FIBROMYALGIA

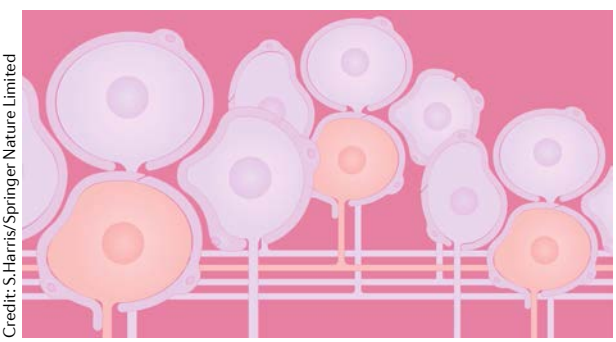
Antibodies induce fibromyalgia symptoms

> the notion of an autoimmune basis would represent a profound shift in the understanding of the disease

The results of a new study suggest that several characteristic symptoms of fibromyalgia are underpinned by antibody-dependent processes, as they could be induced in mice following the transfer of purified serum IgG from patients with fibromyalgia. The aetiopathogenesis of fibromyalgia remains a matter of debate but, if confirmed, the notion of an autoimmune basis would represent a profound shift in the understanding of the disease and could lead to novel treatment approaches.

The study was a collaboration involving research groups at King's College London, the University of Liverpool and the Karolinska Institute. "We all had a well-established interest in pain produced by autoantibodies before we embarked on this collaboration," notes David Andersson, who led the King's College London group.

The researchers first demonstrated that the administration of IgG (8 mg on 4 consecutive days) from individual patients with fibromyalgia from the UK induced mechanical hypersensitivity and increased sensitivity to noxious cold stimuli in recipient mice, with no difference in the response between female and male mice. The effects resolved fully, with the time course being consistent with that of the elimination of IgG from the mice.



Credit: S.Harris/Springer Nature Limited

Notably, IgG perparations pooled from multiple patients with fibromyalgia from Sweden had similar effects. By contrast, transfer of IgG from healthy individuals or groups, or of IgG-depleted serum from patients with fibromyalgia, produced no behavioural effects.

In further investigations, mice that received pooled IgG from patients with fibromyalgia had reduced paw grip strength, displayed less locomotor activity and had a reduced density of intraepidermal nerve fibres compared with mice who received IgG from healthy individuals. Administration of fibromyalgia IgG also increased nociceptor sensitivity in the mice.

IgG from patients with fibromyalgia accumulated in mouse dorsal root ganglia (DRG), primarily localized with satellite glial cells, but not in the brain or spinal cord. In vitro, fibromyalgia IgG bound mouse DRG cells and sectioned human DRG tissue more intensely than IgG from healthy individuals, with the findings suggesting that autoreactive antibodies in IgG solution from patients with fibromyalgia bind antigens expressed in the DRG.

Fibromyalgia IgG did not directly excite isolated DRG neurons, nor did it induce a systemic inflammatory response in mice, supporting the idea that it acts locally in the DRG. Preliminary analysis of sera from several patients with fibromyalgia using a proteome-wide microarray screen (with *Escherichia coli*-produced linear protein fragments) revealed multiple autoreactivities but did not reveal a common pattern.

"Our identification of an antibody-mediated pathophysiology will transform fibromyalgia research and will accelerate development of new therapies," says Andersson. "The findings suggest that therapies that target a reduction in antibody level might be effective against pain associated with fibromyalgia," adds Andreas Goebel, who led the University of Liverpool group.

"If it were demonstrated that some (even if not all) patients with fibromyalgia had an autoimmune pathogenesis, treatment for this subset would be dramatically altered. However, I think much more work should be completed before suggesting that patients with fibromyalgia be treated using immunomodulatory or IgG-depleting treatments," cautions Leslie Crofford, an expert in fibromyalgia who was not involved in the study. Crofford also suggests that the lack of identification of any specific autoantibody is an issue of concern, and that refining the search for characteristic reactivities, perhaps looking at satellite glial cells as a source of antigen, will be a crucial next step.

"Many questions remain to be answered, but our published findings have refined our research objectives," notes Camilla Svensson, primary investigator of the Karolinksa Institute group involved in the study. Future research will aim to determine not only the targets for the pathological antibodies but also the immunological and molecular mechanisms that enable autoreactive IgG to be produced by patients with fibromyalgia, what proportion of patients have these antibodies and the cellular and molecular mechanisms that lead to sensory neuron hyperexcitability and pain.

Sarah Onuora

ORIGINAL ARTICLE Goebel, A. et al. Passive transfer of fibromyalgia symptoms from patients to mice. *J. Clin. Invest.* **131**, e144201 (2021)
RELATED ARTICLE Sarzi-Puttini, P. et al. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. *Nat. Rev. Rheumatol.* **16**, 645–660 (2020)

IN BRIEF

SYSTEMIC LUPUS ERYTHEMATOSUS

Belimumab an option for Black patients with SLE

The first randomized controlled trial of belimumab focusing on individuals with systemic lupus erythematosus (SLE) of Black African ancestry suggests that belimumab could be a suitable treatment option for this group of patients. The international, double blind, placebo-controlled trial of monthly intravenous belimumab (10 mg/kg) in patients with SLE who self-identified as Black did not meet its primary end point of improvement in the SLE responder index with modified proteinuria scoring at week 52. However, disease did improve in those treated with belimumab compared with placebo, with no new safety signals.

ORIGINAL ARTICLE Ginzler, E. et al. EMBRACE: Phase 3/4, randomized, 52-week study of belimumab efficacy and safety in patients of Black African ancestry with systemic lupus erythematosus. *Arthritis Rheumatol.* https://doi.org/10.1002/art.41900 (2021)

PSORIATIC ARTHRITIS

Targeting IL-23 for axial disease in PsA

Post-hoc analysis of data from the phase III DISCOVER-1 and DISCOVER-2 trials suggests that guselkumab, which targets the p19 subunit of IL-23, could be efficacious for treating axial disease in patients with psoriatic arthritis (PsA), despite other IL-23 inhibitors failing to show efficacy for ankylosing spondylitis. Of the 312 patients with active PsA and sacroiliitis included in the analysis, 118 received placebo, 103 received guselkumab every 4 weeks and 91 received guselkumab every 8 weeks. Axial disease activity improved in those receiving either dose of guselkumab compared with placebo up to week 52.

ORIGINAL ARTICLE Mease, P. J. et al. Efficacy of guselkumab on axial involvement in patients with active psoriatic arthritis and sacroiliitis: a post-hoc analysis of the phase 3 DISCOVER-1 and DISCOVER-2 studies. *Lancet Rheumatol.* https://doi.org/10.1016/S2665-9913(21)00105-3 (2021)

OSTEOARTHRITIS

Topical NSAIDs come out top for knee OA

A network meta-analysis has shown that topical and oral NSAIDs produce comparable improvements in function and are superior to paracetamol for knee osteoarthritis (OA). The risk of gastrointestinal adverse effects with topical NSAIDs was lower than that for both paracetamol and oral NSAIDs in data from 122 randomized controlled trials, and overall safety was also superior for topical NSAIDs than oral NSAIDs in data from a real-world OA cohort. Topical NSAIDs also had lower risks of all-cause mortality, cardiovascular disease and gastrointestinal bleeding compared with paracetamol in the real-world data.

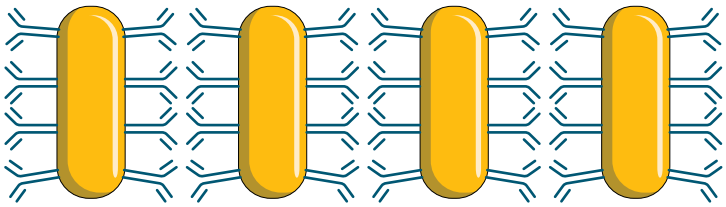
ORIGINAL ARTICLE Zeng, C. et al. Comparative efficacy and safety of acetaminophen, topical and oral non-steroidal anti-inflammatory drugs for knee osteoarthritis: evidence from a network meta-analysis of randomized controlled trials and real-world data. *Osteoarthritis Cartilage* https://doi.org/10.1016/j.joca.2021.06.004 (2021)

SPONDYLOARTHRITIS

HLA-B27 linked to progression to axSpA in FDRs

Seemingly healthy first-degree relatives (FDRs) of patients with axial spondyloarthritis (axSpA) are more likely to progress to clinical axSpA if they are HLA-B27 positive than if they are HLA-B27 negative, according to data from the Pre-SpA cohort. At baseline, 65% of the 151 FDRs reported back pain, 32% had arthralgia, 1% has psoriasis and 1% had uveitis, and clinical and radiographic findings were evenly distributed within the cohort regardless of HLA-B27 status. After 1 year, 6% of FDRs had been diagnosed with axSpA, 86% of whom were HLA-B27 positive.

ORIGINAL ARTICLE de Jong, H. M. Y. et al. Progression from subclinical inflammation to overt SpA in first degree relatives of SpA patients is associated with HLA-B27: the Pre-SpA cohort. *Arthritis Care Res.* https://doi.org/10.1002/acr.24743 (2021)



Credit: Springer Nature Limited

OSTEOARTHRITIS

Going for gold to improve anti-NGF therapy in OA

The development of agents that target nerve growth factor (NGF) as a treatment for osteoarthritis (OA) has not been a smooth process. Associations between anti-NGF antibody therapy and rapidly progressive OA have prompted research into alternative approaches to target NGF that have improved safety profiles. A new study published in *ACS Nano* is championing one such approach: antibody-directed photothermal therapy.

"Anti-NGF therapy improved pain and function in patients with OA in clinical trials. However, there was a major concern related to the development of destructive arthropathy after using high doses of anti-NGF antibody," explains Chunyi Wen, corresponding author of the new study. "To address this concern, we aimed to develop a targeted theranostic approach to locate and ablate NGF in arthritic joints using a minimal dosage of anti-NGF antibody."

To achieve this goal, Wen and colleagues utilized a technique that has been developed for cancer therapy, in which thermally conductive nanoparticles are introduced to a tumour and heated using a near-infrared laser, thereby inducing cell death. The researchers adapted this technique by conjugating gold nanorods coated with molybdenum disulfide (MoS_2; to improve their photothermal properties) to an anti-NGF antibody, thereby aiming to directly bind the nanorods to NGF molecules and induce their destruction by heat upon stimulation with the laser. This technique comes with the added bonus that the nanorods can be tracked using photoacoustic imaging, enabling the researchers to observe their localization within the body over time.

The antibody-conjugated nanorods localized to the injured knee in mice with destabilization of the medial meniscus (DMM)-induced OA, and not to the healthy contralateral knee, showing good specificity for the inflamed synovium in these mice. Following laser stimulation, the antibody-conjugated nanorods reduced signs of pain in mice with both early-stage and late-stage DMM-induced OA for at least 3 days, an effect that regressed by 7-days post-injection in line with the retention time of the therapeutic agent in the body.

Notably, treatment with the antibody-conjugated nanorods and laser stimulation reduced the amount of NGF in joint tissues without affecting the expression of its receptor TRKA compared with antibody-conjugated nanorod treatment alone, and did not cause damage to the surrounding soft tissues or bone.

"As the probe is made of gold nanorod and coated with MoS_2, it has good biocompatibility, and we aim to translate our research findings into a clinical application," says Wen. The researchers hope that their new approach will enable anti-NGF antibodies to be used at reduced doses, thereby improving their safety.

Joanna Clarke

ORIGINAL ARTICLE Au, M. T. et al. Nerve growth factor-targeted molecular theranostics based on molybdenum disulfide nanosheet-coated gold nanorods (MoS_2-AuNR) for osteoarthritis pain. *ACS Nano* https://doi.org/10.1021/acsnano.1c02454 (2021)

RELATED ARTICLE Wise, B. L. et al. The evolution of nerve growth factor inhibition in clinical medicine. *Nat. Rev. Rheumatol.* **17**, 34–46 (2021)

ACUTE INFLAMMATORY ARTHRITIS

Combination therapy for septic arthritis

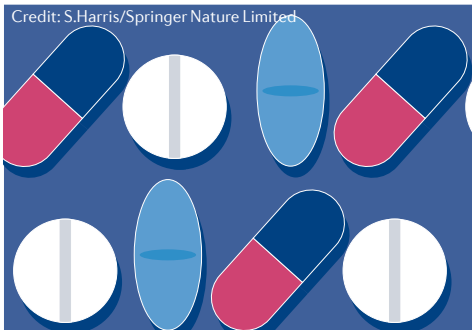
Septic arthritis can result in inflammatory damage to joint tissue, even after bacterial infection is seemingly cleared, as intracellular bacteria inaccessible to systemic antibiotics might persist. A new study in *Science Advances* demonstrates that combination therapy with a cell-penetrating antibiotic and an inflammasome inhibitor markedly reduces intracellular bacteria in synovial tissue while protecting articular cartilage.

The researchers established a mouse model of septic arthritis by intra-articular inoculation with methicillin-resistant *Staphylococcus aureus* (MRSA) under the patella. MRSA injection resulted in clinical signs similar to those in human septic arthritis, such as oedema, immune cell infiltration into the synovial cavity and increased inflammatory markers in synovial fluid and synovial tissue. Similar results were obtained for MRSA-infected human synovial tissue and cartilage in vitro, confirming the model's validity.

Next, the researchers assessed the effects of systemic therapy with vancomycin, a common treatment for human septic arthritis. Vancomycin reduced joint oedema, MRSA abundance in synovial fluid and immune cell infiltration into the synovial cavity. However, although vancomycin ameliorated the reduced articular cartilage thickness following MRSA infections, histopathological signs of osteolysis remained. In fact, pro-inflammatory cytokine levels remained elevated in synovial fluid but not serum, and intracellular MRSA remained, indicating persistent intra-articular inflammation.

Local application of a cell-penetrating antiobiotic, rifampin, rendered intracellular MRSA in synovial tissue inviable. However, even intra-articular injection of heat-killed MRSA can result in persistent inflammation and joint damage, so the researchers included the NLRP3 inflammasome inhibitor OLT1177 in the treatment regimen.

> “combination therapy also preserved joint architecture”


Credit: S.Harris/Springer Nature Limited

Combination therapy with systemic vancomycin and local rifampin and OLT1177 reduced the intracellular reservoir of MRSA, and immune cell and MRSA abundance and pro-inflammatory cytokine levels in synovial fluid. Indeed, micro-CT revealed that combination therapy also preserved joint architecture.

The authors suggest that this cartilage-preserving therapeutic approach might also be effective for the treatment of bacterial septic arthritis in humans.

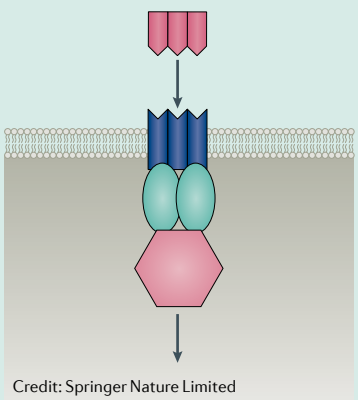
Grant Otto

ORIGINAL ARTICLE Kwon, H.-K. et al. Dual therapeutic targeting of intra-articular inflammation and intracellular bacteria enhances chondroprotection in septic arthritis. *Sci. Adv.* **7**, eabf2665 (2021)

INFLAMMATION

Anti-inflammatory TNF receptor 2 signalling unravelled

TNF, an important cytokine in many inflammatory and autoimmune diseases, can have both pro-inflammatory and anti-inflammatory effects; these opposing effects are thought to be mediated by signalling through TNF receptor 1 (TNFR1) and TNFR2, respectively. TNFR1 signalling has been intensively studied,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> “progranulin could induce a shift towards anti-inflammatory macrophage polarization via TNFR2–14-3-3ε signalling”

but less is known about TNFR2 signalling and how it affects different cell subsets.

“Our lab has a long-standing interest in TNF signalling,” states Chuanju Liu, corresponding author of a new study into the role of TNFR2 signalling in macrophages. “We previously reported that progranulin binds to TNFR1 and TNFR2 and exhibits much higher binding affinity to TNFR2 than TNF. In our new study, we performed an unbiased biochemical co-purification and proteomics screen with progranulin-stimulated macrophages, which led to the discovery of the signalling molecule 14-3-3ε as a previously-unrecognized component of TNFR2 signalling complexes.”

Following the identification of 14-3-3ε, the researchers characterized its effects in the context of chronic inflammation. Knockout of 14-3-3ε in mice with collagen-induced arthritis exacerbated disease, increased the proportion of pro-inflammatory macrophages and decreased the number of regulatory T cells in affected joints. Further in vitro and in vivo work unravelled the signalling pathways responsible for the shift towards pro-inflammatory macrophage polarization upon 14-3-3ε deletion.

Interestingly, the growth factor progranulin could induce a shift towards anti-inflammatory macrophage polarization via TNFR2–14-3-3ε signalling, suggesting that this pathway could be investigated as a potential therapeutic target for inflammatory diseases such as rheumatoid arthritis.

“Although this study discloses the importance of 14-3-3ε in TNFR2 mediated-regulation of inflammation and autoimmunity, there are still many mysteries that remain to be solved,” says Liu. “Moving forward, we will continue to delineate this novel pathway.”

Joanna Clarke

ORIGINAL ARTICLE Fu, W. et al. TNFR2/14-3-3ε signaling complex instructs macrophage plasticity in inflammation and autoimmunity. *J. Clin. Invest.* https://doi.org/10.1172/JCI144016 (2021)
RELATED ARTICLE Salomon, B. L. et al. Insights into the biology and therapeutic implications of TNF and regulatory T cells. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-021-00639-6 (2021)

SYSTEMIC LUPUS ERYTHEMATOSUS

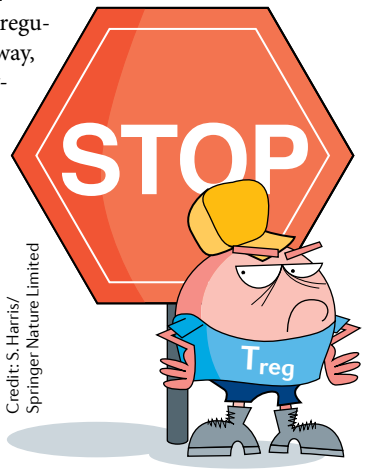
Selectins block T cells in SLE

Systemic lupus erythematosus (SLE) is an autoimmune disease in which regulatory T (T_{reg}) cells are defective. In SLE, platelets express high levels of the adhesion receptor P-selectin and T_{reg} cells express high levels of the P-selectin ligand PSGL1. Now, new research shows that platelets interact with T_{reg} cells via the P-selectin–PSGL1 complex, limiting the immunosuppressive responses of T_{reg} cells.

Among T cell populations, the authors of the new study found that T_{reg} cells had higher PSGL1 expression levels and fucosylation (a post-translational modification required for P-selectin binding) than effector T (T_{eff}) cells. In addition, circulating platelet–T_{reg} cell aggregate abundance but not that of platelet–T_{eff} cell aggregates was higher in patients with SLE than in healthy individuals and correlated with disease activity. Indeed, the platelet–T_{reg} cell interaction blocked T_{reg} cell immunosuppressive activity in vitro, likely via P-selectin–PSGL1, as recombinant P-selectin also inhibited T_{reg} suppressive activity. Similarly, P-selectin also inhibited the immunosuppressive activities of another T_{reg} cell population, follicular T_{reg} cells.

"Mechanistically, P-selectin–PSGL1 engagement induces an intracellular calcium signal mediated by the kinase Syk, which ultimately led to a downregulation of the TGFβ pathway, a major effector underlying T_{reg} cell functions," explains first author Marc Scherlinger. In fact, levels of soluble and platelet-bound P-selectin in platelet-free plasma were higher in patients with active SLE than in those with quiescent SLE or in healthy individuals, and correlated with disease activity.

> blocking P-selectin could be an effective treatment for SLE



Credit: S. Harris/ Springer Nature Limited

Finally, the researchers tested whether blocking the P-selectin–PSGL1 interaction would ameliorate disease symptoms in lupus-prone *Dnase1l3*$^{-/-}$ mice. After confirming that P-selectin similarly inhibited T_{reg} cell immunosuppressive activities in mice, the researchers treated *Dnase1l3*$^{-/-}$ mice with an anti-P-selectin antibody. This treatment reduced the serum levels of anti-double-stranded DNA antibodies and loss of marginal zone B cells in the spleen, and improved kidney pathology, indicating that blocking P-selectin could be an effective treatment for SLE.

"These results could pave the way to the use of anti-P-selectin treatment in SLE, as a multitarget therapy able to restore immune balance and protect against atherosclerosis without promoting infections, unlike classical immunosuppressive drugs," comments Scherlinger.

Grant Otto

ORIGINAL ARTICLE Scherlinger, M. et al. Selectins impair regulatory T cell function and contribute to systemic lupus erythematosus pathogenesis. *Sci. Transl Med.* **13**, eabi4994 (2021)

THERAPY

New treatments for amyloidosis

Amyloidosis is a heterogeneous group of diseases, characterized by the progressive accumulation of amyloid fibrils in tissue, which can arise as a complication of chronic rheumatic diseases and also involve musculoskeletal and articular manifestations. Two new studies published in *The New England Journal of Medicine* highlight advances in treatments for systemic immunoglobulin light-chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis, two progressive and life-threatening forms of amyloidosis.

AL amyloidosis is characterized by deposition of amyloid fibrils of immunoglobulin light chains produced by clonal CD38^{+} plasma cells. The phase III ANDROMEDA trial evaluated the safety and efficacy of daratumumab, a human monoclonal antibody that targets CD38. In the study, 388 patients with newly diagnosed AL amyloidosis were randomly allocated to receive treatment with six cycles of bortezomib, cyclophosphamide and dexamethasone with or without the addition of subcutaneous daratumumab; patients in the daratumumab group then continued to receive the agent as monotherapy every 4 weeks for up to 24 cycles.

After 6 months, haematologic complete response was seen in more patients who received daratumumab than in those who did not (53.3% versus 18.1%) and occurred more rapidly in the daratumumab group. Survival free from major organ deterioration or haematologic progression was also longer in the daratumumab group (hazard ratio 0.58; 95% CI 0.36–0.93), and rates of adverse events and deaths were balanced between the two groups.

> Two new studies … highlight advances in treatments for [AL] amyloidosis and [ATTR] amyloidosis

ATTR amyloidosis involves the accumulation of misfolded transthyretin (TTR) protein in tissue, mainly the heart and nerves; NTLA-2001 is an in vivo gene-editing therapeutic agent based on the CRISPR–Cas9 system that was designed to treat the disease by targeted knockout of *TTR*. Interim data from an ongoing phase I dose-escalation trial in six patients with hereditary ATTR amyloidosis with polyneuropathy indicate that systemic administration of NTLA-2001 at a dose of 0.1 mg/kg or 0.3 mg/kg reduced serum TTR protein concentration by a mean of 52% (range 47–56%) or 87% (range 80–96%), respectively, after 28 days.

Treatment with NTLA-2001 was well-tolerated. The interim results of the study offer proof-of-concept of this in vivo gene-editing approach, and further studies will aim to determine the optimum dose.

Sarah Onuora

ORIGINAL ARTICLES Kastritis, E. et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. *N. Engl. J. Med.* **385**, 46–58 (2021) | Gillmore, J. D. et al. CRISPR-Cas9 in vivo gene editing for transthyretin amyloidosis. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2107454 (2021)

SYSTEMIC SCLEROSIS

Linking autoimmunity, short telomeres and lung fibrosis in SSc

Katja Lakota and John Varga

Short telomere length is implicated in lung diseases and can be caused by mutations in telomere genes. Acquired autoimmunity directed against components of the telomere system is now reported in some patients with systemic sclerosis or idiopathic pulmonary fibrosis, suggesting a novel explanation for short telomeres in these diseases.

Refers to Adler, B. L. et al. Autoantibodies targeting telomere-associated proteins in systemic sclerosis. *Ann. Rheum. Dis.* **80**, 912–919 (2021).

Of the myriad unanswered questions about systemic sclerosis (SSc), one of the most intriguing concerns the origin of disease-specific autoantibodies and their contribution to the multi-organ fibrosis characteristic of SSc. In particular, investigators have long sought to discover the primary antigens that trigger SSc-specific autoimmunity. Although the answer remains elusive, a growing list of autoantibodies have been identified in patients with SSc, making it easier to anticipate particular complications, predict outcomes and individualize treatments. Now, a study by Adler et al.[1] adds to the field by identifying novel autoantibodies that are directed against telomere-maintenance proteins and are associated with abnormally short telomere length in patients with SSc, particularly those with interstitial lung disease (ILD). These intriguing observations not only expand the repertoire of known SSc-associated autoantibodies, but also (re)focuses attention on telomeres in SSc and ILD.

Telomeres are repetitive DNA segments that shield chromosome ends and get progressively shorter with each cell division. Importantly, short telomere length is itself pathogenic, as once telomeres becomes critically short, cells activate the DNA damage response, which triggers apoptosis and cellular senescence. Indeed, telomere shortening has been proposed as an important driver of the ageing process[2]. Telomere attrition has been studied most intensively in lung disease, where short telomere length has been associated with both familial and sporadic forms of ILD[3]. The recognition that short telomere length is also associated with SSc-associated ILD (SSc-ILD) and, as now suggested by Adler et al., might result from autoimmunity[1], has far-reaching implications for the pathogenesis, classification and perhaps even treatment of SSc (FIG. 1).

Interstitial lung involvement can be detected in up to 80% of patients with SSc and is one of the leading causes of SSc-related mortality[4]. Although it shares important characteristics with idiopathic pulmonary fibrosis (IPF), SSc-ILD has distinct genetic risk factors, epidemiology, pulmonary pathology and natural history[4]. In contrast to SSc-ILD, IPF has not been traditionally viewed as an autoimmune condition. Genetic studies uncovered mutations in telomere-related genes (TRGs) in individuals with IPF, and these mutations were associated with abnormally short telomere length. In patients with IPF, short telomere length predicts a more aggressive disease course and reduced survival following lung transplantation[5]. Remarkably, many patients with IPF and short telomere length have no identifiable TRG mutations.

Previous studies examining telomere alterations in SSc demonstrated abnormally short telomere length, but also the opposite[6,7]. Using flow cytometry with fluorescence in situ hybridization (Flow-FISH) to measure age-adjusted telomere length in patients with SSc[6], we found that those with ILD had shorter age-adjusted telomere length in lymphocytes than those without ILD. Notably, patients with SSs who had the greatest reduction in telomere length had more severe lung disease.

Adler et al. now present evidence that patients with SSc mount an autoimmune response to telomere maintenance proteins[1]. Autoantibodies directed against telomere reverse transcriptase or shelterin proteins, most commonly telomeric repeat-binding factor 1 (TERF1), were detected by immunoprecipitation in 7 of 200 patients with SSc (3.5%); in 6 of these 7 patients, the antibodies recognized more than one telomere-associated protein. Using ELISA, 22 of the 200 patients (11%) were found to have anti-TERF1 autoantibodies; this finding was validated in an independent cohort of patients with SSc. Positivity for anti-TERF1 autoantibodies was associated with severe lung disease and low diffusion capacity[1]. Anti-TERF1 autoantibodies were extremely rare in patients with rheumatoid arthritis or myositis (1/60 and 1/60 respectively), but were found in 11/152 (7%) of patients with IPF.

To gain insight into the potential ramifications of autoantibodies targeting the telomere maintenance system, Adler et al. next measured telomere length. Multiple methods are available for determining telomere length in peripheral blood, each with its drawbacks[3]. Using qPCR, Adler et al. found that age-adjusted telomere length was shorter in anti-TERF1 antibody-positive patients with SSc compared to those who were antibody negative. Using Flow-FISH, short telomere length was noted in lymphocytes, but not in granulocytes, from these patients. These findings are consistent with our own study, in which we described short telomere length in lymphocytes, but not granulocytes, in patients with SSc-ILD[6]. A gap between lymphocyte and granulocyte telomere length has been recognized as indicative of a non-genetic cause for short telomere length, potentially attributed to the divisional history of the cell as well as its telomerase activity[8]. In contrast to mature granulocytes that do not undergo cell divisions, lymphocytes are long-lived, and

their telomere length decreases with proliferation and repeated cell activation. Consistent with a non-genetic cause for short telomere length, none of the patients with SSc and very short telomere length in our study[6] was found to have identifiable mutations in TRGs. Indeed, to date neither rare TRG mutations nor common ILD-associated single nucleotide polymorphisms (SNPs) have been reported in SSc.

The intriguing new findings raise important questions. First, what is the origin of anti-telomere autoimmunity in SSc, and is it unique to SSc? The Adler et al. finding of anti-telomere autoimmunity in IPF also suggests revisiting autoimmunity in this disease. Second, in light of the association of anti-telomere autoimmunity in SSc with short telomere length, do these autoantibodies directly influence telomere function (and if so, by what mechanism), or do they represent epiphenomena without a direct pathogenic effect? Alternatively, do these autoantibodies directly impair the function of their targets, such as TERF1, thereby causing tissue damage without causing telomere shortening?

Third, does the association of short telomere length with severe lung involvement in SSc imply a causal role, or are short telomeres simply markers of accelerated cellular ageing due to recurrent injury and activation? To address this question, it would be ideal to know whether parenchymal cells in the lungs of patients with SSc-ILD also have short telomeres, which could provide a plausible mechanistic link between short telomeres and lung injury leading to fibrosis. Indeed, telomere dysfunction has been shown to directly promote myofibroblast transdifferentiation[9].

Fourth, could determining telomere length have utility for predicting progressive lung disease in patients with SSc, and if so which robust yet pragmatic methodology is best suited for clinical practice? In view of preliminary evidence that patients with IPF who have short telomere length have poorer therapeutic responses and a greater risk of adverse events compared with patients with IPF and normal telomere length[10], would detecting short telomere length in patients with SSc influence therapeutic decisions?

If validated and reproduced, the results reported by Adler et al. are highly important. These observations expand the repertoire of SSc-associated autoantibodies and might provide an explanation for short telomere length in patients with SSc-ILD (and possibly other types of ILD) who have no identifiable mutations in TRGs. These findings should stimulate new research into the complex pathogenesis of SSc and the links between autoimmunity and fibrosis.

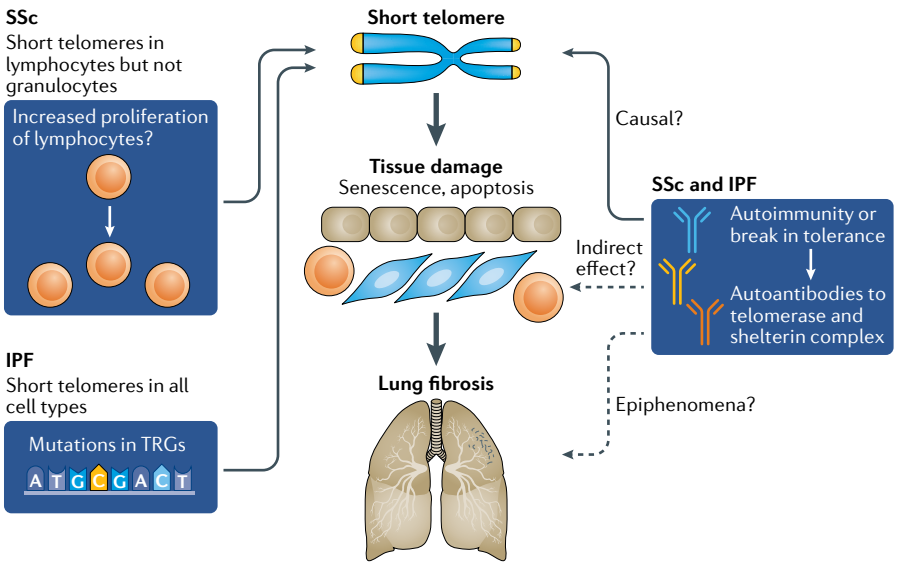


Fig. 1 | **Potential origin and role of SSc-associated anti-telomere autoimmunity in short telomeres and ILD.** A subset of patients with systemic sclerosis (SSc), particularly those with interstitial lung disease (ILD), have short telomeres in lymphocytes, which can be accompanied by circulating autoantibodies against telomerase and members of the shelterin complex, such as telomeric repeat-binding factor 1 (TERF1). Whether these antibodies contribute to short telomere length remains unknown. Patients with idiopathic pulmonary fibrosis (IPF) have short telomere length due to mutations in telomere-related genes (TRGs), contributing directly to lung damage, but the role of short telomere length in SSc-associated ILD is unknown.

Katja Lakota [1] *and John Varga* [2]✉

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https://doi.org/10.1038/s41584-021-00666-3

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Competing interests
The authors declare no competing interests.

RHEUMATOID ARTHRITIS

2021 ACR guideline reflects changes in RA treatment

Rieke Alten and Max Mischkewitz

The 2021 ACR guideline for the treatment of rheumatoid arthritis provides an update on several important topics, including the use of targeted synthetic DMARDs (tsDMARDs). But how does the new guideline compare to EULAR recommendations, and is the growing importance of tsDMARDs adequately accounted for?

Refers to Fraenkel, L. et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol.* https://doi.org/10.1002/art.41752 (2021).

Since the last update of the ACR guideline for the treatment of rheumatoid arthritis[1] (RA) in 2015, several new compounds (such as baricitinib and upadacitinib) have been approved, and new data concerning the safety and efficacy of established DMARDs (tofacitinib in particular) have been published. The 2021 update[2] to the guideline has been eagerly awaited, but does it live up to the expectations of the rheumatology community? And how does it compare to the 2019 EULAR guideline[3]?

The 2021 ACR guideline[2] discusses relevant clinical situations in pharmacological therapy for RA and issues conditional and strong recommendations for action. In particular, we highly appreciate the continued focus on shared decision-making in the guideline's guiding principles. Applying shared decision-making to treatment decisions appropriately involves patients' priorities and can thus result in enhanced therapy adherence[4]. In this context, we consider the participation of a patient panel in developing this guideline to be positive. According to the guideline[2], treatment should aim to achieve a specific target of disease activity. In patients with moderate-to-high disease activity, methotrexate is regarded as the first choice DMARD, whereas in individuals with low disease activity, the guideline favours hydroxychloroquine over other conventional synthetic DMARDs (csDMARDs). The addition of biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is recommended for patients who do not achieve their treatment targets under methotrexate monotherapy, and the use of glucocorticoids is conditionally advised against[2].

In comparison to the most recent update[3] of the EULAR recommendations for the management of RA with csDMARDs and bDMARDs from 2019, a number of differences can be noted (TABLE 1). Whereas the EULAR recommendations favour methotrexate as the csDMARD of first choice regardless of disease activity[3], the ACR guideline conditionally recommends hydroxychloroquine and sulfasalazine over methotrexate in patients with low disease activity to avoid adverse effects associated with methotrexate use — a concern of the patient panel[2]. Nonetheless, methotrexate might still be preferred in some low disease activity settings, such as in the presence of poor prognostic factors[2] (for example, early erosions or the presence of high rheumatoid factor and/or anti-citrullinated protein antibody titres[5]). Methotrexate therefore remains the paramount compound for the pharmacological treatment of RA.

Another major difference between the ACR and EULAR guidelines concerns the use of glucocorticoids during the initiation of DMARDs. The ACR guideline explicitly states a conditional recommendation against the use of short-term glucocorticoid therapy, considering their potential toxicity[2]. By contrast, the EULAR recommendations advise the use of short-term glucocorticoid therapy as a bridging therapy until DMARDs become fully effective[3]. In our clinical experience, short-term glucocorticoid therapy remains a valuable tool to rapidly alleviate patients' symptoms when possible adverse effects are borne in mind and minimized[6]. Considering the usually delayed onset of the effects of csDMARDs, the avoidance of short-term glucocorticoid therapy could be difficult to implement in clinical practice.

In patients who reach their treatment target for at least six months, the ACR guideline favours no modification to DMARD therapy over a dose reduction, and a dose reduction over tapering of DMARDs[2]. If tapering is used, methotrexate should be tapered first in those patient who are treated with both methotrexate and bDMARD or tsDMARD therapy. In the EULAR recommendations, tapering of bDMARDs or tsDMARDs can be considered for patients in persistent remission (after discontinuation of glucocorticoids)[3]. Remarkably, the patient panel involved in creating the ACR guideline clearly spoke out in favour of tapering DMARDs, as they wished to minimize the risk of adverse events[2]. In our clinical experience, patients particularly desire to taper methotrexate owing to symptoms related to drug intolerance. However, the rationale for tapering methotrexate first in the ACR guideline is that patients being treated with methotrexate and bDMARD or tsDMARD therapy usually have a history of an inadequate response to methotrexate monotherapy. Thus, maintenance of the treatment target seems to be more likely in these patients under continued treatment with bDMARDs or tsDMARDs[2]. This notion seems to be reinforced in the results of a randomized controlled trial in which remission rates were compared between methotrexate monotherapy, etanercept monotherapy and methotrexate and etanercept combination therapy[7]. In this study, a greater percentage of patients receiving etanercept monotherapy maintained remission 24 weeks after randomization than those who received methotrexate monotherapy.

Comparing the 2021 guideline with its previous iteration, in the 2015 ACR guideline[1], triple therapy (methotrexate or leflunomide plus hydroxychloroquine and sulfasalazine) was recommended for patients with an inadequate response to csDMARD monotherapy (in addition to other strategies involving csDMARDs, bDMARDs and tofacitinib). By contrast, the 2021 guideline favours the addition of a bDMARD or tsDMARD to methotrexate in such patients over triple therapy[2]. In line with the views of the guideline's patient panel, we welcome the rejection of triple therapy in order to achieve an earlier onset of DMARD effects and a higher treatment persistence.

In addition, since the 2015 guideline, two new tsDMARDs have been approved by the FDA: baricitinib and upadacitinib[8]. Accordingly, their position within the 2021 guideline's treatment sequence is interesting to analyse. Alongside bDMARDs, tsDMARDs are recommended to be added to methotrexate in patients who have an inadequate response to methotrexate monotherapy[2]. Intriguingly, the voting panel debated whether tsDMARDs were preferable to methotrexate as a first-line treatment in patients with moderate-to-high

Table 1 | **Key differences between the 2021 ACR guideline and the 2019 EULAR recommendations for RA treatment**

Clinical scenario	2021 ACR guideline[2]	2019 EULAR recommendations[3]
First-line therapy	Low disease activity: hydroxychloroquine	Methotrexate (in the absence of contraindications)
	Moderate-to-high disease activity: methotrexate	
Use of glucocorticoids	Conditional recommendation against glucocorticoids when starting csDMARDs	Consider short-term glucocorticoids when starting or switching csDMARDs
Insufficient response to methotrexate	Add bDMARDs or tsDMARDs	Poor prognostic factors absent: consider other csDMARDs
		Poor prognostic factors present: add bDMARDs or tsDMARDs
Drug tapering in persistent remission	Continue all DMARDs	Taper glucocorticoids first, then consider tapering bDMARDs or tsDMARDs, then csDMARDs
	If tapering is considered, taper methotrexate, not bDMARDs or tsDMARDs	

bDMARDs; biologic DMARDs; csDMARDs, conventional synthetic DMARDs; RA, rheumatoid arthritis; tsDMARDs, targeted synthetic DMARDs.

disease activity; however, although evidence of moderate certainty indicating a higher efficacy of tsDMARD monotherapy than methotrexate monotherapy is available, long-term safety data for upadacitinib and baricitinib in particular are still scarce, so tsDMARDs were not recommended as a first-line therapy[2]. The results of the SELECT-EARLY study do suggest a greater efficacy of upadacitinib compared with methotrexate in DMARD-naive patients with RA with moderate-to-high disease activity[9]. However, the safety profile of tsDMARDs is not yet entirely clear. Preliminary safety data from the ORAL Surveillance study (a post-marketing safety study of tofacitinib) seem to indicate a higher risk of major cardiovascular events and malignancies (excluding non-melanoma skin cancer) in patients with RA aged 50 years or older with at least one cardiovascular risk factor who received tofacitinib therapy compared with those who received TNF inhibitor therapy[10]. It remains to be seen whether the final results will confirm this conclusion and, if so, whether this safety concern is solely an effect of tofacitinib, or is a drug-class effect. Considering the available evidence, favouring methotrexate over a tsDMARD as the first-line treatment in patients with moderate-to-high disease activity seems reasonable. Yet, if data on tsDMARD efficacy remain promising and acceptable long-time safety can be proven, tsDMARDs will need to be considered as the DMARDs of first choice for RA.

Overall, even though several thousand abstracts and full-text articles were screened for the 2021 ACR guideline[2], the certainty of evidence was low or very low for many recommendations. As such, further research investigating the efficacy and safety of tsDMARDs, comparing specific bDMARD and tsDMARD therapy regimens in individuals with an inadequate response to methotrexate, and minimizing glucocorticoid toxicity will need to be conducted to formulate more solid recommendations. Furthermore, trials comparing different approaches to dose reduction and tapering also remain scarce, yet such concepts are of crucial relevance for the optimal long-term management of RA and are strongly desired by the 2021 ACR guideline's patient panel.

Altogether, the new ACR guideline[2] provides one possible way to balance the rising costs of treating patients to target and maintaining sustained remission. The most important advance is probably the departure from triple therapy and its replacement with bDMARDs and tsDMARDs as second-line therapies. tsDMARDs in particular have received a notable upgrade in comparison with the guideline's last update[1], reflecting not only new data concerning their efficacy and safety, but also patients' preference for oral medications. In the coming months and years, emerging data on tsDMARDs will be interesting to follow, as tsDMARDs have the potential to become increasingly important for the pharmacological treatment of RA.

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Competing interests

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Global epidemiology of systemic lupus erythematosus

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Abstract | Systemic lupus erythematosus (SLE) is an autoimmune disease with protean manifestations that predominantly affects young women. Certain ethnic groups are more vulnerable than others to developing SLE and experience increased morbidity and mortality. Reports of the global incidence and prevalence of SLE vary widely, owing to inherent variation in population demographics, environmental exposures and socioeconomic factors. Differences in study design and case definitions also contribute to inconsistent reporting. Very little is known about the incidence of SLE in Africa and Australasia. Identifying and remediating such gaps in epidemiology is critical to understanding the global burden of SLE and improving patient outcomes. Mortality from SLE is still two to three times higher than that of the general population. Internationally, the frequent causes of death for patients with SLE include infection and cardiovascular disease. Even without new therapies, mortality can potentially be mitigated with enhanced quality of care. This Review focuses primarily on the past 5 years of global epidemiological studies and discusses the regional incidence and prevalence of SLE and top causes of mortality.

Prevalence
The total number of cases of disease in a given timeframe.

Incidence
The number of new cases of disease during a specified timeframe.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with heterogeneous clinical manifestations ranging from mild cutaneous disease to catastrophic organ failure and obstetrical complications. Young women are disproportionately affected by SLE, with a greater prevalence and incidence of this disease in certain ethnic populations such as Black, Asian and Hispanic populations[1,2].

Reports from the past 5 years on the incidence and prevalence of SLE have shown considerable variation across global regions and even within subpopulations[3–5]. These differences are probably attributable to true variation, but also to differences in study design and case definition.

Unfortunately, SLE is one of the leading causes of death in young women[6]. In a meta-analysis of >26,000 female patients with SLE in the USA, the all-cause mortality was 2.6-fold higher than that of the general population, with a standardized mortality ratio (SMR) of more than 2 for cardiovascular disease and SMRs of almost 5 for infection and renal disease[7].

In this Review, we focus on studies that have been published in the past 5 years on SLE epidemiology, and provide an update on the incidence, prevalence and mortality rates of SLE while discussing the leading causes of death in major global geographic regions. We include older studies from regions with very limited data, such as Africa and Australia. We discuss frequent causes of death across international regions that are potentially remediable through improved quality of care[8], and the factors that contribute the most to unfavourable outcomes in each region, such as ethnicity and socioeconomic status. An updated understanding of the international burden of SLE is needed to enable us to allocate resources and address health disparities.

Epidemiology by geographic region

North America

Incidence and prevalence. Estimates of the number of cases of SLE in North America vary widely, with the reported overall incidence ranging between 3.7 per 100,000 person-years and 49 per 100,000 in the US Medicare population[9,10] and the prevalence ranging from 48 to 366.6 per 100,000 individuals[9,11]. In the past few years, data from incidence and prevalence studies from 1946 to 2016 have been comprehensively reviewed[3–5]. Epidemiological efforts conducted in North America from 2015 to 2020 are summarized in TABLE 1 and TABLE 2, and further details are available in Supplementary Information Tables 1 and 2.

Historically, researchers have estimated the burden of SLE in the USA using several different methods of

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Key points

- The estimated incidence, prevalence and mortality of systemic lupus erythematosus (SLE) vary considerably between geographic regions.
- Factors that contribute to the variation across different regions include differences in ethnicity, environmental exposures and socioeconomic status but non-uniform SLE definitions and study design also contribute.
- Population-based studies in the developing world are urgently needed to understand the global burden of disease.
- Mortality in patients with SLE is still unacceptably high, being two to three times higher than that of the general population.
- Infectious diseases and cardiovascular disease are consistently top causes of death in patients with SLE.
- Even without the development of new therapies, SLE outcomes may be improved by focusing on remediable SLE-specific adverse conditions.

Capture-recapture methodology
A method that determines the extent of overlap across multiple case-finding sources to adjust for case under-ascertainment.

case identification, including death registries, clinic and hospital records and claims-based databases that are reliant on International Classification of Disease (ICD) codes[12]. To better capture the extent of the burden of SLE, particularly in minority populations, five regional lupus surveillance projects were funded by the Centers for Disease Control and Prevention (CDC). These rigorous studies used several different clinical and laboratory databases for case finding, and employed capture-recapture methodology, which determines the extent of overlap in multiple case-finding sources to adjust for case under-ascertainment. The first registries from Georgia and Michigan were published in 2014, and reported similar overall incidence (5.6 and 5.5 per 100,000 person-years, respectively) and prevalence (73.0 and 72.8 per 100,000 individuals, respectively) rates[13,14]. These analyses reaffirmed the known disparity between Black and white patients with SLE: the incidence and prevalence of SLE was more than twice as high in Black patients than in white patients and Black patients were diagnosed at an earlier age and experienced renal disease more often (40.5% of Black patients had renal disease versus 18.8% of white patients)[13]. An additional registry focused on American Indian and Alaska Native populations, finding that the estimated prevalence and incidence equalled or exceeded that of the Black population[15].

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Subsequently, registries were formed in California and New York, which provided the first accurate portrayal of the burden of SLE in Hispanic and Asian populations. Findings from the California Lupus Surveillance Project were published in 2017, based on data from San Francisco County between 2007 and 2009 (TABLE 1). The overall annual age-standardized incidence was by far the highest in Black women (30.5 per 100,000 person-years) and lowest in white women (5.3)[1]. Age-standardized prevalence was also higher in the Black female population (458.1 per 100,000 individuals) than in any other ethnicity[1]. Results from the Manhattan Lupus Surveillance Project were published in 2017 and similarly highlighted ethnic disparity inherent to SLE. Incidence rates were highest in non-Hispanic Black women compared with any other group[2]. The prevalence was also highest in non-Hispanic Black women (221.4 per 100,000 individuals), followed by Hispanic and non-Hispanic Asian women (142.7 and 118.5 per 100,000 individuals, respectively). The prevalence was lowest in non-Hispanic white men (6.3 per 100,000 individuals). Other work has emphasized the increased frequency of SLE in minority populations, with the age-adjusted incidence being twice as high in Arab American and Chaldean American populations than in white populations[16].

Emerging data suggest that the prevalence of SLE is rising over time. Analysis of US Medicare data suggest that the age- and sex-adjusted prevalence of SLE was 301.1 per 100,000 individuals in 2009 and rose to 366.6 per 100,000 individuals by 2016 (REF.[9]). The adjusted incidence rates were similar across this time frame (46.9 and 49.0 per 100,000 in the US Medicare population, respectively). The prevalence of SLE is also increasing over time in Canada, with administrative data from Alberta revealing a stable incidence between 2000 and 2015, but an increase in prevalence from 48 per 100,000 individuals in 2000 to 90 per 100,000 individuals in 2015 (REF.[11]).

Mortality. In a comprehensive analysis published in 2017, researchers assessed the trends in mortality of patients with SLE in the USA over almost half a century (1968–2013) using the CDC's National Vital Statistics System and census data[17] (TABLE 2). SLE was the underlying cause of over 50,000 deaths during this period. The annual age-standardized mortality rate (ASMR) for patients with SLE declined between 1968 and 1975, followed by an increase between 1975 and 1999. Between 1999 and 2013, the mortality again declined. The ASMR was 0.45 per 100,000 individuals in 1968 and 0.34 per 100,000 individuals in 2013, representing a decrease of 24.4%. Over this time, annual ASMRs decreased less for patients with SLE than other patients, who experienced a relative decrease of 43.9%. In a multiple logistic regression analysis, female sex, residence in the South or West, age over 65 and minority ethnic group were individual factors independently associated with a higher risk of death[17]. Despite the decreases in mortality, SLE was still a leading cause of death in young women in the USA between 2000 and 2015 (REF.[6]).

Deaths from SLE are unevenly distributed among ethnic groups. In an analysis of data from the Georgia

Table 1 | **International incidence and prevalence of SLE by geographic region**

Region	Study description	Ethnicity and sex (%)	Incidence (cases per 100,000 person-years unless otherwise specified)	Prevalence (cases per 100,000 persons unless otherwise specified)	Ref.
North America					
Southeastern Michigan, USA	Population survey (2002–2005); used the ACR 1997 criteria	Arab or Chaldean American (2); non-Arab, non-Chaldean, white (39); non-Arab, non-Chaldean Black (59); female (91.1); male (8.9)	Arab or Chaldean American: 7.6; non-Arab, non-Chaldean, white: 3.7; non-Arab, non-Chaldean, Black: 8.8	Arab or Chaldean American: 62.6; non-Arab, non-Chaldean, white: 52.3; non-Arab, non-Chaldean, Black: 120.1	16
San Francisco County, CA, USA	Population survey (2007–2009); used ACR 1997 criteria or an alternative definition of SLE (three ACR criteria plus a documented diagnosis of SLE or related renal disease)	Black (20); white (37); Asian or Pacific Islander (37); Hispanic (15); female (88.9); male (11.1)	Overall: 4.6; Black: 15.5; white: 2.8; Asian or Pacific Islander: 4.1; Hispanic: 4.2	Overall: 84.8; Black: 241.0; white: 55.2; Asian or Pacific Islander: 90.5; Hispanic: 94.7	1
Manhattan, NY, USA	Population survey (2007–2009), using the ACR 1997 criteria, SLICC 2012 criteria or treating rheumatologist's diagnosis	Non-Hispanic white (28); non-Hispanic Black (26); Hispanic (32); non-Hispanic Asian (10); non-Hispanic other (3); female (90.6); male (9.4)	Overall: 6.0; non-Hispanic white: 5.6; non-Hispanic Black: 10.1; Hispanic: 4.1; non-Hispanic Asian: 5.4	Overall: 75.9; non-Hispanic white: 51.4; non-Hispanic Black: 133.1; Hispanic: 84.6; non-Hispanic Asian: 75.5	2
Olmsted County, MN, USA	Medical record review (1993–2005); used the ACR 1997 or SLICC 2012 criteria	White (84); Black (7); Asian (5); Native American (2); female (93.2); male (6.8)	ACR 1997: 3.7; SLICC 2012: 4.9	NR	10
Alberta, Canada	Administrative database analysis (2000–2015); used ICD codes	Ethnicity NR; female (85.8); male (14.2)	Overall: 4.4 per 100,000 population; male: 1.3 per 100,000 population; female: 7.7 per 100,000 population	Overall (year 2000): 48; male (year 2000): 13.5; female (year 2000): 83.2; overall (year 2015: 90; male (year 2015): 25.5; female (year 2015): 156.7	11
USA	Cross-sectional analysis (2009–2016); used ICD codes	White (87); Black (7); Asian (2); Hispanic (1); other (3); female (88.0); male (12.0)	Overall (year 2009): 46.9 per 100,000 in the US Medicare population; overall (year 2016): 49.0 per 100,000 in the US Medicare population	Overall (year 2009): 301.1; overall (year 2016): 366.6	9
Europe					
France	Cross-sectional registry analysis (2010); used ICD codes	French population: ethnicity NR; female (86.7); male (13.3)	Overall: 3.3; female: 5.5; male: 0.9	Overall: 47.0; female: 79.1; male: 11.8	28
Sweden	Cross-sectional registry analysis (2010); used ICD codes, physician visits and prescription records	Swedish population: ethnicity NR; female (81–87); male (13–19)	NR	Overall[a]: 46–85; female[a]: 79–144; male[a]: 12–25	29
Val Trompia, Italy	Analysis of data from hospital, general practitioner and laboratory records (2009–2012); used the ACR 1982 criteria	Val Trompia region, defined in northern Italy: ethnicity NR; female (89); male (11)	Overall: 2.0	Overall (year 2012): 39.2; female: 68.8; male: 9.0	32
Germany	Cross sectional registry analysis (2002); used ICD codes	German: ethnicity NR; female (80); male (20)	Female: 1.9; male: 0.9	36.7	24
Southern Sweden	Longitudinal prospective study (1994–2006); potential cases retrieved using ICD codes and ANA testing, and the diagnosis was confirmed through medical file review using Fries & Holman's criteria[110], and thereafter classified using the ACR 1982 criteria	Residents within a defined region in Southern Sweden: female (85); male (15)	2.8	Point prevalence (year 2006): 65	31

Table 1 (cont.) | **International incidence and prevalence of SLE by geographic region**

Region	Study description	Ethnicity and sex (%)	Incidence (cases per 100,000 person-years unless otherwise specified)	Prevalence (cases per 100,000 persons unless otherwise specified)	Ref.
Europe (cont.)					
UK	Longitudinal registry-based study (1999–2012); used Read codes	Ethnicity information available for 61.9% of the study population, distributed as below: white (44.9); Indian (0.8); Black African (0.7); Pakistani (0.6); Black Caribbean (0.4); Chinese (0.2); Bangladeshi (0.2); other/unclassified/mixed (50.3); female (86); male (14)	Overall: 4.9; female: 8.3; male: 1.4	Point prevalence; overall (year 2012): 97.0; in the subgroup where ethnicity was available: white: 134.5; Indian: 193.1; Black African: 179.8; Pakistani: 142.8; Black Caribbean: 517.5; Chinese: 188.4; Bangladeshi: 80.3	27
Crete, Greece	Community-based registry analysis that retrieved cases from multiple sources (1999–2013); used ACR 1997 or SLICC 2012 criteria	Greek, residents of Crete: ethnicity NR; female (92.3); male (7.7)	Overall: 7.4	Point prevalence (year 2013): 123.4	30
Denmark	Longitudinal analysis of the National Patient Registry (1995–2011); used ICD codes	Danish population: ethnicity NR; female (86); male (14)	Overall: 2.3; female: 4.0; male: 0.7	Point prevalence (year 2011): 45.2	25
Estonia	Registry-based study (2006–2010); cases retrieved using ICD codes and a medical file review and the diagnosis verified using the ACR 1982 criteria	Estonian population: ethnicity NR; female (89.7); male (10.3)	Interval[b]: 1.5–1.8	Interval[b]: 37–40	34
Malta	Cross-sectional cohort analysis (2012–2016); used the SLICC 2012 criteria	White (97.2); Asian (0.3); female (93.5); male (6.5)	1.5	29.3	33
Spain	Questionnaire-based cross-sectional analysis (2016–2017); diagnosis confirmed by a medical file review and, if needed, a medical visit	Spanish population: ethnicity NR; female (83); male (17)	NR	210	35
Hungary	Registry based study (2008–2017); used ICD codes	Hungarian population: ethnicity NR; female (85); male (15)	Year (2008–2017): 4.9; year (2016): 3.8	Year (1999): 36.1; year (2016): 70.5	26
South America					
Argentina	Study based on a single private healthcare organization that serves 5–7% of the population (1998–2009); used the ACR 1997 criteria	Predominantly white; female (83.8); male (16.2)	6.3	58.6	48
State of Monagas, Venezuela	Cross-sectional study; used COPCORD methodology	NR	NR	0.07 cases per 100 screened individuals	50
Cuenca City, Ecuador	Cross-sectional study; used COPCORD methodology	NR	NR	0.06 cases per 100 screened individuals	51
Rosario City, Argentina	Cross-sectional study; used COPCORD methodology	Qom indigenous (100)	NR	0.06 cases per 100 screened individuals	52
Colombia	Nationwide database analysis (2012–2016); used ICD codes	Ethnicity NR; female (89); male (11)	NR	Overall (crude): 91.9; individuals aged ≥18 years (crude): 126.3; female (adjusted[c]): 204.3; male (adjusted[c]): 20.2	49
Colombia	Incidence rates were calculated by applying the illness-death model, using age-specific prevalence data (2012–2016) from Fernández-Avila et al.[49], the overall Colombia mortality from the World Health Organization[111] and hazard ratio trends for SLE adapted from Bernatsky et al.[112]	NR	Females (aged 30–39 years): 20; females (aged 45 years): 1; males (aged 20–29 years): 2.5; males (aged ≥75 years): 2.8	NR	47

Table 1 (cont.) | **International incidence and prevalence of SLE by geographic region**

Region	Study description	Ethnicity and sex (%)	Incidence (cases per 100,000 person-years unless otherwise specified)	Prevalence (cases per 100,000 persons unless otherwise specified)	Ref.
South America (cont.)					
Tucumán State, Argentina	Hospital and clinical record review (2005–2012); used the ACR 1997 criteria	Mestizo (83); female (93.5); male (6.5)	Year 2007: 1.4; year 2012: 4.2	34.9	46
Asia					
Taiwan	Retrospective cohort study (2000–2007); used ICD codes	Taiwan Chinese: female (88); male (12)	Average incidence (years 2000–2007): 8.1	Average prevalence (years 2000–2007): 55.6	57
Taiwan	Population-based cohort study (2003–2008); used ICD codes	Taiwan Chinese: female (87.4); male (12.6)	4.9	97.5	61
Korea	Retrospective cohort study (2006–2010); used the ACR 1997 criteria	Korean: female (85.6); male (14.4)	Year 2008: 2.5; year 2009: 2.8	Year 2006: 20.6; year 2007: 21.9; year 2008: 23.5; year 2009: 24.9; year 2010: 26.5	58
China	Population-based case–control study (2009–2010); used the ACR 1997 criteria	Mainland Chinese: female (91.3); male (8.7)	NR	37.6	60
United Arab Emirates	Retrospective cohort study (2009–2012), using ACR (version not specified or SLICC 2012 criteria	Native Arabian (100); female (81.3); male (18.7)	8.6	103	59
Australasia					
New Zealand	Retrospective cohort study and medical records review (1975–1981); used the Fries & Holman criteria[110]	White (71); Polynesian (25); other (4); female (90); male (10)	NR	Overall (Auckland): 18; Polynesian women: 99	81
Australia	Retrospective cohort study and hospital and physician medical records review (1984–1991); used the ACR 1982 criteria	Indigenous Australian (100); female (95)	11	Overall: 52; female: 100	77
Australia	Retrospective cohort study and physician medical records review (1993–1995); used the ACR 1982 criteria	Indigenous Australian (100)	NR	Sydney: 13; North Queensland: 89	79
Australia	Retrospective cohort study and physician medical records review (1996–1998); used the ACR 1982 criteria	White (73); Indigenous Australian (24); other (3); female (86); male (14)	NR	Overall: 45.3; Indigenous Australian: 92.8	80
Australia	Retrospective study and medical records review (1990–1999); used the ACR 1997 criteria	White (25); Indigenous Australian (75); female (83); male (17)	NR	White: 19; Indigenous Australian: 73	78
Africa					
Nairobi, Kenya	Cross-sectional study of a rheumatology clinic (2010–2011); used the ACR 1982 or ACR 1997 criteria	Black African (100); female (100)	NR	Overall: 3,299.5	93
Douala, Cameroon	Cross-sectional study of hospitalized patients in an internal medicine unit (1999–2009); used the ACR 1982 criteria	Black African (100); female (92.3); male (7.7)	NR	Overall: 601.3	91
Port Harcourt, Nigeria	Cross-sectional study of patients at a rheumatology and dermatology clinic (2012–2013); used the SLICC 2012 criteria	Black African (100)	NR	Overall: 2,900.1	92
Nairobi, Kenya	Cross-sectional study of an arthritis clinic (2002–2013); used the SLICC 2012 criteria	Black African (100); female (97); male (3)	NR	Overall: 1,002.5	95
Abidjan, Cote d'Ivoire	Cross-sectional study of a rheumatology clinic (1987–2014); used the ACR 1982 criteria	Black African (100); female (98.3); male (1.7)	NR	Overall: 647.3	94

Table 1 (cont.) | **International incidence and prevalence of SLE by geographic region**

Region	Study description	Ethnicity and sex (%)	Incidence (cases per 100,000 person-years unless otherwise specified)	Prevalence (cases per 100,000 persons unless otherwise specified)	Ref.
Africa (cont.)					
Dakar, Senegal	Cross-sectional study of hospitalized patients in an internal medicine unit (2005–2014); used the ACR 1982 criteria	Black African (100); female (94.5); male (5.5)	NR	Overall: 7,713.5	96
Kampala, Uganda	Cross-sectional study of patients at a rheumatology clinic (2014–2019); used the ACR 1997, SLICC 2012 or EULAR–ACR 2019 criteria	Black African (100); female (91.1); male (8.9)	NR	Overall: 5,495.6	90

Refer to Supplementary Table 1 for further details. ANA, antinuclear antibody; COPCORD, Community Oriented Program for Control of Rheumatic Diseases; ICD, International Classification of Diseases; NR, not reported; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus Erythematosus International Collaborating Clinics. [a]Higher number refers to cases that required just one ICD coded visit, whereas the lower number refers to cases that required several visits or supporting information. [b]Lower number refers to validated cases only, whereas higher number also includes cases with only one ICD code that have not been validated. [c]Adjusted to the 2014 WHO world population.

Lupus Registry from 2002 to 2004, in which cases of SLE were matched to data from the National Death Index from 2002 to 2016, the overall SMR for patients with SLE (adjusted for age, sex and race) was three times higher than that of the general population. Black patients with SLE died approximately 13 years younger than white patients with SLE[18]. The risk of death was also higher in black patients with end-stage renal disease from lupus nephritis than in patients of any other ethnicity with lupus nephritis-related end-stage renal disease (adjusted hazard ratio 1.4, 95% CI 1.2–1.7, in patients aged 18–30 years). When adjusted for area-level median household income, insurance status and renal transplantation, this difference was no longer apparent, suggesting that socioeconomic factors drive the disproportionate mortality[19]. In patients with SLE enrolled in Medicaid, a US government programme that provides health coverage to vulnerable populations, mortality was highest in American Indian patients, followed by Black patients and then white patients. Adjustment for comorbidities and socioeconomic factors attenuated the mortality risk for Black patients, albeit incompletely, but did not affect the mortality risk for American Indian patients. Unusually, the mortality was lower in Hispanic and Asian patients than in white patients, potentially because of the reduced discrepancy in socioeconomic status in the Medicaid population, and lower all-cause mortality in Hispanic patients[20].

The largest study to date of mortality in hospitalized patients with SLE in the USA, which analysed data from the National Inpatient Sample, identified almost two million patients who were discharged from hospital between 2006 and 2016 (REF.[21]). Mortality rates declined from 2006 to 2008 and then remained relatively stable. Black, Hispanic, Asian and Pacific Islander patients had higher in-hospital mortality than white patients[21]. In a study of almost 175,000 SLE-related hospitalizations in the USA in 2016, the leading cause of in-hospital mortality was infection (38.18%), followed by cardiac disease (12.04%)[22]. The National Center for Health Statistics multiple cause of death database has also been used to investigate causes of death in patients with SLE[23]. In this analysis, the most frequently listed conditions among the female patients with SLE who had died were sepsis (4.3%) and hypertension (3.0%), whereas cardiac disease (3.7%) and diabetes mellitus complications (3.6%) were the most frequent conditions among the deceased male patients with SLE. Among the deceased patients, female patients with SLE died on average 22 years younger than female patients without SLE (median age of death for patients with SLE 59 years versus 81 years for those without SLE), whereas this gap was only 12 years for male patients (median age of death for patients with SLE 61 years versus 73 years for those without SLE).

Summary. Epidemiological studies in North America from the past 5 years have reinforced the concept that SLE disproportionately affects women, and racial and ethnic minorities. CDC-funded registries have provided robust data and generally report slightly higher incidence and prevalence rates than previous studies, probably because of more detailed case findings and adjustments for case under-ascertainment. The effect of increased lifetime expectancy on an apparent rise in prevalence cannot be excluded either. Infection and cardiovascular disease are consistently top causes of death.

Europe

Incidence and prevalence. Epidemiological studies in Europe are commonly confined to one location. Many European countries have national registries, often linked to a national health insurance system, which cover the entire or major parts of the population. Various studies of European populations have taken advantage of these registries and thus include large numbers of patients and matched controls[24–29]. However, registry studies rely on case definitions through ICD or similar codes and not on validated clinical cases of SLE. Cohort studies are fewer and smaller than registry studies and describe patients in defined catchment areas and several of these patient populations have been followed over time.

Table 2 | **Mortality in SLE by geographic region**

Region	Study description	Ethnicity (%)	Number of patients and/or deaths	Mortality (standardized mortality ratio if not otherwise specified)	Frequent causes of death (% if not otherwise specified)	Ref.
North America						
USA	Review of billing claims (2000–2006); used ICD codes	Black (40); white (38); Hispanic (15); Asian (4); American Indian (2)	Patients with SLE: 42,221	Crude annual mortality, per 1,000 person-years; overall: 19.1; Black: 24.1; white: 20.2; Hispanic: 7.1; Asian: 5.2; American Indian: 27.5	NR	20
USA	Death certificate analysis (1968–2013); used ICD codes	Black (31); white (65); Asian, Pacific Islander, American Indian or Alaskan Native (4)	SLE-related deaths: 50,249; other deaths (non-SLE related): 100,851,288	Age-standardized mortality (year 2013), per 100,000 persons; overall: 0.34; male: 0.10; female: 0.55; Black: 0.85; white: 0.26; Asian, Pacific Islander, American Indian or Alaskan Native: 0.24	NR	17
Fulton and DeKalb Counties, GA, USA	Incident and prevalent SLE cases from the Georgia Lupus Registry were matched to the National Death Index (2002–2016); used ACR 1997 criteria or an alternative definition of SLE (one of three ACR criteria plus a diagnosis of SLE by a rheumatologist)	Black (77); white (23)	Overall: 400 deaths (out of 1,335 patients with SLE); male: 51 deaths; female: 349 deaths; Black: 324 deaths; white: 76 deaths	Overall: 3.1; male: 3.0; female: 3.1; Black: 3.3; white: 2.4	NR	18
Europe						
UK	Longitudinal prospective study of an inception cohort (1989–2010); used the ACR 1997 criteria	White (51.6); African Caribbean (20.7); South Asian (22); Chinese (2.4)	37 deaths (out of 382 patients with SLE)	2.0	Infection (37.8); cardiovascular disease (27); malignancy (13.5)	41
UK	Cohort study; used ACR 1982 criteria	White (60); Black (35); Asian (10)	76 deaths (out of 511 patients with SLE)	3.1	NR	36
UK	Retrospective registry-based cohort study (1998–2012), using Read codes	Multi-ethnic UK population: ethnicity NR	227 deaths (out of 2,740 patients with SLE)	Mortality rate ratio: overall: 1.7; female: 1.6; male: 1.8	Cardiovascular disease (33); malignancy (25)	40
Italy	Single-centre long-term cohort study (1972–2014); used the ACR 1997 criteria	Italian: ethnicity NR	36 deaths (out of 511 patients with SLE)	NR	Malignancy (33.3); organ failure (22.2); cardiovascular disease (16.7)	42
UK	Population-based matched control cohort study (1999–2014); used Read codes	Multi-ethnic UK population: ethnicity NR	Years 1996–2006: 76 deaths (out of 1,470 patients with SLE); years 2007–2014: 76 deaths (out of 1,666 patients with SLE)	Hazard ratio: years 1996–2006: 2.1; years 2007–2014: 2.1	NR	38
Croatia	Medical file review (2002–2011); used ACR 1982 or ACR 1997 criteria	Croatian: ethnicity NR	90 deaths	NR	Cardiovascular disease (40); infection (33); SLE (29); malignancy (17)	45
Southern Sweden	Longitudinal study of inception cohort (patients recruited 1981–2006 and followed until 2014); used Fries & Holman[110] criteria	Predominantly white: ethnicity NR	60 deaths (out of 175 patients with SLE)	Overall: 2.5; female: 2.7; male: 1.9	Cardiovascular disease (51.7); infection (15.0); malignancy (13.3); SLE (6.7)	37
Norway	Population-based cohort study (patients recruited 1999–2008 and followed until 2014); used ACR 1997 criteria	Non-European origin (16); European (84%)	56 deaths (out of 325 patients with SLE)	Overall: 2.1; patients with lupus nephritis: 3.8; patients without lupus nephritis: 1.7	NR	44

Table 2 (cont.) | **Mortality in SLE by geographic region**

Region	Study description	Ethnicity (%)	Number of patients and/or deaths	Mortality (standardized mortality ratio if not otherwise specified)	Frequent causes of death (% if not otherwise specified)	Ref.
Europe (cont.)						
Hungary	Registry-based study (2008–2017); used ICD codes	Total population of Hungary: ethnicity NR	481 deaths (out of 4,503 patients with SLE)	1.6	Cardiovascular disease (47); infection (43); malignancy (18)	26
UK	Registry-based, prospective, population-based cohort study (1987–2012); used Read codes	8% of British population: ethnicity NR	442 deaths (out of 4,358 patients with SLE)	1.8	Hazard ratio versus 6 matched controls per case: accident and suicide (4.3); infection (3.2); cardiovascular disease (2.5); malignancy (1.4)	39
South America						
Brazil	Ecological study of deaths attributed to SLE using administrative data (2002–2011)	NR	8,761 deaths	4.76 deaths per 1,000,000 inhabitants	SLE (77); cardiovascular disease (6); infection (2.8); respiratory condition (2.2); gastrointestinal condition (2.1); genitourinary condition (1.9)	53
Tucuman state, Argentina	Retrospective cohort study (2005–2012)	NR	32 deaths (out of 353 patients with SLE)	9.1%	Infection (43.8)	46
Asia						
Saudi Arabia	Retrospective cohort study (2001–2009); used; ARA criteria[113]	Middle Eastern population: ethnicity NR	8 deaths (out of 99 patients with SLE)	8.2%	Sepsis (62.5); ischaemic heart disease (12.5); pulmonary embolism (12.5)	62
China	Retrospective multi-centre cohort study (1999–2009); used ACR 1982 or ACR 1997 criteria	Mainland Chinese	166 deaths (out of 1,956 patients with SLE)	8.5%	Infection (25.9); renal failure (19.3); neuropsychiatric lupus (18.7)	67
Thailand	Retrospective multi-centre study (1996–2005); used ACR 1982 criteria	Thai	66 deaths (out of 749 patients with SLE)	Overall: 1.2 deaths per 100 person-years	Active disease and infection (40.9); infection (31.8); active disease (9.1); intracranial haemorrhage (3); renal failure (3); upper gastrointestinal bleeding (1.5)	66
Hong Kong	Prospective cohort study (1995–2011); used ACR 1997 criteria	Hong Kong Chinese	694 patients with SLE; number of deaths NR	Overall: 4.8; patients with lupus nephritis: 9.0; patients with end-stage renal damage: 14	Infection NR	72
Taiwan	Retrospective cohort study (1996–2009); used ICD codes	Predominantly Han Chinese (>98)	4,353 patients with SLE; number of deaths NR	Overall: hazard ratio 2.2	NR	63
Japan	Retrospective cohort study (1984–2010); used ACR 1997 criteria	Japanese (100)	14 deaths (out of 186 patients with SLE)	3.6	Infection (50); suicide (14); acute myocardial infarction (14); stroke (7)	68
Taiwan	Population-based cohort study (2003–2008); used ICD-9 codes	Taiwan Chinese	1,611 deaths (out of 6,675 patients with SLE)	11.1	NR	61
China	Multi-centre nationwide cohort study (2005–2014); used ACR 1982 or ACR 1997 criteria	Mainland Chinese	360 deaths (out of 29,510 patients with SLE)	2.1	Infection (65.8); lupus nephritis (48.6); haematological abnormality (18.1); neuropsychiatric lupus (15.8); interstitial lung disease (13.1)	73
Australasia						
New Zealand	Retrospective chart review (1975–1980); used ACR 1982 criteria	White (71); polynesian (25); other (4)	15 deaths (out of 151 patients with SLE)	2.5–12 deaths per 1,000,000 person years	NR	81

Table 2 (cont.) | **Mortality in SLE by geographic region**

Region	Study description	Ethnicity (%)	Number of patients and/or deaths	Mortality (standardized mortality ratio if not otherwise specified)	Frequent causes of death (% if not otherwise specified)	Ref.
Australasia (cont.)						
Australia	Retrospective chart review (1984–1991); used ACR 1982 criteria	Indigenous Australian (100)	9 deaths (out of 22 patients with SLE)	NR	Active SLE including septic complications (78); cardiovascular events (myocardial infarction) (22)	77
Australia	Retrospective chart review (1996–1998); used ACR 1982 criteria	White (73); Indigenous Australian (24); other (3)	9 deaths (out of 108 patients with SLE)	NR	Cardiovascular events (myocardial infarction, pulmonary embolism or stroke) (67); active SLE (vasculitis, cardiomyopathy) and septic complications (33)	80
Africa						
South Africa	Retrospective chart review of patients with lupus nephritis attending a hospital (1995–2009); used ACR 1982 criteria	Black African (16.7); Asian (4.5); multiracial (77.3); white (1.5)	25 deaths (out of 66 patients with SLE)	NR	Sepsis and/or renal failure (61.5); cardiac failure (15.4); gastrointestinal haemorrhage (3.8); acute pancreatitis (3.8); cerebral vasculitis (3.8); unknown (11.5)	97
Kenya	Cross-sectional study of a rheumatology clinic (2010–2011); used ACR 1982 or ACR 1997 criteria	Black African (100)	0 deaths (out of 24 patients with SLE)	NR	NR	93
Cameroon	Cross-sectional study of hospitalized patients in an internal medicine unit (1999–2009); used ACR 1982 criteria	Black African (100)	2 deaths (out of 39 patients with SLE)	NR	Neurological involvement (50.0); dialysis-related sepsis (50.0)	91
South Africa	Review of hospitalizations at a tertiary referral hospital (2003–2009); used ACR 1982 or ACR 1997 criteria	Black African (33.5); Indian (59.3); multiracial (5.4); white (1.8)	24 deaths (out of 167 patients with SLE)	NR	Infection (62.5); sudden cardiorespiratory event (20.8); neurological event (8.3); renal failure (4.2); bullous lupus erythematous (4.2)	99
South Africa	Retrospective chart review of patients with SLE at a tertiary care university hospital (2003–2012); used ACR 1997 criteria	Black African (33.6); Indian (58.1); multiracial (4.2); white (4.2)	53 deaths (out of 408 patients with SLE)	NR	Infection (49.1); cardiorespiratory event (24.5); neurological event (11.3); malignancy (5.7); renal failure (5.7); unknown (3.8)	98
Ghana	Review of hospitalizations in a teaching hospital (2007–2009); used ACR 1982 criteria	Black African (100)	27 deaths (out of 51 patients with SLE)	NR	Infections and complications NR	100

Refer to Supplementary Table 2 for further details. ARA, American Rheumatism Association; ICD, International Classification of Diseases; NR, not reported; SLE, systemic lupus erythematosus.

In these studies, great effort has been invested in 'multi-source retrieving' whereby all prevalent and incident cases are retrieved through multiple sources including chart review, collaboration with other medical specialties, electronic databases, evaluation of antinuclear antibody (ANA)-positive individuals, patient organizations and public campaigns, and in validating that each diagnosis of SLE fulfils classification criteria[30–33].

The overall incidence of SLE in Europe varies between 1.5 (REFS[33,34]) and 7.4 (REF.[30]) per 100,000 person-years (TABLE 1). Large registry-based studies in the UK[27] and Hungary[26] have reported an overall incidence of 4.9 per 100,000 person-years. Other large registry-based studies in Europe have reported lower incidence rates: 3.3 per 100,000 person-years in France[28], 2.3 per 100,000 person-years in Denmark[25] and between 1.5 and 1.8 per 100,000 person-years in Estonia[34]. The highest annual incidence, 7.4 per 100,000 person-years, comes from a case retrieval study in Crete, Greece[30]. The estimated incidence rates reported in other cohort studies have been similar to that reported by the registry studies: 2.8 per 100,000 person-years in southern Sweden[31], and 2.0 per 100,000 person-years in a confined region in northern Italy[32].

Point prevalence
The prevalence of a disease at a specified point in time.

The estimated prevalence of SLE around Europe varies even more than the estimated incidence, ranging between 29 (REF.[33]) and 210 (REF.[35]) per 100,000 individuals. In most registry studies, the point prevalence ranges between 30 and 70 per 100,000 individuals[24–26,28,29,34], whereas the reported prevalence in the UK is higher, at 97 per 100,000 individuals[27]. An even higher prevalence, 123 per 100,000 individuals, was reported for Crete, Greece, in the case retrieval study[30]. In one study in Spain, researchers used an uncommon methodology whereby questionnaires regarding symptoms were sent to a random selection of the Spanish population and positive responses were followed up by telephone interviews; this approach resulted in a final validation of 12 cases of SLE through medical file review or clinical visits. This study yielded the highest observed prevalence of SLE in Europe, at 210 per 100,000 individuals[35].

The incidence of SLE in women is approximately 5 times higher than in men and peaks earlier (30–50 years of age versus 50–70 years of age)[27,28]. Women are consistently disproportionately affected, representing 85–93% of individuals with SLE (TABLE 1). The prevalence of SLE is about nine times higher in women than in men, with a remarkably steep incline in women starting at puberty, whereas the prevalence curve for men has a slower and more even rise throughout life[25,27,29].

Most European studies do not stratify for ethnicity. An exception is the registry study conducted in the UK[27], which reported a higher incidence and prevalence of SLE in the Black population, especially in individuals of Caribbean descent. Overall, many of the longitudinal studies covering the past few decades describe a declining incidence, but rising prevalence of SLE[26,27,30,31].

The substantial variation in incidence and prevalence is probably due to differences in methodologies and case definitions. Several studies demonstrate that through use of more or less strict case definitions, epidemiological figures will vary considerably in registry-based studies[27,29,34]. The estimates can differ depending on who registered the diagnosis, if the diagnosis is required to be reported only once or several times in the registries, and whether supporting evidence such as medical prescriptions or other data is needed[26,28,29].

Mortality. Studies on SLE-related mortality during the past 5 years have been unevenly distributed across Europe, with five studies from the UK, two from Scandinavia, two from southern Europe and only one from Eastern Europe (TABLE 2). Nevertheless, the SMRs reported in these studies have been fairly consistent, falling between 1.6 and 3.1 (REFS[26,36]). In two longitudinal studies, the SMRs remained consistent over the past three decades[37,38]. One study, which also included patients with juvenile-onset SLE (<18 years of age), reported considerably higher SMRs in those with juvenile-onset SLE (SMR 18.3) than in those with adult-onset disease (SMR 3.1)[36]. Two studies, one from the UK and one from Sweden, reported similar SMRs in men and women[37,39], whereas a registry study in the UK reported higher mortality rates in men than in women[40] (mortality rate of 13.8 per 1,000 person-years in women and 28.1 per 1,000 person-years in men, yielding a female:male ratio of 0.54 (95% CI 0.40–0.73)).

A few studies have looked at risk factors for mortality in European populations, finding that patients with higher damage accrual were at increased risk of mortality in the UK and Italy[41,42]. A subgroup of patients with juvenile-onset SLE from the UK and a subgroup of patients with lupus nephritis (which is associated with an earlier disease onset) in Norway had considerably higher SMRs than patients with SLE with a later disease onset[43,44]. In another separate analysis based on data from the Clinical Practice Research Datalink, comprising 8% of the UK population, higher cumulative glucocorticoid dosage was associated with a higher mortality risk, whereas hydroxychloroquine treatment was associated with a reduced risk of mortality[39].

In the majority of studies, cardiovascular disease is the most common cause of death in patients with SLE, being responsible for 27–52% of fatalities[26,37,40,45] (with the exception of one study in Italy that reported a much lower occurrence of only 17%[42]). Infections are responsible for 15–43% of deaths[26,37,41,45], and malignancies account for 13–33% of deaths[26,37,40,41,45]. Researchers have also investigated the cause-specific mortality for patients with SLE compared with the general population. In one such analysis in Hungary, infections caused a higher percentage of deaths in patients with SLE compared with the general population, whereas malignancy was responsible for a lower percentage of deaths in patients with SLE than in the general population[26]. In a similar study of a UK population that used fully adjusted models, the researchers noted higher relative risks of cardiovascular disease, infection and respiratory disease in patients with SLE than in the general population, whereas malignancy was a less common cause of mortality in these patients compared with the general UK population[39].

Summary. In conclusion, the epidemiological coverage of SLE in Europe is incomplete, with many studies from the UK, several studies from southern Europe and Scandinavia, but few studies from central Europe and eastern Europe. The incidence and prevalence of SLE varies considerably between different European countries; however, because of the different health-care systems and methodologies used, reliable comparisons are not possible. Mortality rates are more consistent across Europe, commonly being about twice that of the general population. Cardiovascular disease and infection are major causes of mortality, together accounting for the increased mortality rate of patients with SLE compared with the general population, whereas malignancies cause proportionally fewer fatalities than in the general population. Standardized mortality rates are higher for patients with high damage scores and those patients with a younger disease onset, nephritis and/or high cumulative doses of glucocorticoids.

South America

Incidence and prevalence. With very limited resources to conduct surveillance studies of chronic conditions, the epidemiology of SLE remains unknown in the majority of South American countries. Moreover, although studies from other parts of the world demonstrate disproportionately higher susceptibility to SLE and SLE-related

mortality in people of colour, compared with white people, studies in South America that assess population-based statistics by race or ethnicity are lacking.

The most recent estimates of the incidence and prevalence of SLE in South America are from a study conducted in the state of Tucumán, Argentina[46] (TABLE 1). The state has a population of nearly one and a half million inhabitants (a predominantly Mestizo population, 60% of whom are under the care of the public health system). In this analysis, individuals aged >16 years with a diagnosis of SLE according to the 1997 ACR revised classification criteria were ascertained across four public hospitals and private rheumatology practices for the period 2005–2012 ($n = 353$). The annual incidence ranged from 1.4 per 100,000 person-years (95% CI 0.7–2.4) in 2007 to 4.2 per 100,000 person-years (95% CI 2.9–5.8) in 2012, with an overall age-adjusted prevalence of 34.9 per 100,000 person-years (95% CI 32.8–41.1) and a female-to-male ratio of 14.3:1.

In a secondary analysis of a prevalence study of SLE in Colombia that was aimed at indirectly calculating age-specific incidence by sex[47] (TABLE 1), researchers found that the incidence for females peaked between the ages of 30 and 39 years, at 20 cases of SLE per 100,000 person-years, and returned to one case of SLE per 100,000 person-years by the age of 45 years[47]. By contrast, the incidence pattern for men showed a flat curve, with two minor peaks: one peak corresponding to men in their early 20s (2.5 per 100,000 person-years) and the other peak corresponding to men older than 75 years (2.8 per 100,000 person-years). In Argentina, researchers have also looked at the incidence of SLE among individuals under the care of a large private health-care system, which serves 5–7% of the population in the city of Buenos Aires[48]. The investigators reviewed data from 140,000 individuals being cared for between January 1998 and January 2009 and found 68 new cases of SLE. The overall incidence within this predominantly white population was 6.3 (95% CI 4.9–7.7) per 100,000 person-years, with 8.9 (95% CI 6.6–11.2) per 100,000 person-years for women and 2.6 (95% CI 1.2–3.9) per 100,000 person-years for men. The age-specific incidence for women peaked between the ages of 18 and 29 years, whereas the incidence remained low across all age groups in men. Among the 127,959 active members registered in the system on January 2009, a total of 75 were classified as having SLE[48]. The overall prevalence was 58.6 (95% CI 46.1–73.5) per 100,000 members (women 83.2 (95% CI 63.9–106.4) and men 23 (95% CI 11.9–40.1)). The age-specific prevalence peaked between the ages of 40 and 59 years for women and between the ages of 40 and 49 years for men.

One of the most recent efforts to estimate the prevalence of SLE in South America was conducted in Colombia, using national health data from a centralized system called the Integrated Social Protection Information System, which compiles health data from 95% of the Colombian population[49]. Cases of SLE were ascertained from 2012 to 2016 using ICD-10 codes. The overall 5-year period crude prevalence was 91.9 per 100,000 individuals, with 126.3 per 100,000 individuals for the population aged over 18 years. After adjustments to the 2014 World Health Organization population, the prevalence rates were 204.3 per 100,000 individuals and 20.2 per 100,000 individuals for females and males, respectively. The crude prevalence in women peaked in the 45–49-year age group (at 391.6 per 100,000 individuals) and in men peaked in the 60–64-year age group (at 46.3 cases per 100,000 individuals).

A population-based study has been conducted to estimate the prevalence of rheumatic diseases in a selected community of Venezuela, using the COPCORD (Community Oriented Program for Control of Rheumatic Diseases) methodology[50]. COPCORD entails three phases: a screening questionnaire provided by trained interviewers to a sample of adult individuals; examination of individuals with musculoskeletal pain by a trained primary care physician; and rheumatic disease confirmation and classification by clinical evaluation (physical examination, labs and radiology) by certified rheumatologists. The study was conducted in a sample of 3,973 individuals from the state of Monagas (population 905,443), and 3 cases of SLE were confirmed. The prevalence of SLE in this sample population was estimated to be 0.07 (95% CI 0.0, 0.2) per 100 individuals[50]. The COPCORD methodology has also more recently been applied to study the prevalence of SLE in two South American populations: individuals in the city of Cuenca (Southern Ecuador)[51] and the indigenous Qom population in Rosario, Argentina[52]. The estimated prevalence of SLE among a sample of adult individuals from each of those communities was 0.06% (95% CI 0.01–0.1 for the Cuenca sample; 95% CI 0.001–0.3 for the Qom sample).

Mortality. Population-based studies of mortality in SLE are scarce in South America. However, epidemiological research conducted in Argentina and Brazil in the past 10 years have provided insights into the magnitude of the problem, high-risk groups and leading causes of death in SLE populations.

A study conducted in the state of Tucumán, Argentina, reported 32 deaths among 353 patients with SLE attending various public hospitals and private rheumatology practices between 2005 and 2012, with an overall mortality rate within the SLE cohort of 9.1% (95% CI 6.3, 12.6)[46] (TABLE 2). An exploratory ecological study[53] that used data from the Mortality Information System of DATASUS, the Department of the Unified Health System (Brazil's National Health System), examined the mortality and causes of death among patients with SLE in Brazil between 2002 and 2011. This study identified 8,761 deaths among patients with SLE in Brazil, yielding a mortality rate of 4.8 deaths per 100,000 inhabitants. SLE alone was mentioned as a underlying cause of death in 77% of these patients. The national mean age at death was 40.7 (standard deviation (s.d.) 18 years), with death occurring at a significantly ($P < 0.0001$) younger age in the northern region (34.1, s.d. 13.7 years) than in the southern region (44.7, s.d. 17 years). Other underlying causes of death reported among the patients with SLE included diseases relating to the circulatory system (6.0%), respiratory system (2.2%), digestive system (2.1%) and genitourinary system (1.9%), and infectious and parasitic diseases (2.8%). In another study assessing

mortality among patients with SLE in São Paulo state, in Brazil's Southeast region, during the period 1985–2004, the mean age at death was 35.1 years (s.d. 15.0 years)[54]. These data together suggest that the survival of patients with SLE might have improved in recent years. However, the data also highlight substantial disparities in age at death, with death from SLE occurring at a lower mean age in the northern and north-eastern regions than that reported for São Paulo state ~10 years prior. As noted by the investigators, the causes of those disparities were multidimensional, including socioeconomic and educational differences, delay in diagnosis, health-care access barriers and more frequent infections and comorbidities in the northern regions of Brazil than in the southern regions[53].

Summary. Only a handful of studies have been conducted investigating the incidence and prevalence of SLE and the mortality among patients with SLE in South American countries. Because of the scarcity of resources to conduct large-scale population-based surveillance, South American studies rely on administrative data or sampling methodologies to find patients, making it difficult to compare estimates with some studies from other parts of the world. Despite these limitations, epidemiological data from South America highlight that SLE begins at a very young age among women, with the incidence peaking in women in their 20s and 30s. Similarly, although the survival of individuals with SLE in Brazil might have improved in the 2000s, the average age of mortality is still very young. Data from these epidemiological studies are fundamental to advance the understanding of health disparities in the burden of SLE and inform resource allocation in specific regions.

Asia

Incidence and prevalence. Compared with North America and western Europe, data regarding the incidence and prevalence of SLE in Asian countries are less robust, although Asian patients with SLE have long been recognized to have a more severe disease course than white patients[4,55]. The largest Asian epidemiological studies have been conducted in Taiwan and South Korea, where large-scale population-based disease registries have been established and properly maintained[56–58]. Although most other SLE epidemiological studies have used retrospective cohorts, these studies nevertheless provide an overview of the prevalence and incidence of SLE in Northeast and East Asia. Data from southern and western parts of Asia, including India, the United Arab Emirates, Israel and Turkey, are generally from studies with relatively smaller sample sizes[59].

The annual incidence of SLE in Asia varies from 2.8 to 8.6 per 100,000 person-years[56–60], and the prevalence ranges from 26.5 to 103 per 100,000 individuals[57–61] (TABLE 1). Most of the Asian cohorts were established in the late 1990s and early 2000s and therefore adopted the 1997 ACR classification criteria for SLE. Data generated from these cohorts, which spanned over a decade, demonstrated that both the prevalence and incidence of SLE seem to be increasing in Asia[58].

Mortality. In addition to population-based SLE registries and related studies conducted in Taiwan and South Korea, other SLE centres in Asia have provided invaluable survival and mortality data for patients with SLE across eastern Asia, China (Mainland) and the Middle East region (TABLE 2). The overall 1-year, 5-year, 10-year and 15-year survival rates range from 93.7 to 98.4%, 80.4 to 98.6%, 56.5 to 98.2% and 31.7 to 88.8%, respectively[56,62–72]. The overall SMRs range between 2.1 and 11.1 (REFS[61,62,68,72,73]). The most common causes of mortality in patients with SLE include sepsis and cardiovascular, cerebrovascular and renal disease[74]. Lupus nephritis is more prevalent and severe in Asia than in Western countries[75]. Notably, patients with lupus nephritis have a higher SMR than patients without lupus nephritis in Asia (9.0 versus 4.8)[72], and patients with proliferative lupus nephritis have a higher SMR than patients with pure membranous lupus nephritis (9.8 versus 6.1)[72]. Furthermore, the SMRs of patients with renal damage or end-stage renal failure are 14.0 and 63.1, respectively[72]. Prompt recognition and treatment of lupus nephritis are crucial for the management of Asian patients with SLE. Results from a meta-analysis of observational studies published between the 1970s and 2010s[76] suggest that renal damage has impeded further improvement of short-term and long-term survival in patients with SLE over the past five decades.

Summary. Serious organ manifestations of SLE, renal disease in particular, remain prevalent in the Asia Pacific region. More work is needed to elucidate the pathophysiology of renal disease in SLE before more effective and targeted disease monitoring and therapy can be implemented. The aggressive nature and poor outcome of renal disease in Asian patients with SLE underscores the urgent need for more efficacious and less toxic regimens.

Australasia

Incidence and prevalence. The incidence and prevalence of SLE in Australia and New Zealand have been difficult to ascertain owing to a lack of large-scale population-based disease registries. All studies have been retrospective in nature, and catchment areas were dependent on participating physicians recording clinical features, diagnosis and other epidemiological data. TABLE 1 presents summarized data from these studies. Limited data have been published on the incidence of SLE, with only one study available that examined new cases of SLE between 1986 and 1990 in the Aboriginal Australian population of the Northern Territory, reporting an annualized incidence of at least 11 per 100,000 person-years[77]. The overall prevalence of SLE has ranged from 13 to 89 per 100,000 individuals on the basis of studies from Australia and New Zealand[77–81]. Two of these studies have also examined ethnic differences in the prevalence of SLE in Australia and New Zealand, finding an increased prevalence in the indigenous (Aboriginal Australian and New Zealand Polynesian) populations (age-adjusted prevalence rates of 51–73 per 100,000, compared with 15–19 per 100,000 white individuals)[78,81].

Most SLE epidemiology studies in Australasia were performed in the 1980s to 1990s, and hence it is difficult

to comment on temporal trends, given the lack of more recent data. A single study used the 1997 ACR classification criteria[82] to define cases of SLE, but no study has used the newer Systemic Lupus International Collaborating Clinics (SLICC)[83] or EULAR–ACR classification criteria[84].

Mortality. SLE-related mortality data in Australasia are limited and mostly presented in studies comparing indigenous (Aboriginal Australian or Torres Strait Islander) populations with white populations[77,78,80] (TABLE 2). Survival rates are lower in indigenous groups than in white populations, with a 5-year survival of 60% in one study[77]. Of the three studies that reported mortality data, the consistent causes of death were active disease associated with intercurrent sepsis or acute thromboembolic events. Poor adherence to medication was also highlighted as a potential factor in one study[78]. The mean disease duration by the time of death was usually short, ranging from 4 months to 8 years[77,78,80]. Deaths during periods of quiescent disease were usually due to cardiovascular disease[77,80].

Ethnicity, as a single demographic variable, has been the most widely reported determinant of unfavourable outcomes in SLE, reported in the literature on Australian and New Zealand populations. Unfortunately, details of the disease course and treatment trajectories were not available from these mortality studies. Ethnicity can certainly have an effect on disease severity, but other socioeconomic factors might also affect certain ethnicity groups, such as access to medical care and adherence to treatment, which might notably influence disease outcomes.

Summary. There have not been many studies exploring the epidemiology of SLE in Australasia. Most studies explored the ethnic difference between the indigenous and white populations, demonstrating an increased prevalence of disease in the indigenous groups. With the changing landscape of demographics in the region, updated studies inclusive of other ethnicities will help to fill the knowledge gap. Furthermore, there has only been one study examining the incidence of SLE in Australia, taking observation from populations living in the Top End of the Northern Territory. The lack of large-scale population-based longitudinal studies has meant that the prevalence and incidence rates may not be reflective of the broader Australasian cities. Most existing studies also relied on relatively dated classification criteria. With the availability of revised classification criteria that have better sensitivity and specificity, future studies to explore longitudinal outcomes such as incidence rates and mortality may find a change in the epidemiology of the disease in the region.

Africa

Incidence and prevalence. In high-income countries, individuals of African ancestry are disproportionately affected by SLE compared with individuals of other ancestries. The burden and natural history of the disease in Black Africans remains a subject of controversy. Two decades ago, epidemiological studies of SLE in Africa were few, limiting the understanding of the disease in the sub-continent. This lack of evidence was often cited as the basis for the assumption that SLE is rarer in Black Africans than in people of African descent in the Americas and Europe, otherwise known as the 'lupus prevalence gradient'[85]. In the past 5–10 years, newer evidence has emerged suggesting that the prevalence gradient hypothesis is an artefact of the limited resources in Africa, including the presence of few specialists and the possibility of missed and misdiagnosis of SLE in these populations[86–88].

An abundance of case series, and more crucially, cross-sectional and cohort studies (albeit hospital-based)[87,89], are now available, enabling an estimation of the burden of disease and phenotype of SLE in Africa. For example, one survey of members of the African League Against Rheumatism in 2013 revealed that 20% of these clinicians (spanning rheumatology, general practice, nephrology and dermatology) had seen more than 50 new patients with SLE in the previous 12 months, indicating that the incidence of this condition is not negligible[87]. However, accurate estimates of the incidence of SLE and longitudinal studies of this disease are unavailable. We identified seven studies from six African countries based on rheumatology clinics and hospitalized patients[90–96] (TABLE 1). There was considerable heterogeneity in prevalence by location among these studies: 601 and 7,713 per 100,000 individuals in Cameroon[91] and Senegal[96], respectively. However, these estimates do not reflect the true population prevalence of SLE in Africa. Although these estimates seem much higher than prevalence estimates from other regions, they are not comparable with population-based (and registry-based) estimates from other settings and might be subject to surveillance bias; for example, hospital-based surveillance systems often comprise individuals with more severe sequelae than in other settings. Similar to the age distribution among Black individuals with SLE in other settings, SLE seems to disproportionately affect young women in Africa. The median age at presentation ranged from 29 to 39 years, and women comprised between 91% and 100% of the patient population in Africa[90,92–96].

Mortality. Assessment of outcomes and comorbidities regarding SLE in Africa confers unique challenges. Serological tests and biopsies are mainstays of the management of SLE; however, the limited availability of these diagnostic and prognostic tools in low-income settings in Africa hinders clinical management[87]. For example, many hospitals in these regions are unable to perform renal biopsies because of the prohibitive costs and the lack of nephrologists and histopathologists[87]. Because of valuable investments in the advancement of nephrology in Africa by the International Society of Nephrology, the increasing prevalence of lupus nephritis in renal registries provides further evidence of the disproportionately high morbidity due to SLE[87]. Synthesis of the evidence from renal registries suggests that lupus nephritis might comprise up to 29% of renal biopsies performed in Africa[87]. Between around 5% and 51% of patients with SLE have renal manifestations[97–99].

Jaccoud arthropathy
A form of chronic, non-erosive, reducible arthropathy that can affect patients with systemic lupus erythematosus.

The other most common SLE manifestations were cutaneous involvement (up to 96% of patients) and arthralgia (up to 53% of patients)[90–96]. In one study, Jaccoud arthropathy was found in 5% of patients[94]. Reported in-hospital mortality in patients with SLE ranges between 0% and 44% in studies, with follow-up times ranging from 3 days to 10 years[91,93,97–100] (summarized in TABLE 2). Frequently listed causes of death in these studies were infections, end-stage renal disease and neuropsychiatric manifestations[91,93,97–100]. The most common treatment regimens for SLE are anti-malarial drugs, corticosteroids, cyclophosphamide, methotrexate, azathioprine and NSAIDs[90–96]. However, the routine use of first-line and second-line drugs might be prohibitive owing to limited affordability and the challenges of counterfeit drugs in some regions[89,101,102].

Summary. Emerging evidence suggests that the burden of disease and natural history of SLE in Africa might be similar to trends identified in patients of African ancestry in other settings. A few considerations unique to this region have also emerged. A sustained investment in SLE research in Africa is needed, as well as capacity building by international rheumatology organizations, including collaborations with programmes such as the Human Heredity and Health in Africa (H3Africa) consortium, funded by the NIH and Wellcome Trust[103]. H3Africa seeks to apply genomic science to understand genetic and environmental contributions to the risk of chronic disease in Africa. Leveraging H3Africa for SLE research would propel the understanding of SLE risk and its clinical course. Another consideration is that the burden of infections in the general population of Africa is high[104]. Co-infection with bacteria (such as those linked with tuberculosis) and/or viruses (such as the human immunodeficiency virus and those linked with hepatitis) can complicate the management of SLE, particularly in the choice of treatment regimens that could potentially reactivate dormant infections[87,89]. Although these conditions are of relatively low prevalence in developed countries, longitudinal studies on the course of these infections in patients with SLE in Africa are warranted.

Global trends

Recent overall SLE incidence rates vary between 3.7 per 100,000 person-years[10] and 49.0 per 100,000 in the US Medicare population[9] in North America, 1.5 and 7.4 per 100,000 person-years in Europe[30,33], 1.4 and 6.3 per 100,000 person-years in South America[46,48] and 2.5 and 8.6 per 100,000 person-years in Asia[58,59]. Estimates of the current incidence of SLE in Australasia or Africa are unavailable. The prevalence of SLE varies between 48 and 366.6 per 100,000 in North America[9,11], 29.3 and 210 in Europe[33,35], 24.3 and 126.3 in South America[46,49], 20.6 and 103 in Asia[58,59], 13 and 52 in Australasia[77,79] and 601.3 and 7,713.5 in Africa[91,96]. These ranges are summarized in FIG. 1 and FIG. 2. Values have not necessarily been adjusted using the same methods, and prevalence estimates seem much higher in Africa than in the rest of the world but are unlikely to reflect true population

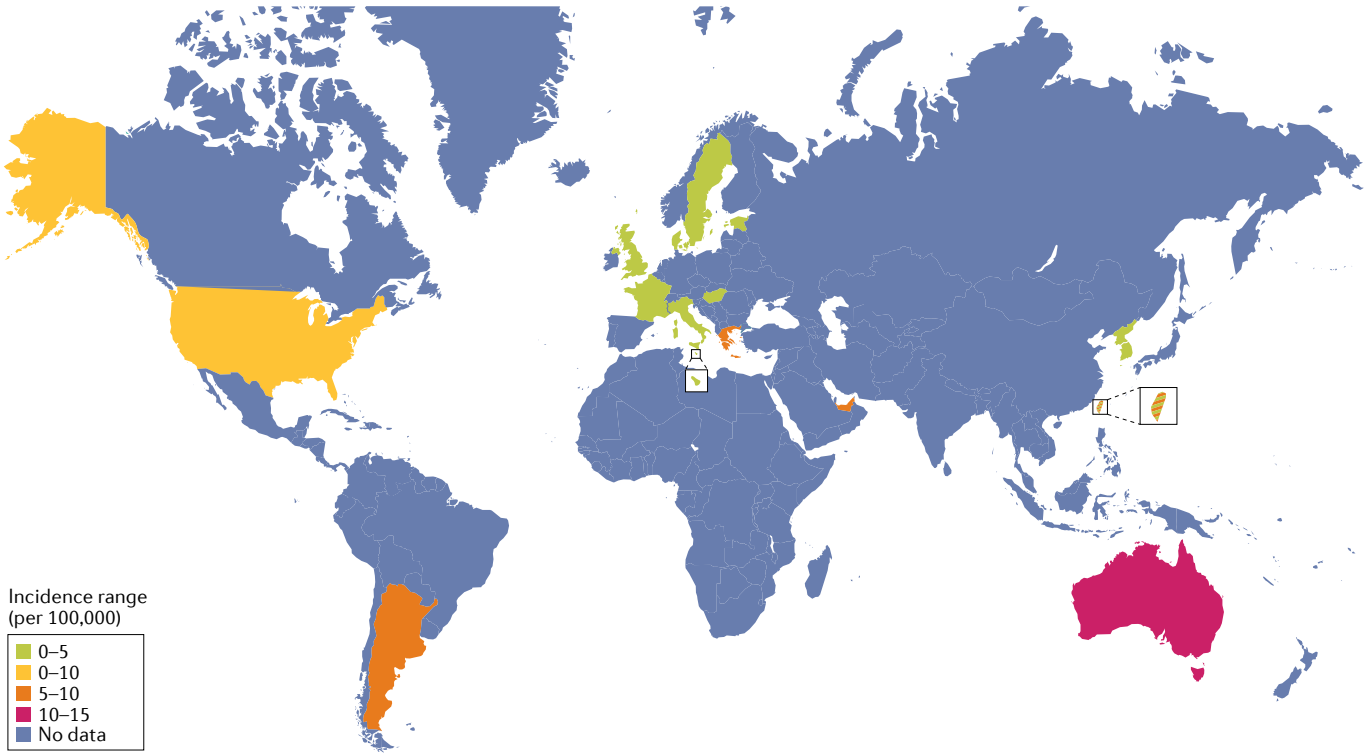

Fig. 1 | **Global incidence estimates for SLE.** The figure shows the reported incidence ranges for systemic lupus erythematosus (SLE) per location (per 100,000 of the population), as denoted by the key. Not all data have been collected and reported uniformly across global regions. Precise overall prevalence ranges per region are outlined in TABLE 1, in which data for China mainland and Taiwan are listed independently. *Nature Reviews Rheumatology* remains neutral with regard to jurisdictional claims in published maps.

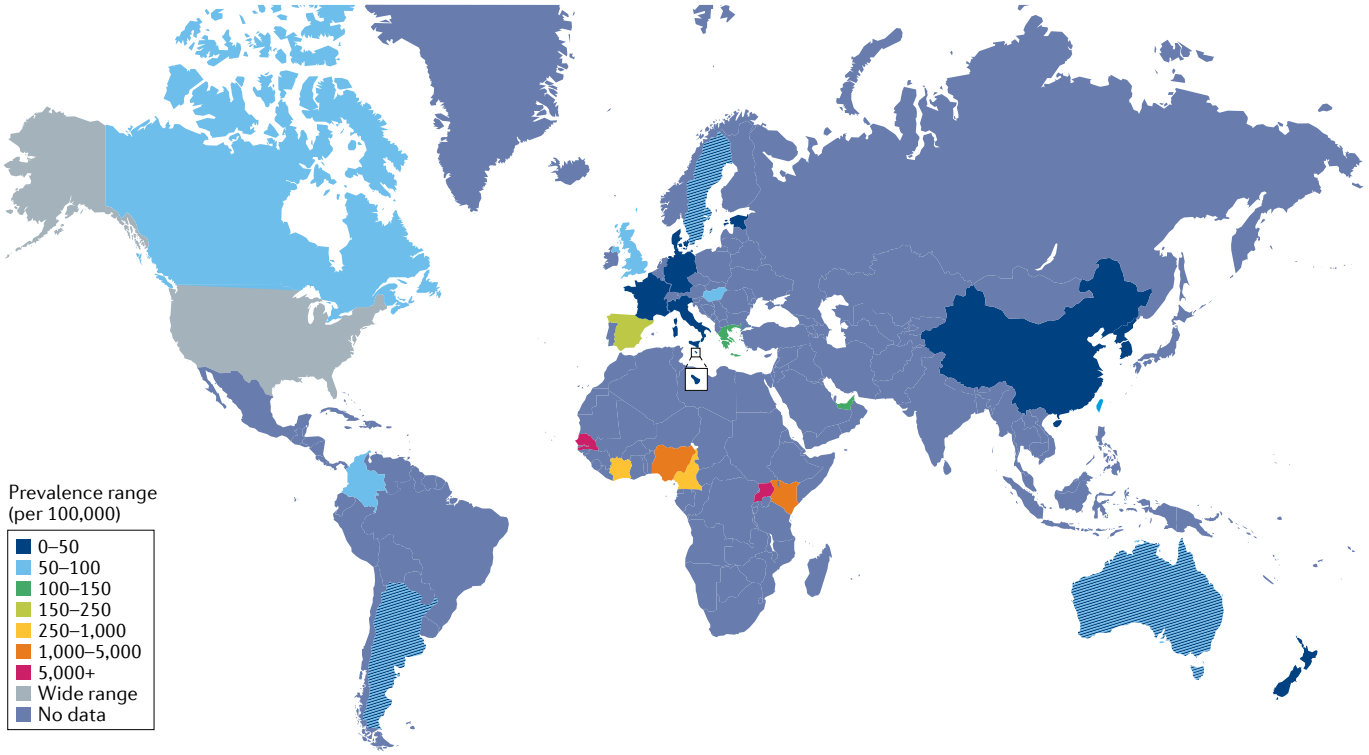

Fig. 2 | **Global prevalence estimates for SLE.** The figure shows the reported prevalence ranges for systemic lupus erythematosus (SLE) per location (per 100,000 of the population), as denoted by the key. Not all data have been collected and reported uniformly across global regions. Prevalence estimates seem much higher in Africa than in the rest of the world but are unlikely to reflect the true population prevalence, as these data are based on hospital and clinic samples. Precise overall prevalence ranges per region are outlined in TABLE 1, in which data for China mainland and Taiwan are listed independently. *Nature Reviews Rheumatology* remains neutral with regard to jurisdictional claims in published maps.

prevalence, as they are based on hospital and clinic samples.

Although comparing regional studies that use distinct methodology is difficult, international studies have offered insight into global trends. Data from the World Health Organization mortality database have been used to calculate an international ASMR for SLE[105]. In 2014, the ASMR was 2.7 deaths per million inhabitants: 4.5 deaths per million inhabitants for women and 0.8 deaths per million inhabitants for men. The ASMR decreased between 2001 and 2003 (−6.4%, $P < 0.05$) followed by a minor increase between 2004 and 2014 (0.6%, $P < 0.01$). Mortality rates were strikingly heterogeneous between countries, with a several hundred-fold variation between countries, from 0.1 deaths per million inhabitants in Morocco to 27.1 deaths per million inhabitants in Saint Lucia. In 2014, the highest overall ASMR was in Latin America and the lowest was in Europe. The researchers suggest that this variation might be because of differences in disease severity, socioeconomic factors, reporting biases and treatment capacity[105]. Mortality rates were higher for SLE than for five other systemic autoimmune diseases, including systemic sclerosis, idiopathic inflammatory myopathies, Sjögren syndrome, mixed connective tissue disease and anti-neutrophil cytoplasm antibody-associated vasculitis.

Frequent causes of mortality include infection, cardiovascular disease, malignancy, as well as sequelae from active disease such as renal failure. A comprehensive international meta-analysis of all-cause and cause-specific SLE mortality was published in 2016 (REF.[7]). In this study, the researchers analysed data from 15 studies, including data from >26,000 patients and >4,640 deaths, and representing data from Asia, Europe and North America from 1999 to 2010. The overall all-cause SMR for patients with SLE was 2.6. The highest cause-specific SMRs were infection (5.0), renal disease (4.7) and cardiovascular disease (2.3).

A systematic review and meta-analysis of survival studies between 1950 and 2016 showed increasing survival in both high-income countries and low- or middle-income countries until the mid-1990s, followed by a persistent plateau. In adults, the 10-year pooled probability of survival estimates were 0.89 in high-income countries and 0.85 in low- or middle-income countries[106]. Infections were the main cause of death in both high-income countries (15.1%) and low- or middle-income countries (37.5%), whereas cardiovascular disease was responsible for 11.3% and 10.6% of deaths, respectively. This knowledge is crucial, because infection might be a modifiable cause of death in patients with SLE.

Although only one new therapy for SLE, belimumab, has been approved in more than half a century, improvements in existing care can likely improve outcomes. In a Delphi consensus study, a multidisciplinary panel of

experts on SLE convened to create a list of 25 SLE-specific adverse outcomes thought to be modifiable[8]. Many of these adverse outcomes relate to frequent causes of mortality such as infections, cardiovascular disease and renal disease. Modifiable infectious outcomes include vaccine-preventable infections including cervical dysplasia from human papillomavirus, herpes zoster, hepatitis B, influenza, meningococcal disease and pneumococcal disease. *Pneumocystis jirovecii* pneumonia in patients receiving moderate to high doses of steroids might also be preventable with prophylaxis[8]. Possibly remediable cardiovascular conditions include recurrent myocardial infarction, and embolic stroke and thrombosis in patients with SLE and antiphospholipid antibody syndrome. The development of end-stage renal disease in patients with lupus nephritis was also thought to be potentially preventable. The consensus study included a list of recommendations to circumvent these poor outcomes[8]. Incorporation of these recommendations into guidelines and clinic quality metrics might improve cause-specific mortality. Future epidemiological studies should determine the incidence and prevalence of potentially remediable SLE-specific adverse conditions and deaths, to help to prioritize resource allocation and improve the quality of care of patients to reduce potentially avoidable deaths. Similar studies should be performed internationally to create regional recommendations for preventable conditions, such as endemic infections.

Methodological issues

Although some variation in the international incidence and prevalence of SLE is accounted for by intrinsic population factors such as ethnicity, environmental exposures and socioeconomic factors, inconsistencies in study design limit the ability to make regional comparisons.

Cohort studies are unable to capture changes in incidence over time, and are typically conducted in tertiary centres, which might attract patients with more complex disease. Studies that use death records might be inaccurate owing to reliance on diagnostic codes, as opposed to physician-confirmed cases. Rigorous registries such as those funded by the CDC in the USA have notable advantages, as these registries interrogate several different databases and utilize capture-recapture methodology, which enables the assessment of whether any cases have been missed. Consequently, these studies are more likely to portray the true burden of SLE. Large registries have also been established in Europe[24–29], South Korea and Taiwan[56–58]. The establishment of further registries that use common methodology across international locations would enable a more accurate comparison between regions.

The definition of SLE also affects epidemiological analyses. The Rochester Epidemiology project identified incident cases of SLE in Olmsted County, Minnesota, that fulfilled either the ACR 1997 or the SLICC 2012 SLE classification criteria. Use of the SLICC 2012 criteria resulted in a higher estimation of the incidence rate than use of the ACR 1997 criteria (4.9 versus 3.7 per 100,000 person-years), due primarily to the identification of cases of renal-limited disease and serological abnormalities[10]. Similarly, in the Manhattan Lupus Surveillance Program, use of the SLICC definition resulted in a higher estimation of the prevalence and incidence rates than the ACR criteria, with 20.2% of patients meeting only the SLICC definition and 4.3% meeting only the ACR criteria[2]. In September 2019, EULAR and the ACR published new criteria for the classification of SLE, which require a patient to have a positive ANA test result at a titre of at least 1:80 to be classified as having SLE[84]. Most epidemiology studies of SLE have used the ACR 1982, ACR 1997 or SLICC 2012 criteria, none of which requires a positive ANA test result. In the SLICC inception cohort, 6.2% of patients with SLE were ANA-negative[107] at cohort enrolment, although a systemic review and meta-regression have shown that only ~2% of patients with SLE remain ANA-negative throughout their disease course[108]. Future epidemiological efforts that use these new EULAR–ACR classification criteria will exclude this subpopulation of ANA-negative patients. Furthermore, the ANA entry criterion might hinder the diagnosis of SLE in regions such as Africa, where serological testing is often sent abroad and is expensive[87]. More research is warranted to understand the unintended consequences of this requirement in resource-limited settings. Disease activity indices that use clinical measures instead of laboratory measures, such as the Lupus Foundation of America Rapid Evaluation of Activity in Lupus Index, might benefit disease management in Africa because these tools reduce the need for cost-prohibitive tests[109].

Conclusion

The overall global incidence of SLE ranges between 1.5 (REF.[33]) and 11 (REF.[77]) per 100,000 person-years, and the global prevalence ranges from 13 to 7,713.5 per 100,000 individuals[79,96]. This striking variation in the reported burden of SLE is in part due to inherent differences in population structure such as sex distribution, ethnicity and environmental exposures. However, reporting bias, study design, case definition and SLE classification criteria also affect estimates of the incidence and prevalence, and variability can be high even within the same region. Women are consistently more affected by SLE than men across international regions. Black, Hispanic and Asian populations are disproportionately affected by SLE, with higher incidence and prevalence rates in these populations than in white populations[1,2]. Several studies from North America, Europe and Asia show a gradual increase in SLE prevalence over time[9,30,31,57], perhaps owing to increased recognition of the disease. Mortality among patients with SLE is still unacceptably high, being two to three times higher than that of the general population. The most consistent causes of death internationally include infection and cardiovascular disease, which can probably be mitigated through improved quality of care. Population-based studies in the developing world are urgently needed to understand the global burden of disease, potentially preventable outcomes and to what the extent lack of specialized health-care providers, diagnostic tests and therapeutics affect SLE diagnosis and care.

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Author contributions

R.R.-G., M.R.W.B., C.D., T.F., A.H., A.M., N.Y.K., E.S. and J.P. researched data for the article; R.R.-G., M.R.W.B. and A.E.C. made substantial contributions to discussions of the content; M.R.W.B., C.D., T.F., A.H., A.M., N.Y.K. and E.S. wrote the article; and R.R.-G., M.R.W.B. and A.E.C. reviewed and edited the manuscript before submission.

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Review criteria

A comprehensive search was developed by J.P. in conjunction with the other authors. The search terms used for this project were "systemic lupus erythematosus", "mortality", "incidence", "prevalence" and "socioeconomic factors". Terms were also compiled for the geographic regions of interest (by continent): North America, South America, Asia, Australia, Africa and Europe. The searches were performed in MEDLINE via PubMed (1966–present). Search results were limited to those items published in the English language and using the MEDLINE human filter. The initial strategy was to include data from the past 5 years, but to represent areas where resources might be limited older studies were included when they were informative. The authors also used additional references of particular interest that were not included in the formal search.

Supplementary information

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Hypertension meets osteoarthritis — revisiting the vascular aetiology hypothesis

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Abstract | Osteoarthritis (OA) is a whole-joint disease characterized by subchondral bone perfusion abnormalities and neovascular invasion into the synovium and articular cartilage. In addition to local vascular disturbance, mounting evidence suggests a pivotal role for systemic vascular pathology in the aetiology of OA. This Review outlines the current understanding of the close relationship between high blood pressure (hypertension) and OA at the crossroads of epidemiology and molecular biology. As one of the most common comorbidities in patients with OA, hypertension can disrupt joint homeostasis both biophysically and biochemically. High blood pressure can increase intraosseous pressure and cause hypoxia, which in turn triggers subchondral bone and osteochondral junction remodelling. Furthermore, systemic activation of the renin–angiotensin and endothelin systems can affect the Wnt–β-catenin signalling pathway locally to govern joint disease. The intimate relationship between hypertension and OA indicates that endothelium-targeted strategies, including re-purposed FDA-approved antihypertensive drugs, could be useful in the treatment of OA.

Osteoarthritis (OA) is a prevalent disease that affects 500 million people worldwide[1] and is not only a leading cause of chronic pain and disability in older adults but also a risk factor for cardiovascular events and all-cause mortality[2–4]. OA is no longer thought of as a simple wear-and-tear problem affecting articular cartilage but rather as a whole-joint disorder subject to interactions between a variety of local and systemic risk factors. The prevalence of knee OA has doubled since the mid-20th century[5], alongside expanding populations of older individuals and those with obesity. However, neither ageing nor obesity can entirely explain the increased prevalence of knee OA. Therefore, interest is growing in metabolic syndrome and its individual components (high blood pressure in particular) as emerging independent risk factors for OA[6,7].

Metabolic syndrome is a cluster of at least three out of the following five conditions: central obesity, high blood pressure (hypertension), hyperglycaemia (often in the form of type 2 diabetes), high cholesterol and low HDL levels. Among these conditions, hypertension and type 2 diabetes are often present in patients with knee OA[8]. After adjustment for body weight or BMI, no statistically significant association exists between any of these conditions and the occurrence of OA, with the exception of hypertension[9]. These results suggest that vascular pathologies, such as hypertension, are likely to be important factors in the pathogenesis of metabolic syndrome-associated OA.

Indeed, vascular dysfunction has already been implicated in the pathogenesis of OA[10]. Emerging evidence is revealing a close association between vascular pathologies and OA in both load-bearing joints (such as the knee) and non-load-bearing joints (such as the joints of the hand)[11]. In a cross-sectional analysis of 254 patients with OA, 63% of patients with knee OA and 40% of patients with hand OA had hypertension[12]. By contrast, Mendelian randomization analysis of data from the UK Biobank has suggested a causal association between low blood pressure and knee OA[13], making a strong case to revisit the interactions between blood vessels and other tissues in joint homeostasis and disease. In this Review, we outline the main findings that link blood pressure and OA from both an epidemiological and a molecular perspective. We also discuss current and emerging therapeutics that target the endothelium and how these might be used in the management of OA.

Epidemiology of hypertension and OA

As a frequently encountered comorbidity in knee OA[14], hypertension confers a high risk of OA progression and a worse outcome for surgical joint replacements[6,15]. However, whether the contribution of hypertension to OA initiation and joint deterioration is biased by

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Key points

- Epidemiologically, high blood pressure (hypertension) has been linked to radiographic and symptomatic knee osteoarthritis.
- At the tissue level, systemic hypertension leads to subchondral bone perfusion abnormalities and ischaemia, which disrupts angiogenic–osteogenic coupling and impairs the integrity of the bone–cartilage functional unit.
- At the molecular level, systemic activation of the renin–angiotensin, endothelin and Wnt–β-catenin signalling pathways induces a phenotypical change in articular chondrocytes and triggers cartilage degradation.
- Antihypertensive medications that exhibit chondroprotective effects in preclinical studies warrant further investigation in patients with osteoarthritis and the frequently encountered comorbidity of systemic hypertension.

potential confounding factors such as BMI is uncertain. Furthermore, contradictory results have been reported regarding the relationship between hypertension and knee OA[9,13,16] (TABLE 1). Higher systolic blood pressure (above 112 mmHg) and pulse pressure (above 39 mmHg) but not diastolic blood pressure were associated with radiographic knee OA in one study that retrieved data from the Osteoarthritis Initiative[16]. However, in another study that retrieved data from the same database, an increase in diastolic blood pressure from baseline was associated with more heterogeneous cartilage T2 values on MRI scans at 48 months in patients with knee OA, indicating increased cartilage degeneration[17]. By contrast, both diastolic and systolic blood pressure were associated with symptomatic knee OA but not with radiographic knee OA in data from the Framingham Osteoarthritis Study[9].

Systematic reviews and meta-analyses of pooled evidence have been performed to decipher the relationship between hypertension and OA. In one systematic review[6], hypertension increased the odds of developing radiographic knee OA by 101% but of developing symptomatic knee OA by only 49%; another meta-analysis also reported a stronger association between hypertension and radiographic knee OA (with increased odds of 89%) than symptomatic knee OA (with increased odds of 39%)[18]. These findings could indicate a closer relationship between hypertension and structural damage in knee OA than between hypertension and joint pain. Notably, a high degree of inter-study heterogeneity was detected when the link between hypertension and radiographic knee OA was explored[6]. Potential confounding factors, such as sex, BMI and ethnicity/race, could affect the relationship between hypertension and knee OA. However, only a few studies have provided sex-specific associations, including showing OA to be more prevalent in women than in men[9]. Ethnicity/race might be another factor that has caused variation in the results of previous studies. For example, a higher prevalence of comorbid hypertension and metabolic syndrome seems to exist in individuals of Asian ancestry with OA than in individuals of non-Asian ancestry with OA[6,19]. This finding might be attributed to the association of an angiotensin-converting enzyme (ACE) gene polymorphism (which is more common in some Asian populations) with knee OA as well as with hypertension[20–23], which warrants further investigation. Given that most studies that have been performed were cross-sectional in nature, the causal relationship between hypertension and knee OA is yet to be confirmed.

Analytical techniques such as Mendelian randomization provide a powerful way to control for confounding and inverse causation[24]. Mendelian randomization deploys genetic variants as instrumental variables to infer whether a risk factor causally affects a health outcome. By using this big data analytics tool, a 2019 study reported an inverse causal association of genetically determined blood pressure with the risk of knee OA, hip OA and surgical joint replacements using data from the UK Biobank[13]. However, the results from the study suggest that low blood pressure is a risk factor for knee OA and high blood pressure is a consequence rather the cause of knee OA. Despite the strong conclusions of this study[13], the findings were limited by the definition of OA that was used. The requirement of a hospital diagnosis of OA in this study implies that only symptomatic OA might have been captured. In addition, whether joint pain relates to intraosseous blood pressure and perfusion in response to alterations of systemic blood pressure remains controversial[25,26]. Moreover, the observation that structural joint damage on a plain radiograph correlates poorly with symptomatic severity in OA is well established. Hence, a critical research gap on the causal relationship between blood pressure and both radiographic and symptomatic OA still exists and needs to be filled.

Joint vascularization in health and OA

Although the concept of OA as a whole-joint disorder has gained much popularity in the past decade, the exact role of the vascular system in joint homeostasis and disease is not fully understood. Experimentally, a reduction of blood flow in postnatal long bones leads to a loss of mineralized bone, whereas bisphosphonate treatment enhances both blood flow and vessel growth in bone[27]. However, these findings were obtained from studying metaphyseal bone and diaphyseal bone in mice under non-inflammatory and non-degenerative conditions. Microangiography of osteoarthritic subchondral bone tissue has revealed an increase in vascular volume and the number of blood vessels in a mouse model of post-traumatic OA, indicating angiogenesis[28]. Optical clearing of bone tissues has also enabled the identification of a previously unknown blood vessel type in cortical bone[29]. Comparatively, it remains technically challenging to visualize and analyse the vascular system and angiogenesis in the subchondral bone of animals and humans in three dimensions. Further exploration of techniques such as optical clearing of bone is warranted to gain insight into the role of the vasculature in the progression of disease.

Articular cartilage is avascular and devoid of nerve endings. The growth and maintenance of articular cartilage therefore heavily rely on the two adjacent tissues — subchondral bone and synovium. The superficial side of articular cartilage is separated from the synovium by a cavity filled with synovial fluid that is mainly produced by synovial cells and, to a lesser extent, by chondrocytes[28]. Synovial fluid serves as a medium for

T2 values
Values obtained in MRI scans that provide information about the water content and organization of the collagen structure in cartilage.

Metaphyseal bone
The transition zone between the shaft and head of long bones; it is the location of the growth plate, which elongates and grows during bone development.

Diaphyseal bone
The midsection of long bones, composed of tubular cortical bone on the outside and a hollow bone marrow cavity on the inside.

Table 1 | **Studies investigating the relationship between hypertension and knee osteoarthritis**

Study (date)	Study design	Cohort	Location (ethnicity/race)	OA classification	Odds ratio (95% CI)	Adjusted factors	Ref.
Bagge et al. (1991)	CSS	70-year-old people in Göteborg	Sweden (NR)	Radiographic	0.96 (0.73–1.27)	BMI	226
Hart et al. (1995)	CSS	Chingford Study	UK (NR)	Radiographic	1.28 (0.76–2.16)	BMI and age	227
				Symptomatic	1.10 (0.53–1.26)		
Sowers et al. (1996)	CSS	Michigan Bone Health Study	USA (white)	Radiographic	6.51 (1.90–21.00)	NR	228
Kim et al. (2010)	CS	NA	Korea (NR)	Radiographic	2.74 (1.66–4.54)	Age, education, BMI, presence of osteoporosis or diabetes mellitus, amount of exercise, smoking, alcohol consumption and occupation	229
				Symptomatic	2.17 (1.30–3.63)		
Reid et al. (2010)	CSS	Southern California American Indian Health Clinic	USA (Native American and Native Alaskan)	Hospital diagnosed	Women 8.46 (4.81–14.90)	Age	230
					Men 12.63 (5.25–30.37)		
Inoue et al. (2011)	CSS	NA	Japan (NR)	Radiographic	Women 5.09 (3.38–7.67)	NR	231
					Men 2.04 (1.08–3.84)		
Yoshimura et al. (2012)	CS	Research on Osteoarthritis/ Osteoporosis Against Disability (ROAD) Study	Japan (NR)	Radiographic	OA onset 2.74 (1.30–5.78)	Age, sex, alcohol consumption, smoking, resident region, BMI, presence of obesity, dyslipidaemia or impaired glucose tolerance	232
					OA progression 1.54 (1.10–2.17)		
Han et al. (2013)	CC	Korean National Health and Nutrition Examination Survey	Korea (NR)	Hospital diagnosed	Women 0.93 (0.65–1.33)	Age, amount of exercise, alcohol consumption and smoking	233
					Men 0.71 (0.36–1.40)		
Shin (2014)	CSS	Korean National Health and Nutrition Examination Survey	Korea (NR)	Radiographic	1.10 (0.89–1.36)	BMI, age, sex, amount of exercise, alcohol consumption, smoking and income	234
Liu et al. (2015)	CSS	NA	China (NR)	Symptomatic	Women 1.42 (1.10–1.84)	NR	235
					Men 1.48 (1.13–1.93)		
Li et al. (2016)	CC	NA	USA (NR)	Radiographic	For stage 3 hypertension 6.75 (0.96–48.67)	NR	236
Kim et al. (2016)	CSS	Korean National Health and Nutrition Examination Survey	Korea (NR)	Radiographic and symptomatic	1.26 (1.08–1.48)	BMI, age, sex, amount of exercise, alcohol consumption, smoking, education, income, occupation and mental health	237
Niu et al. (2017)	CS	Framingham Study	USA (white)	Radiographic	Women 1.30 (0.80–2.00)	BMI, age, amount of exercise, alcohol consumption, smoking and education	9
					Men 1.30 (0.80–2.10)		
				Symptomatic	Women 1.70 (1.00–3.00)		
					Men 1.80 (1.00–3.40)		

Table 1 (cont.) | **Studies investigating the relationship between hypertension and knee osteoarthritis**

Study (date)	Study design	Cohort	Location (ethnicity/race)	OA classification	Odds ratio (95% CI)	Adjusted factors	Ref.
Lo et al. (2017)	CS	Osteoarthritis Initiative	USA (NR)	Radiographic	1.70 (1.00–2.60)	BMI, age, sex and medication use (NSAIDs and antihypertensive, diabetic and cholesterol medications)	16
Zhang et al. (2017)	Meta-analysis	NA	NA	Radiographic	2.01 (1.28–3.15)	Sex, study design, hypertension definition and area	6
				Symptomatic	1.49 (1.26–1.77)		
Xie et al. (2017)	CSS	Xiangya Hospital Health Management Centre Study	China (NR)	Radiographic	1.23 (1.09–1.40)	Age, amount of exercise, alcohol consumption, smoking and education	238
Yasuda et al. (2018)	CSS	NA	Japan (NR)	Symptomatic	3.44 (1.88–10.55)	BMI, age and muscle strength	239
Sanchez-Santos et al. (2019)	CSS	Chingford Study	UK (NR)	Radiographic and symptomatic	1.15 (0.63–2.11)	BMI and age	240
Funck-Brentano et al. (2019)	CSS	UK Biobank	UK (white)	Hospital diagnosed	0.66 (0.57–0.77)	BMI, age and sex	13
Xie et al. (2021)	Meta-analysis	NA	NA	Radiographic	1.70 (1.41–2.05)	NR	7
				Symptomatic	1.32 (1.19–1.48)		
Lo et al. (2021)	Meta-analysis	NA	NA	Radiographic	1.89 (1.40–2.54)	NR	18
				Symptomatic	1.39 (1.17–1.65)		

CC, case–control study; CS, cohort study; CSS, cross-sectional study; NA, not applicable; NR, not reported; OA, osteoarthritis.

chemical exchange between the highly vascularized synovium and the avascular cartilage. For example, nutrients and oxygen from synovial capillaries diffuse to the chondrocytes in the superficial zone of articular cartilage via synovial fluid[30,31]. In its deep zone, articular cartilage is separated from subchondral bone by a thin layer of calcified cartilage[29]. Subchondral bone has a crucial role in nourishing the overlying cartilage[32,33]; indeed, the calcified cartilage is permeable to small molecules such as glucose and nitric oxide[34,35]. The presence of bone-derived proteins within articular cartilage further strengthens the idea of functional biochemical communication and interaction between bone and cartilage tissues[36]. Such interaction could be augmented through microcracks at the interface between bone and cartilage[37–39], through which subchondral bone blood vessels can invade the calcified cartilage layer during the development of OA.

Synovial vasculature

The synovium is highly vascularized, with both fenestrated and continuous capillaries present in relative proportions depending on the anatomical location in the joint[40]. The density of capillaries in the synovium also varies according to the location of the synovium within the joint cavity and the depth below the synovial surface[40]. Capillaries are usually located superficially and their density is high over areolar tissue and adipose tissue and low over tendons[41]. By contrast, lymphatic vessels are mainly located in the deep regions of the synovium[42]. The close proximity to the joint cavity and the fenestration of capillaries in the synovial microcirculation facilitates the exchange of molecules into the synovial fluid and the provision of nourishment to articular cartilage[43].

Modification of the synovial vascular network is a hallmark of the arthritic joint (FIG. 1). The OA synovium is characterized by an increase in microvessel density and endothelial cell proliferation[44,45], and by a decrease in lymphatic vessel density[42]. Synoviocytes isolated from inflamed areas of the OA synovium exhibit high angiogenic potential and have increased expression of vascular endothelial growth factor (VEGF) compared with synoviocytes from adjacent non-inflamed areas[45–47]. VEGF promotes synovial angiogenesis via VEGF receptor 2 (VEGFR2), which is highly expressed by endothelial cells and synoviocytes[47]. Notably, the degree of synovial angiogenesis seems to relate to the severity of synovitis in OA, rather than to the severity of cartilage damage or symptoms[44,48].

Subchondral bone vasculature

Subchondral bone comprises a subchondral trabecular meshwork and a cortical bone plate, which is separated from the calcified cartilage by the cement line. Trabecular bone of the epiphysis is highly vascularized, containing capillaries and a sinusoidal network[49,50]. In the haematopoietic bone marrow of the femoral head, microvessels are sinusoidal in form, whereas in the adipose bone marrow the microvessels are similar to capillaries in other tissues[49]. Cortical bone is penetrated by cavities of different sizes that can be extensions of the marrow space, cylindrical canals containing marrow cells and, occasionally, a blood vessel, or small vascularized channels[51]. These small channels (10–30 μm in diameter) are surrounded by concentric layers of bone that contain thin-walled blood vessels and are the primary conduit for vessels in the subchondral bone[51]. These vascular channels, which contain blood vessels, sympathetic nerves, osteoclasts and osteoblasts[52–54],

Areolar tissue
A type of connective tissue with loosely organized fibres that provides space for interstitial fluid to fill the tissue to provide nourishment.

Epiphysis
The ends of long bones that are covered with articular cartilage and join adjacent bones.

nourish the calcified cartilage and the deep layers of the non-calcified cartilage and govern remodelling at the osteochondral junction[51,52].

Subchondral bone undergoes constant remodelling in response to either physiological or pathological mechanical loading. In the early stages of OA, the cortical plate becomes thinner with less trabecular bone owing to an increase in osteoclast activity and bone turnover rate[55]. In later stages of OA, the subchondral cortical plate becomes thick and sclerotic, whereas the trabecular bone remains osteopenic[55]. Alongside this remodelling process, increased vascularization in the subchondral bone during OA has been well documented in both animals[28] and humans[56].

As bone is a mechanoresponsive tissue, angiogenesis is coupled with osteogenesis under mechanical stimuli during bone modelling and remodelling[57]. During bone repair in mice, osteoblast-derived VEGF regulates osteoblast differentiation and bone formation[58] and osteoblasts can also secrete angiogenic factors in response to mechanical stimuli[59]. Similarly, osteoclast-derived platelet-derived growth factor BB (PDGF-BB) stimulates angiogenesis in subchondral bone in mice and contributes to OA development[60]. Given that aberrant mechanical loading occurs in OA joints as a consequence of cartilage damage, then corresponding vascular modification would be anticipated to take place. Markedly, in a proposed new histological scoring system, subchondral angiogenesis is one of the criteria that must be considered to quantify remodelling of the subchondral bone in mouse models of OA[61]. The inclusion of subchondral angiogenesis marks the recognition of a role for the vasculature in OA assessment and evaluation, implying the importance of angiogenic–osteogenic coupling in disease progression.

In addition to angiogenesis in the subchondral bone, vascular penetration is also observed in human OA at the tidemark that separates the non-calcified from the calcified cartilage[53,62] (FIG. 1). Vascular invasion is accompanied by the expression of matrix metalloproteinases (MMPs) and by the depletion of proteoglycans from the surrounding extracellular matrix (ECM) in cartilage[53]. In addition, vascular channels at the osteochondral junction in OA enable the infiltration of sensory and sympathetic nerve endings that express nerve growth factor and that can generate pain sensation[54,63]. The number of vascular invasion incidents has also been associated with the severity of cartilage damage and clinical symptoms[44,53]. Indeed, the inhibition of angiogenesis successfully preserves joint integrity and reduces pain

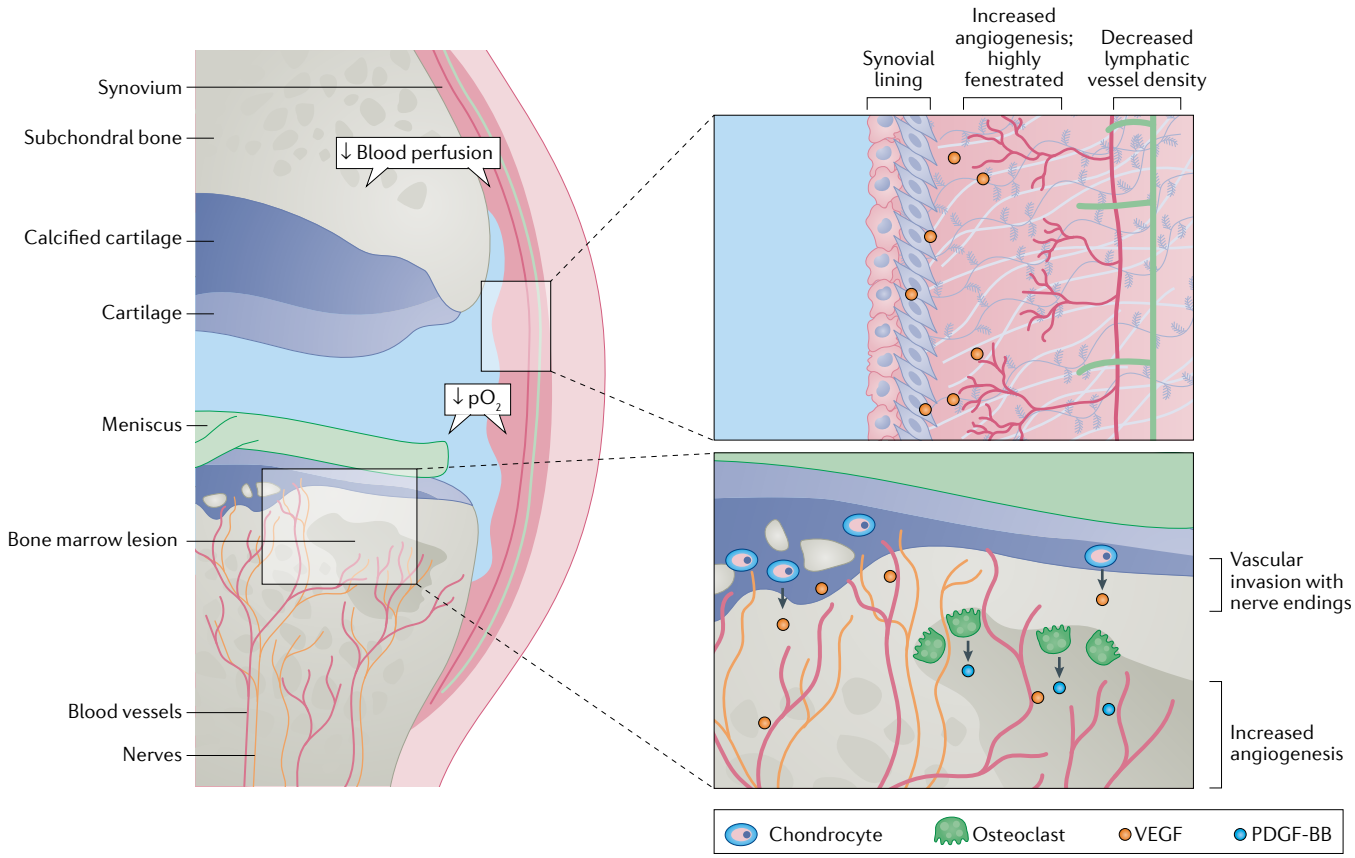

Fig. 1 | **The vasculature and its changes in knee osteoarthritis.** Extensive angiogenesis occurs during knee osteoarthritis. Vascular endothelial growth factor (VEGF) is secreted by various tissues, including the synovium, subchondral bone and cartilage, to promote vessel growth. At sites of aberrant bone remodelling, other angiogenic factors, such as platelet-derived growth factor BB (PDGF-BB), are also secreted. Despite the increase in the number of vessels, local blood flow to the tissue decreases. Perfusion abnormalities, including limited arterial inflow and venous outflow, occur possibly as a result of impaired vessel function and increased intraosseous pressure. The reduced blood flow hinders the supply of oxygen and nutrients to tissues, thus creating an environment of hypoxia and nutritional stress. The formation of highly fenestrated blood vessels and reduction in lymphatic vessel density in osteoarthritic knees also affect synovial fluid drainage, resulting in joint effusion. pO_2, partial pressure of oxygen.

in various experimental models of OA[64]. These findings emphasize the importance of joint vascularization in joint homeostasis and disease.

Notably, angiogenic vessels in OA subchondral bone have a unique molecular phenotype and are known as type H vessels[65]. These blood capillaries are characterized by their high expression of both CD31 and endomucin and were initially described in the metaphysis of young mice[66]. The proportion of type H vessels is maximal after birth and declines in adult and aged mice[66,67]. Type H vessels express large quantities of pro-osteogenic factors and recruit osterix-expressing osteoprogenitor cells, thereby coupling angiogenesis with osteogenesis[66]. The formation of type H vessels also involves preosteoclast-derived PDGF-BB[68]. Interestingly, preosteoclast-derived PDGF-BB can stimulate type H vessel development in the subchondral bone of mice after the induction of OA by destabilization of the medial meniscus (DMM)[60]. Mice that specifically overexpress PDGF-BB in preosteoclasts develop spontaneous OA and are characterized by an increase in H type vessels and nerve endings in the subchondral bone, whereas the specific deletion of PDGF-BB in preosteoclasts provokes the opposite effects[60]. VEGFA secreted by chondrocytes is also involved in type H vessel formation in OA[69] and a proposed crosstalk between endothelial cells and hypertrophic chondrocytes is thought to promote osteogenesis[70].

Hypertension and the joint environment

Given the pivotal roles of alterations in local vascular function and neoangiogenesis in the pathophysiology of OA, the effects of systemic vascular homeostasis on joint health and disease are of great interest. Although not fully understood, systemic vascular pathologies, and particularly hypertension, might contribute to joint disorders both biophysically and biochemically.

Perfusion abnormalities and ischaemia

Hypertension might impair subchondral bone perfusion by altering both fluid flow and intraosseous pressure. Pulse pressure linearly correlates with intraosseous pressure and intraosseous pressure is negatively associated with intraosseous blood flow[71–73]. Therefore, hypertension could potentially contribute to the reduced blood perfusion that occurs in local joint tissues in OA[10] despite compensatory extensive angiogenesis (FIG. 1). Moreover, structural and functional changes in the hypertensive heart could contribute to cardiac arrhythmias that disturb blood flow to the limbs[74].

Bone perfusion abnormalities, characterized by a reduction in both arterial inflow and venous outflow, have indeed been documented in human knee OA[75]. An increase in intraosseous pressure following venous occlusion in hip OA has also been known for a long time[72,76]. In a 2018 study, dynamic contrast-enhanced MRI was used to assess the kinetics of bone perfusion in knee OA[75]. This study revealed a slow clearance of contrast agent in subchondral bone, indicating a reduction of venous outflow in osteoarthritic knees. The patients in this study also showed a limited arterial inflow[75]. Reduction in blood flow could lead to subchondral bone ischaemia and apoptosis of osteocytes that in turn initiates osteoclast-mediated bone resorption[77]. In a mouse model of post-traumatic OA, the disruption of blood flow was detected by power Doppler imaging post-DMM and was associated with the severity of joint damage[78]. In guinea pigs with spontaneous OA, decreased venous outflow in the medial tibial plateau both preceded and was colocalized with cartilage degradation and subchondral bone thickening[79]. Observations from both animals and humans further strengthen the notion of the intimate relationship between blood perfusion and joint destruction.

Hypoxia

The disruption of local blood flow could also trigger a cascade of responses at both the molecular and cellular levels. In OA, both the synovial fluid and the synovium are similarly characterized by a decrease in the partial pressure of oxygen (pO_2)[78,80] (FIG. 1). Interestingly, the importance of circulatory insufficiency relative to synovial tissue metabolism has been highlighted in an effort to explain this observation[81]. The reported link between synovial blood flow and intra-articular hydrostatic pressure could explain the inverse relationship between synovial fluid volume and pO_2[80,82]. In mice with OA induced by DMM, synovial pO_2 (as measured by photoacoustic imaging) progressively decreased with the development and the progression of OA[78]. Synovial hypoxia negatively correlated with synovial blood flow but was positively associated with cartilage damage[78]. Similar features have also been noted in the subchondral bone in human OA; the increased intraosseous pressure found in patients with hip OA is associated with a decreased subchondral pO_2 and an increase in lactate concentration[83].

Impaired nutrition supply

Hypertension-induced perfusion abnormalities cause nutrient deprivation to both bone and cartilage, which ultimately affects their homeostasis[84]. Indeed, osteocytes can only survive nutrient depletion for 4 hours in an experimental setting[85] and 6 hours of bone ischaemia is sufficient to cause osteonecrosis[86].

Subchondral bone perfusion supplies at least 50% of the necessary glucose and oxygen to overlying cartilage[31]. Apart from being a building block for proteoglycan (a major component of cartilage ECM), glucose also regulates catabolic and anabolic gene expression in chondrocytes[87,88]. Changes to the glucose concentration in the ECM can impair insulin growth factor 1-mediated anabolism in chondrocytes, leading to joint pathologies[89]. In a hypoxic environment, the expression of glucose transporter 1 by chondrocytes is upregulated, enabling a more rapid uptake of glucose[90]. However, the intake of nutrients in such an anaerobic environment favours glycolysis, which produces acidic lactate as an end product and further acidifies the cartilage environment[91]. Importantly, acidification of the ECM can alter the synthesis of matrix molecules[92]. The energy depletion caused by the switch to glycolysis is also associated with increased production of nitric oxide as found in osteoarthritic joints[91].

Hypertension and joint structure

Hypertension increases intraosseous stress and causes perfusion abnormalities in joint tissues[72,73]. The resulting physical stress and hypoxic stress could be detrimental to joint homeostasis by dysregulating bone remodelling, altering the osteochondral junction, and provoking inflammation (FIG. 2) and could also explain the comorbid presentation of hypertension and OA, particularly radiographic OA. Clinically, measures of bone quality such as bone mineral density are closely associated with blood flow[27,93]. Researchers have also documented the intracellular and extracellular responses of osteocytes and their progenitor cells towards changes in fluid shear stress[94,95]. Fluid shear stress increases the expression of MMPs and the secretion of osteogenic signalling factors such as nitric oxide and prostaglandins by mesenchymal stem cells, which then trigger the downstream activation of transforming growth factor-β (TGFβ) and cGMP-dependent protein kinase signalling pathways[95,96]. Prolonged exposure to TGFβ can trigger OA-like changes in the knees of mice despite its transient effect on promoting chondrogenesis[97], and nitric oxide upregulates MMPs in a cGMP-dependent manner, further contributing to cartilage destruction[98].

Osteonecrosis

When bone ischaemia and a hypoxic environment are sustained, osteocytes will inevitably undergo apoptosis, which can initiate osteoclast-mediated bone resorption and even lead to osteonecrosis (FIG. 2a). Apoptotic osteocytes are present in the subchondral bone of patients with OA[99]. In murine studies, apoptotic osteocytes could stimulate neighbouring osteocytes to release receptor-activator of NF-κB ligand (RANKL),

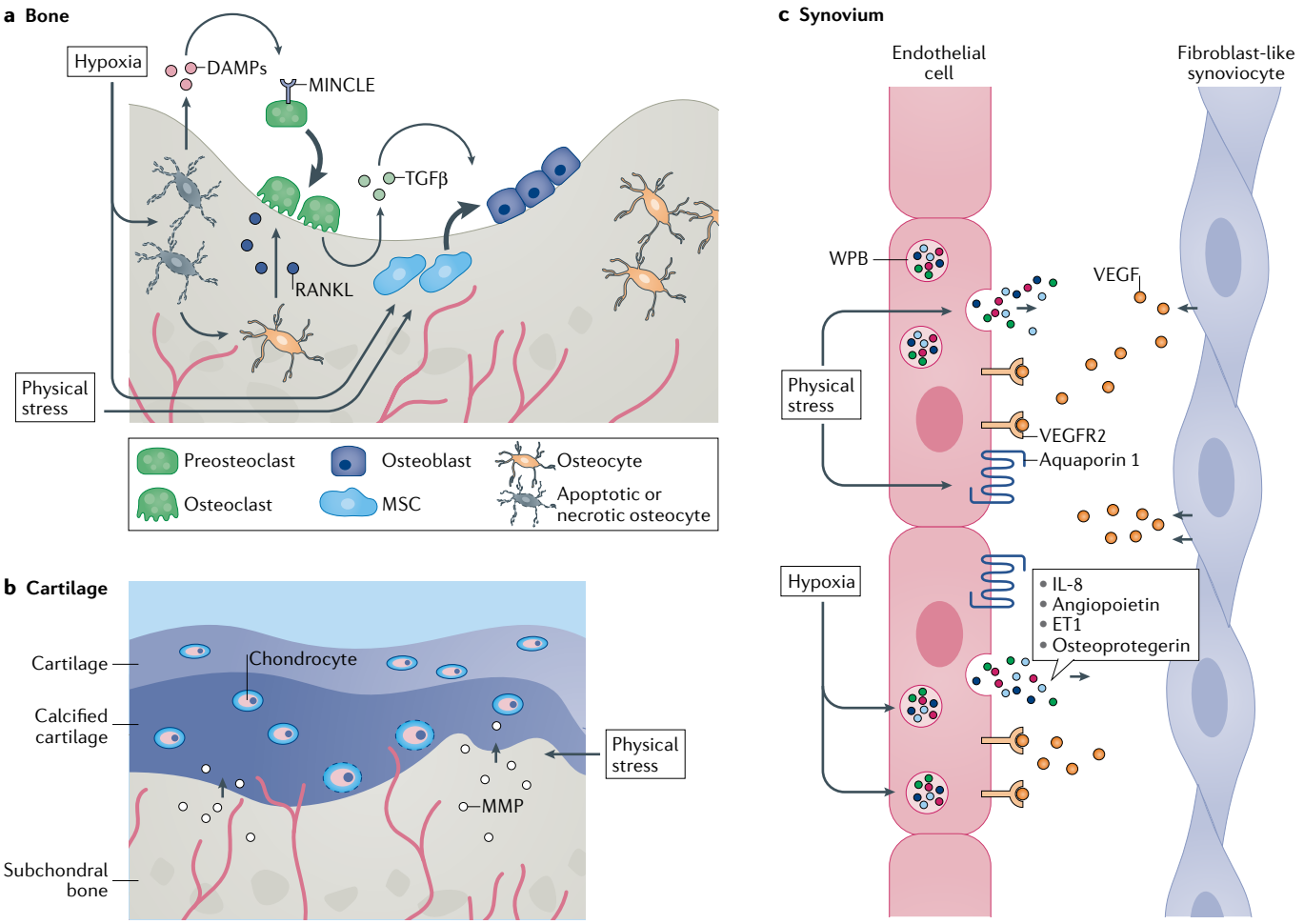

Fig. 2 | **Biophysical effects of hypertension on the joint at the cellular level.** Increased arterial pressure positively correlates with increased intraosseous pressure, while hypertension-induced perfusion abnormalities of vessels limit oxygen supply to joint tissues, creating a hypoxic microenvironment. **a** | Bone undergoes remodelling in response to mechanical changes, resulting in structural changes. Hypoxia triggers osteocyte necrosis. Necrotic osteocytes secrete damage-associated molecular patterns (DAMPs) that can bind to C-type lectin domain family 4 member E (MINCLE) on preosteoclasts and stimulate their differentiation. Apoptotic osteocytes induce the secretion of receptor-activator of NF-κB ligand (RANKL) from neighbouring osteocytes to activate osteoclasts, which initiate the bone remodelling cascade by stimulating osteoblasts (differentiated from mesenchymal stromal cells (MSCs) via transforming growth factor-β (TGFβ)). **b** | The increased physical stress and pressure accelerate the exchange of chemicals (including matrix metalloproteinases (MMPs)) at the osteochondral junction, which promotes cartilage catabolism. **c** | Physical stress increases aquaporin 1 expression on synovial microvessels, contributing to joint effusion and synovial oedema. Hypertensive stretch and hypoxia also aggravate synovial inflammation by promoting the exocytosis of pro-inflammatory cytokine-containing Weibel–Palade bodies (WPBs) from endothelial cells. ET1, endothelin 1; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2.

which induces osteoclast activation[100,101]. In horses with spontaneous equine carpal post-traumatic OA, RANKL expression was increased in the subchondral bone and was linked to increased osteoclast density[102]. In vitro, the secretion of RANKL by the osteocytic MLO-Y4 cell line can be stimulated by hypoxia and favours the differentiation of RAW264.7 cells into osteoclasts[103]. Conversely, conditional knockout of RANKL in osteocytes in mice with surgically induced OA reduces the differentiation of osteoclasts and inhibits the growth of sensory nerves into the subchondral bone and pain hypersensitivity[104].

Macrophage colony-stimulating factor (M-CSF) is another essential cytokine for osteoclastogenesis[105]. M-CSF is secreted by osteoblasts and can direct osteoclast differentiation, thereby promoting bone resorption. The administration of M-CSF can induce bone resorption in wild-type rats and restore bone resorption function and reverse disease phenotypes in mice with osteopetrosis[106,107]. Interestingly, an increase in M-CSF was observed in primary cultured osteoblasts from rats with spontaneous hypertension and was accompanied by a loss of bone mass in the animals[108]. High amounts of circulating IL-6 have also been documented in both humans and rodents with hypertension[109,110]. IL-6 can stimulate osteoclast formation in the presence of M-CSF[111], suggesting that inflammation in hypertension might aggravate osteonecrosis in OA via an interaction between IL-6 and M-CSF.

Recently, a 2020 study has shown that damage-associated molecular patterns released by necrotic osteocytes can be detected by C-type lectin domain family 4 member E (also known as MINCLE) on osteoclasts, which then induces the differentiation of osteoclasts and triggers bone loss[112]. In patients with osteonecrosis, MINCLE was highly expressed in areas of high osteocyte death and correlated with the expression of markers of osteoclast activity[112]. Although a role has not yet been reported for MINCLE in OA, damage-associated molecular patterns are known to be involved in the pathogenesis of OA[113].

Bone marrow oedema

When a joint is mechanically unstable (for example, after anterior cruciate ligament injury[114,115]), the subchondral bone can exhibit a bone bruise (an oedema-like change on MRI scans) known as a bone marrow lesion (BML)[28]. In patients with OA, BMLs are characterized by highly vascularized sclerotic bone tissue with poor mineralization[116,117] and the size of BMLs is inversely proportional to the venous outflow as measured by dynamic contrast-enhanced MRI[26]. The presence of BMLs is strongly associated with increased cartilage erosion and more severe joint pain in patients with knee OA[118,119]. However, it remains controversial whether BMLs resolve or enlarge as OA develops[120,121]. Cystic lesions can develop alongside cartilage loss in both rats with post-traumatic OA and humans with knee OA[122,123]. Some investigators have also suggested that BMLs could be a consequence of ischaemia reperfusion injury[124]. Arterial pressure could conceivably promote capillary oedema, resulting in increased intramedullary pressure and creating a phenomenon that is proposed to be equivalent to BMLs[124]. These results suggest that vascular perfusion and pressure could be determinants of BMLs.

Bone sclerosis

Although patients usually experience temporal bone loss in the early stages of OA, at later stages of disease, bone mass actually increases[125]. The exact mechanism of subchondral bone thickening following the initial osteopenic changes is unclear but hypertension-associated alterations in bone remodelling could account for the sclerotic changes in subchondral bone.

As previously mentioned, pre-osteoclasts secrete PDGF-BB, which stimulates type H vessel development in subchondral bone[60,68]. Type H endothelial cells are capable of inducing osteoblastic differentiation, which could lead to increased bone formation[66]. In addition, osteoclast-mediated bone resorption releases active TGFβ1, which stimulates the recruitment of mesenchymal stromal cells that further differentiate into osteoblasts, thus contributing to subchondral bone sclerosis in OA[28]. Notably, the differentiation of bone marrow mesenchymal stromal cells into osteoblasts can also be directly stimulated by hypoxia[126]. In this context, hypertension-induced hypoxia could aggravate bone sclerosis.

Despite the increase in mass, sclerotic bone is often under-mineralized[127,128]. This impaired mineralization might be linked to an increase in expression of the Wnt antagonist Dickkopf 2 (DKK2). The upregulation of TGFβ1 in osteoarthritic human osteoblasts could stimulate DKK2, a well-known inhibitor of bone mineralization[128]. Thus, the poor mineralization of sclerotic bone might be attributable to changes in Wnt signalling, which is indeed a critical link between hypertension and OA that will be discussed further in another section of this Review.

Osteochondral junction modification

In OA, increased hydraulic conductance has been recorded at the bone–cartilage interface[122]. The pathological remodelling of subchondral bone and vascular invasion into the osteochondral junction is thought to explain the increased ability of biochemical factors to cross the osteochondral junction[129,130] (FIG. 2b). These factors, produced by the damaged bone in OA, can stimulate cartilage degradation[131], particularly by inducing catabolic changes in chondrocyte phenotypes[132]. Considering the increased intraosseous pressure and osteochondral junction modification that occurs in OA, the transport of molecules from the bone to the cartilage might also be accelerated, further facilitating cartilage damage[133,134]. This process could be aggravated by hypertension as intraosseous pressure correlates with blood pressure[72].

Joint effusion

Joint effusion is associated with both radiographic severity and pain in OA[135,136] and could result from an increase in the production of synovial fluid and from abnormalities in synovial fluid drainage in OA. Indeed, an association has been noted between joint effusion and a low density of lymphatic vessels in the synovium

Weibel–Palade bodies
Storage granules in endothelial cells that can be released through exocytosis.

in patients with OA[42]. Synovial oedema is probably also related to an increased vascular permeability of the synovial capillaries[137]. For example, an increased synovial fluid-to-serum ratio of proteins occurs in patients with OA compared with healthy individuals[138]. Immunohistochemical analysis has also revealed an overexpression of the water channel aquaporin 1 in synovitis that contributes to joint swelling and synovial oedema formation in rheumatoid arthritis[139]. Notably, hypertension provokes aquaporin 1 overexpression and activation in aortic endothelial cells in rats[140], suggesting that the upregulation of aquaporin 1 could lead to an increase in hydraulic conductance in OA.

Capillary endothelial cells from the synovium of patients with OA contain more Weibel–Palade bodies (WPBs) than those in the synovium of healthy individuals[141]. WPBs store the adhesive glycoprotein von Willebrand factor, the leukocyte adhesion molecule P-selectin and numerous other pro-inflammatory, angiogenic or vasoactive factors, including IL-8, angiopoietin 2, endothelin 1 (ET1) and osteoprotegerin. The exocytosis of WPBs is tightly regulated by a wide range of physiological signals (hormones and growth factors, thrombin, histamine and mechanical stress) and pathological signals (bacterial toxins)[142–144]. Notably, hypertensive stretch stimulates the exocytosis of WPBs in a mechanism dependent on VEGFR2 (REF.[145]); hence, hypertension could aggravate synovitis in this context (FIG. 2c).

The exocytosis of endothelial WPBs could also be triggered by hypoxia[146], thereby promoting the secretion of pro-inflammatory cytokines. A hypoxic environment also induces the expression of endothelin-converting enzyme (ECE1) and ET1, factors that stimulate the degranulation of WPBs[147,148]; a local amplification loop of ET1 production and secretion is then sustained. The excessive ET1 stimulates the production of pro-inflammatory factors and triggers the catabolic metabolism of articular cartilage as well as synovial thickening in a mechanism that involves a positive feedback loop of reactive oxygen species production[149–151].

Shared molecular pathways

As previously mentioned, hypertension and OA share some basic mechanistic pillars at the tissue, cellular and molecular levels, which largely converge on vasoconstrictors such as the renin–angiotensin system (RAS) and endothelin system[152,153] (FIG. 3). Furthermore, the canonical Wnt–β-catenin pathway has been implicated in both cardiovascular and skeletal diseases[154]. Drugs that target these shared molecular pathways have the potential to demonstrate dual cardioprotective and chondroprotective effects. Further investigation into these shared molecular pathways could lay a foundation for the development of a unified strategy for a variety of age-related pathologies, such as hypertension and OA, in older adults.

Renin–angiotensin system

RAS has a central role in blood pressure regulation, particularly for short-term changes[152], and high circulating concentrations of the RAS component angiotensin II have been reported in individuals with hypertension[155]. Although first identified in the circulatory system, RAS components also exert tissue-specific functions, which are termed local RAS[156]. In the skeletal system, local RAS is particularly important for chondrocyte hypertrophy.

Local RAS expression is found in both human and mouse chondrocytes[157,158]. Although the upregulation of RAS components is greater in synovial fluid from patients with rheumatoid arthritis than in that from patients with OA, ACE expression correlated with concentrations of VEGF and MMP13 in individuals with either type of arthritis[159]. These results suggest a possible role for RAS in synovial angiogenesis as well as in cartilage destruction. At the cellular level, RAS components are involved in different stages of chondrocyte differentiation; however, the respective roles of type 1 angiotensin II receptor (AT1) and AT2 remain controversial. In rats with OA with extensive chondrocyte hypertrophic differentiation, the amount of *AGTR1* mRNA (encoding AT1) was increased, while that of *AGTR2* was reduced[160]. Although the exact roles of the two receptors remain to be elucidated, the findings to date give solid support to the idea of interaction between local RAS and chondrocyte hypertrophy. A study in mice also found that RAS components were expressed exclusively in hypertrophic chondrocytes and not in chondrocytes in hyaline cartilage[158]. Both infusion of angiotensin II and activation of AT2 induced the upregulation of hypertrophy-related genes such as *RUNX2* and *MMP13* in the ATDC5 chondrogenic cell line[161]. Similarly, in vitro administration of the hypertrophy stimulant IL-1β could also initiate expression of AT1 and AT2 by human articular chondrocytes[157]. Contradictory to current understanding, the induced hypertrophic differentiation by angiotensin II protects cells from apoptosis. The anti-apoptotic genes *Bcl2* and *Bcl2l1* were overexpressed in angiotensin II-induced hypertrophic chondrocytes in mice[162], contradicting the idea that angiotensin II promotes cell death via activation of AT2. However, the exact mechanisms involved remain unclear.

In addition to cartilage homeostasis, angiotensin II also has a role in bone remodelling via interaction with RANKL. In the vascular system, angiotensin II activates RANKL, which then accelerates calcium deposition[149]. Vascular calcification reduces vessel elasticity and thereby aggravates systolic hypertension in a vicious cycle[163,164]. In the skeletal system, angiotensin II can induce RANKL expression in osteoblasts, which can then activate osteoclasts and initiate bone remodelling, resulting in aberrant structural changes in OA as previously discussed[165,166].

Endothelin system

In addition to RAS, the endothelin system is a potent vasoconstrictor that helps to control vascular tone and has been implicated in human hypertension[167]. Notably, angiotensin II is an important transcriptional inducer for ET1 and infusion of angiotensin II into normotensive rats enhances both ECE1 activity and renal ET1 concentrations[168].

The endothelin family consists of three isoforms, ET1, ET2 and ET3, which perform their biological functions

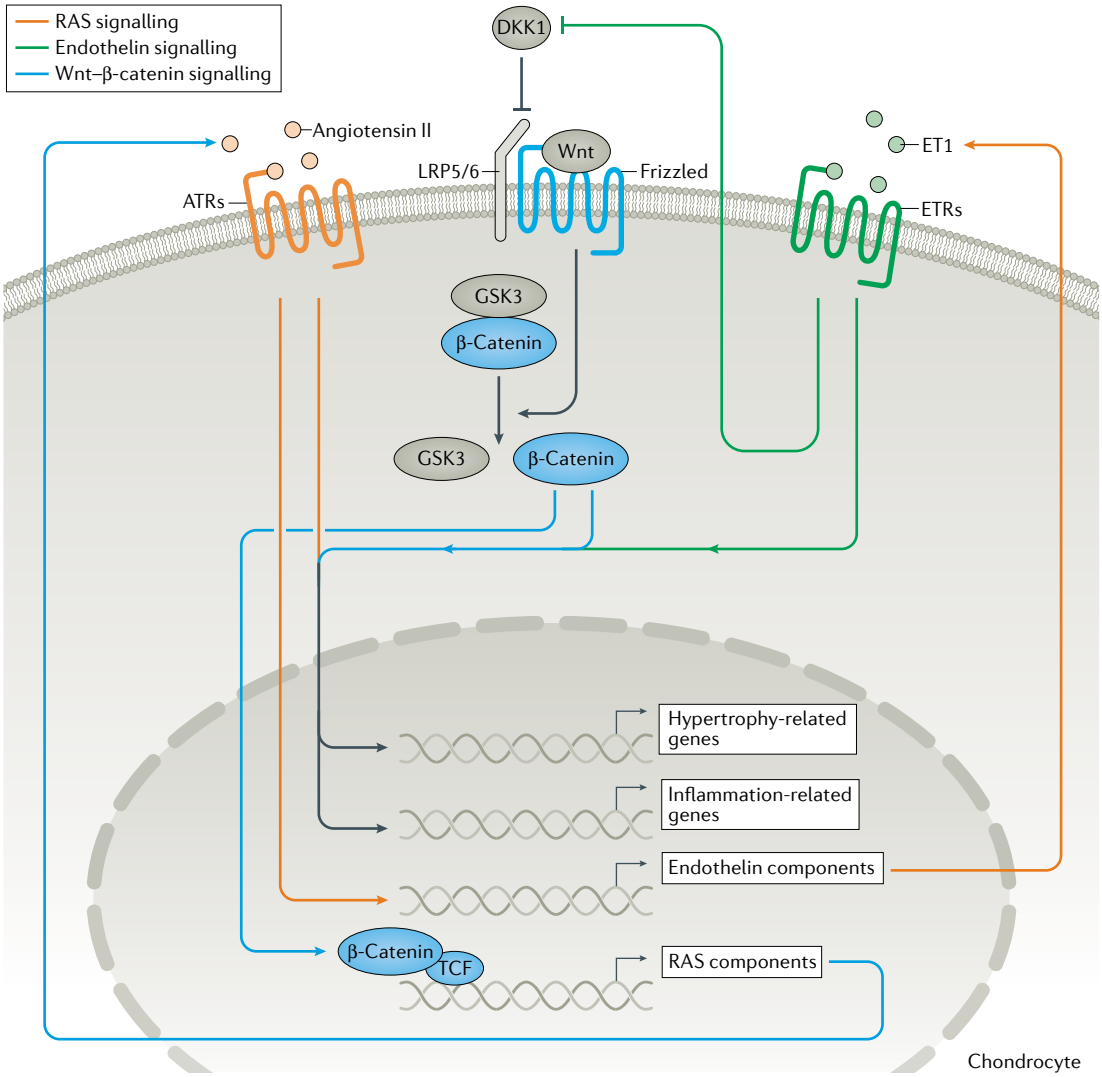

Fig. 3 | **Molecular pathways shared by hypertension and osteoarthritis.** Cartilage is avascular and hypoxic, making it less susceptible to direct physical stress and hypoxic stress brought about by hypertension than bone and the synovium. However, overactivated pathways in hypertension could affect chondrocyte fate. The renin–angiotensin system (RAS), endothelin system and canonical Wnt–β-catenin pathways, which are upregulated in hypertension, induce chondrocyte hypertrophy and an inflammatory response, contributing to joint catabolism. The three pathways are also interconnected. RAS components are transcriptional inducers of endothelin system components. Endothelin 1 (ET1) can suppress Dickkopf protein 1 (DKK1) synthesis and thereby activate the Wnt–β-catenin pathway, which in turn induces the transcription of RAS components. Drugs targeting these shared pathways have shown both cardioprotective and chondroprotective effects, suggesting potential roles in the pathogenesis of both cardiovascular disease and joint disease. ATRs, angiotensin receptors; ETRs, endothelin receptors; GSK3, glycogen synthase kinase 3; LRP, LDL receptor-related protein; TCF, T cell factor.

as vasoconstrictors, mitogens or pro-inflammatory cytokines by activating two G protein-coupled receptors (ET_AR and ET_BR)[169]. Among the endothelins, ET1 is the predominant form in the cardiovascular system and is an aggravating factor in endothelial dysfunction. ET1 is mostly produced by endothelial cells and the counter-effect of the two receptors ensures the precise control of vascular tone[169].

In addition to a role in vascular tone regulation, ET1–ET_AR interactions have also been implicated in articular cartilage degradation and OA development. Clinically, an increase in plasma and synovial ET1 concentrations correlates with the severity of knee OA[170]. Both ET1 and ET_AR are upregulated in all affected joint tissues in OA, including synovial fluid, the synovium and articular cartilage[149,150,171–173]. ET1 in synovial fluid and the synovium can stimulate the production of pro-inflammatory mediators such as IL-1β, IL-6, and IL-8 and can trigger the catabolic metabolism of articular cartilage as well as synovial thickening[149,150]. When used in vitro at similar concentrations to those present systemically and locally in patients with knee OA, ET1 could directly stimulate osteoarthritic chondrocytes to produce MMP1 and MMP13, major enzymes involved in degrading the cartilaginous ECM[171,172]. Underlying mechanisms might involve a positive feedback loop of reactive oxygen species production that activates the transcription factor AP1 and, in turn, increases ECE1 expression and ET1

synthesis[151]. Notably, intra-articular injection of an ET1 antagonist could attenuate articular cartilage degradation following anterior cruciate ligament trauma in a rat model, suggesting that the endothelin system could be a potential therapeutic target for OA management[173].

Wnt–β-catenin signalling

The canonical Wnt–β-catenin signalling pathway governs a wide range of biological activities and, remarkably, the Wnt–β-catenin pathway is upregulated in both individuals with hypertension and in patients with OA[174,175].

A genome-wide association study has revealed a direct correlation between *WNT3* and pulse pressure[176]. Peripheral blood expression of *APC* and *TCF4*, another two genes associated with the Wnt signalling pathway, also showed associations with pulse-wave velocity and arterial stiffness independent of traditional cardiovascular disease risk factors in a population of men with African ancestry from Tobago[177]. Clinically, the overexpression of LDL receptor-related protein 6 (LRP6), a co-receptor for Wnt proteins, has also been found in individuals with hypertension[178]. In fact, interactions between the Wnt–β-catenin pathway and RAS have been widely discussed in relation to cardiovascular diseases. A bioinformatics analysis revealed binding sites for the TCF–LEF family of transcription factors in all RAS genes, including those encoding angiotensinogen, renin, ACE, AT1 and AT2 (REF.[179]). As TCF–LEF transcription factors are part of the Wnt–β-catenin signalling pathway, these results imply that the Wnt–β-catenin pathway could trigger RAS activation. In addition, angiotensin II infusion can induce β-catenin expression and activation[180,181]. The intimate relationship between RAS and the Wnt–β-catenin pathway consolidates the importance of this pathway in vascular homeostasis.

The Wnt signalling pathway has also been extensively studied in skeletal development and degeneration[182]. Wnt signalling helps to maintain the balance between osteogenesis and chondrogenesis as activation of Wnt promotes osteoblast differentiation while repressing chondrogenesis[183]. Wnt–β-catenin signalling also suppresses expression of the chondrogenic gene *Sox9* while enhancing expression of the hypertrophic genes *Runx2* and *Mmp13* in mice[183]. In addition, the overexpression of Wnt genes and β-catenin has been documented in knee OA[175,184,185]. Moreover, Wnt antagonists have shown a beneficial effect on cartilage homeostasis. DKK1 is a Wnt inhibitor that competes with Wnt ligands to bind LRP5 and LRP6 (REF.[186]), thereby blocking the Wnt signalling cascade. A high serum concentration of DKK1 reduced the risk of hip OA in elderly women, whereas an increased serum concentration of another Wnt antagonist, frizzled-related protein, also produced a modest reduction in the risk of hip OA[187]. Frizzled-related protein is a competitive antagonist of frizzled receptors, which are the main receptors for Wnt proteins. A single nucleotide polymorphism in *FRZB*, which encodes frizzled-related protein, increases susceptibility to OA[188,189]. The downregulation of this gene has also been observed in mechanically injured cartilage[185]. All of this evidence hints at the detrimental effect of Wnt–β-catenin pathway upregulation on cartilage homeostasis. Notably, ET1 inhibits DKK1 production in vitro in mouse osteoblasts, thereby activating Wnt signalling[190]. However, although mediation of the Wnt signalling pathway via suppression of Wnt inhibitors by ET1 has been postulated in chondrocytes, experimental proof is required.

Targeting shared molecular pathways

Given that local RAS contributes to various skeletal pathologies, including osteoporosis[191,192], rheumatoid arthritis[193,194] and possibly OA, treatments that target RAS components are being investigated. Aliskiren, a renin inhibitor approved for the treatment of hypertension, has chondroprotective effects by attenuating IL-1, TNF and RUNX2 expression[195]. Aliskiren inhibited chondrocyte hypertrophy, reduced local RAS expression and rescued cartilage destruction in rats with surgically induced OA[195]. Another FDA-approved treatment for hypertension, the ACE inhibitor captopril, has similar effects; captopril suppressed renin, ACE and angiotensin II expression in rats with surgically induced OA by altering the expression of AT1 and AT2 (REF.[160]). The amount of hypertrophic cartilage was greatly reduced by both treatment methods. Furthermore, preliminary results suggest that captopril can attenuate the increased expression of senescence markers that occurs in both subchondral bone and articular cartilage in the deoxycorticosterone acetate salt model of hypertension and in spontaneously hypertensive rats[196].

In addition to chondroprotective effects, antihypertensive drugs can also reduce inflammation. Losartan (an AT1 blocker) and captopril can reduce joint pain and inflammation in rats and mice with experimental models of rheumatoid arthritis[193,197] and rats with experimental OA[160,195,196], respectively, suggesting that the protective effect of antihypertensive drugs on joints was achieved by suppression of local RAS. However, the administration of losartan exacerbated bone loss induced by angiotensin II in mice[166]. This phenomenon might be explained by the opposing roles of AT1 and AT2 in osteoblasts as knockdown of *AGTR2* produced promising effects towards restoring angiotensin II-induced bone loss[166]. By contrast, the ACE inhibitor enalapril improved bone mass and hypertension simultaneously in mice[164] but only marginally in humans[198]. These findings suggest that the beneficial effect of RAS inhibition on joint homeostasis and function might be cell-type specific.

Although the exact role of the endothelin system in OA is yet to be fully defined, ET1 has been linked to chondrocyte hypertrophy and senescence. Preliminary data have also demonstrated that mice with transgenically overexpressed endothelial ET1 have an activated endothelin system and exhibit an OA-like phenotype compared with their littermates, as well as having hypertrophic changes in their cartilage[199,200]. A 2020 study has also demonstrated that ET1 can induce cellular senescence in the murine chondrogenic cell line ATDC5, which could be rescued by ET_BR blockade[201]. Considering that the endothelin system is intertwined with RAS, these effects on chondrocyte fate were anticipated.

The downregulation of Wnt signalling has also been proposed as a strategy to preserve cartilage integrity in

OA management[202]. A variety of Wnt signalling antagonists has been developed and evaluated, including antidepressants, microRNAs, herb extracts and enzymes[203]. These antagonists target components of the Wnt pathway and thereby suppress the signalling cascade, resulting in a reduction in cartilage destruction. Notably, intra-articular injection of the small-molecule Wnt inhibitor SM04690 had promising effects on cartilage rescue in a phase II clinical trial for knee OA with no reported toxicity[204]. Verapamil, a calcium channel blocker generally used for the treatment of hypertension, has also shown a chondroprotective effect through suppression of the Wnt pathway. Verapamil is a potent *FRZB* activator in human OA chondrocytes, in which it was able to downregulate the Wnt pathway and thus inhibit chondrocyte hypertrophic differentiation[205]. Intra-articular injection of verapamil successfully inhibits β-catenin accumulation and OA progression in rats with post-traumatic OA[205]. Taken together, these studies provide preliminary proof of the idea of targeting shared pathways between hypertension and OA for cartilage protection. However, whether these molecules and drugs could rescue OA in a whole-joint manner by restoring bone and synovial function and structure warrants further investigation.

Other antihypertensive drugs for OA

Despite decades of effort in OA research, a cure has not yet been discovered. Research into the causal relationship between hypertension and OA might open the door to the development of disease-modifying OA drugs. The repurposing of FDA-approved drugs for hypertension has the potential for rapid clinical translation as toxicity and pharmacokinetic information for these drugs is readily available. In addition to the RAS, endothelin and Wnt antagonists discussed in the previous section, some other antihypertensive drugs have been trialled for the treatment of OA in various experimental models. Some have already shown promising chondroprotective effects and pain relief whereas others are still being investigated. Among the antihypertensive drugs being investigated, potassium-sparing diuretics and adrenergic antagonists are undergoing the most extensive research for their anti-inflammatory and pain relief effects in OA management.

Potassium-sparing diuretics

Diuretics are drugs that increase sodium and water excretion while retaining potassium reabsorption to prevent hypokalaemia. Diuretics can be further classified into two types: aldosterone antagonists (such as spironolactone and eplerenone) and epithelial sodium channel blockers (such as amiloride). By regulating ion balance and fluid retention, diuretics generally have mild antihypertensive effects and are often used for the treatment of resistant hypertension that is unresponsive to medication[206].

Spironolactone. In patients with OA, low-dose spironolactone improved joint effusion and its associated pain with a higher efficacy than ibuprofen, a commonly used NSAID[207]. Remarkably, low-dose spironolactone (25 mg daily) did not affect blood pressure in individuals who are normotensive [207], implying that this treatment might also be useful in patients with OA who are normotensive. A large-scale clinical study is still needed to further investigate the efficacy of this treatment.

Eplerenone. Eplerenone, also known as mineralocorticoid receptor antagonist, is known to have beneficial effects in experimental models of obesity-related metabolic disorder[208]. Eplerenone also has protective effects on metabolic-associated OA joint lesions; in a rat model of obese spontaneous hypertensive heart failure, treatment with eplerenone also reduced cartilage degradation, osteophyte formation and synovial inflammation[209].

Amiloride. As well as being a diuretic, amiloride also serves as an acid-sensing ion channel blocker[210]. Abnormal activation of acid-sensing ion channels is usually accompanied by a drop in pH and inflammation and can also contribute to cartilage erosion in joints in experimental models of rheumatoid arthritis and to pain and disease progression in models of OA[210,211]. Amiloride inhibits acid-induced cartilage damage and restores type II collagen expression in rats with adjuvant-induced arthritis[210].

Adrenergic antagonists

Adrenergic antagonists are adrenergic receptor blockers that inhibit the action of adrenaline and thereby elicit potent antihypertensive effects. Adrenergic antagonists can be split into two main types: alpha adrenergic antagonists (such as clonidine) and beta adrenergic antagonists (such as beta blockers).

Clonidine. In addition to its antihypertensive effects, clonidine is an effective analgesic that affects the central nervous system. Systemic administration of clonidine was therefore found to be more effective against joint pain than intra-articular injection in a rat model of OA[212]. However, local intravenous anaesthesia seems to be enough to ameliorate joint pain in humans[213].

Beta blockers. Similar to clonidine, beta blockers also have antinociceptive effects. However, although one study reported a reduction in pain in patients with hip or knee OA following beta blocker use, another study has disproved the pain relief effect of this drug[214,215]. Therefore, the efficacy of beta blockers for joint pain is still an open subject for debate. Nevertheless, beta blockers can reduce ET1 synthesis in human endothelial cells, providing further explanation for the antihypertensive effect of the drug[216]. Given that increased concentrations of ET1 correlate with OA severity, evaluating the chondroprotective effects of beta blockers from the perspective of the endothelin family could provide novel insights into OA treatment.

Other therapies

As mentioned in the section on targeting shared molecular pathways, the calcium channel blocker verapamil elicits protective effects on cartilage via inhibition of the Wnt signalling pathway[205]. The same study also reported the efficacy of other antihypertensive calcium

Hypokalaemia
A situation of electrolyte imbalance with low potassium in blood serum.

channel blockers on Wnt signalling inhibition, including nifedipine; however, none of them successfully inhibited Wnt signalling[205]. By contrast, a beneficial effect of nifedipine on chondrocytes has been reported in another study[205,217]. From a metabolic perspective, nifedipine seems to promote the shift from oxidative respiration to glycolysis in chondrocytes. Although this alteration of nutritional pathway was accompanied by nitric oxide production, the drug showed a surprising stimulation of type II collagen and proteoglycan synthesis[217]. This finding feeds into the discussion about the role of nitric oxide, which most studies tend to agree has a catabolic effect on cartilage homeostasis[218].

Future directions

Interactions between body systems is a growing area for understanding pathogenesis and disease aetiology. Given the emerging evidence demonstrating a correlation between the vascular and skeletal systems[219], interventions that have multiple targets could be promising for chronic disease management. Beyond the epidemiological associations between hypertension and OA and the shared role of physical inactivity and weight gain in both diseases, there seem to be direct links between these two diseases at the tissue or cellular level as hypertension can initiate or promote the progression of OA. Therefore, it is conceivable that new therapies with both symptom alleviation and structural aims could be developed based on these new pathophysiological discoveries.

Reducing systemic blood pressure in patients with OA and hypertension should logically have an effect on local tissue and cell regulation by restoring the perfusion abnormalities of the synovial tissue that are responsible for hypoxia-triggered inflammation, improving the nutritional intake of cartilage owing to the reduction of subchondral bone ischaemia induced by hypertension, and reducing intramedullary pressure, which can partly explain the pain that occurs in OA. As discussed in this Review, RAS, endothelin and Wnt signalling inhibitors as well as some existing antihypertensive drugs have already shown positive effects on joint health. The chondroprotective effect of these drugs provides hope for future use in OA treatment. Although it seems intriguing to control hypertension and OA simultaneously, safety issues related to systemically administered drugs need to be considered. Importantly, the shared pathological pathways might also be critical for other biological functions, which could be cell-type specific. More stringent safety assessments of intended therapeutics need to be used to prevent undesired adverse effects. Hence, specific treatments that target local vascular regulation could be considered. Intra-articular injection is an easy route of administration that could be considered as it is well accepted by patients and can be used to achieve high concentrations of a drug in the joint without any major risks or safety concerns.

Although the contribution of hypertension to structural damage in joints is established and supported by evidence, the correlation between blood pressure and nociception remains controversial. Hypertension-associated hypoalgesia has been reported in deoxycorticosterone acetate salt models of hypertension[220] and in rats with spontaneous hypertension[221], which makes the rats less sensitive to acute pain. Similar findings have been obtained in human studies, in which individuals with hypertension had a higher pain tolerance than individuals who are normotensive in acute pain stimulation tests[222,223]. However, such associations between blood pressure and pain sensation are reversed in patients with chronic pain; studies have reported a positive correlation between resting blood pressure and chronic low back pain[224,225]. The proposed mechanism causing alterations to the blood pressure relationship was endogenous opioid dysfunction in chronic pain conditions[225]; although another study did not agree with this notion[224]. The conflicting blood pressure–pain correlation in acute and chronic pain might explain the heterogeneity of findings related to the association between hypertension and symptomatic OA, as some studies have reported positive correlations whereas others reported the opposite. Therefore, the blood pressure–chronic pain relationship warrants further investigation to help consolidate the association between hypertension and symptomatic OA.

Considering that there is currently no cure for OA and the preliminary success of rescuing experimental OA phenotypes using RAS, endothelin and Wnt signalling inhibitors and antihypertensive drugs, the preclinical development of these molecules for therapeutic purposes seems worth investigating.

Conclusions

Existing evidence supports hypertension as being one of the most common metabolic components associated with OA after adjustment for confounding factors. The biophysical and biochemical effects of hypertension on the synovium, subchondral bone and chondrocytes disturb joint homeostasis and could contribute to OA onset and progression. The presence of endothelial–skeletal crosstalk in the pathogenesis of OA emphasizes the potential role of systemic factors such as RAS, endothelins and Wnt signalling in disease management. Forthcoming therapeutic strategies should therefore employ macroscopic approaches that target systemic high blood pressure to resolve local diseases, in particular those with multifactorial aetiologies such as OA.

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Importance of lymphocyte–stromal cell interactions in autoimmune and inflammatory rheumatic diseases

Mélissa Noack and Pierre Miossec ✉

Abstract | Interactions between lymphocytes and stromal cells have an important role in immune cell development and responses. During inflammation, stromal cells contribute to inflammation, from induction to chronicity or resolution, through direct cell interactions and through the secretion of pro-inflammatory and anti-inflammatory mediators. Stromal cells are imprinted with tissue-specific phenotypes and contribute to site-specific lymphocyte recruitment. During chronic inflammation, the modified pro-inflammatory microenvironment leads to changes in the stromal cells, which acquire a pathogenic phenotype. At the site of inflammation, infiltrating B cells and T cells interact with stromal cells. These interactions induce a plasma cell-like phenotype in B cells and T cells, associated with secretion of immunoglobulins and inflammatory cytokines, respectively. B cells and T cells also influence the stromal cells, inducing cell proliferation, molecular changes and cytokine production. This positive feedback loop contributes to disease chronicity. This Review describes the importance of these cell interactions in chronic inflammation, with a focus on human disease, using three selected autoimmune and inflammatory diseases: rheumatoid arthritis, psoriatic arthritis (and psoriasis) and systemic lupus erythematosus. Understanding the importance and disease specificity of these interactions could provide new therapeutic options.

Interactions between stromal cells (BOX 1) and lymphocytes have important functions during the development of a normal immune response. Throughout their early maturation, T cell and B cell precursors interact with stromal cells from the thymus and bone marrow, respectively, enabling the first steps of T cell and B cell differentiation[1,2]. From induction to either resolution or chronicity, stromal cells regulate inflammation through direct and indirect cell contacts with immune cells. Because stromal cells are imprinted with tissue-specific phenotypes, these cells can contribute to site-specific lymphocyte recruitment. This phenotype can undergo molecular and functional changes during chronic inflammation, leading to increased pathogenicity. At the site of inflammation, migrated B cells and T cells interact with local stromal cells, resulting in the secretion of either antigen-specific products, such as immunoglobulins, or non-antigen-specific products, such as cytokines. The interactions and events that occur during normal inflammatory responses are similar, but not identical, to those that occur during chronic inflammation, implying that both stromal cells and lymphocytes undergo several changes in this latter context.

Several chronic inflammatory diseases are characterized by the local infiltration of immune cells and their subsequent direct and indirect interaction with local stromal cells, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), psoriasis and systemic lupus erythematosus (SLE). The involvement of stromal cells at different anatomical positions in different diseases results in different patterns of clinical involvement, such as involvement of the joints in RA or of the skin in psoriasis. A multitude of studies have investigated synoviocytes in the context of RA, whereas fewer studies have investigated stromal cells from other locations in other diseases. Nevertheless, important insights are emerging on stromal cell–immune cell interactions in different diseases and their contribution to disease.

In this Review, we discuss the importance of immune cell–stromal cell interactions during the initiation of inflammation and its transition to chronicity. We outline the critical role of these cell interactions in three selected autoimmune and inflammatory diseases (RA, PsA (and psoriasis) and SLE), with a focus on human studies and stromal cell heterogeneity. We finally discuss how targeting cell interactions, directly and indirectly,

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Key points

- During chronic inflammation, the pro-inflammatory environment leads to changes in stromal cells, and these altered phenotypes contribute to disease induction and chronicity.
- At inflammatory sites, infiltrating B cells and T cells interact with pathogenic stromal cells, promoting inflammation that in turn induces and maintains the pathogenic phenotype of stromal cells.
- Interactions with stromal cells induce accumulation, activation and survival of T lymphocytes and B lymphocytes, through direct cell contact and soluble factors.
- Despite common characteristics such as the involvement of the T helper 17 axis, inflammatory diseases differ, such as in affected sites and types and phenotypes of stromal cells.
- These differences can affect immune cell–stromal cell interactions and their resulting effects on cell activation, proliferation and cytokine production.
- A better understanding of lymphocyte–stromal cell interactions is needed to determine how heterogeneity among these cells, including pathogenic cell subsets, could be used to stratify patients and be targeted more specifically.

could be a useful therapeutic avenue for the treatment of these and other diseases.

Immune cell–stromal cell interactions

Cell interactions are required in secondary lymphoid organs for the development of a fully functional immune system[3]; however, these interactions also promote inflammatory processes in the context of chronic inflammation and disease.

During the early stages of inflammation, lymphocytes are recruited to inflammatory sites via a series of steps involving capture, rolling, adhesion and transmigration of the cells[4]. Subsequently, these cells can form lymphoid organ-like structures, known as ectopic lymphoid organs[5]. Lymphocyte recruitment and migration are controlled by complementary receptor–ligand interactions between the migrating cells and endothelial cells[4]; as some of these molecules are tissue-specific, these interactions influence the tissue specificity of this process[6]. For example, the ligand cutaneous lymphocyte antigen, expressed by T cells, is a skin-homing receptor that binds to E-selectin on endothelial cells at sites in cutaneous inflammation[7,8]. After crossing the endothelium, the phenotype of the lymphocytes switches, which involves an upregulation of adhesion molecules and chemokine receptors that enables increased retention of the cells in local tissues[4].

After this first step of migration, the recruited immune cells interact with local stromal cells. Subsequent interactions in the tissues vary depending on the organ and location within the organ, as well as the disease and disease stage. Crosstalk between immune and stromal cells has effects in both directions and heterogeneity among the stromal cells leads to heterogeneous responses. Indeed, site-specific differences in stromal cells lead to site-specific differences in inflammatory responses[9]. Immune cell–stromal cell interactions also regulate the termination of inflammatory responses. Loss of survival signals from stromal cell interactions leads to the clearance of unwanted effector T cells via apoptosis and phagocytosis of the dead cells[10]. Loss of signals from co-stimulatory molecules such as CD80, CD86 or CD40, and activation of inhibitory signal through cytotoxic T lymphocyte protein 4 (CTLA4), also suppresses T cell activity[11]. Apoptosis, notably through interaction between Fas and FasL, limits the extent of the immune response and triggers the resolution phase[12]. Defects in this regulation contribute to chronic inflammation.

Under chronic exposure to pro-inflammatory mediators, pathogenic changes can occur in stromal cell phenotypes that contribute to chronicity of inflammation. The heterogeneity and tissue specificity of stromal cells could explain in part the disease-specific clinical distribution of chronic inflammation in different tissues. Such heterogeneity can occur across different tissues, across different locations within a tissue and across different cells at the same location, for instance, as a result of acquired mutations[13–18]. Changes in the epigenetic, transcription or translation regulation of gene expression in a cell can modify the cell phenotype[13]; for example, synoviocytes in RA can undergo changes in DNA methylation that are linked to disease[14,15]. For cells at the same anatomical site, accumulation of these differences between diseased and normal tissues has an important function in chronic inflammation[16–18]. These phenotypic changes influence the interactions of stromal cells with immune cells and alter subsequent immune responses, including resolution of inflammation, as exemplified by RA[16,19].

In the following section, we discuss the immune cell–stromal cell interactions that occur during chronic inflammation in three diseases with different levels of B cell and T cell involvement: RA (a disease that involves both B cells and T cells, as well as the production of a few autoantibodies); psoriasis and PsA (a disease that involves predominantly T cells, without autoantibody involvement); and SLE (a disease characterized by the involvement of both T cells and B cells and the production of multiple autoantibodies).

Rheumatoid arthritis

Active RA is characterized by the formation of a hyperplastic and invasive synovium, with leukocyte infiltration and synoviocyte proliferation[20]. This process leads to increased interactions with immune cells, and the production of cytokines and autoantibodies[21]. Most studies have focused on patients positive for rheumatoid factor and anti-CCP antibodies. In this section, we discuss the heterogeneity of RA synoviocytes and their interactions, direct or indirect, with T cells and B cells.

RA synoviocyte heterogeneity

Pathogenic phenotype. RA is characterized by infiltration, inflammation and hyperplasia of the synovium, and eventual joint destruction[21,22]. Synoviocytes (BOX 1) are the main stromal cells of the synovium and these cells undergo increased proliferation[23,24], partly owing to their resistance to apoptosis[25–27], in RA. The invasive capacities of synoviocytes and the amount of metalloproteinase (MMP) the cells produce are also increased in RA compared with osteoarthritis (OA), a context often used as a control comparison[18,27,28]. Various mechanisms contribute to the increased lifespan of synoviocytes in RA. For example, synoviocytes in RA, but not synoviocytes in OA

or dermal fibroblasts in RA, constitutively overexpress the tumour suppressor p53 (REF.[29]). Indeed, researchers have identified mutations in the gene encoding p53 in synoviocytes from patients with RA that are similar or identical to mutations found in some tumours but that are not present in skin fibroblasts from the same patients nor in synoviocytes from patients with OA[30]. In addition, the anti-apoptotic molecule sentrin is overexpressed in the synovial tissue of some patients with RA but not in healthy synovial tissue or synovial tissue of patients with OA[31]. Similarly, another anti-apoptotic molecule, synoviolin, is overexpressed in synoviocytes from patients with RA in response to IL-17 stimulation, promoting resistance to apoptosis and increased survival[32].

These phenotypic changes promote pathogenic functions of synoviocytes, including direct effects on other cell types such as immune cells. For example, local injection of cultured synoviocytes from patients with RA into mice with severe combined immunodeficiency induces RA-like disease, providing strong evidence of the pathogenic effects of these cells[33]. Importantly, the injected synoviocytes maintain their invasive and destructive phenotype and can transfer these properties to a distant and unaffected joint[34].

Anatomical heterogeneity of the RA synovium. Synoviocytes are heterogeneous across different joints and across different locations within the synovium[20,22,35–38] (FIG. 1). Advanced technologies, such as single-cell RNA sequencing combined with machine learning techniques and analysis of histological and transcriptional data sets, have provided insights into the distinct subsets that exist in the RA synovium and their positional identity[35–38]. For example, a high inflammatory subset is present in the RA synovium and is associated with extensive immune infiltration, high levels of inflammation and autoantibody production[36]. Similarly, in a separate analysis, researchers identified a $CD34^{-}THY1^{+}$ subset in the perivascular zone of the deep sub-lining layer of the synovium that is enriched in patients with RA compared with patients with OA[38]. These cells are characterized by the expression of podoplanin (PDPN) and cadherin 11, secrete high levels of pro-inflammatory cytokines and express genes associated with a highly proliferative state[38]. The proportion of $CD34^{-}THY1^{+}$ cells in the RA synovium correlates with the proportion of infiltrating immune cells, including T cells[38]. The presence of $PDPN^{+}$ cells and T cells supports the role of synoviocyte–T cell interactions in promoting the production of cytokines, specifically that of IL-17, in the synovium[39]. This pathogenic subset has also been linked to the expression of fibroblast activation protein-α (FAPα), as FAPα colocalizes with $PDPN^{+}THY1^{+}$ cells in the sub-lining layer of the RA synovium[40]. In mice with serum transfer-induced arthritis, adoptively transferred $PDPN^{+}FAP\alpha^{+}THY1^{+}$ cells assume an immune effector phenotype, expressing high levels of cytokines and promoting severe and persistent inflammatory arthritis[40]. Other studies have identified a critical role for the receptor NOTCH3 in the differentiation and expansion of $THY1^{+}$ synoviocytes[37]. Compared with $THY1^{-}$ cells, the $THY1^{+}$ cells had an enriched NOTCH activation signature, and inhibition of NOTCH blocked $THY1^{+}$ cell differentiation[37]. The ligands needed for NOTCH3 signalling are probably provided by the endothelium, as the NOTCH activation score correlated with the perivascular position of the $THY1^{+}$ cells[37].

In addition to synoviocytes with a high inflammatory phenotype, researchers have also identified a low inflammatory synoviocyte subset that is associated with high pain severity scores and reduced systemic inflammation in patients with RA[36]. This synoviocyte subset likely corresponds to the $CD34^{-}THY1^{-}$ subset found in the lining layer[38], the proportion of which is reduced in swollen joints compared with non-swollen joints[38]. These cells also express FAPα, but, unlike $FAP\alpha^{+}THY1^{+}$ cells, transfer of $FAP\alpha^{+}THY1^{-}$ to mice with serum transfer-induced arthritis is associated with in vivo cartilage damage[40] and in vitro MMP secretion[38].

The presence of different synoviocyte subsets could be linked to different leukocyte infiltration pathotypes in patients with RA. Three pathotypes have been described in patients with early RA: a lympho-myeloid phenotype, a diffuse myeloid phenotype and a pauci-immune pathotype[41]. The high inflammatory synoviocyte subset could be linked to the lympho-myeloid and diffuse myeloid pathotypes. The lympho-myeloid pathotype is characterized by the presence of B cell or plasma cell aggregates and is linked to high titres of anti-citrullinated protein antibodies and a high DAS28-ESR score, whereas the diffuse myeloid pathotype is characterized by a predominance of macrophages in the sub-lining tissue and a high DAS28-ESR score[41]. Both pathotypes are linked to the presence of an extensive immune infiltration in the sub-lining layer, high levels of inflammation and autoantibody positivity, which are associated with the highly inflammatory phenotype of synoviocytes[36]. By contrast, the pauci-immune pathotype is characterized by a scant

Box 1 | **Stromal cell nomenclature**

The nomenclature used for stromal cells can be inconsistent across different studies, and can cause some confusion. The abbreviation 'MSC' is commonly used to refer to mesenchymal stromal cells[161], but is also sometimes mistakenly used to refer to mesenchymal stem cells. Mesenchymal stromal cells are a bulk population of cells and only a small fraction of the cells have stem cell capacities (known as 'stemness'). As such, the International Society for Cellular Therapy has recommended against use of the abbreviation MSC for mesenchymal stem cells and has put forwards three minimal criteria to define mesenchymal stromal cells. First, the cells must be plastic-adherent when maintained in standard culture conditions. Second, the cells must express CD105, CD73 and CD90, and lack the expression of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR surface molecules. Third, the cells must differentiate to osteoblasts, adipocytes and chondroblasts in vitro[162]. This heterogeneous population of stromal cells includes fibroblasts, blood and lymphatic endothelial cells and epithelial cells. All these stromal cells contribute to the tissue architecture and regulate the tissue function in a tissue-specific manner.

Some confusion can also arise with the term synoviocytes. Synoviocytes constitute the main cells of the synovium of joints and can be divided into two cell types: macrophage-like synoviocytes and fibroblast-like synoviocytes (FLS). Macrophage-like synoviocytes express markers of haematopoietic origin and their phenotype is similar to other tissue-resident macrophage populations[60]. FLS are commonly referred to simply as synoviocytes and are mesenchymal cells that display many characteristics of fibroblasts. Surface markers that can be used to characterize FLS include positive staining for vascular cell adhesion molecule 1 (VCAM-1), CD44, CD55, THY1 and cadherin 11, coupled with the absence of macrophage markers such as CD14 or CD68 (REF.[163]). In this Review, we use the term synoviocytes to refer to FLS.

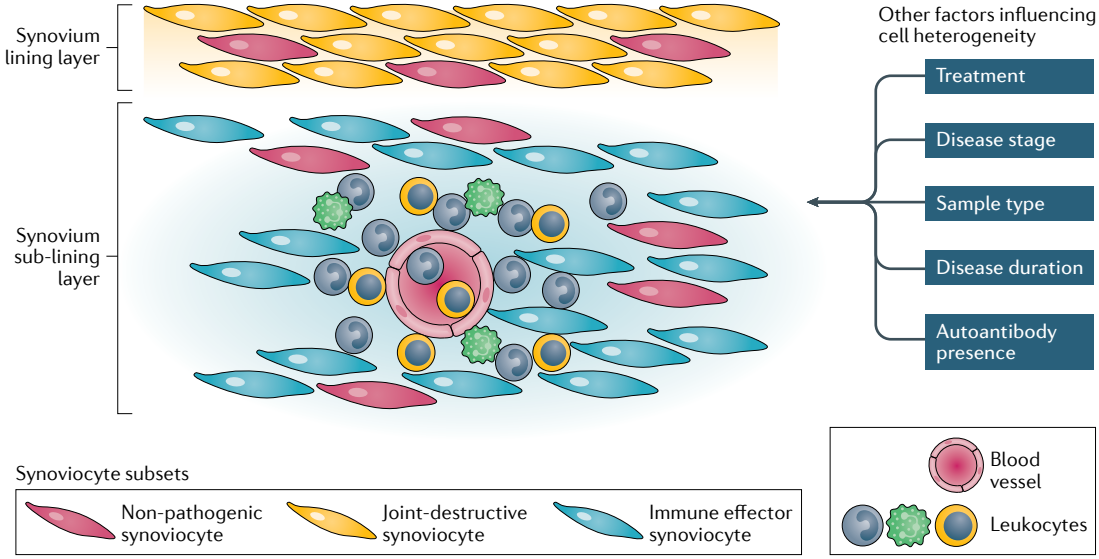

Fig. 1 | **Synoviocyte heterogeneity in RA.** Synoviocytes in rheumatoid arthritis (RA) are a heterogeneous population of cells that can vary in phenotype between different joints and between different locations within the same joint. For example, the phenotypes of synoviocytes of the lining layer and of the sub-lining layer of the synovium can differ, and emerging evidence suggests the presence of two pathogenic $CD34^-$ synoviocyte subsets: synoviocytes with a joint destructive phenotype (characterized by the expression of podoplanin (PDPN) and fibroblast activation protein-α (FAPα) and a lack of expression of THY1) and synoviocytes with an immune effector phenotype (characterized by the expression of PDPN, FAPα, THY1 and NOTCH3)[34–36,38]. Various other factors can also influence this heterogeneity, including the disease stage, type of sample analysed and type of treatment. The figure is based on information from Lefevre et al., Zhang et al., Orange et al. and Mizoguchi et al.[34–36,38].

infiltration of immune cells and a prevalence of resident fibroblasts[41], and aligns with the low inflammatory synoviocyte subset that is associated with reduced systemic inflammation in RA[36].

Overall, RA seems to be characterized by two main subsets of pathogenic synoviocytes. Both subsets express FAPα, PDPN and cadherin 11 but not CD34. The $THY1^+$ subset is found in the sub-lining layer and has immune inflammatory functions, whereas the $THY1^-$ subset is found in the lining layer and has a joint-destructive phenotype. These pathogenic phenotypes lead to altered interactions with immune cells, notably with B cells and T cells, which can increase the inflammatory phenotype of lymphocytes and help to maintain inflammation. As is discussed in the next section, synovial pathotypes of immune infiltrate, synovial and molecular signatures can now be used to predict responses to biologic therapies[41–44].

In addition to considering the anatomical heterogeneity of stromal cells, other types of heterogeneity that influence stromal cell–immune cell interactions must be considered, such as the type of sample assessed (that is, whether the samples were obtained via early biopsy or late, following surgery), the disease stage, autoantibody positivity and the effect of treatment. A better understanding of such heterogeneity is needed in the movement towards personalized treatment. Notably, researchers have begun to focus on synovial signatures of patients to predict and stratify clinical response to therapy[41–44]. Although many current therapies target immune cells and cytokines, no drug has yet been approved that targets synoviocytes specifically, despite the large body of research supporting their important role in RA.

Synoviocyte–lymphocyte crosstalk

Synoviocytes affect RA pathogenesis through direct or indirect interactions with immune cells, most notably, T cells and B cells. The pathogenic phenotype of synoviocytes promotes the recruitment, activation, differentiation and survival of T cells and B cells. In turn, T and B cells induce long-term changes in synoviocytes that contribute to their pathogenic phenotype. This crosstalk creates an activation loop that contributes to chronicity (FIG. 2), as discussed in this next section.

Synoviocyte–T cell interactions. Interactions between synoviocytes and T cells are important in the regulation of immune responses and contribute to disease chronicity[45,46], including by retaining the T cells in the synovium. In RA, synoviocytes produce high amounts of CXCL12 that restrict the egress of lymphocytes from the joint[47]. Synoviocytes also produce large amounts of TGFβ, which induces a persistent expression of CXCR4 by T cells that promotes their retention through CXCL12 (REF.[48]). In addition to having a direct role in the recruitment and retention of lymphocytes, synoviocytes in RA also indirectly promote lymphocyte adhesion to and transmigration through endothelial cell layers[49,50]. For example, in co-cultures, synoviocytes from patients with RA, but not synoviocytes from healthy individuals, upregulate the ability of endothelial cells to adhere to flowing lymphocytes[49]. This effect involves CXCR4–CXCL12 interactions and is dependent on

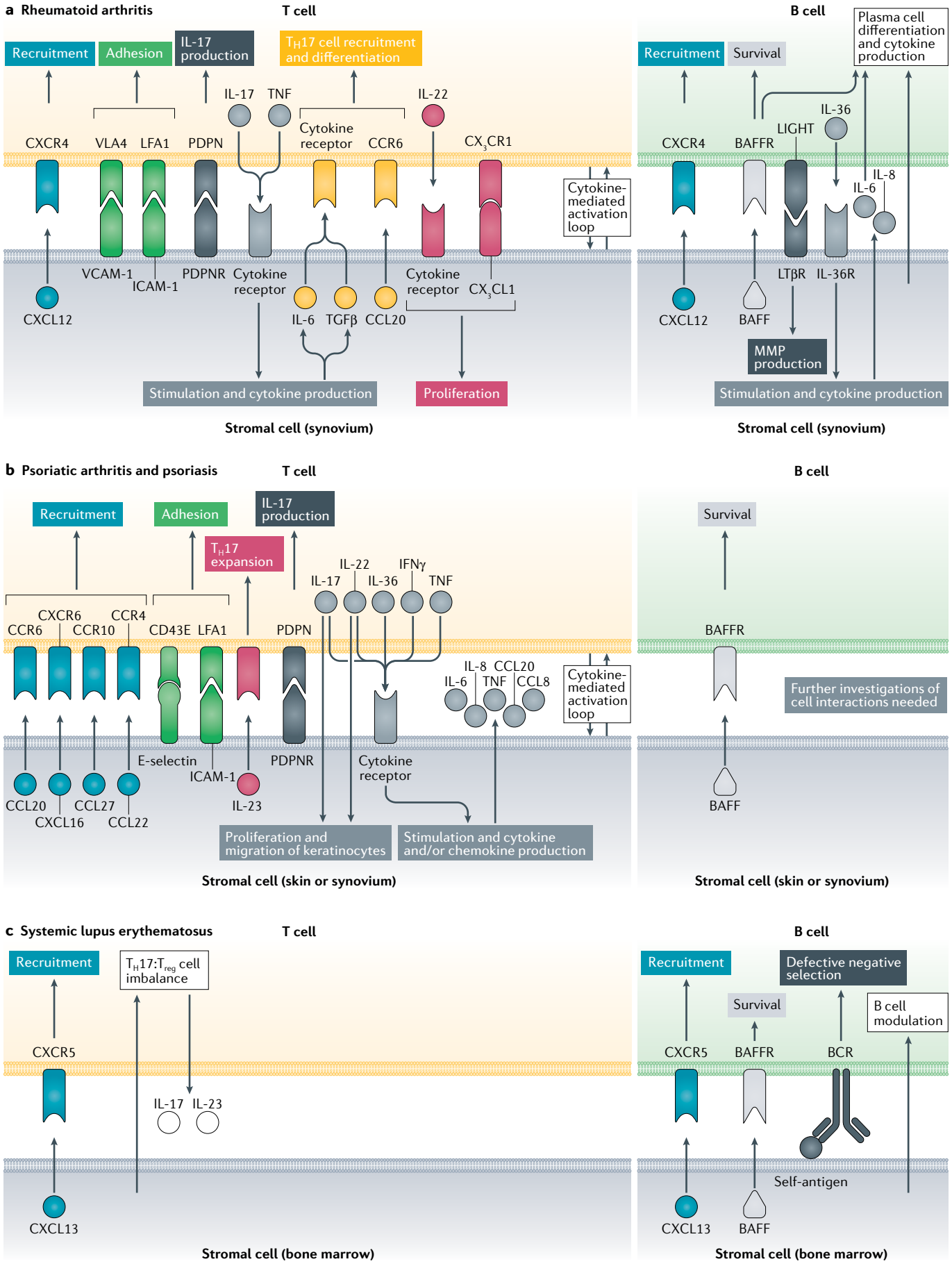
a Rheumatoid arthritis
T cell
B cell
Recruitment
Adhesion
IL-17 production
TH17 cell recruitment and differentiation
Recruitment
Survival
Plasma cell differentiation and cytokine production
IL-17
TNF
IL-22
IL-36
LIGHT
CXCR4
VLA4
LFA1
PDPN
Cytokine receptor
CCR6
CX3CR1
CXCR4
BAFFR
IL-8
IL-6
Cytokine-mediated activation loop
VCAM-1
ICAM-1
PDPNR
Cytokine receptor
IL-6
TGFβ
CCL20
Cytokine receptor
CX3CL1
LTβR
IL-36R
CXCL12
CXCL12
BAFF
MMP production
Stimulation and cytokine production
Proliferation
Stimulation and cytokine production
Stromal cell (synovium)
Stromal cell (synovium)
b Psoriatic arthritis and psoriasis
T cell
B cell
Recruitment
Adhesion
IL-17 production
Survival
TH17 expansion
IL-22
IFNγ
IL-17
IL-36
TNF
CXCR6
CCR4
CCR6
CCR10
CD43E
LFA1
PDPN
BAFFR
IL-8
CCL20
IL-6
TNF
CCL8
Cytokine-mediated activation loop
Further investigations of cell interactions needed
E-selectin
ICAM-1
PDPNR
Cytokine receptor
CCL20
CXCL16
CCL27
CCL22
IL-23
BAFF
Proliferation and migration of keratinocytes
Stimulation and cytokine and/or chemokine production
Stromal cell (skin or synovium)
Stromal cell (skin or synovium)
c Systemic lupus erythematosus
T cell
B cell
Recruitment
TH17:Treg cell imbalance
Recruitment
Defective negative selection
Survival
B cell modulation
CXCR5
IL-17
IL-23
CXCR5
BAFFR
BCR
Self-antigen
CXCL13
CXCL13
BAFF
Stromal cell (bone marrow)
Stromal cell (bone marrow)

Fig. 2 | **Important stromal cell–immune cell interactions during autoimmune and inflammatory diseases.** Various stromal–immune cell interactions that are involved in rheumatoid arthritis (RA), psoriasis, psoriatic arthritis (PsA) and systemic lupus erythematosus (SLE). **a** | In RA synovium, stromal cells (synoviocytes) promote the recruitment (via CXCL12–CXCR4 interaction), activation (via podoplanin (PDPN)–PDPNR interaction), differentiation (via IL-6 and TGFβ secretion) and survival (via B cell activating factor (BAFF)–BAFFR interaction) of T cells and B cells. T cells and B cells, through cytokine secretion (IL-6, IL-17 or IL-36) or cell contact (via CX_3CL1–CX_3CR1 or LTβR–LIGHT interactions), promote the activation of synoviocytes, promoting their pathogenic phenotype. This crosstalk creates an activation loop that contributes to chronicity. **b** | In psoriasis and PsA, cell interactions between stromal cells and mainly T cells, either direct (for example, via PDPN–PDPNR or LFA1–intercellular adhesion molecule 1 (ICAM-1) interactions) or indirect (for example, involving secretion of CCL20, IL-23, IL-6, TNF, IL-17 or IL-36), promote their pathogenic phenotype, contributing to pathogenesis. The stromal environment notably supports T helper 17 (T_H17) cell differentiation (i.e. IL-23 secretion). T_H17 cells are mainly involved in psoriasis and PsA and contribute to the activation of stromal cells (i.e. IL-17 and IL-22 secretion). Alterations in B cells have been described but there is a lack of in-depth studies on their contribution through interactions with stromal cells. **c** | In SLE, abnormal B cell and T cell differentiation and function have been well described, with a defective negative selection of B cells or an imbalance between T_H17 and regulatory T (T_{reg}) cells. Interactions with stromal cells contribute to these defects, but a better description of stromal cell–lymphocyte interactions in SLE will require more work, studying stromal cells from the different organs affected during SLE. MMP, metalloproteinase; VCAM-1, vascular cell adhesion molecule 1.

the anatomical source of the stromal cells, as dermal fibroblasts from the same donor have a limited effect[49].

Synoviocytes also influence T cell differentiation through the production of cytokines. For instance, the secretion of TGFβ and IL-6 by synoviocytes promotes T_H17 cell differentiation[51,52]. In T cell–synoviocyte co-cultures, synoviocytes from patients with RA can promote the expansion of $CD4^+$ T cells and the proportion of T cells that express and produce TNF, IFNγ and IL-17 (REFS[53,54]). After in vitro activation, these IL-17-producing and IFNγ-producing T cells acquire a plasma cell-like morphology, which is associated with a loss of CD3 and high cytokine secretory activity, reflecting the phenotype found in sections of the synovium in patients with RA[55]. These synoviocyte–T cell interactions also induce an aggressive phenotype in synoviocytes, increasing their proliferation, invasive capacity and MMP secretion[53]. This effect of T cells on synoviocyte proliferation occurs via CX_3CL1 (REF.[56]), a chemokine that is expressed by both the T cells and the synoviocytes, is upregulated on the membrane surface of RA synoviocytes and contributes to T cell retention in RA[57]. In co-cultures of sorted $CD4^+$ T cells and synoviocytes from patients with RA, $CD4^+IL\text{-}21^-$ T cells can induce the production of IL-6 by synoviocytes, whereas $CD4^+IL\text{-}21^+$ T cells can also induce the production of MMP[58]. Synoviocytes inhibit T cell apoptosis by maintaining survival signals and inhibiting cell death signals, in part though the production of CXCL12 (REFS[59,60]). Thus, synoviocytes and T cells are able to influence each other's phenotype.

The cytokines secreted by synoviocyte-activated immune cells' feedback create a positive feedback loop. For example, stimulation of RA synoviocytes or RA synovium explants with the pro-inflammatory cytokines IL-1β, TNF and IL-17 induces the secretion of CCL20 by synoviocytes; this chemokine ligand can subsequently promote the recruitment of $CCR6^+$ T_H17 and immature dendritic cells[61,62]. IL-22, a cytokine produced mainly by T_H17 cells, and IL-22-producing T cells are elevated in the synovial fluid of patients with RA compared with that of patients with OA[63]. Notably, T cells from the synovial fluid of patients with RA produce higher amounts of IL-22 than T cells from the peripheral blood, providing evidence that local environment promotes T cell-mediated cytokine production in the RA synovium. IL-22, in turn, induces the proliferation of synoviocytes, an effect that is further increased with soluble TNF[63]. Furthermore, activated T cells can also activate synoviocytes through membrane-bound TNF[64].

Activated T cell–synoviocyte interactions affect both cell types in a cell contact-dependent fashion; for example, direct interactions of T cells with synoviocytes increase the production of TNF, IL-17, IFNγ and IL-6, as well as the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) by synoviocytes[65]. The production of IL-6 and other cytokines by synoviocytes is regulated by a positive feedback loop that involved leukaemia inhibitory factor (LIF), its receptor LIFR, and STAT4. Indeed, silencing the expression of STAT4 in vitro reduces IL-6 transcription in synoviocytes and LIFR inhibition reduces IL-6 production[66]. In co-cultures of RA synoviocytes and peripheral blood mononuclear cells (PBMCs), contact alone between T cells and synoviocytes is sufficient to induce IL-6 and IL-1β production without the need for T cell receptor (TCR) activation[39]. By contrast, both cell contact and TCR activation are required for inducing large amounts of IL-17 secretion[39]. This effect is partly mediated via PDPN, as blocking PDPN with an antibody or small interfering RNA reduces the amount of IL-17 production[39]. Further studies are needed to identify the other molecules involved in amplification of IL-17 production by synoviocytes. When co-cultured with RA synoviocytes, purified T_H17 cells are potent inducers of IL-6, IL-8, MMP1 and MMP3 production, whereas T_H1 cells are not[67], suggesting that T_H17 cells, rather than T_H1 cells, are involved in a pro-inflammatory feedback loop with synoviocytes[67]. After interaction with naive T cells, synoviocytes acquire a more pathogenic phenotype[67] that is maintained over long periods[33]. These in vitro studies provide valuable insight into the role of crosstalk between activated T cells and synoviocytes in RA; however, further studies are needed to determine the long-term role of tissue-resident memory T cells and their interaction with stromal cells in RA.

Overall, T cell activation and infiltration into the synovium are early events in RA, as shown by analysis of early RA synovial tissue[68]. Synoviocytes contribute to T cell accumulation and activation in the RA synovium through directly interacting with the T cells and through the secretion of soluble mediators, such as CXCL12 and IL-6. The synoviocytes promote a pro-inflammatory phenotype in T cells that in turn results in the secretion of an array of pro-inflammatory cytokines, such as IL-17, that stimulate synoviocytes. This positive feedback loop maintains inflammation in the synovium and is regulated by various molecules, including PDPN, although more studies are required to identify other contributors that might represent new therapeutic targets.

Synoviocyte–B cell interactions. As with T cells, RA synoviocytes can also interact with and influence B cells. B cells are first recruited to the synovium via chemokines and adhesion molecules[69,70]. RA synoviocytes support a process known as B cell pseudo-emperipolesis, defined as the migration of B cells beneath the synoviocytes, via a mechanism involving the expression of CXCL12 and VCAM-1 (REF.[71]). Additionally, synoviocytes in RA can inhibit B cell apoptosis[60] via the production of B cell activating factor (BAFF; also known as TNFSF13B)[72]. Both the synovium and synoviocytes express high levels of BAFF in patients with RA compared with patients with OA[72,73]. Notably, pro-inflammatory cytokines that are induced by synoviocyte–T cell interactions, such as TNF and IFNγ, can increase the expression of *BAFF* mRNA[72]. Transmembrane BAFF functions as a first signal for the transcription of recombinase-activating genes (RAGs) in B cells, which are involved in the early steps of antibody affinity maturation followed by IL-6 as the second signal. Inhibition of BAFF expression with mitomycin C or antibody-mediated neutralization of IL-6 blocks the expression of RAG in B cells co-cultured with RA synoviocytes, whereas addition of soluble BAFF to OA synoviocytes has no effect on RAG transcription in B cells[73]. These results suggest that RA synoviocytes have a direct effect on B cell activation through transmembrane BAFF and IL-6 expression. Upon stimulation in vitro, synoviocytes, but not dermal fibroblasts, from patients with RA secrete high levels of BAFF and in co-culture with B cells, these cells promote IgG and IgA class-switching[74]. These results reinforce the idea that the effects and function of stromal cells are dependent on their anatomical location. In co-cultures, B cell–synoviocyte interactions promote terminal differentiation of B cells into mature plasma cells and the secretion of large amounts of IgG antibodies[69]. By contrast, other adherent fibroblast-like human cell lines are much less potent than RA synoviocytes at inducing full B cell differentiation[69]. This full differentiation contributes to antibody secretion, notably autoantibodies that contribute to structural bone damage[75].

B cells can also influence synoviocytes. In RA, the expression of LIGHT is upregulated on B cells, and synoviocytes stimulated with LIGHT in vitro produce MMP and express adhesion molecules such as ICAM-1 (REF.[76]). Plasma cells express IL-36 in the RA synovium and in vitro, IL-36 induces the production of IL-6 and IL-8 by synoviocytes that express IL-36R[77,78]. Furthermore, IL-36 can induce the proliferation and secretion of MMP by synoviocytes in vitro[77]. Unlike IL-36R$^+$ synoviocytes, IL-36R-deficient synoviocytes have a limited capacity to support plasma cell survival in co-cultures[77]. Overall, these findings suggest that crosstalk between B cells and synoviocytes is at least partly dependent on IL-36.

Overall, synoviocytes can promote B cell survival and differentiation directly via transmembrane BAFF and indirectly via soluble BAFF and IL-6 secretion. In turn, activated B cells express some mediators, such as LIGHT or IL-36, that promote the activation of synoviocytes and reinforce their pathogenic phenotype. Hence, similar to with T cell–synoviocyte interactions, a positive feedback loop between B cells and synoviocytes helps maintain the pro-inflammatory microenvironment and contributes to the induction and chronicity of RA.

Psoriatic arthritis and psoriasis

Psoriasis is a chronic T-cell mediated inflammatory skin disease involving hyperproliferation of keratinocytes and skin fibroblasts and infiltration of the skin by activated immune cells[79]. Of patients with psoriasis, 30% progress to developing PsA, a form of arthritis characterized by inflammation of the distal joints and entheses, including in the axial skeleton[80,81]. However, why some patients with psoriasis progress to developing PsA whereas others do not is unclear. Some patients with psoriasis might have sub-clinical changes in the synovium that precede the development of PsA. For example, those patients who develop PsA could have synoviocytes with an altered phenotype that leads to arthritis. This alteration could result from the inflammation linked to psoriasis and/or from other factors. In this section, we describe and compare the interactions between keratinocytes, skin fibroblasts or synoviocytes and T cells in psoriasis and PsA (FIG. 2). Although less research has been performed in PsA than in RA, understanding the differences between the cell interactions in these diseases might explain the differences in clinical manifestations, for example, the involvement of distal arthritis in PsA that does not occur in RA.

The skin in PsA and psoriasis

Pathogenic phenotype of skin stromal cells. Different stromal cells are present in the skin, including keratinocytes in the epidermis and skin fibroblasts in the dermis. Evidence suggest that the characteristics of fibroblasts in the skin are similar in psoriasis and PsA. In psoriatic skin lesions, keratinocytes show signs of defective differentiation and hyperproliferation[79], whereas skin fibroblasts from patients with psoriasis are highly proliferative in vitro[82] and promote keratinocyte proliferation[83]. In skin biopsy samples, the expression of CXCL12 is upregulated in psoriatic skin compared with healthy skin[84]. Skin fibroblasts are the main source of CXCL12, and this chemokine enhances keratinocyte proliferation in vitro[84]. These characteristics of stromal cells during psoriasis and PsA likely influence their interactions with lymphocytes, contributing to maintenance of skin inflammation.

Skin cell–T cell interactions. T cells migrate to the inflamed skin under the control of skin-specific chemokines, such as CCL27 and CXCL16, and adhesion molecules that favour interactions between T cells and skin stromal cells, such as ICAM-1 and E-selectin[85–87]. For example, CXCL16 is upregulated in keratinocytes in psoriatic skin compared with in healthy skin and both in vitro and in vivo experiments have shown that this chemokine can attract T cells to the site of inflammation[85]. Furthermore, IFNγ and TNF can increase the expression of ICAM-1 by healthy keratinocytes in vitro, resulting in increased T cell adhesion[86]. CCL27–CCR10 interactions also have an important role in T cell–mediated skin inflammation in psoriasis[88]. Keratinocytes and fibroblasts from psoriatic

lesions express higher levels of CCL27 than those from healthy or non-lesional skin[88]. Notably, CCR10$^+$ cells are more abundant in the lesional skin of patients with psoriasis than in healthy skin[88]. In vitro stimulation of human keratinocytes with TNF and IL-1β increases the expression of CCL27, and injection of CCL27 into mice induces the recruitment of lymphocytes[88]. Hence, as in the synovium, pathogenic stromal cells in the skin contribute largely to the recruitment and retention of T cells at sites of inflammation.

Various cytokines, most notably IL-17, are implicated in the pathogenesis of psoriasis and PsA and cell contact between T cells with stromal cells promotes their production. In co-cultures of psoriatic skin fibroblasts and PBMCs from patients or healthy donors, cell contact alone is sufficient to induce the production of IL-6, IL-8 and IL-1β by both cell types[89]. By contrast, both cell contact and TCR activation are needed to amplify the production of IL-17 by T cells. Similar to in RA, this amplification involves PDPN[39,89]. However, cell contact between psoriatic skin fibroblasts and PBMCs has no major effect on T_H17 cell differentiation (as assessed by the proportion of intracellular IL-17-expressing CD4$^+$ T cells)[89]. This discrepancy suggests that caution is needed when extrapolating the frequency of T_H17 cells from the amount of IL-17 secretion. In co-cultures, healthy dermal fibroblasts promote the production of IL-23 by dendritic cells, a cytokine known to promote T_H17 cell expansion and pathogenicity[90]. Indeed, the expression of IL-23 by keratinocytes is higher in psoriatic skin than in healthy skin, both in vitro and in situ[91]. Furthermore, in co-culture of healthy keratinocytes and unstimulated T cells, keratinocytes that have been pretreated with IFNγ can activate naive T cells and promote their differentiation into T_H1 and T_H17 cells[92]. Together, these results explain not only the presence of T_H17 cells in the psoriatic skin, but also the large levels of local IL-17 production[93].

Following these initial keratinocyte–T cell interactions, IL-17 activates skin fibroblasts and keratinocytes, promoting their secretion of additional pro-inflammatory cytokines, such as IL-6, and chemokines, such as CCL20 (REFS[94,95]). This secretion is further increased through synergistic effects mediated by IL-17 and TNF[95,96]. IL-17 can also increase keratinocyte proliferation[97]. Keratinocytes are the major source of CCL20 production in psoriasis lesional skin[98]. The CCL20–CCR6 axis has an important effect on T_H17 cell recruitment, which is followed by large amounts of IL-17 secretion in psoriasis[99]. Another T_H17 cytokine, IL-22, can reduce the expression of differentiation-associated genes by keratinocytes and increase the expression of genes involved in mobility and migration[100]. As with IL-17, IL-22 can induce the production of CCL20 by human keratinocytes, through a pathway involving BCL-3; notably, the expression of BCL-3 is increased in psoriatic skin lesions compared with in healthy skin[101]. IL-36, another cytokine involved in psoriasis, has complex effects on keratinocyte differentiation, with inhibition of differentiation and epidermal differentiation markers[102]. The production of IL-36 by primary human keratinocytes is induced by TNF, IL-17, IL-22 and IL-36 itself[103]. IL-22 and IL-36 function in synergy with IL-17 and TNF. As an example, IL-8 and CCL20 production is clearly higher with cytokine combinations than with individual cytokine[101,103]. These results suggest that a feedback loop exists between IL-36 and the T_H17 cytokines IL-17 and IL-22 that is mediated by interactions between keratinocytes and T cells[104].

Overall, pathogenic stromal cells, similar to stromal cells in the synovium, promote the recruitment, differentiation and activation of T cells. The stromal environment notably supports T_H17 cell differentiation, which in turn contributes to the activation of stromal cells, keratinocytes as well as skin fibroblasts. Direct and indirect interactions between skin stromal cells and T cells create a positive loop of activation that promotes the pathogenic phenotype of cells and disease chronicity. The understanding of such mechanisms has already led to the development of therapies that target the T_H17 pathway; indeed, both IL-17 inhibitors and IL-23 inhibitors are effective therapies in psoriasis[105]. An interesting line of investigation could be the effect of inhibiting IL-17 or IL-23 on stromal cell phenotypes and immune cell–stromal cell interactions to better understand their crucial role in pathogenesis.

The synovium in PsA

Synoviocyte phenotype. Fewer studies have investigated the synovium in PsA compared with the skin in psoriasis and PsA or the synovium in RA; furthermore, whereas some evidence suggests that the characteristics of skin fibroblasts are similar in psoriasis and PsA, no study has compared the characteristics of synoviocytes in both these diseases. Stromal cells in the skin are distinct from stromal cells of the synovium, which is linked to differences in their anatomical distribution, cell function and/or the surrounding vasculature. PsA differs from psoriasis by joint manifestations but differs from RA by skin manifestations. Despite common inflammatory mechanisms across these diseases, they affect different organs with different physiology and vascularization. Where PsA stands in relation to psoriasis and RA remains an open question. The global expression of genes in the synovium in PsA is much closer to that of the psoriatic skin than to the synovium in RA[106]. However, some patterns of gene expression differ between paired skin and synovium samples in PsA, including a higher expression of IL-17-related genes in the skin than in the synovium[106]. The synovium in PsA also shares similarities with the synovium in RA. For example, as in RA, synoviocytes in PsA have an abnormal phenotype characterized by increased proliferation, invasiveness and secretion of pro-inflammatory cytokines and MMPs[81,87,107]. More studies are needed to establish the specificity of the changes and heterogeneity observed in PsA, and their link to the pattern of joint involvement in this disease, which is much more asymmetrical in PsA than in RA.

Overall, the pathogenic phenotype of synoviocytes in PsA seems to show some similarities with both skin fibroblasts in psoriasis and synoviocytes in RA. Differences in the interactions between synoviocytes

and immune cells could induce different effects on all these cells, depending on the disease context and joint location, which could explain some of the differences observed between PsA versus RA, for instance, the occurrence of distal arthritis in PsA but not in RA.

Synoviocyte–T cell interactions. In synovium biopsy samples from patients with PsA, the expression of ICAM-1 and VCAM-1 and the numbers of B cells and T cells are similar to that observed in the RA synovium[87]. CCR4 and its ligand CCL22, required for T-cell migration to the skin[108], are expressed in psoriatic skin and increased in the synovial fluid of patients with PsA[109]. Flow cytometry analysis suggests that most $CD4^+CCR4^+$ lymphocytes in the synovium in PsA express CD45RO (a marker of memory T cells), indicating that the CCL22–CCR4 axis has a role in attracting skin-specific memory T cells to the joint[109]. In co-cultures of lymphocytes and synoviocytes from the synovial fluid of patients with PsA, both cell types can produce factors that support osteoclastogenesis, such as RANKL or TNF[110].

As with psoriasis, emerging evidence implicates T_H17 cell cytokine IL-22 in PsA pathogenesis. In the synovial fluid, the concentrations of IL-22 are higher in patients with PsA than in patients with OA[63]; furthermore, T cells from the synovial fluid of patients with PsA secrete more IL-22 than paired T cells from the blood of the patients[63]. In vitro, IL-22 induces the proliferation of PsA synoviocytes, an effect that is further increased in the presence of TNF[63]. Although IL-17 is found in the PsA synovium[107], most studies of synoviocyte–T cell interactions have been performed with RA synoviocytes. Hence, more work is required to investigate the differences between synoviocytes in PsA, skin fibroblasts in psoriasis and synoviocytes in RA and their interactions with immune cells.

Overall, synoviocytes in PsA contribute to the recruitment of T cells to the joint synovium. Cytokines produced by T cells during local interactions modulate the phenotype of the synoviocytes, including their proliferation and cytokine production. However, more work is needed to clarify the differences between synoviocytes in PsA and synoviocytes in RA and their interaction with T cells, which might explain differences in the clinical expression of these diseases. Comparisons between different joints could provide crucial information but such studies are difficult to perform, notably owing to the difficulties in studying the small distal joints.

B cells in PsA and psoriasis

Compared with T cells, B cells have been poorly studied in psoriasis and PsA. Most studies have focused on the number and function of B cells in the circulation, rather than on the effect of the stromal microenvironment on B cells or that of B cells on stromal cells. However, as identified in one study, a large infiltrate of $CD19^+$ B cells is present in the dermis of patients with psoriasis that is not present in healthy skin[111]. In PBMC fractions, the proportion of $CD19^+$ B cells in patients with psoriasis or PsA is higher than in healthy individuals, which correlates positively with disease severity[112]. Conversely, frequency of IL-10-producing B cells, a type of regulatory B cells, is lower in PBMCs from patients with psoriasis than from healthy individuals[113]. Plasmablasts are elevated in the blood of patients with psoriasis compared with in healthy individuals[114]. Furthermore, serum concentrations of BAFF serum are higher in patients with psoriasis, and are even higher in patients with PsA, than in healthy individuals, and these concentrations correlate with disease activity[115]. Notably, researchers have identified populations of clonally expanded B cells in the synovium of patients with PsA, suggesting that local antigen-driven B cell expansion occurs in PsA[116]. However, unlike RA, PsA is characterized by a lack of autoantibodies, making the role of B cells uncertain. This may also apply to seronegative RA, a disease that has not been studied enough[116]. Further studies are needed to clarify whether B cells contribute to psoriasis and PsA pathogenesis, despite this absence of autoantibodies, and to determine the role of interactions with the stromal environment on B cells and consequently on stromal cell responses.

Systemic lupus erythematosus

SLE is an autoimmune disease with a multisystem clinical presentation, including involvement of the skin, joints, kidneys and central nervous system, and is characterized by a wide spectrum of autoantibodies, specifically against cellular components. Dysregulated activation of both B cells and T cells and aberrant production of autoantibodies and pro-inflammatory cytokines are involved in both disease initiation and progression[117]. In this section, we discuss the interactions between stromal cells and B cells, as well as stromal cells and T cells, in SLE (FIG. 2). Compared with in RA and PsA, joint destruction is far less common in SLE. By contrast, this disease is characterized by a more diffuse and systemic clinical expression, indicating that the stromal cell–immune cell interactions that occur in this disease are quite different to those in RA and PsA. The diffuse distribution of clinical features in SLE suggests the involvement of a variety of stromal cells that are likely to have different effects and phenotypes depending on the anatomical location. Investigating the role of immune cell–stromal cell interactions at each site of clinical involvement should provide interesting insights and help to better understand and treat this disease as a whole.

Stromal cell–B cell interactions

Lymphocyte migration to various sites of inflammation in SLE is controlled by chemokines (such as the B cell chemoattractant CXCL13) and chemokine receptors (such as CXCR5, a receptor for CXCL13). Notably, in renal biopsy samples from patients with SLE, CXCL13 is expressed at sites of B cell infiltration[118]. Furthermore, serum concentrations of CXCL13 are increased in patients with SLE compared with healthy individuals, and this expression correlates with disease activity[119]. Prior to migration to inflammatory sites, interactions of stromal cells with B cells can also influence their development and phenotype. Following interactions with local bone marrow stromal cells, B cells and plasma cells

undergo abnormal B cell development in SLE[120] and produce a large number of autoantibodies to self-antigens, mainly nuclear components[121]. Analysis of PBMCs suggest that patients with SLE have higher frequencies of plasma cells and lower number and frequency of memory B cells than healthy individuals[122]. Negative selection of autoreactive B cells is altered in SLE, with B cells displaying amplified B cell receptor (BCR) responses and resistance to regulatory signals[120,123]. Failure to adequately delete these cells could result from defective BCR binding to self-antigens, meaning that this interaction does not induce a strong enough response to trigger clonal deletion[120]. BCR signalling abnormalities could contribute to the large number of pathological memory B cells observed in SLE[120].

Interactions between BAFF and BAFF receptor (BAFFR; also known as TNFRSF13C) are required for B cell survival and regulate the selection of naive autoreactive B cells[124]. Notably, B cells from patients with SLE are aberrantly activated and express upregulated levels of BAFF[122]. Furthermore, plasma concentrations of BAFF are increased in patients with SLE compared with both healthy individuals and patients with RA[125]. However, the association of BAFF concentrations and disease activity is highly variable between different studies[124].

In SLE, few studies have been performed investigating the interactions between immune cells and stromal cells in affected organs. Most studies in humans have assessed mesenchymal stromal cells (MSCs; see BOX 1), mainly derived from the bone marrow (BM-MSCs). Thus, it is difficult to compare these results with those presented above in RA, psoriasis and PsA. However, such missing studies might provide relevant information on the mechanisms and role of stromal cells in SLE pathogenesis for affected organs. In vitro, BM-MSCs from patients with SLE have an abnormal phenotype, including proliferating more slowly, being more prone to ageing and more easily dying after a few passages than cells from healthy individuals[126]. Normally, in the healthy state, BM-MSCs have potent immune-suppressive properties; however, the ability of BM-MSCs to suppress B cells is impaired in SLE. For example, BM-MSCs from patients with SLE have an impaired ability to inhibit B cell proliferation, plasma cell differentiation and IgM and IgG antibody secretion, compared with BM-MSCs from healthy individuals[127,128]. This defect might be explained by a reduction in the expression of CCL2 by BM-MSCs[128,129]. Indeed, BM-MSCs from patients with SLE produce lower amounts of CCL2 than those from healthy individuals; furthermore, treatment with anti-CCL2 antibodies can block the suppressive effects of BM-MSCs on B cell proliferation and differentiation in BM-MSC–B cell co-cultures[128]. However, other analyses have found no differences between the suppressive abilities of BM-MSCs in healthy individuals and BM-MSCs in SLE, and suggest that the effect of BM-MSCs on B cells is mediated through direct cell-to-cell contact with T cells, which is also defective in SLE[130]. These findings suggest that BM-MSCs regulate B cells either directly, through CCL2, or indirectly, through T cell contact.

Studies in SLE have so far focused mainly on alterations in B cells and BM-MSCs. For a better understanding of the role of B cell–stromal cell interactions in SLE, more studies are needed that use stromal cells from the affected organs. SLE involves damage on many organs and studying these interactions in some organs, such as the heart or nervous system, might pose some obvious difficulties. Because of ease of access, a good starting point might be to investigate B cell interactions with stromal cells of the skin or joint, which can then be compared with those interactions that occur in psoriasis or RA, respectively.

Stromal cell–T cell interactions

Interactions between T cells and stromal cells are crucial for modulating B cell function[130]. Several T cell defects have been described in SLE, including abnormal TCR activation that can affect T cell function and differentiation, and aberrant cytokine production[131]. Such defects could result in pathogenic T cell differentiation and impaired number and function of regulatory T (T_{reg}) cells[131]. $CD4^+$ T follicular helper cells can promote autoantibody production and inflammatory T_H17 subsets can promote inflammation in SLE, whereas defective T_{reg} cell function leads to ineffective control of immune responses[131,132]. Indeed, T_H17 cells and IL-17 are implicated in SLE pathogenesis[133]. For example, the proportion of T_H17 cells in blood and concentrations of IL-17 in serum are increased in patients with SLE, especially in patients with kidney disease, compared with healthy individuals[134]. Furthermore, serum concentrations of IL-23 are increased in patients with SLE compared with healthy individuals, which is linked to poor clinical outcomes[135]. This combination leads to an imbalance between T_H17 and T_{reg} cells[136]; this imbalance could result from defective immune regulation by altered interactions with MSCs in SLE[137,138].

As with B cells, few studies have been performed on stromal–T cell interactions. Several findings, such as the increased production of cytokines in SLE, suggest a role for these interactions in the pathogenic phenotypes of these cells. However, more work is needed to better describe stromal–T cell interactions in SLE, including interactions of T cells with stromal cells from the different organs. Although interactions between lymphocytes and stromal cells have an obvious effect on T cell and B cell function in SLE, more in-depth studies are needed to identify the underlying mechanisms involved.

Targeting cell interactions

Cell interactions make an important contribution to autoimmune and inflammatory disorders, in part by inducing the survival of pathogenic cells, as well as by promoting the production of pathogenic autoantibodies and cytokines. Thus, targeting these cell interactions could provide potential new therapeutic options. However, such an approach has so far received less attention than directly targeting cytokines and/or immune cell subsets. Multiple ways of targeting these interactions could be developed, such as directly targeting molecules involved in cell–cell contact and indirectly targeting cytokines and receptors involved in these interactions.

Some currently used treatments can target stromal cell–immune cell interactions, albeit in an indirect

fashion. For example, current therapies used in RA, psoriasis, PsA and SLE[139–141] mainly target cytokines (such as TNF, IL-1, IL-6 and IL-17) or immune cells (such as CD20 on B cells and CTLA4 on T cells) (FIG. 3), which can affect these interactions. Rituximab, an anti-CD20 antibody approved for use in RA[139], depletes B cells and thus eliminates their interactions with other cells. Infliximab, an anti-TNF antibody approved for RA, PsA and psoriasis[139,141], decreases the infiltration of immune cells into the synovium, thus reducing immune cell–stromal cell interactions[142]; similarly, tocilizumab, an anti-IL-6 receptor antibody approved for RA[139], reduces the frequency of T_H17 cells and the production of T_H17-associated cytokines[143].

Currently, few treatments directly target cell interactions. Abatacept, a CTLA–Fc fusion protein, inhibits T cell activation and interactions through the CD28–CD80/CD86 pathway. Abatacept is approved only for RA treatment[139] but has shown promising results in the treatment of PsA[144]. Blocking T cell interactions has shown less promise for SLE, including in studies of abatacept and toralizumab, an anti-CD40L monoclonal antibody[140]. Other molecules might be potential therapeutic targets, such as the PD1–PDL1 complex.

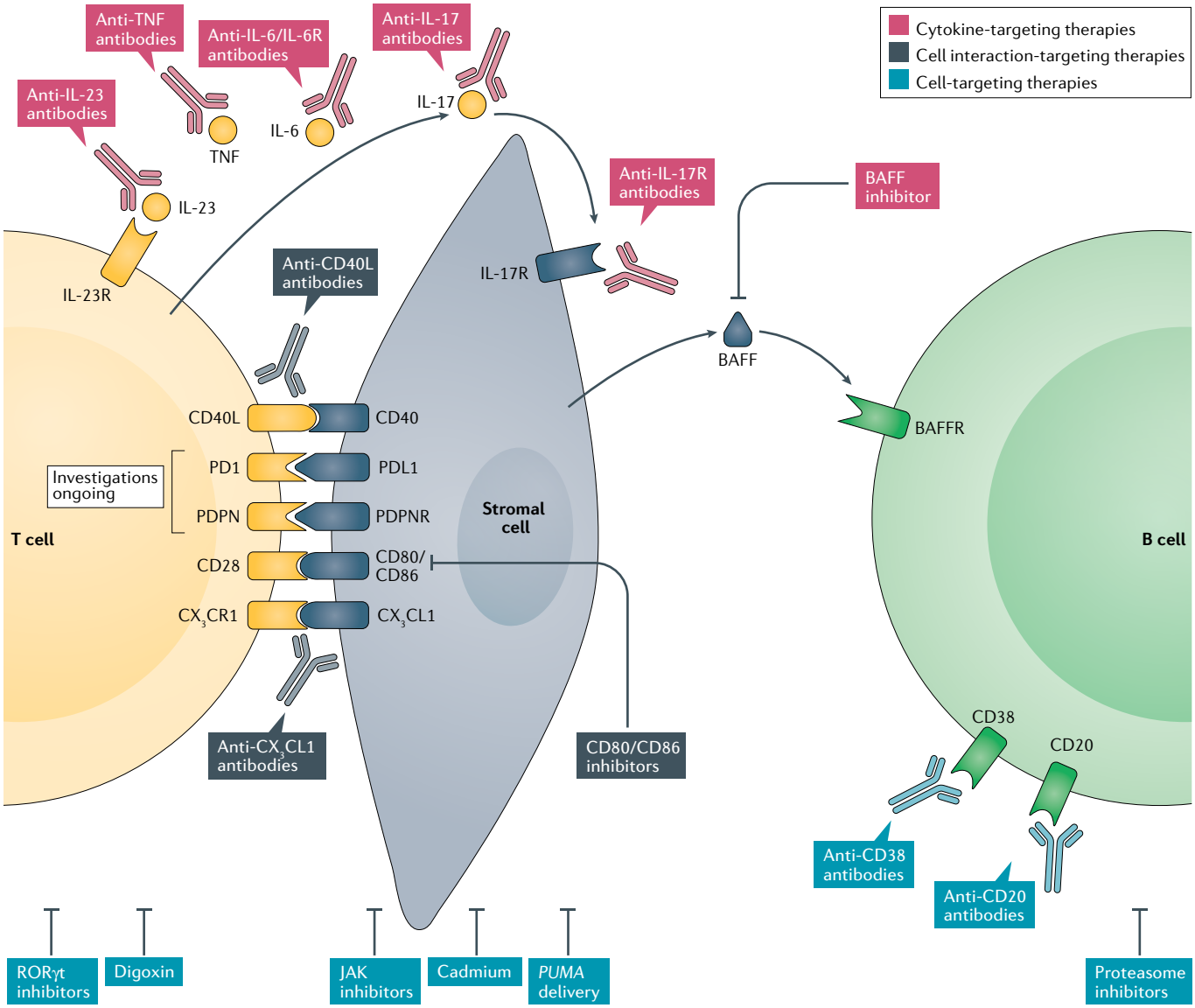

Fig. 3 | **Targeting of cell interactions.** This figure summarizes the current therapies being used or tested to target T cells, B cells and stromal cells, as well as interactions between these cells, in diseases such as rheumatoid arthritis (RA), psoriasis, psoriatic arthritis (PsA) or systemic lupus erythematosus (SLE). These therapies typically target the cytokines (shown in pink) or the cells (shown in blue) involved in stromal cell–immune cell interactions; however, some therapies also target the receptors involved in these interactions (shown in grey). Targeting cytokines (i.e. with anti-TNF, anti-IL-17 antibodies or B cell activating factor (BAFF) inhibitor) or their receptors (with anti-IL-17 receptor (anti-IL-17R) or anti-IL-6 receptor (anti-IL-6R) antibodies) inhibits their activating effect on target cells. Direct inhibition of cell interactions (i.e. with anti-CD40L or anti-CX_3CL1 antibodies, or CD80/CD86, podoplanin (PDPN) or PD1 inhibitors) reduces cell activation. Other strategies shown target immune or stromal cells directly. RORγt inhibitors and digoxin inhibit T helper 17 cell differentiation. Cadmium and *PUMA* delivery induce cell death of synoviocytes. Anti-CD38 and anti-CD20 lead to the depletion of plasma cells and B cells, respectively, and proteasome inhibitors enable a reduction of autoantibody levels. All these strategies contribute to a reduction of the inflammatory environment that is clearly involved in the chronicity of the inflammation related to RA, psoriasis, PsA and SLE, as well as other diseases.

Despite encouraging results in mouse models of RA and psoriasis[145,146], targeting the PD1–PDL1 axis is a complex option, as some patients with cancer being treated with an anti-PD1 or anti-PDL1 antibody can develop immune-related adverse events that resemble autoimmune responses[147,148]. A monoclonal antibody against another potential target, the membrane protein CX_3CL1 that is upregulated in RA T cells[149], has been tested in a first-in-patient phase I–II study. In patients with active RA with an inadequate response to methotrexate or a TNF inhibitor, treatment with this antibody seemed to be safe and patients had a positive clinical response[150].

PDPN expressed by both stromal cells and T cells is another potential therapeutic target that is involved in T cell–stromal cell interactions in RA, PsA and psoriasis. Blocking this transmembrane protein in in vitro and in vivo models has various effects on cells, although the effects are not always protective against disease[151,152]. One important effect of PDPN inhibition is a reduction in the production of IL-17 owing to the blockage of interactions between stromal cells of the skin or synovium and T cells[39,89]. However, in one model of multiple sclerosis, the opposite effect was observed[153].

Targeting directly immune or stromal cells is another option for the treatment of autoimmune and inflammatory diseases[22]. Tofacitinib, a Janus kinase (JAK) inhibitor approved for the treatment of RA[154], can indirectly inhibit TNF-induced production of chemokines by synoviocytes by inhibiting a type I interferon autocrine loop, limiting the recruitment of immune cells[155]. Although the amplification of type I interferon production in SLE is mainly mediated by dendritic cells and not by stromal cells, this approach has received extensive attention following the favourable results observed with blocking the type I interferon signalling pathway in trials of anifrolumab[156]. Treatment of RA synoviocytes with peficitinib, another JAK inhibitor, can also reduce the production of other pro-inflammatory mediators, as well as the proliferation and migration of synoviocytes[157].

Because of the important function of stromal cells in the pathogenesis of various autoimmune and inflammatory diseases, the direct killing of stromal cells is a radical option for not only controlling disease but also for inducing remission and potentially curing the disease. Various preclinical studies have tested this approach using intra-articular delivery. For example, viral vector-mediated delivery of *PUMA*, a pro-apoptotic gene, induces extensive cell death in synoviocytes in vitro and in the joints of rats with adjuvant-induced arthritis can decrease joint inflammation and destruction[158]. Another option for inducing stromal cell death could be the use of the cytotoxic metals. Treatment of RA synoviocytes in vitro with cadmium promotes apoptosis and decreases pro-inflammatory cytokine production[159]. This effect is reduced in the presence of zinc[160]. Intra-articular injection of cadmium in rats with adjuvant-induced arthritis decreases the clinical scores and protects against joint destruction[159]. For RA and PsA, intra-articular administration of these treatments could be useful in patients who have a partial response to systemic treatments, as done with steroid injections. However, treatments that induce stromal cell death non-specifically might be difficult to justify because of off-target effects. Another approach might be to specifically target pathogenic stromal cells; for example, specifically deleting synoviocyte subsets in RA to restore synovial homeostasis[27]. Such an approach could involve the definition of markers to directly target disease-associated stromal cell subsets.

Conclusions

Immune cell–stromal cell interactions are involved in several autoimmune and inflammatory diseases, such as RA, psoriasis, PsA and SLE. The altered phenotype of stromal cells contributes to disease induction and chronicity. Interactions between these cells and immune cells promote inflammation that in turn induces and maintains the pathogenic phenotype of stromal cells. However, an important question that has yet to be clarified is how these interactions and changes in stromal cells contribute to a failure in resolving inflammation in these diseases.

The different diseases discussed in this Review share common characteristics, such as the involvement of T_H17 activation and IL-17 production. However, various aspects of these diseases differ, such as the sites affected and the types and phenotypes of the cells involved within each lesion. These differences can affect immune cell–stromal cell interactions and their resulting effects on cell activation, proliferation and cytokine production.

Although studies from the past few years have provided new information on stromal cell–immune cell interactions in disease, a better understanding of these cell interactions is needed to determine how heterogeneity among these cells, including pathogenic cell subsets, could be targeted or used to stratify patients. The next step is to use synovial cell composition data and molecular signatures to select and predict response to various treatment options in the movement towards personalized treatment.

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Treat-to-target in axial spondyloarthritis — what about physical function and activity?

Jürgen Braun ✉, *Xenofon Baraliakos and Uta Kiltz*

Abstract | In patients with axial spondyloarthritis (axSpA), pain, functional and structural impairments, reduced mobility and potential deformity of the axial skeleton are the most prominent health concerns. Limitations in physical function and spinal mobility are caused by both inflammation and structural damage, and therefore restrictions to physical function must be monitored throughout a patient's life. Consequently, the assessment of physical function is recommended as a key domain in the Assessment of Spondyloarthritis International Society–OMERACT Core Outcome Set. However, in comparison with disease activity, physical function seems to be a relatively neglected target of intervention in patients with axSpA, even though physical function is a major contributor to costs and disability in this disease. This Review aims to reacquaint rheumatologists with the targets for physical function, physical activity and performance by giving guidance on determinants of physical function and how physical function can be examined in patients with axSpA.

Axial spondyloarthritis (axSpA), including radiographic axSpA (r-axSpA) and non-radiographic axSpA (nr-axSpA), is a chronic inflammatory rheumatic disease characterized by pain, functional and structural impairments, reduced mobility and potential deformity of the axial skeleton, as well as by peripheral musculoskeletal and extra-musculoskeletal manifestations[1,2]. Several different health complaints are considered to be important by patients with axSpA and often have a substantial influence on their lives, the most common concerns being stiffness, pain, mobility limitations, fatigue and sleep problems[3,4]. By contrast to the fairly homogeneous group of patients with r-axSpA, which is almost equivalent to the classic ankylosing spondylitis[5] and in which spinal stiffness and functional impairment are often the main clinical features, the total group of patients with axSpA (and also SpA) is diverse and can include individuals with extra-spinal disease manifestations such as arthritis or enthesitis as their main clinical symptoms, which might also lead to functional impairments[2].

Treatment of axSpA includes pharmacological and non-pharmacological therapy and aims to follow a treat-to-target strategy[6]. International recommendations were last updated in 2017 with a focus on disease activity and abrogation of inflammation[7]. Increasing evidence suggests that the presence of so-called 'objective' signs of inflammation, such as increased serum C-reactive protein (CRP) concentrations and bone marrow oedema in the axial skeleton detected on MRI, can predict whether an individual will respond to biologic DMARDs (bDMARDs)[8]. Furthermore, low disease activity is associated with the accrual of less structural damage over time[9]. Limitations in physical function and spinal mobility, which are caused by both inflammation and structural damage[10], are usually also improved in patients with axSpA who are treated with bDMARDs[11], and these improvements seem to last for long periods of time[12]. However, it seems that function, as compared to disease activity, is a relatively neglected target for intervention for patients with axSpA[13–15], even though limitations in physical function are major underlying factors for costs and disability in this disease[16,17].

Physical function usually deteriorates slowly over time in patients with axSpA, with both reversible and irreversible changes occurring that can influence functional capacity[9,18]. Impairments in physical function are most often associated with pain and/or stiffness. Whereas the signs and symptoms caused by inflammation are mostly reversible, those caused by structural damage are irreversible and have a strong influence on patients' functioning, particularly in advanced stages of disease. Although the underlying inflammatory cascade is uniform across the axSpA spectrum, the pathological manifestations and clinical features can differ remarkably, which has an effect on functioning. Data from patients with r-axSpA are robust with respect to physical function, whereas axSpA as a whole (including nr-axSpA) and other aspects of functioning are less

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Key points

- Impairments in physical function are among the most prominent health concerns in patients with axial spondyloarthritis (axSpA); their assessment is a key domain in the ASAS–OMERACT Core Outcome Set.
- The WHO International Classification of Functioning, Disability and Health is the most sophisticated classification system to capture the entire spectrum of functioning and health.
- Physical function can be assessed using self-report tools for physical function and physical activity, objective measurements of spinal mobility and performance-based tests.
- Physical function in patients with axSpA is influenced by inflammation and structural damage, as well as by comorbidities, mental health and various contextual factors.
- Although a combination of pharmacological and non-pharmacological therapy is recommended for the management of axSpA, interventions to improve or maintain function is a relatively neglected target for patients with axSpA.
- Interventions to improve physical function include strategies to enhance physical activity on a regular basis and physiotherapy interventions, often in combination with pharmacological treatments.

well studied. Nevertheless, studies in patients with early axSpA have shown that restricted spinal mobility and a worsened functional status[19] owing to involvement of posterior spinal structures that are not usually part of current scoring protocols might occur in at least some individuals[19,20]. The aim of this Review is to put the targets for improvement or maintenance of physical function, physical activity and performance back into the picture for the rheumatologist, because we are convinced that, for patients with axSpA, a good health status cannot often be reached by pharmacological therapy alone. In this Review, we aim to provide guidance on determinants of physical function and how physical function can be examined in patients with axSpA.

What is physical function?

Definitions of physical function

Physical function is a domain that describes the capability of an organism to independently perform specific tasks[19]. The concept of physical function can be described by conceptually interrelated but distinct domains such as mobility, dexterity of extremities and function of the axial skeleton, as well as by complex activities that require a combination of other basic tasks[21]. In a clinical context, recognition of functional limitations in performing basic tasks is important because impairments in these domains can predict the future development of a physical disability; for example, gait velocity is a single predictor of adverse events in healthy individuals over 75 years of age[22]. Because impairments in physical function are often reversible when assessed at an early stage of disease, we propose that objective measures of physical function should be used more often in patients with axSpA, and also during early disease.

A World Health Organization (WHO) task force introduced the view that functional capacities of people, including respiratory capacity, muscular strength and cardiovascular performance, increase and peak during early adulthood before their linear decline with advancing age, depending on lifestyle and environmental factors[23]. The WHO model classifies tasks into activities considered essential for maintaining independence and those considered discretionary but not required for independent living, even though they might affect quality of life[23]. The term functional capacity (synonymously used with fitness), together with physical function, denotes an individual's capacity to undertake everyday tasks[24].

Importantly, the concept of physical activity has to be distinguished from that of physical function. Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure and that can be measured in kilojoules or kilocalories[25]. Thus, physical activity refers to the amount of energy that is needed to complete a task and not to the capacity to actually perform the task. Physical activity helps improve or maintain muscle and cardiorespiratory functions and subsequently prevents impairment of physical function. Conversely, people who are only able to perform limited amounts of physical activity often have problems with their functional capacity. This relationship can be visualized by analysing performance levels to assess how well a person can execute a piece of work or an activity[26]. However, physical activity is a complex and multidimensional exposure variable, which makes population-based measurements difficult. In addition, all the definitions listed above go beyond the aspect of spinal mobility, which is restricted to physical movements without complex interactions[27,28].

The vast majority of studies concentrate on limitations of physical function because of their widespread prevalence and their links to decreased health-related quality of life (HRQoL), increased risk of disability, falls and fractures, and increased health-care costs[29]. According to the WHO, around 15% of the global population — over a billion people — live with some form of disability, and of these 2–4% experience substantial difficulties in functioning[23]. Therefore, it is essential that the assessment of physical function adequately identifies factors that contribute to physical capacity and the ability to perform a task. To achieve this aim, the measurement of a broad range of impairments is required in patients with axSpA.

Classification of physical function

Owing to the heterogeneity of the different concepts that describe aspects of functioning, it was challenging to classify all aspects systematically and within a meaningful concept. This problem was solved with the publication of the International Classification of Functioning, Disability and Health (ICF) by the WHO in 2001, in which a whole variety of health complaints are systematically classified[23]. The ICF addresses the complex interactions between the functioning and disability components and contextual factors by using the biopsychosocial model, which allows the simultaneous consideration of biological factors, psychological factors and societal factors. Contextual factors consist of environmental and personal factors that can act as facilitators or barriers to functioning[23]. Although this classification system is not specifically focused on a stringent assessment of physical function, it does provide a framework upon which conceptual models can be developed. Moreover, the ICF classification differs fundamentally in its structure from the concept of HRQoL. Within the

framework of the ICF as a standardized classification system, the patient's limitations are objectively assessed, whereas the concept of HRQoL is based on a subjective assessment of the state of health from an individual perspective.

The ICF characterizes disability as a problem in any one of the three biopsychosocial components, body function and body structure, activity and participation (FIG. 1). Deficits in body structure or function are identified as impairments in performing tasks that might have an influence on performing daily activities (activity limitations) or on the realization of social contacts (participation restrictions)[23]. All three domains (impairments, activity limitations and participation restrictions) are considered to be disabilities. This classification can be used to quantify the effect of an impairment on an individual's ability to function in their environment and to assess interventions to minimize disability and maximize functioning.

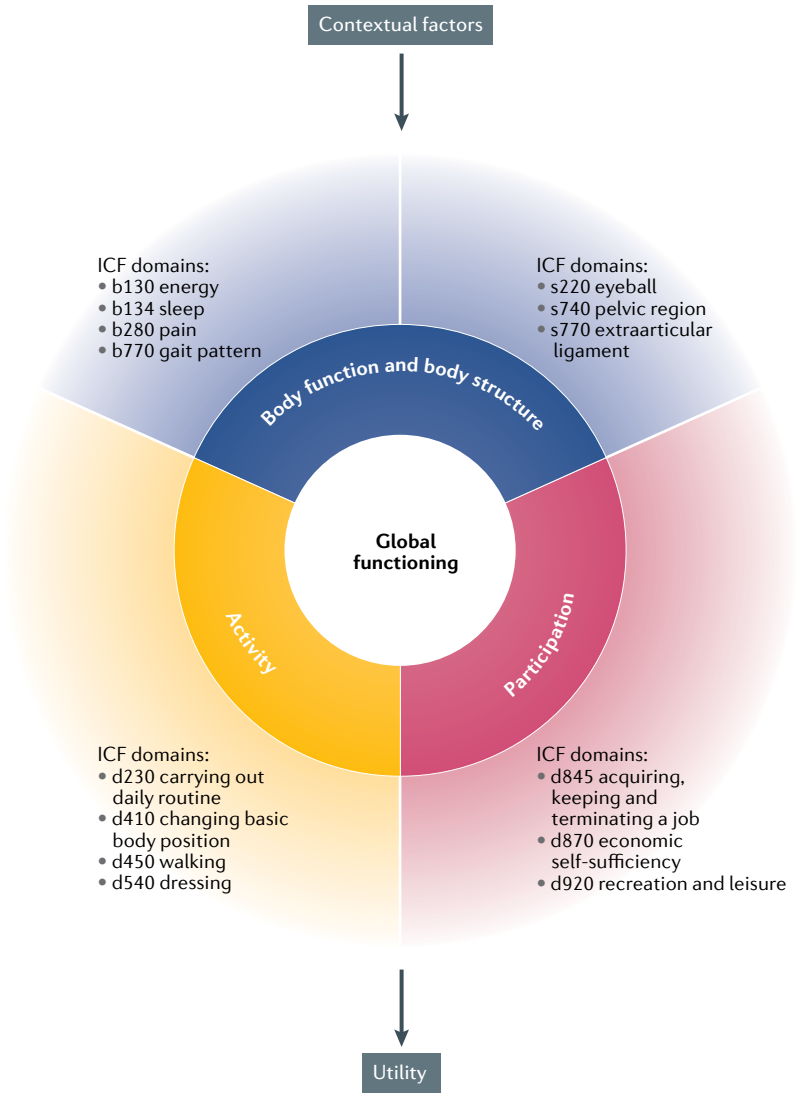

Fig. 1 | **The biopsychosocial model of function in axial spondyloarthritis.** The World Health Organization International Classification of Functioning, Disability and Health (ICF) characterizes disability as a problem in any one of the three biopsychosocial components: body function and body structure, activity and participation. Examples of disease-specific ICF domains that are relevant for individuals with axial spondyloarthritis are provided for each domain. Global functioning is a determinant of utility, and can be affected by contextual factors such as environmental or personal factors.

A disease-specific ICF Core Set was developed in 2010 by the Assessment of Spondyloarthritis International Society (ASAS) to provide a list of ICF categories that are relevant for patients with axSpA[30]. Because the ICF Core Sets provide information on which ICF category to measure, they constitute an evidence-based starting point to develop outcome instruments for functioning and health, such as the ASAS Health Index (ASAS HI), which has been developed on the basis of the ICF Core Set for r-axSpA[31,32].

Tools to assess physical function

Physical function is one of the main domains of the ASAS–OMERACT Core Outcome Set for patients with r-axSpA that was proposed by ASAS over 20 years ago[33]. The list of nine domains to be measured in trials or for clinical record keeping (pain, stiffness, physical function, fatigue, spinal mobility, peripheral joints, enthesses, spinal radiographs and laboratory assessment of inflammation) is currently being updated.

Physical function can be assessed using several different approaches that are characterized by increasing levels of individual appraisal. Examples are self-reported experiences of ability to perform activities, self-reported amounts of physical activity and objectively measured amounts of physical function from applying performance tests (TABLE 1). However, physical function is not a single variable, but rather a collection of health concepts that have to be combined to demonstrate how a patient is affected by a disease in daily life[34]. Discrepancies between ability and actual performance perceived by an individual (underestimation or overestimation) can affect self-reported measures and questionnaires[35]. Such discrepancies can originate from various factors, including education level, cognitive performance, language skills, mental disorders, personality traits, attitudes and somatic disorders such as pain[36]. Thus, self-reported measures might only show perceived limitations rather than 'true' limitations of physical function. For example, compared with matched healthy individuals, patients with r-axSpA both report and objectively perform the same amount of physical activity, despite reporting more difficulties[37].

Self-reported physical function

Aspects of physical function are addressed in tools specifically designed to collect information on physical function, but are also addressed in HRQoL tools. For the measurement of physical function in patients with axSpA the Bath Ankylosing Spondylitis Functional Index (BASFI) is widely used[35]. The BASFI comprises ten questions on activities related to daily living, which are scored with a rating scale from 0 (no functional impairments) to 10 (maximal impairment). The BASFI is reliable, sensitive to change and feasible to use in patients with r-axSpA in clinical practice. However, the self-report style of data collection used by the BASFI limits generalization. International guidelines recommend that non-pharmacological therapy should be

Table 1 | **Tools for assessing physical function, physical activity and performance**

Domain	Tool	Number of items	Application	Ref.
Self-reported physical function	BASFI	10	Disease-specific	35
HRQoL	ASAS HI	17	Disease-specific	32
	ASQoL questionnaire	18	Disease-specific	39
	SF-36	36	Generic	48
Self-reported physical activity	IPAQ	5 domains: 27 items (long), 7 items (short)	Generic	53
	SQUASH	4 domains; number of items depends on actual performance	Generic	54
Objective measure	BASMI	5	Disease-specific	58
	SPPB	3 (balance test with 3 different tasks)	Generic	65
	ASPI	3	Disease-specific	76

ASAS HI, Assessment of Spondyloarthritis International Society Health Index; ASPI, Ankylosing Spondylitis Performance Index; ASQoL, Ankylosing Spondylitis Quality of Life; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; HRQoL, health-related quality of life; IPAQ, International Physical Activity Questionnaire; SF-36, Short Form-36; SPPB, Short Physical Performance Battery Test; SQUASH, Short Questionnaire to Assess Health-Enhancing Physical Activity.

offered to patients with reduced physical function[6]. However, a validated threshold for functional loss or consensus-based guidance as to which kind of physiotherapy or rehabilitation to prescribe for patients with reduced physical function is not available at present. In addition, too much exercise has even been suggested to be deleterious in patients with axSpA[38].

Composite outcome measures such as the disease-specific Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire[39] or the ASAS HI[32] can be used to evaluate HRQoL in patients with axSpA[40]. HRQoL instruments have the advantage of covering aspects beyond physical functioning, such as emotional or social functioning, by assessing the subjective interpretation of a patient. The ASQoL measures the effect of r-axSpA on HRQoL from the patient's perspective[39,41]. This self-reported questionnaire includes 18 items on domains such as sleep, mood, motivation, coping, activities of daily living, independence, relationships and social life. Construct validity and feasibility of the ASQoL has been confirmed in independent cohorts[41,42]. By contrast, the ASAS HI, another patient-reported outcome measure, was developed on the basis of the ICF Core Set to cover the entire spectrum of possible limitations of global functioning in patients with SpA[31,32,43]. The different ways in which the ASAS HI can be used are reviewed in detail elsewhere[44]. The ASAS HI is accompanied by an Environmental Factor Item Set (EFIS) consisting of nine items that address contextual factors that have the potential to influence total functioning of patients[45] and represents a holistic perspective on aspects of health that are typical in patients with axSpA and are important according to patients, health-care providers and researchers. The ASAS HI includes 17 dichotomous items that represent different categories such as pain, emotional function, sleep, sexual function, locomotion, independence, social life and working life. Construct validity and feasibility of the ASAS HI has been confirmed in an independent cohort[46].

In addition to disease-specific questionnaires, generic tools have long been used to assess physical function in individuals with axSpA[47]. The Short Form-36 (SF-36) is one of the most frequently applied generic instruments in individuals with axSpA[48,49]. The SF-36, a 36-item composite self-report measure, was designed to be a short, generic assessment of health that includes physical function in addition to other important aspects, such as physical and emotional roles, bodily pain, general health, vitality, social functioning and mental health. The two main components of the SF-36 are subscores for physical health (the physical component score (PCS)) and mental health (the mental component score (MCS)). Studies have consistently shown that both the PCS and the MCS are reduced in patients with axSpA compared with the general population[50,51]. Activity limitations can be assessed using PCS-related questions. The associated items encompass vigorous activities such as running, lifting heavy objects and participation in strenuous sports, but also moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf, lifting or carrying groceries, climbing stairs, bending, kneeling or stooping, walking, and bathing and dressing without assistance.

Self-reported physical activity

Because the quantitative assessment of physical activity is difficult, self-reported physical activity questionnaires are often used in population-based studies for feasibility reasons. Questionnaires that assess total physical activity need to measure duration and frequency at the very least, but should also cover physical activity in several settings such as home, work, transportation, recreation and sport in order to reach sufficient content validity[52]. The International Physical Activity Questionnaire (IPAQ) and the Short Questionnaire to Assess Health-Enhancing Physical Activity (SQUASH) are recall questionnaires that fulfil these requirements[53,54]. Both questionnaires refer to an average week in the past month and comprise questions in the following domains: occupation, transportation, household activities and gardening, and leisure time and sports activities. Activity scores per domain are calculated by multiplying the number of minutes per week with an intensity score (range 1 to 9) for the activities performed (for SQUASH) or by multiplying the number of minutes per week of the performed activities with the accompanying mean metabolic equivalent (MET) value of these activities, which can be calculated from information provided by IPAQ. The MET is the objective measure of the ratio of the rate at which a person expends energy, relative to the mass of that person, while performing a specific physical activity, compared with a reference (set by convention at 3.5 ml of oxygen per kilogram per minute, which is roughly equivalent to the energy expended when sitting quietly). The Physical Activity Guidelines include a recommendation of 500–1,000 MET-minutes per week for considerable health benefits[55]. In a Dutch cohort of patients with ankylosing spondylitis, increased daily physical activity assessed using an accelerometer, IPAQ and

SQUASH correlated with reduced disease activity and increased physical function and quality of life[56]. In these patients, the median IPAQ total score was almost 6,000 MET-minutes per week, the mean SQUASH total score was close to 7,300, the mean accelerometer outcome was 236 kcounts per day, and the mean wear time of the accelerometer was >14 h per day. In another Dutch study, the total time spent doing physical activity of all different intensities was higher in healthy individuals than in patients with r-axSpA[57]. Notably, the WHO norm of at least moderate physical activity was met by less than half of the patients participating in these studies.

Objective measurements

An important aspect in the assessment of physical function in axSpA is spinal mobility, which is usually assessed by the Bath Ankylosing Spondylitis Metrology Index (BASMI)[58]. The BASMI includes the assessment of lateral and anterior spinal mobility, cervical rotation, tragus-to-wall distance and hip involvement (intermalleolar distance), although chest expansion or thorax excursion is not included despite this and other measures having been shown to improve in response to TNF inhibition[59]. Among several methods that can be used to calculate the BASMI, the linear version has been shown to perform the best[60]. In an analysis of data from two studies in patients with relatively early axSpA (DESIR and SPACE), lateral and anterior spinal flexion (as measured by the modified Schober test) were the most impaired spinal mobility measures, with the authors noting extreme variability in these measures over time[61]. By contrast, in patients with more advanced disease receiving long-term TNF inhibitor therapy, function and spinal mobility remained relatively stable despite increasing radiographic damage during 10 years of therapy[12]. In a natural course of disease study (OASIS), lateral and anterior spinal flexion were similarly the most frequently impaired measures, followed by tragus-to-wall distance, cervical rotation, intermalleolar distance and chest expansion measures, respectively. Notably, this hierarchy was strikingly consistent over time and independent of sex, symptom duration and the presence of syndesmophytes[62].

In contrast to self-reported questionnaires, performance-based tests seem to provide more objective outcome measurements for the evaluation of physical function and deliver relevant additional information. In individuals older than 65 years, physical function tests are strong predictors of important clinical outcomes and adverse health events[63,64]. Physical performance can be assessed as a single task, such as the measurement of grip strength, or as a generic compound measure such as the Short Physical Performance Battery Test (SPPB), which includes gait speed, chair rise and balance tests. In otherwise healthy people over 70 years of age, a low SPPB score can predict physical disability[65] and mortality[66,67]. Similarly, tests to assess gait speed are predictive of several adverse outcomes, such as cognitive decline[68], Activities of Daily Living (ADL) score[69,70], disability[71], hospitalization[72] and mortality[73]. Indeed, the relevance of physical function tests for performance, outcomes and prognosis has been consistently shown across multiple cohorts and different populations. Thus, measuring the actual performance of patients with axSpA could provide a more complete picture of functioning than self-reporting alone.

In addition to measuring mobility, performance measures have also been developed and tested in patients with axSpA[27,74–76]. The first performance test to be designed was the Ankylosing Spondylitis Performance Index (ASPI), which combined three BASFI questions (bending, putting on socks and getting up from the floor) to assess performance-based physical function in patients with axSpA. Improvement was arbitrarily defined as an intra-individual improvement of ≥20% on at least one of the three selected tests, combined with absence of deterioration, defined as worsening of ≥20% in the remaining tests. The time taken to perform the three tasks is totalled to give the final score. Good inter-rater and test–retest reliabilities have been shown for the three ASPI tests with 94% finishing the procedure in <15 min, indicating acceptable feasibility of the test; however, only 82% of patients were able to complete all three tests[75]. When evaluating physical function after an exercise intervention, ASPI performed better than BASFI[77]. Thus, the inclusion of physical performance measures seems to be a good way to assess physical function and what this actually means in axSpA. Preliminary results using performance measures usually used in geriatric medicine such as SPPB have been reported[15], so whether the ASPI will remain the only performance test and whether it will be superior to others remain to be seen. Furthermore, a core strength endurance test battery usually used to test athletes has been adapted for use in patients with axSpA[78]. The adapted test battery was reliable for the assessment of core strength endurance in patients with axSpA, but contrary to what had a priori been hypothesized, its performance was not associated with any disease-specific factor. These results could suggest that this test battery can be performed by patients with axSpA irrespective of their perceived performance and pain, and their actual functional status[78].

Tools to objectively assess physical activity are increasingly becoming available[37,57], but a discussion of the technical aspects of recently developed digital technologies is beyond the scope of this Review.

Physical function in patients with axSpA

Determinants of impaired function

Several factors can influence physical function in patients with axSpA (FIG. 2). Although associations between specific factors and physical function have been consistently described for patients with r-axSpA, impairments in physical function have to be understood as part of a multifaceted picture in a heterogeneous population of patients with axSpA. Available data from cohort studies indicate an association between physical function and disease activity, as well as between physical function and structural damage in patients with r-axSpA[10,18]. The strongest association is between the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS)[29] radiographic scoring system (as a proxy for spinal structural damage) and the BASMI (as a proxy for mobility) and the BASFI (as a proxy for physical function), indicating

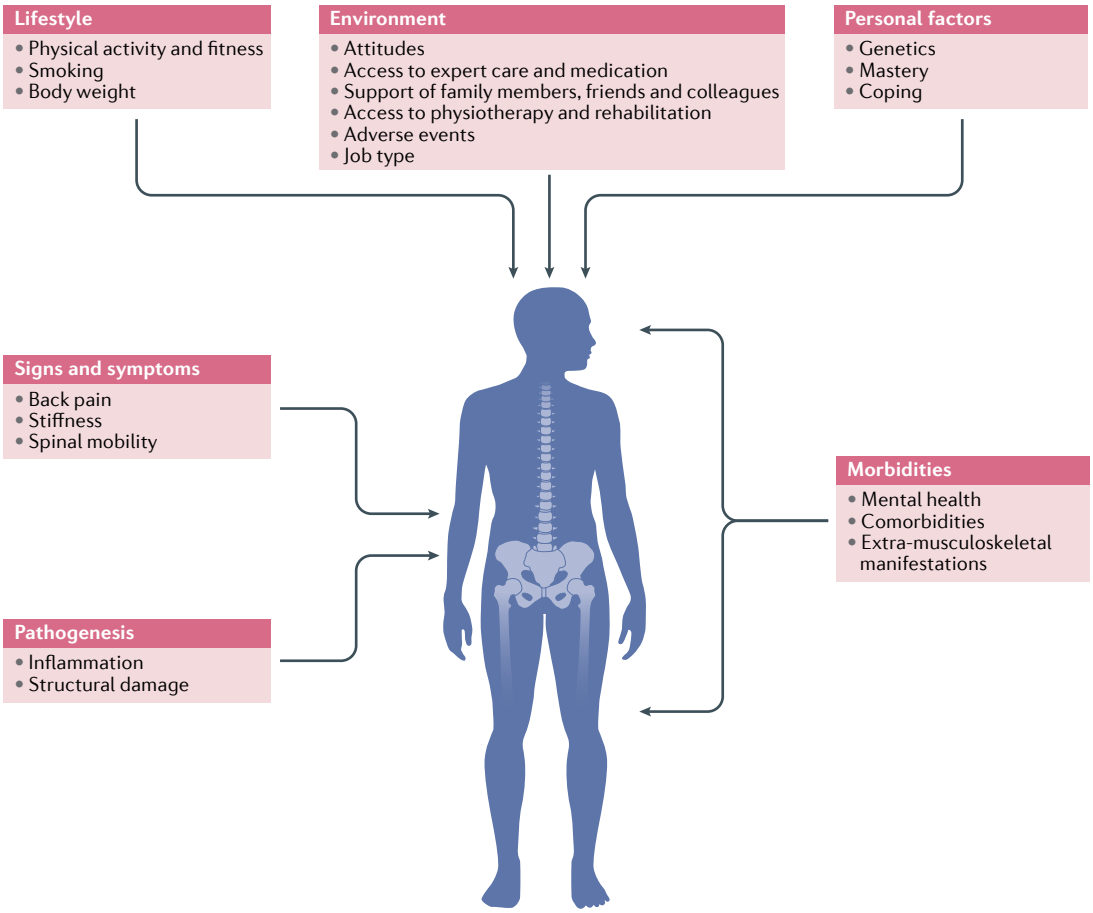

Fig. 2 | **Factors that affect physical function in axial spondyloarthritis.** Physical function is affected by multiple factors related to lifestyle, environment and disease, and thus will have a complex mixture of patient-specific and disease-specific characteristics in each individual with axial spondyloarthritis.

that there are additional determinants that might lead to impairment in physical function[35,58,79,80]. In a 2-year clinical and radiographic follow-up study of the GESPIC cohort, an association was reported between mSASSS and BASFI when adjusted for disease activity parameters (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and CRP), the presence of definite radiographic sacroiliitis and sex[80]. However, the association between mSASSS and BASMI, adjusted for the same parameters, was even stronger. Over time, an increase of 20 or 12 mSASSS points (range 0–72) was required for an increase of one BASFI point (range 0–10) or one BASMI point (range 0–10), respectively[80]. In the same cohort, the association between structural damage in the sacroiliac joints and function was relatively weak[81]. Clinicians should be aware that spinal mobility is a complex outcome that is highly influenced by various clinical and individual factors.

Data from the ASSERT study, in which patients with r-axSpA were treated with infliximab or placebo, confirmed that physical function is associated independently with disease activity, as well as with measures of spinal mobility[82]. In these patients, spinal mobility was an intermediate variable between structural damage and physical function, whereas physical function was an intermediate between spinal mobility and the physical component of SF-36 (REF.[82]). In another subanalysis of data from the ASSERT study, not only was structural damage associated with impairment in spinal mobility, but so was inflammation in the spine (measured using the Ankylosing Spondylitis Spinal MRI Activity (ASspiMRI-a) score)[10]. The ASSERT study researchers calculated that an increase of 10 points in the mSASSS leads to an increase of 0.46 points in the BASMI, independent of the effect of spinal inflammation. Similarly, an increase of 10 units in the ASspiMRI-a score (range 0–138) leads to an increase of 0.33 in the BASMI. In patients with a disease duration of ≤3 years, the association between physical function and inflammation in the spine was greater than that for structural damage (correlation coefficient 0.595 versus 0.380), whereas in patients with a disease duration of >3 years, the opposite was true (correlation coefficient for structural damage of 0.924 versus 0.156 for inflammation in the spine)[10], suggesting that structural damage might not be as relevant in patients with early disease as it is in patients with more advanced disease who might have more severe structural changes and functional impairments. Similarly, in DESIR, a cohort of patients with early axSpA, impairment of spinal mobility was independently determined in terms of disease activity, enthesitis and age[83]. Information on the independent influence of structural

damage and inflammation on spinal mobility as a function of disease duration is very important for the patient. Clinicians should inform patients that the ratio of modifiable to non-modifiable factors can shift over time. This type of information is of critical importance to help patients understand their treatment strategy.

Comorbidities have an important role in the performance of physical function and physical activity. In a large international ASAS comorbidity study[84], the Rheumatic Disease Comorbidity Index (RDCI)[85] was used to assess comorbidity. In this cohort of patients with SpA, at least one comorbidity was reported in 51% of patients, while 9% had three or more comorbidities. A higher RDCI score was independently associated with higher impairments in physical function (BASFI scores), lower utility (EuroQol 5 dimension scores[86]), work impairment, higher absenteeism and higher presenteeism (Work Productivity and Activity Impairment Questionnaire scores)[87]. Health insurance data from Germany confirmed these findings by showing that the number of comorbidities is clearly and statistically significantly associated with both disease activity and physical function[88]. The most prevalent comorbidities in this study were hypertension, depression and chronic pulmonary disorders, whereas in a Dutch study, obesity was found more frequently in patients with axSpA than in the general population (22% versus 15%)[89]. However, a cohort trial from Spain did not confirm an influence of comorbidities on physical function, but rather showed an association with age, disease activity, radiographic damage and the use of bDMARDs[90]. Older age, obesity, smoking and a history of more physically demanding jobs have also been identified as factors that have a negative influence on physical function in patients with axSpA. By contrast, more frequent back exercise, higher levels of education and better social support are associated with better physical function and less disability over time[90–92].

Taken together, there is no doubt that exercise is able to improve physical function. In a survey performed in the UK, patients with r-axSpA who had severe disease and who were motivated to exercise had the most benefit[93]. Motivation to exercise not only had a direct effect on function, but also an indirect effect of improving activity levels. High intrinsic motivation driven by pleasure had the greatest benefit to activity and function[93].

Interaction between physical and mental health. Physical and mental health are strongly linked, but little is known about how they interact. Data from the ASSERT study show that the mental component of SF-36 is independently associated with physical function[82]. Understanding this link is relevant because a high prevalence of depression (up to 35% of individuals) has been found in patients with r-axSpA, as well as an increased risk compared with the general population[94]. In a meta-analysis looking at comorbidities in axSpA that was published in 2020, a higher prevalence of depression was found in patients with axSpA compared with healthy individuals (pooled OR 1.8)[95]. Importantly, being depressed has a large effect on frequent symptoms such as pain and fatigue[96]. German health insurance data[88] showed that depression is rated as one of the most prevalent comorbidities in axSpA, with a prevalence of 26%. The presence of depression was independently associated with worse physical function and disease activity, as well as with 0.7 point and 0.66 point increases in BASFI and BASDAI scores, respectively[88]. Data from the Swedish Skåne Healthcare Register demonstrated a substantial increase in depression in patients with axSpA over the 13-year study period (1999–2011)[97]. The risk of developing depression was higher for women than for men, with a standardized depression rate ratio of 1.81 in women and 1.49 in men[97].

The interactions between physical and mental health have not been well studied in patients with axSpA. In a study using data gathered between 2002 and 2012 as part of the English Longitudinal Study of Ageing[66], in which mental health was assessed by the Centre for Epidemiological Studies Depression Scale and physical health using the ADL instrument[98,99], statistically significant direct and indirect effects for both forms of health were identified among the general population. Indirect effects explained 10% of the effect of past mental health on physical health and 8% of the effect of past physical health on mental health. Importantly, physical activity turned out to be the largest contributor to indirect effects[66]. Strong indirect effects were especially seen in men with regard to mental health. Thus, interventions aimed at changing physical and mental health need to consider not only direct effects, but also the indirect cross-effects between the two forms of health. Studies specifically in patients with axSpA are clearly needed in this area.

Influence of environment on physical function. Understanding the role of an individual's environment in the initiation and progression of physical function limitations is essential. The WHO has acknowledged the central role of a person's environment[23] in the ICF, which takes the social aspects of disability into account and provides a mechanism to document the effect of the social and physical environment on a person's functioning[23,100]. Factors in an individual's environment can range from general exposures, such as climate and general neighbourhood conditions, to more immediate factors such as inadequate lighting. Although the latter will act as barrier to performing physical tasks, other factors such as helpful neighbours could act as facilitators. How somebody handles their diminished abilities and potentially copes with environmental challenges determines how well they will function in daily life, and common compensation and coping strategies often include modifications to the way in which an activity is performed. Conceptual models depicting interactions between the environment and physical function often focus on interventions at the individual level to guide assessment and treatment of patients. For example, the 'universal design movement' recognizes the individual as a key element, but the focal point is the environment, which should be transformed according to the patient's needs. Seven principles have been agreed on to make environments accessible to people with disabilities[101,102].

Many assessments of functioning do not capture the broad dynamic of personal, social, environmental and compensatory strategies, which can all influence physical function and performance. Specific to axSpA, an EFIS has been developed to accompany the ASAS HI to systematically assess such contextual factors[45]. The nine items of the EFIS covers the ICF chapters 'products and technologies', 'support and relationship', 'attitudes' and 'health services'. However, further research is still needed to understand the implications of the EFIS.

Taken together, interrelationships between disability and an individual's environment or community can be understood as a mixture of personal, social, environmental and compensatory strategies, all of which can affect physical function and performance. These personal contexts can be critical aspects for people with disabilities, and need to be taken into account.

Barriers and facilitators to activity

Barriers to being physically active are reported by a substantial number of patients with axSpA[103–106]. The barriers most frequently reported by patients with r-axSpA in a case–control study performed in Norway were pain (48%), stiffness (36%), fatigue (30%) and disability (21%)[104]. Almost two-thirds of patients and healthy individuals in this study reported that they had the potential to become more physically active; the most frequently reported facilitators to increased activity were time and motivation, with stable disease and individually adapted physical activity important for patients with r-axSpA. Almost all participants reported that physical activity had positive effects on their health, including improved fitness and increased vitality, and around one-third of patients reported greater disease stability and pain reduction. In a survey performed in Switzerland, more than half of patients with r-axSpA reported 'low motivation', 'unsuccessful timing in daily routine' and 'hindering disease symptoms' as the top three barriers, whereas the top three facilitators — reported by 40–47% of participants — were 'high motivation', 'good organizational conditions' and 'facilitating disease symptoms'[103]. Notably, physiotherapists found that heterogeneous group composition was also an important barrier, whereas many rheumatologists thought that a lack of information and anticipated or perceived disinterest of their patients were relevant barriers. Individuals from both professions stressed that knowledge and clear evidence for effectiveness of flexibility exercises are important facilitators.

Improving physical function in axSpA

According to recommendations made by the WHO, people of all ages should engage in regular physical activity in moderate amounts to gain considerable health benefits[107]. Importantly, physical activity also improves HRQoL in individuals with functional limitations by enhancing their physical function. Indeed, those patients with SpA, including r-axSpA, from the Skåne Healthcare Register who met the global WHO recommendations for physical activity had lower disease activity, better physical function and superior HRQoL[108]. As already mentioned, disease manifestations can considerably vary in patients with axSpA. Thus, individual treatment recommendations have to be adapted to each patient's health and functional status. Patients who have had the disease for only a short time and who have fully preserved physical function do not require targeted physiotherapeutic interventions, but could benefit from reliable information on the possible gradual process of impairments as their disease progresses and from information on recommendations for physical activity. In young patients with axSpA who have preserved physical function, the recommendation for regular physical activity means that their physical function can be safeguarded as far as possible, and risks to their cardiovascular health reduced.

Physiotherapy

A landmark 2008 Cochrane review on physiotherapy interventions in individuals with r-axSpA found evidence that individual home-based or supervised exercise programmes are better than no intervention; that supervised group physiotherapy is better than at-home exercises; and that combined inpatient spa-based exercise therapy followed by group physiotherapy is better than group physiotherapy alone[109]. These results were largely confirmed in a meta-analysis published in 2020 (REF.[110]). However, the quality and conclusions of published reviews differ, and the authors of the 2008 Cochrane review stated in 2011 that there is room for improvement regarding the quality of interventions in exercise trials in axSpA[111]. They also suggested that measuring physiological responses and the adherence to exercise interventions should be a research focus. In the most recent Cochrane review from 2019, exercise programmes were found to slightly improve function, reduce pain and slightly reduce disease activity (moderate-to-low quality evidence) compared with no intervention[112]. Furthermore, there was moderate-to-low quality evidence that exercise programmes have only limited effects on improving disease activity and function or reducing pain compared with usual care. The authors were uncertain whether exercise programmes can improve spinal mobility, reduce fatigue or even induce adverse effects[112] which, in our experience, is in contrast to patient perception. These results also reflect the difficulty of demonstrating efficacy when studying physiotherapy interventions. Methodological weaknesses of published trials have also been noted in other reviews, such as the often too small number of patients included and the heterogeneity of patients and exercise programmes in randomized controlled trials. The authors of these reviews also stressed the therapeutic potential of exercise programmes to improve disease activity and body function in patients with r-axSpA[112,113]; however, the potential usefulness of physiotherapy in early axSpA (including nr-axSpA) has recently been challenged[114] and is still unclear. New ideas in this area include the use of web-based programmes to motivate patients with axSpA to perform exercises[115]. Further studies are needed to show the utility of such web-based programmes.

Whether the combination of physiotherapeutic interventions and bDMARDs such as TNF inhibitors is superior to medication alone has been addressed by several groups[116–120]. In one study, an intensive

rehabilitation programme in addition to therapy with a TNF inhibitor showed short-term beneficial effects on BASFI scores in patients with r-axSpA[116]. Similarly, in another study, patients with r-axSpA treated with TNF inhibitors were able to perform more exercise when also provided with physiotherapy[117]. Another pilot study suggested that intensive physiotherapy could substitute for a dose reduction of TNF inhibitors in patients with axSpA[118]. Furthermore, a systematic review[119] and a meta-analysis[120], both from 2015, concluded that the concurrent use of TNF inhibition and exercise is probably able to reduce BASMI and BASDAI scores (and BASFI scores to a lesser degree), and that chest expansion remains largely unchanged. Higher quality studies are needed to shed more light on these relevant issues.

Fitness training

A systematic comparison of physical fitness states in patients with r-axSpA (mean Ankylosing Spondylitis Disease Activity Score (ASDAS) 2.3; median disease duration 23 years) and matched individuals from the general population found a higher response rate in patients (59.6%) than in population controls (40.4%)[121]. Even though muscle capacity was not different between patients and population controls, the patients had lower oxygen consumption (VO_2) peak values. Thus, the inferior cardiorespiratory fitness of these patients indicates that physiotherapy programmes should include cardiorespiratory fitness exercises as a basic component. This aspect seems to be particularly relevant given the increased cardiovascular comorbidity of patients with r-axSpA[122,123].

In a meta-analysis of six studies in patients with axSpA, aerobic fitness (defined as exercise performed at 50–90% of the maximal heart rate or between 50% and 80% of the VO_2 peak) had a positive but not statistically significant effect on disease activity (as measured by BASDAI) in the intervention group compared with the control group, but had no effect on BASFI scores, CRP or erythrocyte sedimentation rate (ESR)[124]. Similarly, in a study in 100 patients with axSpA (aged 20–60 years; 97% completed the intervention), in which participants were randomly assigned to an exercise group (high-intensity cardiorespiratory and muscular strength exercises for 3 months) or to a no-intervention group (instructed to maintain their usual level of physical activity), the intervention led to a statistically significant treatment effect on the primary outcome of disease activity (0.6 point reduction in ASDAS score), and also on inflammation, physical function and cardiovascular health[125,126]. When interviewed, patients perceived the supervised high-intensity exercise as challenging for body and mind, but also described a positive experience in which the rapid physical effects strengthened respondents' faith in their own body[127]. The positive experience of participants in this study seems to have changed their attitude towards exercise and their motivation to exercise. In a further analysis of the same study[128], physical activity during leisure time was quantified using a questionnaire in which being physically active was equivalent to ≥1 h per week of moderately or vigorously intense physical activity. At the 12-month follow-up, considerably more individuals from the intervention group than the control group were physically active (67% versus 30%) and performed exercises two or three times per week (58% versus 34%). Participation in the intervention group and being physically active at baseline were the factors most strongly associated with physical activity; however, no differences between the groups were found for disease activity as assessed by ASDAS[128].

To investigate the anti-inflammatory effects and safety of an add-on training programme involving breathing exercises, cold exposure and meditation, an open-label, randomized, one-way crossover clinical proof-of-concept trial has been conducted in patients with axSpA[129]. During the 8-week intervention period, a statistically significant decline in ESR (from 16 to 9 mm/h) was found in the intervention group ($n = 13$) but not in the control group ($n = 11$; from 14 to 16 mm/h); disease activity (measured by ASDAS–CRP) also declined in the intervention group but did not reach statistical significance. No safety signals were reported. The clinical relevance of these findings remains to be determined; nevertheless, the attractive hypothesis that immune responses can be modulated through add-on training programmes deserves further study.

Current recommendations

Several different international recommendations for the management of axSpA address concepts of physical function and physical activity. In addition, the 2020 ASAS quality standards stress that patients with axSpA should be informed about the benefits of regular exercise[130]. However, even though these benefits of physical activity and physiotherapy are highlighted in most recommendations, no treat-to-target approach has been proposed to reach a better physical performance in patients.

The 2016 ASAS–EULAR recommendations for the management of axSpA cover pharmacological and non-pharmacological therapies, including physiotherapy, which has been an important part of the management of r-axSpA for many years[6,131]. The ASAS–EULAR recommendations explicitly mention that the treatment of patients with axSpA needs to be individualized according to the individual's current signs and symptoms of the disease (axial, peripheral and extra-articular manifestations) and to the individual's characteristics, including comorbidities and psychosocial factors[6]. The recommendation for individualized therapy is of particular importance given that patients with axSpA have a high variability of limitations in physical function. The ASAS–EULAR recommendations also emphasize that disease monitoring of patients with axSpA needs to include patient-reported outcomes, clinical findings, laboratory tests and imaging, all obtained using the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring is decided on an individual basis depending on symptoms, severity and treatment[6]. For daily clinical care, this recommendation means that spinal mobility is measured and physical function is regularly assessed. The time interval between examinations needs to be adapted by the rheumatologist in relation to the variable clinical picture.

In the 2020 ASAS quality standards, the suggested time interval was at least once per year[130]. Importantly, the main goals of management are to optimize long-term HRQoL and social participation through the control of signs and symptoms, prevention of structural damage, normalization or preservation of function, avoidance of toxicities and minimization of comorbidities[6]. Furthermore, patients should be educated about the disease and encouraged to exercise on a regular basis and to stop smoking. Physiotherapy is recommended to be considered if present or developing impairments are recognized[5]. However, the health-care systems of many countries could have difficulties in meeting this standard for many different reasons.

The 2017 treat-to-target recommendations for SpA focus on medication use to reduce the burden of inflammation, particularly looking at obtaining clinical remission or inactive disease in musculoskeletal (arthritis, dactylitis, enthesitis and axial disease) and extra-articular (uveitis, psoriasis and colitis) manifestations[6]. Individualizing the treatment target on the basis of the current clinical disease manifestations is important, and can include designing the treatment modality accordingly and considering the time needed to reach the target[7]. Although the outcome variable in treat-to-target recommendations is a reduction in disease activity, for full remission, a well-preserved or good physical function should also be taken into consideration. For example, a patient with bamboo spine might not have any inflammatory disease activity, but will not reach normal levels of function and mobility. In addition, comorbidities, patient factors and drug-related risks have to be taken into account[7]. The treatment finally chosen is based on a shared decision between the patient and the rheumatologist on a background of appropriate information on the treatment target and the risks and benefits of the strategy planned to reach this target[7]. Within this process, the inclusion of patient information and education about regular physical activity and, if necessary physiotherapy, should be mandatory[132].

The 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis include SpA, and stress that physical activity should be performed regularly by individuals with arthritis, and to a similar degree as recommended for healthy individuals[25]. These recommendations suggest that patients with axSpA need to be informed about the benefits of regular exercise[25]. Therefore, there is clear need for improved education and motivation strategies in routine clinical practice for both pharmacological and non-pharmacological options. The 2016 EULAR cardiovascular risk recommendations include lifestyle recommendations that emphasize information on the benefits of a healthy diet, regular exercise and smoking cessation, and the risk-reducing effects of fitness on cardiovascular health[133]. Thus, the promotion of physical activity consistent with general physical activity recommendations has to become an integral part of standard care throughout the course of disease in patients with axSpA[25]. Methodologically, there is a need to evaluate the type, intensity, frequency and duration of an individual's actual physical activity by means of standardized methods to identify which of the four exercise domains (cardiorespiratory, muscle strength, flexibility and neuromotor) should be targeted for improvement[25].

A comprehensive individual assessment should also include a search for general and disease-specific barriers and facilitators related to the performance of physical activity, including knowledge, social support, symptom control and self-regulation[25]. The investigation of disease-specific barriers and facilitators is important for patients and the specific aspects of their health and functional status. Furthermore, a need exists to actually plan physical activity interventions, including behavioural change techniques, self-monitoring, goal setting, action planning, feedback and problem solving, for which a whole range of delivery modes for interventions can and should be considered[25]. A multidisciplinary team is likely to be the best option to care for patients with axSpA with impaired physical function and to promote regular physical activity.

Conclusions

For patients with axSpA, stiffness, pain, mobility limitations, fatigue and sleep problems are the most prominent health concerns and restrictions that influence their quality of life. Current treatment strategies for axSpA include pharmacological and non-pharmacological therapies, with the aim of following a treat-to-target strategy; however, physical function can often be neglected and needs to be put back in focus.

Physical function is not a single variable, but rather a collection of different health concepts that together paint a picture of how a disease affects an individual in daily life (FIG. 2). Self-reported measures, questionnaires and performance-based tests are all available to assess physical function and activity. Functional limitations in performing basic tasks can represent early phases of developing overt physical disability. Therefore, objective measures of physical function are important because poor physical function is often reversible with adequate interventions. A different, albeit related, concept is that of physical activity, which affects and is affected by physical function.

Physical function in individuals with axSpA is influenced by both inflammation and structural damage, and many pharmacological and non-pharmacological interventions have been studied, including combinations of both, with some degree of success. However, the disease spectrum of axSpA includes many different disease manifestations, diagnoses and impairments of physical function. Therefore, to optimize health care for these patients, it is mandatory to understand the different determinants of function, mobility and health (including physical activity) at different stages of disease. The heterogeneous disease course and the different determinants of impairment, which can often change over time, do not make this an easy task, as this disease can affect patients for 50 years or more. Future studies and recommendations should include aspects of physical function and physical activity to reach health benefits for patients with axSpA.

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Combining TNF blockade with immune checkpoint inhibitors in patients with cancer

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TNF is involved in various autoimmune diseases and in immune-related adverse events (irAEs) that occur in patients with cancer being treated with immune checkpoint inhibitors (ICIs)[1,2]. In their Review (Chen, A. Y., Wolchok, J. D., & Bass, A. R. TNF in the era of immune checkpoint inhibitors: friend or foe? *Nat. Rev. Rheumatol.* **17**, 213–223 (2021))[3], Chen and colleagues nicely reviewed the literature, from basic studies[4,5] to clinical observations[6,7], discussing whether TNF can be considered as a putative target in the treatment of irAEs in patients with cancer undergoing ICI therapy. Important questions were raised regarding TNF inhibitor safety and efficacy in this setting, but unfortunately, the authors missed out discussions of the TICIMEL phase Ib clinical trial (NTC03293784), the results of which we think help address some of these questions.

Initiated in 2018, the TICIMEL trial investigated the effects of treatment with the ICIs ipilimumab (an anti-CTLA4 antibody) and nivolumab (an anti-PD1 antibody) in combination with a TNF inhibitor (infliximab or certolizumab) in patients with advanced melanoma[8]. The results from 14 patients enrolled in the first phase of this trial were published in December 2020 (REF.[9]). Although the low number of patients warrants caution as regard to the interpretation of data, the results are informative.

One question raised by Chen and colleagues relates to whether TNF inhibitors are safe in the management of patients with cancer and ICI-induced irAEs. Results from the TICIMEL trial indicate that concomitant administration of ipilimumab, nivolumab and an anti-TNF drug (infliximab or certolizumab) is indeed safe in the short-term and potentially in the long-term.

Chen and colleagues also compiled evidence from pre-clinical studies showing that TNF promotes cancer progression and inhibits anti-tumour immune responses. They conclude that although TNF blockade and/or deficiency in mouse models of cancer can, via the promotion of $CD8^+$ T cell-mediated anti-tumour immune responses and a decrease in immune regulatory responses, impede tumour growth, these observations have to be confirmed in humans. Especially, they noted that this hypothesis has to be evaluated in the context of combined ICI and anti-TNF treatment.

In line with these observations, results from the TICIMEL trial show a high objective response rate in the certolizumab cohort, with all evaluable patients responding to treatment, including four complete responses out of seven objective responses. By comparison, only half of the patients in the infliximab cohort responded to treatment (including one complete response out of three objective responses). These treatments were associated with increased numbers of T helper 1 cells and increased plasma concentrations of IFNγ. Whether and how these responses differ to the ones occurring in patients with advanced melanoma being treated with the combination of ipilimumab and nivolumab remains to be evaluated.

Emerging evidence reported by Chen and colleagues and our recent clinical trial suggest that TNF inhibitors are safe and beneficial in the treatment of patients with cancer and irAEs. We are further assessing these parameters in the second phase of the TICIMEL trial[8,9].

There is a reply to this letter by Chen. A. Y., Wolchock, J. D. & Bass, A. R. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-021-00654-7 (2021).

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Competing interests
B.S. has worked as investigator, consultant and speaker for BMS. N.M. has worked as investigator and/or consultant and/or speaker for BMS, MSD, Roche, Novartis, Pierre Fabre, Amgen, Incyte, Abbvie. B.S. and C.C. have a patent US10144772B2 issued, a patent WO2015173259A1 pending, a patent EP3142685B1 issued, a patent ES2748380T3 issued. B.S., C.C. and N.M. have a patent EP3407911A1 pending, a patent JP2019503384A pending, a patent US20190038763A1 pending, and a patent WO2017129790A1 pending. The other authors declare no competing interests.

Reply to: Combining TNF blockade with immune checkpoint inhibitors in patients with cancer

Allen Y. Chen, Jedd D. Wolchok and Anne R. Bass

We would like to thank Montfort and colleagues for their correspondence (Montfort, A. et al. Combining TNF blockade with immune checkpoint inhibitors in patients with cancer. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-021-00653-8 (2021))[1] on our Review (Chen, A. Y., Wolchok, J. D. & Bass, A. R. TNF in the era of immune checkpoint inhibitors: friend or foe? *Nat. Rev. Rheumatol.* **17**, 213–223 (2021))[2].

We appreciate their highlighting early results of TICIMEL, an open-label phase Ib two-arm study of 14 patients that combined one of two TNF inhibitors, certolizumab or

infliximab, with two immune checkpoint inhibitors (ICIs), ipilimumab and nivolumab, for the treatment of melanoma[3]. This study was published after our manuscript was submitted to reviewers.

The finding in TICIMEL that all seven evaluable patients treated with certolizumab plus ICI therapy achieved an objective response[3] is tantalizing, but the numbers are too small to compare to historical cohorts of patients not treated with a TNF inhibitor. In addition, given that certolizumab and infliximab are both biologic drugs that target TNF (the two drugs differ in that certolizimab is a PEGylated, Fc-free monovalent antibody), how to evaluate the two arms individually is challenging.

An unexpected finding was the high rate of grade 3 or 4 immune-related adverse events (irAEs) in patients in the TICIMEL trial, despite concomitant TNF inhibitor treatment (75% in the certolizumab arm and 50% in the infliximab arm)[3]. The rate of high-grade irAEs was similar to that in CheckMate 067, a large melanoma trial that also used combination ICI therapy in which 59% of patients experienced high grade irAEs[4]. This finding suggests that in TICIMEL, TNF inhibition might not have lessened the rate of adverse events. As with the efficacy analysis, however, the small number of enrolled patients in TICIMEL precludes firm conclusions about toxicity. We look forward to future results, after additional patients have been enrolled in TICIMEL, and congratulate the authors on performing this important study.

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Competing interests

J.D.W. is a consultant for Adaptive Biotech, Amgen, Apricity, Arsenal, Ascentage Pharma, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, F Star, Imvaq, Kyowa Hakko Kirin, Merck, Neon Therapeutics, Psioxus, Recepta, Sellas, Serametrix, Surface Oncology, Syndax and Syntalogic, Takara Bio, Trieza and Truvax; receives research support from AstraZeneca, Bristol Myers Squibb and Sephora; and has equity in Adaptive Biotechnologies, Apricity, Arsenal, BeiGene, Imvaq, Linnaeus, Tizona Pharmaceuticals. The other authors declare no competing interests.