins (Fig. 6a).



RAB4 mediates the recycling of αvβ3 integrin from early endosomes to the plasma membrane, supporting cell migration[209,210]. Further downstream, the RAB4A effector protein Rabip4 mediates cell migration, as shown in NIH 3T3 fibroblasts[210]. Furthermore, deficiency of RAB44, another regulator of endocytic recycling, blocks the development of collagen antibody-induced arthritis in a mouse model of rheumatoid arthritis[109].

Dysregulation of TNF receptor 1 (TNFR1) recycling sustains NF-κB activation in rheumatoid arthritis. Upon TNF stimulation, receptor-interacting protein kinase (RIP) – a death-domain-containing serine–threonine kinase – is heavily ubiquitinated at early cell-surface TNFR1 complexes. The ubiquitin ligase CARP2, which contains a phospholipid-binding domain, localizes to endocytic vesicles and is recruited to internalized early TNFR1 complexes, where CARP2

Fig. 6 | Endosome trafficking in other rheumatic diseases. Involvement of endosome trafficking in rheumatoid arthritis (RA), osteoarthritis (OA), systemic sclerosis (SSc) and Sjögren disease. **a**, In RA synoviocytes (such as macrophages and fibroblast-like synoviocytes), endosomal trafficking promotes various pathogenic processes. For example, neutrophil extracellular traps (NETs) are internalized in macrophages via RAB5A-trafficked endosomes, inducing the production of pro-inflammatory cytokines such as IL-6 and TNF. Lipopolysaccharide (LPS)-induced Toll-like receptor 4 (TLR4)-mediated macrophage activation also depends on RAB5A-mediated endocytic internalization. Integrin trafficking sustains fibroblast migration and cartilage destruction; αvβ3 integrin, expressed on activated macrophages, osteoclasts and endothelial cells[205], mediates fibroblast-like synoviocyte adhesion[206] and is recycled by RAB4 in response to platelet-derived growth factor (PDGF) signalling[209,210], promoting migration. Dysregulation of TNF receptor 1 (TNFR1) recycling sustains NF-κB activation in RA. CARP2, a ubiquitin protein ligase on endocytic vesicles, limits TNF-induced NF-κB activation by targeting internalized TNFR1 for proteasome-mediated degradation[211]. Extracellular vesicles from arthritic mice express glucose transporter 1 (GLUT1)[212], which is trafficked via endosomal pathways involving RAB11 (ref. 215) and RAB21 (ref. 216). **b**, OA chondrocytes exhibit RAB5C-dependent reactive oxygen species (ROS) production[160]; NADPH oxidase 2 (NOX2) is a major source of ROS and is regulated via endosomal traffic by RAB5C and RAB11. ROS-producing endosomes (called redoxosomes) contain NOX2 and mediate αVβ1 integrin signalling. Type II collagen expression is also linked to RAB5A; chondrogenic progenitor cells that lack RAB5C overexpress multiple chondrogenic markers and exhibit increased synthesis and deposition of collagen type II (COL2)[219]. Additionally, RAB4B is overexpressed in OA synovial tissue; however, its protective or permissive role in pathogenesis needs clarification[220]. Chondrocytes express CD71 (ref. 221), which might contribute to their loss in OA via ferroptosis[222]. **c**, SSc is characterized by excessive collagen synthesis resulting in fibrosis across multiple organ systems[223]. Under normal conditions, transforming growth factor-β (TGFβ) receptors (TGFβR) are internalized through clathrin-mediated endocytosis by RAB5A[225], and then returned to the plasma membrane via a RAB11-dependent mechanism[226]. In SSc, impaired endocytosis of TGFβ prolongs surface TGFβ signalling, promoting fibroblast activation and fibrosis[224]. **d**, Sjögren disease is characterized by increased exosome biogenesis. LAMP3 (also known as CD63) is a component of both early and late endosomes and exosomes, and is overexpressed in the salivary gland epithelial cells (SGECs) of people with Sjögren disease, which predisposes these cells to apoptosis[231]. Concurrently, loss of RAB3D from secretory vesicles and increased RAB27-mediated release of cathepsin S in tears amplify local inflammation[233]. Cathepsin S functions as a potent activator of T cells, B cells and other immune cells, fuelling immune responses and perpetuating glandular damage[234]. For all the panels, molecules shown in red are upregulated in disease, those shown in blue are downregulated in disease; dashed arrows indicate endosome trafficking and solid arrows represent other pathways. RIP, receptor-interacting protein kinase; TFR, transferrin; TNFR1, TNF receptor 1.

targets RIP for proteasome-mediated degradation, thereby limiting TNF-induced NF-κB activation[211] (Fig. 6a). CARP2 might thus function as a negative regulator of NF-κB-driven inflammation in rheumatoid arthritis by modulating endosomal trafficking[211].

Extracellular vesicles are also implicated in rheumatoid arthritis. Extracellular vesicles from arthritic mice express the joint-homing receptor αVβ3 integrin[212]. Extracellular vesicles from both arthritic and healthy mice preferentially migrate to the inflamed synovia and avoid healthy joints[212]. Similarly, plasma extracellular vesicles from patients with rheumatoid arthritis overexpress αV integrin, and these vesicles are efficiently internalized by LPS-activated or TNF-activated human synovial cells in vitro. Extracellular vesicles accumulate in both the plasma and synovial fluid of patients with rheumatoid arthritis[213]. Extracellular vesicles contribute to cell-to-cell communication and have a profound effect on immune responses, affecting the production of TNF, IL-6 and IL-1β by monocytes and macrophages[214]. Importantly, extracellular vesicles from arthritic mice express GLUT1 (ref. 212), which is trafficked via endosomal pathways involving RAB11 (ref. 215) and RAB21 (ref. 216). Taken together, these findings indicate that these extracellular vesicles might spread inflammation through the bloodstream of patients with rheumatoid arthritis.

Osteoarthritis

Metabolic dysfunction, including oxidative stress, has long been implicated in osteoarthritis[217]. Reactive oxygen species (ROS)-producing endosomes (called redoxosomes) contain NADPH oxidase 2 (NOX2), which mediates αVβ1 integrin signalling and induces matrix metalloproteinase production in chondrocytes in osteoarthritis[160]. Integrins connect and embed chondrocytes into the extracellular cartilage matrix[218]. RAB5C expression is elevated in ROS-producing chondrocytes in osteoarthritis, suggesting a role for receptor internalization via endosome trafficking[160]. Chondrogenic progenitor cells, present in osteoarthritis cartilage, contribute to fibrocartilaginous extracellular matrix production. Notably, chondrogenic progenitor cells lacking RAB5C overexpress multiple chondrogenic markers and exhibit increased synthesis and deposition of type II collagen[219]. These findings identify RAB5C as a promising therapeutic target to retain chondrocyte integrity and boost type II collagen production in osteoarthritis (Fig. 6b). RAB4B is also overexpressed in osteoarthritis synovial tissue; however, its role in osteoarthritis — whether protective or pathogenic — remains to be clarified[220]. Chondrocytes also express CD71 (ref. 221), which might contribute to the loss of chondrocytes via ferroptosis in osteoarthritis[222]. Thus, targeting CD71-mediated iron uptake could represent a novel therapeutic strategy for osteoarthritis (Table 1).

Systemic sclerosis

Systemic sclerosis (SSc; also referred to as scleroderma) is characterized by excessive collagen synthesis and widespread fibrosis across multiple organ systems[223]. A key driver of this fibrotic process is impaired endocytosis of transforming growth factor-β (TGFβ) receptors[224], which prolongs surface signalling and sustains fibroblast activation[224]. TGFβ receptors are internalized through clathrin-coated pits in a RAB5A-dependent manner[225], and recycled back to the plasma membrane through RAB11-mediated traffic[226] (Fig. 6c). Additionally, TGFβ receptor I might also undergo caveolin-mediated internalization[227]. Importantly, caveolin 1 deficiency disrupts this pathway, resulting in increased receptor retention at the cell surface and prolonged TGFβ signalling[228], thereby promoting excessive extracellular matrix deposition[229]. These findings highlight that both major endocytic pathways (clathrin-mediated endocytosis and caveolin-mediated endocytosis) can independently mediate the internalization of TGFβ receptors. Moreover, clathrin-mediated and caveolin-mediated endocytic pathways can converge during TGFβ receptor endocytic trafficking[227]. Beyond TGFβ signalling, endosomal pathways also influence immune responses in SSc. For example, the expression of endosome-bound sensor TLR9 is increased in patients with SSc and correlates with enhanced type I interferon signalling[230].

Table 1 | Endosome traffic-directed therapeutic targets in rheumatic diseases

Drug	Target	Mechanism	Disease context	Refs.
Targeting RAB GTPases				
3-PEHPC	GGT-II and RAB4A	Endosomal traffic modulation	SLE	31
Neoandrographolide	RAB5A	Inhibition of osteoclast proliferation	OA	254
Targeting TLRs				
Enpatoran (M5049)	TLR7 and TLR8	TLR inhibition and IGS suppression	SLE	104
E6742	TLR7 and TLR8	TLR inhibition and IGS suppression	SLE	247
MHV370	TLR7 and TLR8	TLR inhibition and IGS suppression	SLE	248,249
Modulation of autophagy				
Hydroxychloroquine	Lysosomal v-ATPases	Autophagy inhibition	RA and SLE	268
Rapamycin	mTORC1 (via FKBP12)	mTOR inhibition	SLE	185,261,262, 269–272
Eltrombopag	TFEB	Suppression of autophagy through transcriptional inhibition of TFEB	SLE, ITP and APS	265–267
Modulation of metabolism				
Daratumumab	CD38	Disruption of NAD and calcium metabolism	SLE	188
PPMX-T003	CD71	Disruption of iron metabolism	SLE and PCV	136,251
IGN523	CD98	Inhibition of tryptophan, kynurenine and BCAA transport	SLE and AML	3,273

AML, acute myeloid leukaemia; APS, antiphospholipid syndrome; BCAA, branched-chain amino acids; GGT-II, geranyl-geranyl transferase type II; IGS, interferon gene signature; ITP, immune thrombocytopenia; mTORC1, mechanistic target of rapamycin complex 1; OA, osteoarthritis; PCV, polycythemia vera; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TFEB, transcription factor EB; TLR, Toll-like receptor.

Sjögren syndrome

Sjögren syndrome is an autoimmune sialadenitis of unknown aetiology, characterized by inflammation and dysfunction of the salivary glands. As previously discussed, LAMP3 has a central role in exosome biogenesis. This tetraspanin protein is a component of both early and late endosomes. Within lysosomes, LAMP3 contributes to degradation processes. LAMP3 is also present in exosomes and is used as a reliable marker for these extracellular vesicles[55] (Fig. 6d). In patients with Sjögren syndrome, LAMP3 is overexpressed in salivary gland epithelial cells (SGECs), increasing the susceptibility of the cells to apoptosis[231]. Ectopic, adeno-associated virus-mediated overexpression of LAMP3 enhances SGEC apoptosis and reduces the expression of proteins involved in saliva secretion. Damaged SGECs release DAMPs, which activate immune cells via TLRs. These findings highlight the pathogenic role of distorted endosome trafficking in cells of target organs[232]. Disrupted endosomal and lysosomal trafficking, along with impaired autophagy and increased apoptosis, promotes exosomal release of DAMPs into the extracellular space. These DAMPs activate immune cells, specifically monocytes and macrophages, via TLRs, that amplify the inflammatory cascade in the salivary glands, attracting more immune cells characteristic of Sjögren syndrome[232]. In parallel, loss of RAB3D from secretory vesicles coincides with enhanced RAB27-mediated release of pro-inflammatory cathepsin S in the tears of patients with Sjögren syndrome[233] (Fig. 6d). Cathepsins are potent activators of T cells and B cells, driving inflammation[234]. However, cathepsin S inhibition failed to demonstrate clinical efficacy in a controlled clinical trial[235].

Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a severe, life-threatening hyperinflammatory condition that arises as a form of secondary haemophagocytic lymphohistiocytosis (HLH), typically in the context of rheumatic diseases or haematological malignancies. Mutations of *RAB27A* cause Griscelli syndrome type 2, a genetic form of HLH[236]. RAB27A is crucial for exocytosis of lytic granules by cytotoxic T cells and natural killer cells[236], directing late endosomal perforin-containing and granzyme-containing vesicles to the plasma membrane for targeted delivery to virus-infected or malignant cells via exosome secretion[237]. Loss-of-function mutations in *RAB27A* impair this cytotoxic mechanism, resulting in defective clearance of activated cells and persistent immune stimulation. In addition to impaired cytotoxicity, RAB27A deficiency promotes dysregulated phagocytosis by macrophages[238], prolonging the presence of phagocytosed targets in macrophages and eliciting persistent and uncontrolled activation of these cells. This process promotes haemophagocytosis and heightened production of pro-inflammatory cytokines, creating a 'cytokine storm' characteristic of both HLH and MAS[239]. Heterozygous *RAB27A* mutations might present with delayed-onset HLH or MAS in adulthood[240]. Indeed, secondary HLH, including MAS, is about tenfold more common than the primary form and typically presents in patients with uncontrolled rheumatic disease extending into adulthood[239,241].

Therapeutic implications and opportunities

Several emerging therapeutic strategies aim to restore endosomal homeostasis or target trafficking checkpoints to dampen inflammation in rheumatic diseases (Table 1). Hydroxychloroquine, a cationic amphiphilic compound and mainstay treatment of SLE, rheumatoid arthritis and Sjögren disease, exerts its immunomodulatory effects by increasing endosomal pH[242], thereby inhibiting autophagy and TLR7 activation[243]. Further downstream, this drug can thus suppress type I interferon production in primary pDCs from both healthy individuals and patients with SLE[244].

Small-molecule inhibitors of endosome trafficking are under investigation. These inhibitors include compounds directed against endosome-embedded proteins, such as UNC93B1 (ref. 245) and RAB GTPases[31], as well as upstream regulators, including mTOR and TFEB. For example, the RAB geranyl-geranyl transferase inhibitor 3-PEHPC disrupts RAB4A and RAB5A trafficking in vitro and attenuates ANA production, proteinuria and glomerulonephritis in MRL/lpr lupus-prone mice in vivo[31]. Similarly, the competitive RAB7 inhibitor CID-1067700, which interferes with GTP binding, reduces secretion of several inflammatory cytokines, including IL-1α, IL-8, IL-17A and IL-32, in adipocyte-derived mesenchymal stem cells (ASC52tel) in vitro[246], and suppresses B cell development and autoantibody production in vivo in MRL/lpr mice[30].

A series of dual inhibitors targeting endosome-bound TLR7 and TLR8 has shown preliminary clinical efficacy in SLE. In a double-blind placebo-controlled clinical trial, E6742 was found to be safe and was well tolerated, showing suppression of the interferon gene signature and signals of therapeutic efficacy signals[247]. MHV370, a selective oral inhibitor of TLR7 and TLR8, also restrained the interferon gene signature in mice and patients with SLE in vitro, and was well tolerated in healthy adults[248,249]. Enpatoran, formerly called M5049, exhibited therapeutic efficacy in lupus-prone mice[250] and preliminary evidence of safety and efficacy in human trials[104].

Various inhibitors that target endosomal mediators involved in cell metabolism are also under evaluation. For example, daratumumab, an antibody targeting endosome-trafficked CD38 (ref. 186) that is currently used in the treatment of myeloma, showed clinical benefit in six patients with refractory lupus nephritis[188]. Monoclonal antibodies directed against CD71 (ref. 251) and CD98 (ref. 249) — both trafficked via RAB4A[3] — are currently being evaluated in phase I clinical trials.

Natural compound screening has identified neoandrographolide (NAP), derived from the plant *Andrographis paniculate*, as a potential modulator of endosome traffic. Among 7,459 natural compounds screened, NAP was found to competitively bind the GDP–GTP groove on the surface of RAB5, thereby reducing its GTPase activity and inhibiting cell proliferation in vitro[252]. In addition to its effects on RAB5, NAP suppresses the production of nitric oxide and TNF in activated macrophages[253] and inhibits the formation of mature osteoclasts[254], both processes relevant to inflammation and tissue destruction in rheumatic diseases. RAB5A is overexpressed in T cells both in patients with SLE[60] and lupus-prone mice[31], providing further rationale for assessing the therapeutic potential of NAP in autoimmunity. Moreover, RAB5C expression is increased in ROS-producing chondrocytes in osteoarthritis[160]. Given that the amino acid sequences of RAB5A and RAB5C overlap by 86%, with 100% identity within the GTP-binding domain (Supplementary Fig. 1C), NAP could have therapeutic benefit for a broad range of rheumatic diseases.

Pharmacological inhibition of exosome release and uptake has shown protective effects in osteoarthritis[255] but potentially enhances inflammatory signalling in rheumatoid arthritis[256]. For example, GW4869, a widely used small-molecule inhibitor of neutral sphingomyelinase (a critical enzyme for exosome formation and release[255]), has demonstrated therapeutic benefit in mouse models of osteoarthritis[257]. Treatment with GW4869 increases type II collagen expression and reduces MMP3 expression in cartilage tissues of mice[257]. Moreover, GW4869 blocks the secretion of osteoclast-derived exosomal miR-212-3p, which otherwise suppresses anabolic activity and promotes catabolism in chondrocytes from mice and patients with osteoarthritis[258]. Beyond osteoarthritis, GW4869 also blocks the production of pro-inflammatory cytokines by macrophages and protects against myocarditis in the setting of sepsis[259]. In mice with myosin heavy-chain-directed experimental autoimmune myocarditis, serum exosomes carrying miRNA-142 induce immunometabolic dysfunction in CD4 T cells, contributing to disease pathogenesis. Pharmacological inhibition of exosome secretion with GW4869 mitigates disease severity, underscoring the indispensable role of exosomes in disease development[58]. By contrast, FLSs in rheumatoid arthritis secrete circular RNAs that promote anti-inflammatory polarization of macrophages[256]. Suppressing exosome release in this context might therefore inadvertently disrupt protective immune regulation. These findings highlight the importance of tailoring exosome-targeted therapies to the specific immunopathological context of each rheumatic disease.

TFEB is required for endosome formation during autophagy[62] (Fig. 3a). T_{reg} cells depend on autophagy for survival and, consistent with the role of autophagy in T_{reg} cell development, TFEB responds to T_{reg} cell-related cues in an mTORC1-dependent manner[260]. In SLE, autophagy is generally restrained in T_{reg} cells but increased in effector CD4 T cells[172]. Notably, rapamycin, which inhibits the mTOR pathway and thereby promotes autophagy, has been shown to enhance autophagic activity in T_{reg} cells in SLE[172]. This effect is associated with clinical improvement[185,261–263]. Eltrombopag, an FDA-approved thrombopoietin receptor agonist, has emerged as a direct modulator of TFEB. Eltrombopag binds to the basic helix–loop–helix leucine zipper domain of TFEB, disrupting its DNA-binding activity both in vitro and in vivo[264]. This interaction selectively inhibits the transcriptional activity of TFEB on a genomic scale and blocks autophagy in a dose-dependent manner, opening up new possibilities for cell-type-specific modulation of autophagy[172]. Several case series and retrospective studies have reported potential therapeutic benefit of eltrombopag in SLE[265], immune thrombocytopenia[266] and antiphospholipid syndrome[267], which warrant further investigation in prospective confirmatory studies. However, given that autophagy dysfunction is specific to cell type in SLE[172], systemic blockade of TFEB might be counterproductive in a subset of patients.

Conclusions

Endosomal trafficking has emerged as a central regulator of immune function and tissue homeostasis in rheumatic diseases. Beyond its canonical roles in intracellular sorting and exosome biogenesis, endosomal processing orchestrates antigen presentation, receptor signalling, cytokine secretion and cellular metabolism, processes that collectively shape the inflammatory landscape. Dysregulation of these pathways can lead to abnormal immune responses, inflammation and tissue damage. Continued elucidation of endosomal trafficking regulators across specific immune and end-organ cell subsets — using tools such as imaging flow cytometry, confocal microscopy and single-cell multi-omics — will deepen mechanistic understanding of rheumatic disease pathogenesis and guide the development of precision therapies. A more complete understanding of endosomal pathways in immune and stromal compartments holds promise for restoring immune tolerance and enhancing end-organ resistance, offering new avenues for durable disease control in rheumatic diseases.

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Review article

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Inflammation and pain as interconnected targets in axial spondyloarthritis

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Abstract

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease characterized by complex pain mechanisms that extend beyond inflammation. Although inflammatory nociceptive pain — primarily mediated by pro-inflammatory cytokines — represents the classic pathway and therapeutic target, many patients continue to experience pain despite suppression of inflammation. This residual pain often reflects non-inflammatory processes, including nociplastic and neuropathic pain. Central sensitization, a key mechanism of nociplastic pain, contributes to pain amplification and poor response to treatment. Fibromyalgia, considered the typical phenotype of nociplastic pain, can co-occur with axSpA and is associated with increased symptom burden and reduced efficacy of anti-inflammatory therapies. Neuropathic pain, albeit less common, can result from structural complications and requires targeted therapeutic approaches. In addition, biological sex differences further influence pain perception and treatment outcomes: female patients report more widespread pain, show higher rates of central sensitization and have a worse response to biologic therapies than male patients. Current treatment paradigms are effective for inflammation-driven symptoms but often fail to address the broader spectrum of pain phenotypes in axSpA. Future work should include the development of biomarkers to differentiate pain mechanisms, the refinement of assessment tools and the evaluation of multimodal therapies that target both inflammation and pain processes. This evolving understanding necessitates a shift from an inflammation-centric to a mechanism-informed approach to pain management in axSpA.

Sections

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Key points

- Pain in axial spondyloarthritis (axSpA) is multifactorial. Nociceptive, nociplastic and neuropathic components frequently coexist, and central sensitization is present in about 45–60% of patients, amplifying symptoms beyond their inflammatory origin.
- Fibromyalgia and widespread pain occur in up to one-quarter of patients with axSpA, confound disease activity scores and are linked to worse response to biologic therapies and overall disease burden.
- Sex differences are clinically relevant; women more often present with widespread and thoracic pain, higher central sensitization and worse treatment response, whereas men develop more structural damage but report lower disease activity.
- Cytokines such as TNF and IL-17 drive inflammatory nociceptive pain but also contribute to central and peripheral neuroinflammation, which links inflammation with neuropathic and nociplastic pain mechanisms in axSpA.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that primarily affects the axial skeleton, including the sacroiliac joints and spine. AxSpA includes non-radiographic axSpA, which is defined by the absence of definitive sacroiliac joint changes on conventional radiographs, and radiographic axSpA (formerly referred to as ankylosing spondylitis), for which there is evidence of definite radiographic damage[1]. The hallmark symptom of axSpA is chronic back pain, which often presents before 40 years of age. In axSpA, back pain is frequently described as 'inflammatory back pain' (IBP) (Box 1). IBP refers to a cluster of clinical features that raise suspicion of underlying inflammatory disease. Three sets of IBP criteria — the Calin[2], Berlin[3] and Assessment of Spondyloarthritis International Society (ASAS)[4] criteria — all rely on the characteristic features of IBP; however, the presence of IBP alone does not indicate the presence of underlying rheumatic inflammatory conditions.

Historically, pain in axSpA was viewed almost exclusively through a unidimensional lens, as a direct consequence of inflammation. Although other mechanisms were known, they were largely neglected in clinical practice and research. The advent of highly effective anti-inflammatory therapies shows that despite well-controlled inflammation, many patients continue to experience substantial symptoms. This residual pain often reflects mechanisms beyond inflammation, such as structural damage, altered central pain processing or neuropathic factors[5]. The recognition of these alternative pain mechanisms has prompted a paradigm shift towards a more nuanced, multidimensional understanding of pain in axSpA.

This Review is aimed at providing a comprehensive overview of the different mechanisms that contribute to pain in axSpA and highlights the clinical implications of this broader perspective. By promoting a multidimensional view of pain, we aim to refine disease assessment and management strategies, moving beyond an inflammation-centric model to improve patient outcomes.

Characteristics of pain in axial spondyloarthritis

Following axSpA diagnosis and the initiation of anti-inflammatory therapy, patients might continue to report pain. Pain in axSpA arises from multiple, often overlapping, mechanisms that include all types of pain: nociceptive pain, nociplastic pain and neuropathic pain (Table 1).

Nociceptive pain

Traditionally, axSpA pain was attributed solely to inflammation of the sacroiliac joints, spine or peripheral musculoskeletal structures (arthritis, enthesitis and dactylitis), owing to nociceptive pain[5]. This type of pain is typically localized, deep and aching, and has inflammatory characteristics in most patients (Box 1). Nociceptive pain is mediated by peripheral nociceptors activated by tissue injury or inflammation[6,7]. Inflammatory nociceptive pain responds to anti-inflammatory agents, including NSAIDs, biologic or targeted synthetic DMARDs (bDMARDs and tsDMARDs). However, nociceptive pain can also arise from non-inflammatory sources such as structural damage, concomitant degenerative or mechanical changes or muscle strain[5,8].

In axSpA, inflammation drives structural changes over time[9], including new bone formation leading to syndesmophytes and ankylosis, and bone loss as a result of osteoporosis. These processes alter spinal biomechanics and, at advanced stages, can result in a fully ankylosed spine. Interestingly, in some patients, advanced ankylosis itself might not be directly associated with pain, as inflammatory activity diminishes and movement in the affected segments becomes restricted; however, structural damage can indirectly lead to pain through several mechanisms. First, as motion is lost in ankylosed segments, increased mechanical stress is transferred to the remaining mobile areas of the spine, potentially causing persistent nociceptive pain. Furthermore, secondary osteoarthritis might develop in adjacent mobile spinal segments as a long-term consequence of altered biomechanics and chronic mechanical overload. Imaging has a key role in distinguishing pain related to active inflammation from pain caused by mechanical complications secondary to structural damage[10].

Overall, new bone formation in the sacroiliac joints and spine — the primary mechanism underlying structural damage progression in axSpA — does not necessarily translate into increased pain. In analyses of two long-term extension studies of TNF inhibitor trials, patient-reported outcomes, including pain, remained stable despite ongoing progression of structural damage[11].

Nociplastic pain

Nociplastic pain arises from altered nociception, typically in the absence of ongoing tissue or nerve injury[7,12]. Central sensitization, whereby spinal and supraspinal pain pathways amplify input, is considered the core mechanism of nociplastic pain. Signs of central sensitization occur in 45%–60% of patients with axSpA[13–17]. Fibromyalgia is considered the prototypical nociplastic pain syndrome and can co-occur with axSpA[18].

Currently, nociplastic pain pathophysiology can be broadly divided into two subtypes: descending (top-down) and ascending (bottom-up) pathways. Individuals with top-down nociplastic pain are thought to have a primary brain-based disorder, which often manifests early in life with emerging sleep or memory problems, followed by pain beginning in one body region, then gradually spreading to others into adulthood. The genetic and familial contribution to nociplastic pain seems strongest in these individuals with top-down nociplastic pain[19–21].

By contrast, individuals with bottom-up nociplastic pain usually have an identifiable nociceptive or neuropathic pain condition, upon which nociplastic pain develops secondarily. In these patients, treatment is often most effective when it targets both the central sensitization process and the underlying pain condition, in this case, axSpA[19,22].

In axSpA, nociplastic pain can be suspected if pain persists despite controlled inflammation, especially if pain is in multiple regions of the body. The presence of fatigue, sleep disturbances, cognitive dysfunction, depression and anxiety, all of which are known to occur in axSpA, increases the probability of nociplastic pain[23]. Patients with axSpA who have nociplastic pain frequently show higher scores in axSpA-related patient-reported outcomes[24] and worse response to NSAIDs, bDMARDs and tsDMARDs than those patients with nociceptive pain[24]. For example, a 'possible' or 'likely' nociplastic pain component (defined as a widespread pain index (WPI) of ≥4) was reported in 27% of patients (22% 'possible' and 5% 'likely') with radiographic axSpA receiving bDMARDs for at least 6 months with presumably sufficient control of inflammatory activity (although control of inflammation was not verified with MRI[25]). At the time of assessment, 21% of patients had a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of ≥4, indicating a high symptom burden. In multivariable linear regression, WPI was independently associated with the presence of residual symptoms[25].

Neuropathic pain

Neuropathic pain results from damage or disease of the somatosensory nervous system[7]. Clinically, neuropathic pain presents as burning, electric shock-like or shooting pain, often with paraesthesia or radicular radiation[6]. Although axSpA is not a condition that directly damages the nervous system, the prevalence of neuropathic pain in axSpA ranges between 22% and 56.9%[26,27], and could be caused by structural damage leading to nerve-root or spinal-cord compression, as observed in cauda equina syndrome or concurrent degenerative disease.

Overall, chronic pain in axSpA often involves overlapping phenotypes (Fig. 1), which are not mutually exclusive and might be present at the same time in the same patient[5]. Active inflammation provides 'nociceptive input' that can trigger peripheral sensitization (inflammatory mediators lower the threshold of local nociceptors, causing heightened pain sensitivity in affected tissues). If that input is prolonged, the dorsal horn neurons and pain-processing pathways in the central nervous system undergo neuroplastic changes — a process of central sensitisation — leading to persistent pain perception even after inflammation subsides, which could result in nociplastic pain[8,23]. At the same time, chronic structural damage might cause nerve irritation (neuropathic pain) and mechanical strain (nociceptive pain), all of which contribute to the total pain burden[8] (Fig. 2).

The clinical relevance of this complex construct is high; persistent pain in axSpA should prompt an evaluation for predominant pain mechanisms, rather than reflexively assuming inflammation that is refractory to treatment. Identifying a neuropathic or nociplastic component (including fibromyalgia) has direct treatment implications; instead of switching anti-inflammatory treatment, the rheumatologist might need to address factors associated with nociplastic pain such as anxiety, depression, sleep disturbance and modify the management strategy by addressing non-nociceptive pain mechanisms.

Drivers of pain in axial spondyloarthritis

In axSpA, pain arises from a complex interplay of factors, making it difficult to isolate the contribution of each one individually. Traditionally, nociceptive pain has been attributed to pro-inflammatory cytokines and mechanical stress; however, emerging evidence suggests that these factors might also have a role in neuropathic and nociplastic pain. Additionally, coexisting fibromyalgia and biological sex-related differences are increasingly recognized as considerable contributors to the pain experience in patients with axSpA.

Box 1 | Core clinical features of inflammatory back pain

- Insidious (gradual) onset of chronic back pain
- Morning stiffness in the low back (typically ≥30 min)
- Improvement with exercise or activity (and no sustained relief from rest)
- No improvement with rest (pain might even worsen with inactivity)
- Pain at night, especially in the second half of the night, often improving upon getting up

The role of cytokines

Cytokines have a central role in the pathogenesis and persistence of pain in axSpA by driving inflammation, sensitizing nociceptors and contributing to central pain-processing abnormalities (Table 1). Among these cytokines, TNF and IL-17 are key mediators in the inflammatory response. In addition, these cytokines enhance the production of prostaglandins and other pain mediators, directly activating nociceptors and increasing pain perception.

The central role of TNF was first identified in biopsy-obtained sacroiliac joint samples from patients with axSpA, in which *TNF* mRNA was abundant[28]. TNF is recognized as a common downstream effector pathway in several immune-mediated inflammatory diseases, including axSpA. Functionally, TNF is an important activator and product of macrophages that stimulates cytokine production in immune cells and activates fibroblasts, leading to subsequent tissue remodelling[29,30]. TNF is also produced by neutrophils and activated T cells, which are enriched in the inflamed synovial membrane and entheseal structures[31]. The success of TNF inhibitors, which can reduce both inflammation and pain in axSpA, is the ultimate proof of the pivotal role of this pro-inflammatory cytokine[32,33]. The next successful studies were observed with IL-17 inhibitors and JAK inhibitors. Conversely, trials of drugs that inhibit IL-6, IL-23 and the IL-1 receptor have failed in axSpA[32].

IL-17A constitutes a major cytokine involved in the pathogenesis of axSpA; several IL-17A-producing cell types, including T helper 17 (T_H17) cells, γδ T cells and ILC3s, are present at entheseal vertebral sites. Enthesitis, a key feature of axSpA, arises from robust activation of prostaglandin E_2 (PGE_2) and the IL-23–IL-17 axis. This effect leads to the influx of innate immune cells into the entheses, followed by mesenchymal tissue responses and new bone formation[34,35]. The sustained production of $PGEE_2$ through cyclooxygenase-2 (COX-2) activation is associated with inflammatory responses, such as vasodilatation and neutrophil attraction to tissues, leading to spondylitis[36]. The inhibition of IL-17 and TNF has been shown to be effective for the resolution of enthesitis in axSpA[36].

Notably, IL-17A and PGE_2 are important pain mediators, which are expressed in the dorsal root ganglia. In animal studies, a single injection of IL-17A into the knee joint in rats elicited a slow developing and long-lasting sensitization of nociceptive C fibres of the joint in response to mechanical stimuli, which was not attenuated by neutralizing TNF[37]. Evidence showing successful inhibition of IL-17A–IL-17F heterodimers in axSpA has raised questions about the potential role of IL-17F in pain pathways[31]. This heterodimer shapes the potency, specificity and overall activity of these cytokines. Some studies suggest substantial redundancy between IL-17F and other IL-17 family members, but a distinct function of IL-17F has yet to be clearly defined[38,39].

Table 1 | Characteristics and drivers of pain phenotypes in axial spondyloarthritis

Aspect	Nociceptive pain	Neuropathic pain	Nociplastic pain
Mechanism	Tissue inflammation or damage	Compression of or damage to nerves	Central sensitization with amplified pain processing in the central nervous system
Distribution	Usually localized to affected areas (such as the low back and buttock area)	Pain can follow a radicular or peripheral nerve distribution (for example, sciatica) rather than staying localized to the back	Diffuse and widespread, not confined to sites of inflammation and can be multifocal (affecting the neck, back, peripheral joints and muscles)
Type	Often described as a dull, deep ache or throbbing	Burning, shooting, electric shock-like pain with possible numbness or tingling	Exceeds what objective findings would suggest, along with fatigue, poor sleep and symptoms of anxiety or depression
Timing	For inflammation-related nociceptive pain, symptoms are typically worse with rest and overnight and get better with activity Purely mechanical nociceptive pain might worsen with activity	Can be episodic and lancinating, with paraesthesia or weakness in the affected limb	Non-specific
Physical examination	Localized tenderness and swelling of the peripheral joints and entheses	Sensory loss or reflex changes corresponding to nerve damage along with diminished muscle strength	Physical examination is typically unrevealing apart from widespread tenderness (for example, positive tender points)
Imaging	Imaging can reveal active inflammatory changes in the axial skeleton	Inflammatory lesions do not explain this type of pain	Inflammatory lesions do not explain this type of pain
Main drivers of disease	Pro-inflammatory cytokines	Structural lesions in the peripheral nerve structure caused by mechanical damage or inflammation	Possible role of cytokines
Cytokines	Strong association with TNF and IL-17	Minor involvement of IL-17 and an unknown role of the JAK–STAT pathway	Minor involvement of IL-17 and the role of other cytokines is unclear
Main therapeutic interventions	NSAIDs, TNF inhibitors, IL-17 inhibitors and JAK inhibitors, in combination with non-pharmacological therapies	Gabapentinoids, SNRIs, TCAs, in combination with psychological approaches such as CBT and mindfulness	Gabapentinoids, SNRIs, TCAs, in combination with psychological approaches such as CBT and mindfulness
Mechanical stress	Exaggerated mechanical stress response is associated with enhanced IL-17 production	Role is unclear	Manual work increases pain, whereas regular physical activity is associated with better outcomes
Fibromyalgia	Persistent nociceptive pain is a risk factor for fibromyalgia	Fibromyalgia is associated with this type of pain	Fibromyalgia is considered a typical aspect of central sensitization
Female sex	Hormonal fluctuations, body composition and biomechanics are associated with this type of pain	More common in the female sex than in the male sex	More widespread pain pattern, more abnormalities on neuroimaging and more likely to experience diagnostic delay

CBT, cognitive behavioural therapy; GM–CSF, granulocyte–macrophage colony-stimulating factor; JAK, Janus kinase; SNRIs, serotonin-noradrenaline reuptake inhibitors; STAT, signal transducer and activator of transcription; TCAs, tricyclic antidepressants.

In addition, in some patients, persistent pain despite well-controlled inflammation suggests a major shift towards central pain mechanisms. Indeed, beyond nociceptive pain, cytokines might also contribute to neuropathic and nociplastic pain mechanisms. Chronic inflammation and cytokine-induced neuroinflammation can lead to structural and functional changes in peripheral and central pain pathways, potentially causing neuropathic pain[40,41]. Animal studies have shown that IL-17 is involved in the development and maintenance of neuropathic pain, inflammatory pain and cancer pain[42,43]. Other preclinical studies also suggest a role for IL-17A in neuropathic pain[34].

Additionally, cytokines can influence central sensitization, the hallmark of nociplastic pain, by altering the excitability of neurons in the spinal cord and brain, thereby amplifying pain signals even in the absence of ongoing inflammation[44]. The dependence of central sensitization on the presence of some cytokines such as IL-17, granulocyte–macrophage colony-stimulating factor (GM–CSF) and IL-6 is debated[45].

Data from the British Society for Rheumatology biologics register indicate that high disease activity and widespread pain concomitant to axSpA can predict the development of secondary fibromyalgia, whereas low disease activity, absence of widespread pain and initiation of TNF inhibitors predict resolution of fibromyalgia in axSpA[46]. Subsequently, uncontrolled inflammation (that is, nociceptive pain) during the early stages of axSpA might be associated with the development of nociplastic pain in the long term[46].

Finally, several cytokines, including TNF and IL-17, signal via JAK, which explains the efficacy of JAK inhibitors in axSpA but also the positive effect of these therapies on pain symptoms[47]. The JAK–STAT signalling pathway has been implicated in the processing of pain beyond its role in mediating inflammation. JAK inhibitors can alleviate a broad array of pain outcomes in both axial and peripheral joints[5]. Their effect on nociceptive pain has thus far been assessed using a limited number of questionnaires in cross-sectional studies, restricting firm conclusions; however, the JAK–STAT pathway is receiving increasing attention in the modulation of nociceptive responses given its clear role in cytokine signalling in several immune-mediated inflammatory diseases[5,45,48].

The role of mechanical stress

Mechanical stress has a crucial role in driving pain in axSpA by contributing to both inflammatory and structural disease processes.

In the context of nociceptive pain, mechanical stress might function as a trigger for inflammation. Repetitive mechanical strain, particularly at entheses, can lead to microdamage and elicit an immune system-mediated tissue-repair pathway in tendons and ligaments[49]. Mechanistically, an exaggerated mechanical stress response is associated with enhanced IL-17A production at entheseal sites and sustained production of PGE_2 through COX-2 activation, driving chronic inflammation, pain and progressive structural damage[31,50]. Ongoing inflammation at sites of high mechanical load can result in bone formation, syndesmophytes and ankylosis, leading to spinal stiffness and altered biomechanics[51–53]. As the spine loses flexibility, adjacent segments can experience compensatory mechanical stress, further perpetuating pain and dysfunction. Indeed, physically demanding jobs were traditionally associated with worse outcomes in axSpA, including functional limitation and more new bone formation[54]. Conversely, studies from the past 5 years indicate that exercise is associated with reduced disease activity[55]. In addition, persistent mechanical stress might also contribute to nociplastic pain mechanisms[56].

The role of fibromyalgia and illness perception

The presence of fibromyalgia introduces a nociplastic component, thus contributing to increased pain severity, widespread pain distribution and reduced treatment response. Persistent nociceptive pain is itself a risk factor for the development of nociplastic pain[57] as fibromyalgia is associated with sustained nociceptive pain in axSpA[5]. Studies suggest that fibromyalgia is more prevalent in patients with axSpA than in the general population; the overall prevalence of fibromyalgia in axSpA ranges from 4% to 25%[18,58,59].

In general, the presence of concomitant fibromyalgia in axSpA is associated with higher pain and disease activity scores[24], fatigue, sleep disturbances, functional impairment and reduced quality of life, compared with axSpA without fibromyalgia, even in patients with well-controlled inflammation. Statistically significant differences in the levels of C-reactive protein (CRP) or erythrocyte sedimentation rate are not typically observed when comparing patients with and those without fibromyalgia[58–61].

Finally, response to treatment is negatively affected by concomitant fibromyalgia. In a prospective observational cohort study, the percentage success after 12 weeks of TNF inhibitor treatment was lower in the group with secondary fibromyalgia for most of the efficacy endpoints (BASDAI 50 of 45.3% with fibromyalgia versus 54.1% without fibromyalgia), except for those endpoints related to CRP change[62].

In addition, psychological factors, including illness perceptions, pain-related worrying, coping strategies and overall psychological well-being, are central components of the biopsychosocial model of health in rheumatic diseases and might influence disease activity assessment. In axSpA, negative illness perceptions can affect disease activity as assessed by the Ankylosing Spondylitis Disease Activity Score

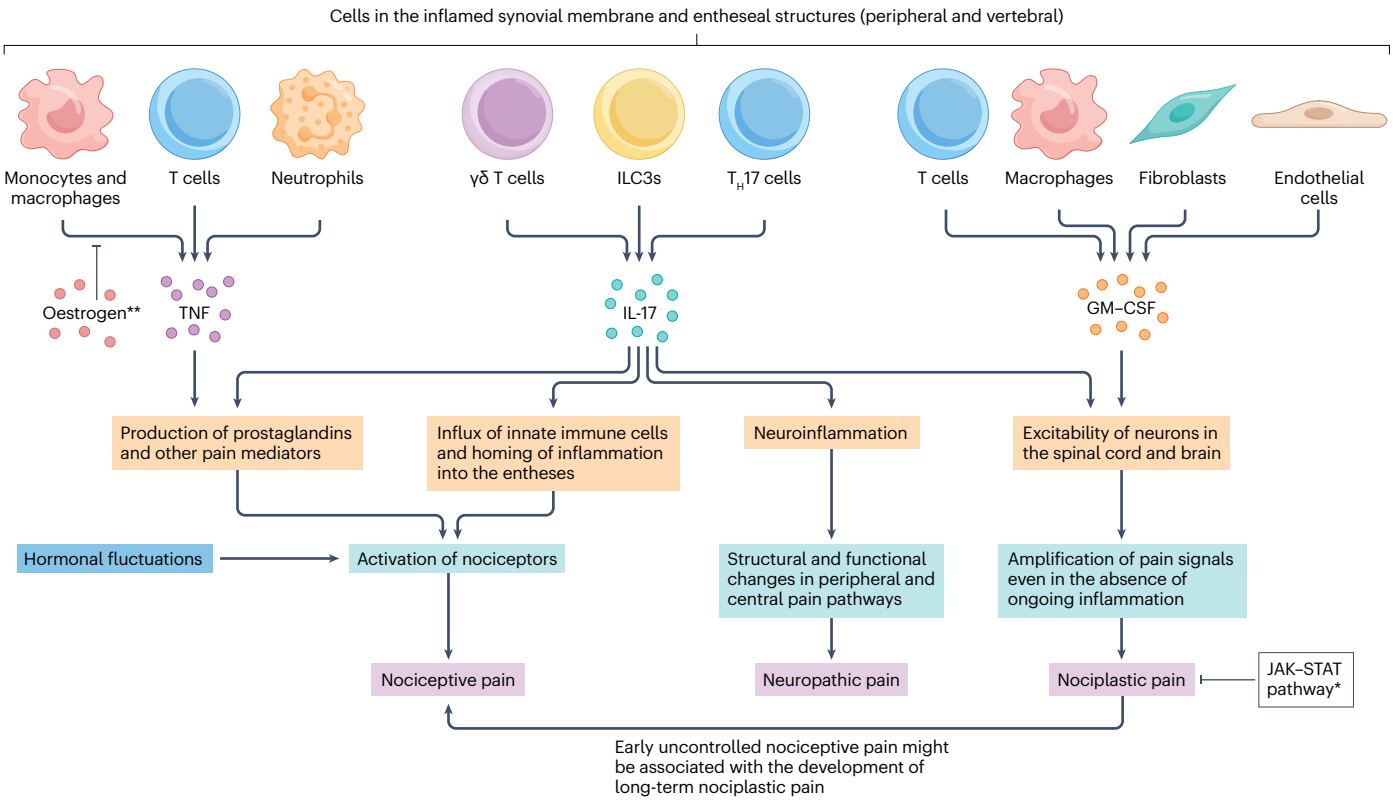

Fig. 1 | Cytokines involved in the development of inflammation in axSpA in relation to pain. Different cytokines are involved in the production and maintenance of high levels of different pro-inflammatory factors and cytokines in axial spondyloarthritis. All these factors drive different pro-inflammatory processes that lead to different types of pain. *For the modulation of neuropathic and nociplastic pain mechanisms, current clinical trials have primarily assessed the efficacy of targeting JAK–STAT pathways in inflammatory pain contexts, but there are no specific methods to assess their impact on other pain phenotypes. **Oestrogen can modulate TNF activity, for example, by inhibiting TNF production by macrophages and monocytes. ILC, innate lymphoid cell; T_H17 cells, T helper 17 cells; GM–CSF, granulocyte–macrophage colony-stimulating factor.

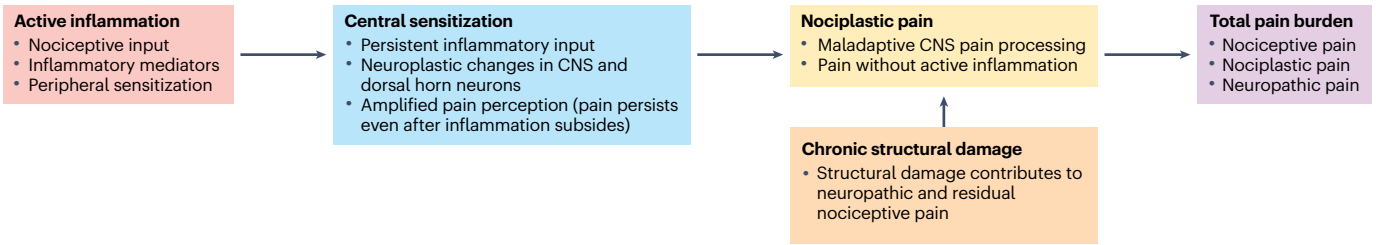

Fig. 2 | Continuum and interconnection of pain mechanisms in inflammatory disease. Active inflammation might lead to different pain types, starting from inflammatory-driven nociceptive input, which develops into neuroplastic changes of the central nervous system and eventually involves the entire pain spectrum when disease becomes chronic. CNS, central nervous system.

(ASDAS)[63,64]. Such negative perceptions, together with pain-related worrying, might encourage passive or avoidant coping strategies when managing symptoms such as pain, stiffness and fatigue[65].

The role of sex differences

Biological sex (that is, sex assigned at birth; throughout this Review, 'sex' is used as a shorthand for biological sex) has a substantial role in shaping the pain experience in axSpA, influencing pain location, severity, reporting and response to treatment. Historically, axSpA was considered to affect male individuals more than female individuals, but growing evidence suggests a more sex-balanced prevalence, especially in the earlier stages of the disease.

A study evaluating pain location in 170 patients with axSpA (63.5% of whom were male patients) found that the location and spread of pain were different in male and female patients and were related to worse clinical status. Axial thoracic pain was the least prevalent overall (lumbar, 74.4%; cervical, 47.6%; cervicothoracic, 47.6%; thoracic, 32.4%), but it was about three times more likely in female patients than in male patients (odds ratio (OR), 2.92; $P = 0.009$). Axial cervicothoracic junction pain spread more diffusely in female patients (OR 2.48; $P = 0.018$). Female individuals had a two- to three-fold higher likelihood of widespread axial (OR 3.33; $P = 0.007$) and peripheral articular (OR 2.34; $P = 0.023$) pain. In this study, widespread non-articular pain and low physician global assessment of disease activity was associated with worse Bath Ankylosing Spondylitis Functional Index (BASFI), BASDAI, Hospital Anxiety and Depression Scale (HADS) subscale anxiety and depression in male patients and worse fear of movement (Tampa Scale for Kinesiophobia (11-item version)) and HADS anxiety in female patients[66]. Female patients were also more likely to have diagnoses of depression and fibromyalgia[67].

Furthermore, similar results were shown in a prospective multicentre cohort study. Of the 494 patients with early axSpA who were followed-up for 6 years (mean ± s.d. age of 31.9 ± 7.5 years, symptom duration of 20.7 ± 11.7 months, 50.4% of whom were male), female patients had higher ASDAS and patient global assessment over time than male patients ($P < 0.0001$ for both), with similar levels of CRP overall ($P = 0.089$), whereas structural damage increased more in male patients ($P < 0.001$)[68].

In addition to high disease activity, female sex in axSpA is associated with increased central sensitization. In a study that compared 116 patients with axSpA with 95 healthy individuals, the Central Sensitization Inventory (CSI) was higher in female individuals than in male individuals[15]. This association is also supported by several neuroimaging studies reporting structural and functional changes in the brains of female patients with axSpA compared with those of healthy individuals[69]. In a study that used modular analysis and machine learning to assess resting-state functional MRI data from 220 individuals with chronic low back pain as a result of axSpA, sex-specific network topological characteristics were observed. Women exhibited atypically higher functional segregation in the mid-cingulate cortex and subgenual anterior cingulate cortex and lower connectivity in the network with the default mode and frontoparietal modules, whereas men exhibited stronger connectivity with the sensorimotor module[70].

The reporting of higher pain levels, more widespread pain and greater functional impairment, despite similar levels of inflammation, suggests that nociplastic pain might be more prominent in female individuals. In addition, a study that used PET to assess neurotransmission during pain in healthy adults suggested that modulation of the endogenous opioid neurotransmitter circuitry by oestrogen might contribute to sex differences in pain sensitivity, in both male and female patients[71,72], which might be of particular interest owing to the high risk of nociplastic pain in axSpA.

In female individuals, low oestrogen was associated with reduced activation of endogenous opioid neurotransmission during a pain stressor and higher pain ratings, whereas a high-oestrogen state showed greater pain-induced regional activation of the endogenous opioid system[72]. Conversely, testosterone might exert anti-nociceptive effects[73], which might also explain differences in the pain occurrence and reporting of pain in patients diagnosed with axSpA.

Moreover, differences in body composition, biomechanics and muscle strength might affect spinal loading and pain perception differently in male and female individuals. Although male individuals have a higher body mass index (BMI) on average, female patients with axSpA have been reported to have a higher adipose tissue mass index and are more likely to have obesity than their male counterparts (28.6% compared with 7.1%), which has been linked to higher disease activity and subsequent pain[71,74].

These sex-related differences (Box 2) have important clinical implications, as female patients with axSpA might experience delayed diagnosis, more frequent misclassification as having fibromyalgia and different responses to biologic therapies. According to a 2025 systematic literature review and meta-analysis, male patients with axSpA are more likely to achieve an ASAS40 response than female patients for all advanced therapies (OR 1.88, 95% CI 1.44–2.46) and for IL-17A inhibitors (OR 1.82) and TNF inhibitors (OR 2.42). Male patients were also more likely to achieve 'low disease activity' or 'inactive disease' status on ASDAS scores (OR 2.19, 95% CI 1.47–3.26) across all advanced therapies and for IL-17A inhibitors (OR 2.08) and TNF inhibitors (OR 2.42) individually[75].

Acknowledging the influence of sex on pain in axSpA can support more personalized approaches to monitoring and treatment.

For example, in female patients, who more often present with widespread pain and features of central sensitization, early screening for fibromyalgia and the use of targeted non-pharmacological interventions such as cognitive behavioural therapy (CBT), exercise programmes and sleep optimization might be prioritized alongside anti-inflammatory therapy. For male patients, who typically present with localized inflammation-driven pain and tend to develop more structural damage than female patients, using imaging to identify the problem and timely initiation or escalation of biologic therapy, where appropriate, might be a better approach. Although these sex-specific considerations could improve treatment selection and reduce misclassification, prospective studies are needed to confirm whether such stratified strategies lead to better outcomes. In summary, a comprehensive understanding of the overlapping pain mechanisms in axSpA is essential for refining disease assessment and implementing effective, multimodal management strategies.

Assessment of pain in axial spondyloarthritis

To ascertain diagnosis, monitoring and treatment evaluation, assessment and measurement of pain in axSpA is crucial both for inflammation-driven but also so-called residual or non-inflammation-driven pain. Owing to the complex and multidimensional nature of pain, various assessments exist, which consider components of pain intensity, pain quality and impact on disease status (Table 2). These tools can be categorized into patient-reported outcome measures, composite indices and functional assessments.

Patient-reported outcome measures

The Visual Analogue Scale (VAS) and the Numerical Rating Scale (NRS) are simple methods for the assessment of general pain. They consist of a scale of 100 mm in length or ranging from 0 to 10, in which the left end represents 'no pain' and the right end represents 'worst pain possible'. Their application in daily practice is considered feasible because of their simplicity[10]. Furthermore, they can be easily adapted to specific painful areas of interest; for example, 'general pain' versus 'pain in the low back', 'pain in the buttocks' or 'pain in the hips'.

Composite indices

The BASDAI[76] comprises six questions that measure disease activity based on the point of view of the patient. Three of the questions in BASDAI refer to pain: overall pain in the neck, back or hip (question 2); pain in joints other than the neck, back or hips (question 3) and discomfort from an area tender to touch or pressure (question 4). Similarly, the ASDAS[77], which was derived from the BASDAI in a validated data-based process, also assesses pain in the back and in areas other than the neck, back or hips in relation to inflammatory complaints. These composite indices are the two most widely used questionnaires in axSpA and are also recommended by the ASAS for use in clinical studies. Overall, the ASDAS is preferred over the BASDAI as the set of questions included in the BASDAI are susceptible to different reasons for having pain, making it more susceptible to the influence of general pain and less likely to differentiative inflammation-related disease-activity complaints. This lack of objectivity has been mainly shown in patients with concomitant fibromyalgia when compared with those without concomitant fibromyalgia, as mentioned previously[62,78].

The PainDETECT questionnaire[79] is a tool for screening for neuropathic pain in patients with low back pain but is also widely used in patients with axSpA. The questionnaire comprises nine questions, seven of which relate to pain quality and sensory symptoms and the other two relate to location of pain and pain progression over time. The patient answers using a scale of 0 to 5, in which 0 stands for no pain and 5 for very strong pain. A score of <13 is interpreted as absence of neuropathic pain, a score of 13–18 as possible presence of neuropathic pain and >18 as likely to have a neuropathic component to their pain[79].

Similarly, the Neuropathic Pain Symptom Inventory (NPSI)[80] also assesses neuropathic pain, in both a qualitative and a quantitative manner. The NPSI consists of 12 items, 10 of which are descriptors of different symptoms of neuropathic pain symptoms and the other 2 evaluate the duration of continuous and paroxysmal spontaneous pain. The average score (0–100) provides an overall measure of neuropathic pain severity. In addition, the NPSI enables the calculation of five subscores, each representing different aspects of neuropathic pain (burning superficial spontaneous pain, squeezing deep spontaneous pain, paroxysmal pain, evoked pain and paraesthesia or dysaesthesia). These subscores can be used to gain a more comprehensive assessment of the pain status of the patient and guide more targeted treatment decisions.

The McGill Pain Questionnaire (MPQ)[81] is designed to capture qualitative aspects of pain, including sensory, affective and evaluative dimensions. The MPQ consists of 78 descriptors divided into 20 sections, enabling detailed description of the nature of pain. Patients select words from each category in the questionnaire that best describe their pain experience, which have an associated point value. This questionnaire also includes sections on pain intensity and temporal patterns. The advantage of the MPQ is that the results can distinguish between different pain qualities (such as throbbing versus stabbing), leading to identification of neuropathic pain components or central sensitization. However, the MPQ is also time consuming and seems to be complex for some patients, making it better suited to detailed assessments or research purposes.

The CSI[82] is a questionnaire designed to identify symptoms related to central sensitization. Although not classed as a primary 'pain assessment tool', the CSI is helpful for distinguishing central from peripheral (inflammatory) pain mechanisms. The questionnaire includes 25 items and patients are asked to rate the frequency of symptoms concerning sleep, concentration difficulties or others on a scale from 0 (never) to 4 (always). Total higher scores indicate a greater likelihood of central sensitization.

Box 2 | Sex-based differences in pain reporting in axial spondyloarthritis

Women

- More widespread pain
- More thoracic location
- Higher self-reported disease activity
- More abnormalities on neuroimaging
- Pain levels are influenced by hormonal fluctuations, body composition and biomechanics
- More components of anxiety and depression

Men

- More radiographic damage
- Better self-reported quality of life
- Better response to therapy

Table 2 | Pain assessment instruments in axial spondyloarthritis

Tool	Assessment method	Pain type	Assessment details	Best used for	Additional notes
VAS	Pain intensity, quantitative	Nociceptive	Mark on a 10-cm line, ranging from 'no pain' at one end to 'worst possible pain' at the other	Quick assessments	Simple and visual
NRS	Pain intensity, quantitative	Nociceptive	Rating of 0–10 given verbally or in writing	Routine tracking	Easy to score
BASDAI	Axial and peripheral pain, quantitative	Nociceptive	Composite measure; six-item questionnaire	Measuring disease activity	Includes pain, fatigue and spinal stiffness
ASDAS	Axial and peripheral pain, quantitative	Nociceptive	Composite measure; four questions answered using a 0–10 scale plus levels of CRP or ESR	Disease-activity assessment	Includes objective inflammatory parameter (CRP or ESR)
PainDETECT	Quantitative	Neuropathic	Composite measure; nine questions	Detecting neuropathic pain	Overlap with nociceptive pain
NPSI	Quantitative and qualitative	Neuropathic	Composite measure; questionnaire that consists of 12 items	Comprehensive assessment of pain levels	Different aspects of neuropathic pain can be assessed
MPQ	Multidimensional, qualitative	Multidimensional	Composite measure; descriptor checklist, two versions (short and long) are available	In research settings or to assess complex pain	Time-intensive
CSI	Central-sensitization symptoms, quantitative	Nociplastic	Composite measure; 25 questions that involve rating symptoms	Non-inflammatory pain	Useful for people with high pain but low inflammation
BPI	Pain intensity and interference, quantitative	Function	Composite measure; questions on pain and function, two versions (short and long) are available	Understanding the impact that pain has on the patient	Quick and informative

ASDAS, Axial Spondyloarthritis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BPI, Brief Pain Inventory; CRP, C-reactive protein; CSI, Central Sensitization Inventory; ESR, erythrocyte sedimentation rate; MPQ; McGill Pain Questionnaire; NPSI, Neuropathic Pain Symptom Inventory; NRS, Numerical Rating Scale; VAS, Visual Analogue Scale.

The Brief Pain Inventory (BPI)[83] assesses both the intensity of pain and its interference with daily functions. It includes items that evaluate pain severity and the extent to which pain hinders activities such as walking, work and sleep, all of which are relevant to axSpA. In the BPI, patients rate their pain at its worst, least, average and current levels over the past 24 h on a scale of 0 (no pain) to 10 (pain as bad as you can imagine).

Overall, the assessment of pain in axSpA requires a combined approach. Different tools capture the different aspects of pain (Table 2), such as inflammatory and non-inflammatory dimensions. Thus far, a single tool that is validated to capture all these aspects does not exist. One in every two patients with axSpA has a high probability of central sensitization, as measured by the CSI. In one study, specific illness perceptions and obesity were independently associated with BASDAI and ASDAS, with CSI scores explaining 38% of the variance in the BASDAI and 23% of the variance in the ASDAS scores[64]. Patients with higher CSI scores include female patients with a history of depression, clinical enthesitis and high scores for ASDAS, and BASDAI[13]. A 'possible' neuropathic component, using the PainDETECT questionnaire, was evident in only 8% and a 'likely' component in 1% of patients. For the 31% of patients with high disease activity, 79.2% showed either a 'possible' or 'likely' nociplastic component and 20.8% a 'possible' or 'likely' neuropathic component. Both neuropathic and nociplastic scores were shown to be independently associated with ASDAS and BASDAI scores[25].

Accurate assessment of pain in axSpA requires recognition of its multifactorial nature, including inflammatory, nociplastic and neuropathic components. A range of tools, including simple scales (VAS and NRS) to composite indices (BASDAI and ASDAS) and specific instruments that target pain mechanisms (PainDETECT, CSI and MPQ), is available to capture different dimensions of pain. Although no single tool comprehensively addresses all aspects, combining multiple assessments can provide a more complete picture of the experience of the patient. Notably, central sensitization is common and might influence composite disease scores substantially.

Interconnection between the different types of pain in axial spondyloarthritis

Although accurate identification of the predominant pain mechanism in patients with axSpA is essential for optimizing management strategies, pain mechanisms are not mutually exclusive and frequently overlap. Bidirectional interactions exist; nociplastic and neuropathic pain might amplify nociceptive pain scores, whereas persistent and inadequately controlled nociceptive pain can facilitate the development of nociplastic and neuropathic pain. Although evidence in axSpA is limited, insights can be extrapolated from other chronic rheumatic and musculoskeletal conditions.

Nociplastic and neuropathic pain as drivers for nociceptive pain scores

In the prospective Groningen Leeuwarden axSpA (GLAS) cohort, which includes 332 patients with axSpA, illness perception, central sensitization (measured by CSI) and BMI had direct effects on ASDAS, beyond inflammatory parameters[63]. In the GESPIC cohort (78 patients with axSpA who were treated with bDMARDs) 22% of patients had nociplastic pain (measured by WPI) and 9% had neuropathic pain (measured by PainDETECT). Both types of pain were associated with the presence of residual symptoms (defined by BASDAI of ≥4)[25]. In the CorEvitas registry (1,823 patients with psoriatic arthritis), 11.1% of patients met

the definition for fibromyalgia and 20.6% were considered to have widespread pain. These patients reported approximately two-fold higher clinical Disease Activity in Psoriatic Arthritis scores, pain, global assessment and tender joint counts compared with those without fibromyalgia[84]. Nociplastic pain thus confounded disease-activity assessment and impaired treat-to-target strategies.

Nociceptive pain as a precursor to nociplastic pain

Data from patients with rheumatoid arthritis (RA) suggest that systemic inflammation might lead to changes in functional central nervous system pathways, leading to the development of nociplastic pain[85]. Emerging neuroimaging studies have helped to provide insights into how inflammation might interact with central pain pathways. Moreover, a post hoc analysis supported by functional MRI studies showed that the erythrocyte sedimentation rate correlated positively with functional connectivity between the insula and the left inferior parietal lobule in patients with RA and concomitant fibromyalgia but not in patients with RA alone[86]. This finding suggests that nociplastic pain might indeed be an intrinsic part of systemic rheumatic diseases, resulting from peripheral inflammation stimuli driving bottom-up processes that trigger the development of nociplastic pain.

The presence of pro-inflammatory cytokines and mediators can contribute to central sensitization via their effect on neuronal transmission, which is characterized by increased excitatory activity and reduced inhibitory activity[87]. In rodent models, the use of lipopolysaccharide as a pro-inflammatory stimulus induced the development of hyperalgesia[88] and other centrally mediated symptoms, including fatigue, sleep and cognitive and mood disturbances[89].

These data indicate a putative role for systemic inflammation in the development of nociplastic pain, in the context of systemic inflammatory disease, offering evidence of a bottom-up nociplastic dimension induced by peripheral inflammatory nociceptive processes that sensitize pronociceptive central nervous system pathways[90,91]. An effective and swift control of inflammation leading to reduced long-term nociplastic pain in axSpA, and in other inflammatory rheumatic disease, has yet to be demonstrated.

Treatment options for pain in axial spondyloarthritis

Effective management of pain in axSpA is challenging as patients might experience multiple pain types. Clinicians must therefore assess the origin of pain (inflammatory versus non-inflammatory) to adjust treatments appropriately. Here, we provide a guide to help manage different sources of pain in patients with axSpA. Nevertheless, highlighting that recommendations for nociplastic and neuropathic pain rely largely on indirect or preclinical evidence is important. Most of the available data are extrapolated from other conditions such as fibromyalgia, diabetic neuropathy or post-herpetic neuralgia, with only limited, indirect or small observational studies directly addressing axSpA.

Inflammation-related nociceptive pain interventions

Non-pharmacological therapies. Non-pharmacological therapies continue to have a crucial role in the management of pain in patients with axSpA[92,93]. Although pharmacological treatments are essential for controlling inflammation and disease progression, non-drug interventions complement these treatments by improving function and reducing pain.

Patient education and self-management are key aspects in the management of axSpA. Understanding pain triggers and how to balance activities can help patients to control their symptoms better. Additionally, smoking cessation is strongly advised, as it exacerbates spinal damage and might worsen pain. Exercise (such as aerobic exercise and range-of-motion or stretching exercises) and physical therapy can also be beneficial for people with axSpA. Regular exercise can improve an inflammatory immune profile, coinciding with pain reduction[94]. In addition, a meta-analysis confirmed that exercise programmes led to considerable improvements in pain and function compared with no exercise[95].

Pharmacological treatments. NSAIDs are first-line therapy in axSpA. NSAIDs target inflammatory nociceptive pain by reducing prostaglandin-mediated inflammation[92]. NSAIDs are recommended at maximum tolerated doses as initial treatment for active axSpA. Most patients experience substantial pain relief with NSAIDs, often within days. Continuous NSAID therapy is preferred in those with persistent symptoms, whereas on-demand use might suffice for milder disease. Common choices of NSAIDs include etoricoxib, naproxen, indomethacin and ibuprofen, with selection guided by patient comorbidities and risk factors (such as gastrointestinal or cardiovascular risk)[92]. NSAID-responsive pain suggests predominantly inflammatory mechanisms. Conversely, lack of NSAID response should prompt evaluation of other pain-type contributors; however, in longstanding disease, the discriminative capacity of NSAIDs response might disappear[96].

In clinical practice, bDMARDs, such as TNF and IL-17 inhibitors are recommended after failure of ≥2 NSAIDs[92,97]. Multiple randomized controlled trials have demonstrated that TNF inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab and golimumab) and IL-17 inhibitors (secukinumab, ixekizumab and bimekizumab) quickly improve total spinal and night pain[98]. These agents target the pro-inflammatory cytokines that promote nociceptive pain, often resulting in substantial pain improvement when successful. Not much is known about the impaired pain pathways in these patients and the effects of bDMARDs on these pathways. In patients with RA and SpA, impaired descending pain modulation (assessed by conditioned pain modulation) improved over 6 months following initiation of TNF inhibitor therapy, whereas no statistically significant difference in thermal pain thresholds was observed, suggesting a possible effect of TNF inhibitors on central pain modulation[99]. Patients with certain extra-musculoskeletal manifestations might have specific biologic preferences; for example, TNF inhibitor monoclonal antibodies are preferred if the patient has coexistent inflammatory bowel disease or recurrent uveitis and IL-17 inhibitors are better for those with severe psoriasis[92].

Treatment with tsDMARDs (such as the JAK inhibitors tofacitinib and upadacitinib) can interrupt multiple cytokine pathways relevant to both inflammation and pain processing[45]. Randomized control trials indicate that JAK inhibitors can produce fast and sustained pain relief in axSpA[93,100,101] and these drugs have demonstrated clinically relevant improvements in patient global pain as early as week 2 of treatment[47,102].

Notably, JAK inhibitors might also modulate neuropathic and nociplastic pain mechanisms via the JAK–STAT pathway. However, current clinical trials (NCT03178487, NCT04169373, NCT03502616) have primarily assessed their efficacy in inflammatory pain contexts, without using specific methodologies to evaluate their impact on other pain phenotypes. Although preclinical and early clinical data suggest a potential role for JAK inhibitors in modulating nociplastic and neuropathic pain, acknowledging that current clinical evidence remains

sparse and exploratory is important. Thus far, studies have not been designed to test the superiority of JAK inhibitors over established treatments, and thus the claim of therapeutic advantage remains unconfirmed by robust clinical data. The UPSTAND trial (NCT04846244) is an ongoing observational study designed to evaluate the real-world effectiveness of upadacitinib in achieving early and sustained pain control in adult patients with axSpA.

Even with optimal anti-inflammatory treatment, some patients still experience residual pain. Studies show that up to 50% of patients with axSpA who are in clinical remission or have low disease activity continue to report substantial pain[97]. This residual pain is often caused by nociplastic or structural mechanisms, which require additional therapies beyond bDMARDs or tsDMARDs, and usually adjunct analgesics are used. Analgesics such as paracetamol (acetaminophen) or opioid-based drugs might be considered for refractory pain after other treatments have failed, are contraindicated or poorly tolerated[92]. Acetaminophen can be useful for mild-to-moderate pain and has a favourable safety profile, although its efficacy in severe axial pain is limited[103]. Tramadol is sometimes used for moderate pain that is not relieved by NSAIDs. Strong opioids (such as morphine or oxycodone) are generally avoided in axSpA owing to modest efficacy for inflammatory pain and considerable long-term risks (including tolerance and dependence)[104].

Interventional and advanced therapies. Intra-articular glucocorticoid injections are particularly useful in managing local pain flares (such as an acutely inflamed sacroiliac joint or a swollen peripheral enthesis) in patients who are on otherwise effective systemic therapy. A 2025 meta-analysis of injectable therapies in SpA found that glucocorticoid injections of the sacroiliac joints led to a large reduction in pain VAS (from ~8/10 to ~3/10) at short-term follow-up[105]. This pain relief tends to persist for several months but might decrease over time and not all patients respond to treatment.

Non-inflammatory nociceptive pain interventions

Non-inflammatory nociceptive pain arises from mechanical or structural abnormalities rather than active inflammation. In axSpA, recognizing factors such as joint damage, altered biomechanics and postural stress is important when selecting the most appropriate treatment as they can contribute to persistent pain, even in the absence of inflammatory activity.

Non-pharmacological therapies. Supervised physical therapy (including hydrotherapy) can adjust an exercise regimen to maintain spinal flexibility, strengthen core muscles and improve posture, all of which help to reduce mechanical pain[106]. Advice on posture and joint protection can mitigate pain from daily mechanical stress. In advanced disease with spinal fusion, physical therapists might recommend adaptive strategies and devices (such as a shower chair or long-handled tools for hygiene) to minimize pain with activities. Although not directly analgesic, these interventions prevent exacerbation of pain owing to poor biomechanics[107].

Interventional therapies. Orthopaedic evaluation is important for structural sources of pain that might be corrected via surgical intervention. Total hip arthroplasty in patients with severe hip-joint arthritis has shown pain relief and function improvement[92]. Patients with fused spines and a severe kyphotic deformity causing pain and functional limitations might benefit from spinal osteotomy procedures to realign the spine[92]. Additionally, if a patient has a spinal fracture, surgical stabilization or decompression could be urgently required to relieve pain and prevent neurological injury.

Nociplastic pain interventions

Importantly, recognizing nociplastic pain prevents unnecessary escalation of anti-inflammatory therapy, which might be ineffective and carry adverse effects.

Non-pharmacological therapies. Exercise is the most effective therapy in the management of fibromyalgia, underscoring its importance for nociplastic pain. Adequate sleep and stress reduction can mitigate central sensitization and fatigue. Mindfulness-based stress reduction and meditative movement therapies have shown improvements in fibromyalgia pain[104].

Chronic pain in axSpA can lead to distress, anxiety, depression and maladaptive coping, which in turn amplify pain perception[108]. Psychological therapies target maladaptive coping and central pain amplification. Established approaches include CBT, acceptance and commitment therapy and interventions such as mindfulness-based stress reduction[109–112]. These methods can reduce fear avoidance, catastrophizing and improve coping strategies, although evidence in inflammatory conditions remains limited[113].

Pain-reprocessing therapy (PRT) is a newer psychological approach designed specifically for chronic nociplastic pain. It focuses on retraining brain pathways that perpetuate pain by combining education, cognitive reframing, somatic tracking (mindful, non-fearful attention to pain sensations) and gradual exposure to feared movements. In a randomized trial of chronic low back pain, PRT led to marked and sustained reductions in pain intensity[113]. However, there is currently no direct evidence supporting the use of PRT in inflammatory diseases such as axSpA, in which pain mechanisms also include active inflammation and structural damage.

Overall, existing evidence supports the importance of combining lifestyle interventions, physical activity and psychological therapies as part of a multimodal strategy in patients with predominantly nociplastic pain, while emphasizing the urgent need for studies specific to inflammatory rheumatic conditions.

Pharmacological therapies. Neurotransmitters have a central role in pain perception by transmitting signals between neurons in the pain pathway, influencing whether pain is amplified or dampened. Excitatory neurotransmitters such as glutamate and substance P enhance pain signalling, whereas inhibitory neurotransmitters such as GABA, serotonin and noradrenaline suppress it. Specifically targeting these neurotransmitters with drugs can reduce pain intensity and alter the way in which the brain processes painful stimuli, which makes neurotransmitter-targeted therapies a scientifically grounded strategy for pain relief. Pharmacological therapies should be considered for those with persistent nociplastic pain. However, evidence of the use of these interventions to improve pain and other symptoms is limited and slow titration of these medications and monitoring for adverse effects (such as sedation and dizziness) is essential[114,115].

Serotonin and noradrenaline reuptake inhibitors (SNRIs; such as duloxetine and milnacipran) have demonstrated analgesic effects in addition to mood-stabilizing properties[115]. Tricyclic anti-depressant medications (such as low-dose amitriptyline) and muscle relaxants (such as cyclobenzaprine) can improve sleep disturbance[116,117].

Gabapentinoids (gabapentin or pregabalin) can improve pain and sleep disturbance[118].

Neuropathic pain interventions

Neuropathic pain arises from dysfunction or injury to the somatosensory nervous system and can be observed in axSpA. Recognizing neuropathic components is crucial for selecting the appropriate pharmacological interventions, such as gabapentinoids or certain anti-depressant medications, which target neural sensitization mechanisms.

Non-pharmacological therapies. Non-pharmacological therapies are vital in the management of neuropathic pain, complementing pharmacological treatments[85]. Physical therapy and structured exercise help to reduce pain and improve function. Psychological approaches such as CBT and mindfulness address emotional aspects and pain perception. Patient education and self-management strategies enhance understanding and adherence. Complementary therapies, including acupuncture and yoga, might provide additional relief[119,120].

Pharmacological therapies. For patients with a clear neuropathic pain component (for example, radiculopathy or peripheral neuropathy), adjuvant neuropathic pain medications are indicated. Gabapentinoids (gabapentin or pregabalin) are useful for nerve pain and are recommended, especially if there are radicular symptoms. In patients with axSpA, pregabalin can help refractory pain while facilitating opioid tapering[121]. SNRIs (such as duloxetine and milnacipran) reduce pain by increasing serotonin and noradrenaline levels in the central nervous system, thereby strengthening the descending inhibitory pathways that suppress pain-signal transmission in the spinal cord[122]. Tricyclic anti-depressant medications (such as low-dose amitriptyline) might be used for certain individuals. Clinical evidence supports the efficacy of amitriptyline in conditions such as diabetic neuropathy and postherpetic neuralgia, often showing moderate pain relief[123].

Interventional and advanced therapies. Interventional and advanced therapies might be considered on a case-by-case basis by pain specialists, especially if imaging shows advanced structural changes that might be causing pain. Epidural steroid injections can be offered for severe radicular pain (for example, disc herniation or spinal stenosis in the context of ankylosis)[124]. If facet joint arthritis or entheseal pain contributes to chronic back pain, local anaesthetic blocks can help. If the latter intervention is effective, longer-term relief can be achieved with radiofrequency ablation[125].

Neuromodulatory therapies, such as transcutaneous electrical nerve stimulation and spinal-cord stimulation, are additional options for difficult-to-treat pain. Transcutaneous electrical nerve stimulation is a non-invasive modality whereby surface electrodes deliver mild electrical currents to modulate pain signalling, which might provide short-term relief for muscle pain or localized back pain. For truly intractable pain for which all conventional therapies have failed, spinal-cord stimulation (implantation of electrodes in the epidural space to deliver electrical pulses) can be considered[126].

In summary, axSpA pain is often multifactorial and requires a multimodal and mechanism-based treatment approach. Recognizing and treating the entire spectrum, from inflammatory to nociceptive, neuropathic and nociplastic pain, require a paradigm shift from inflammation-centric to mechanism-based, individualized therapy. A multidisciplinary, patient-centred approach remains the cornerstone of effective pain management in axSpA.

Future directions and research needs

Although anti-inflammatory therapies have revolutionized axSpA treatment, pain control remains suboptimal for many patients. Future research should be aimed at identifying reliable biomarkers to distinguish pain phenotypes and stratify patients according to predominant pain mechanisms, nociceptive, nociplastic or neuropathic. Stratified treatment algorithms tailored to these profiles might improve outcomes. Novel therapies that target central sensitization and neural mechanisms are especially needed for patients with features of nociplastic or neuropathic pain, who often do not respond to anti-inflammatory agents.

Validated tools to distinguish pain subtypes in clinical practice remain limited and should be prioritized in future work, which is especially relevant in the context of the evolving difficult-to-manage and treatment-refractory axSpA concepts[127]. Moreover, the role of sex differences in pain perception and response to treatment requires further exploration to inform sex-specific management approaches. Digital technologies such as wearable devices and app-based symptom tracking offer opportunities for real-time pain monitoring and might support more personalized, responsive care strategies. In parallel, research into multimodal and multidisciplinary care models, including psychological support and rehabilitation, should be expanded. Altogether, these efforts could bridge the current gap between inflammatory disease control and comprehensive pain relief in axSpA.

Conclusion

Although anti-inflammatory therapies effectively address inflammation-driven nociceptive pain, many patients continue to report pain despite achieving remission or low disease activity by conventional metrics. The achievement of such treatment outcomes underscores the role of additional pain mechanisms, including central sensitization and structural or nerve-related factors. In clinical practice, moving beyond the traditional inflammation-centred model and adopting a multidimensional framework that considers the heterogeneity of pain experiences is crucial for the decision of which pharmacological or non-pharmacological strategy is appropriate for each patient. However, further research on inflammation and pain as interconnected targets in axSpA needs to be considered a high priority in the field of axSpA and beyond. This research should include the improvement of screening and diagnostic tools, tailored interventions and digital solutions. The ultimate goal for axSpA management should be optimal targeting of both aspects of disease burden, inflammation and pain, and their interconnected qualities.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

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Review article

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Cam morphology and the development of femoroacetabular impingement syndrome and hip osteoarthritis

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Abstract

Hip morphology has emerged as an important factor in the development of hip osteoarthritis (OA). Cam morphology is one of the most common hip morphologies, characterized by a bony prominence around the femoral head–neck junction of the hip that alters the normal shape of the femoral head. Cam morphology can contribute to intra-articular joint damage by generating abnormal contact stresses at this junction, initiating femoroacetabular impingement (FAI) syndrome and eventually leading to hip OA. Cam morphology is a causal risk factor for hip OA, but not everybody with this morphology will develop FAI syndrome or OA. The pathogenesis of hip disease is probably driven by the interplay between cam morphology, other coexisting hip morphologies (such as pincer morphology), femoral version, spinopelvic parameters and biomechanical and environmental factors. Early identification of FAI syndrome could enable timely, multidisciplinary intervention and offers the potential to modify the trajectory of disease. Cam morphology can develop during skeletal maturation, particularly in adolescents participating in high-joint-load physical activity, raising important questions about preventative approaches. Management of FAI syndrome includes both surgical and non-surgical approaches. Emerging insights into the pathogenesis and detection of cam morphology are paving the way for more targeted interventions and a deeper understanding of its role in FAI syndrome and hip OA development.

Sections

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Key points

- Cam morphology is a causal risk factor for hip osteoarthritis (OA) and is characterized by excess bone at the anterolateral head–neck junction of the proximal femur.
- Cam morphology probably develops during adolescence as a physiological response to high-joint-load activity, and can lead to femoroacetabular impingement (FAI) syndrome, a symptomatic, motion-related condition linked to hip OA development.
- Specific subtypes of cam morphology and individual characteristics could expedite the development of OA; pincer morphology in the presence of hip pain also seems to be relevant to hip OA development.
- Radiography is the first-line imaging technique for assessing cam and pincer morphology in FAI syndrome, with magnetic resonance imaging providing complementary detail on hip anatomy and intra-articular soft tissues.
- The pathogenesis of FAI syndrome probably results from an imbalance between biological, physical and environmental factors.
- Surgical and non-surgical treatments could be appropriate for people with FAI syndrome.

Introduction

An estimated one in four people will develop hip osteoarthritis (OA) in their lifetime[1]. Hip OA increases the risk of other chronic diseases (such as cardiovascular disease) and imposes a substantial societal and personal burden, including poor quality of life, persistent pain and disability[1–3]. Structural variations in hip morphology are one of the most important risk factors in the development of hip OA[4–7]. Changes in hip morphology are thought to induce pathological tissue forces within the hip joint that can generate clinical symptoms and expedite OA[6,8–10]. Historically, clinical interest has focused on conditions that produce distinct changes to hip morphology, such as hip dysplasia; however, cam morphology (characterized by the presence of additional bone on the anterolateral head–neck junction of the proximal femur) has now been studied in greater detail and seems to have a central causal role in OA pathogenesis[5,8,9,11,12].

Cam morphology can impinge against the acetabulum in positions of hip flexion and internal rotation, causing changes to the articular cartilage and acetabular labrum[7,10,13,14]. However, emerging evidence suggest that pincer morphology, femoral version and spinopelvic alignment also have key roles in modulating the interaction between cam morphology and intra-articular structures[8,15–18]. In some people, this mechanical process can cause femoroacetabular impingement (FAI) syndrome, a symptomatic motion-related condition that can occur in young to middle-aged active adults[10,13]. Over time, this abnormal joint contact might contribute to the development of OA. Although this mechanical pathway towards hip OA might hold true in many individuals, cam morphology is also present in individuals without pain and a large proportion of these people will remain asymptomatic and/or will not develop OA[19–24]. Given that FAI syndrome contributes to the development of hip OA in older adults, early detection in clinical settings could support collaborative management and help to modify disease progression. This Review offers rheumatologists an in-depth update on cam morphology and FAI syndrome, concentrating on three key areas. First, we outline the recommended definitions and terminology for cam morphology and FAI syndrome. Second, we highlight advances in understanding of cam morphology and FAI syndrome, including diagnostic approaches, insights into its pathogenesis (including the involvement of pincer morphology, femoral version and spinopelvic parameters) and its role in the development of hip OA. Third, we summarize the latest clinical trial findings that inform current approaches to the management of FAI syndrome and FAI syndrome with hip OA, as well as potential opportunities for cam morphology prevention.

Clinical definitions and terminology

Consistent use of recommended definitions and terminology improves communication between patients and clinicians, enhancing understanding and contributing to a more effective and positive healthcare experience[25]. In this section, we summarize current definitions and terminology related to cam morphology, pincer morphology and FAI syndrome.

Cam morphology

As our understanding of the contribution of cam morphology to FAI syndrome and hip OA has evolved, so have the associated definitions and recommended terminology[25–27] (Box 1). Cam morphology is defined, according to a concept analysis[26] and the Oxford Consensus study[25], as a cartilage or bony prominence (bump) of varying size at any location around the femoral head–neck junction of the hip that changes the shape of the femoral head from spherical to aspherical. Various forms or subtypes of cam morphology probably exist[28]. These variants of cam morphology may differ substantially in shape and the extent to which each is associated with FAI syndrome and/or OA[28]. An important step forwards in the understanding of cam morphology has been the distinction between primary and secondary forms. Primary cam morphology (the focus of this Review article and hereinafter referred to as cam morphology) develops during skeletal maturation in young adolescents (with no current or previous hip disease), as a normal physiological response to high-joint-load sporting activity and other unconfirmed risk factors[25,26,29–32]. By contrast, secondary cam morphology arises as a consequence of pre-existing hip disease or acute trauma, including Legg–Calvé–Perthes disease, slipped capital femoral epiphysis and healed proximal femoral fractures[25]. Distinguishing between these two subtypes of cam morphology could be important for informing prognosis, guiding treatment decisions and facilitating patient discussions about clinical relevance[25,27].

Pincer morphology

Pincer morphology has yet to be formally defined by consensus studies, but generally refers to focal or global overcoverage of the femoral head by the acetabulum[10,33]. Pincer morphology can result from increased acetabular coverage and/or acetabular retroversion[33] (Fig. 1). As part of its effort to standardize the diagnosis and management of FAI, the Warwick Agreement on FAI syndrome provided recommended terminology for describing pincer morphology[10] (Box 1).

FAI syndrome

Femoroacetabular impingement syndrome is now the widely accepted term to describe a clinical disorder present in young to middle-aged adults (Box 1). The Warwick Agreement defined FAI syndrome as a

Box 1 | Evidence-informed terminology for cam and pincer morphology and FAI syndrome

The terminology surrounding cam and pincer morphology, as well as femoroacetabular impingement (FAI) syndrome, has varied considerably. For cam and pincer morphology, terms such as 'lesion', 'abnormality' or 'deformity' are frequently used[10,26]. However, these terms imply pathological change, which is inappropriate given that cam morphology is also present in asymptomatic individuals[19,23,24,26] and probably reflects a physiological adaptation to high-joint-load activity during adolescence[10,25,27]. Pincer morphology should be considered similarly, although its developmental origins are less well understood. The term 'FAI syndrome' emphasizes the role of symptoms in diagnosis to avoid confusion associated with previous terminology, such as 'asymptomatic FAI'. Evidence-informed terminology for describing cam and pincer morphology, and FAI syndrome, are outlined below.

Recommended terminology:

- Cam morphology
- Pincer morphology
- FAI syndrome
- FAI syndrome with cam morphology (when describing the clinical disorder with cam morphology)
- FAI syndrome with pincer morphology (when describing the clinical disorder with pincer morphology)
- FAI syndrome with mixed morphology (when describing the clinical disorder with cam morphology and pincer morphology)

Terminology to avoid:

- Symptomatic femoroacetabular impingement
- Asymptomatic femoroacetabular impingement
- Cam-type morphology
- Pincer-type morphology
- Cam-type femoroacetabular impingement
- Femoroacetabular impingement morphology
- Deformity, lesion, abnormality or pathology when referring to cam or pincer morphology

motion-related clinical disorder of the hip with a triad of symptoms, clinical signs and imaging findings. It represents symptomatic premature contact between the proximal femur and the acetabulum[10]. FAI syndrome is classified into three subtypes: cam morphology, pincer morphology and mixed morphology. Of these subtypes, FAI syndrome with cam morphology is considered to be the most prevalent[16,24,25,34]. Distinguishing those with FAI syndrome from individuals with either cam or pincer morphology but without symptoms is essential to avoid misdiagnosis and inform treatment. Femoral version and spinopelvic parameters can interact with cam morphology and/or pincer morphology and contribute to the pathogenesis of FAI syndrome. The anatomical, radiological and clinical characteristics of each of these factors, as well as their contribution to FAI syndrome and hip OA, are detailed in the following sections wherever we considered it relevant to the rheumatologist.

Diagnosis and classification

Diagnosis serves as the foundation of clinical care, integrating clinical signs, symptoms and investigations to determine the cause of disease[35]. Conversely, classification is the process of using standardized criteria to create homogeneous patient populations for clinical research[33,36,37]. In this section we discuss the available diagnostic and classification criteria for cam morphology and FAI syndrome, as well as pincer morphology.

Cam morphology

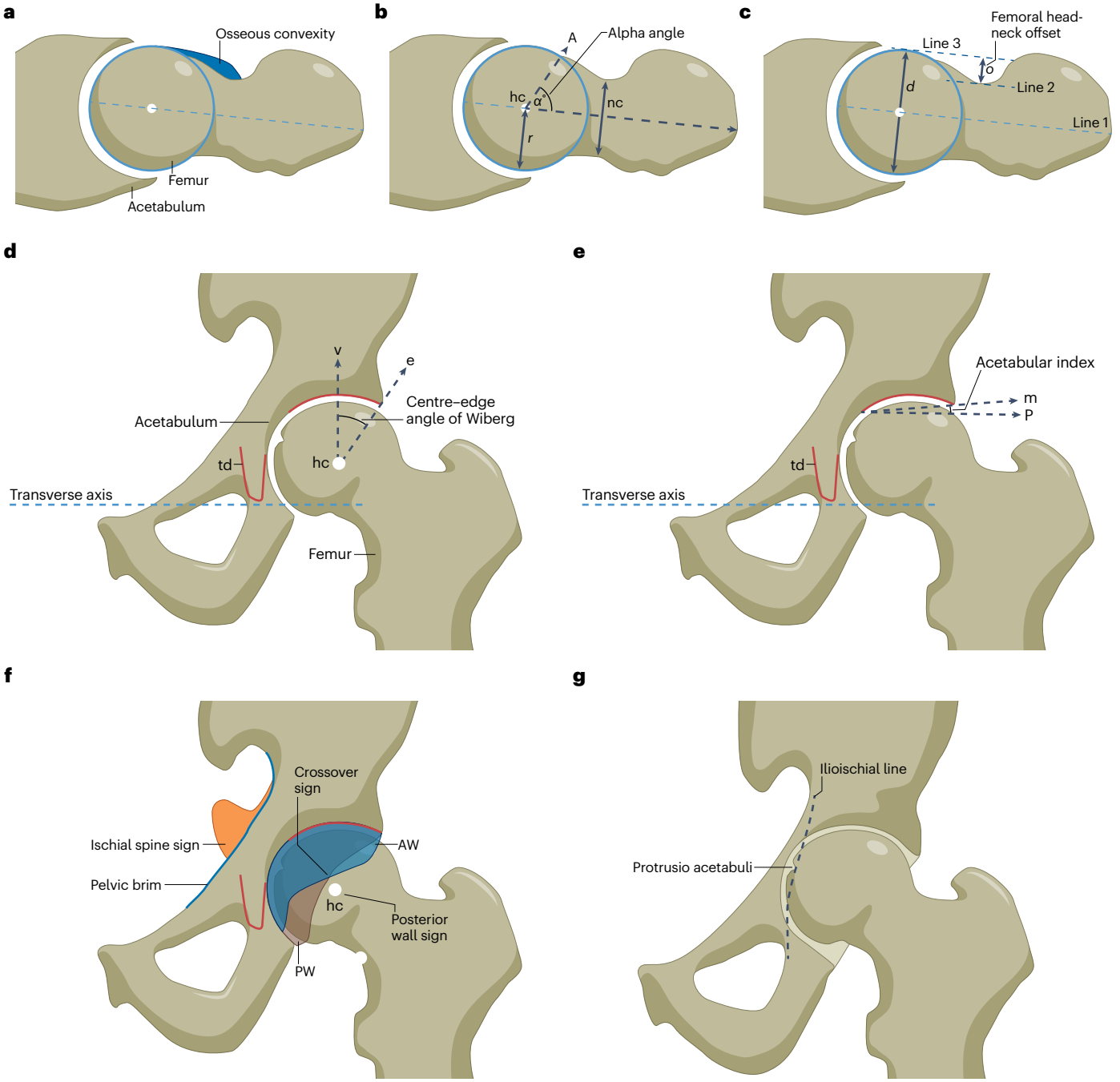
The alpha angle is the most frequently used radiologic metric for assessing cam morphology and is defined as the angle between the femoral neck axis and a line drawn from the centre of the femoral head to the point where the contour diverges from a perfect circle[25,26,38,39] (Fig. 1). This metric quantifies the sphericity of the femoral head–neck junction at specific locations and is widely applicable across various imaging modalities and views[25,38]. Evidence supports a non-sex-specific alpha angle threshold of 60° (at any location around the anterosuperior femoral head–neck junction) (Fig. 2) as a useful discriminator between people with FAI syndrome and pain-free individuals; however, some overlap between these groups still remains around this threshold[16,38,40]. Magnetic resonance imaging (MRI)-based studies have identified additional threshold values for specific locations on the femoral neck, with an alpha angle of 57–60° at the 1:30–2:00 position on the femoral head–neck junction, showing a strong association with symptoms[16].

Pincer morphology

Researchers have proposed various radiologic measures and diagnostic criteria for identifying pincer morphology, but these approaches often produce inconsistent and conflicting findings[33,37,38]. Evaluating acetabular coverage and version is essential, as variations in either can result in pincer morphology[33,37,38]. The centre–edge angle of Wiberg (W-CEA) and the acetabular index are the most used radiologic measures for evaluating the superolateral coverage of the acetabulum[33,37,38] (Figs. 1 and 2). The presence of protrusio acetabuli should also be noted owing to its association with OA[41] (Fig. 1). When evaluating acetabular version, the crossover sign, ischial spine sign and posterior wall sign (Figs. 1 and 2 and Supplementary Table 1) can help to determine the presence of acetabular retroversion (either focal or global)[33,37,38].

FAI syndrome

The diagnosis of FAI syndrome requires a comprehensive approach that integrates both clinical evaluation (Box 2) and imaging assessment (Box 3). Pain is the predominant symptom of FAI syndrome and is often exacerbated with repetitive activity or positions. The location, anatomical spread and severity of pain varies widely, with people often reporting groin pain, but also discomfort in the lateral hip, anterior or posterior thigh, buttock or lower back[10,13]. Mechanical symptoms (clicking, catching and locking) can also be present and often coexist with pain. In symptomatic people presenting with clinical findings, imaging has a pivotal role in the diagnostic work-up for rheumatologists. When cam morphology is used as a diagnostic criterion for FAI syndrome, additional variables must be considered[16,33,37]. For example,



some people exhibit impingement symptoms with an alpha angle below 60°, as this simple radiographic measure might not capture the complexity of FAI syndrome[16,38,42]. A comprehensive assessment should therefore include other anatomical and functional variations — such as pincer morphology, femoral version and spinopelvic parameters, sex and athletic performance — to better understand the diverse clinical phenotypes of FAI syndrome[10,13,42,43].

Classification criteria for clinical research

In the past few years, The Lisbon Agreement has provided imaging-based criteria for classifying cam and pincer morphology (irrespective of symptoms)[33,36,37]. For cam morphology, recommended parameters included the alpha angle, femoral head–neck (FHN) offset, the FHN offset ratio and the osseous convexity of the FHN junction[33] (Fig. 1 and Supplementary Table 1). For pincer morphology, key indicators included the W-CEA, acetabular index, protrusio acetabuli and three measures of retroversion (crossover, ischial spine and posterior wall sign)[33].

Pathogenesis

The formation of cam morphology, and in some cases the subsequent onset of FAI syndrome, are recognized as critical stages within the disease continuum of hip OA[6,40,44]. Understanding the mechanisms

Fig. 1 | Recommended imaging measures for classifying cam and pincer morphology. This figure illustrates key radiographic measures used to identify hip morphology associated with femoroacetabular impingement syndrome, including cam and pincer morphologies. **a**, Osseous convexity is identified by a visible bony prominence at the femoral head–neck junction. **b**, The alpha angle *α* is measured at the anterior point (A) where the contour of the femoral head exceeds its radius *r*. The angle is formed between the centre of the femoral head (hc), the point of deviation and the centre of the femoral neck at its narrowest point (nc). **c**, The femoral head–neck offset *o* is defined as the distance (in millimetres) between the anterior cortex of the femoral neck (line 2) and the outer edge of the femoral head (line 3), measured parallel to the neck (line 1). The offset ratio is calculated by dividing this distance *o* by the diameter *d* of the femoral head. **d**, The centre–edge angle of Wiberg is the angle between a vertical line (v) drawn from the centre of the femoral head (hc) and a line extending to the lateral edge of the acetabular sourcil (e), and is used to assess acetabular coverage. This vertical reference line v is perpendicular to the transverse axis, which is established by connecting the acetabular tear drops (td). **e**, The acetabular index is measured as the angle between a line (m) drawn from the medial aspect of the sclerotic sourcil to the lateral edge of the acetabular weight-bearing surface and a reference line (p) drawn parallel to the transverse axis from the medial aspect of the acetabular weight-bearing surface. **f**, Crossover sign, ischial spine sign and posterior wall sign are indicators of acetabular retroversion. Crossover sign is present when the anterior acetabular wall (AW) crosses over and becomes lateral to the posterior wall (PW). Posterior wall sign is present when the posterior wall lies medial to the centre of the femoral head (hc). Ischial spine sign is present when the triangular shape of the ischial spine protrudes and is visible medially to the pelvic brim. **g**, Protrusio acetabuli is considered to be present when the femoral head crosses or touches the ilioischial line. Parts **d**–**g** adapted with permission from ref. 38, Thieme Medical Publishers.

underlying their formation is essential for identifying opportunities for early intervention and disease modification.

Formation of cam morphology

Existing evidence indicates that cam morphology develops during adolescence through an interplay between femoral growth plate physiology and mechanical loading of the hip joint (such as that caused by athletic activity) that ultimately result in additional bone formation around the femoral head–neck junction[25,26,29,30,32]. Typical high-joint-load activities associated with cam morphology formation include football, ice hockey and basketball[45]. Bone and cartilage are highly responsive to mechanical and physiological stimuli during adolescence, but this adaptive capacity diminishes after growth-plate closure, essentially limiting cam morphology development to the period of active skeletal growth[26,30,32].

Despite considerable advances in understanding, the exact tissue-based mechanism underpinning cam morphology formation remains incompletely understood. Longitudinal studies of physically active, mainly male adolescents have identified increased epiphyseal extension and hypertrophy of the fibrochondro-osseous tissue area at the femoral head–neck junction as important mechanisms in cam morphology development[30,32,46] (Fig. 3). However, the exact contribution of each mechanism differs between studies and populations, and might not be true for cam morphology development in female adolescents[30,32,46]. The developmental time frame for cam morphology is currently best described in male athletes[29–32,46] (Fig. 3). From birth until approximately 8 years of age, the proximal femur typically develops in a physiological manner. Between ages 8 and 10 years, the first signs of soft-tissue hypertrophy arise, primarily of fibrochondro-osseous origin and typically located at the lateral head–neck junction of the femur[29]. Around ages 9 to 10 years, the femoral epiphysis begins to assume an increasingly oblique orientation with progressive lateral extension. From ages 9 to 12 years — depending on sex and occurring just before the second growth spurt — the first osseous changes emerge, marking the earliest visible signs of cam morphology formation[30,31]. At this stage, the anterolateral head–neck junction gradually begins to lose its spherical contour and develops a subtle bony asphericity. As growth-plate closure approaches, the capacity for further osseous remodelling declines[30]. After epiphyseal closure (around age 13 years in women and between ages 13 and 18 years in men), the skeleton loses the capacity for further cam morphology development[30,32,47]. Epiphyseal closure can occur earlier in some individuals. The lower prevalence of cam morphology in women might partly reflect sex-related differences in skeletal maturity during adolescence, as women typically experience earlier femoral growth-plate closure than men. This earlier closure might limit the period of vulnerability during which mechanical loading could induce cam morphology. Notably, the location and size of cam morphology also seems to differ by sex, which might suggest overarching differences in its pathogenesis[48].

The primary causal risk factor for cam morphology development is environment (that is, engagement in high-joint-load sports during adolescence)[29–31,49,50]. In male athletes, both the amount and type of sport played during adolescence are linked to an increased risk of developing cam morphology. For example, one study of professional football players identified a dose–response relationship whereby higher activity levels during adolescence increased the odds of developing cam morphology[50]. Male athletes participating in sports that induce repetitive hip internal rotation and flexion (for example, football and ice hockey) seem to be particularly susceptible[30,32,46,49]. Ethnicity might also influence an individual's risk of developing cam morphology[20,51–53]. For instance, cam morphology is less common in East Asian populations compared with white or Black populations[20,51,52]. These ethnic differences suggest that genetic or cultural factors could be important in the development of cam morphology. Growing interest surround the roles of growth hormones, oestrogen and vitamin D in regulating growth-plate closure[54]. Although the interrelationship between hormonal influence, growth-plate closure and cam morphology remains unclear, specific imbalances or variations during adolescence might affect the growth plate's response to mechanical loading, potentially influencing the formation of cam morphology.

Pathogenesis of FAI syndrome

Considerable interest surrounds the timing and mechanisms by which cam morphology contributes to the development of FAI syndrome[40,44]. The pathogenesis of FAI syndrome probably results from a complex interplay of biological, physical and environmental factors[40,44]. Distinct clinical phenotypes probably exist, with the relevance of each factor varying between individuals and over time. Pincer morphology also contributes to FAI syndrome pathogenesis by increasing bony coverage of the femoral head[7,10,15,33]. When combined with cam morphology, the resulting anatomical configuration leads to earlier bony impingement during hip movement[15].

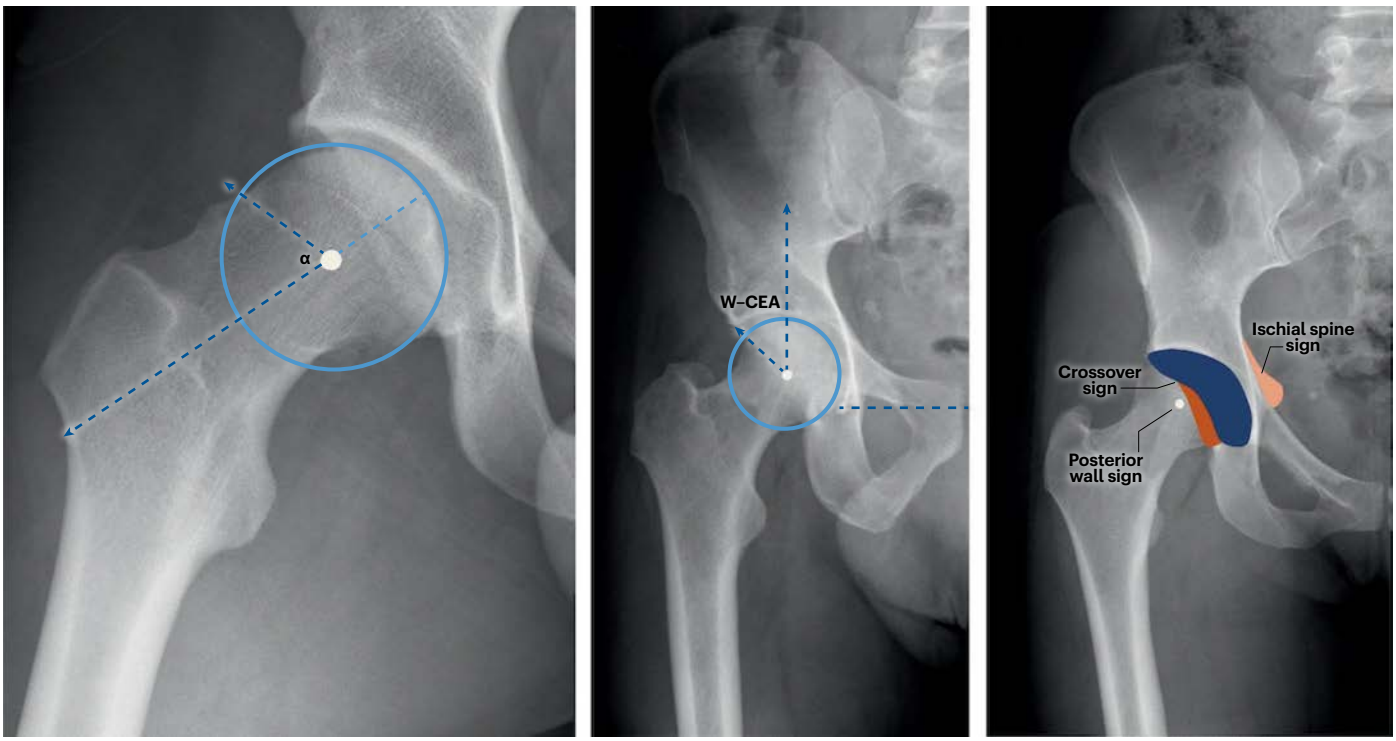


Fig. 2 | Cam morphology and pincer morphology. a, Cam morphology of the right hip, defined by an alpha angle $\alpha \geq 60°$, as visualized on a Dunn 45° lateral radiograph. **b**, Global pincer morphology of the right hip, indicated by a centre–edge angle of Wiberg (W-CEA) ≥40°, on an anteroposterior pelvis radiograph. **c**, Global pincer morphology of the right hip, characterized by the presence of crossover sign, posterior wall sign and ischial spine sign, on an anteroposterior pelvis radiograph.

Emerging evidence highlights the notable role of spinopelvic parameters and variations in femoral version in the development of FAI syndrome[16,17,38,55–57]. The alignment of the spinopelvic complex influences the acetabular orientation and the degree of impingement-free hip motion[16,58]. Several imaging parameters have been used to understand spinopelvic alignment, including pelvic incidence, sacral slope and pelvic tilt (Supplementary Fig. 1). Higher pelvic incidence[16,17] and sacral slope[16] (indicating greater lumbopelvic mobility and increased anterosuperior acetabular coverage) seem to predict symptomatic hip status, although findings remain inconsistent across studies[59]. High or low pelvic incidence has been implicated in the development of FAI syndrome, albeit via different mechanisms[55–57]. For instance, low pelvic incidence (associated with limited lumbopelvic motion) can lead to greater reliance on hip motion during movement and compensatory forward tilt of the pelvis, which can change the functional orientation of the acetabulum and reduce impingement-free hip range motion[55–57]. When paired with cam and/or pincer morphology, these altered biomechanics might heighten the risk of FAI syndrome. Conversely, those individuals with high pelvic incidence are less reliant on hip motion because they possess greater lumbopelvic mobility[55–57]. This increase in mobility might induce compensatory backward tilting of the pelvis, resulting in functional undercoverage of the anterior femoral head and increased loading of the anterior joint structures[55–57].

Femoral version (the amount of rotation between the proximal and distal aspect of the femur; Supplementary Fig. 1) might also have an important role in the pathomechanics of FAI syndrome[18,34,38,60]. Decreased, normal or increased femoral version can be present in hips with cam morphology[34]. Decreased version (known as retroversion) limits hip internal rotation[60] and increases the likelihood of both intra-articular and extra-articular impingement during extreme hip flexion compared to hips with FAI syndrome and normal version[18]. However, the role of femoral version in early-stage pathology remains uncertain, because lower femoral version is linked to better hip cartilage metabolism[61]. Moreover, isolated pathology within pain-generating tissues (such as the acetabular labrum) is unlikely to be the sole mechanism underlying the development of FAI syndrome[8,62]. For example, one large-scale study identified a similar prevalence, location and severity of labral tears in pain-free athletes with cam morphology and in athletes with FAI syndrome[8].

Inflammatory and immunologic mechanisms might also have an important role in FAI syndrome pathogenesis, as shown in OA[63]. Specifically, the synovial tissue of people with FAI syndrome shows elevated levels of synovitis and pro-inflammatory cytokines, which might contribute to symptom development and the degradation of articular cartilage[61,63]. Furthermore, athletes with FAI syndrome also have elevated levels of C-reactive protein compared with pain-free athletes, suggesting the presence of systematic inflammation[51]. However, future exploration is still needed to determine the potential of these and other biomarkers and to identify individuals at risk of FAI syndrome.

Progression to hip OA

Our understanding of the relationship between cam and/or pincer morphology and FAI syndrome continues to evolve, particularly in how these hip morphologies alter hip joint mechanics and accelerate the trajectory of hip OA.

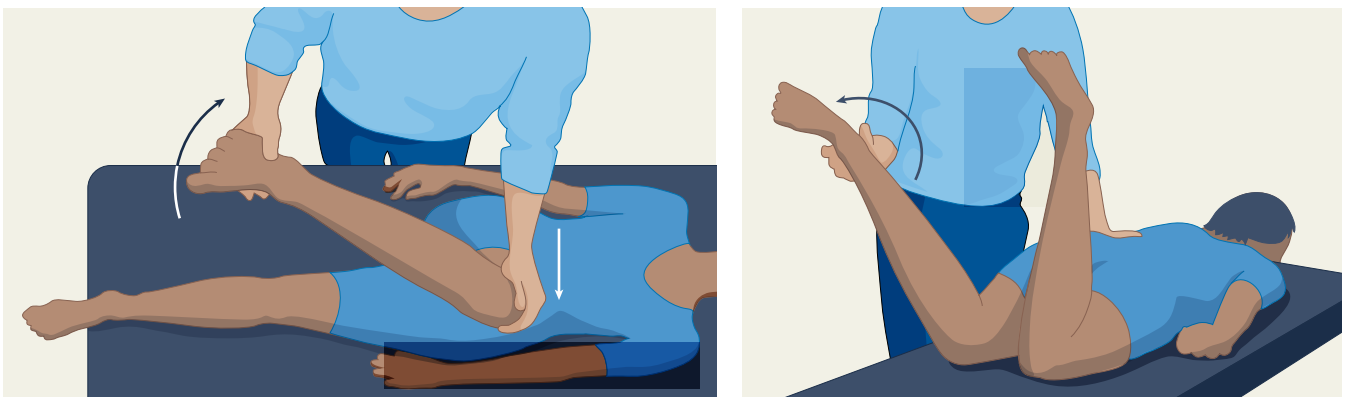
Association of cam and pincer morphology with FAI syndrome

A major limitation of the longitudinal literature is that studies often report on the occurrence of hip pain as a binary variable (that is, present or absent). Hip pain is an umbrella term encompassing various intra-articular conditions, including FAI syndrome, hip dysplasia and labral tears. Longitudinal investigations are also hampered by the slow development of FAI syndrome in those individuals with cam morphology and the difficulty of accurately tracking changes in symptoms over time[47]. The refinement of diagnostic criteria for FAI syndrome (now requiring a triad of symptoms, clinical signs and imaging findings)[10] has also complicated the interpretation of earlier studies that did not use this standardized definition. Finally, most studies investigate hip morphology in isolation rather than the combined effect of femoral, acetabular and spinopelvic anatomy. The following section summarizes evidence linking cam and pincer morphology (and where data permit, femoral version and spinopelvic parameters) to hip pain or FAI syndrome when the appropriate diagnostic criteria have been used.

Longitudinal studies have shown that cam morphology is an inconsistent risk factor for the development of hip pain. A 10-year follow-up of the CHECK study (1,685 hips; mean age 55.9 years) found no association between cam morphology and hip pain in women, and only a weak association in men at the 5-year mark. Cam size also failed to predict symptoms in either sex. However, these findings offer limited insight into younger populations more often affected by FAI syndrome[64]. In a smaller study of 332 asymptomatic hips in younger adults (mean age 29.5 years), MRI-defined cam morphology was associated with an increased risk of developing hip pain within 5 years (relative risk 4.3), although only a small number of hips ($n = 14$) became symptomatic during follow-up[65]. The contralateral pain-free hip of people undergoing hip arthroscopy for ipsilateral FAI syndrome has been used to model the natural history of cam and/or pincer morphology[66,67]. For example, a prospective investigation (mean follow-up of 7.1 years) found that individuals who later developed hip pain had a decreased FHN offset ratio (indicative of a more pronounced cam morphology) in the contralateral hip; no relationship was observed for imaging measures of pincer morphology and subsequent hip pain[66]. Cross-sectional studies have yielded similarly conflicting results across various populations[20]. Cam morphology, but not pincer morphology, differentiated people undergoing or seeking hip arthroscopy for FAI syndrome from pain-free individuals[16,68]. However,

Box 2 | Clinical assessment of FAI syndrome

Clinical tests are often used in the assessment of people suspected of having FAI syndrome[10,13,112,113]. However, most clinical tests have limited diagnostic accuracy and are best suited for screening or ruling out the condition. Importantly, no single clinical test can confirm a diagnosis of FAI syndrome. The flexion–adduction–internal–rotation (FADIR) test (figure, left) is the most frequently used test in clinical settings; however, although this test has high sensitivity, it lacks specificity and can lead to false-positive findings. For the FADIR test, the symptomatic hip is passively moved to 90° of flexion and the knee is bent to 90° of flexion. From this position, the hip is moved into adduction (avoiding movement of the pelvis) and then internally rotated while maintaining both flexion and adduction. The test is deemed to be positive when it reproduces the pain typically experienced by the patient. Passive joint range of motion should also be assessed, with particular attention to hip internal and external rotation in both the neutral hip position and at 90° of hip flexion, because these measures might indicate altered acetabular or femoral version[114]. Notably, reduced hip internal rotation, particularly when assessed in the prone or neutral hip position, is recognized as a useful indicator in the diagnosis of FAI syndrome (figure, right)[115]. For assessing passive hip internal rotation, the symptomatic hip is moved to a neutral position (with the knee bent to 90° of flexion). From this position, the hip is moved into internal rotation. A positive test is indicated by a limited range of motion, regardless of whether the person's familiar pain is reproduced. A comprehensive clinical assessment should also include evaluation of hip, core and lower-limb muscle strength, movement control and palpation of surrounding anatomical structures (such as the hip adductors, iliopsoas and pubic symphysis) because pain arising from these structures can present similarly to FAI syndrome[14,113,116].



Box 3 | Imaging assessment of FAI syndrome

Imaging is pivotal for making informed treatment decisions and determining prognosis in FAI syndrome. Imaging modalities enable detailed characterization of cam and pincer morphology to diagnose the condition, assessment of acetabular and femoral version, evaluation of spinopelvic parameters and identification of labral tears and chondral loss. Imaging also aids in differential diagnoses[10,33,38,40]. Radiography is the crucial first step in assessing hip anatomy and is often paired with MRI as standard imaging modalities for assessing hip disease associated with cam and/or pincer morphology[33,38].

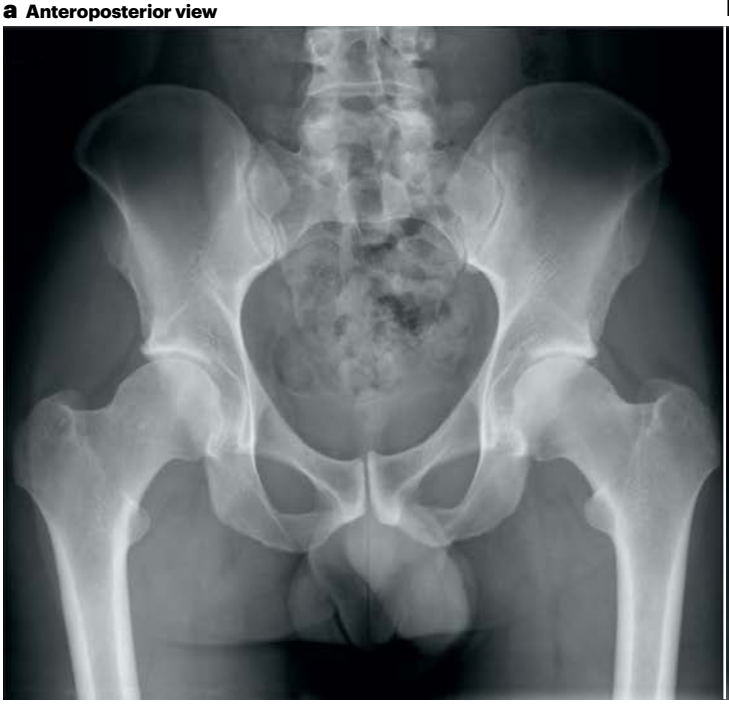
Plain radiographs

The anteroposterior pelvis and lateral views are fundamental to the assessment of cam morphology. The anteroposterior view (figure, panel a) is important for the assessment of pincer morphology (for example, acetabular depth, version and coverage). The lateral view enables assessment of the femoral head–neck junction (best shown with a Dunn 45° view; hips at 45° flexion and 20° abduction (figure, panel b), allowing accurate visualization of cam morphology[33,36,37]. However, these two-dimensional radiographic measurements capture only approximately 50% of proximal femur shape variation, often necessitating advanced imaging for comprehensive evaluation of cam morphology[33,36,37]. Spinopelvic parameters (such as pelvic incidence, sacral slope and pelvic tilt) can be evaluated using lateral lumbosacral radiography[38].

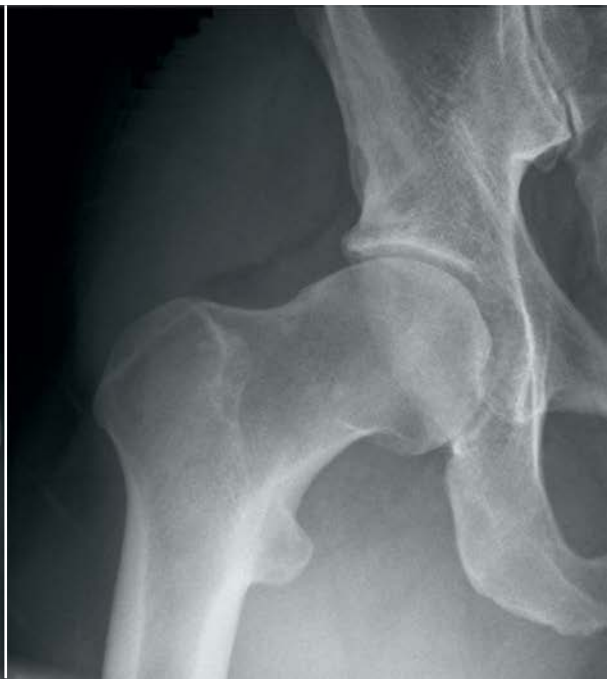
Advanced imaging techniques

MRI and computed tomography imaging provide enhanced three-dimensional (3D) assessment of cam and pincer morphology[36–38]. MRI enables detailed 3D evaluation of hip morphology, including version (acetabular and femoral) and soft tissue structures (for example, cartilage loss and labral tears)[38]. The Lisbon Agreement categorizes MRI with radial imaging and small field-of-view sequences as the gold standard for non-invasive assessment of cam morphology and associated hip joint soft tissues[36]. Computed tomography provides high-resolution 3D visualization of bony detail and is mainly used for surgical planning and virtual range-of-motion simulations[33,36].

a Anteroposterior view



b Lateral view



neither cam nor pincer morphology distinguished individuals with hip pain from those without hip pain in a large general population sample (n = 3,202)[69] or in a cohort of young adult football players[19]. Altered femoral version (whether decreased or increased) exists in both pain-free individuals and individuals with FAI syndrome[16,34]. By contrast, higher pelvic incidence and sacral slope distinguished individuals with FAI syndrome and cam morphology from pain-free individuals with or without cam morphology[16].

As a three-dimensional structure, variations in cam morphology size, location and magnitude probably also influence its reported relationships with hip pain and FAI syndrome. For example, in one study, larger cam morphology size could discriminate collegiate National Football League draftees[70] with prior or current hip pain from players without hip pain. Maximum alpha angle measurements are frequently observed in the anterosuperior region of the femoral head–neck junction[16,37,71,72], with individuals undergoing surgery for

FAI consistently demonstrating larger anterosuperior values than pain-free individuals[16,68]. In a separate study of football players with FAI syndrome, larger anterosuperior, but not superior cam morphology, was modestly associated with worse symptom severity[73]. Finally, greater severity of cam morphology (that is, bony extension over a greater portion of the femoral head–neck junction) has also been associated with FAI syndrome[16]. Evidence on the role of cam and pincer morphology in hip pain is conflicting, and longitudinal studies are needed to clarify their contribution (along with femoral version and spinopelvic parameters) to FAI syndrome pathogenesis.

Association of FAI syndrome with hip OA

FAI syndrome has historically been considered a more clinically relevant predictor of hip OA risk than the presence of cam morphology alone. However, until recently little causal evidence has been available to support this perception. A 10-year longitudinal study of older adults whose hips meet the diagnostic criteria for FAI syndrome (defined by the presence of hip pain, restricted internal rotation (≤25° in 90° of hip flexion) and cam morphology), reported a markedly increased risk of incident end-stage OA, with an adjusted odds ratio of 47.82 (ref. 12). Although only a small proportion of hips (approximately 1.5%) fulfilled the criteria for FAI syndrome, the strength of the association, along with the positive and negative predictive values for OA development, was substantially greater than for cam morphology alone. The distinction between cam morphology and FAI syndrome has important clinical implications when considering hip OA risk. Longitudinal investigations of FAI syndrome that incorporate pincer morphology, femoral version or spinopelvic parameters remain scarce, limiting insight into their role in hip OA development.

Association of cam and pincer morphology with hip OA severity

Hip OA is best conceptualized as a disease continuum that commences early in life (often without clinical symptoms), with initial structural changes occurring within the acetabular labrum and articular cartilage[74–76]. Structural changes can emerge in the absence of radiographic evidence of disease and, although early-stage OA remains undefined for the hip joint, these changes increasingly serve as indicators of early disease development[74,75,77]. Emerging evidence has provided insight into how cam and pincer morphology contribute to early-stage OA. Cross-sectional findings from a large study of adolescent male football players and a general population comparison group suggest that cam morphology does not affect articular cartilage until later in adolescence when the femoral growth plate

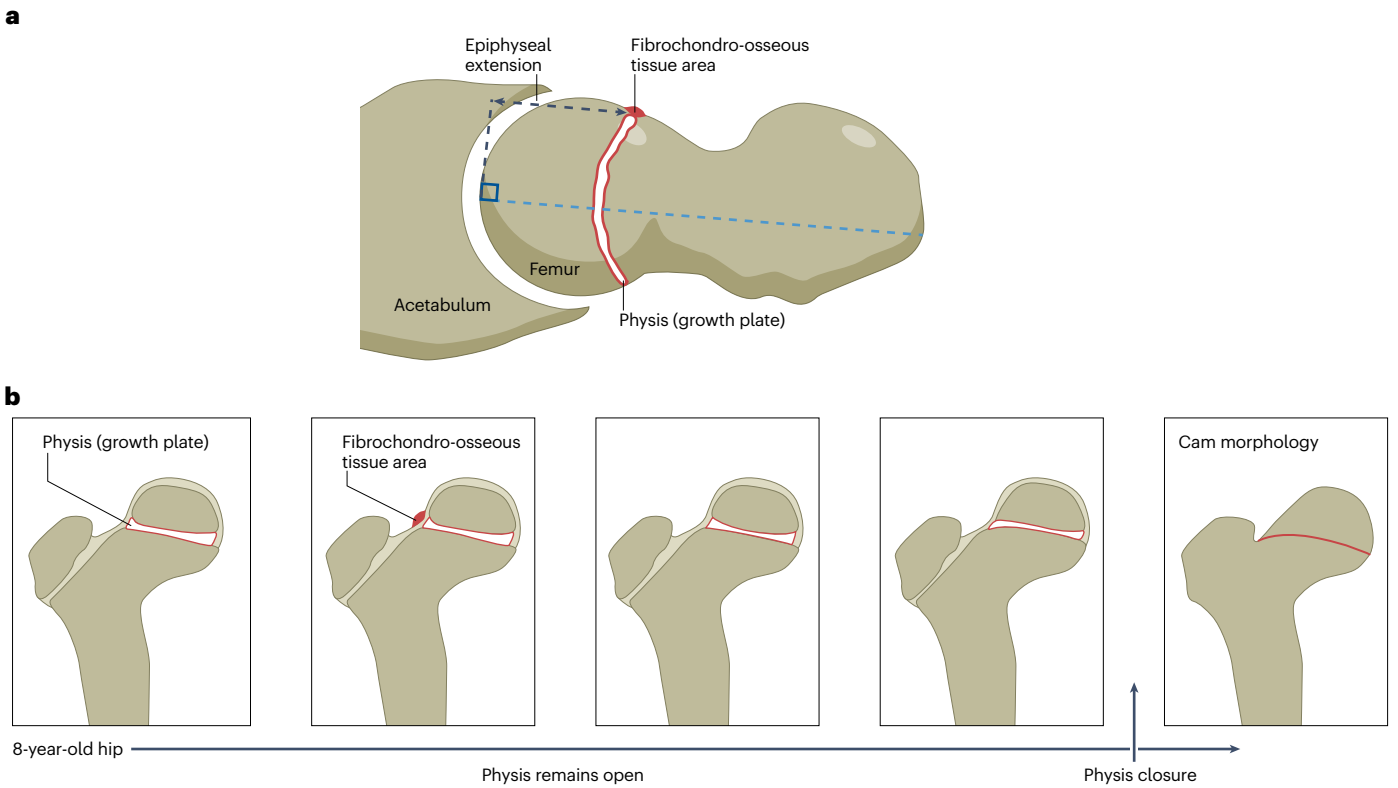


Fig. 3 | Tissue-based mechanisms and development of cam morphology. **a**, Epiphyseal extension and hypertrophy of the fibrochondro-osseous tissue area at the femoral head–neck junction are mechanisms implicated in the development of cam morphology. The fibrochondro-osseous tissue area represents a composite anatomical structure comprising the ossification groove of Ranvier and the perichondral fibrous ring of La Croix. Epiphyseal extension refers to growth or expansion of the epiphysis and is quantified by measuring the distance between the femoral head and the most distal aspect of the physis (growth plate), along a line that is parallel to the long axis of the femoral neck (dashed light blue line). This measure is then normalized to the diameter of the femoral head to account for individual size variation. **b**, At 8 years of age, a normal hip anatomy is observed. Soft-tissue hypertrophy is hypothesized to precede the extension of the femoral epiphysis (red zone), which progresses while the physis remains open. Following physeal closure, cam morphology becomes established. The proposed age ranges for growth-plate closure and cam morphology development might vary between individuals.

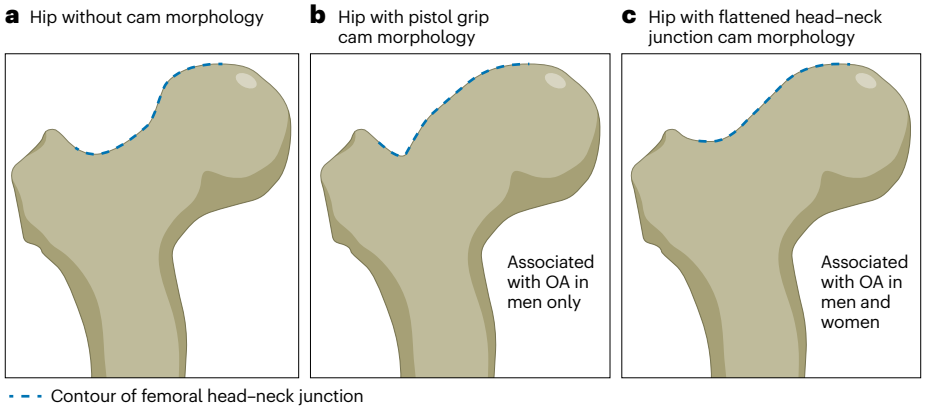


Fig. 4 | Cam morphology subtypes associated with hip osteoarthritis development. Cam morphology is a known risk factor for hip osteoarthritis (OA), with distinct subtypes showing variable associations[28]. **a**, Hip without cam morphology. **b**, Hip with pistol grip cam morphology (associated with hip OA in men only). **c**, Hip with flattened head–neck junction (associated with hip OA in men and women).

closes[78]. This concept is supported by a number of epidemiological and surgical studies[8,62,79,80]. Longitudinal studies of high-school athletes and elite male football players have confirmed an association between cam morphology (but not pincer morphology) and early-stage OA[9,81]. A subsequent cross-sectional study of pain-free elite male Australian football players (mean age 18.6 years) also found that cam rather than pincer morphology is linked to early-stage OA[62]. In adolescents (median age 16.7 years) undergoing surgery for FAI syndrome, greater cam morphology size was associated with surgically identified cartilage loss (with an odds ratio of 1.77 for every 10° increase in alpha angle)[79]. In the same study, the presence of crossover sign seemed to have a protective effect against cartilage loss[79]. Studies of adults aged 20 years and older consistently demonstrate an association between cam morphology and early-stage OA changes, whereas evidence for pincer morphology remains conflicting[8,82–85]. A cross-sectional investigation of young adult football players with and without hip pain identified a modest dose–response relationship between cam morphology and early-stage OA; each 1° increase in alpha angle was associated with a 3% greater odds of cartilage damage[8]. Meta-analytical evidence from surgical studies has also shown a link between greater alpha angle and increased severity of cartilage damage[84]. The relationship between cam morphology and the severity of early-stage OA should be considered when assessing an individual's risk of disease progression.

Extensive evidence shows that cam morphology has an important causal role in the development of hip OA, as confirmed through radiographic or surgical assessment[7,11,20,86]. A meta-analysis of three prospective cohort studies, involving 10,523 hips in older adults aged >45 years, found that cam morphology confers a 2.5-fold increased odds of developing hip OA over a median follow-up of 9 years, relative to hips without cam morphology[11]. Longitudinal data from the CHECK cohort have highlighted a sustained and consistent association between cam morphology and the development of OA, observed across four follow-up assessments over a 10-year period[87]. Nevertheless, the strength of the association between cam morphology and hip OA varies widely, and many individuals with this hip morphology do not go on to develop the disease.

At least two emerging insights could help rheumatologists to identify the type of cam morphology and specific contexts that increase the risk of future hip OA. First, researchers have proposed distinct subtypes of cam morphology, of which only some expedite hip OA. Cam morphology is a collective term for various forms of extra bone formation at the femoral head–neck junction. Although researchers first described subtypes of cam morphology (such as pistol grip deformity) over 50 years ago, robust evidence supporting a causal relationship with OA has remained limited[88]. To date, cam morphology is mostly quantified using an alpha angle threshold greater than 60°. However, this parameter only measures one aspect of cam morphology (that is, sphericity) and such threshold values probably encompass a spectrum of morphological subtypes. Analyses from the CHECK study used statistical shape modelling to characterize subtypes of cam morphology and investigate their associations with the development of hip OA over 10 years[28]. A pistol-grip-shaped femoral head was associated with hip OA exclusively in men, whereas a flattened head–neck junction showed associations with hip OA in both men and women[28] (Fig. 4). These findings confirm that specific subtypes of cam morphology could have greater relevance than others in OA development. The unique characteristics of each subtype cannot be fully captured by the alpha angle alone. Therefore, incorporating additional radiologic measures (such as femoral head–neck offset; Fig. 1) might be needed in clinical settings to better capture cam morphology subtypes and more accurately assess future OA risk.

A second emerging insight relates to the importance of stratifying risk by both sex and age. Data from the World COACH Consortium[5,89] — a global initiative that pooled and harmonized individual participant data from all nine available prospective cohort studies on hip OA, encompassing 23,886 hips — suggests that specific patient subgroups with cam morphology have a greater risk of developing hip OA[89]. Stratified analyses reveal that men with cam morphology have an increased risk of developing hip OA (relative risk 2.50) compared with men without cam morphology. By contrast, women with cam morphology also demonstrate increased risk (relative risk 1.75), but to a lesser extent[89]. Age-specific analyses further identify individuals aged 51–60 years with cam morphology as being at particularly high risk (relative risk of 2.15), with this subgroup exhibiting a higher relative risk than other age groups (40–50, 61–70 and >70 years). These findings further highlight the importance of risk stratification when evaluating the relevance of cam morphology in hip OA development.

Meta-analytical evidence from three prospective cohort studies (mean age >55 years, including 10,481 hips) indicates that pincer morphology does not increase the likelihood of OA development (odds ratio of 1.08) when compared with individuals without pincer morphology[11]. However, newly analysed data from the CHECK study indicates that hip pain might modify the relationship between pincer

morphology and OA[90]. For example, individuals presenting with a combination of baseline hip pain and pincer morphology (defined by an anterior centre edge angle >40°) had an increased odds of developing hip OA at 5-year (odds ratio of 3.41), 8-year (odds ratio of 2.36) and 10-year (1.97) follow-up, compared with individuals who had pincer morphology but no hip pain[90]. Finally, evidence of an association between protrusio acetabuli and hip OA development remains inconclusive. Two population-based prospective studies have reported conflicting evidence: the Johnston County OA Project[41] found a fourfold increased risk of hip OA in women with protrusio acetabuli, but not in men, whereas the Chingford Study[91] did not find any association.

Management

Over the past decade, considerable progress has been made in the management of FAI syndrome, with emerging clinical trial evidence supporting both surgical and non-surgical treatment approaches[92–99].

FAI syndrome

FAI syndrome can be managed with surgical and non-surgical treatments[10,100]. The current evidence, discussed in this section, is derived from studies involving people with FAI syndrome without coexisting radiographic hip OA. Hip arthroscopy is the most common surgical technique for FAI syndrome, with its use largely concentrated in high-income countries. The procedure typically involves resection of the cam and/or pincer morphology, and is frequently accompanied by treatment of co-existing cartilage and labral pathology[10]. Common non-surgical strategies include activity modification, education, intra-articular injections and physiotherapy-led incremental exercise rehabilitation[92,93,100]. Patient education is a cornerstone of non-surgical treatment and centres on activity modification, recommending avoidance of positions and activities usually associated with pain (for example, squatting, leg crossing, pivoting, high-joint-load activity and floor sitting)[101]. Patients should also be made aware of the high prevalence of cam and pincer morphology in pain-free individuals to help them contextualize their imaging findings[23]. Therapeutic intra-articular injections are often used in clinical settings in conjunction with exercise rehabilitation or in those with high pain levels[10,92]. Both corticosteroids and hyaluronic acid can provide modest short-term pain relief, although longer-term effects seem to vary considerably between individuals[92]. Importantly, the potential for either injection to modify disease progression remains unclear. Despite growing interest in orthobiologic injections (for example, platelet-rich plasma and mesenchymal stem cells), at present no clinical trial evidence is available to support the effectiveness of such approaches in people with FAI syndrome[92].

A growing body of research is focused on examining the effectiveness of hip arthroscopy and physiotherapy-led treatments in improving patient-reported outcomes and modifying disease progression in individuals with FAI syndrome. Three randomized controlled trials have compared surgery to physiotherapist-led treatment for FAI syndrome, examining the effects on pain and quality of life[94,95,99]. Although both treatment groups showed improvements in pain, the superiority of arthroscopy compared over physiotherapy was modest at 6–12 months. At two-year follow-up, one trial reported no advantage of arthroscopy over physiotherapist-led treatment in terms of pain relief or quality-of-life outcomes[93]. However, a more recent randomized controlled trial reported that, at 3-year follow-up, arthroscopy was superior to physiotherapist-led treatment, resulting in an 8.9-point improvement (out of 100; 95% confidence interval 7.0–10.8) in activities of daily living compared with physiotherapy-led treatment, among the 77% of participants who completed follow-up[96].

Consensus from the International Hip Pain Research Network recommends physiotherapist-led treatment as the first-line approach for managing FAI syndrome[100]. Several small-scale studies have compared different physiotherapy-led treatments[100], and a full-scale randomized controlled trial (PhysioFIRST)[102] is under way. This trial is comparing a targeted strengthening intervention with standardized stretching in 154 individuals with FAI syndrome[102], and is expected to provide robust evidence on the comparative effect of these approaches on patient outcomes. Optimal treatment (surgical or non-surgical) of FAI syndrome should involve shared decision-making, enabling patients to make informed choices. Clinicians should work within a multidisciplinary team with access to all treatment options.

Although both surgical and non-surgical treatments are primarily aimed at reducing pain and improving quality of life, growing interest has emerged in their potential to modify the course of OA[27,98,103]. So far, two randomized controlled trials have investigated the effects of arthroscopy versus physiotherapy on MRI-defined hip joint structure: one study with a 12-month follow-up[98] and the other with a 3-year follow-up[96]. At 12 months, no difference was observed between the surgery and physiotherapy groups in terms of hip joint structure[98]. At 3-year follow-up, radiographic joint space width remained similar across both groups, but the Scoring Hip OA with MRI[104,105] score was lower in the arthroscopy group (mean 9.22, standard deviation 11.43)

Glossary

Acetabular labrum
An intra-articular fibrocartilaginous triangle that traverses the anterior and posterior acetabular rim, joining with the transverse acetabular ligament inferiorly to create a continuous ring. It functions to improve joint stability, distribute joint forces and preserve articular cartilage.

Acetabular version
The orientation of the acetabulum in the horizontal plane.

Acetabulum
The cup-shaped bony socket in the pelvis that forms the hip joint by articulating with the head of the femur.

Crossover sign
A radiographic indicator of acetabular retroversion; present when the anterior acetabular wall crosses over the posterior acetabular wall.

Femoral version
The amount of rotation or torsion between the proximal and distal parts of the femur.

Ischial spine sign
A radiographic feature associated with acetabular retroversion; considered present when the triangular ischial spine protrudes medially into the pelvic cavity.

Posterior wall sign
A radiographic sign of insufficient posterior acetabular coverage; considered present when the projection of the posterior acetabular wall is medial to the centre of the femoral head.

Protrusio acetabuli
A radiographic finding indicating medial displacement of the acetabulum; occurs when the medial wall of the acetabulum projects into the pelvic cavity, resulting in the femoral head crossing or touching the ilioischial line.

Spinopelvic parameters
A set of radiographic measurements used to assess the relationship between the hip, pelvis and lumbar spine in the sagittal plane (namely pelvic incidence, sacral slope and spinopelvic tilt).

compared with the physiotherapy group (mean 22.76, standard deviation 15.26), suggesting that arthroscopy might be associated with reduced MRI-detected joint damage relative to physiotherapy[96]. No clinical trials have examined the effects of exercise-based treatments on the trajectory of hip OA in individuals with FAI syndrome. Hip muscle weakness, altered movement and changes to physical activity are usually seen in individuals with FAI syndrome[106], and might also alter hip joint forces, influencing the trajectory to hip OA[107]. Exercise-based treatment programmes that target hip muscle weakness, enhance movement control and improve physical activity might be especially beneficial in altering the risk of future hip OA. However, these interventions must be delivered at a sufficient dosage to effectively target impairments and alter joint forces[108], an aspect that might have been suboptimal in the reported randomized controlled trials[94,96,98].

FAI syndrome with hip OA

People with FAI syndrome and established radiographic hip OA present a complex therapeutic challenge in rheumatology practice[109]. An expert-panel Delphi study identified genuine uncertainty — clinical equipoise — among experts regarding which treatment is superior for this patient population[110]. The expert group recommended that physiotherapy-led treatments should consist of core and hip muscle strengthening, enhancement of lumbo-pelvic mobility, avoidance of high-joint-load positions and activity modification. Hip arthroscopy could be considered for younger patients and/or those with a normal body mass index[110]. By contrast, people with severe joint space narrowing, advanced radiographic disease (that is, Tönnis grade 3 OA) or bilateral cartilage damage involving both the acetabular and femoral head as identified on MRI should be regarded as poor candidates for hip arthroscopy[110]. For young adults who are not candidates for arthroscopy and do not respond to physiotherapy-led interventions, total hip arthroplasty might be considered as a treatment option[111].

Opportunities for cam morphology prevention

Growing interest surrounds the prevention of cam morphology in children and adolescents, because of its associated increased risk of FAI syndrome and hip OA in later life[44]. However, despite this increased risk, not all people with cam morphology develop hip OA[11,28,86,89]. Young athletes with open femoral epiphyseal growth plates represent a critical target population for primary prevention strategies[29,30,32,46]. The cornerstone of a prevention programme would probably involve reducing sporting load during periods of skeletal growth, particularly in young athletes engaged in high-joint-load sports linked to cam morphology formation (such as football and ice hockey). However, findings from the Oxford Consensus study (parts 1 and 2), which included input from parents, athletes, coaches, clinicians and scientists, emphasized the need for further research to identify risk factors for cam morphology in youth athletes before implementing prevention programmes[25,27]. Without such knowledge, the benefits of sports participation during youth far outweigh the risks and consequences of cam morphology, and thus primary prevention interventions for cam morphology cannot currently be recommended[44].

Conclusion

Cam morphology is present in individuals with and without FAI syndrome and is associated with an increased risk of developing early hip OA. Evidence suggests that exposure to high-joint-load physical activity during skeletal maturation has an important role in cam morphology formation. Imaging remains a cornerstone of the diagnosis of hip morphology but should always be interpreted with caution and in conjunction with clinical symptoms and physical findings. Cam morphology might contribute to the onset of early-stage hip OA from late adolescence, whereas additional factors such as pincer morphology, femoral version and spinopelvic parameters probably influence FAI syndrome development. Longitudinal mechanistic evidence supports cam morphology as a well defined causal risk factor for hip OA, and emerging data also highlight the importance of FAI syndrome in disease development. Specific subtypes of cam morphology and demographic characteristics seem to be more strongly associated with hip OA than others and could inform patient stratification. Although both surgical and non-surgical interventions are available for managing FAI syndrome, existing clinical trial evidence supporting these approaches is predominantly derived from people without coexisting hip OA. At present, strategies to prevent cam morphology development (primary prevention) are not considered feasible. Continued efforts are needed to advance diagnostic approaches for FAI syndrome and to individualize surgical, non-surgical and orthobiologic treatments to enhance clinical outcomes and reduce the future burden of hip OA.

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Author contributions

All authors researched data for the article and wrote the article. J.H., J.K., P.v.K., V.M., M.S., K.C., F.B., P.D., S.B-Z. and R.A. contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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Check for updates

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In the version of the article initially published, in the "Nociplastic pain" section, the sentence "Patients with axSpA who have nociplastic pain frequently show higher scores in axSpA-related patient-reported outcomes and worse response to NSAIDs, bDMARDs and tsDMARDs than those patients with nociplastic pain" should have read "Patients with axSpA who have nociplastic pain frequently show higher scores in axSpA-related patient-reported outcomes and worse response to NSAIDs, bDMARDs and tsDMARDs than those patients with nociceptive pain." In the "Nociplastic and neuropathic pain as drivers for nociceptive pain scores" section, the text "In the GESPIC cohort (78 patients with axSpA who were treated with bDMARDs) 22% of patients had nociceptive pain (measured by WPI)..." should have read "In the GESPIC cohort (78 patients with axSpA who were treated with bDMARDs) 22% of patients had nociplastic pain (measured by WPI)... ". These corrections have been made to the HTML and PDF versions of the article.