GENETICS

Potential causal variants for RA identified

> Raychaudhuri and colleagues narrowed down the possible genetic associations to six potentially causal variants for RA

Genome-wide association studies (GWASs) have previously revealed 101 non-MHC loci associated with rheumatoid arthritis (RA), but the causal genetic variants had not been defined. By combining fine-mapping techniques with functional studies, the authors of a new study published in *Nature Genetics* have identified strong candidate causal genetic variants for RA and for type 1 diabetes mellitus (T1DM).

"In this study we used statistical genetic strategies, dense genotyping data, functional investigation of non-coding variants and a combined analysis of data from patients with RA and patients with T1DM," explains corresponding author Soumya Raychaudhuri. "Statistical data for non-coding variation is important but often insufficient for identifying functional alleles, so using the statistical data, and combining it with non-coding functional assays to demonstrate that the candidate alleles had the potential to alter enhancer function, was key to defining causal variation."

Starting with a fine-mapping approach, the researchers investigated 76 non-MHC risk-associated loci for RA (11,475 cases and 15,870 controls) and T1DM (9,334 cases and 11,111 controls). The resulting list was refined to include only loci with ≤10 variants in their credible sets, and these loci were taken forward for functional studies (electrophoretic mobility shift assays and allele-specific luciferase assays) using immortalized T cell and monocyte lines.

Using this integrated approach, Raychaudhuri and colleagues narrowed down the possible genetic associations to six potentially causal variants for RA. These variants included missense mutations in *TYK2* (rs35018800) and *DNASE1L3* (rs35677470), an indel in *TNFAIP3* (rs35926684) and a non-coding mutation in the *CD28–CTLA4* locus (rs117701653). Shared missense mutations with T1DM in *PTPN22* and *TYK2* that had been previously described in GWASs were also confirmed.

"Amongst the most exciting results are a loss-of-function allele in *DNASE1L3* and non-coding causal alleles in *TNFAIP3* and *CD28–CTLA4*," says Raychaudhuri. "These results point to key pathways and genes that are driving RA risk."

The loss-of-function missense mutation in *DNASE1L3* produced a nuclease that could no longer cleave DNA during apoptosis. Importantly, similar missense mutations in *DNASE1L3* have previously been reported for systemic sclerosis and systemic lupus erythematosus (SLE).

Similarly, variants of *TNFAIP3* are associated with several autoimmune diseases, including SLE and Sjögren syndrome. A20, the protein coded for by *TNFAIP3*, reduces signalling via the transcription factor NF-κB and thereby inhibits apoptosis. Interestingly, the results of Hi-C promoter-capture analysis suggested that the rs35926684 region interacts with the promoters for *TNFAIP3*, *IL22RA* (involved in inflammation, apoptosis and angiogenesis) and *IFNGR1* (involved in interferon responses), indicating that several genes could be influenced by this one variant.

The rs117701653 variant of *CD28–CTLA4* (located in the CD28 region) also showed interactions with multiple promoters via Hi-C analysis, suggesting that this variant might affect *CTLA4* (involved in T cell co-stimulation) and *RAPH1* (involved in cell adhesion).

"The success of this study is to identify primary disease-associated variants," says Gerry Wilson, an expert in the genetics that underlie RA who was not involved in this study. "It's a great example of integration of state-of-the-art statistical analysis and straightforward biological experiments. Moving forward, it will be important to determine if the functional effects observed are specific to T cells or potentially occur in other relevant cell types such as synovial fibroblasts or B cells."

"There remain questions as to what context these alleles are working in, both in terms of cell-type and cell-state, what the downstream genes are that are regulated by the RA risk alleles and what the upstream regulatory machineries are that are driving RA risk," concludes Raychaudhuri. "Additional cellular investigations including CRISPR strategies and single cell investigation of inflamed tissues in RA will be critical to define the set of candidate genes driving cellular phenotypes."

Joanna Collison

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ORIGINAL ARTICLE Westra, H.-J. et al. Fine-mapping and functional studies highlight potential causal variants for rheumatoid arthritis and type 1 diabetes. *Nat. Genet.* **50**, 1366–1374 (2018)

IN BRIEF

PAEDIATRIC RHEUMATOLOGY

Long-term safety of canakinumab in systemic JIA

In a long-term extension of two phase III studies assessing the safety and efficacy of canakinumab (a fully human anti-IL-1β monoclonal antibody) in patients with active systemic juvenile idiopathic arthritis (JIA), treatment efficacy at 6 months was maintained for up to 5 years. No new safety findings were reported and treatment was associated with glucocorticoid discontinuation or substantial reduction in glucocorticoid dose. Overall, 102 patients (58%) discontinued canakinumab, mainly because of treatment inefficacy. A higher rate of discontinuation was noted for late responders than for early responders (81% versus 29%), indicating that early response is a predictive factor of long-term outcome.

ORIGINAL ARTICLE Ruperto, N. et al. Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: results from the 5-year long-term extension of the phase III pivotal trials. *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2018-213150 (2018)

SYSTEMIC LUPUS ERYTHEMATOSUS

Ustekinumab — a novel treatment?

The addition of ustekinumab, an IL-12 and IL-23 inhibitor, to standard-of-care treatment was more efficacious than placebo in the treatment of patients with active systemic lupus erythematosus (SLE) in a double-blind phase II randomized controlled trial. More patients in the ustekinumab group achieved an SLE responder index-4 (SRI-4) response at week 24 than in the placebo group (37 (62%) versus 14 (33%); $P = 0.006$). The safety profile of ustekinumab was consistent with that reported in previous trials of ustekinumab for other diseases.

ORIGINAL ARTICLE van Vollenhoven, R. F. et al. Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. *Lancet.* https://doi.org/10.1016/S0140-6736(18)32167-6 (2018)

GOUT

IL-1β blockade prevents gout attacks

In a post hoc analysis of data from CANTOS, a large double-blind placebo-controlled trial of canakinumab treatment for patients with established atherosclerotic disease, canakinumab treatment was associated with a ~50% reduction in risk of a first gout attack, but not with a change in serum uric acid levels. The reduction in risk of incidence gout was observed for all baseline concentrations of serum uric acid, suggesting that IL-1β blockade can prevent gout attacks independent of serum uric acid levels.

ORIGINAL ARTICLE Solomon, D. H. et al. Relationship of interleukin-1β blockade with incident gout and serum uric acid levels: exploratory analysis of a randomized controlled trial. *Ann. Intern. Med.* https://doi.org/10.7326/M18-1167 (2018)

RHEUMATOID ARTHRITIS

DMARD-related adverse events lower persistence

In a study of patients with methotrexate-refractory rheumatoid arthritis, the addition of sulfasalazine and hydroxychloroquine to methotrexate (triple therapy; $n = 171$) resulted in a lower persistence rate (defined as treatment without a ≥90-day gap in therapy) than the addition of a TNF inhibitor ($n = 2,125$). Over a 12 month period, 45% of patients in the TNF inhibitor group persisted with treatment, compared with 18% of patients in the triple therapy group. Treatment discontinuation was most often because of sulfasalazine-related adverse drug events.

ORIGINAL ARTICLE Erhardt, D. P. et al. Low persistence rates in rheumatoid arthritis patients treated with triple therapy are attributed to adverse drug events associated with sulfasalazine. *Arthritis Care Res.* https://doi.org/10.1002/acr.23759 (2018)

RHEUMATOID ARTHRITIS

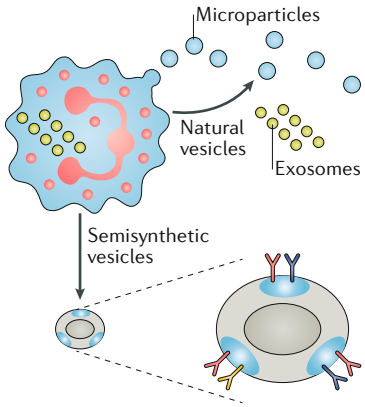
Nanoparticles in neutrophil clothing

Neutrophils are key immune cells in rheumatoid arthritis (RA) that are known for their involvement in perpetuating, but also in resolving, inflammation. One mechanism used by neutrophils to control inflammation is the production of natural vesicles (such as exosomes and microparticles), which have been shown to be joint-protective in mouse models of RA.

In a new study published in *Nature Nanotechnology*, researchers show how semisynthetic nanoparticles (NPs) coated in neutrophil cell membrane can also have joint-protective effects in mouse models of RA. "We collected the plasma membrane of activated neutrophil cells and then coated the membrane onto a synthetic nanoscale particle core, forming neutrophil-membrane-coated nanoparticles (neutrophil-NPs)," states corresponding author Liangfang Zhang. "The resulting neutrophil-NPs were then applied locally to inflamed joints."

Intra-articular injection of neutrophil-NPs reduced disease severity and joint damage in two mouse models of RA (collagen-induced arthritis and a transgenic model of inflammatory arthritis) to a level comparable with mice treated with anti-TNF or anti-IL-1β antibodies. "Neutrophil-NPs were able to effectively interact with and absorb various types of inflammatory cytokines that would otherwise have interacted with real neutrophils," says Zhang.

The researchers also investigated the ability of neutrophil-NPs to penetrate cartilage. Fluorescently labelled neutrophil-NPs could be detected to a depth of 140 μm from the cartilage surface in explants, whereas erythrocyte-membrane-coated NPs could only be detected to a depth of 30 μm. Neutrophil-NPs were also seen in close proximity to chondrocyte nuclei, indicating that the NPs might have been taken up by the chondrocytes. In explants



Credit: Adapted from Thomas, B.L. & Perretti, M. Neutrophil wrap. *Nat. Nanotechnol.* https://doi.org/10.1038/s41565-018-0260-6 (2018)

treated with IL-1β, neutrophil-NPs reduced cartilage damage by removing IL-1β from the environment.

"The development of therapeutic approaches based on the modification of NPs with cell membrane represents an important leap forward in the field of nanomedicine since they combine the benefits of both human-made and natural materials," explains Massimo Bottini, who was not involved in this study. "Although the authors did not assess the mechanism of interaction between neutrophil-NPs and chondrocytes, the ability of neutrophil-NPs to enter the cartilage and target the chondrocytes is an important finding," he continues. "The next step should be to test the therapeutic efficacy of systemically administered neutrophil-NPs in mouse models of arthritis as both a therapeutic agent and a chondrocyte-specific drug delivery system."

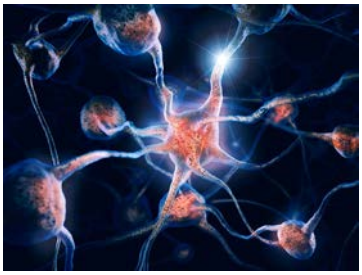
"We are very interested in moving this technology forward to evaluate its clinical application potential; however, a major challenge that we have to overcome is the large-scale manufacturing of the neutrophil-NPs to GMP quality," concludes Zhang.

Joanna Collison

ORIGINAL ARTICLE Zhang, Q. et al. Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis. *Nat. Nanotechnol.* https://doi.org/10.1038/s41565-018-0254-4 (2018)

SYSTEMIC LUPUS ERYTHEMATOSUS

ACE inhibitors preserve cognitive function



Credit: Oleksiy Maksymenko Photography/Alamy Stock Photo

In a mouse model of brain pathology mediated by a subset of anti-DNA antibodies found in patients with systemic lupus erythematosus (SLE), ACE inhibition can preserve cognitive function, according to a new study. "The most important aspect of the study is that the results showed that damaged neurons can recover and cognition can be improved if microglial activation is controlled," reports Betty Diamond, corresponding author of the study.

Her group has previously demonstrated that this subset of anti-DNA antibodies, which they term DNRAbs, cross-react with the *N*-methyl-d-aspartate receptor (NMDAR). "We have been studying how and when these antibodies can contribute to the neuropsychiatric symptoms of SLE," says Diamond. They developed a two-stage mouse model of neuropsychiatric lupus, in which DNRAbs are first induced by immunizing with a DWEYS peptide and the blood-brain barrier (BBB) is then disrupted using LPS treatment, resulting in acute excitotoxic neuron loss followed by long-term alterations in neuronal integrity and by spatial memory impairment.

In this study, Diamond and colleagues sought to understand the mechanisms underlying the long-term cognitive impairment in this model. "We demonstrate that the antibody-mediated neuronal death leads to microglial cell activation, and that microglial suppression can improve neuronal integrity and cognitive problems," explains Diamond.

Using C1q-deficient mice, they showed that the decrease in dendritic complexity and spine density, but not the acute neuronal death, was dependent on C1q. Unlike wild-type DNRAb$^+$ mice, C1q-deficient DNRAb$^+$ mice behaved normally in an object-place memory task that tests spatial memory.

ACE inhibitors, commonly used to lower blood pressure, have previously been shown to suppress microglial activation. In the new study, treatment with a BBB-permeable ACE inhibitor, but not with a BBB-impermeable ACE inhibitor or saline, suppressed microglial activation and preserved dendritic integrity and cognitive function in the DNRAb$^+$ mice.

> "Treatment with a BBB-permeable ACE inhibitor… suppressed microglial activation and preserved dendritic integrity and cognitive function in the DNRAb$^+$ mice"

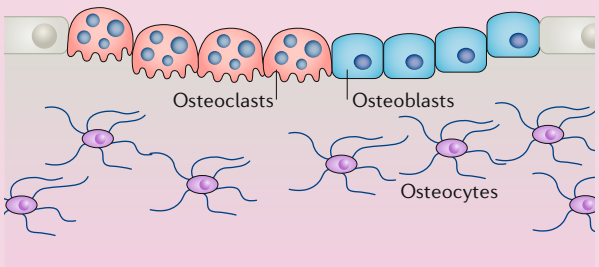
"We plan to study the mechanisms for microglial activation, which might lead to therapeutic targets" says Diamond. "We also think clinical trials of ACE inhibitors in neuropsychiatric SLE are now warranted."

Jessica McHugh

ORIGINAL ARTICLE Nestor, J. et al. Lupus antibodies induce behavioral changes mediated by microglia and blocked by ACE inhibitors. *J. Exp. Med.* https://doi.org/10.1084/jem.20180776 (2018)

BONE

RANKL reverse signalling and bone



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New research by Hiroshi Suzuki and colleagues shows that reverse signalling of receptor activator of nuclear factor-κB (RANK; also known as TNFRSF11A) ligand (RANKL; also known as TNFSF11) in osteoblasts has a role in linking bone resorption and formation.

RANKL belongs to the tumour necrosis factor family, which is a group of proteins that act as bidirectional signalling molecules and produce intracellular reverse signalling. Previously, osteoblasts were thought to be the main producers of RANKL; however, mounting evidence suggests that osteocytes are the main source during bone remodelling. "Because of this finding, we hypothesized that osteoblastic RANKL might have a different physiological role than that of osteocytic RANKL," explains corresponding author Masashi Honma.

In this study, the researchers showed that maturing osteoclasts secreted vesicular RANK (vRANK), which binds to osteoblastic RANKL and activates reverse signalling through *Runx2*. The stimulation also increased the mineralization of osteoblasts.

Next, the authors created a mouse model (*Rankl*^{P29A}) to suppress reverse signalling of RANKL but not forward signalling, which triggers osteoclastogenesis. When recombinant RANKL was administered, osteoclast maturation in both *Rankl*^{P29A} and wild-type mice was increased; however, bone formation was disrupted in *Rankl*^{P29A} mice compared with wild-type mice. The results suggest that osteoblastic RANKL reverse signalling is involved in linking bone resorption and formation.

> "…activation of RANKL reverse signalling inhibited reduced bone formation"

Finally, Suzuki and colleagues targeted RANKL reverse signalling in an ovariectomized mouse model to test whether it is a possible pharmacological target for the treatment of osteoporosis. They found that activation of RANKL reverse signalling inhibited reduced bone formation. "Our findings indicate that the role of RANKL is the accelerator of bone turnover rather than the stimulator of bone resorption," concludes Honma.

Ivone Leong,
Nature Reviews Endocrinology

This article is modified from the original in *Nat. Rev. Endo.* (https://doi.org/10.1038/s41574-018-0094-1).

ORIGINAL ARTICLE Ikebuchi, Y. et al. Coupling of bone resorption and formation by RANKL reverse signalling. *Nature* **561**, 195–200 (2018)

PAEDIATRIC RHEUMATOLOGY

Some PD-1$^+$ CD8$^+$ T cells are not exhausted

New research shows that PD-1$^+$ CD8$^+$ T cells that accumulate in the synovial fluid of patients with juvenile idiopathic arthritis (JIA) are not in an exhausted state. These cells are mostly memory T cells with an effector signature and probably derive from local antigenic stimulation to contribute to joint pathology.

PD-1 is a negative co-stimulatory receptor best known for its function as an immune checkpoint. In chronic inflammatory environments such as cancer and some infectious diseases, PD-1 expression is induced on CD8$^+$ T cells and is associated with loss of effector functions and the entry of those cells into a state known as exhaustion.

To see if PD-1$^+$ CD8$^+$ T cells in the joints are similarly exhausted, the researchers performed whole-transcriptome sequencing of T cell subsets from the synovial fluid of patients with JIA or from healthy individuals. The JIA PD-1$^+$ cells were enriched for gene expression pathways that are typical of effector T cells, such as the cell cycle, proliferation, cytotoxicity and pro-inflammatory signalling.

The researchers also showed that these PD-1$^+$ cells are primarily glycolytic and have not switched cellular metabolism to oxidative phosphorylation, as is expected of exhausted T cells. Furthermore, these cells were functionally active in response to in vitro stimulation with PMA and ionomycin or with anti-CD3 and anti-CD28 antibodies.

The researchers also characterized the T cell receptor (TCR) Vβ repertoires, showing that TCR diversity is lower in the PD-1$^+$ subset than in the PD-1$^-$ population, suggesting that PD-1$^+$ cells in the synovial fluid of patients with JIA proliferate in response to locally expressed antigens and that PD-1 marks a distinct CD8$^+$ T cell subset.

"At the target site of chronic inflammatory diseases, enrichment

> "…PD-1$^+$ cells are primarily glycolytic and have not switched cellular metabolism to oxidative phospho-rylation…

Credit: Springer Nature Limited/Neil Smith

of PD-1$^+$ CD8$^+$ T cells doesn't mean exhaustion, but rather functional adaptation and local antigen-driven clonal expansion," explains Alessandra Petrelli, first author of the new study. "Therefore, our paper supports the idea of functional T cell adaptation to the local inflammatory environment. The data also suggest that these cells may have a pathogenic function in chronic inflammation and could be interesting targets for therapy," she concludes.

Nicholas J. Bernard

ORIGINAL ARTICLE Petrelli, A. et al. PD-1$^+$CD8$^+$ T cells are clonally expanding effectors in human chronic inflammation. *J. Clin. Invest.* https://doi.org/10.1172/JCI96107 (2018)

OSTEOARTHRITIS

Brains and bones and joints

The nuclear phosphoprotein ANP32A protects against oxidative degeneration of brain, bone and cartilage tissue, according to a study published in *Science Translational Medicine*.

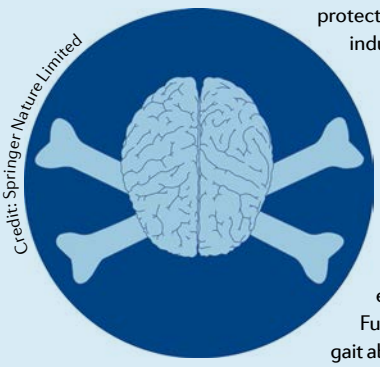
To understand an already established association between risk of osteoarthritis and *ANP32A* polymorphisms, the researchers show that compared with patients admitted for trauma surgery, patients with hip osteoarthritis (OA) have lower gene and protein expression of ANP32A in cartilage. The protein is also expressed less in damaged areas than in healthy areas of the cartilage.

These findings are mirrored in both surgically-induced and age-induced mouse models of OA. Furthermore, *Anp32a*$^{-/-}$ mice are more susceptible to cartilage degeneration in a variety of OA models.

To understand the mechanism of this protective function of ANP32A, the researchers conducted genome-wide transcriptomic analyses. One of the top hits, *Atm*, drew their attention owing to the known anti-oxidant function of the protein kinase it encodes. They show that *Atm* is barely expressed in cartilage from *Anp32a*$^{-/-}$ mice and in patients with OA, especially in damaged areas of cartilage, and knockdown of *ANP32A* in human cartilage samples results in lower expression of *ATM*.

Using ChIP-qPCR and RNA polymerase II analysis the researchers found that ANP32A directly activates transcription at the *ATM* promoter in chondrocytes.

The therapeutic implications of these findings were probed by feeding the antioxidant *N*-acetyl-cysteine (NAC) to *Anp32a*$^{-/-}$ mice, resulting in cartilage protection against surgically induced OA.



Credit: Springer Nature Limited

Intriguingly, the pathology in *Anp32a*$^{-/-}$ mice is not restricted to cartilage as the mice also developed osteopenia plus ataxia that is associated with reduced cerebellar expression of *Atm*. Furthermore, the ataxic gait abnormality in these mice was reversed by NAC treatment.

"Oxidative stress has been suggested to play an important role in the progression of osteoarthritis and other degenerative or ageing-associated diseases," explains corresponding author Rik Lories. "Our data suggest that increasing levels of ANP32A in the target tissues may be a strategy to act against these processes and treat OA and other diseases," he concludes.

> "…*Anp32a*$^{-/-}$ mice are more susceptible to cartilage degeneration…

Nicholas J. Bernard

ORIGINAL ARTICLE Cornelis, F. M. F. et al. ANP32A regulates ATM expression and prevents oxidative stress in cartilage, brain, and bone. *Sci. Transl. Med.* **10**, eaar8426 (2018)

THERAPY

How to be NICEr in treating osteoarthritis

Philip G. Conaghan

Current guidelines for the treatment of osteoarthritis involve exercise and lifestyle modifications as well as pharmaceutical therapeutics for effective pain management. Is this message reaching patients, and are they exercising enough?

Refers to Healey, E. L. et al. Uptake of the NICE osteoarthritis guidelines in primary care: a survey of older adults with joint pain. *BMC Musculoskelet. Disord.* **19**, 295 (2018).

Osteoarthritis (OA) is an increasing problem for individuals and for health-care systems, especially with ageing societies and the increasing prevalence of obesity[1]. Healey et al.[2] have reported a large (4,059 respondents who consulted their primary care physician about joint pain in the previous 12 months) UK community-based patient survey of OA management. They used this survey to evaluate how people with OA have been using the therapies recommended by the UK National Institute for Health and Clinical Excellence (NICE). NICE provides national clinical guidance on the basis of a robust synthesis of systematic literature reviews, health economic data, expert opinion and patient input. Although these guidelines are primarily aimed at NHS health-care providers, the Healey et al.[2] survey (performed between May 2011 and April 2012) enables us to see what patients registered in 8 sites in the West Midlands and North West of England were doing a few years after the first NICE OA clinical guidelines were published in 2008 (REF.[3]). The survey is, of course, reported information and therefore is limited by patient recall bias.

An important issue raised by Healey et al.[2] is that of multi-site joint pain: 80% of participants in the study reported such pain. However, guidelines have failed to advise on how to manage this group of patients, in part because there are very few trials in this area. Treating the whole patient is critical and needs to be the focus of future musculoskeletal research and therapy.

Healey et al.[2] report that patterns of usage of most OA therapies were depressingly low, especially for muscle-strengthening exercises, but mostly in line with other surveys that have looked at use of current OA therapies in the UK[4], EU[5,6] and USA[7]; however, these surveys often focus on pharmacological therapies[4,5]. The uptake of therapies was generally lower than in another survey (from 2011–2012) of approximately 2,000 patients[4] from the broader UK population rather than the regional population surveyed by Healey et al.[2] Therefore, the reduction in uptake and other differences might reflect the larger sample size in the Healey et al.[2] study, or might be reflective of issues that are specific to some regions of the UK.

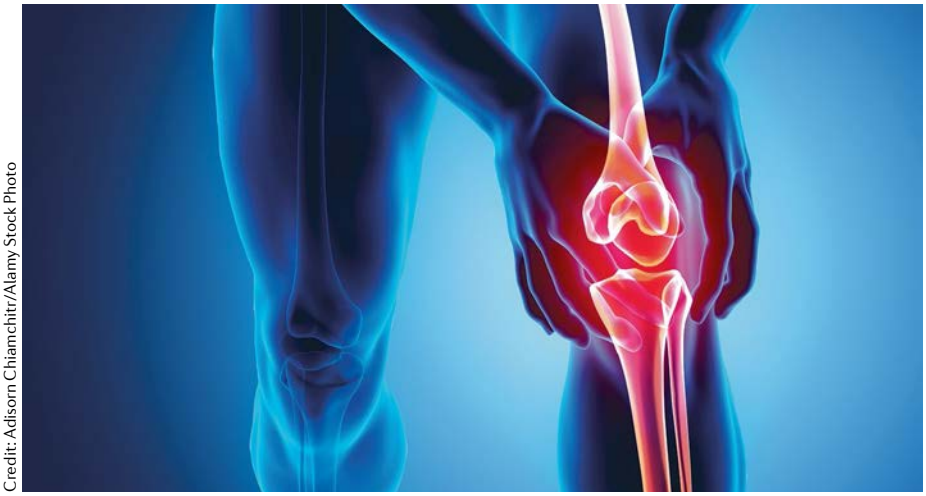
> We must rebuff the view that joint pain is an inevitable part of ageing

One similarity across international studies has been the limited use of pharmacological therapies such as oral NSAIDs and opioids, probably reflecting the limitations of these therapies (rather than lack of prescription), especially their toxicities and contra-indications which substantially limit application to people who might have multiple comorbidities. A diminishing use of drug therapy is especially appropriate among an velderly population. The usage of these therapies might also reflect some dissatisfaction with the perceived benefits — a large proportion of people with OA pain have substantial levels of persistent pain despite using existing pharmacological therapies including NSAIDs and opioids[6]. Therefore, we have a real problem in that it seems we are not treating joint pain very well in the community and patients are not following the principles laid out in clinical guidance.

So what can we do to treat OA better and more easily? Something not often looked at in such surveys is the provision of written information to patients; overall, only 23% of respondents in the Healey survey reported being given this information. Apart from talking about pain management, patients often report discussing with doctors their fears about OA and its impact on their lives, and about primary health-care support[4]. Many of these important issues can be addressed with adequate provision of information, advice on local facilities and directing patients to trusted, evidence-based information websites. Creating a list of such information for patients for each local practice is a relatively quick task and probably would only require annual updates.

In the Healey at al[2]. survey, it is unclear if uptake of muscle-strengthening exercises and manual therapy reflect exposure of these patients to physiotherapy programs. Also, there is often a lack of community understanding of what constitutes aerobic activity; some patients mistakenly think this means being part of a supervised activity. Despite the efficacy of simple and safe non-pharmacological interventions (such as exercise) for OA, and indeed all mechanical joint pain, why is there a failure of patients to participate in these important aspects of daily care? NICE emphasizes that muscle strengthening should come before increasing aerobic activity; telling physically weak people to go for a walk is not an effective strategy. A particular challenge in our ageing society is the reduction in frequency of exercise as people age, as reported by Healey et al.[2] Whether this problem reflects a failure of health-care professionals to engage older patients in exercise therapy or a possible attitude among patients that 'my muscle weakness is just part of ageing' is unclear. We must educate our patients that only by getting strong and subsequently fit will their joint pain diminish in a sustainable way. Teaching a single exercise to patients with weak grip or weak quadriceps can take as little as a few minutes, and the analgesic benefits can be clear in just a few weeks of appropriate muscle strengthening, even in people aged >75 years[8].

It would be wise to prevent or reduce muscle weakness through community



Credit: Adisorn Chiamchitr/Alamy Stock Photo

interventions, as recommended in a recent tiered approach to physical activity supported by a range of important UK health providers[9]. This approach starts with accessible community facilities (like parks and swimming pools), then supervised physical programmes (such as aqua-aerobics or dance clubs), progressing through structured community-based rehabilitation programmes (that need not be supervised by clinicians). If people have problems despite accessing these tiers, individual programmes supervised by physical therapists will be required, but clinicians need to direct patients to these tiered activities first[9].

The reported rates of dieting to lose weight (<10%) are not unexpectedly low, and it is not clear if this refers to being part of an effective, supervised diet programme. Being overweight is certainly a contributor to joint pain, with trials suggesting that 5–10% of bodyweight must be lost to achieve symptomatic benefits[10]. We have been spectacularly unsuccessful in Western societies in turning around the obesity epidemic and we need new strategies, bearing in mind the success and beneficial effect of government societal interventions that have reduced the prevalence of smoking, for example.

Even in the absence of new pharmacological therapies, there are things health-care professionals can do better and quickly in line with NICE guidance. All practitioners who treat musculoskeletal problems should provide their patients with hard-copy or electronic exercise sheets and provide directions to appropriate web information on the nature and treatment of osteoarthritis. We must rebuff the view that joint pain is an inevitable part of ageing. We must promote muscle strengthening as a critical component of osteoarthritis care, no matter the age of the patient, and we must support our patients with guided activity plans to reduce the burden of joint pain.

Philip G. Conaghan[1,2]

[1]*Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK.*

[2]*NIHR Leeds Biomedical Research Centre, Leeds, UK.*

e-mail: p.conaghan@leeds.ac.uk

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Competing interests
The author declares no competing interests

RHEUMATOID ARTHRITIS

The parallel worlds of ACPA-positive and RF-positive B cells

Vivianne Malmström and Caroline Grönwall

Seropositive RA can present with two different types of autoantibodies that have distinct features: anti-citrullinated protein antibodies (ACPAs) and rheumatoid factors (RFs). With a single-cell approach, researchers provide evidence that the underlying B cell subsets of these autoantibody specificities develop in parallel by different mechanisms.

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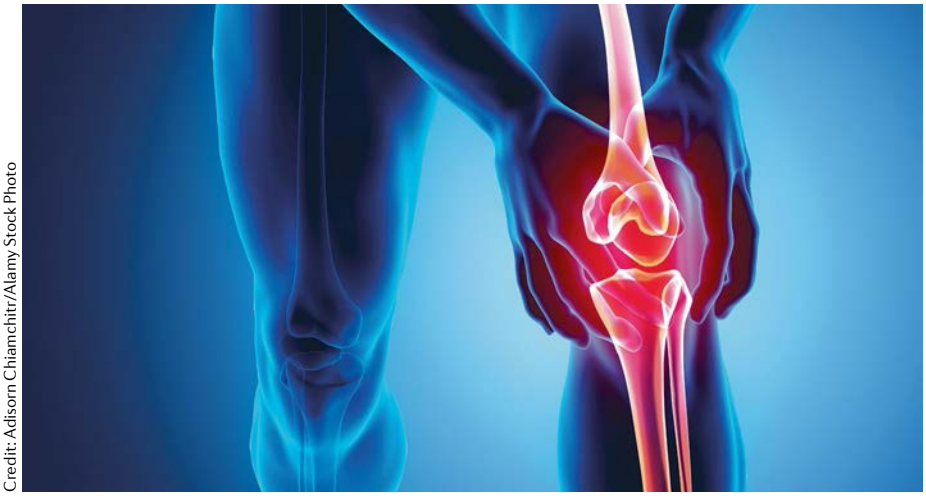
The major subset of rheumatoid arthritis (RA), known as seropositive RA, is characterized by the presence of rheumatoid factors (RFs) and anti-citrullinated protein antibodies (ACPAs) in the serum. These two sets of autoantibodies have some contrasting features, even though they often co-occur in seropositive RA, and might function synergistically. ACPAs are specific for RA[1], whereas RFs are relatively common in other autoimmune diseases and can be present in infection[2]. Even though RFs have undergone somatic hypermutation, these molecules generally carry only a modest number of somatic mutations[2]; by contrast, ACPAs are reported to have high levels of somatic mutations[3–6]. Increased knowledge about how these two major autoreactivities arise is crucial for understanding how RA develops and what mechanisms drive pathogenesis. In a new study, Lu et al.[7] explore the differences between autoreactive B cells expressing



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interventions, as recommended in a recent tiered approach to physical activity supported by a range of important UK health providers[9]. This approach starts with accessible community facilities (like parks and swimming pools), then supervised physical programmes (such as aqua-aerobics or dance clubs), progressing through structured community-based rehabilitation programmes (that need not be supervised by clinicians). If people have problems despite accessing these tiers, individual programmes supervised by physical therapists will be required, but clinicians need to direct patients to these tiered activities first[9].

The reported rates of dieting to lose weight (<10%) are not unexpectedly low, and it is not clear if this refers to being part of an effective, supervised diet programme. Being overweight is certainly a contributor to joint pain, with trials suggesting that 5–10% of bodyweight must be lost to achieve symptomatic benefits[10]. We have been spectacularly unsuccessful in Western societies in turning around the obesity epidemic and we need new strategies, bearing in mind the success and beneficial effect of government societal interventions that have reduced the prevalence of smoking, for example.

Even in the absence of new pharmacological therapies, there are things health-care professionals can do better and quickly in line with NICE guidance. All practitioners who treat musculoskeletal problems should provide their patients with hard-copy or electronic exercise sheets and provide directions to appropriate web information on the nature and treatment of osteoarthritis. We must rebuff the view that joint pain is an inevitable part of ageing. We must promote muscle strengthening as a critical component of osteoarthritis care, no matter the age of the patient, and we must support our patients with guided activity plans to reduce the burden of joint pain.

Philip G. Conaghan[1,2]

[1]*Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK.*

[2]*NIHR Leeds Biomedical Research Centre, Leeds, UK.*

e-mail: p.conaghan@leeds.ac.uk

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Competing interests
The author declares no competing interests

RHEUMATOID ARTHRITIS

The parallel worlds of ACPA-positive and RF-positive B cells

Vivianne Malmström and Caroline Grönwall

Seropositive RA can present with two different types of autoantibodies that have distinct features: anti-citrullinated protein antibodies (ACPAs) and rheumatoid factors (RFs). With a single-cell approach, researchers provide evidence that the underlying B cell subsets of these autoantibody specificities develop in parallel by different mechanisms.

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either RFs or ACPAs by characterizing the immunoglobulin repertoire and transcriptional programmes of autoantigen-specific B cells captured from six patients with RA.

The isolation of lymphocytes using antigen-labelled tetramers (the technique used by Lu et al.[7]) enables in-depth analysis of autoantigen-specific B (or T) cells. This technique is being increasingly used for the study of clinical samples of patients with RA[3–5] and is a promising approach for use in immune surveillance studies to track autoreactive B cells (and their phenotype) in repeat blood samples of patients with RA. In their study, Lu et al.[7] combine this technology with single-cell RNA sequencing, enabling the investigators to study the transcriptional programmes used by the different captured cells and to discriminate captured B cells that have a naive, memory or plasmablast phenotype as well as to simultaneously conduct somatic hypermutation and class-switch analyses.

All six patients of the Lu et al.[7] study had both ACPA-positive and RF-positive B cells, which were present in similar frequencies (1–4 cells per 1,000 B cells), but interestingly they found striking differences between the two B cell subpopulations. These differences, which were both at the transcriptional level and within the immunoglobulin gene sequences themselves, suggest contrasting trajectories in the development of the two B cell subpopulations.

The maturation of B cell responses normally involves the interaction of B cells with antigens in the germinal centres, leading to somatic hypermutation and the selection of high-affinity somatically hypermutated B cells (in a process known as the germinal centre reaction) as well as class-switching. In the study by Lu et al.[7], a higher proportion of the ACPA-positive B cells had signs of antigen-experience and class switching compared with the RF-positive B cells. Furthermore, the somatic hypermutation rates of ACPA-positive B cells were considerably higher than those of RF-positive B cells, suggesting that the ACPA-positive B cells had undergone more cycles of B cell selection in the germinal centres. These findings could imply that ACPA B cells are part of a chronic response whereas the RF B cells are part of a short-term response (FIG. 1).

Looking further into the transcriptomic profiles, the investigators developed their own analysis pipeline for characterizing the differentially expressed genes (DEGs) in B cells at distinct stages of differentiation (to discriminate B cells that have a naive, memory or plasmablast phenotype). The DEGs in the ACPA-positive B cells were enriched for genes involved in the promotion of T cell-dependent B cell differentiation, class switching and nuclear factor-kB signalling.

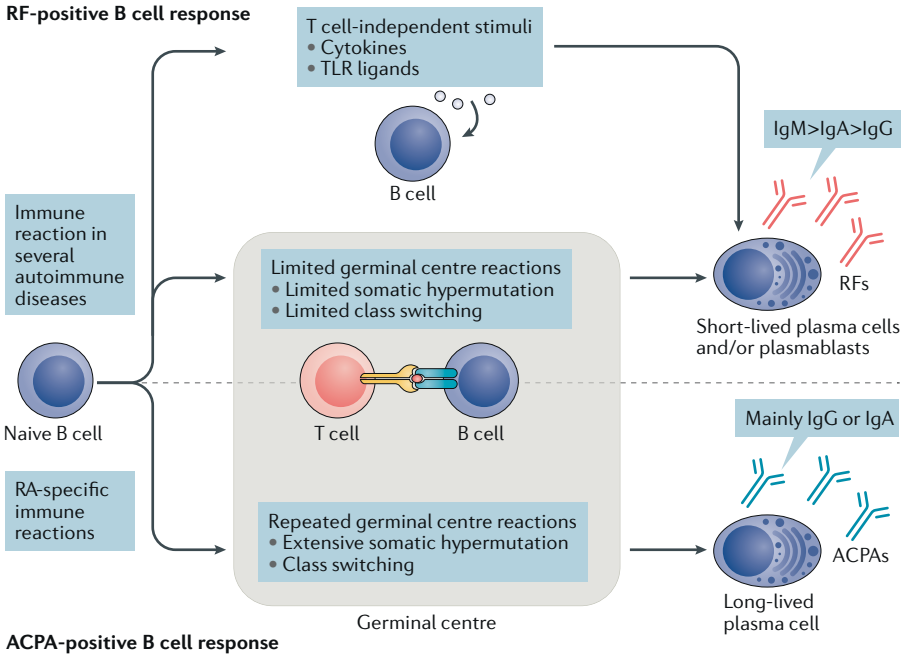

Fig. 1 | **The maturation of RF-positive and ACPA-positive B cell responses.** Anti-citrullinated protein antibodies (ACPA)-positive B cells undergo multiple rounds of germinal centre reactions whereby they accumulate somatic hypermutations and undergo isotype switching. By contrast, rheumatoid factor (RF)-positive B cells undergo few rounds of germinal centre reactions and might instead be activated by innate immune mechanisms. Thus, the citrulline-specific immune response generates long-lived plasma cells and ACPA autoantibodies that are relatively stable, whereas the RF response is characterized by the generation of short-lived plasma cells and fluctuating RF levels. Ig, immunoglobulin; RA, rheumatoid arthritis; TLR, Toll-like receptor.

Conversely, the DEGs in RF-positive B cells included two transcription factors (BACH2 and SOX11) that might be associated with rapid IgM responses and reduced germinal centre responses. Co-expression of innate immune genes and plasmablast differentiation markers in RF-positive B cells further support the association between RF-positive B cells and rapidly induced but short-lived responses rather than responses involving prolonged affinity maturation. Altogether, these findings support the concept that parallel pathways are used in the maturation of ACPA-positive and RF-positive B cells (FIG. 1).

These results[7] lend support to a scenario in which the citrulline-specific response is governed by a robust RA-specific $CD4^+$ T cell response with repeated germinal centre selection, whereas RF production is also driven by intrinsic factors, such as Toll-like receptor stimuli, and possibly involves B cells with a more innate-like profile associated with a rapid response. Relevant to this discussion, other investigators have demonstrated that the immunoglobulins of ACPA-positive B cells have unique features, consistent with several rounds of germinal centre reactions[3,5]. These features include the accumulation of *N*-glycosylation sites in the Fab region of IgG ACPAs, which is driven by somatic hypermutation[8,9] and implicates the existence of a gradually or continually evolving citrulline-specific autoimmune response. However, the exact mechanisms driving ACPA B cell selection are not yet fully delineated.

Yet, even though RFs are less specific to RA than ACPAs, RF-positive B cells might have important roles in amplifying immune responses by functioning as potent antigen-presenting cells[10]. Given that RF-positive B cells can internalize immune complexes that contain any (auto)antigen and present these antigens to T cells, these B cells might contribute to ACPA expansion and epitope spreading.

With regard to the pathogenic role of autoantibodies in RA, the extent to which autoantibodies directly contribute to arthritis development is unknown, even if accumulating evidence suggests that they have a functional role[1,3]. Clearly, both immune complexes and antigen capture and presentation contribute to arthritis development. The expression of recombinant monoclonal antibodies from sequenced B cells will enable researchers to continue dissecting the effector functions pertinent to RA pathology.

There is a growing interest in monitoring the autoreactive B cell and T cell repertoires of patients with RA, and tetramer technology is one useful approach that can be combined with

several methodologies such as RNA sequencing and time-of-flight mass cytometry (CyToF) for this purpose. The isolation of antigen-specific lymphocytes (both B and T cells) might reveal signals that would otherwise be easily missed by generic approaches that analyse entire subsets of cells without pre-selecting for the autoreactive cells. Using tetramer methodology, Lu et al.[7] provide intriguing insight into RA pathogenesis and implicate the existence of distinct scenarios that shape the respective autoreactive B cell subpopulations in RA. Studies like this one will hopefully inspire future efforts to characterize the underlying activation and differentiation history of autoreactive lymphocyte populations to help understand the mechanisms by which B cell tolerance breaks down in RA. Such insights could ultimately lead to therapeutic approaches that interfere with RA pathogenesis.

Vivianne Malmström * *and Caroline Grönwall*

Division of Rheumatology, Department of Medicine, Karolinska Institutet, Karolinska University Hospital, Center for Molecular Medicine, Stockholm, Sweden.

**e-mail: Vivianne.Malmstrom@ki.se*

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GOUT

Hyperferritinaemia and hyperuricaemia — a causal connection?

Pascal Richette and Augustin Latourte

A variety of comorbidities of gout exist, but most of these associations are not causally linked. Mendelian randomization analysis of genome-wide association study data now suggests that iron overload might increase serum uric acid levels and hence the risk of gout flares.

Refers to Fatima, T. et al. The relationship between ferritin and urate levels and risk of gout. *Arthritis Res. Ther.* **20**, 179 (2018).

People with gout or isolated hyperuricaemia often have a variety of comorbidities, such as renal failure and hypertension, as well as other components of metabolic syndrome, such as obesity. These comorbidities contribute to the high levels of cardiovascular mortality in gout, but the link between comorbidities and hyperuricaemia is complex. Obesity and comorbidities such as chronic kidney disease increase the risk of developing gout because they both increase serum uric acid levels by impairing urinary uric acid excretion[1]. Some observational studies indicate that hyperuricaemia and gout might contribute to cardiovascular diseases, metabolic syndrome and renal failure[1]. However, exploring the causality between hyperuricaemia and outcomes from observational studies is limited by potential confounders and reverse causality. Hence, a new study from Fatima et al.[2] utilizes Mendelian randomization, which has been used previously to detect causal associations. An earlier umbrella review (a review that analyses data from multiple sources) of associations between hyperuricaemia and multiple health outcomes from observational studies concluded that causality of these associations disappears once Mendelian randomization analysis is applied[3]. Thus, convincing evidence has been lacking to add a causal link to the association of serum uric acid levels and comorbidities.

Fatima et al.[2] add to our understanding of the relationship between hyperuricaemia and hyperferritinaemia, a relatively neglected association given the clinical focus has been on the high prevalence of obesity and liver function abnormality in patients with gout. Elevated serum ferritin levels are fairly common in the general population and can result either from increased ferritin synthesis or from increased release of ferritin by damaged cells, as can occur in patients with metabolic disorder. Not surprisingly, an association between hyperferritinaemia and hyperuricaemia has been reported previously[4]. However, whether this association is causal has not been investigated until now.

Fatima et al.[2] aimed to replicate the observational association between hyperferritinaemia and hyperuricaemia or gout using large data sets from New Zealand ($n = 320$ participants) and the USA ($n = 10{,}976$ participants). It needs to be noted that the majority of participants were overweight (BMI >25 kg/m^2) or obese (BMI >30 kg/m^2) and hence the population probably included many individuals with metabolic syndrome. Furthermore, ~90% of patients with hyperferritinaemia in routine medical practice do not actually have iron overload. Hyperferritinaemia and iron overload should not be confused or used as interchangeable terms, and given that all data sets studied by Fatima et al.[2] show the mean transferrin saturation coefficient is lower than 45% (the cut-off for iron overload), conclusions regarding the association between gout and iron overload should be made with some caution. Nevertheless, the association with ferritin levels is of interest.

Using regression analyses adjusted for age, sex, BMI and C-reactive protein levels, the researchers identified a positive association between ferritin levels and serum urate, and also between ferritin levels and gout in some, but not all, data sets. This heterogeneity of results across the different studied populations and the non-adjustment for factors known to increase ferritin levels raises some issues with regards to the robustness

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of the findings. It is tempting to speculate that the positive association might arise from confounders, particularly metabolic syndrome and non-alcoholic fatty liver disease[5], in which both urate and ferritin levels are elevated[6].

An intriguing finding from the observational analysis was the association between ferritin and gout flares, but the mechanism underlying this association is unclear. The authors speculate that the iron content of animal-based foods could contribute to the risk of flares, as occurs with high dietary purine intake. Because iron-rich foods are unlikely to trigger flare by causing acute crystallization of monosodium urate in synovial fluid, one hypothesis could be that other components in food are responsible for triggering gout attacks. One candidate might be free fatty acids, which are sharply increased after heavy eating[7].

Interestingly, the authors tried to identify causality between iron and urate (or ferritin and urate) using a two-sample Mendelian randomization analysis. The genetic variants used as instrumental variables were five single nucleotide polymorphisms (SNPs) associated with iron-related phenotypes and three SNPs associated with serum urate levels. These SNPs were selected from two previously published genome-wide association studies (GWAS) the Genetics of Iron Status Consortium and the Global Urate Genetics Consortium. In single-instrument analysis, the rs1800562 variant of *HFE* (encoding the human haemochromatosis protein), which is strongly associated with both iron and ferritin levels in GWAS[8], was shown to causally increase serum uric acid levels. By contrast, causality was not detected between any of the three urate instruments *SLC2A9* rs12498742, *SLC16A9* rs1171614 or *SLC22A12* rs478607 and iron or ferritin levels, a finding similar to that reported in a phenome-wide association study and Mendelian randomization analysis of the UK Biobank[9]. This exciting finding suggests that genetically controlled iron overload could be a risk factor for hyperuricaemia. Surprisingly, so far the association between hereditary haemochromatosis (the prototype disease for primary iron overload caused by homozygous or compound heterozygous mutation of *HFE*) and gout has not been reported.

Credit: Erhui1979/DigitalVision Vectors

However, one study of 738 patients with the *HFE* mutation C282Y found an association between ferritin and serum uric acid levels in multivariate analysis[10], supporting the findings of Fatima et al.[2]

Although a mechanism by which iron overload might raise serum uric acid levels is not known, one explanation could be that iron induces expression of the enzyme xanthine oxidase and thus increases production of uric acid, as has been reported previously[10]. This increase in serum uric acid levels could, in turn, protect from the oxidative stress generated by non-transferrin-bound iron. Indeed, uric acid could function as an iron chelator by generating a urate-Fe^{3+} complex, limiting the production of hydroxyl radicals[10].

In conclusion, iron overload might be added to the list of factors known to increase serum uric acid levels. However, this finding is quite unexpected, as an association between hereditary haemochromatosis and gout has not been reported in observational studies. Further data are therefore required to confirm a causal association, for example by showing that phlebotomy, which is the standard of care for patients with hereditary haemochromatosis and iron overload, can decrease serum uric acid levels.

Pascal Richette and Augustin Latourte*

Rheumatology Department, Hôpital Lariboisière, INSERM U1132, 2 rue Ambroise Paré, Paris, France.

**e-mail: pascal.richette@aphp.fr*

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Effects of the IL-23–IL-17 pathway on bone in spondyloarthritis

Ellen M. Gravallese[1]* *and Georg Schett*[2]

Abstract | Over the past several years, a pathophysiological role for the IL-23–IL-17 pathway in human disease has been defined. A subset of rheumatic diseases, including psoriatic arthritis (PsA) and ankylosing spondylitis (AS), are now acknowledged to be triggered by dysregulated IL-23–IL-17 pathway activation. Genetic evidence links the IL-23–IL-17 pathway to inflammation in these rheumatic diseases, and mechanistic data from mice support a functional role for IL-23–IL-17 pathway activation in the development of enthesitis and in entheseal bone formation. Furthermore, analysis of human tissue samples, as well as data from clinical trials, also supports a role for activation of the IL-23–IL-17 pathway in these diseases. The unique bone phenotype that occurs in PsA and AS is a surprising coexistence of both systemic bone loss and periosteal and entheseal bone formation and is likely to be the result of the actions of IL-23 and/or IL-17 on bone. However, the effects of these cytokines on bone cells are complex, and controversy remains regarding their exact roles in the specific bone microenvironments relevant to PsA and AS.

Experimental evidence has increasingly demonstrated that several human diseases, including psoriatic arthritis (PsA) and ankylosing spondylitis (AS), which are included under the heading of spondyloarthritis (SpA), as well as psoriasis and Crohn's disease, are triggered by activation of the IL-23–IL-17 pathway. The pro-inflammatory cytokines IL-23 and IL-17 are important targets for current anti-inflammatory drug therapies, and activation of the IL-23–IL-17 pathway is required during immune activation in host defence against invading pathogens, as well as for maintaining the barrier function of mucosal and other body surfaces[1]. Pathological activation of the IL-23–IL-17 pathway, in the context of certain genetic backgrounds, can lead to chronic inflammatory diseases including psoriasis, PsA and AS. Rheumatic diseases that are associated with activation of the IL-23–IL-17 pathway have a distinct skeletal phenotype that is characterized by the concomitant presence of bone loss and pathological new bone formation. Although the roles of IL-23 and IL-17 in precipitating inflammatory diseases have been reviewed elsewhere[2,3], this Review focuses specifically on the changes to bone that are seen in conjunction with chronic, pathological activation of the IL-23–IL-17 pathway. Current understanding of the molecular regulation of bone by these cytokines in the light of both mechanistic and clinical data is also discussed.

The IL-23–IL-17 pathway

IL-23 is a heterodimeric cytokine comprising two subunits (p19 and p40) and is produced by activated myeloid cells, predominantly dendritic cells (DCs) and monocyte or macrophage lineage cells, whereas IL-17 is produced by T cells, natural killer cells and innate lymphoid cells (ILCs)[4,5]. Production of IL-23 is induced by the engagement of pattern recognition receptors on myeloid cells by bacterial products such as lipopolysaccharide and other danger-associated molecular patterns[5]. IL-23 is critically involved in the communication between myeloid cells and T cells and, together with IL-1β, IL-6 and transforming growth factor-β (TGFβ), promotes the polarization of activated T cells into T helper 17 (T_H17) cells[6]. IL-23 also stabilizes the phenotype of T_H17 cells and improves the pro-inflammatory potential of these cells[7,8]. To date, T_H17 cells are the best described source of IL-17A, a pro-inflammatory effector cytokine that is physiologically involved in immune responses and in the homeostasis of epithelial barriers such as the skin and the intestine[1]. Although T_H17 cells constitute an important source of IL-17A, other immune cells bearing the IL-23 receptor (IL-23R), including group 3 ILCs (ILC3s)[9], γδ T cells and $CD8^+$ cytotoxic T cells, can also produce IL-17A when activated[10]. Notably, IL-23 not only induces IL-17A production but also triggers the activation of other cytokines, including IL-21, IL-22 and IL-17F, which orchestrate epithelial responses, lymphocyte proliferation and augmentation of inflammation[11].

IL-23–IL-17 in pathogenesis

Genetic, mechanistic and clinical data support the concept that IL-23–IL-17 pathway activation is associated with the development of a distinct group of inflammatory rheumatic diseases, including PsA and AS.

[1]*Division of Rheumatology, Department of Medicine, University of Massachusetts Medical School, Worcester, MA, USA.*

[2]*Department of Internal Medicine 3, Friedrich Alexander University Erlangen-Nuremberg and Universitatsklinikum Erlangen, Erlangen, Germany.*

**e-mail: ellen.gravallese@umassmed.edu*

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Key points

- IL-23 is produced by activated myeloid cells, whereas IL-17 is predominantly produced by T cells and innate lymphoid cells.
- Several lines of evidence support a role for the IL-23–IL-17 pathway in the pathogenesis of psoriatic arthritis (PsA) and ankylosing spondylitis (AS).
- Bone changes that occur in PsA and AS include systemic bone loss, articular erosions and entheseal bone formation and reflect the combined effects of IL-23 and IL-17.
- IL-17A promotes osteoclastogenesis directly, as well as indirectly, through the production or induction of receptor-activator of nuclear factor-κB ligand (RANKL) expression, whereas the effects of IL-23 on osteoclasts are pleotropic.
- IL-17A exhibits differential effects on the maturation of osteoblast precursor cells to osteoblasts depending upon the stage of differentiation of the cellular precursor.
- IL-17A blockade inhibits articular bone erosion and might also retard systemic bone loss in PsA and AS and enthesophyte formation in PsA.

Genetic evidence

The results of gene association studies have shown that patients with PsA share the same variants of *IL23R* as do patients with psoriasis[12]. An association between the *IL23R* locus and AS also exists[13], suggesting common pathogenic mechanisms in these diseases. Genetic and epigenetic fine mapping studies of inflammatory diseases and their causal variants also provide evidence for a close relationship between AS and non-rheumatic inflammatory diseases, including psoriasis and inflammatory bowel disease, that are associated with alterations in mucosal barrier functions[14]. In addition, overlap exists between risk alleles for AS and genes related to the IL-17 pathway, as demonstrated in a study that used an integrated genomics approach[15]. The identification of protective alleles in *IL23R* that lead to diminished phosphorylation of signal transducer and activator of transcription 3 (STAT3) and impaired production of IL-17 supports the idea that activation of the IL-23–IL-17 pathway is controlled at a genetic level[16,17].

HLA-B27 is strongly associated with the risk of developing AS, and HLA-B27 transgenic rats develop inflammation, articular erosions and bone proliferation similar to that seen in humans with AS[18]. In addition, evidence exists that the presence of HLA-B27 is associated with factors that regulate bone remodelling. For example, a study in which the sera of 241 individuals was examined demonstrated that HLA-B27-positive individuals had substantially lower serum concentrations of sclerostin and Dickkopf-related protein 1 (DKK1), which are both inhibitors of the Wnt signalling pathway, than HLA-B27-negative individuals regardless of whether they had SpA or uveitis alone or were healthy[19]. Low serum sclerostin concentrations have also been linked to increased formation of syndesmophytes in patients with AS[20]. By contrast, serum concentrations of Indian hedgehog, a regulator of endochondral ossification, were substantially higher in HLA-B27-positive individuals than in HLA-B27-negative individuals[19]; these data suggest that the presence of HLA-B27 itself modulates the expression of these important regulators of bone homeostasis. Conversely, a study that used in vitro differentiation systems to examine both direct bone formation and bone formation that occurs through endochondral ossification found no difference in bone formation in the presence or absence of HLA-B27 (REF.[21]). Therefore, additional studies are needed to further clarify the direct role of HLA-B27 in bone formation in SpA.

Mechanistic evidence from animal models

In addition to genetic evidence that links the IL-23–IL-17 pathway to specific rheumatic diseases, mechanistic data in mice support the functional role of IL-23–IL-17 pathway activation in the development of these diseases. Hence, mice that overexpress IL-23 develop enthesitis and peripheral arthritis[22]. In this model, IL-23 activated resident T cells within entheseal sites, causing them to produce IL-17A, IL-22 and IL-17F and trigger local inflammation[22]. Other rodent models that have features that mimic human PsA or AS are also characterized by IL-23–IL-17 pathway activation. For example, $CD4^+$ T cells in HLA-B27 transgenic rats produce IL-17 (REF.[23]). Furthermore, blockade of IL-17A function with anti-IL-17 antibodies prevented the development of AS-like features in the spine of SKG mice (which spontaneously develop arthritis and peri-spinal inflammation)[24]. Finally, male BXSB × NZB mice, which spontaneously develop enthesitis, are characterized by expansion of the IL-17-secreting T_H17 cell population[25]. Taken together, these data[22–25] imply a causal relationship between IL-23–IL-17 pathway activation and the development of entheseal inflammation, which is a hallmark of human PsA and AS.

Clinical evidence

Evidence from analyses of cell and tissue samples from patients with PsA or AS also supports a role for activation of the IL-23–IL-17 pathway in human disease. In AS, peripheral blood samples from patients have increased numbers of T_H17 cells[26], T_H22 cells[27] and γδ T cells[28], and serum concentrations of IL-17 and IL-23 are also increased compared with those in healthy individuals[29]. Furthermore, synovial tissue from patients with PsA contains cells that express IL-23 and/or IL-17 (REF.[30]), and IL-17-producing cells are present in the facet joints of patients with AS[31]. ILC3s are also present in human entheseal tissue[32].

Additionally, data from clinical trials in patients with PsA or AS support the relevance of IL-17 in these diseases; targeting IL-17A by use of the neutralizing antibodies secukinumab and ixekizumab ameliorated inflammation in both PsA and AS[33–35]. A direct role for IL-23 in the pathogenesis of PsA has been shown by the clinical efficacy of ustekinumab, an antibody directed against the common p40 subunit of IL-12 and IL-23 (REFS[36,37]). Furthermore, IL-23 targeting has been shown to achieve superior control of enthesitis over targeting TNF in patients with PsA[38]. However, although targeting IL-23 is effective in PsA, the results of a 2018 randomized, double-blind, phase II study of risankizumab, an antibody directed against the p19 subunit of IL-23, showed no efficacy for this approach in patients with AS[39] despite promising initial data from an open label trial of ustekinumab in patients with AS[40]. These results suggest that IL-23 might not be an essential cytokine in the pathogenesis of inflammation in patients with established AS but might have a role in the initiation phase of this disease.

Bone phenotype in PsA and AS

Diseases such as PsA and AS have a profound effect on bone and serve to highlight the unique and specific microenvironments that exist within bone[41]. Given that in both diseases there is evidence for robust activation of the IL-23–IL-17 pathway, the manifestations of bone changes in PsA and AS reflect the specific signature of the combined effects of IL-23 and IL-17 on the human skeleton. Similar to other chronic inflammatory diseases, including rheumatoid arthritis (RA) and Crohn's disease, PsA and AS are associated with premature systemic bone loss (FIG. 1a). Hence, in the long bones and vertebrae of patients with PsA or AS, both trabecular and cortical bone are lost and osteopenia and/or osteoporosis ensue[42,43]. AS is associated with increased fracture risk[44], a fact that seems also to be true in PsA[45]. Overall, systemic bone loss in AS and PsA seems to be somewhat less pronounced than that observed in RA, which might reflect the absence of additional factors in AS and PsA that promote bone loss, such as antibodies directed towards citrullinated proteins, an important pathogenic feature in RA but not in AS or PsA. These anti-citrullinated protein antibodies (ACPAs) promote osteoclastogenesis even in the absence of inflammation[46] and are associated with systemic bone loss in RA before the onset of clinical disease[47].

By contrast, prominent focal new bone formation occurs in AS and PsA (FIG. 1b), which distinguishes these diseases from RA, in which localized bone changes are essentially catabolic in nature. New bone formation in

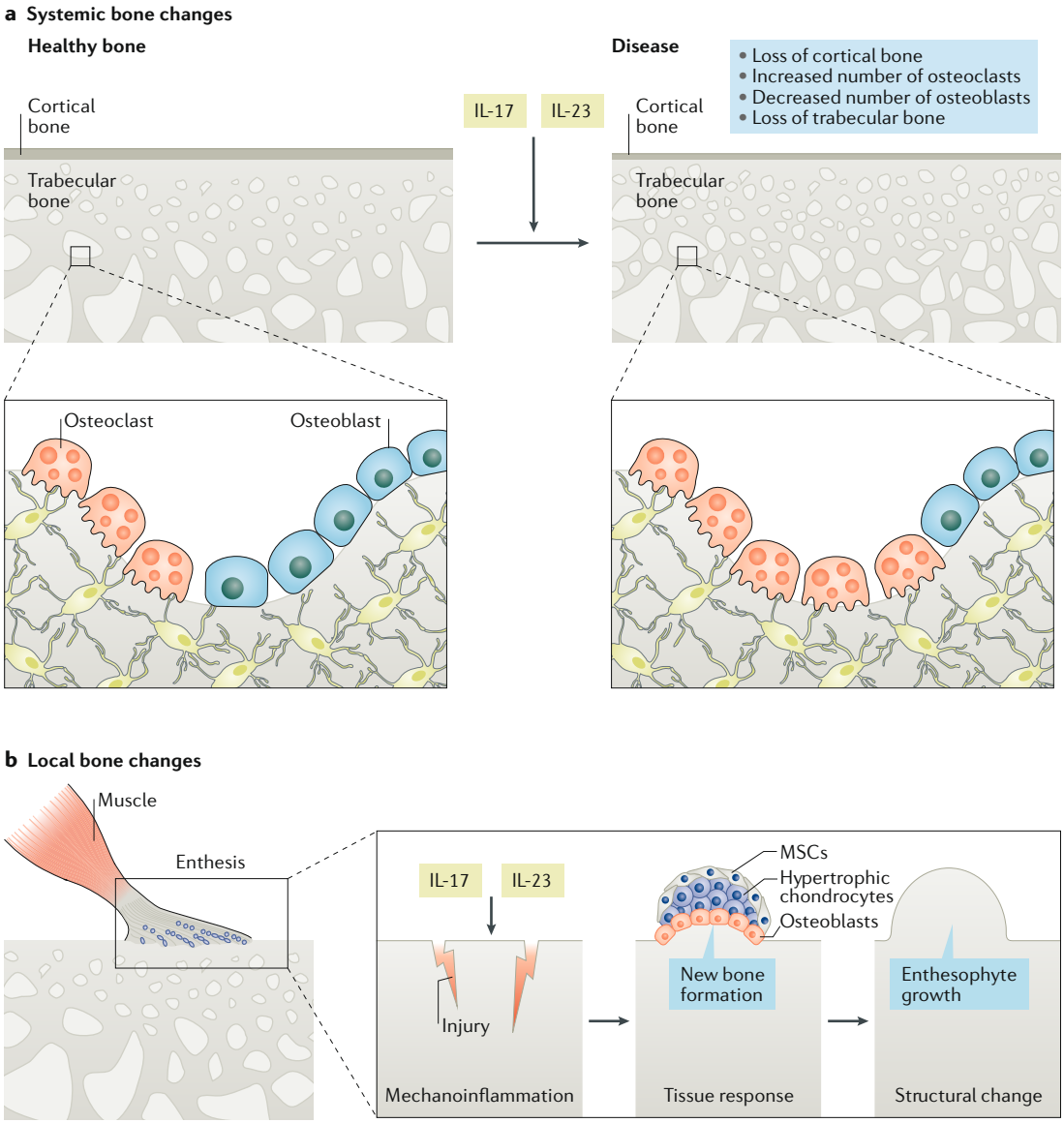

Fig. 1 | **Effects of IL-23 and IL-17 on bone. a** | Diseases associated with overexpression of IL-23 and/or IL-17 induce systemic bone loss characterized by a decrease in cortical and trabecular bone. This effect is caused by a negative net balance of bone remodelling in which increased osteoclast-mediated bone resorption and decreased osteoblast-mediated bone formation occur. **b** | At the local level, particularly at entheseal sites, IL-23 and/or IL-17 instigate an inflammatory response at periosteal areas, which leads to fracture repair-like bone apposition and to the formation of enthesophytes. MSC, mesenchymal stem cell.

AS and PsA is a localized process that begins at specific anatomical sites[48,49]; entheseal inflammation seems to be closely linked to new bone formation in PsA and AS. Newly formed bone appears as bony spurs originating from periosteal sites that are juxtaposed to the insertions of tendons and ligaments. Notably, this process is not linked to the remodelling process within the skeleton but rather resembles a response-to-injury process. Mechanistically, bony spurs that form in PsA and AS at both peripheral and axial skeletal sites are generated through an endochondral bone formation sequence that in many instances mimics fracture healing, in which a cartilage scaffold is formed and then subsequently remodelled into bone. Paradoxically, IL-23 and IL-17 seem to indirectly promote this process at entheseal sites, as both cytokines are involved in expanding entheseal inflammation, thereby instigating an exaggerated repair response in bone. Thus, IL-23–IL-17 pathway activation is associated with both systemic catabolic and localized anabolic bone changes.

Immune regulation of bone

Whereas glucocorticoid treatment, age and the postmenopausal state are classically seen as the main risk factors for bone loss in inflammatory diseases, the central role of inflammation as a direct trigger for bone loss has long been underappreciated. In fact, inflammation is one of the most powerful triggers of bone loss in mammalian species[50]. The net loss of bone in the context of inflammation is usually a result of an increase in bone resorption by osteoclasts combined with a decrease in bone formation by osteoblasts. This imbalance in bone homeostasis elicited by inflammation is powerful enough to precipitate premature bone loss and to increase fracture risk. Moreover, chronically high concentrations of acute phase reactants are associated with an increase in fracture risk[51], underscoring the key role of inflammation in controlling bone mass.

Increasingly, insights into the molecular regulation of osteoclasts and osteoblasts by inflammation-borne factors, and into specific immune–bone cell interactions, have led to an improved understanding of the determinants of bone changes during inflammation. For example, the expression of receptor-activator of nuclear factor-κB ligand (RANKL; also known as TNFSF11) by activated T cells[52–54] links immune activation with increased bone resorption. Furthermore, RANKL expression is induced in resident mesenchymal cells by several key pro-inflammatory cytokines, including TNF, IL-1 and IL-6 (REF.[55]). One study of cell type-specific deletion of RANKL has shown that synovial fibroblast-derived, but not T cell-derived, RANKL has a key role in articular bone erosion in the setting of inflammatory arthritis[56]. In addition, the anti-RANKL antibody denosumab also inhibits inflammatory bone loss[57,58], supporting the concept that the induction of osteoclast differentiation is an important effector pathway by which inflammation promotes the degradation of bone in human rheumatic diseases. Consequently, the use of denosumab has been approved in Japan to protect patients with RA from bone erosion[59].

Notably, the cytokine repertoire that is engaged in specific disease processes determines the pattern of bone disease that manifests. TNF, IL-1 and IL-6 are classic bone-degrading cytokines that directly (by binding to osteoclasts or their precursor cells) or indirectly (by inducing RANKL expression on mesenchymal cells) induce osteoclast differentiation and bone resorption. Thus, in diseases in which these cytokines are prevalent, such as RA, the resulting bone phenotype is one of bone loss. Other cytokines, however, have markedly different regulatory effects on bone. For example, type I and type II interferons effectively antagonize RANKL-mediated signalling in osteoclasts and thereby protect bone from osteoclast-mediated resorption[60]. Other cytokines that inhibit bone loss include IL-4, IL-13 and IL-33, which are involved in the differentiation of T_H2 cells and are upregulated in allergic diseases such as asthma. These cytokines effectively inhibit osteoclast differentiation by both direct and indirect mechanisms[61]. Therefore, the predominant cytokines expressed in a given immune-mediated or inflammatory disease determine the respective outcome for bone. In this respect, an in-depth understanding of the influence of the IL-23–IL-17 pathway on bone cells is required to fully explain the bone changes that occur in PsA and AS (FIG. 2).

Effects of IL-17 on bone

IL-17 and osteoclasts. The systemic bone loss and focal bone erosions that occur in PsA (and also in some patients with AS) suggest that activation of the IL-23–IL-17 pathway induces the differentiation of bone-resorbing osteoclasts. The first recognition that IL-17 influences bone homeostasis came from Kotake and colleagues, who reported that IL-17 potently induces osteoclastogenesis in an osteoblast–osteoclast co-culture system[62]. Mechanistically, in this setting, IL-17 induced the expression of RANKL on osteoblasts, which promoted the robust induction of osteoclast differentiation. The notion that IL-17-induced osteoclast differentiation is RANKL-dependent was additionally supported by the fact that osteoprotegerin (OPG; also known as TNFRSF11B), a soluble decoy receptor for RANKL, completely blocked IL-17-mediated osteoclastogenesis[62]. Subsequent studies confirmed the pro-osteoclastogenic effect of IL-17 (REFS[63,64]), and T_H17 cells are now known to be a key T cell subset in the stimulation of osteoclastogenesis, supporting osteoclast differentiation by releasing IL-17 and by expressing RANKL[65]. In a mouse model of collagen-induced arthritis and in patients with RA, so-called exFOXP3 T_H17 cells, which are T_H17 cells that have lost expression of the regulatory T cell-associated transcription factor FOXP3 and that express high levels of RANKL, seem to be the most potently osteoclastogenic T cell subset[66]. Classic T_H17 cells also have a more potent pro-osteoclastogenic effect than γδ T cells, which represent an additional source of IL-17 (REF.[67]).

IL-17 also exerts direct effects on osteoclasts[68,69]. Most prominently, osteoclast lineage cells exposed to IL-17 upregulate RANK, the receptor for RANKL, which improves the osteoclastogenic potential of RANKL in these cells[69]. In addition to its direct effects on bone cells, IL-17 is also pro-inflammatory, which adds to its effects on bone resorption in arthritis. For instance, IL-17A induces the expression of classic pro-inflammatory

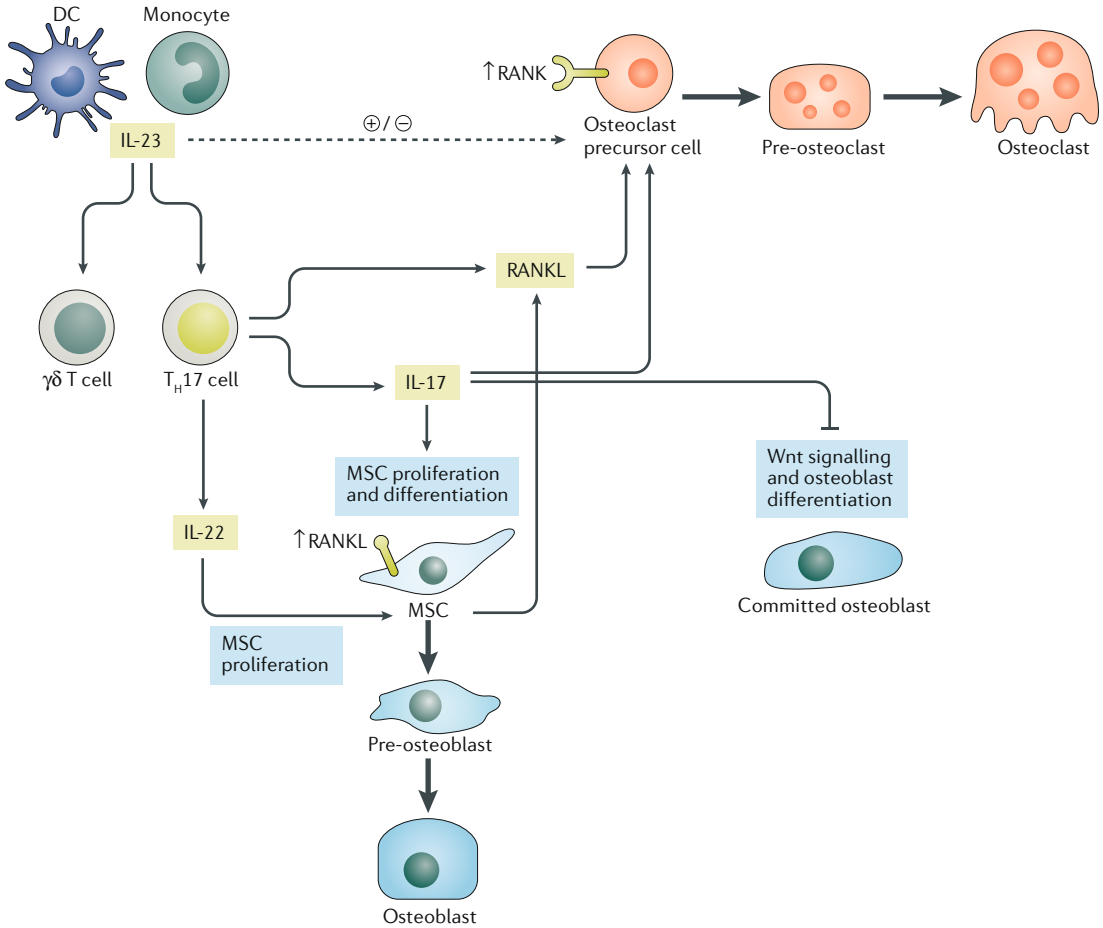

Fig. 2 | **Effects of IL-23 and IL-17 on osteoclasts and osteoblasts.** Dendritic cells (DCs) and monocytes produce IL-23, which induces the production of IL-17 by T helper 17 (T_H17) cells and γδ T cells. IL-17 increases receptor-activator of nuclear factor-κB (RANK) expression on osteoclast precursor cells and RANK ligand (RANKL) expression on mesenchymal stem cells (MSCs). T_H17 cells and γδ T cells also produce RANKL themselves. These processes induce osteoclast differentiation. The direct effect of IL-23 on osteoclast precursor cells to induce or inhibit osteoclastogenesis remains controversial. IL-17 also has an effect on MSCs, potentially inducing MSC proliferation and promoting their differentiation into osteoblasts. However, IL-17 causes the inhibition of Wnt signalling and osteoblast differentiation in committed osteoblasts. T_H17 cells also produce IL-22 in response to IL-23, which in turn has an effect on inflammation and possibly also on bone formation in spondyloarthritis.

cytokines (including TNF, IL-1 and IL-6)[70,71] by stromal cells and macrophages, and these cytokines function downstream of IL-17A to affect osteoclastogenesis.

Overall, current data provide substantial evidence for a catabolic function for IL-17A in bone homeostasis that is mirrored by the induction of osteoclastogenesis, thereby explaining the development of bone erosions and osteopenia and/or osteoporosis typically seen in patients with PsA or AS. In support of this concept, blockade of IL-17A by the neutralizing antibodies ixekizumab and secukinumab retarded the progression of bone erosions in patients with PsA[35,72].

IL-17 and osteoblasts. In addition to the articular and systemic bone loss that occurs in PsA and AS, the prominent entheseal bone formation that occurs in these diseases suggests that either IL-17 or IL-23 itself promotes osteoblast differentiation and subsequent bone formation. Osteoblasts are derived from cells of the mesenchymal lineage, but controversy remains regarding the effects of IL-17A on the differentiation and function of these cells. The results of some studies indicate that IL-17A induces osteoblast differentiation from human mesenchymal stem cells (MSCs)[73,74], suggesting that IL-17A would be protective against generalized bone loss. In support of this concept, bone loss induced by ovariectomy was increased in mice deficient for IL-17 receptor A (IL-17RA), the receptor for IL-17A[75].

However, conflicting data have shown that IL-17A inhibits osteoblast differentiation, as blockade of IL-17A and IL-17RA-deficiency protected mice from bone loss following ovariectomy[76]. Further support for this concept came from two studies that demonstrated that IL-17A exerts inhibitory effects on osteoblast differentiation and function. In one study, Uluckan et al.[77] investigated whether IL-17A expression in skin could result in systemic bone loss using two mouse models that mimic human psoriasis: the *K14IL17A*^{ind} mouse, in which IL-17A is expressed under the control of the keratin 14 promoter, leading to epidermal IL-17A expression

and a psoriasis-like skin condition, and mice with epithelial deletion of transcription factor JUNB ($JUNB^{\Delta ep}$ mice), which also results in epidermal IL-17A expression. These models both resulted in systemic bone loss caused by a decrease in osteoblast activity rather than by an increase in osteoclast activity. Furthermore, blockade of IL-17A signalling using an IL-17A blocking antibody reversed the bone loss phenotype in $JUNB^{\Delta ep}$ mice[77], consistent with the concept that IL-17A is an inhibitor of osteoblast function and bone formation and that blockade of IL-17A promotes bone formation. In murine cells, IL-17A inhibited the mRNA and protein expression of markers of late osteoblast differentiation, such as osteocalcin, and of early osteocyte differentiation, such as dentin matrix acidic phosphoprotein 1 (DMP1) and phosphate-regulating neutral endopeptidase[77]. This effect was associated with the profound downregulation of genes involved in the Wnt pathway, including *Axin2*, *Wisp1* and *Bmp4*, suggesting that IL-17A actively suppresses the differentiation of osteoblast precursor cells into osteoblasts and osteocytes.

In another study, Shaw et al.[78] also found an osteoblast inhibitory effect of IL-17A. In the K/B × N serum transfer model of arthritis, IL-17A-deficient mice developed more periosteal bone formation than wild-type mice despite the fact that the severities of inflammation and articular bone erosion were similar in both groups of mice[78]. IL-17A also inhibited calvarial osteoblast differentiation in vitro and affected the Wnt signalling pathway by inducing expression of the Wnt antagonist soluble frizzled related protein 1 (sFRP1), which inhibits bone formation. Notably, antibody blockade of sFRP1 led to a reduction in the inhibitory effect of IL-17A on osteoblast differentiation[78]. The results of these studies[77,78] that indicate that IL-17A inhibits osteoblast differentiation are also in agreement with the results of a study by Kim et al.[79] that showed the suppressive effects of IL-17 on rat calvarial osteoblast differentiation in vitro and on bone regeneration in a rat calvarial defect model in vivo.

By contrast, however, Ono et al.[80] used a femoral cortical bone defect drill hole model to demonstrate that IL-17A, which is produced in large amounts by γδ T cells immediately after injury to bone, promoted bone formation and healing by stimulating mesenchymal progenitor cells to proliferate and differentiate into osteoblasts. This model recapitulated the process of intramembranous bone formation. In this study[80], IL-17A-deficient mice had impaired fracture healing owing to defective osteoblast-mediated bone formation. These results are consistent with the results of a previous study[81] that showed that T cells promote osteoblast differentiation in early fracture repair via the production of IL-17F.

Although these data[77–80] are seemingly contradictory, the osteoblast precursor cells that were examined in vitro in these studies were different. Uluckan et al.[77], Shaw et al.[78] and Kim et al.[79] used calvarial osteoblasts, which are cells already committed to the osteoblast lineage, whereas Ono et al.[80] negatively selected a population of mesenchymal precursor cells from repair tissue within the cortical bone defects. Finally, human MSCs express IL-17RA[73], and IL-17A and IL-17F derived from T_H17 cells induce the differentiation of MSCs into osteoblasts in vitro, as evidenced by the induction of alkaline phosphatase activity and matrix mineralization[82]. Taken together, these data[73–82] suggest that the effect of IL-17A on osteoblast differentiation probably depends upon the cell type exposed to IL-17A, the differentiation stage of that cell and perhaps also the timing and duration of cytokine exposure (FIG. 2).

Effects of IL-23 on bone

IL-23 and osteoclasts. Conflicting data exist as to how IL-23, an essential inducer of T_H17 cell differentiation, influences osteoclast formation. Clearly, IL-23 promotes the differentiation of osteoclasts indirectly via the induction of T_H17 cell polarization and IL-17A production in vivo[83–85]; however, the direct effects of IL-23 on osteoclastogenesis are less well understood. IL-23 has been suggested to induce osteoclastogenesis directly in human cells in the absence of osteoblasts or exogenous soluble RANKL[83]. Osteoclastogenesis induced by IL-23 from monocyte lineage cells was inhibited by an anti-IL-17 antibody, by etanercept (a TNF inhibitor) and by OPG, demonstrating that IL-17, TNF and RANKL are all involved in IL-23-mediated osteoclastogenesis[83]. However, questions remain as to whether these direct effects of IL-23 have been clearly demonstrated, as monocyte lineage cells are poor sources of RANKL and IL-17. More convincing evidence that IL-23 might directly promote osteoclast differentiation comes from studies that demonstrated the induction of RANK expression on osteoclast precursor cells upon stimulation by IL-23 (REF.[86]) and the activation of DNAX-activation protein 12 (DAP12; also known as TYROBP) by IL-23, which is part of a RANKL-independent pathway for osteoclast differentiation[87].

Conversely, direct inhibitory (rather than stimulatory) effects of IL-23 on osteoclasts have been reported. For example, exposure of monocytes to IL-23 inhibited osteoclast differentiation in murine cells in vitro and in an in vivo model[88,89]. Furthermore, genetic data from mice suggest that IL-23 has protective effects on bone under steady state conditions, as a 30% decrease in bone mass was demonstrated in mice deficient for the p19 subunit of IL-23 (REF.[89]). In addition, IL-23 induced the production of granulocyte–macrophage colony-stimulating factor (GM-CSF), a well-known inhibitor of osteoclast differentiation, by T_H17 cells, and this induction limited bone resorption[89]. However, as IL-17 and RANKL expressed by T_H17 cells favour osteoclast differentiation and bone resorption, the net effect of IL-23 on bone might therefore be converted to a catabolic one[83–85] (which might additionally be supported by the pro-inflammatory actions of IL-23 demonstrated in mouse models of arthritis[83,84,90]). Hence, although the net effect of IL-23 on osteoclasts during steady state conditions might be regulatory in nature, IL-23 could also activate osteoclast differentiation in the context of inflammatory disease. This concept is also supported by data showing that therapeutic inhibition of IL-23 by ustekinumab limits the progression of bone erosions in patients with PsA[91].

An important, yet underappreciated, effect of IL-23 on osteoclastogenesis and early bone loss in

autoimmune diseases is the ability of IL-23 to downregulate the enzyme β-galactoside α-2,6-sialyltransferase 1 (ST6Gal1), which controls the sialylation of antibodies[92]. De-sialylated antibodies, which are generated in the pro-inflammatory environment triggered by IL-23, not only induced the release of effector cytokines by macrophages but also strongly induced osteoclast differentiation and bone resorption in vitro and in vivo in mice[93]. Hence, IL-23 might be important in autoimmune-mediated bone loss, especially in the early phases of diseases such as RA, in which ACPAs and rheumatoid factor are important triggers of osteoclast differentiation[46]. However, the effects of IL-23 on ST6Gal1 in PsA and AS remain unknown.

IL-23 and osteoblasts. In contrast to IL-17, IL-23 did not have any effects on the differentiation of osteoblasts (as measured by alkaline phosphatase activity), or on their proliferation, nor did it induce RANKL expression in osteoblasts[88] in vitro. In addition, although mesenchymal cells and osteoblasts express IL-17RA, they lack expression of IL-23R[94].

Potential effects of IL-22 on bone

Another important cytokine in the IL-23–IL-17 pathway is IL-22, which is produced by a number of immune cells, including bone marrow DCs, T_H17 cells, T_H22 cells, ILC3s, γδ T cells and $CD8^+IL\text{-}17^+$ T cells[95]. IL-22 is thought to be important in the pathogenesis of PsA and AS, as it is produced by enthesis-resident T cells in mice that overexpress IL-23 (REF.[22]). IL-22 also promoted local osteoblast differentiation in these mice through the upregulation of STAT3 (presumably in osteoblast precursor cells), thereby inducing the expression of genes that regulate bone formation[22]. Additionally, IL-22 promotes hyperproliferation of keratinocytes in the skin and of synovial fibroblasts derived from the joints of patients with PsA[96,97]. The results of a 2018 study[98] lend support for a role for IL-22 in the pathogenesis of PsA. The authors used a new model of PsA in which mice have T cell-specific expression of a hyperactive *Stat3* allele ($R26Stat3C^{stopfl/fl}CD4Cre$ mice) and develop IL-17-driven psoriasiform skin lesions, tendonitis and/or enthesitis, articular bone erosion and osteopenia. Treatment of these mice with an IL-17-neutralizing antibody or deletion of IL-22 led to an improvement in both skin and bone disease manifestations[98], thereby implicating IL-22 as well as IL-17 in the pathogenesis of PsA.

IL-22 can also promote osteoclastogenesis through the induction of RANKL expression by synovial fibroblasts[99]. However, whether IL-22 is involved in articular bone erosion in PsA or AS is not yet known. IL-22 might also affect osteoblast differentiation. The results of a study in which the effects of IL-22 on human MSCs were examined demonstrate that IL-22 promotes the proliferation and migration of MSCs in an inflammatory environment[94] and might directly promote their differentiation into osteoblasts[100]. In addition, primary osteoblasts do not express receptors for IL-22 (REF.[94]). Therefore, additional studies are needed to clarify the effects of IL-22 on bone in PsA and AS.

Emerging concepts

Bone changes in PsA and AS are a remarkable combination of exaggerated bone resorption with a simultaneous increase in bone formation. In this regard, PsA and AS exhibit a unique bone phenotype that is probably a result of the distinct cytokine activation pattern in these diseases. Substantial evidence exists in support of the hypothesis that both IL-17 and IL-23 are involved in the pathogenesis of inflammation in PsA and AS. Inflammation of the synovial membrane in these diseases might be caused by a direct extension of disease activity at inflamed entheseal sites, especially if these structures are adjacent to one another, as in so-called synovio-entheseal complexes[101]. Both cytokines also have profound effects on bone remodelling. So how can such diverse effects be explained, and why does it seem that bone responds differently to IL-17 and IL-23 at specific anatomical sites?

The prevailing evidence from studies on the effects of IL-17 and IL-23 on bone suggests that both cytokines trigger net bone loss by directly or indirectly affecting osteoclasts; IL-17 and IL-23 stimulate the bone-resorbing behaviour of osteoclasts and downregulate compensatory bone formation. This IL-23–IL-17 pathway-induced imbalance in bone homeostasis would explain, at least in part, the systemic bone loss that occurs in patients with AS or PsA, and these cytokines therefore represent two specific effector molecules involved in immune-mediated bone loss in these diseases. Bone erosions arise from an imbalance in bone remodelling at skeletal sites that are directly exposed to the inflamed, cytokine-rich synovial membrane. As a consequence of interactions with the inflamed synovium, osteoclastogenesis is induced, leading to the degradation of bone. The IL-23–IL-17 pathway-mediated skewing of physiological bone remodelling towards a negative net balance, and the induction of progressive bone loss, might therefore also contribute to the articular bone erosions that form in the peripheral joints and the sacroiliac joints of patients with these diseases.

By contrast, new bone formation in patients with PsA or AS is a localized process that affects distinct anatomical sites. In this process, IL-23 and IL-17 are involved in an inflammatory stress response to injury, which is accompanied by localized new bone formation in the cortical bone that resembles fracture repair. In this context, IL-23 and IL-17 might produce an inflammatory microenvironment that encourages bone responses rather than directly executing such responses. Other factors are also likely to be involved, including prostaglandin E_2 (a known inducer of osteoblast differentiation[102] and IL-22 (REF.[100]). IL-17A, despite being an inhibitor of osteoblast function and being able to trigger systemic bone loss, might also directly contribute to this process by promoting the local differentiation of mesenchymal precursor cells in this response-to-injury setting[103], as results gained using the cortical bone defect drill hole model would suggest[80]. Notably, however, if IL-17A does indeed inhibit osteoblast differentiation, then blockade of this cytokine could help to promote bone formation, particularly if the inhibition of IL-17A does not also eliminate inflammation, as it might not in all clinical settings.

	PsA and AS	RA
Mechanisms	Mechano-inflammation	Autoimmune inflammation
	Mild or no acute phase	Acute phase
	MHC class I (HLA-Cw6 and HLA-B27)	MHC class II (HLA-DR4)
	No humoral autoreactivity	Autoantibodies
Manifestations	Enthesitis	Synovitis
	Axial disease frequent	Axial disease rare
	DIP disease frequent	DIP disease absent
	Bony spur formation	Bone erosion
Medications	IL-17 (and/or IL-23) inhibitors and TNF inhibitors	IL-6 inhibitors and TNF inhibitors

Fig. 3 | **Essential characteristics of IL-17-dependent forms of arthritis.** A '3M-model' (mechanisms, manifestations and medications) of the key differences between spondyloarthritis (namely, psoriatic arthritis (PsA) and ankylosing spondylitis (AS)) and rheumatoid arthritis (RA). With respect to bone, PsA and AS are characterized by an entheseal-driven, IL-17-dependent inflammation that leads to new bone formation (enthesophytes). DIP, distal interphalangeal joint.

Implications for treatment

Blockade of IL-17A is an effective approach for controlling the clinical signs and symptoms of inflammation in patients with PsA and AS. By contrast, IL-17 blockade is not effective in patients with RA, suggesting the existence of essential differences between different forms of arthritis in their mechanistic origin and clinical manifestations (FIG. 3). Hence, the 'mechano-inflammation' that occurs in PsA and AS, which is MHC class I-mediated, is essentially not autoimmune in origin and is not dependent on IL-6 but is dependent on IL-17. Accordingly, blockade of IL-17A with ixekizumab or secukinumab, as well as of IL-12 and/or IL-23 with ustekinumab, inhibited the progression of bone erosions in peripheral arthritis in patients with PsA[35,72,91]. Furthermore, in two double-blind, placebo-controlled trials (MEASURE 1 and MEASURE 2), treatment with secukinumab led to substantial improvements in the signs and symptoms of AS[33,104]. Structural bone changes in patients with AS have also been assessed by measuring the progression of syndesmophyte formation in the spine using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)[105]. These analyses showed a mild retardation of syndesmophyte formation in patients with AS upon secukinumab treatment[105]. This outcome is important, as structural bone damage in patients with AS is associated with a decline in function in these patients[106]. Supporting this concept, the results of a 2018 study[107] in which comprehensive high-resolution imaging was used on patients with PsA suggest that IL-17 inhibition arrests the progression of not only bone erosion but also enthesophyte formation. This effect is accompanied by the preservation of bone mass and bone functional properties in patients with PsA[107].

Overall, the current evidence for the effects of IL-17 and/or IL-23 inhibition on halting osteoclast-mediated bone erosion is strong, whereas data on the effects of inhibition of these cytokines on new bone formation are scarce. Despite having negative effects on bone formation in the context of bone remodelling, IL-17A can also trigger entheseal inflammation and thereby influence local bone formation. This function might enable IL-17 blockade to beneficially influence enthesophyte formation in the peripheral joints and the spine of patients with PsA or AS. Additional studies to investigate the interactions between IL-17A and the regulation of inflammation and new bone formation in PsA and AS are essential.

Conclusions

The effects of IL-17A and IL-23 on bone in PsA and AS are complex. The direct effects of these cytokines on osteoclasts and on bone resorption suggest that these cytokines have a catabolic effect on bone, whereas the effects of IL-17A on osteoblast lineage cells seem to differ depending on the stage of differentiation of the cell at the time of exposure to this cytokine. Furthermore, indirect effects of IL-23 and IL-17 that encourage periosteal repair responses probably explain the seemingly paradoxical anabolic effect of these two cytokines on bone in patients with PsA or AS. The effect of the IL-23–IL-17 pathway on bone is an area of active research, and the results of both basic and clinical investigations should shed further light on these mechanisms and help to advise future therapeutic approaches.

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Both authors researched the data for the article, provided substantial contributions to discussions of its content, wrote the article and reviewed and/or edited the manuscript before submission.

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Hand osteoarthritis: clinical phenotypes, molecular mechanisms and disease management

*Michelle Marshall[1], Fiona E. Watt[2], Tonia L. Vincent[2] and Krysia Dziedzic[1]**

Abstract | Osteoarthritis (OA) is a highly prevalent condition, and the hand is the most commonly affected site. Patients with hand OA frequently report symptoms of pain, functional limitations and frustration in undertaking everyday activities. The condition presents clinically with changes to the bone, ligaments, cartilage and synovial tissue, which can be observed using radiography, ultrasonography or MRI. Hand OA is a heterogeneous disorder and is considered to be multifactorial in aetiology. This Review provides an overview of the epidemiology, presentation and burden of hand OA, including an update on hand OA imaging (including the development of novel techniques), disease mechanisms and management. In particular, areas for which new evidence has substantially changed the way we understand, consider and treat hand OA are highlighted. For example, genetic studies, clinical trials and careful prospective imaging studies from the past 5 years are beginning to provide insights into the pathogenesis of hand OA that might uncover new therapeutic targets in the disease.

Osteoarthritis (OA) is one of the leading causes of disability worldwide[1]. With the average age of the general population increasing, the impact of OA and joint pain is set to rise[2]. Disabling hand pain is a common complaint, affecting ~12% of individuals aged over 50 years in the UK general population[3]. For many of these individuals, this symptom can be ascribed to hand OA, which is the most common form of OA. Hand OA is a heterogeneous condition, often involving multiple joints[4], and can have distinct (but sometimes overlapping) patterns of joint involvement: for example, OA of the interphalangeal joints (IPJs) and/or the first carpometacarpal joint (CMCJ)[5].

A gap exists between guidelines for the management of hand OA and current standards of treatment[6]. Health-care inititatives such as JIGSAW-E (Joint Implementation of Guidelines for Osteoarthritis in Western Europe; funded by EIT-Health) aim to close the evidence–practice gap for OA[7] by implementing international guidelines and quality standards[8,9]. A common misconception is that OA of the hands affects the quality of life of individuals less than OA of the lower limbs, and many patients are encouraged to believe that hand OA is an inevitable result of ageing and that nothing can be done to improve the disease symptoms[10]. These unfounded assumptions make prioritizing health care for hand OA a challenge.

In this Review, we provide an overview of the epidemiology, presentation and burden of hand OA and present areas where in the past 5 years new evidence has substantially changed the way we understand, consider and treat hand OA. We include updates on the imaging of hand OA and the development of novel imaging techniques, and advances in knowledge of disease mechanisms and the management of hand OA.

Epidemiology

Definitions of hand OA

Hand OA can be defined in a number of ways: by the ACR clinical criteria[11]; by structural changes determined by imaging (most frequently using plain radiography; so-called radiographic hand OA); and by radiographic changes accompanied by the presence of typical symptoms (pain, aching or stiffness; referred to as symptomatic hand OA). For the latter two categories, a range of different definitions, particularly radiographic definitions[12], has been used in the study of hand OA (BOX 1).

Radiographically, hand OA is characterized, as with other forms of OA, by joint space narrowing (JSN), osteophyte formation (which, for any joint, is pathognomonic of radiographic OA), subchondral sclerosis and subchondral cyst formation. Researchers have attempted to improve the detection of early disease features (including features that might not be evident by plain radiograph) by using MRI or ultrasonography; however, these techniques have not found a place in the diagnosis of hand OA in the clinic to date[13].

[1]*Research Institute for Primary Care and Health Sciences, Arthritis Research UK Primary Care Centre, David Weatherall Building, Keele University, Keele, UK.*

[2]*Arthritis Research UK Centre for Osteoarthritis Pathogenesis, Kennedy Institute of Rheumatology, University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), Oxford, UK.*

**e-mail: k.s.dziedzic@keele.ac.uk*

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Key points

- Hand osteoarthritis (OA) is highly prevalent, and individuals with this condition frequently report symptoms of pain, functional limitations and frustration in undertaking everyday activities.
- Clinical imaging is not recommended for the diagnosis or routine monitoring of patients with hand OA unless an alternative diagnosis is suspected.
- MRI and ultrasonography findings have provided insight into hand OA pathology, but further prospective studies are required to inform on how features of the disease change over time.
- Hand OA is multifactorial in aetiology with evidence for the involvement of abnormal mechanical loading and hereditary factors, whereas the contribution of inflammation to pathogenesis remains contentious.
- Recommendations for core treatments in the management of hand OA should be integrated into clinical practice to improve the quality of care for patients.
- A greater understanding of the presentation, pathogenesis and disease course is needed to help provide targeted therapy with existing and new treatments.

Prevalence

Hand OA is a highly prevalent condition with a well-recognized female preponderance that is particularly notable in patients with severe symptomatic disease presenting to secondary care[14,15]. Estimates of the prevalence of hand OA vary depending on the definition of hand OA used, as well as by the age, sex and geographical area of the population studied, and can also be influenced by genetic factors, occupation and diet. Of the various hand OA definitions, radiographic hand OA is associated with the highest prevalence, ranging from 21% in a US population to 92% in a Japanese population[16–18]. By contrast, the prevalence of symptomatic hand OA is much lower than radiographic hand OA, ranging from 3% in Iranian and Chinese populations to 16% in a US population[19–21]. Prevalence estimates for hand OA are generally higher than those reported for hip and knee OA (hip OA: radiographic 1.0–45.0% and symptomatic 0.9–7.4%; knee OA: radiographic 7.1– 70.8% and symptomatic 5.4–24.2%)[16]. The prevalence of hand OA is also higher in some groups of individuals, such as in patients with an HIV-1 infection, than in the general population[22].

Incidence and progression

The distinction between incidence (occurrence of the disease) and progression (development towards a more advanced stage of the disease) of hand OA is somewhat arbitrary and depends on the case definition of the disease used. With this caveat in mind, in one study of a US population, the lifetime risk of developing symptomatic hand OA in at least one hand by the age of 85 years was estimated at 40%, with 47% of women and 25% of men developing the disease in this population[23]. The annual incidence of hand OA varies between 0.2% and 4.7% for radiographic hand OA and between 0.1% and 1.1% for symptomatic hand OA irrespective of age, sex and geographical location[24–26] (TABLE 1). The incidence of hand OA peaks at the age of 50 in women and greatly exceeds the incidence measured for men at that age[27]. Progression of hand OA is usually slow, and only few hand joints exhibit changes in each patient[25]. The rates of radiographic progression vary from 3.2% to 23.5% per year depending on the population studied, the grading scale used and whether the definition of progression also incorporates incident OA (that is, new-onset OA)[24,28] (TABLE 2).

Disease presentation and burden

Signs and symptoms

OA is considered a condition of the whole joint, rather than just the articular cartilage, and signs and symptoms can arise from the cartilage, underlying bone, synovium, muscles, tendons and ligaments (or the sites of ligament insertion into the bone)[29,30]. Symptoms commonly include pain, stiffness and limitation or restriction of movement such as a decrease of grip and/or pinch strength. Signs of hand OA include 'nodes' of the affected IPJs (firm swellings over the superolateral and dorsal aspects of the distal interphalangeal joints (DIPJs) and proximal interphalangeal joints (PIPJs), known as Heberden and Bouchard nodes, respectively) and deformities such as squaring of the thumb base (FIG. 1). Inflammation can produce redness, warmth, effusion and/or soft tissue swelling.

Individuals with hand OA can be divided into different subgroups depending on the joints in the hands that are affected; these subgroups consist of nodal OA, first CMCJ OA and another presentation called erosive hand OA, in which the subchondral bone is affected by central erosions. First CMCJ OA is thought to occur most frequently, followed by nodal IPJ OA, a non-nodal form of IPJ OA and erosive hand OA[5]. However, apart from first CMCJ OA, which frequently occurs in isolation, there is considerable overlap in presentations among these subgroups, suggesting shared aetiologies[5].

First CMCJ OA. Patients with first CMCJ OA have increased pain sensitivity, a reduced range of motion in thumb abduction and a decreased combined thumb abduction and index finger extension strength compared with healthy individuals[31]. Notable associations between self-reported pain and function have been reported for these patients. Furthermore, compared with healthy individuals, patients with this condition have reduced grip and pinch strength[32], including a decrease in cylindrical grasp and key pinch strength that can begin in the early stages of disease[33,34]. Some of these presentations might be due to changes in the structure and composition of the joint and changes in the innervation of the dorsal radial ligament, which has an important proprioceptive and stabilizing role for the thumb base[35]. In individuals with symptomatic first CMCJ OA, the presence of both ligament ruptures and dorsal subluxation is a common finding on MRI[36,37]. The grind test (where the examiner exerts pressure while rotating the joint to test whether pain or crepitus are elicited) has frequently been used to determine the presence of first CMCJ OA[38]. However, in a 2014 study, the traction-shift (subluxation-relocation) test (where the examiner provokes subluxation and relocation of the joint passively to test whether pain is elicited) had higher sensitivity, specificity and positive and negative predictive values for first CMCJ OA than the grind test[39].

Box 1 | **Commonly used definitions of hand OA by category**

Clinical

- ACR hand osteoarthritis (OA) criteria[11]: hand pain, aching or stiffness and three of the following four criteria:
  - Hard tissue enlargement of two or more of ten selected joints[a]
  - Hard tissue enlargement of two or more distal interphalangeal joints (DIPJs)
  - Fewer than three swollen metacarpophalangeal joints (MCPJs)
  - Deformity of at least one of ten selected joints[a]

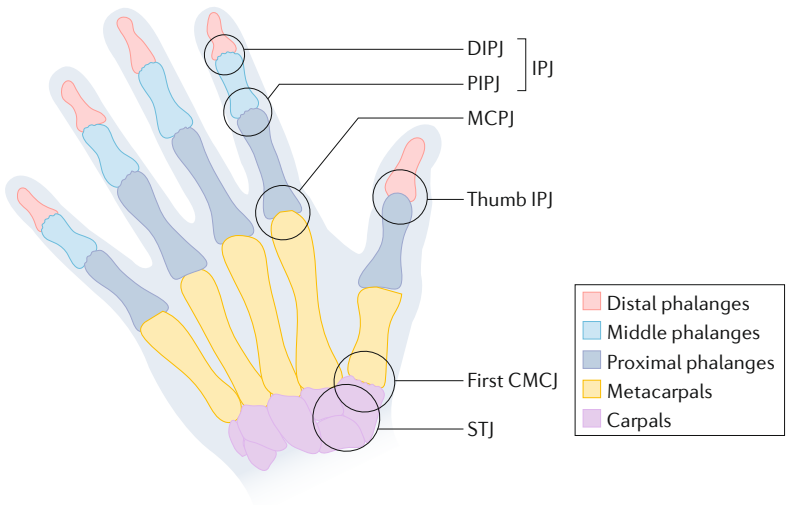
(As used in REFS[55,75,211–213])

Radiographic

- Kellgren–Lawrence[214,215] grade 2 or greater in at least one hand joint (as used in REFS[21,22,26,75,216–221])
- Kellgren–Lawrence grade 2 or greater in at least two hand joints (as used in REFS[135,222])
- Kellgren–Lawrence grade 2 or greater in two of three groups of hand joints (DIPJs, proximal interphalangeal joints (PIPJs), the first carpometacarpal joint (CMCJ) and/or the scaphotrapezial joint (STJ)) (as used in REFS[223–225])
- Altman atlas score[44] of 1 or more for osteophytes or joint space narrowing in one or more hand joints (as used in REFS[226–228])

Symptomatic

- Hand pain, aching or stiffness and the presence of at least one hand joint with a Kellgren–Lawrence grade 2 or greater (as used in REFS[20,21,229])
- Hand pain, aching or stiffness and the presence of Kellgren–Lawrence grade 2 or greater in the same joint, with at least one hand joint affected (as used in REF.[26])
- Hand joint symptoms and the presence of at least one hand joint with radiographic OA in the same hand (as used in REF.[23])



[a]The ten selected joints refers to the second and third DIPJ, the second and third PIPJ and the CMCJ of both hands

Nodal OA. Nodes are the hallmark of nodal OA and most frequently affect the DIPJs (Heberden nodes), followed by the thumb IPJs and the PIPJs (Bouchard nodes). The pattern of joints affected by nodes is similar to the pattern of joints affected by radiographic features[40], but although the presence of nodes is associated with underlying radiographic OA, IPJ OA can present with tenderness and bony enlargement without nodal involvement[41]. Nodal OA occurs more often in women than in men and occurs most often in the dominant hand, suggesting the involvement of mechanical and hormonal factors[40]. Patients with nodal OA frequently have synovitis, osteophytes, cartilage loss and central and marginal erosions[42]; aesthetic discomfort is also common[43]. A strong positive association between the presence of nodes and radiographic OA (in particular, the occurrence of JSN) supports the notion that a clinical observation of nodes can be taken as an indication of hand OA without the need for radiographic assessment[40].

Erosive hand OA. The predominant features of erosive hand OA are central erosions and collapse of the subchondral bone. The term erosive OA is arguably a misnomer, as central erosions are evident in many patients to some degree depending on the imaging modality used[44,45]; hence, this condition probably represents an extreme phenotype of these changes. Although erosive hand OA is commonly considered a separate disease, increasing evidence suggest that this condition is a severe form of hand OA[42,46,47]. Erosive hand OA can affect the first CMCJ as well as the IPJs, but patients rarely have erosive OA of both the first CMCJ and the IPJs (most patients have central erosions exclusively in one or the other)[48]. Erosive OA of the IPJ occurs predominantly in women, whereas erosive OA of the first CMCJ occurs more often in men than in women[48]. Erosive hand OA has a higher clinical burden than non-erosive forms of hand OA, and the associated disability might be as severe as that associated with rheumatoid arthritis (RA), depending on the setting[49,50].

Inflammatory changes, including synovitis and tenosynovitis (determined clinically as soft tissue swelling and by ultrasonography) and effusions and central and marginal erosions (determined by MRI), are frequently observed in patients with either erosive hand OA or nodal OA[42]. The frequency and patterns of joints affected by erosive disease and severe non-erosive forms of hand OA are similar[46,47]. However, progression of synovitis, joint effusion and radiographic OA occurs more frequently in patients with erosive hand OA than in patients with non-erosive forms of hand OA (independently of the amount of synovitis and radiographic structural damage present at baseline)[51,52]. Furthermore, the findings of a 2016 study indicated that patients with erosive hand OA had a higher level of inflammation (including a higher power Doppler activity, which is an indicator of the level of vascularization) than patients with non-erosive hand OA, suggesting that the inflammatory phenotype differs in erosive and non-erosive forms of hand OA[52]. This concept requires further investigation.

Individual and societal burden

The presence of hand OA frequently affects the ability of an individual to undertake everyday activities[53,54]. Symptomatic hand OA is associated with poor self-reported general health, although the strength of this association varies by country and is often partially mediated by impaired physical hand function[55]. In a number of studies, the presence of hand OA and pain related to hand OA has been associated with atherosclerosis and cardiovascular disease[56–60]. This association is analogous to the increased cardiovascular mortality observed in patients with painful OA of the large joints compared with the general population[61]; this increased

Table 1 | **Reported incidence rates for hand osteoarthritis**

Study	Population	*n*	Incidence	Follow-up time period	Annual incidence
Radiographic hand osteoarthritis					
Haugen et al. (2017)[25]	OAI (study cohort), USA	407	18.9%	4 years	4.7%
Haugen et al. (2011)[21]	Framingham, USA	810	• Women: 34.6% • Men: 33.7%	Median 8.7 (IQR 7.9–9.5) years	• Women: 4.0% • Men: 3.9%
Paradowski et al. (2010)[244]	Lund, Sweden	97	14.4%	Mean 9.6 (SD 0.4) years	1.5%
Chaisson et al. (1997)[221]	Framingham, USA	458	• Overall: 83% • Women: 87% • Men: 76%	24 years	• Overall: 3.5% • Women: 3.6% • Men: 3.2%
Bagge et al. (1992)[245]	Goteborg, Sweden	74	• DIPJ: 13.6% • PIPJ: 13.6% • First CMCJ: 4.9%	4 years	• DIPJ: 3.4% • PIPJ: 3.4% • First CMCJ: 1.2%
Kallman et al. (1990)[24]	BLSA (study cohort), USA	84	• Individuals aged <40 years: 56/1,000 person-years • Individuals aged 40–59 years: 69/1,000 person-years • Individuals aged ≥60 years: 106/1,000 person-years	• Age < 60: mean 23.5 (SEM ± 0.25) years • Age ≥ 60: mean 16.9 (SEM ± 0.45)	• Individuals aged ≤40 years: 0.2% • Individuals aged 40–59 years: 0.3% • Individuals aged ≥60 years: 0.6%
Plato et al. (1979)[246]	BLSA (study cohort), USA	65	47.7%	Mean 13.45 (range 12.00–16.00) years	3.5%
Symptomatic hand osteoarthritis					
Haugen et al. (2011)[21]	Framingham, USA	810	• Women: 9.7% • Men: 4.0%	Median 8.7 (IQR 7.9–9.5) years	• Women: 1.1% • Men: 0.5%
Oliveria et al. (1995)[26]	Massachusetts, USA	~130,000	100/100,000 person-years	1 year	0.1%
Clinical diagnosis of hand osteoarthritis[a]					
Yu et al. (2015)[247]	CIPCA (database), UK	94,955	1.3%	1 year	1.3%
Prieto-Alhambra et al. (2014)[27]	SIDIAP (database), Spain	3,266,826	2.4/1,000 person-years	Median 4.45 (IQR 4.19–4.98) years	0.1%

BLSA, Baltimore Longitudinal Study of Aging; CIPCA, Consultations in Primary Care Archive; CMCJ, carpometacarpal joint; DIPJ, distal interphalangeal joint; IQR, interquartile range; OAI, Osteoarthritis Initiative; PIPJ, proximal interphalangeal joint; SD, standard deviation; SEM, standard error of the mean; SIDIAP, Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària. [a]Consultation rate for clinical diagnosis.

mortality is assumed to be caused by decreased load-bearing exercises, but the association with hand OA suggests the involvement of other factors. Conversely, some data from the past 3 years would indicate that individuals with hand OA have a similar risk of all-cause and cardiovascular disease-specific mortality to the general population[61,62].

Patients with hand OA are frequently dissatisfied with the appearance of their hands, especially patients with Heberden and Bouchard nodes, joint deformity and/or erosive hand OA[43]. Aesthetic dissatisfaction has negative effects on the patient symptoms, including increasing the level of pain and stiffness and decreasing the function of the hand; aesthetic dissatisfaction is also associated with depression, anxiety and negative perceptions by the patients about their illness[43,63,64]. Patients with hand OA can have a distorted mental representation of pain in the hand, and normalization of this distortion by multisensory illusions might offer pain relief[65].

Although much is known about the economic burden of hand OA in terms of the direct costs of some treatments, less is known about the indirect costs of this condition such as loss of productivity[66–68]. For example, in one study, arthroplasty surgery for first CMCJ OA often resulted in substantial time off work[69]. Further research is required in this area.

Imaging

Radiography

For decades, radiography has been used to determine the presence and severity of hand OA and to examine disease progression in both clinical and research settings, including in randomized controlled trials (RCTs)[70,71]. This technology is widely available, inexpensive and is an acceptable procedure to patients. However, the inability to view non-bony structures (such as the joint capsule, synovium, ligaments and tendons and their entheseal attachment to the bone) using radiography and the insensitivity of this technique in detecting structural pathology limit its utility in both settings compared with other imaging modalities. For these reasons, and as hand OA can often be reliably diagnosed on the basis of clinical presentations, EULAR and the National Institute for Health and Care Excellence (NICE) do not recommend imaging for the routine diagnosis of hand OA[8,72], although imaging might be useful in excluding other conditions[72,73]. Routine imaging is not recommended for clinical monitoring unless there is an unexpected and

Table 2 | **Reported progression rates for hand osteoarthritis**

Study	Population	*n*	Progression	Follow-up time period	Annual progression rate
Radiographic definition (with incorporation of incidence rate)					
Haugen et al. (2017)[25]	OAI (study cohort), USA	994	59.4%	4 years	14.9%
Haugen et al. (2017)[76]	Oslo, Norway	69	62.3%	Mean 4.7 (SD 0.4) years	13.3%
Bijsterbosch et al. (2014)[248] and Bijsterbosch et al. (2011)[249]	GARP (study cohort), Netherlands	236	• Overall: 52.5% • Osteophyte progression: 44.9% • JSN progression: 25.8%	Mean 6.1 (range 5.0–7.8) years	• Overall: 8.6% • Osteophyte progression: 7.4% • JSN progression: 4.2%
Bijsterbosch et al. (2013)[131]	GARP (study cohort), Netherlands	161	• Overall: 60% • Osteophyte progression: 53% • JSN progression: 32%	6 years	• Overall: 10.0% • Osteophyte progression: 8.8% • JSN progression: 5.3%
Bijsterbosch et al. (2013)[131]	GARP (study cohort), Netherlands	128	• Overall: 39% • Osteophyte progression: 24% • JSN progression: 29%	2 years	• Overall: 19.5% • Osteophyte progression: 12.0% • JSN progression: 14.5%
Paradowski et al. (2013)[250] and Paradowski et al. (2010)[244]	Lund, Sweden	118	59.3%	Mean 9.6 (SD 0.4) years	6.2%
Yusuf et al. (2011)[251]	GARP (study cohort), Netherlands	164	33.5%	Mean 6.0 (SD 0.6)	5.6%
Botha-Scheepers et al. (2009)[252]	GARP (study cohort), Netherlands	172	• Osteophyte progression: 21.5% • JSN progression: 19.2%	2 years	• Osteophyte progression: 10.8% • JSN progression: 9.6%
Botha-Scheepers et al. (2007)[28]	GARP (study cohort), Netherlands	184	• Osteophyte progression: 47% (probands) and 42% (siblings) • JSN progression: 34% (probands) and 37% (siblings)	2 years	• Osteophyte progression: 23.5% (probands) and 21.0% (siblings) • JSN progression: 17.0% (probands) and 18.5% (siblings)
Cvijetić et al. (2004)[253]	Croatia	186	• DIPJs: 59.9% (women) and 54.5% (men) • PIPJs: 34.9% (women) and 33.7% (men) • First CMCJ: 41.2% (women) and 49.9% (men)	10 years	• DIPJs: 6.0% (women) and 5.5% (men) • PIPJs: 3.5% (women) and 3.4% (men) • First CMCJ: 4.1% (women) and 5.0% (men)
Kallman et al. (1990)[24]	BLSA (study cohort), USA	177	• Individuals aged <40 years: 50% • Individuals aged 40–59 years: 50% • Individuals aged ≥60 years: 50%	• Individuals aged <40 years: 15.8 years • Individuals aged 40–59 years: 12.4 years • Individuals aged ≥60 years: 8.9 years	• Individuals aged <40 years: 3.2% • Individuals aged 40–59 years: 4.0% • Individuals aged ≥60 years: 5.6%
Radiographic definition (without incorporation of incidence rate)					
Haugen et al. (2011)[21]	Framingham, USA	464	• Women: 96.4% • Men: 91.4%	Median 8.7 (IQR 7.9–9.5) years	• Women: 11.1% • Men: 10.5%
Güler-Yüksel et al. (2011)[222]	GARP (study cohort), Netherlands	181	31.7%	2 years	15.9%
Hassett et al. (2006)[254]	Chingford, UK	• Osteophytes: 222 • JSN: 308	• Osteophyte progression: 72.5% • JSN progression: 64.0%	11 years	• Osteophyte progression: 6.6% • JSN progression: 5.8%
Plato et al. (1979)[246]	BLSA (study cohort), USA	29	72.4%	Mean 13.45 (range 12.00–16.00) years	5.4%
MRI-based definition (with incorporation of incidence rate)					
Haugen et al. (2017)[76]	Oslo, Norway	69	58.0%	Mean 4.7 (SD 0.4) years	12.3%

BLSA, Baltimore Longitudinal Study of Aging; CMCJ, carpometacarpal joint; DIPJ, distal interphalangeal joint; GARP, Genetics, Arthrosis and Progression; IQR, interquartile range; JSN, joint space narrowing; OAI, Osteoarthritis Initiative; PIPJ, proximal interphalangeal joint; SD, standard deviation.

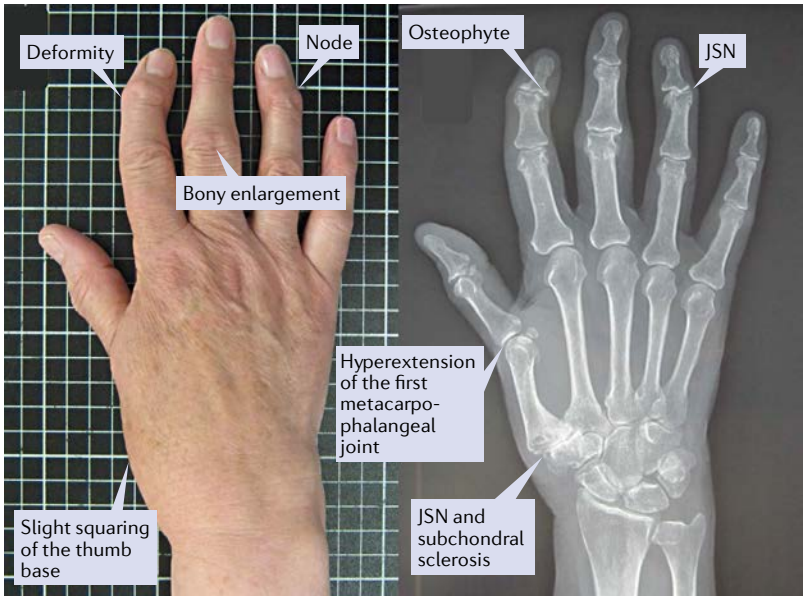


Fig. 1 | **Features of hand osteoarthritis.** A photographic image of an individual's hand showing squaring of the thumb base and bony enlargement, nodes and deformity of the interphalangeal joints and the corresponding radiograph displaying osteophytes, joint space narrowing (JSN) and subchondral sclerosis at the thumb base and interphalangeal joints are provided.

rapid change in symptoms or clinical characteristics that suggest an alternative diagnosis such as RA or psoriatic arthritis (PsA[72].)

Radiography still has a place in the research setting; however, which scoring methods to use are still debated and might depend on the objective of the study and the population studied (for example, patients with erosive versus patients with non-erosive forms of hand OA)[74,75]. Although radiography might have a low sensitivity in detecting features in early disease, the ability of this technique to detect hand OA progression over 5 years is similar to that of 1.0 Tesla MRI, although these imaging modalities do not always detect progression in the same joints[76]. Given that the cost of radiography is lower than that of MRI, radiography is the suggested imaging modality of choice in observational studies with a long follow-up period[76].

Advances in ultrasonography and MRI

In the past 10 years, the use of ultrasonography and MRI for assessing patients with hand OA has increased, providing greater insight into the pathology of the disease and increased evidence that these imaging modalities have a higher sensitivity than radiography in determining the presence of pathological features such as osteophytes, JSN and central erosions[47,77–81]. Using ultrasonography and MRI, researchers have shown that inflammatory changes in the synovium and at the enthesis of the hands are a common finding in hand OA[30,82,83]. Bone marrow lesions (BMLs) are also detectable in the hands by MRI (consistent with other joints affected by OA)[30,84].

Ultrasonography enables real-time multiplanar imaging at a relatively low cost. With this approach, inflammatory and structural changes can be observed without the use of ionizing radiation or the need for a contrast agent; however, this technique is operator-dependent, and bony structures such as cysts and BMLs cannot be detected. Several ultrasonography scoring systems for hand OA have been developed for grading pathological features as well as for use in research studies[80,85,86]. On the basis of inter-observer and inter-reliability scores, the Outcome Measures in Rheumatology (OMERACT) group has endorsed the scoring of osteophytes using the Mathiessen atlas[13,80]. However, although ultrasonography is reliable for determining healthy cartilage or a total loss of cartilage, the use of the ultrasonographic atlas for grading the severity of cartilage pathology is not supported[13]. Ultrasonography findings have good concordance with MRI findings[42,87], but the associations between ultrasonography findings and symptoms have differed across various studies[36,82,83,88,89].

Although MRI is more expensive and takes a longer time to scan patients than other imaging modalities, this imaging modality is important in OA research (including in clinical trials), as it enables the visualization of all joint structures through different pulse sequences in multiple planes[90]. The Oslo hand OA MRI scoring system includes assessments of osteophytes, JSN, central erosions, cysts, BMLs, malalignment, collateral ligament pathology, synovitis and flexor tenosynovitis in the DIPJs and PIPJs[91]. This scoring system has good intra-rater and inter-rater reliability, has good construct validity (in relation to joint tenderness) and has higher sensitivity in determining the presence of osteophytes and erosions than radiography, CT or ultrasonography; however, this approach is time consuming because of the number of features and sites that require examination[81,91–93]. In patients with erosive hand OA, the presence of synovitis and BMLs has been assessed by the Oslo hand OA MRI scoring system, and has shown good intra-rater and inter-rater reliability and is associated with clinical symptoms, demonstrating good construct validity[94].

The Oslo hand OA MRI scoring system has been refined, and the updated version, referred to as the HOAMRIS scoring system, includes measurements of the volume and extent of damage to the joint surface (to enable an improved assessment of central erosions compared with the Oslo hand MRI scoring system), excludes the assessment of collateral ligament pathology and flexor tenosynovitis and combines the assessments of the proximal and the distal joint surfaces (which were graded separately for the Oslo scoring system) for grading central erosions, cysts and BMLs[95]. The HOAMRIS scoring system has good inter-reader reliability for cross-sectional readings but has lower longitudinal reliability, which is thought to be because of the small range of change scores for many of the features. The responsiveness of this scoring system to change (as assessed by the standardized response means) at the patient level (that is, the sum scores for all DIPJs and PIPJs) is good for all assessed features, except for cysts and BMLs[96].

A number of imaging features are associated with disease progression. For example, incident synovitis and BMLs determined on MRI are associated with incident joint tenderness after 5 years[97]. Baseline MRI-defined

synovitis, BMLs and JSN predict radiographic progression in hand OA over 2 and 5 years[98,99]. Baseline and persistent ultrasonography features including synovitis, joint effusion and power Doppler ultrasonographic activity in hand joints are associated with radiographic progression in the same joints after 2 and 5 years[100,101].

Researchers have used ultrasonography to measure the treatment response of individuals with hand OA after intramuscular and intra-articular injections of steroid or other agents[36,102,103]. However, understanding how inflammatory features in individual hand joints change over time is important to determine whether ultrasonography is a valid measure of assessing response to treatment. In a longitudinal study of patients with hand OA, inflammatory features that included synovial thickening, effusion or a power Doppler ultrasonography signal were consistently present in most patients over a 3-month period; however, in individual joints, the inflammatory features changed over time, with persistent inflammatory features found in only 19% of the hand joints[104]. Further investigation in other study populations and over different time periods is recommended before ultrasonography is used as the primary outcome measure in assessing treatment response in individuals' hand joints.

Developments in CT

CT enables more detailed visualization of the bone structures than radiography, MRI or ultrasonography (although this approach requires a high dose of ionizing radiation); hence, in the past few years, this technology has been used for research purposes in hand OA. By using high-resolution peripheral quantitative CT (HR-pQCT), a technique that is based on CT but is able to achieve higher resolution images over a smaller field of view, researchers could show that new bone formation is more common at the cartilage–bone interface and joint margins in hand OA than in PsA[105]. Additionally, disease-associated bone formation is located predominately on the palmar and dorsal sites in hand OA, whereas PsA has more widespread involvement, suggesting that different mechanisms of aberrant bone formation occur in these two conditions[105]. Findings from 3D CT imaging show that the curvature of the trapezial and first metacarpal articular surface of patients with early CMCJ OA differs from that of younger or older healthy individuals[106]. Additionally, using MicroCT (radiographic imaging in 3D on a small scale), researchers have identified differences in the structure and configuration of the trapezium trabecular bone in individuals with and without first CMCJ OA[107]. These findings indicate that morphological changes of the bones and joints can occur at the thumb base in hand OA.

Novel imaging methods in development

Following the advancement of laser technology, several optical imaging modalities have been developed that might be applicable to hand OA[108] (BOX 2), including diffuse optical tomography, fluorescence optical imaging and optical coherence tomography as well as related techniques such as photoacoustic imaging. These techniques offer low-risk (non-ionizing radiation) imaging, differentiation between the soft tissues in the hand and fast processing times[108]. To date, these techniques have been predominantly used for in vitro and ex vivo applications, whereas their use in vivo, particularly in patients with hand OA, is limited and is still undergoing development and testing[109]. The use of systemic contrast agents for some of these applications might limit their use and acceptability to patients.

Symptoms and structural pathology

Discordance or weak associations between clinical symptoms and radiographic structural changes are frequently reported in OA, and hand OA is no exception[110]. However, it is possible that imaging modalities that are more sensitive than those currently in use could reveal stronger associations. In a 2015 systematic review of various cross-sectional studies, the researchers concluded that MRI-defined BMLs, osteophytes, bone attrition and cysts were not associated with hand pain severity[111]. However, various MRI-defined features (such as moderate or severe synovitis, BMLs, central erosions, cartilage attrition and osteophytes), in addition to various ultrasonography-determined features (such as osteophytes, synovitis and the absence of joint cartilage), have been associated with tenderness in the same joints[79,92,110]. Furthermore, the cumulative effects of OA in multiple hand joints is associated with more severe hand pain[112], functional limitation[92] and weaker grip and pinch strength[18,92,113]. Little is known about the course of symptoms in hand OA over time and how they relate to structural pathology. Inflammation (as determined by ultrasonography) has been associated with the progression of radiographic hand OA and the subsequent development of bone erosions[114,115]; however, further longitudinal research will enable a better understating of the disease processes and could help identify potential targets for treatment.

Disease mechanisms

Studying the pathogenesis of hand OA is difficult: researchers have limited access to diseased tissue, and for tissue that is available, the quantities obtained for molecular analysis are small. Healthy donor tissue (to use as a control) is rarely available, and no animal models of hand OA exist. In addition to the epidemiological and in depth prospective imaging studies detailed above, our understanding of hand OA disease pathways comes from a combination of genetic data analysis and the outcomes (positive or negative) of clinical studies.

An important question to address is whether hand OA shares similar pathogenic pathways with OA at other joint sites. Of the common aetiological factors, perhaps the most important factor is abnormal mechanical loading. Although the joints of the hands are not weight bearing, they are nonetheless load bearing. Evidence for the involvement of mechanical loading in the development of hand OA is best demonstrated by the higher prevalence of OA in the dominant hand than in the non-dominant hand (80% of right-handed individuals with hand OA are predominately affected in their right hand)[116] and the lack of disease in the immobilized hand (for example, owing to hemiparesis or polio) of some

Box 2 | **Novel and alternative imaging methods in development applicable to hand OA**

Diffuse optical tomography and photoacoustic imaging
In diffuse optical tomography (DOT), light from the near-infrared spectral region is passed through tissues, and the spatial and temporal variation in light absorption and scattering is measured and used to construct tomographic images[230]. Using 3D DOT, researchers could distinguish between distal interphalangeal joints affected by osteoarthritis (OA) and healthy joints[231]. After further methodological refinements, this technique could distinguish between patients with hand OA and patients with psoriatic arthritis or healthy individuals[232]. Incorporating photoacoustic imaging with DOT improves the image resolution, enabling better differentiation of bone from soft tissue[233].

Fluorescence optical imaging
In fluorescence optical imaging (FOI), tissues are illuminated with a light source that can range from ultraviolet to infrared; this light excites fluorophores that have been introduced through a fluorescence contrast media that accumulates at sites of inflammation[234,235]. In one study investigating the use of FOI in OA, which looked at joints of the hand, the researchers noted that although similar proportions of individuals with inflammation were distinguished using FOI and grey-scale or power Doppler ultrasonography in patients with either OA or rheumatoid arthritis, a particular phase of fluorescent dye flooding in (phase 2) FOI might be more informative in OA[236].

Optical coherence tomography
Optical coherence tomography (OCT) employs light from the infrared end of the spectrum, which is passed through the tissues under investigation; the resulting reflections are measured, and cross-sectional images are produced. OCT can be used to visualize cartilage in the first carpometacarpal joint and to detect early changes including thickening of the cartilage and changes to the articular surface that are consistent with histology findings[237]. Additionally, overlaying the OCT images onto CT images can help with the visualization of cartilage[237].

Trabecular bone texture
The texture of trabecular bone is quantifiable, and changes in bone texture are observable in early OA at the knee[238,239]. Work using directional fractal signals has now extended this finding to the smaller regions of the hands, and the use of augmented variance orientation transform (AVOT) has the potential to be useful in the early detection and prediction of hand OA[240].

Positron emission mammography
Positron emission mammography (PEM) is a nuclear medicine modality that has been used to detect or characterize breast cancer. The PEM scanner has a small field of view but is comparable to a standard PET or CT scan for evaluating hand OA[241].

Photography
A system for scoring hand OA from photographs offers an alternative method of diagnosing hand OA to clinical or radiographic assessment and is a commonly used, reliable and valid method of scoring hand OA[242,243]. It offers researchers a feasible alternative method of data collection, which might be of particular use for large population-based studies or studies covering wide geographic or remote areas.

patients with OA of the other hand[117,118]. Inflammatory changes in the entheses of the interphalangeal joints of patients with hand OA suggest that this tissue is an important area of stress[119]. Several features are unique to hand OA. For instance, unlike OA of the large joints, the incidence of hand OA peaks around the time of menopause[27], the early inflammatory phase of disease seems to pre-date bone remodelling, and joint tenderness often seems to improve in individuals over time (T.L.V., unpublished observations).

Genetics of hand OA

Genetic studies can provide powerful insights into pathogenesis. Hand OA has the highest estimated heritability of all types of OA (approximately 60%)[120]. A comprehensive review published in 2008 summarized all genetic studies in hand, hip, knee and spine OA, drawing from the literature published up until 2006[121]. This study revealed just two candidate gene associations that had been replicated for hand OA: genetic variants in *ACAN* (encoding aggrecan, an integral component of the extracellular matrix in cartilaginous tissue) and *HFE* (encoding homeostatic iron regulator, a protein associated with haemochromatosis)[121]. Since this study, five genome-wide association studies (GWASs)[122–126] and numerous candidate gene studies have been published. For convenience, gene candidates can be grouped into three areas according to their putative role in disease (FIG. 2): those that are associated with growth factor signalling[123,124,127–130], those that contribute to the integrity and calcification of the extracellular matrix of cartilage[122,125,131–135] and those that relate to inflammatory pathways[126,136–140]. Two GWASs in hand OA deserve further attention. The first was a study in Iceland in which two loci were identified: one on chromosome 1, a rare variant associated with severe hand OA (no further allelic characterization was given), and a second common set of variants on chromosome 15, all in *ALDH1A2* (REF.[126]). *ALDH1A2* encodes the enzyme retinal dehydrogenase 2 (ALDH1A2), which catalyses the synthesis of cellular retinoic acid. The polymorphic variants in *ALDH1A2* are hypomorphic (that is, associated with lower levels of ALDH1A2 in hand OA cartilage)[141]. Retinoic acid is essential for forelimb development in the embryo and is a potentially interesting target, as this metabolite has anti-inflammatory effects on many different cell types including chondrocytes[142]. Paradoxically, chondrocyte biologists use retinoic acid to stimulate cartilage catabolism (albeit at supra-physiological levels)[143].

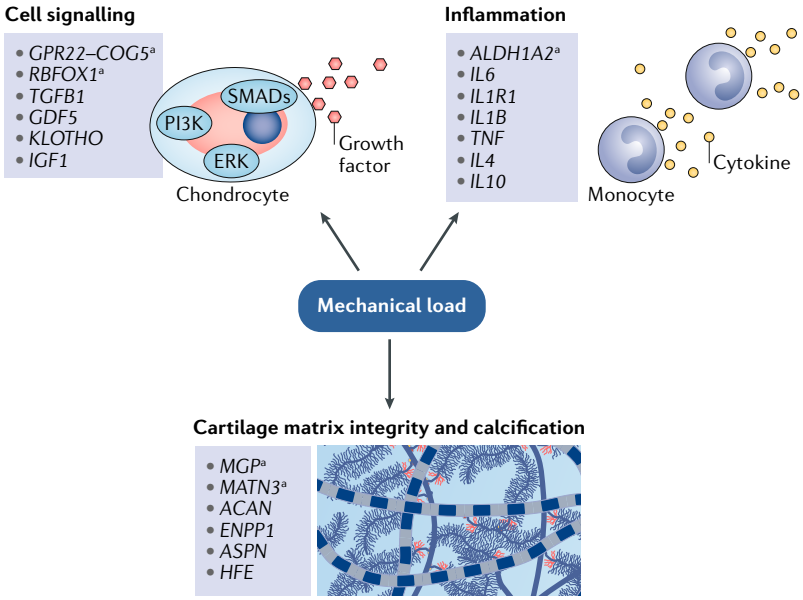


Fig. 2 | **Predicted molecular drivers of hand osteoarthritis by genetic association.** Mechanical load is central to the pathogenesis of hand osteoarthritis (OA) and influences growth factor bioavailability, inflammation and matrix degradation. The genes shown in this figure have been linked to radiographic or symptomatic hand OA in at least one study (some of which have not been replicated). ERK; extracellular-signal-regulated kinase; PI3K, phosphoinositide 3-kinase. [a]Genetic associations that were identified by genome-wide scans (the other associations were identified using candidate gene approaches).

The second study, a 2017 GWAS from the Netherlands, identified a locus on chromosome 12, close to *MGP*[125]. This gene, also identified in a previous candidate gene study[133], encodes matrix Gla protein (MGP), which is responsible for preventing calcification of cartilage; the hypomorphic function associated with the risk variant might predispose individuals to abnormal chondrocalcinosis and altered biomechanical properties of the cartilage. MGP is known to be regulated by transforming growth factor-β (TGFβ), and so it is of interest that candidate gene studies from the past few years have added further support for the association of hand OA with polymorphic variants in genes encoding TGFβ family members[131,132,136]. These associations are consistent with the purported chondroprotective role of TGFβ in the joint.

Sex hormones and hand OA

All types of OA have a higher prevalence in postmenopausal women than in premenopausal women, but the relationship that hand OA has with the typical time of menopause onset seems to be unique and robust[27,144]. For instance, perimenopausal symptoms (such as hot flushes and irregular menstrual cycles) commonly occur at the time of presentation with hand OA[144]. Whether this relationship is due to the loss of the established anti-inflammatory and pro-reparative effects of oestrogen or related to fluctuations in other sex hormones is currently unclear. Both oestrogen and testosterone regulate the expression of ALDH1A family members[145], and it is tempting to speculate that there might be important crosstalk between retinoic acid and oestrogen signalling in the perimenopausal period.

Inflammation and hand OA

The role of inflammation in hand OA remains particularly contentious. Although it is widely accepted that inflammatory changes (including clinical and imaging-based synovitis) occur in disease, these changes are typically relatively modest in hand OA compared with inflammatory arthritides such as RA[146], and the pathogenic role of inflammation is far from certain. Data from prospective imaging studies show that baseline synovitis on MRI or ultrasonography predicts radiographic progression or central erosion, respectively[99,114,115,147] However, it is worth bearing in mind that the presence of BMLs and JSN also predicts progressive disease[99], and so it is possible that inflammation is a consequence rather than a cause of progressive disease.

A wide range of OA serum or plasma biomarkers have been investigated in hand OA, which can provide insight into disease development. These biomarkers include various inflammatory markers, such as C-reactive protein and adipokines, and markers of cartilage or bone homeostasis, such as type II collagen[148,149]. In one small sub-study of 18 patients from a 2016 hand OA clinical trial, serum IL-1 levels were associated with loss of hand function and radiological erosions[150]. Although this study raises the possibility that erosive and non-erosive OA have different biomarker profiles, to date, biomarker characterization remains less developed for hand OA than it is for OA at other sites such as the knee. Currently, there are no validated serum or plasma biomarkers for diagnosing hand OA, stratifying its severity or predicting its progression or response to treatment.

Results from clinical trials can also aid in the understanding of disease pathogenesis. Intra-articular steroid therapy is routinely used in many cases to treat symptomatic hand OA. A 2015 RCT of 60 patients with symptomatic hand OA showed that steroid (triamcinolone) injection in combination with lidocaine (a local anaesthetic) resulted in a statistically significant improvement in the patients' hands in terms of pain on movement and physician's assessment of swelling compared with treatment with lidocaine alone[151]. Interestingly, lidocaine injection alone resulted in a striking response in the patients in this study, and five secondary disease activity measures did not differ between the two groups. The emphasis on targeting inflammation in hand OA has been further unsettled by the negative results of several RCTs in hand OA using traditional anti-inflammatory or 'anti-synovial' agents. These findings include a failure to demonstrate a difference between placebo treatment and treatment with hydroxychloroquine[152,153], anti-TNF agents[154,155] or IL-1-targeting strategies[156].

Advances in therapy

The management of hand OA combines both non-pharmacological and pharmacological approaches. Surgical treatments are offered to those with severe symptoms and for whom conservative approaches have failed[29]. In this section, we describe findings from original studies produced within the past 5 years for core recommendations (a range of self-management support), first-line analgesia and novel pharmacological targets.

Non-pharmacological therapies

In a 2017 systemic review, Lue and colleagues[157] provided an update on an earlier review[158] of non-surgical therapies for hand OA, and the reader is directed to this manuscript for an appraisal of the quality of some of the studies discussed below. In this section, a summary of the core and adjunctive treatments and surgery are briefly provided.

Core interventions: self-management support. Self-management programmes for hand OA can include a range of approaches such as providing the patient with written information on hand OA and self-management approaches, giving advice on hand exercises and joint education (such as joint protection strategies and pacing of activities), weight management strategies and using new models of care[159,160]. For example, Moe et al.[160] concluded that the use of an integrated, multidisciplinary care model, although not superior in clinical outcomes, resulted in greater patient-reported satisfaction than usual care.

Written information on the underlying disease and self-management approaches, such as the OA guidebook[161], are essential components of the core management of hand OA, although limited evidence is available for the effectiveness of hand OA education alone. In the trial that tested an OA consultation model (which consisted of an OA guidebook, an OA consultation with a general practitioner and a subsequent follow-up with a practice nurse in a dedicated OA clinic), the supply of written information by general practitioners and practice nurses to patients increased from 4% to 28% in the model OA consultation arm, whereas no changes from baseline were observed in the control arm (which consisted of usual care alongside a resource pack of written advice for patients)[162]. Although implementation of this model did not improve the health status of patients, it did improve the implementation of clinical guidelines (the NICE OA recommendations) by clinicians and allied health professionals, along with the use of self-management approaches[159].

Education on maintaining joint health is often described as 'joint protection education' or 'joint education'. In the SMOOTH (Self-Management of Osteoarthritis of the Hand) study, which included community-dwelling adults (aged 50 years and over) with ACR-defined hand OA, the individuals who attended occupational therapy classes for joint protection education (using written patient information from an Arthritis Research UK booklet[163]) were twice as likely to respond to treatment than those who did not attend the classes[164].

Several trials of hand exercise for hand OA[165–167] have been published in the past few years, along with a Cochrane systematic review[168]. Exercise is recognized as an effective analgesic therapy for those with OA at any site[169]. However, despite continued efforts to identify the specific benefits of exercises for hand OA, the Cochrane review[168] found that the magnitude of the benefit of exercise and which exercises should be prescribed are still uncertain. For complex interventions, blinding the therapist or patient to the intervention is difficult, and in large studies, self-report questionnaires are often used, which contribute to a low quality rating of the study when assessed in systematic reviews. The findings suggest that recommending one approach to exercise over another is not possible at present for hand OA. Few studies have investigated the cost-effectiveness of exercise in the management of hand OA, but findings from the SMOOTH study show that hand exercises, delivered in classes by occupational therapists, could be a cost-effective approach over 12 months[66].

The association of obesity and hand OA is continually debated[170,171]. Weight management forms part of a holistic approach to managing OA in general, and as hand OA often coexists with OA in other sites, consultations for hand OA provide an opportunity to offer weight management advice and referral to services if a patient is overweight, as recommended by NICE quality standards[8,9].

Adjunctive conservative therapies. Several systematic reviews have been published in the past few years on the use of non-surgical treatments for first CMCJ OA[172,173]. Local treatments such as splints (pre-fabricated or custom orthotics worn on the affected joint) might offer warmth, support and stabilization of joints that are normally painful on movement. However, there continues to be uncertainty about the exact mechanism of action of splints and regarding their optimal design and instructions for use to maximize adherence and safety. Soft splints, off the shelf splints and splints worn at night-time might be more acceptable to patients than hard splints, custom made splints or splints to be worn during the day[174–176].

Researchers have investigated splints or orthoses for first CMCJ OA[177–181] and IPJ OA[157,172,173,182] as well as pressure gloves for hand arthritis[183]. However, currently, what type of splint is best is unclear, and data are inconsistent as to whether splints provide symptom relief in the hand[157]. The use of splints does improve function and pinch strength in patients with first CMCJ OA[172,173]. Most studies of splinting have a high risk of bias because of difficulties in establishing or maintaining participant blinding or including true sham devices, but the inclusion of a placebo splint in new upcoming studies such as the OTTER (OA of the Thumb Therapy) trial gives an opportunity to address some of the key limitations of previous trials of splinting[174–176].

Other non-pharmacological therapies. Several other therapies that have been tested for the treatment of hand OA include spa therapy[184], joint mobilization[185], taping[186] and ultrasound therapy[187]. Although evidence is limited for the efficacy of such treatments, these approaches have been recommended in various clinical guidelines for the management of hand OA such as the EULAR Hand OA recommendations[29,188,189].

Pharmacological therapies

First-line analgesia: topical treatments. Topical NSAIDs are recommended in international and national guidelines as a first-line pharmacological treatment option for symptomatic hand OA (owing to their superior safety profile to oral analgesics[8,188] and improved efficacy

compared with oral paracatamol[190] and placebo[191]). Overall, topical NSAIDs are superior to placebo for relieving pain and improving function in OA[191]. Although salicylate gel is associated with higher withdrawal rates owing to adverse events, the remaining topical NSAIDs are not associated with any increased local or systemic adverse events[191]. The benefits of topical NSAIDs have been summarized elsewhere[192], but there is still uncertainty over the relative efficacy of topical NSAIDs compared with the efficacy of other topical treatments such as capsaicin.

Topical capsaicin, an extract of hot chilli pepper, is recommended for the treatment of OA pain[8], but studies of this treatment in hand OA are limited. In a 2014 systematic review[193] of RCTs of topical capsaicin use in OA, which included five double-blind RCTs and one case-crossover trial, only one study included patients with hand OA. Capsaicin was reported to be safe and well tolerated across all the included studies, with no evidence of systemic toxicity[193]. This treatment is associated with mild burning at the application site, which peaks after 1 week and declines over time[193]. Capsaicin might therefore be more suited to patients who lack inflammatory signs and have persistent pain or neuropathic symptoms, which aligns with the use of capsaicin for neuropathic pain associated with other conditions. Capsaicin treatment efficacy warrants further investigation.

Local analgesia. Injecting drugs such as glucocorticoids directly into the joints provides local symptomatic relief and offers another option in addition to core treatment. Interest in the use of intra-articular injection therapy in hand OA continues[151,194–198], as this approach is preferable to surgical approaches in elderly patients with comorbidities[198].

The benefits and harms of intra-articular therapies were assessed in a 2016 systematic literature review and meta-analysis; this analysis included trials that investigated the efficacy or safety of any intra-articular therapy in first CMCJ and IPJ OA compared with placebo or other treatments for which pain was the main outcome[198]. A total of 13 trials (including 864 patients with hand OA, 11 trials of patients with OA of the first CMCJ and 2 trials of patients with OA of the IPJs) were included. The results of a meta-analysis of two trials comparing intra-articular corticosteroids and placebo treatment in patients with first CMCJ OA indicated that intra-articular corticosteroids resulted in no improvement in pain. Synthetic hyaluronan also seemed inefficacious compared with placebo in patients with first CMCJ OA. However, in one trial of patients with OA of the IPJs, the patients receiving corticosteroids had considerable improvements in pain during movement compared with the patients receiving placebo[151]. The authors of the systematic review[198] concluded that intra-articular injection of corticosteroids or hyaluronan do not seem more effective than placebo in first CMCJ OA. However, the placebo response can be large, and intra-articular use in combination with other modalities such as splinting might still be a relevant option.

Adjunctive analgesia. Paracetamol is prescribed for hand OA if topical treatments are ineffective or not tolerated[8], although the effect size of this therapy in the treatment of large joint OA might be smaller than previously thought[190]. If ineffective, and following careful assessment of the risks and benefits to the individual, oral NSAIDs (such as naproxen), cyclooxygenase 2 (COX2; also known as PTGS2) inhibitors or opiates might be introduced. These drugs should generally be used sparingly and only when required to limit the risk of toxicity. A proton pump inhibitor should be prescribed along with NSAIDs to protect against NSAID-induced gastrointestinal adverse events[199]. In a 2015 study of patients with first CMCJ OA[200], in the small number of participants included in the final analysis ($n = 19$), the patients receiving naproxen had a considerable reduction in brain activity in areas commonly associated with pain perception compared with those patients receiving placebo.

The use of several novel agents has been investigated for the treatment of hand OA and typically involves the re-purposing of disease-modifying anti-rheumatic drugs or biologic therapies licensed for use in RA: these therapies include adalimumab, a monoclonal antibody to TNF[154], hydroxychloroquine[153], doxycycline[201] and GCSB-5, a herb extract[202]. Evidence from these studies suggests that adalimumab and hydroxychloroquine are not effective in treating hand OA pain[153,154]. Further studies are needed to identify oral treatments that improve hand pain or modify the course of disease. Several drug trials in OA, including ongoing trials, might be relevant to hand OA and have been reviewed elsewhere[203]. The ongoing clinical trials include drugs that inhibit inflammatory mechanisms (such as GM-CSF[204] and anti-IL-6 (REF.[205])), but novel targets relevant to other OA mechanisms might be needed to move the field forward.

Nutraceuticals are not recommended by NICE for the management of OA, but researchers have investigated their effects in hand OA. In a systematic review of oral chondroitin for OA, including hand OA, chondroitin treatment (alone or in combination with glucosamine) was associated with a short-term benefit in terms of pain relief compared with placebo (although most of the studies assessed were of low quality)[206]. The low risks associated with chondroitin might account for its popularity as an over-the-counter supplement in individuals with hand OA, but more evidence is needed to advocate the use of this supplement in routine clinical practice.

Surgery. Surgery in hand OA is recommended for patients who are refractory to non-surgical management[8]. In a survey of 163 patients with first CMCJ OA, the results confirmed that patients predominantly visit hand surgeons seeking treatment to reduce pain and that improvements in function and aesthetic image are a lower priority for these patients[207]. The findings highlight the need to elicit patients' expectations before treatment and to discuss potential treatment outcomes in order to achieve optimal gain from surgery. Placebo-controlled RCTs for many surgical procedures carried out for the treatment of hand OA are lacking.

Guidelines and implementation

Guidelines have previously been published that address the clinical management of hand OA[8,29,208,209], including the newly released 2018 update from EULAR[188]. However, ensuring the uptake of guidelines in clinical practice is challenging[159,162]. Improvements are needed in the ways of recording hand OA diagnosis in primary care and evaluating the quality of hand OA care, including the implementation of guidelines. Demonstrating an association between the implementation of clinical guidelines and improvements in the health status and function of patients is difficult in real world settings[159]. This field of investigation is growing; for example, ways in which to measure the quality of care that include valid quality indicators and demonstrate the effects of implementation are now high on the research agenda.

Regarding research guidelines, a preliminary core set of outcomes has been developed by OMERACT using Delphi exercises and systematic literature review[210]. In clinical trials of symptom modification, the minimum outcomes should include assessments of pain, physical function, joint activity and hand strength as well as global patient assessment. For clinical trials examining structure modification as well as observational studies, structural damage should also be examined[210]. Finally, guidelines on imaging in hand OA clinical trials are also available[71].

Conclusion

Hand OA is a common, disabling, heterogeneous condition. Studies in the past few years have provided some advances in our understanding of the burden and underlying mechanisms of hand OA as well as regarding hand OA therapy, but there is much still to understand. Localized therapies for hand OA such as hand exercises and topical treatments offer small but clinically important amounts of symptomatic relief in hand OA and should arguably be more widely used. Hydroxychloroquine, previously used anecdotally off label to treat severe forms of the disease, is now known to be ineffective in the treatment of established symptomatic radiographic hand OA and should not be used in such patients. The lack of efficacy of many anti-rheumatic drugs in hand OA has catalysed a re-evaluation of potential disease targets. The disappointing results from clinical trials reaffirm the need for a better understanding of basic underlying disease mechanisms, and arguably a better method for identifying and stratifying patients with early disease and/or who are at high risk of progression, at a time when disease processes might be susceptible to intervention.

In primary care management, the diagnosis of hand OA without the use of imaging is still recommended by international guidelines[8]. A better approach for classifying and coding the disease is needed. Such an approach is essential for improving the delivery of quality care for this common condition. Guidelines such as the newly updated 2018 EULAR recommendations[188] for the management of hand OA will continue to improve the quality of care for patients with hand OA, provided that steps are taken to accelerate the implementation of such guidance into every day practice.

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Review criteria
The aim of this Review is to update earlier reviews[4,6] published in *Nature Reviews Rheumatology* with evidence from a search over the past 5 years for new original studies, Cochrane reviews and international guidelines. A search for original articles that examined hand osteoarthritis and were published between 1 January 2012 and 10 October 2017 was performed in MEDLINE. The title and abstracts were searched using the following terms: "osteoarthritis" or "OA" and "hand", "finger", "thumb", "interphalangeal", "inter phalangeal", "IPJ", "metacarpophalangeal", "metacarpo phalangeal", "MCP", "carpometacarpal", "carpo metacarpal", "CMC", "trapezioscaphoid", "trapezio scaphoid", "TS", "erosive", "nodal" or "node". All full-text papers and articles in the English language were reviewed. The authors also searched the reference lists of identified articles for further relevant papers.

New insights into the genetics and epigenetics of systemic sclerosis

Chiara Angiolilli[1,2,3], *Wioleta Marut*[1,2,3], *Maarten van der Kroef*[1,2], *Eleni Chouri*[1,2], *Kris A. Reedquist*[1,2] *and Timothy R. D. J. Radstake*[1,2]*

Abstract | Systemic sclerosis (SSc) is a severe autoimmune disease that is characterized by vascular abnormalities, immunological alterations and fibrosis of the skin and internal organs. The results of genetic studies in patients with SSc have revealed statistically significant genetic associations with disease manifestations and progression. Nevertheless, genetic susceptibility to SSc is moderate, and the functional consequences of genetic associations remain only partially characterized. A current hypothesis is that, in genetically susceptible individuals, epigenetic modifications constitute the driving force for disease initiation. As epigenetic alterations can occur years before fibrosis appears, these changes could represent a potential link between inflammation and tissue fibrosis. Epigenetics is a fast-growing discipline, and a considerable number of important epigenetic studies in SSc have been published in the past few years that span histone post-translational modifications, DNA methylation, microRNAs and long non-coding RNAs. This Review describes the latest insights into genetic and epigenetic contributions to the pathogenesis of SSc and aims to provide an improved understanding of the molecular pathways that link inflammation and fibrosis. This knowledge will be of paramount importance for the development of medicines that are effective in treating or even reversing tissue fibrosis.

DNA methylation
An epigenetic change to DNA that conventionally creates a close, inactive chromatin state that results in transcriptional repression.

[1]*Department of Rheumatology and Clinical Immunology, University Medical Centre Utrecht, Utrecht University, Utrecht, Netherlands.*

[2]*Laboratory of Translational Immunology, Department of Immunology, University Medical Centre Utrecht, Utrecht University, Utrecht, Netherlands.*

[3]*These authors contributed equally: Chiara Angiolilli, Wioleta Marut.*

**e-mail: t.r.d.j.radstake@umcutrecht.nl*

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Systemic sclerosis (SSc) is a severe disease that is characterized by damage to small blood vessels and immune system alterations that leads to fibrosis of the skin and internal organs[1]. Such fibrosis can cause severe damage to internal organs, leading to conditions such as pulmonary arterial hypertension and pulmonary fibrosis, both of which are major causes of disease-associated morbidity and mortality[2,3]. On the basis of skin involvement, SSc is classified into two main subtypes: limited cutaneous SSc (lcSSc), in which skin fibrosis is restricted to the distal areas of the hands and fingers, and diffuse cutaneous SSc (dcSSc), in which skin fibrosis can affect the whole body[1]. Patients with SSc who do not have fibrosis, but who do have Raynaud phenomenon and either a marker autoantibody (for instance, anti-centromere antibodies (ACAs), anti-telomere antibodies (ATAs) or antinuclear antibodies (ANAs)) or abnormalities in nail fold capillaroscopy results, are identified as having early SSc[4]. Given the heterogeneity in disease that occurs between patients with SSc, in 2013 (REF.[5]) the ACR and EULAR proposed new criteria[6] for the classification of SSc that incorporate additional clinical manifestations and features of the disease to enable improved and earlier diagnosis than was possible using previous criteria[2].

SSc is a rare disease with a prevalence that ranges from 7 to 489 individuals per million[7]. This variability is likely to be the result of a high degree of variation across geographic regions as SSc is more prevalent in the USA, Australia and southern Europe than in northern Europe and Japan[7–9]. Moreover, in the USA, African Americans have a higher probability of developing SSc than white Americans and experience an earlier age of onset and increased morbidity[7–9]. SSc development is also sex-dependent, being more common in women than in men, with ratios varying from 3:1 to 14:1 depending on the geographical region[8]. Notably, although SSc is more prevalent in women, men with SSc seem to develop more severe disease outcomes than do women with SSc[7].

Currently, the pathogenesis of SSc remains ambiguous; however, the consensus is that in genetically susceptible individuals, the disease is triggered by exposure to environmental factors. These factors, such as exposure to silica or viruses[10–12], can lead to modifications at the epigenetic level[10–12] (such as DNA methylation and histone post-translational modifications (FIG. 1)) that ultimately cause a series of molecular events that lead to the development of SSc. In this Review, we present an overview of developments in our understanding of the genetic and epigenetic landscape of SSc pathogenesis.

Key points

- Systemic sclerosis (SSc) is a complex fibrotic, autoimmune disease, the manifestations of which are only partially explained by genetic predisposition.
- The concordance rate for SSc in monozygotic twins is low, indicating that genetic predisposition is insufficient to explain disease development and suggesting a role for environmental factors and epigenetic influences.
- Epigenetic factors associated with SSc include changes in DNA methylation, histone modifications and the expression of microRNAs and long non-coding RNAs, which together drive aberrant immune activation and fibrosis.
- Integration of the knowledge derived from genomic and epigenomic studies in SSc is needed to improve the characterization of the disease.
- Therapies that target epigenetic pathways are emerging as promising therapeutic tools in experimental models of fibrosis, raising hope for future applications in SSc.

As previous literature on the subject has been reviewed elsewhere[13], we concentrate on research from the past 4 years. We also highlight new directions that could be taken in diagnostic and therapeutic approaches to SSc.

Genetic involvement in SSc

SSc is a complex autoimmune disease with regard to genetic susceptibility. The relative risk of developing SSc is 1.6% in families with a history of SSc and 0.026% in the general population[14,15]. Interestingly, the concordance rate of SSc in monozygotic twins is only 4.2%[16], which is a much lower rate than that of other autoimmune diseases, including rheumatoid arthritis (RA; 12.3%)[17], multiple sclerosis (16.7%)[18] and primary biliary cholangitis (77%)[19]. However, the gene expression profiles of dermal fibroblasts isolated from patients with SSc and their unaffected monozygotic, but not dizygotic, twins are similar[20], indicating that a substantial genetic component exists in the development of this disease. The presence of SSc is also associated with the risk of developing other autoimmune diseases. For instance, first-degree relatives of patients with SSc have a high prevalence of autoimmune thyroid disease[21], RA[21] and systemic lupus erythematosus (SLE)[22].

Nevertheless, over the past few years, intense research has led to insights into the genetic basis of this disease. Similar to most autoimmune diseases, SSc is not the result of a single polymorphism but rather results from multiple genetic variants that predispose individuals to developing SSc. Many HLA and non-HLA genes are associated with susceptibility to SSc (TABLE 1). In the following section, we focus on genetic associations with SSc that have been identified over the past 4 years.

HLA genes

The HLA region is a highly polymorphic part of the genome that contains the first identified genetic associations with SSc. The results of multiple studies, some of which included genome-wide association studies (GWASs) and Immunochip data analysis, have shown associations between HLA polymorphisms and susceptibility to SSc (TABLE 1). According to the results of a 2017 systematic review[23], class II HLA genes have the highest statistically significant association with SSc; in particular, genetic polymorphisms in *HLA-DQA1*, *HLA-DQB1*, *HLA-DPB1* and *HLA-DRB1* have been associated with SSc in more than five different studies[23,24]. In general, the majority of studies have reported that the presence of HLA alleles is linked with general susceptibility to SSc, although some studies have shown a protective effect of HLA alleles in SSc (TABLE 1). These associations can be specific for certain populations or common between different ethnic populations[25,26]. For instance, the results of a 2015 study in patients with SSc from a Mexican cohort showed that *HLA-DRB1*11:04* was associated with susceptibility to SSc, whereas *HLA-DQB1*03:01* was associated with protection from SSc[27]. A separate 2016 study confirmed the protective role of *HLA-DQB1*03:01*, but this time in Japanese patients with SSc[28]. In the same study[28], *HLA-DQB1*05:01* and *HLA-DQB1*06:01* were also found to positively associate with the presence of autoantibodies in patients with SSc. By contrast, the results of another study in the USA showed that *HLA-DQB1*03:01* was associated with susceptibility to SSc, rather than protection, in white, African-American and Hispanic individuals[25].

Many studies have also reported that HLA genes and/or haplotypes associate with subsets of patients with SSc and with some clinical features of SSc. For example, in a Chinese cohort, lung fibrosis was most common in patients with SSc who carried the *HLA-DPB1*03:01* haplotype, whereas ACA-positive patients were more likely to carry the *HLA-DPB1*04* haplotype than ACA-negative patients[29]. By contrast, these clinical features of SSc had a negative relationship of borderline significance with homozygous expression of *HLA-DPB1*05:01* (REF.[29]). The results of another study provided evidence that class II HLA alleles within the *HLA-DQ5–HLA-DR1* haplotype are associated with low rates of progression from early SSc to established SSc[30].

The importance of class II HLA gene associations in SSc has also been confirmed in juvenile-onset SSc. In particular, *HLA-DQA1*05*, which had been previously identified as a risk factor in adult males with SSc[31], was more prevalent in patients with juvenile-onset SSc than in healthy controls[32]. Moreover, a new association between SSc and *HLA-DRB1*10* was reported in children[32], suggesting a distinction between the HLA gene associations for juvenile-onset and adult-onset SSc.

Finally, the results of Immunochip data analysis have provided a comprehensive overview of the HLA region, confirming a strong association between the HLA region and SSc[24]. In this study[24], seven single-nucleotide polymorphisms (SNPs) and six polymorphic amino acid positions in the HLA region were associated with either SSc or with specific autoantibody profiles.

Non-HLA genes

Many of the different genes associated with SSc are found in non-HLA loci, with the strongest associations being with genes related to the immune system (FIG. 2a; TABLE 1). For example, in line with the type I interferon signature found in patients with SSc[33], polymorphisms in interferon regulatory factor (IRF) genes are associated with SSc[34]. *IRF5* was the first IRF gene reported to be associated with SSc, an observation that was replicated in several studies[34]. In 2016, another IRF family member, *IRF4*, was identified as a common susceptibility locus for SSc and RA in a cross-disease GWAS meta-analysis[35].

Histone post-translational modifications
Chemical modifications to histone tails (such as acetylation and methylation) that influence the accessibility of the DNA to the transcription machinery, thereby allowing or repressing gene expression.

Immunochip
Single nucleotide polymorphism microarrays designed to replicate and establish statistically significant genome-wide association study loci associated with autoimmune and inflammatory disorders.

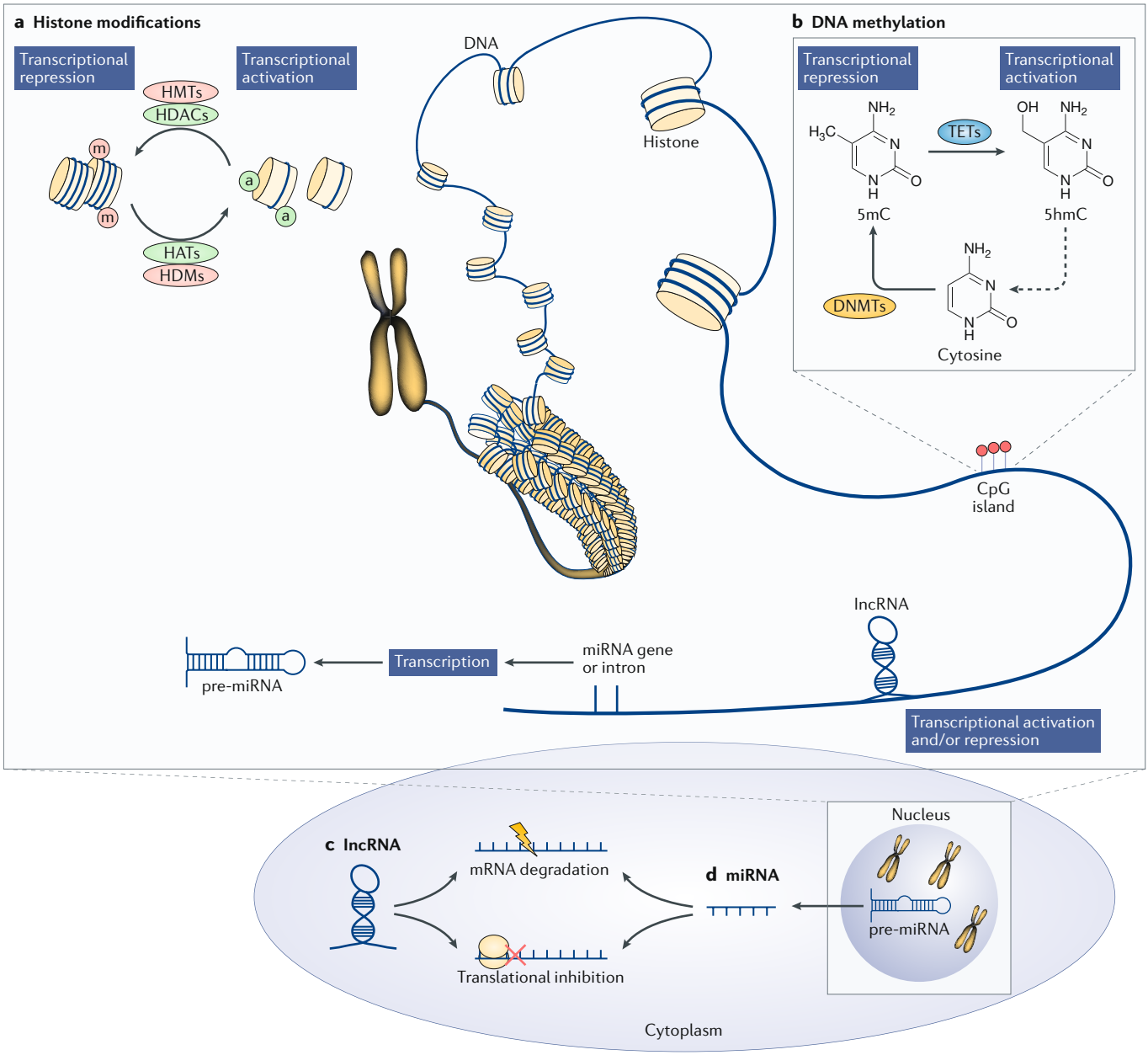


Fig. 1 | **Key epigenetic processes. a** | Histone acetyltransferases (HATs) mediate the transfer of acetyl groups to lysine residues on histone tails. Histone deacetylases (HDACs) counterbalance HAT activity by deacetylating histones (as well as non-histone proteins). Histone methyltransferases (HMTs) and histone demethylases (HDMs) catalyse the transfer and the removal, respectively, of methyl groups on lysine and arginine residues on histones. A specific example of how H3K27 methylation (H3K27me3) and acetylation (H3K27a) can influence transcriptional regulation is given in the figure. **b** | DNA methyltransferases (DNMTs) convert cytosine to 5-methylcytosine (5mC) and promote transcriptional repression; conversely, ten-eleven translocation methylcytosine dioxygenase (TET) proteins convert 5mC to 5-hydroxymethylcytosine (5hmC) and, after intermediate reactions, promote DNA demethylation. **c** | Long non-coding RNAs (lncRNAs) have a wide range of functions, including establishing transcriptional initiation or repression and controlling mRNA decay and protein translation. **d** | MicroRNAs (miRNAs) with near-perfect complementarity preferentially block protein synthesis by inhibiting translation, whereas miRNAs with perfect complementarity accelerate mRNA degradation. a, acetyl group; m, methyl group; pre-miRNA, precursor-miRNA.

Unsurprisingly, given that T cells are involved in the pathogenesis of SSc, several genes expressed by T cells have also been identified as being associated with susceptibility to SSc. For example, *CD247* encodes the T cell receptor CD3ζ subunit, which modulates antigen-dependent activation of T cells. The results of three GWASs have revealed an association between the *CD247* rs2056626 variant and susceptibility to SSc[36–38]; however, this association was not confirmed in a Han Chinese cohort of patients with SSc[39], highlighting the difficulties that arise from the heterogeneity of disease in patients with SSc and the influence of ethnicity. The

Table 1 | **Genes associated with systemic sclerosis**

Function	Gene	Allele or variant (location)	Disease association	Refs
Susceptibility to SSc				
MHC class II	*HLA-DR*	*DRB1*11:04*	SSc	27
		*DRB1*01:01*	Presence of ACAs	28
		*DRB1*10:01*	Presence of ACAs	28
		*DPB1*04:02*	Presence of ACAs	28
		*DRB1*15:02*	Presence of ATAs	28
		*DRB1*10*	Juvenile SSc	32
	HLA-DQ	*DQB1*05:01*	Presence of ACAs	28
		*DQB1*06:01*	Presence of ATAs	28
		*DQA1*05*	Juvenile SSc	32
	HLA-DP	*DPB1*03:01*	Presence of ATAs	28
		*DPB1*09:01*	Presence of ATAs	28
		*DPB1*03:01*	Pulmonary fibrosis	29
		*DPB1*04*	Presence of ACAs	29
Transcription factors involved in interferon signalling	*IRF4*	rs9328192 (intergenic)	SSc	35
	IRF5	rs2004640 (intronic)	SSc and pulmonary fibrosis in SSc	34,150–152
	IRF5–TNPO3	• rs4728142 (intergenic) • rs10488631 (intergenic) • rs12531711 (intronic)	SSc	52
	STAT4	rs7574865 (intronic)	SSc and pulmonary fibrosis in SSc	34,152
T helper 2 cell-associated cytokine	*IL12A*	rs77583790 (intronic)	SSc	24
IL-12 receptor subunit	*IL12RB1*	rs436857 (coding)	SSc	42
B cell-specific regulator of intracellular calcium storage	*BANK1*	rs10516487 (coding)	dcSSc and interstitial lung disease	58
Subunit of the telomerase enzyme	*TERT*	rs34094720 (coding)	dcSSc and interstitial lung disease	58
Ubiquitin-editing enzyme involved in TNF signalling	*TNFAIP3*	rs58905141 (intergenic)	Pro-fibrotic responses in fibroblasts	53
Protein involved in vesicular trafficking and autophagosome formation	*ATG5*	rs9373839 (intronic)	SSc	24
Protein that mediates DNA cleavage	*DNASE1L3*	rs35677470 (coding)	ACA-positive SSc	24,52
Cell adhesion and co-stimulatory molecule found on T cells and natural killer cells	*CD2*	rs624988 (intergenic)	ACA-positive SSc	50
ATPase with phospholipid-transporting functions	*ATP8B4*	rs55687265 (coding)	SSc	56
Extracellular matrix components	*COL4A3*	rs55816283 (coding)	dcSSc	58
	COL4A4	rs200450557 (intronic)	dcSSc and interstitial lung disease	58
	COL5A2	rs116298748 (coding)	dcSSc	58
	COL22A1	rs72727814 (coding)	dcSSc	58
	COL13A1	rs41277962 (coding)	dcSSc	58
	CTGF	G-945C (coding)	Pulmonary fibrosis in SSc	152
A kinase associated with IL-1 signalling	*IRAK1*	rs1059702 (coding)	Pulmonary fibrosis in SSc	152
Protection from SSc				
MHC class II	*HLA-DR*	*DRB1*13:02*	SSc	28
		*DRB1*14:06*	SSc	28
	HLA-DQ	*DQB1*03:01*	SSc	27,28
		*DQB1*03:01*	SSc	28
		DQ5-DR1	SSc progression	30
		*DPB1*02:01*	SSc	28

ACA, anti-centromere antibody; ATA, anti-telomere antibody; dcSSc, diffuse cutaneous SSc; SSc, systemic sclerosis.

concentration of IL-12, a cytokine involved in the regulation and differentiation of T cells towards a T helper 1 (T_H1) cell phenotype, is also increased in patients with SSc and might serve as a marker for disease activity[40]. The results of genetic association studies have revealed several IL-12-related loci to be associated with susceptibility to SSc, including the rs3790567 SNP in *IL12RB2* (REF.[41]) and the rs436857 SNP in the promoter region of *IL12RB1* (REF.[42]), emphasizing the suggested role of the IL-12 pathway in the pathogenesis of SSc. Moreover, *STAT4*, which encodes a transcription factor that is involved in IL-12 signalling, was identified and confirmed as an SSc risk factor in several studies[34,43,44].

Interestingly, most of the genetic variants identified in SSc overlap with those implicated in other autoimmune diseases, such as RA, SLE or Sjögren syndrome. For instance, associations with *STAT4* have been found in at least six other autoimmune diseases[45–48], and associations with *IRF5* have also been found in patients with SLE and patients with multiple sclerosis[48,49]. In 2016, *CD2* was identified as a novel risk factor for SSc in a European cohort[50], adding yet another genetic risk factor to the list of those shared between SSc and RA. Overall, these gene variants seem likely to be involved in processes that are linked to autoimmune diseases in general rather than just one particular disease.

Other genes that are associated with SSc are involved in extracellular matrix (ECM) deposition, apoptosis or autophagy (TABLE 1). The results of two meta-analyses[35,43] of GWASs revealed SNPs in *ATG5*, which encodes a protein involved in autophagosome elongation, to be associated with SSc. These findings were confirmed by analysis of Immunochip data[24], suggesting that the autophagy process is important in SSc. *DNASE1L3* encodes a protein in the deoxyribonuclease 1 family that mediates the breakdown of DNA during apoptosis[51]. The rs35677470 SNP in *DNASE1L3* was associated with ACA-positive patients with SSc in two Immunochip studies[24,52] and represents one of the most statistically significant non-HLA genetic associations reported in SSc. Notably, two 2016 studies have highlighted interactions between genes and environmental factors in SSc[53,54]. A strong association has been found between the previously identified rs58905141 SNP in *TNFAIP3*, a gene encoding a ubiquitin-editing enzyme involved in TNF-mediated immune responses, and silica-induced pro-fibrotic responses in fibroblasts[53], and exposure to certain solvents seems to be a risk factor for the development of SSc, particularly in men[54].

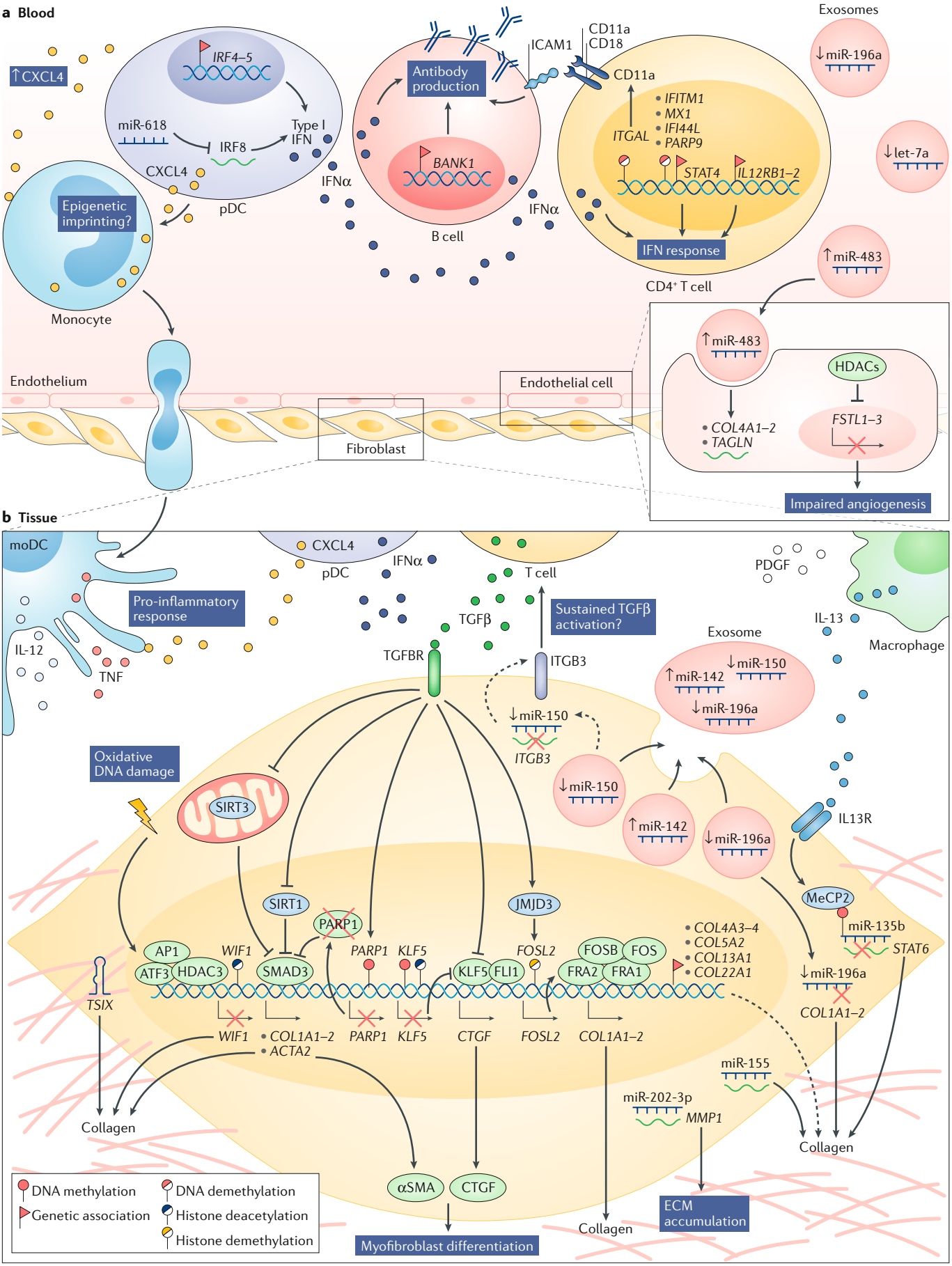
Although analysis of GWAS and Immunochip data has provided crucial information that has helped to shape our understanding of SSc pathogenesis, the authors of these studies focused only on common variants. By contrast, next-generation sequencing techniques have enabled whole-genome sequencing, as well as regional genomic sequencing, such as whole-exome sequencing (WES) of gene coding regions. WES offers a quick and cost-effective platform to identify rare coding variants[55]. In the first WES study of SSc, the authors identified variants of *ATP8B4*, a gene encoding an ATPase enzyme involved in the translocation of phospholipids in the cell membrane, as a novel genetic risk factor for the disease[56], although this association was not confirmed in a follow-up study[57]. In another WES study, the authors identified 68 new genes associated with SSc[58]. Consistent with the results of previous GWASs[59], the results of this study[58] confirmed a variant of *BANK1*, a gene encoding a B cell-specific scaffold protein involved in calcium storage, as a candidate risk factor for dcSSc, as well as variants in other genes previously implicated in SSc pathogenesis, such as *IRF5*. In addition, newly identified genetic variants associated with SSc were located in the ECM-related pathway, which is crucial for the fibrotic characteristics of dcSSc[58]. Although WES is the most popular method to detect rare coding variants in autoimmune diseases, the decreasing costs of whole-genome sequencing will enable the sequencing of both the non-coding and coding regions of the genome in the future. Moreover, next-generation sequencing techniques could also be used to improve the diagnosis of rare autoimmune diseases by providing clinicians with more accurate genetic information.

Epigenetic modifications in SSc

As previously mentioned, rapid progress has been made in outlining the genomic landscape of SSc. Continued refinement of this developing map and integration with GWAS and transcriptomic data will be an essential component of a systems medicine approach to the personalized treatment of patients with SSc. However, genetic predisposition only partially explains disease onset in SSc, suggesting that epigenetic processes (BOX 1; FIG. 1) could be involved in the pathogenesis of SSc. The literature suggests that immune cells from patients with SSc retain a pro-inflammatory phenotype that persists for days after being taken out of their original environment[60,61]. In particular CXC-chemokine ligand 4 (CXCL4), an important chemokine in SSc pathogenesis[60,62], could be essential for the aberrant imprinting of immune cells at an epigenetic level[63], thereby potentially triggering the pro-inflammatory and pro-fibrotic responses required for disease manifestations. However, the cell-specific expression patterns of proteins that regulate epigenetic processes in patients with SSc at distinct stages of the disease are not fully understood. In this section, we discuss insights gained over the past 4 years into epigenetic modifications associated with the pathophysiology of SSc.

DNA methylation

Fibroblasts. Over the past few years, two studies have confirmed that an altered global hypomethylation state contributes to the pathological phenotype of fibroblasts from patients with SSc[64,65]. The results of a large-scale DNA methylation analysis revealed 916 CpG sites in dermal fibroblasts from patients with lcSSc and 1,653 CpG sites in fibroblasts from patients with dcSSc that were hypomethylated compared with sites in fibroblasts from healthy individuals, as well as a marked increase in differentially methylated genes in fibroblasts from patients with dcSSc[64]. Interestingly, although some of the genes associated with SSc pathology, such as *COL23A1*, *COL4A2*, *RUNX2*, *RUNX3*, *ITGA9* and *ADAM12*, were commonly hypomethylated in both lcSSc and dcSSc fibroblasts, only 6% of the differentially methylated


a Blood
↑CXCL4
IRF4–5
miR-618
IRF8
Type I IFN
CXCL4
pDC
Epigenetic imprinting?
Monocyte
IFNα
Antibody production
BANK1
B cell
ICAM1
CD11a
CD18
CD11a
ITGAL
• IFITM1
• MX1
• IFI44L
• PARP9
STAT4
IL12RB1–2
IFN response
CD4⁺ T cell
Exosomes
↓miR-196a
↓let-7a
↑miR-483
↑miR-483
HDACs
• COL4A1–2
• TAGLN
FSTL1–3
Impaired angiogenesis
Endothelium
Fibroblast
Endothelial cell
b Tissue
moDC
CXCL4
pDC
IFNα
T cell
PDGF
Macrophage
IL-13
Pro-inflammatory response
IL-12
TNF
TGFβ
TGFBR
Sustained TGFβ activation?
ITGB3
Exosome
↑miR-142
↓miR-150
↓miR-196a
↓miR-150
ITGB3
↓miR-150
↑miR-142
↓miR-196a
IL13R
Oxidative DNA damage
SIRT3
SIRT1
PARP1
JMJD3
AP1
ATF3
HDAC3
WIF1
SMAD3
PARP1
KLF5
KLF5
FLI1
FOSL2
FOSB
FOS
FRA2
FRA1
• COL4A3–4
• COL5A2
• COL13A1
• COL22A1
MeCP2
miR-135b
STAT6
↓miR-196a
COL1A1–2
TSIX
WIF1
• COL1A1–2
• ACTA2
PARP1
KLF5
CTGF
FOSL2
COL1A1–2
Collagen
miR-155
miR-202-3p
MMP1
Collagen
αSMA
CTGF
Collagen
ECM accumulation
Myofibroblast differentiation
DNA methylation
Genetic association
DNA demethylation
Histone deacetylation
Histone demethylation

◀ Fig. 2 | **Genetic and epigenetic influences on the pathogenesis of systemic sclerosis.** The figure highlights the genetic and epigenetic findings in systemic sclerosis (SSc) made over the past 4 years. Selected examples are described. **a** | In the blood, circulating immune cells and microRNA (miRNA)-containing extracellular vesicles contribute to the pro-inflammatory and autoimmune responses that are the hallmarks of SSc. In plasmacytoid dendritic cells (pDCs), a type I interferon (IFN) signature is potentially sustained by both genetic and epigenetic alterations that regulate interferon regulatory factor (IRF) proteins. Together, these alterations promote IFNα secretion, which in turn activates multiple immune cell subsets. High concentrations of CXC-chemokine ligand 4 (CXCL4) in the circulation, in part produced by pDCs, could possibly function as an imprinting factor during the differentiation of monocytes into monocyte-derived dendritic cells (moDCs) and further increase the inflammatory responses of the latter. In T cells, both the hypomethylation of DNA at IFN genes and the genetic risk associated with the signal transducer and activator of transcription 4 (STAT4)–IL-12 pathway could increase type I and type II IFN responses. T cells from patients with SSc are epigenetically imprinted to have increased amounts of CD11a at the cell surface. Interaction of CD11a with intercellular adhesion molecule 1 (ICAM1) on B cells could be involved in sustaining autoantibody production. Circulating miRNAs in extracellular vesicles, such as miR-483, can regulate pro-fibrotic and anti-fibrotic responses in endothelial cells. **b** | In fibroblasts from patients with SSc or fibroblasts exposed to transforming growth factor-β (TGFβ), the diminished activity of sirtuins (SIRTs)1–3 and the epigenetic-mediated repression of *PARP1* sustain the transcription factor SMAD3 signalling pathway and collagen and α-smooth muscle actin (αSMA) synthesis. Together with the decreased activity of the KLF5–FLI1 transcription factor complex at the *CTGF* promoter region, these alterations initiate myofibroblast differentiation processes. Additional epigenetic changes in the *FOSL2* promoter region, genetic variants in collagen genes and aberrant miR-202-3p, miR-155 and miR-135b regulation further contribute to collagen release and altered extracellular matrix (ECM) deposition processes. Oxidative DNA damage leads to the recruitment of the transcription factors AP1, ATF3 and histone deacetylase 3 (HDAC3) to the *WIF1* promoter region, favouring Wnt signalling and collagen production. Additionally, downregulation of miR-150 in fibroblasts from patients with SSc could lead to sustained integrin expression, which could, in turn, also amplify TGFβ signalling. CTGF, connective tissue growth factor; IL13R, IL-13 receptor; ITGB3, β3 integrin; JMJD3, jumonji domain-containing protein 3; MeCP2, methyl-CpG-binding protein 2; PARP1, poly(ADP-ribose) polymerase 1; PDGF, platelet-derived growth factor; TGFBR, TGFβ receptor; TSIX, XIST antisense RNA.

genes were shared between the two SSc subgroups. Various collagen and catenin family genes were remarkably hypomethylated in fibroblasts from patients with dcSSc compared with those from patients with lcSSc (Supplementary Table 1). Additionally, distinct integrin genes were hypomethylated in fibroblasts from patients with dcSSc[64], which could potentially contribute to the sustained activation of transforming growth factor-β (TGFβ) that occurs in these patients[66,67]. No differences in the methylation pattern of *FLI1*, *DKK1* and *SFRP1*, genes previously described as being hypermethylated in patients with SSc and negatively regulating fibrotic processes[68], were detected in fibroblasts from either of the two SSc subsets[64]. However, genes encoding downstream targets of DKK1 and SFRP1 in the Wnt signalling pathway, such as *CTNNB1* and *AXIN2*, were hypomethylated in fibroblasts from patients with dcSSc[64]. In another study[69], altered DNA methylation and histone acetylation at *KLF5*, which encodes a transcription factor that works synergistically with the transcription factor FLI1 to modulate fibrotic processes, contributed to impaired KLF5–FLI1 activity in fibroblasts from patients with SSc. Taken together, these results support the idea that heterogeneous, yet overlapping, epigenetic mechanisms could be behind the altered phenotype of fibroblasts in SSc (FIG. 2b).

The results of a 2018 study[70] showed that hypermethylation of *PARP1*, which encodes the negative regulator of fibroblast activation poly(ADP-ribose) polymerase 1 (PARP1), occurred in fibroblasts and keratinocytes from patients with SSc. In this study[70], the suppressed expression of PARP1 that occurs in fibroblasts from patients with SSc was mimicked in vitro by the long-term exposure of fibroblasts to TGFβ, which acted as an imprinting factor, thereby causing increased DNA methylation in the *PARP1* promoter region. As reduced expression of PARP1 was slightly more pronounced in fibroblasts from patients with dcSSc than in those from patients with lcSSc, it is plausible that increased TGFβ signalling (or increased exposure to TGFβ), could be one of the driving forces behind the different methylation patterns observed in the two disease subgroups[66,67].

Although altered DNA methylation was previously associated with reduced DNA (cytosine-5)-methyltransferase 1 (DNMT1) expression in both fibroblasts and T cells[71,72], new evidence also suggests a role for ten-eleven translocation methylcytosine dioxygenase (TET) enzymes, which convert 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) and catalyse the initial step of DNA demethylation (FIG. 1b). In-depth evaluation of 5mC and 5hmC activity in SSc is still lacking, as a complete understanding of DNA demethylation processes will be made possible only by novel technologies that enable the sensitive quantification of these marks[73]. Nevertheless, total 5hmC was shown to be increased in skin from patients with SSc[65]. In line with this finding, *TET1* mRNA was increased in fibroblasts from patients with SSc and was modestly regulated by hypoxic conditions[65]. Notably, TET1 was also consistently upregulated in the lungs of bleomycin-treated mice and has been proposed to be a primary target for therapy targeting epigenetic processes in idiopathic pulmonary fibrosis (IPF)[74]. By contrast, TET1 was not differentially expressed in dermal fibroblasts from patients with SSc compared with those from healthy individuals; however, a prominent upregulation of the DNA methylation binding protein methyl-CpG-binding protein 2 (MeCP2) was noted in fibroblasts from patients with SSc[75]. MeCP2 was also upregulated in the dermal fibroblasts of patients with dcSSc in a separate study[76] and is thought to be a key regulator of fibrotic events.

In lung fibroblasts from patients with SSc or IPF, defects in the prostaglandin G/H synthase 2 (PTGS2)–prostaglandin E_2 pathway, an important negative modulator of the fibrotic responses in vivo[77], were caused by alterations in DNA methylation processes[78]. Reduced expression of transcriptional and immune response regulator (TC1), a positive regulator of PTGS2 expression[79], was specifically dependent upon methylation in these cells, as treatment with DNMT inhibitors but not with histone deacetylase (HDAC) inhibitors restored TC1 expression to physiological levels[78].

Immune cells. Similar to dermal fibroblasts, general hypomethylation has been found in the whole blood and in the T cells of patients with SSc[80,81]. In a genome-wide DNA methylation study[81], a total of 696 and 2,283 unique sites in $CD4^+$ and $CD8^+$ T cells, respectively, were differentially methylated in patients with SSc compared with healthy individuals. Three-hundred and thirty sites were differentially methylated in both

Box 1 | **Epigenetic modifications**

In eukaryotes, DNA is located within the nucleus and is highly compacted into chromatin, a complex of DNA and proteins that forms chromosomes. Unwinding the chromatin reveals sites at which a variety of epigenetic changes influence gene transcription without altering the DNA sequence. Chromatin condensation and relaxation, associated with transcriptional silencing and initiation, respectively, are regulated by the activity of histone-modifying enzymes. The most common histone modifications are methylation and acetylation (FIG. 1a). Access to the DNA by the transcriptional machinery is influenced by the addition of methyl groups at sites with high amounts of cytosine and guanine, known as CpG islands. Although predominantly occurring in gene promoter regions, DNA methylation exists in diverse genomic contexts, including in regulatory elements and gene bodies, and is catalysed by DNA methyltransferases (FIG. 1b). Additional layers of epigenetic control are mediated by RNA molecules. Long non-coding RNAs are transcribed RNA molecules with a length of ~200 nucleotides that have a wide range of functions (FIG. 1c), whereas microRNAs are short RNAs of 20–25 nucleotides that bind to complementary sequences in target mRNAs and control post-transcriptional events (FIG. 1d).

cell types, which remarkably showed the same patterns of either hypomethylation or hypermethylation. Independently of the subtype of T cell analysed, hypomethylation was predominantly found in type I interferon-related genes, such as *IFI44L*, *IFITM1*, *MX1*, *PARP9* and *EIF2AK2* (REF.[81]).

Hypomethylation of the promoter region of *ITGAL* (which encodes CD11a, a cell-surface molecule involved in T cell co-stimulation[82]) was also detected in $CD4^+$ T cells from patients with SSc and inversely correlated with patient disease activity scores[83]. Reduced methylation of *ITGAL* and the association between DNA methylation and a type I interferon signature have similarly been described as common hallmarks of $CD4^+$ T cells from patients with SLE[84,85]. The results of DNA methylation analysis of whole blood from patients with SSc or SLE reinforced results that had been previously gained from isolated $CD4^+$ T cells. In this study[80], *FOXP3* was hypermethylated and *TNFSF7* (encoding CD70) was hypomethylated in both diseases compared with healthy individuals. Similarly, single-target screening of *IRF7*, a type I interferon transcription factor associated with the production of autoantibodies in SSc[86], revealed hypomethylation in peripheral blood mononuclear cells from patients with SSc, results that support the increased expression of *IRF7* in both lcSSc and dcSSc[87]. Conflicting results have arisen with respect to *FOXP3*, which has been shown to be hypermethylated and downregulated in $CD4^+$ T cells from patients with SSc[88] yet to be hypomethylated in total peripheral blood mononuclear cells in a different study[89]. Although this second study[89] demonstrates global alterations in regulatory and inflammatory T cell subsets in patients with SSc, it also highlights the limitations of examining epigenetic changes using mixed cell populations rather than isolated cell subsets.

Taken together, the results of different studies aiming to map differential DNA methylation in SSc indicate that alterations in canonical pathways regulating fibrosis and immune cell activation can be imprinted at the DNA methylation level (FIG. 2; Supplementary Table 1). Furthermore, as the methylation signatures in dcSSc and lcSSc are only partly overlapping, it is possible that epigenetic divergences are at the root of these two disease subgroups.

Histone post-translational modifications

Aberrant gene expression as a result of histone post-translational modifications is known to be involved in the pathogenesis of SSc[13] (Supplementary Table 2). Histone acetylation and methylation (FIG. 1a) are currently the most commonly described epigenetic modifications in the field of SSc research; therefore, elucidating the role of histone-modifying enzymes in this disease could provide insights into novel therapeutic strategies. For example, the expression of the histone deacetylase genes *HDAC4* and *HDAC5* are increased in endothelial cells from patients with SSc compared with those from healthy individuals, whereas *HDAC6* expression is decreased[90]. Many genes that are regulated by the action of HDAC5 are involved in angiogenesis[90], suggesting that the overexpression of *HDAC5* contributes to disrupted angiogenic processes in SSc.

Histone acetylation. Histone acetylation is associated with a more open chromatin structure, enabling the binding of the transcriptional machinery and thereby promoting gene transcription. The potential effect of chromatin deacetylation in SSc was highlighted by a study in which the expression of *KLF5* was decreased in fibroblasts from patients with SSc compared with fibroblasts from healthy individuals[69]. The degree of histone 3 (H3) and H4 acetylation at the promoter of this gene was lower in the fibroblasts from patients with SSc than in the healthy control fibroblasts, and treatment with HDAC inhibitors or DNMT inhibitors recovered *KLF5* expression[69]. Similar epigenetic repression was observed for *FLI1* (REF.[69]), validating the results of a previous study[91]. The combined downregulation of these two transcription factors is thought to be important in the pathogenesis of SSc, as mice with double heterozygous deficiency of KLF5 and FLI1 produced autoantibodies and developed spontaneous skin and lung fibrosis[69]. KLF5 and FLI1 synergistically repressed the expression of connective tissue growth factor (CTGF), which is a known regulator of tissue remodelling and fibrosis. These findings suggest that the epigenetic repression of *KLF5* and *FLI1* in fibroblasts from patients with SSc is likely to underlie the increased *CTGF* expression observed in these cells[69].

The sirtuins (class III HDACs involved in cell survival and inflammation) SIRT1, SIRT3 and SIRT7 are regulators of SMAD transcription factor–TGFβ signalling in fibroblasts and have been implicated in the pathogenesis of SSc[92–97]. The expression of these sirtuins is generally decreased in dermal and pulmonary fibroblasts from patients with SSc. In two studies[93,94], the decrease in SIRT1 correlated inversely with the modified Rodnan skin score (mRSS), a measure of disease activity. The results of another study[92] suggested that the decrease in SIRT1 was greater in patients with dcSSc and patients with pulmonary fibrosis than in patients with lcSSc and patients who did not have pulmonary fibrosis, respectively. Activation of SIRT1 with either resveratrol or the more specific activators SA3 and SRT1720 led to a less fibrotic and inflammatory phenotype in both cultured fibroblasts and in the bleomycin-induced mouse model of SSc[92,94,98]. Similarly, in vitro activation of SIRT3 with hexafluoro in fibroblasts inhibited the activation of

SMAD2, SMAD3 and STAT3 upon TGFβ stimulation, and mice treated with hexafluoro showed attenuation of bleomycin-induced fibrosis in the lung and skin[97].

Histone methylation. Histone methylation can result in either increased or suppressed transcription of nearby genes. Global levels of H3K27me3, a known repressive mark, were lower in $CD4^+$ T cells from patients with SSc than in $CD4^+$ T cells from healthy individuals[99]. This decrease in expression inversely correlated with an increase in expression of *JMJD3* (also known as *KDM6B*), which encodes the histone demethylase jumonji domain-containing protein 3 (JMJD3), whereas the expression of genes encoding other histone demethylases, such as *UTX* (also known as *KDM6A*) and *EZH2*, was unchanged[99]. This same pattern of increased expression of *JMJD3* and unchanged expression of *UTX* was also found in fibroblasts from patients with SSc (compared with fibroblasts from healthy individuals), although the number of H3K27me3-positive fibroblasts in the skin of patients with SSc compared with in healthy skin was increased rather than decreased[100]. Increased concentrations of JMJD3 caused reduced H3K27me3 at the promoter of *FOSL2*, which encodes the transcription factor FRA2 thought to be involved in regulating ECM production, the expression of which is increased in fibroblasts from patients with SSc[100]. Stimulation of fibroblasts from healthy individuals with TGFβ caused the upregulation of *JMJD3* expression in a SMAD3-dependent manner and a general decrease of H3K27me3 (REF.[95]). Treating rat fibroblasts with TGFβ also led to an accumulation of the activating histone mark H3K4me3 at the promoters of *COL1A1*, *COL1A2* and *ACTA2*, genes encoding the ECM components collagen I and II and α-smooth muscle actin (αSMA)[101]. Altogether, these results show that TGFβ–SMAD signalling pathways, which are implicated in the pathogenic ECM production that occurs in SSc (FIG. 2b), are closely linked to targetable epigenetic histone-modifying enzymes.

Non-coding RNAs

MicroRNAs in immune cells and fibroblasts. To date, a limited number of studies have investigated microRNA (miRNA) expression changes in immune cells from patients with SSc[102,103] (TABLE 2). For example, the role of miRNAs in plasmacytoid dendritic cells (pDCs) from patients with SSc was addressed for the first time in a 2017 study[102]. The results of this study suggested that increased levels of miR-618 in pDCs lead to decreased expression of IRF8 in patients with SSc. Overexpression of miR-618 inhibited pDC differentiation and activation and led to increased IFNα release upon Toll-like receptor 9 (TLR9) stimulation[102]. The function of miRNAs in the development of fibrosis, however, has been addressed in greater detail. The previously identified anti-fibrotic miRNA miR-29a[13] has now also been shown to reduce the expression of TGFβ-activated kinase 1 binding protein 1 (TAB1), a protein involved in the downregulation of tissue inhibitor metalloproteinase 1 (TIMP1) expression and collagen degradation[104]. In addition to its anti-fibrotic properties, miR-29a is thought to modulate apoptosis[105]. Fibroblasts from patients with SSc that overexpressed miR-29a had reduced amounts of the anti-apoptotic proteins BCL-2 and BCL-X_L and were susceptible to cell death[105]. Inhibition of the pro-fibrotic miRNA miR-21, which is upregulated in SSc[13], also increased apoptosis in fibroblasts from patients with SSc[106]. These results[106] confirm miR-29a and miR-21 as candidate molecules for use or targeting to reduce fibrosis.

Upregulation of miR-202-3p in the skin of patients with SSc contributed to the suppression of matrix metalloproteinase 1 (MMP1), a protein known to be decreased in the skin of these patients[107]. Specifically, miR-202-3p was shown to bind to the 3′ untranslated region of MMP1 mRNA and to repress its expression. Expression of miR-202-3p could be induced in a time-dependent and dose-dependent manner by TGFβ stimulation[107], suggesting a role for this pro-fibrotic cytokine in the regulation of miR-202-3p expression. Yet another miRNA that is present at increased frequencies in the skin and lungs of patients with SSc[108,109], as well as in mice with bleomycin-induced skin fibrosis[108], is miR-155. In a 2017 study[110], miR-155 was shown to be a positive regulator of NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome-mediated collagen synthesis in fibroblasts, a pathway that had been previously implicated in fibrosis in SSc[111]. Collagen production in fibroblasts from patients with SSc was further shown to be induced by the activation of STAT6-dependent IL-13 signalling and the concomitant suppression of miR135b expression[75]. Concentrations of this miRNA were also reduced in the serum and monocytes of patients with SSc[75]. The authors of this study[75] proposed that the expression of miR-135b could be regulated by methylation events in dermal fibroblasts. Furthermore, decreased concentrations of miR-193b were present in fibroblasts and skin from patients with SSc[112]. This decrease in miR-193b promoted the expression of urokinase-type plasminogen activator (uPA), a protein that induced the proliferation of vascular smooth muscle cells and inhibited apoptosis[112], suggesting that miR-193b might contribute to proliferative vasculopathy in SSc.

Circulating microRNAs. Circulating miRNAs could potentially serve as clinical biomarkers in patients with SSc. In fact, the direct measurement of miRNA concentrations in body fluids such as serum or plasma is already proving to be a useful tool to monitor disease manifestations and progression[113]. Building on the work of previous publications[13], researchers are now evaluating a broad range of circulating miRNAs in SSc. A 2015 study, in which the expression of 45 circulating miRNAs was examined in plasma from patients with SSc, identified a network of 21 miRNAs that could discriminate patients with SSc from healthy individuals and patients with SLE[114]. The miRNA profile that could discriminate between healthy individuals and patients with SSc was characterized by miRNAs from the miR-17~92 cluster and by miR-16, miR-223 and miR-638[114]. In a separate study, the plasma miRNA profile of patients with SSc was correlated with disease phenotypes; miR-223, miR-181b, miR-342-3p and miR-184 were differentially expressed between patients with lcSSc and those with dcSSc, and the expression of miR-409-3p, miR-184, miR-92a, miR-29a

MicroRNA
A short non-coding RNA of 18–24 nucleotides in length that regulates gene expression by binding to its complementary sequence within a target mRNA.

Table 2 | **Non-coding RNAs in systemic sclerosis**

Non-coding RNA	Expression level in SSc	Tissue or cell type	Target mRNA	Implication	Refs
miRNA					
miR-618	↑	pDCs	IRF8	Overexpressed miR-618 reduced pDC development and enhanced IFNα release upon TLR9 stimulation	102
miR-193b	↓	Skin tissue and dermal fibroblasts	uPA	miR-193b induced proliferative vasculopathy in human pulmonary artery smooth muscle cells	112
miR-202-3p	↑	Skin tissue and dermal fibroblasts	MMP1	miR-202-3p induced pro-fibrotic effects by targeting MMP1	107
miR-155	↑	Dermal and lung fibroblasts	ND	miR-155 is induced by inflammasome activation and regulated inflammasome-driven collagen production	110
miR-155	↑	Human skin tissue and skin tissue from bleomycin-treated mice	CK1α and SHIP1	miR-155 regulated Wnt–β-catenin and AKT signalling pathways by targeting CK1α and SHIP1 in a mouse model of SSc	108
miR-155 and miR-182	↑	Lung tissue	ND	• miR-155 levels correlated with progressive SSc ILD • miR-155-knockout mice with bleomycin-induced disease had reduced lung fibrosis and reduced arginase 1 and TIMP1 production compared with wild-type mice	109
miR-130b	↑	Human skin tissue and dermal fibroblasts; skin tissue from bleomycin-treated mice	PPARγ	miR-130b induced pro-fibrotic effect via regulation of PPARγ expression	153
miR-483-5p	↑	Serum and serum exosomes	Fibrosis-related genes	miR-483-5p overexpression in fibroblasts and endothelial cells dysregulated the expression of fibrosis-related genes, such as those for type I and type IV collagen	116
miR-4458 and miR-18a	↑, ↓	Dermal fibroblasts	Type I collagen and CTGF	IL-23 and TGFβ signalling mediated the upregulation of miR-4458 and the downregulation of miR-18a expression. In turn, miR-4458 and miR-18a regulated type I collagen and CTGF expression, respectively	154
miR-135b	↓	Human dermal fibroblasts, serum and monocytes; skin tissue from bleomycin-treated mice	STAT6	miR-135b regulated IL-13-mediated collagen production via STAT6 signalling	75
miR-638, miR-181b, miR-29b-3p, miR-590-5p and miR-150	↑	Plasma	ND	Circulating plasma miRNA profiles discriminated patients with SSc from healthy individuals	114
miR-106a, miR-16, miR-223, miR-92a, miR-17, miR-20a, miR-146a, miR-146b, miR-192-5p, miR-24, miR-221, miR-142-3p and miR-342-3p	↓	Plasma	ND	Circulating plasma miRNA profiles discriminated patients with SSc from healthy individuals	114
miR-181b and miR-184	↑	Plasma	ND	Circulating miRNA profile discriminated patients with lcSSc from those with dcSSc	115
miR-223 and miR-342-3p	↓	Plasma	ND	Circulating miRNA profile discriminated patients with lcSSc from those with dcSSc	115
let7g-5p, miR17-5p, miR-21-5p, miR-23b-5p, mir29a-3p, miR-150-5p, miR-155-5p, miR-215-5p and miR-503-5p	↑	Serum exosomes	ND	Distinct pro-fibrotic and anti-fibrotic miRNAs contained in exosomes from patients with SSc compared with exosomes from healthy individuals	118
let7a-5p, miR-92a-3p, miR-125b-5p, miR-133a-3p, miR-140-5p, miR-145-5p, miR-146a-5p, miR-196a-5p, miR-200a-3p, miR-200b-3p and miR-223-3p	↓	Serum exosomes	ND	Distinct pro-fibrotic and anti-fibrotic miRNAs contained in exosomes from patients with SSc compared with exosomes from healthy individuals	118

Table 2 (cont.) | **Non-coding RNAs in systemic sclerosis**

Non-coding RNA	Expression level in SSc	Tissue or cell type	Target mRNA	Implication	Refs
miRNA (cont.)					
miR-142-3p	↑	Dermal fibroblast exosomes	ND	SSc fibroblasts released increased amounts of exosomes, compared with fibroblasts from healthy individuals, that stimulated type I collagen expression	117
miR-150 and miR-196a	↓	Dermal fibroblast exosomes	ND	SSc fibroblasts released increased amounts of exosomes, compared with fibroblasts from healthy individuals, that stimulated type I collagen expression	117
miR-5196	↑	Monocytes and serum	FRA2	miR-5196 mimic caused inhibition of FRA2 and TIMP1 production in monocytes upon DZNep and TLR8 stimulation	103
lncRNA					
CTBP1-AS2 and *AGAP2-AS1*	↑	Skin tissue	ND	Differentially expressed lncRNAs in SSc skin	119
OTUD6B-AS1	↓	Skin tissue	ND	Differentially expressed lncRNAs in SSc skin	119
TSIX	↑	Skin tissue, dermal fibroblasts and serum	Type I collagen	*TSIX* regulates type I collagen expression	120

CK1α, casein kinase 1α; CTGF, connective tissue growth factor; dcSSc, diffuse cutaneous SSc; ILD, interstitial lung disease; IRF8, interferon regulatory factor 8; lcSSc, limited cutaneous SSc; lncRNA, long non-coding RNA; miRNA, microRNA; MMP, matrix metalloproteinase; ND, not defined; pDC, plasmacytoid dendritic cells; SHIP1, SH2 domain-containing inositol phosphatase 1; SSc, systemic sclerosis; STAT6, signal transducer and activator of transcription 6; TGFβ, transforming growth factor-β; TIMP1, tissue inhibitor metalloproteinase 1; TLR, Toll-like receptor; uPA, urokinase-type plasminogen activator.

and miR-101 correlated with an SSc autoantibody signature[115]. Moreover, the results of a comprehensive screening of 758 circulating miRNAs revealed 30 miRNAs that are altered in the serum of patients with SSc compared with that of healthy individuals[116]. The results of this study[116] also demonstrated the consistent upregulation of miR-483-5p from the earliest stages of SSc.

A growing body of evidence has revealed an important role for extracellular vesicles, including exosomes, and their miRNA content in SSc. The amount of exosomes is decreased in the serum of patients with SSc compared with healthy individuals[117], and these exosomes contain distinct pro-fibrotic and anti-fibrotic miRNAs[118]. Interestingly, exosomes from patients with SSc induced a pro-fibrotic phenotype in healthy fibroblasts in vitro[118], suggesting that exosomes might mediate the cellular crosstalk that is necessary to initiate pro-fibrotic events. In line with these findings[118], circulating miR-483-5p, which is upregulated in patients with SSc, was also enclosed in serum exosomes, and overexpression of miR-483-5p in healthy fibroblasts and endothelial cells altered fibrosis-related gene expression[116]. Taken together, these studies[118] indicate that miRNAs present in exosomes might contribute to the pathogenesis of SSc (FIG. 2).

Long non-coding RNAs. The role of long non-coding RNA (lncRNA) in SSc is still poorly understood. RNA sequencing of skin tissue from patients with SSc revealed 676 lncRNAs that were differentially expressed between patients and healthy individuals[119]. A substantial fraction of the lncRNAs identified were antisense lncRNAs, which might function as co-regulators of their coding sense genes. Three antisense lncRNAs, *CTBP1-AS2*, *OTUD6B-AS1* and *AGAP2-AS1*, were further validated and their expression correlated strongly with the expression of their paired sense genes[119]. Another study showed that the lncRNA *TSIX* was upregulated in dermal fibroblasts from patients with SSc and was involved in the regulation of type I collagen production via mRNA stabilization[120]. Furthermore, concentrations of *TSIX* were increased in the serum of patients with SSc, leading the authors to propose *TSIX* as a potential disease biomarker[120]. These initial studies highlight the need for the further investigation of lncRNAs in SSc (TABLE 2).

Long non-coding RNA
A long non-coding RNA ~200 nucleotides in length that functions as a molecular scaffold to regulate gene expression at the transcriptional, post-transcriptional and epigenetic levels.

Targeting epigenetic processes

Although the results of many studies have indicated that a number of epigenetic regulatory proteins have altered expression in SSc, a more comprehensive approach is needed to fully take advantage of and guide the development of epigenomic pharmacological inhibitors and agonists. Of particular importance are studies aimed at understanding how the epigenetic code is either aberrantly written or read at the molecular level in SSc, which are currently lagging behind those in other rheumatic diseases such as RA[121]. An overview of epigenetic compounds that have been investigated in the context of SSc and in experimental models of fibrosis is included in TABLE 3. In the following section, the discussion is divided by therapeutic target.

DNA methylation

Two DNMT inhibitors that share similar mechanisms of action, 5-azacytidine and 5-aza-2′-deoxycytidine (collectively referred to as 5-aza) are, to date, the most commonly used compounds for investigations into the therapeutic targeting of DNA methylation in fibrosis.

Treatment with 5-aza is known to have a beneficial effect on dermal fibroblasts derived from patients with

SSc[68,122]. In particular, treatment of these cells with 5-aza upregulated the expression of both KLF5, a transcription factor known to modulate fibrotic responses[69], and PARP1, an enzyme involved in the regulation of SMAD-mediated transcription[70], and suppressed the expression of collagen genes[75]. In pulmonary fibroblasts from patients with SSc, 5-aza treatment restored PTGS2 and prostaglandin E_2 production, and in TGFβ-stimulated pulmonary fibroblasts from mice, it attenuated *COL1A1* and *ACTA2* expression[78].

The outcomes of the studies addressing the effects of 5-aza treatment on T cells are less conclusive than those in studies on fibroblasts with regard to the potential therapeutic benefit of this compound. In fact, although previously shown to reduce *FOXP3* methylation and to increase the frequency of regulatory T cells among $CD4^+$ T cells in patients with SSc[88], treatment with 5-aza was subsequently shown to cause the hypomethylation of *ITGAL* and thereby induce *ITGAL* expression in $CD4^+$ T cells from healthy individuals, causing a pro-fibrotic phenotype in fibroblasts and immune responses in T cells and B cells in co-culture experiments[83]. Similarly, exposure of $CD4^+$ T cells from healthy individuals to 5-aza increased the percentage of $CD3^+CD4^+CD28^+CD11a^{hi}KIR^+$ T cells, a subset that is increased in patients with dcSSc, active SLE or active RA[123].

5-Aza-mediated triggering of autoreactive processes in the T cells of healthy individuals has been well documented[124]; however, firm conclusions as to the potential disadvantages of the use of 5-aza in SSc are limited as only a few studies have utilized T cells from patients with SSc[83,123]. Most studies have utilized single-cell subsets, but the use of 5-aza in systems that might more closely reflect the complexity of SSc, such as organoids, tissue explants from patients or animal models of fibrosis, would be preferable. For example, in vivo, intraperitoneal injections of 5-aza resulted in reduced skin fibrosis in bleomycin-treated mice[68].

Histone post-translational modification

Therapies aimed at epigenetic processes that attempt to confer balance to dysregulated histone modifications are currently under investigation. For example, the HDAC inhibitor trichostatin A (TSA) restored the expression of Wnt inhibitory factor 1 (WIF1), an inhibitory regulator of Wnt signalling that is suppressed in fibroblasts from patients with SSc[125]. In vivo, TSA reduced disease in a bleomycin-induced mouse model of skin fibrosis by suppressing β-catenin, type I collagen and αSMA expression[125], results that were in line with previous findings[126]. However, in a bleomycin-induced pulmonary fibrosis model, the anti-fibrotic properties of TSA were limited[127]. Although the expression of *Sftpc*, which is necessary for correct alveolar function, and the epithelial marker *Cdh1* were clearly increased, no reduction in expression of the mesenchymal gene *VIM* was observed and epithelial-to-mesenchymal transition was not inhibited in vitro. Additionally, in both the inflammatory and fibrotic phases of bleomycin treatment in vivo, TSA did not reduce immune cell infiltrates in the airspaces, nor did it have a statistically significant anti-fibrotic effect[127]. In line with these findings, the HDAC inhibitor valproic acid induced the production of IL-6, a pro-fibrotic cytokine, in a paraquat-induced mouse model of pulmonary fibrosis, whereas the histone acetyltransferase (HAT) inhibitor anacardic acid had the opposite effect[128].

Aberrant regulation of HATs, as previously observed to occur in fibroblasts from patients with SSc[129], might have a role in fibrosis. Resveratrol, a nonspecific compound that activates the class III HDAC SIRT1, had anti-fibrotic effects in vitro concomitant with a reduction in HAT p300 activity[94]. Treatment of fibroblasts from patients with SSc with resveratrol resulted in reduced collagen and αSMA expression, and in bleomycin-challenged mice, resveratrol attenuated lung and skin fibrosis[92,94,98]. However, fibroblast-specific knockout of SIRT1 led to a decrease in skin thickness and a reduced number of myofibroblasts in bleomycin-treated mice[93]. These contrasting findings might be caused by the well-known off-targets effects of resveratrol[130], but they might also result from the cell-specific and tissue-specific functions of SIRT1 in fibrosis. The use of selective activators of SIRT1 and/or knockdown technologies, pharmacological treatment strategies (such as therapeutic versus prophylactic models) and treatment timing should be given close attention.

Histone demethylase and histone methyltransferase inhibitors (GSKJ4 and DZNep, respectively) both reduced fibrosis in experimental models[100,131]. However, although reducing collagen and αSMA expression in bleomycin-challenged lung tissue[131] and displaying protective functions in experimental liver fibrosis[132], in vitro, DZNep increased the TLR8-mediated production of two pro-fibrotic factors, TIMP1 and FRA2, in monocytes[103] and induced collagen and αSMA expression in skin fibroblasts co-cultured with TIMP1-producing monocytes[133]. Furthermore, DZNep has also previously been shown to exacerbate bleomycin-induced skin fibrosis[134]. Taken together, these results might indicate organ-specific functions for DZNep.

Bromodomain and extra-terminal domain (BET) proteins are also critical epigenetic regulators of gene transcription. In fact, BET proteins recognize acetylated lysine residues and therefore have a role in acetylation-mediated transcriptional activation or suppression[135]. Despite not being fully characterized in SSc, BET proteins were shown to modulate fibrotic processes[136]. Further evaluation of BET inhibitors will thus be useful to understand how abrogation of the reading of the epigenetic code can affect pathological processes in SSc.

MicroRNA expression. Candidate miRNAs known to be dysregulated in SSc and in experimental models of fibrosis constitute appealing targets for therapeutic approaches. Topical application of an inhibitor for miR-155, an miRNA upregulated in lesional skin from patients with SSc or morphea (a localized form of scleroderma), suppressed collagen deposition in a bleomycin-induced mouse model of skin fibrosis[108]. In addition to possible implications for miR-155 inhibitors as anti-fibrotic compounds, these findings[108] also suggest that delivery of miRNA modulators directly onto the skin surface could be a promising therapeutic strategy that would overcome the undesirable effects of intradermal injection[137]. In another study, an miR-30a mimic was nebulized into

Table 3 | **Therapies that target epigenetic processes — experimental evidence in systemic sclerosis**

Therapy	Tissue or cell type	Outcome	Refs
DNMT inhibitor			
Zebularine; 5-aza-2′-deoxycytidine	Lung fibroblasts from patients with SSc and patients with IPF	↑ PTGS2 expression	78
5-Aza-2′-deoxycytidine	Dermal fibroblasts from patients with SSc and healthy individuals	↑ PARP1 and transcription factor KLF5 expression	69,70
5-Aza-2′-deoxycytidine	TGFβ-stimulated mouse lung fibroblasts	• ↓ αSMA and type I collagen expression • ↓ Stress fibre formation	155
5-Azacytidine	Healthy $CD4^+$ T cells co-cultured with either PBMCs, B cells or dermal fibroblasts	• ↑ Proliferative response to autologous PBMCs • ↑ IgG production • ↑ Collagen expression	83
5-Azacytidine	PHA-stimulated $CD3^+CD4^+CD28^+KIR^+$ T cells	↑ Percentage of $CD11a^+$ cells	123
HDAC inhibitor			
TSA	• Dermal fibroblasts from patients with SSc and healthy individuals • Mouse skin tissue	↑ WIF1 expression	125
TSA	Monocytic cell line	↓ Transcription factor FRA2 and TIMP1 expression	133
TSA	Skin and lung tissue from bleomycin-challenged mice	• ↓ β-catenin, type I collagen and αSMA expression in the skin • ↓ Pulmonary fibrosis	125,127
Valproic acid	Lung tissue from paraquat-challenged mice	• ↑ IL-6 expression • ↑ Pulmonary inflammation	128
MC1568	TGFβ-stimulated dermal fibroblasts	• ↑ Transcription factor NR4A1 expression • ↓ Collagen release	156
Divalproex sodium[a]	Digital ulcer tissue from patients with SSc	• ↓ Digital ulcers • ↓ Swelling of fingers	157
Mycophenolate mofetil[a]	Skin and lung tissue from patients with SSc	• ↓ mRSS • ↑ Lung function	158–161
HAT inhibitor			
Anacardic acid	Lung tissue from paraquat-challenged mice	• ↓ Fibrosis and lung inflammation • ↓ Type I collagen, TGFβ, αSMA and fibronectin 1 expression	128
Sirtuin activator			
Resveratrol	Dermal fibroblasts from patients with SSc	• ↓ Collagen production • ↓ αSMA and fibronectin extracellular domain A expression	94,98
Resveratrol	TGFβ-stimulated dermal fibroblasts	• ↓ Cell migration and contractility • ↑ Stress fibre formation • ↑ Collagen expression	93,94
Resveratrol	Lung fibroblast cell line stimulated with TGFβ or bleomycin	↓ mTOR activation	92,98
Resveratrol	TNF-stimulated lung fibroblast cell line	• ↓ IL-6, IL-1β and iNOS expression • ↓ p65 acetylation	92
Resveratrol	TGFβ-stimulated dermal fibroblasts and lung fibroblast cell line	• ↓ Collagen and αSMA expression • ↓ Transcription factor SMAD3 activation	92,94,98
Resveratrol	Lung tissue from bleomycin-challenged mice	• ↓ Alveolar epithelial injury • ↓ Collagen expression	92
Resveratrol	Skin tissue from bleomycin-challenged mice	• ↓ Dermal thickness • ↓ Collagen expression	94,98
Hexafluoro	TGFβ-stimulated lung fibroblasts	• ↓ αSMA, fibronectin extracellular domain A and collagen expression • ↓ Cell migration and contraction • ↓ ROS production • ↓ Transcription factor SMAD3 activation	97
Hexafluoro	Lung and skin tissue from bleomycin-challenged mice	• ↓ Lung fibrosis • ↓ Dermal thickness • ↓ Collagen production	97

Table 3 (cont.) | **Therapies that target epigenetic processes — experimental evidence in systemic sclerosis**

Therapy	Tissue or cell type	Outcome	Refs
HMT inhibitor			
DZNep	TGFβ-stimulated healthy lung fibroblasts	• ↓ αSMA and fibronectin 1 expression • ↓ Fibroblast contractility • ↓ SMAD transcription factor nuclear translocation	131
DZNep	Monocytic cell line	• ↑ Transcription factor FRA2 and TIMP1 expression	133
DZNep	Lung tissue from bleomycin-challenged mice	• ↓ Lung fibrosis • ↓ αSMA and collagen expression	131
HDM inhibitor			
GSKJ4	Dermal fibroblasts from patients with SSc stimulated with TGFβ or PDGF	• ↓ TGFβ-induced transcription factor FRA2 expression • ↓ Cell migration	100
GSKJ4	Skin and lung tissue from mice challenged with bleomycin or topoisomerase I	• ↓ Dermal thickness • ↓ Myofibroblast counts • ↑ Hydroxyproline levels • ↓ Skin-infiltrating T cells	100
miRNA mimic			
miR-29a mimic	Dermal fibroblasts from patients with SSc	• ↓ Collagen and TIMP1 expression • ↑ Apoptosis	104,105
miR-30 agomir	Lung tissue from bleomycin-challenged mice	• ↓ Lung fibrosis and collagen deposition • ↓ DRP1 and TET1 expression • ↓ Hydroxyproline, αSMA and vimentin expression	74
miR-29b mimic	Lung tissue from bleomycin-challenged mice	• ↓ Pulmonary fibrosis • ↓ Collagen expression	139
miR-29b mimic	Skin tissue from healthy individuals	• ↓ Fibroplasia • ↓ Collagen expression	140
miRNA inhibitor			
miR-21 inhibitor	Dermal fibroblasts from patients with SSc	↑ Apoptosis	106
miR-155 antagomir	Skin tissue from bleomycin-challenged mice	• ↓ Skin thickness • ↓ Collagen type I expression • ↓ αSMA-positive fibroblasts	108

αSMA, α-smooth muscle actin; DNMT, DNA methyltransferase; DRP1, dynamin-related protein 1; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDM, histone demethylase; HMT, histone methyltransferase; IgG, immunoglobulin G; iNOS, inducible nitric oxide synthase; IPF, idiopathic pulmonary fibrosis; miRNA, microRNA; mRSS, modified Rodnan skin score; mTOR, serine/threonine-protein kinase mTOR; PARP1, poly(ADP-ribose) polymerase 1; PBMCs, peripheral blood mononuclear cells; PDGF, platelet-derived growth factor; PHA, phytohaemagglutinin; PTGS2, prostaglandin G/H synthase 2; ROS, reactive oxygen species; SSc, systemic sclerosis; TET1, ten-eleven translocation methylcytosine dioxygenase 1; TGFβ, transforming growth factor-β; TIMP1, tissue inhibitor metalloproteinase 1; TSA, trichostatin A; WIF1, Wnt inhibitory factor 1. [a]Partial HDAC inhibitory effects.

the lungs of bleomycin-challenged mice, resulting in reduced production of collagen, reduced expression of myofibroblast differentiation markers and the amelioration of lung fibrosis[74]. As circulating levels of different miR-30 family members are reduced in patients with IPF, as well as in patients with SSc[138], these results[74] provide evidence for the beneficial effects of therapies that aim to induce miR-30 expression. Lastly, an oligonucleotide mimic of miR-29b (MRG-201) has been developed as a possible anti-fibrotic treatment. Systemic treatment with MRG-201 reduced collagen production and disease in a bleomycin-induced mouse model of fibrosis[139]. MRG-201 has been further evaluated in a phase I clinical trial in skin incisions in healthy individuals, the preliminary results of which showed its administration lessened collagen expression and prevented fibroplasia[140].

Conclusions

Over the past few years, it has become clear that a complete characterization of the pathophysiological features of SSc can be accomplished only by the careful examination of both the genetic and epigenetic influences that affect this disease (FIG. 2). Despite the concordance of findings between a number of studies, divergences between findings in some studies constitute a major drawback. These different outcomes could be partially explained by the heterogeneity of SSc, further indicating the need for the data-driven molecular reclassification of the disease. Additionally, the diverse techniques used to evaluate genetic and epigenetic marks, as well as non-disease-related factors, such as ethnicity, sex, age, lifestyle and therapeutics, could explain data irreproducibility[141]. Hence, the inclusion of necessary controls, large sample sizes and the recruitment of therapy-naive patients are crucial in future preclinical studies.

The variability in miRNA expression between studies highlights the need for methodological standardization and data validation in independent cohorts of patients. The therapeutic targeting of miRNA has been facilitated by the development of delivery strategies that partially solve problems related to the biopharmaceutical properties of the molecules. Chemical nucleoside modifications and locked nucleic acid technology provide resistance against nucleases, and the introduction of

lipid nanocarriers for miRNA mimics or anti-miRNAs confers miRNA stability and limits immune rejection[142]. Additionally, topical miRNA-directed therapies are showing promising results when applied to patient-derived skin samples, thereby encouraging further preclinical evaluation in SSc[143].

Inhibitors that affect DNA methylation necessarily require further characterization in vivo. In fact, as DNA methylation is pivotal in physiological processes, broadly specific targeting of these mechanisms would be expected to cause unwanted adverse effects[144]. Similar considerations exist around the use of inhibitors to either sustain or repress HDAC activity as targeting different classes or members of histone-modifying enzymes could have distinct, or even opposite, effects on disease manifestations. Low therapeutic doses of pan-HDAC inhibitors have shown clinical efficacy and safety in systemic-onset juvenile idiopathic arthritis[145]; however, the benefits of using HDAC inhibitors in SSc are still debatable.

In this Review, we have described highlights from the field of genetics and epigenetics in SSc made over the past 4 years. As epigenetic changes might occur very early in the disease course, potentially years before fibrosis appears, they might constitute a link between inflammation and tissue fibrosis that has hitherto not been understood. Understanding this link is important as, although fibrosis was previously considered to be an end-stage condition, it is now thought to be potentially reversibile[146–148]. As fibrosis is shared between many acute and chronic diseases and still accounts for one-third of deaths worldwide[149], understanding the underlying molecular pathways that link inflammation with fibrosis will be paramount for the development of medicines that are effective in treating or even reversing tissue fibrosis[149]. Despite advances in this field, an urgent need remains for more large-scale population studies and longitudinal measurements in patients with SSc. The integration of multi-omics data, including genomic, epigenomic, transcriptomic, proteomic and metabolomic data, is hoped to deliver a more holistic understanding of the pathogenesis of SSc and to pave the way for novel therapies to halt or even prevent fibrosis.

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Author contributions

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OPINION

Modern-day environmental factors in the pathogenesis of osteoarthritis

Francis Berenbaum, Ian J. Wallace, Daniel E. Lieberman and David T. Felson

Abstract | The prevalence of osteoarthritis (OA) is rising for reasons that are not fully understood. In this Opinion article, we review the possibility that OA is an evolutionary mismatch disease, which is a disease more common today than in the past because genes inherited from previous generations are inadequately or imperfectly adapted to modern environmental conditions. We focus on four major environmental factors in OA pathogenesis that have become ubiquitous within the past half-century: obesity, metabolic syndrome, dietary changes and physical inactivity. Because a cure for OA does not yet exist, prevention strategies that target these modifiable environmental factors are needed to curb further increases in OA prevalence.

To a large extent, osteoarthritis (OA) is a disease of old age, so its prevalence might be expected to be higher today than in the past simply because more people are living longer, especially in Europe, the United States and other developed nations[1,2]. However, evidence exists that increased longevity is probably not the sole reason for the high prevalence of OA. Wallace et al.[3] traced long-term trends in the prevalence of knee OA in the United States using skeletal remains from 2,576 adults over the age of 50, spanning from prehistoric hunter–gatherers to 21st century city-dwellers. The results show that people who died since the mid-20th century were approximately twice as likely to have OA as those who died during earlier times, confirming expectations that the disease has become more common[4–6]. However, this spike in prevalence is apparent even after controlling for age in a generalized linear model, indicating the presence of additional major risk factors that have become ubiquitous only within the past half-century.

OA pathogenesis, like all disease aetiologies, involves interactions between genes and the environment[7], but the increase in OA prevalence in just the past few generations indicates that environmental changes are a major contributor to the current high prevalence of OA. On this basis, OA seems to fit the definition of what evolutionary biologists refer to as a 'mismatch disease', that is, a condition that is more common today than in the past because the human body is not well adapted to certain features common to modern environments[8,9]. As there is no cure for OA, classification of it (at least partly) as a mismatch disease is of clinical consequence, as environmental factors are potentially modifiable targets for prevention.

Here, we discuss the effect of the environment on OA pathogenesis, focusing on factors that have become ubiquitous since the mid-20th century. To contextualize this evidence, we begin with an overview of the concept of mismatch diseases and conclude with a discussion of how understanding modern-day environmental factors is relevant to disease prevention.

Mismatch diseases

The concept of mismatch diseases derives from two basic principles of evolutionary biology: the theory of adaptation and the fact that interactions between genes and the environment are in constant flux[8,9]. Each individual inherits genes that interact with the environment, and most of these genes were favoured by natural selection because they improved the ability to survive and reproduce under particular environmental conditions. As a result, all organisms are adapted in varying degrees to aspects of the environment in which their ancestors existed, including associated diets and patterns of physical activity. When environments change, as they inevitably do, ancestral alleles once favoured by natural selection can become mismatched to features of the new environment. Ultimately, as a result of such mismatches, individuals have an increased susceptibility to illnesses that were once rare or nonexistent among earlier generations.

Mismatches between inherited genetic variants and changing environments are a fundamental engine of evolution[10], but an abundance of evidence indicates that such mismatches are becoming more common and severe in humans owing to rapid environmental changes related to the cultural evolution of our species (reviewed elsewhere[9]).

Although humans have been hunter–gatherers for almost all of our >200,000-year evolutionary history, in just the past ~12,000 years, a large proportion of the global population has transitioned from being physically active hunter–gatherers, mainly consuming wild plants and animals, to being farmers settled in agricultural communities reliant on cereals and other domesticated foods to being post-industrial workers engaged in low levels of physical activity and eating highly processed foods. Although these changes in the environment, which have occurred in a blink of the eye in evolutionary time, have brought many benefits and comforts, they are also thought to be responsible for the emergence of a variety of mismatch diseases. For example, owing to the long evolutionary history of humans as physically active hunter–gatherers and consuming a diet rich in fibre but low in sugar[9], the rising prevalence of type 2 diabetes is widely considered to be related to recent shifts towards physical inactivity and overconsumption of foods high in sugar but low in fibre, resulting in persistent positive energy balance, increased adiposity and chronic low-grade inflammation, which can lead to insulin insensitivity[11].

When considering whether conditions such as OA are examples of mismatch

Box 1 | **Effect of the obesity epidemic on osteoarthritis prevalence**

Although it is difficult to quantify precisely how much of the current prevalence of osteoarthritis (OA) is attributable to any given environmental change, data from Wallace et al.[3] provide a rough indication of the influence of the obesity epidemic on knee OA levels in the United States. Among individuals in their skeletal sample for which BMI at the time of death was documented, 25% of people who died in the past few decades were obese, compared with only 1% from earlier times, and individuals with obesity had a 2.2 times higher (95% CI 1.6–3.0) prevalence of knee OA than non-obese individuals. These data suggest that today obesity doubles the risk of knee OA in roughly 1 in 4 people over the age of 50, whereas only 1 in 100 people were at a similarly heightened risk of knee OA roughly a half-century ago. Although Wallace et al.[3] were limited in their ability to assess the full effect of obesity on knee OA prevalence because BMI is a fairly inaccurate measure of excess adiposity and BMI was known only from individuals' time of death and not at the time they developed OA, these data provide strong evidence that the recent steep rise in obesity levels has led to substantially more people being at greater risk of developing knee OA.

diseases, however, caution is required, as the mismatch concept is often applied to a wide range of health disorders, in both the scientific literature and popular press, as more a matter of assumption than a hypothesis to be carefully tested. As with the so-called 'Paleo diet', overly simplistic claims are sometimes made about the potential health benefits associated with living more like our ancient ancestors and are based on misleading caricatures of past environments[12] and the false assumption that humans evolved to be healthy[9]. Clearly, not all features specific to modern environments interact negatively with the genes we inherit, and many environmental alterations can be beneficial, such as antibiotics, refrigeration or the use of casts for bone fractures. With this caveat in mind, we suggest two principal criteria for rigorously testing the mismatch hypothesis for diseases such as OA: first, that the disease is more prevalent today than among past populations after accounting for variation in lifespan and, second, that preventable contributors to the disease are more common in modern environments. Although OA is not a new disease and has been documented among Palaeolithic hunter–gatherers[13] and Neolithic farmers[14], the study by Wallace et al.[3] and prior studies of smaller archaeological samples[15,16] provide compelling evidence that OA meets the first criterion of a mismatch disease as being more prevalent today than in the past. Such studies, however, are retrospective and cannot identify all the causes of recent increases in OA. Nevertheless, evidence that the prevalence of OA in developed nations has spiked in the past half-century provides important clues about which preventable contributors to OA might be responsible, the most conspicuous candidates being obesity, metabolic syndrome, dietary changes and physical inactivity (FIG. 1).

Mismatch factors

Obesity. Obesity is commonly attributed as a source of mismatch diseases, as until modern times, most human bodies were rarely, if ever, exposed to long-term high levels of positive energy balance and hence rarely evolved adaptations to cope with the consequences of excess adipose tissue, especially visceral stores[17]. Unsurprisingly, obesity is a strong and well-established risk factor for OA[18], especially knee OA[19]. Incidence of knee OA among adults aged ≥40 years is reported to be approximately three times as frequent among obese individuals (BMI ≥ 30) and five times as frequent among morbidly obese individuals (BMI ≥ 35) compared with individuals of a healthy weight (BMI < 25)[18]. Given such a strong association, the rising prevalence of OA in developed nations is in some measure clearly attributable to the recent burgeoning obesity epidemic[20] (BOX 1).

The link between obesity and knee OA is especially pernicious because it creates a vicious cycle in which pain from OA can greatly limit a person's physical activity, thus promoting further weight gain and weakening of muscles that stabilize and protect joints, which in turn can exacerbate pain and OA progression[21]. A negative feedback loop of this kind could just as easily be triggered by joint pain as by obesity, but evidence indicates that in the majority of cases, obesity precedes the onset of OA[22,23]. The driving, causal role of obesity in OA pathogenesis is further highlighted by evidence that most individuals with OA who have undergone bariatric surgery to induce weight loss experience a substantial reduction in joint pain and other symptoms[24,25]. Evidence suggests that cartilage loss can be slowed if an obese person loses 10% or more of their original weight[26]. Weight loss may also reduce pain sensitivity and thereby contribute to pain relief[27].

Although the precise mechanisms by which obesity affects OA incidence are not completely understood, the longest-standing and perhaps most intuitive explanation is that obesity creates an abnormal loading environment for weight-bearing joints[28].

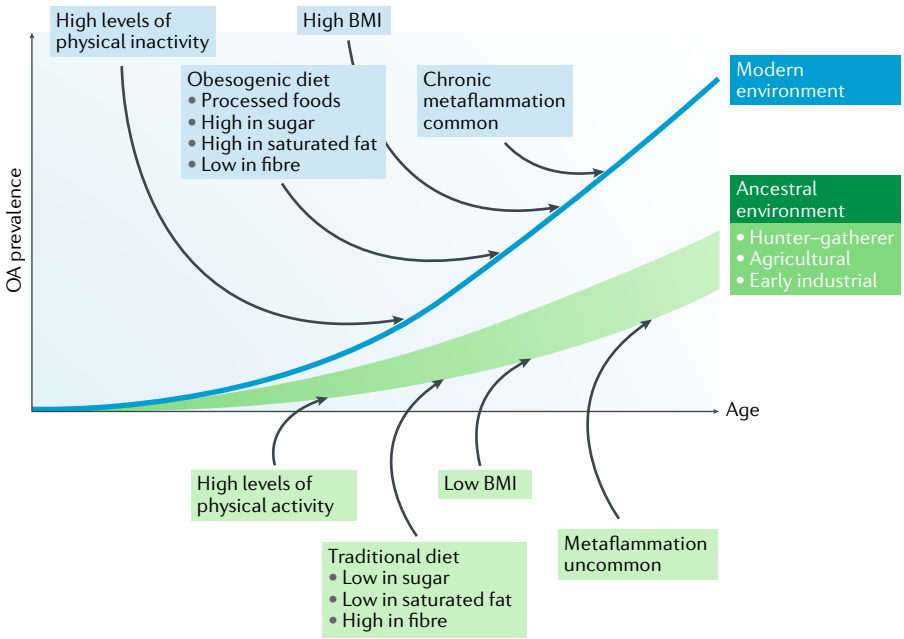

Fig. 1 | **Model of osteoarthritis as a mismatch disease.** In all populations, the prevalence of osteoarthritis (OA) rises with age, but the hypothesis of mismatch predicts that prevalence at any given age is higher in modern environments because of high levels of obesity, chronic metaflammation and physical inactivity, and diets of processed foods that are rich in sugar and saturated fats and low in fibre.

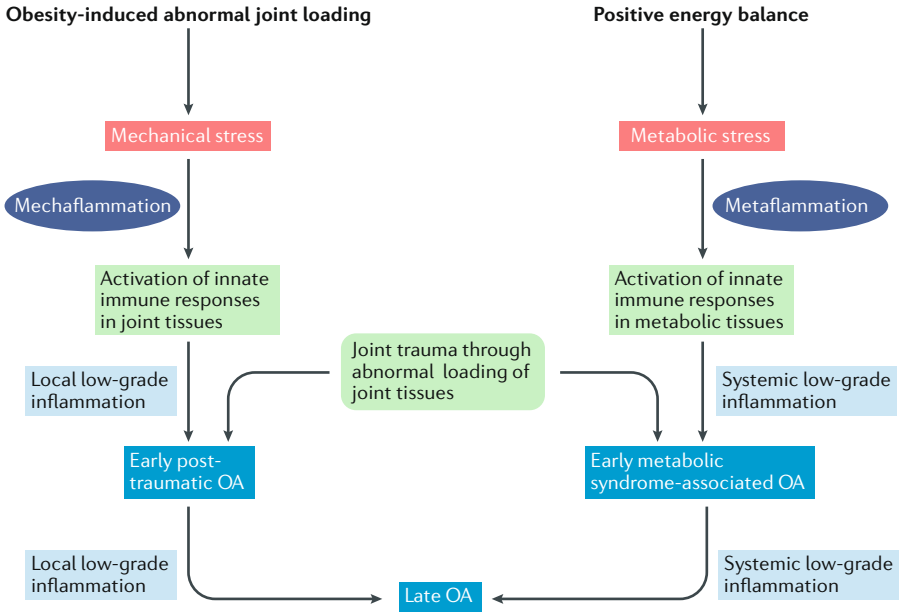

Fig. 2 | **Mechaflammation versus metaflammation.** Both osteoarthritis (OA) and obesity begin with activation of the innate immune system, which occurs by a local stimulus from joint tissues experiencing abnormal loading or a systemic stimulus from the adipose tissue. Triggering of innate immune responses can result in two types of low-grade inflammation, mechaflammation and metaflammation. Low-grade inflammation, in turn, weakens joint tissues, increasing their vulnerability to damage by subsequent loading and the initiation of OA.

Loading per se is not bad for joints, as it is necessary for normal joint development and maintenance[29,30], but some loads clearly have the potential to damage cartilage and other joint tissues and thus increase OA susceptibility, a fact highlighted by the strong link between traumatic injuries and OA[31]. The added body weight associated with obesity increases the magnitude of axial loads sustained by weight-bearing joints, which may impart some of the risk of OA caused by obesity. Among people with varus malalignment of the knee, such high-magnitude loads could be especially harmful, as they can magnify knee adduction moments[32]. Furthermore, low muscle strength relative to body weight may reduce the capacity of transarticular muscles to absorb shock and increase the rate and variability of joint loading[33]. A compromised ability to stabilize joints could cause forces to become concentrated in joint regions that are inadequately adapted for such loads and thus vulnerable to damage.

The primary result of aberrant loading of cartilage is damage to the structure of the cartilage matrix of collagen fibrils and proteoglycans[34,35]. Cartilage degradation caused by abnormal loads may occur to some extent through wear and tear, but evidence suggests that the primary effect of such loads is to stimulate the production of metalloproteinases by chondrocytes and to activate these proteins in the matrix[36]. Abnormal loads trigger mechanoreceptors on the chondrocyte surface, which, in turn, trigger intracellular signalling pathways (for example, mitogen-activated protein kinase (MAPK) or nuclear factor-κB (NF-κB)) and the production of pro-inflammatory and catabolic mediators[37,38]. Matrix fragments released into the joint cavity can then provoke synoviocyte and macrophage responses and further release these pro-inflammatory and catabolic mediators, a process we refer to as mechaflammation[39] (FIG. 2).

Mechanical factors are probably not the only contributors to obesity-induced OA, as obesity increases OA risk in not only weight-bearing joints but also non-weight-bearing regions, such as hands[40]. The association between obesity and OA is generally stronger for weight-bearing than non-weight-bearing joints, but this difference in susceptibility across joints is evidence that the effect of obesity on OA involves complex interactions between mechanical and systemic factors[41]. Although much remains to be learned about these systemic factors, evidence indicates that a predominant source is adipose tissue, which produces and releases cytokines (including adipokines) into the bloodstream, many of which (such as IL-1, IL-6, IL-8, IFNγ, TNF, leptin and resistin) promote chronic low-grade inflammation, also termed metaflammation, for which the body is not well adapted[42] (FIG. 2). Several of these cytokines have been shown experimentally to have an important function in initiating OA[43]. The adipokine leptin seems to be especially important in initiating OA, as age-related knee OA does not occur in leptin-deficient obese mice[44]. The most direct pathway by which high levels of leptin and other cytokines in the bloodstream affect OA is by diffusing into the synovial fluid and locally activating proteolytic enzymes, such as matrix metalloproteinase 1 (MMP1), MMP3 and MMP13 (REF.[45]), which can trigger matrix degradation in cartilage and other joint tissues[46]. However, obesity-induced metaflammation may also affect OA more indirectly by modulating other critical metabolic factors, as discussed in the next section.

Metabolic syndrome. Another common source of mismatch diseases that also stems from excessive and long-term positive energy balance is metabolic syndrome, which is defined by a cluster of cardiometabolic factors that commonly accompany obesity, including central adiposity, dyslipidaemia, impaired fasting glucose levels and hypertension. Individuals with metabolic syndrome are at increased risk of a variety of health disorders, especially cardiovascular disease, type 2 diabetes and some cancers[47]. An abundance of evidence indicates that metabolic syndrome was once a rare (almost nonexistent) disease in nonindustrial populations[48–50]. Given the increase in prevalence of metabolic syndrome in developed nations, and an association with obesity, it is unsurprising that metabolic syndrome has been hypothesized to be a major risk factor for OA[40,51].

Adipose-induced metaflammation is almost always associated with metabolic syndrome[42] and strongly affects the metabolic dysregulation underlying multiple metabolic components[52]. In turn, these individual components of metabolic syndrome might affect the initiation or progression of OA[53,54]. For example, experimental evidence suggests that hyperglycaemia can have adverse effects on chondrocyte metabolism[55–58], and type 2 diabetes can alter the structure of extracellular matrices, causing enrichment of advanced glycation endproducts (AGEs). In cartilage, AGEs stiffen the matrix, preventing optimal cushioning of the joints under a mechanical load[59]. Moreover, AGEs can signal chondrocytes through specific AGE receptors to increase

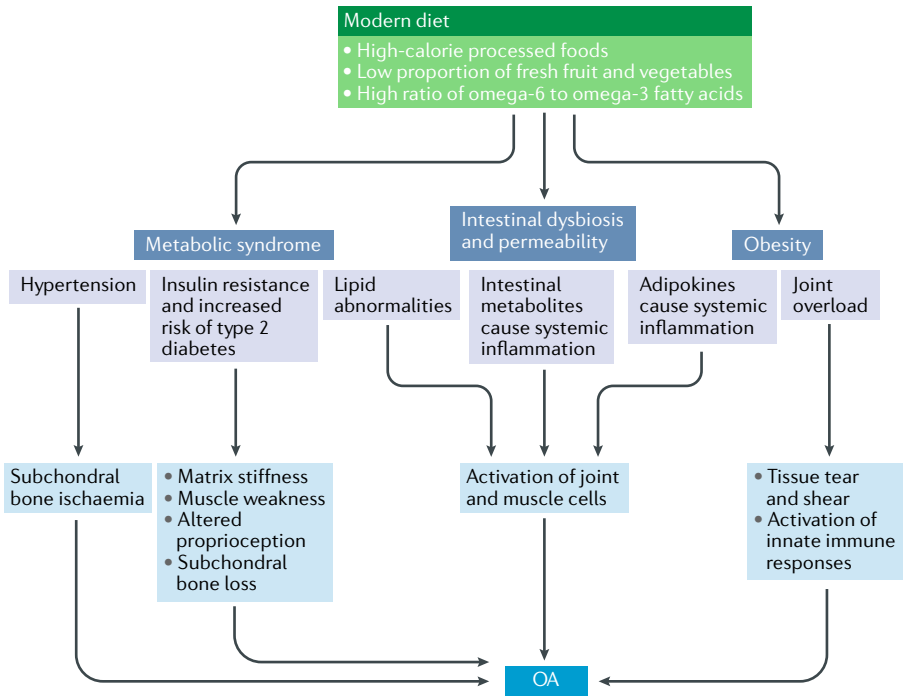

Fig. 3 | **Diet as a mismatch factor.** The deleterious effects of modern diets on osteoarthritis (OA) arise from increased adiposity and body mass, which leads to joint overload, a well-established risk factor for OA. Moreover, high caloric intake, a low proportion of fresh fruit and vegetables and a high ratio of omega-6 to omega-3 fatty acids, which are all hallmarks of a modern diet, participate in an increase in intestinal dysbiosis and permeability. These intestinal alterations increase systemic low-grade inflammation, a biological response suggested to trigger joint cell activation in OA. Modern diets are also considered the main cause of metabolic syndrome, which includes hypertension, insulin resistance and lipid abnormalities. Each of these pathologies could indirectly have an important function in OA pathogenesis through deleterious effects on joint tissues.

synthesis of metalloproteinases[60] and thus should eventually lead to increased cartilage matrix degradation. Oxidized LDL, a pro-inflammatory peroxidized lipid detected at high concentration in plasma from patients with metabolic syndrome, can stimulate the production of reactive oxygen species by chondrocytes, propelling matrix degradation[61]. Hypertension might also be implicated in OA pathogenesis owing to induction of downstream tissue ischaemia. If ischaemia affects the blood vessels of the subchondral bone, the nutritional exchange between the subchondral bone and the cartilage might be compromised, resulting in altered metabolism of cells in the joints[62].

Nevertheless, despite experimental evidence of multiple potential pathways linking metabolic syndrome and OA, data from human studies are conflicting, with most studies showing no association of metabolic syndrome with knee OA after taking into account BMI. For example, in a study of 991 individuals, metabolic syndrome was strongly associated with incident knee OA, but after controlling for body weight, the associations disappeared[63]. Other studies, however, have found that hand OA (but not knee OA) is strongly associated with metabolic syndrome even after adjusting for body weight[41]. Interestingly, people with hypertension have been shown to have an elevated risk of knee OA independent of obesity[63], and OA prevalence was higher among people with type 2 diabetes than among people without diabetes, independent of weight differences[64]. Moreover, an MRI study indicates that patients with type 2 diabetes have accelerated knee cartilage matrix degeneration compared with individuals without diabetes, even after correcting for ethnicity, age, sex, baseline BMI and severity of OA as measured by baseline Kellgren – Lawrence score[65]. Although experimental research and some human studies provide evidence that individual components of metabolic syndrome (aside from adiposity) contribute to OA pathogenesis, more data are necessary to resolve the degree to which the current prevalence of OA is attributable to modern increases in metabolic syndrome prevalence.

Dietary changes. The increase in OA prevalence in developed nations raises the question of whether changes in diet cause mismatches that contribute to OA. Modern diets in many developed countries differ from those of earlier generations in being substantially more energy dense and processed, with added sugar, salt and saturated fats but less fibre, fresh fruits and vegetables[9]. These dietary shifts almost certainly affect OA risk by promoting prolonged positive energy balance and excess adiposity but also perhaps by increasing the probability of hyperglycaemia, dyslipidaemia and hypertension.

Aside from promoting metabolic dysregulation, however, modern dietary changes potentially affect OA risk in other ways. An additional dietary factor of particular relevance is a reduced intake of antioxidants[66]. Reactive oxygen species are involved in chondrocyte senescence, extracellular matrix degradation, synovial inflammation and subchondral bone alteration[67]. Diets in many developed nations are characterized by an increase in the ratio of pro-inflammatory omega-6 fatty acids to anti-inflammatory omega-3 polyunsaturated fatty acids[68]. However, evidence that this imbalance contributes to disease remains a contested point of debate. In one study, supplementing the diet with omega-3 fatty acids reduced the severity of post-traumatic OA in mice and limited attendant synovitis[69], whereas in another study, dietary enrichment of omega-3 fatty acids did not reduce the onset of knee OA in mice[70]. In humans, the effect of omega-3 fatty acid supplements in OA trials has not been reported to affect joint pain[71,72]. Moreover, sulforaphane, an isothiocyanate abundant in broccoli, decreased the severity of OA in mice, possibly by protecting against damage from reactive oxygen species[73,74]; plans now exist to test the consumption of broccoli in an OA clinical trial[75]. Conflicting evidence exists regarding the effect of the antioxidant vitamin C on OA in humans[76–79], with experiments in mice, rats and guinea pigs showing that vitamin C may increase OA risk[80]. On the other hand, vitamin K, present in green leafy vegetables like spinach, kale and broccoli, is a necessary cofactor for the γ-carboxylation of some calcium-binding proteins, including matrix gla protein, a vitamin K-dependent mineralization inhibitor expressed in human articular cartilage. Many human observational studies have reported that vitamin K deficiency increases the risk of OA[81–83], but clinical trials testing vitamin K treatment have not yet been performed. Experimental

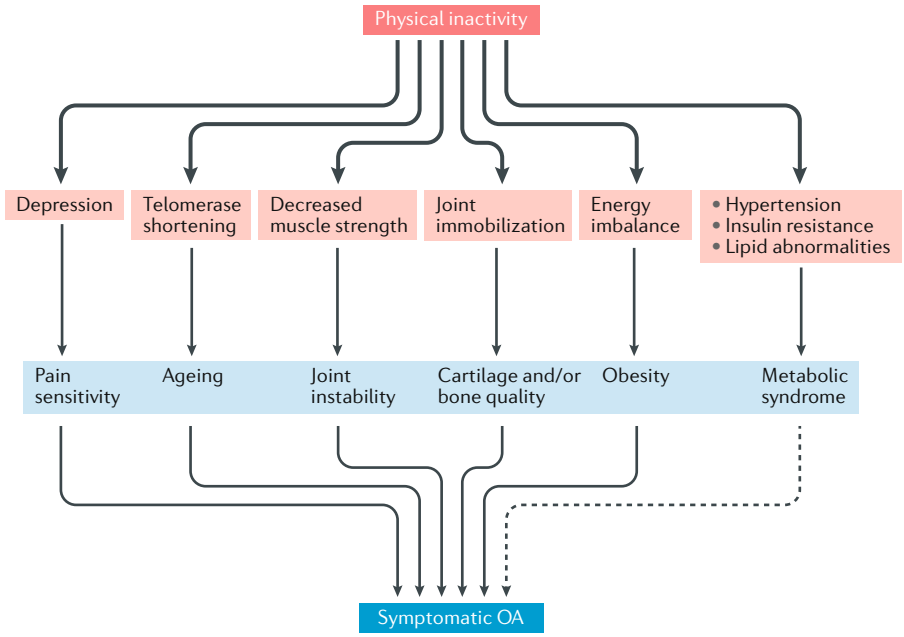

Fig. 4 | **Physical inactivity as a mismatch factor.** A sedentary lifestyle and physical inactivity might initiate and aggravate osteoarthritis (OA) and its symptoms via a variety of pathways.

studies point to other dietary factors that are potentially implicated in OA but have not yet been carefully examined in human studies (FIG. 3). Some groups have shown that dietary high-fat overload can increase the severity of post-traumatic OA in mice and rats[69,84,85]. Interestingly, for the same quantity of calories, severity of OA was exacerbated by a diet rich in saturated as opposed to unsaturated fatty acids[69].

Obesity and ageing are associated with intestinal dysbiosis that may cause metabolic age-related chronic diseases[86,87]. The function of the diet in modulating the composition and metabolic activity of the intestinal microbiome is now recognized[88]. Diffusion of biologically active metabolites (such as acetate, propionate and butyrate) and lipopolysaccharide, a microbial cell wall constituent, from the gut to bloodstream related to increased intestinal permeability and dysbiosis in patients with obesity is associated with low-grade systemic inflammation[89–91]. Although evidence that these dysbiosis-derived metabolites have a direct pathophysiological function in OA is lacking, the results of some experimental studies are consistent with this hypothesis[92,93]. One important dietary factor that modifies the gut microbiota is fibre; changes in the intestinal microbiome might be related to a paucity of fibre in the modern diet. In two cohorts, volunteers in the highest quartile of total fibre intake had lower rates of new-onset symptomatic OA than those in the lowest quartile of total fibre intake[94,95]. In fact, the higher the fibre intake, the less knee pain experienced by patients with OA[94]. Fibre intake has not yet been tested as a treatment in human OA trials. Animal studies also suggest that the gut microbiota affects OA; for example, a reduction in *Bifidobacterium* spp. in obese mice has been associated with increased migration of macrophages into the synovial tissue, which accelerates OA, whereas dietary supplementation with oligofructose, a non-digestible fibre, was associated with protection of joints in obese mice[96].

Physical inactivity. Mechanical loading has a major function in nearly all cases of OA, and as physical activity is the most common source of joint loading and is an environmental factor that has changed in the modern world, any consideration of OA as a mismatch disease requires examining shifts in activity patterns[31]. As already noted, one important and well-established risk factor for knee OA is joint trauma, especially meniscal and anterior cruciate ligament tears, which can lead to abnormal stress gradients and excess focal stress within cartilage. Thus, increased participation in sports and other athletic activities that frequently cause such injuries has been hypothesized to underlie current high levels of OA[97]. However, this hypothesis is conjectural, given that earlier generations, particularly prehistoric populations, almost certainly engaged in high levels of moderate and vigorous physical activity and yet had lower prevalence of OA[98,99]. Whether people today are, on average, more susceptible to injury and post-traumatic OA than in the past is highly speculative.

Although trauma unquestionably increases OA risk, a more likely contributor to the increased prevalence of OA is physical inactivity, which has become epidemic in the past few decades, especially in many developed nations[100]. Pathways by which physical inactivity can increase OA risk include indirect promotion of obesity and metaflammation, depression[101] or telomere shortening[102] (FIG. 4). However, physical inactivity might also contribute to OA pathogenesis directly. Because the musculoskeletal system, like many physiological systems, evolved to require biophysical stimuli from the environment to adjust capacity to demand[103], mechanical loads engendered by activity are critical to the development and maintenance of optimal structure and strength of joint tissues and their surrounding muscles[29,104]. Moreover, a reduction in loading as a result of a physically inactive lifestyle might cause formation of weaker and less stable joints that are more susceptible to damage and deterioration[105,106]. In other words, physical inactivity leads to an absence of normal demand, whereby individuals are unlikely to attain or maintain normal joint capacity.

To illustrate this 'use it or lose it' principle in cartilage, patients with paralysed limbs exhibit marked knee cartilage thinning[106,107], whereas MRI studies have shown that people who regularly engage in weight-bearing exercise maintain thicker cartilage, and in one study, these individuals were even noted to have fewer cartilage defects, than people who are physically inactive[108–110]. Animal experiments have yielded similar findings: disuse experiments (for example, rodent limb immobilization or unloading) consistently demonstrate multiple catabolic effects on joint tissues, including thinning of all cartilage layers, decreased cartilage proteoglycan content by increased expression of metalloproteinases and demineralization of subchondral bone by osteoclast activation[111–114]. By contrast, a meta-analysis of exercise in various animal species showed that, compared with animals on a moderate daily exercise regimen, non-exercising control animals had thinner knee cartilage with lower aggrecan content[115]. Thinner cartilage with lower aggrecan content is not necessarily osteoarthritic cartilage (for example, paralysed limbs

rarely get OA), but it is biomechanically vulnerable cartilage[116].

Even if physical inactivity is detrimental to joint health, this does not mean that all forms of physical activity are beneficial for joints. As already discussed, some types of loading can threaten the integrity of joint tissues, and loads that are extreme or otherwise abnormal, either in terms of magnitude, frequency or some other parameter, which are produced by active lifestyles through occupation (for example, jobs requiring frequent knee bending) or recreation (for example, sports injuries) can culminate in damaged joints that are more prone to OA. Thus, risk of OA is probably increased by both extreme physical inactivity and activity[35,117]. However, although considerable research and clinical attention has been paid to the potential negative consequences of some types of physical activity for joint health, greater attention ought to be devoted to understanding the degree to which decreases in physical activity underlie high levels of OA today.

Conclusions

Although the causes of the high and rising prevalence of OA are still not entirely understood, one important conclusion of this article is that OA fits the criteria of a mismatch disease in that the current OA prevalence seems to be partly attributable to environmental risk factors that have become amplified in the modern world. These factors probably include obesity, metabolic syndrome, dietary changes and physical inactivity. A second and even more important conclusion is that, although OA risk is influenced by intrinsic factors such as age and genetics, OA is partly a mismatch disease affected by modifiable factors, indicating substantial potential for prevention. This is a critical insight given that available nonsurgical treatments for OA provide relief from symptoms only, and no disease-modifying drugs exist. In short, although OA may seem to be mainly a disease of old age, from an evolutionary perspective, it is not age per se that causes the disease but an accumulation of joint tissue deterioration arising from interactions between the genes we inherited from our ancestors and the environments — many of them novel yet modifiable — that we encounter as we grow older.

Because of human evolutionary origins as physically active hunter–gatherers on the margin of energy balance, human joints probably evolved to require routine mechanical loading in the absence of adiposity-induced metaflammation to grow and function optimally with age. However, even if OA is partly a mismatch disease, the disease would not cease to occur even if everyone on the planet adjusted their lifestyles to more closely match the conditions for which the human musculoskeletal system is adapted. As the incidence of OA in prehistoric populations testifies, trauma and other risk factors have always predisposed some people to OA. Nevertheless, on the basis of the available evidence reviewed here, it seems unlikely that the OA epidemic will be curbed without at least beginning to reverse declines in physical activity levels and the quality of our diets, along with attendant effects on obesity and metabolic dysregulation. How to promote such lifestyle changes is a major challenge.

Glossary

Adaptation
A phenotypic trait favoured by natural selection because it improves an organism's ability to survive and reproduce.

Developed nations
Wealthy countries with post-industrial economies and advanced technological infrastructure.

Hunter–gatherers
People who subsist on foraged wild plants and hunted wild animals, in contrast to agriculturalists who subsist mainly on domesticated plants and animals.

Knee adduction moments
Dynamic rotational forces (torques) that act on the knee in the coronal plane, applying a compressive force to the medial side of the knee.

Kellgren–Lawrence score
A common method of classifying the severity of knee osteoarthritis using radiography.

Mechaflammation
Focal inflammation owing to a local mechanical insult.

Metaflammation
Chronic, low-grade, metabolic and systemic inflammation.

Varus malalignment
A deformity of the knee in which the distal leg is angled medially in relation to the axis of the thigh, resulting in a bowlegged appearance.

Francis Berenbaum[1]*, *Ian J. Wallace*[2], *Daniel E. Lieberman*[2] *and David T. Felson*[3,4]

[1]*Sorbonne Université, INSERM, DHU i2B, AP-HP, Hôpital Saint-Antoine, Paris, France.*

[2]*Department of Human Evolutionary Biology, Peabody Museum, Harvard University, Cambridge, MA, USA.*

[3]*Clinical Epidemiology Unit, Boston University School of Medicine, Boston, MA, USA.*

[4]*NIHR Manchester Musculoskeletal Biomedical Research Centre, University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.*

**e-mail: francis.berenbaum@aphp.fr*

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All authors researched data for the article, wrote the article, made substantial contribution to discussions of the content and reviewed and/or edited the manuscript before submission.

Competing interests
The authors declare no competing interests.

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Author Correction: Major lung complications of systemic sclerosis

Christopher P. Denton, Athol U. Wells and John G. Coghlan

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In the originally published version of this article, Table 2 contained an error. In this table, the statement "Also licensed for CTEPH; cannot be combined with a PDE5 inhibitor" was in the wrong row and incorrectly attributed to the drug selexipag, whereas this statement was actually referring to the drug riociguat. Furthermore, the reference supporting this statement was incorrect. These errors have now been corrected in the HTML and PDF versions of the manuscript.

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