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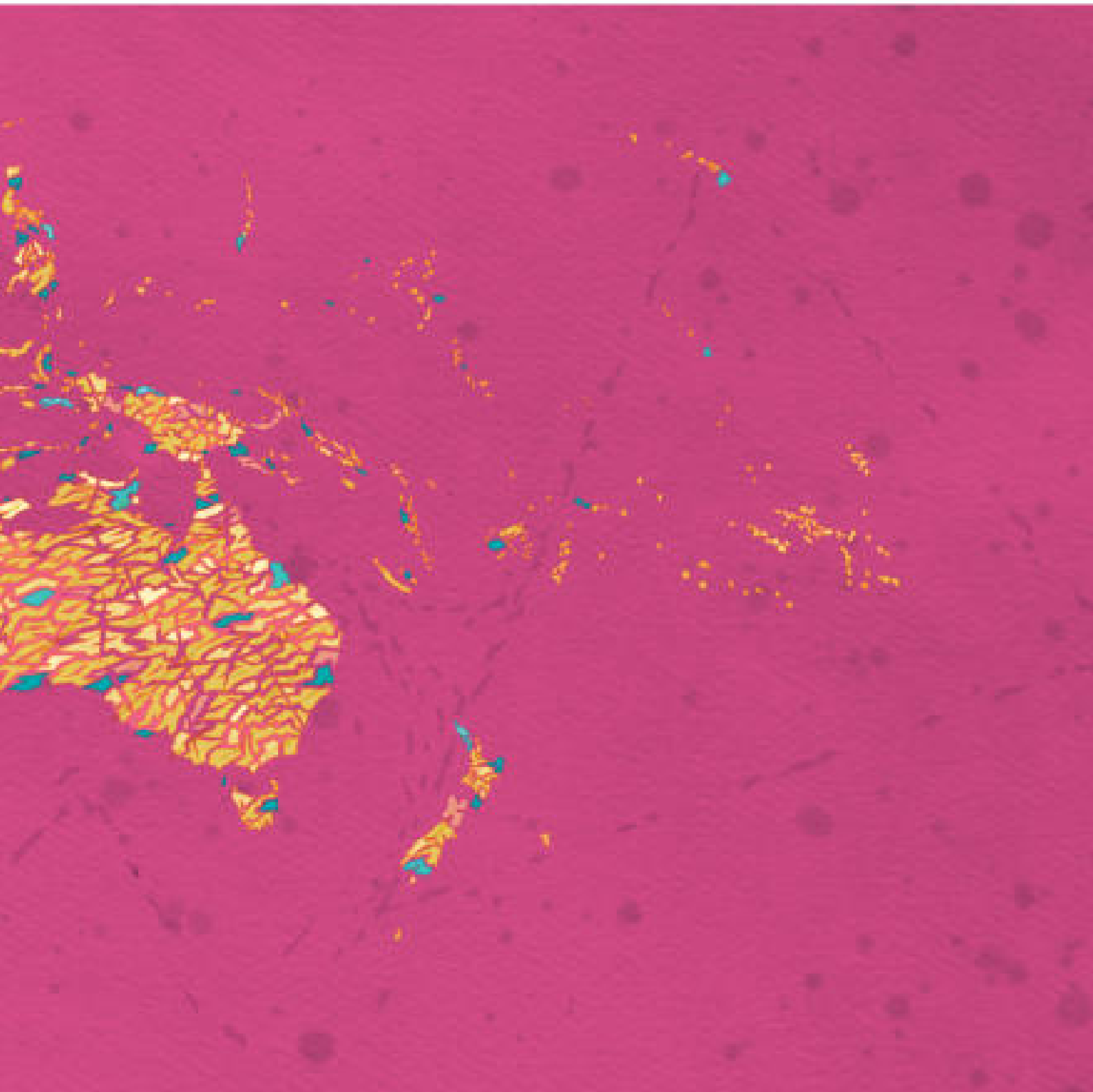

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Connecting the structure and function of cartilage using spatial omics

Indira Prasadam & Xiwei Fan

Advances in spatial omics, such as transcriptomics and proteomics, have provided vital insights into cartilage microenvironments, revealing cellular diversity, zonal organization and links between cartilage structure and function. Analysing cartilage using spatial omics could deepen the understanding of diseases such as osteoarthritis and guide the development of targeted, disease-modifying therapies.

Structure and function are intrinsically linked in biological systems, with articular cartilage exemplifying this relationship. As a specialized connective tissue, cartilage can preserve joint integrity even with substantial mechanical stress. This resilience stems from the unique 3D zonal spatial organization of cartilage and the functional adaptability of its sole cellular component, chondrocytes. However, the limited regenerative capacity of cartilage and the pathological changes observed in osteoarthritis (OA) present substantial challenges for clinical intervention. Advances in single-cell and spatial omics technologies, including spatial proteomics and transcriptomics, are transforming the understanding of cartilage biology by uncovering its molecular complexity and redefining established paradigms. In this Comment, we highlight the need to leverage spatial omics technologies to address critical gaps in cartilage research, with the goal of translating these advancements into personalized therapies and improved patient outcomes for OA.

Spatial organization of articular cartilage

The distinct zones of cartilage optimise mechanical load distribution and maintain cartilage function, and, combined with the spatial patterns of chondrocytes, these zonal arrangements collectively facilitate nutrient diffusion and intercellular communication[1]. Chondrocytes are heterogeneous, consisting of subpopulations with zone-specific gene and protein expression and functions. In OA, chondrocytes can undergo phenotypic changes, such as becoming senescent and pro-inflammatory, which contributes to extracellular matrix degradation and zonal disintegration[1]. These changes accelerate disease progression; thus, understanding chondrocyte heterogeneity and spatial dynamics in this context could contribute to the development of targeted therapies. Moreover, the zonal organization of cartilage and its disruption during OA progression offer unique opportunities for therapeutic intervention, emphasizing the importance of preserving structural integrity to maintain function.

Single-cell and spatial omics in cartilage biology

Historically, research on the structure and function of cartilage has relied on histology, immunohistochemistry and imaging techniques. In the past decade, considerable advances have been made through the use of bulk omics approaches to analyse joint tissues from patients with OA and from animal models of OA[2]. For example, large-scale genetic studies in humans have uncovered loci and pathways associated with OA[3], and studies using transcriptomics have classified OA into subtypes on the basis of mechanisms such as inflammation, cartilage degradation and metabolic dysregulation[4]. This stratification underscores the molecular heterogeneity of OA cartilage and highlights the need for subtype-specific therapeutic strategies. However, bulk omics analyses lack the resolution to distinguish individual cell types or capture spatial organization, limiting insights into cartilage microenvironments.

Single-cell RNA sequencing (scRNA-seq) has addressed this gap somewhat by providing high-resolution data on chondrocyte heterogeneity. For instance, a study analysing 1,464 chondrocytes from ten patients with OA undergoing knee arthroplasty identified seven distinct chondrocyte populations, including three novel phenotypes with unique functions[5]. Another study that combined scRNA-seq with spatial transcriptomics examined human knee articular cartilage from both patients with OA and healthy individuals and identified 11 chondrocyte populations[6]. These populations included inflammatory, hypertrophic and prefibrocartilage chondrocytes and could facilitate patient stratification, and highlighted dynamic chondrocyte transitions and zone-specific expression of genes that are essential for OA progression[6]. However, scRNA-seq inherently loses the spatial and zonal context of these cells, which limits the ability to map their precise organization and interactions within cartilage and therefore highlights the need to use spatial omics to capture the molecular and structural intricacies of the tissue.

Spatial transcriptomics and proteomics can bridge this gap. For example, spatial transcriptomic platforms capture spatially resolved gene expression data and enable researchers to map molecular processes whilst maintaining structural integrity. Although spatial transcriptomics are widely used in fields such as oncology, their application in cartilage biology and OA research remains unexplored[7], thus providing a research opportunity for uncovering the spatially regulated mechanisms underlying OA. Integrating these advanced technologies into OA studies could reveal previously unrecognized zonal patterns of gene and protein expression, paving the way for the discovery of novel therapeutic targets.

Although the central dogma suggests a linear flow from DNA to RNA to protein, the reality is far more complex. The relationship between messenger RNA and its corresponding proteins is highly regulated and non-linear, with multiple control points affecting protein expression. Compared with transcriptomics, spatial proteomics has provided greater insights into cartilage biology by enabling

high-resolution analysis of protein expression, localization and interactions within native tissue. To obtain meaningful insights into the relationships between structure and function, proteins should be studied directly, as post-transcriptional and post-translational modifications can occur.

Techniques such as mass spectrometry imaging (MSI), including MALDI-MSI (matrix-assisted laser desorption/ionization), TOF-SIMS (time-of-flight secondary ion mass spectrometry) and DESI-MSI (desorption electrospray ionization), have been used to analyse proteins, lipids and metabolites in cartilage. MALDI-MSI has revealed spatially distinct protein alterations linked to OA progression[8]. A newly developed type of functional MSI has confirmed enzymes, such as phospholipase A2 group IIA, as important contributors to disease progression, offering insights to guide therapeutic strategies[9]. Additionally, laser-capture microdissection combined with liquid chromatography–mass spectrometry has been used to examine zonal differences in cartilage, including calcified regions, revealing region-specific protein alterations[10]. By directly mapping protein expression, these approaches provide critical information that transcends transcriptomics and reflects the functional heterogeneity of the tissue.

Despite some advances, the application of spatial proteomics in OA research remains limited. Current efforts have barely begun to explore the potential of this technique, but rapidly advancing technologies and computational tools, including machine learning, offer promising opportunities for addressing the complex molecular heterogeneity of OA. It is becoming increasingly apparent that the integration of spatial transcriptomics and proteomics is essential to unravelling the multifaceted biology of cartilage and OA.

Addressing challenges and advancing spatial omics in cartilage research

Compared with other fields, spatial omics remains underutilized in cartilage research, owing to complex workflows, high costs and challenges associated with the low chondrocyte density in cartilage. This cellular sparsity complicates imaging and sequencing, as highly sensitive tools are needed to extract meaningful data. Rapid technological advancements in the past 5 years have enabled the effective analysis of low cell numbers. The optimization of workflows, from sample preparation to data analysis, can yield valuable insights into zonal differences, trends in gene and protein expression, and markers of cartilage degeneration.

Scalability and resolution remain critical challenges, particularly in cartilage zones with lower chondrocyte activity. Emerging technologies, such as enhanced multiplexed imaging and advanced single-molecule sequencing, are being developed to improve resolution in these regions. Innovations in optics for deep tissue imaging and machine learning algorithms to interpret complex datasets offer promising solutions to overcome these limitations and extract meaningful insights from low-abundance transcripts and proteins.

The development of a 3D molecular map of chondrocytes that integrates spatial, molecular and functional data would provide unparalleled insights into zonal adaptations and pathological changes in OA. Samples that are discarded during surgery, which can be graded by disease severity, represent an accessible resource for studying chondrocyte behaviour in both healthy states and diseased states. To ensure reproducibility and clinical relevance, it will be essential to develop standardized markers, protocols and reference atlases that can be replicated across laboratories. Future research that aims to identify the phenotypes and endotypes of OA should also investigate interactions between chondrocytes and other cell types in the joint, such as synoviocytes and immune cells, and systemic factors, such as aging, obesity and metabolic disorders, which can influence chondrocyte behaviour and spatial organization, should also be considered. Addressing these challenges will deepen understanding of cartilage biology and support the development of precision therapies for OA. Integrating spatial omics will be crucial, as it reveals distinct molecular patterns and identifies potential biomarkers for targeted interventions.

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References

1. Fukui, N. et al. Zonal gene expression of chondrocytes in osteoarthritic cartilage. *Arthritis Rheum.* **58**, 3843–3853 (2008).
2. Beier, F. The impact of '-omics' research on our understanding of osteoarthritis and future treatments. *Curr. Opin. Rheumatol.* **35**, 55–60 (2023).
3. McDonald, M. N. et al. Novel genetic loci associated with osteoarthritis in multi-ancestry analyses in the Million Veteran Program and UK Biobank. *Nat. Genet.* **54**, 1816–1826 (2022).
4. Yuan, C. et al. Classification of four distinct osteoarthritis subtypes with a knee joint tissue transcriptome atlas. *Bone Res.* **8**, 38 (2020).
5. Ji, Q. et al. Single-cell RNA-seq analysis reveals the progression of human osteoarthritis. *Ann. Rheum. Dis.* **78**, 100–110 (2019).
6. Fan, Y. et al. Unveiling inflammatory and prehypertrophic cell populations as key contributors to knee cartilage degeneration in osteoarthritis using multi-omics data integration. *Ann. Rheum. Dis.* **83**, 926–944 (2024).
7. Marx, V. Method of the Year: spatially resolved transcriptomics. *Nat. Methods* **18**, 9–14 (2021).
8. Eveque-Mourroux, M. R., Rocha, B., Barre, F. P. Y., Heeren, R. M. A. & Cillero-Pastor, B. Spatially resolved proteomics in osteoarthritis: State of the art and new perspectives. *J. Proteomics* **215**, 103637 (2020).
9. Fan, X. et al. Functional mass spectrometry imaging maps phospholipase-A2 enzyme activity during osteoarthritis progression. *Theranostics* **13**, 4636–4649 (2023).
10. Fan, X. et al. The deterioration of calcified cartilage integrity reflects the severity of osteoarthritis-A structural, molecular, and biochemical analysis. *FASEB J.* **36**, e22142 (2022).

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Competing interests

The authors declare no competing interests.

Immunology

Targeting T cell-activating NETs in uveitis

Retinal vasculitis is a common complication of autoimmune uveitis that leads to vision loss. It is associated with a breach in the blood–retina barrier (BRB) and the concomitant retinal accumulation of pro-inflammatory immune cells, mainly neutrophils and $CD4^+$ T cells. A study by Li. et al. now sheds light onto the mechanistic link between neutrophils and $CD4^+$ T cells in the pathogenesis of autoimmune uveitis.

Activated neutrophils produce extracellular DNA–protein complexes termed neutrophil extracellular traps (NETs). NET levels were higher in the blood of patients with idiopathic uveitis or Behçet uveitis than in the blood of healthy donors, and were correlated with disease activity. In addition, in vitro activation of neutrophils from the blood of patients with autoimmune uveitis resulted in more NET formation (NETosis) than the NETosis that resulted from activated neutrophils from healthy donors.

On the basis of those observations, the authors investigated the mechanistic links between increased NETosis in uveitis and retinal infiltration by activated $CD4^+$ T cells in a mouse model of experimental autoimmune uveitis (EAU). Administration of the NET-degrading enzyme DNAse I or a neutrophil-depleting antibody to mice with EAU reduced disease severity by both minimizing the frequency of intraocular T helper 1 (T_H1) and T_H17 $CD4^+$ T cells and restoring the balance between splenic $CD4^+$ regulatory T cells and effector T cells. In vitro assays with primary human retinal microvascular endothelial cells (RMECs) or mouse-derived endothelial cells further showed that NETs increase endothelial cell permeability, thereby potentially disrupting the BRB, and also upregulate the expression of molecules associated with cell adhesion and antigen presentation. Co-culture assays with human RMECs and patient-derived $CD4^+$ T cells showed that the presence of NETs increases the adhesion of $CD4^+$ T cells to RMECs and consequent effector T cell differentiation. Moreover, preliminary in vitro results indicated that NETs sensed by the cGAS–STING pathway in endothelial cells induce a pro-senescent gene expression programme in these cells. Thus, the authors suggest that targeting of NETs or treatment with either senolytics — to remove senescent RMECs — or with a cGAS–STING pathway inhibitor might help restore the BRB and dampen $CD4^+$ T cell-mediated autoimmunity in uveitis.

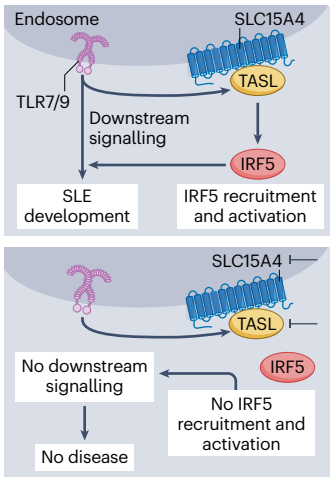
Maria Papatriantafyllou

Original article: Li, Z. et al. Neutrophil extracellular traps potentiate effector T cells via endothelial senescence in uveitis. *JCI Insight* https://doi.org/10.1172/jci.insight.180248 (2025)

Related article: Clarke, S. L. N. et al. The management of adult and paediatric uveitis for rheumatologists. *Nat. Rev. Rheumatol.* **20**, 795–808 (2024)

Immunopathogenesis

TASL has a key role in SLE



Genome-wide association studies have identified numerous genes that are linked to the development of systemic lupus erythematosus (SLE), including *TASL*, *IRF5*, *TLR7*, *TLR9* and *SLC15A4*. Both Toll-like receptor 7 (TLR7) and TLR9 have known pathogenic roles in SLE pathogenesis; TASL–SLC15A4 interactions mediate the activation of IRF5 downstream of TLR7 and TLR9 signalling. Despite the identification of this signalling cascade, the functional role that it has in SLE pathogenesis is unclear.

Now, two studies published simultaneously in *Nature Communications*, by Lau et al. and by Drobek et al., provide insights into the function of TASL in the pathogenesis of SLE. Paolo Manzanillo, the corresponding author of the Lau et al. study, comments that "Our studies not only verify and repeat the key data of one another but also highlight unique aspects of TASL biology," and the corresponding author of the Drobek et al. study, Manuele Rebsamen, notes that "Both papers mutually support each other's findings and conclusions, with virtually no discrepancies."

The studies by Drobek et al. and Lau et al. both demonstrate that mice lacking TASL have diminished TLR7 and TLR9 responses; in these mice, IRF5 activation and cytokine production are impaired. Notably, although loss of TASL diminished these responses, they were not fully impaired. In both studies, *Tasl*-deficient mice were protected from pristane-induced lupus.

In the Drobek et al. study, the authors note that loss of SLC15A4 results in a complete loss of IRF5 activation, whereas loss of TASL only impairs this activation. Research to understand this disparity led to the identification of a novel paralogue of TASL, termed TASL2, which is not found in humans. The phenotype of *Tasl* and *Tasl2* double-knockout mice was identical to that of mice with mutant Slc15a4 (known as *feeble* mice). This study provides evidence that the primary function of the TASL–SLC15A4 axis in the TLR7 and TLR9 signalling pathway is downstream activation of IRF5 and that loss of this axis is protective in mouse models of SLE.

Lau et al. also explored the functional link between an SLE-associated single-nucleotide polymorphism (SNP) and TASL. They show that this SNP alters the expression of TASL, cytokine production and TLR signalling in human cells. This research demonstrates the key role of TASL in SLE in cells from mice and humans.

When asked about the future of this research, both Manzanillo and Rebsamen noted that as TASL is found on the X chromosome and is reported to escape X chromosome inactivation, the role of TASL as a potential explanation for why autoimmune diseases (including SLE) preferentially affect women should be explored.

Taken together, these studies indicate that the SLC15A4–TASL axis is key in the pathogenesis of SLE and that targeting this axis could have therapeutic potential for SLE and other autoimmune diseases.

Holly Webster

Original articles: Drobek, A. et al. The TLR7/9 adaptors TASL and TASL2 mediate IRF5-dependent antiviral responses and autoimmunity in mouse. *Nat. Commun.* https://doi.org/10.1038/s41467-024-55692-y (2025); Lau, L. et al. An essential role for TASL in mouse autoimmune pathogenesis and Toll-like receptor signaling. *Nat. Commun.* https://doi.org/10.1038/s41467-024-55690-0 (2025)

Bone

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Towards better management of sterile bone inflammation

Jürgen Braun

The first expert consensus recommendations for the treatment and diagnosis of adult sterile bone inflammation have been developed, in which the term 'chronic non-bacterial osteitis' is proposed as a disease definition. Will these recommendations pave the way for better diagnosis, management and treatment of this rare disease?

Refers to Winter, E. M. et al. Expert consensus recommendations for the diagnosis and treatment of chronic non-bacterial osteitis (CNO) in adults. *Ann. Rheum. Dis.* https://doi.org/10.1136/ard-2024-226446 (2024).

Sterile bone inflammation is a rare and heterogeneous syndrome that affects children and adults. In the past, various terms have been used to describe sterile bone inflammation, including chronic non-bacterial osteomyelitis, chronic recurrent multifocal osteomyelitis (CRMO), synovitis, acne, pustulosis, hyperostosis, osteitis syndrome, diffuse sclerosing osteomyelitis, pustulotic arthro-osteitis, sternocostoclavicular hyperostosis and others. Now, an international panel of experts has proposed the term 'chronic non-bacterial osteitis' (CNO) as a disease definition and has provided 16 recommendations for the management of CNO[1].

The development of these recommendations is a good step forward to increase awareness of this health problem, and to prompt much-needed patient registries, translational research and multicenter trials. This need is particularly pressing, owing to the lack of diagnostic and classification criteria and standard outcome measures and the impact of bone pain on the daily life of patients.

Notably, although CNO occurs more frequently in children, these recommendations are specifically for adult-onset CNO. In a 2018 study of 486 cases from the Eurofever international registry, the mean age at disease onset was around 10 years[2]. In this study, the reported disease manifestations were rather heterogenous and included acne, palmoplantar pustulosis, psoriasis and papulopustular lesions, which together made up to <20% of the entire cohort. There are important differences between childhood-onset CNO and adult-onset CNO. In childhood-onset CNO, there is more systemic inflammation, and the course of disease is often recurrent and multifocal and also involves appendicular bones. By contrast, adults typically present with lesions confined to one or two areas in the axial skeleton, often as osteitis of the anterior chest wall, including the clavicles, upper ribs and sternum, but vertebrae, mandible and pelvis can also be involved[3,4].

The recommendations for the initial laboratory tests for CNO include a complete blood count with white cell differential, and measuring the levels of inflammatory markers, renal function, alkaline phosphatase, calcium, 25-hydroxy vitamin D, parathyroid hormone, phosphate and, in some cases, bone-turnover makers and HLA-B27 positivity[1]. For the initial imaging evaluation of adults with suspected CNO, whole-body MRI is recommended. Routine bone biopsies are discouraged[1,4]. The most important recommendations are shown in Box 1.

For therapy, the expert panel recommends NSAIDs as a first-line treatment of active CNO; for second-line treatment, individualised management, intravenous bisphosphonates (this option is preferred) and tumour necrosis factor inhibitors are recommended[1]. A relevant healthcare problem is that it is often unclear who is responsible for the care of patients with CNO. My personal view is that inflammatory changes should be taken care of by rheumatologists.

When considering adult CNO in general, it is important to realize that the initial MRI findings of bone marrow oedema and osteolysis can be later followed by structural changes, such as sclerosis, hyperostosis, erosions, soft-tissue ossification and ankylosis[3]. Apart from bone inflammation, patients can present with musculoskeletal features (arthritis, sacroiliitis, dactylitis and enthesitis), dermatological features, uveitis and inflammatory bowel disease[3]. The role of these manifestations in disease pathogenesis is unclear, which is similar to axial spondyloarthritis (axSpA). The similarity between these two related diseases in several clinical feature is evident in the literature[5] and in the Venn diagram presented in the new recommendations[1]. In axSpA, bone marrow oedema is frequently observed in the axial skeleton but is often related to entheseal structures; however, the appearance of spondylitic lesions in axSpA[5] can be difficult to distinguish from those observed in CRMO.

The most severe multifocal form of CNO, CRMO, first described in 1972 (ref. 6), has similarities to reactive arthritis. An infectious aetiology had been considered for CRMO for decades, owing to the isolation of *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) from bone lesions of individual patients[7]. However, this concept has now been discarded, as even long-term antibiotic therapy did not change the course of disease, and PCR tests failed to detect bacterial DNA in bone specimens; similar observations have been made in reactive arthritis. Patients with psoriatic arthritis can have axial involvement, and an association with skin changes related to inflammatory bone disorders has also been described for synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome; this term was first proposed in 1987 (ref. 8).

In CNO, SAPHO and axSpA, osteodestructive changes (such as erosions) can follow the initial inflammatory changes (such as bone marrow oedema), especially in the sacroiliac joints. Such erosive changes rarely occur in the spine and are dependent on the degree and duration of inflammation in axSpA[5]. However, inflammation can also lead to osteoproliferative changes, which can manifest as hyperostosis and ankylosis. These changes have a pathognomonic appearance in axSpA,

Box 1 | The most important recommendations for the management of CNO

Although all the new recommendations[1] for the management of chronic non-bacterial osteitis (CNO) should be considered, some of these recommendations are particularly important.

- Consider performing whole-body imaging, preferably MRI, in all patients at the initial evaluation to detect both clinically silent and active lesions.
- Routine bone biopsies are not necessary. Bone biopsies should be reserved for cases with inconclusive imaging and/or suspicion of malignancy or infectious osteomyelitis.
- Assess disease activity on the basis of clinical symptoms (bone pain is likely to be caused by osteitis) and radiological disease activity; consider all possible combinations (presence of both, one or neither).
- Initially treatment response evaluations should be conducted after 2–4 weeks, and then every 12 weeks (treat-to-target approach).
- For cases that resemble axial spondyloarthritis, intravenous bisphosphonates (which is generally preferred) or tumour necrosis factor inhibitors should be used (no randomized controlled trials are available thus fat for either treatment in CNO). Prior treatment with conventional DMARDs, such as methotrexate, is not required.

with syndesmophytes and ankylosis of the spine (accordingly, axSpA was previously known as ankylosing spondylitis). Another rather frequent form of bone formation is diffuse skeletal hyperostosis, which shows some similarities to but also distinct differences from axSpA. Among the differences are the much younger disease onset and the genetic association with HLA-B27 in axSpA.

However, osteodestructive and osteoproliferative changes, many of which are degenerative, occur in numerous rheumatic musculoskeletal diseases, including osteoarthritis. A common example of degenerative changes occurring at entheses are calcaneal spurs, which occur in about 15% of the general population but do not typically cause symptoms[9], whereas inflammation-induced heel pain in the form of Achilles enthesitis or plantar fasciitis is frequently observed in spondyloarthritides. Another example is Tietze's syndrome, a benign, self-limiting entity with tender, non-suppurative swelling in the upper anterior chest wall, especially at the second and third costosternal junctions and the sternoclavicular joint[10]. In the most common manifestation of CNO, the anterior chest wall is also involved, but the location of this involvement is often slightly different than that in axSpA, and the early inflammatory phase of CNO more often causes clinical symptoms.

Thus, there is substantial overlap among CNO, axSpA, SAPHO and other rheumatic musculoskeletal diseases; however, osteitis that does not present at entheses is more specific to CNO. The whole spectrum of these diseases could, for example, be named 'spondylorthritis-like diseases'. However, to find out more about the pathogenesis of these disease, it will be necessary to look at the individual clinical presentations and disease tropism. The role of the bone and possibly the bone marrow is an area of particular interest in the pathogenesis of these diseases.

These recommendations for the management of CNO will hopefully trigger research and international collaborations to improve disease management for patients. This research should include quantification of the duration of response to therapy and better evaluation of the burden of this orphan disease, which clearly needs to be communicated to rheumatologists and other healthcare professionals who treat patients with CNO.

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References

1. Winter, E. M. et al. Expert consensus recommendations for the diagnosis and treatment of chronic non-bacterial osteitis (CNO) in adults. *Ann. Rheum. Dis.* https://doi.org/10.1136/ard-2024-226446 (2024).
2. Girschick, H. et al. The multifaceted presentation of chronic recurrent multifocal osteomyelitis: a series of 486 cases from the Eurofever international registry. *Rheumatology* **57**, 1203–1211 (2018).
3. Buch, K., Thuesen, A. C. B., Brøns, C. & Schwarz, P. Chronic non-bacterial osteomyelitis: a review. *Calcif. Tissue Int.* **104**, 544–553 (2018).
4. Leerling, A. T., Dekkers, O. M., Appelman-Dijkstra, N. M. & Winter, E. M. Clinical and therapeutic diversity in adult chronic nonbacterial osteomyelitis (CNO) of the sternocostoclavicular region: a meta-analysis. *Rheumatology* **62**, 512–522 (2023).
5. Sieper, J. et al. Axial spondyloarthritis. *Nat. Rev. Dis. Primers* **1**, 15013 (2015).
6. Giedion, A., Holthusen, W., Masel, L. F. & Vischer, D. [Subacute and chronic "symmetrical" osteomyelitis]. *Ann Radiol.* **15**, 329–342 (1972).
7. Girschick, H. J. et al. Chronic recurrent multifocal osteomyelitis in children: diagnostic value of histopathology and microbial testing. *Hum. Pathol.* **30**, 59–65 (1999).
8. Chamot, A. M. et al. Le syndrome acné pustulose hyperostose ostéite (SAPHO). Résultats d'une enquête nationale. 85 observations [Acne-pustulosis-hyperostosis-osteitis syndrome. Results of a national survey. 85 cases]. *Rev. Rhum. Mal. Osteoartic.* **54**, 187–196 (1987).
9. Kirkpatrick, J., Yassaie, O. & Mirjalili, S. A. The plantar calcaneal spur: a review of anatomy, histology, etiology and key associations. *J. Anat.* **230**, 743–751 (2017).
10. Tietze, A. Über eine eigenartige Häufung von Fällen mit Dystrophie der Rippenknorpel. *Klin. Wochenschr.* **58**, 829–831 (1921).

Competing interests

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Review article

Check for updates

Hyperuricaemia and gout in the Pacific

Baptiste Gérard[1], Megan Leask[2], Tony R. Merriman[3,4], Thomas Bardin[5], Erwan Oehler[6], Aniva Lawrence[7], Satupaitea Viali[8], Samuela 'Ofanoa[9], Leanne Te Karu[10], Lisa K. Stamp[11], Nicola Dalbeth[12] & Tristan Pascart[13]

Abstract

Gout is the most common form of inflammatory arthritis in adults worldwide. There has been a steady increase in prevalence, which varies across different geographic areas and is high in the Indigenous (First Nations) peoples of the Pacific region. Palaeo-archaeological studies demonstrate that gout was present in the Pacific region prior to European colonization, which is suggestive of genetic predisposition. Genetic risk factors, including population-specific genetic variants and genetic variants shared across populations, particularly those influencing urate transporters, have been identified in Indigenous peoples of the Pacific that partly explain the earlier age of onset of gout. Indigenous peoples of the Pacific experience severe gout, with frequent flares, high hospitalization rates and tophaceous gout, all aggravated by socio-cultural factors. Despite a specific need for effective gout management, Indigenous peoples of the Pacific are under-represented in gout research and inequities in care continue. Indigenous peoples-led, holistic gout management programmes are systematically and urgently required in this region, where gout is a major public health issue. Importantly, a foundation of cultural safety is necessary to underpin such programmes.

Sections

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Key points

- Indigenous peoples of the Pacific, particularly those of Polynesian descent, have a high prevalence of hyperuricaemia and gout.
- The genetic basis of gout in Indigenous peoples of the Pacific is a composite of risk alleles shared between populations and population-specific risk alleles.
- Gout in Indigenous peoples of the Pacific is severe, associated with family history and is experienced at a relatively young age.
- Cardiometabolic and renal comorbidities are common in people with gout throughout the Pacific region, and their management and prevention are also required.
- Health inequities continue to affect gout care for Indigenous peoples of the Pacific region.
- Territorial, holistic health programmes are systematically and urgently required in this region, particularly to improve access to urate-lowering therapy.

Introduction

Gout is the most common type of inflammatory arthritis in adults worldwide[1,2]. It is the result of high levels of urate in the serum (hyperuricaemia), which leads to crystallization of monosodium urate (MSU) and the deposition of MSU crystals in and around the joints[3]. Persistent hyperuricaemia is the causal prerequisite for developing gout and reducing serum-urate levels is therefore the main target for long-term treatments[4]. The phases of this chronic disease are typically a progression from hyperuricaemia to the deposition of MSU crystals to the subsequent immune response to these crystals, which trigger severely painful episodes of arthritis, known as gout flares[5,6]. Without appropriate treatment with urate-lowering therapy (ULT), people experience recurrent flares, and eventually tophi develop and joint damage known as erosive gout occurs[3]. Comorbidities, including cardiovascular diseases, chronic kidney disease, diabetes mellitus and obesity often accompany gout, with a causal role for hyperuricaemia and gout either strongly suspected or established[1,7–10], and there is evidence that gout flares have a causal role in cardiovascular events[11]. Despite being a potentially 'curable' rheumatic disease, with many guidelines for readily available and inexpensive medications, gout remains poorly managed throughout the world[12–14], incurring a burden on quality of life with substantial societal costs[15–19].

Epidemiological studies demonstrate that the prevalence of gout continues to increase worldwide. This prevalence varies widely, according to age, sex, the population studied and the study methods used, from 0.9% in metropolitan France[20] to 5.1% in the USA[21] and 6.2% in Taiwan[22]. Prevalence of gout in Indigenous (First Nations) peoples of the Pacific region often exceeds 5% of the adult population[23] (Box 1 and Fig. 1). The high prevalence of gout in these populations has been attributed to genetic predisposition and possibly unique environmental and socio-cultural exposures.

Gout represents a central public health issue for the Pacific region, and people with gout in the Pacific continue to be adversely affected by suboptimal management, despite the development of some local programmes to address this issue. This narrative Review is aimed at providing an overview of gout and hyperuricaemia in the Pacific, including discussion of trends over time, and to provide a better understanding of the disease and its genetic, clinical and cultural aspects. It is also a call to prioritize gout as an urgent public health issue.

Epidemiology of hyperuricaemia and gout in the Pacific

Early findings

Early epidemiological studies from the 1950s to the 1980s consistently reported high serum-urate levels but varying prevalences of gout in Indigenous peoples of the Pacific, particularly in people of Polynesian ancestry[24–30]. It was reported that men in American Samoa had high serum-urate levels, comparable with the values in Māori (Indigenous Aotearoa New Zealanders), Indigenous peoples of Pukapuka and Rarotonga (Cook Islands), and higher than in Native Hawaiians and men of European ancestry[24]. In Fiji, hyperuricaemia was notably high (27%) among Indigenous men and women, although clinically diagnosed gout was uncommon (2 cases described out of 1,340 patients)[31]. High serum-urate levels and a low frequency of clinical gout were also found in individuals from the Marshall Islands (mean serum urate 6.6 mg dl^{-1} for men and 5.6 mg dl^{-1} for women; gout prevalence 1.7%)[32]. In the Mariana Islands, data from a survey designed for a study of neurological disorders that included 390 Pacific people >40 years of age showed that 22.8% had hyperuricaemia (defined as a serum-urate level >7.0 mg dl^{-1} in men and >6.0 mg dl^{-1} in women) and an estimated 11.5% had definite gout[33].

Trends over time

Epidemiological data over time show that the prevalence of gout in peoples throughout the Pacific is increasing, whereas serum-urate levels seem to be consistent (Table 1). In Aotearoa New Zealand, significantly more cases of clinical gout were reported in Māori than in non-Māori people in two surveys during the 1950s[30], and in the 1970s a gout prevalence of 10.2% was reported in Māori men compared with 2% in non-Māori men[34]. In 1978, in the first epidemiological study to focus on Māori, the prevalence of hyperuricaemia (defined as a serum-urate level >7.0 mg dl^{-1} in men and >6.0 mg dl^{-1} in women) was 49% in men and 42% in women, whereas the prevalence of gout was 8.8% in men and 0.8% in women[35]. In a follow-up study involving 531 of the 766 initial participants, re-interviewed 11 years later, the incidence of gout in the intervening period was 10.3% for men and 4.3% for women[35]. In the past six decades, the prevalence of gout has increased throughout the Pacific, as it has elsewhere in the world[1,36]. The relationship between the prevalence of hyperuricaemia and time in Pacific populations is less clear. In Aotearoa New Zealand, the prevalence of hyperuricaemia was more than 45% in Māori in the 1960s[27] and 1970s[35], greater than its prevalence in the 2010s (17.0% with serum-urate levels >0.40 mmol/l (6.8 mg dl^{-1}))[37].

Contemporary data

A national-level survey from 2019 showed that Māori and Pacific Peoples living in Aotearoa New Zealand had a prevalence of gout of 8.5% and 14.8%, respectively (by comparison, for other non-Māori, non-Pacific New Zealanders the prevalence was 4.7%)[38]. Moreover, a previous study published in 2012 based on drug-dispensing data estimated the prevalence of gout in older (≥65 years of age) Māori and Pacific men to be >30%, whereas the prevalence of gout for all men >20 years old was estimated to be 7.3%[39,40]. The first cross-sectional epidemiological study in

New Caledonia, published in 2021 and involving 1,144 people, reported a 3.3% adjusted prevalence of gout and a 67% prevalence of hyperuricaemia, with prevalence of both being highest in people of Polynesian descent (6.7% for gout; 86.3% for hyperuricaemia)[41]. To estimate the prevalence of gout in this study, an algorithm for epidemiological studies using a questionnaire to detect gout by non-physicians that was applicable to large-scale (in-person or remote) surveys developed in France[42] was adapted to the New Caledonian perceptions of disease, to be used in the national health survey. Self-reported gout data and application of the algorithm showed that gout was less prevalent in Kanak people (Indigenous people of New Caledonia) (2.6%) than in people of European descent (4.1%) whereas hyperuricaemia was greater among people of Polynesian and Kanak descent[41]. French Polynesia comprises more than 120 islands spread over five archipelagos covering an area the size of Europe in the Southeast Pacific, with Tahiti being the largest island in which 80% of the country's population resides. A total of 896 randomly selected individuals from French Polynesia were interviewed in the epidemiological *Ma'i u'u* survey conducted in 2021 (ref. 23]), and their data were extrapolated nationwide in a modelling study to represent the country's 196,630 inhabitants. Using the same algorithm as that used in New Caledonia[41,42], the study showed that hyperuricaemia prevalence was 71.6%, and that gout prevalence was 14.5% (3.5% in women and 25.5% in men), among the general adult population. Self-report of gout provided a similar prevalence of the disease[23]. A 2018 review of gout in Hawai'i showed that nearly every major ethnocultural group, including Native Hawaiians, has an increased risk of hyperuricaemia compared with US mainland populations[43]. A study using 2011–2017 data from the Hawaiian healthcare system showed that Native Hawaiians with gout had a more severe disease, younger age at onset, more tophi and higher serum-urate levels than people of European descent (mean serum-urate level 7.6 mg dl^{-1} versus 6.9 mg dl^{-1}, respectively)[44]. The results of a study performed in Guam from 2019 to 2022, including 356 participants, 221 (62%) of whom declared Chamorro (Indigenous people of the Mariana Islands) ancestry, showed an estimated 28% prevalence of gout, and 42% of participants had serum-urate levels >6.8 mg dl^{-1} [45]. These studies suggest that the reported prevalence of gout is increasing in the Pacific, based on both self-reports by study participants and classification by algorithms, probably reflecting a genuine increase in the prevalence of the disease over the past 10 years.

Environmental influence

The influence of environmental factors on gout in the Pacific, for example, the westernization of diets, particularly in urban areas, is unclear[25,27,46,47]. An attempt was made from the 1960s to the 1980s to examine the role of different environments by comparing serum-urate levels and gout prevalence in migration studies. A comparison between two populations from Tokelau, one that migrated to an urban lifestyle in Aotearoa New Zealand and the other of which stayed in their atoll homeland, had similar serum-urate levels but the risk of gout was significantly higher among migrant men (relative risk 3.7)[48]. Gout occurred at a younger age and became more common as the length of stay of Tokelau men in Aotearoa New Zealand increased. Gout was more prevalent in Māori who lived in urban Aotearoa New Zealand, particularly in men (10.2%), than in Pukapuka men (5.3%) who lived in rural conditions in the isolated atoll of Pukapuka (Cook Islands), whereas hyperuricaemia was reported in more than 40% of both men and women in all groups[27]. On the central Pacific island of Nauru, a high prevalence of hyperuricaemia (64% of men with a serum-urate level >7.0 mg dl^{-1} and 60% of women with a serum-urate level >6.0 mg dl^{-1}), with a high prevalence of gout in men (6.9%, defined by prior episodes of podagra), was observed in an urbanized population[25]. By contrast, Chamorro people who had migrated to California had significantly lower serum-urate levels than Chamorro people living in Guam and in Rota (Mariana Islands) and who had a rural way of life, and Palaua (Western Caroline Islands) people had similar serum-urate values regardless of environmental conditions[49]. Indigenous people in the Eastern Highlands of New Guinea with a traditional diet and no exposure to alcohol also had significantly higher serum-urate levels than Indigenous people and Europeans living in urban areas in New Guinea[50]. In Samoa, hyperuricaemia was high in both rural and urban regions in both men and women[51]. All of these studies consistently suggested that most Pacific peoples are inherently hyperuricaemic, with serum-urate levels unaffected by migration, and that the western environment promotes the progression from hyperuricaemia to gout. Factors contributing to the transition from asymptomatic hyperuricaemia are, however, still unknown. Food triggers similar to those established as triggers of gout flares in people with gout could be suspected, and can be hypothesized as being involved in the transition from hyperuricaemia to gout[52]. These factors will hopefully be elucidated by the results of the TIGER (Transition in Gout Research) international cohort study, which completed enrolment in August 2024 with 270 participants (more than half from Aotearoa New Zealand) with asymptomatic hyperuricaemia; these participants will be followed up for 5 years, with a primary end point of the development of gout[53].

Box 1 | The Pacific region and its peoples

The Pacific region is a large area spanning one-third of the planet, encompassing many countries and comprising three large territories historically described by European geographers of the nineteenth century. The Polynesian triangle is geographically delimited by Hawai'i to the north, Rapa Nui (Easter Island) to the east and Aotearoa New Zealand to the south, with French Polynesia, Cook Islands, Tuvalu, Tokelau, Niue, Wallis (Uvea) and Futuna in the centre, and Samoa and Tonga on the Western boundary of the triangle. To the west of the Polynesian triangle is Melanesia, which includes Papua New-Guinea, the Solomon and Fiji Islands, Vanuatu and New Caledonia. Micronesia comprises ~2,000 islands, including the Federated States of Micronesia, Kiribati and the Marshall Islands. However, these geographical groupings, which are sometimes based on linguistic commonalities, do not represent the diversity of the people inhabiting this region. Beyond an obvious historical, cultural and linguistic diversity, the complex and recurrently redefined history of migrations of the Indigenous peoples of the Pacific Islands contributed to a diversity of genetic ancestries[74,76], both locally and throughout the region.

For the purposes of this paper, Indigenous peoples of the Pacific are collective terms for individuals who have a Pacific nation genealogical connection, and do not imply homogeneity, but are terms that are generally accepted. Use of terminology describing populations originating from certain geographic areas, such as 'Micronesians' or 'Melanesians', ascribed by early European geographers, and often used in articles reporting study results that are included in this Review, is minimized in this article to reduce colonial reduction of the multiplicity of ancestors, cultures, languages, beliefs and environments that are widespread in the Pacific region.

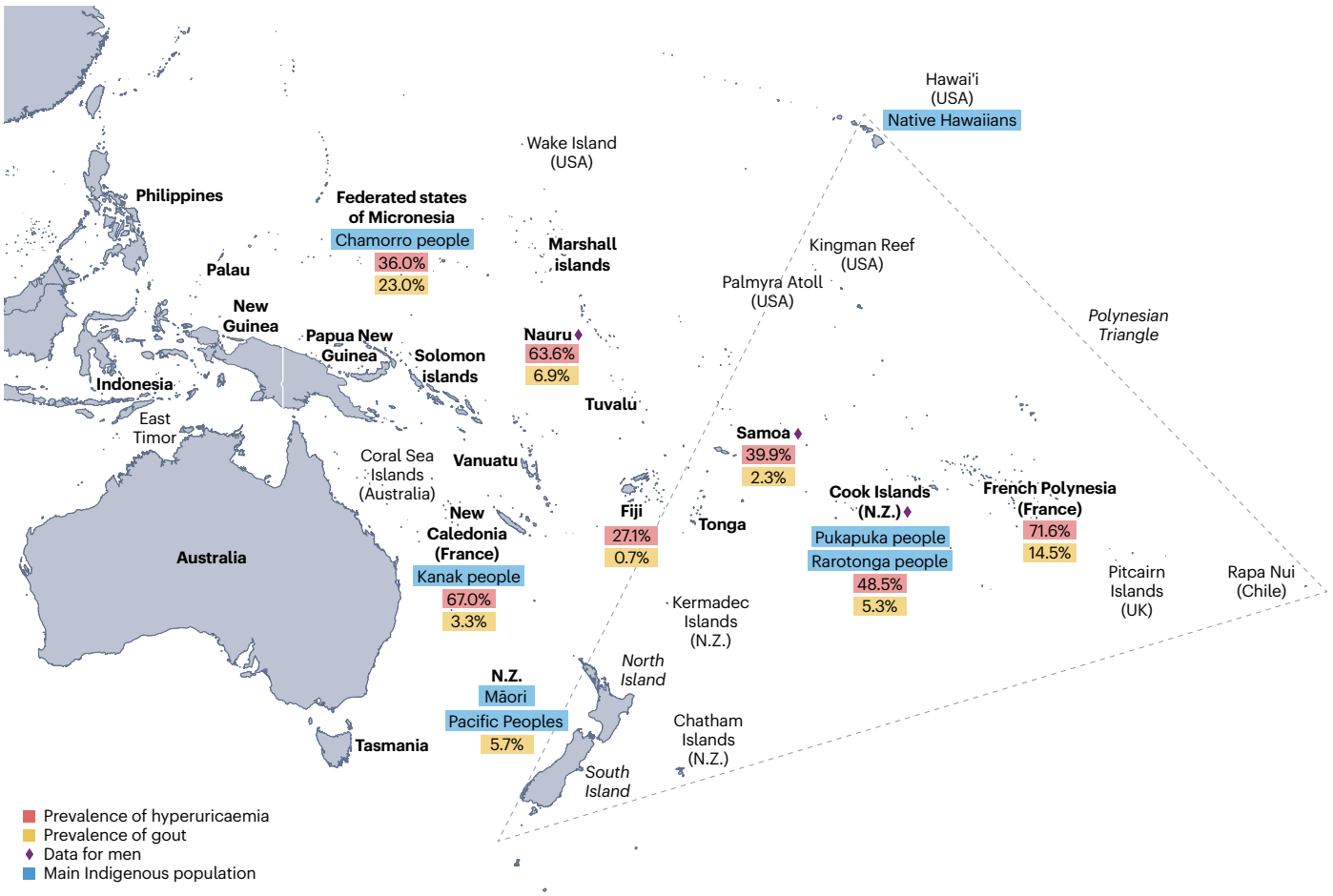

Fig. 1 | Map of the Pacific region with the known national prevalences of hyperuricaemia and gout. The prevalence of gout and hyperuricaemia is high throughout the Pacific region, comprising the Polynesian triangle and the Western Pacific (see Box 1). The values shown are the latest available for each country (see Table 1). There is lack of data for certain locations, and for some locations (denoted by a black diamond symbol) the values shown are the prevalence of gout and hyperuricaemia in men only. The names of the Indigenous peoples of the Pacific are provided for some countries for the reader's information. N.Z., New Zealand.

Palaeopathological studies of gout in the Pacific

Gout has affected humanity for thousands of years. Bioarchaeological studies have shown skeletal evidence of gout worldwide, including in prehistoric Pacific populations[54]. A common thread is that the number of individuals with features of gout in skeletal remains reflects modern-day prevalences. Skeletal evidence of gout was found in 7 out of 20 male adults from a ~3,000-year-old site in Teouma, Vanuatu, and bony lesions consistent with gout were identified in 6 out of 42 male adults from a settlement dating from ~1288–1300 AD in Aotearoa New Zealand[55,56]. Fifteen cases of gout were reported from a skeletal assemblage dating between 950 and 1450 AD in Guam, with bone erosions consistent with gout in 7 female and 8 male individuals, mostly young and middle-aged adults, representing 5.6% of all individuals[57]. At a second site in Guam from the same period skeletal evidence of gout was found in 4 individuals, 3 men and 1 woman, out of 152 individuals[58]. An exception is a study that reported possible evidence of gout in only one individual from among 349 individuals from the Mokapu site in Hawai'i[59]. In general, bone changes consistent with gout seem to reflect modern-day prevalences in all populations, including in Europe, among whom the prevalence of gout in skeletons in medieval Britain (fourteenth and fifteenth centuries) was estimated to be between 1 and 3%[54,60,61].

Known genetic determinants of gout in the Pacific

In people of European and East Asian ancestry, it has been convincingly demonstrated during the past two decades that genetics has a central role in the determination of gout and hyperuricaemia, with genetic variants explaining a substantial component of variance in serum-urate levels[62–65]. The heritability of serum-urate levels is estimated at ~50%[66]; thus, the prevalence of gout and hyperuricaemia in Pacific peoples, particularly pre-colonization in the eighteenth and nineteenth centuries, has generated the hypothesis that Pacific peoples have a genetic background that increases the risk of gout.

Common risk-conferring genetic variants shared between populations tend to have similar effect sizes across populations[63], including those populations indigenous to the Pacific. Genome-wide association studies (GWAS) have provided insight into the molecular pathogenesis of hyperuricaemia and gout in non-Pacific populations[63] and these findings have been strengthened by genetic studies involving Indigenous

Table 1 | Prevalence of hyperuricaemia and gout across the Pacific region

Location	Setting	Data collection period	Age (years)	Definition of hyperuricaemia	Prevalence of hyperuricaemia (%)	Prevalence of gout (%)	Ref.
French Polynesia	Random samples of households; self-questionnaire for gout diagnosis	2021	>18	>6.0 mg dl^{-1}	71.6 (66.7–76.6)	Overall: 14.5 Men: 25.5% Women: 3.5%	23
Guam	Stratified sampling in local census; questionnaire for gout diagnosis	2019–2022	>18	>6.8 mg dl^{-1}	Overall: 36.0 Chamorro people: 42.1 Other Micronesian[a]: 25.3 Filipino: 26.8 (16–41)	Overall: 23.0 Chamorro people: 28.5 Other Micronesian[a]: 8.9 Filipino:	45
Aotearoa New Zealand	Hospitalization rate and drug-dispensing claims from two independent data sources	2019	>20	NR	NR	Overall: 5.7 Men: 9.0 Women: 2.7 Māori: men: 13.1; women: 4.3 Pacific Peoples: men: 22.8; women: 7.0 Others: men: 7.4; women: 2.1	38
New Caledonia	Random samples of households; questionnaire for gout diagnosis	2015–2016	18–60	>6.0 mg dl^{-1}	Overall: 67.0 (61.9–71.6) Polynesian: 86.3 (72.3–93.8) Kanak people: 74.7 (67.8–80.6) European: 49.3 (38.8–60.0) Others: 61.6 (49.5–72.4)	Overall: 3.3 (3.5–8.5) Polynesian: 6.7 (2.5–16.8) Kanak people: 4.1 (1.8–8.9) European: 2.6 (1.4-4.7) Others: 1.9 (0.5–6.6)	41
Aotearoa New Zealand	Random selection from the electoral roll; self-declared diagnosis	2012	20–64	>6.8 mg dl^{-1}	Overall: 13.7 Māori: 17.0 Non-Māori: 7.5	Overall: 7.6 Māori: 10.3 Non-Māori: 2.3	37
Aotearoa New Zealand	Hospitalization rate and drug-dispensing claims from two independent data sources	2009	>20		NR	Overall: 3.8 Men: 6.0 Women: 1.8 Māori: 6.1 Pacific Peoples: 7.6 Asian: 2.0 European or other: 3.2	39
Tokelau	Cross-sectional survey based on registers; diagnosis based on history of typical flare	1968–1982	>15		NR	Migrant men: 5.1 Non-migrant men: 1.5	48
Marshall Islands	Annual medical examinations from one site	1974–1978	>15		NR	Men: 1.7	32
Fiji	Random selection in two areas (urban and rural)	1980	>20	>7.0 mg dl^{-1} for men, >6.0 mg dl^{-1} for women	Indigenous Fijian men: 26.6 Indigenous Fijian women: 27.1 Asian Indian men: 21.7 Asian Indian women: 10.9	Indigenous Fijian men: 0.2 Indigenous Fijian women: 0.2 Asian Indian men: 0.7 Asian Indian women: 0.3	31
Aotearoa New Zealand	Random selection of Māori peoples	1978	>15	>7.0 mg dl^{-1} for men, >6.0 mg dl^{-1} for women	Māori men 49% Māori women 42%	Māori men 8.8% Māori women 0.8%	35
Western Samoa	House-to-house census	1978	>20	>0.7 mg l^{-1} men; >0.6 mg l^{-1} women	Indigenous Samoan men: 39.9; women: 26.4	Indigenous Samoan men: 2.3 Indigenous Samoan women: 1.3	51
Nauru	Random selection	1978	>0	>7.0 mg dl^{-1} men; >6.0 mg dl^{-1} women	Indigenous people of Nauru: men: 63.6; women: 60.0	Indigenous people of Nauru: men: 6.9; women: 0.4	25

Table 1 (continued) | Prevalence of hyperuricaemia and gout across the Pacific region

Location	Setting	Data collection period	Age (years)	Definition of hyperuricaemia	Prevalence of hyperuricaemia (%)	Prevalence of gout (%)	Ref.
Aotearoa New Zealand and Cook Islands	Random selection from household census	1966	>20	>7.0 mg dl^{-1} men; >6.0 mg dl^{-1} women	NZ Māori: 47.5; Rarotongan: 44; Pukapukan: 48.5	NZ Māori men: 10.2 NZ Māori women: 1.8 Rarotonga men: 2.4 Rarotonga women: 0 Pukapuka men: 5.3 Pukapuka women: 0	27
Aotearoa New Zealand	Two separate surveys in Māori and non-Māori	1960	Adults	NR	NR	Whanau-a-apanui tribe Māori: 4.7 Arawa tribe Māori: 2.7 Non-Māori: 0.3%	30

[a]Including Chuukese, Kosraean, Marshallese, Palauan, Pohnpeian and Yapese. NR, not reported; NZ, New Zealand.

peoples of the Pacific (Table 2). Genetic variants involved in controlling renal clearance of urate contribute to differences in hyperuricaemia and gout prevalence. ABCG2 is an ATP-dependent exogenous transporter located both on the apical membrane in the proximal renal tubule and in enterocytes, and mediates the excretion of uric acid in the urine and intestinal lumen[67]. The *ABCG2* missense Q141K variant is associated with both age at onset and tophaceous disease[68–70], higher serum-urate levels, a higher risk of gout and gout flare frequency[71] in Pacific Peoples residing in Aotearoa New Zealand.

Selective pressures and/or bottlenecking events could partly underlie the high occurrence of gout across the Pacific region. Archaeological, linguistic and palaeogenomic studies tracing human migration indicate that early individuals migrated from East Asia and moved to Southeast Asia and the wider Pacific ~4,000 years ago. Subsequent studies suggest serial migrations expanding between unoccupied archipelagos, with a final expansion to Rapa Nui (Easter Island) and Aotearoa New Zealand approximately 800 years ago[72–74]. Indigenous knowledge, however, indicates that Māori presence in Aotearoa New Zealand dates back even further and puts the studies often performed by European scholars into perspective[75]. The history of these migrations provides insight into the shared ancestral features of predisposition to gout shared by Indigenous Taiwanese and Indigenous peoples of the Pacific, as Indigenous Taiwanese peoples also exhibit a high contemporary prevalence of gout[22,76,77]. The history of Pacific migrations, which involved long sea journeys followed by settlement in insular environments, thus likely contributing to genetic drift and bottlenecking events, could have contributed to changing allele frequencies from the ancestral population, which in turn can be expected to influence the prevalence of conditions with a genetic basis[78]. In support of this idea, the aforementioned *ABCG2* gout-risk variant is fivefold more prevalent in people of Western Polynesian ancestry than in those of Eastern Polynesian ancestry[71], and whole-genome sequencing indicates that Pacific peoples (Polynesian people in Aotearoa New Zealand) have thousands of genetic variants potentially influencing protein function that are either unique to these populations or much more common in these populations than in others[79].

Further supporting the theory of an increased prevalence of genetic risk alleles in Indigenous peoples of the Pacific, there is increasing evidence that population-specific genetic variants also contribute to the risk of gout in these populations[68]. A variant in *ABCC4*, which encodes the unidirectional renal urate efflux pump MRP4, was associated with gout in Māori and Indigenous Pacific male individuals[80]. Polymorphisms of the *SLC2A9* gene, which encodes a renal transporter involved in urate excretion in the urine, are associated with higher serum-urate levels and gout[81,82], with *SLC2A9* variants affecting renal handling of hyperuricaemia induced by sugar-sweetened beverage intake in Māori and Pacific Peoples living in Aotearoa New Zealand[83,84]. *SLC22A12* encodes the URAT1 transporter, responsible for most renal-urate reabsorption. Alleles of SNP variant across the *SLC22A11–SLC22A12* locus were associated with an increased risk of gout in Māori and people of Western Polynesian ancestry[85].

Although the variants described so far probably increase the risk of gout by increasing serum-urate levels, other variants are likely to be involved in increased inflammatory responsiveness. IL-37 is a pivotal anti-inflammatory cytokine that suppresses the activity of IL-1β, which mediates MSU crystal-induced inflammation. Variants in the *IL37* gene are associated with an increased risk of gout in hyperuricaemic individuals of self-reported Eastern or Western Polynesian ancestry[86]. Variants in *CLNK*, a gene in close proximity to the *SLC2A9* locus, were suspected to confer, through the modulation of innate immunity, a higher risk of gout in a Polynesian population, including Māori from Aotearoa New Zealand and the Cook Islands and Pacific people from Samoa, Tonga, Tuvalu, Tokelau and Niue residing in Aotearoa New Zealand[87]. Wang et al.[88] identified a Polynesian-specific deletion associated with gout that implicated class-I MHC-mediated antigen presentation in gout. Finally, a rare variant of *LDHD* leading to lactate dehydrogenase D deficiency and associated with autosomal-recessive early-onset gout was reported in a Kanak family from New Caledonia[89].

Beyond a dominant role in determining the onset of hyperuricaemia and gout, genetics has an important influence on treatment outcomes, particularly the safety of the main first-line ULT allopurinol, which inhibits xanthine oxidoreductase. *HLA-B*58:01* has been shown to increase the risk of severe cutaneous events during allopurinol use and explains the increased frequency of these events in specific populations, notably Han Chinese and Vietnamese populations[90–92]. *HLA-B*58:01* was found to be almost absent in Indigenous peoples of French Polynesia, in contrast to people living in French Polynesia reporting Chinese ancestry, providing reassurance about the safety of allopurinol to reduce the burden of gout in Indigenous peoples in French Polynesia[23]. Furthermore, poor metabolizers of CYP2C9 could be at increased risk of hepatotoxicity induced by the uricosuric

drug benzbromarone, and frequencies of *CYP2C9* poor-metabolizer alleles were found to be significantly lower in peoples reporting Eastern and Western Polynesian ancestries than in individuals of European descent[93].

Identifying genetic signatures of gout holds considerable promise for the future healthcare of all populations. For other cardiometabolic conditions, diagnostic panels and genetic scores are already being used in clinic settings for assessing drug reactions and successful early disease-risk predictions (for example, clinical implementation by the eMERGE Network in the USA[94]. However, the large genetic studies driving these clinical advances lack data from Indigenous peoples, including Pacific populations (Box 2).

Clinical presentation and experience of gout in the Pacific

In addition to a high prevalence of gout (Table 1), Indigenous peoples of the Pacific experience early-onset and severe gout. Family history of gout and earlier age of onset are more common in these groups than in other ethnic groups according to most epidemiological studies of gout in the Pacific[23,36,44,95]. In Aotearoa New Zealand, first-degree relatives with gout have been reported for 71.8% of Māori and 62.8% of Pacific Peoples, compared with 51.2% of non-Māori, non-Pacific Peoples[95]. In French Polynesia, 51.9% of the population reported having at least one first-degree relative affected by gout[23]. The estimated mean age at onset was 39 years for Māori and 34 years for Pacific Peoples living in Aotearoa New Zealand, compared with 46 years for non-Māori, non-Pacific Peoples[95,96]. The 2021 epidemiological *Ma'i u'u* survey conducted in French Polynesia showed a prevalence of 1.6% in the 18–29 years age group rising to 16.9% in the 30–39 years age group[23], being particularly high in men (32.3%), whereas the prevalence of gout (determined using the same algorithm to classify people with and without gout that was used in French Polynesia and metropolitan France[42]) in New Caledonia, where Kanak ancestry is predominant, was estimated to be 1.1% in the 18–39 years age group[41]. Earlier onset of disease is also observed in Native Hawaiians than in individuals of European descent (50 versus 57 years of age)[44]. An earlier onset of gout is logically associated with a longer disease duration, which no doubt contributes to a more severe clinical presentation of gout, particularly in the setting of suboptimal treatment[97]. Cases of extensive tophaceous disease and a high flare frequency are also present in Indigenous peoples of the Pacific, with a reported mean of 2.3 flares in 3 months in Māori or Pacific Peoples compared with 0.3 flares in non-Māori non-Pacific Peoples, and a higher number of tophi in Native Hawaiians compared with people from other ancestries living in Hawai'i[36,44,98–100]. As a consequence, hospitalization rates for gout are high[44,100,101]. In a national study of hospital admissions in Aotearoa New Zealand from 1999 to 2009 that were attributable to or complicated by gout, Pacific Peoples and Māori were over-represented (2.5% and 2.2% of 1-year hospital admissions, respectively) compared with people of Asian (0.6%) and European or other (0.8%) ancestry[102]. A qualitative study demonstrated that the personal impact of gout for Māori was considerable and worsened the experience of the disease[103]. Māori men with gout experienced

Table 2 | Genetic variants associated with gout in Indigenous peoples of the Pacific

Gene name	Gene product	Function	Cell or tissue distribution	Associated risks with variants	Population	Refs.
ABCG2	ABCG2	Urate excretion	Kidney and other tissues	Increased serum urate levels and gout risk Increased gout flare frequency Tophaceous disease Earlier gout onset	Polynesian	68–71
SLC2A9	GLUT9	Urate reabsorption	Liver and kidney	Increased serum-urate levels and gout risk	Polynesian Māori	81,82,84
SLC22A12	URAT1	Urate reabsorption	Kidney	Increased serum-urate levels and gout risk	Western Polynesian Māori	85
ABCC4	MRP4	Urate excretion	Kidney and other tissues	Increased serum-urate levels and gout risk	Western Polynesian Māori	80
MICA	MHC class I polypeptide-related sequence A	Immune response	Cell surface receptor, non-specific	Increased gout risk	Western Polynesian Māori	88
CLNK	Cytokine-dependent hematopoietic cell linker	Immune response	T cells, natural killer cells, mast cells	Increased gout risk	Eastern and Western Polynesian Māori	87
IL37	IL-37	Immune response	Skin, lung	Increased gout risk in hyperuricaemic individuals	Eastern and Western Polynesian Māori	86
LDHD	LDHD	Urate excretion	Non-specific	Autosomal-recessive early-onset gout	Kanaks (New Caledonia)	89

ABCG2, ATP-binding cassette subfamily G member 2; CLNK, cytokine-dependant hematopoietic cell linker; GLUT9, glucose transporter protein 9; LDHD, lactate dehydrogenase D; MRP4, multidrug resistance protein 4; URAT1, urate transporter 1.

Box 2 | Addressing underrepresentation in gout genetics research

Less than 1% of genome-wide association studies (GWAS) include participants from Oceania and this underrepresentation threatens to exacerbate the health inequities already faced by these populations[141]. Additionally, commonly overlooked is the fundamental right that Indigenous populations have to equitable representation in research projects. For example, in Aotearoa New Zealand, there is a responsibility under *Te Tiriti o Waitangi* (The Treaty between Indigenous Māori and the Crown) to ensure equitable health outcomes (Article 3 of *Te Tiriti*) for Māori while guaranteeing *tino rangatiratanga* (absolute sovereignty) over genetic data[95]. Appropriate and ethical representation of Indigenous peoples in genetic datasets is also crucial to ensure that these data are used to maximize benefits for Indigenous peoples[118].

Underrepresentation of Indigenous populations in genetic research is a result of several issues that do not affect genetics research in larger population groups, and which need to be addressed if Indigenous peoples are to receive equitable representation in genetic studies that would translate into equitable medical care. These issues include mistrust of Western institutions, ongoing colonization, misuse of samples and deficit framing (that is, defining groups of people by their problems) in study reporting[141,142]. An additional issue for genetics research in Indigenous populations in the Pacific is the generation of datasets of a sufficient size to enable the conceptual advances that routinely come from genetics studies in major population groups (for example, GWAS). Moreover, ancillary data such as reference panels for imputation and expression data such as Genotype–Tissue Expression database[143,144], equivalent data for identification of candidate causal genes from GWAS and linking to molecular mechanisms are lacking for populations of Pacific ancestry. Further compounding these issues is a scarcity of Indigenous researchers with the human genetics capabilities to rectify these shortcomings.

To combat the issues described above, research projects must ensure authentic engagement and partnership in the long term. In the past decade there have been numerous examples of successful engagement, consultation, relationship building, workforce development and application of Indigenous-centric ethical frameworks in genomics research with Indigenous Pacific communities[23,144–146]. For example, consistent and continuous engagement with Ngāti Porou Oranga, an *Iwi* (tribe)-led health provider in Aotearoa New Zealand has led to a formalized agreement between the Ngāti Porou Oranga Charitable Trust and the University of Otago outlining a framework for the use, storage and protection of genetic data from participants, to workforce development in the field of genetics of gout for young Māori who *whakapapa* (genealogically connect) to the *Ngāti Porou iwi* with participants from the *iwi* included in genetic studies of gout[68,80,86,88,147], and to additional genetics projects including the Variome and Rakeiora projects established by Genomics Aotearoa. Programmes focused on workforce development and upskilling of Pacific researchers have also been established, through which dozens of Indigenous peoples from the Pacific are trained every year[148–150]. Capacity and capability in genetic research are critical to ensuring that Indigenous peoples retain *rangatiratanga* (self-determination). In French Polynesia, community engagement through interviews with community leaders was undertaken prior to the *Ma'i u'u* study to assess the acceptability of the study, and to determine how the collected data could be used and returned to the community[23,118]. In summary, Indigenous-centric ethical frameworks and approaches are essential for genetic studies partnering Indigenous peoples with common principles of genetic data sovereignty, transparency in data collection, culturally appropriate narratives, dissemination of findings and resources enabling communities to co-govern in the research processes[45,151]. Studies prioritizing these frameworks have the potential to address the critical issue of the inequity of Indigenous participations in genetic research, furthering genomic justice and equity in genomics research for all population groups.

overwhelming pain symptoms, isolation and a negative effect of gout on employment and relationships, not just for the individual but for their *whānau* (family) and the wider community[103]. Most considered the disease with stoicism and all participants believed or had been informed that gout is caused by dietary habits and/or drinking habits, which led to a perception of self-inflicted disease and a feeling of guilt.

Gout, comorbidities and social determinants of health in the Pacific

Gout is strongly associated with renal, cardiovascular and metabolic diseases[10]. These common comorbidities impose considerable challenges for the management and outcomes of gout, with cardiovascular disease being the major cause of increased mortality in people with gout[104]. In Aotearoa New Zealand, metabolic syndrome, diabetes mellitus, cardiovascular disease and hypertension are common in people with gout[105]. The risk of cardiovascular disease remains high among Māori and Pacific Peoples, with or without the additional risk factor of gout[106]. Social determinants of health, including income, housing conditions, work opportunities and access to health services, are central in explaining the increased risk of cardiovascular disease in Māori and Pacific Peoples living in Aotearoa New Zealand[107]. An association between gout and cardiovascular disease was reported in a study using linked administrative data, highlighting worse outcomes for Māori. For both men and women, compared with New Zealanders of European descent, Māori had a much higher risk of a fatal or non-fatal cardiovascular event within 5 years irrespective of gout status (adjusted hazard ratio (HR) 1.79 for women and 1.59 for men)[106]. Gout was associated was cardiovascular disease in both sexes (HR for women 1.34 and 1.18 for men). Although NSAIDs are generally recommended for the treatment of gout flares, repeated courses of NSAIDs for gout flares without the use of ULT reflect poor care and contribute to the risk of kidney and cardiovascular disease[108–111]. In 2016, 37% of people with gout were dispensed an NSAID compared with 23% of the resident adult population in Aotearoa New Zealand; moreover, 47% of Pacific Peoples and 41% of Māori with gout aged 20–44 years were dispensed an NSAID compared with 34% of non-Māori non-Pacific Peoples, according to National drug-dispensing claims[101]. In the epidemiological *Ma'i u'u* study in French Polynesia, strong associations were

shown between gout and type 2 diabetes mellitus (odds ratio (OR) 2.1), particularly in women with gout, 73.4% of whom also had diabetes[23]. In New Caledonia, gout prevalence was associated overall with BMI (adjusted OR, 1.2 per kg/m^2) and waist circumference (adjusted OR 1.1 per cm)[41]. In Hawai'i, diabetes mellitus, obesity and hypertension were common among Native Hawaiian people with gout, at rates of 10.4%, 22.2% and 60.7%, respectively[44]. Putting these numbers into context, the NHANES studies, which involved a representative sample of US adults, showed that type 2 diabetes mellitus was present in 33.1% of people with gout versus 10.8% of those without, and the prevalence of abdominal obesity was greater in people with gout (62.9% versus 35.3%), as was hypertension (69.1% versus 30.3%)[112]. These comorbidities are therefore common in people with gout worldwide[1] but are of considerable importance in the Pacific and they are highly influenced by social inequities, as the same barriers that prevent optimal management of gout also affect management of these comorbidities. Inequity occurs for Māori and Pacific Peoples across the entire causal pathway of these co-morbidities.

Chronic inflammation secondary to uncontrolled gout might also explain other associated comorbidities. A report from New Caledonia showed an overrepresentation of amyloid A amyloidosis among people of Kanak and Wallisian ancestry, being notably associated with gout in a case series of 20 patients[113]. Amyloid A amyloidosis is generally secondary to chronic inflammatory diseases. This association with gout could be explained by much longer and polyarticular flares, and also by a high rate of skin infections, which frequently trigger local gout flares.

Cultural experiences of illness and gout in the Pacific

Experiences of gout in the Pacific have a specific impact because the disease is omnipresent in daily life owing to its high prevalence, and because of local perceptions of disease and medicine. Contemporary legacies of colonialism led among other effects to the eradication of traditional practices, and current systems are designed around western perceptions of illness and healthcare (Box 3). In Aotearoa New Zealand, the traditional Māori perception of illnesses considers the general balance of health rather than each specific disease, and gout is seen as an inherent part of this balance, which might not be compatible with the perceptions of disease and medicine held by European physicians[114,115]. To Māori, *hauora* refers to 'holistic health and wellbeing', which means being well and in balance with the physical, spiritual and environmental community in which people live, domains that are not all captured by quality-of-life indicators usually used in clinical studies[114]. Participants in interview studies have described the recurrent experience of gout as eroding their *wairua* (spirit)[114]. Also, the role of *whānau*, a Māori concept of the collective representation of generations who share genealogical descent (biologically or not), is important in how an individual perceives the disease and how it should be managed. "Gout runs in the whānau" has been reported in participants' interviews, demonstrating not only a cultural understanding of the heredity of gout but also a shared experience of how it should be managed (with ULT and/or symptomatic treatment depending on how other members of the *whānau* had been treated)[114].

Box 3 | Colonization and its impact on the health of Indigenous peoples of the Pacific

The arrival of European settlers in the South Pacific during the eighteenth and nineteenth centuries had an enormous effect on the region and its population. In addition to introducing infectious diseases that took a heavy toll on Indigenous peoples of the Pacific, colonization imposed abusive, exploitative and racist power relations on local societies, and imposed Christianity. In Aotearoa New Zealand, the confiscation of most of the *whenua* (land) by the British Crown led to deep and consistent hardship, with resultant effects on critical cultural assets by preventing Māori knowledge from being passed on between generations[152,153]. Historical trauma caused by land loss was also experienced by many other Indigenous peoples of the Pacific, with inequitable health outcomes[154,155]. The consequences of land alienation for wellbeing and health, including debilitating sadness, grief, anger, identity damage and cultural erosion[156], reverberate down the generations and continue to this day, affecting interpersonal and environmental relationships in communities[156,157]. Demography and life expectancy as crude markers of health and wellbeing were seriously affected, with a drastically contracted (almost halved) Māori population until the twentieth century, as mortality increased and fertility decreased owing to epidemics, warfare, land confiscation, economic impoverishment and mass settler immigration[158]. Disparities between Māori and non-Māori life expectancy of ~7 years have continued since the mid-1990s[159]. Contemporary legacies of colonialism are ongoing in the oppression and marginalization of many Indigenous peoples of the Pacific, which are also reflected in the eradication of ways of life, including traditional practices, social structures, or traditional ways of knowing or knowledge creation[160]. Most local health systems are primarily designed around a Western model of health and illness in which Indigenous healthcare providers are under-represented, far removed from traditional medicine and the traditional views of health. This maladaptation of the health system and social inequities contribute to the unequal access to health and social services by Indigenous peoples[160].

Language can also be a substantial barrier to healthcare, as healthcare providers usually use the language of the colonizers. In the case of French Polynesia, although seven different Indigenous languages are used across the >100 islands, doctors use French to communicate with patients, whose command of the language varies depending on their age, educational level and the remoteness of their island from Tahiti[116]. Social determinants of health also contribute to ethnic differences in gout outcomes[161,162]. The historical context is important when considering health outcomes in Indigenous peoples of the Pacific, and it gives the opportunity to reflect on how Indigenous knowledge can provide possible solutions for current public health crises and well-being in general[163,164]. Interventions founded on these insights are relevant on a cultural and a community level, to enable healing from historic injustices inherited from colonization. In addition, local measures and health providers must increasingly attempt to encompass traditional models of health to promote holistic approaches and decolonize healthcare[165]. Dealing with the consequences of colonization has been a consistent part of the Pacific region's history for a long period of time.

Similar representations of gout have been described in French Polynesia. However, the perception of gout as a self-inflicted disease can also affect representations and experience of the disease. Excessive intake of alcohol and food are seen as major determinants of the disease and increase the perceived guilt (*whakamā*) of being 'afflicted' by it, and this message continues to be conveyed by healthcare professionals[114,116]. This sense of guilt from being afflicted with a disease considered to be the consequence of 'sins' is fuelled by the strong presence of European settler religions[117]. However, the literature does not uphold the perception of gout as self-inflicted owing to diet and alcohol. For example, the *Ma'i u'u* survey in French Polynesia demonstrated that alcohol consumption did not correlate with having developed gout[23], and gout was not associated with dietary factors in New Caledonia[41]. Genuine community engagement has also helped to destigmatize gout; providing the results of the 2021 study to people with gout living in Tahiti in 2023 was extremely beneficial to the participants as it improved the perception of the disease in the general population[23,118]. The understanding of the importance of genetics in gout and genetic literacy is also helping to eradicate this view[119].

Current management and health programmes for gout in the Pacific

Gout management methods are well established, with many treatment guidelines recommending what should be the standard of care[109,111,120,121]. Nevertheless, although the burden of gout continues to rise, its management in clinical practice worldwide is not improving, including throughout the Pacific[122]. Multiple factors explain the poor management of gout, from social inequities in access to the health system and medicines to inadequate training for health professionals in gout management. According to a 2012 French Polynesian survey of general practitioners comparing common practices there and in metropolitan France, doctors in French Polynesia had sufficient theoretical knowledge of how to manage gout, but, despite the high prevalence of the disease, they did not adhere to international guidelines; all of the physicians surveyed identified patients' poor compliance and failure to attend follow-up consultations as the main obstacles[123]. A decade later, despite doctors dealing with gout on a daily basis, only a minority of people with gout received an appropriate prescription of ULT. Indeed, only 16.2% of participants with gout had a serum-urate level of <6.0 mg dl^{-1}, and many patients had never heard of ULT[23]. In addition to being a potential sign of miscommunication between doctors and people with gout, this under-prescribing and lack of information about the importance of ULT whilst providing symptomatic treatment alone has been perceived in French Polynesia and Aotearoa New Zealand as working in health professionals' favour by ensuring revenue[114,117]. In the survey from New Caledonia, less than half of people with gout were receiving ULT (45.9%), and only 29.6% of them were at the target serum-urate level of <6.0 mg dl^{-1}, despite the fact that the cost of these drugs were covered by the healthcare system[41].

The cost of chronic disease management and long-term medications is a further barrier for patients throughout the Pacific region. An overview by the Pharmaceutical Management agency of New Zealand emphasized inequities in gout management, including that the ULT dispensing rate according to clinical need was lower for Pacific Peoples living in Aotearoa New Zealand than for non-Pacific Peoples, which was attributed to reduced access to primary healthcare[124]. In addition to the cost and physical barriers from reaching clinics to seek healthcare (for example, lack of public transport, opening hours)[114], structural barriers created by prescribing biases and a lack of cultural safety further limit effective gout management. In Aotearoa New Zealand, Māori and Pacific Peoples also receive less regular ULT[95]. There is no evidence that the available gout treatments are less effective in Indigenous peoples of the Pacific, but higher doses of ULT can be required to achieve therapeutic targets[125]. Indeed, Wright et al. showed that Pacific Peoples living in Aotearoa New Zealand need higher doses of allopurinol than Māori and other New Zealanders to achieve the target serum-urate level[126]. This need might be attributable to the ABCG2 rs2231142 (Q141K) gout-risk allele, which is more common in Pacific Peoples and which is consistently associated with the need for more allopurinol to achieve the target serum-urate level[96,127,128].

Aotearoa New Zealand national health data from 2016–2017 found that 13.8% of Māori adults and 15.5% of Pacific Peoples adults did not take prescribed medications because of costs. Health-related costs (for example, for medicines, travel to clinics or time off work) are also commonly seen to compete with the primary needs of daily life, particularly for younger people with gout[114]. From the perspective of patients, the community and health professionals in general practice, when inequity remains pervasive, general-practice initiatives are inhibited without aligned resourcing or incentives[129].

Table 3 | Examples of current programmes for the management of gout in the Pacific region

Location	Programme	Description	Ref.
Aotearoa New Zealand	Ola Manuia: Pacific Health and Wellbeing Action Plan 2020-2025	Accompanying actions for the health and disability system for Pacific Peoples to achieve equitable health outcomes	139
Aotearoa New Zealand	Counties Manukau DHB 'Owning My Gout'	Improving ULT using culturally appropriate communication in Māori and Pacific Peoples with gout	131
Aotearoa New Zealand	Northland DHB 'Gout Stop'	Improving ULT using culturally appropriate communication in Māori and Pacific Peoples with gout	130
Aotearoa New Zealand	Quantitative assessment of Pacific Peoples' gout health burden and treatment need	Observational study using routinely collected data to determine the prevalence of patients with gout, the proportion whose serum urate level is monitored and prescriptions of ULT	138
French Polynesia	Local therapeutic education focusing on gout	People with gout diagnosed at the Taaone hospital Individual interviews and providing of information on gout and its treatments	117

DHB, district health board; ULT, urate-lowering therapy.

Future directions for research and management of gout in the Pacific

Recognizing the needs of Māori and Pacific Peoples in Aotearoa New Zealand, the 'Gout Stop' and 'Owning My Gout' programmes were developed for primary care to optimize the use of ULT[130]. These programmes included culturally appropriate education and support for patients and primary healthcare professionals. In the Gout Stop programme, more non-Māori non-Pacific New Zealanders fully completed the programme (that is, they achieved full titration of ULT doses), but of those who completed the programme, more Māori than non-Māori maintained long-term adherence to ULT. Initially, 179 people were enrolled but 64% were not visibly active in the programme after 3 months. Of those who achieved a serum-urate level <0.36 mmol l^{-1} (<0.6 mg dl^{-1}), 17% identified as Māori and 29% as Pacific Peoples, compared with 40% non-Māori, non-Pacific New Zealanders, making this an anti-equity programme[131]. Similarly, with Gout Stop the programme completion rate was 55% for Māori and Pacific Peoples compared with 84% in the non-Māori, non-Pacific Peoples group. Non-Māori, non-Pacific participants were more likely to achieve the target serum-urate level (50%) than Māori (39%) or Pacific Peoples (30%) participants. These results from real-life clinical interventions demonstrated an improvement of ULT prescription and adherence, but were still far from the near-perfect results reported in the nurse-led care randomized controlled trial carried out in the UK[132,133]. Patient preconceptions relating to gout were identified as strongly influencing participation in the Gout Stop and Owning My Gout programmes[131]. These preconceptions included old beliefs about the causes of gout, *whakamā* or shame associated with gout and lack of acceptance that gout is a long-term condition.

Driving change in gout management for Indigenous peoples of the Pacific requires partnership with recognition of their realities, worldviews and health[134–137]. New endeavours in Aotearoa New Zealand are taking place (Table 3); for example, a new programme is being co-designed with community members from the Pacific People's Health Advisory Group, clinical staff from the Pacific Practice-Based Research Network and University of Auckland researchers to improve successful ULT management in Pacific Peoples from Aotearoa New Zealand[138]. Another example is the Pacific Health and Wellbeing Action Plan 2020–2025, a holistic approach to healthcare that includes recognition of traditional healing modalities of Pacific Peoples[139]; there are no implementation data yet from this programme. The community's involvement in developing, implementing and delivering a Pacific-specific ULT management programme was recommended as part of the *Te Mana Ola* (Pacific Health Strategy plan), one of the five key priorities of which is Autonomy/Determination (*Soalaupule*), on which these new approaches are based. Others have called for a national gout-specific strategy, with the development being framed authentically with co-creation in structure, legislation, policy and delivery[140]. Finally, including Indigenous people of the Pacific in the early phases of new drug development is needed.

Conclusions

Hyperuricaemia and gout are notably prevalent in Indigenous peoples throughout the Pacific. Cardiometabolic and renal comorbidities are often present, and associated mortality is high. The genetic basis of gout in Indigenous peoples of the Pacific is a composite of risk alleles shared between populations and population-specific risk alleles. Gout remains an equity issue with suboptimal management, particularly for Indigenous Peoples of the Pacific. Culturally safe programmes that deliver appropriate patient information and enable the diagnosis and management of gout and its comorbidities are needed to control this major public health issue in the Pacific region. Adequate teaching and activation of the health workforce should be prioritized around appropriate ULT prescribing and management, and debunking colonial views of gout as a self-inflicted disease caused by dietary indiscretion. Respective governments should ensure the urgent implementation of pro-equity strategies in partnership with Indigenous communities. This approach could be overseen in a multi-country, pan-Pacific approach, with appropriate resourcing and sharing of knowledge.

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References

1. Dehlin, M., Jacobsson, L. & Roddy, E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. *Nat. Rev. Rheumatol.* **16**, 380–390 (2020).
2. GBD 2021 Gout Collaborators. Global, regional, and national burden of gout, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol.* **6**, e507–e517 (2024).
3. Dalbeth, N., Gosling, A. L., Gaffo, A. & Abhishek, A. Gout. *Lancet* **397**, 1843–1855 (2021).
4. Stamp, L. K., Christensen, R. & Morillon, M. B. Serum urate as a surrogate outcome for gout flares: where do we stand today? *Gout Urate Cryst. Depos. Dis.* **2**, 70–76 (2024).
5. Pascart, T. & Lioté, F. Gout: state of the art after a decade of developments. *Rheumatology* **58**, 27–44 (2019).
6. Muntiu, M., Joosten, L. A. B. & Crișan, T. O. Gout basic research: 2023 in review. *Gout Urate Cryst. Depos. Dis.* **2**, 220–235 (2024).
7. Singh, J. A. & Gaffo, A. Gout epidemiology and comorbidities. *Semin. Arthritis Rheum.* **50**, S11–S16 (2020).
8. Andrés, M. Gout and cardiovascular disease: mechanisms, risk estimations, and the impact of therapies. *Gout Urate Cryst. Depos. Dis.* **1**, 152–166 (2023).
9. Urquiaga, M. & Gaffo, A. L. Year in review: gout clinical research. *Gout Urate Cryst. Depos. Dis.* **1**, 37–48 (2023).
10. Choi, H. K., McCormick, N. & Yokose, C. Excess comorbidities in gout: the causal paradigm and pleiotropic approaches to care. *Nat. Rev. Rheumatol.* **18**, 97–111 (2022).
11. Cipolletta, E. et al. Association between gout flare and subsequent cardiovascular events among patients with gout. *JAMA* **328**, 440–450 (2022).
12. Doherty, M. et al. Gout: why is this curable disease so seldom cured? *Ann. Rheum. Dis.* **71**, 1765–1770 (2012).
13. Te Kampe, R. et al. Outcomes of care among patients with gout in Europe: a cross-sectional survey. *J. Rheumatol.* **49**, 312–319 (2022).
14. Scheepers, L. E. J. M. et al. Medication adherence among patients with gout: a systematic review and meta-analysis. *Semin. Arthritis Rheum.* **47**, 689–702 (2018).
15. Lee, S. J. et al. Perceptions of disease and health-related quality of life among patients with gout. *Rheumatology* **48**, 582–586 (2009).
16. Rai, S. K. et al. The economic burden of gout: a systematic review. *Semin. Arthritis Rheum.* **45**, 75–80 (2015).
17. Stewart, S. et al. The experience of a gout flare: a meta-synthesis of qualitative studies. *Semin. Arthritis Rheum.* **50**, 805–811 (2020).
18. Shields, G. E. & Beard, S. M. A systematic review of the economic and humanistic burden of gout. *Pharmacoeconomics* **33**, 1029–1047 (2015).
19. Roddy, E., Zhang, W. & Doherty, M. Is gout associated with reduced quality of life? A case-control study. *Rheumatology* **46**, 1441–1444 (2007).
20. Bardin, T. et al. Prevalence of gout in the adult population of France. *Arthritis Care Res.* **68**, 261–266 (2016).
21. Yokose, C. et al. Trends in prevalence of gout among US Asian Adults, 2011-2018. *JAMA Netw. Open.* **6**, e239501 (2023).
22. Kuo, C.-F. et al. Epidemiology and management of gout in Taiwan: a nationwide population study. *Arthritis Res. Ther.* **17**, 13 (2015).
23. Pascart, T. et al. The gout epidemic in French Polynesia: a modelling study of data from the Ma'i u'u epidemiological survey. *Lancet Glob. Health* **12**, e685–e696 (2024).
24. Healey, L. A. & Jones, K. W. Hyperuricemia in American Samoans. *Arthritis Rheum.* **14**, 283–285 (1971).
25. Zimmet, P. Z., Whitehouse, S., Jackson, L. & Thoma, K. High prevalence of hyperuricaemia and gout in an urbanised Micronesian population. *Br. Med. J.* **1**, 1237–1239 (1978).
26. Gibson, T., Waterworth, R., Hatfield, P., Robinson, G. & Bremner, K. Hyperuricaemia, gout and kidney function in New Zealand Maori men. *Br. J. Rheumatol.* **23**, 276–282 (1984).
27. Prior, I. A., Rose, B. S., Harvey, H. P. & Davidson, F. Hyperuricaemia, gout, and diabetic abnormality in Polynesian people. *Lancet* **1**, 333–338 (1966).
28. Prior, I. A. & Rose, B. S. Uric acid, gout and public health in the South Pacific. *N. Z. Med. J.* **65**, 295–300 (1966).
29. Prior, L. Epidemiology of Rheumatic disorders in the Pacific with particular emphasis on hyperuricaemia and gout. *Semin. Arthritis Rheum.* **11**, 213–229 (1981).
30. Lennane, G. A. Q., Rose, B. S. & Isdale, I. C. Gout in the Maori. *Ann. Rheum. Dis.* **19**, 120–125 (1960).

31. Tuomilehto, J. et al. Plasma uric acid level and its association with diabetes mellitus and some biologic parameters in a biracial population of Fiji. *Am. J. Epidemiol.* **127**, 321–336 (1988).
32. Adams, W. H., Harper, J. A., Heotis, P. M. & Jamner, A. H. Hyperuricemia in the inhabitants of the Marshall Islands. *Arthritis Rheum.* **27**, 713–716 (1984).
33. Burch, T. A., O'Brien, W. M., Need, R. & Kurland, L. T. Hyperuricaemia and gout in the Mariana Islands. *Ann. Rheum. Dis.* **25**, 114–116 (1966).
34. Rose, B. S. Gout in Maoris. *Semin. Arthritis Rheum.* **5**, 121–145 (1975).
35. Brauer, G. W. & Prior, I. A. A prospective study of gout in New Zealand Maoris. *Ann. Rheum. Dis.* **37**, 466–472 (1978).
36. Klemp, P., Stansfield, S. A., Castle, B. & Robertson, M. C. Gout is on the increase in New Zealand. *Ann. Rheum. Dis.* **56**, 22–26 (1997).
37. Stamp, L. K. et al. Hyperuricaemia and gout in New Zealand rural and urban Māori and non-Māori communities. *Intern. Med. J.* **43**, 678–684 (2013).
38. Gout. *Te Tāhū Hauora Health Quality & Safety Commission*. https://www.hqsc.govt.nz/our-data/atlas-of-healthcare-variation/gout/ (accessed 2025).
39. Winnard, D. et al. National prevalence of gout derived from administrative health data in Aotearoa New Zealand. *Rheumatology* **51**, 901–909 (2012).
40. Jackson, G. et al. Potential unmet need for gout diagnosis and treatment: capture–recapture analysis of a national administrative dataset. *Rheumatology* **51**, 1820–1824 (2012).
41. Bardin, T., Magnat, E., Clerson, P., Richette, P. & Rouchon, B. Epidemiology of gout and hyperuricemia in New Caledonia. *Jt. Bone Spine* **89**, 105286 (2022).
42. Richette, P. et al. Identification of patients with gout: elaboration of a questionnaire for epidemiological studies. *Ann. Rheum. Dis.* **74**, 1684 (2015).
43. Thompson, M. D. Insights in public health: hyperuricemia and gout in Hawai'i. *Hawaii J. Med. Public Health* **77**, 121–124 (2018).
44. Chang, C. et al. Gout in native Hawaiian Patients in Hawai'i: clinical characteristics and disparities. *Arthritis Care Res.* **76**, 712–719 (2024).
45. Paulino, Y. C. et al. Conducting genetic epidemiology research on hyperuricaemia and gout in an indigenous community in Guam — a feasibility study. *BMC Public Health* **25**, 484 (2025).
46. Serra-Mallol, C. et al. Eating well' in Pacific Islands countries and territories: a qualitative and normative approach to food cultures in New Caledonia. *Appetite* **163**, 105192 (2021).
47. Davila, F., Burkhart, S. & O'Connell, T. State of food and nutrition security in the Pacific. in: Dansie, A., Alleway, H. K. & Böer, B. (eds) *The Water, Energy, and Food Security Nexus in Asia and the Pacific: The Pacific*. 85–106 (Springer International Publishing, 2024).
48. Prior, I. A., Welby, T. J., Ostbye, T., Salmond, C. E. & Stokes, Y. M. Migration and gout: the Tokelau Island migrant study. *Br. Med. J. Clin. Res. Ed.* **295**, 457–461 (1987).
49. Reed, D., Labarthe, D. & Stallones, R. Epidemiologic studies of serum uric acid levels among Micronesians. *Arthritis Rheum.* **15**, 381–390 (1972).
50. Jeremy, R. & Rhodes, F. A. Studies of serum urate levels in New Guineans living in different environments. *Med. J. Aust.* **1**, 897–899 (1971).
51. Jackson, L. et al. Hyperuricaemia and gout in Western Samoans. *J. Chronic Dis.* **34**, 65–75 (1981).
52. Helget, L. N. & Mikuls, T. R. Environmental triggers of hyperuricemia and gout. *Rheum. Dis. Clin. North. Am.* **48**, 891 (2022).
53. Stewart, S. et al. Development of gout in people with asymptomatic hyperuricemia: study protocol for a 5-year prospective cohort. *BMJ Open.* **14**, e090415 (2024).
54. Ling, N. Y., Halcrow, S. E. & Buckley, H. R. Gout in paleopathology: a review with some etiological considerations. *Gout Urate Cryst. Depos. Dis.* **1**, 217–233 (2023).
55. Buckley, H. R., Tayles, N., Halcrow, S. E., Robb, K. & Fyfe, R. The people of Wairau Bar: a re-examination. *J. Pac. Archaeol.* **1**, 1–20 (2010).
56. Buckley, H. R. Possible gouty arthritis in lapita-associated skeletons from Teouma, Efate Island, Central Vanuatu. *Curr. Anthropol.* **48**, 741–749 (2007).
57. Rothschild, B. M. & Heathcote, G. M. Characterization of gout in a skeletal population sample: presumptive diagnosis in a Micronesian population. *Am. J. Phys. Anthropol.* **98**, 519–525 (1995).
58. Douglas, M. T., Pietrusewsky, M. & Ikehara-Quebral, R. M. Skeletal biology of Apurguan: a precontact Chamorro site on Guam. *Am. J. Phys. Anthropol.* **104**, 291–313 (1997).
59. Suzuki, T. Paleopathological and paleoepidemiological investigation of human skeletal remains of early Hawaiians from Mokapu Site, Oahu Island, Hawaii. *Jpn. Rev.* **83**, 128 (1993).
60. Dittmar, J. M. et al. Gout and 'Podagra' in medieval Cambridge, England. *Int. J. Paleopathol.* **33**, 170–181 (2021).
61. Rothschild, B. M., Coppa, A. & Petrone, P. P. 'Like a virgin': absence of rheumatoid arthritis and treponematosis, good sanitation and only rare gout in Italy prior to the 15th century. *Reumatismo* **56**, 61–66 (2004).
62. Major, T. J., Topless, R. K., Dalbeth, N. & Merriman, T. R. Evaluation of the diet wide contribution to serum urate levels: meta-analysis of population based cohorts. *BMJ* **363**, k3951 (2018).
63. Leask, M. P. et al. The pathogenesis of gout: molecular insights from genetic, epigenomic and transcriptomic studies. *Nat. Rev. Rheumatol.* **20**, 510–523 (2024).
64. Major, T. J. et al. A genome-wide association analysis reveals new pathogenic pathways in gout. *Nat. Genet.* **56**, 2392–2406 (2024).
65. Butler, F., Alghubayshi, A. & Roman, Y. The epidemiology and genetics of hyperuricemia and gout across major racial groups: a literature review and population genetics secondary database analysis. *J. Pers. Med.* **11**, 231 (2021).
66. Krishnan, E., Lessov-Schlaggar, C. N., Krasnow, R. E. & Swan, G. E. Nature versus nurture in gout: a twin study. *Am. J. Med.* **125**, 499–504 (2012).
67. Nian, Y.-L. & You, C.-G. Susceptibility genes of hyperuricemia and gout. *Hereditas* **159**, 30 (2022).
68. Sumpter, N. A. et al. Association of gout polygenic risk score with age at disease onset and tophaceous disease in European and Polynesian men with gout. *Arthritis Rheumatol. Hoboken NJ* **75**, 816–825 (2023).
69. Zaidi, F. et al. Systematic genetic analysis of early-onset gout: *ABCG2* is the only associated locus. *Rheumatol. Oxf. Engl.* **59**, 2544–2549 (2020).
70. He, W., Phipps-Green, A., Stamp, L. K., Merriman, T. R. & Dalbeth, N. Population-specific association between *ABCG2* variants and tophaceous disease in people with gout. *Arthritis Res. Ther.* **19**, 43 (2017).
71. Wrigley, R. et al. Pleiotropic effect of the *ABCG2* gene in gout: involvement in serum urate levels and progression from hyperuricemia to gout. *Arthritis Res. Ther.* **22**, 45 (2020).
72. Ioannidis, A. G. et al. Paths and timings of the peopling of Polynesia inferred from genomic networks. *Nature* **597**, 522–526 (2021).
73. Gosling, A. L. & Matisoo-Smith, E. A. The evolutionary history and human settlement of Australia and the Pacific. *Curr. Opin. Genet. Dev.* **53**, 53–59 (2018).
74. Arauna, L. R. et al. The genomic landscape of contemporary western Remote Oceanians. *Curr. Biol. CB* **32**, 4565–4575.e6 (2022).
75. Taonui, R. Whakapapa – genealogy. What is whakapapa? Te Ara, the Encyclopedia of New Zealand; http://www.TeAra.govt.nz/en/whakapapa-genealogy/page-1 (accessed 2025).
76. Gosling, A. L., Buckley, H. R., Matisoo-Smith, E. & Merriman, T. R. Pacific populations, metabolic disease and 'Just-So Stories': a critique of the 'Thrifty Genotype' hypothesis in Oceania. *Ann. Hum. Genet.* **79**, 470–480 (2015).
77. Lipson, M. et al. Reconstructing Austronesian population history in Island Southeast Asia. *Nat. Commun.* **5**, 4689 (2014).
78. Choin, J. et al. Genomic insights into population history and biological adaptation in Oceania. *Nature* **592**, 583–589 (2021).
79. Emde, A.-K. et al. Mid-pass whole genome sequencing enables biomedical genetic studies of diverse populations. *BMC Genomics* **22**, 666 (2021).
80. Tanner, C. et al. Population-specific resequencing associates the ATP-binding cassette subfamily C member 4 gene with gout in New Zealand Māori and Pacific men. *Arthritis Rheumatol. Hoboken NJ* **69**, 1461–1469 (2017).
81. Narang, R. K. et al. Population-specific factors associated with fractional excretion of uric acid. *Arthritis Res. Ther.* **21**, 234 (2019).
82. Hollis-Moffatt, J. E. et al. Role of the urate transporter *SLC2A9* gene in susceptibility to gout in New Zealand Māori, Pacific Island, and Caucasian case-control sample sets. *Arthritis Rheum.* **60**, 3485–3492 (2009).
83. Dalbeth, N. et al. Population-specific influence of *SLC2A9* genotype on the acute hyperuricaemic response to a fructose load. *Ann. Rheum. Dis.* **72**, 1868–1873 (2013).
84. Batt, C. et al. Sugar-sweetened beverage consumption: a risk factor for prevalent gout with *SLC2A9* genotype-specific effects on serum urate and risk of gout. *Ann. Rheum. Dis.* **73**, 2101–2106 (2014).
85. Flynn, T. J. et al. Association analysis of the *SLC22A11* (organic anion transporter 4) and *SLC22A12* (urate transporter 1) urate transporter locus with gout in New Zealand case-control sample sets reveals multiple ancestral-specific effects. *Arthritis Res. Ther.* **15**, R220 (2013).
86. Klück, V. et al. Rare genetic variants in interleukin-37 link this anti-inflammatory cytokine to the pathogenesis and treatment of gout. *Ann. Rheum. Dis.* **79**, 536–544 (2020).
87. Ji, A. et al. Aotearoa New Zealand Māori and Pacific population-amplified gout risk variants: *CLNK* is a separate risk gene at the *SLC2A9* locus. *J. Rheumatol.* **48**, 1736–1744 (2021).
88. Wang, K. et al. A Polynesian-specific copy number variant encompassing the MICA gene associates with gout. *Hum. Mol. Genet.* **31**, 3757–3768 (2022).
89. Bardin, T. et al. Early-onset gout and rare deficient variants of the lactate dehydrogenase D gene. *Rheumatology* **62**, 3978–3983 (2023).
90. Ha Pham, T. T. et al. Allopurinol-induced severe cutaneous adverse reactions in Vietnamese: the role of HLA alleles and other risk factors. *Pharmacogenomics* **23**, 303–313 (2022).
91. Chiu, M. L. S. et al. Association between HLA-B*58:01 allele and severe cutaneous adverse reactions with allopurinol in Han Chinese in Hong Kong. *Br. J. Dermatol.* **167**, 44–49 (2012).
92. Stamp, L. K., Day, R. O. & Yun, J. Allopurinol hypersensitivity: investigating the cause and minimizing the risk. *Nat. Rev. Rheumatol.* **12**, 235–242 (2016).
93. Roberts, R. L. et al. Frequency of CYP2C9 polymorphisms in Polynesian people and potential relevance to management of gout with benzbromarone. *Jt. Bone Spine* **81**, 160–163 (2014).
94. Gottesman, O. et al. The Electronic Medical Records and Genomics (eMERGE) network: past, present, and future. *Genet. Med.* **15**, 761–771 (2013).
95. Te Karu, L., Dalbeth, N. & Stamp, L. K. Inequities in people with gout: a focus on Māori (Indigenous People) of Aotearoa New Zealand. *Ther. Adv. Musculoskelet. Dis.* **13**, 1759720X211028007 (2021).
96. Phipps-Green, A. J. et al. A strong role for the *ABCG2* gene in susceptibility to gout in New Zealand Pacific Island and Caucasian, but not Māori, case and control sample sets. *Hum. Mol. Genet.* **19**, 4813–4819 (2010).
97. Pascart, T., Ducoulombier, V. & Jauffret, C. Early-onset gout. *Jt. Bone Spine* **91**, 105704 (2024).
98. Oehler, E. & Pascart, T. Severe tophaceous gout with radiograph examination of diffused calcified soft tissue tophi. *J. Rheumatol.* **42**, 1259–1260 (2015).

99. McLean, L. Tophaceous pseudotumors in Polynesian patients with gout. *J. Rheumatol.* **31**, 1866–1868 (2004).
100. Dalbeth, N. et al. The experience and impact of gout in Māori and Pacific people: a prospective observational study. *Clin. Rheumatol.* **32**, 247–251 (2013).
101. Dalbeth, N. et al. Gout in Aotearoa New Zealand: the equity crisis continues in plain sight. *N. Z. Med. J.* **131**, 8–12 (2018).
102. Robinson, P. C., Merriman, T. R., Herbison, P. & Highton, J. Hospital admissions associated with gout and their comorbidities in New Zealand and England 1999–2009. *Rheumatology* **52**, 118–126 (2013).
103. Te Karu, L., Bryant, L. & Elley, C. R. Maori experiences and perceptions of gout and its treatment: a kaupapa Maori qualitative study. *J. Prim. Health Care* **5**, 214–222 (2013).
104. Clarson, L. E. et al. Increased cardiovascular mortality associated with gout: a systematic review and meta-analysis. *Eur. J. Prev. Cardiol.* **22**, 335–343 (2015).
105. Te Karu, L., Harwood, M., Arroll, B., Bryant, L. & Kenealy, T. The inequity of access to health: a case study of patients with gout in one general practice. *N. Z. Med. J.* **134**, 51–58 (2021).
106. Cai, K. et al. Association between gout and cardiovascular outcomes in adults with no history of cardiovascular disease: large data linkage study in New Zealand. *BMJ Med.* **1**, e000081 (2022).
107. Tane, T., Selak, V., Eggleton, K. & Harwood, M. Drivers of access to cardiovascular health care for rural Indigenous Peoples: a scoping review. *Rural. Remote. Health* **24**, 8674 (2024).
108. Moon, K. W. et al. Risk factors for acute kidney injury by non-steroidal anti-inflammatory drugs in patients with hyperuricaemia. *Rheumatology* **50**, 2278–2282 (2011).
109. FitzGerald, J. D. et al. 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Rheumatol.* **72**, 879–895 (2020).
110. Latourte, A. et al. 2020 Recommendations from the French Society of Rheumatology for the management of gout: management of acute flares. *Jt. Bone Spine* **87**, 387–393 (2020).
111. Richette, P. et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann. Rheum. Dis.* **76**, 29–42 (2017).
112. Bardin, T. & Richette, P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. *BMC Med.* **15**, 123 (2017).
113. Rech, J.-S. et al. AA amyloidosis of unknown origin in New-Caledonia with focus on the association with gout: a consecutive case series of 20 patients. *Amyloid* **29**, 68–69 (2022).
114. Te Karu, L., Kenealy, T., Bryant, L., Arroll, B. & Harwood, M. The long shadow of inequity for Māori with gout. *MAI J.* **9**, 152–165 (2020).
115. Gosling, A. L., Matisoo-Smith, E. & Merriman, T. R. Gout in Māori. *Rheumatology* **53**, 773–774 (2014).
116. Roussey, A. *Culture Polynésienne et Maladies Chroniques: une Étude Qualitative des Déterminants de Santé Culturels dans la Prise en Charge des Maladies Chroniques*. MD thesis, Univ. Nantes (2018).
117. Boivin, R., Pascart, T. & Oehler, E. Goutte de la personne âgée: comment l'éduquer en Polynésie française? *Gérontologie Société* **46174**, 21–38 (2024).
118. LeBaron von Baeyer, S. et al. Nothing about us without us: sharing results with communities that provide genomic data. *Cell* **87**, 5483–5489 (2024).
119. Arnold, J., Harris, R. & Graham, K. *Pharmac Te Pātaka Whaioranga: Gout insights — Impact on Māori;* https://pharmac.govt.nz/about/access-equity/medicine-access-equity-monitoring-and-outcomes-framework/gout-insights-impact-on-maori (Pharmac, 2021).
120. Pascart, T. et al. 2020 recommendations from the French Society of Rheumatology for the management of gout: urate-lowering therapy. *Joint Bone Spine* **87**, 395–404 (2020).
121. Dahanayake, C., Jordan, K. M. & Roddy, E. Crystal Clear? The 2022 NICE guideline for the diagnosis and management of gout. *Gout Urate Cryst. Depos. Dis.* **1**, 7–10 (2023).
122. Dalbeth, N., Te Karu, L. & Stamp, L. K. Gout and its management. *Intern. Med. J.* **54**, 716–723 (2024).
123. Pascart, T., Oehler, E. & Flipo, R.-M. Gout in French Polynesia: a survey of common practices. *Joint Bone Spine* **81**, 374–375 (2014).
124. Arnold, J., Harris, R., Masina, L. A. & Graham, K. *Pacific Peoples Health - Gout Data Insights;* https://pharmac.govt.nz/assets/2022-04-11-PacificPeoples-Health-Gout-Data-Insights.pdf (Pharmac, 2022).
125. Fanning, N. C. et al. Association of rare and common genetic variants in *MOCOS* with inadequate response to allopurinol. *Rheumatology* **63**, 3025–3032 (2024).
126. Wright, D. F. B. et al. The development and evaluation of dose-prediction tools for allopurinol therapy (Easy-Allo tools). *Br. J. Clin. Pharmacol.* **90**, 1268–1279 (2024).
127. Wallace, M. C. et al. Association between *ABCG2 rs2231142* and poor response to allopurinol: replication and meta-analysis. *Rheumatology* **57**, 656–660 (2018).
128. Hishe, H. Z. et al. The impact of genetic variability in urate transporters on oxypurinol pharmacokinetics. *Clin. Transl. Sci.* **16**, 422–428 (2023).
129. Te Karu, L., Harwood, M., Bryant, L., Kenealy, T. & Arroll, B. Compounding inequity: a qualitative study of gout management in an urban marae clinic in Auckland. *J. Prim. Health Care* **13**, 27–35 (2021).
130. Lawrence, A. et al. Facilitating equitable prevention and management of gout for Māori in Northland, New Zealand, through a collaborative primary care approach. *J. Prim. Health Care* **11**, 117–127 (2019).
131. Andrews, S., Gasparini, J. & Henderson, G. *Evaluation of Gout Stop and Owning My Gout Management Programmes: Final Report for Arthritis New Zealand and Its Partners* (Synergia Limited, 2020).
132. Doherty, M. et al. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. *Lancet* **392**, 1403–1412 (2018).
133. Fuller, A., Jenkins, W., Doherty, M. & Abhishek, A. Nurse-led care is preferred over GP-led care of gout and improves gout outcomes: results of Nottingham Gout Treatment Trial follow-up study. *Rheumatology* **59**, 575–579 (2020).
134. Kawakami, K. L. et al. The lives of native Hawaiian elders and their experiences with healthcare: a qualitative analysis. *Front. Public Health* **10**, 787215 (2022).
135. Neville, S. et al. Barriers to older Pacific peoples' participation in the health-care system in Aotearoa New Zealand. *J. Prim. Health Care* **14**, 124–129 (2022).
136. Roman, Y. M. Moving the needle in gout management: the role of culture, diet, genetics, and personalized patient care practices. *Nutrients* **14**, 3590 (2022).
137. Curtis, E. et al. Why cultural safety rather than cultural competency is required to achieve health equity: a literature review and recommended definition. *Int. J. Equity Health* **18**, 174 (2019).
138. Ofanoa, M. et al. Design and implementation of a Pacific intervention to increase uptake of urate-lowering therapy for gout: a study protocol. *Int. J. Equity Health* **20**, 262 (2021).
139. Ministry of Health. *Ola Manuia: Pacific Health and Wellbeing Action Plan 2020-2025* (2020).
140. Te Karu, L. Guest editorial: restoration of the health system must not neglect medicines — but who has the power of reform? *J. Prim. Health Care* **13**, 96–101 (2021).
141. Sirugo, G., Williams, S. M. & Tishkoff, S. A. The missing diversity in human genetic studies. *Cell* **177**, 26–31 (2019).
142. Curtis, E. et al. Indigenous adaptation of a model for understanding the determinants of ethnic health inequities. *Discov. Soc. Sci. Health* **3**, 10 (2023).
143. García-Pérez, R. et al. The landscape of expression and alternative splicing variation across human traits. *Cell Genomics* **3**, 100244 (2023).
144. Abolins-Thompson, H. et al. Culturally responsive strategies and practical considerations for live tissue studies in Māori participant cohorts. *Front. Res. Metr. Anal.* **9**, 1468400 (2024).
145. Beaton, A. et al. Engaging Māori in biobanking and genomic research: a model for biobanks to guide culturally informed governance, operational, and community engagement activities. *Genet. Med.* **19**, 345–351 (2017).
146. Moors, J. et al. A Polynesian-specific missense CETP variant alters the lipid profile. *HGG Adv.* **4**, 100204 (2023).
147. Rasheed, H. et al. Association of the lipoprotein receptor-related protein 2 gene with gout and non-additive interaction with alcohol consumption. *Arthritis Res. Ther.* **15**, R177 (2013).
148. University of Illinois. Summer Internship for INdigenous Peoples in Genomics; https://sing.igb.illinois.edu/ (2020).
149. University of Utah Health. Haumana 'O Pasifika Program; https://uofuhealth.utah.edu/haumana-o-pasifika-program (2023).
150. Genomics Aotearoa. *Ruatau* https://www.genomics-aotearoa.org.nz/our-work/te-ao-maori-projects/ruatau.
151. Bardill, J. et al. Advancing the ethics of paleogenomics. *Science* **360**, 384–385 (2018).
152. Koea, J. B. Indigenous trauma: a New Zealand perspective. *Injury* **39**, S11–S18 (2008).
153. Thom, R. R. M. & Grimes, A. Land loss and the intergenerational transmission of wellbeing: the experience of iwi in Aotearoa New Zealand. *Soc. Sci. Med. 1982* **296**, 114804 (2022).
154. Anderson, I. et al. Indigenous and tribal peoples' health (The Lancet-Lowitja Institute Global Collaboration): a population study. *Lancet* **388**, 131–157 (2016).
155. Paradies, Y. Colonisation, racism and indigenous health. *J. Popul. Res.* **33**, 83–96 (2016).
156. Moewaka Barnes, H. & McCreanor, T. Colonisation, hauora and whenua in Aotearoa. *J. R. Soc. N. Z.* **49**, 19–33 (2019).
157. Wirihana, R. & Smith, C. Historical trauma, healing and well-being in Māori communities. *MAI J.* **3**, 197–210 (2014).
158. Pool, I. & Kukutai, T. *Taupori Māori — Māori population change, Te Ara — the Encyclopedia of New Zealand*. http://www.TeAra.govt.nz/en/taupori-maori-maori-population-change/print (2025).
159. Ministry of Health. *Tatau Kahukura Māori Health Chart Book 2015, 3rd edn* (Ministry of Health, 2015).
160. Reid, P., Cormack, D. & Paine, S.-J. Colonial histories, racism and health — the experience of Māori and Indigenous peoples. *Public Health* **172**, 119–124 (2019).
161. Yokose, C. et al. Nationwide racial/ethnic disparities in US emergency department visits and hospitalizations for gout. *Rheumatology* **62**, 2247–2251 (2023).
162. McCormick, N., Yokose, C. & Choi, H. K. What drives the contemporary black–white racial disparities in gout in the US? Impact of social determinants of health. *Gout Urate Cryst. Depos. Dis.* **1**, 99–114 (2023).
163. Daniels, S.-A. P., Kauahikaua, L., Kaio, C., Casson-Fisher, J. N. & Ku, T. Conceptualizing a new system of care in Hawai'i for native Hawaiians and substance use. *Hawaii. J. Health Soc. Welf.* **81**, 43–51 (2022).
164. Smith, L. T., Maxwell, T. K., Puke, H. & Temara, P. Indigenous knowledge, methodology and mayhem: what is the role of methodology in producing indigenous insights? A discussion from mātauranga Maori. *Knowl. Cult.* **4**, 131–156 (2016).
165. Chung-Do, J. J. et al. Waimānalo pono research hui: a community-academic partnership to promote native Hawaiian wellness through culturally grounded and community-driven research and programming. *Am. J. Community Psychol.* **64**, 107–117 (2019).

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Review article

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Stem and progenitor cells in the synovial joint as targets for regenerative therapy

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Abstract

Damage to articular cartilage, tendons, ligaments and entheses as a result of trauma, degeneration or inflammation in rheumatic diseases is prevalent. Regenerative medicine offers promising strategies for repairing damaged tissues, with the aim of restoring both their structure and function. While these strategies have traditionally relied on tissue engineering approaches using exogenous cells, interventions based on the activation of endogenous repair mechanisms are an attractive alternative. Key to advancing such approaches is a comprehensive understanding of the diversity of the stem and progenitor cells that reside in the adult synovial joint and how they function to repair damaged tissues. Advances in developmental biology have provided a lens through which to understand the origins, identities and functions of these cells, and insights into the roles of stem and progenitor cells in joint tissue repair, as well as their complex relationship with fibroblasts, have emerged. Integration of knowledge obtained through studies using advanced single-cell technologies will be crucial to establishing unified models of cell populations, lineage hierarchies and their molecular regulation. Ultimately, a more complete understanding of how cells repair tissues in adult life will guide the development of innovative pro-regenerative drugs, which are poised to enter clinical practice in musculoskeletal medicine.

Sections

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Key points

- Joint tissues are susceptible to damage that often does not adequately heal without intervention and can predispose to osteoarthritis.
- Understanding the regenerative biology of the synovial joint will guide the development of therapeutic strategies to activate endogenous repair mechanisms and improve outcomes.
- In adult joint tissues, stem and progenitor cell niches are present in the synovial lining and sublining, the paratenon and tendon sheath, the superficial zone of cartilage and the subchondral bone marrow.
- The identity and functions of the different stem and progenitor cell populations in adult joint tissues can be understood in the context of their diverse developmental origins.
- The synovium could be a reservoir of joint-repairing cells, and cells from bone marrow can contribute to the repair of osteochondral defects.
- Single-cell technologies offer the opportunity to establish integrated models of cell populations and lineage hierarchies and their molecular regulation.

Introduction

Damage of joint tissues is very common and is typically the result of high-impact or cumulative low-impact repetitive trauma, age-related degeneration or inflammation in rheumatic conditions. Cartilage defects are detected in ~60% of all arthroscopic procedures[1,2]. Osteoarthritis (OA) is a degenerative joint disease characterized by loss of cartilage, and its prevalence is increasing owing to ageing of the population[3]. The incidence of early-onset OA is also rising, attributable in part to the increased prevalence of obesity[4]. Knee OA is the most common and disabling form of OA and accounts for ~85% of the disability burden of OA[3,5]. In addition, patients with inflammatory arthritis often develop cartilage and enthesis damage. Repair of damaged tissues is therefore an unmet clinical need in rheumatology.

Regenerative medicine, which is aimed at repairing damaged tissues without scar formation and restoring structure and function, involves two main therapeutic strategies. The first strategy reflects traditional tissue engineering and relies on implantation at the site of damage of exogenous cells, often after expansion in culture, or of tissue constructs generated in vitro by combining cells and biomaterials, with or without growth factors (Box 1). The second approach relies on the activation of intrinsic repair mechanisms by pharmacologically targeting endogenous stem and progenitor cells and related morphogenetic pathways[6]. Although tissue engineering approaches can, theoretically, provide a lifelong solution, the manufacturing is expensive and laborious, leads to a product that is often unreliable and is subject to the substantial challenges posed by the regulatory requirements for advanced therapy medicinal products, which are primarily related to the ex vivo manipulation of cells. Instead, a traditional pharmacological approach based on pro-regenerative drugs with consistent composition and reliable potency would be highly desirable for ease of production and regulation. The development of these pro-regenerative drugs would be enabled by an in-depth understanding of the regenerative biology of the tissues to be repaired.

For centuries, the articular cartilage has been deemed unable to heal itself after injury. However, growing evidence suggests that, under certain conditions, the joint surface has intrinsic healing ability[7]. In humans, interventions that target joint biomechanics, such as joint distraction, can result in increased cartilage thickness, presumably due to intrinsic repair[8]. Similarly, some mouse strains have the capacity to heal cartilage defects[9,10]. These observations prompted investigation of the underpinning repair mechanisms.

Postnatally, tissue healing is believed to recapitulate, to some extent, the processes of tissue formation during embryonic development, involving a series of spatiotemporally patterned events that include the proliferation of stem and progenitor cells and their migration and differentiation into mature cell types[11]. In adult life, stem-cell function persists in tissues and organs, including the synovial joint, to replace cells that are lost to physiological turnover, injury or disease. Numerous studies have identified stem cells in bone marrow, which are often referred to as skeletal stem cells. However, the distinction between stem cells and progenitor cells is often not clear, primarily owing to limited evidence of self-renewal ability, and we therefore collectively refer to stem cells and progenitor cells as SPCs throughout this Review. In this article, we review from a developmental perspective the endogenous SPCs that reside in various niches in the adult synovial joint in mammals and their roles in repair, and provide examples of how this knowledge is informing the development of pro-regenerative drugs.

Regenerative biology of the synovial joint

The musculoskeletal system is a complex integration of morphologically heterogeneous components and different tissues. It seems unlikely that a single hierarchical cell-lineage tree similar to, for example, the haematopoietic system, could exist to maintain and repair skeletal tissues in adult life. Instead, accumulating evidence points to the existence of multiple SPC populations with diverse developmental origins and functions residing in the various tissues. Of note, skeletal cells remain confined within their local environment. Tracing of perichondrial cells from mouse embryonic life on the basis of expression of *Hoxa11*, which has a critical role in morphogenesis, specifically of the zeugopod (consisting of the radius and ulna, and the tibia and fibula)[12], showed that these cells give rise to chondrocytes, osteoblasts and bone-marrow adipocytes, and persist up to at least 1 year of age, while remaining restricted to their anatomical domain, the zeugopod[13] (Fig. 1). Hoxa11 continues to be expressed in the zeugopod tissues in adult mice[13,14], and *Hox11* loss of function results in impaired fracture healing in the ulna (zeugopod) but not the femur (stylopod)[14], indicating that *Hox* genes remain functionally important in adult SPCs. These findings support a model whereby the 'seeding' of skeletal tissues with lifelong SPCs occurs around the time that tissues form and mature, in the embryo or in early postnatal life, and these cells specialize to locally maintain and repair the tissue and/or organ they reside in.

Stem and progenitor cells in bone marrow

Fibroblast-like cells with chondro-osteogenic differentiation potency can be isolated and culture expanded from bone marrow. This observation, together with the view that microfracture would enable subchondral marrow cells to move into the cartilage lesion and promote repair, contributed to the idea that bone marrow could be a source of cartilage-repairing cells. Prospective isolation of cells from human bone marrow using cell-surface markers such as STRO-1 (ref. 15), CD271

Box 1 | Exogenous cell therapy

Cell therapy for repair of cartilage defects

Most defects of the articular cartilage are partial thickness and do not reach bone, and only about 5% are full thickness[1]. However, as partial-thickness lesions are debrided during surgery to full thickness, repair strategies focus on the treatment of full-thickness cartilage defects.

Autologous chondrocyte implantation (ACI): culture-expanded chondrocytes, isolated from a biopsy sample taken from a healthy and unloaded area of knee cartilage, are implanted into the defect[112].

- Results from up to 20 years' follow-up demonstrated that ACI is an effective and durable treatment of large cartilage defects in the knee[113].
- Prospective, randomized, multicentre trials comparing ACI with microfracture, in which subchondral bone is perforated to enable cells and factors from bone marrow to stimulate repair[114], have shown structurally superior repair tissue following ACI at 12 months[115], with a superior clinical outcome at 36 months[116]. A clinically superior outcome at 5 years was reported only in participants with symptom duration <3 years[117]. A separate study reported no difference between ACI and microfracture at 14–15 years' follow-up[118].
- ACI has evolved through studies aiming to improve and standardize the manufacturing of the chondrocyte preparation and to optimize delivery, for example, through arthroscopy, the use of a hydrogel as a carrier and the implantation of cultured chondrocytes seeded on a collagen membrane[106].
- A further advancement is matrix-associated ACI using spheroids, which utilizes aggregates of culture-expanded autologous chondrocytes and their self-synthesized extracellular matrix[119].

Mesenchymal stromal cell (MSC) implantation: culture-expanded or minimally manipulated MSCs are used in an ACI-like procedure.

- Several clinical studies using MSCs, primarily from bone marrow or adipose tissue, for cartilage repair have shown promising results, albeit with variable structural outcomes ranging from hyaline-like cartilage to fibrous tissue, and allogeneic MSCs have shown a satisfactory safety profile[106,120].

Cell therapy for osteoarthritis

- A systematic review of evidence from 16 randomized clinical trials that included 612 patients showed that intra-articular injection of autologous or allogeneic MSCs provides better pain relief and functional improvement than cell-free therapy for knee OA[121].
- MSCs seem to mediate beneficial effects primarily via paracrine signals such as the release of growth factors and immunomodulatory properties[106].
- However, a multicentre, single-blind randomized controlled trial involving 480 patients with knee OA investigated the safety and efficacy of cell injections from autologous bone marrow aspirate concentrate, autologous adipose stromal vascular fraction and allogeneic human umbilical cord tissue-derived MSCs, in comparison with corticosteroid injection. At 1-year post-injection, there was no difference in clinical outcome between groups, and no evidence of structural improvement on MRI[122].

(ref. 16), CD146 (ref. 17), CD51 and PDGFRα[18], or a more elaborate combination of markers[19], together with cell transplantation experiments in animal models to demonstrate in vivo multipotency, and in some cases self-renewal ability, identified partly overlapping SPC populations. Genetic cell-labelling and tracing studies in mice further enhanced our understanding of the identity, location and function of the SPCs in bone marrow. Seminal studies identified perivascular SPCs marked by expression of Pdgfrα and Sca1 (ref. 20), Nestin[21,22] or leptin receptor (LepR)[23,24], again with some overlap between populations, which were found to support haematopoiesis and to contribute to osteogenic and adipogenic lineages[21,24]. In addition, a distinct population of osteochondroreticular SPCs expressing Gremlin-1 was described and shown to contribute to early postnatal bone growth and fracture repair in adult mice[25]. These and other studies revealed how SPCs identified in adult bone marrow are heterogeneous and specialize to primarily support bone turnover and repair, or marrow functions[26]. The existence of a single stem cell giving rise to all cartilage, bone and stromal lineages through a defined hierarchy of lineage-restricted progenitors that could each be identified by a combination of cell-surface markers was proposed in mice[27] and humans[19], although the co-existence of distinct stem cells has since been recognized[28], as supported by previous studies (reviewed elsewhere[26]). Studies from the past few years have continued to add to our understanding of how SPC populations change at different stages of life to support development, postnatal growth, homeostasis and repair after injury[13,29,30], and how alterations in SPCs, including reduction in their skeletogenic potential, can contribute to or result from ageing[31,32]. Key studies and their findings are summarized in Table 1. It remains challenging, however, to integrate findings from various studies into unified models, partly owing to the use of different markers that could identify cells at different stages of lineage commitment and might not retain consistent expression patterns at different life stages or in different contexts, such as after injury.

Many studies have shown that various SPC populations contribute to the transient cartilage of the callus in models of bone fracture (Table 1). However, few studies have evaluated their response in models of osteochondral injury. *Lepr*-lineage cells were found to make a minor contribution to the repair of deep osteochondral defects[24], and SPCs as previously defined by a set of cell-surface markers[27] were detected in the repair tissue of osteochondral lesions that were deep enough to access the underlying bone marrow[31]. Conversely, tracing of SPCs marked by perinatal and postnatal expression of osterix, which had previously been shown to contribute to fracture callus formation[33], showed that these cells made a negligible contribution to the repair tissue filling the osteochondral defects[34]. The extent of the contribution of bone marrow SPCs to the repair of osteochondral defects thus remains unclear and could represent a context-dependent stochastic event.

Stem and progenitor cells in the synovial joint

Initial evidence of the existence of SPCs in the synovial joint in vivo came from a study that used a double-nucleoside-analogue labelling scheme in a mouse model of articular cartilage injury to show the presence of label-retaining (that is, slow-cycling) cells in both the lining

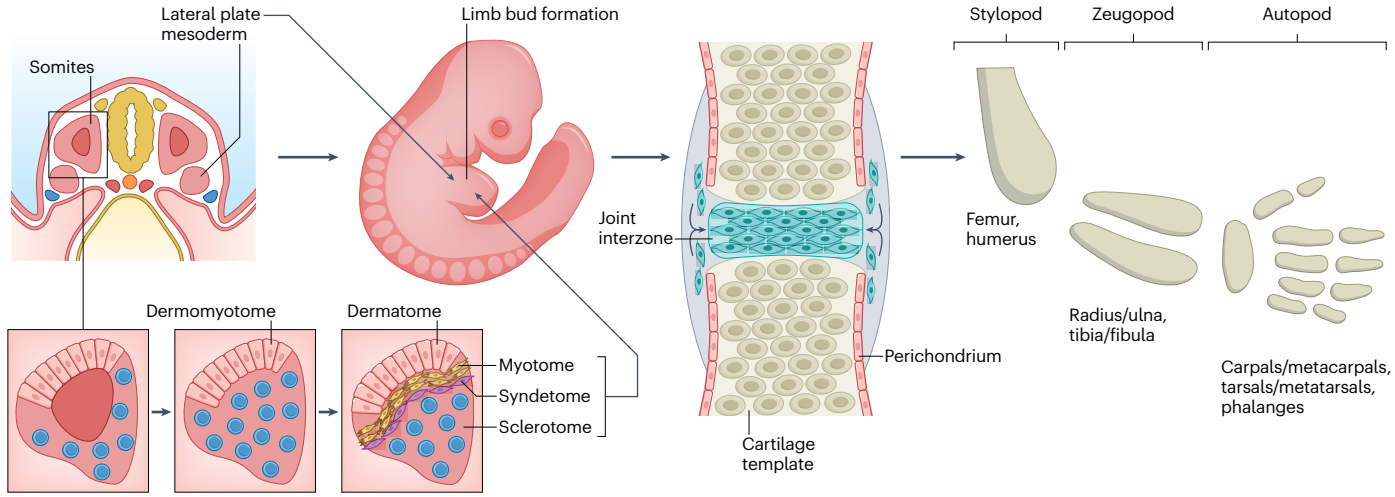

Fig. 1 | Overview of limb development and synovial joint formation. During embryogenesis, the embryo organizes into three germ layers, the ectoderm, mesoderm and endoderm, in a process called gastrulation. The mesoderm, which eventually gives rise to tissues that include muscle, dermis, cartilage and bone, undergoes segmentation to form axial, paraxial, intermediate and lateral domains. The paraxial mesoderm segments into somites, which later contribute to the formation of the axial skeleton and skeletal muscles of the trunk. As the somites mature, different regions of the somites commit to diverging cell fates. The sclerotome, which eventually forms cartilage and bone, differentiates first, followed by differentiation of the dermomyotome into the dermatome and myotome. Finally, the syndetome, which gives rise to tendons, forms from the dorsolateral domain of the sclerotome, induced by signals from the adjacent myotome. Cells within the sclerotome, myotome and syndetome migrate into the developing limb bud and contribute to fibroblast populations within the limb and to the formation of entheses, myotendinous junctions and bone superstructures. The limb bud mainly forms from the somatic layer of the lateral plate mesoderm, with patterning across the limb directed by the differential expression of *Hox* genes. Cartilage templates, from which the long bones form, develop by chondrogenesis of mesenchymal condensations and are surrounded by the perichondrium. At the site of a prospective joint, a cluster of mesenchymal cells assembles, called the joint interzone. Characterized by the expression of genes involved in the specification of cells for joint formation, such as *Gdf5*, the joint interzone cells give rise to various joint tissues, contributed to by a continuous influx of cells from the surrounding tissue. Further development of the limb occurs in a proximodistal fashion, starting with the proximal-most compartment of the limb (humerus or femur), called the stylopod, followed by development of the middle limb compartment (radius/ulna or tibia/fibula), the zeugopod, then the distal-most limb compartment (carpals/metacarpals, tarsals/metatarsals, phalanges), the autopod.

and sublining synovium that were distinct from pericytes and that, after cartilage injury, proliferated and formed ectopic cartilage in the synovium[35]. Subsequently, lineage-tracing studies advanced the understanding of the developmental origins and biology of SPCs in the joint tissues. In mouse embryos, the development of the appendicular skeleton starts with the emergence of the limb bud from the lateral plate mesoderm at around embryonic day 9 (E9). From around E11.5, mesenchymal cell condensations undergo chondrogenesis to give rise to cylindrical primary cartilage templates sheathed by perichondrium. At the site of a prospective joint, a stripe of mesenchymal cells, called the joint interzone and characterized by the expression of distinct genes such as *Gdf5* (encoding growth differentiation factor 5), emerges that segments the cartilage template. Lineage-tracing of *Gdf5*-expressing joint interzone cells revealed that these cells give rise to various joint tissues, including articular cartilage, intra-articular ligaments and parts of the synovium[36–39]. The joint interzone cells are recruited, at least in part, from the surrounding tissue flanking the cartilage template[40], and the continuous influx of SPCs into the joint interzone sustains joint development[41] (Fig. 1). Tracing of *Gdf5*-lineage cells into adulthood, using a model controlled by a *Gdf5* regulatory sequence that is active in the mouse knee joint interzone during development but not in adult knees[42–44] showed that *Gdf5*-lineage cells persist in the joint tissues throughout life[36–38], suggesting that this lineage contains lifelong self-renewing stem cells. In adult synovium, *Gdf5*-lineage cells are a subpopulation of Pdgfrα-expressing stromal cells with minimal overlap with cells expressing the bone marrow SPC markers Nestin, LepR or Gremlin-1, and were shown in vitro to have superior ability to form cartilage and a synovial-lining-like layer but poor osteogenic capacity[38]. After cartilage injury, the *Gdf5*-lineage cells proliferated (resulting in synovial hyperplasia), populated the cartilage defect and underwent chondrogenic differentiation to effect cartilage repair[38]. Conditional ablation of the transcriptional cofactor Yes-associated protein in the *Gdf5*-lineage cells prevented synovial lining hyperplasia and markedly reduced the contribution of *Gdf5*-lineage cells to cartilage repair[38]. These findings demonstrated a functional heterogeneity of joint-resident SPCs, with *Gdf5*-lineage cells repairing articular cartilage after injury. However, the tissue of origin of the cartilage-repairing cells remains undefined.

Articular cartilage itself contains progenitor cells located at the surface of the tissue[45]. Tracing of *Prg4*-expressing cells from the superficial layer of the developing articular cartilage showed that their progeny gradually gave rise to chondrocytes into deeper regions of the cartilage as mice aged[46]. Cells in the superficial layer of cartilage were also shown to divide slowly and to express SPC markers[47]. *Prg4*-lineage cells have been shown to populate cartilage defects after injury[34,48], and to differentiate into aggrecan-expressing chondrocytes[34]. However, *Prg4* is also expressed by *Gdf5*-lineage cells in the synovial lining, and the extensive expansion of both *Gdf5* and *Prg4* lineages in the hyperplastic synovium following cartilage injury, together with a general absence of proliferating cells in the cartilage surrounding the defect[38,48] and a lack

of detectable contribution from lineage-traced Aggrecan-expressing cartilage cells to the repair tissue[34], led to the suggestion that the chondroprogenitors that repair cartilage could originate primarily from synovium rather than the superficial zone of cartilage. The in vivo chondrogenic potency of *Prg4*-expressing cells in the synovial lining is further demonstrated by their progeny giving rise to chondrocytes in developing osteophytes in experimental OA, with lineage-traced *Prg4*-expressing cells persisting in the cartilage cap of mature osteophytes[49], which overlies the newly formed bone, likely originating from SPCs in the periosteum[49,50]. Of note, *Prg4* expression itself is downregulated after injury[48] and *Prg4*-null mice display extensive ectopic chondrogenesis, as demonstrated in the temporomandibular joint[51].

The adult subchondral bone and marrow are also populated by *Gdf5*-lineage cells[38], which probably arise during formation of the secondary ossification centre. Unlike the primary ossification centre, which forms in the embryo through the invasion of the mineralized cartilage by blood vessels and associated osteoprogenitors from the surrounding perichondrium[52], secondary ossification is initiated after birth by invagination at the periarticular surface and the invasion of SPCs into the epiphyseal cartilage, which precedes mineralization and vascular invasion[53,54]. These invading periarticular cells give rise to osteo-lineage cells, adipocytes and perivascular cells within the epiphyseal bone compartment[54]. It thus seems that the subchondral bone compartment houses a distinct stromal cell lineage that shares a developmental origin with the overlying cartilage. Whether these cells are functionally distinct from other bone marrow SPCs and have a role in maintaining or repairing cartilage is unclear.

Table 1 | Key studies reporting skeletal stem and progenitor cell populations in mouse bone

Refs.	Main marker(s)	Other marker(s)	Anatomical site	Function
Morikawa et al.[20]	Pdgfrα, Sca-1	CD29, CD49e, CD44, CD105, CD133, Pdgfrβ, Ang-1	Perivascular	Differentiate into osteoblasts, adipocytes and HSC niche cells following transplantation
Méndez-Ferrer et al.[21]	Nestin	Cxcl12, Adrb3, Ang-1	Perivascular	Contribute to skeletal remodelling and HSC maintenance
Kunisaki et al.[107]	Nestin	Nes-GFP^{bright}: Ng2; Nes-GFP^{dim}: Lepr	Nes-GFP^{bright}: periarteriolar; Nes-GFP^{dim}: perisinusoidal	Periarteriolar Nestin-expressing cells co-expressing the pericyte marker NG2 are required for HSC maintenance and to promote HSC quiescence
Arranz et al.[108]	Nestin	Cxcl12	Perivascular	Cxcl12 production by Nestin-expressing cells negatively regulates HSC activity
Ding et al.[23]	Lepr	Scf, Pdgfrα, Pdgfrβ, Cxcl12	Perivascular	Support HSC maintenance in adult bone marrow
Zhou et al.[24]	Lepr	Prx1, Pdgfrα, CD51, Pdgfrβ, CD105, Scf, Cxcl12	Perisinusoidal, periarteriolar	Main source of new bone and adipocytes in adult bone marrow; contribute to repair following bone fracture or osteochondral injury
Shen et al.[109]	Lepr	Oln	Periarteriolar	Osteogenic progenitors maintained by mechanical stimulation; increase in number after fracture and are depleted during ageing
Pineault et al.[13], Rux et al.[14]	Hoxa11	Pdgfrα, CD51, Lepr	Zeugopod	Contribute to bone, cartilage and bone marrow adipocytes; contribute to fracture repair in the zeugopod
Worthley et al.[25]	Grem1	CD105, distinct from Nes-GFP cells	Trabecular bone and growth plate region; not perisinusoidal	Osteochondroreticular cells; lack adipogenic potential; involved in postnatal bone growth, bone remodelling and fracture repair
Chan et al.[27]	CD45$^-$Ter119$^-$Tie2$^-$ CD51$^+$ CD90$^-$ 6C3$^-$CD105$^-$CD200$^+$	Not reported	Isolated from long bones	Expand following fracture; give rise to chondrocytes and osteocytes following transplantation
Ambrosi et al.[32]	CD45$^-$Ter119$^-$Tie2$^-$ CD51$^+$ CD90$^-$ 6C3$^-$CD105$^-$CD200$^+$	Not reported	Isolated from long bone	Decreased activity in aged mice compared with young mature mice following transplantation and in fracture repair
Mizuhashi et al.[110]	Pthrp	Subset of CD45$^-$Ter119$^-$ CD31$^-$CD51$^+$CD90$^-$CD105$^-$ CD200$^+$ cells	Growth plate (resting zone)	Contribute to growth plate, bone and bone marrow stromal cells but not adipocytes
Muruganandan et al.[111]	Foxa2	Not reported	Growth plate (resting zone)	Can become Pthrp$^+$ cells; contribute to growth plate cartilage maintenance and repair following injury
Matsushita et al.[30]	Fgfr3	Subset of CD45$^-$Ter119$^-$ CD31$^-$CD51$^+$CD90$^-$ CD200$^+$ cells	Endosteum	Following transplantation, contribute to chondrocytes and osteoblasts in fracture callus, as well as reticular cells and marrow adipocytes; supply osteoblasts to the repair of cortical bone injury in juvenile mice but not in aged mice

HSC, haematopoietic stem cell; MSC, mesenchymal stromal cell; Nes–GFP, Nestin–green fluorescent protein.

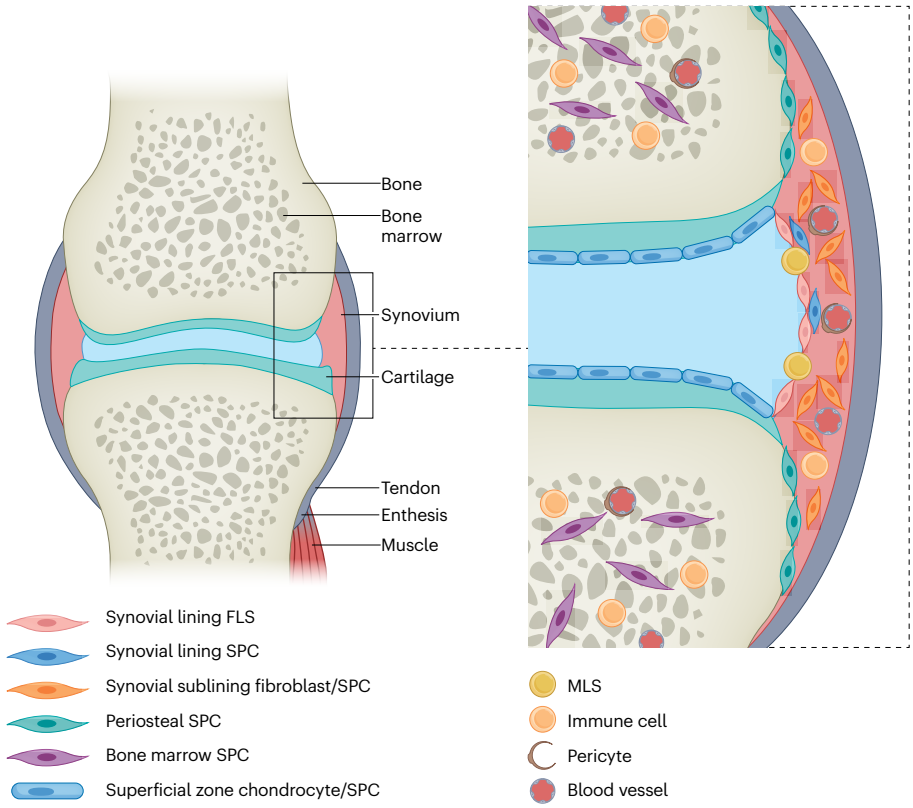

Fig. 2 | Overview of skeletal stem and progenitor cell populations in the synovial joint. Stem and progenitor cells (SPCs) have been identified within various joint-associated tissues. Among the most highly investigated are SPC populations residing within bone marrow, which include cells around sinusoids and arterioles, and at endosteal surfaces. SPCs are also present in the superficial zone of articular cartilage and in the membranes that surround the joint and its related structures, including the synovium and periosteum. In the synovium, SPCs are present among the Prg4-expressing cells in the lining and among the fibroblasts in the vascularized sublining. FLS, fibroblast-like synoviocyte; MLS, macrophage-like synoviocyte.

In summary, the synovial joint holds multiple spatially distinct SPCs across its tissues (Fig. 2), with the ability to repair cartilage and participate in tissue-remodelling processes such as osteophyte formation in OA. It remains to be fully clarified whether these tissue-resident SPCs in the synovial joint have equal functional plasticity with stochastic, context-dependent outcomes or diverse, intrinsic tissue-formation abilities.

Stem and progenitor cells in the tendon and enthesis

Tendons and ligaments insert into intra-articular or periarticular bone via fibrocartilaginous entheses, which are vulnerable to inflammation and injury[55]. Damage to the enthesis in adulthood often results in a disorganized, scar-mediated repair tissue with inferior biomechanical properties and susceptibility to repeat injuries. In the past decade or so, elegant studies have uncovered mechanisms of bone superstructure formation that result in the three-dimensional shaping of the bones, including condyles at articulating surfaces, bone eminences that serve as tendon-attachment sites and sesamoid bones[56–60]. Shortly after the establishment of the cartilage template, distinct bipotent Sox9$^+$Scx$^+$ progenitors arise at its boundaries with the surrounding Scx-expressing tendon primordia[56–60] and differentiate into either chondrocytes or tenocytes to form the bone eminences and attachment units[61,62], which postnatally mature to form the entheses. Interestingly, although the cells in the early lateral plate mesodermal condensations are generally thought to give rise to the limb mesenchymal cells[63], an SPC population characterized and regulated by expression of the transcription factor Hic1 was shown to migrate into the developing limb bud from the syndetome and sclerotome compartments of the somite, alongside myogenic progenitors migrating from the dermomyotome and projecting nerve axons[64] (Fig. 1). Progeny of Hic1$^+$ cells gave rise to various fibroblast populations throughout the limb[64], as well as the bipotent progenitors forming the bone eminences and fibrocartilaginous entheses[65]. The latter also derive from *Gdf5*-lineage progenitors[66,67], indicating at least partial overlap between the somite-derived migratory progenitor population and the cells of the joint interzone that give rise to the joint tissues.

Both articular hyaline cartilage and entheseal fibrocartilage continue to develop and mature postnatally under the influence of mechanical forces, with interstitial growth of the tissue driven primarily by an increase in cell size and extracellular matrix deposition rather than by proliferation, and these cartilage tissues are protected from undergoing remodelling to bone[48,67–69]. Enthesis formation is driven by Hedgehog signalling[67,68,70,71], which is regulated by primary cilia that link mechanosensing to enthesis formation and response to loading[72]. Hedgehog-responsive Gli1$^+$ cells persist in the mature enthesis at the border between the non-mineralized and mineralized fibrocartilage, but their repair response was shown to be overwhelmed by fibrous scarring in a mouse model of full-depth supraspinatus enthesis injury[73]. Interestingly, sorted and cultured Gli1$^+$ cells isolated from developing entheses in early postnatal mice promoted regeneration after transplantation into the same adult injury model[74], suggesting that failure to repair might be attributable to a limited presence or reduced activity of SPCs in the mature enthesis. This and other studies using single-cell transcriptomics are corroborating and extending our understanding of the cellular and molecular mechanisms of enthesis development and maturation[69,74,75], which could help to inform strategies to promote

repair of the mature enthesis, for example, through moderate exercise to stimulate the recruitment of Prrx1$^+$ progenitors via ciliary TGFβ receptor 2 signalling[75].

Cells have been isolated from tendons that, following culture expansion, were able to form tendon-like or enthesis-like tissues in models of heterotopic transplantation[76]. On the basis of the presence of nucleoside-analogue-retaining cells, it was suggested that these SPCs reside within the tendon midsubstance, interspersed among tenocytes[76]. However, convincing evidence of their in vivo location was lacking. The tendon midsubstance is surrounded by membranes, the epitenon and paratenon, and at areas of high friction is wrapped in synovium, known as the tendon sheath. Lineage-tracing and single-cell transcriptomic studies have revealed that tendon repair following injury is mediated primarily by SPCs in the paratenon or synovial tendon sheath[66,77–82]. These cells extensively proliferate after injury and supply progeny that infiltrate the injured tendon and undergo tenocyte differentiation[77–80,82]. Sheath SPCs were identified as a Tppp3$^+$ subset of Pdgfrα$^+$ cells[77] that are also marked by expression of *Bglap* (encoding osteocalcin)[79]. Hedgehog signalling is upregulated after tendon injury and stimulates Tgfβ signalling that promotes the proliferation of tendon sheath cells and upregulates tenogenic gene expression, mediated at least in part by Smad3 binding to the Mohawk promoter[79], a key tenogenic transcription factor[83]. Their proliferation and tenogenic differentiation is also dependent on Pdgf signalling, with conditional knockout of *Pdgfra* in Tppp3$^+$ cells resulting in impaired proliferation and tenocyte differentiation, leading instead to poor fibrotic repair by other Pdgfrα$^+$ cells[77]. This observation highlights the notion that injury-induced signals in the synovial joint can drive different repair outcomes depending on local target cell populations, with tendon-sheath SPCs possibly primed to undergo tenocyte differentiation. However, they show multilineage potential in vitro[79], and Tppp3$^+$ cells can contribute to ectopic cartilage formation and subsequent endochondral bone formation induced either by tendon injury or by hip dislocation and acetabular reaming as a model of osteophyte formation after arthroplasty[80]. It is unclear whether the Tppp3$^+$ SPCs that form ectopic cartilage are distinct from the Tppp3$^+$ SPCs that undergo tenocyte differentiation to repair the tendon or whether these are the same cells with dual potency.

Relationship between stem and progenitor cells and fibroblasts

The relationship between SPCs and fibroblasts has long been undefined. Cells with the ability to form fibroblastoid colonies and multilineage differentiation in vitro have been derived from most connective tissues. The protocols to obtain mesenchymal stromal cells (MSCs) in vitro, based on attachment to tissue-culture plastic, are identical to those used to obtain fibroblasts and no markers discriminate between cultured MSCs and fibroblasts. Whether SPCs are distinct from fibroblasts in their native tissues remains a matter of debate. Single-cell technologies have greatly advanced our understanding of the fibroblasts and are defining spatiotemporal hierarchies in physiology and pathology. Large-scale integration of single-cell RNA-sequencing data from fibroblasts derived from multiple tissues and disease states identified a common population of fibroblasts thought to reside near blood vessels, marked by expression of *Pi16 and Dpp4*, that was postulated to represent a reservoir of non-specialized, universal fibroblasts that can develop into specialized, tissue-specific fibroblasts[84]. An equivalent fibroblast subpopulation was shown to be present in mouse knee joints within both the *Gdf5*-lineage population and other fibroblasts and was bioinformatically predicted to give rise to differentiated cell types[39,85]. Lineage tracing of *Dpp4*-expressing cells, which include cells in synovium lining the infrapatellat fat pad, demonstrated that cells expressing *Dpp4* possess SPC properties with the ability to give rise to both fibroblast-like synoviocytes (FLSs, a specialized subset of synovial fibroblasts residing in synovial lining) and adipocytes in the fat during growth and OA progression[86]. The equivalent cells were also identified in humans[87]. It is possible, however, that in response to challenging scenarios such as an acute injury, the proliferation and adoption of a multipotent state represents an opportunistic functional state of plastic fibroblasts, a concept that is supported by the apparent de novo emergence of fibroblasts co-expressing *Sox9*, *Runx2* and *Scx* in a model of joint-surface injury[39]. Indeed, it is becoming increasingly apparent that the traditional stem-cell hierarchical model inspired by the haematopoietic system might not universally apply, and that in other adult tissues and organs, potentially any cell type can adopt stem-cell functions to repair damage[88].

Single-cell transcriptomic analysis has also uncovered heterogeneity in the *Prg4*-expressing synovial lining fibroblasts, with a distinct population of *Prg4*-expressing SPCs that are located adjacent to the mature FLSs (Fig. 2) and proliferate to supply new FLSs in response to injury[39]. The existence of synovial lining SPCs could help to explain why the FLSs remain largely of *Gdf5*-lineage ontogeny in adult life, whereas the sub-lining is of mixed ontogeny, although there is compensatory recruitment from both *Gdf5*-lineage and non-*Gdf5*-lineage sub-lining cells into the *Prg4*-expressing synovial-lining population after injury[39]. The discovery of synovial-lining SPCs also sheds new light on the identification of *Prg4*-expressing cells as chondroprogenitors in models of articular cartilage repair[34,48] and osteophyte formation[49] discussed above, suggesting that this chondrogenic activity results from the bipotency of *Prg4*-expressing SPCs in the synovial lining towards FLSs and chondrocytes, rather than the differentiation of FLSs into chondrocytes, although direct evidence is awaited. In this respect, trajectory and gene-regulatory network analysis based on single-cell transcriptomic data obtained from models of acute joint-surface injury, and of anterior-cruciate-ligament rupture leading to post-traumatic OA, identified *Sox5* and *Foxo1* as candidate transcription factors regulating FLS differentiation[39,85]. These transcription factors also have key roles in articular chondrocytes[89–92], with *Foxo1* upregulation due to lipid scarcity in an avascular environment driving *Sox9*-mediated chondrogenesis and cellular metabolic adaptation[93]. Thus, there seem to be commonalities in the molecular mechanisms governing the differentiation and maintenance of FLSs and chondrocytes, suggesting an intricate balance in the regulation of SPC fate that remains to be elucidated.

Finally, the relationship between tendon and enthesis SPCs and synovial fibroblasts remains to be clarified. Tendon and enthesis SPCs identified via single-cell RNA-sequencing analyses[74,77,78] show overlap in their marker gene expression profile with synovial fibroblasts[39,85]. Notably, *Prg4*, *Itga6* and *Tspan15* were reported to be expressed by a cell cluster identified as undifferentiated tendon and ligament SPCs[78], but these markers are now widely recognized as identifiers of mature FLSs[39,94]. Such findings might be explained by the small number of cells typically obtained from mouse joint tissues, which provides limited ability to discriminate the rare *Prg4*-expressing SPCs from the *Prg4*-expressing FLSs[39]. The integration of single-cell datasets together with spatial expression data will help to increase resolution to reveal the full scale of cellular heterogeneity, while at the same time unifying cell populations, lineages and molecular pathways across time and space.

Towards pro-regenerative therapies

Since adult cartilage was regarded as having poor repair capacity, therapeutic development over the past decades focused primarily on targeting inflammatory and catabolic pathways to halt tissue damage and deterioration. However, so far, none of the randomized controlled clinical trials targeting pro-inflammatory cytokines or proteases in OA has met its primary endpoints[95]. Studies in the past decade are providing support to a different approach to disease modification in OA that is based on targeting cartilage anabolism and regeneration. Some anabolic or pro-regenerative drugs are already in advanced stages of clinical testing for OA. These drugs include sprifermin (recombinant FGF18), which promotes cartilage anabolism through the activation of FGF receptor 3 (refs. 96–99), lorecivivint (SM04690), a small molecule inhibitor of Wnt signalling downstream of β-catenin[100–102], and LNA043, a deletion mutant of angiopoietin-like 3 encompassing the C-terminal fibrinogen-like domain to remove its pro-angiogenic effect while preserving chondrogenic activity[103]. Meanwhile, advances in our understanding of the developmental and regenerative biology of the synovial-joint tissues are inspiring preclinical studies aimed at promoting endogenous repair via targeting SPCs and related signalling pathways.

The canonical Wnt signalling, mediated by β-catenin, is known to have key roles in cartilage formation, maintenance and repair, and excessive activation of Wnt signalling results in cartilage breakdown and development and progression of OA (reviewed elsewhere[11]). The signalling proteoglycan Agrin, which was shown to have pro-regenerative and chondrogenic effects dependent on the activation of CREB signalling and simultaneous suppression of canonical Wnt signalling, when delivered in a collagen gel into an osteochondral defect in mice, enhanced regeneration through the recruitment of endogenous *Gdf5*-lineage SPCs[104]. The results of this study indicate the importance of timely targeting of the morphogenetic pathways that orchestrate regeneration. In a 2023 study in rodents, researchers used the temporomandibular joint, in which the adult condylar cartilage is covered by a perichondrium-like fibrous tissue, as a model to identify *Lgr5*-expressing secretory cells in the outer zone of the perichondrium as crucial for inhibiting the canonical Wnt signalling pathway in the underlying chondroprogenitors and chondrocytes, thereby acting as a Wnt-inhibitory niche for cartilage[105]. Diphtheria-toxin-mediated ablation of the *Lgr5*-expressing cells during joint development resulted in depletion of chondroprogenitors and marked chondrocyte phenotypic instability with expression of osteoblast markers, presumably secondary to high canonical Wnt signalling activity[105]. Lgr5$^+$ cells decreased in ageing and OA, with a concomitant increase in canonical Wnt signalling activity in cartilage[105]. These findings inspired the development of an injectable hydrogel therapy combining hyaluronic acid and the Wnt inhibitor sclerostin, which, delivered intra-articularly to post-traumatic osteoarthritic jaw and knee joints in rabbit, rat, and minipig models, ameliorated OA by suppressing Wnt activity and restoring chondrocyte phenotypic identity[105].

It is likely that the type and quality of the endogenous repair tissue ultimately result from combinations of context-dependent environmental cues, reflecting the site and extent of damage, the anatomical proximity of the SPCs that might be opportunistically recruited to the site of injury, and their cell-intrinsic differentiation potency. In the case of joint-surface defects, the repairing cells can originate from the articular cartilage itself, the synovium and/or the subchondral bone marrow, depending on the size and depth of the defect, for example, whether the defect is a partial-thickness or full-thickness chondral defect confined to the articular cartilage or an osteochondral defect extending through the underlying subchondral bone to its marrow content. From a clinical perspective, opportunity lies in activating and influencing endogenous reparative processes towards the best possible structural outcome. For example, microfracture typically results in a fibrocartilaginous repair tissue, which is generally accepted to be biomechanically inferior to hyaline cartilage and not durable[106]. The outcome of cartilage repair could be improved by locally delivering factors that enhance the quality of the repair tissue, as demonstrated in a proof-of-concept study in which co-delivery of BMP2 and soluble VEGFR1, a VEGF receptor antagonist, in a hydrogel into an osteochondral defect in mice skewed differentiation from fibrous to cartilage tissue[31].

Most studies are typically performed in young adult mice, and often do not address the quality and durability of the repair tissue; hence, it is unclear to what extent these models study true tissue regeneration. Complete regeneration of joint tissues to their complex and non-uniform structures will depend on appropriate spatiotemporal activation and control of morphogenetic mechanisms, a consideration that emphasizes the importance of developmental biology studies to understand joint morphogenesis. Altogether, these studies are generating essential knowledge that is informing the development of novel pro-regenerative drugs. Translation to clinical use will require suitable models that address the shortcomings of mouse models.

Conclusions

In summary, regenerative medicine and tissue engineering have entered orthopaedic clinical practice. The development of injectable pro-regenerative drugs and biologics will introduce regenerative medicine to the armamentarium of the rheumatologist, not only for the treatment of joints damaged by trauma and OA but also for the holistic management of inflammatory arthritis that causes damage to the articular cartilage and other joint structures. The mounting knowledge of the mechanisms of joint homeostasis, remodelling, scarless repair or regeneration, and disease progression is helping to inform the development of pharmacological interventions. These advances, together with patient phenotyping and stratification, will enable the delivery of the right treatment to the right patient at the right time.

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References

1. Hjelle, K., Solheim, E., Strand, T., Muri, R. & Brittberg, M. Articular cartilage defects in 1,000 knee arthroscopies. *Arthroscopy* **18**, 730–734 (2002).
2. Widuchowski, W., Widuchowski, J. & Trzaska, T. Articular cartilage defects: study of 25,124 knee arthroscopies. *Knee* **14**, 177–182 (2007).
3. Hunter, D. J. & Bierma-Zeinstra, S. Osteoarthritis. *Lancet* **393**, 1745–1759 (2019).
4. Weng, Q. et al. Global burden of early-onset osteoarthritis, 1990–2019: results from the Global Burden of Disease Study 2019. *Ann. Rheum. Dis.* **83**, 915–925 (2024).
5. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **388**, 1545–1602 (2016).
6. De Bari, C. & Roelofs, A. J. Stem cell-based therapeutic strategies for cartilage defects and osteoarthritis. *Curr. Opin. Pharmacol.* **40**, 74–80 (2018).
7. Dell'accio, F. & Vincent, T. L. Joint surface defects: clinical course and cellular response in spontaneous and experimental lesions. *Eur. Cell Mater.* **20**, 210–217 (2010).
8. Jansen, M. P. & Mastbergen, S. C. Joint distraction for osteoarthritis: clinical evidence and molecular mechanisms. *Nat. Rev. Rheumatol.* **18**, 35–46 (2022).
9. Eltawil, N. M., De Bari, C., Achan, P., Pitzalis, C. & Dell'accio, F. A novel in vivo murine model of cartilage regeneration. Age and strain-dependent outcome after joint surface injury. *Osteoarthritis Cartilage* **17**, 695–704 (2009).
10. Rai, M. F. et al. Heritability of articular cartilage regeneration and its association with ear wound healing in mice. *Arthritis Rheum.* **64**, 2300–2310 (2012).
11. Thorup, A.-S., Dell'Accio, F. & Eldridge, S. E. Lessons from joint development for cartilage repair in the clinic. *Dev. Dyn.* **250**, 360–376 (2021).

12. Pineault, K. M. & Wellik, D. M. Hox genes and limb musculoskeletal development. *Curr. Osteoporos. Rep.* **12**, 420–427 (2014).
13. Pineault, K. M., Song, J. Y., Kozloff, K. M., Lucas, D. & Wellik, D. M. Hox11 expressing regional skeletal stem cells are progenitors for osteoblasts, chondrocytes and adipocytes throughout life. *Nat. Commun.* **10**, 3168 (2019).
14. Rux, D. R. et al. Regionally restricted *Hox* function in adult bone marrow multipotent mesenchymal stem/stromal cells. *Dev. Cell* **39**, 653–666 (2016).
15. Gronthos, S., Graves, S. E., Ohta, S. & Simmons, P. J. The STRO-1$^+$ fraction of adult human bone marrow contains the osteogenic precursors. *Blood* **84**, 4164–4173 (1994).
16. Jones, E. A. et al. Optimization of a flow cytometry-based protocol for detection and phenotypic characterization of multipotent mesenchymal stromal cells from human bone marrow. *Cytometry B Clin. Cytom.* **70**, 391–399 (2006).
17. Sacchetti, B. et al. Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment. *Cell* **131**, 324–336 (2007).
18. Pinho, S. et al. PDGFRα and CD51 mark human Nestin$^+$ sphere-forming mesenchymal stem cells capable of hematopoietic progenitor cell expansion. *J. Exp. Med.* **210**, 1351–1367 (2013).
19. Chan, C. K. F. et al. Identification of the human skeletal stem cell. *Cell* **175**, 43–56.e21 (2018).
20. Morikawa, S. et al. Prospective identification, isolation, and systemic transplantation of multipotent mesenchymal stem cells in murine bone marrow. *J. Exp. Med.* **206**, 2483–2496 (2009).
21. Méndez-Ferrer, S. et al. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. *Nature* **466**, 829–834 (2010).
22. Isern, J. et al. The neural crest is a source of mesenchymal stem cells with specialized hematopoietic stem cell niche function. *Elife* **3**, e03696 (2014).
23. Ding, L., Saunders, T. L., Enikolopov, G. & Morrison, S. J. Endothelial and perivascular cells maintain haematopoietic stem cells. *Nature* **481**, 457–462 (2012).
24. Zhou, B. O., Yue, R., Murphy, M. M., Peyer, J. G. & Morrison, S. J. Leptin-receptor-expressing mesenchymal stromal cells represent the main source of bone formed by adult bone marrow. *Cell Stem Cell* **15**, 154–168 (2014).
25. Worthley, D. L. et al. Gremlin 1 identifies a skeletal stem cell with bone, cartilage, and reticular stromal potential. *Cell* **160**, 269–284 (2015).
26. Kfoury, Y. & Scadden, D. T. Mesenchymal cell contributions to the stem cell niche. *Cell Stem Cell* **16**, 239–253 (2015).
27. Chan, C. K. F. et al. Identification and specification of the mouse skeletal stem cell. *Cell* **160**, 285–298 (2015).
28. Ambrosi, T. H. et al. Distinct skeletal stem cell types orchestrate long bone skeletogenesis. *Elife* **10**, e66063 (2021).
29. Shu, H. S. et al. Tracing the skeletal progenitor transition during postnatal bone formation. *Cell Stem Cell* **28**, 2122–2136.e3 (2021).
30. Matsushita, Y. et al. Bone marrow endosteal stem cells dictate active osteogenesis and aggressive tumorigenesis. *Nat. Commun.* **14**, 2383 (2023).
31. Murphy, M. P. et al. Articular cartilage regeneration by activated skeletal stem cells. *Nat. Med.* **26**, 1583–1592 (2020).
32. Ambrosi, T. H. et al. Aged skeletal stem cells generate an inflammatory degenerative niche. *Nature* **597**, 256–262 (2021).
33. Mizoguchi, T. et al. Osterix marks distinct waves of primitive and definitive stromal progenitors during bone marrow development. *Dev. Cell* **29**, 340–349 (2014).
34. Massengale, M. et al. Adult Prg4$^+$ progenitors repair long-term articular cartilage wounds in vivo. *JCI Insight* **8**, e167858 (2023).
35. Kurth, T. B. et al. Functional mesenchymal stem cell niches in adult mouse knee joint synovium in vivo. *Arthritis Rheum.* **63**, 1289–1300 (2011).
36. Rountree, R. B. et al. BMP receptor signaling is required for postnatal maintenance of articular cartilage. *PLoS Biol.* **2**, e355 (2004).
37. Koyama, E. et al. A distinct cohort of progenitor cells participates in synovial joint and articular cartilage formation during mouse limb skeletogenesis. *Dev. Biol.* **316**, 62–73 (2008).
38. Roelofs, A. J. et al. Joint morphogenetic cells in the adult mammalian synovium. *Nat. Commun.* **8**, 15040 (2017).
39. Collins, F. L. et al. Taxonomy of fibroblasts and progenitors in the synovial joint at single-cell resolution. *Ann. Rheum. Dis.* **82**, 428–437 (2023).
40. Decker, R. S., Koyama, E. & Pacifici, M. Genesis and morphogenesis of limb synovial joints and articular cartilage. *Matrix Biol.* **39**, 5–10 (2014).
41. Shwartz, Y., Viukov, S., Krief, S. & Zelzer, E. Joint development involves a continuous influx of gdf5-positive cells. *Cell Rep.* **15**, 2577–2587 (2016).
42. Chen, H. et al. Heads, shoulders, elbows, knees, and toes: modular *Gdf5* enhancers control different joints in the vertebrate skeleton. *PLoS Genet.* **12**, e1006454 (2016).
43. Pregizer, S. K. et al. Impact of broad regulatory regions on Gdf5 expression and function in knee development and susceptibility to osteoarthritis. *Ann. Rheum. Dis.* **77**, 450 (2018).
44. Kania, K. et al. Regulation of *Gdf5* expression in joint remodelling, repair and osteoarthritis. *Sci. Rep.* **10**, 157 (2020).
45. Dowthwaite, G. P. et al. The surface of articular cartilage contains a progenitor cell population. *J. Cell Sci.* **117**, 889–897 (2004).
46. Kozhemyakina, E. et al. Identification of a *Prg4*-expressing articular cartilage progenitor cell population in mice. *Arthritis Rheumatol.* **67**, 1261–1273 (2015).
47. Li, L. et al. Superficial cells are self-renewing chondrocyte progenitors, which form the articular cartilage in juvenile mice. *FASEB J.* **31**, 1067–1084 (2017).
48. Decker, R. S. et al. Cell origin, volume and arrangement are drivers of articular cartilage formation, morphogenesis and response to injury in mouse limbs. *Dev. Biol.* **426**, 56–68 (2017).
49. Roelofs, A. J. et al. Identification of the skeletal progenitor cells forming osteophytes in osteoarthritis. *Ann. Rheum. Dis.* **79**, 1625–1634 (2020).
50. Debnath, S. et al. Discovery of a periosteal stem cell mediating intramembranous bone formation. *Nature* **562**, 133–139 (2018).
51. Bechtold, T. E. et al. Osteophyte formation and matrix mineralization in a TMJ osteoarthritis mouse model are associated with ectopic hedgehog signaling. *Matrix Biol.* **52–54**, 339–354 (2016).
52. Maes, C. et al. Osteoblast precursors, but not mature osteoblasts, move into developing and fractured bones along with invading blood vessels. *Dev. Cell* **19**, 329–344 (2010).
53. Xie, M. & Chagin, A. S. The epiphyseal secondary ossification center: evolution, development and function. *Bone* **142**, 115701 (2021).
54. Tong, W. et al. Periarticular mesenchymal progenitors initiate and contribute to secondary ossification center formation during mouse long bone development. *Stem Cell* **37**, 677–689 (2019).
55. Schett, G. et al. Enthesitis: from pathophysiology to treatment. *Nat. Rev. Rheumatol.* **13**, 731–741 (2017).
56. Blitz, E., Sharir, A., Akiyama, H. & Zelzer, E. Tendon-bone attachment unit is formed modularly by a distinct pool of Scx- and Sox9-positive progenitors. *Development* **140**, 2680–2690 (2013).
57. Sugimoto, Y. et al. *Scx*$^+$/*Sox9*$^+$ progenitors contribute to the establishment of the junction between cartilage and tendon/ligament. *Development* **140**, 2280–2288 (2013).
58. Eyal, S. et al. On the development of the patella. *Development* **142**, 1831–1839 (2015).
59. Eyal, S. et al. Bone morphology is regulated modularly by global and regional genetic programs. *Development* **146**, dev167882 (2019).
60. Eyal, S., Rubin, S., Krief, S., Levin, L. & Zelzer, E. Common cellular origin and diverging developmental programs for different sesamoid bones. *Development* **146**, dev167452 (2019).
61. Blitz, E. et al. Bone ridge patterning during musculoskeletal assembly is mediated through SCX regulation of Bmp4 at the tendon-skeleton junction. *Dev. Cell* **17**, 861–873 (2009).
62. Roberts, R. R. et al. FGF signaling patterns cell fate at the interface between tendon and bone. *Development* **146**, dev170241 (2019).
63. Ono, N. & Kronenberg, H. M. Mesenchymal progenitor cells for the osteogenic lineage. *Curr. Mol. Biol. Rep.* **1**, 95–100 (2015).
64. Arostegui, M., Scott, R. W., Böse, K. & Underhill, T. M. Cellular taxonomy of Hic1$^+$ mesenchymal progenitor derivatives in the limb: from embryo to adult. *Nat. Commun.* **13**, 4989 (2022).
65. Arostegui, M., Scott, R. W. & Underhill, T. M. Hic1 identifies a specialized mesenchymal progenitor population in the embryonic limb responsible for bone superstructure formation. *Cell Rep.* **42**, 112325 (2023).
66. Dyment, N. A. et al. Lineage tracing of resident tendon progenitor cells during growth and natural healing. *PLoS ONE* **9**, e96113 (2014).
67. Dyment, N. A. et al. Gdf5 progenitors give rise to fibrocartilage cells that mineralize via hedgehog signaling to form the zonal enthesis. *Dev. Biol.* **405**, 96–107 (2015).
68. Schwartz, A. G., Long, F. & Thomopoulos, S. Enthesis fibrocartilage cells originate from a population of Hedgehog-responsive cells modulated by the loading environment. *Development* **142**, 196–206 (2015).
69. Zhang, T. et al. Single-cell RNA sequencing reveals cellular and molecular heterogeneity in fibrocartilaginous enthesis formation. *Elife* **12**, e85873 (2023).
70. Liu, C.-F., Breidenbach, A., Aschbacher-Smith, L., Butler, D. & Wylie, C. A role for hedgehog signaling in the differentiation of the insertion site of the patellar tendon in the mouse. *PLoS ONE* **8**, e65411 (2013).
71. Felsenthal, N. et al. Development of migrating tendon-bone attachments involves replacement of progenitor populations. *Development* **145**, dev165381 (2018).
72. Fang, F., Schwartz, A. G., Moore, E. R., Sup, M. E. & Thomopoulos, S. Primary cilia as the nexus of biophysical and hedgehog signaling at the tendon enthesis. *Sci. Adv.* **6**, eabc1799 (2020).
73. Schwartz, A. G., Galatz, L. M. & Thomopoulos, S. Enthesis regeneration: a role for Gli1+ progenitor cells. *Development* **144**, 1159–1164 (2017).
74. Fang, F., Xiao, Y., Zelzer, E., Leong, K. W. & Thomopoulos, S. A mineralizing pool of Gli1-expressing progenitors builds the tendon enthesis and demonstrates therapeutic potential. *Cell Stem Cell* **29**, 1669–1684.e6 (2022).
75. Xiao, H. et al. Mechanical stimulation promotes enthesis injury repair by mobilizing *Prrx1*$^+$ cells via ciliary TGF-β signaling. *Elife* **11**, e73614 (2022).
76. Bi, Y. et al. Identification of tendon stem/progenitor cells and the role of the extracellular matrix in their niche. *Nat. Med.* **13**, 1219–1227 (2007).
77. Harvey, T., Flamenco, S. & Fan, C.-M. A *Tppp3*$^+$*Pdgfra*$^+$ tendon stem cell population contributes to regeneration and reveals a shared role for PDGF signalling in regeneration and fibrosis. *Nat. Cell Biol.* **21**, 1490–1503 (2019).
78. Tachibana, N. et al. RSPO2 defines a distinct undifferentiated progenitor in the tendon/ligament and suppresses ectopic ossification. *Sci. Adv.* **8**, eabn2138 (2022).
79. Wang, Y. et al. Osteocalcin expressing cells from tendon sheaths in mice contribute to tendon repair by activating Hedgehog signaling. *Elife* **6**, e30474 (2017).
80. Yea, J.-H. et al. *Tppp3*$^+$ synovial/tendon sheath progenitor cells contribute to heterotopic bone after trauma. *Bone Res.* **11**, 39 (2023).
81. Dyment, N. A. et al. The paratenon contributes to scleraxis-expressing cells during patellar tendon healing. *PLoS ONE* **8**, e59944 (2013).
82. Sakabe, T. et al. Transcription factor scleraxis vitally contributes to progenitor lineage direction in wound healing of adult tendon in mice. *J. Biol. Chem.* **293**, 5766–5780 (2018).

83. Liu, W. et al. The atypical homeodomain transcription factor Mohawk controls tendon morphogenesis. *Mol. Cell Biol.* **30**, 4797–4807 (2010).
84. Buechler, M. B. et al. Cross-tissue organization of the fibroblast lineage. *Nature* **593**, 575–579 (2021).
85. Knights, A. J. et al. Synovial fibroblasts assume distinct functional identities and secrete R-spondin 2 in osteoarthritis. *Ann. Rheum. Dis.* **82**, 272–282 (2023).
86. Li, J. et al. Synovium and infrapatellar fat pad share common mesenchymal progenitors and undergo coordinated changes in osteoarthritis. *J. Bone Miner. Res.* **39**, 161–176 (2024).
87. Tang, S. et al. Single-cell atlas of human infrapatellar fat pad and synovium implicates APOE signaling in osteoarthritis pathology. *Sci. Transl. Med.* **16**, eadf4590 (2024).
88. Clevers, H. & Watt, F. M. Defining adult stem cells by function, not by phenotype. *Annu. Rev. Biochem.* **87**, 1015–1027 (2018).
89. Ng, J. Q. et al. Loss of Grem1-lineage chondrogenic progenitor cells causes osteoarthritis. *Nat. Commun.* **14**, 6909 (2023).
90. Matsuzaki, T. et al. FoxO transcription factors modulate autophagy and proteoglycan 4 in cartilage homeostasis and osteoarthritis. *Sci. Transl. Med.* **10**, eaan0746 (2018).
91. Wang, C., Shen, J., Ying, J., Xiao, D. & O'Keefe, R. J. FoxO1 is a crucial mediator of TGF-β/TAK1 signaling and protects against osteoarthritis by maintaining articular cartilage homeostasis. *Proc. Natl Acad. Sci. USA* **117**, 30488–30497 (2020).
92. Lefebvre, V. Roles and regulation of SOX transcription factors in skeletogenesis. *Curr. Top. Dev. Biol.* **133**, 171–193 (2019).
93. van Gastel, N. et al. Lipid availability determines fate of skeletal progenitor cells via SOX9. *Nature* **579**, 111–117 (2020).
94. Croft, A. P. et al. Distinct fibroblast subsets drive inflammation and damage in arthritis. *Nature* **570**, 246–251 (2019).
95. Vincent, T. L. Of mice and men: converging on a common molecular understanding of osteoarthritis. *Lancet Rheumatol.* **2**, e633–e645 (2020).
96. Lohmander, L. S. et al. Intraarticular sprifermin (recombinant human fibroblast growth factor 18) in knee osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol.* **66**, 1820–1831 (2014).
97. Hochberg, M. C. et al. Effect of intra-articular sprifermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: the FORWARD randomized clinical trial. *JAMA* **322**, 1360–1370 (2019).
98. Guehring, H. et al. The effects of sprifermin on symptoms and structure in a subgroup at risk of progression in the FORWARD knee osteoarthritis trial. *Semin. Arthritis Rheum.* **51**, 450–456 (2021).
99. Eckstein, F. et al. Long-term structural and symptomatic effects of intra-articular sprifermin in patients with knee osteoarthritis: 5-year results from the FORWARD study. *Ann. Rheum. Dis.* **80**, 1062–1069 (2021).
100. Deshmukh, V. et al. A small-molecule inhibitor of the Wnt pathway (SM04690) as a potential disease modifying agent for the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage* **26**, 18–27 (2018).
101. Yazici, Y. et al. A novel Wnt pathway inhibitor, SM04690, for the treatment of moderate to severe osteoarthritis of the knee: results of a 24-week, randomized, controlled, phase 1 study. *Osteoarthritis Cartilage* **25**, 1598–1606 (2017).
102. Yazici, Y. et al. Lorecivivint, a novel intraarticular CDC-like kinase 2 and dual-specificity tyrosine phosphorylation-regulated kinase 1a inhibitor and Wnt pathway modulator for the treatment of knee osteoarthritis: a phase II randomized trial. *Arthritis Rheumatol.* **72**, 1694–1706 (2020).
103. Gerwin, N. et al. Angiopoietin-like 3-derivative LNA043 for cartilage regeneration in osteoarthritis: a randomized phase 1 trial. *Nat. Med.* **28**, 2633–2645 (2022).
104. Eldridge, S. E. et al. Agrin induces long-term osteochondral regeneration by supporting repair morphogenesis. *Sci. Transl. Med.* **12**, eaax9086 (2020).
105. Ruscitto, A. et al. Lgr5-expressing secretory cells form a Wnt inhibitory niche in cartilage critical for chondrocyte identity. *Cell Stem Cell* **30**, 1179–1198.e7 (2023).
106. Zelinka, A., Roelofs, A. J., Kandel, R. A. & De Bari, C. Cellular therapy and tissue engineering for cartilage repair. *Osteoarthritis Cartilage* **30**, 1547–1560 (2022).
107. Kunisaki, Y. et al. Arteriolar niches maintain haematopoietic stem cell quiescence. *Nature* **502**, 637–643 (2013).
108. Arranz, L. et al. Neuropathy of haematopoietic stem cell niche is essential for myeloproliferative neoplasms. *Nature* **512**, 78–81 (2014).
109. Shen, B. et al. A mechanosensitive peri-arteriolar niche for osteogenesis and lymphopoiesis. *Nature* **591**, 438–444 (2021).
110. Mizuhashi, K. et al. Resting zone of the growth plate houses a unique class of skeletal stem cells. *Nature* **563**, 254–258 (2018).
111. Muruganandan, S. et al. A FoxA2+ long-term stem cell population is necessary for growth plate cartilage regeneration after injury. *Nat. Commun.* **13**, 2515 (2022).
112. Brittberg, M. et al. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N. Engl. J. Med.* **331**, 889–895 (1994).
113. Ogura, T., Mosier, B. A., Bryant, T. & Minas, T. A 20-year follow-up after first-generation autologous chondrocyte implantation. *Am. J. Sports Med.* **45**, 2751–2761 (2017).
114. Steadman, J. R., Rodkey, W. G. & Rodrigo, J. J. Microfracture: surgical technique and rehabilitation to treat chondral defects. *Clin. Orthop. Relat. Res.* S362–S369 (2001).
115. Saris, D. B. F. et al. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. *Am. J. Sports Med.* **36**, 235–246 (2008).
116. Saris, D. B. F. et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. *Am. J. Sports Med.* **37**, 10S–19S (2009).
117. Vanlauwe, J. et al. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. *Am. J. Sports Med.* **39**, 2566–2574 (2011).
118. Knutsen, G. et al. A randomized multicenter trial comparing autologous chondrocyte implantation with microfracture: long-term follow-up at 14 to 15 years. *J. Bone Jt. Surg. Am.* **98**, 1332–1339 (2016).
119. Hoburg, A. et al. Sustained superiority in KOOS subscores after matrix-associated chondrocyte implantation using spheroids compared to microfracture. *Knee Surg. Sports Traumatol. Arthrosc.* **31**, 2482–2493 (2023).
120. Barry, F. & Murphy, M. Mesenchymal stem cells in joint disease and repair. *Nat. Rev. Rheumatol.* **9**, 584–594 (2013).
121. Zhang, Y., Yang, H., He, F. & Zhu, X. Intra-articular injection choice for osteoarthritis: making sense of cell source-an updated systematic review and dual network meta-analysis. *Arthritis Res. Ther.* **24**, 260 (2022).
122. Mautner, K. et al. Cell-based versus corticosteroid injections for knee pain in osteoarthritis: a randomized phase 3 trial. *Nat. Med.* **29**, 3120–3126 (2023).

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Review article

Check for updates

The role of the immune system in osteoarthritis: mechanisms, challenges and future directions

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Abstract

Osteoarthritis (OA) is a chronic joint disease that has long been considered a simple wear-and-tear condition. Over the past decade, research has revealed that various inflammatory features of OA, such as low-grade peripheral inflammation and synovitis, contribute substantially to the pathophysiology of the disease. Technological advances in the past 5 years have revealed a large diversity of innate and adaptive immune cells in the joints, particularly in the synovium and infrapatellar fat pad. Notably, the presence of synovial lymphoid structures, circulating autoantibodies and alterations in memory T cell and B cell populations have been documented in OA. These data indicate a potential contribution of self-reactivity to the disease pathogenesis, blurring the often narrow and inaccurate line between chronic inflammatory and autoimmune diseases. The diverse immune changes associated with OA pathogenesis can vary across disease phenotypes, and a better characterization of their underlying molecular endotypes will be key to stratifying patients, designing novel therapeutic approaches and ultimately ameliorating treatment allocation. Furthermore, examining both articular and systemic alterations, including changes in the gut–joint axis and microbial dysbiosis, could open up novel avenues for OA management.

Sections

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Key points

- Technological advances, such as single-cell RNA sequencing, have revealed an unexpected diversity of immune cells within joint tissues in osteoarthritis (OA), particularly in the synovium and infrapatellar fat pad.
- At advanced stages of OA, aggregates that comprise B cells and T cells surrounded by plasma cells are observed in synovial tissues.
- The presence of circulating autoantibodies and alterations in memory T cell and B cell populations that are reported in OA indicate a potential contribution of self-reactivity to disease pathogenesis.
- Immune changes in OA contribute to both articular and systemic low-grade inflammation, the underlying mechanisms of which might vary depending on the OA phenotype, representing potential clinically relevant therapeutic targets.
- The gut microbiota and associated immune responses have a role in OA pathophysiology, and potentially represent novel therapeutic targets.

Introduction

Osteoarthritis (OA) is the most common rheumatic disease, causing pain, stiffness and loss of joint function. The prevalence of this disease is steadily rising[1] and, although OA represents a major socio-economic burden, only temporary symptomatic treatments are available to relieve pain and swelling. Ultimately, total joint replacement, an expensive and sometimes unsatisfactory procedure[2,3], is often inevitable in the late stages of the disease. As a result, OA has been included in the WHO list of top priority diseases and, as of 2018, is considered a serious condition by the FDA[4].

OA is a whole-joint disease that encompasses cartilage and bone damage, synovial tissue inflammation (synovitis) and infrapatellar fat pad (IFP, also known as Hoffa's fat pad) inflammation and fibrosis, as well as systemic changes such as low-grade inflammation and gut microbiota alterations[5]. In the past 10 years, data have revealed a large diversity of immune cell types present in different organs including connective tissues, such as synovial tissue, thanks to technological advancements in bulk, single-cell and spatial transcriptomics[6–8]. The understanding of the complexity of synovial tissue composition has now greatly advanced, particularly through studies of rheumatoid arthritis (RA), a prototypical synovitis-driven disease. Longitudinal in-depth characterization of RA synovial tissue, which has been facilitated by the development of minimally invasive and safe ultrasound-guided biopsies[9] and the optimization of cryopreservation and dissociation procedures[6], has revealed that the array of cell populations and subsets within the synovium, including fibroblasts, macrophages, T cells and B cells, are more detailed and diverse than previously known[10–16]. Similarly, the development of high-throughput approaches has enabled an unprecedented description of the cellular changes associated with OA progression. Notably, these approaches have assisted in the identification of multiple immune cell types in the joint, including neutrophils, monocytes, macrophages, B cells, T cells, natural killer (NK) cells and dendritic cells. Of these cells, monocyte and macrophage populations are the most abundant synovial immune cells[17] and two studies, one of which is a preprint[18], highlighted that these cells exhibit the most considerable changes across disease stages in mouse models[19]. Alongside this molecular characterization, the understanding of OA has also evolved towards a more holistic medical approach. OA is now recognized as a multifaceted joint disease involving systemic modifications and a wide range of comorbidities (including cardiovascular disease, type 2 diabetes mellitus, obesity and metabolic syndrome) that influence the overall health, quality of life and the therapeutic management of patients[20]. In addition, low-grade systemic inflammation might have a key role in the progression of OA and pain, particularly in the context of obesity and metabolic syndrome. Adipose tissue can release pro-inflammatory cytokines and other soluble mediators that could contribute to both systemic inflammation and joint damage[21].

Here, we provide a narrative Review that contextualizes the literature from the past 20 years on the involvement of innate and adaptive immune cells in the pathophysiology of OA, both from a local and a systemic perspective. Special attention is given to the relationship between the dysregulated immune response in the joint, and its effect on low-grade inflammation and gut microbiota dysbiosis. Finally, we summarize the current development of immunomodulatory and biologic drugs aimed at addressing the challenge of personalized and targeted treatment approaches for patients with OA. We also address whether cell-based therapies, initially contemplated for their regenerative and structural effects, could be considered clinically relevant because of their immunomodulatory properties.

Insights into innate immune cell diversity in osteoarthritis

For decades, synovial tissue has been described as a connective tissue composed mainly of type A (macrophage-like) synoviocytes, which are responsible for maintaining joint integrity and defence against infection, and type B (fibroblast-like) synoviocytes, described as the sole producers of synovial fluid. In this binary and oversimplified picture, only a few immune cells were described as immune sentinels. The understanding of the complex composition of OA synovial tissue has greatly evolved and highlights a notable involvement of innate immune cells in the pathophysiology of the disease. Indeed, innate receptors, inflammasome pathways, proteins of the complement cascade[22] and cytokines and chemokines released by activated innate immune cells have been shown to mediate joint damage and pain in OA[23,24].

Initial joint damage can have diverse origins related to the various aetiologies of OA (such as ageing, metabolic disease and traumatic injuries), notably involving cartilage degradation owing to the loss of proteoglycans and collagen, chondrocyte stress or death, and subchondral bone remodelling (such as sclerosis and bone marrow lesions). Damage to cartilage extracellular matrix triggers the innate immune system by releasing damage-associated molecular patterns, which, in turn, activate pattern recognition receptors (such as Toll-like receptors (TLRs)) on immune cells. Triggering the innate immune system leads to the production of pro-inflammatory cytokines and matrix-degrading enzymes. Notably, the pathological cleavage of several matrix components (such as collagen and aggrecan) and pro-inflammatory molecules (such as C-reactive protein) leads to the development of neoepitopes that might enhance the inflammatory processes involved in OA; this concept has been reviewed elsewhere[25]. Moreover, damage to the meniscus, ligaments or joint capsule can destabilize the joint and exacerbate wear. Mild synovitis occurs early in disease development[26], with synovial immune cells releasing pro-inflammatory cytokines. Both inflammation and tissue damage create a vicious circle that further enhances damage and the release of self-antigens, which are presented by antigen-presenting cells to T cells, thereby engaging the adaptive immune system. Table 1 summarizes the phenotypic markers described to characterize each innate immune cell type and subtype observed in the OA joint.

Table 1 | High-throughput identification of innate immune cell subtypes in OA tissues

Tissue	Cell type			Technical approaches	Ref.
	Name	Subtype	Phenotypic markers		
Human					
Synovium	Macrophages	Immune regulatory macrophages	*CD14, CD163, FCGR3A, CD169, STAB1, TXNIP, SEPP1, FLOR2*	Single-cell RNA sequencing	33
		Inflammatory macrophages	*CD14, CD163, IL1B, IL1A, IL6, TNF, CCL2, CCL3, CCL4*		
	Dendritic cells	N/A	*FCER1A, CD1C*		
	Mast cells	N/A	N/A		
Synovium	Myeloid cells	15 subclusters	Various myeloid and NK cell-associated markers	Single-cell CITE sequencing	10
	NK cells	14 subclusters			
Synovium and IFP	Macrophages	Resident macrophages	*F13A1, SELENOP, LYVE1, MAN1A1, SLC40A1*	Single-cell and single-nuclei RNA sequencing	36
		Inflammatory macrophages	*CCL3, TNF, IL1B, OLR1, CCL3L1*		
	Monocytes	N/A	*FCGR3A, TIMD4, MARCO, FN1*		
	Dendritic cells	N/A	*HLA-DPB1, HLA-DQA1, HLA-DQB1, FCER1A, CD1C*		
	Mast cells	N/A	*TPSB2, TPSAB1, CPA3, MS4A2, CD69*		
	Granulocytes	N/A	*FCN1, S100A9, S100A12, EREG, S100A8*		
	Osteoclast-like cells	N/A	*ACP5, CTSK, SPP1, MMP9, TNFRSF11A*		
Synovium and IFP	Macrophages	Monocytes/macrophages	LY6C, CD14, CX3CR1, VIM	Imaging mass cytometry	37
		Mature myeloid cells	F4/80 (*ADGRE1*)		
		Antigen-presenting cells	MHCII		
		Undefined myeloid cells	$F4/80^{+/-}$, various myeloid-associated markers		
IFP	Macrophages	Subcluster 0	*P2RY14, MAN1A1, FGF13, DSCAML1, PID1*	Single-nuclei RNA sequencing and spatial transcriptomics	38
		Subcluster 1	*FN1, TPRG1, KCNQ3, PDE3A, FMNL2*		
		Subcluster 2	*TTN, STAB1, AHNAK, RBM25, PRRC2C*		
		Subcluster 3	*ADH1B, DLC1, FBN1, NEGR1*		
	Dendritic cells	N/A	*ITGAX, HLA-DRB1, HLA-DRA*		
	Mast cells	N/A	*KIT*		
Mouse					
Joint (cartilage, synovial fluid, synovium and IFP)	Macrophages	$Trem2^{hi}Fcrls^{+}$	*Itgam, Cd14, Cd68, Trem2, Fcrls, Ms4a7, Apoe, Fabp5, Cd63, C1qa, C1qb, C1qc, Mrc1*	Single-cell RNA sequencing	19
		$Crip1^{hi}Cav1^{+}$	*Itgam, Cd14, Cd68, Trem2, Ms4a7, C1qa, C1qb, C1qc, Crip1, S100a4, Vim, Tagln2, Cspg4*		
		$MHCII^{hi}$	*Itgam, Cd14, Cd68, Cd74, H2-Aa, H2-Ab1, H2-Eb1, Il1b*		
		$Lyve1^{hi}Folr2^{hi}$	*Itgam, Cd14, Cd68, Adgre1, Lyve1, Folr2, Timd4, Sparc, Vsig4, Mrc1*		
	Monocytes and Macrophages	Ifn-r	*Itgam, Cd14, Ifit1, Ifit2, Ifit3, Isg15, Cxcl10, Cccl12*		
	Monocytes	$S100a8^{hi}$	*Itgam, Cd14, S100a8, Lcn2, Retnlg, Mmp8, Mmp9, Il1b, Ly6c2, Plac8*		
		$Ly6c2^{hi}$	*Itgam, Cd14, Ly6c2, Plac8, Il1b*		
		$Hspa1b^{hi}$	*Itgam, Cd14, Ly6c2, Plac8, Hspa1b, Ccr2, Tmpo, Rhob*		
	Dendritic cells	moDC	*Itgam, Cd14, Cd74, H2-Aa, H2-Ab1, H2-Eb1, Il1b*		
		N/A	*Cd209a, Lag3*		
	Neutrophils	$Ccrl2^{hi}$	*S100a8, Ccrl2, Il1b, Ptgs2, Cxcl2*		
		$Mmp8^{hi}$	*S100a8, Mmp8, Mmp9, Retnlg, Ly6c2*		
		$Chil3^{hi}$	*S100a8, Chi3l1, Ngp, Lcn2*		
		Ifn-r	*S100a8, Ifit1, Isg15*		
	NK cells	N/A	*Gzma, Nkg7*		

Table 1 (continued) | High-throughput identification of innate immune cell subtypes in OA tissues

Tissue	Cell type			Technical approaches	Ref.
	Name	Subtype	Phenotypic markers		
Mouse (continued)					
Synovium	Macrophages	Basal resident	*Timd4, Lyve1, Folr2*	Single-cell RNA sequencing	18
		Resident-like A	*Mrc1, Ly6e, Gas6*		
		Resident-like B	*Cd9, Spp1, Trem2*		
		Infiltrating	*Ccr2, MHC Class II*		
	Dendritic cells	N/A	*C1qa, Cd209a*		
	Monocytes	N/A	*Ly6c2, Plac8, Chil3*		
	Neutrophils	1 and 2	*Retnlg, Ly6c2*		
		3	*Retnlg, Ly6c2, Cd79a*		
	Mast cells	N/A	*Fcer1a*		

CITE sequencing, cellular indexing of transcriptomes and epitopes by sequencing; IFP, infrapatellar fat pad; N/A, not applicable; NK cells, natural killer cells.

Macrophages in the synovium, infrapatellar fat pad and other tissues

Importantly, synovitis, subsequent joint effusion and particularly the infiltration of macrophages, correlate with osteophyte formation, OA-related pain and severity, loss of joint function and the likelihood of joint replacement[27–30]. Experiments in mouse models of OA have provided a causal mechanistic link between synovial macrophage infiltrates and cartilage destruction and pain[31,32]. This section describes both how human studies have demonstrated the diversity of macrophage populations and how animal experiments further established the fundamental role of these cells in the OA joint.

Descriptive findings from human studies. Through the use of flow cytometry and RNA sequencing, a 2019 study identified two main subgroups of patients on the basis of the presence of distinct macrophage subpopulations, namely classical OA and inflammatory-like OA, but not characterized by specific clinical features[17]. Beyond this preliminary characterization, the presence of 12 clusters of cells in the synovium (including innate immune cells such as pro-inflammatory and regulatory macrophages, dendritic cells and mast cells) have been identified by single-cell RNA sequencing[33]. The diversity of synovial immune cells has further been investigated by integrating single-cell transcriptomics and mass cytometry, focusing primarily on RA but including nine patients with OA as comparators, shedding light on the rich synovial immune cell component in OA[10]. Overall, synovial macrophage phenotypes are altered in OA, and might even show an altered response to palliative treatments, such as glucocorticoids[34].

During the past decade, several studies have suggested that macrophages infiltrating other joint tissues, such as the IFP of the knee, could also influence joint pathology. Indeed, the IFP is in direct contact with the synovium via its sublining layer on the joint capsule side, forming an anatomo-functional unit[35] (Fig. 1), and crosstalk therefore exists between these tissues. Accordingly, the immune-cell diversity revealed by single-cell RNA sequencing in both tissues is very similar[36]. Imaging mass-cytometry analyses have also identified 11 myeloid-cell populations in the synovium and IFP[37]. Importantly, apolipoprotein E, which is predominantly expressed by synovial macrophages, has been shown to mediate a deleterious crosstalk between IFP and cartilage, but also synovium and cartilage[36]. Moreover, a small population of osteoclast-like cells, characterized by the expression of receptor activator of NF-κB (RANK), cathepsin K (CTSK) and matrix metalloproteinase-9 (MMP-9) are found in the synovium and IFP, which could contribute to articular destruction[36]. In a 2024 study, an intricate relationship between fibroblasts and other cell types, such as macrophages, was identified in the human IFP through the use of single-nuclei and spatial transcriptomics[38]. Interestingly, this study indicates that macrophage–fibroblast interactions are stronger in knee OA than in healthy counterparts; these interactions involve diverse pathways and molecules (such as peroxisome proliferator-activated receptor α, fibronectin-1 and platelet-derived growth factors)[38].

Functional findings from animal studies. Similar to observations made in human studies, mouse models of joint destabilization-induced OA describe innate immune cell diversity[18,19] and substantial alterations in the innate immune cell compartment in the joint, which can be observed from day 1 to day 30 after injury[19]. Macrophages represent the main synovial immune cells in mice and their phenotypes are altered in OA models. In particular, a preprint published in 2023 demonstrated that the role of key transcription factors, such as CCAAT/enhancer-binding protein (C/EBP) family members or JUN, are predicted to drive pro-inflammatory synovial macrophage differentiation[18]. Notably, in a rat destabilization-induced model of OA, signal transducer and activator of transcription 6 (STAT6) signalling has been shown to be a major driver of macrophage activation and is likely to be involved in macrophage-associated pain sensitivity[39]. In line with the findings from a 2024 study[40], which demonstrated that the macrophages from patients with OA experiencing worse pain had a lower phagocytic capacity than macrophages from patients with less pain, future studies should further investigate the link between macrophage functions and pain in OA. In a mouse model of OA, the deficiency of TREM2 (triggering receptor expressed on myeloid cells 2) significantly exacerbates the joint inflammatory response and accelerates disease progression, highlighting its protective function[41]. In accordance with the expression and role of TREM2$^+$ synovial macrophages, which form a tight anti-inflammatory immune barrier in the healthy synovial tissue in both mice and humans[16], it seems important to decipher the function of these cells in the human OA synovium. Consistent with human

findings, anti-apolipoprotein E antibodies can attenuate synovial inflammation and cartilage degradation in a collagenase-induced murine model of OA[36].

Macrophages also infiltrate lumbar dorsal root ganglia (DRG) on the ipsilateral side during murine OA. Total depletion of macrophages or switching these macrophages from pro-inflammatory to anti-inflammatory phenotypes leads to an alleviation of OA pain in animal models. Both CXCL11 and myostatin can be involved in the interaction between macrophages and nociceptive neurons (neuro-immune communication), and to subsequent OA pain[23,42,43]. Furthermore, 20-month-old mice with mild OA associated with mechanical allodynia also exhibit joint hyperalgesia[44]. Moreover, this study highlighted that ageing was associated with significant and sex-specific immune-cell phenotype changes in DRG, a feature that was also observed in older humans. Collectively, dissecting neurogenic inflammation and especially the crosstalk between macrophages and afferent nociceptive neurons seems critical for understanding the inflammatory mechanisms of OA-related pain and hyperalgesia[45]. In addition, in an organ culture of rat lumbar DRG, treatment with conditioned media prepared with synovial cells from patients with worse pain increased neuronal stress signals compared with DRGs treated with unconditioned media[40].

Overall, the heterogeneity of macrophages and the complex crosstalk these cells have with other innate and adaptive immune cells and stromal cells might have a key role in orchestrating joint homeostasis and OA development. As described later in this Review, other innate immune cells, such as neutrophils, mast cells, NK cells and innate lymphoid cells (ILCs) can also contribute to perpetuating the inflammatory milieu within the joint (Fig. 1).

Mast cells in the synovial joint

Mast cells are typically known for their involvement in IgE-mediated allergic reactions but are increasingly recognized for their multifunctionality in several health and disease states[46], including inflammatory disorders and autoimmune diseases. Mast cells are present in healthy synovium and represent up to 3% of total cells, which increases further in the inflamed synovium[46]. The presence of mast cells in the synovial tissue in OA is one of the defining factors that discriminates OA from RA in the histopathological classification of tissue[47]. Mast cells are also part of the rich cellular composition of IFP[38]. Through their expression of IL-18, mast cells are believed to influence the phenotypic changes of chondrocytes in OA cartilage[33]. Mast cells are also capable of producing tryptase β, which in turn has been shown to cleave proteoglycan 4, leading to a reduction in joint lubrication and this process is associated with OA severity in a post-traumatic OA mouse model[48]. Tryptase levels are significantly higher in the synovial fluid of patients with OA than in healthy individuals; genetic or pharmacological ablation of mast cells in mice confirmed their pathogenic involvement in the development of OA, through mast-cell-derived tryptase[49]. More specifically, IgE-mediated activation of mast cells via binding to the high-affinity IgE

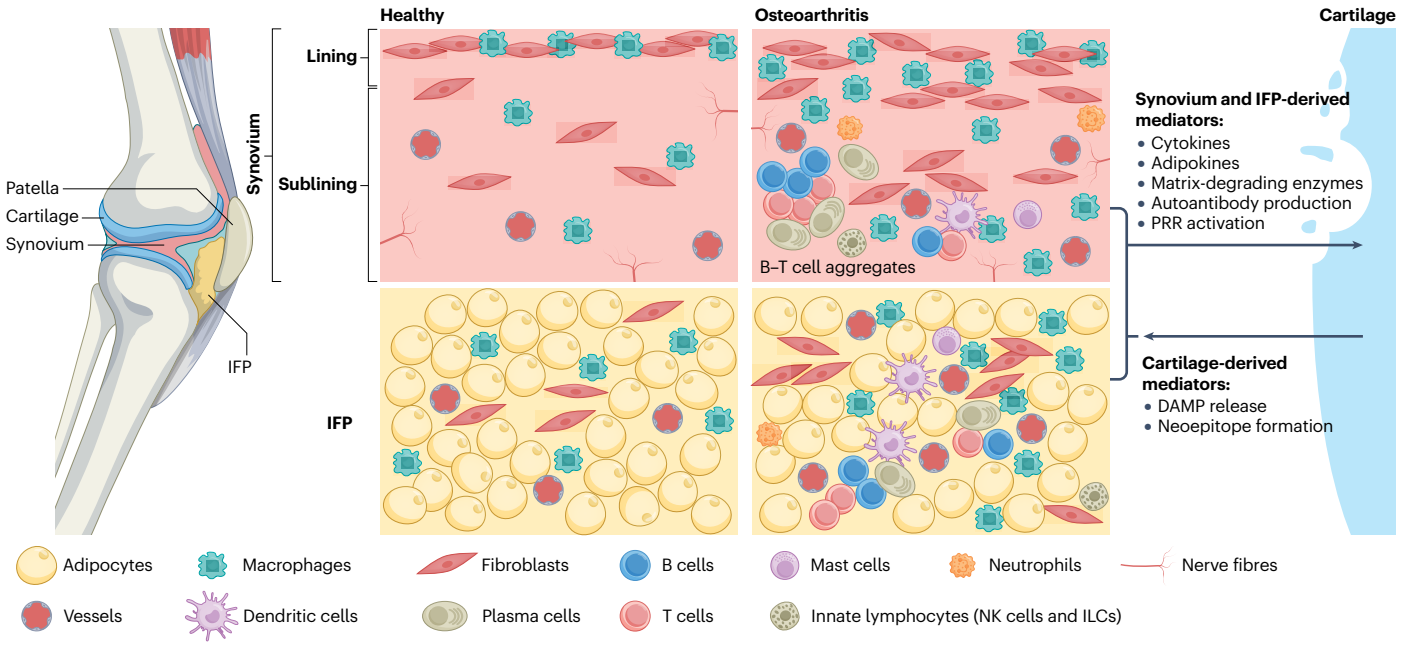

Fig. 1 | Immune cells in the synovium and infrapatellar fat pad in health and osteoarthritis. Various innate and adaptive immune cells are differently distributed in the synovial tissue and infrapatellar fat pad (IFP) in healthy joints and those with osteoarthritis (OA). The diversity and distribution of innate immune cells (macrophages, dendritic cells, mast cells, neutrophils and innate lymphocytes, including natural killer (NK) cells and innate lymphoid cells (ILCs)) and adaptive immune cells (plasma cells, B cells and T cells, which form aggregates in OA) in the synovium (lining and sublining) and IFP of healthy joints and those with OA are represented. Structural cells, including adipocytes, fibroblasts and endothelial cells forming vessels and nerve fibres are also represented. In OA, the synovial lining thickens and the protective barrier that hinders immune-cell trafficking in the steady state is disrupted. Neovascularization also occurs in OA tissues. Numerous mediators (such as cytokines, adipokines or matrix-degrading enzymes) are released by cells in the synovium and IFP and can induce cartilage damage in OA. In turn, the degraded cartilage produces damage-associated molecular patterns (DAMPs) that further enhance pattern-recognition receptors (PRR) activation and synovial and IFP inflammation. The cleavage of matrix components increases the formation of neoepitopes and can enhance the inflammatory processes involved in OA.

receptor (FcεRI) activates the spleen tyrosine kinase (SYK) pathway, and mediates inflammation and tissue damage[49]. These findings align with data from a 2024 study that suggested that atopic diseases, such as asthma and/or allergic rhinitis, could be risk factors for OA owing to shared genetic variants between diseases[50].

Neutrophils in the synovial joint

Neutrophils have a role in the pathogenesis of joint diseases, particularly in driving inflammation and contributing to joint damage. Neutrophils release pro-inflammatory cytokines (such as IL-1β and IL-6), reactive oxygen species and contribute to the activation of matrix-degrading enzymes (such as MMP)[51], which contribute to cartilage breakdown. Notably, the most important cartilage-degrading collagenase involved in OA, MMP-13, is activated by neutrophil elastase[51]. Furthermore, neutrophil extracellular traps are known to amplify joint inflammation and tissue destruction in RA, and are also highly suspected for their role in the pathophysiology of OA[52,53]. Neutrophils are mostly found in the synovial fluid and the bloodstream. Although neutrophils can be observed in 20% of RA synovial tissues, they infiltrate less than 1% of OA tissues[47]. Notably, synovial fluid neutrophils collected from the knee of patients with OA are phenotypically altered and are characterized by a decreased expression of CD11b, CD54 and CD64, increased expression of CD62L, TLR2 and TLR4 and increased production of reactive oxygen species and phagocytic activity when compared with neutrophils collected from individuals with knee infections[54].

Other innate immune cells in the synovial joint

ILCs (including ILC1, ILC2 and ILC3) are innate lymphocytes characterized by their lack of the recombinant activating gene (RAG)-dependent rearranged antigen receptors. The function of ILCs in the OA synovium is poorly described. In the blood, the percentage of ILC3s is notably reduced in several autoimmune and autoinflammatory diseases, including OA[55]. NK cells have been shown to infiltrate the OA synovium[56]. Given the role of both NK cells and ILCs in the context of chronic inflammation[57], the distribution and diversity of these cells in OA would be worth investigating in the future.

Peripheral innate immune cells in osteoarthritis

Circulating innate immune cells are also altered in OA; dysregulation of the local innate immune response could have substantial effects on circulating immune cells and soluble biomarkers. Joint degeneration products, such as cartilage oligomeric matrix protein[58], can diffuse into the blood and might also activate circulating innate immune cells. A study published in 2018 suggested that circulating monocytes present several features of activation, such as higher expression of CD16, CCR2 and MHCII in women with knee OA[59]. In a study published in 2020, the majority of circulating monocytes in OA were shown to express CCR1 and CCR2, resulting in these cells migrating to the joint through chemoattraction[60]. The data connecting the diversity and abundance of peripheral immune cells to OA features remain scarce, and further studies are needed to refine this concept.

Overall, a wide range of innate immune cells are described in the OA joint, and their role as drivers of disease is increasingly recognized. The complex and interactive crosstalk between innate and adaptive immune cells, a hallmark of several chronic and inflammatory diseases[61], is an important aspect of the pathophysiology of OA. How the activation of innate immune cells and their intricate relationship with adaptive immune cells relates to OA progression is discussed in the next section.

Effect of adaptive immune cell activation on chronic inflammation in osteoarthritis

Chronic inflammation is a prolonged and persistent inflammatory response that can last for months or even years. Such inflammation in OA might sometimes remain silent before the onset of established disease and symptoms, such as articular pain and articular damage. In vivo mouse studies and analysis of samples obtained from organ donors have revealed the complex development of the adaptive immune system throughout life, from embryonic stages to adulthood, both in physiological and disease conditions, including in the context of chronic inflammation. In particular, T cell subsets with specialized functions vary according to life stage and anatomical location, showing distinct patterns of change in blood, lymphoid organs and tissues with age[62]. This concept is particularly relevant to OA, given that ageing is a major risk factor for this chronic inflammatory disease; the few studies that have investigated the presence, distribution and repertoires of B cells and T cells in OA joint tissues, how their circulating counterparts vary across disease stages and the overall contribution of these cells to the pathogenesis of OA are detailed in this section.

Subsets of T cells and B cells in the osteoarthritis synovium

Within the OA synovium, T cell infiltration and polarization occur early in disease development[63]; in a post-traumatic mouse model of OA, $CD4^+$ T cell deficiency reduces cartilage degeneration[64]. Although $CD8^+$ cytotoxic T cells can be found in OA tissues, $CD4^+$ T helper cells are the major T cell subtype present in the synovial tissue[65]. The study of T cell-deficient mice ($TCR\alpha^{-/-}$ mice) with OA has demonstrated reduced cartilage degeneration and osteophyte formation compared with wild type mice with OA[66]. Additionally, inhibiting T cell egress from lymph nodes using fingolimod reduces load-induced cartilage degradation and the number of T cells in the synovium in mice with OA[66]. A low proportion of infiltrating regulatory T (T_{reg}) cells ($CD4^+CD25^{+/high}CD127^{low/-}$) in the synovial tissue also relates to increased pain and functional disability in knee OA[67]. Changes in the proportion of $CD8^+$ T cells have been observed in OA blood, synovial fluid and tissue[68–70]. Notably, compared with peripheral blood, the proportion of activated cytotoxic $CD8^+$ $IFN\gamma^+$ cells (known as Tc1 cells) and cytotoxic $CD8^+$ $IL\text{-}17A^+$ cells (known as Tc17 cells) is significantly higher in the synovial fluid, suggesting a localized activation within the OA joint. Furthermore, the proportion of such $CD8^+$ T cell subtypes vary depending on the stage and localization of OA[70]. In the synovial fluid collected from 119 patients with OA, a 2022 study also identified four immune-phenotypes associated with distinct clinical trajectories that were based on the proportion of T cells and monocyte-macrophage lineage cells[71]. Importantly, the authors of this study defined an 'aggressive' phenotype that was characterized by a high percentage of synovial fluid monocytes and macrophages, neutrophils, $HLA\text{-}DR^+$ $CD4^+$ T cells and $CD8^+$ T cells; this 'aggressive' phenotype was associated with the poorest disease outcome[71]. Although several studies have highlighted that distinct populations of T cells might not just be innocent bystanders in OA, studies on B cells in OA remain sparse, but these cells are becoming an increasing area of interest in OA research[72]. IgM^+ $CD27^+$ B cells are present in the synovial fluid of patients with OA and can secrete the regulatory cytokine IL-10, which can exert regulatory functions[73]. Naive and memory B cells with specific transcriptomic signatures can be found in the synovial tissue and IFP of patients with OA; however, as shown in Table 2, data on the diversity of B cells and T cells in OA tissues remain fragmented.

Table 2 | High-throughput identification of adaptive immune cell subtypes in OA

Tissue	Cell type			Technical approaches	Ref.
	Name	Subtype	Phenotypic markers		
Human					
Synovium	B cells	N/A	*MZB1, TNFRSF17, CD79A*	Single-cell RNA sequencing	33
	T cells	N/A	*CD3*		
Synovium	B cells	9 subclusters	Various B cell- and T cell-associated markers	Single-cell CITE sequencing	10
	T cells	24 subclusters			
Synovium and IFP	B cells	Naive	CD79A, HLA-DRA, MS4A1, CD74, CD83	Imaging mass cytometry	36
		Memory	IGHG4, IGLC1, IGKC, IGLC2, IGLC3		
	T cells	N/A	IL7R, FOS, FOSB, LTB, KLF6		
	NKT cell	N/A	NKG7, GZMB, KLRD1, GZMH, GNLY		
Fat pad	T cells		*CD247, THEMIS*	Single-nuclei RNA sequencing and spatial transcriptomics	38
Mouse					
Synovium	B cells	N/A	*CD79a*	Single-cell RNA sequencing	18
	T cells and NK cells	N/A	*Lck, Ly6c2*		
Joint (cartilage, synovial fluid, synovium and IFP)	B cells	Rag1^{hi}	*Cd79a, Rag1, Sox4, Myb*	Single-cell RNA sequencing	19
		Lcn2^{hi}	*Cd79a, Lcn2, Retnlg, Mmp8*		
		Ms4a1^{hi}	*Cd79a, Ms4a1, Igkc, Ifi30*		
		Cd74^{hi}	*Cd79a, CD74, H2-Ab1, H2-Eb1*		
	T cells	N/A	*Thy1, Cd3e*		

CITE sequencing, cellular indexing of transcriptomes and epitopes by sequencing; IFP, infrapatellar fat pad; N/A, not applicable; NK cells, natural killer cells; NKT cells, natural killer T cells.

Function of T cells and B cells in osteoarthritis joint tissues

T cells and B cells that are present in the OA synovium can contribute to joint inflammation through the release of cytokines and to the degradation of the cartilage matrix. Indeed, B cells can directly or indirectly promote the production of MMPs and aggrecanases (ADAMTS), which leads to the breakdown of cartilage[74]. Synovial B cells can also function as antigen-presenting cells and could also potentially contribute to local autoimmune responses, as suggested by the observed retention of autoantibodies within the OA joint[75]. In addition, pro-inflammatory cytokines produced by T cells, such as IL-17 and TNF, induce oxidative stress and apoptosis in chondrocytes, resulting in chondrocyte death[76], a typical feature observed in the cartilage of patients with OA.

In the synovial tissue, it is likely that T cell-derived IL-17 drives synovitis by activating synovial fibroblasts and stimulating the release of pro-inflammatory cytokines[77]. Such cytokine production driven by lymphocytes induces synovial MMP-9 (ref. 78), which contributes to the degradation of cartilage and has effects on adipose tissue, notably the IFP, causing the increased production of adipokines, such as leptin and resistin[79]. Adipokines have been shown to accelerate cartilage catabolism and synovitis[80]. Furthermore, the infiltration of T cells and B cells into the IFP sustains a pro-inflammatory environment, perpetuating joint inflammation and damage[81]. Although the exact role of adaptive immunity in OA remains to be fully elucidated, a 2024 Mendelian randomization study suggested a causal link between dysregulated innate and adaptive immune cells, including T_{reg} cells, and OA at various anatomical sites[82].

Peripheral T cells and B cells in osteoarthritis

Beyond the synovial tissue, emerging evidence indicates systemic changes in the adaptive immune system in OA. Notably, alterations in the peripheral blood immune cell composition, particularly in memory T cells and B cells, have been observed in patients with OA[83], an observation that is independent of age[68]. Deep immunophenotyping of blood samples from patients with knee OA, compared with 15 other autoimmune and autoinflammatory diseases (including RA, spondyloarthritis and Crohn's disease), reveals distinct immune alterations. Specifically, T_{reg} cell subsets are generally over-represented in patients with OA compared with healthy individuals, although the percentage of T_{reg} cells expressing ICOS (inducible T cell costimulator) is significantly reduced in OA[55]. Interestingly, in a 2024 preprint, an association was identified between peripheral T_{reg} cell dysfunction and OA-related pain in patients with knee OA[84]. Patients with OA who experienced pain exhibited a reduction in functional T_{reg} cell subsets ($CD95^+$ T_{reg} cells, $FOXP3^+$ $CTLA4^+$ T_{reg} cells and $CD45RA^-$ T_{reg} cells). B cell subsets are also altered in OA; there are substantially fewer $CD32^-$ B cells and transitional B cells in the blood of patients with OA than in healthy individuals[55]. Circulating B cells in individuals with OA have a more mature phenotype than those from healthy individuals, suggesting an immunological memory response and a potential role of these B cells in sustaining inflammation and tissue damage[69]. It will be important to determine if this B cell activation is a result of the chronic low-grade inflammation that is associated with OA or if it represents an active and targetable pathophysiological process directed against specific antigens[72].

Overall, future studies are needed to better understand the effect of peripheral adaptive immune cell alterations on features of OA and disease location (such as single-joint versus multi-joint involvement).

Evidence for T cells and B cells driving autoimmunity in osteoarthritis

Early studies have identified that T cells infiltrating the synovium exhibit a restricted repertoire[85], primarily targeting products of cartilage breakdown such as chitinase-3-like protein 2 and type II collagen[86,87]. This observation is supported by findings that indicate that peripheral T cells from patients with OA show a stronger response to autologous chondrocytes than those from healthy individuals[88]. This response is partially inhibited by antibodies against HLA class I and HLA class II, as well as CD4 and CD8 (ref. 88). Additionally, some individuals with OA have T cells that recognize peptides from specific regions (such as the amino acid regions 16–39 and 263–282) of the human cartilage proteoglycan aggrecan[89]; peripheral blood mononuclear cells from these individuals produce higher levels of pro-inflammatory cytokines and chemokines when stimulated with human cartilage proteoglycan aggrecan peptides than unstimulated cells. Moreover, autoantibodies against methionine adenosyltransferase 2 β have been detected in patients with OA, suggesting that mechanisms of self-reactivity are involved in disease pathogenesis[90]. These autoantibodies might target cartilage components, contributing to further tissue damage and inflammation. Interestingly, autoantibodies against post-translationally modified proteins are found in the sera of patients with OA, but, as expected, at a lower frequency than in patients with RA[75]. T cell and B cell aggregates that are surrounded by plasma cells have been identified in the synovial tissue of more than half of patients with OA in the late stages of the disease[91] (Fig. 1). Such organized synovial structures are associated with peripheral inflammatory changes, such as the ratio of monocytes to lymphocytes and neutrophils to lymphocytes, and further investigation is required to better decipher the pathogenic role of these aggregates in OA. Notably, the infiltration of adaptive immune cells is also observed in the IFP[92], but their histological organization is not described.

Technological advances in single-cell sequencing approaches have enabled the definition of the sequences recognized by T cell and B cell receptors. By combining methods that can predict the structure of epitopes recognized by these sequences and the current accelerated development of artificial intelligence and machine-learning structure prediction tools, it will soon be possible to identify the antigen specificity of these adaptive immune cells, which will advance the understanding of numerous diseases, including OA.

Systemic consequences of osteoarthritis-related immune dysregulation

It is now well-recognized that disease is not restricted to the joint in OA and systemic immune dysregulation in OA can affect the entire body. This section explores the underlying causes and consequences of systemic inflammation, the interplay between disease features and gut microbiota alterations and the multi-tissue damage associated with OA.

Consequences of systemic inflammation

The development of OA is often accompanied by comorbidities such as cardiovascular disease, obesity and metabolic syndrome[93]. Distinguishing OA-induced systemic inflammation and immune dysfunction from responses that are a result of associated diseases is challenging owing to their close interdependency. This interdependency is particularly relevant for obesity, a major systemic risk factor for knee and hip OA, which underscores the importance of studying inflammatory and immune processes in non-weight-bearing joints, such as the hands, to better understand the effect of systemic inflammation on OA[94].

From a whole-body perspective, however, low-grade systemic inflammation clearly seems to be a biologically and clinically relevant hallmark of OA. This inflammation is associated with pain regardless of its location[95], as well as with radiographic severity and disease progression[96]. The origins of this low-grade inflammation are multifaceted and closely linked to different risk factor-based OA phenotypes, such as metabolic and age-related OA. Specifically, these phenotypes involve two underlying biological processes: metainflammation[97] (which refers to inflammation driven by metabolic disorders) and inflammaging[98] (which describes the chronic inflammatory state associated with ageing). Although both processes contribute to chronic systemic low-grade inflammation, they manifest through distinct immune dysregulation that can disrupt joint homeostasis and contribute to the development of OA. There are numerous different types of inflammation and tissue sources of inflammation, which are discussed in this section.

Metainflammation. Metainflammation serves as the systemic pathway that links obesity, metabolic syndrome and OA, in addition to the effects of mechanical overload[99]. It is the consequence of excessive unhealthy visceral fat accumulation and adipose tissue dysfunction that strongly contributes to the onset of obesity-related comorbidities including OA. The underlying mechanisms of adipose tissue dysfunction include adipocyte hypertrophy and the infiltration of pro-inflammatory macrophages to adipose tissue. This dysfunction results in the release of various mediators from adipose tissue, including pro-inflammatory cytokines (such as TNF and IL-6), adipokines, free fatty acids, lipid mediators and reactive oxygen species[100,101]. Adipokines, such as leptin, adiponectin and visfatin, have been extensively studied for their pro-inflammatory and/or anti-inflammatory properties and their effects on joint homeostasis. Their assessment as biomarkers in biological samples (including blood and synovial fluid) has been the focus of numerous studies[102]. Notably, the serum leptin:adiponectin ratio is considered an accurate estimate of visceral adipose tissue dysfunction[103] and is associated with pain levels in lower limb OA, independent of radiographic severity[104].

Inflammaging and senescence. Inflammaging is a hallmark of age-related chronic diseases such as OA[98]. This complex process involves many biological phenomena (such as defective autophagy, epigenetic changes, telomere shortening and oxidative stress). As individuals age, damage-associated molecular patterns, such as alarmins, serve as danger signals, leading to the activation of inflammasomes such as NLRP3. This activation is crucial for promoting systemic inflammation and joint destruction[105,106]. Another mechanism by which ageing promotes inflammation is cellular senescence. Although senescence is a physiological response that prevents the accumulation of damaged cells, senescent cells can accumulate in the OA joint, leading to a senescence-associated secretory phenotype (SASP)[105]. SASP is characterized by the increased production of cytokines, chemokines, growth factors and MMPs and can lead to joint damage[107]. During ageing, senescence also affects the immune system, a process known as immunosenescence, which results from the accumulation of 'antigenic load' over time[108]. This process has specific effects on both the adaptive immune system (including thymic

involution, a decrease in the number of naive T cells, impaired efficient adaptive immune responses and alterations of the immune synapse) and the innate immune system leading to a sustained activated state. A 2023 preprint suggests that pathogenic B cell subsets can also drive immunosenescence of T cells via clonal TCR restriction[109]. In this context, treatment with anti-CD20 monoclonal antibodies seems to be an interesting strategy to counteract T cell ageing and associated immunosenescence. Various immune cells, including lymphocytes, macrophages and mast cells, are involved in senescence-related processes associated with OA[110]. Immunosenescence can lead to a defective immune response and chronic low-grade inflammation, which could also be involved in OA per se[98]. Senescent immune cells, via their SASP, which sustains chronic joint inflammation, can also induce senescence in surrounding resident joint cells, such as chondrocytes or synovial fibroblasts, and contribute to tissue damage that spans the entire joint[110]; this process is known as bystander senescence. Among the wide range of mediators released in SASP, IL-6 is particularly notable, as its elevated blood levels are associated with overall mortality[111]. IL-6 can function as an enhancer of chronic inflammation and oxidative stress associated with both ageing and pathological conditions such as OA; this cytokine could represent a 'gerokine' (soluble molecule associated with ageing), which is involved in the switch from physiological ageing to age-related diseases[112]. IL-11, another cytokine in the IL-6 family, has also been proposed as a 'gerokine' that is involved in the pathological processes related to ageing[113]. Collectively, joint inflammation drives immunosenescence, and senescent immune cells, in turn, exacerbate chronic inflammation in OA, providing an explanation for the chronicity of the disease.

Overall, understanding the immunological aspects of metabolic dysregulation and ageing at both the joint and the systemic levels in the context of OA will be critical for developing targeted interventions that address the unique needs of older patients or patients with obesity.

Effects of immune dysregulation on gut microbiota in osteoarthritis

Increasing evidence suggests a link between OA and the gut microbiota, but the current understanding of this relationship remains limited[114]. Gut microbiota and immunity are deeply intertwined; gut microbes influence both intestinal and systemic immunity, and, conversely, immunogenetics regulate microbiota composition[115]. Mouse models of OA have demonstrated that alterations in gut microbiota can alter disease progression[116,117]. Prebiotic agents can mitigate the effects of a high-fat diet on OA by modulating gut microbiota, thereby attenuating metainflammation[118]. In addition, the disruption of the gut microbiota through antibiotic treatment can also alleviate the progression of OA[116]. These findings are in line with previous work showing that germ-free mice have a reduced OA severity and synovitis following joint destabilization compared with specific pathogen-free mice, emphasizing that gut microbiota-related factors promote post-traumatic OA development[117].

Multiple studies in human cohorts further support the hypothesis that gut bacteria and their metabolites have an active role in OA aetiology[119–121]. High levels of lipopolysaccharide and lipopolysaccharide-binding protein, which are indicators of systemic chronic low-grade inflammation and intestinal barrier dysfunction, are positively associated with the severity of knee OA and the abundance of activated macrophages in the synovium[119,122]. As for systemic low-grade inflammation, discriminating microbiota alterations related to OA from those related to obesity in the context of weight-bearing joints is a challenge; however, gut dysbiosis has also been found in people with hand OA[123]. Moreover, an increased abundance of *Streptococcus* in the microbiome correlates with knee OA pain, probably through the modulation of synovial inflammation, reinforcing the connection between gut dysbiosis and joint pathology[120]. A striking example of the gut–joint relationship is the change in the tryptophan metabolic pathway, which is linked to both gut microbiota and intestinal permeability biomarkers. The changes in this pathway are associated with erosive hand OA and pain, emphasizing the role of low-grade inflammation and gut dysbiosis in disease[124,125]. This association is in line with a 2023 study in RA, which found that tryptophan metabolism had an active role in the pathogenesis of the disease[126]. Short-chain fatty acids, such as butyrate, might also be involved in the modulation of the disease course and pain in OA[127]. Notably, faecal microbiota transplantation from patients with OA and metabolic syndrome to germ-free mice significantly exacerbates disease severity and systemic alterations compared with transplants from healthy donors[128].

Collectively, these findings underscore the intricate relationship between gut microbiota and OA pathogenesis, notably through innate immune response and low-grade inflammation (Fig. 2). Thus, modulating the microbiota through the use of prebiotics and probiotics could represent a potential therapeutic strategy for OA.

Deciphering immune dysregulation: an integrative approach to understanding multi-tissue damage in osteoarthritis

Chronic low-grade inflammation and immune responses form the common foundation of many chronic diseases, including OA, cardiovascular diseases, metabolic disorders, neurodegenerative conditions and other comorbidities associated with OA[129]. Moreover, patients often present with a combination of these conditions. Therefore, these shared systemic biological phenomena and the overlap of these diseases in patients encourage an integrated approach to understanding their pathophysiology, including that of OA.

It is increasingly recognized that OA should be studied within the context of various interconnected axes, such as the brain–joint axis, gut–joint axis and cardiovascular–joint axis as all are involved in chronic systemic inflammation. Interestingly, a 2024 study suggests that genetic factors shared between OA and cardiovascular diseases might contribute to the development of both conditions[130]. This finding challenges the simplistic notion that the link between OA and cardiovascular diseases can be solely attributed to physical inactivity. Similarly, epidemiological studies suggest an association between OA and dementia[131]. In line with this work, the induction of OA in a murine model of Alzheimer's disease was shown to exacerbate and accelerate the progression of neuroinflammation and amyloid plaque deposition[132].

These emerging insights highlight the need to view OA as a condition deeply interconnected with systemic, multi-organ low-grade inflammation, warranting a more integrated and interdisciplinary research approach to improve patient care.

Future strategies for targeting the immune system in osteoarthritis

This Review underscores the considerable advances made over the past decade in understanding the immune components of OA; however, the therapeutic benefits of these discoveries have yet to be appreciated. This section is aimed at highlighting the avenues pursued thus far, including the development of conventional and biologic therapies and the use of cell therapy for the treatment of OA.

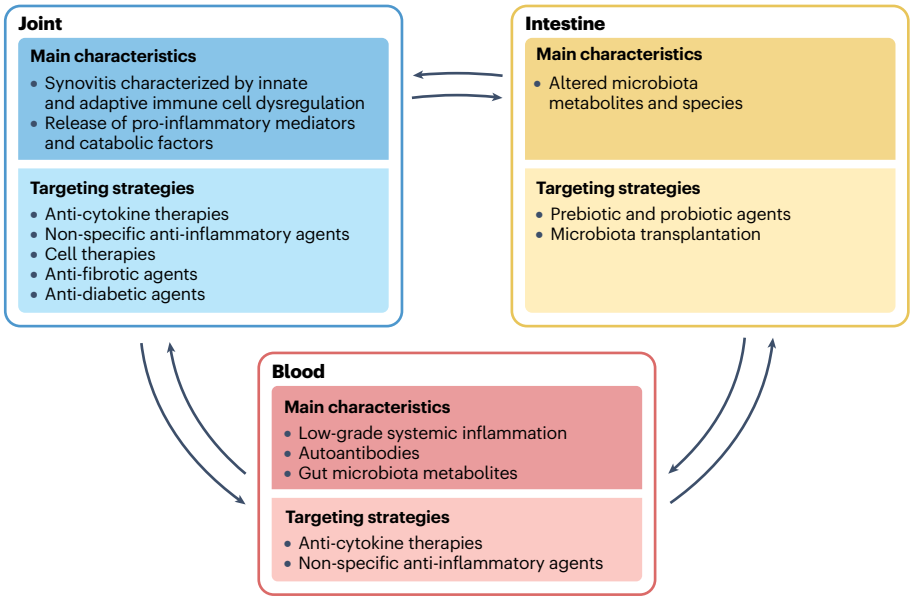

Fig. 2 | The influence of the immune system on the joint and the periphery in osteoarthritis. Innate and adaptive immune cells can have bidirectional effects (black arrows) at the peripheral and joint levels in the context of osteoarthritis (OA). The main characteristics observed in the blood (red), joint (blue) and gut (yellow) and the treatments approved or currently under development for OA, which target each compartment, are represented.

Conventional and biologic therapies to target immune dysregulation in osteoarthritis

Building on the extensive data from clinical studies in RA, conventional and biologic therapies, such as anti-cytokine strategies and non-specific anti-inflammatory agents, have emerged as promising approaches to targeting immune dysregulation in OA, with the goal of mitigating inflammation and ameliorating disease progression. The development of novel approaches, specifically those targeting disease-specific pathways, and better stratification of patients with OA, are important for improving patient care.

Anti-cytokine therapeutic approaches. Various anti-cytokine strategies have been explored in OA with the objective of replicating what has been achieved in RA, on the assumption that there are sufficient similarities between the immune abnormalities found in OA and those found in RA to reposition treatments. Notably, many of the studies of conventional and biologic therapies have primarily been conducted in erosive hand OA because of the recognized importance of the inflammatory component in this disease subtype[133]. Etanercept, a soluble TNF receptor, showed no symptomatic benefit in 90 patients treated for 24 weeks[134], nor did adalimumab, an anti-TNF antibody, in a 6-month randomized controlled trial in 85 patients treated with two subcutaneous injections 15 days apart or with placebo[135]. Targeting IL-6 also failed in a 6-week study of 91 patients who received two infusions 4 weeks apart (weeks 0 and 4) of tocilizumab, a humanized anti-IL-6 receptor antibody, or placebo[136]. Moreover, a clinical trial testing the efficacy of the anti-granulocyte–macrophage colony-stimulating factor antibody otilimab demonstrated no benefit in a pilot study of 44 patients who received either subcutaneous otilimab or placebo administered weekly from week 0 to week 4, then every 2 weeks until week 10 (ref. 137). Finally, targeting IL-1, considered as the most potent pro-inflammatory and pro-damaging mediator in OA, has also been evaluated. Lutikizumab, an antibody that inhibits IL-1α and IL-1β, has been tested in two pivotal clinical trials, both in patients with erosive hand OA and in patients with knee OA presenting with synovitis[138,139]. Both trials failed to demonstrate a superior efficacy of lutikizumab over placebo. However, a post hoc analysis from the CANTOS trial, a randomized, placebo-controlled trial that evaluated the anti-IL-1 antibody canakinumab (subcutaneous injection once every 3 months) in 10,061 patients with prior myocardial infarction and elevated C-reactive protein (15.6% of whom reported a medical history of OA) at baseline, showed a 40% reduction in the rate of total knee replacement after a mean follow-up of 3.7 years, re-opening the door for anti-IL-1 therapies in knee OA[140]. In 2024, a randomized controlled trial demonstrated that denosumab, an inhibitor of receptor activator of nuclear NF-κB ligand (RANKL), had a structural effect on erosive hand OA by inducing remodelling and preventing new erosive lesions[141]. Interestingly, such an effect could be mediated by targeting synovitis since denosumab reduced synovitis and effusion scores compared with baseline[141].

Despite these efforts, it remains unclear whether systemically delivered therapies effectively reach the joint space in sufficient concentrations to modulate local inflammation and joint damage. This limitation could contribute to the lack of efficacy observed in these studies.

Non-specific anti-inflammatory therapeutic agents. Beyond the specific targeting of pro-inflammatory cytokines, non-specific anti-inflammatory strategies have been tested in the context of OA. Methotrexate, the gold-standard treatment for RA, showed a moderate effect on pain in two independent 6-month randomized, placebo-controlled trials in symptomatic knee and hand OA[142,143]. Compared with previous trials showing no effect of methotrexate on pain relief[144], these studies, published in 2023 and 2024, call for a better definition of the appropriate methotrexate dose to administer, and an evaluation of its cost-effectiveness before considering this therapy for a larger population of patients. The efficacy of glucocorticoids, potent anti-inflammatory agents with known immunomodulatory effects, following intra-articular injection has long been established for OA[145]; however, the benefit–risk balance of repeated intra-articular injections of glucocorticoids remains debatable[146]. The randomized, placebo-controlled HOPE trial, in which the efficacy of a short (6-week) course

of oral prednisolone or placebo was evaluated in 92 patients with hand OA presenting with synovitis, demonstrated that prednisolone had a clinically relevant effect on pain[147]. Other drugs with anti-inflammatory or immunomodulatory properties, such as colchicine[148,149], hydroxychloroquine[150] and statins[151], have been examined in clinical investigations in the context of OA. Although interesting, these drugs have so far failed to demonstrate their efficacy for this indication.

Future directions. Overall, except for non-specific treatments such as glucocorticoids, targeting the immune system in OA has not yet proven to be highly beneficial. Beyond the disappointing evidence available, several explanations could be proposed.

First, although the repositioning of RA treatment initially seemed to be a relevant strategy, it is not clear whether inflammatory and catabolic mediators involved in OA are the same as those involved in RA, and whether these mediators function within the same time and spatial frameworks following disease initiation. Given the clinical and structural differences between these rheumatic conditions, the development of therapeutic strategies targeting pro-inflammatory pathways and/or fibrosis associated with OA is utterly indispensable. Current therapeutic strategies under development include targeting IL-10 using gene therapy and the use of liraglutide, a glucagon-like peptide-1 receptor agonist used in type 2 diabetes mellitus and obesity management that has been shown to reduce synovitis in experimental models of OA; both of these strategies are being tested in humans[152,153]. In advanced OA, chronic synovial inflammation can progress to synovial fibrosis, characterized by excessive collagen accumulation, abnormal fibrin deposition and synovial fibroblast proliferation[154]. Nintedanib, an antifibrotic agent, attenuates synovial inflammation, fibrosis and cartilage degradation through the inhibition of pro-inflammatory polarization of OA synovial macrophages in a destabilization-induced mouse model of OA[155]. Future directions for the treatment of OA also include modulation of the gut microbiota through distinct strategies, including the use of prebiotic and probiotic agents and faecal microbiota transplantation. None of these strategies is yet included in the guidelines of scientific societies for alleviating OA symptoms[156], although clinical studies are emerging (for example, NCT06459700); however, physical activity and a healthy whole-food plant-based diet both exert beneficial effects on OA symptoms, in part through the modulation of the gut microbiota[157].

Second, past clinical failures could be attributed to the current inability to differentiate between OA endotypes, which influence clinical phenotypes[158]. It is now clear that there are different joint and peripheral molecular signatures in OA and that inclusion and exclusion criteria for different signatures should be incorporated into clinical trials to facilitate more targeted treatment approaches in OA (Fig. 3). The presence of soluble biomarkers in the blood of patients with OA might help to define disease subgroups linked to phenotypes and endotypes and stratify patients. In 2022, three endotypes (low tissue turnover, structural damage and systemic inflammation) were defined on the basis of the expression of 14 circulating biochemical markers, and were shown to be associated with clinical phenotypes and disease evolution[159]. Future studies should further explore the relationship between these biochemical biomarkers and the phenotypic, genomic and demographic characteristics of patients with OA to enhance patient stratification and advance the challenging development of precision medicine[160]. Several other challenges must be addressed to improve the stratification of patients with OA. They include, but are not limited to, the technical approaches needed for routine implementation in patient care, the economic implications of such advancements and the associated ethical considerations.

Immunomodulatory properties of cell therapy for osteoarthritis management

Cell-based therapies have gained attention for their immunomodulatory properties, offering a novel approach to managing immune dysregulation and inflammation in OA. Among these therapies, mesenchymal stem cells (MSCs) are the most extensively studied; in this section we also discuss emergent strategies such as the injection of genetically modified chondrocytes, macrophages and stem cells.

Mesenchymal stem cell-based cell therapy. Interest in MSCs (also known as mesenchymal stromal cells) has grown in rheumatology, especially in the context of OA, owing to their trophic and immunomodulatory properties[161]. MSCs are found in almost all tissues and were originally identified in the bone marrow as haematopoietic support cells. Over the past decade, MSCs have elicited enthusiasm in a wide range of clinical applications owing to the ease of collecting these cells, not only from the bone marrow but also from other accessible sources such as adipose tissue, synovium and umbilical cord.

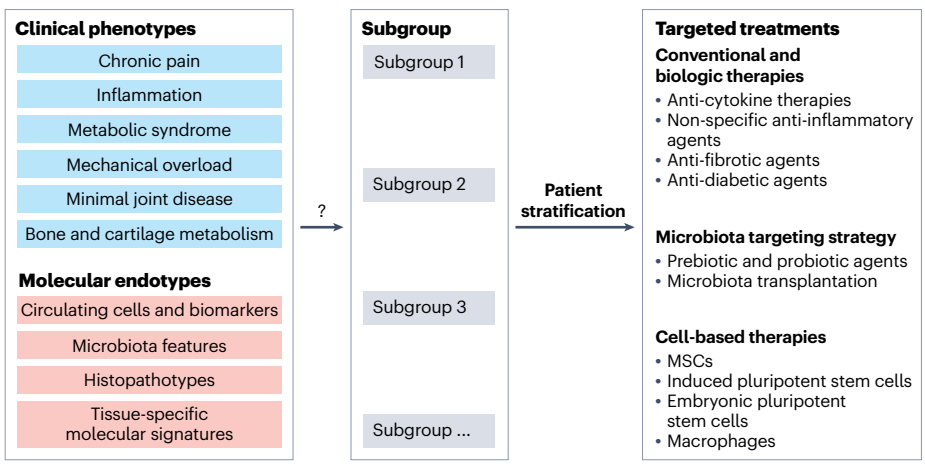

Fig. 3 | Towards personalized medicine in osteoarthritis. Schematic representation of the concept of personalized medicine in osteoarthritis (OA). The main clinical phenotypes of OA, which have previously described[187], could be associated with distinct or overlapping molecular endotypes; the number of possible subgroups based on these associations is still to be clarified in OA (as indicated by '?'). In the future, identifying clear subgroups in OA (by identifying associated clinical phenotypes and molecular endotypes) could enable better allocation of targeted treatments for each patient with OA. MSCs, mesenchymal stem cells.

MSCs are characterized by their immune-evading properties[162]; they express low levels of MHC class I and do not typically express MHC class II under normal conditions, thereby reducing the detection of these cells by the host immune system. In addition, MSCs express complement regulatory proteins, such as CD46, CD55 and CD59 (ref. 163), which protect them from complement-mediated lysis. Such features have made allogeneic MSCs particularly attractive for the development of cell-based therapy in OA as they offer several advantages over autologous MSCs, including off-the-shelf availability, reduced inter-donor variability, enhanced clinical consistency and reduced cost and logistical complexity[164]. Although allogeneic cell therapies are promising, further research is needed to establish their long-term safety, notably related to immunogenicity, rejection risk and adaptive immune response after repeated injections.

Although still controversial, it is increasingly accepted that MSCs respond to their environment by secreting (either directly or mediated via the production of extracellular vesicles containing specific cargo[165]) trophic and immunomodulatory factors, such as prostaglandin E_2, transforming growth factor β (TGFβ), indoleamine 2,3-dioxygenase, IL-10 and hepatocyte growth factor[166]. As such, MSCs have immunomodulatory and anti-inflammatory capabilities[167]. Of relevance to OA management, the ability of MSCs to produce biomolecules that can modulate innate and adaptive immunity was first identified in graft-versus-host disease[168]. In particular, MSCs can alter macrophage polarization from a pro-inflammatory to a pro-regenerative state[169]. MSCs also affect the differentiation, maturation and function of dendritic cells, resulting in reduced antigen presentation and T cell activation[170]. In addition, MSCs inhibit the proliferation, cytokine production and cytotoxic activity of NK cells[171]. These cells also inhibit T cell proliferation and activity[172] but stimulate the development of T_{reg} cells, which are essential for maintaining immune tolerance and preventing autoimmune responses[173]. Likewise, MSCs reduce B cell proliferation and differentiation, thereby reducing antibody production[174]. Overall, the interactions between MSCs and various immune cells exert a global anti-inflammatory and immunomodulatory effect, which, in the context of OA, could lead to a reduction in disease severity.

Owing to the effects of MSCs on immune cells in OA, a large number of human clinical trials have been initiated. A comprehensive meta-analysis of randomized and non-randomized controlled trials through the use of intra-articular injections of MSCs in patients with knee OA indicates clinically relevant pain reduction, improved joint function and cartilage protection at final follow-up endpoints[175]. Limitations such as small sample size, lack of clear patient stratification and variability in cell origin and dosage prevent definitive conclusions. This difficulty to unequivocally address the relevance of MSCs has been further reinforced by a multicentre human phase II–III clinical trial that failed to demonstrate the therapeutic superiority of MSCs over glucocorticoids 1 year after intra-articular injection in knee OA[176].

Future research on MSCs in OA should focus on defining the subsets of patients that could benefit from MSC-base cell therapy, identifying the optimal cell sources and dosages and establishing standards and quality-control procedures for the production of MSCs. In addition, issues related to the administration route and cell-delivery system should also be addressed. Therefore, preclinical developments now include the use of biomaterial scaffolds to promote MSC secretory functions and improve MSC-based therapy for OA[177]. Hopefully, such improvements could help clinicians to match available treatment options with the clinical phenotypes and molecular endotypes of patients with OA to ensure consistent and reproducible clinical outcomes from a personalized medicine perspective.

Other cell-based therapies. Beyond the aforementioned applications of MSCs, other immunomodulatory cell-based therapies have shown promise in preclinical and clinical trials for patients with OA, although the results of these trials still require further validation. These innovative approaches include intra-articular injection of genetically modified allogeneic chondrocytes that overexpress TGFβ[178] and of autologous peripheral blood mononuclear cells[179].

Given the pivotal role of macrophages in OA pathogenesis, several macrophage-based immunomodulatory cell therapies are also under investigation. These studies are investigating approaches that include intra-articular injection of genetically engineered macrophages that are 'locked' in an anti-inflammatory and pro-regenerative M2-like phenotype[180] or of allogeneic mononuclear cells from non-HLA-matched healthy donors induced to a stable apoptotic state (NCT06459063) to promote the pro-resolving features of macrophages. Furthermore, macrophage derivatives, including exosomes[181] and cytoplasmic membrane fragments[182] could also be used to bypass regulatory hurdles related to classical cell therapies.

Finally, induced pluripotent stem cells and embryonic pluripotent stem cells have been contemplated with interest because of their unprecedented capabilities of indefinite self-renewal and differentiation into any somatic cell lineages, including those found in joints[183,184]. These properties have made these cells attractive for in vitro OA disease modelling. Interestingly, the ability of induced pluripotent stem cells to give rise to MSCs (known as iMSCs) which exhibit similar biological behaviour to classical MSCs but with enhanced scalability, inter-donor reproducibility and improved immune properties, have also made iMSCs candidates for immunomodulatory intervention in various diseases[185]. iMSCs are being assessed in a multicentre, single-arm, phase I trial (NCT06049342) for safety and efficacy assessment in knee OA.

Altogether, these transformative therapies hold potential as optimal strategies for disease-modifying OA therapy by simultaneously delivering anti-inflammatory and pro-regenerative signals. However, extensive experiments are required before clinical translation can reasonably be considered and rigorous evaluation of the safety, efficacy and long-term outcomes of these therapies remains paramount in advancing these innovative approaches from bench to bedside.

Overall, the OA therapeutic landscape is evolving with the exploration of conventional, biological, gene- and cell-therapy approaches. Although current clinical results are not yet satisfactory, specific subsets of patients with OA presenting with clinical phenotypes, associated with precisely defined underlying molecular endotypes, will probably benefit from these therapies. By taking advantage of the development of cutting-edge technologies during the past decade and by improving patient stratification, the ultimate goal is to improve therapeutic outcomes and quality of life for individuals with OA. Notably, high-throughput omics approaches provide sensitivity and accuracy to gene- and protein-expression analyses and could be of prognostic and therapeutic relevance; however, the high cost and lack of reproducibility and standardization across centres still limit their clinical use[186].

Conclusions

The relationship between OA and the immune system is both multifaceted and dynamic. Although inflammation is a central feature in

OA pathogenesis, the interplay between innate and adaptive immune responses adds substantial complexity to the understanding of the disease. The involvement of various immune cells, cytokines and signalling pathways underscores the need for a nuanced approach to OA management.

Research published in the past 20 years highlights the potential of exploring novel therapeutic avenues, particularly through immunomodulatory strategies and regenerative medicine. These approaches are aimed at addressing not only the symptoms of OA but also the underlying immune mechanisms driving disease progression. Immunomodulatory therapies, such as targeting specific cytokines or immune cell subsets, offer the promise of reducing inflammation and slowing disease advancement. Regenerative medicine, including the use of MSCs and tissue engineering, holds potential for repairing damaged cartilage and restoring joint function.

As research continues to delve into the immunological intricacies of OA, a more comprehensive understanding of innate and adaptive immune cells in OA will be crucial. This knowledge will pave the way for innovative and targeted interventions, potentially transforming the management of OA. By integrating insights from both basic and clinical research, future therapies could offer more effective and personalized treatments, ultimately improving outcomes and quality of life for individuals affected by OA.

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References

1. Safiri, S. et al. Global, regional and national burden of osteoarthritis 1990–2017: a systematic analysis of the Global Burden of Disease Study 2017. *Ann. Rheum. Dis.* **79**, 819–828 (2020).
2. Price, A. J. et al. Knee replacement. *Lancet* **392**, 1672–1682 (2018).
3. Ferguson, R. J. et al. Hip replacement. *Lancet* **392**, 1662–1671 (2018).
4. Osteoarthritis Research Society International. *Osteoarthritis: A Serious Disease, Submitted to the U.S. Food and Drug Administration* White Paper (OARSI, 2016).
5. Sanchez-Lopez, E., Coras, R., Torres, A., Lane, N. E. & Guma, M. Synovial inflammation in osteoarthritis progression. *Nat. Rev. Rheumatol.* **18**, 258–275 (2022).
6. Stephenson, W. et al. Single-cell RNA-seq of rheumatoid arthritis synovial tissue using low-cost microfluidic instrumentation. *Nat. Commun.* **9**, 791 (2018).
7. Marx, V. Method of the year: spatially resolved transcriptomics. *Nat. Methods* **18**, 9–14 (2021).
8. Mandelin, A. M. et al. Transcriptional profiling of synovial macrophages using minimally invasive ultrasound-guided synovial biopsies in rheumatoid arthritis. *Arthritis Rheumatol.* **70**, 841–854 (2018).
9. Kelly, S. et al. Ultrasound-guided synovial biopsy: a safe, well-tolerated and reliable technique for obtaining high-quality synovial tissue from both large and small joints in early arthritis patients. *Ann. Rheum. Dis.* **74**, 611–617 (2015).
10. Zhang, F. et al. Deconstruction of rheumatoid arthritis synovium defines inflammatory subtypes. *Nature* **623**, 616–624 (2023).
11. Alivernini, S. et al. Distinct synovial tissue macrophage subsets regulate inflammation and remission in rheumatoid arthritis. *Nat. Med.* **26**, 1295–1306 (2020).
12. Accelerating Medicines Partnership Rheumatoid Arthritis and Systemic Lupus Erythematosus (AMP RA/SLE) Consortium. et al. Defining inflammatory cell states in rheumatoid arthritis joint synovial tissues by integrating single-cell transcriptomics and mass cytometry. *Nat. Immunol.* **20**, 928–942 (2019).
13. Smith, M. H. et al. Drivers of heterogeneity in synovial fibroblasts in rheumatoid arthritis. *Nat. Immunol.* **24**, 1200–1210 (2023).
14. Mizoguchi, F. et al. Functionally distinct disease-associated fibroblast subsets in rheumatoid arthritis. *Nat. Commun.* **9**, 789 (2018).
15. Croft, A. P. et al. Distinct fibroblast subsets drive inflammation and damage in arthritis. *Nature* **570**, 246–251 (2019).
16. Culemann, S. et al. Locally renewing resident synovial macrophages provide a protective barrier for the joint. *Nature* **572**, 670–675 (2019).
17. Wood, M. J. et al. Macrophage proliferation distinguishes 2 subgroups of knee osteoarthritis patients. *JCI Insight* **4**, e125325 (2019).
18. Knights, A. J. et al. Synovial macrophage diversity and activation of M-CSF signaling in post-traumatic osteoarthritis. Preprint at *bioRxiv* https://doi.org/10.1101/2023.10.03.559514 (2023).
19. Sebastian, A. et al. Single-cell RNA-Seq reveals changes in immune landscape in post-traumatic osteoarthritis. *Front. Immunol.* **13**, 938075 (2022).
20. Herrero-Beaumont, G. et al. Systemic osteoarthritis: the difficulty of categorically naming a continuous condition. *Aging Clin. Exp. Res.* **36**, 45 (2024).
21. McAlindon, T. E. et al. Associations of inflammatory and metabolic biomarkers with incident erosive hand osteoarthritis in the osteoarthritis initiative cohort. *Osteoarthr. Cartil.* **32**, 592–600 (2024).
22. Wang, Q. et al. Identification of a central role for complement in osteoarthritis. *Nat. Med.* **17**, 1674–1679 (2011).
23. Silva Santos Ribeiro, P., Willemen, H. L. D. M., Versteeg, S., Martin Gil, C. & Eijkelkamp, N. NLRP3 inflammasome activation in sensory neurons promotes chronic inflammatory and osteoarthritis pain. *Immunother. Adv.* **3**, ltad022 (2023).
24. Miller, R. J., Malfait, A.-M. & Miller, R. E. The innate immune response as a mediator of osteoarthritis pain. *Osteoarthr. Cartil.* **28**, 562–571 (2020).
25. Hannani, M. T. et al. From biochemical markers to molecular endotypes of osteoarthritis: a review on validated biomarkers. *Expert. Rev. Mol. Diagnostics* **24**, 23–38 (2024).
26. Atukorala, I. et al. Synovitis in knee osteoarthritis: a precursor of disease? *Ann. Rheum. Dis.* **75**, 390–395 (2016).
27. Conaghan, P. G. et al. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: results from a large, 3-year, prospective EULAR study. *Ann. Rheum. Dis.* **69**, 644–647 (2010).
28. Eitner, A. et al. Pain sensation in human osteoarthritic knee joints is strongly enhanced by diabetes mellitus. *Pain* **158**, 1743–1753 (2017).
29. Zhang, H. et al. Synovial macrophage M1 polarisation exacerbates experimental osteoarthritis partially through R-spondin-2. *Ann. Rheum. Dis.* **77**, 1524–1534 (2018).
30. Raghu, H. et al. CCL2/CCR2, but not CCL5/CCR5, mediates monocyte recruitment, inflammation and cartilage destruction in osteoarthritis. *Ann. Rheum. Dis.* **76**, 914–922 (2017).
31. Sakurai, Y. et al. Contribution of synovial macrophages to rat advanced osteoarthritis pain resistant to cyclooxygenase inhibitors. *Pain* **160**, 895–907 (2019).
32. Blom, A. B. et al. Crucial role of macrophages in matrix metalloproteinase-mediated cartilage destruction during experimental osteoarthritis: involvement of matrix metalloproteinase 3. *Arthritis Rheum.* **56**, 147–157 (2007).
33. Chou, C.-H. et al. Synovial cell cross-talk with cartilage plays a major role in the pathogenesis of osteoarthritis. *Sci. Rep.* **10**, 10868 (2020).
34. Wang, C. et al. Transcriptomic profiling of osteoarthritis synovial macrophages reveals a tolerized phenotype compounded by a weak corticosteroid response. *Rheumatology* **64**, 860–869 (2024).
35. Macchi, V. et al. The infrapatellar fat pad and the synovial membrane: an anatomo-functional unit. *J. Anat.* **233**, 146–154 (2018).
36. Tang, S. et al. Single-cell atlas of human infrapatellar fat pad and synovium implicates APOE signaling in osteoarthritis pathology. *Sci. Transl. Med.* **16**, eadf4590 (2024).
37. South, S. M. et al. Imaging mass cytometry reveals tissue-specific cellular immune phenotypes in the mouse knee following ACL injury. *Osteoarthr. Cartil. Open.* **5**, 100416 (2023).
38. Peters, H. et al. Cell and transcriptomic diversity of infrapatellar fat pad during knee osteoarthritis. *Ann. Rheum. Dis.* **84**, 351–367 (2025).
39. Blackler, G. et al. Targeting STAT6-mediated synovial macrophage activation improves pain in experimental knee osteoarthritis. *Arthritis Res. Ther.* **26**, 73 (2024).
40. Philpott, H. T. et al. Synovial innate immune exhaustion is associated with worse pain in knee osteoarthritis. *Arthritis Rheumatol.* https://doi.org/10.1002/art.43089 (2024).
41. Fang, C. et al. TREM2 promotes macrophage polarization from M1 to M2 and suppresses osteoarthritis through the NF-κB/CXCL3 axis. *Int. J. Biol. Sci.* **20**, 1992–2007 (2024).
42. Raoof, R. et al. Dorsal root ganglia macrophages maintain osteoarthritis pain. *J. Neurosci.* **41**, 8249–8261 (2021).
43. Martin Gil, C. et al. Myostatin and CXCL11 promote nervous tissue macrophages to maintain osteoarthritis pain. *Brain Behav. Immun.* **116**, 203–215 (2024).
44. Geraghty, T. et al. Age-associated changes in knee osteoarthritis, pain-related behaviors, and dorsal root ganglia immunophenotyping of male and female mice. *Arthritis Rheumatol.* **75**, 1770–1780 (2023).
45. Domoto, R., Sekiguchi, F., Tsubota, M. & Kawabata, A. Macrophage as a peripheral pain regulator. *Cells* **10**, 1881 (2021).
46. Nigrovic, P. A. & Lee, D. M. Mast cells in inflammatory arthritis. *Arthritis Res. Ther.* **7**, 1–11 (2005).
47. Mehta, B. et al. Machine learning identification of thresholds to discriminate osteoarthritis and rheumatoid arthritis synovial inflammation. *Arthritis Res. Ther.* **25**, 31 (2023).
48. Das, N. et al. Tryptase β regulation of joint lubrication and inflammation via proteoglycan-4 in osteoarthritis. *Nat. Commun.* **14**, 1910 (2023).
49. Wang, Q. et al. IgE-mediated mast cell activation promotes inflammation and cartilage destruction in osteoarthritis. *eLife* **8**, e39905 (2019).
50. Baker, M. C., Robinson, W. H. & Ostrom, Q. Genetic association between atopic disease and osteoarthritis. *Osteoarthr. Cartil.* **32**, 220–225 (2024).
51. Wilkinson, D. J. et al. Matrix metalloproteinase-13 is fully activated by neutrophil elastase and inactivates its serpin inhibitor, alpha-1 antitrypsin: implications for osteoarthritis. *FEBS J.* **289**, 121–139 (2022).
52. Mehrani, Y. et al. The importance of neutrophils in osteoarthritis: current concepts and therapeutic perspectives. *Immuno* **3**, 250–272 (2023).
53. Luan, T. et al. Identification and analysis of neutrophil extracellular trap-related genes in osteoarthritis by bioinformatics and experimental verification. *J. Inflamm. Res.* **16**, 3837–3852 (2023).
54. Manukyan, G. et al. Phenotypic and functional characterisation of synovial fluid-derived neutrophils in knee osteoarthritis and knee infection. *Osteoarthr. Cartil.* **31**, 72–82 (2023).

55. Tchitchek, N. et al. Deep immunophenotyping reveals that autoimmune and autoinflammatory disorders are spread along two immunological axes capturing disease inflammation levels and types. *Ann. Rheum. Dis.* **83**, 638–650 (2024).
56. Huss, R. S., Huddleston, J. I., Goodman, S. B., Butcher, E. C. & Zabel, B. A. Synovial tissue-infiltrating natural killer cells in osteoarthritis and periprosthetic inflammation: NK cells in degenerative joint disease. *Arthritis Rheum.* **62**, 3799–3805 (2010).
57. Vivier, E. et al. Innate lymphoid cells: 10 years on. *Cell* **174**, 1054–1066 (2018).
58. Kraus, V. B. et al. An osteoarthritis pathophysiological continuum revealed by molecular biomarkers. *Sci. Adv.* **10**, eadj6814 (2024).
59. Loukov, D., Karampatos, S., Maly, M. R. & Bowdish, D. M. E. Monocyte activation is elevated in women with knee-osteoarthritis and associated with inflammation, BMI and pain. *Osteoarthr. Cartil.* **26**, 255–263 (2018).
60. Zhao, X. et al. CCL3/CCR1 mediates $CD14^{+}CD16^{-}$ circulating monocyte recruitment in knee osteoarthritis progression. *Osteoarthr. Cartil.* **28**, 613–625 (2020).
61. Dong Kim, K. et al. Adaptive immune cells temper initial innate responses. *Nat. Med.* **13**, 1248–1252 (2007).
62. Kumar, B. V., Connors, T. J. & Farber, D. L. Human T cell development, localization, and function throughout life. *Immunity* **48**, 202–213 (2018).
63. Rosshirt, N. et al. Proinflammatory T cell polarization is already present in patients with early knee osteoarthritis. *Arthritis Res. Ther.* **23**, 37 (2021).
64. Shen, P.-C. et al. T helper cells promote disease progression of osteoarthritis by inducing macrophage inflammatory protein-1γ. *Osteoarthr. Cartil.* **19**, 728–736 (2011).
65. Nees, T. A. et al. T helper cell infiltration in osteoarthritis-related knee pain and disability. *J. Clin. Med.* **9**, 2423 (2020).
66. Wheeler, T. A. et al. Mechanical loading of joint modulates T cells in lymph nodes to regulate osteoarthritis. *Osteoarthr. Cartil.* **32**, 287–298 (2024).
67. Nees, T. A. et al. Infiltration profile of regulatory T cells in osteoarthritis-related pain and disability. *Biomedicines* **10**, 2111 (2022).
68. Ponchel, F. et al. Changes in peripheral blood immune cell composition in osteoarthritis. *Osteoarthr. Cartil.* **23**, 1870–1878 (2015).
69. Xie, X., Doody, G. M., Shuweihdi, F., Conaghan, P. G. & Ponchel, F. B-cell capacity for expansion and differentiation into plasma cells are altered in osteoarthritis. *Osteoarthr. Cartil.* **31**, 1176–1188 (2023).
70. Platzer, H. et al. $CD8^{+}$ T cells in OA knee joints are differentiated into subsets depending on OA stage and compartment. *J. Clin. Med.* **11**, 2814 (2022).
71. Trajerova, M. et al. Knee osteoarthritis phenotypes based on synovial fluid immune cells correlate with clinical outcome trajectories. *Osteoarthr. Cartil.* **30**, 1583–1592 (2022).
72. Burt, K. G. & Scanzello, C. R. B cells in osteoarthritis: simply a sign or a target for therapy? *Osteoarthr. Cartil.* **31**, 1148–1151 (2023).
73. Sun, H. et al. $IgM^{+}CD27^{+}$ B cells possessed regulatory function and represented the main source of B cell-derived IL-10 in the synovial fluid of osteoarthritis patients. *Hum. Immunol.* **80**, 263–269 (2019).
74. Kapoor, M., Martel-Pelletier, J., Lajeunesse, D., Pelletier, J.-P. & Fahmi, H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat. Rev. Rheumatol.* **7**, 33–42 (2011).
75. Xie, X. et al. Auto-antibodies to post-translationally modified proteins in osteoarthritis. *Osteoarthr. Cartil.* **29**, 924–933 (2021).
76. Pacquelet, S. et al. Interleukin 17, a nitric oxide-producing cytokine with a peroxynitrite-independent inhibitory effect on proteoglycan synthesis. *J. Rheumatol.* **29**, 2602–2610 (2002).
77. Sun, W. et al. IL-17A exacerbates synovial inflammation in osteoarthritis via activation of endoplasmic reticulum stress. *Int. Immunopharmacol.* **145**, 113733 (2025).
78. Sinkeviciute, D., Aspberg, A., He, Y., Bay-Jensen, A.-C. & Önnerfjord, P. Characterization of the interleukin-17 effect on articular cartilage in a translational model: an explorative study. *BMC Rheumatol.* **4**, 30 (2020).
79. Wisniewska, E. et al. Infrapatellar fat pad modulates osteoarthritis-associated cytokine and MMP expression in human articular chondrocytes. *Cells* **12**, 2850 (2023).
80. Zapata-Linares, N. et al. Systemic and joint adipose tissue lipids and their role in osteoarthritis. *Biochimie* **227**, 130–138 (2024).
81. Apinun, J. et al. Immune mediators in osteoarthritis: infrapatellar fat pad-infiltrating CD8+ T cells are increased in osteoarthritic patients with higher clinical radiographic grading. *Int. J. Rheumatol.* **2016**, 9525724 (2016).
82. Xu, C. et al. Causal associations between circulating immune cells and osteoarthritis: a bidirectional Mendelian randomization study. *Int. Immunopharmacol.* **142**, 113156 (2024).
83. Zhu, W. et al. Alterations in peripheral T cell and B cell subsets in patients with osteoarthritis. *Clin. Rheumatol.* **39**, 523–532 (2020).
84. Binvignat, M. et al. Immunological profiling in knee osteoarthritis: Treg dysfunction as key driver of pain. Preprint at *bioRxiv* https://doi.org/10.1101/2024.10.12.618016 (2024).
85. Nakamura, H., Yoshino, S., Kato, T., Tsuruha, J. & Nishioka, K. T-cell mediated inflammatory pathway in osteoarthritis. *Osteoarthr. Cartil.* **7**, 401–402 (1999).
86. Kim, H.-Y. et al. Enhanced T cell proliferative response to type II collagen and synthetic peptide CII (255–274) in patients with rheumatoid arthritis. *Arthritis Rheum.* **42**, 2085–2093 (1999).
87. Tsuruha, J.-I. et al. Autoimmunity against YKL-39, a human cartilage derived protein, in patients with osteoarthritis. *J. Rheumatol.* **29**, 1459–1466 (2002).
88. Sakata, M. et al. Osteoarthritic articular chondrocytes stimulate autologous T cell responses in vitro. *Clin. Exp. Rheumatol.* **21**, 704–710 (2003).
89. De Jong, H. et al. Cartilage proteoglycan aggrecan epitopes induce proinflammatory autoreactive T-cell responses in rheumatoid arthritis and osteoarthritis. *Ann. Rheum. Dis.* **69**, 255–262 (2010).
90. Camacho-Encina, M. et al. Discovery of an autoantibody signature for the early diagnosis of knee osteoarthritis: data from the Osteoarthritis Initiative. *Ann. Rheum. Dis.* **78**, 1699–1705 (2019).
91. Boutet, M.-A. et al. Comparative analysis of late-stage rheumatoid arthritis and osteoarthritis reveals shared histopathological features. *Osteoarthr. Cartil.* **32**, 166–176 (2024).
92. Favero, M. et al. Infrapatellar fat pad features in osteoarthritis: a histopathological and molecular study. *Rheumatology* **56**, 1784–1793 (2017).
93. Marshall, D. A. et al. Existing comorbidities in people with osteoarthritis: a retrospective analysis of a population-based cohort in Alberta, Canada. *BMJ Open.* **9**, e033334 (2019).
94. Visser, A. W. et al. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. *Ann. Rheum. Dis.* **74**, 1842–1847 (2015).
95. Jin, X. et al. Circulating C reactive protein in osteoarthritis: a systematic review and meta-analysis. *Ann. Rheum. Dis.* **74**, 703–710 (2015).
96. Attur, M. et al. Plasma levels of interleukin-1 receptor antagonist (IL1Ra) predict radiographic progression of symptomatic knee osteoarthritis. *Osteoarthr. Cartil.* **23**, 1915–1924 (2015).
97. Hotamisligil, G. S. Inflammation, metaflammation and immunometabolic disorders. *Nature* **542**, 177–185 (2017).
98. Fulop, T. et al. Immunology of aging: the birth of inflammaging. *Clin. Rev. Allerg. Immunol.* **64**, 109–122 (2021).
99. Courties, A., Berenbaum, F. & Sellam, J. The phenotypic approach to osteoarthritis: a look at metabolic syndrome-associated osteoarthritis. *Jt Bone Spine* **86**, 725–730 (2019).
100. Binvignat, M., Sellam, J., Berenbaum, F. & Felson, D. T. The role of obesity and adipose tissue dysfunction in osteoarthritis pain. *Nat. Rev. Rheumatol.* **20**, 565–584 (2024).
101. Unamuno, X. et al. Adipokine dysregulation and adipose tissue inflammation in human obesity. *Eur. J. Clin. Invest.* **48**, e12997 (2018).
102. Francisco, V. et al. Adipokines: linking metabolic syndrome, the immune system, and arthritic diseases. *Biochem. Pharmacol.* **165**, 196–206 (2019).
103. Frühbeck, G., Catalán, V., Rodríguez, A. & Gómez-Ambrosi, J. Adiponectin-leptin ratio: a promising index to estimate adipose tissue dysfunction. Relation with obesity-associated cardiometabolic risk. *Adipocyte* **7**, 57–62 (2018).
104. Sellam, J. et al. Pain in women with knee and/or hip osteoarthritis is related to systemic inflammation and to adipose tissue dysfunction: cross-sectional results of the KHOALA cohort. *Semin. Arthritis Rheum.* **51**, 129–136 (2021).
105. De Roover, A., Escribano-Núñez, A., Monteagudo, S. & Lories, R. Fundamentals of osteoarthritis: inflammatory mediators in osteoarthritis. *Osteoarthr. Cartil.* **31**, 1303–1311 (2023).
106. Swindell, W. R. et al. Robust shifts in S100a9 expression with aging: a novel mechanism for chronic inflammation. *Sci. Rep.* **3**, 1215 (2013).
107. Greene, M. A. & Loeser, R. F. Aging-related inflammation in osteoarthritis. *Osteoarthr. Cartil.* **23**, 1966–1971 (2015).
108. Liu, Z. et al. Immunosenescence: molecular mechanisms and diseases. *Sig. Transduct. Target. Ther.* **8**, 200 (2023).
109. Khan, S. et al. B cells promote T cell immunosenescence and mammalian aging parameters. Preprint at *bioRxiv* https://doi.org/10.1101/2023.09.12.556363 (2023).
110. Han, Z., Wang, K., Ding, S. & Zhang, M. Cross-talk of inflammation and cellular senescence: a new insight into the occurrence and progression of osteoarthritis. *Bone Res.* **12**, 69 (2024).
111. Li, H., Liu, W. & Xie, J. Circulating interleukin-6 levels and cardiovascular and all-cause mortality in the elderly population: a meta-analysis. *Arch. Gerontol. Geriatr.* **73**, 257–262 (2017).
112. Forcina, L., Franceschi, C. & Musarò, A. The hormetic and hermetic role of IL-6. *Ageing Res. Rev.* **80**, 101697 (2022).
113. Widjaja, A. A. et al. Inhibition of IL-11 signalling extends mammalian healthspan and lifespan. *Nature* **632**, 157–165 (2024).
114. Binvignat, M., Sokol, H., Mariotti-Ferrandiz, E., Berenbaum, F. & Sellam, J. Osteoarthritis and gut microbiome. *Jt Bone Spine* **88**, 105203 (2021).
115. Marietta, E., Rishi, A. & Taneja, V. Immunogenetic control of the intestinal microbiota. *Immunology* **145**, 313–322 (2015).
116. Guan, Z. et al. Gut microbiome dysbiosis alleviates the progression of osteoarthritis in mice. *Clin. Sci.* **134**, 3159–3174 (2020).
117. Ulici, V. et al. Osteoarthritis induced by destabilization of the medial meniscus is reduced in germ-free mice. *Osteoarthr. Cartil.* **26**, 1098–1109 (2018).
118. Schott, E. M. et al. Targeting the gut microbiome to treat the osteoarthritis of obesity. *JCI Insight* **3**, e95997 (2018).
119. Huang, Z. Y., Stabler, T., Pei, F. X. & Kraus, V. B. Both systemic and local lipopolysaccharide (LPS) burden are associated with knee OA severity and inflammation. *Osteoarthr. Cartil.* **24**, 1769–1775 (2016).
120. Boer, C. G. et al. Intestinal microbiome composition and its relation to joint pain and inflammation. *Nat. Commun.* **10**, 4881 (2019).
121. Dunn, C. M. et al. Identification of cartilage microbial DNA signatures and associations with knee and hip osteoarthritis. *Arthritis Rheumatol.* **72**, 1111–1122 (2020).
122. Huang, Z. Y. et al. Biomarkers of inflammation — LBP and TLR — predict progression of knee osteoarthritis in the DOXY clinical trial. *Osteoarthr. Cartil.* **26**, 1658–1665 (2018).

123. Wei, J. et al. Association between gut microbiota and symptomatic hand osteoarthritis: data from the Xiangya Osteoarthritis Study. *Arthritis Rheumatol.* **73**, 1656–1662 (2021).
124. Binvignat, M. et al. Serum tryptophan metabolites are associated with erosive hand osteoarthritis and pain: results from the DIGICOD cohort. *Osteoarthr. Cartil.* **31**, 1132–1143 (2023).
125. Binvignat, M. et al. Serum intestinal permeability biomarkers are associated with erosive hand osteoarthritis and radiographic severity: results from the DIGICOD cohort. *Osteoarthr. Cartil.* **32**, 747 (2024).
126. Moulin, D. et al. Counteracting tryptophan metabolism alterations as a new therapeutic strategy for rheumatoid arthritis. *Ann. Rheum. Dis.* **83**, 312–323 (2024).
127. Cho, K.-H. et al. Lactobacillus (LA-1) and butyrate inhibit osteoarthritis by controlling autophagy and inflammatory cell death of chondrocytes. *Front. Immunol.* **13**, 930511 (2022).
128. Huang, Z. et al. Faecal microbiota transplantation from metabolically compromised human donors accelerates osteoarthritis in mice. *Ann. Rheum. Dis.* **79**, 646–656 (2020).
129. Kamps, A. et al. Occurrence of comorbidity following osteoarthritis diagnosis: a cohort study in the Netherlands. *Osteoarthr. Cartil.* **31**, 519–528 (2023).
130. Magnusson, K., Turkiewicz, A., Dell'Isola, A. & Englund, M. Shared genetic factors between osteoarthritis and cardiovascular disease may underlie common etiology. *Nat. Commun.* **15**, 9569 (2024).
131. Weber, A. et al. Association between osteoarthritis and increased risk of dementia: a systemic review and meta-analysis. *Medicine* **98**, e14355 (2019).
132. Kyrkanides, S. et al. Osteoarthritis accelerates and exacerbates Alzheimer's disease pathology in mice. *J. Neuroinflammation* **8**, 112 (2011).
133. Favero, M. et al. Erosive hand osteoarthritis: latest findings and outlook. *Nat. Rev. Rheumatol.* **18**, 171–183 (2022).
134. Kloppenburg, M. et al. Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **77**, 1757–1764 (2018).
135. Chevalier, X. et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **74**, 1697–1705 (2015).
136. Richette, P. et al. Efficacy of tocilizumab in patients with hand osteoarthritis: double blind, randomised, placebo-controlled, multicentre trial. *Ann. Rheum. Dis.* **80**, 349–355 (2021).
137. Schett, G. et al. Anti-granulocyte-macrophage colony-stimulating factor antibody otilimab in patients with hand osteoarthritis: a phase 2a randomised trial. *Lancet Rheumatol.* **2**, e623–e632 (2020).
138. Fleischmann, R. M. et al. A phase II trial of lutikizumab, an anti-interleukin-1α/β dual variable domain immunoglobulin, in knee osteoarthritis patients with synovitis. *Arthritis Rheumatol.* **71**, 1056–1069 (2019).
139. Kloppenburg, M. et al. Phase IIa, placebo-controlled, randomised study of lutikizumab, an anti-interleukin-1α and anti-interleukin-1β dual variable domain immunoglobulin, in patients with erosive hand osteoarthritis. *Ann. Rheum. Dis.* **78**, 413–420 (2019).
140. Schieker, M. et al. Effects of interleukin-1β inhibition on incident hip and knee replacement: exploratory analyses from a randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* **173**, 509–515 (2020).
141. Wittoek, R., Verbruggen, G., Vanhaverbeke, T., Colman, R. & Elewaut, D. RANKL blockade for erosive hand osteoarthritis: a randomized placebo-controlled phase 2a trial. *Nat. Med.* **30**, 829–836 (2024).
142. Kingsbury, S. R. et al. Pain reduction with oral methotrexate in knee osteoarthritis: a randomized, placebo-controlled clinical trial. *Ann. Intern. Med.* **177**, 1145–1156 (2024).
143. Wang, Y. et al. Methotrexate to treat hand osteoarthritis with synovitis (METHODS): an Australian, multisite, parallel-group, double-blind, randomised, placebo-controlled trial. *Lancet* **402**, 1764–1772 (2023).
144. Ferrero, S. et al. Methotrexate treatment in hand osteoarthritis refractory to usual treatments: a randomised, double-blind, placebo-controlled trial. *Semin. Arthritis Rheum.* **51**, 831–838 (2021).
145. Najm, A., Alunno, A., Gwinnutt, J. M., Weill, C. & Berenbaum, F. Efficacy of intra-articular corticosteroid injections in knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Jt Bone Spine* **88**, 105198 (2021).
146. Guermazi, A., Hunter, D. J. & Kloppenburg, M. Debate: intra-articular steroid injections for osteoarthritis — harmful or helpful? *Osteoarthr. Imaging* **3**, 100163 (2023).
147. Kroon, F. P. B. et al. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. *Lancet* **394**, 1993–2001 (2019).
148. Døssing, A. et al. Colchicine twice a day for hand osteoarthritis (COLOR): a double-blind, randomised, placebo-controlled trial. *Lancet Rheumatol.* **5**, e254–e262 (2023).
149. Heijman, M. W. J. et al. Association of low-dose colchicine with incidence of knee and hip replacements: exploratory analyses from a randomized, controlled, double-blind trial. *Ann. Intern. Med.* **176**, 737–742 (2023).
150. Kingsbury, S. R. et al. Hydroxychloroquine effectiveness in reducing symptoms of hand osteoarthritis: a randomized trial. *Ann. Intern. Med.* **168**, 385 (2018).
151. Wang, Y. et al. Effect of atorvastatin on knee cartilage volume in patients with symptomatic knee osteoarthritis: results from a randomized placebo-controlled trial. *Arthritis Rheumatol.* **73**, 2035–2043 (2021).
152. Grigsby, E. et al. XT-150 — a novel immunomodulatory gene therapy for osteoarthritis pain in phase 2b development. *Osteoarthr. Cartil.* **29**, S12 (2021).
153. Meurot, C. et al. Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis. *Sci. Rep.* **12**, 1567 (2022).
154. Remst, D. F. G. et al. Gene expression analysis of murine and human osteoarthritis synovium reveals elevation of transforming growth factor β-responsive genes in osteoarthritis-related fibrosis. *Arthritis Rheumatol.* **66**, 647–656 (2014).
155. Yan, J. et al. Nintedanib ameliorates osteoarthritis in mice by inhibiting synovial inflammation and fibrosis caused by M1 polarization of synovial macrophages via the MAPK / PI3K-AKT pathway. *FASEB J.* **37**, e23177 (2023).
156. Pers, Y.-M. et al. Recommendations from the French Societies of Rheumatology and Physical Medicine and Rehabilitation on the non-pharmacological management of knee osteoarthritis. *Ann. Phys. Rehabil. Med.* **67**, 101883 (2024).
157. Walrabenstein, W. et al. A multidisciplinary lifestyle program for metabolic syndrome-associated osteoarthritis: the 'Plants for Joints' randomized controlled trial. *Osteoarthr. Cartil.* **31**, 1491–1500 (2023).
158. Mobasheri, A. & Loeser, R. Clinical phenotypes, molecular endotypes and theratypes in OA therapeutic development. *Nat. Rev. Rheumatol.* **20**, 525–526 (2024).
159. Angelini, F. et al. Osteoarthritis endotype discovery via clustering of biochemical marker data. *Ann. Rheum. Dis.* **81**, 666–675 (2022).
160. Siaton, B. C., Hogans, B. H. & Hochberg, M. C. Precision medicine in osteoarthritis: not yet ready for prime time. *Expert. Rev. Precis. Med. Drug. Dev.* **6**, 5–8 (2021).
161. Barry, F. & Murphy, M. Mesenchymal stem cells in joint disease and repair. *Nat. Rev. Rheumatol.* **9**, 584–594 (2013).
162. Ankrum, J. A., Ong, J. F. & Karp, J. M. Mesenchymal stem cells: immune evasive, not immune privileged. *Nat. Biotechnol.* **32**, 252–260 (2014).
163. Moll, G. et al. Mesenchymal stromal cells engage complement and complement receptor bearing innate effector cells to modulate immune responses. *PLoS ONE* **6**, e21703 (2011).
164. Chen, C.-F. et al. Treatment of knee osteoarthritis with intra-articular injection of allogeneic adipose-derived stem cells (ADSCs) ELIXCYTE®: a phase I/II, randomized, active-control, single-blind, multiple-center clinical trial. *Stem Cell Res. Ther.* **12**, 562 (2021).
165. Bertolino, G. M., Maumus, M., Jorgensen, C. & Noël, D. Therapeutic potential in rheumatic diseases of extracellular vesicles derived from mesenchymal stromal cells. *Nat. Rev. Rheumatol.* **19**, 682–694 (2023).
166. Najar, M. et al. Mesenchymal stromal cells and immunomodulation: a gathering of regulatory immune cells. *Cytotherapy* **18**, 160–171 (2016).
167. Wang, Y., Fang, J., Liu, B., Shao, C. & Shi, Y. Reciprocal regulation of mesenchymal stem cells and immune responses. *Cell Stem Cell* **29**, 1515–1530 (2022).
168. Le Blanc, K. et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. *Lancet* **371**, 1579–1586 (2008).
169. Giri, J., Das, R., Nylen, E., Chinnadurai, R. & Galipeau, J. CCL2 and CXCL12 derived from mesenchymal stromal cells cooperatively polarize IL-10+ tissue macrophages to mitigate gut injury. *Cell Rep.* **30**, 1923–1934.e4 (2020).
170. Chiesa, S. et al. Mesenchymal stem cells impair in vivo T-cell priming by dendritic cells. *Proc. Natl Acad. Sci. USA* **108**, 17384–17389 (2011).
171. Abbasi, B., Shamsasenjan, K., Ahmadi, M., Beheshti, S. A. & Saleh, M. Mesenchymal stem cells and natural killer cells interaction mechanisms and potential clinical applications. *Stem Cell Res. Ther.* **13**, 97 (2022).
172. Glennie, S., Soeiro, I., Dyson, P. J., Lam, E. W.-F. & Dazzi, F. Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. *Blood* **105**, 2821–2827 (2005).
173. Hagmann, S. et al. The influence of bone marrow- and synovium-derived mesenchymal stromal cells from osteoarthritis patients on regulatory T cells in co-culture. *Clin. Exp. Immunol.* **173**, 454–462 (2013).
174. Corcione, A. et al. Human mesenchymal stem cells modulate B-cell functions. *Blood* **107**, 367–372 (2006).
175. Copp, G., Robb, K. P. & Viswanathan, S. Culture-expanded mesenchymal stromal cell therapy: does it work in knee osteoarthritis? A pathway to clinical success. *Cell Mol. Immunol.* **20**, 626–650 (2023).
176. Mautner, K. et al. Cell-based versus corticosteroid injections for knee pain in osteoarthritis: a randomized phase 3 trial. *Nat. Med.* **29**, 3120–3126 (2023).
177. Lagneau, N. et al. Harnessing cell-material interactions to control stem cell secretion for osteoarthritis treatment. *Biomaterials* **296**, 122091 (2023).
178. Cherian, J. J. et al. Preliminary results of a phase II randomized study to determine the efficacy and safety of genetically engineered allogeneic human chondrocytes expressing TGF-β1 in patients with grade 3 chronic degenerative joint disease of the knee. *Osteoarthr. Cartil.* **23**, 2109–2118 (2015).
179. Chuang, C.-H. et al. Enriched peripheral blood-derived mononuclear cells for treating knee osteoarthritis. *Cell Transpl.* **32**, 09636897221149445 (2023).
180. Liang, C. et al. Engineered M2a macrophages for the treatment of osteoarthritis. *Front. Immunol.* **13**, 1054938 (2022).
181. Song, X. et al. An injectable thermosensitive hydrogel delivering M2 macrophage-derived exosomes alleviates osteoarthritis by promoting synovial lymphangiogenesis. *Acta Biomater.* **189**, 130–142 (2024).
182. Ma, Y. et al. Artificial M2 macrophages for disease-modifying osteoarthritis therapeutics. *Biomaterials* **274**, 120865 (2021).
183. Craft, A. M. et al. Generation of articular chondrocytes from human pluripotent stem cells. *Nat. Biotechnol.* **33**, 638–645 (2015).
184. Tiwari, S. K., Wong, W. J., Moreira, M., Pasqualini, C. & Ginhoux, F. Induced pluripotent stem cell-derived macrophages as a platform for modelling human disease. *Nat. Rev. Immunol.* **25**, 108–124 (2025).

185. Kelly, K. et al. Two-year safety outcomes of iPS cell-derived mesenchymal stromal cells in acute steroid-resistant graft-versus-host disease. *Nat. Med.* **30**, 1556–1558 (2024).
186. Byron, S. A., Van Keuren-Jensen, K. R., Engelthaler, D. M., Carpten, J. D. & Craig, D. W. Translating RNA sequencing into clinical diagnostics: opportunities and challenges. *Nat. Rev. Genet.* **17**, 257–271 (2016).
187. Mobasheri, A. et al. Recent advances in understanding the phenotypes of osteoarthritis. *F1000Res* **8**, 2091 (2019).

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Perspective

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Delineating inflammatory from non-inflammatory mechanisms for therapy optimization in psoriatic arthritis

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Abstract

Psoriatic arthritis (PsA) is anatomically much more heterogeneous than rheumatoid arthritis, as, beyond synovitis, it often also involves enthesitis, peritendinitis, tenosynovitis, osteitis and periostitis. This heterogeneity currently precludes a gold standard for objectively defining resolution of inflammation following treatment, with enthesitis posing a particular challenge. Despite these difficulties, we apply lessons learned from rheumatoid arthritis to describe how patients with PsA and an inadequate response to therapy can be designated within two patient subgroups, characterized by persistent inflammatory PsA (PIPsA) and non-inflammatory PsA (NIPsA), respectively. The NIPsA phenotype is defined by the lack of ongoing joint inflammation, as confirmed through clinical assessment and imaging, along with normalized inflammatory marker levels. NIPsA might be associated with obesity, biomechanical-related pain, osteoarthritis, fibromyalgia, secondary post-inflammatory damage and central pain mechanisms. In this article, we frame PsA composite outcomes measures in relationship to the PIPsA and NIPsA phenotypes and propose that this approach might help to minimize unnecessary or ineffective cycling of PsA therapy in patients who acquire dominant non-inflammatory mechanisms and might also inform future trial design.

Sections

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Key points

- For optimal management of patients with psoriatic arthritis (PsA) and an inadequate response to treatment (particularly in cases that are difficult to treat or refractory), we propose two main disease subcategories: persistent inflammatory PsA (PIPsA) and non-inflammatory PsA (NIPsA).
- Despite the complexity of PsA in terms of the structures involved (enthesis, synovium, tendons, para-tendinous soft tissue and bone), the best clinical feature for the routine recognition of genuine inflammatory arthritis is joint swelling (synovitis or dactylitis), which can be confirmed by ultrasonography (PIPsA phenotype).
- In symptomatic patients with persistent pain and high composite scores, but without objective clinical signs of inflammation, the absence of 'active' inflammation on ultrasonography suggests a NIPsA phenotype that is likely to be associated with comorbidities, such as obesity and osteoarthritis; however, distinguishing 'pure' and less common isolated entheseal phenotypes remains challenging for this less common clinical phenotype.
- The exhaustion of therapeutic options define treatment-refractory PsA; however, it is recognized that non-response, as measured by composite outcomes, might involve non-inflammatory components, highlighting the need for imaging.
- Accurate characterization of the PIPsA phenotype will facilitate clinical trials, including combinations of advanced therapies using existing composite outcomes for PsA.

Introduction

The success of biological disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) in rheumatology for both rheumatoid arthritis (RA) and psoriatic arthritis (PsA) has revolutionized the management and even resulted in dose optimization or tapering strategies as key features in disease management[1,2]. Despite these therapeutic advances, there has been increasing recognition of patients with inflammatory arthritis that is non-responsive or refractory to treatment, initially in RA and later in PsA[3–7].

Patients with RA who have been exposed to multiple DMARDs without apparent benefit are variously designated as having 'difficult-to-treat', 'treatment-resistant' or 'refractory' RA[4,6]. We previously suggested that patients with RA in whom all available classes of drug have failed could be designated as having 'poly-refractory RA', as there are no therapeutic options left[8]. In RA, the 'difficult-to-treat' terminology is the best agreed term and defines individuals with signs of active disease in whom at least two bDMARD or tsDMARD classes have failed following conventional DMARDs[4]. The 'difficult-to-treat' terminology as articulated for RA was also used in PsA, with 'difficult-to-treat' PsA having been suggested to also represent failure of at least one conventional DMARD and two bDMARD or tsDMARD classes[3,9] (Table 1). An attempt has also been made to differentiate 'difficult-to-treat' PsA from 'treatment-resistant' PsA driven by comorbidities (also defined as 'complex-to-manage' PsA, abbreviated to C2M PsA)[9,10]. However, universal agreement on these definitions is still lacking.

In this article, we propose that patients with PsA and an inadequate response to therapy, starting with patients who are unresponsive to conventional DMARDs and extending to individuals with 'difficult-to-treat' PsA and refractory PsA (in whom treatments from all available classes have failed) can be classified into two distinct disease subgroups: a subgroup with a persistent inflammatory PsA (PIPsA) phenotype, which is marked by active joint inflammation (typically clinically manifesting as joint swelling) and confirmed on imaging; and a subgroup with non-inflammatory PsA (NIPsA) phenotype, which is often linked to comorbidities such as obesity and osteoarthritis (OA). In addition, we discuss potential mechanisms underlying these phenotypes, as well as considerations for treatment strategies and trial design.

Inadequate therapy responses in PsA

A Northern European registry study of over 10,000 patients demonstrated that patients with PsA who received more than four bDMARDs or tsDMARDs — that is, patients representing an approximation for a refractory or near-refractory state — have a very low likelihood of achieving remission as assessed using the Disease Activity in Psoriatic Arthritis (DAPSA) score, with number needed to treat of 63 (ref. 11). In such patients, differentiation between inflammatory (that is PIPsA-associated) and non-inflammatory (that is NIPsA-associated) mechanisms, is vital to prevent futile therapy cycling and ensure optimal PsA management in the real-world setting.

Multiple treatment failures make it essential to identify the underlying mechanisms driving inadequate responses to therapy. Several patients with PsA who are cycling through bDMARDs or tsDMARDs show little objective evidence of joint inflammation. International registries data, observational studies and clinical trials reveal that only 10% to 40% of patients with PsA achieve remission[12–14] despite very low rates of radiographic disease progression. Hence, a failure to differentiate between PsA associated with traceable inflammatory mechanisms (that is, PIPsA) versus PsA where non-inflammatory mechanisms might be in place (that is, NIPsA) might explain why a large population of patients with PsA do not achieve remission or low disease activity. The existing burden of apparent treatment failure in PsA has shifted the focus from Minimal Disease Activity (MDA) or DAPSA remission onto 'Patient Acceptable Symptom State'[15,16], which we propose should be assessed through the perspective of both inflammatory and non-inflammatory mechanisms to optimize treatment strategies. At first glance, our newly suggested term NIPsA might appear to be contradictory, as the term 'arthritis' inherently implies the presence of inflammation. However, chronic inflammatory conditions, including PsA, often progress through an initial inflammatory phase to post-inflammatory phases. The latter may be characterized by secondary OA and joint malalignment, both of which involve pain sensitization mechanisms and are, thus, painful. Differentiating between disease phases presents a clinical challenge, as purely inflammatory or non-inflammatory states are rarely observed, not only in PsA but also in conditions such as RA, and overlapping mechanisms frequently coexist[17].

Outside of rheumatology, similar dynamics between pro-inflammatory and post-inflammatory disease states are observed. For instance, in multiple sclerosis, patients with severe disability are unlikely to respond to therapy if inflammation is no longer active, as evidenced by negative MRI scans[18,19]. Similarly, validated composite outcome measures in PsA, such as DAPSA, Psoriatic Arthritis Disease Activity Score (PASDAS) and MDA, encompass patients with treatment-resistant disease. Such apparent resistance, which emerges from the clinimetric indices, might stem not from active inflammation

Table 1 | Psoriatic arthritis phenotypes: terms and definitions

Difficult to treat PsA (*clinical classification*)	Patients with active disease in whom at least two different lines of biologic or targeted synthetic therapy and at least one conventional DMARD have failed
Refractory PsA (*clinical classification*)	Failure owing to treatment inefficacy or intolerance, or treatment exclusion based on contraindications, for at least one drug of each advanced therapy (biologic or targeted synthetic DMARDs) licensed for PsA. This criterion applies to patients with active disease as determined by a validated composite outcome measure
Persistent inflammatory PsA (*clinical and imaging classification*)	Patients with active disease with imaging evidence of ongoing inflammation (based on ultrasonography or MRI), despite undergoing at least one recommended therapy from any single DMARD class (either conventional or biologic and targeted synthetic DMARDs)
Non-inflammatory PsA (*clinical and imaging classification*)	Patients with active disease without imaging evidence of ongoing inflammation (based on ultrasonography or MRI), despite undergoing at least one recommended therapy from any single DMARD class (either conventional or biologic and targeted synthetic DMARDs)
Active disease (*clinical classification*)	Ongoing peripheral and/or axial musculoskeletal symptoms. Conventionally characterized by a DAPSA score >14 or an alternative validated outcome measure and ASDAS ≥2.1 for isolated spinal symptoms

ASDAS, Ankylosing Spondylitis Disease Activity Score; DAPSA score, Disease Activity in Psoriatic Arthritis score; PsA, psoriatic arthritis.

at the time of assessment but rather from the residual damage inflicted by prior inflammation.

To avoid confusion and the implication that such patients with high composite scores are no longer considered to have PsA, it is more accurate to describe the mechanisms driving their symptoms as non-inflammatory or representative of a NIPsA phenotype. This terminology provides a nuanced perspective on their condition, acknowledging its complexity while maintaining the validity of their diagnosis.

Anatomical challenges in PsA

The heterogeneity of musculoskeletal involvement in PsA, including synovitis, osteitis, enthesitis, peritendinitis and periostitis, complicates the detection and definition of PsA with inadequate response to treatement[20,21]. Isolated axial disease or peripheral enthesitis without adjacent synovio-entheseal involvement are rare manifestations but important to recognize in order to avoid misdiagnoses and inappropriate therapeutic approaches (Fig. 1). Furthermore, it is acknowledged that the persistence of pain and joint tenderness in the absence of joint swelling and of elevated C-reactive protein (CRP) levels are more likely to be reported in PsA than in RA, owing to the entheseal and extracapsular centric inflammation in PsA[22] (Fig. 1). Such PsA cases might represent immunologically driven refractory disease that is difficult to demonstrate objectively[20,23–25]. The pathological variability of the affected tissues, combined with the challenges in assessing enthesitis, makes distinguishing between inflammatory and non-inflammatory mechanisms more challenging than RA (Fig. 1). In particular, the correlation between entheseal tenderness and imaging findings varies according to the studies from poor to suboptimal, hence a gold standard test is lacking[26–28]. However, similar to RA, PsA is most commonly characterized by joint swelling, and the presence or absence of this clinical lesion is also a key parameter for the delineation between inflammatory and non-inflammatory mechanisms in PsA.

Lessons from refractory RA

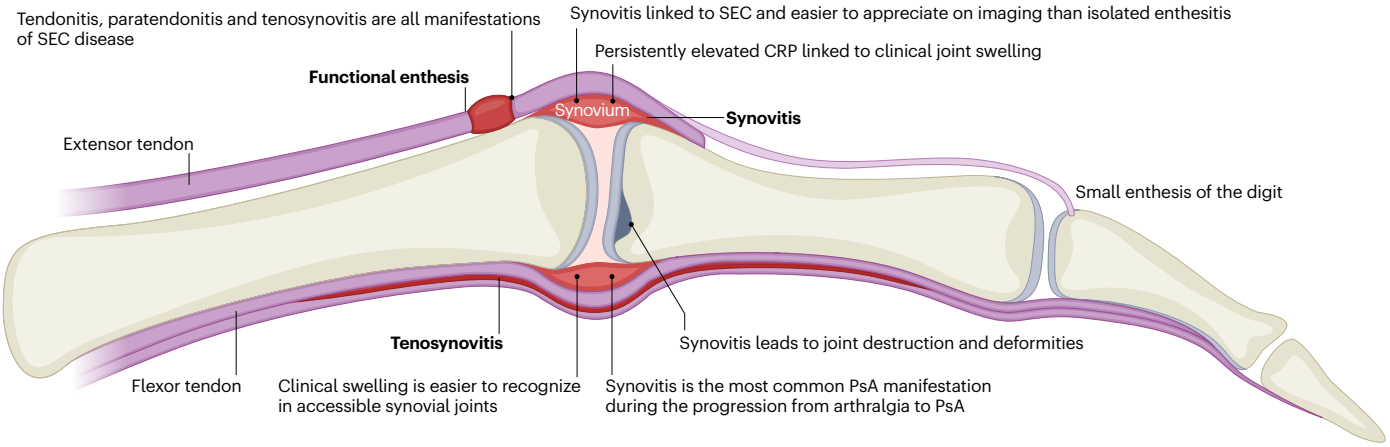
Lessons learned from refractory RA can help to better understand inflammatory mechanisms in PsA patients with inadequate response to therapy. We previously proposed two major subdivisions for the clinical assessment of RA towards switching DMARD class and especially switching across bDMARDs or tsDMARDs: non-inflammatory refractory RA (NIRRA) and persistent inflammatory refractory RA (PIRRA)[8,17]. The NIRRA group, as designated by the absence of ultrasonographic power Doppler changes in clinically swollen joints correlated more strongly with obesity, OA and fibromyalgia, as well as with lower CRP and lower SJC compared with the PIRRA group, with NIRRA representing 40% of total refractory RA cases[8]. The primacy of synovitis and secondary nature of erosion in RA is well established, as is the control of joint inflammation towards structural damage prevention[2,29]. RA-associated synovitis is readily evaluable using ultrasonography in clinically accessible locations and furthermore[30], there is a clear link between synovial inflammation and bone erosion — a key prognostic surrogate in RA.

Compared with RA, erosive disease is less prevalent and disease progression is slower in PsA, with only a subset of patients experiencing substantial radiographic progression[31,32]. However, analogous to RA, baseline radiographic erosive damage, raised CRP levels and persistent synovitis are also major risk factors for PsA progression[31,33–35], underscoring the key importance of synovitis and outcomes in PsA. Damage in PsA also includes post-inflammatory lesions including both juxta-articular and entheseal new bone formation in both the peripheral and axial skeleton[21,36], but at the population level persistent inflammatory disease is mostly readily recognized in relation to joint swelling associated with synovitis.

Recognizing the PIPsA landscape

PIPsA refers to cases where patients continue to show active disease with clear imaging evidence of ongoing inflammation, such as through ultrasonography or MRI, despite having received at least one recommended therapy from a DMARD class, including conventional, biologic, or targeted synthetic options (Table 1). The temporal concept referenced with 'persistent' in the PIPsA classification is important and refers to a lack of reduction in disease activity by at least 50% within 3 months or not reaching the treatment target within 6 months, in accordance with the treat-to-target approach and the European Alliance of Associations for Rheumatology (EULAR) recommendation on PsA treatment[1].

Both animal studies and human imaging analyses suggest that initial PsA involvement is entheseal and includes the synovio-entheseal complex (SEC) structure, and this explains the focal joint swelling (Fig. 1a) or entire digital swelling (dactylitis)[24,37–40]. Dactylitis encompasses most of the primary lesions of psoriatic finger involvement, ranging from tenosynovitis and subcutaneous edema (also called pseudotenosynovitis), which are characteristic of the acute phases, to articular synovitis and erosions observed in the chronic phases (Fig. 1a). Indeed, apart from the rare pure axial PsA phenotypes or isolated peripheral entheseal phenotypes, persistent swelling is clearly linked to PsA clinical expression, progression joint erosion, destruction and joint deformity (Fig. 1). Accordingly, the concept of NIRRA and PIRRA relating to objective evidence of synovitis in RA may be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Tendonitis, paratendonitis and tenosynovitis are all manifestations of SEC disease
Synovitis linked to SEC and easier to appreciate on imaging than isolated enthesitis
Persistently elevated CRP linked to clinical joint swelling
Functional enthesis
Synovium
Synovitis
Extensor tendon
Small enthesis of the digit
Tenosynovitis
Synovitis leads to joint destruction and deformities
Flexor tendon
Clinical swelling is easier to recognize in accessible synovial joints
Synovitis is the most common PsA manifestation during the progression from arthralgia to PsA

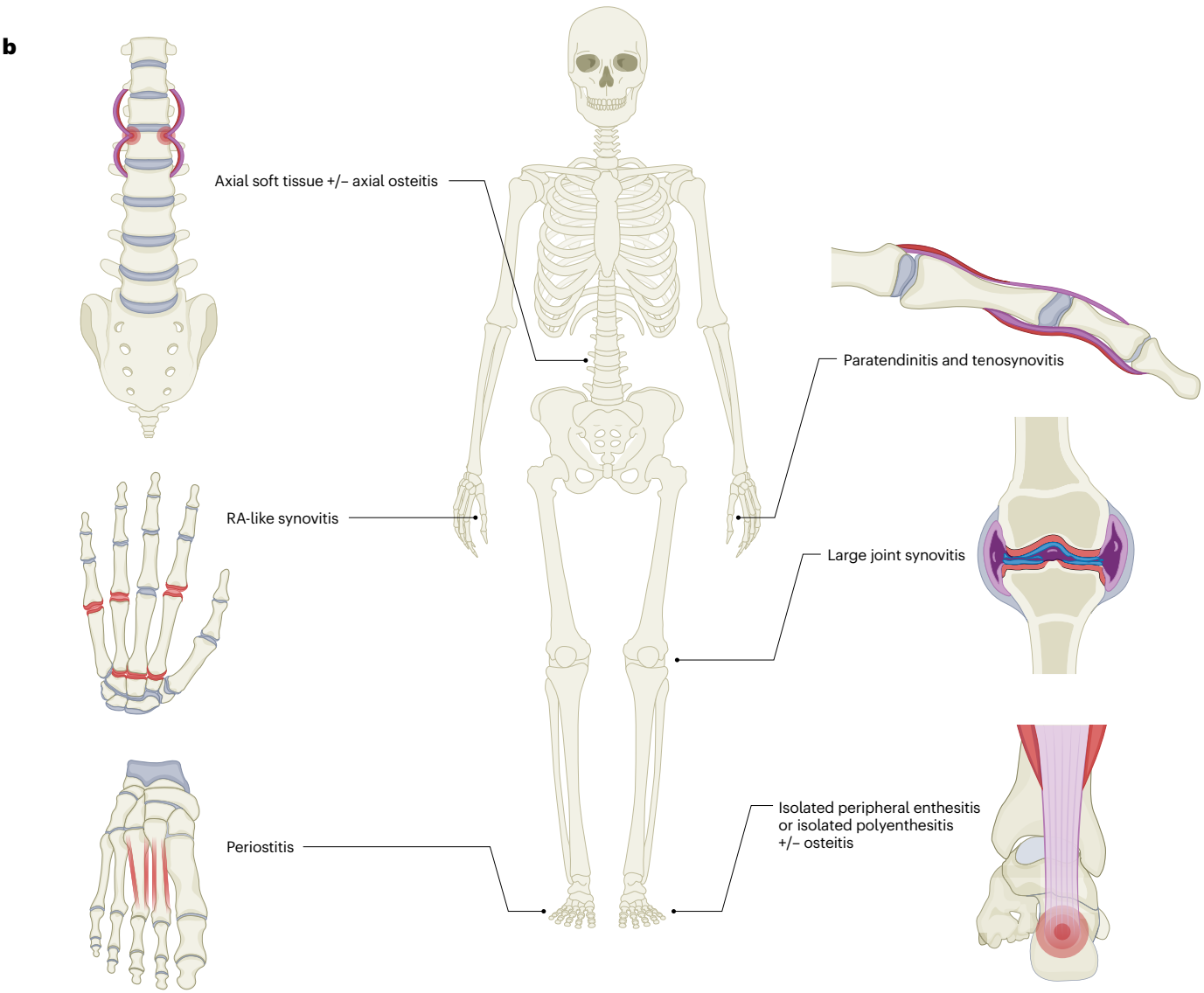

b
Axial soft tissue +/– axial osteitis
Paratendinitis and tenosynovitis
RA-like synovitis
Large joint synovitis
Periostitis
Isolated peripheral enthesitis or isolated polyenthesitis +/– osteitis

Fig. 1 | The complexity of psoriatic arthritis-related joint disease. **a**, The central role of synovitis in psoriatic arthritis (PsA) and its various clinical implications are highlighted towards defining imaging and possibly tissue assessment as the gold standard for exclusion of non-inflammatory PsA (NIPsA) phenotypes. Synovitis is the most common manifestation of early PsA in patients with arthralgia follow-up. Synovitis linked with the synovio-entheseal complex (SEC) is easier to detect than enthesitis alone, with synovitis often acting as a 'smoking gun' for other pathology. Clinically, synovitis is easy to recognize owing to visible joint swelling and can be confirmed through imaging techniques. Persistent raised C-reactive protein (CRP) levels in trials, indicating a non-response, are linked to joint swelling. Additionally, synovitis contributes to joint destruction and deformity like those observed in rheumatoid arthritis (RA) and is associated with PsA-related erosion and outcomes. **b**, The pathological tissue heterogeneity of musculoskeletal pathological involvement in PsA-related joint disease, and the associated difficulty in objectively measuring joint target tissues, complicates the detection and definition of refractory PsA. PsA involvements include not only synovitis but also osteitis, enthesitis, peritendinitis, and periostitis of both the peripheral and axial skeleton. At the population level, isolated axial disease and isolated peripheral enthesitis without adjacent synovio-entheseal soft-tissue involvement are uncommon PsA manifestations. Ultrasonography can be used to identify inflammatory changes in all soft-tissue structures that are affected in PsA, including the synovial cavities and bursae, tenosynovial structures and adjacent soft tissues, enabling the diagnosis of PsA with inadequate response to treatment.

broadly applicable to PsA patients with inadequate response to therapy where joint synovitis is often central to the patient outcomes[8]. Hence, most NIPsA and PIPsA phenotypes can be clinically gleaned from joint tenderness and swelling, as documented by ultrasonography (Fig. 2).

Assessing enthesitis, peritendinitis, periostitis and osteitis is comparatively more challenging than evaluating clinical joint swelling that is often associated with joint cavity synovitis and effusion[1,41] (Fig. 1b). When clinically accessible, entheseal structures are, unlike the synovium, relatively avascular and, although painful or tender, might not display ultrasonographic changes. In addition, whereas the association between joint synovitis and structural damage has been well established, especially in RA, the link between the involvement of peri-articular structures (such as peritendinitis), which are commonly seen in PsA, and structural damage is less defined. Results from the phase IIIb ACHILLES randomized controlled trial, where secukinumab for peripheral enthesitis showed statistically significant improvements over the placebo only in the retrocalcaneal bursitis component of the SEC structure, thus highlight the utility of synovitis evaluation in a primary entheseal pathology[42,43]. These findings suggest that the synovial component of the SEC is more responsive to change, which is why we will focus on this SEC component in PIPsA phenotype definitions — even when enthesitis is the specific lesion under evaluation[44–48].

Importance of objective measurement of joint inflammation

PsA-related oligoarthritis and PsA-polyarthritis (the latter defined by the presence of at least five swollen joints, which is considered a poor prognostic factor according to EULAR recommendations[1]) are readily evaluable in the clinic, and the presence or absence of synovitis or peritendinitis can be easily detected using ultrasonography (Fig. 2). Dactylitis is included in the EULAR recommendations for polyarthritis owing to the presence of synovitis and has a poor prognosis for the association with radiographic damage, especially when more than one finger or toe are affected[1,39].

Compared with joint swelling with evidence of active inflammation on imaging, PIPsA phenotypes with isolated entheseal involvement are substantially more challenging to objectively assess, especially in patients with persistent inflammatory enthesitis symptoms despite treatment[49]. Also, the persistence of pain in a particular enthesis might be related to mechanical enthesopathies or non-inflammatory pain mechanisms triggered after an inflammatory process, or a combination of both[20,24,50,51]. In this scenario, detection of entheseal tenderness during the physical examination would not be sufficient to define a PIPsA phenotype. The same limitation applies to the axial disease, where the inflammatory and non-inflammatory mechanisms are both likely to impact the same patient, sometimes simultaneously. In patients with axial symptomatic PsA, and especially in HLA-B27-negative individuals, MRI is often negative despite the presence of inflammation[52]. Thus, although collectively there might be imaging "blind spots" for the detection of both isolated peripheral entheseal and axial inflammation, joint or digit swelling appearing at physical examination in patients with inadequate response to therapy can still be an indicator of a PIPsA phenotype, hence the suggested focus on swelling that is likely to be linked to SEC disease (Fig. 1).

Ultrasonography for defining PIPsA and NIPsA

Despite the challenges posed by the heterogeneity of the structures involved, especially when compared with RA, imaging has potentially a key role in defining PIPsA and NIPsA phenotypes. In patients with elevated disease activity scores and joint swelling (which is the best surrogate for joint inflammation in PsA), the presence of 'active' inflammation on ultrasonography should be used for confirming the PIPsA phenotype, especially in doubtful cases, as in the presence of obesity or joint deformities[45,46,53]. In a patient with a confirmed PIPsA phenotype, imaging can also help to identify the specific anatomical site involved (for example, in the case of a mini-enthesitis of the digit)[45,54,55]. In addition, ultrasonography has the potential to detect PsA-independent factors that promote persistent inflammation, such as concomitant crystal arthritis[44,56,57]. In patients with joint tenderness but without any clinical evidence of inflammation, for example, in those with no joint swelling and normal CRP levels[58–62], in whom a NIPsA is suspected, imaging, and particularly ultrasonography, can be used to exclude the presence of SEC inflammation[63]. Furthermore, although isolated enthesitis (that is, enthesitis without joint or tendon manifestations) is uncommon in patients with PsA, the detection of an entheseal power Doppler signal, with or without other indicators of 'active' entheseal inflammation (such as hypoechoic areas or entheseal thickening[47,64]) or structural damage (such as bone erosions) — especially at the Achilles enthesis, might indicate an entheseal PIPsA phenotype. Whereas ultrasonography is an affordable and accessible approach to assessing synovitis in PsA it is still not able to detect peri-entheseal osteitis. Therefore, in patients with ongoing features of inflammatory pain, an MRI scan should be considered for further evaluation if ultrasonography findings are negative.

Potential pathogenetic mechanisms in PIPsA

The immunopathogenesis of PIPsA is poorly understood, as few studies have so far focused on treatment-refractory PsA. Genome-Wide Association Studies (GWAS), as well as results from translational studies

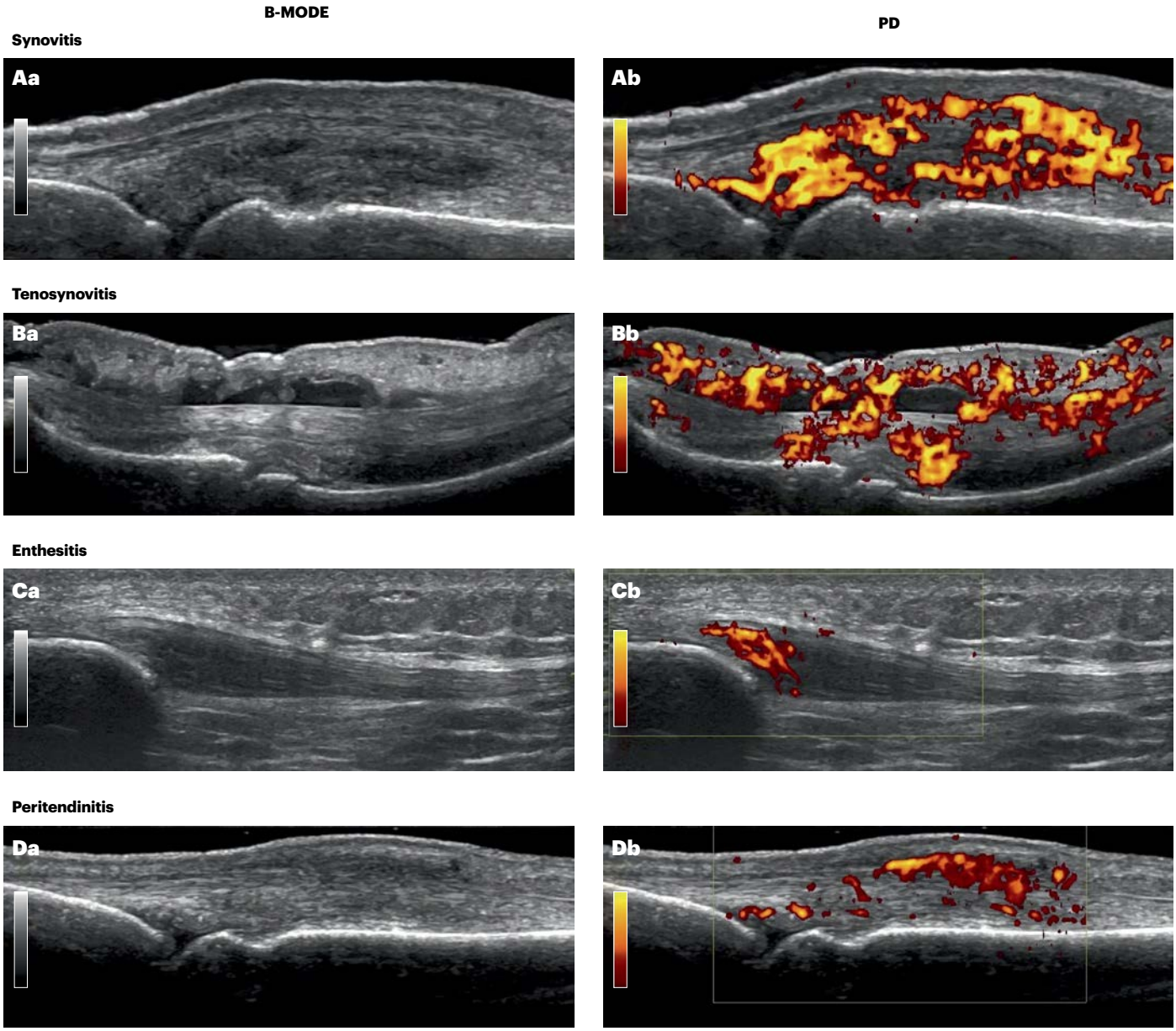


Fig. 2 | Imaging peripheral inflammation in psoriatic arthritis. In rheumatoid arthritis (RA), the persistent inflammatory refractory RA (PIRRA) phenotype is based on the presence of joint synovitis, as determined in B-mode, as synovial hypertrophy (Aa) and concomitant power Doppler (PD) changes (Ab). Likewise, in psoriatic arthritis (PsA), synovitis is a central disease component to the persistent inflammatory PsA (PIPsA) phenotype. However, given the synovio-entheseal complex (SEC) centricity of disease, other lesions, including tenosynovitis (Ba and Bb), enthesitis (Ca and Cb) and peritendinitis (Da and Db), should be evaluated in a patient with an inadequate response to therapy.

testing inhibitors of the tumour necrosis factor (TNF), interleukin-23 (IL-23) and IL-17 pathways strongly incriminate the IL-23–IL-17 axis and the NF-κB–TNF pathways in PsA pathogenesis[65], but there are very limited data on the contribution of these pathways to treatment-refractory disease. Also, the MHC-1 associations beyond HLA-B27 in PsA, as well as mechanistic studies using patient-derived samples or humanized mouse models of PsA all point to a key role for $CD8^+$ T cells and their associated cytokines[66–68].

As the PIPsA phenotype is likely to arise in patients previously exposed to TNF, IL-17 or IL-23 inhibition, and in cases where drug compliance and the absence of neutralizing antibodies are confirmed, genetic associations might help to explain PIPsA immunopathogenesis. In fact, genetic variants affecting many cytokine pathways including those downstream of IL-1, IL-4 or IL-13 and IL-6 have emerged from GWAS[69]. The reverse translational immunology studies investigating a role for these cytokines in refractory PsA are rudimentary, but

case series of refractory PsA responding to IL-6 inhibition have been reported[70]. Furthermore, the use of IL-4- or IL-13-blocking strategies for eczema is associated with the development of both psoriasis and PsA, implicating type 2 cytokine dysregulation in the induction of PsA[71]. GWAS have also linked genetic variants of the type 1 interferon and JAK–STAT pathways with PsA. Accordingly, it will be interesting to see how many patients in whom JAK pathway inhibition has failed have a PIPsA phenotype. Other potential molecular mechanisms leading to PIPsA might include rare monogenic forms of PsA, especially in younger patients, epigenetic modifications and somatic mutations, but this is largely speculative owing to the paucity of data. Synovial biopsies from patients with a defined PIPsA phenotype might help to dissect the immunopathogenesis of non-response to two or more classes of therapy in PsA[72,73].

Potential mechanisms in NIPsA

Evidence supporting the concept that the NIPsA phenotype is common comes from evaluations of patients with PsA 12 months after initiating a first anti-TNF therapy, which showed that almost 40% reported unacceptable pain and that nearly two-thirds of this remaining pain load was attributed to a pain pattern indicative of a non-inflammatory mechanism (defined as refractory pain in that study)[74]. The refractory pain was defined as a combination of pain of >40 mm on the visual analogue scale, a CRP value of below 10 mg/l and fewer than one swollen joint[74]. More swollen joints and higher global assessment at the start of anti-TNF therapy were associated with a significantly lower risk of 12-month refractory pain, suggesting that patients with higher initial inflammation might be less prone to present with unresolved pain indicative of a non-inflammatory mechanism later on[75].

One of the most interesting research areas in difficult-to-treat or refractory PsA, as defined by composite outcome measures, is the exploration of pain persistence mechanisms that are not directly mediated by active inflammation. The International Association for the Study of Pain has developed definitions for three general categories of pain: nociceptive, neuropathic and nociplastic[76]. These types of pain can occur simultaneously, increasing both the severity and the interference of the overall pain experience[77]. In patients with NIPsA, persistence of disease activity assessed using traditional composite scores is likely to be mediated by nociplastic and neuropathic pain mechanisms, rather than nociceptive mechanisms[78]. Accurately and reliably characterizing these complex types of pain is crucial for customizing appropriate treatment strategies and enhancing patient outcomes. Even when inflammation is clinically controlled, patients with chronic arthritis still experience pain and this residual pain appears to be more pronounced in PsA than in RA[79].

In patients with a NIPsA phenotype it is also important to exclude any recurrent, short-duration, inflammatory flares that have subsided prior to clinical assessment, as these might warrant therapy switching. Using a statistical methodology known as mediation analysis, various DMARDs have been assessed for pain reduction resulting from inflammation and neuroinflammation control versus a direct pain-relieving effect, as some DMARDs might act directly on the nervous system as neuromodulatory agents[77,80].

Local and systemic inflammation might contribute to nociplastic pain, and detecting systemic inflammation can be challenging, especially in PsA, where systemic inflammation levels are frequently low[81]. Neuroinflammation has been associated with a specific inflammatory pattern in PsA, that involves IL-23 and IL-17 signalling, the JAK–STAT pathway, TNF and IL-6 cytokines, although the field is still rudimentary compared with knowledge about central pain mechanisms and how these impact neural connectivity in RA[81]. Disentangling the NIPsA phenotype will also facilitate research into how pro-inflammatory cytokines might contribute to pain via neuropathic pain mechanisms in nerves and dorsal root ganglia and also in nociplastic pain mechanisms in the central nervous system.

Composite outcomes through the NIPsA and PIPsA lens

Contemporary composite outcomes represent the mainstay of disease activity and response assessment in PsA and mainly include DAPSA, Disease Activity Score 28 and MDA[82–84] (Fig. 3). There are important variations in the frequency of remission status according to the definition used, varying between 13.1% (very low disease activity) to 42.1% (Disease Activity Score 28), depending on the score used, and this indicates that achieving remission in PsA might be unattainable for many patients[12]. There has been a shift towards a more patient-centred disease perspective with increased adoption of patient-reported outcomes[85]. Given the multifaceted nature of pain in chronic PsA, we believe that a more formal differentiation between PIPsA and NIPsA components might not only benefit patients, but also help physicians and the pharmaceutical industry to better charter novel therapy development courses. We propose that the non-inflammatory and persistent inflammatory aspects of PsA composite outcomes can be set out along a continuum of inflammatory to non-inflammatory features and a dissociation between these features will help to quickly delineate PIPsA or NIPsA phenotypes (Fig. 3).

In composite PsA indices, pain has a substantial impact on the total score as, for example, in MDA, 3 out of 7 components are patient-reported outcomes (pain visual analogue scale, patient global assessment and health assessment questionnaire), 2 out of 7 components are related to tenderness in joints and entheses, although not necessarily indicating inflammation, and only two MDA components are associated with objective signs of inflammation (PASI and swollen joints). The proportion of subjective measures in those scores partly explains discrepancies in reported responses to bDMARDs or tsDMARDs, where a PASI90 response is generally expected in over 80% of treated patients with psoriasis[86], whereas an MDA response is expected in only 30–40% of patients treated for PsA[29,87] (Fig. 3). This disparity certainly reflects the complexity of PsA, with possible involvement of multiple domains (joints, entheses, axial), but failure to achieve MDA might be mediated independently of PsA-driven inflammation with a strong NIPsA component. Thus, the persistence of inflammation in a patient with PsA showing inadequate response to therapy ideally requires investigation of the inflammation in all potential domains, before concluding by classifying them under a NIPsA phenotype.

With respect to enthesitis, a high number of tender entheseal points, is more suggestive of widespread pain syndromes than genuine inflammatory disease[58,59,88]. Improvement in SJC and CRP values, for example, alongside dramatic concurrent improvements in other composite outcome measure components, attests to the utility of composite outcome measures in capturing excellent clinical responses. By contrast improvement in joint swelling, psoriasis and CRP but not composite outcome measure components is more likely to indicate a NIPsA phenotype (Fig. 3). Accordingly, we propose that a focus on the NIPsA and PIPsA phenotype with objective measurement of the most measurable PsA lesion, that is, synovitis, is key to avoiding futile or erroneous switching of therapy and for dissecting disease mechanisms (Fig. 3).

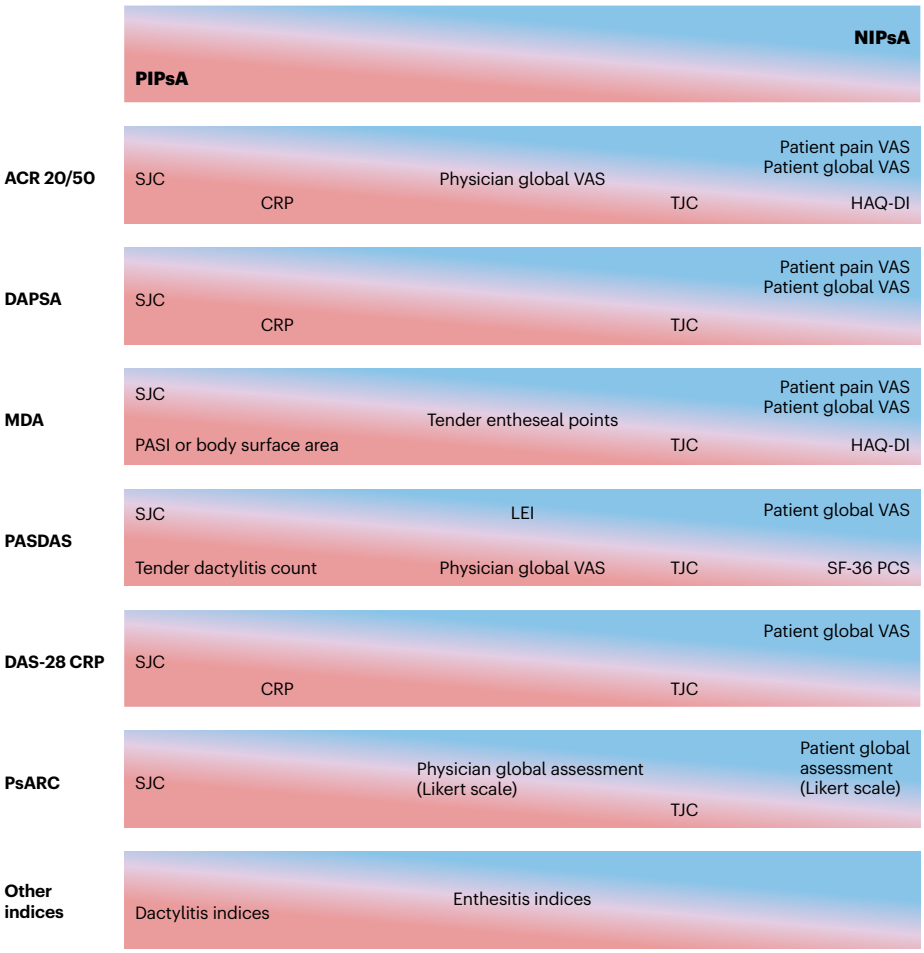


Fig. 3 | Evaluating psoriatic arthritis through the perspective of composite outcomes. Psoriatic arthritis (PsA) is a clinically defined multidomain disease, typically assessed using composite outcomes. Some composite outcome components might strongly align with non-inflammatory PsA (NIPsA) and others with persistent inflammatory PsA (PIPsA) phenotypes. Common composite outcome measures, including American College of Rheumatology 20 (ACR20)[123] and ACR50 (ref. 123), are used in clinical trials. In addition, Disease Activity in Psoriatic Arthritis (DAPSA) score[124], minimal disease activity (MDA)[82], Psoriatic Arthritis Disease Activity Score (PASDAS)[125], Disease Activity Score 28 (DAS28)[126] and Psoriatic Arthritis Response Criteria (PsARC)[127,128] are also used regularly in the clinic. Here, we display how certain domains, including swollen joint count (SJC), dactylitis resolution, C-reactive protein (CRP) and Psoriasis Area Severity Index (PASI), are strongly aligned with PIPsA immune mechanisms, whereas other domains, including patient visual analogue scale (VAS) pain and global assessment, are aligned more closely with NIPsA and are likely to inflate composite outcomes via the non-inflammatory component of the disease. Unfortunately, outcome domains, such as enthesitis, or the cardinal lesion, are difficult to measure objectively and align more closely with the NIPsA rather than the PIPsA concept. Isolated high patient-reported outcome measures with resolution of joint swelling, CRP normalization (if elevated initially) and substantial skin improvement or clearance point towards NIPsA mechanisms. HAQ-DI, Health Assessment Questionnaire-Disability Index; SF-36 PCS, Short Form 36 Physical Component Summary; TJC, tender joint count.

Comorbidity factors in refractory PsA

Various comorbidities, including obesity, depression, fibromyalgia and concomitant or secondary post-inflammatory OA, might affect the development of NIPsA phenotypes and thus contribute to reduced PsA therapy responses and an apparent refractory PsA phenotype[5,10,89]. The link between obesity and persistent inflammatory or non-inflammatory phenotypes might be much more complex in PsA than in RA, as obesity is a risk factor for PsA development[90,91], with weight loss being associated with non-progression to PsA and with improved efficacy of biological therapy[92]. Furthermore, obesity is linked to an increased rate of subclinical entheseal sonographic abnormalities in healthy people, thus complicating the interpretation of imaging in PsA[20,27,93]. In addition, increased skeletal stress in obesity might also contribute to the Koebner phenomenon, biomechanical-related pain, or physical stress-related enthesitis, which is well described in animal models[20,94]. Thus, mechanical enthesopathies in obesity and inflammatory enthesitis pose a particular challenge in defining immune or non-immune disease mechanisms, with the likelihood of both mechanisms being integrated or overlapping. In terms of comorbidity, such as obesity, PsA sits at the boundary between inflammatory and metabolic rheumatism with the frequent co-occurrence of gout[95]. In patients with PIPsA, the presence of monosodium urate crystals might promote the persistence of synovial inflammation through mechanisms that differ from those observed in PsA[95]. Concomitant gout or calcium pyrophosphate deposition disease might also contribute to refractory RA, especially in seronegative disease[96,97]. Concomitant gout should be evaluated in the PIPsA phenotype and treated with urate-lowering therapy if confirmed or suspected.

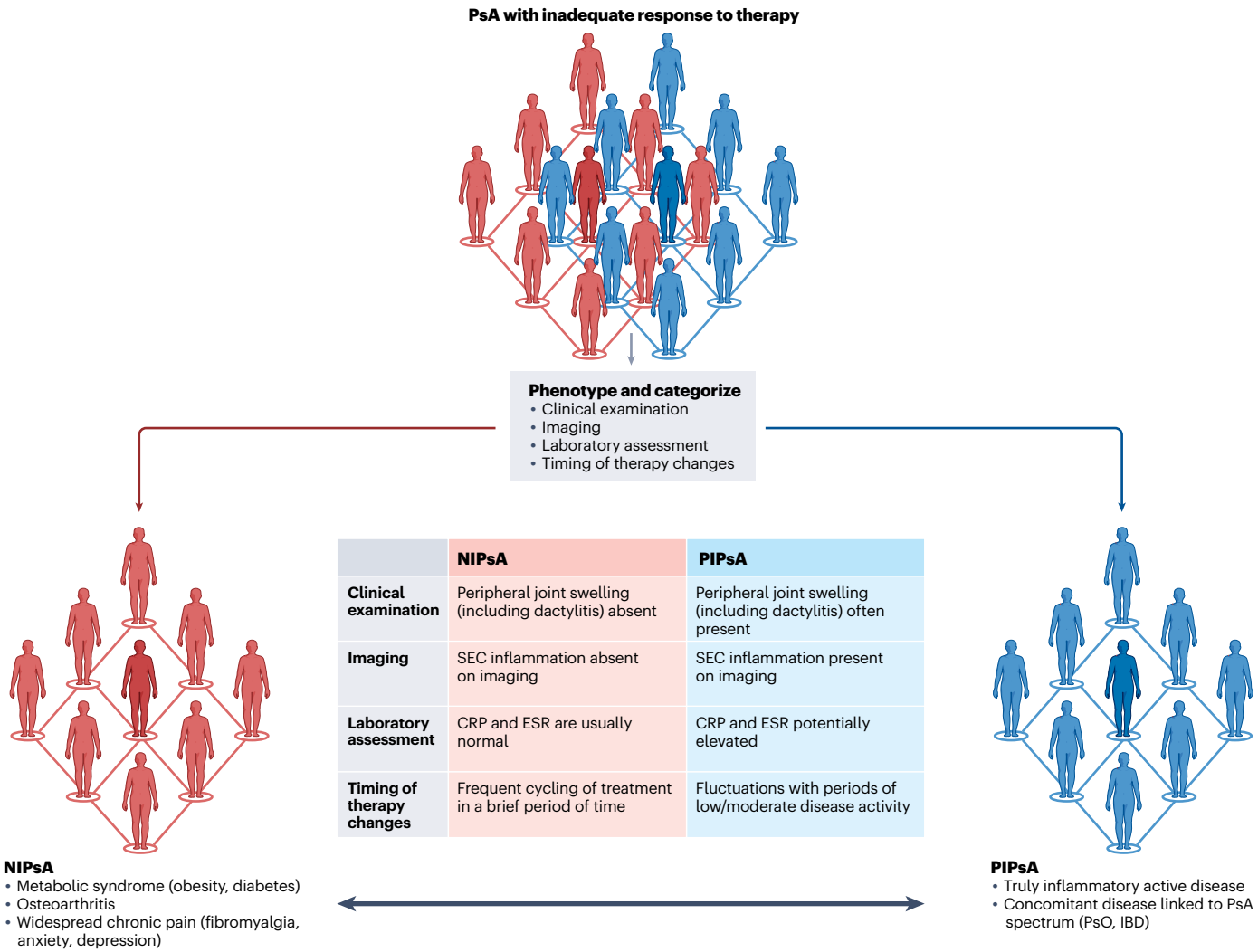
Other considerations on NIPsA and PIPsA

The lack of a "gold-standard" histological confirmation, tissue inaccessibility, difficulty visualizing painful entheseal structures and the usually modest inflammatory responses make the differentiation between a persistent inflammatory and a non-inflammatory phenotype more challenging in PsA than in RA. Also, some manifestations of PsA, such as axial disease, show a disconnect between symptoms and imaging, as asymptomatic new bone formation is sometimes detected. Clearly, such silent lesions do not warrant therapy unless it is considered that there is a risk of inflammation-driven extensive spinal fusion, something that has not been addressed to date. Not being able to objectively distinguish NIPsA from PIPsA mechanisms in such cases thus shifts the option more towards drug cycling or a trial of therapy to support a PIPsA phenotype.

Treating PsA with extra-articular inflammatory manifestations

Patients with PsA often have extra-articular inflammatory manifestations, including anterior uveitis, inflammatory bowel disease (IBD) and psoriasis, and therapy selection for PsA is usually based on ability to treat these associated extra-articular manifestations, if present[41,87,98–100]. However, the coexistence of articular and extra-articular involvement is certainly an element that might complicate treatment and promote a PIPsA pattern (Fig. 4) or limit therapy options, for example, in the case of patients with PsA and IBD, where the IL-17 inhibitor should be avoided[101,102]. An asynchronous response, when, for example, cutaneous involvement but not joint involvement might respond to treatment, or the persistence of activity at the extra-articular level, as in the case of IBD, can contribute to the persistence of disease activity at the articular level and impact patients' function and quality of life, even in the absence of joint disease[85,103].

Although RA is associated with some extra-articular or extra-synovial features that might render disease more 'complex to manage', we did not find these to be major considerations in our refractory RA cohort[8]. Other non-articular features, including interstitial lung disease[104,105] and vasculitis[106], might contribute to difficult-to-treat RA, but in our cohort of 1600 patients on biologic drugs these were relatively uncommon[8]. The term C2M-PsA, emphasizing the potential influence of comorbidities in influencing disease treatment and outcomes, has recently been introduced for PsA but this did not include any criteria for stratification into inflammatory and non-inflammatory



	NIPsA	PIPsA
Clinical examination	Peripheral joint swelling (including dactylitis) absent	Peripheral joint swelling (including dactylitis) often present
Imaging	SEC inflammation absent on imaging	SEC inflammation present on imaging
Laboratory assessment	CRP and ESR are usually normal	CRP and ESR potentially elevated
Timing of therapy changes	Frequent cycling of treatment in a brief period of time	Fluctuations with periods of low/moderate disease activity

Fig. 4 | Stratification of patients with psoriatic arthritis who respond inadequately to therapy. This figure illustrates the categorization of psoriatic arthritis (PsA) into two distinct phenotypes: non-inflammatory PsA (NIPsA) and persistent inflammatory PsA (PIPsA). Patients with PsA can be classified into one of these two phenotypes based on their clinical features, imaging features, timing of treatment responses and laboratory examinations. Patients with NIPsA do not exhibit objective inflammation but have other conditions contributing to their symptoms, such as osteoarthritis and fibromyalgia. These patients often have obesity or diabetes as well. By contrast, PIPsA is defined by continuous objective inflammatory activity including joint swelling, raised C-reactive protein (CRP) levels and imaging abnormalities indicative of active disease. The figure highlights the main features and differences between these two phenotypes, showing that although they are distinct, they can be interchangeable over time in a single patient, as their conditions evolve. ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; PsO, psoriasis; SEC, synovio-entheseal complex.

mechanisms[9,107]. Given the relative safety of the IL-23 and IL-17 targeting monoclonal antibody therapies, management is potentially more straightforward in complex cases.

In RA, the presence of OA is unsurprisingly associated with a NIRRA phenotype[8]. However, the influence of OA on refractory PsA phenotypes might be much more complex, as some forms of OA and PsA share similar features, including distal interphalangeal joint and cervical spine involvement that can complicate both diagnosis evaluation of the response to therapy[108,109]. The processes of joint degeneration and remodelling, which are typical of OA, and of inflammation, which is usually linked to PsA, are often considered to be distinct; nevertheless, the psoriatic phenotype might influence the underlying OA, making it more inflammatory in nature and responsive to systemic treatment, especially in the early, inflammatory, disease phase. This opens up the possibility that OA as a comorbidity might frequently promote a NIPsA phenotype[110,111] but also generate an initial PIPsA phenotype.

Finally, clinicians need to consider sex-related differences in the context of difficult-to-treat and refractory[112] PsA. Observational studies investigating the effectiveness of bDMARDs consistently report that women have poorer treatment outcomes and lower drug persistence rates than men[113,114], and that this is primarily due to higher levels of pain, fatigue and worse quality of life. By contrast, men with PsA often exhibit more severe radiographic structural damage in both axial and peripheral joints, as well as greater progression of this damage, than women[115,116]. This highlights the necessity of gaining a deeper understanding of the mechanisms behind arthritis pain and how the mechanisms that promote PIPsA and NIPsA may be sex- and gender-related[117,118].

Implications for clinical trials designs

The selection of patients with a PIPsA phenotype, based on the presence of joint swelling with imaging-confirmed synovitis, is likely to increase the chances of success for any inflammation-targeting interventions, including the combination of bDMARDs and tsDMARDs. Conversely, excluding the NIPsA phenotype from the trial landscape might help to minimize inconsistencies in the next phase of trials in PsA (Fig. 4). Combinations of bDMARDs and tsDMARDs have the potential for improved disease control but are currently underutilized in PsA and in rheumatic and musculoskeletal diseases in general[119–122]. Data from the VEGA trial in IBD suggests that combination therapy with the IL-23 inhibitor guselkumab and the TNF inhibitor golimumab might be more effective for ulcerative colitis than therapy with either drug alone[123]. A similar trial in PsA is comparing guselkumab in combination with golimumab, versus guselkumab or golimumab alone in patients with an inadequate response to TNF inhibitors alone (NCT05071664). Whereas the IBD combination trial includes objective colonoscopic and histological confirmation of intestinal inflammation, the PsA trials lack objective confirmation of joint inflammation. These differences could have disappointing translational consequences. Nevertheless, the preliminary case series in PsA and spondyloarthritis support the use of bDMARD and tsDMARDs in combination or as add-on therapies in disease settings[119,121], and the implementation of a strategy for improved patient stratification might help to deliver promising results.

Conclusions

In this article, we have pragmatically extrapolated the similarities between 'difficult-to-treat' and refractory RA and PsA, with a focus on synovial and soft-tissue inflammation, and delineate the PIPsA and NIPsA phenotypes for patient stratification. In the absence of reliable serum biomarkers that predict responses to advanced therapies for PsA, we propose a focus on imaging, and particularly the use of ultrasonography, to identify clinically accessible inflamed structures at the peripheral skeleton and disentangle the PIPsA phenotype from the NIPsA phenotype. We next propose that new biological therapy strategies, including combination therapy strategies, should be focussed on patients with a PIPsA phenotype. Ultimately, this will help to optimize use of biological therapy and identify truly refractory PIPsA. Furthermore, a formal focus on the NIPsA phenotypes will facilitate new research avenues in patients without any objectively detectable ongoing inflammation who still experience disabling pain, and this dichotomy will be important for targeting central pain mechanisms.

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References

1. Gossec, L. et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2023 update. *Ann. Rheum. Dis.* **83**, 706–719 (2024).
2. Smolen, J. S. et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann. Rheum. Dis.* **82**, 3–18 (2023).
3. Marzo-Ortega, H. et al. Time to address the challenge of difficult to treat psoriatic arthritis: results from an international survey. *Ann. Rheum. Dis.* **83**, 403–404 (2024).
4. Nagy, G. et al. EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann. Rheum. Dis.* **80**, 31–35 (2021).
5. Perrotta, F. M., Scriffignano, S., Ciccia, F. & Lubrano, E. Clinical characteristics of potential 'Difficult-to-treat' patients with psoriatic arthritis: a retrospective analysis of a longitudinal cohort. *Rheumatol. Ther.* **9**, 1193–1201 (2022).
6. Paudel, M. L. et al. Prevalence and characteristics of adults with difficult-to-treat rheumatoid arthritis in a large patient registry. *Rheumatology* https://doi.org/10.1093/rheumatology/keae318 (2024).
7. Winthrop, K. L. et al. Unmet need in rheumatology: reports from the advances in targeted therapies meeting, 2023. *Ann. Rheum. Dis.* **83**, 409–416 (2024).
8. David, P. et al. Poly-refractory rheumatoid arthritis: an uncommon subset of difficult to treat disease with distinct inflammatory and noninflammatory phenotypes. *Arthritis Rheumatol.* **76**, 510–521 (2024).
9. Singla, S., Ribeiro, A., Torgutalp, M., Mease, P. J. & Proft, F. Difficult-to-treat psoriatic arthritis (D2T PsA): a scoping literature review informing a GRAPPA research project. *RMD Open.* **10**, e003809 (2024).
10. Lubrano, E., Scriffignano, S. & Perrotta, F. M. Difficult to treat and refractory to treatment in psoriatic arthritis. *Rheumatol. Ther.* **10**, 1119–1125 (2023).
11. Glintborg, B. et al. Uptake and effectiveness of newer biologic and targeted synthetic disease-modifying antirheumatic drugs in psoriatic arthritis: results from five Nordic biologics registries. *Ann. Rheum. Dis.* **82**, 820–828 (2023).
12. Hagège, B. et al. Remission and low disease activity in psoriatic arthritis publications: a systematic literature review with meta-analysis. *Rheumatology* **59**, 1818–1825 (2020).
13. Gladman, D. D. et al. Residual disease activity in Canadian patients with psoriatic arthritis treated with advanced therapies: results from a multiregistry analysis (UNISON-PsA). *J. Rheumatol.* **51**, 479–487 (2024).
14. Lubrano, E., Perrotta, F. M., Scriffignano, S., Coates, L. C. & Helliwell, P. Sustained very low disease activity and remission in psoriatic arthritis patients. *Rheumatol. Ther.* **6**, 521–528 (2019).
15. Lubrano, E. et al. Assessment of the Patient Acceptable Symptom State (PASS) in psoriatic arthritis: association with disease activity and quality of life indices. *RMD Open.* **6**, e001170 (2020).
16. S, S. et al. Psoriatic arthritis acceptable symptoms state: does sex make a difference? *Rheumatol. Ther.* **11**, 1393–1402 (2024).
17. Buch, M. H., Eyre, S. & McGonagle, D. Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. *Nat. Rev. Rheumatol.* **17**, 17–33 (2021).
18. Eshaghi, A. et al. Identifying multiple sclerosis subtypes using unsupervised machine learning and MRI data. *Nat. Commun.* **12**, 2078 (2021).
19. Kuhlmann, T. et al. Multiple sclerosis progression: time for a new mechanism-driven framework. *Lancet Neurol.* **22**, 78–88 (2023).
20. Schett, G. et al. Enthesitis: from pathophysiology to treatment. *Nat. Rev. Rheumatol.* **13**, 731–741 (2017).
21. Gladman, D. D., Antoni, C., Mease, P., Clegg, D. O. & Nash, P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann. Rheum. Dis.* **64**, ii14–741 (2005). ii14-17.
22. Lindqvist, U. R. C. et al. The Swedish early psoriatic arthritis register — 2-year followup: a comparison with early rheumatoid arthritis. *J. Rheumatol.* **35**, 668–673 (2008).
23. McGonagle, D., Lories, R. J. U., Tan, A. L. & Benjamin, M. The concept of a 'synovio-entheseal complex' and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. *Arthritis Rheum.* **56**, 2482–2491 (2007).

24. Aydin, S. Z., Bridgewood, C., Zabotti, A., Girolimetto, N. & McGonagle, D. The transition from enthesis physiological responses in health to aberrant responses that underpin spondyloarthritis mechanisms. *Curr. Opin. Rheumatol.* **33**, 64–73 (2021).
25. McGonagle, D. G., Helliwell, P. & Veale, D. Enthesitis in psoriatic disease. *Dermatol. Basel Switz.* **225**, 100–109 (2012).
26. Di Matteo, A. et al. Relationship Between ultrasound and physical examination in the assessment of enthesitis in patients with spondyloarthritis: results from the DEUS multicenter study. *Arthritis Rheumatol.* **77**, 22–33 (2024).
27. Bakirci, S. et al. Entheseal changes in response to age, body mass index, and physical activity: an ultrasound study in healthy people. *J. Rheumatol.* **47**, 968–972 (2020).
28. Michelsen, B. et al. Achilles enthesitis defined by ultrasound is not associated with clinical enthesitis in patients with psoriatic arthritis. *RMD Open.* **3**, e000486 (2017).
29. Kerschbaumer, A. et al. Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann. Rheum. Dis.* **82**, 95–106 (2023).
30. Terslev, L. et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce — part 2: reliability and application to multiple joints of a standardised consensus-based scoring system. *RMD Open.* **3**, e000427 (2017).
31. Reddy, S. M. et al. Comparative analysis of disease activity measures, use of biologic agents, body mass index, radiographic features, and bone density in psoriatic arthritis and rheumatoid arthritis patients followed in a large U.S. disease registry. *J. Rheumatol.* **37**, 2566–2572 (2010).
32. Merola, J. F., Chakravarty, S. D., Choi, O., Chan, D. & Gottlieb, A. B. A clinical review of structural damage in psoriatic arthritis for dermatologists: from pathogenesis to ongoing controversies. *J. Am. Acad. Dermatol.* **90**, 349–357 (2024).
33. Honda, S. et al. Association of polygenic risk scores with radiographic progression in patients with rheumatoid arthritis. *Arthritis Rheumatol.* **74**, 791–800 (2022).
34. Koc, G. H. et al. Determinants of radiographic progression in early psoriatic arthritis: insights from a real-world cohort. *RMD Open.* **10**, e004080 (2024).
35. van der Heijde, D. et al. Radiographic progression according to baseline C-reactive protein levels and other risk factors in psoriatic arthritis treated with tofacitinib or adalimumab. *J. Rheumatol.* **46**, 1089–1096 (2019).
36. Taylor, W. et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum.* **54**, 2665–2673 (2006).
37. Zabotti, A. et al. Risk of developing psoriatic arthritis in psoriasis cohorts with arthralgia: exploring the subclinical psoriatic arthritis stage. *RMD Open.* **10**, e004314 (2024).
38. Mease, P. et al. Quantification of pre-existing radiographic damage and its relationship with joint activity and long-term clinical outcomes with secukinumab therapy in patients with psoriatic arthritis. *Arthritis Res. Ther.* **24**, 283 (2022).
39. Dubash, S. et al. Dactylitis is an indicator of a more severe phenotype independently associated with greater SJC, CRP, ultrasound synovitis and erosive damage in DMARD-naive early psoriatic arthritis. *Ann. Rheum. Dis.* **81**, 490–495 (2022).
40. Girolimetto, N. et al. Ultrasonographic evidence of predominance of acute extracapsular and chronic intrasynovial patterns in 100 cases of psoriatic hand dactylitis. *J. Rheumatol.* **47**, 227–233 (2020).
41. Coates, L. C. et al. Group for research and assessment of psoriasis and psoriatic arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat. Rev. Rheumatol.* **18**, 465–479 (2022).
42. Behrens, F. et al. Efficacy and safety of secukinumab in patients with spondyloarthritis and enthesitis at the Achilles tendon: results from a phase 3b trial. *Rheumatology* **61**, 2856–2866 (2022).
43. Baraliakos, X. et al. Magnetic resonance imaging characteristics in patients with spondyloarthritis and clinical diagnosis of heel enthesitis: post hoc analysis from the phase 3 ACHILLES trial. *Arthritis Res. Ther.* **24**, 111 (2022).
44. Zabotti, A. et al. Musculoskeletal ultrasonography for psoriatic arthritis and psoriasis patients: a systematic literature review. *Rheumatology* **56**, 1518–1532 (2017).
45. Naredo, E. et al. Validation and incorporation of digital entheses into a preliminary GLobal OMERACT Ultrasound DActylitis Score (GLOUDAS) in psoriatic arthritis. *Ann. Rheum. Dis.* **83**, 1060–1071 (2024).
46. Zabotti, A. et al. Novel and reliable DACTylitis glObal Sonographic (DACTOS) score in psoriatic arthritis. *Ann. Rheum. Dis.* **79**, 1037–1043 (2020).
47. Di Matteo, A. et al. Power Doppler signal at the enthesis and bone erosions are the most discriminative OMERACT ultrasound lesions for SpA: results from the DEUS (Defining Enthesitis on Ultrasound in Spondyloarthritis) multicentre study. *Ann. Rheum. Dis.* **83**, 847–857 (2024).
48. Gessl, I. et al. Tenderness and radiographic progression in rheumatoid arthritis and psoriatic arthritis. *Ann. Rheum. Dis.* **82**, 344–350 (2023).
49. Smerilli, G. et al. Double target' ultrasound monitoring of biologic therapy in psoriatic arthritis. *Clin. Exp. Rheumatol.* **42**, 626–632 (2024).
50. Schett, G. et al. Psoriatic arthritis from a mechanistic perspective. *Nat. Rev. Rheumatol.* **18**, 311–325 (2022).
51. Savage, L. et al. Defining pre-clinical psoriatic arthritis in an integrated dermato-rheumatology environment. *J. Clin. Med.* **9**, 3262 (2020).
52. Castillo-Gallego, C., Aydin, S. Z., Emery, P., McGonagle, D. G. & Marzo-Ortega, H. Magnetic resonance imaging assessment of axial psoriatic arthritis: extent of disease relates to HLA-B27. *Arthritis Rheum.* **65**, 2274–2278 (2013).
53. Girolimetto, N. et al. Sensitivity to change and clinical correlations of the novel DACtylitis glObal Sonographic (DACTOS) score in psoriatic arthritis. *Rheumatology* **60**, 4103–4111 (2021).
54. Zabotti, A. et al. Ultrasonography in psoriatic arthritis: which sites should we scan? *Ann. Rheum. Dis.* **77**, 1537–1538 (2018).
55. Aydin, S. Z. & Deodhar, A. Are all entheses the same? *Rheumatology* **63**, 1–2 (2024).
56. Sakellariou, G. et al. Differential diagnosis of inflammatory arthropathies by musculoskeletal ultrasonography: a systematic literature review. *Front. Med.* **7**, 141 (2020).
57. Gessl, I. et al. Systematic literature review to inform the EULAR recommendations for the use of imaging in crystal-induced arthropathies in clinical practice. *Ann. Rheum. Dis.* **83**, 1208–1224 (2024).
58. Marchesoni, A. et al. The problem in differentiation between psoriatic-related polyenthesitis and fibromyalgia. *Rheumatology* **57**, 32–40 (2018).
59. Marchesoni, A., De Lucia, O., Rotunno, L., De Marco, G. & Manara, M. Entheseal power Doppler ultrasonography: a comparison of psoriatic arthritis and fibromyalgia. *J. Rheumatol. Suppl.* **89**, 29–31 (2012).
60. Zabotti, A., Mandl, P., Zampogna, G., Dejaco, C. & Iagnocco, A. One year in review 2018: ultrasonography in rheumatoid arthritis and psoriatic arthritis. *Clin. Exp. Rheumatol.* **36**, 519–525 (2018).
61. Zabotti, A. et al. Enthesitis of the hands in psoriatic arthritis: an ultrasonographic perspective. *Med. Ultrason.* **19**, 438–443 (2017).
62. Mandl, P. & Aletaha, D. The role of ultrasound and magnetic resonance imaging for treat to target in rheumatoid arthritis and psoriatic arthritis. *Rheumatology* **58**, 2091–2098 (2019).
63. Dubash, S. R. et al. Ultrasound shows swollen joints are the better proxy for synovitis than tender joints in DMARD-naïve early psoriatic arthritis. *Rheumatol. Adv. Pract.* **5**, rkab086 (2021).
64. Balint, P. V. et al. Reliability of a consensus-based ultrasound definition and scoring for enthesitis in spondyloarthritis and psoriatic arthritis: an OMERACT US initiative. *Ann. Rheum. Dis.* **77**, 1730–1735 (2018).
65. Chandran, V., Liao, W. & de Vlam, K. Biomarkers in psoriasis and psoriatic arthritis: where are we now? *J. Rheumatol.* **51**, 74–76 (2024).
66. Bowes, J. et al. Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis. *Nat. Commun.* **6**, 6046 (2015).
67. Ritchlin, C. T. et al. Psoriatic arthritis subtypes are phenocopied in humanized mice. *JCI Insight* **9**, e178213 (2024).
68. Kuiper, J. J. et al. EULAR study group on 'MHC-I-opathy': identifying disease-overarching mechanisms across disciplines and borders. *Ann. Rheum. Dis.* **82**, 887–896 (2023).
69. O'Rielly, D. D., Jani, M., Rahman, P. & Elder, J. T. The genetics of psoriasis and psoriatic arthritis. *J. Rheumatol. Suppl.* **95**, 46–50 (2019).
70. Merashli, M., De Marco, G., Podgorski, M., McGonagle, D. & Marzo-Ortega, H. Evidence of response to IL-6 inhibition in some cases of refractory spondyloarthritis-associated peripheral synovitis. *Ann. Rheum. Dis.* **75**, 1418–1420 (2016).
71. Bridgewood, C. et al. T Helper 2 IL-4/IL-13 dual blockade with dupilumab is linked to some emergent T helper 17–type diseases, including seronegative arthritis and enthesitis/enthesopathy, but not to humoral autoimmune diseases. *J. Investig. Dermatol.* **142**, 2660–2667 (2022).
72. Ciliento, M. S. et al. Evaluation of the synovial effects of biological and targeted synthetic DMARDs in patients with psoriatic arthritis: a systematic literature review and meta-analysis. *Int. J. Mol. Sci.* **24**, 5006 (2023).
73. Garaffoni, C. et al. High-grade synovitis associates with clinical markers and response to therapy in chronic inflammatory arthritis: post hoc analysis of a synovial biomarkers prospective cohort study. *Front. Immunol.* **14**, 1298583 (2023).
74. Roseman, C. et al. Persistent pain and its predictors after starting anti-tumour necrosis factor therapy in psoriatic arthritis: what is the role of inflammation control? *Scand. J. Rheumatol.* **53**, 94–103 (2024).
75. Samuel, C. et al. Characteristics associated with patient-reported treatment success in psoriatic arthritis. *Rheumatology* https://doi.org/10.1093/rheumatology/keae149 (2024).
76. Trouvin, A.-P. & Perrot, S. New concepts of pain. *Best. Pract. Res. Clin. Rheumatol.* **33**, 101415 (2019).
77. Mease, P. J. Navigating the complexity of pain in psoriatic arthritis and axial spondyloarthritis. *Curr. Opin. Rheumatol.* **36**, 282–288 (2024).
78. Horbal, N. & Maksymowych, W. P. Nociplastic pain in axial spondyloarthritis and psoriatic arthritis: role of JAK kinases in immunopathology and therapeutic impact of JAK inhibitors. *Expert. Rev. Clin. Immunol.* **21**, 137–152 (2025).
79. Rifbjerg-Madsen, S. et al. Pain and pain mechanisms in patients with inflammatory arthritis: a Danish nationwide cross-sectional DANBIO registry survey. *PLoS ONE* **12**, e0180014 (2017).
80. de Vlam, K. et al. Identifying and quantifying the role of inflammation in pain reduction for patients with psoriatic arthritis treated with tofacitinib: a mediation analysis. *Rheumatol. Ther.* **9**, 1451–1464 (2022).
81. Sunzini, F., Schrepf, A., Clauw, D. J. & Basu, N. The biology of pain: through the rheumatology lens. *Arthritis Rheumatol.* **75**, 650–660 (2023).
82. Aletaha, D., Alasti, F. & Smolen, J. S. Disease activity states of the DAPSA, a psoriatic arthritis specific instrument, are valid against functional status and structural progression. *Ann. Rheum. Dis.* **76**, 418–421 (2017).
83. Coates, L. C., Fransen, J. & Helliwell, P. S. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann. Rheum. Dis.* **69**, 48–53 (2010).
84. Leeb, B. F. et al. The disease activity score in 28 joints in rheumatoid arthritis and psoriatic arthritis patients. *Arthritis Rheum.* **57**, 256–260 (2007).

85. Orbai, A.-M. et al. Updating the psoriatic arthritis (PsA) core domain set: a report from the PsA workshop at OMERACT 2016. *J. Rheumatol.* **44**, 1522–1528 (2017).
86. Hjort, G., Schwarz, C. W., Skov, L. & Loft, N. Clinical characteristics associated with response to biologics in the treatment of psoriasis: a meta-analysis. *JAMA Dermatol.* **160**, 830–837 (2024).
87. Gossec, L. et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann. Rheum. Dis.* **79**, 700–712 (2020).
88. Macchioni, P. et al. Ultrasonographic and clinical assessment of peripheral enthesitis in patients with psoriatic arthritis, psoriasis, and fibromyalgia syndrome: the ULISSE study. *J. Rheumatol.* **46**, 904–911 (2019).
89. Mease, P., Reed, G., Ogdie, A., Pappas, D. A. & Kremer, J. M. Prevalence of fibromyalgia and widespread pain in psoriatic arthritis: association with disease severity assessment in a large US registry. *Arthritis Care Res* **76**, 1313–1321 (2024).
90. Love, T. J. et al. Obesity and the risk of psoriatic arthritis: a population-based study. *Ann. Rheum. Dis.* **71**, 1273–1277 (2012).
91. Green, A. et al. Modifiable risk factors and the development of psoriatic arthritis in people with psoriasis. *Br. J. Dermatol.* **182**, 714–720 (2020).
92. Højgaard, P. et al. The influence of obesity on response to tumour necrosis factor-α inhibitors in psoriatic arthritis: results from the DANBIO and ICEBIO registries. *Rheumatology* **55**, 2191–2199 (2016).
93. Di Matteo, A. et al. How normal is the enthesis by ultrasound in healthy subjects? *Clin. Exp. Rheumatol.* **38**, 472–478 (2020).
94. Jacques, P. et al. Proof of concept: enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells. *Ann. Rheum. Dis.* **73**, 437–445 (2014).
95. Felten, R., Duret, P.-M., Gottenberg, J.-E., Spielmann, L. & Messer, L. At the crossroads of gout and psoriatic arthritis: 'psout'. *Clin. Rheumatol.* **39**, 1405–1413 (2020).
96. Petsch, C. et al. Prevalence of monosodium urate deposits in a population of rheumatoid arthritis patients with hyperuricemia. *Semin. Arthritis Rheum.* **45**, 663–668 (2016).
97. Krekeler, M., Baraliakos, X., Tsiami, S. & Braun, J. High prevalence of chondrocalcinosis and frequent comorbidity with calcium pyrophosphate deposition disease in patients with seronegative rheumatoid arthritis. *RMD Open.* **8**, e002383 (2022).
98. Lubrano, E., Scriffignano, S. & Perrotta, F. M. Multimorbidity and comorbidity in psoriatic arthritis — a perspective. *Expert. Rev. Clin. Immunol.* **16**, 963–972 (2020).
99. De Vicente Delmás, A. et al. Uveitis in psoriatic arthritis: study of 406 patients in a single university center and literature review. *RMD Open.* **9**, e002781 (2023).
100. Zabotti, A. et al. The challenge of IBD-related arthritis screening questionnaires in early and predominantly entheseal phenotypes. *Rheumatol. Ther.* **11**, 1321–1331 (2024).
101. Hueber, W. et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut* **61**, 1693–1700 (2012).
102. Fobelo Lozano, M. J., Serrano Giménez, R. & Castro Fernández, M. Emergence of inflammatory bowel disease during treatment with secukinumab. *J. Crohns Colitis* **12**, 1131–1133 (2018).
103. Ogdie, A. et al. Defining outcome measures for psoriatic arthritis: a report from the GRAPPA-OMERACT working group. *J. Rheumatol.* **44**, 697–700 (2017).
104. Koduri, G. & Solomon, J. J. Identification, monitoring, and management of rheumatoid arthritis-associated interstitial lung disease. *Arthritis Rheumatol.* **75**, 2067–2077 (2023).
105. Bongartz, T. et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. *Arthritis Rheum.* **62**, 1583–1591 (2010).
106. Radic, M., Martinovic Kaliterna, D. & Radic, J. Overview of vasculitis and vasculopathy in rheumatoid arthritis — something to think about. *Clin. Rheumatol.* **32**, 937–942 (2013).
107. Ribeiro, A. L. et al. Deciphering difficult-to-treat psoriatic arthritis (D2T-PsA): a GRAPPA perspective from an international survey of healthcare professionals. *Rheumatol. Adv. Pract.* **8**, rkae074 (2024).
108. McGonagle, D., Hermann, K.-G. A. & Tan, A. L. Differentiation between osteoarthritis and psoriatic arthritis: implications for pathogenesis and treatment in the biologic therapy era. *Rheumatology* **54**, 29–38 (2015).
109. Tan, A. L., Grainger, A. J., Tanner, S. F., Emery, P. & McGonagle, D. A high-resolution magnetic resonance imaging study of distal interphalangeal joint arthropathy in psoriatic arthritis and osteoarthritis: are they the same? *Arthritis Rheum.* **54**, 1328–1333 (2006).
110. Geenen, R. et al. EULAR recommendations for the health professional's approach to pain management in inflammatory arthritis and osteoarthritis. *Ann. Rheum. Dis.* **77**, 797–807 (2018).
111. Vela, J. et al. Quantitative sensory testing, psychological profiles and clinical pain in patients with psoriatic arthritis and hand osteoarthritis experiencing pain of at least moderate intensity. *Eur. J. Pain* **28**, 310–321 (2024).
112. Tarannum, S. et al. Sex- and gender-related differences in psoriatic arthritis. *Nat. Rev. Rheumatol.* **18**, 513–526 (2022).
113. Højgaard, P. et al. Gender differences in biologic treatment outcomes — a study of 1750 patients with psoriatic arthritis using Danish Health Care Registers. *Rheumatology* **57**, 1651–1660 (2018).
114. Stober, C. et al. Prevalence and predictors of tumour necrosis factor inhibitor persistence in psoriatic arthritis. *Rheumatology* **57**, 158–163 (2018).
115. Eder, L., Thavaneswaran, A., Chandran, V. & Gladman, D. D. Gender difference in disease expression, radiographic damage and disability among patients with psoriatic arthritis. *Ann. Rheum. Dis.* **72**, 578–582 (2013).
116. Geijer, M. et al. The Swedish early psoriatic arthritis registry 5-year followup: substantial radiographic progression mainly in men with high disease activity and development of dactylitis. *J. Rheumatol.* **42**, 2110–2117 (2015).
117. Kim, J.-R. & Kim, H. A. Molecular mechanisms of sex-related differences in arthritis and associated pain. *Int. J. Mol. Sci.* **21**, 7938 (2020).
118. Luo, X. et al. IL-23/IL-17A/TRPV1 axis produces mechanical pain via macrophage-sensory neuron crosstalk in female mice. *Neuron* **109**, 2691–2706.e5 (2021).
119. Valero-Martínez, C. et al. Dual targeted therapy in patients with psoriatic arthritis and spondyloarthritis: a real-world multicenter experience from Spain. *Front. Immunol.* **14**, 1283251 (2023).
120. Cuchacovich, R., Garcia-Valladares, I. & Espinoza, L. R. Combination biologic treatment of refractory psoriasis and psoriatic arthritis. *J. Rheumatol.* **39**, 187–193 (2012).
121. Simon, D., Fagni, F. & Schett, G. Sequential interleukin-17/interleukin-23 inhibition in treatment-refractory psoriatic arthritis. *Ann. Rheum. Dis.* **81**, 1334–1336 (2022).
122. Hren, M. G. & Khattri, S. Treatment of recalcitrant psoriasis and psoriatic arthritis with a combination of a biologic plus an oral JAK or TYK2 inhibitor: a case series. *Ann. Rheum. Dis.* **83**, 1392–1393 (2024).
123. Feagan, B. G. et al. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. *Lancet Gastroenterol. Hepatol.* **8**, 307–320 (2023).
124. van Gestel, A. M., Haagsma, C. J. & van Riel, P. L. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum.* **41**, 1845–1850 (1998).
125. Nell-Duxneuner, V. P. et al. Evaluation of the appropriateness of composite disease activity measures for assessment of psoriatic arthritis. *Ann. Rheum. Dis.* **69**, 546–549 (2010).
126. Helliwell, P. S. et al. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). *Ann. Rheum. Dis.* **72**, 986–991 (2013).
127. Prevoo, M. L. et al. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br. J. Rheumatol.* **35**, 1101–1105 (1996).
128. Fransen, J. et al. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomised controlled trials of two tumour necrosis factor inhibitors. *Ann. Rheum. Dis.* **65**, 1373–1378 (2006).

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A.Z., S.Z.A., A.D.M. and D.M. conceived the main concepts and equally described the newly suggested terminology. A.Z., S.Z.A., P.D., A.D.M. and D.M. contributed to writing. A.Z., A.D.M. and D.M. revised the final version of the manuscript.

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In the version of the article initially published, an incorrect version of Fig. 3 was included. Fig. 3 has now been updated in the HTML and PDF versions of the article, as seen in Fig. 1.

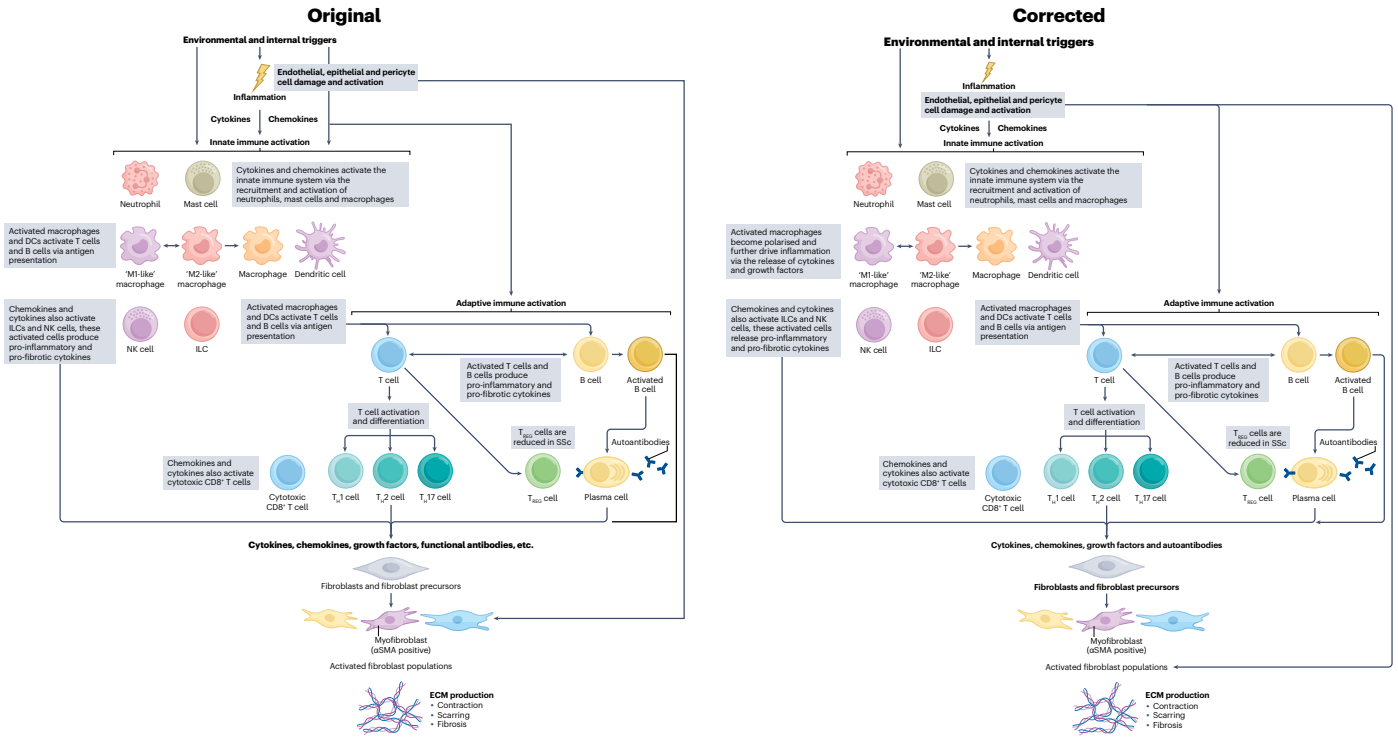

Fig. 1 | Original and corrected Fig. 3.