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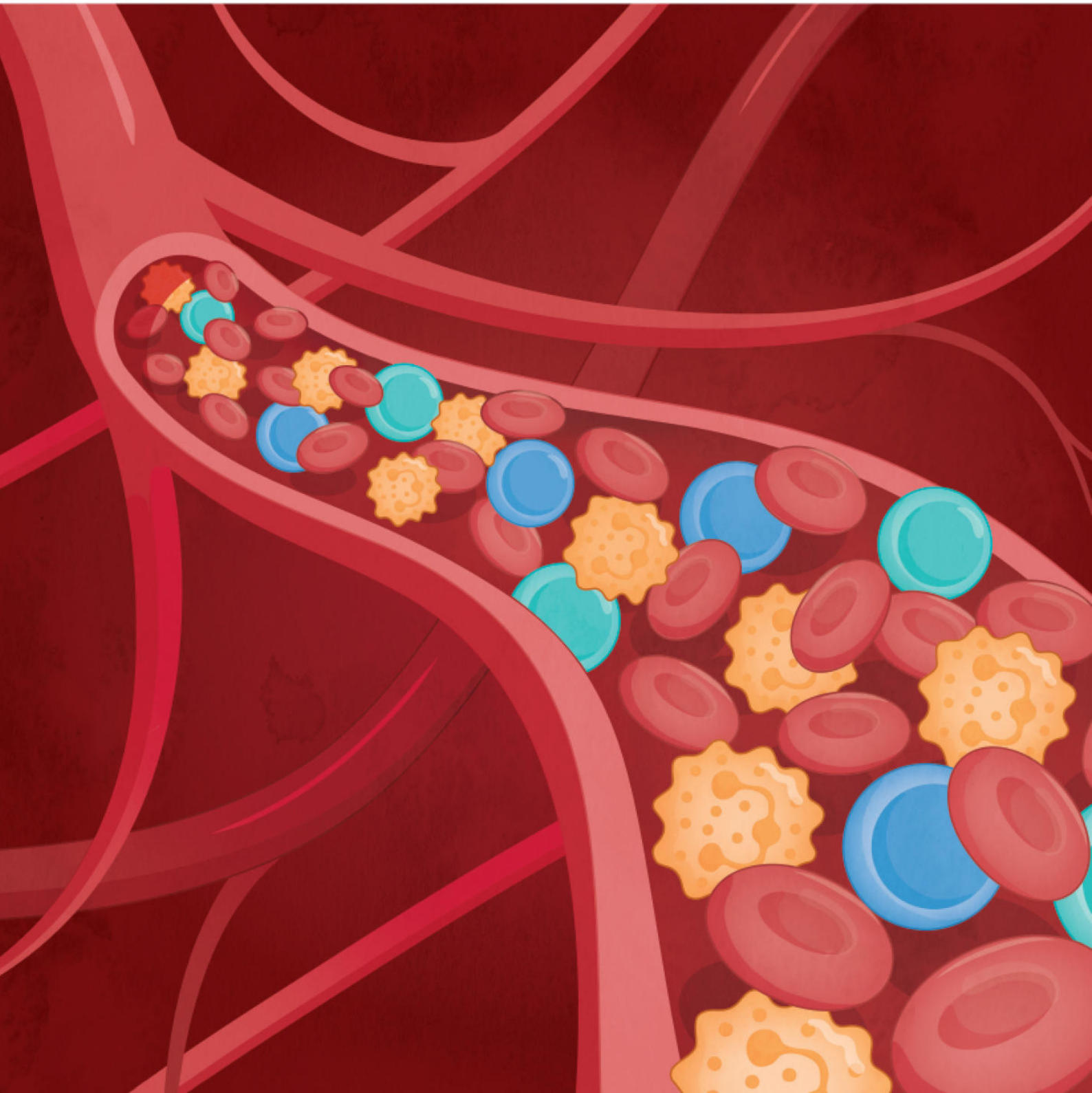

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Factors beyond urate levels for managing gout flares

Hang Korng Ea & Pascal Richette

Urate crystals alone are required but not sufficient to trigger gout flares; they can also be modulated by environmental, metabolic, genetic and epigenetic factors. Avoiding large variation in urate levels, maintaining prophylaxis until crystal clearance and initiating low-dose urate-lowering therapy are efficient strategies for disease management.

Gout flare is an extremely painful form of inflammatory arthritis that was first described by Sydenham in 1683 as an intense pain that seized and awakened him in the night and made him feel as though he had a dislocated bone. The inflammatory reaction associated with gout flares is triggered by monosodium urate (MSU) crystals; this was demonstrated in 1962 by James Faires and Daniel McCarthy who self-injected MSU crystals into their knees. Besides local pain and substantial effects on quality of life, gout flares are associated with a transient increased risk of major adverse cardiovascular events. Consequently, avoiding recurrent flares is an important part of gout management and can be achieved through the dissolution of MSU crystals by urate-lowering therapy (ULT) using a treat-to-target strategy and managing factors that promote flare. Although MSU crystals are required for the initiation of gout flare, there are other important factors that modulate flare initiation (Table 1); for example, genetic studies have identified 22 loci that are associated with gout but not with urate level, which directly implicates these candidate genes in gout inflammation. Notably, these genes are involved in NLRP3 inflammasome activity, IL-1 cytokine family signalling, cell osmolarity and cell metabolism[1]. MSU crystals form when chronic elevation of serum urate levels (SULs) reach above 70 mg l^{-1}, but these crystals can remain silent for long periods of time. Thus, ultrasonography assessment shows MSU crystal deposition (observed as a double contour pattern) in around one-third of asymptomatic individuals with hyperuricemia[2]. Moreover, flare scarcely develops around tophus (a clinically detectable deposition of MSU crystals), as observed by our own experience and other experts in the field.

At ULT initiation, considering factors that decrease risk of flare will improve patient observance and adherence, which are essential for curing gout. Decreasing the risk of flare when starting ULT is a crucial challenge as there is a paradoxical increased risk of flare in the period following ULT initiation; this paradoxical effect is usually associated with high-dose initiation of ULT. Informing patients of this increased risk of flare is essential and a 6-month flare prophylaxis is recommended by international societies when commencing ULT, which should be started at a low dose[3]; however, flare rebound is observed after cessation of the 6-month flare prophylaxis. Thus, whether prophylaxis must be maintained until complete dissolution of MSU crystals (which can be confirmed by ultrasonography) needs to be investigated. In fact, with the current recommended SUL target (below 60 or 50 mg l^{-1}), MSU crystal dissolution occurs slowly with a very small change in MSU crystal deposition after 1 year of ULT[4]. Consequently, 36% to 54% of patients still have flare after 1 year of ULT, despite 81% to 87% of individuals reaching the SUL target[5]. Moreover, MSU crystal deposition is still detectable in 21.1% of patients after 2 years of ULT with SUL at target. In theory, these patients are still at risk of flares. Thus, to accelerate MSU crystal dissolution and stop flare, a lower SUL target might be discussed with these patients.

Among mediators that contribute to gout flare, IL-1β is considered as the chief orchestrator. After MSU crystal detection, resident macrophages release IL-1β, which then amplifies the inflammatory response through recruitment of innate immune cells including neutrophils and monocytes. IL-1β production is a two-step process. The first step involves engagement of pathogen recognition receptors (such as Toll-like receptors), which leads to the activation of transcription factors (such as NF-κB and activator protein-1) and formation of pro-IL-1β. The second step activates the NLRP3 inflammasome platform, leading to the formation of active caspase 1, which promotes IL-1β maturation and secretion. MSU crystals activate both of these steps, especially the NLRP3 inflammasome, through several mechanisms, including cell membrane interactions, crystal phagocytosis, lysosome damage, mitochondrial dysfunction, excessive production of reactive oxygen species, increased oxidative stress, cell metabolism reprogramming, dysregulation of cell volume and peripheral circadian rhythm.

The risk of gout flare is 2.4 times higher at night than during the day, and flares are more frequent in winter and early spring than in summer[6]. Virtually all cellular processes and gene expression function with a circadian rhythm, including the endocrine system and the immune system. The production of corticosteroid, a stress hormone with anti-inflammatory properties, increases at the start of the day in diurnal animals, including humans, peaking at 8 a.m. and reaching its lowest levels between 8 p.m. and 4 a.m. SUL also displays a circadian variation, but the 24-h variation between the peak and nadir of SUL is less than 5 mg l^{-1}, and this small variation might not contribute to flare. MSU crystals decrease the gene expression and protein production of BMAL (brain and muscle ARNT-like 1), which is one of the central core regulators of the circadian clock. BMAL inhibits the expression of NF-κB and the NLRP3 inflammasome. BMAL expression is naturally low at night and high during the day; BMAL expression in monocytes and macrophages is even lower at night in the presence of MSU crystals, which results in a high risk of overactivation of NF-κB and the NLRP3 inflammasome and overproduction of IL-1β[6]. Finally, cold temperatures can also increase the risk of flare by promoting MSU crystal formation and NLRP3 inflammasome activation. The NLRP3 protein (previously known as cryopyrin) and its gain-of-function variants are associated with familial cold-induced autoinflammatory syndrome.

Besides circadian rhythm, ULT initiation (especially at a high dose) and MSU crystal deposition (which increases with disease duration),

Table 1 | Factors that modulate gout flare

Factors associated with gout flare	Mechanisms	Intervention
MSU crystals	Chronic elevation of serum urate level (hyperuricemia) Activation of macrophages and other immune cells	Lower target serum urate level to accelerate crystal dissolution
Circadian rhythm	MSU crystals inhibit BMAL expression, which is naturally low at night BMAL inhibits both NF-κB and NLRP3	Prophylaxis at night
Alcohol intake Purine intake	Considerable elevation of serum urate level Soluble urate possesses pro-inflammatory properties Urate induces trained immunity and epigenetic reprogramming of myeloid precursors Possible formation of new MSU crystals	Diet modification at the beginning of ULT, including lower intake of alcohol and purine-rich foods
Diuretics	Increased serum urate levels Possible modification of plasma osmolarity	Initiation of prophylaxis might alleviate symptoms
High-dose ULT initiation	Considerable decrease of serum urate levels Reduced intracellular antioxidant capacity Possible shedding of MSU crystal deposition	Initiate low-dose ULT (allopurinol 50 mg per day or febuxostat 20 mg per day) Initiation of antioxidant supplementation might also help to alleviate symptoms
History of flare	IL-1β release during flare can induce trained immunity and epigenetic changes in myeloid precursors	Initiate ULT at first flare
Prophylaxis withdrawal	Unknown	Maintain prophylaxis until complete dissolution of MSU crystals

MSU, monosodium urate; ULT, urate-lowering therapy.

several other factors and conditions are associated with gout flare: patients having a history of flare, high-calorie and lipid-enriched meals, high intake of alcohol and purine-rich foods, introduction of diuretics, hospitalization, trauma, vaccination, air pollutants and withdrawal of flare prophylaxis[7]. The mechanisms that cause these factors to promote flare remain unclear. Western-enriched caloric diets can lead to substantial elevation in soluble urate levels, which can then promote flare through priming and training of innate immune cells to a pro-inflammatory state[8]. In serum from patients with asymptomatic hyperuricemia, the concentration of inflammatory mediators is higher than in serum from healthy individuals (with normal levels of serum urate). Similarly, serum from mice on a Western diet has higher levels of inflammatory mediators than serum from mice on a standard chow diet[8]. Monocytes primed with soluble urate produce less IL-1Ra (a natural inhibitor of the IL-1 family of cytokines) and more IL-1β. Soluble urate can also change the epigenetic programming of monocytes and macrophages, inducing both histone methylation (histone 3 lysine 4 trimethylation) and acetylation (histone 3 lysine 27 acetylation). These epigenetic modifications alter the transcriptional program of monocytes and macrophages, which leads to a pro-inflammatory phenotype, and so these cells become more reactive to MSU crystals. Interestingly, the epigenetic reprogramming of myeloid precursors in the context of a Western diet relies on NLRP3 inflammasome activation and IL-1β production[8]. These data suggest that gout flare could perhaps, through IL-1β release from monocytes and macrophages, promote these epigenetic modifications. Finally, soluble urate possesses antioxidant properties and is a scavenger of reactive oxygen species and singlet oxygen. Urate reduces haemoglobin oxidation by peroxide, protects erythrocytes against lipid peroxidation and prevents erythrocyte lysis induced by peroxidation damage[9]. The antioxidant potential of soluble urate is similar to that of vitamin C. The considerable decrease of urate when initiating ULT, especially at high doses, could reduce intracellular antioxidant capacity, which increases oxidative stress and might subsequently contribute to gout flare through NLRP3 inflammasome activation.

In conclusion, initiation of low-dose ULT, maintaining prophylaxis until complete crystal dissolution, avoiding a Western diet, alcohol and purine-rich foods and lowering of the SUL target are all important to preventing gout flare prior to crystal clearance. Considering factors beyond urate levels that can prevent gout flares is essential to the management of this disease and for improving the quality of life of individuals with gout.

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Competing interests

The authors declare no competing interests.

Rheumatoid arthritis

Targeting anti-PAD4 autoantibodies in RA

Autoantibodies that target PAD4, an enzyme involved in citrullination, have been identified in individuals with rheumatoid arthritis (RA) and are associated with severe joint disease. Despite the discovery of these autoantibodies and their association with disease, their role in the pathogenesis of RA is unclear. Now, a study in *Arthritis Rheumatology* provides the first in vivo findings that directly implicate anti-PAD4 autoantibodies in the pathogenesis of RA.

To test the function of anti-PAD4 antibodies in vivo and in vitro, the researchers cloned five monoclonal anti-PAD4 antibodies that were derived from individuals with RA. They generated a chimeric antibody from the clone with the highest binding affinity and injected this into mice with collagen-induced arthritis (CIA). Mice injected with the anti-PAD4 antibody had exacerbated disease, more-severe synovial fibroblast hyperplasia and higher innate and adaptive immune cell infiltrates (including monocytes, neutrophils and T cells) in the joints than control animals.

PAD4 is expressed on the surface of neutrophils and monocytes, and analysis revealed that monocytes in the joint were preferentially targeted by anti-PAD4 antibodies in both naive mice and those with CIA, although binding was higher in mice with CIA. In the blood, anti-PAD4 antibodies also bound to monocytes and, to a lesser extent, neutrophils.

In an assessment of the binding of the five cloned anti-PAD4 antibodies to human peripheral blood mononuclear cells in vitro, four of five of the antibodies targeted monocytes over other immune cells (neutrophil binding was variable). Anti-PAD4 antibodies also enhanced the secretion of pro-inflammatory meditators from human monocytes. "These findings challenge the existing concept that neutrophils are the main target of these autoantibodies," notes Taejoon Won, first author of this study.

The researchers then sought to determine the mechanism by which anti-PAD4 antibody treatment induced mouse synovial fibroblast hyperplasia. They hypothesised that the increased T cell infiltrates in treated mice might indirectly activate synovial fibroblasts. Indeed, stimulating human fibroblast-like synoviocytes isolated from individuals with RA with T cell-derived cytokines (such as IL-17A) led to an activated and invasive fibroblast state.

"Our work supports the rationale for the development of antigen-specific therapy to specifically deplete PAD4 reactive B cells or autoantibodies, thereby precisely removing pathogenic humoral immune elements, whilst minimizing adverse effects associated with broader depletion," comments Erika Darrah, one of the corresponding authors of this study.

Holly Webster

Original article: Won, T. et al. Anti-peptidylarginine-4 autoantibodies derived from patients with rheumatoid arthritis exert pathogenic effects by activating monocytes and exacerbating inflammatory arthritis. *Arthritis Rheumatol.* https://doi.org/10.1002/art.43168 (2025)

Vasculitis

Upadacitinib effective for GCA in phase III trial

In the phase III SELECT-GCA trial, treatment with the JAK1 inhibitor upadacitinib at a dose of 15 mg (but not 7.5 mg) once a day in combination with a 26-week glucocorticoid taper had superior efficacy and reduced glucocorticoid use compared with placebo in combination with a 52-week glucocorticoid taper.

The double-blinded, randomized study, conducted at 100 sites across 24 countries, enrolled 428 adults aged 50 or over with active giant cell arteritis (GCA), 70% of whom had new-onset GCA and 30% with relapsing disease. All participants had received treatment with prednisone at a dose of ≥40 mg per day any time before enrolment and were receiving 20–60 mg prednisone per day at the start of the study.

Sustained remission at week 52 was observed in 46.4% of those in the 15 mg upadacitinib group, compared with 29.0% of those in the placebo group ($P = 0.002$). The remission rate in the 7.5 mg upadacitinib group (41.1%) was not significantly different from the placebo group.

The 15 mg dose of upadacitinib was also superior to placebo with respect to cumulative glucocorticoid exposure over 52 weeks, risk of disease flare, fatigue and quality of life. Safety profiles were similar across all three treatment groups, and no major cardiovascular events were reported in the upadacitinib groups.

Sarah Onuora

Original article: Blockmans, D. et al. A phase 3 trial of upadacitinib for giant-cell arteritis. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2413449 (2025)

Therapy

Methotrexate as first-line therapy for pulmonary sarcoidosis

First-line treatment for pulmonary sarcoidosis is generally prednisone, but the need for alternative, evidence-based treatments has long been recognized. The results of the PREDMETH trial now suggest that methotrexate, which is currently recommended as second-line treatment, could be an alternative to prednisone as first-line treatment for pulmonary sarcoidosis.

In this open-label, non-inferiority trial, which involved 138 participants from 17 hospitals in the Netherlands, the unadjusted mean change from baseline to week 24 in the percentage of the predicted forced vital capacity was 6.75% among those who initiated treatment with prednisone and 6.11% in those treated with methotrexate, with the between-group difference indicating that methotrexate was non-inferior to prednisone.

Improvement in the percentage of the predicted forced vital capacity was quicker with prednisolone than with methotrexate, but similar improvements were seen in both treatment groups over 24 weeks. The rate of adverse events was also similar in both groups, although the types of events that were most frequently reported differed with each treatment. The researchers suggest that these findings could help inform the choice of the most appropriate first-line treatment for an individual with pulmonary sarcoidosis.

Sarah Onuora

Original article: Kahlmann, V. et al. First-line treatment of pulmonary sarcoidosis with prednisone or methotrexate. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2501443 (2025)

Lyme arthritis

Insights into Lyme arthritis

Lyme disease is caused by *Borrelia burgdorferi* infection, which is transmitted via a tick vector. Lyme arthritis can be a postinfection, inflammatory complication of Lyme disease. Treatment with immunosuppressive agents is effective, which indicates that this disease is mediated by the immune system. Previous work has shown that *B. burgdorferi* produces peptidoglycan during growth, fragments of which can be detected in the synovial tissue of individuals with Lyme arthritis. How the *B. burgdorferi* peptidoglycan persists and drives chronic, postinfectious Lyme disease complications remains unclear. Two complimentary studies have now been published that provide insights into *B. burgdorferi* persistence and identify a potential treatment for Lyme disease.

McClune et al. used a mouse model that enabled real-time tracking of *B. burgdorferi* peptidoglycan and found that, unlike other peptidoglycans, it accumulates in the liver and persists for weeks, altering the immune profile of the liver. Analysis of synovial samples from individuals with Lyme arthritis showed that polymeric *B. burgdorferi* peptidoglycan, rather than fragments, persists in the synovium. Together, these findings indicate that *B. burgdorferi*-derived peptidoglycan might act as a persistent source of antigen that drives chronic inflammation in Lyme arthritis and other complications of Lyme disease.

Gabby et al. aimed to identify safter therapeutic agents for Lyme disease than those currently in use, which can have adverse effects, particularly in children. Using high-throughput screening, the authors identified the β-lactam, piperacillin, which specifically inhibited the growth of *B. burgdorferi*. Piperacillin was able to alter the unusual peptidoglycan synthesis in *B. burgdorferi*. Using a mouse model of infection, the authors treated mice with either piperacillin or doxycycline (a broad-spectrum antibiotic used to treat Lyme disease) and found that piperacillin was more effective at lower doses than doxycycline, and did not alter the microbiome. The *B. burgdorferi*-specific effects of this treatment indicate that piperacillin might be a safter alternative to current available therapies.

"Both studies offer hope to patients through new, innovative ways to potentially treat Lyme disease and Lyme disease-related afflictions, such as Lyme arthritis. Piperacillin is an excellent candidate for human trials in this context and might work very well for acute stages of disease, or even prophylactically. By masking or targeting the lingering peptidoglycans for destruction, we might be able to treat patients for whom typical treatments have failed and enable them to return to health, faster" comments Brandon Jutras, the corresponding author of the two studies.

Holly Webster

Original articles: McClune, M. E. et al. The peptidoglycan *of Borrelia burgdorferi* can persist in discrete tissues and cause systemic responses consistent with chronic illness. *Sci. Transl. Med.* **17**, eadr2955 (2025); Gabby, M. E. et al. A high-resolution screen identifies a preexisting beta-lactam that specifically treats Lyme disease in mice. *Sci. Transl. Med.* **17**, eadr9091 (2025)

Osteoarthritis

Methotrexate does not improve knee OA

Findings from clinical trials have suggested that methotrexate could be an effective treatment for hand osteoarthritis (OA), particularly when inflammation is present, but the efficacy of this approach for inflammatory knee OA is unclear. Now, the results of the MESKO trial indicate that low-dose methotrexate did not improve pain or effusion-synovitis in individuals with knee OA over 52 weeks.

In the trial, conducted at 11 sites in China, 215 people with knee OA and effusion-synovitis on MRI were randomly allocated to treatment with either methotrexate (up to 15 mg weekly) or placebo; 175 participants completed the 52-week follow-up. The mean change in knee pain (assessed on a 0–100-mm visual analogue scale (VAS)) from baseline to 52 weeks did not differ significantly between the methotrexate and placebo groups (−29.5 mm versus −29.8 mm). Moreover, there were no differences in mean change in MRI-measured knee effusion-synovitis maximal area (−0.2 cm^2 versus −0.3 cm^2) or in any of the pre-specified secondary outcomes between the groups over 52 weeks.

Methotrexate did significantly improve OA symptoms compared with placebo in the subgroup of participants with severe pain (VAS score ≥ 80 mm) at baseline; however, as this subgroup was small (16 participants) further research is needed to confirm this finding.

Sarah Onuora

Original article: Zhu, Z. et al. Low-dose methotrexate for the treatment of inflammatory knee osteoarthritis: a randomized clinical trial. *JAMA Intern. Med.* https://doi.org/10.1001/jamainternmed.2025.1359 (2025)

Biomarkers

https://doi.org/10.1038/s41584-025-01249-2

Decoding the adaptive immune repertoire for disease prediction

Laura F. Su

A simple blood test that can diagnose or predict one's risk for autoimmune diseases would revolutionize medicine and transform patient care. Published in *Science*, Zaslavsky et al. advance this vision with a powerful machine learning framework that leverages immune receptor sequences from T cells and B cells for disease classification.

REFERS TO Zaslavsky, M. E. et al. Disease diagnostics using machine learning of B cell and T cell receptor sequences. *Science* **387**, eadp2407 (2025).

The diagnosis of autoimmune diseases is a complex process that relies on a combination of patient history, physical examinations and laboratory tests, often requiring specialist expertise. However, many patients present with non-specific symptoms or atypical disease manifestations that do not fit neatly into standard diagnostic frameworks, leading to delays or misdiagnoses. Although autoantibodies are a key component of the diagnostic toolkit, they are rarely restricted to a single disease. Low titres of autoantibodies are also present in healthy individuals and only a subset of seropositive individuals will progress to clinical disease[1]. These challenges emphasize the need for more precise methods to diagnose autoimmune diseases and stratify at-risk individuals.

T cells and B cells are essential for immune defence but also have key roles in autoimmune diseases. They recognize antigens through specialized receptors — T cell receptors (TCRs) and B cell receptors (BCRs). TCRs consist of pairs of α- and β-chains, whereas BCRs are dimers made up of light and heavy chains. These receptors are generated through the recombination of variable (V), diversity (D) — for TCRβ and the BCR heavy chain — and joining (J) gene segments, with further diversity introduced by random nucleotide insertions and deletions at the junctional regions. Somatic hypermutation of BCRs in activated B cells further introduces point mutations into the variable region of the immunoglobulin gene to refine antibody affinity. Together, these mechanisms generate an immense diversity of receptors, enabling the adaptive immune system to recognize a vast array of antigens. Activated T cells and B cells proliferate. Unique receptor sequences from expanding antigen-stimulated cells leave behind a mosaic of molecular traces that preserve a history of past and present antigenic encounters.

Unlocking the information within adaptive immune receptors for biomarkers and therapeutics is a highly active area of research with substantial progress and ongoing challenges[2]. Efforts to mine sequences associated with immune activity have successfully identified signatures of infection[3,4], cancer[5] and autoimmune diseases[6,7]. However, disease classifiers have yet to capture the broader immune patterns and interactions and typically focus on specific conditions with either TCR or BCR data.

The study by Zaslavsky et al.[8] marks an important advancement in the field, leveraging TCR and BCR sequences to develop an integrated ensemble approach for disease classification. The authors developed a machine learning framework, termed 'machine learning for immunological diagnosis' (Mal-ID), that utilizes TCR β-chain (TRB) and immunoglobulin heavy chain (IgH) sequences from bulk RNA-sequencing datasets to identify disease-associated signatures (Fig. 1). Mal-ID integrates the output from three base models. Model 1 analyses V gene usage and quantifies mutation rates in the BCR. Model 2 clusters TCRs with similar complementarity-determining region 3 (CDR3) sequences, which are crucial for antigen recognition. Model 3 goes beyond known aspects of immune receptors by using a self-supervised language model trained on millions of diverse proteins to learn the underlying patterns of each receptor sequence. These representations are then combined with results from the first two models to predict a disease state in the final output. Mal-ID was applied to 16.2 million IgH and 23.5 million TRB sequences from peripheral blood samples of 220 healthy individuals, 63 patients with COVID-19, 37 recipients of influenza vaccines at day 7 post vaccination, 95 patients with HIV infection, 86 patients with systemic lupus erythematosus (SLE) and 92 patients with type 1 diabetes. Individuals were divided into three cross-validation folds. Each fold was separated into a training set and testing set. Importantly, repeat samples from the same donor were kept together to ensure that the test set did not include data from the same individual used for training, which could otherwise lead to artificially inflated performance. Mal-ID integrated the outputs from these models to predict the probability of an individual belonging to each disease category. An individual was then assigned to the disease predicted to have the highest probability.

Mal-ID trained on BCR and TCR data achieved an impressive area under the receiver operating characteristic curve (AUROC) of 0.99. As a pan-disease classifier, Mal-ID correctly assigned immune states 85.3% of the time. As expected, combining BCR and TCR data improved accuracy compared to using either alone. When Mal-ID was trained to be an SLE-specific classifier, it achieved an AUROC of 0.98, with 93% sensitivity and 90% specificity. This is a remarkable result, especially considering disease heterogeneity and the limited BCR and TCR sequence data from just 64 patients with SLE. Age, sex and race showed a modest effect on disease classifications. For validation, the authors trained Mal-ID on an external TCR dataset containing samples from patients with other autoimmune diseases and infections. Here, Mal-ID performed well overall, but misclassified 12% of healthy donors as having a disease. This issue is not new; past efforts in autoimmunity have faced similar challenges owing to low disease prevalence, leading to false positives that lower the accuracy of prediction[9,10]. Immune receptor-based methods will need to address these challenges. Additionally, the binary

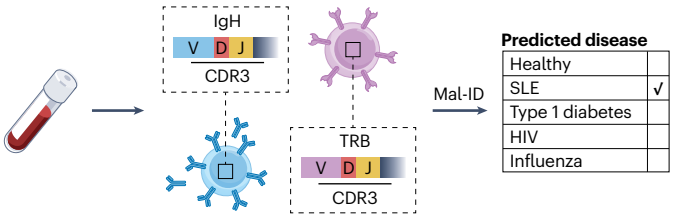

Fig. 1 | BCR- and TCR-based disease classification. Machine learning for immunological diagnosis (Mal-ID) integrates variable (V) gene usage, B cell receptor (BCR) mutation rates, complementarity-determining region 3 (CDR3) clustering and protein modelling of BCR heavy chain (IgH) and T cell receptor (TCR) β-chain (TRB) to classify patients with various diseases. It successfully identified systemic lupus erythematosus (SLE) with a strong area under the receiver operating characteristic curve (AUROC) score, highlighting the potential of immune receptor-based diagnostics for disease prediction. D, diversity; J, joining.

classification framework that assigns a single disease label is limiting, as individuals might have multiple diseases, have been vaccinated or have a simultaneous infection. The ability to resolve competing diagnostic possibilities and prioritize co-occurring conditions will be crucial for successful translation into clinical settings. Another important consideration is the time dimension. Mal-ID takes a single shot in time, whereas immune responses are dynamic. Future large-scale immune receptor sequencing and artificial intelligence-driven analysis that incorporate longitudinal data have the potential to move beyond disease classification to predict risk, guide treatment selection and assess prognosis. These advancements have the potential to revolutionize diagnosis and treatment treatment, but will need to address potential confounding factors and undergo rigorous validation.

Beyond biomarker discovery, Mal-ID and other future advancement in this space might help identify relevant antigen-specific responses in autoimmune diseases. Mal-ID showed promise by assigning higher COVID-19 probabilities to known SARS-CoV-2-binding BCRs. This ability to detect signals in the blood suggests that a subset of cells expressing disease-associated receptors actively circulate rather than being confined to target tissues. Whether these cells are bystanders or direct mediators of disease remains a crucial unanswered question. Future research linking immune repertoire signatures to their antigens and disease mechanisms might uncover new targets for immune-based therapies.

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Competing interests

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Review article

Check for updates

Immunometabolism in systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disorder characterized by chronic inflammation, tissue damage, accelerated cardiovascular disease and the synthesis of autoantibodies that target nucleic acids and nuclear protein complexes. Emerging evidence underscores the key role of immune metabolic dysregulation in SLE, revealing how metabolic reprogramming during immune cell activation influences disease development and progression. Alterations in key metabolic pathways such as glycolysis and oxidative phosphorylation profoundly affect the activation, differentiation and function of B and T cells, monocytes, neutrophils and other immune cells, driving inflammation and tissue injury. This Review synthesizes current findings on immune cell metabolism in animal models of lupus and in patients with SLE, highlighting the interplay of metabolic disturbances, mitochondrial dysfunction and disease pathogenesis. Furthermore, it explores the potential of targeting metabolic pathways as therapeutic strategies to mitigate organ damage and improve outcomes in SLE.

Sections

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Key points

- Metabolomic profiling in patients with systemic lupus erythematosus (SLE) has revealed substantial alterations in amino acid, lipid and energy metabolism, especially linked to oxidative stress and mitochondrial dysfunction, providing valuable indicators of disease activity and severity.
- Altered glucose metabolism influences the function and activation of T cells, B cells and macrophages, contributing to SLE pathogenesis.
- Mitochondrial dysfunction and excessive production of reactive oxygen species promote inflammation and immune dysregulation in SLE. Indicatively, mitochondrial dysfunction in neutrophils enhances the formation of neutrophil extracellular traps, contributing to tissue damage and autoimmunity in SLE.
- Long-term clinical trials with diverse patient populations are vital for evaluating therapies that target cellular metabolism. Combining metabolic modulators with immune-regulating therapies represents a promising strategy for improving SLE treatment outcomes.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune syndrome characterized by dysregulated immune responses, leading to widespread inflammation and multisystem organ damage. Patients with SLE face increased risks of morbidity and mortality, particularly from lupus nephritis, atherosclerotic cardiovascular disease and infections. SLE is marked by substantial clinical heterogeneity and an unpredictable course, with periods of remission and flares that can culminate in end-stage organ damage. SLE predominantly affects women, with a female-to-male ratio of 9:1, and disproportionally afflicts minorities[1,2]. Although an armamentarium of therapies is currently available to treat SLE, many of these drugs have substantial side effects owing to their strong immunosuppressive roles and, in the case of corticosteroids, deleterious cardiometabolic effects. Thus, improved therapies that have immunomodulatory roles without establishing persistent immunosuppression are needed.

The pathogenesis of SLE remains incompletely understood, and involves a complex interplay of genetic, epigenetic, environmental and metabolic factors that promote immune dysregulation and lower the threshold for pathogenic autoimmunity. Dysregulated innate and adaptive immune responses[3], including heightened type I interferon (IFN) signalling in immune and stromal cells, overactivation of myeloid cells, excessive production of modified autoantigens, at least in part through aberrant cell death, and defective clearance of dead cells, are key features of SLE pathogenesis[4]. Furthermore, profound abnormalities in lymphocyte phenotypes and functions seem to have fundamental roles in driving autoimmune processes in SLE.

Innate immune cells that are activated by microbial components or other danger signals promote tissue damage and cell death. These processes generate and modify danger-associated molecular patterns (DAMPs), autoantigens, or neoantigens (including nucleic acids, lipids, carbohydrates, and proteins)[5]. Increased oxidative stress and the production of reactive oxygen species contribute to antigen modifications[6]. In individuals with a genetic predisposition, inflammatory responses to autoantigens or neoantigens are amplified. Inefficiently cleared dead cells and debris release altered nuclear and mitochondrial DNA (mtDNA), as well as RNA and modified proteins, which all trigger pro-inflammatory responses in target cells. These responses activate Toll-like receptors (TLRs) and other nucleic acid sensors, further amplifying inflammation[7].

In addition to innate immune dysregulation, adaptive immune responses are involved in SLE pathogenesis. Autoreactive T cells that have evaded thymic elimination are likely to cross-react with microbial products or danger signals resembling autoantigens, potentially triggering autoimmune responses[8]. T helper (T_H) cell subsets have distinct roles in orchestrating immune responses, with T_H1, T_H2, T_H17 and follicular helper T (T_{FH}) cells contributing in different ways to immune regulation and autoimmunity. Failures in the development or function of regulatory T (T_{reg}) cells[9] and regulatory B (B_{reg}) cells[10] undermine the maintenance of immune tolerance and further exacerbate these processes[11]. B cells contribute to immune dysregulation and tissue damage through the production of autoantibodies[2,8]. Autoantibody production by B cells and plasma cells promotes the accumulation of immune complexes in tissues, including the skin and kidneys, where they activate the complement system. Immune complex deposition supports the recruitment of inflammatory cells that release enzymes and free radicals. This process perpetuates the dysregulation of various immune cells, including $CD4^+$ T cells, dendritic cells (DCs), monocytes, macrophages and neutrophils[5,12].

The metabolic state of the host impacts immune responses[13], which usually require the metabolic reprogramming of immune cells to cover the energy and biosynthetic demands of immune cell activation, differentiation and function. The concept of immunometabolism highlights how these metabolic demands of immune cells might vary depending on the immune context and cell type[14,15]. After activation, immune cells rapidly grow and differentiate into specialized effector cells, requiring substantial nutrient uptake[16,17] and the activation of various metabolic pathways (Box 1). In SLE, chronic inflammation and metabolic dysfunction coexist, creating a feedback loop that exacerbates immune and metabolic dysregulation[5]. Although existing SLE treatments modulate the immune system, targeting the immunometabolism might hold promise for therapies that restore immune cell homeostasis without causing extensive immunosuppression.

Given the latest advances in understanding the role of immunometabolism in immune dysregulation, as well as the potential therapeutic implications, we highlight the links between altered immunometabolism and SLE. This Review discusses in detail how SLE is associated with changes in metabolic pathways and mitochondrial function in innate immune cells, such as neutrophils, monocytes and macrophages, as well as in T cells and B cells. Moreover, it briefly explores the potential of metabolic biomarkers in SLE, and outlines the contribution of metabolic changes to SLE pathogenesis, with an emphasis on targeting immune metabolism for the potential treatment of SLE and SLE-associated complications.

Immunometabolism and metabolic dysregulation

Metabolic pathways

Cellular and microenvironmental signals regulate metabolic pathways in immune cells, including glycolysis, the pentose phosphate pathway (PPP), the tricarboxylic acid (TCA) cycle (also known as the Krebs cycle), oxidative phosphorylation and the lipid- and amino acid metabolic pathways, linking metabolic pathway activity to cellular needs[18] (Box 1). Immune cell activation and proliferation often involves a switch to glycolysis, even in oxygen-rich conditions, a phenomenon

known as the Warburg effect[19], as glycolysis covers the increased energy demands. In addition, changes in various pathways of lipid metabolism, including fatty-acid oxidation, lipid synthesis and lipid signalling, enable the formation of lipid rafts, which are required to maintain the biophysical properties of the plasma membrane in T cells and to support T cell receptor (TCR) clustering and subsequent signal transduction. Indeed, alterations in lipid raft composition have been associated with impaired T cell signalling, affecting the activation and expansion of T cells[20].

Oxygen levels, nutrient availability and inflammatory mediators further shape immune cell metabolism[15]. Hypoxic conditions tend to drive glycolysis via the activation of hypoxia-inducible factor 1-alpha (HIF-1α), a key regulator of metabolic adaptation under hypoxic and inflamed conditions that inhibits oxidative phosphorylation and alters the functional capabilities of innate immune cells during infections[21,22]. The serine/threonine protein kinase mammalian target of rapamycin (mTOR) also serves as a central regulator of immune metabolism, among other cellular processes. mTOR operates through two distinct complexes, mTORC1 and mTORC2, which both integrate diverse environmental signals, such as hormones, nutrients and energy levels, to modulate cellular responses and maintain anabolic processes[23]. By contrast, in catabolic processes, nutrient levels are sensed via the serine/threonine kinase AMP-activated protein kinase (AMPK). AMPK is activated by hypoxia and nutrient deprivation and promotes ATP production through several catabolic pathways while simultaneously inhibiting ATP consumption[24].

Immune cell-derived metabolites or cytokines further influence the metabolic states of neighbouring immune cells. For example, the TCA cycle intermediate succinate accumulates during inflammatory states and stabilizes HIF-1α, which leads to the induction of interleukin-1β (IL-1β)[25]. Conversely, the TCA cycle metabolite itaconate exhibits anti-inflammatory properties and decreases succinate levels through the inhibition of succinate dehydrogenase, thereby reducing the production of pro-inflammatory cytokines[26].

The gut microbiome interacts with host immune cells and metabolic pathways, modulating both innate and adaptive immune responses[27]. Short-chain fatty acids (SCFAs) produced by anaerobic bacteria modulate immune cell metabolism through multiple mechanisms, including metabolic assimilation, acetyl-CoA production, G protein-coupled receptor (GPCR) signalling and histone deacetylase (HDAC) inhibition, impacting immune cell function and differentiation[28]. The SCFA-mediated inhibition of HDAC in peripheral T cells promotes anti-inflammatory effects by expanding and supporting T_{reg} cell differentiation in various conditions, including cancer[29,30]. Gut bacteria also metabolize tryptophan into indole derivatives, which can influence the activity of T cells, DCs and macrophages via the activation of aryl hydrocarbon receptor (AHR)-mediated transcription[31]. Conversely, immune cells affect the composition and diversity of the gut microbiota, for example, via the activity of T_{reg} cells and IgA[32].

Changes in cellular metabolism induce epigenetic modifications, which in turn can influence cellular behaviour and disease progression[33]. As an example, the cholesterol precursor mevalonate inhibits lysine-specific demethylase 5 (KDM5), thereby promoting epigenetic changes[34]. Alpha-ketoglutarate (α-KG), a metabolite derived from glutamine, regulates gene expression as it is a cofactor for histone demethylases[35]. Thus, metabolic changes often lead to substantial alterations in chromatin structure and gene expression, thereby contributing to changes in immunological responses. Conversely, epigenetic modifications, including DNA methylation, histone modifications and non-coding RNA regulation, influence gene expression patterns that control key metabolic pathways[36].

Box 1 | Key metabolic pathways in immune cells

- **Glycolysis** occurs in the cytoplasm and converts glucose into pyruvate, while also generating adenosine triphosphate, the key fuel of cellular energy, and reducing nicotinamide adenine dinucleotide (NAD^+) to NADH[18].
- The **pentose phosphate pathway** operates alongside glycolysis and focuses on producing nicotinamide adenine dinucleotide phosphate and ribose-5-phosphate. The pentose phosphate pathway has two phases: the oxidative phase, in which glucose-6-phosphate is oxidized by enzymes such as glucose-6-phosphate dehydrogenase to generate nicotinamide adenine dinucleotide phosphate for biosynthesis and redox balance, and the non-oxidative phase, which provides precursors for nucleotide synthesis[209].
- The **tricarboxylic acid cycle** (also known as the Krebs cycle) occurs in the mitochondria and is central to energy production. In the tricarboxylic acid cycle, acetyl-CoA derived from the catabolism of carbohydrates, fats and proteins, is oxidized into carbon dioxide with the generation of high-energy electron carriers, NADH and FADH2, which all fuel the electron transport chain for adenosine triphosphate synthesis via oxidative phosphorylation[18].
- **Oxidative phosphorylation** in the mitochondria uses the electron transport chain to produce ATP. Nutrient-derived electrons pass through a series of complexes (I–IV) in the inner mitochondrial membrane, releasing energy to pump protons into the intermembrane space. This creates a proton gradient, driving ATP synthesis as protons flow back into the matrix through ATP synthase[18].
- **Glutaminolysis** is a metabolic pathway that catabolizes glutamine to generate ATP, lactate and α-ketoglutarate (α-KG)[18].
- **Lipid metabolism** encompasses anabolic and catabolic processes. Anabolic pathways synthesize fatty acids and triglycerides for energy storage and the maintenance of cellular membranes. Catabolic processes break down triglycerides into free fatty acids and glycerol. Enzymes such as hormone-sensitive lipase (HSL) hydrolyse triglycerides, with free fatty acids undergoing β-oxidation in the mitochondria to produce ATP[209].
- **Amino acid metabolism** involves synthesizing, degrading, and interconverting amino acids, which support protein synthesis, energy production and metabolic regulation[209].

Mitochondrial metabolic dysfunction

Mitochondrial dysfunction occurs when the mitochondria fail to function properly, leading to inadequate energy production, enhanced production of reactive oxygen species and the formation of superoxide radicals. Reactive oxygen species synthesis and enhanced oxidative stress can damage mitochondrial components, including lipids, proteins and mtDNA[5].

Oxidative stress contributes to inflammatory processes in many conditions, including metabolic syndrome, in which mitochondrial integrity is often compromised, leading to increased reactive oxygen

species production, decreased mitochondrial membrane potential and impaired energy metabolism[37]. Mitochondrial dysfunction can disrupt calcium homeostasis and results in excessive calcium accumulation within mitochondria. Calcium accumulation in turn triggers oxidative stress, mitochondrial membrane permeabilization and, ultimately, cell death[38]. In addition, abnormal mitophagy, a process through which damaged mitochondria are removed, has been shown to exacerbate metabolic stress and contribute to tissue injury[39]. SLE platelets release mDNA following FcγRIIA stimulation by immune complexes, with prointerferogenic consequences[40]. Overall, the dysregulation of metabolic pathways in immune cells via cell-extrinsic signals, such as nutrient and oxygen availability or the composition of the gut microbiota, and cell-intrinsic processes, such as the dysregulation of mitophagy and mitochondrial function, is likely to occur under the conditions of chronic autoimmune and autoinflammatory diseases, such as SLE. In the following sections, we discuss how this metabolic dysregulation has been associated with inflammation in SLE and highlight potential diagnostic and therapeutic targets in these pathways.

Identification of metabolic biomarkers in systemic lupus erythematosus

Given the complexity and clinical heterogeneity of SLE, the identification of biomarkers to assist in the diagnosis, predict clinical flares and monitor treatment responses remains an important goal. Various approaches that detect metabolic changes at both a cellular and a systemic level[18], through the quantification of metabolites in cells, tissues, serum, plasma or urine, might help to identify SLE biomarkers (Box 2).

Metabolic profiling in patients with SLE has revealed substantial metabolic alterations. For instance, elevated levels of urea, cystine (which is the oxidized form of cysteine), threonine and glucose have been reported in the serum of patients with SLE when compared with healthy donors. Conversely, the levels of lactic acid, cysteine, citric acid and tryptophan were found to be decreased in patients with SLE, supporting the hypothesis that the levels of oxidative stress are elevated in these patients[41,42]. Reduced lactate levels in patients with SLE potentially indicate a transition from aerobic to anaerobic metabolism, potentially owing to mitochondrial dysfunction or altered glycolytic regulation, as both of these processes have been linked to oxidative stress. Decreased citrate levels in these patients possibly point towards impaired mitochondrial function or a shift in metabolic processes that disrupt normal mitochondrial energy production, both of which might reflect oxidative stress. Alternatively, altered citrate levels might reflect altered metabolic demand in cells facing oxidative damage in SLE.

Analysis of immune cell transcriptional signatures in individuals with subclinical antinuclear autoantibody seropositivity that did or did not progress to SLE linked the downregulation of gene expression

Box 2 | Summary of studies reporting metabolic biomarkers in patients with systemic lupus erythematosus

Metabolomics

- Increased levels of oxidative stress activity, increased activity in the urea cycle (decreased arginine and ornithine, increased levels of urea), increased levels of cystine (while cysteine depleted) and decreased levels of tryptophan metabolites in the serum of patients with systemic lupus erythematosus (SLE)[41].
- Decreased levels of HDL, HDL-bound apolipoprotein A1 and increased levels of glycoprotein acetyls (which reflects the measurement of glycosylation of major plasma proteins and is used as a reflector of chronic and accumulative inflammation) and glycolysis metabolites (citrate/creatinine/glycerol/lactate/pyruvate) in the serum of patients with SLE[48].
- Increased levels of cystine (while cysteine depleted), pentose phosphate pathway metabolites, methionine sulfoxide, kynurenine, cytosine and deoxycytidine triphosphate in peripheral blood lymphocytes of patients with SLE[46].
- Increased oxidative phosphorylation in plasmablasts and decreased histidine levels in the plasma of patients with SLE[52].

Gene expression analyses using microarrays

- Increased oxidative stress and increased expression of pentose phosphate pathway-associated enzymes in micro-dissected renal biopsies from patients with SLE[44].
- Increased gene expression of the oxidative phosphorylation-associated genes cytochrome C oxidase COX6A1, succinate dehydrogenase complex, subunit D and succinate-CoA ligase GDP-forming subunit alpha in $CD4^+$ T cells from patients with SLE[50].

Gene expression analyses using RNA sequencing

- Analysis of cells from patients with discoid lupus and lupus nephritis showed decreases in genes controlling glucose and lipid metabolism in lupus-affected skin and kidney, respectively[45].
- Multiomics analysis revealed downregulation of the oxidative phosphorylation-regulating gene *PRDX6* in SLE B cells. *PRDX6*-deficient B cells showed upregulated mitochondrial respiration, as well as antibody production[51].
- mRNA analysis and genotyping in blood from healthy individuals and patients with SLE found a total of 365 differentially expressed genes, which were enriched for genes involved in oxidative phosphorylation[49].
- Decreased gene expression of mitochondrial oxidative phosphorylation complex I components in peripheral blood mononuclear cells from patients with anti-nuclear antibody positivity who progress to classifiable SLE, suggesting mitochondrial dysfunction in these cells[43].
- Increased expression of genes of the metallothionein gene family (MT1E, MT1F and MT1HL1), suggesting an increase in oxidative stress, was identified by a multicohort analysis of transcriptomic profiles from 40 independent studies on peripheral blood mononuclear cells or whole blood from patients with SLE. During oxidative stress, metallothioneins are upregulated to protect the cells, and metallothionein upregulation in SLE might be a protective response[47].
- Gene pathways indicating elevated oxidative stress, altered metabolism and mitochondrial dysfunction were found to be upregulated in whole-blood analyses of patients of Asian ancestry with SLE compared with healthy individuals and patients of European ancestry[54].

of mitochondrial oxidative phosphorylation complex I components to disease progression, supporting the concept that mitochondrial dysfunction is an early event during the development of autoimmune responses and organ damage in SLE[43]. Transcriptomic alterations reflecting upregulation of the oxidative phosphorylation pathway and PPP have been correlated with kidney injury in patients with lupus nephritis[44,45].

Metabolome profiling of lymphocytes from patients with SLE found elevated levels of cystine, kynurenine, cytosine and dCTP, overall suggesting enhanced oxidative stress, chronic immune activation, altered nucleotide metabolism and DNA damage responses[46]. Moreover, some patients with SLE have displayed elevated levels of metallothioneins, cysteine-rich proteins involved in metal detoxification, and metallothionein upregulation has been proposed as a protective response against chronic inflammation-induced oxidative stress[47]. A broader metabolomic analysis identified 25 metabolites that are significantly altered in patients with SLE and cardiometabolic dysfunction, including decreased levels of atheroprotective high-density lipoprotein (HDL) subsets and HDL-bound apolipoprotein A1, as well as increased levels of glycoprotein acetyls (GlycA)[48].

Gene expression related to proteins involved in oxidative phosphorylation has been found to be increased in T cells and B cells from patients with active versus inactive SLE. In the case of T cells, this enrichment correlated with increases in mitochondrial mass, mitochondrial membrane potential and oxidative stress[49–51]. A separate analysis suggested decreased histidine levels as a potential biomarker for organ damage, independent of the type I IFN signature[52]. The decreased levels of histidine in SLE might reflect altered amino acid metabolism, potentially driven by oxidative stress, inflammation and immune dysregulation.

Metabolic changes observed in patients with SLE, such as disruptions in glycolysis and the TCA cycle, have also been reported in animal models of lupus across different ages. This finding suggests that metabolic disturbances have a crucial role in SLE pathophysiology[53].

Comparison of the genetic and molecular mechanisms that underlie severe manifestations of SLE in individuals of Asian ancestry versus patients of European ancestry showed altered glycolysis and fatty-acid biosynthesis, upregulation of pathways related to oxidative stress and mitochondrial dysfunction in the former versus increased IFN responses linked to cytosolic nucleic acid sensing in the latter[54]. The relevance of these findings to disease phenotype and severity remains to be determined.

Overall, all these studies reveal substantial disruptions in metabolic pathways, including oxidative stress, mitochondrial function and amino acid metabolism, highlighting the putative importance of metabolic profiling as a tool for biomarker identification for the clinical diagnosis and management of SLE. In the next sections, we will explore immunometabolic dysregulation in specific immune cell subsets in SLE and how this can impact disease pathogenesis.

Metabolic changes in neutrophils in systemic lupus erythematosus

Neutrophils are the first cells to migrate to sites of inflammation and infection, where they modify their metabolism to support an inflammatory response[55]. Activated neutrophils often display a substantial rise in glycolysis[56,57] and, eventually, initiate a cell death programme that is regulated by the mitochondria[58]. In addition to microbes, neutrophils respond to endogenous signals such as DAMPs, cytokines and immune complexes, which trigger their activation and, in the context of SLE, exacerbate tissue inflammation and organ damage[59]. Furthermore, dysregulation in various neutrophil function contributes to vascular damage[60,61].

Compared with neutrophils from healthy individuals, neutrophils from patients with SLE exhibit hyperreactivity, accelerated apoptosis coupled with decreased clearance mechanisms of dead neutrophils, and enhanced production of mitochondrial reactive oxygen species and proteolytic enzymes[47,59] (Fig. 1a). Impaired mitophagy has also been reported in SLE neutrophils, with retention of oxidized nucleotides in the mitochondria[62]. In addition, patients with SLE have enriched numbers of circulating low-density granulocytes (LDGs), a pro-inflammatory subset of neutrophils with dysregulated formation of neutrophil extracellular traps (NETs)[60,63,64] (Fig. 1b), NET formation in SLE has been associated with the release of modified autoantigens and the induction of type I IFNs[65].

In addition to displaying increased spontaneous NET formation, LDGs synthesize higher levels of mitochondrial reactive oxygen species and display higher amounts of oxidized mtDNA than normal-density granulocytes from patients with SLE and healthy controls[66,67]. Proteomic analyses have revealed that LDGs, as compared to normal-density granulocytes, are enriched in enzymes of the oxidative phosphorylation pathway, and this is likely to facilitate NET formation[68]. Although the molecular pathways leading to NET formation are not fully understood, they have been shown to involve histone citrullination[69] and reactive oxygen species production[70]. Elevated glycolytic activity in neutrophils correlates with increased reactive oxygen species production, creating a vicious cycle enhancing glycolysis, reactive oxygen species generation, and NET release that further promotes inflammation[71,72] (Fig. 1a). Ribonucleoprotein (RNP)-immune complexes and other immune complexes that are typically seen in patients with SLE contribute to inflammation by further driving neutrophils to produce enhanced levels of mitochondrial reactive oxygen species. These reactive oxygen species have been associated with increased oxidation of mtDNA and genomic DNA that are released in NETs[60,73,74]. Oxidized DNA triggers pro-inflammatory responses, including type I IFN production via the cGAS–STING pathway[73,75] and endosomal TLRs[74]. Furthermore, oxidized mtDNA has been implicated in inflammasome activation and in cell death via gasdermin D oligomerization[76] (Fig. 1a). DNA oxidation in the presence of mitochondrial reactive oxygen species confers resistance to DNA digestion by nucleases and oxidation of other autoantigens also prolongs their half-life, thereby perpetuating downstream inflammatory responses[77]. Indeed, neutrophils have been found to accumulate oxidized mtDNA in SLE, and this reinforces interferogenic responses and production of autoantibodies that are specific against mtDNA[78]. This is particularly the case for LDGs[73].

In addition, under conditions of enhanced oxidative stress such as SLE, the voltage-dependent anion channel in the mitochondrial outer membrane oligomerizes and interacts via its positively charged N-terminal domain with mtDNA, promoting mtDNA release to the cytoplasm (Fig. 1a). As mentioned above, cytoplasmic mtDNA activates cGAS–STING and a downstream pro-inflammatory gene expression programme[79].

The NADPH oxidase 2 (NOX2) complex is the catalytic subunit of NADPH oxidase, a protein complex that produces superoxide and has a crucial role in innate and adaptive immune responses[80].

Mutations in the genes encoding subunits of this complex, particularly in *NCF1* and *NCF2*, have been associated with altered neutrophil function and increased susceptibility to SLE in humans[81]. For example, *NCF2* displays allelic heterogeneity and certain *NCF2* variants have been associated with increased susceptibility to SLE in various ethnic populations[82], with the potential contribution of B cell activation and the production of autoantibodies[83]. In addition, mice with mutations in *NCF1* exhibit spontaneous production of lupus autoantibodies,

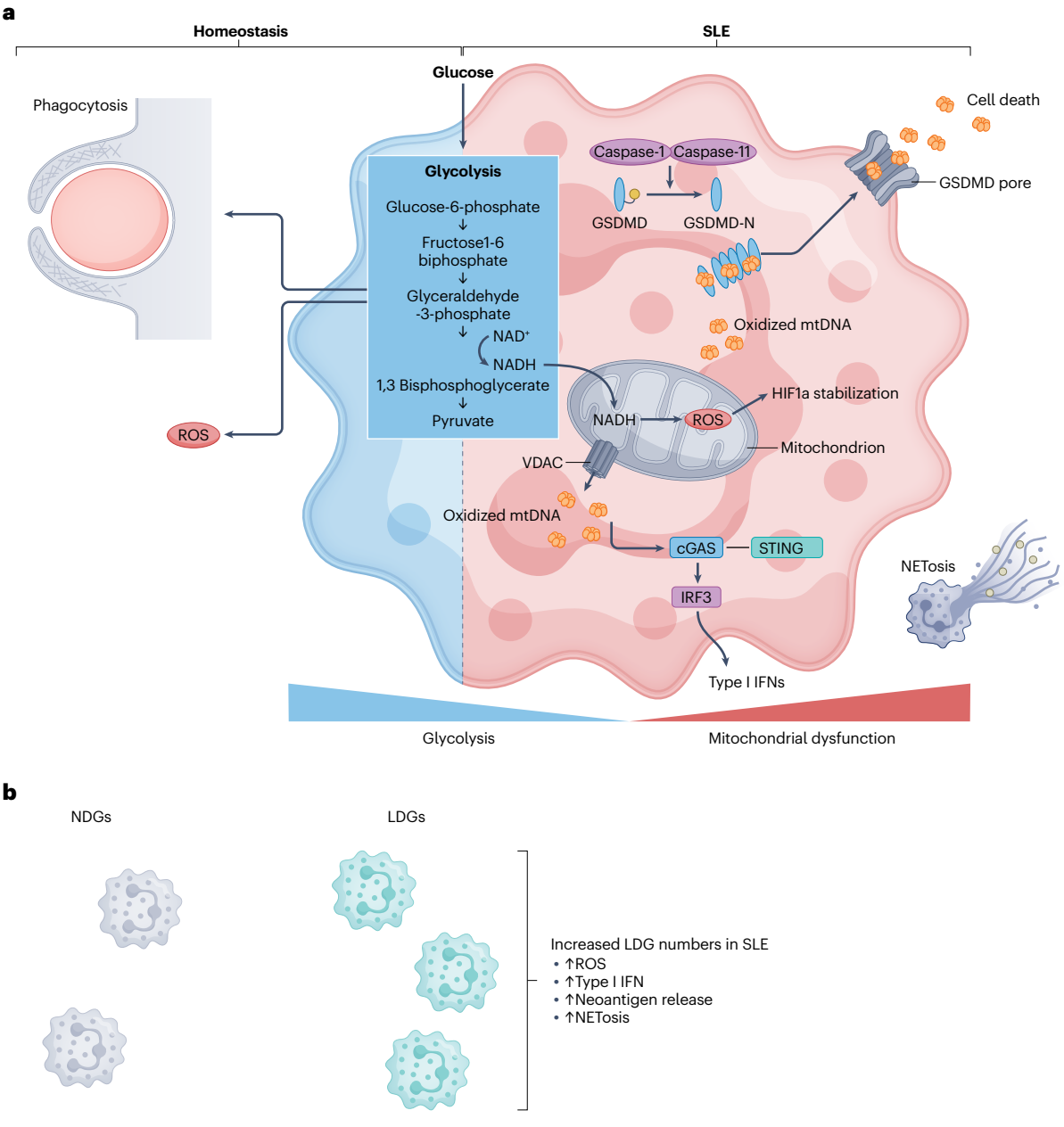

Fig. 1 | Oxidative stress and mitochondrial dysfunction in neutrophils in systemic lupus erythematosus. a, Under homeostatic conditions, neutrophils depend on glycolysis to mediate effector functions such as phagocytosis and reactive oxygen species (ROS) production, whereas cell death is mediated by the mitochondria. A glycolytic state in neutrophils leads to increased NADH internalization by the mitochondria and the subsequent generation of mitochondrial reactive oxygen species. Reactive oxygen species in turn blocks the degradation of hypoxia inducible factor α (HIF-1α) by prolyl-hydroxylases (not shown), increasing HIF-1α stability. Reactive oxygen species production also mediates the release of neutrophil extracellular traps (NETs) and oxidation of mitochondrial DNA (mtDNA). Oxidized mtDNA accumulates in systemic lupus erythematosus (SLE) neutrophils, and induces interferogenic responses after being released to the cytoplasm through the oligomerization of the voltage-dependent anion channel (VDAC) in the mitochondrial outer membrane. The cytoplasmic oxidized mtDNA triggers pro-inflammatory responses, including type I IFN production via the cGAS–STING pathway and endosomal TLRs (not shown). Oxidized mtDNA has also been implicated in cell death via gasdermin D (GSDMD) oligomerization and in inflammasome activation (not shown). **b**, In patients with SLE, two populations of neutrophils have been identified: normal-density granulocytes (NDG) and low-density granulocytes (LDG); LDGs exhibit an increase in NET formation (NETosis) oxidative phosphorylation and oxidative stress.

whereas haploinsufficiency of *NCF2* seems to accelerate lupus in mice, highlighting the direct link between impaired NOX2 function and lupus pathogenesis[84–86].

Targeting metabolic dysregulation in SLE neutrophils offers a potentially promising therapeutic approach for managing SLE. Intervening in the pathways that drive increased glycolysis, mitochondrial dysfunction and aberrant reactive oxygen species production might help to mitigate the excessive inflammatory response and NET formation that contribute to tissue damage. This is explored in more detail later in the last section of this Review.

Metabolic changes in monocytes and macrophages in systemic lupus erythematosus

The balance between pro-inflammatory and anti-inflammatory states is influenced, in part, by the metabolic pathways that govern macrophage responses during inflammation and tissue injury[87]. After activation, macrophages shift from oxidative phosphorylation to glycolysis, and this supports their proliferative capacities and enhances their effector functions in inflammatory responses[88,89].

In SLE, monocytes and macrophages are recruited to sites of inflammation, in part by cytokines, autoantibodies and immune complexes that activate macrophages through Fc receptor engagement, leading to enhanced inflammatory cytokine synthesis[90]. The continued activation of macrophages further promotes immune cell recruitment, thereby perpetuating tissue inflammation in various organs, including the kidneys, and promoting tissue remodelling, glomerular injury and fibrosis[91,92]. Overall, macrophage dysfunction in SLE has been linked to the dysregulation of apoptotic cell clearance[93], TLR activation[94] and type I IFN signalling[95] (Fig. 2).

Defective apoptotic cell clearance by macrophages

Macrophages have a crucial role in clearing apoptotic cells, as exemplified by splenic marginal zone macrophages under homeostatic conditions, and this function contributes to immune tolerance[93,96]. Apoptotic cells drive macrophages into a stress response that is mediated mainly by the amino acid sensor general control nonderepressible 2 (GCN2) (Fig. 2). GCN2 enhances the production of the anti-inflammatory cytokines IL-10 and TGF-β. As a result, *GCN2* deletion in myeloid cells of lupus-prone mice increases immune activation and humoral autoimmunity, worsens renal pathology and is associated with higher mortality[97].

Dysregulated Toll-like receptor activation in systemic lupus erythematosus macrophages

The endolysosomal solute carrier family 15 member 4 (SLC15A4; also known as PHT1) regulates macrophage metabolism by maintaining respiratory homeostasis and modulating glycolysis and glutaminolysis[98], and also has a role in the colocalization of nucleic acid-sensing TLRs and their ligands into endolysosomes[99]. The conversion of pyruvate into the TCA cycle has been shown to be impaired in macrophages from SLC15A4-deficient mice. As a compensatory response, these macrophages increasingly rely on glutaminolysis for energy production[98]. Interestingly, genome-wide association studies have implicated polymorphisms in *SLC15A4* in the pathogenesis of SLE, and has associated some *SLC15A4* variants with increased susceptibility to this condition[100–102]. In vitro studies have shown that SLC15A4 increases metabolic flexibility, predisposing macrophages towards a M1-like metabolic profile[98]. Furthermore, studies utilizing mouse models of lupus with genetic deficiency of SLC15A4 have reported improvement in disease severity, at least in part, through impairments in TLR activation[103].

Another key metabolic regulator implicated in SLE is pyruvate kinase M2 (PKM2), a glycolytic enzyme that is upregulated in macrophages, DCs, T cells and B cells from patients with SLE, in association with increased immune activation[94,104] (Fig. 2). PKM2 activity drives pro-inflammatory responses following TLR activation, as it regulates the activation of protein tyrosine kinase 2-beta, a protein that is involved in cell adhesion, motility and gene expression[94]. Pharmacological inhibition of PMK2 has been reported to decrease SLE progression in two mouse models of lupus, indicating a role for PKM2 in the inflammatory response associated with SLE[94].

The transcription factor TonEBP (also known as nuclear factor of activated T cells 5 (NFAT5)) has also been reported to contribute to SLE pathophysiology[105] (Fig. 2). Mechanistically, TonEBP, controls the expression of genes that respond to osmotic stress and has been proposed to contribute to lupus nephritis by promoting macrophage activation through TLR signalling and NFκB and mTOR pathway regulation. Indeed, TonEBP-deficient macrophages display reduced activation and enhanced efferocytosis, whereas TonEBP deficiency has also been linked with decreased differentiation of T_h1 cells and T_h17 cells[105].

Epigenetics and macrophage metabolism in systemic lupus erythematosus

Epigenetic changes influence macrophage metabolism and vice versa. IFNα primes monocytes and induces metabolic programming, enhancing both glycolysis and oxidative phosphorylation, and increasing the activity of the TCA cycle component isocitrate dehydrogenase, which produces α-KG[35]. An increase in glycolysis covers immediate energy demands and an increase in oxidative phosphorylation sustains energy production, enabling the cells to respond energetically to inflammation and immune challenges. As mentioned above, α-KG regulates KDM6 histone demethylases, which are crucial for the epigenetic modulation of IFN-sensitive gene (ISG) promoters, sustaining inflammatory responses. Indeed, inhibition of histone demethylases such as KDM6A and KDM6B has been reported to reduce autoimmunity, highlighting the intersection of metabolism, epigenetics and inflammation in SLE[35].

The IFN response-associated transcription factor IRF5 regulates the expression of oxidative phosphorylation-associated genes in monocytes and plasmacytoid dendritic cells (pDCs). IRF5 deficiency reduces mitochondrial activity, suppressing inflammatory pathways[106]. Additionally, deficiency in ubiquitin-specific protease 18 (USP18), a crucial regulator of IFN signalling and the downstream JAK/STAT pathway, enhances M1 macrophage polarization, glycolysis and reactive oxygen species production, promoting mitochondrial dysfunction and mtDNA release, further driving inflammation[107]. Transfection of mtDNA in macrophage cell lines activates glycolysis and lactate production, which sustains cGAS activity through lactylation, preventing its degradation and amplifying IFN-I responses[95].

Mitochondrial fatty-acid oxidation has emerged as a regulator on type I-IFN responses in monocytes that acts via epigenetic modifications. The observation that fatty-acid oxidation might have crucial epigenetic roles in myeloid cells in controlling inflammation further emphasizes nutrient-linked immunomodulation[108]. Also, erythroid mitochondrial retention, which is associated with impairments in the ubiquitin-proteasome system, is detected in a subset of patients with paediatric SLE and is associated with activation of the type I IFN pathway[109].

In summary, metabolic dysfunction in monocytes and macrophages is a well-described phenomenon in SLE. These metabolic changes drive

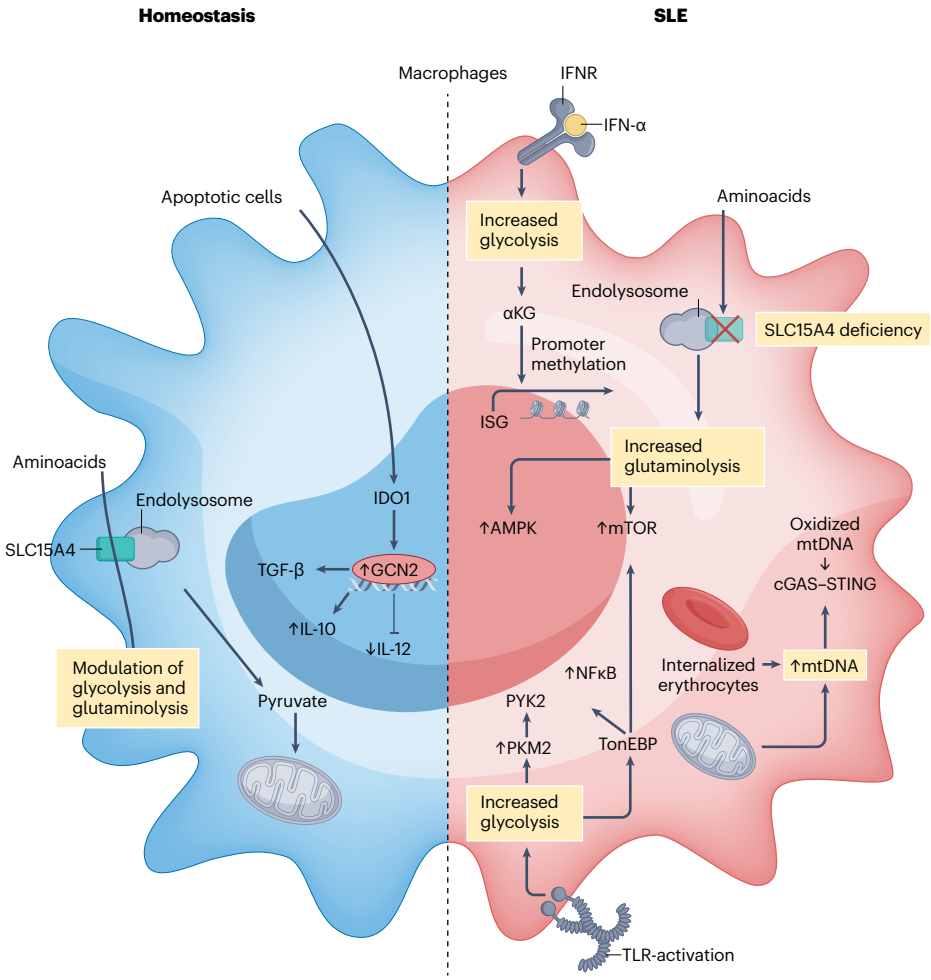

Fig. 2 | Metabolic alterations in monocytes and macrophages in systemic lupus erythematosus. Apoptotic cells induce a tolerogenic response in macrophages. This response is mediated by the induction of the aryl hydrocarbon receptor ligand IDO1 and the production of interleukin 10 (IL-10) and transforming growth factor β (TGFβ) downstream of the transcription factor GCN2. Deficiency in GCN2 has been associated with increased inflammation in systemic lupus erythematosus (SLE). Under homeostatic conditions, the amino acid transporter solute carrier family 15 member 4 (SLC15A4) regulates macrophage metabolism by maintaining respiratory homeostasis and modulating glycolysis and glutaminolysis. SLC15A4 deficiency increases glutaminolysis and promotes M1 macrophage polarization. SLC15A4 mediates activation of TLR pathways, particularly through AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR). Pyruvate kinase M2 (PKM2), a glycolytic enzyme that is upregulated in macrophages from patients with SLE, drives pro-inflammatory responses following TLR engagement, as it regulates the activation of protein tyrosine kinase 2-beta (PYK2), a protein that is involved in cell adhesion, motility and gene expression. SLE monocytes and macrophages have also shown an increase in the levels of PKM2 and TonEBP activation, both leading to TLR activation in an NFκB- and mTOR-dependent regulation, as well as increasing efferocytosis. Interferon α (IFNα) increases glycolysis and enhances production of alpha-ketoglutarate (α-KG), which in turn increases histone methylation at ISG promoters. Monocytes from patients with SLE were found to contain high levels of oxidized mitochondrial DNA (mtDNA), which in turn activates the cGAS–STING pathway. Erythrocytes from patients with SLE retain their mitochondria and mtDNA. These can be internalized by macrophages or other target cells during the clearance of erythrocytes and produce an inflammatory response.

immune activation and contribute to chronic inflammation and organ damage. Targeting these metabolic pathways might offer new therapeutic strategies for managing SLE and correcting immune imbalances.

Metabolic changes in other innate immune cells in systemic lupus erythematosus

Plasmacytoid dendritic cells

pDCs are robust producers of type I IFNs[110]. When pDCs are activated, they undergo metabolic reprogramming that enhances mitochondrial respiration and production of ATP, which is required for the synthesis of IFNs[111]. The activation of TLR9 on pDCs triggers signalling pathways that promote fatty-acid oxidation and oxidative phosphorylation[112]. At the mitochondrial level, NCF1-dependent reactive oxygen species production is important in the regulation of pDC development and function. Indeed, the *NCF1* variant p.R90H exacerbates autoimmunity, at least in part, by facilitating the activation of pDCs[113].

Conventional myeloid dendritic cells

Conventional myeloid DCs contribute substantially to SLE pathology[114]. In lupus-prone mice, conventional myeloid DCs exhibit

higher metabolic activity, evidenced by the downregulation of pyruvate dehydrogenase kinase 1 (Pdk1), an inhibitory regulator of the TCA cycle[115]. Additionally, FcγRs that recognize IgG immune complexes interact with TLRs to trigger the production of pro-inflammatory cytokines. Although the crosstalk between FcγRs and TLRs is essential for immune defence, it can become pathogenic when activated by autoantibodies in SLE. A key mediator of this process is IRF5 (ref. 106), which is activated via two distinct signalling pathways: activation via TBK1 and IKKε downstream of TLR stimulation, and nuclear translocation triggered by FcγR signalling. After activation downstream of TLR stimulation and FcγR signalling, IRF5 promotes inflammatory cytokine production and shifts DCs to glycolysis. This metabolic reprogramming provides the energy required for immune activation and cytokine secretion, ensuring that DCs can support heightened immune responses, but this process also fuels inflammatory responses characteristic of SLE[106,116].

Metabolic changes in T cells in systemic lupus erythematosus

The adaptive immune response involves multiple steps, each requiring distinct metabolic states to support T and B cell activation, proliferation and differentiation into effector cells. Naïve T cells have low energy demands and rely on minimal levels of glycolysis and oxidative phosphorylation. However, after activation, T cells increase the use of glucose, amino acids and fatty acids to meet the high energy requirements of effector functions.

T cells have a key role in SLE; $CD4^+$ T cells help activate B cells and display autoreactive features, whereas cytotoxic $CD8^+$ T cells are directly involved in organ damage. T_H1) $CD4^+$ T cells produce IFNγ, which activates macrophages and enhances inflammation[4], whereas T_H17 $CD4^+$ T cells produce IL-17, which contributes to the recruitment of additional inflammatory cells and exacerbates tissue damage, especially in the kidneys[117,118]. Furthermore, elevated levels of T_H2 cytokines, such as IL-4, have been linked with SLE pathogenesis and disease activity[119]. As mentioned above, dysfunction in T_{reg} cells can also play important roles in SLE pathogenesis[120].

Mitochondrial metabolism in T cells

T cells from patients with SLE exhibit mitochondrial abnormalities compared with T cells from healthy controls (Fig. 3). Unlike normal peripheral blood lymphocytes that undergo apoptosis in response to oxidative stress, SLE T cells are more prone to necrosis, with a greater percentage of them showing this tendency owing to ATP depletion caused by mitochondrial hyperpolarization[121,122]. SLE T cells show prominent increases in mitochondrial mass and mitochondrial and cytoplasmic calcium levels compared with those from healthy controls. Indeed, electron microscopy analyses have revealed that lymphocytes isolated from the peripheral blood of patients with SLE have a significant increase in mitochondria numbers per cell, compared with control peripheral blood lymphocytes from healthy donors[123]. mTOR activation leads to lysosomal degradation of the TCRζ chain via HRES-1–Rab4-dependent pathways, perturbing the assembly, expression and stability of the TCR–CD3 complex, which contributes to immune dysregulation characterized by impaired T cell activation and response in SLE[124]. Importantly, the deficiency of the TCRζ has been reversed in patients treated with rapamycin, an inhibitor of mTOR[124].

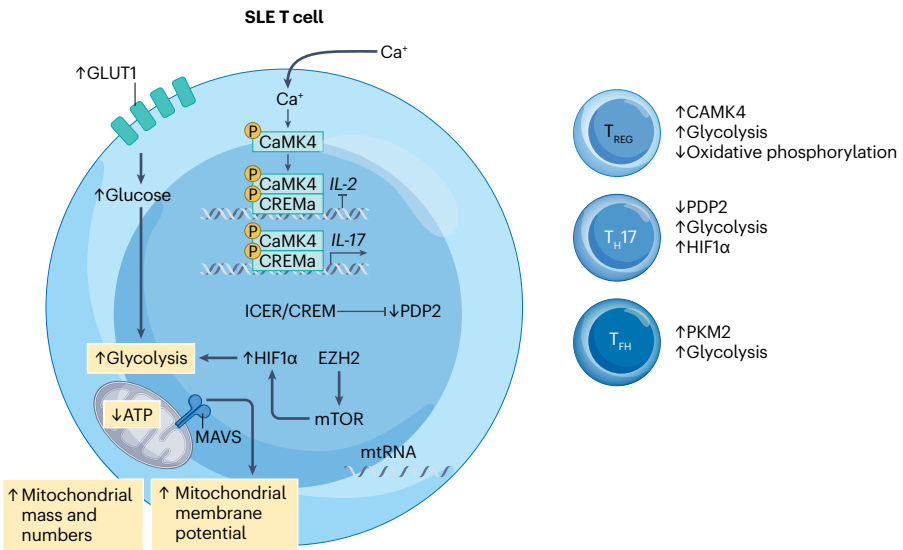

Fig. 3 | Metabolic alterations in T cells in systemic lupus erythematosus. Compared with T cells from healthy donors, T cells from patients with systemic lupus erythematosus (SLE) show profound increases in mitochondrial mass and mitochondrial and cytoplasmic calcium levels. SLE T cells have a substantial increase in the number of mitochondria per cell. Calcium flux in SLE T cells induces nuclear calcium/calmodulin-dependent protein kinase IV CaMK4, and enhances cAMP responsive element modulator (CREM expression), which form a transcriptional complex that downregulates expression of interleukin-2 (IL-2) and upregulates expression of IL-17. Upregulation of the histone methyltransferase enhancer of zeste homologue 2 (EZH2) increases expression of mammalian target of rapamycin (mTOR), leading to HIF1α activation and maintaining glycolytic activity. Oligomerization of the mitochondrial antiviral signalling protein MAVS contributes to mitochondrial hyperpolarization and decreased ATP production. Inducible cAMP early repressor (ICER) reduces PDP2, favouring glycolysis over oxidative phosphorylation. In general, SLE regulatory T (T_{reg}) cells display increased CaMK4 signalling, increased glycolysis and decreased oxidative phosphorylation. SLE T helper 17 (T_H17) cells present low expression of pyruvate dehydrogenase phosphatase subunit 2 (PDP2), high glycolysis and increased activation of hypoxia inducible factor α (HIF1α), whereas follicular T helper (T_{FH}) cells display increased levels of pyruvate kinase M2 (PKM2) and glycolysis. mtRNA, mitochondrial RNA.

Mitochondrial antiviral signalling (MAVS) oligomerization, a process that occurs when MAVS proteins form large aggregates that amplify antiviral signalling, also contribute to mitochondrial hyperpolarization, and decrease ATP production. MAVS oligomerization has been reported to limit the respiratory capacity of peripheral blood mononuclear cells from patients with SLE and thereby induce mitochondrial reactive oxygen species production and type I IFN responses[125,126].

Glucose metabolism in T cells

In addition to mitochondrial dysfunction, altered glucose metabolism is a hallmark of SLE T cells. Both glycolysis and mitochondrial oxygen consumption are elevated in $CD4^+$ T cells from patients with SLE compared with $CD4^+$ T cells from healthy individuals[127–129].

Mechanisms that drive enhanced glycolysis in T cells include the upregulation of transcription factors, such as ICER and CREM in T_H17 cells (Fig. 3). Overexpression of ICER reduces pyruvate dehydrogenase phosphatase subunit 2 (PDP2) at the mRNA and protein levels, favouring glycolysis over oxidative phosphorylation. Indeed, restoring PDP2 expression in $CD4^+$ T cells suppresses T_H17 cell differentiation[130]. HIF-1α is overexpressed in SLE T cells and this correlates with T_H17-related gene expression[131], indicating that additional factors contribute to glycolysis dependence in T_H17 cells. Increased expression of glucose transporters such as GLUT1 and the increased activity of calcium–calmodulin-dependent protein kinase IV (CaMK4) also drive glycolysis in SLE T cells. Indeed, one study suggests that inhibition of CaMK4 decreases GLUT1 expression during Th17 cell differentiation, leading to reduced IL-17 production[132]. However, whether CaMK4 directly regulates the expression of GLUT1, requires further exploration. CaMK4 enhances CREM expression, a CAMP response element modulator, that acts as a repressor, reducing IL-2 production[133]. This process might contribute to the lower IL-2 synthesis reported in human SLE T cells[134]. Furthermore, CaMK4 promotes mTOR activity[135], and this might contribute to the described activation of the mTOR pathway in SLE T cells[136]. Specifically, mTOR activation drives glycolysis in double-negative (DN) T cells from patients with SLE, leading to IL-4 production and necrotic cell death during disease flares[137].

Epigenetic modifications mediated by mTOR further amplify glycolysis. Upregulation in $CD4^+$ T cells of the histone methyltransferase Enhancer of zeste homologue 2 (EZH2) correlates with mTORC1 activation, and promotes a feedback loop that sustains inflammation. EZH2 expression is modulated by miRNAs suppressed by mTOR, linking metabolic and epigenetic changes in SLE[138].

Immunometabolism and T cell subset imbalance in systemic lupus erythematosus

$CD4^+CD25^+FOXP3^+$ T_{reg} cells secrete anti-inflammatory cytokines such as IL-10 and TGF-β to suppress effector T cell responses and maintain immune tolerance[139]. In vivo studies have demonstrated that TGF-β and IL-10 effectively suppress TLR-mediated antigen-specific immune responses and improve disease in lupus-prone models. Mechanistically, TGF-β and IL-10 modulate transcriptional programmes and suppress glycolysis and oxidative phosphorylation by inhibiting the mTORC1–S6 kinase 1 (S6K1) pathway in TLR-stimulated B cells[139].

SLE has been associated with impaired T_{reg} cell function and an imbalance between T_{reg} cells and T_H17 cells, with elevated IL-17 levels potentially contributing to SLE pathogenesis[140–142]. T_H17 cells can transdifferentiate into $IL17A^+IFNγ^+T_H17$–T_H1 cells at inflammatory sites, thereby exacerbating inflammation through IFNγ and IL-17A production[143]. mTOR activation increases expression of the IFNγ-inducing transcription factor T-bet, thereby supporting this pro-inflammatory shift, in T cells from patients with SLE[144]. Nicotinamide phosphoribosyltransferase (NAMPT), an enzyme essential for NAD^+ biosynthesis, is upregulated in lupus nephritis, enhancing glycolysis and mitochondrial respiration in T cells. This metabolic shift supports IFNγ production, linking NAMPT activity to T cell metabolic dysfunction in SLE[145]. Increased glycolysis in SLE T_{reg} cells is driven, in part, by the CaMK4-mediated phosphorylation of phosphofructokinase platelet type. This process suppresses oxidative metabolism, impairs T_{reg} cell stability and exacerbates autoimmunity. Interestingly, modulation of the T_{reg} cell metabolism via CRISPR–Cas9-mediated deletion of phosphofructokinase platelet type was able to reverse the defects in T_{reg} cell function[146].

Follicular helper T (T_{FH}) cells from SLE patients and MRL/lpr lupus-prone mice are essential for B cell activation and autoantibody production, and also exhibit increased glycolysis. PKM2 supports T_{FH} cell differentiation by enhancing glycolytic flux. Pharmacological inhibition of PKM2 reduces T_{FH} cell-driven inflammation, highlighting its potential as a therapeutic target[147].

Overall, several abnormalities are observed in various important immunometabolic pathways in T cells in SLE and are likely to contribute to important alterations in their phenotype and function (Fig. 3). Dysfunctional mitochondrial metabolism, enhanced glycolysis and impaired immune regulation in T cells contribute to chronic inflammation and immune dysregulation characteristic of SLE. Shifts in T cell subsets, such as an imbalance between T_{reg} cells and T_H17 cells, as well as alterations in metabolic regulators such as mTOR, contribute to exacerbated autoimmunity and organ damage. These metabolic changes not only influence T cell activation and function but are also likely to drive the persistence of inflammation and tissue damage seen in SLE.

Metabolic alterations in B cells in systemic lupus erythematosus

Glucose metabolism in B cells

Metabolic reprogramming drives B cell hyperactivity and underlies the altered B cell subset composition in patients with SLE (Fig. 4). B cell activating factor (BAFF), which has increased expression in patients with SLE, promotes aerobic glycolysis in B cells, supporting their proliferation and antibody production[148,149]. Monocarboxylate transporter 1 (MCT1), a protein that transports lactate, pyruvate and ketone bodies across cell membranes, modulates B cell activation, influencing class-switch recombination and antibody production[150]. In patients with SLE, MCT1 expression levels are significantly upregulated compared with healthy individuals, and Mct1 deficiency decreased disease severity in a mouse model of lupus. MCT1-mediated pyruvate metabolism is necessary for generating the acetyl-CoA required for H3K27 acetylation, facilitating the transcriptional activation of genes needed for effective class-switching[150].

Glucose metabolism seems to have an important role in B cell subsets that are most relevant in SLE pathology. Under homeostatic conditions, germinal centre B cells selectively oxidize fatty acids for energy and display minimal glycolysis[151]. By contrast, in a mouse model of lupus germinal centre B cells exhibited a high reliance on glucose oxidation for survival and were vulnerable to glycolysis inhibition[152].

Human $CD27^+IgD^+$ unswitched memory B cells respond to stimulation with the TLR9 ligand CpG and IFNα by undergoing a metabolic shift towards glycolysis, and this metabolic shift facilitates memory

B cell differentiation into CD27^{hi}CD38^{hi} plasmablasts, which are precursors to antibody-secreting plasma cells. This process involves activation of mTORC1 and increased lactate production. Notably, heightened mTORC1 activation has been observed in CD19^{+} B cells from patients with SLE, correlating with plasmablast differentiation and disease activity[153] (Fig. 4).

Disruptions in these metabolic pathways can promote the development of autoreactive B cells that produce autoantibodies. Autoantibodies against glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a multifunctional protein known mainly for its role in glycolysis, have been implicated in the pathogenesis of SLE, particularly in patients presenting with neuropsychiatric symptoms[154]. GAPDH-specific autoantibodies have been associated with increased disease activity in patients with SLE and with complications such as increased intracranial pressure, which may exacerbate neuropsychiatric conditions[155]. However, further investigation is needed to understand the mechanism by which these autoantibodies cause damage.

Mitochondrial metabolism in B cells

Enhanced mitochondrial activity, including increased membrane hyperpolarization, has been noted in CD19^{+} B cells from patients with SLE compared with CD19^{+} B cells from healthy individuals[156]. Treatment of B cells with a TLR9 ligand and IFNα upregulates mitochondrial function, glycolysis and oxidative phosphorylation, supporting plasmablast differentiation[156]. Conversely, use of a glutaminase inhibitor to target glutamine metabolism, a metabolic pathway that provides key substrates for mitochondrial function, reduces oxidative phosphorylation, reactive oxygen species production, ATP production and plasmablast differentiation without affecting glycolysis[156]. These findings underscore the importance of mitochondrial metabolic pathways in sustaining plasmablast differentiation.

Combined analyses of plasma levels of histidine (an amino acid reported to be abundant in mitochondria[157]) and transcriptomic data revealed a negative correlation between histidine levels and oxidative phosphorylation (a marker of mitochondrial activity) in plasmablasts, suggesting that decreased plasma histidine levels might reflect increased uptake of histidine by B cells[52]. Further exploration is needed to understand how histidine levels directly or indirectly regulate mitochondrial activity.

NOX2 generates reactive oxygen species, and TLR-dependent NOX2 activation promotes maturation of TLR-containing endosomes, resulting in signal termination and preventing excessive immune activation to nucleic acid-containing antigens[158]. Primary human B cells with NOX2 loss of function induced through the expression of defective *NCF1* and *NCF2* variants had enhanced signalling downstream of endosomal TLRs, and exhibited increased humoral responses, leading to stronger or prolonged response to the activation of endosomal TLRs. Low reactive oxygen species production in the absence of NOX2 was also found to contribute to autoimmune B cell responses by impairing endosomal maturation[158].

Additionally, mitochondria and mtDNA might serve as sources of autoantigens in SLE, as evidenced by the presence of autoantibodies targeting mitochondrial RNA and other targets in these organelles[159]. Indeed, antibodies against the mitochondrial outer membrane and mitochondrial DNA are increased in both patients with SLE and mouse models of SLE, in association with anti-dsDNA and lupus nephritis[78].

Immunometabolism and B cell subsets in systemic lupus erythematosus

The age-associated B cell (ABC) subset is expanded in patients with SLE[160], and has been linked to increased autoantibody production in mouse models of lupus[161]. Unlike germinal centre B cells, ABCs produce inflammatory cytokines, take up antigen, and preferentially induce T_{FH} cell differentiation, which might drive autoimmune responses[161]. ABCs display unique metabolic profiles that enhance their survival and function: glycolytic and oxidative metabolism is elevated in ABCs compared with other follicular B cells, and this adaptation seems to support the enhanced antigen uptake and presentation abilities of ABCs[161] (Fig. 4). In mice, the increased glycolytic activity of ABCs seems to be driven by IFNγ signalling, whereby the transcription factor

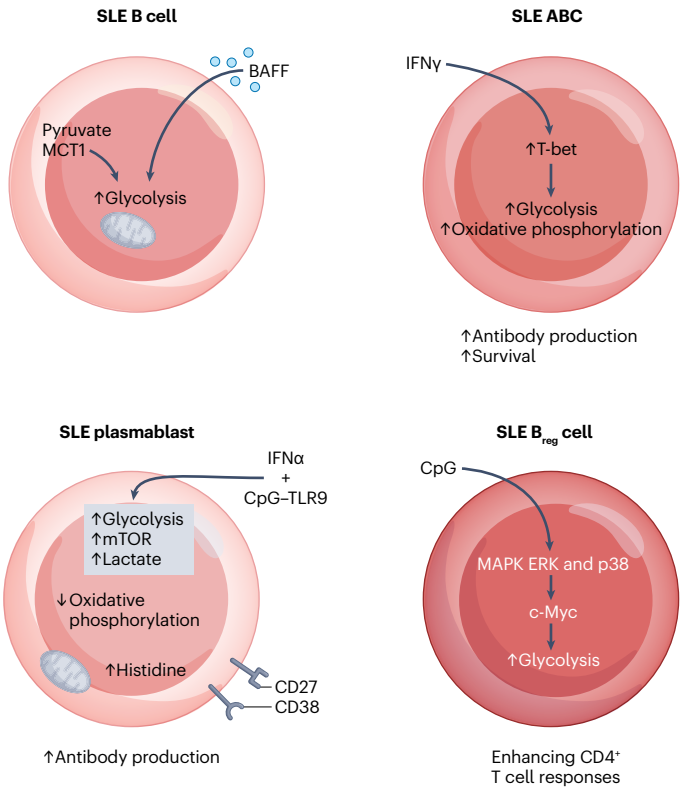

Fig. 4 | Metabolic dysregulation of B cells in systemic lupus erythematosus. High levels of the B cell activating factor BAFF predispose B cells to aerobic glycolysis, supporting their proliferation and antibody production. Monocarboxylate transporter 1 (MCT1) modulates B cell activation by regulating pyruvate uptake and glycolysis. Activation of the Toll-like receptor 9 (TLR9) with CpG and stimulation with interferon α (IFNα), induces a metabolic shift towards glycolysis in CD27^{+}IgD^{+} unswitched memory B cells, facilitating their differentiation into CD27^{hi}CD38^{hi} plasmablasts. This process involves activation of mammalian target of rapamycin complex 1 (mTORC1) and increased lactate production. Histidine is essential for plasmablast differentiation induced by innate immune signals. In systemic lupus erythematosus (SLE), IL-10^{+} regulatory B (B_{reg}) cells often adopt a pathogenic phenotype, enhancing CD4^{+} T cell responses. This shift seems to be driven by CpG and the upregulation of c-Myc mediated by the mitogen activated protein kinases (MAPK) ERK and p38. The increased glycolytic activity in age-associated B cells (ABCs) is driven by IFNγ signalling, in which the transcription factor T-bet, downstream of IFNγ, regulates glycolysis-related genes by repressing expression of the transcription factor BCL6.

T-bet, acting downstream of IFNγ, regulates glycolysis-related genes by repressing BCL6 expression[162]. This metabolic reprogramming is crucial for the pro-inflammatory functions of ABCs, including their induced activation of T cells.

Memory B cells from patients with SLE exhibit gene expression patterns that are associated with increased oxidative phosphorylation and mitochondrial dysfunction[51]. Mouse B cells that were deficient in Peroxiredoxin 6 (PRDX6), a protein that regulates oxidative phosphorylation, had enhanced oxidative stress[51].

Regulatory B (B_{reg}) cells are important in maintaining immune tolerance. Under homeostasis, cholesterol metabolism regulates human B_{reg} cell functions by driving IL-10 synthesis in these cells[163]. In patients with SLE, IL-10$^+$ B_{reg} cells often adopt a pathogenic phenotype that enhances CD4$^+$ T cell responses (Fig. 4). This shift seems to be driven by environmental factors and the upregulation of the transcription factor c-Myc, which is activated by ERK and p38 MAPK signalling pathways, leading to a glycolytic reprogramming and a pro-inflammatory phenotype in B_{reg} cells[164].

In conclusion, metabolic reprogramming in B cells has a crucial role in the pathogenesis of SLE, contributing to the altered subset composition and hyperactivity of these cells. Elevated glycolysis and oxidative phosphorylation in B cells support their proliferation, antibody production and class-switch recombination, which are key features of SLE. Additionally, the increased expression of molecules such as BAFF and MCT1 further exacerbate these processes, promoting the development of autoreactive B cells that contribute to disease progression. The dysregulated metabolic pathways also impact various B cell subsets, including memory B cells, ABCs, and B_{reg} cells, highlighting the complex interplay between metabolic changes and immune dysfunction in SLE.

Metabolic targets for the treatment of systemic lupus erythematosus

Therapeutic approaches targeting glycolysis

As mentioned in previous sections, immune cells exhibit increased glycolytic activity contributing to SLE. Pharmacological inhibition of glycolysis with 2-deoxy-D-glucose (2-DG) reduces lupus severity in animal models by normalizing T cell metabolism and decreasing IFNγ production[129]. Furthermore, inhibition of glycolysis in lupus-prone mice treated with 2-DG impairs B cell function by selectively reducing autoantibody synthesis[149]. Of note, 2-DG has already been tested in other conditions, such as various cancers, which has provided data on 2-DG safety and tolerability that has accelerated the path to clinical applications based on 2-DG in other inflammatory conditions.

The activity of other glycolytic enzymes can also be targeted in SLE (Fig. 5). For instance, the allosteric activator of PKM2 TEPP-46 induces PKM2 tetramerization and thereby inhibits glycolysis in T_{FH} cells. In mouse models of SLE, TEPP-46 reduced inflammatory damage by decreasing nuclear PKM2 and limiting BCL6-mediated glycolysis during T_{FH} cell differentiation[147]. Similarly, an inhibitor of PKM2 activity in macrophages, DCs and B cells reduced inflammation in various mouse models of lupus[94].

In addition to targeting glycolytic enzymes, targeting glucose transport has recently emerged as a potential alternative for the treatment of SLE (Fig. 5). In vitro, the glucose transporter inhibitor CG-5 targets glucose uptake by T cells, inhibiting T_H1 and T_H17 cell differentiation and promoting T_{reg} cell induction[127]. In the triple-congenic model and chronic graft-versus-host-disease model of lupus, CG-5 decreased the numbers of germinal centre B cells, autoantibody production and mitigated lupus phenotypes[127]. The CaMK4 inhibitor KN-93 reduces GLUT1 expression and GLUT1-mediated glucose uptake in CD4$^+$ T cells, and this effect of KN-93 was associated with decreased disease activity and enhancement of T_{reg} cell generation in MRL/lpr mice[132,146]. However, targeting glycolytic enzymes or glucose transport are not specific to immune cells and may affect other tissues that rely on glucose metabolism, raising concerns about off-target effects and systemic toxicity. With continued research, these alternatives could lead to more selective and safer approaches that improve SLE disease by targeting glucose metabolism (Fig. 5).

Therapeutic approaches targeting both glucose and mitochondrial metabolism

Metformin, which inhibits mitochondrial complex I, leading to decreased oxidative phosphorylation, has demonstrated the ability to inhibit the transcription of IFN-stimulated genes in CD4$^+$ T cells that were isolated from patients with SLE and stimulated in vitro with IFNα[165]. Furthermore, metformin hampers NET formation and IFNα induction in pDCs from healthy donors[166]. Therapeutic targeting of ABC metabolism with metformin, reduces ABC-mediated antigen presentation and T_{FH} cell differentiation, highlighting the potential for metabolic modulation to mitigate ABC-driven autoimmunity[161].

In preclinical studies, treatment of MRL/lpr lupus-prone mice with metformin downregulated systemic and renal inflammation, increased the levels of phosphorylated AMPK, decreased the levels of phosphorylated STAT3 and lowered the renal expression of necroptosis markers, leading to the reduction of renal macrophage infiltration and pro-inflammatory cytokine production[167]. These results and the established safety profile of metformin, makes it a potentially attractive option for targeting immunometabolic disturbances in SLE.

As immune cells shift between glycolysis and oxidative phosphorylation in SLE, dual inhibition with metformin and 2-DG provides a more comprehensive metabolic blockade. The synergistic effects of metformin and 2-DG have been particularly effective in the lupus-prone B6.NZM2410.Sle1.Sle2.Sle3 triple-congenic mouse model, showing reduced disease activity, normalized T cell metabolism, decreased mTORC1 activation, reduced numbers of autoreactive T_{FH} cells and alleviated lupus nephritis[128,129,168,169].

Metformin and 2-DG also influence the metabolic profiles of B cells[148,161,162] and macrophages[170]. Overall, metformin and 2-DG have favourable safety profiles, and metformin achieved reductions in disease flares in preliminary clinical trials with patients with SLE[171,172]. Furthermore, when combined with the CD28 inhibitor CTLA4-Ig, metformin has improved lupus phenotypes in the NZB/NZW F1 lupus model[173]. These results encourage further exploration of combination therapies targeting both metabolic dysregulation and immunological activation to improve lupus outcomes.

Therapeutic approaches targeting mammalian target of rapamycin

Dysregulated mTOR signalling is a hallmark of SLE and has been associated with dysregulation of glycolysis. The inhibition of mTOR signalling (Fig. 5), using rapamycin or rapamycin analogues, has shown efficacy in both mouse models and early-phase clinical trials. Indeed, rapamycin, which is a specific mTORC1 inhibitor, has shown efficacy in mouse models of lupus by decreasing anti-dsDNA autoantibodies and

proteinuria and improving survival[174]. Clinical trials have further demonstrated the effectiveness of rapamycin in reducing disease activity and corticosteroid dependence in patients with refractory SLE[175,176], suggesting that mTOR inhibitors are likely to be useful in patients with severe disease who are refractory to conventional therapies, or as adjuvant combination therapy. Mechanistically, rapamycin has been shown to inhibit IL-4 production, necrosis of double-negative T cells and Ca^{2+} influx in CD28-costimulated T cells, and to restore T_{reg} cell function, among other benefits[137,177,178]. These effects have been observed mainly in mouse models, although human-specific data on the effects of rapamycin in SLE are emerging. Long-term studies will be required to assess the safety and efficacy of these compounds, as well as any potential for adverse effects associated with their use in SLE.

Targeting lipid metabolism in systemic lupus erythematosus

Statins have lipid-lowering and immunomodulatory effects and and have been proposed as potential therapeutics in SLE. Atorvastatin has been shown to reverse lipid raft abnormalities in T cells from patients with SLE, normalizing lipid raft signalling, which is required for the formation of the immunological synapse[179–182]. Additionally, inhibition of glycosphingolipid biosynthesis with N-butyldeoxynojirimycin, a glucosylceramide synthase inhibitor, improved $CD4^+$ T cell signalling and decreased autoantibody production in vitro[183]. Simvastatin,

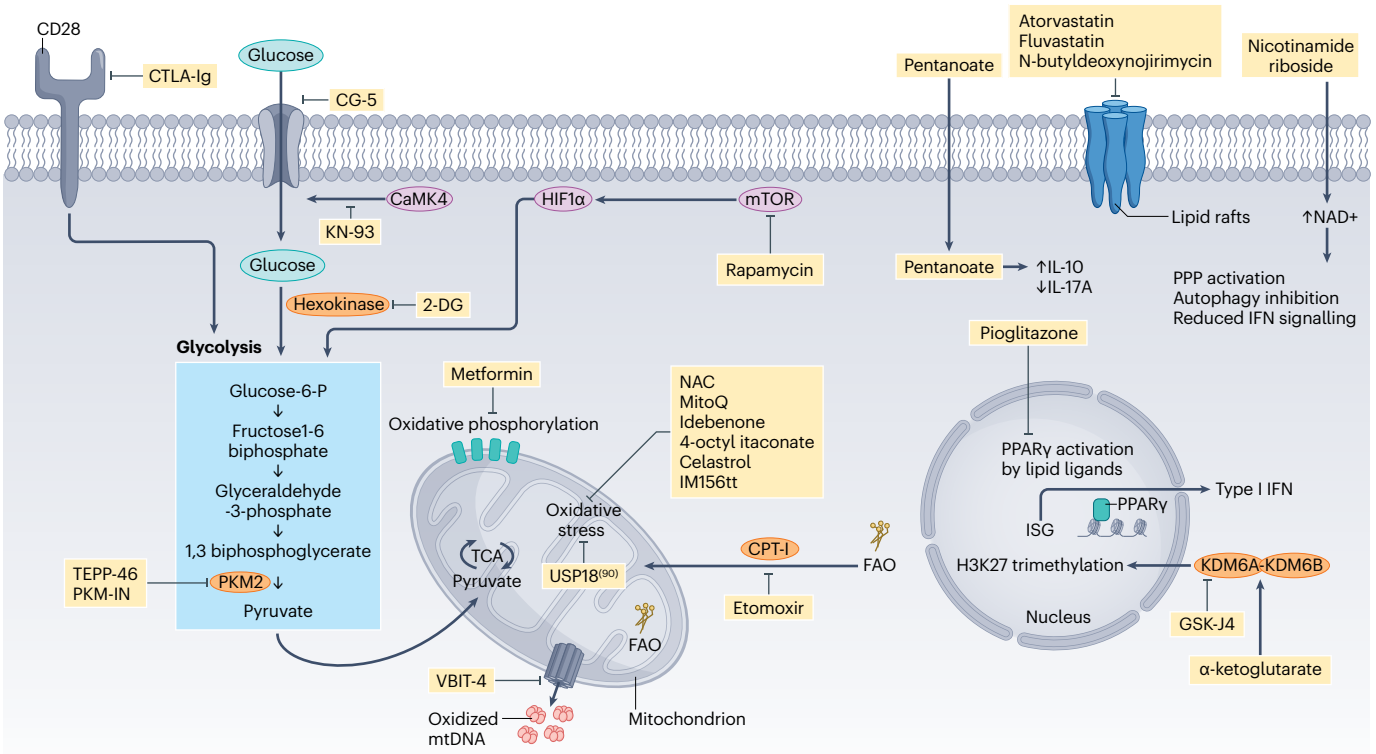

Fig. 5 | Metabolic targets for the treatment of systemic lupus erythematosus. Various metabolic approaches for the treatment of systemic lupus erythematosus (SLE) have been studied in vitro, in preclinical models or clinical studies. Here, we show some representative examples. Metformin and 2-deoxy-D-glucose (2-DG) have been shown to reduce pathogenic activity in T cells, macrophages and B cells in SLE, through the inhibition of mitochondrial complex 1 and the glycolytic enzyme hexokinase, respectively. The glucose transporter (GLUT1) inhibitor CG-5 also inhibits glucose uptake in T cells. Blocking glucose uptake with CG-5 ameliorates autoimmune activation in animal models of lupus. By inhibiting the kinase CaMK4, KN-93 reduces GLUT1 expression and GLUT1-mediated glucose uptake in $CD4^+$ T cells, decreases disease activity, and enhances the generation of regulatory T (T_{reg}) cells. The pyruvate kinase M2 (PKM2) inhibitors TEPP-46 and PKM-IN downregulate glycolysis in macrophages, dendritic cells (DCs), B cells and follicular helper T (T_{FH}) cells, and have been shown to reduce inflammation in various mouse models of lupus. In addition, the CD28 antagonist CTLA4-Ig has been shown to reduce glycolysis downstream of CD28 signalling. Rapamycin (sirolimus), a specific inhibitor of mammalian target of rapamycin complex 1 (mTORC1), has shown efficacy in preclinical models of SLE by decreasing anti-dsDNA antibodies, lowering proteinuria and improving survival. Statins have gained attention for their lipid-lowering effects in SLE. Atorvastatin reverses lipid raft abnormalities in SLE T cells, normalizing signalling pathways. Simvastatin improves mitochondrial function in DCs. The short-chain fatty acid (SCFA) pentanoate suppresses autoimmunity by enhancing production of interleukin 10 (IL-10) in B cells and reducing the expression of interleukin-17A (IL-17A) in $CD4^+$ cells. Omega-3 fatty acids, such as eicosapentaenoic acid, reduce pro-inflammatory cytokines and improve T_{reg} cell function in mouse models of SLE. Etomoxir, a carnitine palmitoyltransferase I (CPT-I) inhibitor, suppresses production of interferon γ (IFNγ) and reduces inflammation. The anti-oxidants *N*-acetylcysteine (NAC), MitoQ, idebenone and 4-octyl itaconate also alleviate renal and systemic inflammation in SLE cells or animal models. Nicotinamide riboside is absorbed into cells and converted to NAD^+, increasing NAD^+ levels and the activity of the pentose–phosphate pathway (PPP), blunts autophagy and type I IFN production in patients with SLE. Blocking the release of oxidized mitochondrial DNA (mtDNA) via the inhibitor of voltage-dependent anion channel (VDAC) oligomerization VBIT-4 has been proposed to be effective in the treatment of SLE. In vitro treatment with pioglitazone, a PPARγ agonist, induced transcriptional repression of genes implicated in T cell responses, decreasing effector $CD4^+$ T cell activation and proliferation, while increasing T_{reg} cell proliferation.

Glossary

B6.NZM2410.Sle1.Sle2.Sle3 triple-congenic mouse model
A genetically engineered model on a C57BL/6 background combining three susceptibility loci from Sle, Sle2 and Sle3, leading to spontaneous lupus-like disease.

Chronic graft-versus-host-disease model
A model of lupus induced by transferring splenocytes from autoimmune-prone Bm12 mice into C57BL/6 recipients, triggering lupus-like autoimmunity within 2–5 weeks.

MRL/lpr mice
A mouse strain with an Fs gene mutation (lpr) leading to defective lymphocyte apoptosis and lupus-like symptoms.

NZB/NZW F1 lupus model
A spontaneous model of lupus generated by crossing NZB and NZW mice, producing offspring (F1) that develop a female-biased, late-onset lupus-like disease.

an inhibitor of the enzyme HMG-CoA reductase that has a key role in cholesterol production in the liver, improved mitochondrial function in DCs and reduced systemic inflammation in a mouse model of pristane-induced lupus[184]. However, the effectiveness of statins in managing symptoms and complications of SLE remains to be systematically determined, and results have been mixed with regard to their immunomodulatory roles[185,186].

SCFAs produced by gut microbiota also modulate immune responses[187]. The SCFA pentanoate suppressed autoimmunity by enhancing IL-10 production in B cells and reducing the expression of IL-17A in a model of autoimmune encephalomyelitis[188]. Omega-3 fatty acids, such as eicosapentaenoic acid, have shown the ability to reduce pro-inflammatory cytokine synthesis and improve T_{reg} cell function in mouse models of lupus[189,190]. The carnitine palmitoyltransferase I (CPT-I) inhibitor etomoxir was shown to suppress IFNγ production in memory $CD4^+$ T cells from patients with SLE[144] and decrease the production of IL-6 and CXCL10 by in vitro activated DCs[191], thereby reducing inflammation. CPT-I inhibition with etomoxir might offer a therapeutic strategy to modulate T_H cell subset imbalances, potentially alleviating inflammation in SLE. Furthermore, vitamin D3 has been shown to ameliorate lupus nephritis by inhibiting NFκB and MAPK pathways while enhancing T_{reg} cell function in MRL/lpr mice[192,193] Activation of peroxisome proliferator-activated receptor-γ (PPARγ), a nuclear receptor that acts as a lipid sensor, with its agonist pioglitazone, downregulated the activation and proliferation of $CD4^+$ T cells isolated from patients with SLE, while enhancing the proliferation and function of T_{reg} cells from the same patients[194].

Therapeutic approaches targeting oxidative stress

Elevated levels of reactive oxygen species exacerbate SLE symptoms and organ damage[5]. Anti-oxidants such as *N*-acetylcysteine (a stable amino acid precursor that increases glutathione levels in peripheral blood lymphocytes) and the coenzyme Q analogues MitoQ and idebenone have been demonstrated to reduce oxidative stress markers and improve mitochondrial function in vitro, in animal models of lupus, as well as in patients with SLE[195–198]. The compound 4-octyl itaconate, a cell-permeable itaconate derivative with anti-oxidant properties, alleviated renal and systemic inflammation in mouse models of lupus and improved the in vitro function of myeloid cells derived from patients with SLE[199]. The exact mechanism by which 4-octyl itaconate mitigates disease in mouse models of lupus is still under investigation, although 4-octyl itaconate has been reported to decrease oxidative stress through the activation of nuclear factor erythroid-related factor 2 (NRF2)[200]. Indeed, levels of serum endogenous itaconate were found to be decreased in patients with SLE compared with healthy individuals[201]. Additionally, glucocorticoids exert some of their therapeutic effects by increasing levels of itaconate, through promoting transport of cytosolic pyruvate dehydrogenase to the mitochondria[202].

Another compound with anti-oxidant properties is dimethyl fumarate (DMF, a fumaric ester), an established therapeutic agent for psoriasis that has been used as a potential treatment for severe cutaneous manifestations of lupus[203,204]. DMF acts mainly through activation of the NRF2, which regulates the expression of genes involved in oxidative stress response[205]. Therefore, activating NRF2 through DMF or 4-octyl itaconate is a potential strategy for mitigating cellular damage and alleviating disease symptoms in patients with SLE.

The balance between NAD^+ and its reduced form, NADH, is crucial for maintaining cellular redox balance and mitochondrial integrity[206]. Normalizing the redox imbalance by raising NAD^+ through NAD^+-boosting compounds, such as the NAD^+ precursor nicotinamide riboside were shown to increase the activity of the PPP and to blunt autophagy and type I IFN production in healthy volunteers. NAD^+ boosting with nicotinamide riboside in vitro also blunted the type I IFN response in monocytes from SLE patients[207]. An ongoing clinical trial is assessing the potential of nicotinamide riboside to modify clinical activity, immune dysregulation and vascular dysfunction in patients with SLE (NCT06032923)[208].

Furthermore, blocking the release of oxidized mtDNA to the cytoplasm might hold potential for the treatment of SLE. The voltage-dependent anion channel oligomerization inhibitor VBIT-4 decreases disease severity in mouse models of lupus and has been shown to improve mtDNA release, IFN signalling and NET formation in myeloid cells from patients with SLE[79]. Together, these findings highlight the growing repertoire of therapeutic strategies aimed at restoring redox balance and mitochondrial function (Fig. 5). Targeting oxidative stress, whether through anti-oxidant compounds, NRF2 activation, NAD^+ boosting, or inhibition of mitochondrial DNA release, offers promising alternatives to dampen immune dysregulation and reduce disease severity.

Conclusion

Preclinical and early clinical data show a promising potential for strategies targeting immunometabolism for the modulation of autoimmunity (Table 1 and Supplementary Table 1). These data suggest that therapies targeting glycolysis, mTOR signalling, lipid metabolism and oxidative stress have the ability to modulate the underlying immune dysregulation and metabolic disturbances of SLE. Such approaches might offer improved, personalized treatment options for patients with SLE, with the potential to reduce disease flares, improve organ function and minimize reliance on corticosteroids and other immunosuppresants.

However, several challenges must be addressed before metabolic therapies are widely adopted in clinical practice. Most importantly, there is a need for robust clinical trials involving large and diverse patient cohorts to better understand the full range of effects, safety profiles and optimal treatment regimens for metabolic interventions in SLE. Although early-phase studies have provided valuable insights,

Table 1 | Metabolic therapeutic targets in systemic lupus erythematosus

Drug	Targeted molecules	Mechanisms of action
Strategies targeting glucose metabolism and mitochondria metabolism		
2-DG and metformin	Hexokinase (2-DG) and mitochondria complex I (metformin)	Reduction of IFNγ production and restoration of IL-2 production in $CD4^+$ T cells from a triple-congenic mouse model of lupus and in $CD4^+$ T cells from patients with SLE[129]
Strategies targeting glucose metabolism		
KN-93	CaMK4	Normalized PFKP activity in $CD4^+$ T cells from patients with SLE, leading to enhanced T_{reg} cell function[146]
Strategies targeting mitochondrial metabolism		
Metformin	Mitochondria complex I	Reduced the occurrence of major flares by 41% compared with placebo[172]
Idebenone	Mitochondrial reactive oxygen species	Reduced mortality, glomerular inflammation and fibrosis, and improved renal function in MRL/lpr mice. In vitro, idebenone reduced NET formation by neutrophils from patients with SLE[198]
4-octyl itaconate	NRF2 and reactive oxygen species production	Reduced proteinuria, kidney immune complex deposition, renal scores of severity and inflammation in a mouse model of lupus. When applied on cells from patients with SLE in vitro, it reduced B cell responses and macrophage activation[199]
Dimethyl fumarate and monoethyl hydrogen fumarate salts	NRF2	Decreased disease activity in three patients with cutaneous lupus manifestations[204]
N-acetylcysteine	Mitochondria complex I	Decreased oxygen consumption in peripheral blood lymphocytes from patients with SLE[195]
VBIT-4	VDAC1 oligomerization	Decreased mtDNA release, IFN signalling, skin lesions, alopecia, renal immune complex deposition, proteinuria and autoantibody production in MRL/lpr mice. Reduced NET formation by NDG and LDG from patients with SLE in vitro[79]
Strategies targeting mTOR		
Rapamycin	mTOR	Reduced erythema and tenderness of involved areas on the skin of a patient with discoid SLE[176]
		Induced autophagy, restored the expression of GATA3 and CTLA4, and corrected T_{reg} cell function in T cells from patients with SLE[177]
		Blocked the IL-4 production and necrosis of $CD4^-CD8^-$ double-negative T cells, increased the expression of FOXP3 in $CD25^+CD4^+$ T cells, and expanded $CD25^+CD19^+$ B cells in patients with SLE[137]
		Decreased mitochondrial hyperpolarization and calcium flux in T cells from patients with SLE[178]
		Expanded $CD4^+CD25^+FoxP3^+$ T_{reg} cells and $CD8^+$ memory T cell populations and inhibited IL-4 and IL-17 production by $CD4^+$ T and $CD4^-CD8^-$ double-negative T cells in patients with SLE[175]
Strategies targeting lipid metabolism		
Atorvastatin	Lipid rafts	Reduced the active form of LCK, IL-10 and IL-6, and increased ERK phosphorylation in T cells from patients with SLE[181]
N-butyldeoxynojirimycin	Glucosylceramide synthase inhibitor	Normalized glycosphingolipid metabolism, corrected $CD4^+$ T cell signalling and functional defects, and decreased anti-dsDNA antibody production by autologous B cells in patients with SLE[183]
Fluvastatin	HMG-CoA reductase inhibitor	Reduced the SLE Disease Activity Index, anti-dsDNA and lipid levels, in patients with SLE[180]
Pioglitazone	PPAR-γ agonists PBMCs and T $CD4^+$	Decreased proliferation and activation of effector $CD4^+$ T cells from patients with SLE[194]
Etomoxir	Carnitine palmitoyltransferase 1 inhibitor	Increased fatty-acid synthesis/suppressed IFNγ production and upregulated FOXP3 expression in T-bet^+FoxP3^+ cells from patients with SLE[144]
Strategies targeting diverse aspects of metabolism		
Nicotinamide riboside	Boosts NAD^+ levels	Reduced autophagy and IFNβ release in monocytes from patients with SLE[207]

2-DG, 2-deoxy-D-glucose; CaMK4, calcium/calmodulin dependent protein kinase IV; CTLA4, cytotoxic T lymphocyte protein 4; ERK, extracellular signal-regulated kinase; FOXP3, forkhead box P3; GATA3, GATA-binding protein 3; LDG, low-density granulocytes; mTOR, mammalian target of rapamycin; mtRNA, mitochondrial RNA; NDG, normal-density granulocytes; NET, neutrophil extracellular traps; NRF2, factor erythroid-related factor 2; PFKP, phosphofructokinase platelet type; PPARγ, peroxisome proliferator-activated receptor-γ; SLE, systemic lupus erythematosus; T_{reg} cells, regulatory T cells.

long-term, multicentre trials are necessary to assess the sustainability of benefits, identify any long-term side effects and evaluate the effectiveness of these treatments across different stages of the disease. Additionally, research that examines the synergy between metabolic inhibitors and existing immunomodulatory treatments will be crucial for optimizing combination therapy strategies.

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Review article

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Advances in the treatment of ANCA-associated vasculitis

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Abstract

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) consists of a group of small-vessel vasculitides that often present with organ-threatening or life-threatening manifestations. Current immunosuppressive treatments have improved survival and rates of remission, but are not curative, have frequent toxicities, and do not effectively prevent relapse. Clinical trials have established the role of rituximab, an anti-CD20 B cell-depleting monoclonal antibody, in both the remission-induction and maintenance phases of the disease and demonstrated that glucocorticoid doses can be substantially reduced from historical dosing levels without affecting treatment efficacy. Therapies that have the potential to be more effective and safer have become available or are under investigation. Avacopan, an oral C5a receptor antagonist, was approved as an adjunctive treatment for AAV and use of this drug in combination with rituximab or cyclophosphamide and markedly reduced glucocorticoid dosing demonstrated superior efficacy and potentially greater kidney recovery than prior standard of care. Other agents under study for treatment of AAV include next-generation anti-CD20 monoclonal antibodies, anti-CD19 chimeric antigen receptor T cells, novel complement inhibitors and agents that can target fibrosis. Alongside traditional randomized controlled trials with clinical endpoints, experimental medicine studies are focusing on mechanistic endpoints and disease biomarkers. This Review discusses current treatments and the advances in the management of AAV.

Sections

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Key points

- The main regimen of remission induction in antineutrophil cytoplasmic antibody-associated vasculitis is based on high-dose glucocorticoids combined with rituximab or cyclophosphamide.
- The initial approach to treatment induces remission of vasculitis in most patients but does not prevent relapse in a substantial number of people and has multiple toxicities.
- Clinical trial data show that reduced-dose regimens of glucocorticoids are non-inferior to standard-dose regimens and have a lower risk of serious infections; rituximab is superior to azathioprine in maintaining disease remission.
- B cell-targeting therapies under evaluation for antineutrophil cytoplasmic antibody-associated vasculitis treatment include anti-CD20 monoclonal antibodies with increased B cell depletion capacity compared with rituximab, chimeric antigen receptor T cells and B cell-inhibiting antibodies.
- Avacopan in combination with rituximab or cyclophosphamide and markedly reduced glucocorticoids has superior efficacy, kidney function recovery and improvement in quality of life to regimens based on standard glucocorticoid dose.
- Novel targets include pathways involved in antineutrophil cytoplasmic antibody-induced inflammation and fibrosis, which could be combined with immunosuppressive therapies. Strategies to reduce cardiovascular risk and improve response to vaccines are being tested.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) encompasses three rare disorders — microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) — which are characterized by inflammation of small blood vessels and scarce immune deposition[1]. MPA and GPA show high frequencies of necrotizing crescentic glomerulonephritis and alveolar haemorrhage that result from small-vessel vasculitis and are usually associated with ANCA positivity. Furthermore, a key component of GPA but not MPA is granulomatous inflammation, which mainly affects the ears, nose and throat (ENT) and lungs[2]. The main features of EGPA are asthma and eosinophilia; glomerulonephritis is rare and only 30–40% of patients test positive for ANCA[3,4]. The treatment of EGPA, which differs substantially from that of GPA and MPA, is not discussed in this Review and evidence-based guidelines for the management of this disorder were published in 2023 (ref. 5).

In individuals with MPA and GPA, ANCAs mainly target myeloperoxidase (MPO) or proteinase 3 (PR3), which are primarily found in neutrophils, but also in monocytes and macrophages. Antigen specificity is associated with clinical phenotype and prognosis[6]. PR3-ANCA is more common in GPA and is associated with younger age at onset, higher rates of relapse and lower mortality, whereas MPO-ANCA is prevalent in MPA and portends a higher risk of kidney involvement, progression to end-stage kidney disease (ESKD) and death[7–11]. Genetic associations align more with the type of ANCA than with clinical diagnosis[12,13]; hence, distinguishing between PR3-AAV and MPO-AAV, as opposed to GPA and MPA, could improve risk stratification of patients and reflect more accurately pathogenic differences[14,15]. However, even such an ANCA-based classification fails to separate AAV into two distinct entities as both show overlapping features and substantial heterogeneity. PR3-AAV can be associated with localized ENT disease or with systemic presentation dominated by kidney involvement indistinguishable from that seen in MPO-AAV, whereas some patients classified as GPA are positive for MPO-ANCA; this finding is mainly reported in regions such as China and Japan, where MPO-ANCA is the dominant serotype[16,17]. Model-based clustering of large patient datasets have identified multiple disease clusters, such as non-renal AAV, renal AAV with or without PR3-ANCA and smaller clusters that are characterized by gastrointestinal and central nervous system involvement, thereby providing evidence that a binary classification will not resolve the complexity of the AAV spectrum[18–20]. Defining patient subgroups based on the presence of granulomatous features or kidney involvement, which confer an increased risk of relapse and death, respectively, has also been proposed[21].

Although the aetiology of AAV remains unknown in most cases, the pathogenesis of vasculitic lesions has been delineated more clearly[22]. Autoreactive B cells, assisted by T cells, give rise to ANCA-producing plasmablasts and plasma cells. Circulating ANCAs bind to cell-surface MPO and PR3 expressed by neutrophils and monocytes, which, in the presence of pro-inflammatory cytokines and complement factors, causes neutrophil activation, degranulation and release of neutrophil extracellular traps (NETs). The subsequent tissue inflammation ultimately results in fibrosis[23]; however, although ANCAs have an established pathogenetic role in AAV, other factors also contribute. Notably, individuals with active disease might be ANCA-negative and others that do not exhibit any features of AAV can test positive for ANCA[24]. Multiple MPO and PR3 epitopes, as well as alternative ANCA specificities, could account for differences in pathogenicity[25,26].

The use of standard immunosuppressive therapies, such as cyclophosphamide, has improved survival in patients with AAV and converted a frequently fatal condition to one that follows a chronic relapsing–remitting course[27,28]. However, a substantial proportion of patients still develop end-organ damage, such as ESKD, experience disease relapse or suffer toxicities from treatment, which affects quality of life and life expectancy[29,30]. The identification of key pathogenetic players, including B cells and the complement system, supports the development of so-called 'targeted' therapies, such as rituximab and avacopan, and fosters the evaluation of innovative treatments that could expand therapeutic options for AAV. Furthermore, strategies to reduce the occurrence of infections, a leading cause of death among patients with AAV, and to address comorbidities that often accompany vasculitis, such as chronic kidney disease (CKD), are being investigated or are already available. This Review discusses current treatment, advances and controversies in the management of AAV.

Current treatment and controversies

Patients with MPA and GPA are often grouped together in clinical trials and receive similar immunosuppressive regimens, which typically includes a 3–6-month phase of 'induction of remission' followed by a prolonged phase of 'maintenance of remission'. Remission is defined as the cessation of disease activity, and should be qualified by time since treatment start, and the need for ongoing therapy, such as oral glucocorticoid dose[31]. These parameters have varied between trials, meaning that remission rates cannot be directly compared between studies, although two major trials have used a Birmingham Vasculitis

Activity Score of zero at 6 months and glucocorticoid withdrawal in their remission definitions[32,33]. As biomarkers for active disease and remission are scarce, disease activity is quantified using the validated Birmingham Vasculitis Activity Score, or its derivatives, a checklist of clinical features of active disease, such as haematuria and nasal crusting[34]. Certain clinical features are not unique to vasculitis and thus distinguishing those symptoms that occur as a result of other causes, including damage (that is, irreversible organ dysfunction no longer responsive to immunosuppression), can be problematic. Long-term sequelae of disease and/or treatment also include infertility, malignancy and cardiovascular disease.

Guidelines for the management of AAV have been updated by international societies in the past 5 years[35–37]. The following sections discuss the induction and maintenance of remission, with Table 1 and Table 2 outlining features of the main therapies. The main controversies on the use of current treatments are summarized in Table 3.

Induction of remission

The main regimen to induce remission in AAV is a combination of glucocorticoids with rituximab or cyclophosphamide. This approach results in remission within 6 months in 70–90% of patients, depending on the stringency of the definition, the threshold dose of glucocorticoids applied and the other immunosuppressive therapies used[36]. For patients without organ-threatening or life-threatening manifestations, such as glomerulonephritis, alveolar haemorrhage, mononeuritis multiplex, meningeal involvement and retro-orbital disease[36,38], alternatives to cyclophosphamide and rituximab include mycophenolate mofetil and methotrexate but use of these drugs is complicated by higher relapse rates than cyclophosphamide[39–42]. Furthermore, plasma exchange (PLEX) and intravenous immunoglobin are used in addition to immunosuppressive therapies for selected patients. In 2021, avacopan, an oral complement inhibitor, was approved as an adjunctive treatment to cyclophosphamide or rituximab and a lower than standard dosing regimen of glucocorticoids.

Refractory disease, that is, failure to achieve remission with standard treatment protocols, inability to taper glucocorticoids to a low dose or disease progression, occurs in 10–30% of patients with AAV[31]. Treatment options include switching from rituximab to cyclophosphamide and vice versa, adding avacopan, PLEX or intravenous immunoglobin, but the prognosis and quality of life remain poor in this group[31,43]. Causes of secondary vasculitis, including recreational drugs and malignancy, should be considered in all patients, particularly those with refractory disease[44].

Glucocorticoids. Findings from clinical trials indicate that the dose of glucocorticoids, a major determinant of toxicity, can be substantially reduced from the previous standard dosing without affecting treatment efficacy (Table 1). In the international PEXIVAS trial of over 700 patients with AAV with kidney involvement (estimated glomerular filtration rate (eGFR) < 50 ml/min/1.73 m^2) and/or alveolar haemorrhage treated with cyclophosphamide or rituximab, a reduced glucocorticoid tapering regimen, resulting in a 40% lower cumulative dose of oral prednisone at 6 months than the standard tapering regimen, was non-inferior for efficacy and associated with fewer serious infections[45]. The LoVAS trial also found reduced-dose prednisolone (0.5 mg/kg per day) in combination with rituximab to be non-inferior to high-dose prednisolone (1 mg/kg per day). However, in this study, all of the patients were from Japan and had predominantly newly diagnosed AAV with MPO-ANCA and mild kidney involvement, potentially limiting the generalizability of the results[46]. In the international RITAZAREM trial, which enrolled patients with relapsing disease, investigators were allowed to choose between prednisone starting at 0.5 or 1 mg/kg per day, alongside rituximab, and no difference in remission rates was observed between the two glucocorticoid regimens[47]. Overall, these results encourage minimization of the dose of glucocorticoids, but these drugs remain a highly valuable treatment in the initial management of AAV. High-dose intravenous glucocorticoids, usually 1–3 g of pulse methylprednisolone over 3 days, are often administered prior to commencing oral prednisolone, and their use was allowed in most trials, including those investigating oral glucocorticoid reduction[33,45,47,48]. No randomized trial has assessed whether the addition of methylprednisolone pulses is beneficial in AAV; hence, evidence is lacking to support this practice (Table 3). Some studies report no difference in efficacy but an increased risk of infections with intravenous glucocorticoids, and their use is recommended only for patients with features of organ-threatening or life-threatening disease, such as those in the PEXIVAS trial[36,49,50].

Rituximab and cyclophosphamide. Rituximab, a B cell-depleting, chimeric monoclonal antibody that targets CD20, has been increasingly used since the RAVE study found it to be non-inferior for remission induction to cyclophosphamide, a cytotoxic agent that has long been standard of care in AAV, followed by azathioprine[32]. Compared with cyclophosphamide, rituximab is not associated with an increased risk of malignancy or infertility, and was superior for those individuals with relapsing disease and PR3-ANCA positivity[51,52] (Table 1). Furthermore, a post hoc analysis of the same trial showed no difference in kidney outcomes between the two regimens[53].

However, because those with creatinine >4 g/dl were excluded from the RAVE trial, it remains unknown whether rituximab and cyclophosphamide are also equivalent in patients with a substantially reduced eGFR. Retrospective observations show similar results of both regimens among those with advanced kidney failure and in the PEXIVAS trial the type of induction therapy was not associated with the composite outcome, although the trial was not powered to compare rituximab and cyclophosphamide[45,54–56]. Notably, the current recommended PEXIVAS reduced-dose glucocorticoid schedule is lower than the oral glucocorticoid regimen used in the RAVE trial; however, most patients in the PEXIVAS trial received cyclophosphamide and among those treated with rituximab there was a trend favouring the standard-dose glucocorticoid regimen, which raises concern that reduced-dose glucocorticoids might be less effective than the standard dose when given with rituximab[45]. Unlike cyclophosphamide, rituximab does not have a direct effect on myeloid cells that drive inflammation, such as neutrophils and monocytes, which might result in a slower control of disease manifestations[57,58].

Another option is the combined use of rituximab and cyclophosphamide (Table 3). The RITUXVAS trial showed that rituximab could be cyclophosphamide sparing among patients with severe renal AAV, including those with dialysis dependence. The rituximab treatment group only had 2–3 doses of intravenous cyclophosphamide, compared with 6–10 doses in the standard cyclophosphamide-only group, with no difference in the frequency of adverse events[59]. The combination of rituximab and low-dose cyclophosphamide has also been shown in observational studies to be potentially glucocorticoid sparing[60]. A randomized trial is currently underway to test whether the addition of cyclophosphamide pulses to rituximab enables a more sustained remission compared with standard rituximab therapy (NCT03942887).

Table 1 | Main therapies used for induction of remission in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)

Therapy	Mechanism	Usual dosing	Use	Adverse effects	Key studies	Considerations
Glucocorticoids	Binding of the glucocorticoid receptor inhibits innate and adaptive immune cells	Intravenous: 1–3 g[a] Oral: 50–70 mg per day or 0.5 mg/kg per day[b]	Almost all patients will receive oral glucocorticoids in combination with immunosuppressive agents; intravenous use is not established but is often used in organ-threatening or life-threatening disease[e]	Infections, diabetes mellitus, hypertension, obesity, osteoporosis, cataracts and psychosis	PEXIVAS[45] LoVAS[46] RITAZAREM[47]	Rapid tapering to 5 mg per day over 3 months is effective and associated with fewer serious infections than standard tapering; use of lower doses is possible for selected patients, especially with avacopan
Rituximab	Depletion of $CD20^+$ B cells via ADCC, CDC or DCD	Intravenous: 1 g on days 0 and 14 or 375 mg/m^2 weekly for 4 weeks	All patients	Infusion reactions, infections, hypogammaglobulinaemia, poor vaccine responses, late-onset neutropenia and PML (rare)	RAVE[32] RITUXVAS[59]	Superior to cyclophosphamide in PR3-AAV and relapsing disease but not formally compared in most severe kidney presentations[c]
Cyclophosphamide	Alkylating agent that suppresses the proliferation of innate and adaptive immune cells	Intravenous:15 mg/kg[d] every 2–3 weeks for 6–10 doses Oral: 2 mg/kg per day[d] for 3–6 months	Administered for organ-threatening or life-threatening disease[e] if rituximab is not available or in combination with rituximab	Bone marrow suppression, infections, cystitis, sterility and malignancy (skin, bladder and bone marrow)	CYCLOPS[200,201] RITUXVAS[59]	Intravenous route is preferred (~50% lower cumulative dose); the addition of rituximab could be dose-sparing
Avacopan	C5aR antagonist that inhibits neutrophil chemotaxis, priming and activation	Oral: 30 mg twice daily for 1 year	Adjunctive therapy in patients at risk of glucocorticoid-related adverse effects, organ-threatening or life-threatening disease[e]	Liver toxicity (rare) Leukopenia (rare)	ADVOCATE[33]	Large glucocorticoid-sparing effect that enables quick tapering; kidney function recovery is greatest with poor baseline eGFR
Plasma exchange	Removal of circulating ANCA	Seven exchanges (60 ml/kg)	Adjunctive therapy for patients with kidney involvement and creatinine >300 µmol/l (3.4 mg/dl)	Increased risk of serious infections and bleeding and infusion reactions (uncommon)	PEXIVAS[45] MEPEX[48] Walsh et al.[64]	No effect on mortality; possible lower risk of ESKD at 1 year but also more infections; recommended for individuals with double-positive ANCA and anti-GBM antibodies
Mycophenolate mofetil	Inhibition of de novo purine synthesis, which suppresses lymphocyte proliferation	Oral: 1–1.5 g twice daily	Used as an alternative to rituximab in new-onset, non-organ-threatening[f] AAV	Poor gastrointestinal tolerance, bone marrow suppression and herpes zoster	MYCYC[39]	Higher relapse rate than cyclophosphamide in PR3-AAV
Methotrexate	Increased adenosine release, NOS uncoupling and increased sensitivity of T cells to apoptosis	20–25 mg per week oral or subcutaneous	Alternative to rituximab in new-onset, non-organ-threatening AAV[f]; contraindicated in eGFR <30 ml/min/1.73 m^2	Nausea, diarrhoea, liver toxicity, leukopenia, chemical pneumonitis, liver fibrosis and dose adjustment needed with CKD	NORAM[42]	Less effective than cyclophosphamide in multiorgan and pulmonary disease
IVIG	Immunomodulating effects that are mediated by FcγR and FcRn	2 g/kg	Adjunctive therapy in refractory AAV (not recommended)	Adverse reactions (which are usually mild) and anaphylaxis in IgA deficiency	Jayne et al.[202]	Effects are not sustained in the long term; beneficial in patients with hypogammaglobulinaemia, high infection risk and PML

ADCC, antibody-dependent cytotoxicity; CDC, complement-dependent cytotoxicity; CKD, chronic kidney disease; DCD, direct cell death; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FcγR, factor crystallizable gamma receptors; FcRn, neonatal factor crystallizable receptor; GBM, glomerular basement membrane; IVIG, intravenous immunoglobulin; NOS, nitric oxide synthase; PML, progressive multifocal leukoencephalopathy; PR3, proteinase 3. [a]Methylprednisolone or equivalent. [b]Prednisone or equivalent. [c]Serum creatinine > 354 µmol/l (4 mg/dl) or alveolar haemorrhage requiring mechanical ventilation. [d]Dose adjusted to age and estimated glomerular filtration rate. [e]Glomerulonephritis, alveolar haemorrhage, mononeuritis multiplex, meningeal involvement, central nervous system involvement, retro-orbital disease, mesenteric involvement and cardiac involvement[36]. [f]ENT disease without bone involvement, cartilage collapse or deafness, skin involvement without ulceration, non-cavitating lung nodules and episcleritis[36].

Plasma exchange. PLEX is aimed at rapidly removing ANCAs and has been in use for 40 years as an adjunctive treatment for life-threatening manifestations of AAV (Table 1). The MEPEX trial reported a reduced risk of ESKD at 1 year for patients presenting with a serum creatinine >500 µmol/l (5.7 mg/dl) who received PLEX. However, results from the PEXIVAS trial, which was larger than the MEPEX trial, did not show a significant reduction in time to the composite outcome of death and/or ESKD over an average follow-up of 3 years for patients presenting with

a eGFR <50 ml/min/1.73 m^2. There was a trend in the PEXIVAS trial that favoured PLEX on ESKD for the subgroup of patients with creatinine >500 µmol/l (5.7 mg/dl) but no effect on mortality was observed, which is perhaps explained by the multi-factorial nature of this end point. However, a post hoc analysis of the PEXIVAS trial found that early recovery of kidney function was significantly improved with PLEX and was associated with a reduced risk of ESKD at 12 months[61]. Furthermore, although PR3-ANCA is associated with more active histological lesions and greater kidney recovery than MPO-ANCA, eGFR improved with PLEX similarly in both groups, compared with individuals who did not receive PLEX, which indicates that the response to PLEX does not differ according to ANCA serotype[10,61–63].

An updated meta-analysis of nine randomized trials, including MEPEX and PEXIVAS, identified a significant reduction in the risk of ESKD, but not death, at 1 year in patients who received PLEX. Notably, the estimated absolute risk reduction was greater with increasing baseline creatinine, which was 5% for those with creatinine 300–499 µmol/l (3.4–5.6 mg/dl) and 16% for those with creatinine >500 µmol/l (5.7 mg/dl), suggesting that PLEX provides greater benefit in those at a higher risk of ESKD[64]. The meta-analysis also concluded that PLEX increases the risk of serious infections and benefits on kidney survival attenuate with time. As a result of these analyses, current guidelines and recommendations state that PLEX can be considered for patients with a serum creatinine >300 µmol/l[36,37,65] (Table 3). By contrast, PLEX should always be used in patients who are double-seropositive for ANCA and anti-glomerular basement membrane (GBM) antibodies; however, PLEX dosing in AAV is uncertain, with the probability that ANCA removal is incomplete, and no studies have used a PLEX regimen aimed at ANCA negativity, as is recommended for anti-GBM disease. Using more effective methods of reducing ANCA levels, such as immunoadsorption or imlifidase, will better address the question of the therapeutic benefit of this approach[66].

Therapies used for maintenance of remission

Relapse, which is defined as the reappearance of active manifestations following remission, occurs in one third of patients with AAV within 18 months of induction therapy[52,67]. Traditional disease-related risk factors include diagnosis of GPA, PR3-ANCA positivity, ENT involvement and previous history of relapse, but translating these risk factors into personalized strategies remains challenging[52,67,68]. In view of their toxicity, glucocorticoids should be reduced to low doses, such as 5 mg per day, by 6 months or earlier (Table 2). The effect of glucocorticoid discontinuation is unclear and has been investigated in patients with GPA who achieved remission by the TAPIR trial (NCT01933724). Preliminary results show that patients who discontinued treatment with prednisone had a higher frequency of 'minor' but not 'major' relapses

Table 2 | Main therapies used for maintenance of remission in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)

Therapy	Mechanism	Usual dosing	Indication	Adverse effects	Key studies	Considerations
Glucocorticoids	Binding of glucocorticoid receptor inhibits innate and adaptive immune cells	Oral: 5 mg per day[a] or less, discontinuation should be considered	Not always required	Obesity, diabetes mellitus, hypertension, osteoporosis, infections, cardiovascular disease, adrenal insufficiency, cataracts and psychosis	LoVAS[203] RITAZAREM[71] TAPIR[69]	Cumulative dose is associated with toxicity; discontinuation appears to be safe in patients on rituximab
Rituximab	Depletion of CD20$^+$ B cells via ADCC, CDC or DCD	Intravenous: 0.5–1 g every 6 months for 24 months or more	First choice for all patients	Infusion reactions, infections, hypogammaglobulinaemia, poor vaccine responses, late-onset neutropenia and PML (rare)	MAINRITSAN[70] RITAZAREM[71] MAINRITSAN-3[72]	Patients who frequently relapse might benefit from 4-monthly dosing and extended course (such as 1 g per year)
Azathioprine	Purine analogue that suppresses lymphocyte proliferation	Oral: 2 mg/kg per day orally for 24 months	Inferior alternative to rituximab; used after cyclophosphamide induction	Bone marrow suppression and liver toxicity	CYCAZAREM[204] REMAIN[73]	Prolonged course of >24 months is associated with fewer relapses; safe in pregnancy
Mycophenolate mofetil	Inhibition of de novo purine synthesis, which suppresses lymphocyte proliferation	Oral: 0.5–1 g twice daily for 24 months	Inferior to azathioprine in non-organ-threatening AAV[b]	Poor gastrointestinal tolerance, bone marrow suppression, herpes zoster and malignancy	IMPROVE[205]	Higher relapse rates and no safety advantage compared with azathioprine
Methotrexate	Increased adenosine release, NOS uncoupling and increased sensitivity of T cells to apoptosis	20–25 mg per week (oral or subcutaneous) for 24 months	Alternative to azathioprine in non-organ-threatening AAV[b]; contraindicated in eGFR <30 ml/min/1.73 m^2	Nausea, diarrhoea, liver toxicity, leukopenia, chemical pneumonitis, liver fibrosis, dose adjustment with CKD	WEGENT[206,207]	Similar rate of relapse to azathioprine but trend towards more adverse events
Leflunomide	Inhibition of uridine monophosphate synthesis and suppression of lymphocyte proliferation	Oral: 30 mg per day for 24 months	Alternative to azathioprine in non-organ-threatening AAV[b]	Hypertension, liver toxicity, leukopenia, rash, chemical pneumonitis and peripheral neuropathy	Metzler et al.[208]	Possibly superior to methotrexate but with a higher rate of adverse effects

ADCC, antibody-dependent cytotoxicity; CDC, complement-dependent cytotoxicity; CKD, chronic kidney disease; DCD, direct cell death; eGFR, estimated glomerular filtration rate; NOS, nitric oxide synthase; PML, progressive multifocal leukoencephalopathy. [a]Prednisone or equivalent. [b]Ear, nose and throat disease without bone involvement, cartilage collapse or deafness, skin involvement without ulceration, non-cavitating lung nodules and episcleritis[36].

Table 3 | Main controversies on current treatments for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and potential solutions

Issue	Pro	Con	Considerations
Should treatment start with IV glucocorticoids?	Immediately available Possibly faster control of inflammation Used in several clinical trials	Benefit not assessed in clinical trials Substantial increase in cumulative glucocorticoid dose Possible higher risk of serious infections	Recommended only for organ-threatening or life-threatening presentations
Should a PEXIVAS reduced-dose regimen of oral glucocorticoids be used in patients with kidney involvement and/or alveolar haemorrhage?	Non-inferior to a standard-dose regimen in combination with cyclophosphamide followed by azathioprine or rituximab Reduced serious infections and GTI than standard-dose regimen	Trend favouring higher-dose regimen among patients on rituximab	Currently recommended Early use of avacopan could enable quicker and more effective tapering Caution in patients on rituximab only
Should low-dose cyclophosphamide be combined with rituximab in organ-threatening or life-threatening presentations (such as creatinine >300 µmol/l)?	Broad suppression of lymphocytes and myeloid cells Possibly faster acting than rituximab alone Cyclophosphamide sparing in severe renal AAV (RITUXVAS[59])	No data on comparison with rituximab alone No reduction in adverse events compared with standard cyclophosphamide	Suggested benefits include a glucocorticoid-sparing effect Often also used in patients with refractory disease
Should PLEX be used to improve overall survival and the rate of kidney failure?	Greater early kidney recovery Reduced risk of ESKD at 1 year (meta-analysis)[64] Renal benefits are greatest in patients with highest baseline creatinine	No demonstrated effect on mortality Benefits for ESKD risk attenuate after 1 year Costly and invasive procedure Increased risk of infection Dosing is unclear, and was not aimed at ANCA negativity in clinical trials	Possibly only short-term benefits Consider for individuals who have creatinine levels of >300 µmol/l Imlifidase might enable more complete ANCA removal
Is a tailored rituximab regimen based on changes in ANCA levels and B cell numbers a convenient strategy to maintain remission?	Lower cumulative rituximab exposure compared with a fixed-schedule regimen Possible avoidance of unnecessary treatment in patients with a lower risk of relapse Possible lower risk of acquired immunodeficiency	Higher rates of relapse compared with a fixed-schedule regimen Inconsistent association between changes in ANCA levels and B cell numbers and relapse (particularly in GPA and PR3-AAV) Need for closer monitoring and more frequent visits to detect changes	Expectant approach could be acceptable in patients at a lower risk of relapse and milder disease or renal-limited AAV with ESKD More definitive treatments needed (next-generation anti-CD20 monoclonal antibodies, BiTE and CAR T cell therapy)

BiTE, bispecific T cell engager; CAR, chimeric antigen receptor; ESKD, end-stage kidney disease; GPA, granulomatosis with polyangiitis; GTI, glucocorticoid toxicity index; MPL, methylprednisolone.

at 6 months than those who continued on 5 mg per day (15.5% versus 4.2%, $P = 0.022$). However, no difference was observed among patients who received rituximab[69].

Both the MAINRITSAN trial, which enrolled newly diagnosed patients induced with cyclophosphamide, and the RITAZAREM trial, which recruited patients with relapsing AAV who received rituximab for induction, showed the superiority of rituximab over azathioprine for maintenance of remission, with a comparable safety profile[70,71] (Table 2). The dose of rituximab varied in these studies from 0.5 g every 6 months to 1 g every 4 months for 2 years, respectively. Relapse rates after completion of 2 years of therapy were similar in the rituximab and azathioprine arms of the RITAZAREM trial, despite a high cumulative dose, which indicates that the effect of these treatments wears off[71]. Thus, there is no evidence that prolonged treatment with rituximab 'resets' the immune system in patients with relapsing AAV and prevents the return of autoimmune manifestations, thereby modifying the long-term disease course. As a result, repeat dosing is often needed and extended therapy beyond 2 years results in fewer relapses, but the optimal duration of treatment is not established[72,73]; however, rituximab increases the risk of acquired immunodeficiency, which causes hypogammaglobulinaemia, reduces response to vaccines and infections, and tailored regimens have been used to limit exposure[74]. In a randomized clinical trial, administering rituximab upon an increase in ANCA levels or B cell repopulation was associated with a lower cumulative rituximab dose than a fixed-schedule regimen, but with a numerically higher risk of relapse, which raises questions about the ability of these biomarkers to guide individual therapy[75].

Persistent ANCA positivity or reappearance after induction therapy is associated with a higher risk of relapse than stable ANCA negativity, and might warrant continuation of rituximab. However, only half of the patients who are ANCA-positive experience a relapse, whereas episodes of minor relapse can occur without changes in ANCA level or in patients who are ANCA negative[52,68,73,76–78]. Clinical phenotype could facilitate the interpretation of serial ANCA measurements, as an increase in ANCA levels seems to be more strongly associated with relapse in patients with vasculitic manifestations, particularly kidney involvement, than in those with non-renal and granulomatous disease[78]. Similarly, MPO-ANCA status shows a higher association with risk of relapse than PR3-ANCA, possibly because it is more strongly associated with vasculitic manifestations. A study of a large cohort of patients with MPO-AAV and kidney involvement found that relapses are virtually absent in patients who achieve and maintain MPO-ANCA negativity, whereas the risk is markedly increased with reoccurrence or persistence of MPO-ANCA[77]. Hence, rituximab could be discontinued in patients with renal-limited involvement who achieve MPO-ANCA negativity, given the low likelihood of relapse, and be resumed in the case of seroconversion, which shows good predictability, but decisions are more challenging for patients with PR3-ANCA and extra-renal disease.

Although a reappearance of B cell number indicates that the effects of rituximab are waning, the association of B cell repopulation

with relapse is variable. Some studies have reported that B cell reconstitution by 12–18 months preceded all episodes of relapse, whereas in other cohorts relapse occurred regardless of B cell counts[52,75,79,80]. A single-centre, randomized trial compared rituximab given upon B cell repopulation with that given after an increase in the level of ANCAs in patients who had completed 24 months of fixed-schedule rituximab[81]. The former led to fewer relapses but was associated with a higher rituximab exposure (average 1 g per year), which confirms the limitations of tailored approaches and the short-term effects of rituximab.

An advantage of the rituximab fixed interval approach is the low rate of relapse and the predictability and probable reduction in monitoring visits; however, the cumulative dose and the risk of infection and secondary immunodeficiency with rituximab could be higher than with a tailored regimen[74,82]. Using an expectant approach, whereby further rituximab treatment is only given when disease returns or an increase in ANCA levels occurs, requires close monitoring and good communication with the managing centre (Table 3). The consequences of a potential relapse should be considered based on patient prior disease course. If the effects of a relapse are likely to be mild, such as constitutional symptoms and ENT symptoms only, then an expectant approach is acceptable, whereas if major complications have occurred previously, such as loss of kidney function, then this approach would increase the risk of substantial organ damage, such as ESKD.

Advances in B cell-targeting and T cell-targeting therapies

The efficacy of rituximab supports the concept that B cells have a pivotal role in AAV[32,59,71,83,84]. B cells are precursors of plasmablasts and plasma cells, which are short-lived and long-lived antibody-producing cells, respectively, and can present antigens to T cells and orchestrate the immune response by secreting cytokines. Notably, rituximab does not target the progenitor cells that reconstitute the B cell pool, plasmablasts or plasma cells, all of which are CD20-negative and could account for persistent or recurrent ANCA positivity that underlies refractory and relapsing disease[52]. Furthermore, although complete B cell depletion is usually observed in the peripheral blood following rituximab treatment, memory B cells persist in lymphoid and target organs and have been associated with active disease[85–88]. B cell repopulation following rituximab is more frequently delayed in AAV than in other diseases, and has been associated with inherent defects in B cell development that predate the start of immunosuppression, which raises concerns about the toxicity of this therapy[89].

T cells are involved in the pathogenesis of AAV[90]. Serum markers of T cell activation, such as soluble IL-2 receptor, are elevated in patients with AAV and correlate with disease activity, whereas the expression of transcriptomic profiles of T cell exhaustion is associated with prolonged remission[91,92]. T helper (T_H) cells support B cell responses to ANCA antigens and the production of ANCAs, which are high-affinity, class-switched IgG1 antibodies. Furthermore, T_H cells are expanded in active disease and secrete cytokines that are associated with a T_H1 (IL-12 and IFNγ) and T_H17 profile (IL-6 and IL-17), which promote inflammation and damage[93,94].

Emerging B cell-depleting and B cell-inhibiting therapies developed for lymphoproliferative disorders and autoimmune diseases and agents that affect T cells have been studied in AAV. The following paragraphs discuss B cell-targeting and T cell-targeting treatments of interest for AAV (Table 4 presents the main characteristics of these therapies and Fig. 1 depicts their targets).

B cell-depleting therapies

The next-generation anti-CD20 monoclonal antibodies show greater B cell-depleting capacity and better tolerability than rituximab[95,96]. Ofatumumab, a fully human monoclonal antibody that elicits increased complement-dependent cytotoxicity, was used in seven patients with AAV, some of whom were intolerant or unresponsive to rituximab (Table 4). The treatment was effective and well tolerated, but no trial has been conducted with this agent[97]. Obinutuzumab is a humanized monoclonal antibody that causes increased antibody-dependent cytotoxicity and direct cell death via a glycoengineered Fc and has been used to successfully treat a small number of patients[98] (Fig. 1). The ongoing ObiVas trial (ISRCTN13069630) is testing the hypothesis that obinutuzumab is superior to rituximab at inducing tissue B cell depletion in patients with PR3-AAV, the primary end point being the relative percentage change from baseline in the number of $CD19^+$ cells in the nasal associated lymphoid tissue at week 26 (ref. 99). The ObiVas trial is not powered to compare the clinical efficacy of obinutuzumab with rituximab, but results could provide biological evidence of its superiority. Deeper B cell depletion might translate into a more complete and durable remission, which would be particularly beneficial for patients with refractory disease and would reduce the need for retreatment compared with rituximab. Obinutuzumab has shown promising results in lupus nephritis and membranous nephropathy, in which response to rituximab is often incomplete, but its effect in AAV will need to be determined[100,101].

Anti-CD19 monoclonal antibodies, such as inebilizumab, hold promise, because they can deplete CD20-negative plasmablasts, but they have not yet been used in AAV[102,103]. Daratumumab, an anti-CD38 monoclonal antibody that primarily targets plasma cells, seemed to be successful in a few patients with AAV who were refractory to rituximab and other treatments, which suggests that targeting the broader B cell lineage improves remission rates in AAV[104–106] (Fig. 1). The combination of an anti-CD20 and an anti-CD38 therapy has proved beneficial in some autoimmune diseases and is being evaluated in paediatric nephrotic syndrome (NCT05704400)[107,108]. Notably, CD38 is also expressed on myeloid cells and some B cell subsets; hence, the beneficial effects of daratumumab might also come about, because this therapy targets these cells in addition to plasma cells.

B cell-inhibiting therapies

Targeting molecules involved in B cell development and maturation, such as B cell activating factor (BAFF, which is also known as BLyS), could inhibit pathogenic responses without B cell depletion[109]. BAFF promotes the survival of autoreactive B cells and levels of BAFF are increased in patients with AAV compared with healthy individuals[110–114] (Fig. 1). The BREVAS trial assessed the addition of monthly intravenous belimumab, a human monoclonal antibody that neutralizes soluble BAFF and is licensed for systemic lupus erythematosus (SLE), to azathioprine for remission maintenance in GPA and MPA[115] (Table 4). Recruitment in this trial was terminated early owing to a shift towards rituximab as a maintenance agent and no effect of belimumab on relapse rate was observed; however, among the 14 patients in the belimumab arm who received rituximab at induction, no relapse occurred, suggesting that combining the two agents could have additive effects. The randomized, placebo-controlled COMBIVAS trial is evaluating the addition of subcutaneous belimumab (200 mg weekly from day 1 for 52 weeks) to a standard induction regimen of rituximab (1,000 mg on day 8 and 22) in PR3-AAV[116]. This small study (36 patients) has a primary mechanistic end point of time to PR3-ANCA negativity. Exploratory endpoints were

Table 4 | Characteristics of B cell-targeting and T cell-targeting therapies under evaluation in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)

Therapy	Target	Features	Mechanism	Strengths	Main study	Comments
B cell-depleting agents						
Obinutuzumab	CD20	Humanized IgG1 monoclonal antibody with a glycoengineered Fc	B cell depletion via enhanced ADCC and DCD Internalized less than rituximab	Improved tissue B cell depletion compared with rituximab	ObiVas (ISRCTN13069630)[99]	Potential for more complete and durable remission than rituximab
Ofatumumab	CD20	Fully human IgG1 monoclonal antibody	B cell depletion, enhanced CDC and slower dissociation than rituximab	Improved tolerability compared with rituximab	McAdoo et al. (case series)[97]	Encouraging results in patients who are intolerant or unresponsive to rituximab
Daratumumab	CD38	Humanized IgG1 monoclonal antibody	Depletion of plasmablasts and plasma cells, also targets T cells, memory B cells and NK cells	Depletion of autoantibody-producing cells	Ostendorf et al. (case report)[105] and Rixecker et al. (case report)[106]	Effective in patients who were refractory to rituximab
CAR T cells	CD19	Engineered autologous T cells	Virtually complete depletion of B cells and plasmablasts	Eradication of autoreactive B cell clones and rapid repopulation with immature, non-autoreactive B cells	Mouse model[124] and several trials in humans (NCT06152172, NCT06590545, NCT06508346)	Potential for long-term drug-free remission High costs and limited safety data
B cell-inhibiting agents						
Belimumab	BAFF	Fully human IgG1 monoclonal antibody	Inhibition of B cell survival and maturation	Preferential inhibition of autoreactive B cells	BREVAS[115]	Fewer relapses only in patients treated with belimumab and rituximab at induction
Combination of rituximab and belimumab	CD20 and BAFF	Chimeric IgG1 and fully human IgG1	Combined B cell depletion and inhibition	Increased mobilization of memory B cells and block of post-rituximab surge in BAFF	COMBIVAS[116]	Potential for enhanced response to rituximab and longer time to relapse
Telitacicept	BAFF and APRIL	TACI-Fc fusion protein	Inhibition of B cell differentiation and plasma cell functions	Potent inhibition of autoantibody production	TTCAAVREM (NCT05962840)	Findings limited to Chinese studies of patients with other rheumatic diseases (such as SLE)
Povetacicept	BAFF and APRIL	TACI-Fc fusion protein	Superior inhibition of B cell differentiation and plasma-cell functions than telitacicept	Potent inhibition of autoantibody production	RUBY-3 (NCT05732402)	Open-label study on various immune-mediated kidney diseases
T cell-targeting agents						
Alemtuzumab	CD52	Humanized IgG1 monoclonal antibody	Prolonged depletion of T cells and, to a lesser extent, B cells, NK cells and other innate immune cells	Expansion of tolerogenic T regulatory cells at reconstitution	ALEVIATE[132]	Low rate of complete response in patients with refractory AAV and high frequency of early relapses
Abatacept	CD80	CTLA4-Fc fusion protein	Inhibition of co-stimulatory signals of B cells and other APCs	Inhibition of T cell activation	Langford et al.[133] ABROGATE[134]	Preliminary results show no effect on the rate of treatment failure in relapsing, non-severe GPA
Ustekinumab	p40 subunit of IL-12 and IL-23	Humanized IgG1 monoclonal antibody	Inhibition of T helper 1 and T helper 17 responses	Reduced neutrophil priming and recruitment and reduced macrophage activation	Engesser et al.[135]	Supported by transcriptome data of kidney tissue from patients with AAV and glomerulonephritis

ADCC, antibody-mediated cytotoxicity; APCs, antigen-presenting cells; APRIL, A proliferation-inducing ligand; BAFF, B cell activating factor of the tumour necrosis factor family; CDC, complement-dependent cytotoxicity; CTLA4, cytotoxic, T lymphocyte-associated protein 4; DCD, direct cell death; GPA, granulomatosis with polyangiitis; NK, natural killer; SLE, systemic lupus erythematosus, TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor.

designed to assess the effect of the rituximab–belimumab combination therapy within both peripheral blood and lymphoid tissues. Observations that BAFF protects B cells from rituximab-induced depletion and promotes their reconstitution suggests that belimumab could enhance response to B cell-depleting therapy and consolidate remission of AAV[117]; however, this combination therapy has shown conflicting results in SLE[118,119].

A proliferation-inducing ligand (APRIL) is another cytokine of the TNF family that promotes B cell functions and shares receptors with BAFF, which includes transmembrane activator and calcium

modulator and cyclophilin ligand interactor (TACI). Dysregulation of the BAFF–APRIL system has been implicated in AAV and trials of telitacicept (NCT05962840) and povetacicept (NCT05732402), dual BAFF and APRIL inhibitors (that are based on TACI), have been launched in GPA and MPA[120] (Fig. 1).

Cell-based therapies

Anti-CD19 chimeric antigen receptor (CAR) T cells are engineered autologous lymphocytes that can eliminate CD19$^+$ cells[121] (Fig. 1). This therapy induces a profound depletion of B cells and plasmablasts and has achieved a sustained clinical and serological drug-free remission in patients with autoimmune diseases refractory to conventional treatment[122,123]. Anti-CD19 CAR T cells protected mice from MPO-ANCA-induced glomerulonephritis and also attained ANCA negativity and complete B cell depletion in the bone marrow of a patient with refractory AAV[124,125]. Several phase I–II studies will evaluate CAR T cell therapy in patients with AAV.

Despite the potential of anti-CD19 CAR T cells providing a cure by eradicating autoreactive cells, implementing this therapy in AAV remains challenging (Table 4). The production of CAR T cells is expensive and involves several steps, including leukapheresis, lentivirus-based transduction and in vitro expansion. Furthermore, patients need to receive a lymphodepleting conditioning regimen before reinfusion and be on low doses of glucocorticoids to enable good in vivo cell expansion. Therefore, the treatment requires clinical stability and might not be compatible with remission induction regimens for acute presentations of AAV. A more suitable population to treat might be patients with non-severe, refractory or frequently relapsing disease who need longer-term drug-free complete remission, thus perhaps justifying the high costs of the treatment. The risks of the known adverse events of CAR T therapy in AAV, including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, are not known but could also alter the risk-to-benefit ratio and influence patient selection.

The use of allogeneic CAR T cells from healthy donors, which, unlike autologous ones, can be immediately available, has been proposed, but these cells might cause graft-versus-host disease and be rapidly rejected by the recipient[126]. Furthermore, T cells or natural

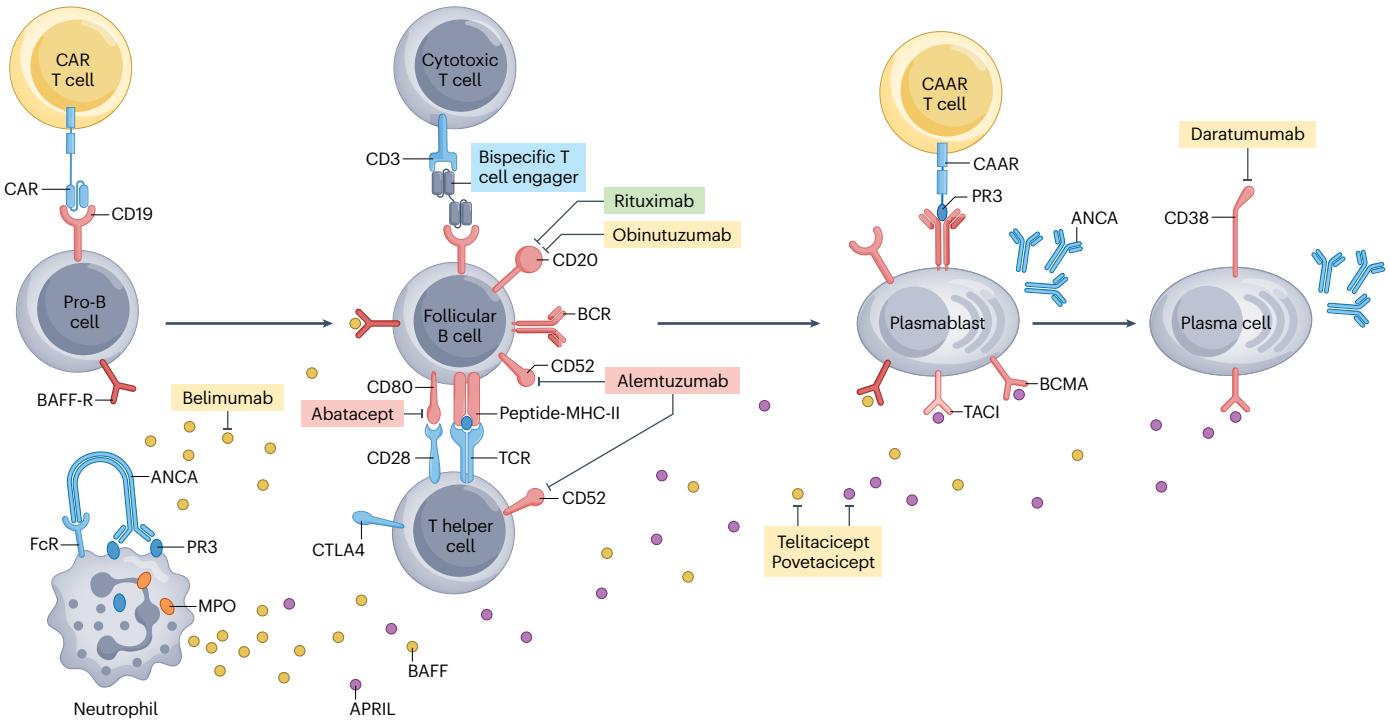

Fig. 1 | B cell-targeting and T cell-targeting therapies for AAV. Therapies that are currently approved for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are shown in green; therapies in red are those that do not have a major effect in AAV; therapies highlighted in yellow are currently under investigation or show positive results in case reports; and therapies in blue have been proposed for AAV but thus far have only been used for other conditions. CD19 is expressed by pro-B cells, B cells and plasmablasts, which can be depleted by chimeric antigen receptor (CAR) T cells or by bispecific T cell engagers. Immature, mature and memory B cells (not shown) express CD20 and are depleted by rituximab, obinutuzumab and ofatumumab (not shown), whereas plasma cells are targeted by daratumumab, which binds to CD38. Autoreactive B cells that recognize molecules such as proteinase 3 (PR3) via their B cell receptor (BCR) could be selectively eliminated by chimeric autoantigen receptor (CAAR) T cells with PR3 as the autoantigen. B cells and T cells express CD52, which is the target of alemtuzumab. Follicular B cells provide co-stimulatory signals to T helper cells and can be inhibited by abatacept, a CTLA4-like fusion protein. ANCA-stimulated neutrophils produce B cell-activating factor of the TNF family (BAFF), a pro-survival B cell factor, which is antagonized by belimumab. The B cell-stimulating cytokines BAFF and APRIL share receptors, such as TACI; TACI-like fusion proteins, including telitacicept and povetacicept, can neutralize both ligands. Other BAFF receptors include BAFF-R and BCMA, expressed at various stages of the B cell lineage. APRIL, A proliferation-inducing ligand; BAFF-R, BAFF receptor; BCMA, B cell maturation antigen; CTLA4, Cytotoxic T-Lymphocyte Antigen 4; MPO, myeloperoxidase; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor.

killer cells engineered to express a chimeric autoantigen receptor (CAAR) have been studied in some autoantibody-mediated conditions and might be used in AAV[127,128] (Fig. 1). CAAR cells are recognized by autoreactive cells and can selectively eradicate them, thereby sparing the rest of the B cell pool. Another option is bispecific T cell engagers, antibodies that target a B cell marker, such as CD19, and CD3 on T cells to create an immunological synapsis and enhance killing of B cells, which has been used in rheumatoid arthritis[129] (Fig. 1). The field of cell-based therapy is rapidly evolving and several approaches to in vivo cell production are being explored.

T cell-targeting therapies

T cells are affected by several therapies used in AAV, including glucocorticoids, cyclophosphamide, azathioprine and mycophenolate mofetil. Furthermore, cyclosporine A, a calcineurin inhibitor that suppresses activation and proliferation of T cells, showed positive results as a maintenance agent in a small trial of patients with GPA[130]. An analysis of the RITUXVAS trial found that the presence of T cell tubulitis was associated with a poor response to treatment with rituximab, highlighting the clinical relevance of targeting T cells in therapy[131]. Emerging T cell-targeted therapies have been evaluated in AAV.

Alemtuzumab is an anti-CD52 monoclonal antibody licensed for multiple sclerosis that induces sustained depletion of T cells, and to a lesser extent of B cells, monocytes and eosinophils (Fig. 1). The phase IIb ALEVIATE trial included 12 patients with AAV who were refractory to standard therapy, and compared 30 mg with 60 mg of alemtuzumab. Complete remission was only achieved in one third of patients and relapses were frequent; hence, alemtuzumab has not been proposed as an alternative to rituximab[132].

Abatacept, a fusion protein comprising an inert Fc portion and the extracellular domain of the cytotoxic T lymphocyte-associated protein 4 (CTLA-4), binds to the costimulatory proteins CD80 and CD86 and prevents T cell activation (Fig. 1). Despite good results in a pilot study[133], the phase III ABROGATE trial (NCT02108860), which compared abatacept with placebo in relapsing, non-severe GPA, demonstrated no difference in the rate of treatment failure, arguing against major benefits of this therapy in AAV[134].

Evidence of enrichment of $CD4^+$ T cells that produce T_H1 and T_H17 cytokines in the kidneys of patients with renal AAV has prompted consideration of ustekinumab, a human monoclonal antibody targeting the p40 subunit common to both IL-12 and IL-23, which promote the differentiation of T_H1 and T_H17 cells respectively (Fig. 2). Use of ustekinumab in combination with glucocorticoids and low-dose cyclophosphamide was associated with good clinical response in four patients with relapsing AAV[135].

Advances in complement-targeting therapies

The complement system comprises the classical, lectin and alternative pathways, which converge into the generation of complement component 5 (C5), which is cleaved into the anaphylatoxin C5a and the membrane attack complex, also known as C5b-9. The role of complement in AAV has long been considered minor, although complement breakdown products are detected in the serum and tissues of several patients, and correlate with disease activity[136–139]. In the past two decades, animal models have shown that the complement system, particularly the alternative complement pathway, is crucial in the development of vasculitic lesions[140–142]. C5a was identified as a critical primer of neutrophils and monocytes for ANCA-induced activation, which results in further C5a generation, sustaining the amplification of the process (Fig. 2). Genetic deletion of C5a and pharmacological inhibition of the C5a receptor (C5aR1, also known as CD88) prevents the formation of glomerular crescents in a mouse model of MPO-ANCA-induced glomerulonephritis and led to the development of therapies that target the C5a–C5aR1 axis[142,143]. The following sections discuss complement inhibition in AAV.

Avacopan

Avacopan (formally known as CCX168), an orally administered small molecule, inhibits C5aR1 but does not interfere with C5b-9, which has an important role in the defence from encapsulated bacteria, such as *Neisseria meningitidis* (Fig. 2). Its approval in 2021 as a first-in-class complement inhibitor was a milestone in the field of AAV, because avacopan is the first therapy developed with GPA and MPA as the primary indication. The phase II trials CLEAR and CLASSIC, and the phase III trial ADVOCATE showed efficacy and good tolerability of avacopan as an adjunctive therapy and its potential as a glucocorticoid-sparing therapy[33,144,145].

ADVOCATE, a double-blind, double-dummy trial, compared avacopan 30 mg twice daily for 52 weeks with prednisone 60 mg per day, tapered to discontinuation at 21 weeks, in combination with cyclophosphamide followed by azathioprine or rituximab without azathioprine, among 330 patients with newly diagnosed or relapsing AAV[33]. Participants could receive open-label intravenous methylprednisolone and oral prednisone for up to 4 weeks. Avacopan was non-inferior to prednisone in achieving remission at week 26 and superior in sustaining remission up to the end of the study (52 weeks). The avacopan group received two-thirds lower mean cumulative glucocorticoid dose than the prednisone group and suffered less glucocorticoid toxicity. Furthermore, patients on avacopan reported greater improvements in health-related quality of life than those on prednisone, which might reflect better disease control and a reduction in some of the adverse effects of glucocorticoids, such as insomnia, weight increase and skin fragility[146].

Avacopan was also associated with earlier reductions in proteinuria and greater kidney function recovery, with the best improvements observed in those patients with lower baseline eGFR (15–30 ml/min/1.73 m^2). The increase in eGFR continued beyond week 26 with avacopan, but not with prednisone, indicating sustained beneficial effects[147].

Current guidelines recommend considering avacopan as an alternative to the extensive use of glucocorticoids, in addition to cyclophosphamide or rituximab, in patients with active disease, particularly in those at an increased risk of glucocorticoid toxicity and in those with severe kidney involvement[36]. With use of avacopan, which is immediately active, rapid withdrawal of glucocorticoids at 4 weeks can be achieved for most patients. Furthermore, although avacopan has efficacy in maintaining remission, whether it has additive benefits for patients receiving rituximab for maintenance and whether it should be continued beyond 1 year remains unknown. The inhibition of neutrophil activation and degranulation by avacopan, which results in reduced release of MPO and PR3, might lower the antigenic drive that promotes the immune response towards ANCA antigens, thereby contributing to relapse prevention.

Currently, the high costs of avacopan limits both access to this therapy and the duration of treatment, and long-term treatment outcomes are not available. Post-authorization studies, such as a phase IV randomized trial (NCT06072482) and a prospective registry (NCT05897684), will further evaluate the safety of avacopan and clarify whether treatment translates into improved rates of kidney failure and overall survival[148]. Reassuringly, avacopan seemed beneficial in

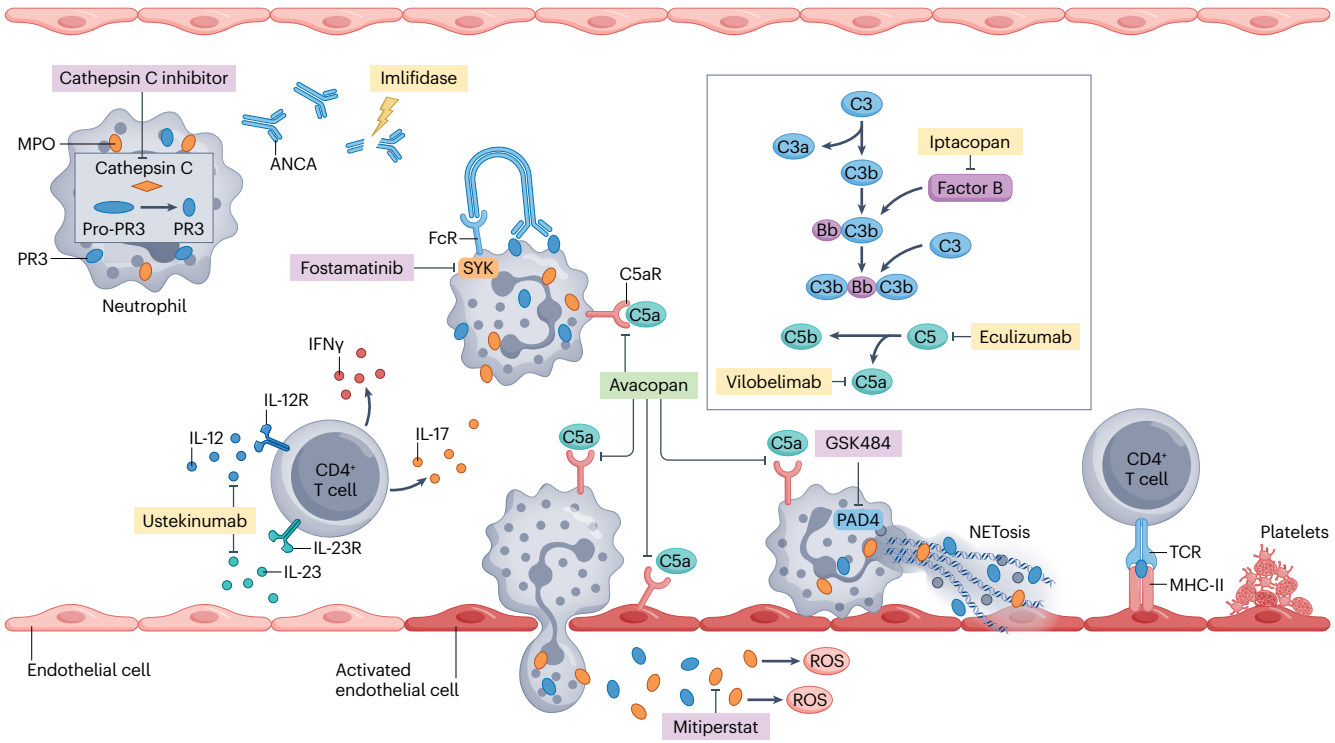

Fig. 2 | Innovative therapies targeting mechanisms of ANCA-induced inflammation. Highlighted in green are therapies currently approved for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; highlighted in yellow are therapies that have been used or are being tested in patients with ANCA-associated vasculitis; and therapies highlighted in purple show benefits in vitro or in other conditions. Cathepsin C inhibitors might prevent the activation of proteinase 3 (PR3) in the lysosomes of immature neutrophils. ANCAs can be degraded by imlifidase, ANCA-induced activation of neutrophils and monocytes (not shown) through engagement of the Fc receptor (FcR) and subsequent SYK signalling can be inhibited by fostamatinib. The alternative complement pathway, which leads to the generation of C5a, is crucial for neutrophil priming, chemotaxis and degranulation, as well as endothelium activation. Complement activation can be targeted at different stages by iptacopan (factor B), eculizumab (C5), vilobelimab (C5a) and avacopan (C5aR). Activated neutrophils release PR3 and myeloperoxidase (MPO), which enhances reactive oxygen species (ROS) production and subsequent endothelial inflammation. This process can be inhibited by mitiperstat. Neutrophils also undergo NETosis, extruding decondensed chromatin and toxic proteins, such as MPO and PR3, which are recognized by T cells. GSK484 inhibits PAD4, a key enzyme for neutrophil extracellular trap (NET) formation. IL-12 and IL-23 promote T_H1 and T_H17 cell differentiation, respectively, which results in the release of pro-inflammatory T_H1 and T_H17 cytokines, such as IFNγ and IL-17, and these pathways can be inhibited by ustekinumab. Endothelial cells become activated in response to inflammation and acquire a pro-thrombotic phenotype, which facilitates platelet aggregation. PAD4, peptidilarginine deiminase 4.

real-world populations, including in patients with hypoxic alveolar haemorrhage and eGFR <15 ml/min/1.73 m^2 or those requiring dialysis, who were excluded from the ADVOCATE trial, suggesting an effect across a wider range of presentations[149–151].

Other complement-targeting therapies

Vilobelimab (IFX-1) neutralizes C5a and prevents binding to C5aR1 and also C5L2, the other receptor for C5a, which might serve as negative modulator of the C5aR signalling pathway[152] (Fig. 2). Two phase II trials, IXPLORE (NCT03712345) and IXCHANGE (NCT03895801), showed the safety and efficacy of vilobelimab compared with prednisone, with a lower glucocorticoid cumulative dose, but further studies are not currently planned[153].

Eculizumab, and the longer-acting ravulizumab, inhibit C5 and prevent the generation of C5a and also C5b-9, which has a central role in the pathogenesis of complement-mediated thrombotic microangiopathy (Fig. 2). A few patients with AAV, including those complicated by thrombotic microangiopathy, have been successfully treated with eculizumab[154–156]. Unlike avacopan, anti-C5 therapies require vaccination and antibiotic prophylaxis against encapsulated bacteria.

Targeting components of the alternative pathway proximal to C5, such as C3, factor B and factor D, is supported by observations that their breakdown products correlate with disease activity in AAV[137,157–159]. Iptacopan, an oral inhibitor of factor B, will be investigated in a phase II study in AAV (NCT06388941) (Fig. 2); in addition, factor H-related proteins, which inhibit the main regulator of the alternative pathway, are increased in AAV and have been proposed as a therapeutic target[157]. Other emerging agents that target C3 and other aspects of the complement pathway are under consideration for treatment of autoimmune diseases, including AAV.

Although deposition of C3 and factor B in the kidney and reduced serum levels of C3 have been consistently associated with a more severe disease phenotype, no study has assessed how these factors affect response to complement antagonists[137,139,158]. Patients with signs of complement activation might benefit more from therapies that target the complement pathway and future work could identify markers that could guide the use of these therapies.

Novel targets and biomarkers

Several therapies that could complement immunosuppressive treatment in AAV are being developed. An improved understanding of disease pathogenesis has enabled the identification of novel therapeutic targets to prevent inflammation induced by ANCA. Furthermore, there is increasing awareness that fibrosis and other comorbidities, such as cardiovascular disease and immunodeficiency, contribute substantially to damage in patients with AAV and should be specifically treated. Biomarkers that enable early identification of disease and anticipate relapse could also improve management. The following section discusses advances in novel targets and biomarkers (Table 5 presents features of these therapies and Fig. 2 illustrates some of the drugs and their targets.)

Targeting antineutrophil cytoplasmic antibody-induced inflammation

Imlifidase, a recombinant protease derived from *Streptococcus pyogenes*, degrades circulating and tissue-bound human IgG and rapidly cleared ANCAs in patients with anti-GBM disease who were double-seropositive for anti-GBM antibodies and ANCA in the GOOD-IdeS-01 trial[160] (Fig. 2). Successful use of imlifidase in a patient with PR3-AAV and refractory lung haemorrhage has been reported[161]. The phase II study INFLIMIDARDSe (EudraCT-Nr. 2021-004706-22) will evaluate imlifidase in patients with AAV-related alveolar haemorrhage (Table 5).

PR3 requires activation by the lysosomal protease cathepsin C during neutrophil maturation. In vitro, cathepsin C inhibition diminishes neutrophil cell-surface PR3 expression, resulting in reduced capacity for PR3-ANCA to induce cell activation, NET formation and glomerular endothelial cell injury[162,163] (Fig. 2). These findings might prompt further investigation of cathepsin C inhibitors in AAV, which are under evaluation for bronchiectasis[164] (Table 5). MPO secreted by activated neutrophils mediates oxidative injury and correlates with kidney disease severity[165]. Inhibition of MPO ameliorated kidney inflammation in a mouse model of crescentic glomerulonephritis[166]. Mitiperstat (AZM198), an oral MPO inhibitor, has been studied in heart failure and could be considered for the treatment of AAV[167] (Fig. 2).

Spleen tyrosine kinase (SYK) mediates intracellular signalling of various receptors, including Fc engagement by ANCAs, and is upregulated in ANCA-activated neutrophils and monocytes[168] (Table 5). Increased expression of SYK is noted in glomeruli of patients with active

Table 5 | Potential strategies for the management of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)

Agent	Type	Mechanism	Effect	Main study
ANCA-induced inflammation				
Imlifidase	Recombinant IgG protease	Cleavage of IgG	Rapid clearance of ANCA	INFLIMIDARDSe (EudraCT-Nr. 2021-004706-22)
BI-9740	Oral cathepsin C inhibitor	Reduced expression of PR3	Reduced PR3-ANCA-induced neutrophil activation and NET formation	Jerke et al. (in vitro study)[163]
Niclosamide	Oral anthelminthic	Inhibition of the IL-6– STAT3 pathway and other pathways	Reduced PR3-stimulated formation of granuloma	Henderson et al. (in vitro study)[209] and Lim et al.[210]
Mitiperstat (AZM198)	Oral MPO inhibitor	Inhibition of ROS generation and NET formation	Reduced neutrophil degranulation and oxidative injury	Antonelou et al. (mouse model)[166]
Fostamatinib	Oral SYK inhibitor	Inhibition of SYK activation through ANCA engagement of Fc receptors	Reduced neutrophil and monocyte activation	McAdoo et al. (mouse model)[170]
GSK484	Oral PAD4-inhibitor	Inhibition of NET formation	Reduced MPO tissue deposition and immune response to MPO	O'Sullivan et al. (mouse model)[174]
Vilobelimab	Anti-C5a monoclonal antibody	Inhibition of C5a-mediated chemotaxis and priming of neutrophils	Inhibition of ANCA-induced neutrophil activation and glucocorticoid-sparing	IXPLORE IXCHANGE[153]
Other pro-inflammatory pathways				
Iptacopan	Oral Factor B inhibitor	Inhibition of the alternative complement pathway	Reduced complement-mediated neutrophil chemotaxis and priming	NCT06388941
Hydroxychloroquine	Oral antimalarial	Inhibition of lysosomal activity and signalling of TLR7 and TLR9	Reduced secretion of pro-inflammatory cytokines	HAVEN (NCT04316494)[211]
Fibrosis				
Lixudebart (ALE. F02)	Anti-claudin-1 monoclonal antibody	Targeting epitopes of exposed, non-junctional claudin-1	Reduced activation of pro-fibrogenic pathways	RENAL F02 (2022-502184-38)
Pirfenidone	Oral anti-fibrotic agent	Inhibition of TGFβ, PDGF, MMP and anti-inflammatory effects	Reduced fibroblast activity and chronic inflammation	NCT03385668
Cardiovascular disease				
Sparsentan	Endothelin A and angiotensin II receptor antagonist	Reduced vasoconstriction and pro-thrombotic effects	Improved endothelial dysfunction, fibrinolysis and nephroprotection	SPARVASC (NCT05630612)

ANCA, antineutrophil cytoplasmic antibody; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NET, neutrophil extracellular trap; PAD4, peptidylarginine deiminase 4; PDGF, platelet-derived growth factor; PR3, proteinase 3; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; SYK, spleen tyrosine kinase; TGFβ, transforming growth factor β; TLR, Toll-like receptor.

Glossary

Alternative complement pathway
This pathway does not require a trigger, such as immune complexes, but is instead constitutively activated through the 'tick over' of C3 and regulatory factors, such as factor H, which are required to prevent widespread activation in the absence of pathogenic stimuli.

Anaphylatoxin
A cytokine that mediates the recruitment and activation of innate immune cells.

Chimeric antigen receptor
(CAR). An engineered receptor that contains an antibody fragment that recognizes unprocessed antigen, such as CD19, and transmembrane and intracellular signalling domains of the T cell receptor complex, which provide activation and co-stimulatory signals in response to antigen binding.

Chimeric autoantigen receptor
(CAAR). An engineered receptor that contains a portion of an autoantigen, potentially PR3, which can be recognized by autoreactive cells, and transmembrane and intracellular domains of the T cell receptor complex.

Cytokine release syndrome
A supraphysiologic inflammatory response (which can progress to multiorgan failure) that can occur following treatment with any immune therapy that activates or engages endogenous or infused T cells and/or other immune effector cells.

Granulomatous inflammation
A form of tissue inflammation that is characterized by the presence of granulomas, structures in which palisading macrophages, including multinucleated giant cells and epithelioid cells and lymphocytes aggregate to surround a core of material, such as apoptotic neutrophils, that cannot be eliminated.

Immune effector cell-associated neurotoxicity syndrome
Neurological symptoms (ranging from mild confusion to seizures and cerebral oedema) that can occur after treatment with any immune therapies that activate or engage endogenous or infused T cells and/or other immune effector cells, leading to damage of the blood–brain barrier.

Immune checkpoints
Molecules that provide co-stimulatory or co-inhibitory signals to T cells that can support or inhibit their activation.

Membrane attack complex
A structure that occurs when the components of the terminal complement pathway assemble and form pores in the cell membrane that can lead to cell lysis.

Neutrophil extracellular traps
(NETs). Net-like structures composed of decondensed chromatin and granule proteins, such as MPO and PR3, that are released as a form of programmed cell death by neutrophils.

T cell tubulitis
Inflammation in the tubule-interstitial compartment of the kidney predominantly driven by T cells.

renal AAV[169]. Fostamatinib, an oral SYK inhibitor licensed for immune thrombocytopenia, ameliorated both kidney and lung lesions in a mouse model of MPO-AAV[170] (Fig. 2).

ANCAs also induce NETs, which are toxic to the endothelium and stimulate further ANCA responses[171]. Peptidylarginine deiminase 4 (PAD4) citrullinates histones and is essential for NET formation[172,173] (Fig. 2). GSK484, an oral inhibitor of PAD4, abrogated NET production, MPO deposition and glomerular inflammation in a mouse model of MPO ANCA-induced glomerulonephritis, and might have a role in the treatment of AAV[174] (Table 5).

Fibrosis

Claudin-1, a component of the epithelial tight junctions that is overexpressed and exposed at non-junctional sites by parietal epithelial cells in glomerular crescents, has been associated with glomerulosclerosis (fibrosis within the glomeruli)[175,176]. Lixudebart (ALE.01), a monoclonal antibody that targets an epitope of the exposed, non-junctional claudin-1, reduced proteinuria and fibrosis in a mouse model of MPO-ANCA-induced glomerulonephritis[177]. The phase II trial RENAL-F02 (NCT06047171) is investigating whether lixudebart slows the progression to CKD in patients with renal AAV (Table 5).

Interstitial lung disease (ILD) is common in patients who are MPO-ANCA positive, and portends a poor prognosis[178,179]. Anti-fibrotic therapies, such as nintedanib and pirfenidone, are now approved for idiopathic pulmonary fibrosis, but evaluation in MPO-ANCA-ILD is limited to retrospective series[180,181]. A pilot study on pirfenidone in MPO-ANCA-ILD (NCT03385668) has completed recruitment and the results are awaited (Table 5).

Biomarkers

In the past decade, urine biomarkers with the potential to improve detection of a renal flare have been evaluated (Supplementary Table 1). Levels of urinary soluble CD163 (usCD163), a macrophage-shed scavenger receptor, are increased in AAV-related glomerulonephritis and can differentiate patients with active renal vasculitis from healthy individuals and those in remission[182,183]. A large multicentre analysis defined a usCD163–creatinine ratio threshold of 250 ng/mmol as a cut-off for active renal vasculitis and a validated diagnostic kit is now commercially available[184]. Notably, usCD163 levels reflect glomerular inflammation but are not specific to AAV and are also being evaluated in other types of glomerulonephritis[185].

Further potential blood and urinary biomarkers of disease activity have been proposed and might be combined to improve accuracy in detecting and monitoring disease flares (Supplementary Table 1). In the RAVE trial, levels of circulating immune checkpoints at study enrolment were associated with failure of rituximab and with both sustained remission and infections[186]. If these findings are replicated in independent cohorts, the use of these markers might facilitate personalized immunosuppressive treatment.

Preventing infections

During the COVID-19 pandemic, the negative effects of immunosuppressive therapies, particularly rituximab, on the development of protective antibodies following vaccination were highlighted[187,188]. In patients treated with rituximab, T cell responses do not seem to be affected, whereas B cell depletion predicted failure to achieve seroconversion[189,190]. Humoral response could be increased by additional booster vaccine doses and even with undetectable anti-spike antibodies, vaccinated individuals had a five-fold reduced risk of moderate or severe COVID-19, compared with unvaccinated individuals[191]. The PNEUMOVAS trial compared a single versus double or quadruple dose of conjugated pneumococcal vaccines (PCV13) at the start of treatment with rituximab, prior to a dose of pneumococcal polysaccharide vaccine (PPV23), in 95 patients with active AAV. Preliminary results showed that no strategy achieved response to all serotypes but when stratified for age, patients on the double dose of PCV13 had a higher probability of response than those on the single or quadruple

dose[192]. ACQUIVAS (NCT03514979) is an open-label, phase IIb study also assessing response to single doses of PCV13 and PPV23 in patients with AAV in remission. Immunogenicity of those treated with rituximab and those who received other regimens will be compared.

Chronic kidney and cardiovascular disease

Cardiovascular morbidity and mortality are elevated in patients with AAV, and the risk is particularly high among those with CKD[28,193–195]. Sodium glucose cotransporter-2 inhibitors are now a mainstay in the treatment of CKD and are used in patients with AAV, although trials leading to approval of these drugs either excluded (the DAPA-CKD trial) or only included a small number of patients with AAV (the EMPA-KIDNEY trial)[196,197]. Patients with AAV-related glomerulonephritis have also been excluded from trials of mineralocorticoid agonists[198]. Exclusion of this high-risk group contributes to care inequity and therapeutic disenfranchisement.

An investigator-initiated study found that plasma endothelin-1 is increased in patients with AAV in remission, compared with healthy volunteers, and correlates with arterial stiffness and endothelial dysfunction, which are known to increase the risk of cardiovascular events. Endothelin-1 inhibition was able to attenuate these changes and sparsentan, a dual endothelin-1 receptor A and angiotensin II receptor antagonist, is being evaluated (NCT05630612) in patients with AAV[199].

Conclusions

Current treatments for AAV achieve high rates of survival and remission but patients remain burdened with a substantial risk of relapse and toxicity. Emerging therapies provide promising opportunities to further improve outcomes. The excellent results of rituximab encourage the evaluation of next-generation anti-CD20 monoclonal antibodies, whereas use of B cell-inhibiting therapies, such as belimumab, and T cell-targeting agents, such as abatacept, seems less successful. Furthermore, recognition of the importance of the complement system in the pathogenesis of AAV has led to the approval of avacopan, which holds promise in achieving a substantial reduction in glucocorticoid dose, with better disease control and greater kidney recovery. A major unmet need is the development of a safe, long-term treatment for AAV; cell-based therapies are rapidly evolving and might offer a cure to patients with AAV, although translation of these therapies into clinical practice is challenging. Furthermore, pathways involved in ANCA-induced inflammation and fibrosis have been identified as potential targets. Improving trial endpoints will also be crucial to show the superiority of emerging therapies to those currently available. In this regard, alongside large global trials, studies on smaller and homogeneous populations can focus on mechanistic endpoints and biomarkers. The management of AAV has made major steps forward in the past decades and continues to advance steadily.

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Author contributions

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Review article

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The pathogenesis, clinical presentations and treatment of monogenic systemic vasculitis

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Abstract

Many monogenic autoinflammatory diseases, including DADA2 (deficiency of adenosine deaminase 2), HA20 (haploinsufficiency of A20), SAVI (STING-associated vasculopathy with onset in infancy), COPA syndrome, LAVLI (LYN kinase-associated vasculopathy and liver fibrosis) and VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, present predominantly with vasculitis and constitute a substantial subgroup of vasculitic conditions associated with a 'probable aetiology'. The spectrum of monogenic vasculitis encompasses all sizes and types of blood vessel, ranging from large vessels to medium-size and small vessels, and from the arterial side to the venous side of the vasculature. Monogenic vasculitis typically starts early in life during infancy or childhood; VEXAS syndrome, which presents in late adulthood, is an exception. The activation of myeloid cells via inflammasome and nuclear factor-κB pathways, type I interferon-enhanced autoimmune mechanisms and/or dysregulated adaptive immune responses have an important role in the development of immune-mediated endothelial dysfunction and vascular damage. Genetic testing is essential for the diagnosis of underlying monogenic autoinflammatory diseases; however, the penetrance of genetic variants can vary. Increased awareness and recognition of distinctive clinical findings could facilitate earlier diagnosis and allow for more-targeted treatments.

Sections

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Key points

- Monogenic vasculitis usually starts during early childhood, whereas VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome typically develops in late adulthood.
- Early recognition of distinctive clinical findings (such as early strokes) might aid diagnosis.
- Genetic diagnosis is crucial, but variable penetrance of variants should be kept in mind when interpreting findings and during genetic counselling.
- Activation of myeloid cells, type I interferon-enhanced autoimmune responses and endothelial dysfunction contribute to vascular damage.
- Increased awareness of these rare diseases could aid earlier diagnosis and initiation of targeted treatments.

Introduction

Primary systemic vasculitides are multifactorial diseases; however, in the past decade, new monogenic autoinflammatory diseases have emerged that can present with vasculitis as one of their main manifestations, diseases such as deficiency of adenosine deaminase 2 (DADA2), haploinsufficiency of A20 (HA20), LYN kinase-associated vasculopathy and liver fibrosis (LAVLI), type I interferon-mediated diseases (known as interferonopathies) such as stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) and COPA syndrome, and vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome[1–6]. Vasculitic manifestations have also been reported in association with other autoinflammatory diseases, such as familial Mediterranean fever (FMF) and mevalonate kinase deficiency (MKD), in addition to the characteristic features of these diseases[7–16]. Individuals with monogenic forms of vasculitis usually have early disease onset with distinctive manifestations along with a prominent inflammatory response. By contrast, VEXAS syndrome, which is associated with somatic variants in the *UBA1* gene, usually presents as an autoinflammatory disease of the elderly, and a considerable proportion of patients develop systemic vasculitis and thrombosis[6,17,18].

This Review aims to increase awareness of these rare autoinflammatory diseases by focusing on their vasculitic features, as they are in the differential diagnosis of the relatively more common primary systemic vasculitides. Early recognition of these monogenic conditions and initiation of targeted treatments ultimately lead to improved outcomes. We discuss the molecular pathways associated with these monogenic diseases, which affect both innate and adaptive immune responses and increase the risk of vascular inflammation and thrombosis. Some of these pathways overlap with those observed in idiopathic multifactorial forms of systemic vasculitis; thus, the identification of new targets in these pathways could lead to effective treatments for the multifactorial forms of vasculitis. Future studies that investigate the role of somatic mutations in the blood and other tissue compartments could also provide insights into the pathogenesis of different forms of vasculitis.

The spectrum of vasculitis and monogenic autoinflammatory diseases

The revised version of the international Chapel Hill Consensus Conference (CHCC) nomenclature of systemic vasculitis in 2012 includes subgroups of vasculitic conditions that are associated with a systemic disease or with a 'probable aetiology', such as infections, drugs and cancer[19]. During the past decade, several new monogenic autoinflammatory diseases have been identified with a wide spectrum of clinical features, including systemic vasculitis, which could fit into the CHCC category of 'vasculitides with probable aetiology'.

The vessels that are affected by monogenic autoinflammatory diseases can vary, but mainly involve small and/or medium-size vessels. The identification of VEXAS syndrome broadened the spectrum of affected vessels to include the involvement of large vessels. VEXAS syndrome and HA20 can also affect the venous side of the vasculature[17,18] (Fig. 1).

The CHCC nomenclature aims to define the types and sizes of affected vessels to help to differentiate and diagnose systemic vasculitides. However, patients with monogenic forms of vasculitis usually have some other distinctive features (including early age of disease onset, familial aggregation) and certain non-vasculitic clinical findings (such as orogenital ulcers, interstitial lung disease (ILD) and relapsing polychondritis) that make the differential diagnosis with idiopathic systemic vasculitides possible in both paediatric and adult patients. Table 1 summarizes the distinctive features of the inherited and somatic genetic diseases covered in this Review.

Inherited monogenic vasculitides

Most monogenic autoinflammatory vasculitides follow an autosomal recessive inheritance pattern owing to loss-of-function (LOF) mutations with variable penetrance. In HA20, haploinsufficiency resulting from LOF mutations leads to an autosomal dominant inheritance pattern. By contrast, gain-of-function (GOF) variants are responsible for SAVI and LAVLI, with most arising as de novo mutations.

DADA2

DADA2 revolutionized the field as the first well-described mimic of one of the primary vasculitides, classic polyarteritis nodosa (PAN), in patients with early-onset disease. The DADA2 disease-causing mutations were originally defined in 2014 by two consortia[1,2], both of which highlight the association of the biallelic LOF variants in the *ADA2* gene (previously known as *CECR1*, which encodes adenosine deaminase 2 (ADA2)) with inflammatory systemic vasculitis and early-onset stroke.

Clinical features. DADA2 causes medium-vessel necrotizing vasculitis with systemic or skin-confined disease[20,21]. The most prominent clinical features are livedo racemosa, systemic vasculitis, early-onset stroke (often with increased acute-phase response) and varying degrees of haematological and immunological abnormalities. In a 2022 consensus report, the authors classified four DADA2 disease phenotypes: pre-symptomatic; inflammatory and/or vasculitic; haematological and immune deficient[22]. Inflammatory and/or vasculitic disease has been defined for patients with recurrent episodes of fever, acute-phase response along with findings of vasculitis involving the skin (cutaneous vasculitis and skin necrosis), nervous system (ischaemic stroke, intracranial haemorrhage and neuropathy) and other visceral organs (vascular aneurysm, ischaemia and infarction) leading to the diagnosis of classic or cutaneous PAN or Sneddon syndrome[22]. In a systematic review that compared 613 children with PAN with 207 children

with DADA2, neurological, gastrointestinal and cardiac involvements were more frequent in DADA2, whereas constitutional symptoms (such as fever and weight loss), and testis involvement, were more common in idiopathic PAN[23]. However, a major limitation of this article is that not all the historic 'idiopathic' PAN cases would have been tested for *ADA2* variants. The predilection for central nervous system involvement in DADA2 is crucial in distinguishing it from classic PAN[24]. In a single-centre study, it was suggested that the lack of marked thrombocytosis observed in patients with DADA2 could serve as a laboratory marker to facilitate the differentiation between DADA2 and classic PAN[20].

Haematological involvement can be in the form of anaemia, thrombocytopenia or even pancytopenia. The anaemia could be either red cell aplasia presenting as a mimic of Diamond–Blackfan anaemia or autoimmune haemolytic anaemia[22]. The differential diagnosis of DADA2 also includes idiopathic thrombocytopenia and Evans syndrome. Patients can also present with lymphoproliferation that resembles autoimmune lymphoproliferative syndrome or even lymphoma. Finally, the immune dysregulation of DADA2 can mimic common variable immunodeficiency; however, the most common immune abnormality is hypogammaglobulinaemia[21,22,25].

Pathogenesis. The pathogenesis of both haematological and immune dysregulation in DADA2 remains unclear. The enzyme ADA2 is highly expressed and secreted by myeloid cells; macrophage polarization and the polarization of pro-inflammatory 'M1-like' macrophages has been implicated in the promotion of inflammation and vascular damage[21]. In addition, increased interferon signatures in peripheral blood cells during the active stages of the disease have been reported[21,26,27]. An important study highlighted the role of neutrophils and neutrophil extracellular trap (NET) formation (known as NETosis) in DADA2; ADA2 enzyme deficiency can result in enhanced adenosine-mediated NETosis and subsequent TNF production[28]. Together, these studies suggest that inflammation in DADA2 is predominantly driven by activated immune cells including 'M1-like' macrophages and neutrophils. ADA2 deficiency and reduced adenosine receptor A_2R signalling might also affect haematopoietic stem cell differentiation[29]. Furthermore, disrupted T cell and B cell homeostasis is reported in DADA2, which indicates that the adaptive immune system probably also contributes to disease pathogenesis[26].

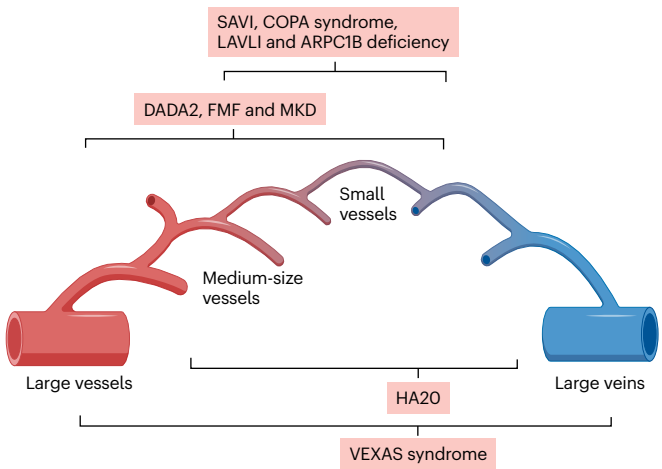

Fig. 1 | Spectrum of vascular involvement in monogenic vasculitis. Types and sizes of vascular involvement in monogenic vasculitis are given within the Chapel Hill Consensus Conference (CHCC) nomenclature figure. We modified the CHCC vascular tree, which extends from large arteries to veins, by incorporating large veins to better represent the full spectrum of vascular involvement. Small vessels are preferentially involved in stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), COPA syndrome, LYN kinase-associated vasculopathy and liver fibrosis (LAVLI) and ARPC1B deficiency; small and medium-size vessels are involved in deficiency of adenosine deaminase 2 (DADA2), haploinsufficiency of A20 (HA20), familial Mediterranean fever (FMF) and mevalonate kinase deficiency (MKD); and all types and sizes of vessels are affected in vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome. Veins are more frequently affected than arteries in HA20 and VEXAS syndrome. Adapted with permission from ref. 19, Wiley.

Diagnosis and management. The aforementioned 2022 consensus article proposed that the diagnosis of DADA2 is established by biochemical testing of ADA2 enzymatic activity in the blood (plasma or serum) and/or genetic testing[22]. Near-absent ADA2 enzymatic activity in the blood indicates DADA2, and normal ADA2 enzymatic activity excludes the diagnosis of DADA2. Genetically, the presence of biallelic pathogenic or likely pathogenic variants in *ADA2* defines a confirmatory genotype and is diagnostic of DADA2 (ref. 30). Individuals with clinical features of DADA2 and nonconfirmatory genotypes should undergo further evaluation with ADA2 enzyme activity and/or genetic testing for copy number variations and non-coding variants[22,31]. *ADA2* variants exhibit a spectrum of effects, with 91% of the DADA2-associated variants showing more than a 75% reduction in enzymatic activity[32]. The carrier frequency (when using <25% enzymatic activity as a threshold) in the healthy population is estimated to be at least 1 in 236 (refs. 32,33). Some residual activity is necessary for the development of vasculitic manifestations, and variants that cause very low or no enzymatic activity are associated with bone marrow failure and tend to present in the first year of life. Otherwise, the disease is highly heterogeneous, and although more common in children, it can also present in adulthood.

There are no randomized controlled trials of treatments for DADA2. Therapeutic recommendations are therefore based on case series and expert opinion. Retrospective studies consistently demonstrate a clear beneficial role of TNF inhibition, which substantially lowers the risk of vasculitic complications including haemorrhagic stroke[22,34,35]. No particular anti-TNF agent is more effective than others; however, etanercept is the least immunogenic and it might be favoured as it is associated with a low risk of anti-drug antibodies[22]. Glucocorticoids, conventional DMARDs, IL-1 blockade and IL-6 blockade have also been reported in the treatment of DADA2, but the long-term efficacy of these approaches seems limited in comparison with TNF inhibition[22]. TNF inhibition is beneficial for the inflammatory disease features of DADA2 but does not improve bone marrow failure or immunodeficiency[34]. The use of anti-aggregants or anticoagulants is not recommended owing to the risk of haemorrhagic stroke[22].

Allogeneic haematopoietic stem cell transplantation (HSCT) is suggested for patients with severe haematological and inflammatory phenotypes who have not responded to conventional therapy[22]. Given the relatively high frequency of pathogenic variants in the general population[32], potential donors (both unrelated and family donors) should be genetically tested before donation. Enzyme replacement and gene therapy are not available yet but could be options in the future[36].

Treatment of pre-symptomatic individuals with DADA2 is a subject of ongoing debate; however, given the unpredictable nature of the

Table 1 | Distinctive features of monogenic forms of systemic vasculitis

Disease	Gene	Inheritance pattern	Clinical findings		Pathogenesis	Treatment
			Vasculitic	Others		
DADA2	*ADA2* (also known as *CECR1*)	Autosomal recessive	Livedo racemosa, polyarteritis nodosa, early-onset strokes with lacunar infarcts, cutaneous vasculitis and skin necrosis[1,2]	Recurrent fever episodes, elevated inflammatory markers, cytopenias, lack of marked thrombocytosis, immunodeficiency and lymphoproliferation	'M1-like' polarization of monocytes and neutrophil NET formation	Anti-TNF agents and HSCT
HA20	*TNFAIP3*	Autosomal dominant (haploinsufficiency)	Retinal vasculitis, necrotizing chorioretinitis, venous thrombosis and CNS vasculitis[3]	Orogenital ulcers, intestinal ulcers, autoimmune hepatitis, thrombocytopenia, immunodeficiency and lymphoproliferation	NF-κB activation and inflammasome activation owing to defective ubiquitylation	Colchicine, glucocorticoids, immunosuppressive agents, anti-TNF agents, anti-IL-1 inhibitors, JAK inhibitors and HSCT
SAVI	*STING1*	De novo, autosomal recessive and autosomal dominant	Skin vasculopathy, peripheral ulcerative lesions, extensive tissue loss (particularly of peripheral tissues) and nasal septum perforation[4]	Interstitial lung disease, arthralgia and/or arthritis	Increased type I interferon production and NF-κB activation	JAK inhibitors and anifrolumab
COPA syndrome	*COPA*	Autosomal dominant	Skin and intestinal vasculitis and livedo reticularis[63,65]	Interstitial lung disease, arthralgia and/or arthritis, neuromyelitis optica and transverse myelitis and IgA nephropathy	Increased type I interferon production, NF-κB activation	Immunosuppressive agents, JAK inhibitors and rituximab
LYN	*LYN*	De novo	Purpuric skin rash[5]	Systemic inflammation, liver fibrosis, hepatosplenomegaly, abdominal pain, arthritis, oral ulcers, GVHD-like colitis, anaemia, leukocytosis, thrombocytopenia and autoantibodies		Dasatinib and anti-TNF agents
HCK	*HCK*	De novo	Neonatal-onset petechial skin lesions[87]	Hepatosplenomegaly, lung infiltrates (including haemorrhage) and fibrosis	Enhanced activation and migration of myeloid cells and increased β2-integrin expression	Ruxolitinib
Actinopathies	*ARPC1B*	Autosomal recessive	Cutaneous vasculitis[11,102]	Skin rash, infections and gastrointestinal bleeding	Actin cytoskeleton defects	Glucocorticoid, mycophenolate mofetil, sirolimus and HSCT
VEXAS syndrome	*UBA1*	Somatic	Leukocytoclastic vasculitis, polyarteritis nodosa and giant cell arteritis[6]	Relapsing polychondritis, neutrophilic dermatosis, macrocytic anaemia, lymphopenia, monocytopenia, thrombocytopenia and vacuoles in early erythroid and myeloid precursors	Defective ubiquitylation, protein misfolding and ER stress	Glucocorticoid, JAK inhibitors, anti-IL-6 inhibitors, azacytidine and HSCT
FMF	*MEFV*	Autosomal recessive	Protracted febrile myalgia, increased risk of IgAV and polyarteritis nososa[7,8]	Fever, peritonitis, pleuritis, arthritis and erysipelas-like erythema	Inflammasome-mediated myeloid cell activation	Colchicine and anti-IL-1 inhibitors
MKD	*MVK*	Autosomal recessive	IgAV, Kawasaki disease-like and Behçet disease-like clinical findings[14–16]	Recurrent fever from early in life, nausea, vomiting and diarrhoea	Inflammasome-mediated myeloid cell activation	Symptomatic treatment and anti-IL-1 inhibitors

CNS, central nervous system; DADA2, deficiency of adenosine deaminase 2; ER, endoplasmic reticulum; FMF, familial Mediterranean fever; GVHD, graft-versus-host disease; HA20, haploinsufficiency of A20; HCK, haematopoietic cell kinase; HSCT, haematopoietic stem cell transplantation; IgAV, IgA vasculitis; JAK, Janus kinase; LYN, LYN kinase deficiency; MKD, mevalonate kinase deficiency; NET, neutrophil extracellular trap; NF-κB, nuclear factor-κB; SAVI, stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy; VEXAS syndrome, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome.

disease, this approach is probably warranted to prevent catastrophic complications such as stroke[22].

HA20

HA20 was first described in a family of European ancestry in association with heterozygous LOF mutations in the *TNFAIP3* gene, which encodes the A20 protein[3]. The disease was described as a monogenic form of Behçet disease (a form of multifactorial variable vessel vasculitis) with early-onset systemic inflammation and other manifestations, including orogenital ulcers, anterior uveitis, skin and gastrointestinal inflammation and arthralgia and/or arthritis[3]. Examination of a larger group of patients revealed the complexity of the clinical manifestations in

HA20, including autoimmunity and lymphoproliferation[37–39], which makes the diagnosis of HA20 challenging owing to its heterogeneous presentation and the lack of pathognomonic symptoms.

Clinical features. HA20 encompasses both autoinflammatory and autoimmune features such as episodes of fever, orogenital and gastrointestinal ulcers, serositis, uveitis, choroiditis, neuroinflammation, autoantibodies, autoimmune hepatitis, haemolytic anaemia, thrombocytopenia, lupus nephritis and allergic responses including eczema, and asthma[38,39]. Some patients present with mild immunodeficiency including hypogammaglobulinaemia, IgA deficiency and recurrent infections, and some can even develop B cell lymphoma and autoimmune lymphoproliferative syndrome-like disease[38–40].

The proposal of HA20 as the monogenic form of Behçet disease was mainly owing to similarities of the mucocutaneous findings and uveitis[37]. Behçet disease involves all sizes and types of blood vessel with a preference for the venous side of the vasculature[41]. Vasculitis was reported relatively less frequently in HA20, but venous involvement was a predominant feature. Vascular pathology was reported in 5 of 177 patients (3%) in one study and 22 of 199 patients (11.06%) in another study[38,39]. Four patients from one of the studies[38,39] had venous involvement characterized as superficial thrombophlebitis, catheter-induced thrombosis, lower extremity or cerebral sinus thrombosis; two patients from the same study reported having strokes[39]. Instances of central nervous system vasculitis were also reported in the original series of patients[3]. There was only a single report of medium-size vessel vasculitis manifestations that were compatible with the diagnosis of PAN[42]. Ocular involvement was reported in 7.3–8.5% of the patients[38,39], and included retinal vasculitis, choroiditis and even necrotizing chorioretinitis; but the latter two are not features of Behçet disease[37].

The current reported cases of HA20 indicate regional and ancestral differences in the clinical presentation of the disease[38,39,43]. Recurrent fever episodes and gastrointestinal inflammation were more frequently reported in patients from East Asia than patients from other regions, whereas Behçet disease-associated symptoms, such as genital ulcers and skin findings, were observed less frequently[43]. In addition, autoantibodies and autoimmune features were detected at lower rates in patients from East Asia[43].

Pathogenesis. The protein A20 has crucial regulatory and anti-inflammatory functions in various cells including monocytes, macrophages, neutrophils, B cells and T cells. The deubiquitinase and ubiquitin-ligase activity of A20 controls the turnover of several proteins involved in intracellular signalling, including those involved in pro-inflammatory and cell-survival pathways[34,44,45]. The amino-terminal ovarian tumour domain of A20 mediates deubiquitinase activity and the carboxy-terminal seven zinc-finger (ZnF) domains, particularly ZnF4 and ZnF7, mediate the ubiquitin-ligase activity[38]. Mouse studies revealed that the deletion of the ZnF7 domain results in a spontaneous inflammatory disease that is mainly characterized by digital arthritis; however, the deletion of ZnF4 only or the ovarian tumour domains does not result in a similar phenotype[46,47]. In humans, although most disease-causing variants are truncating or nonsense mutations, several pathogenic missense variants that affect protein folding and stability have been reported[38].

Diagnosis and management. HA20 is diagnosed by genetic testing. The complex function of A20 means that genotype–phenotype correlation is not clear, although some clusters have been defined for autoimmune, gastrointestinal or mucocutaneous manifestations in association with LOF or missense variations[38,39]. Patients are usually treated with colchicine, glucocorticoids and immunosuppressive drugs, which can be effective in patients with mild disease. For refractory manifestations of HA20, anti-TNF agents are the preferred option because of the crucial role that A20 has in nuclear factor-κB (NF-κB)-mediated inflammation; blocking IL-1 signalling (using anakinra and Janus kinase (JAK) inhibitors) has also shown favourable responses[37–39]. For individuals with severe disease, HSCT could be curative[48].

SAVI, COPA and other interferonopathies

Type I interferon-mediated diseases (known as interferonopathies) are associated with GOF or LOF mutations in proteins that have a role in the sensing and degradation of intracellular viral and self nucleic acids, assembly of proteasome complexes and negative regulation of the downstream JAK–signal transducer and activator of transcription (STAT) signalling pathway[49]. Interferonopathies, including the prototypical Aicardi–Goutières syndrome, exhibit a broad spectrum of clinical manifestations, including small-vessel vasculitis that affects the skin and brain[50]. In some of these conditions, such as SAVI and COPA syndrome, vasculitic features can be more predominant.

Monoallelic GOF mutations in the *STING1* gene (previously known as *TMEM173*), which encodes STING, a key adaptor protein involved in DNA sensing and interferon production, were first reported in 2014 to induce a severe inflammatory phenotype, characterized by ILD and systemic inflammation[4,51]. Most SAVI-associated mutations are de novo and reside in the highly conserved dimerization domain[52]. The heterozygous substitution c.463G>A p.V155M accounts for 42% of reported patients with SAVI[52]. Although monoallelic inheritance is the common feature[51,53–59], biallelic (homozygous) mutations outside of the dimerization domain have also been reported in patients with SAVI[60–62]. Heterozygous, milder, mutations were associated with familial chilblain lupus[57].

Heterozygous missense mutations in COPI coat complex subunit-α (*COPA*) result in increased interferon signalling, similar to *STING1* variants, and are associated with a syndrome characterized by high titres of autoantibodies, ILD with or without alveolar haemorrhage, arthritis and nephritis[63,64]. These features were originally described in patients with heterozygous dominant LOF mutations in the N-terminal WD40 domain of COPA; however, heterozygous C-terminal variants are also reported to result in a similar phenotype of autoinflammation and autoimmunity owing to their effect on the integrity and function of coatomer protein complex I (COPI)[65]. COPI is essential to maintain STING trafficking and intracellular protein homeostasis[66].

Clinical features. Disease onset is early, often in infancy, and lung involvement is the main cause of morbidity and mortality in SAVI. More than 75% of patients described thus far present with ILD[52]. Alveolar haemorrhage has been reported in a few individuals[67]. Joint involvement, mostly polyarticular, has been reported in up to one-third of patients with SAVI[53,54,68]. Glomerulopathy has been described in only five patients with SAVI[55,68–71], notably all of whom were positive for anti-neutrophil cytoplasmic antibodies (ANCA)[72], and in one instance with adult-onset disease[55]. Skin vasculopathy, which ranges from a mild rash or livedo to severe peripheral ulcerative lesions, extensive tissue loss and nasal septum perforation, is a core feature of SAVI and has been described in 77% of patients[52].

The clinical spectrum of COPA syndrome is similar, but the age of onset and clinical severity associated with the reduced penetrance

of the variants can vary[63,65,73]. In the original 2014 study, eight of ten patients with N-terminal mutations were ANCA positive (myeloperoxidase or proteinase 3) and one patient was reported to have ANCA-associated vasculitis[63,74]; however, only one of six patients with C-terminal mutations was ANCA positive. Patients with COPA syndrome develop rheumatoid factor-positive arthritis; as this manifestation is very unusual in young patients, it could serve as a biomarker for COPA syndrome. Patients with mutations in the C-terminal domain had additional manifestations such as neuromyelitis optica and transverse myelitis in association with anti-aquaporin 4 autoantibodies, IgA nephropathy and livedo reticularis[65].

Vasculitic manifestations have also been reported in other interferonopathies, such as proteasome-associated autoinflammatory syndromes (PRAAS, also known as CANDLE). In addition to neutrophilic dermatosis with histological features of leukocytoclastic vasculitis, ANCA-associated renal vasculitis has also been reported anecdotally[75,76].

Pathogenesis. Immune responses to viral infection involve host-encoded nucleic acid-binding pattern recognition receptors, including cyclic GMP–AMP synthase (cGAS), which senses double-stranded (ds) DNA and signals through cGAMP and STING to upregulate interferon responses[52]. Upon DNA sensing by cGAS, cGAMP binds to STING, and STING activation in the Golgi leads to type I interferon production, NF-κB pathway activation and cell death induction through endoplasmic reticulum stress. SAVI-associated GOF mutations lead to constitutive activation of STING and enhance type I interferon production through IRF3 phosphorylation and inflammatory cytokine production by activating the NF-κB pathway[77].

COPA variants result in dysfunction of COPI, which affects the retrograde Golgi-to-endoplasmic reticulum transport of STING, causes endoplasmic reticulum stress and enhanced interferon production as well as the polarization of T helper 17 cells[63]. C-terminal mutations affect both anterograde and retrograde STING trafficking and activate type I interferon signalling, endoplasmic reticulum stress and NF-κB signalling[65]. Essentially, LOF mutations in COPA and GOF mutations in STING cause an accumulation of active STING and result in enhanced expression of interferon and NF-κB-induced transcripts. Type I interferonopathy is considered to have a crucial role in developing immune-mediated renal and vascular pathologies[78].

Diagnosis and management. Patients with suspected interferonopathies are diagnosed through genetic testing. In addition, transcriptomic analysis (such as measuring interferon gene signature), cytokine profiling and protein analysis (such as measuring phosphorylated STATs) are used to record the level of interferon production. Reduced penetrance is a feature of many interferonopathies, which complicates molecular diagnosis.

JAK inhibitors have been the mainstay therapy for interferonopathies. Use of baricitinib to treat monogenic interferonopathies, such as SAVI and PRAAS, can improve clinical manifestations and suppression of inflammatory biomarkers; however, full remission is not achieved in most patients, and monitoring safety and efficacy is important in risk–benefit assessment[79]. Efficacy of anifrolumab, a monoclonal antibody that binds to type I interferon receptor subunit 1 was also reported in patients with SAVI[80,81]. A EULAR and ACR task force has outlined points to consider for the clinical management of interferonopathies, including SAVI, which feature recommendations for use of glucocorticoids and baricitinib to improve symptoms[82]. These recommendations emphasize maintenance of the lowest possible glucocorticoid dose to maintain disease control to prevent organ damage[82]. Various immunosuppressive treatments, including azathioprine, mycophenolate mofetil, cyclophosphamide and cyclosporine and rituximab, are used to treat patients with COPA syndrome depending on the underlying clinical findings[63,65,73]. Baricitinib was also reported to be effective in controlling systemic inflammation and pulmonary manifestations in patients with COPA syndrome[83], and HSCT has been a successful treatment option for individuals with severe disease[84,85]. Therapies that aim to inhibit STING are in the early stages of development.

LYN kinase and HCK-associated vasculopathies

Monoallelic GOF variants in the Src family of non-receptor protein kinases, LYN kinase, are linked to severe neonatal-onset disease and vasculitis of small-vessel arteries, now known as LAVLI[5,86]. In addition, a mutation in haematopoietic cell kinase (*HCK*), which encodes another molecule that belongs to the Src family, was identified in 2022 in a patient who presented with neonatal-onset petechial skin lesions[87]. Phosphorylation at specific tyrosine residues is crucial for keeping these molecules in an inactive, closed conformation.

Clinical features. Individuals with heterozygous mutations that affect the residue Y508 in the *LYN* gene present with severe systemic inflammation and a propensity to develop liver fibrosis. Other clinical features comprise purpuric skin rash, hepatosplenomegaly, abdominal pain, arthritis, oral ulcers and graft-versus-host disease-like colitis[5,86]. Biopsy-obtained skin samples from lesions demonstrated the disruption of small vessels and myeloid cell infiltrates[5]. Haematological findings include elevated acute-phase reactants, anaemia, leukocytosis, moderate-to-severe thrombocytopenia, elevated liver enzymes and the presence of autoantibodies (including anti-Sm, anti-Ro, anti-phospholipid, anti-thyroid peroxidase and antinuclear antibodies)[5]. B cell stimulation experiments suggest a defect in central and peripheral B cell tolerance in LAVLI, which might predispose these patients to autoimmunity later in life[5]. Liver studies revealed cholestasis, microcalcifications, infiltrations with lymphocytes, macrophages and neutrophils and peri-sinusoidal fibrosis. One patient presented with liver cirrhosis at the age of 5 months[5]. One patient with a *HCK* mutation developed persistent purpura, hepatosplenomegaly, lung infiltrates and fibrosis and died from respiratory failure[87].

Pathogenesis. LYN is highly expressed in haematopoietic and endothelial cells and has an essential role in haematopoiesis and in regulating innate and adaptive immune responses. It functions primarily as a negative regulator of several signalling cascades, such as STAT5, NF-κB and mitogen-activated protein kinase (MAPK). LYN kinase autoinhibition is mediated by intramolecular interactions between the C-terminal tail and the SH2 domain. Within the short-tail R domain (amino acids 501–512), the phosphorylation at Y508 is crucial for its autoinhibition[88]. Thus far, only four patients with LAVLI have been identified, and three of the four carry monoallelic mutations that affect Y508 (Y508H/F and Y508*)[5]. One patient is a carrier for a truncating mutation Y507* (ref. 5). Mechanistically, all pathogenic variants lead to constitutive activation of LYN and its downstream target proteins. At a cellular level, LYN activation results in the upregulation of neutrophils (indicated by high β2-integrin expression) and endothelial cells (indicated by high expression of intercellular adhesion molecule 1 and E-selectin)[5]. Activated neutrophils have a higher capacity for adhesion and diapedesis through endothelial cells; activation

of endothelial cells causes loss of VE-cadherin and disruption in the endothelial barrier function. Pro-inflammatory cytokines and chemokines, such as IL-6, IL-1, IL-18, TNF and CXCL10, were increased in serum and in lipopolysaccharide-stimulated monocytes from patients with LAVLI[5].

Similarly to LYN, HCK phosphorylation at Tyr522 (Y522) is crucial to keep the molecule inactive. A de novo truncating mutation at Tyr515*, reported in a single patient, removes the inhibitory tail domain, resulting in increased protein kinase activity, enhanced activation and migration of myeloid cells and high levels of pro-inflammatory cytokine production. Mutant myeloid cells displayed high expression of β2-integrins and high capacity for binding to endothelial cells, consistent with a vasculitic phenotype[87].

Diagnosis and management. LAVLI is diagnosed using genetic testing. All reported patients were carriers of a de novo mutation[5,86]. LYN kinase activity can be inhibited by a pan-SRC kinase inhibitor, dasatinib, which is an anticancer drug used to treat chronic myeloid leukaemia and acute lymphoblastic leukaemia[89]. In patients with LAVLI, treatment with dasatinib resulted in normalization of acute-phase reactants, a substantial reduction in the pro-inflammatory immune response and regression of liver fibrosis in one patient[5]. In addition, treatment with the TNF inhibitor etanercept might help to suppress systemic inflammation. A combination therapy of dasatinib and etanercept could also be another potential therapeutic option[5].

Other monogenic diseases

Vasculitic features can emerge during other monogenic autoinflammatory diseases, or their underlying pathogenic mechanisms might contribute to an increased risk of primary vasculitides.

FMF is the most common monogenic autoinflammatory disease and is associated with pathogenic variants that affect the *MEFV* gene (which encodes pyrin[90]). Besides recurrent fever and serositis, patients with FMF might present with some typical cutaneous manifestations. Erysipelas-like erythema is the characteristic skin rash observed in patients with FMF; however, the histopathological features of these lesions are not consistent with vasculitis[91]. Protracted febrile myalgia is characterized by severe, crippling myalgia, high fever, abdominal pain, diarrhoea, arthritis and/or arthralgia and transient purpura. The vasculitic pathology observed in protracted febrile myalgia is thought to be caused by the presence of granulocytic infiltration in the walls of arterioles and the deposition of IgA in pathological specimens[92].

Patients with FMF have a higher rate of other vasculitides than the general population[7,93]. The most common form of vasculitis associated with FMF is IgA-associated vasculitis (IgAV, previously called Henoch–Schönlein purpura). In FMF, IgAV tends to recur several times, is observed in younger children and the rash can develop in unusual locations, such as the face and trunk. Biopsy-obtained skin samples typically show leukocytoclastic vasculitis without IgA deposition[94]. Another common vasculitis observed in FMF is classical PAN, which can be found in 1% of patients with FMF. Individuals with PAN and FMF tend to have earlier disease onset, more frequent perirenal haematomas, more severe myalgia and a good overall prognosis[95]. Most patients with FMF who present with PAN display high titres of antistreptolysin O[95]. There is still no consensus on whether instances of IgAV and PAN observed in FMF are coincidental or directly associated. It is highly possible that the presence of pro-inflammatory *MEFV* variants could function as a trigger for the more severe course of IgAV or provoke a pro-inflammatory reaction against streptococcal infection in PAN. The risk of Behçet disease was also found to be higher in patients with FMF than in healthy individuals[9].

Vasculitic manifestations, including IgAV, Kawasaki disease-like and Behçet disease-like clinical findings, were also observed in patients with MKD but were rare[14–16,96]. Large-vessel vasculitis that resembles Takayasu arteritis was reported in some patients with Blau syndrome[97,98].

Heterozygous LOF variants in the *RELA* gene have been linked to a Behçet disease-like condition, which is driven by NF-κB signalling defects, TNF-mediated mucosal apoptosis and impaired epithelial recovery[99,100]. However, the resemblance to Behçet disease is mainly limited to mucocutaneous findings, as vasculitis is not a characteristic feature of this mimicker, although it has been reported[99].

A growing number of monogenic immune-mediated diseases have been related to genes involved in pathways of actin cytoskeleton remodelling and identified under the term 'immuno-actinopathies'[101]. Actin is the most abundant intracellular protein in most eukaryotic cells, contributing to the acquisition and maintenance of cell structure and function. Some of these conditions can present with cutaneous vasculitis[102].

Homozygous LOF variants of the *ARPC1B* gene, which encodes the p41 regulatory subunits of the ARP2/3 complex, cause platelet abnormalities with eosinophilia and immune-mediated inflammatory disease[11]. The disease is characterized by very early clinical onset. Presenting symptoms include skin rash, infections and gastrointestinal bleeding[102,103]. Early-onset cutaneous vasculitis is one of the earliest manifestations of this condition, presenting as a maculopapular rash, erythema nodosum or vasculitic purpura. Purpuric lesions can affect the trunk, legs and scrotum. In all skin biopsy-obtained samples, there was clear leukocytoclastic vasculitis with multiple microthrombi in the vascular lesions[12,104]. Most patients experience recurrent or severe bleeding episodes, most frequently represented by gastrointestinal haemorrhage, and platelet counts are usually low. An increased rate of respiratory tract infections and skin infections, as well as atopic findings, are also observed, and *ARPC1B* deficiency is classified among the inborn errors of immunity with atopic phenotypes[102,105]. The inflammatory manifestations of this condition might respond to glucocorticoids, mycophenolate mofetil and sirolimus; co-existence of a severe immunodeficiency might necessitate HSCT treatment in a relevant percentage of patients[103].

Somatic mutations and systemic vasculitis

Mutations that arise in somatic cells later in life (somatic mosaicism) can lead to systemic inflammatory disorders, including vasculitis. VEXAS syndrome is the first identified example of monogenic vasculitis caused by somatic mutations.

VEXAS syndrome

The discovery of VEXAS syndrome in 2020 represents a paradigm shift in understanding causal relationships between genetics and complex inflammatory diseases[6]. VEXAS syndrome was initially discovered using a 'genotype-first' approach whereby genetic databases were queried for novel, deleterious variants common to patients, without consideration of clinical phenotype[6]. The results of such an approach led to the characterization of an extremely clinically heterogeneous disease that would otherwise have been challenging to appreciate fully by clinical observation alone. VEXAS syndrome is a monogenic disease of adulthood caused by somatic mutations acquired later in life within the haematopoietic system[106]. As *UBA1* is located on the X chromosome,

the disease is almost entirely restricted to men, particularly those over the age of 50 years.

Clinical features. VEXAS syndrome is considered a prototype for a new class of diseases, termed 'haemato-inflammatory diseases'[107]. Recurrent inflammation in the skin, cartilage, lungs, arteries and eyes combined with progressive bone marrow failure phenotypically defines the disease. Patients develop features suggestive of relapsing polychondritis, neutrophilic dermatosis and multiple different forms of systemic vasculitis including leukocytoclastic vasculitis, PAN and giant cell arteritis[108,109]. Macrocytic anaemia, lymphopenia, monocytopenia and thrombocytopenia are the most common haematological abnormalities[110]. The presence of vacuoles in early erythroid and myeloid precursor cells from bone marrow aspirates is strongly suggestive of the disease. Treatment-refractory systemic inflammation with progressive bone marrow failure leading to transfusion dependence and myelodysplastic syndrome often typifies disease trajectory. Pleuropulmonary manifestations, including ground-glass opacities, consolidations and pleural effusion, are also frequent; however, the response to glucocorticoids is favourable, with no progression to interstitial fibrosis[111].

Pathogenesis. The genetic landscape of VEXAS syndrome continues to evolve since its initial discovery[112]. Canonical mutations at exon 3, including missense mutations in codon Met41, define most cases and might have prognostic value[113]. These mutations cause reduced translation of the cytoplasmic isoform of UBA1 with resultant cellular stress from unfolded protein response[114]. Another set of mutations has been described that affect cytoplasmic UBA1 function instead of translational efficiency[112]. VEXAS syndrome is typically associated with a high clonal burden of disease that is readily detectable in bone marrow or peripheral blood.

Beyond being remarkably prevalent for a newly discovered disease, with estimates of 1 in 4,000 men over the age of 50 years, VEXAS syndrome demonstrates that somatic mutations and clonal populations of cells can cause complex inflammatory diseases of adulthood with vasculitic features[115]. Previously, efforts to discover somatic drivers of vasculitis were focused on a set of genes associated with clonal haematopoiesis. Acquired mutations in *DNMT3A* and *TET2*, the two most common genes associated with clonal haematopoiesis, have been detected in multiple forms of systemic vasculitis in association with ageing[116]. A relationship between the incidence of giant cell arteritis and clonal mutations in *TET2* has been reported[117]. Mutations associated with clonal haematopoiesis probably prime myeloid cells towards a pro-inflammatory phenotype and might modulate the disease course but are unlikely to be primary causal drivers of vasculitis. A similar set of mutations has been demonstrated in VEXAS syndrome, often co-occurring within *UBA1* mutant clones, in association with increased mortality risk[118].

Diagnosis and management. Genetic testing for somatic variants of the *UBA1* gene is essential to confirm diagnosis in individuals with suspected VEXAS syndrome, as indicated by clinical and haematological findings. Mutations can be detected in peripheral blood or bone marrow[119]. There are no current guidelines regarding whom to test for VEXAS syndrome. Options for genetic testing include targeted sequencing for exon 3 variants in *UBA1* or next-generation sequencing testing. Sanger sequencing, although potentially useful as a cost-effective screening test, is not sensitive enough to detect a lower clonal burden of disease (such as variant allele fractions of <20%). Although most pathogenic variants are clustered within exon 3, additional variants have been reported in other locations in association with VEXAS syndrome[112]. Next-generation sequencing panels might be useful to detect concomitant secondary mutations related to clonal haematopoiesis.

Despite advances in the understanding of disease pathophysiology, VEXAS syndrome is often refractory to treatments other than glucocorticoids, although JAK inhibitors, IL-6-directed therapies and hypomethylating agents such as azacytidine can be effective[120]. Median survival is 10 years from symptom onset, and allogenic HSCT can be curative but should be reserved for select patients, given the associated risks[72].

Inflammatory pathways and implications for idiopathic systemic vasculitis

The discovery of rare monogenic diseases manifesting with vasculitis indicated the contribution of various inflammatory pathways in the molecular pathogenesis of vascular inflammation. Thus far, most efforts to understand the pathophysiology of monogenic forms of vasculitis have primarily focused on the haematopoietic system, as peripheral blood samples are readily available from affected patients. Understanding disease biology within the vascular wall poses further challenges, given the often limited access to vascular tissue from patients and lack of animal models for most of these conditions. Although the precise pathogenic mechanisms of vasculitis remain unclear, four key pathways have a crucial role, sometimes overlapping in certain conditions (Box 1).

The physiological function of ADA2 is still enigmatic, and understanding has been hampered in part because mice lack an ADA2 orthologue, making animal studies challenging. Studies in other species, such as *Drosophila*, suggest that it could be involved in growth factor activity[121]. ADA2 has traditionally been considered an extracellular enzyme; however, its hypoglycosylated low-molecular-weight form might have intracellular functions in monocytes and macrophages, and pathogenic variants can disrupt this intracellular form in patients[122]. Transcriptomic analysis of peripheral blood mononuclear cells from patients with DADA2 revealed the upregulation of TNF, type I interferon and type II interferon pathways in both vasculitic and haematological phenotypes of DADA2 and even in asymptomatic patients[123]. ADA2 functions as a negative regulator of IFNβ and transcription of type I interferon-stimulated genes in endothelial cells, and loss of ADA2 function results in increased activity of dsRNA-sensing mechanisms and TBK1 and IRF3-mediated production of IFNβ, but its contribution to disease pathogenesis remains unclear[24,122]. Treatment with TNF inhibitors leads to a reduction in inflammation and restores the integrity of endothelial cells in blood vessels[124]. Deficiency of ADA2 results in DADA2; however, elevated ADA2 activity has been reported in patients with infections and systemic juvenile idiopathic arthritis with macrophage activation syndrome[125]. Whether aberrations in ADA2 activity contribute to the pathogenesis of multifactorial late-onset vasculitides and strokes remains to be seen. One study demonstrated that only 3.4% of patients with idiopathic PAN, who were relatively young and undiagnosed for a long time, had biallelic pathogenic or likely pathogenic variants in ADA2, and 4.2% were monoallelic carriers for three variants of uncertain importance and two likely pathogenic variants; however, none of the patients with granulomatosis with polyangiitis or microscopic polyangiitis had biallelic variants[126].

Ubiquitylation is an essential post-translational regulatory mechanism for innate immune responses, and it provides a rapid-acting control of inflammatory pathways[127]. Autoinflammatory pathogenic pathways are associated with defects in ubiquitylation in vasculitis in individuals with HA20 and VEXAS syndrome[38,106]. The A20 protein has an important 'checkpoint' function, controlling both innate and adaptive immune responses. The ligase activity of A20 adds lysin 48-linked ubiquitin chains to the targeted proteins and activates their proteasome-mediated degradation. The malfunctioning ubiquitin-ligase activity of the C terminus of the A20 protein is linked to defective inactivation of the NF-κB and inflammasome pathways, which are considered to have a main role in the inflammatory manifestations observed in these patients[38,45,128,129]. By contract, A20 might also provide fine-tuning deubiquitinase activity by cleaving lysin 63-linked polyubiquitin chains and regulating intracellular signalling through crucial components of the NF-κB pathway such as NF-κB essential modulator (NEMO), receptor-interacting serine/threonine protein kinase 1 (RIPK1) and TNF receptor-associated factor 6 (TRAF6)[38,45].

Common SNPs within the *TNFAIP3* gene locus have been associated with several autoimmune diseases[44,130,131], but the mechanisms associated with pathogenic variants and autoimmune features of HA20 have not been clarified yet. A20 might also have an inhibitory role in type I and type II interferon downstream signalling via suppression of STAT1 expression[38].

The VEXAS syndrome-associated E1 enzyme UBA1 is involved in most ubiquitylation events[112]. Loss of cytoplasmic isoform because of substitution of Met41 results in protein misfolding, endoplasmic reticulum stress and activation of inflammatory pathways[6]. Monocytes from patients with VEXAS syndrome show signs of exhaustion and aberrant expression of chemokine receptors[132]. Increased plasma concentrations of IL-1β and IL-18 owing to inflammasome activation and enrichment of TNF and NF-κB pathways in gene expression analysis of peripheral blood supports the involvement of myeloid cells in the inflammatory pathogenesis of VEXAS syndrome[132]. Inflammation-associated thrombosis, which is observed in half of patients with VEXAS syndrome, is an important vasculitic feature in this condition[17]. Venous thrombosis is more common than arterial thrombosis (cumulative incidence is 40% for venous and 11% for arterial thrombosis at 5 years after disease onset) and is usually unprovoked and recurrent despite treatments with anticoagulants[17]. A predilection for the venous side of the vasculature in HA20 and VEXAS syndrome, both linked to ubiquitylation defects, warrants further investigation.

Lastly, diseases associated with increased type I interferon signalling result in vasculitis that usually affects small vessels. The pathogenesis of vasculitis is similar to that of ANCA-associated vasculitis (typically in patients with autoantibodies to myeloperoxidase and proteinase 3) with the activation of neutrophils and stimulation of NETosis driving disease; however, other immune-mediated mechanisms might also have a role in endothelial dysfunction, thrombotic microangiopathy and endothelial barrier disruption[78]. The cGAS–STING pathway can also induce NF-κB-mediated pro-inflammatory cytokine production and myeloid cell activation[133]. Studies using the STING N153S/wild type animal model of SAVI further supports the involvement of other interferon-independent mechanisms that lead to disrupted αβ T cell development and an increased γδ T cell population[134]. Similarly, the *Copa*$^{E241K/+}$ knock-in mouse model reveals defective thymic tolerance, characterized by an increase in autoreactive T cells and a decrease in regulatory T cells, suggesting an additional potential pathogenic mechanism[135].

STING and *ADA2* genes are also expressed in endothelial cells, but the potential role of pathogenic variants in triggering intrinsic defects that lead to endothelial activation and/or dysfunction in vasculitis pathogenesis remains to be fully elucidated[4,122,136].

Box 1 | Inflammatory pathways implicated in the pathogenesis of monogenic systemic vasculitis

Although the underlying mechanisms remain unclear, numerous inflammatory pathways are implicated in the pathogenesis of monogenic systemic vasculitis.

Activation of myeloid cells
- Inflammasome-mediated upregulation of IL-1 and IL-18 pathway (FMF and MKD)
- 'M1-like' macrophage polarization and NETosis (DADA2)
- Defective ubiquitylation (HA20 and VEXAS syndrome)
- Defective regulation of immunoreceptors (LAVLI and HCK)

Type I interferon-enhanced autoimmune pathologies
- Endothelial dysfunction and damage (SAVI and COPA syndrome)
- Thrombotic microangiopathy (SAVI and COPA syndrome)
- Barrier dysfunction (SAVI and COPA syndrome)
- ANCA-associated vasculitis (SAVI and COPA syndrome)

Dysregulated adaptive immunity
- Increased autoreactive T cells (SAVI and COPA syndrome)
- Decreased regulatory T cells (SAVI and COPA syndrome)

Endothelial dysfunction
- Intrinsic defects (SAVI and COPA syndrome)

ANCA, anti-neutrophil cytoplasmic antibodies; DADA2, deficiency of adenosine deaminase 2; FMF, familial Mediterranean fever; HA20, haploinsufficiency of A20; HCK, haematopoietic cell kinase; LAVLI, LYN kinase-associated vasculopathy and liver fibrosis; MKD, mevalonate kinase deficiency; NETosis, neutrophil extracellular trap formation; SAVI, stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy; VEXAS syndrome, vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome.

Clinical considerations

The identification of several monogenic autoinflammatory vasculitides has expanded the spectrum of diseases that should be considered in the differential diagnosis of patients presenting with findings of systemic vasculitis. Although most genetic vasculitic diseases have a very early onset, some patients can be diagnosed during adulthood owing to variable penetrance of pathogenic variants or relatively mild cases that are associated with variants of unknown importance. By contrast, the development of VEXAS syndrome later in life, which is caused by somatic mutations, again emphasizes that late-onset autoinflammation can result from somatic mutations, as previously described for cryopyrinopathies and TNF receptor-associated periodic syndrome[137]. The association of idiopathic late-onset vasculitides with somatic mutations in *UBA1* and other immune and haematopoietic genes remains unclear[116,117].

Although it is important to consider all monogenic autoinflammatory vasculitides initially with their distinctive clinical findings, laboratory tests are ultimately needed to confirm diagnosis. Measuring ADA2 enzyme activity is an effective alternative to genetic analysis in patients with DADA2. Every child with PAN should be tested for enzyme activity or *ADA2* variants, whereas the necessity for testing in adults remains uncertain because of the low frequency of positive results in this age group. However, for all other monogenic conditions, genetic testing is necessary when disease is suspected. The frequency of positive results depends on the characteristics of the screened patient. For HA20, screening is advised only in patients with disease with very early onset (<5 years) that is characterized by episodic manifestations with accompanying high acute-phase response and autoimmune features[37]. In the original 2014 study, A20 variants were found to be very rare in adult patients with Behçet disease[3]. For the diagnosis of VEXAS syndrome, appropriate genetic analysis methods should be chosen for the detection of somatic variants. The likelihood of detecting a pathogenic variant depends on patient characteristics, with higher positivity rates observed in those with myelodysplastic syndrome and systemic inflammatory features or in patients with refractory vasculitis requiring ongoing glucocorticoid treatment despite the use of synthetic or biologic DMARDs[119,138].

Correct diagnosis of the vasculitic conditions associated with monogenic diseases could enable the administration of more-targeted treatments that target specific pathogenic pathways, ranging from colchicine to anti-TNF agents, anti-IL-1 inhibitors or JAK inhibitors. HSCT might be a preferred treatment option, with favourable outcomes reported in patients with DADA2 with haematological manifestations associated with very low or absent enzymatic activity or in selected cases of severe forms of other monogenic vasculitides[33,139].

Successful use of treatments such as anti-TNF agents, anti-IL-1 inhibitors or JAK inhibitors that target the primary pathogenic mechanisms in monogenic diseases suggests the potential of these therapies in multifactorial systemic vasculitides with similar clinical findings.

Conclusions

Monogenic autoinflammatory diseases constitute an important group within the vasculitic conditions and can be classified under 'vasculitis associated with probable aetiology' in the 2012 CHCC. DADA2, HA20, SAVI, COPA syndrome, LAVLI and VEXAS syndrome can present with predominantly vasculitic manifestations[1–6,63]. The spectrum of vasculitis covers all sizes and types of blood vessel, ranging from large vessels to medium-sized and small vessels, and from the arterial side to the venous side of the vasculature. Activation of myeloid cells through inflammasome and NF-κB pathways, type I interferon-enhanced autoimmune pathologies that involve B cells, autoreactive T cells, dysfunctional regulatory T cells and endothelial cells have an important role in the development of immune-mediated vascular damage. Increased awareness of these rare diseases can facilitate earlier diagnosis and allow for more-targeted treatments.

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Author contributions

The authors contributed equally to all aspects of the article.

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Consensus statement

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2023 International Rome consensus for the nomenclature of Sjögren disease

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Abstract

Nomenclature for the disease widely known as Sjögren syndrome has proven unsatisfactory. Patients have perceived 'syndrome' as indicative of a vague collection of symptoms, prompting the Sjögren's Foundation to abandon the term. Furthermore, the traditional distinction between 'primary' and 'secondary' forms fails to account for the complex interplay between overlapping autoimmune diseases. Following a bibliometric analysis, systematic literature review and a Delphi consensus process with equal involvement of professional and patient representatives, five recommendations are now issued. First, the term 'Sjögren disease' should replace 'Sjögren syndrome'. Second, the acronym 'SjD' should be used as an abbreviation for 'Sjögren disease'. Third, the descriptor 'associated' should be used in lieu of 'secondary' for Sjögren disease occurring in association with a second systemic autoimmune disease for which classification criteria are fulfilled. Fourth, Sjögren disease is the preferred terminology in common parlance and in clinical diagnosis, without differentiation as to primary and associated forms. Fifth, the differentiation between primary and associated Sjögren is recommended for scientific studies to define a homogeneous population. In conclusion, the consensus endorses 'Sjögren disease' as the official nomenclature to acknowledge the distinct pathogenesis of this disorder and to improve clarity in both clinical practice and research.

Sections

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Introduction

The disease known widely as Sjögren syndrome affects 1–72 per 10,000 people[1] and presents with a diverse spectrum of clinical manifestations[2,3]. The first cases were reported during the late nineteenth century and were manifested by severe ocular and oral dryness. In 1926, Henri Gougerot[4] reported the association of several sicca manifestations in what was probably the first description of the disease. However, there is unanimous agreement in the scientific community that its first comprehensive description as a specific disease was made by the Swedish ophthalmologist Henrik Sjögren in his doctoral thesis published in 1933 (refs. 5,6). In 1936, Stephan Von Grósz[7] honoured Sjögren by describing the disease as Sjögren syndrome. The disease received broader recognition after Sjögren's thesis, which was originally published in German, was translated into English in 1943 (ref. 8). The occurrence of Sjögren syndrome as a 'sicca complex' in association with rheumatoid arthritis (RA), systemic sclerosis (SSc) or myositis or as a 'stand-alone' disease was highlighted by researchers at the NIH in the early 1960s[9]. In 1979, Haralampos M. Moutsopoulos et al.[10] coined the terms 'primary' and 'secondary' Sjögren syndrome, considering clinical, serological and genetic characteristics of individuals presenting with sicca-related manifestations, either alone or coexisting with RA; these terms have since been used almost universally to refer to and classify this medical condition. This nomenclature and classification approach has been debated in recent years, as researchers have highlighted concerns about the inaccuracy of referring to a disease as a syndrome[11,12] and also the lack of value in distinguishing primary from secondary forms of the disease[1,13–17].

During preliminary discussions for the organization of the International Symposium on Sjögren Syndrome (ISSS) in Rome, Italy (7–10 September 2022), two different nomenclature-focused projects emerged: one from the USA (led by A.N.B.) and one from Europe (led by M.R.-C.). These two proposals were merged, and an international Task Force was created with the aim of developing a rational consensus on the nomenclature of Sjögren syndrome (referred to hereafter in this manuscript as 'Sjögren') based on the clinical experience of international professionals, current scientific knowledge and the perception and experience of patients.

We report herein the results of a comprehensive process to validate a change in nomenclature for Sjögren, including a bibliometric analysis to determine current terminologies applied to this disease across several languages and countries, a systematic literature review (SLR) to define a rationale for distinguishing primary from secondary forms of the disease, and a Delphi consensus process with respect to disease nomenclature, involving both international professionals and patient groups.

Methods

The convenors (M.R.-C. and A.N.B.) invited international experts with an established record of clinical research in Sjögren to participate in the Delphi consensus process. The Steering Committee (M.R.-C., A.N.B., E.K.A., C. Baldini, H.B., C. Bouillot, S.J.B., T.D., K.M.H., L.L., S.M.L., X.M., S.C.P., V.S., A.G.T., M.d.P.B.-Z., B.A.F.) included eight rheumatologists, two internal medicine specialists, two ophthalmologists, two oral medicine specialists, one paediatrician and two patient representatives. The Working Group (J.-M.A., B.A., M.B., S.C., S.d.V., R.I.F., R. Gerli, R. Giacomelli, J.-E.G., G.H.-M., R.J., A.K., S.K.-K., X.L., S.S.M., H.M.M., W.-F.N., P.O., S.R., M.R., A.S., R.H.S., A.S.-A., V.V., C.V., F.V., M.W.-H.) and the Task Force (see list at the end of the article) included 79 specialists in rheumatology, internal medicine, oral medicine, family medicine, paediatrics, ophthalmology, otolaryngology, genetics and other health professionals from 28 countries (Australia, Brazil, Canada, China, Colombia, Egypt, France, Germany, Greece, Hungary, India, Italy, Japan, Mexico, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, South Korea, Spain, Sweden, Turkey, Uruguay, UK and USA). Members of the Working Group were experts with a strong background in clinical research on Sjögren from centres not represented in the Steering Committee; they contributed to the drafting of the Delphi consensus questions and reviewed the manuscript critically before providing final approval. To ensure patient representation, a worldwide participative process was coordinated by K.M.H. and C. Bouillot through their roles in the US Sjögren's Foundation and Sjögren Europe, respectively. The opinions of 1,431 patients from 23 countries (Argentina, Australia, Cameroon, Canada, Denmark, Finland, France, Germany, Greece, India, Ireland, Japan, Netherlands, New Zealand, Norway, Poland, Portugal, Romania, South Korea, Spain, Switzerland, UK and USA) were canvassed via e-mail and the cumulative results were then reported to the Task Force.

In the absence of international guidelines or recommendations for a definitive methodological approach to developing a consensus on the nomenclature of a disease, the convenors searched for changes in nomenclature in the field of autoimmune diseases. Among the few precedents found, the reasons for changing the nomenclature of an autoimmune disease were diverse, including the avoidance of eponyms from physicians involved with the Nazi regime (for example, Reiter or Wegener) or the use of terms not acceptable for patients (such as primary biliary 'cirrhosis'), or to achieve 'nomenclature symmetry' with respect to previous nomenclature changes in similar diseases (for example, Churg–Strauss Syndrome)[18–21]. The number of experts consulted with respect to the name changes varied widely from four[18] to twenty-five[19], and the inclusion of patient representatives was only reported in relation to the nomenclature of primary biliary cholangitis[21]. The methodologies for establishing convergence and agreement were diverse, including a consensus letter (in the case of Reiter's syndrome)[18], a face-to-face meeting[20], an e-mail exchange plus a face-to-face meeting[19] and online surveys distributed among physicians and patients[21]. Although many methodological approaches have been developed to achieve consensus on disease classification[22], we modelled our approach after those used for nomenclature because we felt that it was important to include the opinion of patients in the process. The convenors allowed themselves a degree of methodological flexibility in gathering international patients' perspectives, taking into account the clear differences between the design of a study aimed at professionals and one aimed at patients.

The convenors then presented the Steering Committee with a proposed rationale, based on this review of historical methodological precedent, for seeking international consensus on a change in the name for Sjögren and its classification as primary versus secondary based. The Steering Committee in turn agreed to define two main areas of analysis and their corresponding core methodological approaches: a nomenclature area (coordinated by A.N.B., with use of a bibliometric analysis) and a classification area (coordinated by M.R.-C., with use of an SLR).

Bibliometric analysis

Experts in linguistics (A.M., D.Y.) carried out a bibliometric analysis with the aid of professional informationists (J.B., B.T.) to determine the frequency (percentage of usage) and yearly trends in use of the terms 'Sjögren', 'Sjögren's', 'disease', 'syndrome', 'secondary' and 'associated'.

Linguistic analyses were performed on three corpora of literature. The first corpus was 34,589 unique medical citations and abstracts (duplicates were removed from the 86,909 total records retrieved) published in journals between 1992 and 2022 and identified from five medical literature databases (MEDLINE via PubMed, Embase, CINAHL, Web of Science and Scopus) using the search terms listed in Supplementary Box 1. This first corpus included non-English-language papers with translated titles and abstracts. The second corpus was scanned books contained in the Google Books n-gram database with the search restricted to 1980–2018. The third corpus was scholarly and popular news, spanning multiple world languages and including encyclopedias, Wikipedia, book titles, journal titles and abstracts and general web matches (using Google Translate to generate possible translations of the various English alternatives and then searching for attestation of those candidate phrases on the web in scientific and medical literature). The analyses utilized linguistically normalized n-gram techniques to enumerate the usage of selected search phrases, both in aggregate and as a trend over time.

Systematic literature review

An SLR is aimed at identifying and evaluating all relevant literature on a topic to draw conclusions about a question. The SLR was carried out to characterize the overlap of Sjögren with each systemic autoimmune disease included in Supplementary Box 2 in terms of frequency and differences in the disease phenotype (epidemiological profile, frequency of ocular and oral dryness, frequency of glandular dysfunction, and histopathological and immunological profiles). The SLR was performed by M.R.-C., M.d.P.B.-Z., S.R. and A.S.-A., using MEDLINE with the MeSH term 'Sjögren syndrome' and the search terms included in Supplementary Box 2 with restrictions for date (after 1986), studies (humans) and age of study participants (adults). Other databases, such as EMBASE and Cochrane Library, were also searched. Eligible studies for inclusion were those in which the study population included adults (age > 16 years), used the 2002 American–European Consensus Group or 2016 ACR–EULAR classification criteria for Sjögren[23,24] (a retrospective check for the fulfilment of these criteria was allowed for studies published before these years), and used the current classification criteria for the concomitant autoimmune diseases in effect at the time of article publication. We only included individuals who fulfilled the 2002 or 2016 classification criteria as these criteria were developed through international collaboration and were more rigorous than earlier criteria, which did not mandate the presence of positivity for anti-SSA or anti-SSB autoantibodies and/or the presence of a positive minor salivary gland biopsy[25]. Studies were excluded if the classification criteria used (for Sjögren and/or the autoimmune disease) were not detailed in the methods section or if there was a lack of clinical information about patients with Sjögren overlapping with a second disease ('overlap Sjögren'). For the analysis, the frequencies of key phenotypic features of individuals with overlap Sjögren were compared with those reported in the Sjögren Big Data Consortium cohort (the largest international cohort of patients with Sjögren classified as 'primary')[26].

Delphi process

The Delphi technique is a systematic process of surveying a panel of experts to arrive at a group opinion or decision. The Delphi process used here was designed by M.d.P.B.-Z., M.R.-C. and A.N.B. and used the Google Forms platform; the patient groups provided responses via Survey Monkey. All participants were assured as a function of this process that their responses to the surveys would remain confidential. A series of statements were made by M.R.-C. and A.N.B. (Supplementary Box 3), and participants were asked to express their agreement or disagreement with each statement on a 1–5 Likert scale, with 1 representing strong disagreement and 5 representing strong agreement with the statement. For statistical analysis, scores of 1 and 2 were grouped as disagreement, 3 was listed as neutral, and 4 and 5 were grouped as agreement. In the first Delphi round, the task force was asked about their agreement with the use of the following individual terms: the eponym 'Sjögren', 'syndrome', 'disease', 'primary', 'secondary' and 'associated' (Supplementary Fig. 1a). Supplementary Box 3 provides the wording of each statement and its particular pros and cons as discussed by the Steering Committee. A consensus was considered achieved when there was an initial majority in favour (defined as more than two-thirds of participants indicating agreement) or against (more than two-thirds of participants indicating disagreement) each statement. For this first Delphi round, the results from the survey of patients were evaluated quantitatively (arithmetic mean). The results of the first Delphi round were presented and discussed in a plenary session at the 2022 ISSS in Rome to garner the collective opinion of those professionals and patient representatives in attendance. After collecting the arguments for and against each option, the Steering Committee selected five nomenclature options for the second Delphi round. The selection process was conducted entirely online. Steering Committee members were invited to submit their proposed nomenclature options along with a supporting rationale. The convenors compiled all suggestions and subsequently conducted an online survey among the Steering Committee members, asking them to rank their top five options. The five options with the highest rankings were then forwarded to the second Delphi round.

The second Delphi round had two main objectives (Supplementary Box 4). The first objective was to evaluate the degree of support of the scientific community and patient representatives for the usage of each of the five nomenclature options selected by the Steering Committee after collecting feedback from the ISSS meeting in Rome. The number of Delphi rounds for choosing the nomenclature was initially set to two consecutive elimination rounds by seeking a majority opinion (more than two-thirds of participants scoring agreement) (Supplementary Fig. 1b).

The second objective was to assess the majority opinion among task force participants regarding the use of the terms 'primary' and 'associated' for Sjögren occurring, respectively, alone or in association with another systemic autoimmune disease, by posing three general questions.

Drafting and approval of the manuscript

The manuscript was drafted by M.R.-C., A.N.B. and M.d.P.B.-Z. and was sent sequentially to the Steering Committee and Working Group members for review and approval. The final document is intended to be useful for the international community of health care professionals, doctors and dentists in specialist training, medical students, patients, the pharmaceutical industry and drug regulatory organizations. Industry involvement was not permitted at any stage of the project.

Results

Bibliometric results

As shown in Table 1, 'Sjögren syndrome' and its linguistic and spelling variants were the predominant terms for the disease in the literature, accounting for 75% of the identified usage as assessed by an analysis of PubMed citations. In an n-gram analysis of 86,909 medical abstracts of

articles (including their titles and keywords) published between 1992 and 2022, the term 'Sjögren syndrome' was used 97.8% of the time, with 'Sjögren disease' used 1% of the time, 'autoimmune exocrinopathy' used 0.4% of the time and 'Gougerot-Sjögren' used 0.8% of the time. Among 82,901 medical citations, the possessive form 'Sjögren's' was utilized 72.6% of the time, compared with 26.6% of the time for Sjögren and 0.8% for Sjögrens (including all spelling and linguistic variants for each term). Usage of the possessive form was 82% in the 1993–1997 period but only 70% in the 2018–2022 period, indicating a trend in the published literature away from the use of the possessive Sjögren's, Sjögren's and Sjoegren's (and other spelling variants). There was also a substantial trend over time in the published medical literature away from the usage of 'secondary Sjögren('s)' and its multiple variants with respect to spelling, capitalization, hyphenation and use of the possessive.

Systematic literature review

A total of 55 individual studies fulfilled the SLR inclusion criteria[27–81] and included a total of 1,931 patients diagnosed with both Sjögren and an associated systemic autoimmune disease (Table 2). Figure 1 summarizes the frequency of Sjögren in people with other systemic autoimmune diseases. The frequency of Sjögren varied widely depending on the associated disease, ranging from 34% in those diagnosed with inflammatory myopathies to 1.7% in individuals with sarcoidosis. The main epidemiological characteristics of patients at the time of Sjögren diagnosis varied substantially depending on the associated disease. The association between Sjögren and some diseases (such as anti-neutrophil cytoplasmic antibody-associated vasculitis, SSc, spondyloarthritis and sarcoidosis) had a substantially reduced female predominance than that reported in Sjögren in the absence of another coexisting disease ('primary' form) (93.4% women) (Fig. 2). With respect to age at diagnosis of Sjögren, the coexistence of anti-neutrophil cytoplasmic antibody-associated vasculitis with Sjögren raised this figure from 52 years (reported in the Sjögren Big Data Consortium cohort[26]) to 62 years, whereas the coexistence of systemic lupus erythematosus (SLE) lowered the age at diagnosis of Sjögren to below 45 years (Supplementary Fig. 2). There were notable differences in the frequency of glandular involvement (Supplementary Figs. 3 and 4) and the immunological profile (Supplementary Fig. 5) in comparison with what was reported in the Sjögren Big Data Consortium cohort[26].

In summary, the results generated from the SLR demonstrate the enormous influence of the association with another systemic autoimmune disease, with substantial alteration of both the epidemiological profile and the phenotype of Sjögren compared with the characteristics observed in the absence of another coexisting disease.

Delphi process on terms to name the condition

In the first Delphi round, which assessed the extent of agreement on the use of individual terms, 88% of the Task Force participants agreed with the statement about maintaining the use of the eponym 'Sjögren', 31% agreed with the statement about maintaining the term 'syndrome' and 53% agreed with the statements about changing the term 'syndrome' to 'disease'. With respect to patients' opinions, on a numeric scale on which 5 was the maximum level of agreement, mean scores were 4.35 for maintaining the use of the eponym 'Sjögren', 1.87 for using the term 'syndrome', and 4.23 for using the term 'disease' (Supplementary Table 1).

After discussion online among the Steering Committee members, we opted to forego any effort to reach consensus on the use of the possessive or non-possessive form of Sjögren in English publications, or of spelling variants (o, oe, ö), and left this up to individual or journal preference.

Table 1 | Synonyms and classification terms for Sjögren and their relative frequencies

Synonym or classification term	PubMed citations, *n* (%)
Sjögren's syndrome	18,040 (62.6)
Sjögren syndrome	3,269 (11.3)
Sjoegren syndrome	158 (0.5)
Sjoegren's syndrome	68 (0.2)
Sjögren's disease	320 (1.1)
Sjögren disease	102 (0.4)
Sjoegren disease	0
Sjoegren's disease	0
Gougerot-Sjögren syndrome	277 (1.0)
Gougerot-Sjögren's syndrome	50 (0.2)
Gougerot Sjoegren syndrome	9 (0.03)
Gougerot Sjoegren's syndrome	2 (0.01)
Gougerot-Houwer-Sjoegren or Houwer-Gougerot-Sjögren's syndrome	5 (0.02)
Gougerot-Mulock Houwer-Sjögren syndrome	1 (0.003)
Mikulicz Gougerot Sjoegren syndrome	1 (0.003)
Mikulicz-Radecki syndrome	0
Gougerot-Sjögren disease	15 (0.05)
Gougerot-Sjögren's disease	7 (0.02)
autoimmune exocrinopathy	170 (0.6)
systemic autoimmune exocrinopathy	5 (0.02)
dacryosialoadenopathia atrophicans	3 (0.01)
mucoserous dyssecretosis	1 (0.003)
oculobuccopharyngeal dryness	0
rheumatic sialosis	0
sicca syndrome	940 (3.3)
primary Sjögren/Sjögren's	4,857 (16.9)
primary Sjoegren/Sjoegren's	2 (0.01)
secondary Sjögren/Sjögren's	482 (1.7)
secondary Sjoegren/Sjoegren's	2 (0.01)
associated Sjögren/Sjögren's	38 (0.13)

Usage was assessed by a count of PubMed citations. The assessment was not time restricted and was performed on 6 May 2022.

In the second Delphi round, which assessed the extent of agreement with the use of the five proposed nomenclature terms, 63% of the task force participants supported the use of 'Sjögren disease' (with the abbreviation SjD), 28% supported the use of a novel acronym 'S.J.Ö.G.R.E.N.' (salivary gland swelling, joint pain/swelling, ocular/oral dryness, general symptoms, renal/respiratory manifestations, exocrinopathy, non-Hodgkin lymphoma), 22% supported the use of 'Sjögren syndrome', 12% supported the use of 'Sjögren autoimmune epithelitis' and 5% the use of 'Sjögren autoimmune exocrinopathy'. Among the patients, 77% supported the use of 'Sjögren disease' followed by 25% supporting the acronym S.J.Ö.G.R.E.N. (Supplementary Table 2).

After combining the results of the two arms, 70% of participants (professionals plus patients) supported the use of the term Sjögren disease, avoiding the need for a subsequent Delphi round because a majority opinion had been obtained (Fig. 3).

Delphi process on classification nomenclature

In the first Delphi round, which assessed the extent of agreement by clinicians on the individual terms used in the classification of Sjögren, there was a similar level of support for either maintaining the term

Table 2 | Key features of patients with Sjögren and an associated systemic autoimmune disease

Feature	Primary Sjögren	Sjögren plus systemic autoimmune disease							
		SLE	SSc	RA	SpA	Sarcoidosis	IIM	AAV	IgG4-RD
Number of studies	NA	13	4	24	3	5	3	2	1
Number of European studies	NA	7	4	9	3	3	3	2	1
Prevalence of Sjögren in AD[a]	NA	606/4,133 (14.7)	222/1,511 (14.7)	361/3,681 (9.8)	20/111 (18.0)	50/2,974 (1.7)	34/99 (34.3)	No data	No data
Prevalence of AD in Sjögren[b]	NA	56/670 (8.4)	No data	68/994 (6.8)	23/148 (15.5)	No data	21/1715 (1.2)	No data	10/133 (7.5)
Total patients with Sjögren plus AD	NA	726	222	673	91	88	55	66	10
Women, *n*/*N* (%)	14,308 (93.4)	637/652 (97.6)	349/441 (79.1)	466/505 (92.3)	66/91 (72.5)	48/88 (54.5)	50/55 (90.9)	55/66 (83.3)	9/10 (90.0)
Mean age at Sjögren diagnosis, years (range)	51.7 (NA)	42.4 (31–51.8)	52	55.1 (48–63.4)	45.7 (44–47)	50.4 (47–52.4)	54.3 (53–55.5)	61.9 (60–63.9)	No data
Dry mouth, *n*/*N* (%)	13,939 (91.0)	181/222 (81.5)	85/85 (100)	380/474 (80.2)	69/78 (88.4)	36/38 (94.7)	No data	22/22 (100)	10/10 (100)
Dry eyes, *n*/*N* (%)	14,059 (91.8)	175/222 (78.8)	85/85 (100)	395/475 (83.2)	67/78 (85.8)	33/34 (97.0)	No data	22/22 (100)	8/10 (80.0)
Abnormal Schirmer's test, *n*/*N* (%)	10,037/12,709 (79.0)	137/181 (75.6)	19/19 (100)	225/331 (68.0)	No data	4/5 (80.0)	26/34 (76.5)	No data	No data
Positive corneal staining, *n*/*N* (%)	4,103/5,931 (69.2)	53/76 (69.7)	No data	158/256 (61.7)	No data	5/5 (100)	No data	No data	No data
Abnormal ocular tests, *n*/*N* (%)	11,495/13,569 (84.7)	78/90 (86.6)	24/28 (85.7)	152/207 (73.4)	No data	5/5 (100)	No data	No data	No data
Abnormal salivary flow test, *n*/*N* (%)	6,251/8,418 (74.3)	108/122 (88.5)	No data	168/220 (76.4)	12/13 (92.3)	No data	3/7 (42.9)	No data	No data
Abnormal parotid scintigraphy, *n*/*N* (%)	2,396/2,922 (82.0)	35/50 (70.0)	No data	97/122 (79.5)	ND	16/25 (64)	No data	No data	No data
Salivary biopsy grade 3–4, *n*/*N* (%)	8,974/10,379 (86.5)	67/77 (87.0)	58/59 (98.3)	120/158 (75.9)	77/91 (84.6)	34/37 (91.8)	27/30 (90.0)	56/66 (84.8)	No data
ANA, *n*/*N* (%)	11,383/15,180 (75.0)	98/127 (77.1)	53/59 (89.8)	227/300 (75.7)	33/43 (76.7)	18/26 (69.2)	22/28 (78.6)	18/22 (81.8)	6/10 (60)
RF, *n*/*N* (%)	6,265/15,056 (41.6)	124/334 (37.1)	56/85 (65.9)	441/518 (85.1)	13/78 (16.6)	11/26 (42.3)	No data	29/66 (43.9)	No data
Anti-SSA antibodies, *n*/*N* (%)	12,191/14,644 (83.2)	352/611 (57.6)	27/85 (31.7)	213/358 (59.5)	16/43 (37.2)	14/26 (53.8)	32/55 (58.2)	42/66 (63.6)	4/10 (40)
Anti-SSB antibodies, *n*/*N* (%)	6,090/1,3212 (46.1)	210/611 (34.3)	9/66 (13.6)	10/36 (27.8)	1/7 (14.2)	9/26 (34.6)	9/38 (23.7)	18/66 (27.2)	2/10 (20)
Low C3, *n*/*N* (%)	1,691/12,646 (13.4)	199/434 (45.8)	7/26 (26.9)	No data	2/23 (8.6)	No data	No data	No data	No data
Low C4, *n*/*N* (%)	1,685/12,615 (13.4)	203/434 (46.7)	3/26 (11.5)	No data	2/23 (8.6)	No data	No data	No data	2/10 (20)

The table summarizes the key features of 1,931 patients with Sjögren disease (SjD) and an associated systemic autoimmune disease, from 55 individual studies identified in a systematic literature review[27–81]. Values in the 'primary Sjögren' column are derived from the Sjögren Big Data Consortium cohort[26]. Where data are expressed as '*n*/*N*', *n* refers to the number of patients who have the evaluated feature, and *N* refers to the number of patients for whom information on that feature is available in the manuscript. [a]Studies focused on patients diagnosed with a specific autoimmune disease within which the occurrence of SjD was assessed. [b]Studies focused on patients with SjD within which the frequency of a concomitant autoimmune disease was assessed.AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; AD, autoimmune disease; ANA, antinuclear antibodies; IgG4-RD, IgG4-related disease; NA, not applicable; RA, rheumatoid arthritis; RF, rheumatoid factor; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis.

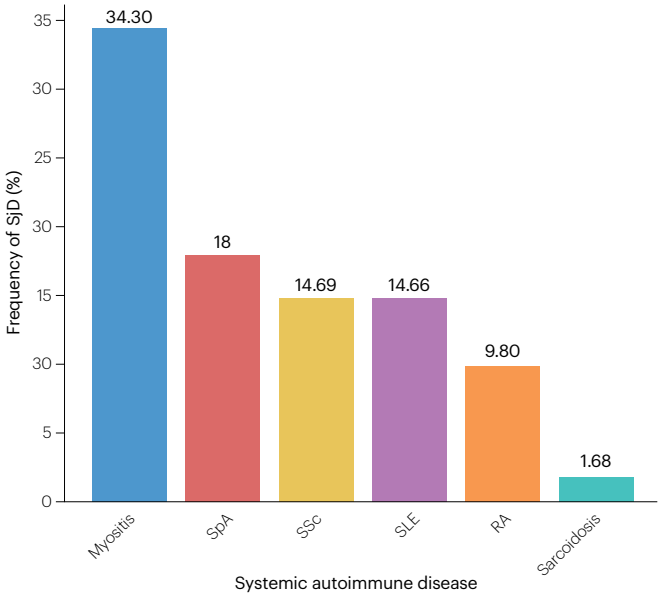

Fig. 1 | Frequency of Sjögren disease among individuals with another concomitant systemic autoimmune disease. The figure summarizes the frequency of Sjögren disease (SjD) in the studies included in a systematic literature review[27–81]; the 55 studies that met the inclusion criteria involved a total of 1,931 patients diagnosed with both Sjögren and an associated systemic autoimmune disease (see Table 2). The frequency of SjD varied widely depending on the associated disease. RA, rheumatoid arthritis; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis.

'primary' (44%) or not maintaining it (41%), whereas a majority (73%) agreed on not maintaining the term 'secondary'. If the term 'secondary' was not maintained, 75% agreed on using the alternative term 'associated'. Patients' opinions were quantified on a numeric scale on which 5 was the maximum level of agreement; the mean score was 2.51 for maintaining the use of the term 'primary', 2.15 for maintaining the term 'secondary' and 3.08 for changing the term 'secondary' to 'associated' (Supplementary Table 1).

In the second Delphi round, those surveyed were asked if there were objective reasons to differentiate between primary and associated Sjögren for disease nomenclature, specifically given that this distinction is not applied to other systemic autoimmune diseases (Supplementary Table 2), which do not always occur in isolation. Most professionals (76%) and patients (79%) agreed that there were no reasons to apply this differentiation specifically to Sjögren when it is not applied to the autoimmune diseases commonly associated with Sjögren. However, 54% of professionals and 44% of patients replied that the distinction between primary and associated Sjögren still had potential importance, with 30% of professionals stating that this importance is contextual (as indicated by the response "It depends"). When professionals were asked in which field it is necessary to differentiate between primary and associated Sjögren, 50% indicated mainly in the scientific field (for the purpose of defining a study population) and 25% indicated in all fields, including in clinical practice for individual diagnosis. Overall, 82% of experts and 55% of patients agreed that it was important to differentiate primary Sjögren from associated Sjögren for scientific studies, clinical practice or both. These results were discussed online among the Steering Committee members (including patient representatives), and it was agreed with the patient representatives to formulate two recommendations that reflected an agreement position (recommendations 4 and 5 in Box 1). These recommendations were sent electronically to the entire task force and were approved by all Task Force members after making exclusively minor semantic (not substantive) changes. The survey did not specifically address the need of clinicians to differentiate between primary and associated disease for clinical decision making, such as the attribution of specific systemic features to Sjögren or an overlap systemic disease and the choice of specific treatments.

Consensus was not reached with respect to the importance of the differentiation between primary and associated Sjögren in the field of research. As evidenced by the SLR, the Sjögren phenotype is substantially influenced by the association with other systemic autoimmune diseases (Figs. 1 and 2; Supplementary Fig. 2–5). Thus, it is recommended that researchers detail in future scientific publications on Sjögren whether patients with other autoimmune diseases (either systemic or organ-specific) were excluded from studies (detailing the excluded diseases if so) or, if they were not excluded, the percentage of patients who had other autoimmune disease(s) (whenever possible). Furthermore, it might be necessary to conduct a separate sensitivity study and subgroup analysis, especially in experimental or interventional studies. The scientific rationale for this recommendation is to maintain the comparability of results from new studies with those carried out in the past

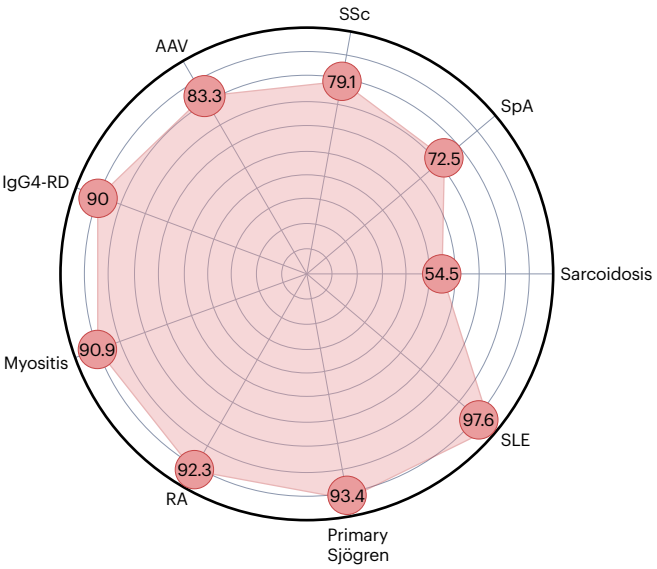

Fig. 2 | Frequency of women among patients with Sjögren disease and other systemic autoimmune diseases. The radar chart depicts the percentage of patients with Sjögren disease and another concomitant systemic autoimmune disease who are women. The values are derived from those studies included in the systematic review that provided sex-specific patient information[27–81]; the 55 studies that met the inclusion criteria involved a total of 1,931 patients diagnosed with both Sjögren and an associated systemic autoimmune disease (see Table 2). In the figure, the label 'primary Sjögren' corresponds to patients classified as having 'primary' Sjögren (that is, Sjögren in the absence of another coexisting disease) in the Sjögren Big Data Consortium cohort[26]. AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; IgG4-RD, IgG4-related disease; RA, rheumatoid arthritis; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis.

(practically all of which were carried out in people classified as having 'primary' Sjögren).

Discussion

The recommendations of the 2023 International Rome consensus for the nomenclature of Sjögren are summarized in Box 1. We have obtained a clear international consensus that the medical condition known as Sjögren syndrome should be re-named and hereafter referred to as Sjögren (or Sjögren's) disease or with the abbreviation SjD. This change in nomenclature has been reached and endorsed via a Delphi process with the participation of 79 professionals and 1,431 patients from 34 countries. There are two key arguments in favour of this change in nomenclature. First, it is important to recognize that SjD is not a syndrome, namely an aggregate of symptoms and signs that are associated with a morbid process independent of pathogenesis[82,83]. Instead, SjD is widely accepted as a distinct autoimmune disease, with characteristic autoantibodies, glandular histopathology and a specific pattern of systemic involvement. Some members of the Task Force thought that changing the term from 'syndrome' to 'disease' could have positive outcomes regarding research and funding attention. The second argument emerged principally from patients' beliefs that the term 'syndrome' can be counterproductive, indicating that SjD is a loose collection of ill-defined or 'nuisance' symptoms (overwhelmingly sicca) rather than the actuality, which is that it is a disease with serious morbidity and, for some, increased mortality[84].

Regarding the use of the eponym Sjögren, most patients and professionals supported maintaining its use. Although some experts argued strongly that the eponym should be abandoned in favour of a histopathological descriptor (for example, autoimmune epithelitis), patient representatives argued that it would be very difficult for their advocacy organizations to promote awareness and education and obtain increased funding for research with such a technical disease name. In addition, 'autoimmune epithelitis' is hard to remember and does not convey to the public or to patients what the disease is any more than 'Sjögren' does.

Finally, the choice of a disease abbreviation (SjD) was also important, not only for conformity but also to ensure that it does not have negative connotations. Until now, the abbreviation SS (commonly used for Sjögren syndrome) applies to 337 terms[85], including some with potentially offensive connotations. Similarly, the abbreviation SD applies to over 209 terms, including the medical terms sudden death, senile dementia and sexual dysfunction. By contrast, SjD is more specific and has only one other medical connotation (sacroiliac joint dysfunction).

A clear consensus was also reached on abandoning the term 'secondary' in favour of 'associated' when classifying patients with SjD co-occurring with another systemic autoimmune disease. An issue that remained without clear resolution was whether there was importance, value or utility in differentiating primary and associated forms of SjD. Nearly 80% of professionals and patients agreed that there are no reasons to label a given patient as having either primary Sjögren or associated Sjögren, particularly as these labels are not applied to patients with SLE, SSc or RA that is 'stand-alone' or overlapping with a second disease. Sjögren should be considered a disease in its own right, rather than a secondary manifestation of another disease. The patient representatives made it clear that the use of the terms 'secondary' and 'associated' gives the impression that their Sjögren disease is less important than other concomitant conditions. However, a majority of professionals and patients appreciated the necessity of distinguishing primary versus associated Sjögren in research studies or clinical practice, or both.

The coexistence in a single patient of more than one autoimmune disease, both systemic and organ-specific, is a well-recognized clinical occurrence with a reported frequency ranging between 8% and 53%[86–91]. In fact, SjD is the systemic autoimmune disease that most commonly overlaps with another[92,93]. The terms 'primary' and 'secondary' are misleading when applied to SjD, as they suggest that primary disease is idiopathic whereas secondary disease is derived from a definable related condition. Instead, the co-existence of two or more autoimmune diseases, termed polyautoimmunity, can simply

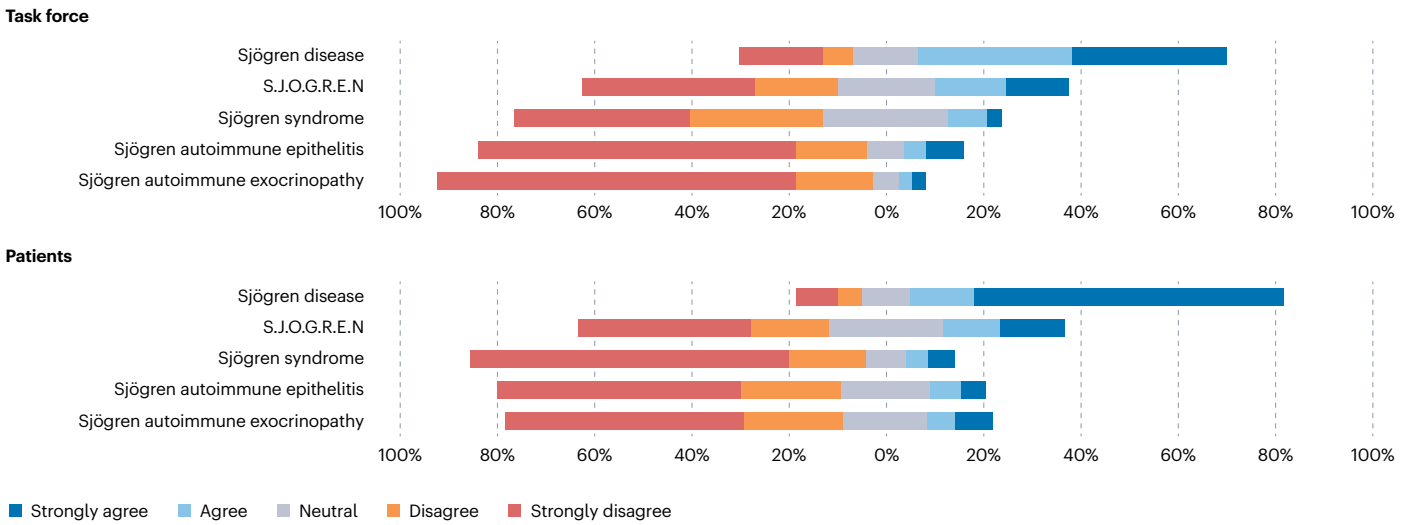

Fig. 3 | Agreement on the use of proposed nomenclature terms for Sjögren. The figure summarizes the results of the second Delphi round, in which Task Force participants and patient representatives were surveyed regarding their support for the usage of each of five nomenclature options. Participants were asked to express their agreement or disagreement with the use of each term on a 1–5 Likert scale, with 1 representing strong disagreement and 5 representing strong agreement; results of the survey are provided in Supplementary Table 2. Overall, a majority of participants supported the use of the term 'Sjögren disease'.

reflect shared genetic and environmental predisposing factors and pathogenetic pathways[94,95]. In addition, some patients might present with an illness best characterized as SLE or RA but that evolves over time into one best characterized as SjD. The absence of an objective criterion to help differentiate between primary and secondary SjD has resulted in complex issues of classification. Thus, the term 'secondary' has been overwhelmingly used when SjD is associated with RA, SSc or SLE, whereas it has been rarely used when it is associated with other systemic autoimmune diseases (including antiphospholipid antibody syndrome, sarcoidosis, myopathies, vasculitis and IgG4-related disease). Why this differentiation is applied to SjD and not to the other systemic autoimmune diseases is unclear but might relate to the initial perception by rheumatologists that SjD was a variant form of RA[96]. The fact that SjD could occur alone, in the absence of a second autoimmune disease, was first highlighted in landmark studies at the NIH in the early 1960s[9]. The distinction between primary and secondary forms of the disease was advanced by Moutsopoulos et al.[10] and predicated on the concept that each form had unique clinical, serological and genetic characteristics that could influence disease prognosis and appropriate therapeutic strategies. However, in 2019 Mavragani and Moutsopoulos wrote that splitting SjD into 'primary' and 'secondary' forms fails to fully reveal the wide clinical spectrum of the disease[14]. The distinction between primary and associated SjD reflects only the frequently reported clinical situation of the coexistence or overlap of SjD in patients with other autoimmune diseases.

An issue that was not specifically addressed in the Delphi process was the value of defining whether specific systemic manifestations of SjD relate to an associated condition, such as a myositis syndrome for patients with interstitial lung disease or neuromyelitis optica or multiple sclerosis for patients with central nervous system demyelination. In these examples, diagnosis of the associated condition might influence a clinician's choice of therapy. Clinicians often judge whether a patient has primary or associated SjD on the basis of the predominant phenotype, an assessment that can change during the natural history of the patient's disease. Recognizing a clinical overlap could be valuable as it could influence how we can manage the patient (for example, when interpreting new symptoms, ordering organ-specific tests during follow-up or even choosing a different therapeutic approach). The overlap of two systemic autoimmune diseases can also affect overall disease burden and severity[91]. This clinical distinction is increasingly murky and awaits advances in new classification tools and molecular markers for clarification.

The distinction between 'primary' and 'secondary' forms of SjD has had substantial consequences for research, as most published scientific studies in SjD focus on the primary form, excluding patients with an associated systemic autoimmune disease. This differentiation has been maintained until now in both the current classification criteria and activity rating scales. The developers of the current ACR–EULAR classification criteria stated that they "focus on primary rather than secondary [Sjögren syndrome]. Patients with the latter would typically not be eligible for experimental treatments for [Sjögren syndrome]"[24]. Consistent with this statement, therapeutic studies on SjD, especially randomized controlled trials, systematically exclude patients with other associated systemic autoimmune diseases. Why this occurs only in trials carried out in people with SjD and not in those affected by other systemic autoimmune diseases is difficult to explain from a methodological point of view. Post hoc analyses have even investigated why therapeutic responses can be different in patients with and without associated SjD[97,98].

Box 1 | Summary of the 2023 International Rome consensus for the nomenclature of Sjögren disease

1. The term 'Sjögren disease' should replace 'Sjögren syndrome'.
2. 'SjD' should be used as an abbreviation for 'Sjögren disease'.
3. The descriptor 'associated' should be used in lieu of 'secondary' for Sjögren disease occurring in association with a second systemic autoimmune disease for which classification criteria are fulfilled.
4. The term Sjögren disease is preferred in common parlance and in clinical diagnosis, without differentiation as to primary and associated forms. However, an appreciation of the common association of Sjögren disease with other systemic autoimmune diseases could have value in the clinical evaluation of affected patients and in clinical decision-making.
5. The differentiation between primary and associated Sjögren disease is recommended for scientific studies in order to define a homogeneous population.
6. The choice of using the possessive or non-possessive form of Sjögren and spelling variants (o, oe, ö), should be left to the individual or journal preference.

Our SLR demonstrated that the coexistence of another systemic autoimmune disease heavily influences the phenotype of SjD. Thus, the inclusion of patients with both primary and associated SjD in a clinical study or therapeutic trial can alter the homogeneity of the study population and affect patterns of results. In cases in which study design allows for the inclusion of patients with SjD who have associated diseases, it would seem reasonable to conduct a specific sensitivity analysis excluding these patients.

Conclusions

The 2023 Rome International Consensus on Sjögren Nomenclature strongly endorses the transition from the term 'Sjögren syndrome' to 'Sjögren disease' (SjD) to better reflect its definition as a distinct systemic autoimmune disease. The term 'associated' is recommended instead of 'secondary' to indicate Sjögren when it is occurring with another systemic autoimmune disease for which classification criteria are fulfilled. It may be unnecessary to label patients with primary versus associated Sjögren in clinical practice, as this distinction is not routinely applied to other systemic autoimmune diseases. However, this recommendation does not negate the potential value of recognizing the overlap of SjD with other systemic diseases in individual patients and its impact on the attribution of systemic manifestations and treatment choices. Similarly, this distinction is useful for research purposes to ensure a uniform study population. This consensus marks a significant stride towards a more streamlined and precise understanding of SjD within both clinical and research settings.

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Competing interests
A.N.B., S.M.L., S.S.M. and V.S. are members of the Board of Directors of the Sjögren's Foundation. A.N.B. is Chair of the Medical and Scientific Advisory Council of the Sjögren's Foundation. K.M.H. is Vice President of Medical and Scientific Affairs of the Sjögren's Foundation. C. Bouillot is General Secretary of Sjögren Europe. C .Baldini, H.B., X.M., A.G.T. and W.-F.N. are members of the Medical Board of Sjögren Europe. L.L. is President of the Sjögren's Society of Canada, a member of its Board of Directors and co-chair of its Medical Advisory Board. None of the other authors has any relevant competing interests to report.

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