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What rheumatology can learn from oncology: a patient's perspective

By Sarah Sisbot

Drawing on my contrasting experiences as a patient in oncology and rheumatology, I have seen how the lack of precision-based diagnostics and meaningful endpoints limits progress in rheumatic disease. I believe biologically grounded classification systems and greater patient involvement are essential for more effective and responsive care.

As a woman in my thirties who has undergone treatment for hereditary breast cancer and is now navigating a severely disabling autoimmune disease, I have been struck by the stark contrast between oncology and rheumatology. My cancer diagnosis was informed by precise genetic insights and my treatment guided by biomarkers and frequent monitoring, even including enrolment into a clinical trial. After entering remission, I became an Advocate in Science with the Susan G. Komen Foundation to help ensure that research keeps the patient perspective close to heart. By contrast, during the 1,000 days that I have battled a disabling autoimmune disease, what has disappointed me even more than the 7 failed lines of treatment is the realization that had rheumatology adopted structures for disease classification, trial endpoints and grant development that mirrored those in oncology, my outcome might have been better.

When I first developed systemic joint inflammation, I expected a path similar to oncology: tissue assessment leading to a precise diagnosis and treatment informed by frequently updated practice guidelines. What I got instead were months-long delays between appointments for endless antibody tests, in which the presence or absence of specific antibodies could neither fully confirm nor deny the existence of a specific autoimmune disease. Many autoimmune diseases are believed to involve T cell dysregulation, yet my T cells were not assessed. In addition to countless blood draws, I had numerous joints aspirated and multiple biopsies, none of which provided actionable insights or were used to look at my cells. Out of desperation, I paid privately for flow cytometry to quantify my immune cells; the result — elevated T helper 17 (T_H17) cells — potentially supported my rheumatologist's decision to pursue an IL-17 blocker. Securing approval for treatment has taken months, and any benefit will take longer still to assess.

The treatments that I have tried and failed, perhaps unnecessarily, have resulted in severe adverse effects. Six weeks after starting sulfasalazine, I developed agranulocytosis complicated by preseptal cellulitis and required hospitalization for intravenous antibiotics. I happen to carry an HLA allele associated with severe sulfasalazine-induced neutropenia (M. Wadelius et al., *Clin. Pharmacol. Ther.* **103**, 843–853; 2018). Given that HLA-B alleles are routinely checked (for example, to identify HLA-B27), I urge rheumatologists to consider the risks of sulfasalazine treatment in patients who carry the same allele that I do.

This autoimmune disease has taken so much away from me. I lost a job I treasure. I can no longer care for my young children in the way I would like to. Even walking across a room can bring me to tears. Despite near-weekly appointments, no combination of DMARDs, biologics, steroids or pain relievers has meaningfully reduced the inflammation. The toll on my body far exceeds what can be assessed within a 15-minute check-in — or in a 2,000-page medical record that contains duplications and inaccuracies. As my health declines, I increasingly worry that my non-response to treatment will be read as a personal failing rather than a signal that current therapeutic frameworks are misaligned with disease biology.

What would it take to bring rheumatology closer to the precision that reshaped oncology? I would start with a longitudinal, multi-centre registry that collects deep clinical, immunological and genomic data from patients. This approach would include precision methods, such as single-cell sequencing, flow cytometry, complete HLA typing, cytokine profiling and, of course, antibody profiling. Then I would collect data about which treatments those patients respond to and how their cells and cell populations, cytokines and antibodies change over time. The resulting information could then be used to determine whether existing disease categories really reflect underlying biology, or whether mechanistic clusters (for example, disease driven primarily by IL-6, IL-23, IL-17, TNF or IFNγ, or by a particular HLA allele) better predict response to treatment. These categories need not be mutually exclusive.

> "What would it take to bring rheumatology closer to the precision that reshaped oncology?"

Clinical trial endpoints should also better reflect what matters to patients. Common composite measures, such as ACR20 or DAS28, can feel misaligned with lived experience. More than once, my doctors and I have disagreed about whether a particular drug was helping, which makes me question the inclusion — and influence — of a physician global assessment of disease activity within ACR20. Similarly, DAS28 excludes joints in the feet, a choice that surprises me given how much those joints contribute to my disability. And can any patient truly be sure of a 20% improvement in symptoms over 6 months? Until endpoints more accurately reflect the underlying biological mechanisms and pathways, raising the bar from modest improvement towards more meaningful change in symptoms (for example, 50% improvement) could make trials both more relevant and more informative.

> "Perhaps the most important change is to include patients in the research process"

Perhaps the most important change is to include patients in the research process. Professional societies and research funders can lower barriers by offering fee waivers and travel support for patients, caregivers and trainees

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to attend relevant conferences at no cost. My voice is just one of many, and others deserve to be heard just as clearly, if not more so. I believe that listening to patients will reveal the structural gaps in rheumatology and the opportunity to rebuild on stronger foundations. Oncology shows that this goal is achievable. My dream is that a patient who wakes up one morning with disabling chronic joint inflammation, as I once did, will receive a tissue-informed assessment of the cells, cytokines and antibodies driving their disease, and begin targeted treatment with the opportunity to contribute to research. That was my experience in oncology, and I firmly believe that this goal is possible and worthwhile for rheumatology.

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Research highlights

Degenerative disc disease

Lactylation of SOD1 promotes oxidative damage in IVDD

Intervertebral disc degeneration (IVDD) is strongly associated with lactate accumulation, but the molecular pathways that connect lactate to tissue damage have remained unclear. A new study identifies protein lactylation as an important mediator of oxidative stress in IVDD, highlighting a critical disease-promoting modification of superoxide dismutase 1 (SOD1).

Using an integrated multi-omics approach, including metabolomics, single-cell RNA sequencing and lactylation proteomics, the researchers systematically mapped the global lactylome landscape of nucleus pulposus tissue from patients with mild or severe IVDD, as well as that of rats with puncture-induced or ageing-induced disc degeneration. The analysis revealed widespread increases in protein lactylation associated with oxidative damage in nucleus pulposus cells.

"The most striking finding was that the key antioxidant enzyme SOD1 showed markedly increased lactylation at lysine 123 during intervertebral disc degeneration," remarks Yu Zhai, a co-corresponding author on the study. Mechanistically, this modification ($SOD1^{K123la}$) induces a previously unreported conformational change that disrupts substrate binding and suppresses enzymatic activity, leading to increased reactive oxygen species, DNA damage and cellular senescence via activation of the p53 pathway.

Genetic mutation of the lactylation site (K123R) restored SOD1 activity, diminished oxidative damage and alleviated disc degeneration in the rat puncture-induced model of IVDD.

In terms of therapeutic targeting of $SOD1^{K123la}$, the researchers moved beyond inhibiting upstream lactyltransferases, given the poor specificity of these enzymes, to identify a more precise strategy. They performed a large-scale structure-guided virtual screening of approximately 1.6 million compounds and identified a site-specific lactylation inhibitor, which they named ZL-01.

Intradiscal administration of ZL-01 alleviated puncture-induced disc degeneration in rats. Although rapid clearance of this inhibitor limited drug bioavailability, targeted delivery via type II collagen affinity peptide-modified extracellular vesicles enhanced retention in nucleus pulposus tissue and improved therapeutic efficacy in vivo.

"In future work, we plan to validate the functional role of $SOD1^{K123}$ lactylation in large animal models to determine whether this mechanism is conserved across species," explains Minghan Liu, a co-corresponding author on the study. "We also aim to further characterize the therapeutic potential of ZL-01 by defining its optimal dosage, safety profile and pharmacokinetic properties, which will provide essential preclinical evidence for the potential clinical translational of this strategy."

Jessica McHugh

Original article: Zhang, Y. et al. SOD1 lactylation impairs its enzymatic activity by conformational change to aggravate intervertebral disc degeneration. *Nat. Commun.* https://doi.org/10.1038/s41467-026-69127-3 (2026)

Therapy

IgG4 surge predicts relapse in IgG4-RD

Increased serum levels of IgG4 over time can indicate relapse in IgG4-related disease (IgG4-RD). Now, findings from a longitudinal cohort study indicate an optimal change threshold in IgG4 levels for predicting relapse.

The study involved 155 patients with active IgG4-RD, who had ≥6 months of follow-up and at least three IgG4 measurements. IgG4 levels assessed at a single time point were not associated with relapse. However, relapse was predicted by an 'IgG4 surge', defined as an increase in IgG4 level of >60% between assessments over a median 3-month interval. Fluctuations in IgG4 were common; 61% of patients whose IgG4 levels had previously normalized regained IgG4 positivity.

For patients with IgG4 surge, the use of intensified treatment with glucocorticoids and/or immunosuppressive drugs reduced the risk of relapse by 68.3%, compared with non-intensified treatment (hazard ratio 0.317). Thus, repeated assessment of serum IgG4 levels to identify 'IgG4 surge' as a warning sign of relapse could provide an opportunity for intervention.

Holly Webster

Original article: Wang, Y. et al. IgG4 surge and relapse: determining the predictive threshold for IgG4 rising kinetics in IgG4-related disease. *Rheumatology* https://doi.org/10.1093/rheumatology/keag034 (2026)

Related article: Peyronel, F. et al. IgG4-related disease and other fibro-inflammatory conditions. *Nat. Rev. Rheumatol.* **21**, 275–290 (2025)

Systemic lupus erythematosus

Positive results for obinutuzumab in SLE phase III trial

The glycoengineered type II CD20-specific monoclonal antibody obinutuzumab, which induces more-potent B cell depletion than type I anti-CD20 monoclonal antibodies such as rituximab do, is approved for the treatment of lupus nephritis. The results of the phase III ALLEGORY trial now show that when added to standard therapy, treatment with obinutuzumab reduces disease activity in adults with active systemic lupus erythematosus (SLE).

In this trial, 303 participants were randomly allocated to receive treatment with either obinutuzumab or placebo, in addition to standard therapy. At week 52, the proportion of participants who achieved the primary end point — SLE responder index 4 (SRI-4) response — was significantly greater in the obinutuzumab group than in the placebo group (76.7% versus 53.5%).

Obinutuzumab was also superior to placebo with respect to secondary end points, including BICLA response at week 52, sustained reduction in glucocorticoid dose from week 40 to week 52, sustained SRI-4 response from week 40 to week 52, SRI-6 response at week 52, and median time to first BILAG-defined flare.

Remission and low disease activity (measured by DORIS response and LLDAS score, respectively) at week 52 also seemed to occur more frequently in the obinutuzumab group than in the placebo group, although these additional secondary end points were not controlled for type I error. No new safety signals were identified, and the safety profile of obinutuzumab was consistent with previously reported trial results.

> **"obinutuzumab can lead to clinically meaningful reductions in SLE disease activity"**

The results of the ALLEGORY trial suggest that targeting B cells with obinutuzumab can lead to clinically meaningful reductions in SLE disease activity, with sustained disease control and reduced reliance on glucocorticoid therapy.

Sarah Onuora

Original article: Furie, R. A. et al. Efficacy and safety of obinutuzumab in active systemic lupus erythematosus. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2516150 (2026)

Related articles: Stockfelt, M. et al. Opportunities and limitations of B cell depletion in SLE. *Nat. Rev. Rheumatol.* **21**, 111–126 (2025)

Lupus nephritis

Repurposing vamifeport for lupus nephritis

Vamiferport (an oral ferroportin inhibitor) has demonstrated good safety and tolerability in sickle cell anaemia. In lupus nephritis, excess iron exacerbates disease, and targeting iron with hepcidin (which binds to ferroportin and regulates iron metabolism) has shown promise. Now, results from a preclinical pilot study show that vamiferport could be a promising adjunct therapy for lupus nephritis.

Importantly, treatment of lupus-prone MRL/*lpr* mice with oral vamiferport did not worsen systemic lupus erythematosus-associated anaemia, compared with vehicle control. Dermatitis and splenomegaly, both indicators of worse outcomes in this model, were reduced in vamiferport treated mice.

Vamiferport treatment attenuated renal pathology compared with control treatment, evidenced by decreased *Ngal* gene expression and a lower urinary albumin-to-creatinine ratio, independently of both glomerular immune complex deposition and circulating levels of anti-dsDNA antibodies. Kidney inflammation and immune cell infiltration were also reduced after treatment.

Mechanistically, vamiferport targeted kidney-infiltrating monocytes (which express ferroportin and differentiate into pro-inflammatory macrophages), but not renal proximal tubular epithelial cells. These results support further research into repurposing vamiferport for lupus nephritis.

Holly Webster

Original article: Katikaneni, D. et al. Vamifeport, a clinical stage oral ferroportin inhibitor, alleviates murine lupus nephritis: a pilot study. *Clin. Immunol.* https://doi.org/10.1016/j.clim.2026.110699 (2026)

Fibromyalgia

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Identifying fibromyalgia phenotypes based on psychological symptom burden

Ana Margarida Pinto & José A. P. da Silva

Psychological symptoms have a pivotal role in determining the severity of fibromyalgia. Findings now show that identifying and managing these symptoms during the early stages of disease could reveal disease phenotypes and improve the management of fibromyalgia.

Refers to *Lee, K.-W. et al. Alleviation of depression rather than pain predicts disease improvement in fibromyalgia patients with prominent psychological symptoms–a prospective observational study. Semin. Arthritis Rheum.* **77**, 152920 (2026).

Fibromyalgia has long challenged clinicians with a troubling paradox: despite decades of advances in the understanding of pathophysiological mechanisms and therapeutic agents, pain remains remarkably refractory to analgesic intervention[1]. A study by Lee et al.[2] published in *Seminars in Arthritis and Rheumatism* offers a potential explanation and a possible path forward.

In the study, 112 patients with newly diagnosed fibromyalgia were treated with pregabalin with or without low-dose imipramine with 4 weeks of follow-up. Using cluster analysis of baseline anxiety and depression scores, they identified two distinct phenotypes: FM-AD (prominent affective disturbance, 47% of individuals) and FM-nAD (lower psychological burden, 53% of individuals). Both groups experienced pain reduction and improvement of anxiety at the 4 week follow-up. The factors that predicted disease improvement differed considerably between groups. For the FM-nAD subgroup, pain intensity was the sole predictor of disease severity as measured by the Revised Fibromyalgia Impact Questionnaire; however, depression, rather than pain, predicted disease severity in the FM-AD subgroup. Mediation analyses confirmed that treating depression had beneficial effects on disease, independent of pain reduction.

Current understanding frames fibromyalgia as a nociplastic pain condition, that is, pain arising from altered pain processing within the central nervous system, without apparent tissue damage[3]. The crucial question is whether this central dysregulation is the primary driver of disease or if it is shaped — perhaps even driven — by emotional, cognitive and social factors. Data from the study by Lee et al.[2] indicates that the latter might have a role in driving disease.

Empirical research published in the past 2 years supports these observations[4,5]. The use of the Emotions-Affect Systems ELicitation (EASEL-3) scale (validated in over 2,000 patients with fibromyalgia across multiple countries) shows that individuals with fibromyalgia exhibit a distinctive emotional profile: heightened activation of threat-related emotions (such as anger, fear, anxiety or sadness) and diminished engagement of positive emotions involved in soothing and motivation (for example, pleasure, pride, contentment or relaxation) compared with healthy individuals[4]. Importantly, activation of the soothing system moderates the relationship between threat and fibromyalgia symptoms — a higher capacity for soothing attenuates the effect of threat activation[4]. Data-driven methods show that psychological distress (depression and anxiety) outperform pain-related measures in distinguishing fibromyalgia severity, achieving moderate-to-high discriminative accuracy across categorical and dimensional severity approaches[5].

The longitudinal clinical data from the study by Lee et al.[2] add a crucial temporal and treatment responsiveness dimension to this picture. Their mediation analyses reveal not only that depression correlates with disease severity, but that alleviation of depression is clinically beneficial for those patients with the FM-AD phenotype. The pathway through which pain relief improved depression in this subgroup is equally telling; it occurred entirely through anxiety reduction, which suggests an interconnected and complex emotional cascade rather than independent symptom domains.

The abovementioned clinical, psychometric and computational evidence support the FITSS (Fibromyalgia: Imbalance of Threat and Soothing Systems) model that we proposed in 2023[6]. This model frames fibromyalgia as a consequence of a long-standing imbalance of the emotional regulation systems in the brain. According to this model, the 'threat system' (which is designed to detect danger) becomes overactive, whereas the 'soothing system' (which promotes calm and recovery) is underactive. This imbalance keeps brain networks in a constant state of alert, leading to a persistent fight-or-flight state. Symptoms such as pain, fatigue and heightened vigilance stem from and are continuously reinforced by this state. Emotional dysregulation has a central role in sustaining this cycle by further amplifying threat processing. This re-framing does not challenge the legitimacy of the disease but instead highlights the potential of targeting these mechanisms therapeutically.

Thus, early psychological screening has emerged as an essential assessment for phenotype stratification. The use of brief screening tools, such as the Hospital Anxiety and Depression Scale, which was used in the study by Lee et al.[2] to identify the FM-AD subgroup, offers a practical approach that can be readily implemented in routine care. At the same time, the FM-AD–FM-nAD dichotomy, which is based on clinical thresholds for anxiety and depression, might underestimate the relevance of emotional dimensions across the entire fibromyalgia spectrum. Patients classified as being in the FM-nAD group — those below the clinical cut-off for psychiatric comorbidity — might nonetheless harbour relevant imbalances in their underlying emotional landscape. Dimensional measures of affect system activation, rather than categorical psychiatric screening, might reveal therapeutically relevant subgroups that are currently being overlooked. The EASEL-3 scale represents a first step in this direction, although more refined

tools for mapping the emotional topography of fibromyalgia will probably emerge as this field evolves.

Treatment algorithms might also require revision. Current guidelines recommend psychotherapy as an adjunct to pharmacological and physical interventions[7]. Data from the study by Lee et al.[2] suggest that using psychological intervention as the primary modality for patients with the FM-AD phenotype could be warranted. 'Classical' cognitive behavioural therapy[8], compassion-focused therapy, mindfulness and acceptance-based approaches — all of which target emotional processing and regulation — have demonstrated efficacy in fibromyalgia but are underused relative to pharmacotherapy.

Several caveats merit consideration. It remains unknown whether the observed clinical benefits of treating depression persist in the long term, given the short follow-up period of the study. The absence of a placebo arm and reliance on self-reported measures introduce potential biases. The FM-AD–FM-nAD distinction, although clinically intuitive, requires replication across diverse populations.

Nevertheless, this study represents an important step towards precision medicine in fibromyalgia. By demonstrating that different patient phenotypes respond through fundamentally different mechanisms, the authors reinforce earlier research that challenges the 'one-size-fits-all' approach and advocates for more personalized management of fibromyalgia[9] This perspective aligns with evidence that somatic and affective patterns in fibromyalgia are person-specific rather than generalizable from group averages, emphasizing the importance of individualized approaches that consider the heterogeneous and dynamic nature of person-specific factors[10]. The path forward probably lies not in better pharmacological agents, but in matching patients to interventions based on their underlying pathophysiology — be it predominantly neurophysiological, predominantly emotional or, as is probably most common, a complex interplay of both.

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Competing interests

J.A.P.d.S. is the founder and co-owner of myfibromyalgia.com. A.M.P. declares no competing interests.

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Review article

Check for updates

Germinal-centre and extrafollicular B cell pathways in systemic lupus erythematosus

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Abstract

Autoantibody flares are important drivers of pathology in systemic lupus erythematosus (SLE), highlighting the pivotal role of B cells in initiating and propagating chronic autoimmunity. Although autoreactive specificities are a normal feature of the naive B cell repertoire, these cells are normally suppressed by layered tolerance checkpoints that limit inappropriate activation. Autoimmune-prone environments can lower these tolerance thresholds, rendering naive autoreactive B cells more sensitive to aberrant cues. Cytokines and other microenvironmental signals shape tissue niches that direct autoreactive B cells towards either germinal-centre or extrafollicular differentiation pathways. Germinal centres support the entry, selection and diversification of autoreactive B cells, with T cell help sustaining these repertoires. By contrast, naive autoreactive B cells entering the extrafollicular pathway exhibit an attenuated requirement for cognate T cell help and strong dependence on complement and TLR signalling. Emerging evidence continues to refine our understanding of germinal-centre and extrafollicular responses as complementary sources of autoreactive effector cells. With this progress, investigations into the origin, development, longevity and tissue dynamics of autoreactive memory B cells as chronic sources of autoantibodies are warranted. Although broad B cell depletion therapies have yielded benefit, a key challenge now is developing precision strategies that selectively target pathogenic B cell subsets.

Sections

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Key points

- Intrinsic autoreactivity is embedded in naive T cell and B cell repertoires and autoimmune environments drive autoreactive B cells towards germinal-centre or extrafollicular fates.
- Autoreactive B cell fate commitment is shaped by contextual, genetic and metabolic cues.
- Autoreactive germinal centres indicate peripheral B cell tolerance breakdown in systemic lupus erythematosus (SLE) and serve as T cell-dependent sites of pathogenic autoantibody diversification.
- Extrafollicular B cell responses provide rapid production of autoantibodies in SLE, supported by heterogeneous $CD4^+$ T cell help.
- Mechanistic characterization of autoreactive B cell fate decisions informs memory B cell dynamics and supports the development of precision therapies in SLE.

Introduction

Systemic lupus erythematosus (SLE) is often used as the prototype disease model for studying the mechanisms that drive autoantibody-mediated systemic autoimmunity. In SLE, the production of autoantibodies reflects a breach in B cell tolerance, in which B cells bearing autoreactive B cell receptors (BCRs) — also termed naive autoreactive B cells — are inappropriately selected for activation, proliferation and differentiation. Similar to responses against foreign antigens, autoreactive B cells can either enter the germinal centre, where the cells undergo extensive affinity-based selection, or differentiate extrafollicularly, undergoing more limited selection over a shorter time window[1–5]. Together, these pathways contribute to the diverse autoantibody landscape characteristic of SLE, reflecting serological activity and potentially contributing to substantial disease heterogeneity[6]. The germinal-centre response contributes to disease progression through a process known as epitope spreading[7,8]. In parallel, recent studies within the past decade highlight a major role for the extrafollicular pathway in generating pathogenic B cells in SLE, underscoring the need for in-depth mechanistic investigations[9–12].

Research into fate bifurcation between extrafollicular and germinal-centre pathways has long been intertwined with studies of primary immune responses, follicular exclusion and the mechanisms underlying tolerance breakage in secondary lymphoid organs. Work in mouse models using transgenic antigens and BCRs, as well as studies of vaccination and infection, has shown that extrafollicular responses do not always preclude the formation of a germinal-centre response but rather precede it. As accumulating evidence highlights the critical roles of extrafollicular B differentiation in SLE, our understanding of how germinal-centre and extrafollicular pathways collectively shape autoimmune responses continues to rapidly evolve. This growing body of work provides a timely foundation for reviewing the context-specific factors that drive these responses and for considering their broader implications for disease.

In this Review, we first outline the key regulators that govern germinal-centre versus extrafollicular fate decisions in conventional secondary lymphoid organs, with a particular focus on the environmental cues that activate naive autoreactive B cells and selectively steer them towards one differentiation pathway over the other. We then examine autoreactive germinal centres as open structures capable of supporting the entry and persistence of autoreactive B cells that have surpassed tolerance thresholds, aided by autoreactive T cell help. We also highlight early and recent efforts to identify and functionally characterize the various T cell subsets that support pathogenic extrafollicular B cell responses, and we discuss the potential challenges that arise when attempting to dissect these T cell–B cell interactions at a mechanistic level. Finally, we survey emerging areas of investigation and therapeutic advances in SLE. Together, these discussions underscore the importance of defining key cellular and molecular triggers that shape SLE pathogenesis.

Intrinsic B cell autoreactivity

A fundamental trigger of autoimmunity lies in the inherent self-reactivity embedded within the naive B cell and T cell repertoires. Pioneering work has shown that although many self-reactive clones are progressively removed during early B cell maturation, approximately 20% of the mature human naive B cell repertoire exhibit detectable self-reactivity against cellular antigens in vitro[13,14]. Autoreactive T cells are similarly present in healthy tissues and in circulating peripheral blood[15,16], suggesting that cognate T cell help is available to support a peripheral breach of B cell tolerance under permissive conditions[17]. Such 'hidden' self-reactivity can become activated under the influence of genetic factors and/or various contextual environmental cues, such as exposure to cytokines and autoantigens, arising from both systemic inflammation and local tissue microenvironments (Fig. 1).

B cell clones bearing self-reactive specificities are normally constrained by multiple tolerance checkpoints[18–21]. Nevertheless, some degree of residual self-reactivity is retained as a trade-off for maintaining the breadth of responses needed to defend against diverse foreign antigens. In this context, rather than defining a fixed threshold for the frequency of self-reactive B cells, researchers have introduced a spectrum-based view of autoreactivity, in which B cell repertoires exhibit a continuum of self-reactivity, including clones that fall below the detection limits of current ex vivo antigen-binding assays yet remain biologically and functionally relevant in vivo[21]. Further work suggests that certain autoreactive clones are actively selected into the mature repertoire through autoantigen engagement, and that distinct B cell lineages (such as B1a cells, follicular B cells and marginal-zone B cells) might follow lineage-specific antigen-dependent positive selection thresholds. Adding further complexity, genetic polymorphisms within the germline antibody repertoire influence antibody specificity and function, complicating efforts to define inherent self-reactivity[22–24]. For example, allelic variation at the *IGHV1-69* locus can fine-tune the self-reactive features of broadly neutralizing antibodies against influenza A virus, contributing to population-level variation in autoimmune susceptibility[23].

The conversion of germline-encoded autoreactivity into autoimmune disease has been demonstrated across numerous human and murine studies. For example, although SLE flares involve highly polyclonal differentiation of antibody-secreting cells (ASCs), cells expressing one heavy-chain variable gene segment — *IGHV4-34* — become disproportionately expanded. *IGHV4-34* can be targeted by the 9G4 anti-idiotype antibody, and is over-represented in naive B cells, memory B cells and ASCs during flares, highlighting the selective expansion of a pre-existing autoreactive clone[25–27]. Similarly, *IGHV1-69* is distinctly dominant in cryoglobulinaemic vasculitis following hepatitis C virus

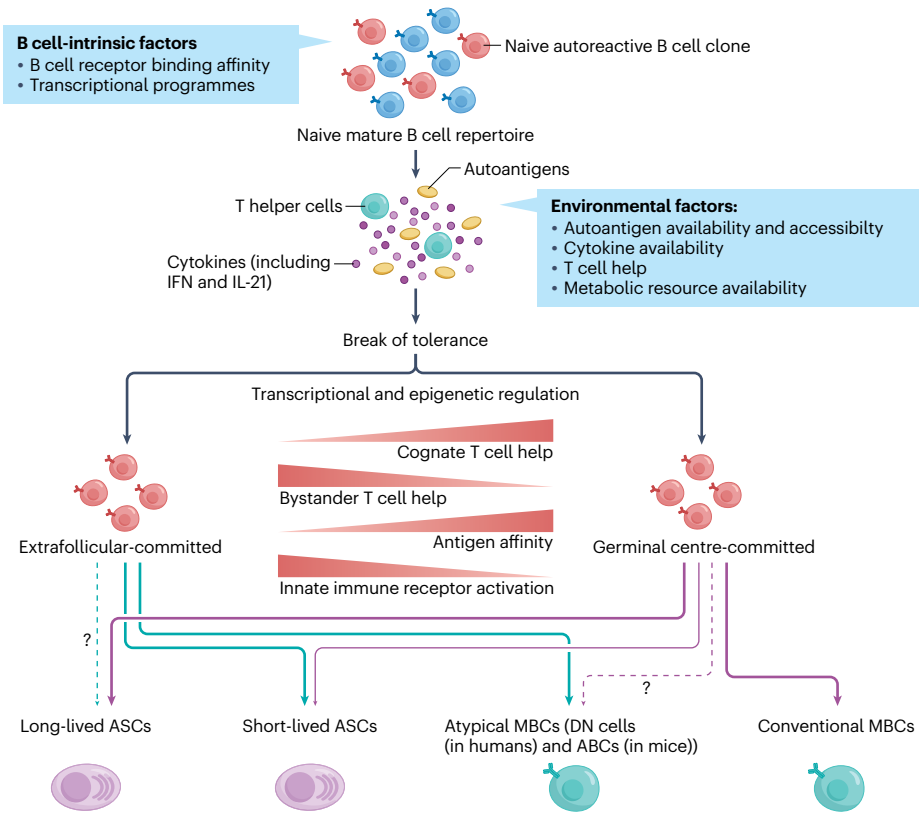


Fig. 1 | Drivers of autoreactive B cell activation and differentiation. A healthy B cell repertoire naturally contains clones with varying degrees of autoreactivity. Naive B cells that carry self-reactive B cell receptor (BCRs) have the potential to drive autoimmunity under chronic exposure to their cognate self-antigens. B cell-intrinsic factors (such as BCR binding affinity and transcriptional programmes) and extrinsic signals (including autoantigen availability, cytokine milieu, T cell help and metabolic resources) collectively contribute to an autoreactive environment and shape the fate of a naive autoreactive B cell. Upon activation, naive autoreactive B cells can differentiate through either the germinal-centre or the extrafollicular pathway to generate antibody-secreting cells (ASCs) and memory B cells (MBCs), guided by coordinated transcriptional and epigenetic programmes. B cell commitment to either developmental pathway is influenced by the extent of cognate and bystander T cell help, antigen affinity and innate immune receptor engagement (represented as gradient-shaded triangles). Arrow thickness denotes the relative contributions of each pathway to the production of long-lived and short-lived ASCs, and atypical and conventional memory B cells. Dotted arrows with question marks indicate processes in which experimental evidence is suggestive but not yet fully established. DN, double negative. ABCs, age-associated B cells.

infection[28,29]. Mixed bone marrow chimeric autoimmune mice (Box 1) further demonstrate selective clonal expansion of wild-type B cells within germinal centres when subjected to autoimmune pressure imposed by an autoreactive BCR transgenic compartment[1]. These chimeras also show shared baseline B cell clones across germinal-centre-derived ASC and memory compartments, albeit expanded to different degrees, suggesting functional divergence among redundant autoreactive clones. Notably, the autoimmune chimeras also showed heavy usage of *IGHV3-6*, the murine orthologue of human *IGHV4-34* (ref. 30). Altogether, these studies illustrate that intrinsic autoreactivity within immune cell repertoires functions as a double-edged sword, with both local and systemic environments functioning as critical modulators that selectively skew this intricate balance. Although inherent autoreactivity does not predetermine autoimmune diseases, such in-born self-reactivity provides the substrate for germinal-centre and extrafollicular B cell responses in autoimmune diseases such as SLE by supplying B cell clones that can be preferentially recruited under autoimmune-prone conditions.

Germinal-centre and extrafollicular B cell pathways

With intrinsic self-reactivity providing the substrate for B cell-driven autoimmunity, activated autoreactive B cells commit to either germinal-centre or extrafollicular differentiation pathways. Mechanistic insights into these processes have come largely from mouse models tailored to specific questions. Together, these pathways converge as complementary routes that shape the diverse autoantibody landscape of SLE.

Germinal-centre dynamics

The germinal centre is classically regarded as the site of B cell selection, class-switch recombination and antibody affinity maturation, and contemporary vaccine development is accordingly aimed at eliciting robust germinal-centre responses. However, analyses of germinal-centre output over the past 2–3 years have prompted a re-evaluation of the long-held view that germinal centres exclusively produce high-affinity antibodies. Studies examining the affinity of antibodies produced by germinal-centre-derived plasma cells have revealed a broad continuum of low-affinity to high-affinity specificities[31,32]. Such observations reframe earlier work describing the germinal centre as an open structure for B cell circulation[33], challenging the assumption that high affinity is a requirement for plasma-cell differentiation[34]. The nature of B cell selection and differentiation in the germinal centre has fundamental implications for the cycling and selection of self-reactive B cells. Using the anti-idiotype antibody 9G4, which detects human B cells expressing the autoreactivity-associated *IGHV4-34* gene segment, researchers have demonstrated that 9G4-positive self-reactive B cells are excluded from the germinal centre in the tonsils of otherwise healthy individuals. By contrast, these cells are present within the germinal centre B cell compartment in patients with SLE, indicating that defective exclusion of autoreactive B cell exclusion from germinal centres represents a hallmark of SLE[35]. Additionally, work in multiple mouse models demonstrates that self-reactive B cells can form spontaneous germinal centres and undergo affinity maturation, establishing germinal centres as potent sources of autoantibodies with diverse reactivity[1,36–39]. Thus, spontaneous germinal-centre formation is a

Box 1 | Models of systemic lupus erythematosus for studying germinal-centre and extrafollicular B cell responses

SW_{HEL} mice[36]
- Express high-affinity anti-egg lysozyme (HEL) B cell receptors (BCRs) and undergo normal somatic hypermutation.
- Used to study how self-antigen affinity and accessibility influence germinal-centre recruitment.

TLR7 gain-of-function (kika) mice[180]
- Carry the gain-of-function $TLR7^{Y264H}$ mutation identified in paediatric systemic lupus erythematosus.
- Develop spontaneous germinal centres plus extrafollicular T helper cells and age-associated B cells (ABCs).
- Crossing onto a germinal-centre B cell-depleted *Cd23-cre* $Bcl6^{fl/fl}$ background highlights strong germinal-centre-independent activity.

MRL/lpr mice[181–183]
- Fas^{lpr} mutation arising spontaneously within the MRL autoimmune strain.
- Accelerated disease development, including broad autoantibodies and systemic disease; autoreactive responses are predominantly extrafollicular.

AM14 H-Tg, Fas-deficient mice[42,184,185]
- AM14 heavy-chain transgene encodes rheumatoid factor specifically.
- Crossing onto the *Fas*-deficient MRL/lpr background yields age-dependent, spontaneous extrafollicular autoantibody-forming cells.
- Robust extrafollicular B cell responses and somatic hypermutation after IgG anti-chromatin antibody challenge.

The 564Igi mouse[37]
- Knock-in model expressing pre-arranged autoreactive heavy and light chains to nuclear antigens.
- Creates an autoantigen-rich and IFN-rich environment promoting tolerance breach; autoimmunity is TLR7-driven.

Mixed bone-marrow chimeras[1,17,70]
- Wild-type (WT) and 564Igi bone marrow are co-transferred into irradiated B6 recipients; 564Igi B cells initiate autoimmunity but are deleted, whereas WT B cells sustain spontaneous germinal centres.
- Enables study of normal autoreactive B cell dynamics, repertoire evolution and follicular T cell responses; germinal-centre reporters (such as $S1PR2\text{-}Cre^{ERT2}$ TdTomato) can be used to track germinal-centre-experienced donor cells.
- Not suitable for extrafollicular studies owing to the lack of extrafollicular-specific labelling.

B cell adoptive transfer and parabiosis models[2,11]
- WT or gene-modified B cells transferred into 564Igi recipients to track early tolerance breakdown. Adoptive transfer enables rapid tracking of donor B cell germinal-centre entry, clonal evolution, and time-stamped extrafollicular responses.
- Parabiosis (WT–564Igi pairs) enables study of WT cell invasion into autoreactive germinal centres.

key signature of peripheral B cell tolerance breakdown in SLE and contributes to the pool of pathogenic autoantibodies.

The extrafollicular response

In contrast to the germinal-centre response, the extrafollicular pathway is characterized by rapid differentiation of ASCs and prompt production of antibodies, where plasma cells expand exponentially within extrafollicular foci by ~4–5 days after immunization[5,40]. In mice, extrafollicular differentiation during the foreign antigen response has traditionally been described as occurring through four stages, beginning with the initial antigen encounter, progressing through T cell–B cell interactions, B cell expansion and subsequent plasmablast and plasma-cell differentiation, and, ultimately, the development of long-lived plasma cells[41]. In autoimmunity, the longevity of plasma cells produced during extrafollicular response remains incompletely understood. Studies in mice more often point towards a transient lifespan for extrafollicularly derived plasma cells[42–44] (Fig. 1). However, in-depth assessments across different model systems and in humans are needed to fully define plasma-cell longevity and the regulatory factors that support plasma-cell survival. The complexity of B cells destined for the extrafollicular pathway has been extensively reviewed elsewhere[45]. Marginal-zone B cells were traditionally regarded as a major source of extrafollicular ASCs[5,46–48], but more recent work in both humans and mice has shown that naive follicular B cells can also substantially contribute[9,11]. Autoantibodies produced through this route are usually of lower affinity and can display polyreactivity towards multiple autoantigens[13,49].

In SLE, accumulating evidence supports a major contribution for the extrafollicular pathway in autoantibody production. BCR sequencing of circulating ASCs from patients with SLE during flares has revealed markedly lower rates of somatic hypermutation than in healthy individuals, along with marked polyclonality, consistent with autoantibody production occurring largely outside germinal centres[26]. Within this ASC population, expansions of *IGHV4-34*-expressing clones display hallmarks of naive B cell origin and broad polyreactivity, suggesting antigen-driven selection of germline-encoded autoreactivity without extensive somatic hypermutation[26]. The contribution of the extrafollicular pathway to human SLE has been further clarified by characterization of $IgD^{-}CD27^{-}$ double-negative (DN) B cells in the peripheral blood of patients. These cells arise from activated naive B cells[9,50], and can be subdivided into DN1–DN4 subsets on the basis of CXCR5 and CD11c expression. Among these subsets, the DN2 subset ($IgD^{-}CD27^{-}CXCR5^{-}CD11c^{+}$) shows particularly robust expansion in SLE and displays features of extrafollicular origin, including the absence of CXCR5 (ref. 9). DN2 cells readily differentiate into ASCs and thus have considerable clinical relevance. A key feature of DN2 cells is the low or absent expression of complement receptor 2 (CR2; also known as CD21) (Box 2).

Mechanistic insight from mouse models aligns closely with these human observations. When B cells from healthy mice are transferred

into 564Igi transgenic autoimmune mice, a subset of naive follicular B cells rapidly downregulate the expression of CD21 immediately after activation and before proliferation[2,11] (Box 1). These CD21^{lo} cells, which resemble human DN2 cells, are potent producers of autoantibodies in autoimmune environments and seem to represent a transitional state preceding extrafollicular ASC differentiation[11]. Crucially, functionally blocking the CD21 receptor reduces donor-cell proliferation and diminishes extrafollicular ASC formation[11]. Thus, the phenotypic characterization of disease-associated human B cell subsets is complemented by mouse studies that permit tissue-level investigation of mechanisms relevant to SLE pathogenesis. Because nomenclature for B cells destined for extrafollicular differentiation has varied across studies and biological contexts, in this Review, we refer to the classic naive-activated, circulating human extrafollicular B cell subset as DN2 cells; to phenotypically similar populations first described in aged and autoimmune mice as age-associated B cells (ABCs); and to analogous subsets identified during infections, such as *Plasmodium falciparum* and *Salmonella* infections, as atypical B cells (atBCs)[9,45,51–55].

Mouse models for studying autoreactive B cell fate

Transgenic and spontaneous models of SLE enable mechanistic characterization of autoreactive B cell fate, germinal-centre dynamics and extrafollicular responses, although their often-complex genetics limit direct translation to human SLE[56,57]. Much of our understanding of systemic B cell tolerance, and how it is shaped by BCR specificities, derives from studies using transgenic mice expressing defined BCRs (immunoglobulin transgenic mouse models) that typically bind antigen with affinities higher than those present in a physiologically naive repertoire and exhibit a restricted B cell repertoire that limits BCR evolution. These models commonly rely on direct challenging by cognate 'self' antigen, or adoptive transfer of antigen-specific B cells into autoimmune-prone recipient mice, followed by donor cell-specific antigen inoculation. Classic systems, such as the hen egg lysozyme (HEL) models or the AM14 anti-chromatin model, have been instrumental in defining the fundamental principles of B cell tolerance[42,58–64]. Additional examples are highlighted in Box 1. However, dissecting how B cells commit to germinal-centre and extrafollicular fates requires spatial and kinetic insight from secondary lymphoid organs in settings that more accurately mirror the complexity of human autoimmunity. For example, clarifying how contextual factors — such as the timing and source of inflammation — shape the B cell responses and evolution would benefit from systems that preserve a fully diverse B cell repertoire. In this context, the 564Igi mouse model offers distinct advantages: through wild type mixed bone-marrow chimeras and adoptive B cell transfers, this approach provides a more modular and physiologically relevant alternative to fixed transgenic models, enabling analysis of the role of naturally autoreactive B cells in autoimmunity, while also providing precise kinetic windows, to understand how individual cells commit to extrafollicular or germinal-centre fates[1,11,17,65] (Box 1 and Fig. 2).

Determinants of germinal-centre versus extrafollicular fate

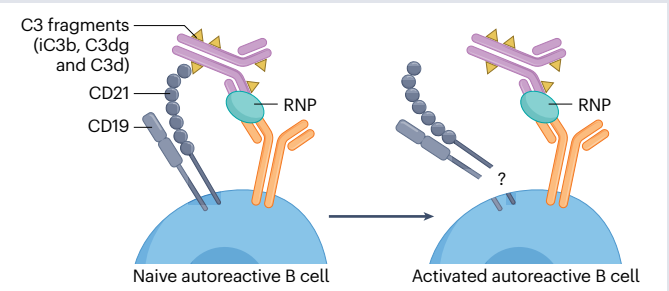
The mechanisms that precisely direct B cell differentiation along the germinal-centre or extrafollicular pathway remain incompletely defined. Proposed determinants include the strength and quality of BCR signalling, the nature of cognate T cell interactions, and the influence of local environmental cues, including cytokines and metabolic resources. Other reviews have examined BCR signalling and extrafollicular differentiation in detail[66–68], and T cell help is discussed in a later section. Hence, in this section we focus on the importance of a pro-inflammatory environment in shaping fate commitment among B cells with diverse BCR repertoires (Fig. 2).

Antigen stability and availability

Understanding the dynamics of B cell differentiation pathways in response to self-antigens requires careful consideration of antigen recognition within a physiological context. Responses to self differ fundamentally from responses to infection or vaccination, because self-antigens often remain continuously present. Kinetic tracing of antigen-specific B cell dynamics in humans remains nearly impossible,

Box 2 | The complement pathway in B cell activation and differentiation

Complement C3 is a central component of the complement cascade and, upon activation, is cleaved into C3a and C3b. C3a functions as an anaphylatoxin that facilitates immune-cell recruitment, whereas C3b opsonizes antigen surfaces to facilitate phagocytosis. C3b is further cleaved into iC3b and, upon cofactor binding, into C3dg and C3d, all of which remain bound to the antigen surface and can engage the complement receptor CD21 (ref. 186). CD21 forms a heterodimer with CD19 and is part of the B cell co-receptor complex. Co-ligation of the CD19–CD21 complex with the B cell receptor (BCR) by antigen opsonized with C3d or iC3b — including immune complexes containing small nuclear ribonucleoproteins (RNPs), a major complement-opsonized autoantigen in systemic lupus erythematosus — induces signal transduction through the BCR and CD19 and lowers the activation threshold for naive autoreactive B cells[187] (see the figure). Following ligand engagement, surface CD21 on naive autoreactive B cells is rapidly downregulated together with CD19. The precise mechanism(s) of this downregulation is unknown, although early biochemical data point to receptor shedding as a possible explanation[188–190]. Early naive-activated CD21^{lo} DN2-like



cells preferentially undergo extrafollicular differentiation into antibody-secreting cells. Inhibition of CD21 ligand binding impairs B cell proliferation and antibody-secreting cell formation, indicating that CD21 functions as an initiator of autoimmune B cell activation and extrafollicular differentiation[51]. Although the precise role of CD21 in autoreactive germinal-centre responses is still under investigation, the receptor probably exhibits nuanced functions on follicular dendritic cells and on germinal-centre B cells.

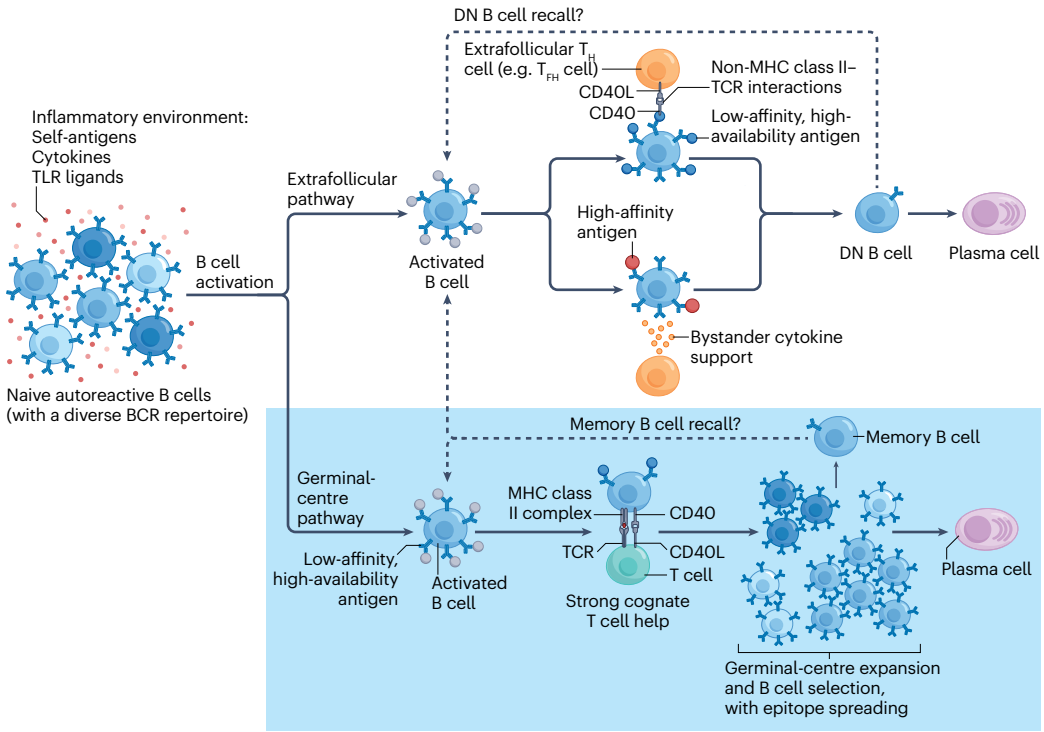


Fig. 2 | Contextual determinants of extrafollicular and germinal-centre B cell pathways. In an autoimmune environment, naive autoreactive B cells are activated through recognition of self-antigens via the B cell receptor (BCR) and by sensing TLR agonists, together with exposure to inflammatory cytokines such as interferons. The activated B cells can follow distinct pathways, shaped by antigen availability and the nature of T cell help. Top: in the extrafollicular response, which is rapid and often driven by abundant antigen together with bystander T cell support, activated naive B cells differentiate into double-negative (DN) B cells (IgD^-CD27^-) and subsequently into plasma cells. Bottom: in the germinal-centre pathway, strong and sustained cognate interactions with T cells drive affinity maturation clonal diversification and epitope spreading, culminating in the generation of self-reactive plasma cells. Both pathways also generate memory B cells and sustain disease through the production of pathogenic autoantibodies. TCR, T cell receptor; T_{FH} cells, T follicular helper cells; T_H cells, T helper cells.

but knockout in mouse models with defined BCR specificities allows time-resolved analyses of the activation of antigen-specific B cells. During primary murine immune response to foreign challenge, ASCs emerge in the splenic red pulp within 2–4 days following challenge, for T cell-dependent and T cell-independent stimuli, and appear in the medullary cords of lymph nodes[41]. Similarly, in human studies, circulating ASCs become detectable in the blood 4–7 days after vaccination or infection[69,70]. Notably, these events coincide with two sometimes overlooked milestones: the intrinsic timing necessary for activated B cells to differentiate into ASCs[71] and, crucially, the disappearance of antigen from the splenic red pulp, accompanied by subsequent accumulation within follicles[72–74].

In vivo, the amount and persistence of antigen shape the timing and relative prominence of extrafollicular responses versus the emergence of the germinal-centre pathway. In the B1-8^{hi} mouse model, in which B cells recognize a defined model antigen (4-hydroxy-3-nitrophenylacetyl), this antigen remains detectable in the spleen for roughly 4 days after immunization. This window coincides with key events, including B cells moving to the germinal centre[72], the surge of plasmablasts and the emergence of a subset of memory-like B cells that express the key ABC-fate transcription factor ZEB2 (as discussed in a later section)[75,76]. Detailed analysis using fluorescence resonance energy transfer-based cleavage-sensitive probes demonstrate that antigens are protected from degradation within B cell follicles, but are rapidly degraded by metalloproteases outside follicles within 3 days after immunization[73]. Indeed, these observations help to explain the longstanding proposal that controlling antigen release and delivery can enhance the efficacy of vaccines designed to elicit strong germinal-centre reactions[74,77]. Inside follicles, follicular dendritic cells protect antigens over time, sustaining germinal-centre activity[78]. In autoimmune settings, by contrast, antigen is often abundant and continually available, making it unlikely to constrain extrafollicular expansion. Although extrafollicular responses are commonly associated with high-affinity B cells, work in the HEL system shows that increased antigen density — even when antibody affinity is modest — can bias activated B cells towards extrafollicular differentiation, whereas reduced antigen density favours germinal-centre commitment[58]. These findings suggest that abundant antigen can override affinity thresholds that normally limit extrafollicular predominance, probably in conjunction with some T cell help. Indeed, distinct T cell subsets can provide signals that support, but do not by themselves dictate, whether activated B cells follow extrafollicular versus germinal-centre trajectories; this influence is largely dependent on the spatial and inflammatory context in which the interaction occurs.

Thus, defective clearance of self-antigens could contribute to downstream autoimmune phenotypes and skew the balance between extrafollicular and germinal-centre responses. Failures in nuclease activity exemplify this principle: the absence or failure of DNases

results in accumulation of extracellular DNA and drives autoimmune disease[79–82]. Complement components similarly maintain tolerance by supporting efficient removal of apoptotic material[83–85]. Mice deficient in complement C4 develop autoantibodies and exhibit defective clearance of apoptotic debris[86,87], and mixed bone marrow chimeras generated between C4-sufficient or C4-deficient mice and 564Igi lupus mice demonstrate that C4 has a critical role in maintaining B cell tolerance at the transitional stage. Notably, 564Igi mice expressing different C4A or C4B isotypes have distinct patterns of self-reactivity[88,89]. Beyond antigen availability, the relevance of the nature of an antigen (including the molecular form, such as nucleic acids or proteins) and its size in modulating autoreactive B cell fate remains unclear. Studies indicate that antigens above roughly 70 kDa differ markedly from smaller molecules in their capacity to access specific microenvironments, altering their availability for extrafollicular or germinal-centre responses. Antigens of varying size and physicochemical properties follow distinct kinetic routes and have different distributional limits within secondary lymphoid organs[90–92]. Antigen availability clearly represents a predominant feature to explore in human autoimmune disease and might help to explain the evolution and heterogeneity of self-reactivity in patients with SLE.

Cytokine regulation

During differentiation, autoreactive B cells encounter diverse local environments and are shaped in part by cytokine signals that influence their fate. One of the best defined examples of cytokine-driven extrafollicular bias comes from studies of immune responses to *Salmonella enterica* serovar Typhimurium. In this infection model, IL-12 alone drives robust extrafollicular plasmablast formation and suppresses the germinal-centre pathway by modulating and hampering the differentiation of T helper cells[93]. Related work in the same system showed that Sca1^{+} monocytes dampen germinal-centre activity, reinforcing the idea that identifying factors that inhibit germinal-centre activity can reveal drivers of the extrafollicular pathway[94]. IL-12-stimulated B cells responding to *Salmonella* also secrete IFNγ, establishing a B cell-intrinsic positive feedback loop that strengthens the extrafollicular trajectory[95]. Interferon signatures are a hallmark of SLE, although the specific contributions of type I, type II and type III interferons to B cell fate and disease progression continue to be defined[96]. T cell-derived IFNγ is a central driver of DN2 cell development in human SLE, and promotes the differentiation of ABCs and atBCs in mice[9,52,53,97,98], in part through induction of the transcription factor T-bet. Additionally, T cell-derived IL-2 in mice drives the differentiation of B cells into plasma cells in vitro and in vivo, biasing B cells towards an extrafollicular fate through mTOR-dependent signalling that precedes IRF4 upregulation, a major regulator of plasma-cell differentiation[99]. IL-21 and IL-10 further modulate T cell-dependent extrafollicular responses, as discussed in more detail in later sections[100,101]. Collectively, these studies highlight that cytokines — including IL-2, IL-10, IL-12, IL-21 and interferons — shape the inflammatory microenvironments that direct B cell fate decisions with lasting effects.

Transcriptional and epigenetic regulation

Commitment to extrafollicular and germinal-centre pathways is regulated by multilayered transcriptional programmes (as reviewed elsewhere[4]). Cytokine signalling in B cells often leads to transcriptional and epigenetic changes that could amplify local inflammation through the release of additional cytokines, creating feedforward circuits that reinforce specific effector fates. One illustrated example is ZEB2, a transcription factor required for the development of ABCs in autoimmune settings and atBCs during *P. falciparum* infection, where this transcription factor drives the expression of characteristic surface markers[54,75]. ZEB2 also regulates the balance between the expression of MEF2B and MEF2C, two transcriptional regulators whose relative abundance influences whether activated B cells can enter the germinal centre, with MEF2B required for germinal-centre transition. In addition, ZEB2 deficiency impairs B cell-intrinsic IFNγ production, further disrupting extrafollicular development[75]. Although genetic predisposition contributes to SLE, chronic inflammation and cytokine exposure can impose epigenetic modulations that precondition B cells towards a specific pathway[102]. Indeed, naive B cells in individuals with SLE exhibit an epigenetic profile consistent with a predisposition towards extrafollicular differentiation[103,104].

Metabolic regulation

Metabolic resources represent an additional important limiting factor in B cell-fate bifurcation. Clinical and rodent studies of *P. falciparum* infection have long documented an impairment of germinal-centre responses accompanied by a marked expansion of the extrafollicular B cell compartment and poor establishment of B cell memory. One proposed mechanism is that the high metabolic requirements of extrafollicular plasmablasts might starve the environment and limit the development of germinal centres. In a mouse model of *P. falciparum* infection, this nutrient limitation was traced specifically to the availability of L-glutamine; supplementation of L-glutamine during an ongoing *P. falciparum* infection reestablished the germinal-centre responses. Consistent with this observation, malaria-naive humans exposed to *P. falciparum* develop a strong plasmablast response in their first encounter with the parasite[105].

B cells have distinct metabolic requirements at different stages of differentiation and across subsets[106,107]. For example, dynamic mTOR complex 1 (mTORC1) activity is essential for regulating the proliferative cycling of germinal-centre B cells[108,109]. Notably, genetic disruption of lactate dehydrogenase A (LDHA) — the enzyme responsible for converting pyruvate to lactate — in 'resting' naive B cells abolishes germinal-centre responses while leaving extrafollicular response intact. By contrast, deletion of LDHA in activated B cells does not affect their capacity to undergo germinal-centre maturation. Thus, requirements for aerobic glycolysis differ across the various stages of B cell activation[110].

Clinically, individuals with severe COVID-19 exhibit a markedly expanded extrafollicular response, whereas mild disease is dominated by germinal-centre responses[111,112]. Uncontrolled B cell activation and aberrant extrafollicular reactions are normally restrained by the induction of mitochondrial dysfunction[113]. Reduced levels of mitochondrial dysfunction is associated with severe COVID-19, resulting in pathogenic extrafollicular B cell expansion and a limited capacity to produce germinal-centre-derived antibodies necessary to curtail the infection. These observations suggest that mitochondrial dysfunction serves as a regulatory mechanism to block exacerbated extrafollicular B cell differentiation in humans.

Comparative studies of B cells from healthy individuals and patients with SLE have helped to identify disease-metabolic pathways. However, limited information exists regarding the specific contributions of metabolic programmes to the development of extrafollicular versus germinal-centre responses in autoimmunity[114]. Work shows that DN2-like CD11c^{+} B cells in SLE exhibit increased expression of the 6-methyladenosine (m^{6}A) demethylase fat mass and obesity-associated protein (FTO).

Mechanistically, epigenetic modification of m^{6}A promotes human extrafollicular DN2 formation through a TLR7–FTO–ATPase H$^+$-transporting V1 subunit G1 (ATP6V1G1) signalling axis that enhances mitochondrial oxidative phosphorylation[115]. These findings suggest that strong TLR7 signalling can skew B cells towards the extrafollicular fate by triggering distinct metabolic programmes. Collectively, further mechanistic insights are required to better determine the contribution of metabolic resources to autoreactive B cell fate commitment.

Germinal-centre dynamics in systemic lupus erythematosus

Germinal centres are fundamental for protective immunity, refining B cell clones into highly specific and durable responders following infection or vaccination. In SLE, however, these same structures operate under altered regulatory conditions, enabling breaches in tolerance that intensify and support the evolution of autoreactive B cell populations.

Germinal centres support autoreactive B cell evolution

Germinal centres can generate autoreactive B cells through two main routes: intrinsically self-reactive clones that enter germinal-centre reactions despite tolerance mechanisms, and initially non-self-reactive B cells that acquire self-reactivity through the germinal-centre reaction and are not effectively purged. Self-reactive clones already present in the repertoire can also diversify further within germinal centres, broadening their specificities towards new targets as they evolve[116,117]. Thus, in SLE, breaches in tolerance in the pre-germinal-centre compartments are often amplified during germinal-centre maturation. Work in the 564Igi lupus model illustrates this amplification. Germinal centres seeded by autoreactive 564Igi B cells can recruit B cells from a wild-type repertoire[118]. In mixed bone-marrow chimeras containing both 564Igi and wild-type B cell populations, these wild-type B cells enter autoreactive germinal centres and undergo clonal expansion and diversification[1]. This recruitment contributes to epitope spreading[1], broadening antigen reactivity beyond the initiating 564Igi specificity, while maintaining similar germline BCR usage in autoimmune and immunized settings[30]. Notably, although germinal centres amplify and diversify autoreactive clones, they are not required for the production of self-reactive antibody-secreting cells. Systemic abrogation of the germinal-centre response via genetic deletion of B cell-specific B cell lymphoma 6 (BCL6) — a critical transcriptional repressor essential for germinal-centre differentiation — does not dampen the development of self-reactive ASCs and instead enhances extrafollicular pathways and expands the pool of self-reactive ASCs[10].

Interestingly, B cells that acquire self-reactivity during germinal-centre evolution are only eliminated when the relevant self-antigen is locally available; by contrast, self-reactivity to antigens expressed in distant organs is not necessarily eliminated, suggesting that systemic patterns of antigen localization help to maintain a peripheral tolerance threshold[36]. Why, then, does the immune system retain self-reactive clones that are permitted to enter and participate in germinal centres? One proposed explanation is clonal redemption, in which problematic B cell clones can undergo somatic mutation within germinal centres to lose self-reactivity and acquire foreign-antigen specificity. However, clonal redemption alone does not explain how these self-reactive clones gain entry, survive selection and persist long enough within germinal centres to undergo such re-shaping, highlighting that additional mechanisms governing germinal-centre tolerance remain to be fully defined[119,120].

T follicular helper cells propagate autoreactive germinal centres

Within the autoreactive germinal centre, T follicular helper cells (T_{FH} cells) and T follicular regulatory cells (T_{FR} cells) interact with B cells to shape peripheral tolerance. An imbalance — with pathogenic T_{FH} cells promoting autoimmunity and regulatory T_{FR} cells failing to constrain it — contributes to dysregulated B cell responses[121] (Fig. 3). Circulating human CCR7^{lo}PD1^{hi}CXCR5$^+$ T_{FH} precursor cells also support T_{FH} cell activity and are expanded in autoimmune disease[122]. Across mouse and human studies, T_{FH} cells show altered frequency, function, gene expression and metabolic profiles in autoimmune disease[17,123–129]. Mounting evidence suggests that T_{FH} cells adopt a permissive — rather than regulatory — role in the loss of B cell tolerance. Indeed, similar to the B cell repertoire, the endogenous CD4$^+$ T cell repertoire naturally contains self-reactive clones capable of driving autoantibody production. Notably, these autoreactive T cells spontaneously adopt T_{FH}-like phenotypes when transferred in mice, potentially providing an abundant source of support for autoreactive germinal-centre B cells[16]. Genetic studies further underscore the centrality of T_{FH} cells: deficiency of BCL6 or SLAM-associated protein (SAP) — both essential for T_{FH} and germinal-centre formation — abrogates autoimmune disease in Roquin$^{san/san}$ mice[130]. Similarly, in mixed bone-marrow chimeras, inducible T cell co-stimulator (ICOS) or SAP deficiency prevents the formation of autoimmune germinal centres following epitope spreading[17]. Continuous T cell help is necessary to maintain autoimmune germinal centres, as T cell-specific deletion of BCL6 reduces the frequency of autoimmune germinal centres[17]. Furthermore, although follicular T cell repertoires from immunized and autoimmune mice are polyclonal and share predicted specificities[131], a minority of clonotypes become selectively enriched in autoimmune settings[132]. Retrogenic chimeras show that these enriched T cell receptors (TCRs) are sufficient to rescue autoimmune germinal-centre formation and epitope spreading[17], suggesting that follicular T cell specificity can influence loss of B cell tolerance.

Evidence suggests that autoreactive germinal centres originate from an initiator B cell clone positioned in the extrafollicular bridging channel — the anatomical corridors in the spleen that guide activated B cells from the marginal zone towards the T cell–B cell border. In this niche, B cells present self-antigen to a cognate autoreactive T cell, which in turn provides the helper signals required to establish and propagate an autoreactive germinal centre[8]. Bystander expansion of T cells further complicates this process. This phenomenon refers to the non-specific activation of T cells with specificities for antigens other than those inducing the primary response, either through dendritic-cell presentation of alternative antigens, or through cytokine-driven activation[131,133,134]. Repertoire analyses of mouse T_{FH} and T_{FR} cells suggest that follicular T cells undergo substantial bystander expansion[131–134] and harbour autoreactive TCRs[16,135,136]. The combined effects of bystander expansion and endogenous T cell autoreactivity probably broaden foreign-antigen coverage, but at the evolutionary cost of permitting autoreactivity. Indeed, mounting evidence suggests that similar mechanisms exist in the B cell repertoire and are responsible for both diverse immunity and the development of autoimmunity[23,137–140]. Therefore, these observations support a model in which loss of tolerance in the germinal centre occurs when an autoreactive B cell gains access to T cell help and an autoreactive T cell, in turn, engages B cells, an outcome made possible by the inherent autoreactivity embedded within both repertoires. The mechanisms responsible for preventing such reciprocal breaks

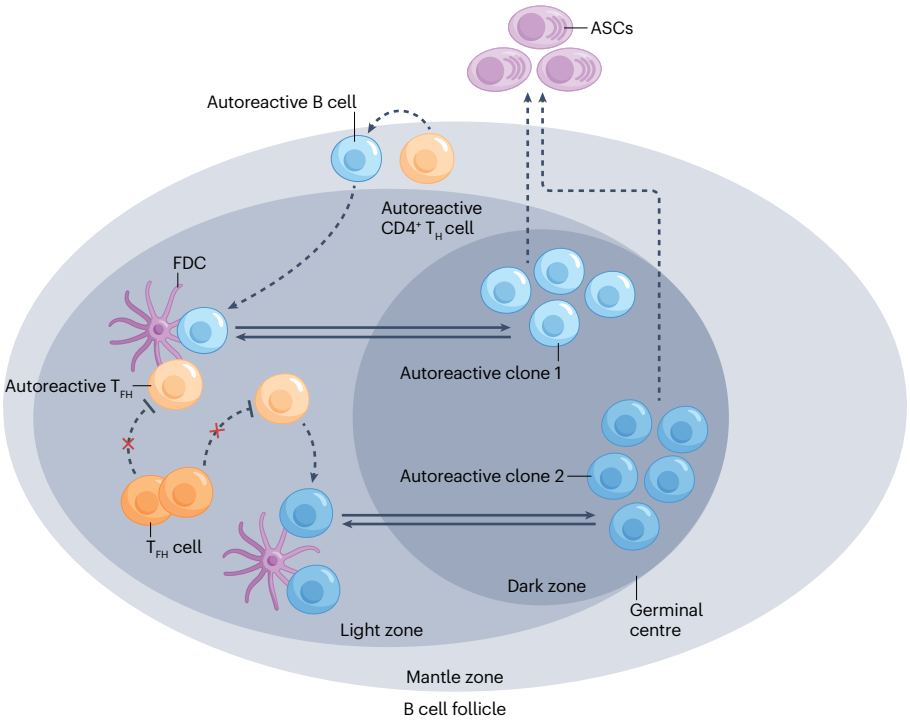


Fig. 3 | Components of an autoreactive germinal centre. Spontaneous autoreactive germinal centres arise during chronic exposure to autoantigens and function as open structures that permit the entry, selection, evolution and expansion of autoreactive B cell clones. Within these germinal centres, autoreactive B cells evolve towards pauciclonality as selected clones undergo extensive proliferation and somatic hypermutation, ultimately differentiating into antibody-secreting cells (ASCs)[1]. Under homeostatic conditions, self-reactive T follicular helper cells (T_{FH} cells) are regulated by T follicular regulatory cells (T_{FR} cells) to prevent aberrant activation and autoimmunity. In autoimmune conditions, activated autoreactive T_{FH} cells promote the establishment of autoreactive germinal centres, and impaired T_{FR} cell function further supports the persistence of these germinal centres[17,121]. FDC, follicular dendritic cell; T_H cell, T helper cell.

in tolerance, including clonal anergy and T cell ignorance, remain incompletely defined.

T cell-dependent extrafollicular B cell responses in systemic lupus erythematosus

Although germinal-centre response drives clonal diversification, selection and epitope spreading, extrafollicular responses provide a rapid and persistent source of autoantibodies in SLE. Research progress over the past decade on various aspects of extrafollicular B cell responses has been extensively reviewed[44,45,66,68,141,142]. Historical and current experimental evidence indicates that extrafollicular B cell responses depend on T cell help. However, substantial gaps remain regarding the heterogeneity and variability of the T cell subsets involved and the requirement for direct T cell–B cell interactions. This section therefore summarizes existing studies and highlights areas in need of further investigation.

T cell-derived signals governing extrafollicular autoimmunity

As outlined in an earlier section, the extrafollicular antibody response proceeds through a defined series of stages, with T cell–B cell interactions and rapid B cell expansion occurring within 24 h after the primary antigen encounter[41]. Mechanistic studies of T cell-dependent extrafollicular B cell response in autoimmunity remain limited, and much of our understanding derives from immunization and infection models using foreign antigens (Box 3). In autoimmunity, B cells that break tolerance typically exhibit low antigen-binding affinity and yet display substantial clonal diversity, reflecting activation by a diverse pool of autoantigens. The enormous diversity of the T cell repertoire further complicates T cell–B cell interactions in the extrafollicular pathway and potentially shapes distinct cellular dynamics within the lymphoid environment[143]. Although T cell help is widely recognized as a positive regulator of the extrafollicular response, the relative contributions of antigen-specific versus bystander T cells remain debated. In acute lymphocytic choriomeningitis virus (LCMV) infection in mice, germinal-centre-independent T_{FH} cell help is necessary for the generation of ABC-like T-bet$^+$CD11c$^+$ B cells[144]. By contrast, extrafollicular T cell help is ICOS dependent[145] yet SAP independent in autoimmune mouse models[17], suggesting that stable, long-lived T cell–B cell contacts — crucial for germinal-centre reactions — are less essential in the extrafollicular pathway.

Dnase1l3$^{-/-}$ mice generate autoantibodies via extrafollicular ASCs, a process that requires T cell help mediated by CD40L[82]. Consistent with this requirement, MHC class II-deficient B cells — which cannot receive cognate T cell help — produce markedly fewer plasma cells when transferred into 564Igi hosts, suggesting that extrafollicular ASC differentiation depends on antigen-specific T cell interactions[118,141]. In the MRL/lpr lupus strain, PSGL1^{lo} T cells represent a distinct population of ICOS-dependent extrafollicular helper T cells that drive extrafollicular B cell responses through IL-21 and CD40L production. Notably, these PSGL1^{lo} T cells also require B cells for their own development, demonstrating a reciprocal extrafollicular T cell–B cell co-dependency[145]. Conversely, some studies suggest that T cell help augments extrafollicular B cell responses, but does not constitute a strict requirement. For example, in MLR/lpr mice expressing the AM14 heavy-chain transgene (Box 1), extrafollicular activation and somatic hypermutation of anti-chromatin AM14 B cells occur independently of T cells and instead rely on TLR7 and TLR9 signalling, although CD4$^+$ T cells amplify the response[64]. Therefore, the requirement for T cell help during extrafollicular B cell responses seem to be in part dependent on the presence of TLR co-stimulation. Nevertheless, T cells do seem necessary for spontaneous conversion of autoreactivity in this model when mice are not experimentally stimulated with anti-chromatin antibodies[64]. Similarly, AM14 BCR-transgenic BALB/c B cells generate antibody-forming cells within 6 days of IgG2a anti-chromatin antibody stimulation, even in hosts lacking T cells or expressing non-cognate

Box 3 | Early insights into T cell help in extrafollicular B cell responses

Early work challenged the notion that T cell help is restricted to thymus-dependent antigen responses. These studies showed that antibody production against thymus-independent type 2 antigens nevertheless requires antigen-primed $CD4^+$ T cells[191,192]. Subsequent investigations showed that T cells can deliver bystander help through 'soluble helper factors' to facilitate antibody response to the thymus-independent type 2 antigen DAGG–Ficoll[193].

A clearer extrafollicular T cell identity emerged with the discovery of a specific $BCL6^+PD1^{lo}$ population of pre-germinal-centre T follicular helper cells (T_{FH} cells) located at the T cell–B cell border in mice. These pre-germinal-centre T_{FH} cells prime B cells for early extrafollicular responses. Although BCL6 was often described as a key transcription factor that drives germinal-centre B cell differentiation, these pre-germinal-centre T_{FH} cells also require BCL6 to drive extrafollicular plasmablast differentiation and antibody production[194]. $BCL6^+$ pre-germinal-centre T_{FH} cells mediate extrafollicular antibody response through IL-21, consistent with previous reports[63,145,195,196]. During *Salmonella* infection, pre-germinal-centre T_{FH} cells emerge 4 days post-transfer at the T cell–B cell border and initiate the extrafollicular plasmablast response, preceding the emergence of $PD1^{hi}$ T cells. Immunization with hen-egg lysozyme-ovalbumin further confirmed that BCL6-dependent pre-germinal-centre T_{FH} cells function in an antigen-specific manner[194].

TCRs, albeit at lower levels than in wild-type recipients[63]. These findings indicate that antigen-specific T cells enhance but do not dictate extrafollicular B cell response in this setting. IL-21 and CD40L mediate bystander and cognate T cell help, respectively, in this model and notably these T cell-derived signals persist despite inducible T cell co-stimulator ligand blockade[63]. Collectively, these observations show that, unlike germinal-centre-dependent autoreactivity, the degree and nature of T cell dependence in extrafollicular responses varies across model systems, with TLR signalling having a substantial role in calibrating this dependence.

Although the abovementioned mouse studies point to distinct subsets of T cells that support extrafollicular B cell differentiation in SLE, considerable technical and conceptual challenges in defining TCR antigen specificity continue to limit detailed exploration of cognate T cell–B cell interactions during the extrafollicular B cell response. Notably, autoreactive T cell clones that accumulate in the spleen and non-lymphoid tissue after sustained T_{FR} depletion in mice exhibit a T_{FH}-like phenotype and secrete IFNγ, yet have low BCL6 expression[16]. However, characterization of the autoreactive potential of T cell repertoires equipped with extrafollicular B helper functions remains limited. Given that a single self-reactive T_{FH} clone can drive autoreactive germinal-centre development, an intriguing question is whether such a clone could also support extrafollicular responses[17]. Furthermore, given that a subset of extrafollicularly destined B cells can differentiate independently of T cell help, comprehensive characterization of the corresponding BCR repertoire and antigen specificities remains essential for defining the factors that determine reliance on T cell help during tolerance breakdown. For example, in the absence of TLR and/or complement receptor stimulation, extrafollicularly destined autoreactive B cells might show increased dependence on T cell help for differentiation.

Extrafollicular T helper cell subsets driving pathogenic responses

Following numerous patient studies describing pathogenic extrafollicular B cells such as DN2 cells and ABCs, considerable effort has been made in characterizing the T cell populations that provide extrafollicular help and promote pathogenic antibody responses. Among these cells, T peripheral helper cells (T_{PH} cells) and T helper 10 cells (T_H10 cells) have emerged as major T cell subsets supporting extrafollicular B cell responses in SLE, albeit through distinct mechanisms (Fig. 4a). T_{PH} cells were initially identified in the synovium of patients with rheumatoid arthritis (RA) and were later also described in the peripheral blood of patients with SLE, where their frequency correlated with that of $CD11c^+$ B cells[146,147]. T_{PH} cells exhibit a $PD1^{hi}CXCR5^-CD4^+$ surface signature and express high levels of IL-21, CXCL13 and SAP[148], in part consistent with a potent capacity to drive extrafollicular B cell activation. However, as the cognate receptor for CXCL13, CXCR5, is not expressed on bona fide extrafollicular B cells, T_{PH} cells might also perform functions beyond direct recruitment and activation of these B cells. T_{PH} cells also have unique expression of CCR2, CX3CR1 and CCR5, possibly driving the migration of T_{PH} cells to sites of inflammation.

In paediatric-onset SLE, a phenotypically similar yet functionally distinct subset of $CXCR5^-CXCR3^+PD1^{hi}CD4^+$ helper T cells — referred to as T_H10 cells owing to their IL-10-producing capacity — has been identified in the blood and in the tubulointerstitial compartment of individuals with proliferative lupus nephritis. This subset lacks IL-21 and BCL6 expression, indicating IL-21-independent activity. The lack of CXCR5 expression combined with CXCR4 expression suggests extrafollicular confinement. In contrast to T_{PH} cells, T_H10 cell B helper function is driven by IL-10 and succinate, and is amplified by oxidized mitochondrial DNA (mtDNA)-activated plasmacytoid dendritic cells, potentially through ICOS engagement and IFN-mediated signalling[149] (Fig. 4a). The precise roles of IL-10 and succinate in promoting pathogenic B cell autoantibody production remain unresolved. Moreover, T_H10 cells can promote IgD^-CD27^+ B cell and $CD27^+CD38^+$ plasmablast differentiation and antibody production in vitro, and correlate with ABC expansion in SLE, but whether these cells also support extrafollicular IgD^-CD27^- double-negative cells, including DN2 cells, is unknown.

As previously discussed, the transcription factor ZEB2 drives ABC development and possibly also promotes CD11c expression[75]. A related role has been proposed for ZEB2 in promoting the B helper functions of a $CXCR3^{mid}CD4^+$ effector memory T cell subset, named age-associated T helper cells (T_HA cells). These cells represent another subset distinct from T_{PH} cells and are characterized by a surface phenotype of $CD25^-CXCR5^-CCR6^-CCR4^-$ and the unique feature of age-dependent expansion[76] (Fig. 4a). Interestingly, the expression of granzyme A, granzyme B and perforin in these cells suggests cytotoxic potential, pointing to functional diversity within the subset. Whether T_HA cells support B cells with an ABC-like or DN2-like phenotype remains unresolved. Their phenotypic profile, including the expression of *TBX21* (encoding T-bet), raises the possibility of cytokine-mediated polarization in parallel with their B cell counterparts.

IL-21 signals through IL-21R on B cells via the JAK–STAT pathway by phosphorylating and activating STAT3, which in turn, induces a transcriptional programme that includes B lymphocyte-induced maturation protein 1 (BLIMP1) and activation-induced cytidine deaminase, thereby

promoting plasma-cell differentiation and potent immunoglobulin production[150–153]. Interestingly, IL-21 exhibits context-dependent functions that vary according to co-stimulatory conditions and B cell states. In addition to inducing plasma-cell differentiation, IL-21 can support germinal-centre entry and maintenance and, in the absence of BCR co-stimulation, promotes B cell apoptosis[100]. Notably, positive IL-21 signalling is considerably amplified with CD40 co-stimulation, underscoring the synergistic functions of multiple T cell-derived helper signals[152,154]. The outcome of IL-21 signalling also seems to depend on the expression level of IL-21R across B cell subsets. For instance, CD11c^{hi}CD21^{lo} B cells demonstrate substantially elevated expression of IL-21R compared with naive and CD27^{+} memory cells, alongside a corresponding increased expression of IL-21-inducible genes[155]. Consequently, IL-21 drives the expansion and plasma-cell differentiation of DN2-like CD11c^{hi} cells in both patients with SLE and infected mice[155,156]. T_{PH} cells expressed higher levels of IL-21 than CXCR5^{+} T cell populations, and together with the elevated expression of IL-21R on extrafollicularly committed B cells, this cytokine environment probably promotes B cell retention and activation in extrafollicular niches, facilitating terminal ASC differentiation[143]. Interestingly, the requirement for CD40 engagement in the development and activity of extrafollicular B cells remains contentious across species (particularly mice versus humans). For instance, in humans, stimulation with trimerized CD40L activates resting naive B cells, but not DN2 cells, as demonstrated by the lack of CD25 upregulation[9]. Instead, DN2 cells are highly responsive to TLR7 signalling, suggesting a reduced reliance on cognate T cell help.

The identification of different extrafollicular T cell subsets highlights the unique developmental and metabolic requirements of disease-associated B cell subsets in SLE (Fig. 4b), while also raising several unresolved questions. For instance, a key priority is to delineate the developmental trajectories of extrafollicular T helper cells and identify the signals that drive their polarization. T_{PH} cells share substantial clonal overlap with T_{FH} cells in both patients with SLE and pristane-treated mice[143]. In patients with SLE, transcriptomic pseudotime analysis positions T_{PH} cells downstream of T_{FH} cells in the developmental hierarchy[143]. However, this proposed trajectory requires further experimental validation and characterization. Variability in B helper T cell subsets between childhood-onset and adult-onset SLE could potentially reflect differences in organ involvement, including the higher frequency of renal manifestations in paediatric disease[157]. Another open question is whether distinct extrafollicular T cell and B cell subsets preferentially interact as functional pairs in mediating antibody responses. More stringent definitions of extrafollicular development are needed, particularly in the context of SLE. The assignment of pathogenic B cell subsets to either germinal-centre or extrafollicular developmental origin is further complicated by evidence that somatic hypermutation and affinity maturation can occur at extrafollicular sites[42,158,159]. Thus, as with the expanding catalogue of extrafollicular B cell subsets, rigorous functional and tissue-specific characterization — beyond

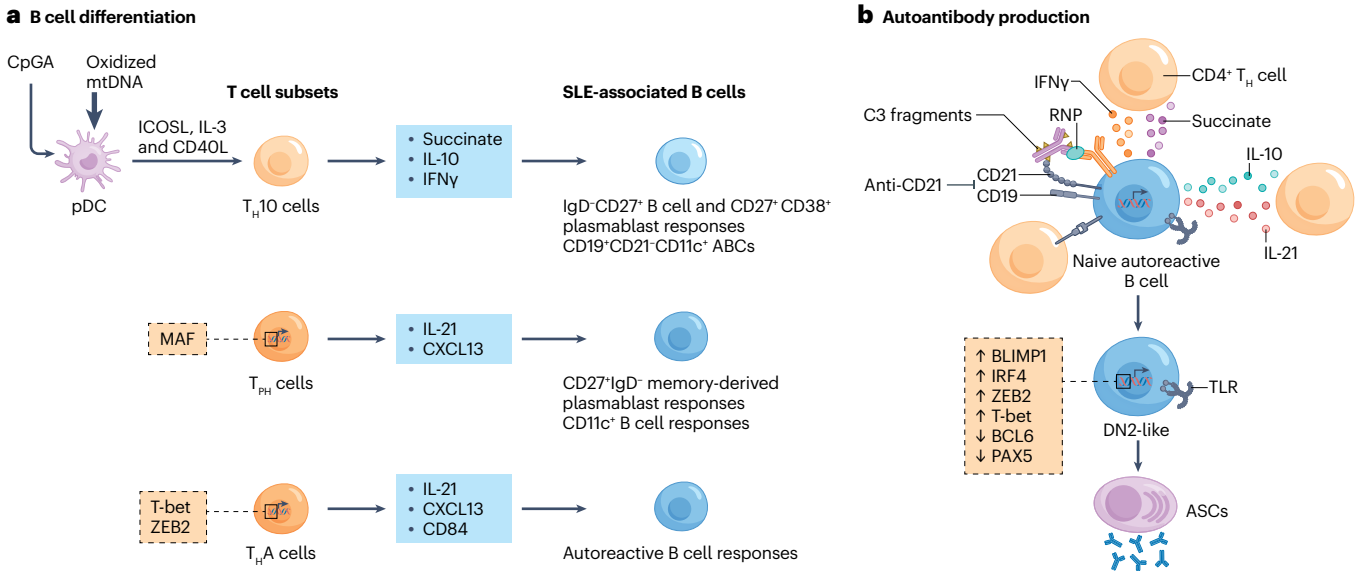


Fig. 4 | Germinal-centre-independent T cell help in extrafollicular B cell responses. Multiple helper T cell subsets and co-stimulatory pathways could coordinate to drive extrafollicular autoreactive B cell responses. **a**, Extrafollicular T cell help contributes to the activation and differentiation of systemic lupus erythematosus (SLE)-associated B cells. Top: plasmacytoid dendritic cells (pDCs) are activated by neutrophil-derived oxidized mitochondrial DNA (mtDNA), and to a lesser extent, CpGA, leading to the induction of T helper 10 cells (T_H10 cells) (PD1^{hi}CXCR3$^+$CXCR5$^-$CD4$^+$). These inducible T cell co-stimulator ligand (ICOSL)-dependent T_H10 cells produce succinate, IL-10 and IFNγ and promote IgD$^-$CD27$^+$ B cell and CD27$^+$CD38$^+$ plasmablast differentiation in vitro[149]. Middle: MAF-dependent T peripheral helper cells (T_{PH} cells) (PD1^{hi}CXCR5$^-$CD4$^+$) produce IL-21 and CXCL13, drive plasmablast differentiation from CD27$^+$IgD$^-$ memory cells in vitro, and correlate with CD11c$^+$ B cell responses in patients with SLE[146,147]. Bottom: age-associated T helper cell (T_HA cell) (CXCR3^{mid}CXCR5$^-$CD4$^+$) development is driven by T-bet and ZEB2; these cells secrete IL-21 and CXCL13, and also express CD84 to facilitate T cell–B cell interactions[76]. **b**, Cognate and bystander signals shape extrafollicular differentiation of autoreactive B cells. Naive autoreactive B cells commit to extrafollicular differentiation pathways via cognate CD4$^+$ T helper cell (T_H cell) interactions, indirect T cell help (through IL-21, succinate, IL-10 and IFNγ) and B cell-intrinsic TLR signalling and CD21 engagement. BLIMP1, IRF4, ZEB2 and T-bet are key transcription factors driving extrafollicular B cell responses and a DN2-like phenotype, whereas BCL6 and PAX5 activities are suppressed. Blocking the interaction between C3d or iC3b and CD21 with an anti-human CD21 antibody disrupts complement-mediated co-stimulation and thereby interferes with B cell activation. ABCs, age-associated B cells; ASCs, antibody-secreting cells; RNP, ribonucleoprotein.

surface receptor phenotyping — is needed to establish the identity and developmental programmes of extrafollicular T cells.

Future perspectives

Both germinal-centre and extrafollicular responses generate memory B cells, albeit with important phenotypic and functional distinctions that remain incompletely understood. A deeper mechanistic understanding of the germinal-centre and extrafollicular B cell differentiation pathways is essential for guiding the development of non-depleting, pathogenic target-specific therapeutic strategies. In this section, we summarize advances and future perspectives in these two areas.

Memory B cell response and dynamics

An intriguing and debated area of SLE research concerns the nature of the memory B cell response and the relative contributions of the extrafollicular and germinal-centre pathways. Conventional switched memory B cells (IgD^-CD27^+), generally considered to be germinal-centre derived, seem largely unaffected in SLE[9]. By contrast, potential extrafollicular B cell memory responses in autoimmunity have received comparatively little attention, although early studies provide compelling evidence for germinal-centre-independent waves of memory B cells. For example, 4-hydroxy-3-nitrophenylacetyl-specific $IgG1^+$ B cells with a resting phenotype emerge in *Rag1*$^{-/-}$ mice reconstituted with *Bcl6*$^{-/-}$ bone marrow 60 days after primary immunization with 4-hydroxy-3-nitrophenylacetyl-CG[160]. Similarly, $IgG1^{hi}CD38^+$ B cells with low somatic hypermutation develop in C57BL/6 mice 10–70 days after immunization with 4-hydroxy-3-nitrophenylacetyl-CG when germinal-centre formation is blocked by anti-ICOS antibody administration[161]. In another model, non-proliferating, non-germinal-centre, unmutated $B220^{high}BCR^{high}$ B cells develop as early as 5 days after HEL^{2x}-SRBC immunization and are characterized as possible early memory B cells[40].

A major challenge in defining the extrafollicular versus germinal-centre developmental origins of disease-associated memory B cell populations in SLE is the absence of definitive surface markers for a specific memory subset, coupled with limited insight into their longevity in tissue. DN2-like cells, often labelled 'atypical memory B cells' in bacterial and parasitic infections, are frequently assumed to be extrafollicularly derived[162,163]. However, accumulating evidence suggests that DN2 cells actually emerge from naive precursors and function primarily as immediate ASC progenitors, rather than forming a stable, long-lived memory pool[9,164].

In infectious settings, integrated single-cell transcriptomics and pseudotime lineage analyses suggest that certain memory B cell and atBC subsets develop along pathways divergent from conventional memory B cells. Notably, atBCs can be effectively recalled following *P. falciparum* sporozoite vaccine boosts, supporting their functional memory identity[163]. However, the lack of subset-specific markers complicates lineage tracking in vivo. This ambiguity is exemplified by T-bet, which characterizes non-recirculating, spleen-restricted, influenza HA-specific memory B cells of possible germinal-centre origin, but is also expressed by DN2 cells in patients with SLE and a subset of ABCs in mice[9,155,165–168].

Studies of mRNA vaccination and acute SARS-CoV-2 infection have further investigated the durability of memory B cell subsets[164,169]. Spike-specific DN cells showed overall durability, but the persistence of specific sub-populations varied across studies. Beyond conventional germinal-centre-derived memory B cells ($IgD^-CD27^+CXCR5^+CD11c^-$), DN1 B cells ($IgD^-CD27^-CXCR5^+CD11c^-CD21^+$) were identified as durable memory subsets, with relatively low mutation frequencies, suggesting a possible extrafollicular origin. However, DN1 cells express CXCR5, contrasting with conventional germinal-centre-independent subsets[9]. By contrast, DN2 cells showed limited durability in one study (disappearing within 2 months post-boost), but persisted for over 4 months in healthy individuals and patients with SLE in another study[164,169]. All together, these findings underscore the need for comprehensive developmental and functional characterization of various memory B cell populations in SLE. Establishing a widely applicable and consistent nomenclature system will be essential for clarifying their contribution to SLE and, potentially to the pathogenesis of other autoimmune diseases.

B cell-targeted therapies in systemic lupus erythematosus

A range of therapies has been developed or repurposed in recent decades to achieve broad removal of B cell repertoires in SLE and other autoimmune diseases. Monoclonal antibodies targeting CD19, CD20 and BAFF, as well as small-molecule BTK inhibitors, have shown variable efficacy[170]. CD19-targeted and B cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR) T cell therapies have produced promising early results, including possible long-term remission and evidence of an immunological 'reset' in which reconstituting B cell repertoires remain non-autoreactive following depletion of the CAR T cells[171]. Notably, minimal circulating self-reactive antibodies and $CD11c^+CD21^-$ B cells were detected at 6 months to 1 year following CD19 CAR T cell therapy in patients with SLE[172,173]. However, a modest rebound in circulating memory B cells was observed at 1-year follow-up, suggesting potential re-emergence of germinal-centre-mediated activity[173]. Persistence of long-lived plasma cells and antibody response has also been reported in recipients of the CD19-targeted CAR T cell therapy CTL019 (ref. 174).

These findings highlight the importance of the long-term monitoring of reconstituting B cell clonal repertoires, as well as potential shifts in T cell clonality following B cell depletion, to better understand treatment biology and to capture any repertoire shifts that might imply return of autoreactivity. Access to tissue biopsies would further enable surveillance of 'hidden' long-lived populations that might evade initial deletion yet retain pathogenic potential. Work in TLR7 gain-in-function mice provides additional insight: autoantibody relapse after CD19-targeted CAR T cell treatment was probably largely driven by newly generated B cells rather than treatment-resistant plasma cells, whereas relapse following BCMA-targeted CAR T cell treatment showed a mixed origin[175]. These early results highlight both the variable efficacy and distinct mechanisms of depletion across CAR T cell platforms, as well as the enduring influence of an autoimmune environment. Additional work is needed to define the environmental changes induced by B cell depletion — particularly those that might predict the nature and fate of returning repertoires and shape the antibody landscape. Close monitoring of factors such as cytokine profiles and interferon activity will be essential, given their modulatory functions in antibody responses discussed throughout this Review.

Last, DN2 and resting naive B cells from patients with SLE exhibit an epigenetic predisposition to activation[100]. Disease-associated epigenetic imprinting in naive B cells, together with developmental defects in progenitor B cells, suggest sustained changes in B cell physiology that could be resistant to peripheral B cell depletion[103,176]. These insights underscore the need to continue exploring other non-pan B cell-targeted treatments aimed at modulating pathogenic B cell functions. For instance, targeting the BCR complex, CD19, IFN receptors and complement receptors such as CD21 represent one such strategy, as targeting these pathways could modulate activation signalling and B cell differentiation without eliminating the entire repertoire[177,178].

Glossary

Affinity maturation
The process by which B cells progressively acquire increased antigen-binding specificity and affinity through somatic hypermutation and selection in the germinal centre[197].

Age-associated B cells
(ABCs). A non-germinal-centre non-antibody-secreting murine B cell subset that expands with age and accumulates more rapidly in autoimmune strains, initially defined as $CD19^{+}B220^{+}CD11c^{+}CD21^{-}CD23^{-}$[52,53,198].

Atypical B cells
(atBCs). A pathogenic B cell subset observed in infectious settings and phenotypically analogous to age-associated B cells[199].

B1a cells
A self-renewing, innate-like B cell lineage that resides mostly in the peritoneal and pleural cavities; these cells carry repertoires biased towards bacterial and self-antigens and produce naturally occurring polyreactive IgM antibodies[200].

Class-switch recombination
A B cell-specific DNA rearrangement mechanism that replaces IgM expression with IgG, IgE or IgA[201].

Clonal anergy
A peripheral tolerance mechanism in which a self-reactive B cell is reprogrammed to become functionally unresponsive, exhibiting reduced responsiveness to B cell receptor stimulation and diminished expression of IgM[120,202].

Clonal redemption
The process by which anergic self-reactive B cell clones regain functionality through the selection of mutated progeny with reduced inherent autoreactivity compared with before entry into the germinal centre[119,120,203].

Epitope spreading
The diversification and shifting of antigenic targets recognized by the autoantibody repertoire[7].

Extrafollicular bridging channel
An anatomical region in the spleen that bridges the T cell zone and the red pulp[45].

Follicular B cells
Recirculating mature B cells derived from bone-marrow B2 lineage precursors; these cells localize to the B cell follicles and typically display an $IgD^{hi}IgM^{low}CD21^{mid}$ (follicular type 1) or $IgD^{hi}IgM^{hi}CD21^{mid}$ (follicular type 2) phenotype[204].

Marginal-zone B cells
A B2-derived B cell enriched in the splenic marginal zone between marginal sinus and red pulp; in rodents, these cells are non-recirculating and characterized by $IgM^{hi}IgD^{low}CD21^{hi}CD1d^{hi}CD23^{-}$ and mount rapid responses to blood-borne pathogens and lipid antigens[204,205]. In humans, marginal-zone B cells are found in the lymphoid organs and circulation, and exhibit a $IgM^{hi}IgD^{lo}CD23^{-}CD21^{+}CD1c^{+}$ surface phenotype[206].

Secondary lymphoid organs
Lymph nodes, spleen, Peyer's patches, tonsils, adenoids and (in rodents) nasal-associated lymphoid tissue; these anatomically organized lymphoid structures serve as major sites of immune responses and tolerance induction[207].

Somatic hypermutation
A diversification process in which antigen-experienced B cells acquire rapid point mutations in immunoglobulin V-region genes, mediated by the enzyme activation-induced cytidine deaminase (AID); occurs at high frequency in germinal-centre B cells and at a low frequency in extrafollicular responses[64,197].

T cell ignorance
A form of immunological tolerance in which antigen-specific T cells remain clonally ignorant despite the presence of their target antigen, maintaining a naive phenotype[208].

T follicular helper cells
(T_{FH} cells). Specialized $CD4^{+}CCR7^{low}PSGL1^{low}$ helper T cells that are essential for germinal-centre formation and antibody production; the majority of germinal-centre T follicular helper cells are $PD1^{hi}BCL6^{hi}SAP^{hi}CXCR5^{hi}$. B cells receive cognate and indirect help from T follicular helper cells via CD40L, IL-4 and IL-21 for activation and differentiation[17,121,209].

T follicular regulatory cells
(T_{FR} cells). A population of $CD4^{+}$ T cells that differentiate from $CD25^{hi}FOXP3^{+}$ regulatory T cells and that migrate to B cell follicles and germinal centres upon antigen stimulation and regulate development and differentiation of T follicular helper cells[210].

The autoreactive B cell repertoire might also be indirectly modulated by targeting T cell populations that provide B-helper or supportive functions[121]. In addition, CAR T cells that specifically target B cells expressing SLE-associated *IGHV4-34* show early promise as a non-depleting therapeutic approach[179]. As discussed earlier in this Review, germinal-centre and extrafollicular B cell differentiation lead to the production of autoantibodies with distinct kinetics and properties. Thus, instead of depleting B cells altogether, selectively modulating or redirecting the routes of autoantibody production in a reversible way might suppress autoreactivity while preserving protective immunity during vaccination or infection. Hence, an improved mechanistic understanding of the germinal-centre and extrafollicular B cell responses — and the embedded T cell–B cell interactions within these pathways in health and autoimmunity — could effectively inform the development of targeted therapies in the treatment of SLE.

Conclusion

Inherent autoreactivity within healthy B cell and T cell repertoires provides the foundation for autoantibody responses in SLE, and various exogenous factors converge to drive tolerance breakdown and promote the positive selection of specific autoreactive clones into effector pathways. The choice between extrafollicular and germinal-centre pathways is shaped by the combined selection pressure exerted by environmental cues, including antigen accessibility, metabolic resources and cytokine exposure. Autoreactive germinal centres are open structures that permit clonal entry and facilitate diversification of autoreactive B cells and epitope spreading. T cell help is a cornerstone in shaping the development and clonal composition of autoreactive germinal centres. Meanwhile, both historical and emerging evidence indicate that the extrafollicular antibody response is also guided by cognate and bystander help conferred by distinct, extrafollicularly confined T cell subsets. Overall, our evolving narrative of B cell-driven autoreactivity increasingly emphasizes the importance of studying B cells in the context of their inflammatory milieu and cellular interactors, rather than as isolated producers of autoantibodies.

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Review article

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Fertility, pregnancy and lactation in women with systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that predominantly affects women of childbearing age. As the prevalence of SLE rises, and advances since the 1960s have substantially improved survival and quality of life, the number of women with SLE who become pregnant is steadily increasing. Although pregnancy is feasible for most patients with well-controlled SLE, pregnancy remains challenging for both women with SLE and clinicians because the risk of maternal complications and adverse fetal outcomes is higher than that in the general population. Moreover, the increased risk of pregnancy complications persists in subsequent pregnancies in women with SLE, whereas in healthy women this risk decreases owing to the development of maternal–fetal immune tolerance. During pregnancy and the postpartum period, women remain at risk of disease flares and other complications, particularly those with active disease at conception, a history of lupus nephritis, antiphospholipid syndrome or recent medication withdrawal. Important knowledge gaps persist regarding the mechanisms underlying these complications and the safety of treatment during conception, pregnancy and lactation. Preconception counselling, assessment of risk factors for adverse outcomes, pregnancy planning, timely medication adjustment and multidisciplinary management are essential to improve the maternal and fetal outcomes in women with SLE.

Sections

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Key points

- In women with systemic lupus erythematosus (SLE), pregnancy is associated with higher risks of maternal complications and adverse fetal outcomes than in women in the general population.
- Fertility in women with SLE might be reduced owing to disease activity, renal failure, cyclophosphamide exposure, age-related decline in ovarian reserve and lifestyle factors.
- Achieving ≥6–12 months of inactive SLE on pregnancy-compatible medication before conception reduces the risks of disease flare and pregnancy complications.
- Preconception counselling, pregnancy planning, adjustment of medication, multidisciplinary management and shared decision-making are central to achieving safe pregnancies in women with SLE.
- Elucidating the pathogenesis of pregnancy complications in women with SLE is crucial for improving maternal and fetal outcomes.
- Important gaps persist regarding the safety of antirheumatic medication use during conception, pregnancy and lactation, and so further research is required.

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease, characterized by episodes of disease activity and disease remission. The disease predominantly affects women of childbearing age, and pregnancy represents a major challenge for both women with SLE and clinicians, as SLE can adversely affect the pregnancy course and outcomes, and pregnancy itself can exacerbate disease activity. Despite improvements in the management of pregnant women with SLE over the past three decades — and a documented decline in adverse pregnancy outcomes between 2003 and 2022 in a Swedish nationwide study[1] — pregnancy in women with SLE continues to carry a higher risk of maternal complications and adverse fetal outcomes compared with the general population[2,3]. Moreover, the increased risk of pregnancy complications persists in subsequent pregnancies in women with SLE, in contrast to a declining trend in healthy women[4]. In addition, patients are at risk of SLE flares throughout pregnancy and the postpartum period[5].

Despite the increasing number of pregnant women with SLE[6], studies over the past three decades have shown that patients with SLE have fewer children than women in the general population[7–10], and fewer children than originally planned[11]. A Finnish nationwide study found higher rates of childlessness among both women and men with SLE (9.3% and 4.7%, respectively) compared with the rates in the general population[10]. Reduced family sizes in individuals with SLE can be attributed to the cumulative effects of previous adverse pregnancy outcomes, chronic disease, medication required to control the disease, treatment-related gonadotoxicity, reduced libido, sexual dysfunction and psychological factors, including concerns about the ability to parent and fears of transmission of the disease to offspring owing to hereditary factors[12–14]. The physical and psychological impacts of SLE affect reproductive health in both men and women[15–18].

In this Review, we provide an overview of current insights into fertility in women with SLE, the bidirectional relationship between SLE and pregnancy and the pathophysiology of pregnancy complications in women with SLE. We also summarize contemporary standards of clinical care for women during the periconception period, pregnancy and lactation, and outline key priorities for future research.

Fertility

Since 2016, several guidelines have been published to support the clinical management of patients with SLE, including the British Society for Rheumatology (BSR) guidelines[19–21], the European Alliance of Associations for Rheumatology (EULAR) recommendations for family planning, assisted reproduction and pregnancy in women with SLE and/or antiphospholipid syndrome (APS)[22], the American College of Rheumatology (ACR) guidelines on reproductive health in rheumatic diseases, including SLE[23], and updated EULAR recommendations for the use of antirheumatic drugs during reproduction and pregnancy[24]. These guidelines address key aspects of fertility including the impact of SLE and its treatments, assisted reproductive techniques and contraception — topics explored in detail in this section.

Impact of SLE

Fertility is defined as the natural ability to conceive, and SLE does not seem to impair the function of the fallopian tubes[22]. Nevertheless, a systematic review of 1,272 women with SLE and 555 healthy individuals showed reduced concentrations of anti-Müllerian hormone (a marker for ovarian reserve) in women with SLE, especially those previously exposed to cyclophosphamide[25]. Active autoimmune disease and renal failure independently contribute to impaired fertility[26,27]. Age-related decline in ovarian reserve, comorbid conditions and lifestyle factors such as smoking and obesity affect women with SLE in the same way as in the general population, underscoring the importance of early counselling on family planning and reproduction during the reproductive years.

Influence of medication

The productive effects of conventional synthetic DMARDs (csDMARDs) differ by the drug, safety profile, reversibility and timing of discontinuation (Table 1). Biologic DMARDs (bDMARDs), such as belimumab and rituximab, generally have a compatible safety profile, whereas evidence on targeted synthetic DMARDs and small molecules remains limited[24]. Use of TNF inhibitors in SLE varies widely, influenced by concerns about their potential to induce anti-double-stranded DNA antibodies[28].

Prior exposure to cyclophosphamide or other alkylating agents is linked to reduced ovarian reserve and an increased risk of premature ovarian failure, particularly in patients who receive cumulative cyclophosphamide doses exceeding 7.5–10 g or who are older than 30 years at the time of first exposure[29,30]. The Euro-Lupus low-dose cyclophosphamide regimen (six fortnightly pulses at a fixed dose of 500 mg) is therefore generally preferred in women with SLE, as its much lower cumulative exposure confers only a low risk of infertility in women younger than 30 years[31,32].

Fertility preservation using gonadotropin-releasing hormone analogues should be considered in women prior to treatment with alkylating agents[22]. Against this background of well-established gonadotoxicity associated with alkylating agents, the potential reproductive effects of more commonly used agents, including NSAIDs, have also been explored. Although a prospective study in 2,573 women suggested that NSAIDs might adversely affect ovulation and implantation[33], the overall evidence on NSAID-related impairment of fertility is limited

Table 1 | Safety of antirheumatic drugs preconception, during pregnancy and during lactation

Drug	Before conception	During pregnancy	During lactation
Drugs widely used before conception, during pregnancy and during lactation			
Hydroxychloroquine	Compatible	Compatible	Compatible
Chloroquine	Compatible	Compatible	Compatible
Azathioprine	Compatible	Compatible	Compatible
Cyclosporine	Compatible	Compatible	Compatible
Tacrolimus	Compatible	Compatible	Compatible
Colchicine	Compatible	Compatible	Compatible
Prednisone and prednisolone	Compatible (aim for ≤5 mg/day[a])	Compatible (aim for ≤5 mg/day[a])	Compatible (aim for ≤5 mg/day[a])
Drugs used only in selected circumstances[b]			
NSAIDs (ibuprofen as first choice; only intermittent use)	Compatible (stop if conception is difficult)	Compatible (stop at 20 weeks of gestation)	Compatible
IVIG	Compatible	Compatible[c]	Compatible
Belimumab	Compatible	Compatible[c]	Compatible
Rituximab	Compatible	Compatible[c]	Compatible
TNF inhibitors	Compatible	Compatible	Compatible
Anifrolumab	Not compatible[d]	Not compatible[d,e]	Compatible
Drugs contraindicated during pregnancy (teratogenic or harmful)			
Cyclophosphamide	Not compatible[f] (stop 3 months before conception)	Not compatible[f,g]	Not compatible[f]
Methotrexate	Not compatible[f] (stop 1–3 months before conception)	Not compatible[f]	Not compatible[f,h]
Mycophenolate mofetil	Not compatible[f] (stop ≥6 weeks before conception)	Not compatible[f,g]	Not compatible[f]
Leflunomide	Not compatible[d] (cholestyramine washout if needed[i])	Not compatible[d]	Not compatible[d]
Voclosporin	Not compatible[d]	Not compatible[d]	Not compatible[d]

Data from refs. 22,23. IVIG, intravenous immunoglobulin. [a]Use only if possible without provoking a disease flare. [b]Only use when necessary, such as during disease flares or uncontrolled disease, failure, if other (pregnancy-compatible) options are contraindicated, or to reduce the need for higher than optimal predniso(lo)ne doses. [c]Can be used during pregnancy if needed to effectively control maternal disease. [d]Not compatible because of insufficient evidence to establish safety. [e]Should be used during pregnancy only if no pregnancy-compatible medication can effectively control maternal disease. [f]Not compatible because of proven harm or teratogenicity. [g]In severe, refractory maternal disease during pregnancy, IVIG, or (in the second and third trimester) cyclophosphamide or mycophenolate mofetil can be considered. [h]Methotrexate ≤25 mg weekly can be considered during lactation if no safer alternative can be used. [i]Cholestyramine washout is recommended only if leflunomide discontinued <3.5 months before conception.

and does not require stopping NSAIDs when attempting to conceive. Nevertheless, NSAID withdrawal might be considered if conception takes longer than expected[23,24].

Assisted reproductive techniques

Assisted reproductive techniques are generally safe in women with well-controlled SLE[22,34,35], provided that management includes multidisciplinary assessment and thrombotic risk stratification owing to the use of oestrogen-containing agents with prothrombotic potential. Indications for assisted reproductive techniques are the same as for women without chronic diseases. Because twin and higher-order multiple pregnancies are associated with adverse outcomes — most notably preterm birth[36], a complication that is already more frequent in women with SLE[2] — ovarian stimulation should be carried out with caution, and single-embryo transfer should be routinely recommended, as supported by prior literature[37]. The use of adjusted ovarian stimulation protocols aimed at minimizing peak oestrogen levels might further improve safety and reduce complications in women with rheumatic diseases, including SLE and APS[38–40]. Furthermore, prophylactic anticoagulation therapy with low-molecular-weight heparin (LMWH) or heparin should be considered in asymptomatic antiphospholipid antibody (aPL)-positive women and is recommended in women with obstetric APS undergoing assisted reproductive techniques, in line with the ACR guidelines and EULAR recommendations[22,23].

Contraception

Effective contraception — tailored to the patient's comorbidities and individual thrombosis risk, and balanced against the risks of an unplanned pregnancy — remains essential, and should be actively discussed with all women with SLE of childbearing age to prevent unplanned pregnancy and to enable optimization of disease control and medication regimens before conception[22,23]. Thrombosis risk is mainly associated with the presence of aPLs or APS[22,23], although consideration of factors such as hypertension, obesity and smoking is also warranted.

Both copper and progesterone-containing intrauterine devices are safe options in women with SLE in the absence of gynaecological contraindications[22,23]. As copper intrauterine devices are more likely

to be associated with increased menstrual bleeding[41], progesterone-containing intrauterine devices are often preferred; importantly, intrauterine devices, including progesterone-containing devices, are not associated with an increased risk of venous thromboembolism (VTE) or arterial thromboembolism[42].

Use of oestrogen-containing contraceptives is associated with a twofold to threefold increased risk of VTE compared with non-use in the general population, and this risk seems to be further amplified in women with SLE, particularly in aPL-positive women[43]. Therefore, women with an increased thrombosis risk are advised against using oestrogen-containing contraceptives[22,23,44]. However, combined hormonal contraceptives can be considered in women with inactive disease and absence of aPLs[45]. By contrast, women with SLE who are persistently aPL-positive, regardless of whether they fulfil criteria for APS, should avoid combined contraceptives[22]. For these women, progesterone-only contraception pills are an alternative option[42]. Although limited data are available, the use of depot medroxyprogesterone acetate in aPL-positive women should be avoided as use of this agent is associated with an increased risk of thrombosis in the general population, unlike progesterone-only pills and progesterone-containing intrauterine devices[23,46]. In practice, women with SLE and a low thrombotic risk and inactive disease can use combined hormonal contraceptives or any intrauterine device. In those with higher thrombotic risk or persistent aPL positivity, progesterone-only options or progesterone-containing intrauterine devices are generally more suitable; the latter is especially useful in women with SLE who are receiving anticoagulation therapy because this method minimizes menstrual blood loss while maintaining highly effective contraception.

The impact of pregnancy on SLE

Pregnancy in women with SLE involves a finely regulated interplay between maternal immune adaptations and underlying autoimmune activity. Over the past three to five decades, substantial progress has been made in characterizing the frequency and spectrum of disease flares during pregnancy and the postpartum period, as well as factors that predispose to these events.

Disease flares during pregnancy

SLE flares occur in approximately 2.5–35% of pregnancies, most frequently during the second and third trimesters or in the early postpartum period[4,47,48]. The spectrum of flares ranges from mild mucocutaneous or musculoskeletal manifestations to severe renal, haematological or neuropsychiatric involvement. Whether flare risk is increased during pregnancy and the postpartum period remains debated, as studies on this topic have yielded conflicting results, possibly owing to differences in study design, inclusion criteria, flare definitions and pregnancy management[49,50]. Evidence from the Hopkins Pregnancy Cohort, which included 1,349 women with SLE and 398 pregnancies in 304 women[5], showed higher flare rates during pregnancy than in non-pregnancy periods, and an additional increase during the first 3 months after birth. Notably, the increased risk of flares occurred exclusively among women not taking hydroxychloroquine, aligning with prior observational data showing that continuous hydroxychloroquine use before conception and throughout pregnancy reduces the risk of flares during gestation and the early postpartum period[51,52].

Risk factors for disease flares

Hydroxychloroquine is recommended as baseline therapy in all pregnant women with SLE to help maintain disease control[5,51]. Discontinuation of hydroxychloroquine[5,51], active disease at conception[52–55], and a history of active or previous lupus nephritis[47,56,57] are major risk factors for flare during pregnancy and the postpartum period. High disease activity at conception or within the 6 months preceding conception, as well as serologically active disease in the first trimester (characterized by hypocomplementaemia or failure to increase to supranormal complement levels) are also associated with an increased risk of flare during pregnancy[52–55,58].

Past lupus nephritis has been identified as a risk factor for both renal and non-renal flares in prospective studies[47,56]. Moreover, renal flare risk also varies substantially with disease activity: in one cohort of women with lupus nephritis, the renal relapse rate was 72% among those with an unplanned pregnancy or who were not in complete remission, compared with 11.3% among women who had achieved complete renal remission at conception[57]. Furthermore, a systematic review published in 2025 showed that younger age is associated with an increased risk of disease flares during pregnancy[59], and in another study primigravida was linked to a higher risk of both renal and non-renal flares[60].

In summary, maintaining low disease activity, continuing treatment with hydroxychloroquine and achieving complete remission of prior lupus nephritis are major factors in preventing disease flares during pregnancy and the postpartum period.

The impact of SLE on pregnancy

Despite improvements in the management of pregnancies in women with SLE, these pregnancies remain associated with higher risks of both maternal and fetal complications compared with pregnancies in the general population[1,61]. Moreover, complications arising during pregnancy in women with SLE not only endanger the health of the mother and child during pregnancy, but are also linked to an increased risk of several health complications later in life for both mother and child[62,63]. In the following section, we first outline the pregnancy complications associated with SLE, and then provide an overview of current knowledge regarding the pathophysiology of these complications in SLE.

Pregnancy complications and adverse outcomes

Several studies have shown that women with SLE have higher rates of obstetric complications than women in the general population, including pregnancy loss, fetal death, (pre-)eclampsia, fetal growth restriction (FGR), low birthweight and preterm birth[1,64,65]. Moreover, in a population-based study from the USA, maternal mortality was 20-fold higher among women with SLE[64]. Despite a decrease in maternal and fetal mortality and obstetric complications over the past decades (with fetal loss falling from 43% in the 1960s to 17% in the early 2000s)[61,66], overall complication rates and the associated health-care costs remain higher than in pregnancies in women without SLE[67]. Furthermore, the increased risk of hypertensive disorders of pregnancy (HDP), FGR, fetal death and premature birth persist across subsequent pregnancies in women with SLE, contrasting with the declining risk typically observed in healthy women[4]. When considering population-level temporal trends, a nationwide Swedish study examining the past two decades found that adverse pregnancy outcomes declined more markedly in nulliparous than in parous pregnancies in women with SLE, whereas the rates of adverse outcomes remained unchanged in the general population[1].

SLE-specific risk factors for adverse pregnancy outcomes include active disease prior to or at conception, lupus flares during pregnancy, hypertension, a history of lupus nephritis, severe organ failure (such as of the kidneys, heart or lungs), the presence of aPLs

or established APS, anti-Ro/SSA and/or anti-La/SSB antibodies and thrombocytopenia[47,68–73]. A retrospective cohort study of 347 pregnancies in 332 Chinese women with SLE showed that women who fulfilled a combination of favourable preconception conditions (such as stable disease for at least 6 months, absence of active vital organ involvement, use of hydroxychloroquine, and glucocorticoid doses not exceeding the dose equivalent to prednisone 7.5 mg per day) had the highest chance of achieving a favourable pregnancy outcome[74]. The results of this study support previous observations identifying factors associated with more favourable pregnancy outcomes and show that the likelihood of a favourable outcome increases when multiple favourable preconception conditions are present[74]. The combination of favourable preconception factors in this retrospective Chinese study might also apply to patients of other ethnic backgrounds, but confirmation in future (preferably prospective) studies is needed.

Evidence on ethnic and racial disparities in adverse pregnancy outcomes in women with SLE remains scarce[75,76] and existing studies do not provide definitive conclusions. In the PROMISSE cohort, Black women with SLE had higher rates of adverse pregnancy outcomes than white women; however, this difference was not statistically significant when adjusted for disease activity and socioeconomic status[75].

Pregnancy loss. Over the past six decades, the frequency of pregnancy loss in women with SLE has declined markedly. A US study found a decline in pregnancy loss rate from 43% in 1960–1965 to 17% in 2000–2003, a rate approaching that in the general US population (10–15%)[66]. Key predictors of pregnancy loss in women with SLE include APS (especially in women with persistent lupus anticoagulant positivity), clinical and serological disease activity, hypertension, proteinuria and low platelet count[3,77–79]. The highest risk occurs in women with concurrent high disease activity, low complement levels and elevated anti-dsDNA titres in the second trimester[77].

(Pre-)eclampsia. Pre-eclampsia is a pregnancy complication characterized by newly developed hypertension and proteinuria, as well as other organ involvement, after 20 weeks of gestation. In the general obstetric population, pre-eclampsia occurs in approximately 5% of pregnancies[80], but in women with SLE, the reported incidence rates are considerably higher, ranging from 6.1% to 25%[4,52,64,81,82]. Beyond established general obstetric risk factors — including maternal age, obesity and diabetes mellitus — SLE-specific predictors of pre-eclampsia include history of lupus nephritis, active disease at or before conception, pre-existing hypertension, aPL positivity and thrombocytopenia[3,47,49].

Fetal growth restriction and small for gestational age infant. FGR is a pregnancy condition in which the fetus does not reach its biological growth potential owing to impaired placental function, and is diagnosed using both biometric and functional parameters[83]. Fetuses with FGR are at increased risk of perinatal morbidity and mortality, as well as adverse long-term health outcomes[83]. Small for gestational age infant refers to a birthweight below the tenth percentile, and includes both growth-restricted and constitutionally small but healthy infants. Population-based data indicate that FGR occurs more often in pregnancies in women with SLE than in the general obstetric population (5.3% versus 1.6%)[84]. Independent risk factors for FGR in women with SLE include active disease at or before conception, lupus nephritis and aPL positivity[49,85,86]. Conversely, hydroxychloroquine use during pregnancy has been associated with a reduced FGR rate compared with non-use[87]. In addition, the rate of small for gestational age infants is markedly higher in pregnancies in women with SLE than in age-matched and parity-matched women from the general population (25% versus 4.5%)[88].

Preterm birth. Preterm birth — defined as delivery before 37 weeks of gestation — is among the most frequent complications of pregnancy in women with SLE. A systematic review and meta-analysis of 8,157 pregnancies in women with SLE found a preterm birth rate of 31% (95% CI 0.14–0.50), markedly higher than the 6–10% observed in the general obstetric population[72]. Risk factors for preterm birth in women with SLE include active disease, past or active lupus nephritis and glucocorticoid therapy[89,90]. Remarkably, preterm births in women with SLE show an almost equal distribution between spontaneous and medically indicated deliveries. Spontaneous preterm birth beginning with preterm prelabour rupture of membranes occurs twice as frequently in pregnant women with SLE than does spontaneous preterm birth in the general population (51% versus 25%)[2].

Neonatal lupus syndrome. Anti-Ro/SSA and/or anti-La/SSB autoantibodies are present in approximately 40% of women with SLE and can lead to fetal and neonatal manifestations through FcγR-mediated transplacental transfer of maternal IgG autoantibodies, which begins at 16 weeks of gestation[91]. The most severe and usually permanent manifestations involve the fetal heart. The risk of congenital heart block (CHB) in the fetus is 1–2% in women without previously affected offspring, but increases to 17% in women with a previous child with CHB[92,93], and usually develops during the second trimester, and rarely occurs after 26 weeks of gestation. The results of the STOP-BLOC study highlight high-titre anti-Ro antibodies as an important risk factor for CHB, but also emphasize the importance of yet-unidentified factors[94]. CHB is associated with substantial mortality and morbidity; approximately 20% of affected fetuses do not survive, and among survivors, around two-thirds require permanent pacemaker implantation[95,96]; a minority later develop dilated cardiomyopathy[97]. Hydroxychloroquine use during pregnancy has been associated with a 50% reduction in recurrence rate of CHB in a subsequent pregnancy among anti-Ro/SSA-positive women with a previous baby with CHB, as shown in an open-label study of 54 pregnancies (7.4%; 90% CI 3.4–15.9%)[98]. Neonatal lupus includes transient cutaneous lesions and, more rarely, hepatomegaly, elevated liver enzymes, splenomegaly, anaemia and thrombocytopenia[99].

Long-term consequences of pregnancy complications. Pregnancy complications in women with SLE not only endanger the health of the mother and child during pregnancy but can also confer long-term health consequences for both mother and child. In general, pregnancy can be regarded as a stress test for future cardiovascular risk: HDP are associated with an increased risk of subsequent cardiovascular disease, depending on gestational age and the severity of the HDP, and with a twofold to threefold increase in cardiovascular mortality[100]. Data specifically addressing long-term cardiovascular risk after HDP in women with SLE are limited. In a population-based study from Sweden, women with SLE who experienced a HDP, including pre-eclampsia, had a twofold higher rate of major cardiovascular events (including myocardial infarction, stroke and heart failure) and a threefold higher rate of incident hypertension compared with women from the general population, after a median follow-up of 10.8 years[62].

Preterm birth and low birthweight are leading causes of mortality in children under 5 years of age and are associated with an increased

risk of several health complications (including cognitive impairment and developmental delays), and development of cardiovascular and chronic kidney disease later in life[63]. Given the approximately three-fold higher rate of preterm birth[2] and the at least twofold increased risk of low birthweight[1,84] in women with SLE, these long-term risks are especially relevant to this population. In addition, children with cardiac manifestations of neonatal lupus might experience lifelong cardiac complications.

Pathophysiology of pregnancy complications in SLE

Although several risk factors for adverse pregnancy outcomes in SLE have been identified, they do not reliably predict which patients will develop complications. This limitation has led to growing interest in the biological mechanisms underlying pregnancy complications in SLE.

A healthy pregnancy depends on precisely regulated maternal immune responses. The maternal immune system works in concert with placental extravillous trophoblasts to remodel spiral arteries, ensure adequate placental blood flow and repair decidual tissue damage caused by implantation[101–103]. The immune system must also establish maternal–fetal tolerance to prevent rejection of the semi-allogeneic fetus, through interactions with both extravillous trophoblasts and syncytiotrophoblasts at the maternal–fetal interface, and contributes to the initiation of labour at term[102,103]. In SLE, the immune system is dysregulated[104] and is therefore likely to disrupt these processes and contribute to pregnancy complications. Although the full mechanisms underlying SLE-related pregnancy complications remain to be elucidated, the presence of aPLs, increased activation of neutrophils and other immune cells and insufficient downregulation of type I interferon response are potential pathophysiological drivers, as detailed below and summarized in Fig. 1.

Autoantibodies — particularly aPLs — are among the most prominent molecular risk factors for pregnancy complications in women with SLE[3]. The prevailing hypothesis is that aPLs bind to trophoblasts, triggering complement factor C5a generation and neutrophil recruitment[105,106]. Neutrophils can then promote placental damage through natural killer cell recruitment[107], release of reactive oxygen species[108], and formation of immunogenic neutrophil extracellular traps (NETs)[106], which are also thrombogenic and might contribute to the increased thrombosis risk in women with aPL-positive SLE and APS[106]. Although much of this evidence comes from animal models, increased NET deposition in placentas from women with SLE supports the relevance of these mechanisms in humans[107,109,110]. However, the role of complement in SLE-related pregnancy complications remains unclear: placentas from women with SLE show increased C3 and C4 deposition, whereas C5 levels are often decreased or unchanged[109,111,112].

The presence of elevated NET and increased C3 and C4 deposition in placentas from women with aPL-negative SLE and in women with

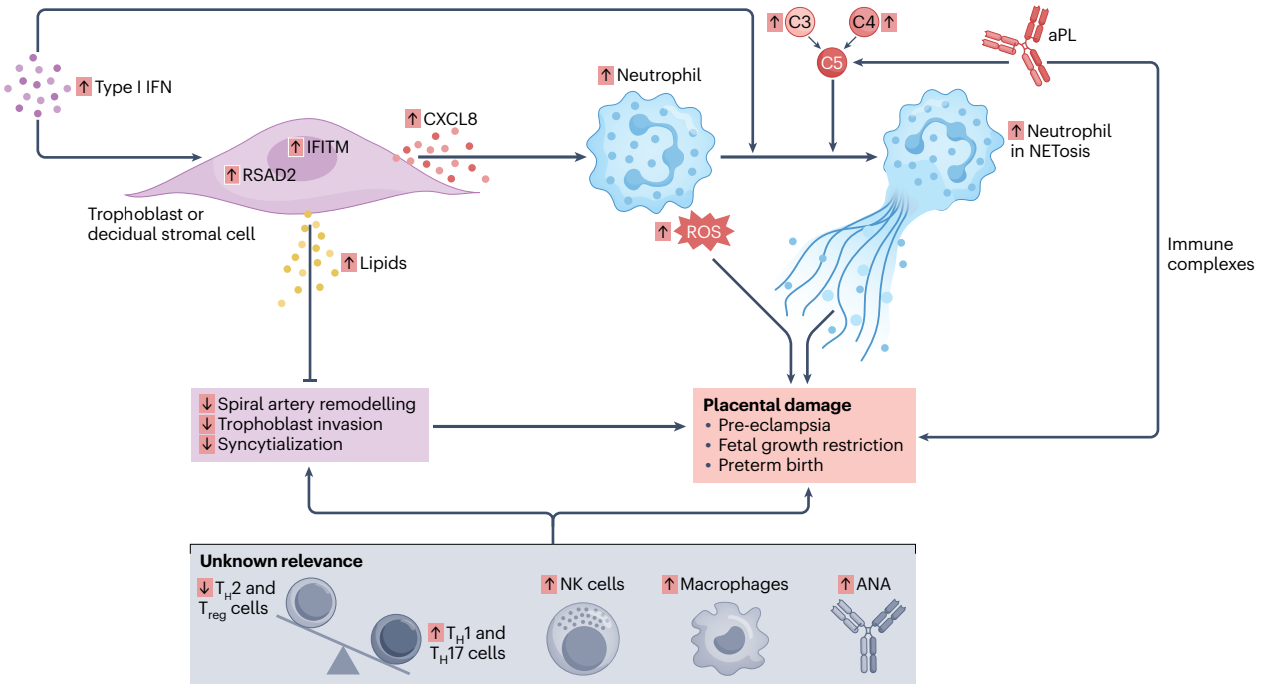

Fig. 1 | Immunological processes involved in placental dysfunction in SLE. In pregnancies in women with systemic lupus erythematosus (SLE), type I interferon (IFN) activity is increased and induces the expression of radical *S*-adenosyl methionine domain-containing protein (RSAD2), interferon-inducible transmembrane protein (IFITM) and CXCL8 in trophoblasts and/or decidual stromal cells, which together contribute to placental damage and impaired placental development by promoting lipid accumulation (RSAD2), inhibiting cytotrophoblast fusion (via IFITM-mediated syncytialization) and recruiting neutrophils (CXCL8). Recruited neutrophils can release neutrophil extracellular traps (NETosis), triggered by type I IFN or by activated complement (C3, C4 and C5) generated in response to antiphospholipid antibodies (aPL). Activated complement, together with aPLs, can also form immune complexes that further contribute to placental damage. Additional abnormalities reported in pregnancies in women with SLE, including altered T cell balance, increased natural killer (NK) cell and macrophage populations and deposition of antinuclear antibodies (ANA), might contribute to placental dysfunction, although their mechanistic roles remain unclear. C3, complement factor 3; C4, complement factor 4; C5, complement factor 5; ROS, reactive oxygen species; T_H cells; T helper cells; T_{reg} cell, regulatory T cell. Original figure created using BioRender.

pre-eclampsia without SLE or aPLs[107,109,110], indicates that neutrophil activation and complement dysregulation contribute more broadly to the pathogenesis of pregnancy complications. In SLE, this broader contribution is supported by associations between adverse pregnancy outcomes and higher circulating and intervillous neutrophil levels[113–116], together with reduced circulating C3 and C4, consistent with increased complement consumption[3]. Mechanistically, activation of C5a might initiate this inflammatory cascade even in the absence of antibody stimulation[117], with aPLs serving as an additional trigger for placental injury and subsequent complications.

Another hallmark of SLE that might contribute to pregnancy complications is elevated type I interferon activity, measured by increased expression of type I interferon-stimulated genes (the so-called type I interferon signature). In healthy pregnancy, this signature is downregulated relative to the non-pregnant state, as indicated by longitudinal analysis of blood samples[118]. By contrast, women with SLE exhibit an elevated signature prior to conception that is less effectively downregulated during pregnancy, with the smallest reduction observed in those who later develop complications such as pre-eclampsia or FGR[118]. Type I interferons might contribute to placental dysfunction through several mechanisms. IFNα induces RSAD2 in trophoblasts, decidual stromal cells and macrophages, leading to lipid accumulation and impaired placental vascular development[119]. Type I interferons also induce upregulation of interferon-inducible transmembrane proteins (IFITMs), which inhibit cytotrophoblast fusion into syncytiotrophoblasts, a key process in placental development[120]. Finally, IFNα stimulates CXCL8 production in decidual stromal cells, promoting neutrophil recruitment[115]. However, studies in patients with multiple sclerosis treated with IFNβ have shown no changes in preterm birth rate, birthweight or live birth rate[121–123], even though IFNβ also induces RSAD2, IFITMs and CXCL8. Combined with the fact that 50–70% of patients with SLE have elevated type I interferon[124] but not all develop pregnancy complications, these data suggest that additional mechanisms contribute to the increased risk of such complications.

Beyond neutrophils and type I interferon, other immune alterations have been described in pregnant women with SLE, including high levels of cytokines (such as CXCL8 and IL-10)[125], an increase in circulating $CCR5^{+}CD16^{+}$ monocytes[126], and a reduced T helper 1 to T helper 2 immunological shift[127]. Reported placental abnormalities in women with SLE include reduced monocytes and resting mast cells[128], altered long non-coding RNA expression[128], increased macrophage infiltration[129] and deposition of antinuclear antibodies[111]. Findings regarding elevated natural killer cells in the placenta are inconsistent[107,129]. Although understanding of the mechanisms underlying pregnancy complications in women with SLE continues to advance, further insight is needed to predict, prevent and treat these outcomes. Progress is limited by the fact that much mechanistic evidence was derived from animal models or small studies in humans that compared pregnancies in women with SLE with pregnancies in healthy women without stratifying by pregnancy outcomes, and by considerable methodological variability, factors that limit direct translation into risk prediction and treatment.

Preconception counselling

Preconception counselling is the cornerstone of reproductive health care and family planning for women with SLE and is required to evaluate and reduce risks of adverse pregnancy outcomes for each patient (Table 2). During this process, women should be informed about the importance of timing — specifically that pregnancy outcomes are optimized when conception occurs during a period of quiescent disease — as well as the potential bidirectional effects of SLE and pregnancy. Counselling should also address the potential need for medication alterations before conception, throughout pregnancy and during breastfeeding[22,23].

Early, structured and multidisciplinary collaboration among rheumatologists, obstetricians, general practitioners, pharmacists and other allied health-care professionals is essential. Such coordination ensures consistent counselling messages, clear communication of treatment plans across teams and easy avenues for patients to seek clarification, particularly when they encounter conflicting messages. Providing patients with written, lay-friendly information that summarizes agreed recommendations allows patients to share consistent guidance with family members and external health-care providers. This written information equips patients to respond confidently if their treatment plan is questioned (for example, by pharmacists or other health-care professionals unfamiliar with SLE-specific pregnancy management).

Importance of preconception counselling

Although fertility and sexual health have historically been under-prioritized areas in the care of patients with rheumatic musculoskeletal diseases[130], updated EULAR recommendations and the 2020 ACR guidelines call for reproductive health to be addressed in clinical practice with "early and regular counselling" and with discussion of family planning "early and often"[23,24]. Effective preconception counselling is the cornerstone of optimizing the reproductive journey for women with SLE. Such counselling relies on multidisciplinary collaboration, when needed, and is built on several key components: a comprehensive medical assessment of each individual patient, careful review and adjustment of medications, and evaluation of the individual risk profile associated with the specific SLE phenotype (Table 2).

Clinical review

The main priority of the clinical review is to ensure that women are receiving pregnancy-compatible medication before conception (Tables 1 and 2 and Box 1). Any necessary treatment changes should be made prior to pregnancy, as achieving remission on an optimal and pregnancy-safe regimen is essential to reducing the risks of flare, miscarriage and FGR[22]. Discontinuing or modification of pregnancy-compatible SLE medication should be strongly discouraged in women with SLE planning to conceive (even in those with low disease activity or in remission), because medication withdrawal is a common trigger for disease flares[22].

Sustained remission for 6 to 12 months before conception remains a key determinant of favourable pregnancy outcomes[131], particularly in women with a history of lupus nephritis[68] or involvement of other important organs[3,23,24,132]. Conception should be avoided during periods of active disease or in the presence of severe organ dysfunction, including renal failure[49], pulmonary hypertension[132] or recent cerebrovascular accident, owing to the increased risks of maternal flares and maternal and fetal complications[23,24].

Women with SLE are, on average, older at first conception than women in the general population, and this age trend is accompanied by higher BMI[133] as well as increased use of assisted reproductive techniques[10]. In this context, a comprehensive thrombosis risk assessment is more crucial than ever, given that VTE remains the leading direct cause of maternal death[134]. Contemporary registry and cohort data indicate that women with rheumatic musculoskeletal diseases, including SLE, now conceive at a median age in the mid-30s, mirroring broader trends in high-income countries[10,48,135].

Table 2 | Counselling and management during all stages of pregnancy in women with SLE

	Before conception	During pregnancy	After birth and between pregnancies
Clinical review	Achieve and maintain remission for ≥6–12 months on pregnancy-compatible medication; perform VTE assessment; address modifiable risk factors (such as smoking, depression and obesity)	Regular multidisciplinary monitoring; assess kidney function, blood pressure, urine protein and disease biomarkers; monitor fetal growth and placental blood flow; timely induction of labour, weighing all parameters	Monitor for flares (common in the first 3–6 months after delivery); use postpartum period for future pregnancy planning
Medication management	Discontinue teratogens (MMF, MTX and cyclophosphamide) per washout; initiate hydroxychloroquine (if not already prescribed); continue or transition to pregnancy-compatible immunosuppressants (azathioprine, cyclosporine or tacrolimus) and ensure remission; continue pregnancy-compatible biologic DMARDs if patient is in remission	Continue hydroxychloroquine; use DMARDs as needed to control the disease (see Table 1 and main text); use lowest effective glucocorticoid dose; initiate low-dose aspirin in the first trimester in women at increased risk of pre-eclampsia; add LMWH in high-risk patients as indicated; supplement calcium and vitamin D	Adjust medication as needed; most pregnancy-compatible drugs are safe during breastfeeding; re-establish VKA when indicated; continue bone health supplements if on long-term glucocorticoids or heparin, particularly when breastfeeding
Autoantibody assessment	Test for aPLs, anti-Ro/SSA and anti-La/SSB antibodies	If anti-Ro/SSA-positive and/or anti-La/SSB-positive, fetal echocardiography at 18–20 weeks and, if indicated, repeated fetal heart rate surveillance for CHB; if aPL-positive, follow thromboprophylaxis protocols; coordinate aspirin cessation with multidisciplinary team if epidural anaesthesia is planned	If aPL-positive, follow specific local postpartum thromboprophylaxis protocols
Contraception counselling	Avoid conception during active disease or ongoing severe organ dysfunction; provide effective contraception	NA	Discuss effective contraception to prevent unplanned pregnancy, especially with active disease or teratogenic drugs
Pregnancy follow-up and counselling	Provide information on pregnancy expectations; involve family and multidisciplinary team as appropriate	Provide ongoing counselling evolving risks and preferences	Counselling on the consequences of pregnancy outcome on subsequent pregnancy; discuss long-term cardiovascular risk

Data from refs. 22–24. aPLs, anti-phospholipid antibodies; CHB, congenital heart block; LMWH, low-molecular-weight heparin; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not appropriate; SLE, systemic lupus erythematosus; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Risk factors for adverse pregnancy outcomes in the general population, such as overweight and obesity, are also relevant for women with SLE. In women with SLE specifically, obesity compounds the effects of disease activity and is associated with a higher likelihood of adverse pregnancy outcomes[136]. Evidence from a systematic review indicates that a prepregnancy BMI of >25 kg/m^2 confers an increased risk of fetal death and preterm birth (HR 3.58, 95% CI 1.45–8.83)[136]. Cohort and population-based studies over the past two decades have shown greater use of assisted reproductive techniques among women with rheumatic musculoskeletal diseases, including SLE, than among women in the general population[10,48], reflecting higher infertility rates, older maternal age and evolving patient expectations.

Autoantibody assessment

Testing for aPLs, anti-Ro/SSA autoantibodies and anti-La/SSB autoantibodies is a critical component of preconception evaluation in women with SLE[22,23], as these autoantibodies directly inform risk stratification, perinatal management (including antepartum and postpartum thromboprophylaxis) and fetal monitoring strategies. aPLs (including the presence of lupus anticoagulant, anticardiolipin IgG or IgM antibodies and anti-β_2-glycoprotein-I IgG or IgM antibodies) identify women with a specific risk profile that includes recurrent pregnancy loss before 10 weeks of gestation, pregnancy loss after 12 weeks and adverse pregnancy outcomes related to placental dysfunction, as well as maternal arterial and venous thrombosis typical of APS[137]. Importantly, the clinical relevance of low titre or IgA isotypes of classic aPLs, or of non-classic aPLs (such as antibodies against the phosphatidylserine–prothrombin complex) remains unclear. These situations necessitate careful assessment of other thrombosis risk factors, the patient's broader clinical context and individual preferences. It is important to emphasize that the updated 2023 ACR–EULAR APS classification criteria are more complex, weighted criteria than the earlier 2006 APS criteria, yet these criteria are still not intended as diagnostic criteria[138].

Communication and planning

Effective communication and strategic planning are the cornerstones of optimal care for women with SLE who are contemplating pregnancy. Early and regular involvement[24] of the patient, the patient's family and the multidisciplinary team, including rheumatologists, gynaecologists and other allied health-care professionals, ensures a foundation of shared decision-making. The process goes beyond discussing medical risks, medication adjustments, adherence and lifestyle advice, extending to an exploration of the patient's reproductive goals, personal values and psychosocial context[12]. Thorough counselling, ideally involving both family members and the multidisciplinary team, not only ensures that the patient is fully informed about the interplay between SLE and reproductive health but also allows the patient to express concerns and set realistic expectations[12]. The importance of shared decision-making for providing optimal clinical care to pregnant women with SLE is illustrated by the two case vignettes presented in Box 1.

Box 1 | Case vignettes illustrating shared decision-making

Case vignette 1: medication safety in pregnancy planning
A 28-year-old nulliparous woman with stable systemic lupus erythematosus (SLE) for 2 months wishes to conceive. She has no history of lupus nephritis, organ involvement or antiphospholipid antibodies.

- The clinician recommends postponing conception until 6–12 months of quiescent disease, emphasizing the importance of continuing hydroxychloroquine owing to established safety and beneficial effects on disease control and pregnancy outcomes. The woman, however, is anxious about fetal medication exposure and expresses a preference to stop all therapy before conceiving.
- Through shared discussions, the clinician explains that active SLE poses greater risks to both parent and fetus than the recommended medications, and they review guideline-based evidence together. They agree on a plan to maintain hydroxychloroquine, begin low-dose aspirin in early pregnancy, delay conception until stable disease is achieved, and arrange multidisciplinary monitoring to optimize outcomes.

Case vignette 2: pregnancy planning in a high-risk patient
A 28-year-old nulliparous woman with SLE and prior lupus nephritis seeks preconception counselling. A previous pregnancy was complicated by severe pre-eclampsia with fetal growth restriction at 25 weeks, despite multidisciplinary management, ongoing treatment with hydroxychloroquine and azathioprine, and initiation of low-dose aspirin at 10 weeks of gestation, culminating in fetal death. At that time, lupus nephritis had not reached complete remission, and a postpartum non-renal flare followed.

- The woman now wishes to pursue another pregnancy and demonstrates understanding of the prior complications. Her disease has been stable for 6 months on hydroxychloroquine, low-dose prednisone and azathioprine, with minimal proteinuria, stable renal function and well-controlled blood pressure.
- Her clinician outlines the high recurrence risk of severe complications — pre-eclampsia, preterm birth and fetal loss — drawing on guidelines and registry data, while acknowledging the woman's grief, hopes and values.
- Should she choose to proceed, the plan would include ≥12 months of stable remission, optimization of renal and cardiovascular health, low-dose aspirin, close monitoring of blood pressure and serology (including complement levels) and care within a highly specialized, multidisciplinary team. The limitations of preventive strategies are discussed openly, with emphasis on ongoing emotional and psychological support

These composite vignettes illustrate the complexity and high stakes of reproductive decision-making in women with SLE and the differences in risk perception of the woman. Shared decision-making integrates the best available evidence with individual preferences, fears, values and priorities. Open communication, collaborative planning and mutual respect underpin tailored management strategies

Management during pregnancy

Pregnancy in women with SLE is a high-risk period, with several potential complications that can influence both the outcome of pregnancy and the course of the disease. Therefore, careful multidisciplinary management and close monitoring throughout pregnancy, together with timely adjustment of medication, are of the utmost importance to reduce the risks of obstetric complications and disease flares.

Multidisciplinary management and pregnancy monitoring

Pregnancies in women with SLE are best managed within a specialized combined rheumatological–obstetric clinic throughout pregnancy and the postpartum period, following local protocols for high-risk pregnancies and shared-care protocols. The general schedule comprises regular clinic visits, with the frequency varying depending on SLE disease activity, organ involvement, autoantibody profile, comorbidities and the course of pregnancy[22,23]. Close monitoring of blood pressure is vital for early detection of pre-eclampsia, and home blood pressure measurements should be encouraged in women with hypertension, a history of HDP, or past or present lupus nephritis[139].

Regular blood and urine investigations are necessary for monitoring disease activity and early detection of pregnancy complications[22,23]. Haemoglobin levels and platelet counts can fall as a result of SLE-related immune haemolytic anaemia, thrombocytopenia or pre-eclampsia with haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome[139]. Regular urine investigations are also essential for detecting proteinuria, which could be the earliest sign of pre-eclampsia or a renal flare.

Distinguishing pre-eclampsia from a renal lupus flare is often challenging because hypertension, oedema, proteinuria and impaired renal function can occur in both conditions (Box 2). Yet making this distinction is crucial, given the differences in management. Pre-eclampsia, by definition, arises only after 20 weeks of gestation and is characterized by a new-onset hypertension. The only effective treatment for pre-eclampsia is delivery of the fetus and placenta. Furthermore, pre-eclampsia and active lupus nephritis can co-occur, further complicating clinical assessment.

Routine ultrasonographic screening should be performed in all pregnant women with SLE[22]. Additional fetal echocardiographic surveillance is advised for those women who are anti-Ro/SSA-positive and/or anti-La/SSB-positive, commencing at 16–20 weeks of gestation and repeated at appropriate intervals up to 26 weeks of gestation. Enhanced monitoring is warranted in high-risk patients, specifically those with high-titre anti-Ro/SSA antibodies or a prior infant with neonatal lupus or CHB[22,23]. In the third trimester, supplementary fetal growth assessments, including Doppler measurements, are advised for the early detection of placental insufficiency and/or FGR, in accordance with EULAR recommendations and the 2020 ACR guidelines[22,23].

Prevention of obstetric complications

Treatment with hydroxychloroquine, low-dose aspirin and adjunctive folic acid, vitamin D and calcium supplementation is strongly recommended during pregnancy for all women with SLE to reduce the risk of pregnancy complications[22–24,140]. In addition, antenatal and

postpartum thromboprophylaxis should be considered and discussed with all pregnant women with SLE[22,23].

Hydroxychloroquine. Hydroxychloroquine use is strongly advised before conception, during pregnancy and during lactation, according to EULAR, ACR and BSR guidelines[23,24,140], owing to its well-established role in reducing flare risk and improving pregnancy outcomes. Continued use during pregnancy is associated with a reduced risk of pre-eclampsia and FGR[141] as well as a favourable effect on the risk of preterm birth[142]. In addition, a prospective open-label study demonstrated that hydroxychloroquine use during pregnancy reduces the recurrence of CHB in a subsequent pregnancy in anti-Ro/SSA-positive women who have previously given birth to an infant with CHB[98]. Experts broadly agree that the risk–benefit profile of hydroxychloroquine in pregnancy in SLE strongly supports its use[143].

Low-dose aspirin. Low-dose aspirin is a cornerstone of preterm pre-eclampsia prevention and is generally recommended for all pregnant women at increased risk of HDP following an individualized risk–benefit assessment[144,145]. In women with SLE, the use of low-dose aspirin during pregnancy is similarly recommended[22,23], given the markedly increased risk of HDP and other pregnancy-related complications. Low-dose aspirin reduces platelet aggregation and vasoconstriction, which are important contributors to the pathogenesis of pre-eclampsia and FGR[23]. Evidence from randomized controlled trials[144] and meta-analyses[145] in high-risk obstetric populations (including women with autoimmune diseases) have shown that daily low-dose aspirin, when initiated before 16 weeks of gestation, considerably reduces the risk of preterm pre-eclampsia and related complications[144]. This benefit is also considered applicable to women with SLE by many experts in the field, particularly women with SLE with additional risk factors such as hypertension, prior lupus nephritis or the presence of aPLs or APS, who are at increased risk of pre-eclampsia.

Heparin. Pregnancy is a procoagulant state associated with an increased risk of VTE, a risk that is particularly important to consider in women with predisposing conditions such as SLE with or without aPLs. Compared with pregnant women in the general population, pregnant women with SLE have a higher incidence of VTE (7.2 versus 62 per 10,000 pregnancies)[146]. A retrospective analysis of the National Inpatient Sample database, including 8,040 pregnancies in women with SLE, showed markedly increased rates of deep vein thrombosis (42 per 10,000 in SLE pregnancies versus 5.34 per 10,000 in the general pregnant population) and pulmonary embolism (adjusted OR 9.76, 95% CI 6.13–15.55)[146].

Antenatal and postpartum thromboprophylaxis must therefore be considered and discussed with all patients with SLE[23]. Evidence quantifying the contribution of SLE disease activity to VTE risk in pregnancy remains limited. One study[147] based on a secondary analysis of a prospective registry involving 55 pregnancies in 49 patients with SLE, evaluated the Royal College of Obstetricians and Gynaecologists VTE risk model alongside SLE activity defined by the Definition Of Remission In SLE (DORIS) remission criteria[148] to guide postpartum VTE prophylaxis. The findings suggest that not all patients with SLE automatically require postpartum VTE prophylaxis, but rather only those with active SLE or additional non-SLE VTE risk factors. The study also highlighted underuse of recommended prophylaxis even among individuals with elevated risk scores, underscoring the need for refined, individualized risk assessment rather than a blanket thromboprophylaxis approach in all pregnancies in women with SLE[147]. In the absence of data from larger, prospective studies, antenatal and postpartum VTE prophylaxis should be guided by an individualized risk assessment that incorporates each patient's full risk factor profile. For the postpartum prophylaxis, additional peripartum risk factors, such as a caesarean delivery, postpartum haemorrhage, pre-eclampsia and proteinuria, should also be considered. Heparins remain the mainstay of antenatal and postpartum thromboprophylaxis and are widely recommended in clinical guidelines owing to their well-established safety profile in pregnancy[23,140]. For individuals who require long-term anticoagulation outside pregnancy (for example, patients with thrombotic APS), switching from vitamin K antagonists to LMWH should be discussed prior to pregnancy, as vitamin K antagonists are contraindicated during pregnancy[24]. The usual practice is to advise switching from vitamin K antagonists to LMWH upon confirmation of pregnancy.

Box 2 | Distinguishing renal lupus flare from hypertension-related pregnancy disorder

Features common to both conditions

- Medical history and clinical manifestations:
  - Hypertension
  - Oedema
- Laboratory investigations:
  - Decline in renal function
  - Proteinuria
  - Reduced platelet count

Features more suggestive of a renal lupus flare

- Medical history and clinical manifestations:
  - History of lupus nephritis (especially if not in complete remission at conception)
  - Other clinical signs of active systemic lupus erythematosus
- Laboratory investigations:
  - Active urine sediment
  - Decline in complement component 3 (C3) and/or C4 levels (or a failure of complement levels to rise as expected during pregnancy)
  - Increase in anti-double-stranded DNA antibody titre

Features more suggestive of a hypertension-related pregnancy disorder

- Medical history and clinical manifestations:
  - History of antiphospholipid syndrome
  - No history of lupus nephritis
  - Absence of other clinical signs of active systemic lupus erythematosus
  - Headache or visual complaints
  - Right upper-quadrant abdominal pain
- Laboratory investigations
  - Normal urinary sediment
  - No decline in C3 and/or C4 levels
  - No increase in anti-dsDNA titre
  - Elevated liver enzymes

Data from refs. 50,139.

Adjunctive treatment. Any woman planning to conceive should take 400 µg of folic acid daily to reduce the risk of fetal neural tube defects, ideally beginning 3 months before conception and continuing through the first trimester[22]. Additionally, all pregnant and lactating women with SLE should receive 1,000 IU of vitamin D supplementation daily, as higher dosages have been associated with greater reduction in pre-eclampsia risk[149], and vitamin D deficiency is common in women with SLE[150]. Furthermore, since 2014, daily 1,000 mg of calcium supplementation has been recommended in pregnancy, based on evidence from the general obstetric population demonstrating reduced risks of pre-eclampsia and preterm birth compared with placebo[151]. An updated Cochrane systematic review, however, reported little to no difference in pre-eclampsia risk between calcium users and non-users in the general obstetric population (relative risk 0.83, 95% CI 0.67–1.04; six randomized controlled trials, 15,304 women)[152]. This finding should not be interpreted as a reason to discontinue calcium supplementation in women with SLE, for several reasons. Beyond increased physiological calcium requirements during pregnancy, supplementation is widely recommended because of the high prevalence of insufficient dietary calcium intake[153,154], the increased burden of osteoporosis and osteopenia[150], and the frequent use of glucocorticoids and heparin, both of which adversely affect bone metabolism.

Prevention of disease flares

Maintaining stable, low disease activity and continuing hydroxychloroquine and other pregnancy-compatible DMARDs throughout pregnancy are essential for preventing disease flares. In particular, hydroxychloroquine adherence seems particularly important; a pharmacokinetic study in pregnant women with SLE demonstrated higher odds of preterm birth among women with non-adherent hydroxychloroquine concentrations, compared with those among women maintaining therapeutic concentrations, even after adjusting for lupus nephritis and race (OR 11.2, 95% CI 2.3–54.2; $p = 0.003$)[155].

Additionally, timely adjustment of immunosuppressive therapy is essential for individuals who require ongoing treatment during pregnancy. Several drugs used in the management of SLE are compatible with the periconception period and throughout pregnancy, whereas others are contraindicated (Table 1). Ensuring effective treatment of the disease during pregnancy can be challenging. If necessary, switching to pregnancy-compatible immunosuppressive drugs should be performed 4 to 6 months before conception, as such changes can trigger disease flares. This interval also allows for the recommended 6–12 months of sustained disease remission on stable therapy prior to conception, necessitating an adequate observation period after any treatment adjustment[22]. Women receiving long-term low-dose glucocorticoids should not abruptly discontinue therapy, owing to the risk of disease flare and stress-induced adrenal crisis, and the potential need for stress-dose glucocorticoids during labour should be discussed with the obstetric team (see the section 'Glucocorticoids').

Safety of antirheumatic medication use during pregnancy

Over the past 5 years, ACR and BSR guidelines and updated EULAR recommendations on the use of antirheumatic drugs during pregnancy and lactation have provided important guidance for health-care professionals and patients[21,23,24]. In line with preconception counselling and these recommendations, emphasis should be placed on continuing pregnancy-compatible medication to maintain disease control throughout pregnancy. Table 1 provides an overview of pregnancy-compatible drugs that are considered safe and are widely used during pregnancy, alongside those that are contraindicated because of known teratogenicity or insufficient safety data, and outlines the implications of exposure. Further detail on individual therapeutic agents can be found in the published international guidelines and recommendations[21,23,24].

Conventional synthetic DMARDs. No csDMARDs are formally licensed for use during pregnancy in women with SLE. Health-care professionals and patients therefore rely on guidance from major societies to inform csDMARD use during pregnancy and lactation. These guidelines are developed according to rigorous standards based on systematic reviews of the literature[21,23,24,140]. Data from a global survey of 414 health-care professionals indicate that such guidance is widely used in daily clinical practice, underscoring the importance of these documents as essential clinical references[156]. As evidence on the safety of DMARD use in pregnancy and lactation continues to expand — primarily through observational studies — shared decision-making remains crucial when discussing medication choices.

NSAIDs. According to BSR and updated EULAR recommendations[21,24], NSAIDs should only be used intermittently during pregnancy and discontinued after 28 weeks of gestation to avoid adverse fetal effects. The FDA advises caution with NSAID use even after 20 weeks of gestation, as these agents might cause rare but serious kidney problems in the fetus, leading to complications caused by low levels of amniotic fluid[157]. Cyclooxygenase-2 inhibitors should be avoided owing to insufficient data on safety in pregnancy.

Glucocorticoids. Non-fluorinated glucocorticoids, including prednisone, prednisolone, hydrocortisone and methylprednisolone, are considered compatible with pregnancy[24]. Doses should be titrated to the lowest effective level to minimize maternal complications such as hypertension, infection and gestational diabetes mellitus[23]. Although glucocorticoid therapy can precipitate gestational diabetes mellitus in any pregnancy, particular attention to this risk warranted in SLE, as glucocorticoids are frequently used to maintain disease control. A systematic review and meta-analysis of five studies involving 3,432 pregnancies in women with SLE and 248 gestational diabetes mellitus events demonstrated a notable association between pregnancy and gestational diabetes mellitus in women with SLE[158]. Moreover, high-dose or prolonged glucocorticoid use are associated with increased risks of premature birth[159], and some studies have linked glucocorticoid use to increased risk of premature rupture of membranes, although evidence is mixed[160]. In women with SLE treated with the equivalent of ≥5 mg prednisolone daily for longer than about 3 weeks, as well as those on long-term lower doses after tapering from higher doses, the need for stress dose therapy before labour should be discussed within the multidisciplinary team, including endocrine expertise.

Fluorinated glucocorticoids, such as dexamethasone and betamethasone, readily cross the placenta and should be reserved primarily for accelerating fetal lung maturation in the setting of impending preterm birth. Fluorinated glucocorticoids have been used with the aim of reversing CHB, albeit in the absence of evidence to support the practice[161].

Biologic DMARDs. Historically, the use of bDMARDs during conception and pregnancy was approached with considerable caution, given the evidence available at the time, often leading to withdrawal of therapy and potential harm owing to increased disease activity[162]. However, cumulative data and expert reviews now support the selective

use of certain bDMARDs, where clinically indicated, to mitigate the risks of active disease and support a successful pregnancy[21,23,24,52,162]. bDMARDs cross the placenta through active transfer only after placental expression of neonatal Fc receptors begins around 16 weeks of gestation, after which active transplacental transport increases progressively towards term[163].

Although TNF-inhibiting agents are not standard first-line therapy for SLE, these drugs are used in some regions in selected patients — either to maintain disease control or to manage coexisting inflammatory diseases[164] — and are considered compatible throughout pregnancy. B cell-targeted therapies such as rituximab, belimumab and the more recently approved interferon-blocking agent anifrolumab are used in severe or refractory SLE when conventional DMARDs are insufficient or contraindicated[24,162]. Studies have shown minimal to no increased risk of congenital malformations, low birthweight or other major adverse outcomes in infants exposed antenatally to belimumab, rituximab or TNF-inhibiting agents, when these therapies are used judiciously for maternal benefit[21,23,24]. Administration of B cell-targeted agents after 20 weeks of gestation can lead to transient neonatal B cell depletion, although this effect has not been associated with serious infections, and B cells typically normalize within 6 months[165–167]. Regarding infant vaccination, the 2024 updated EULAR guidelines recommend avoiding live infant vaccines (such as the BCG vaccine) during the first 6 months of life in infants born to women who received B cell-depleting therapy in the second or third trimester or TNF-inhibiting agents that undergo active transplacental transfer during the second half of pregnancy[24].

Lactation

Breastfeeding is an important aspect of postpartum care for both parent and infant, and several SLE-specific considerations deserve attention. In general, breastfeeding should be encouraged in all women with SLE.

General aspects of breastfeeding

Breast milk is widely regarded as the optimal source of infant nutrition, providing protection against infections and dental malocclusion, supporting cognitive development, and probably reducing the risk of overweight and diabetes in later life[168]. For the mother, breastfeeding offers several long-term health benefits including protection against breast cancer and potentially also against ovarian cancer and type 2 diabetes[168]. Moreover, breastfeeding is an important bonding component for mother and baby. However, no data are currently available on the long-term effects of breastfeeding on the mother, specifically in women with SLE.

Specific aspects of lactation in women with SLE

Breastfeeding initiation rate and duration are lower in women with SLE than in women without SLE[169,170]. A qualitative study showed that attitudes on breastfeeding vary widely and are strongly shaped by personal preferences and lived experience[171]. Specifically, support from health-care professionals in reassuring patients that breastfeeding is safe with their medication is important[171]. Also important is the need to support whatever decision the woman makes[171]. Breastfeeding can be physically and emotionally demanding, and some women, especially those with a chronic illness such as SLE, might feel they lack the stamina to breastfeed, worry about insufficient milk or feel more confident using formula[171]. These concerns must be respected, as women can experience stress from being responsible for their child's health[171]. Mixed feeding, combining breastfeeding with formula supplementation, should also be recognized as a pragmatic and acceptable option, offering flexibility for those women with SLE in whom exclusive breastfeeding is challenging — whether due to medication regimens, maternal fatigue or other disease-related factors.

The evidence on the effects of medication exposure on breast milk remains limited for most drugs. Nevertheless, only a small number of medications are now considered absolutely contraindicated during breastfeeding[23,24]. Accurate counselling requires an assessment of the extent to which each drug is transferred into breast milk. Several factors influence infant exposure, including the route of administration, dosage, duration of use, half-life and timing of administration in relation to breastfeeding, as well as the volume of breast milk consumed by the infant[172].

Women with SLE have an increased likelihood of giving birth to a premature[2] or growth-restricted[84] infant compared with women from the general population. For these babies, breast milk is particularly important. However, the risk of medication exposure through breast milk could be higher because drug elimination might be slower, increasing the potential for accumulation. In these situations, the risks and benefits should be carefully evaluated and discussed with the neonatologist[24].

Safety of antirheumatic medication use during lactation

For many drugs, direct evidence regarding the effects of maternal drug use during breastfeeding remains limited. Nevertheless, pharmacological principles allow reasonable estimation of infant exposure and associated risk, and these assessments are now incorporated in updated evidence-based BSR, EULAR and ACR guidelines[21,23,24,140]. Most drugs commonly used to treat SLE are considered compatible with breastfeeding[24] (Table 1). These drugs are either not transferred — or only minimally transferred — into breast milk, or sufficient evidence supports their safety in breastfed infants. For mothers receiving intravenous methylprednisolone pulse therapy, a breastfeeding delay of approximately 2–4 h after administration is recommended to minimize infant exposure[24].

bDMARDs are considered safe for use during lactation[21,23,24]. Owing to the large molecular size of these agents, which impedes passive diffusion through the intercellular space between mammary cells into breast milk[173], no or only minimal transfer of bDMARDs into breast milk is expected[174]. Moreover, any bDMARD in breast milk is unlikely to be absorbed in active form after oral administration owing to digestion in the infant's gastrointestinal tract[23,24]. Methotrexate at doses of ≤25 mg weekly might be considered during lactation when no suitable alternative is available, given the very low concentrations detected in breast milk and the absence of reported harm[24].

Drugs that should be avoided during breastfeeding owing to insufficient safety data include cyclophosphamide, mycophenolate mofetil, leflunomide, voclosporin, etoricoxib and targeted synthetic DMARDs, such as Janus kinase inhibitors[21,24]. The decisions around breastfeeding in women with SLE involve careful counselling, before and after birth, taking into account the mother's desire to breastfeed, physical condition, medication safety and the necessity of continuing a particular medication or switching to an available alternative.

Future research directions

To improve the course and outcomes of pregnancy in women with SLE, future research should prioritize closing key knowledge gaps in two major areas: the pathogenesis of pregnancy complications in SLE

and the effects of immunosuppressive medications during pregnancy and lactation (Box 3).

To better predict and prevent the occurrence of adverse outcomes of pregnancy in women with SLE, elucidating the pathogenesis of pregnancy complications in SLE is crucial. Most current translational studies are underpowered to distinguish between complicated and uncomplicated pregnancies in women with SLE and often focus on differences in between pregnancies in women with SLE and pregnancies in healthy women, where the type I interferon signature predominates[175]. Robust progress will therefore depend on larger, prospective, multi-ethnic cohort studies and registries ideally linked to high-quality biobanking to enable direct comparisons between pregnancies in women with SLE with and without complications. Further research should also address additional immune processes that are central to normal pregnancy, including maternal–fetal tolerance and the initiation of parturition. Mechanistic studies are required to determine whether placental abnormalities are a cause or consequence of adverse outcomes and how these processes intersect with SLE-related immune dysregulation. With advances in organoid models of placental development, the field is now poised to move beyond observational studies towards functional experiments that could provide deeper mechanistic insights into pregnancy complications in SLE.

In addition, several key research questions regarding the use of immunosuppressive medications during pregnancy and lactation in women with SLE remain unresolved. Progress in this area will require prospective pregnancy registries and, where feasible, pragmatic trials or comparative-effectiveness studies to move beyond the limitations of small, largely underpowered, retrospective analyses and to address specific safety signals identified in preliminary reports. Research in this field should not only seek to close knowledge gaps regarding the safety of currently used immunosuppressive medications in SLE and newly developed therapeutic agents during pregnancy and lactation, but also evaluate the efficacy of drugs in improving pregnancy outcomes. Clinical trials involving patients at high risk of adverse pregnancy outcomes are urgently needed[176]. Securing approval for, and conducting, clinical trials in pregnant women with SLE remains a major challenge, but is of great importance to patients, and therefore deserves joint efforts from health-care professionals, regulatory authorities and other stakeholders.

Further research is also needed on the risk of infections, the response to vaccinations and the long-term development of children exposed in utero to antirheumatic drugs. Several additional questions, although not unique to SLE, remain highly relevant for women with SLE and other autoimmune diseases, including the optimization of assisted reproductive techniques, contraception strategies in the context of thrombosis risk and models of multidisciplinary preconception counselling and pregnancy care. These broader issues lend themselves well to disease-agnostic registries and implementation studies that can compare different service configurations and care pathways. Moreover, large multiethnic, multinational studies are needed to clarify whether socioeconomic, ethnic or other structural disparities contribute to differences in pregnancy outcomes among women with SLE.

Finally, the practical obstacles to conducting high-quality research in pregnant women with SLE must be acknowledged and addressed. These include ethical and regulatory constraints, liability concerns, the routine exclusion of pregnant women from clinical trials and the logistical complexity and cost of long-term mother–child follow-up. Progress will require collaborative research networks that bring together rheumatologists, obstetricians, neonatologists, paediatricians and patient partners, alongside harmonized data standards and dedicated funding mechanisms that explicitly support pregnancy research. Such coordinated efforts will be essential to close the critical knowledge gaps outlined throughout this Review.

Box 3 | Future research agenda

Pathogenesis of pregnancy complications

- Identify early pregnancy biomarkers that predict later complications through prospective, multiethnic registries and harmonized biobanks, overcoming the limitations of small, retrospective, single-centre studies.
- Clarify how maternal–fetal immune tolerance fails in systemic lupus erythematosus (SLE) and contributes to adverse pregnancy outcomes.
- Investigate the effects of therapeutic agents on biological processes at the maternal–fetal interface using placental organoid models, examining both established and emerging therapies.
- Elucidate the mechanisms of spontaneous preterm birth in SLE.
- Determine how ethnic, socioeconomic and other structural disparities shape pregnancy outcomes.
- Assess, in large multiethnic cohorts, the impact of parity on flare risk and pregnancy outcomes.
- Evaluate the feasibility of a treat-to-target approach aimed at remission or low disease activity in women with SLE planning pregnancy or already pregnant.

Antirheumatic medication during pregnancy and lactation

- Define the safety profiles of antirheumatic drugs with limited or no pregnancy and lactation data.
- Conduct clinical trials in high-risk individuals, including women with persistent antiphospholipid antibodies.
- Study the safety of newly developed SLE therapies during pregnancy and lactation, and their efficacy in improving pregnancy outcomes.
- Characterize drug transfer by measuring medication levels in maternal blood, breast milk and infant blood in both term and preterm infants during lactation.
- Investigate infection risk, vaccine responses and long-term development in children exposed in utero to antirheumatic therapies, particularly biologic DMARDs administered after 20 weeks of gestation.
- Advance care model and implementation research, including optimization of multidisciplinary preconception and pregnancy pathways, and address barriers (such as ethical and regulatory constraints, exclusion of pregnant women from clinical trials and costs and logistics of long-term follow-up). Collaborative networks and dedicated funding mechanisms will be essential.

Conclusions

Pregnancy outcomes in women with SLE have substantially improved over the past four decades; however, the risks of maternal complications and adverse fetal outcomes remain substantially higher than in the general population. Optimizing care therefore requires a comprehensive approach that begins well before conception and extends throughout pregnancy and the postpartum period. Preconception

counselling, careful pregnancy planning, systematic assessment of risk factors, timely adjustment of medication and coordinated multidisciplinary management all have central roles in minimizing the likelihood of disease flares and pregnancy complications. Impaired fertility in women with SLE, associated with disease activity, renal failure, medication exposure, age-related decline in ovarian reserve and lifestyle factors, underscores the importance of early counselling about family planning during the reproductive years. Lactation rates in women with SLE are reduced owing to safety concerns, disease flares, physical limitations and mental challenges, illustrating the need to integrate multidisciplinary care and breastfeeding support into postpartum care. Continued research and sustained collaboration between patients and multidisciplinary teams is essential to further improve outcomes for families affected by SLE.

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Perspective

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Bridging the gap: combining treat-to-target and difficult-to-treat strategies in the management of rheumatoid arthritis

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Abstract

The treat-to-target (T2T) strategy, which involves predefined therapy objectives and a focused monitoring system, has substantially improved the management of rheumatoid arthritis (RA). These benefits probably result from a reduction in undertreatment, prevention of overtreatment and thus an improvement in long-term outcomes for both articular manifestations and comorbidities. However, T2T has also revealed a subgroup of patients who, despite following guideline-based treatment, do not reach the predefined outcomes. This finding has led to the emerging concept of 'difficult-to-treat' (D2T) RA. D2T-RA might reflect true pharmacological refractoriness, but D2T-RA is also increasingly recognized as having broader underlying causes, including psychosocial distress, comorbidities, chronic pain syndromes and patient or system-related barriers. If these underlying factors remain unidentified, unnecessary treatment escalation can occur, which could worsen long-term outcomes. Although T2T focuses on predefined targets and regular monitoring, which works well for the majority of patients, the structured multidomain approach characteristic of the D2T framework might provide a guide for managing patients who do not reach these targets despite guideline-based care. For this population, the D2T approach could offer better stratification and serve as a practical, precision-medicine-oriented extension of T2T by providing a more mechanism-informed, personalized management strategy. Integrating this D2T perspective into T2T practices keeps the strengths of T2T while also offering individualized care for patients with more complex disease trajectories, representing an unmet need.

Sections

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Introduction

The implementation of the treat-to-target (T2T) strategy, together with novel therapeutic innovations, has transformed the treatment of rheumatoid arthritis (RA). Prior to the adoption of the T2T strategy, therapeutic decisions were often led by empirical clinical evaluation rather than measurable metrics that sought predefined goals. This framework brought a paradigm shift by implementing a management algorithm based on regular assessment and timely treatment adjustments, which has enabled optimal and dynamic disease control. As a result, many patients have achieved remission or low disease activity, which demonstrates the effectiveness of this strategy in everyday clinical practice. Furthermore, T2T has helped to prevent both undertreatment and overtreatment, which has also contributed to improved long-term outcomes across musculoskeletal and comorbid disease domains[1–3].

Paradoxically, the success of the T2T approach has also brought to light a distinct subset of patients who do not respond adequately to treatment despite optimal disease management. In other words, by standardizing treatment goals and ensuring that most patients achieve remission, the T2T framework has made it possible to clearly identify those who remain refractory to current therapeutic options despite following a structured guideline. This population, defined as those with 'difficult-to-treat' RA (D2T-RA), has gained increasing attention in the past decade, owing to the considerable clinical and socioeconomic burden associated with D2T-RA[4]. Although the T2T strategy has optimized inflammatory disease control for the majority of patients, the persistence of a D2T subset suggests a more complex and multifactorial cause of therapeutic resistance in RA. Understanding these underlying mechanisms of the D2T disease state could contribute to improved outcomes and tailored therapeutic approaches. By further investigating inflammatory processes and factors beyond inflammation, including pain processing, comorbidities, adherence and socioeconomic and psychosocial determinants, new perspectives might emerge that could help to improve treatment strategies and prevent progression towards a D2T disease state.

Although the T2T strategy includes individualized targets and shared decision-making, those who continue to experience active symptoms despite proper treatment might benefit from an even more personalized approach using the D2T strategy. By re-evaluating why therapy is not effective, whether the reason is biological, psychological or related to other conditions, this structured reassessment inherently enables a more personalized approach that remains aligned with the T2T framework. Precision medicine refers to tailoring therapeutic approaches to the individual needs of patients based on specific clinical, biological, psychological and other circumstantial factors that influence the disease course[5,6]. Although this goal is still evolving in RA, a more mechanism-informed, individualized assessment could become important for patients for whom conventional targets no longer accurately capture the individual course of the disease, primarily in the case of the D2T state.

In this Perspective, we propose a complementary relationship between T2T and D2T that reflects not a limitation of current therapeutic strategies but an opportunity and a guide for the management of people who have a poor response to treatment and represent an unmet clinical need. By considering these frameworks as complementary rather than distinct, through a novel lens, a model of care that remains structured and evidence-based can be conceptualized, that is also flexible enough to address the biological and personal variability that is characteristic of the real-world patient experience.

The use of treat-to-target to assess treatment failure

The implementation of T2T has clearly demonstrated considerable advancements in the treatment of RA. T2T has consistently been associated with higher remission rates, faster suppression of inflammation, reduced radiographic progression and improved functional outcomes compared with routine care approaches[7,8]. Despite these clear benefits of the T2T approach in RA, as with any structured treatment framework, exceptions inevitably arise. Some individuals fail to reach their predefined targets even when the strategy is rigorously applied. By corollary, the T2T approach is not just a treatment algorithm to direct therapeutics but comprises a more complex system that can also reveal non-optimal RA disease trajectories. These trajectories can include persistent or relapsing disease activity despite adequate suppression of inflammation, a progressive loss of treatment efficacy or tolerance after multiple DMARDs or limited improvement in pain, fatigue and function even when inflammatory markers normalize[9,10]. Such patterns highlight that suboptimal outcomes in RA might arise from mechanisms beyond pharmacological failure, involving the interplay of immune, neurobiological and psychosocial factors. T2T offers a structure to identify characteristics that are associated with such treatment failure and might enable earlier prediction. These signs could serve as clinical indicators for the risk of developing a D2T disease state. Such early indicators might include persistent or fluctuating disease activity despite optimized therapy, repeated drug intolerance or loss of efficacy, ongoing glucocorticoid dependence or discordance between objective disease control and patient-reported outcomes, such as pain and fatigue. Psychological distress and comorbidities can further contribute to this profile, highlighting an increased risk of progressing towards a D2T state. Therefore, we propose that the structure of the T2T algorithm itself affirms the importance of the D2T concept by identifying in real time those patients who, despite appropriate management, deviate from a positive, health-associated, therapeutic trajectory (Fig. 1).

Reframing treatment resistance using difficult-to-treat

Ideally, patients reach remission or low disease activity after the application of recommendation-driven T2T strategy; however, a considerable proportion (6–28%) of patients still fail to achieve these predefined therapeutic goals[9]. A EULAR taskforce was established to form a definition of D2T-RA that describes this group of patients with RA who remain symptomatic despite multiple treatment efforts[4]. Furthermore, EULAR also proposed an approach to managing such D2T disease (including both pharmacological and non-pharmacological therapies), parsing out the various domains in which therapeutic decisions should be considered[10]. Importantly, D2T-RA is not a definitive diagnosis but rather a clinical state; by defining such a state, the clinician–patient partnership can focus on manageable elements across affected domains via a step-by-step approach aimed at altering that state towards that of 'wellbeing'.

Although D2T suggests pharmacological or pathogenetic refractoriness, it should be considered as an overarching term for all patients whose disease remains challenging. Although true 'patho-refractory' disease might be present, for many patients, the factors that contribute to the D2T state extend beyond 'conventional' articular inflammation. Many of these proposed contributors can be conceptualized within a triad of three core considerations. First, ensuring that the correct diagnosis has been made (for example, RA could be a misdiagnosis or complicated by a coexisting condition). Second, checking for objective

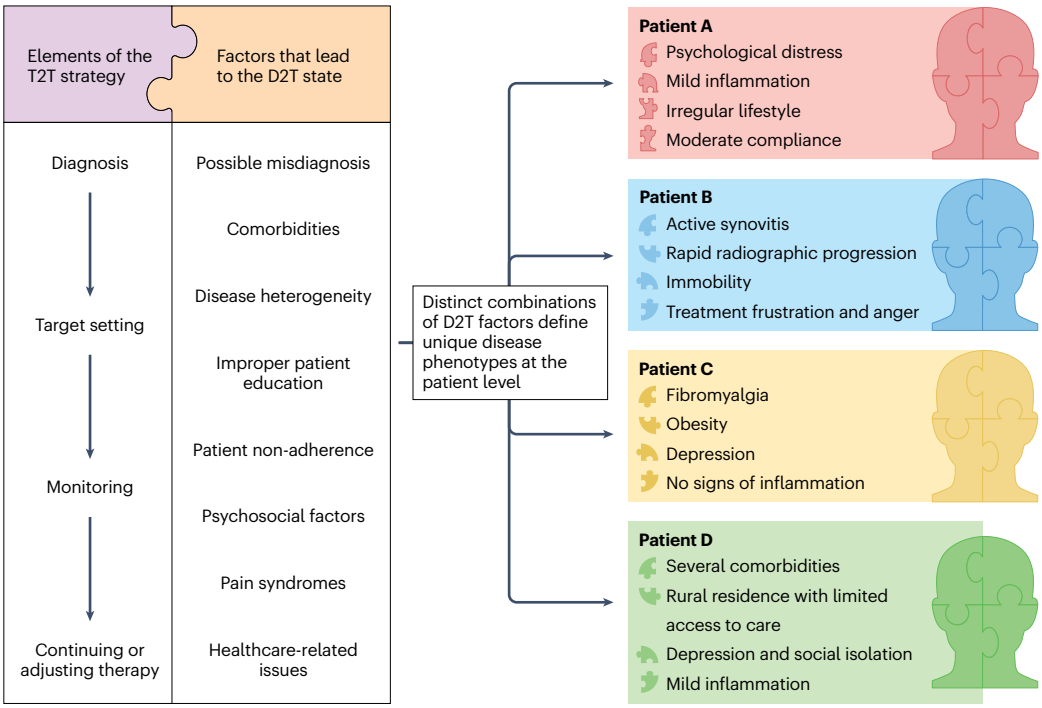

Fig. 1 | The difficult-to-treat puzzle: the treat-to-target framework uncovers unmet needs in rheumatoid arthritis. The treat-to-target (T2T) approach provides a structured framework in rheumatoid arthritis (RA) management. However, when therapeutic goals are not met, this structure can reveal gaps ('missing pieces') that signal the presence of difficult-to-treat (D2T) disease. D2T-RA is not a single phenotype but a diverse spectrum of patient-specific profiles characterized by shared biological, psychological and systemic features. Although T2T helps to identify when treatment goals remain unmet, the D2T perspective offers direction for stratifying patients who do not respond to pharmacological therapy and require a more individualized approach. Understanding how shared factors such as inflammation, comorbidities, pain sensitization or psychosocial stress combine uniquely in each patient enables smarter, adaptive strategies beyond escalation, ultimately improving long-term outcomes. Furthermore, integrating D2T elements into the T2T pathway might facilitate the earlier recognition of patients who are at a high risk of developing D2T-RA, enable more personalized care and help to optimize long-term disease outcomes.

evidence of ongoing biologically active disease (such as symptoms that are being driven or amplified by pain syndromes, secondary osteoarthritis or psychological distress). Finally, consider if the presence of inflammation indicates pharmacological refractoriness or if other factors (for example, non-adherence, socioeconomic barriers, treatment limitations owing to intolerance or perceived adverse effects) could be contributing to the sustained activity[11–15]. Each patient with D2T-RA represents a unique combination of contributing factors, such as pieces of a puzzle that differ in both composition and interaction. These variations reflect the individual balance of biological, psychological and social elements that shape the disease course in each patient. Recognizing this individuality highlights the need for a personalized approach in which assessment and management are guided by factors that directly contribute to the unique D2T state in each patient, rather than a uniform therapeutic pathway.

This diversity of mechanisms also helps to explain the emergence of various terms in the literature that attempt to capture different aspects of the same complex state. The coexistence of multiple overlapping terms reflects different emphases, some prioritizing pharmacological refractoriness, and others the broader clinical or psychological complexity, but they all broadly describe the same underlying state[16,17]. Although this state was defined as D2T in RA, the phrase 'difficult to manage' is used in other conditions to capture the broader, multidomain challenges, and indeed other taskforces have preferred this term[18,19], highlighting that terminology is not fully consistent across inflammatory arthritides. Perhaps, although RA is always multifaceted in terms of clinical presentation and consequence, this more problematic phenotype is most simply described as 'complex RA'. Mechanistic perspectives have also been proposed, including labels such as persistent inflammatory refractory RA (PIRRA) and non-inflammatory refractory RA (NIRRA), which are aimed at separating predominantly inflammatory from non-inflammatory refractory presentations based on objective evidence of synovitis[20,21]. Since the introduction of the EULAR definition of D2T-RA, an increasing number of cohort- and registry-based studies have used this definition to classify D2T-RA, leading to greater harmonization of reporting across datasets[9,14,21]; however, accumulating experience from routine care and research might contribute to refining the definition and improving stratification over time[21].

Early factors that predict treatment resistance

Although many clinical and biological features have been associated with the D2T phenotype, it is self-evident that risk factors might already be present before or at the time of RA diagnosis. Clinical factors, such as obesity, fibromyalgia or psychological distress, increase the likelihood of developing D2T disease and infer worse long-term outcomes[14,15,22].

Evaluating and managing these factors should be mandatory in the early and ongoing management of RA.

An intriguing but as yet unanswered question concerns the role of primary pathogenesis in D2T-RA. In theory, different pathological trajectories could correlate with distinct clinical presentations. For example, biopsy-obtained synovial tissue samples with highly inflammatory leukocyte-rich profiles are more likely to be associated with erosion progression than those with pauci-immune features. In the latter, by contrast, fibroblasts interact with nociceptive neurons, which potentially contributes to peripheral pain sensitization with relatively lower levels of peripheral inflammation[23–28]. Moreover, whether these synovial immune profiles define disease (truly pathogenetically differentiated disease subsets) or simply a function of different disease kinetics is unclear. Regardless, they could confer clinical importance. A 2024 study in which single-cell RNA sequencing and receptor–ligand analysis highlighted fibroblast–neuron crosstalk and pain-related gene signatures in synovial tissue with a low level of inflammation supports the idea that tissue-specific mechanisms might be related to treatment refractoriness[29]. More studies of this nature are required across different tissue domains.

Although joint involvement is the primary concern in RA, disease pathogenesis extends far beyond the joints. Structural and network-wide brain alterations observed in RA are associated with inflammatory activity[30], which suggests that inflammation can 'rewire' brain networks in a way that might contribute to symptom persistence, including pain, fatigue and cognitive impairments. Notably, central nervous system alterations can also contribute to symptom persistence despite peripheral inflammation being under control[20]. Therefore, pain in RA is increasingly recognized as mixed, arising partly from nociceptive components linked to joint inflammation and partly from nociplastic components involving central mechanisms that modify pain perception[31]. Clinically, this nociplastic component is also demonstrated by the higher prevalence of fibromyalgia among patients with RA compared with the general population. Fibromyalgia is characterized by central sensitization and altered pain processing, which can amplify pain perception even in the absence of joint inflammation[15,32]. Psychosocial distress, anxiety and depression can also contribute to altered central functioning and influence brain connectivity patterns, which can amplify pain perception and further reduce response to treatment[33]. The fact that these alterations can also occur before the onset of disease, shaping pain processing, ways of coping and adherence to treatment, might influence the treatment course from the start. Therefore, unravelling the relationship of peripheral inflammation with nociplastic pain and psychological comorbidities is an area of crucial importance for future RA studies, especially in the context of D2T disease. Multidomain assessment and integrated care might therefore be useful in preventing or slowing down the development of a D2T state.

Integrating a difficult-to-treat approach into treat-to-target practice

Clinical experience with D2T reveals an important limitation of the T2T approach that cannot necessarily be attributed to the treatment strategy itself but rather to the composite disease activity indices commonly used in routine care, such as the Disease Activity Score in 28 Joints (DAS28)[34], the Simplified Disease Activity Index (SDAI)[35] or the Clinical Disease Activity Index (CDAI)[36]. However, these indices might not always capture inflammatory activity (synovitis) comprehensively and can be influenced by non-inflammatory symptom drivers; therefore, they might not consistently guide appropriate adjustments in therapy for all patients[37]. In such instances, the apparent 'failure' of T2T could reflect measurement limitations (over- or underestimation of inflammation) rather than an inherent deficiency of target-driven care.

Although DAS28, CDAI and SDAI are widely adopted in both clinical practice and clinical trials, they have important shortcomings in routine practice and should be interpreted alongside clinical judgement and shared decision making[38–40]. First, factors associated with altered pain processing, such as central sensitization, depression and anxiety, sleep disturbance, comorbid fibromyalgia and other comorbidities (such as obesity) can disproportionately influence the subjective components of disease activity indices, including tender joint counts or patient global assessment, resulting in the overestimation of disease activity and potentially prompting unnecessary escalation of immunomodulatory treatment[15,41,42]. In such instances, treatment based solely on composite scores can fail to address the true drivers of symptoms, enabling the persistence of chronic pain and an increased risk of a D2T state. Importantly, these factors do not exclude the presence of residual synovitis and might coexist with ongoing inflammatory activity, further complicating the interpretation of composite scores and disease management. Second, many composite indices do not include the assessment of feet and ankles, which are frequently affected in RA. As a result, patients might be classified as being in remission despite having active inflammation in these joints, potentially leading to an underestimation of the disease activity, consequent undertreatment, and, over time, irreversible joint erosions and chronic pain[43,44]. These limitations are especially relevant in D2T disease, raising the question of whether, for certain patients with D2T-RA, alternative or more comprehensive targets should be considered along with broader multidimensional assessment strategies.

T2T applies a structured, target-oriented treatment principle by focusing mainly on inflammatory control and, potentially, on other predefined targets that can be influenced by individual factors. These elements make T2T practical for large-scale implementation and help to reduce over- and undertreatment through objective monitoring and decision-making. However, building on this strategy, the D2T approach applies a multimodal framework for reassessment to evaluate the full range of clinical, biological and psychosocial factors when patients remain symptomatic despite guideline-recommended care. Although this individualized approach is less suited to broad, population-wide implementation, it highlights the notion that composite targets might not suit all patients and encourages tailoring therapy to the individual patient (Fig. 2).

To improve patient outcomes, the T2T approach could benefit from incorporating elements of the D2T strategy. Recognizing the signs of D2T disease early could contribute to more effective patient stratification and enable more personalized interventions, potentially improving long-term outcomes. Such signs also include clinical and non-inflammatory factors that can limit the effectiveness of standard treatment modalities. For example, if the application of two or more biologic or targeted synthetic DMARDs (bDMARDs or tsDMARDs) has failed, reassessing the original diagnosis is important[10]. In addition, when C-reactive protein levels are low, but the patient continues to report pain, central sensitization, psychological distress or nociplastic pain should be considered, as these factors are unlikely to benefit from escalating therapy[4,22]. Furthermore, inflammatory activity should not be excluded on the basis of acute phase reactants alone. Even though strategy trials have not demonstrated the superiority of routine imaging-driven T2T over conventional approaches[45–47], in selected instances, ultrasonography might help to evaluate the presence of

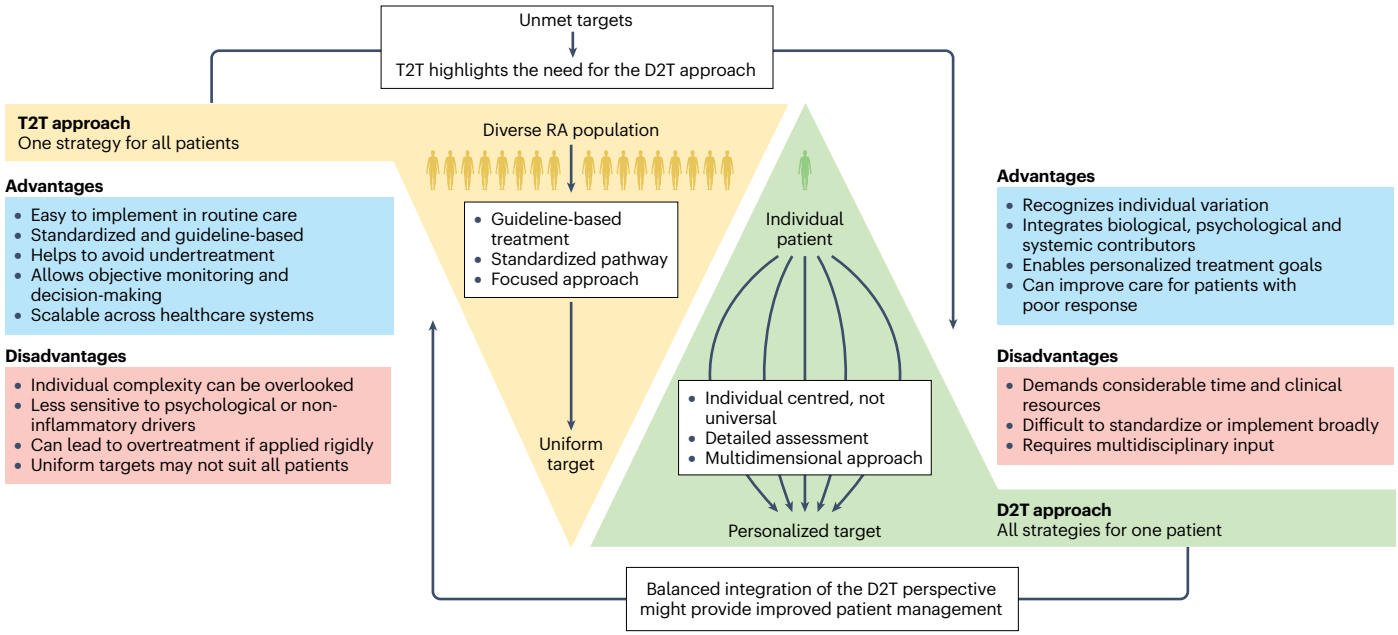

Fig. 2 | Integrating difficult-to-treat with treat-to-target: from standardized targets to personalized adaptation. Although the treat-to-target (T2T) strategy offers a clear, focused structure and common treatment goals for all patients, the difficult-to-treat (D2T) perspective focuses on the individual, taking into account clinical, biological and psychosocial factors that might affect response to treatment. Both T2T and D2T have advantages and disadvantages, but combining these two different perspectives can improve treatment strategies and might help to balance standardization with the need for personalized care and improve long-term outcomes.

residual synovitis that is potentially associated with flare risk, which could inform therapeutic decision-making[37,48,49]. Repeated dose reductions owing to comorbidities or adverse effects also often occur and should prompt a comprehensive reassessment of the overall health status, with analysis of comorbidity burden, therapeutic tolerability and risk–benefit balance.

Several of these early indicators of D2T-RA overlap with the 'poor prognostic factors' described in earlier EULAR recommendations[3], including moderate-to-high disease activity after conventional synthetic DMARD (csDMARD) therapy, persistently elevated acute-phase reactants, high swollen joint counts, seropositivity for rheumatoid factor and/or anti-citrullinated protein antibodies, early radiographic erosions and failure of two or more csDMARDs. However, the D2T framework integrates these predictors into a broader, multidomain perspective that also encompasses comorbidities, pain mechanisms and psychosocial contributors, better reflecting the heterogeneity of real-world RA. For some patients, addressing these factors might require shared decision-making from a multidisciplinary team including rheumatologists, cardiologists, nephrologists, pulmonologists, neurologists, pain specialists, psychologists and other healthcare professionals[14,50]. Furthermore, although synovial phenotyping, synovial fluid analysis or assessing nervous system involvement are currently not part of everyday practice, they might help in the future to better stratify patients and determine more personalized therapeutic approaches[25,26,29].

Integrating these two perspectives could provide a more balanced strategy that is structured enough to enable standardized monitoring but flexible enough to address real-life complexity with the help of multidomain assessment and shared decision-making. The primary objective should be to identify those patients with potentially challenging disease earlier and address contributing factors before refractoriness develops. Early recognition of the signs of the D2T state within the T2T framework could provide an opportunity for timely adjustments to therapy, optimization of the management of different comorbidities and additional targeted non-pharmacological support, potentially preventing the development of chronic refractoriness. However, at the same time, the T2T framework itself can also help to identify those who have already entered a D2T state by detecting persistent disease activity or non-inflammatory contributors to poor outcomes despite optimal management. Overall, the D2T state should not be seen as the end of the treatment pathway but as a signal to adapt and broaden the T2T approach to meet the complexity of real-world RA care (Fig. 2).

The difficult-to-treat strategy in personalized rheumatoid arthritis treatment

Patients with clinically challenging disease provide a basis for the legitimacy of the D2T concept, and its implementation and the recommended algorithm of its management offered novel ways of addressing the underlying reasons for treatment refractoriness[4,10]. Rather than differentiating single biological entities, the current D2T framework encompasses all patients facing difficulties during their treatment trajectories, accurately reflecting the heterogeneity of this population, and despite its complexity, it still provides a useful management strategy that could be universally implemented in everyday clinical care, and help to guide more patients towards remission[10] (Fig. 3).

At the same time, the D2T framework also conveys a broader message, namely that these patients reach this state for different reasons, such as persistent inflammation, the presence of comorbidities,

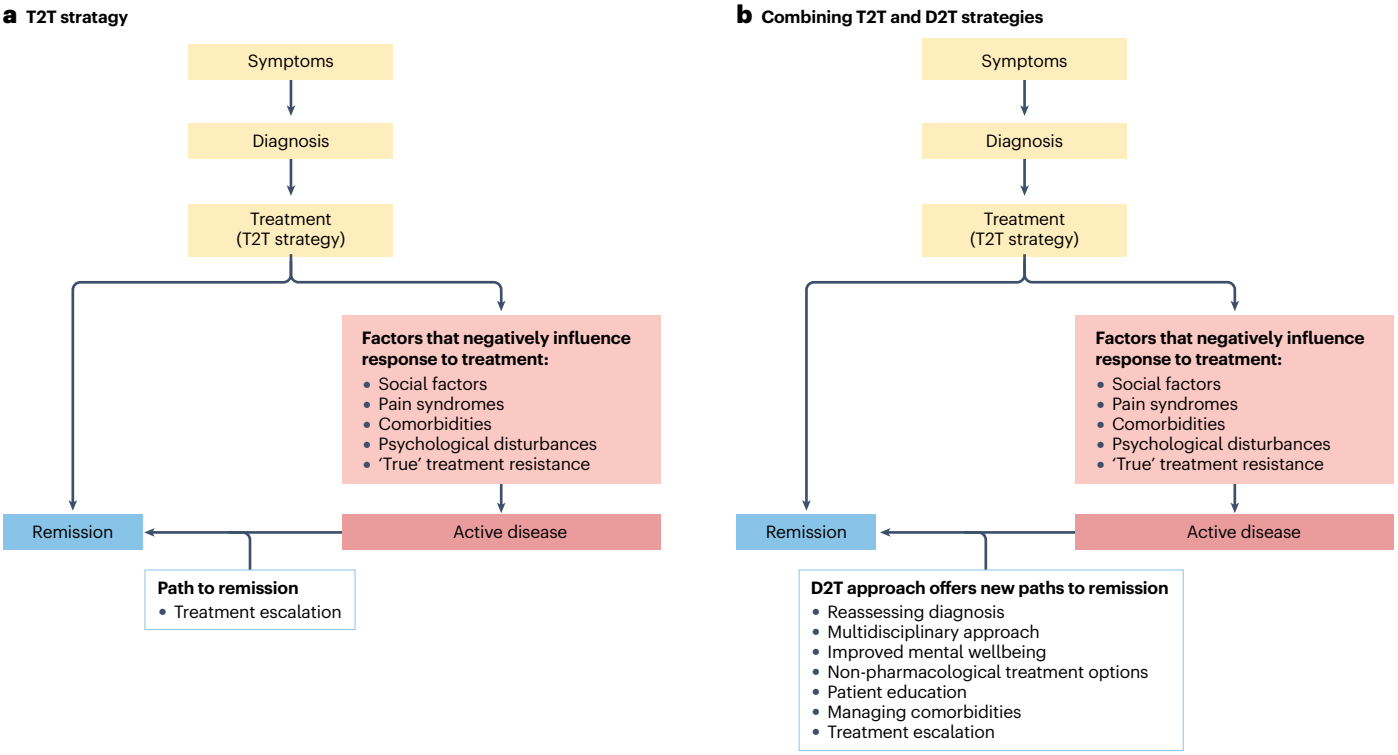

Fig. 3 | Difficult-to-treat approach offers new ways to remission. The treat-to-target (T2T) strategy has been a major advance in rheumatoid arthritis care, establishing a standardized and effective pathway wherein many patients can achieve remission through timely treatment strategies and systematic follow-up. However, remission is still not universally achievable. Patients might deviate from this straight road owing to multiple and interrelated factors, including diagnostic delay, misclassification, heterogeneous disease biology, comorbidities, treatment adherence, psychosocial and pain-related issues and health system barriers. **a**, In the conventional approach, many patients are often managed through repeated therapeutic escalation; however, escalation alone is not always sufficient, leaving many with persistently active disease. **b**, The D2T approach reframes the patient journey by addressing this complexity through a comprehensive, individualized patient assessment, including diagnosis reassessment, comorbidity control, multidisciplinary care, patient education, mental health support and non-pharmacological interventions. By offering multiple alternative routes to remission or low disease activity, this paradigm represents a step towards truly personalized medicine.

sustained pain or psychosocial burden and systematically mapping these factors can help with disease management. In that sense, the D2T concept inherently incorporates ideas typically associated with precision medicine, highlighting that each patient with D2T-RA has a unique biological and personal story that must be understood to achieve effective treatment. Precision medicine refers to an innovative, evidence-based treatment approach in which the genomic, environmental and lifestyle information guides decisions related to patient management[5,6]. For RA, precision medicine involves identifying molecular and clinical subgroups within the context of what is currently perceived as a single disease[20,51,52].

The first step towards personalization would be proper patient stratification. RA is probably heterogeneous from a pathological perspective[28,52]. Although clinical parameters, such as disease duration or autoantibody status, remain important reference points, even with broader patient profiling that includes the assessment of fatigue, sleep quality, physical functioning or psychosocial distress, these parameters cannot clearly describe the variability in disease course and response to treatment[51]. Therefore, focusing on cellular, molecular and functional phenotyping related to tissue-specific processes in peripheral blood, the joints and even the brain became a central aim to identify different pathophysiological mechanisms that might contribute to symptom persistence[16,23–25,27–31,52]. Notably, even though some biomarkers seem to be promising in research settings[53,54], none has yet demonstrated a consistent, clinically meaningful predictive effect[55–57]. However, these multidomain evaluations bring the field closer to understanding the complex role of inflammatory, neural and behavioural factors in disease pathophysiology, which together with future studies could potentially provide novel biomarkers that might be useful for stratification or predicting response to treatment. Moreover, these findings highlight the notion that managing RA effectively would potentially require therapy that mainly targets the most dominant driving factors in patients with refractory disease[58].

Another important aspect of precision medicine involves novel data-driven approaches aimed at predicting disease trajectories and response to treatment. Approaches based on the integration of clinical and laboratory data obtained from registries and electronic health record systems have shown an ability to predict disease outcomes[59–63]. In a 2025 study, the effectiveness of machine-learning algorithms was shown in this clinically highly heterogeneous D2T population. Several clinical factors were identified, including disease activity measures, patient-reported outcomes and treatment duration, as key early

predictors of transition to a D2T state[64]. Importantly, in another study, an externally validated multivariable prediction model identified patient-reported outcomes (such as functional status, pain and fatigue) and other disease-related factors as being among the top predictors of progression to D2T-RA[65]. However, in a large registry-based study, younger age at onset, high autoantibody titre and comorbidities were also shown to be possible predictors of D2T-RA[66]. Although these computational methods are currently present only in research settings with a rather modest predictive performance, requiring robust validation and further methodological optimization, they point towards a future in which data-driven insights derived from real-world patient populations could guide therapeutic decision-making at the individual level.

Although patient management according to the T2T strategy requires frequent patient visits, patients cannot be continuously monitored. However, digital health monitoring tools, another emerging pillar of personalized medicine (including in rheumatology), also provide details about the disease course, which are otherwise missed between patient appointments. Health-tracking devices, including smartphone applications for patient-reported outcomes or wearable devices that continuously monitor vital parameters and record data regarding daily activity or sleep quality, are valuable tools in the assessment of the everyday functioning of patients[6]. Although telehealth methods cannot replace in-person visits and proper disease monitoring, evidence from randomized controlled trials and systematic reviews suggests beneficial effects of selected digital methods, but the overall evidence remains heterogeneous[67,68]. For example, the results of a study in which application-based daily symptom tracking was used show that this method can be useful in predicting RA flares. This finding suggests that integrating self-monitoring into everyday clinical practice not only enriches the clinical data by providing more details of the patient-perceived disease course, but might also be beneficial in motivating patients to take an active role in their disease management and in improving patient–provider connections[69]. In a randomized controlled trial, connected monitoring via a smartphone application reduced the number of in-person visits and was associated with improved quality of life[70]. These novel approaches might hold the key to capturing the subtle fluctuations in disease activity that conventional follow-ups might miss. In addition, the integration of this multidomain information into routine care could provide an opportunity for a nearly real-time treatment adaptation in the future, but more robust evidence is needed before considering implementation.

The field of precision medicine is rapidly growing as increasing amounts of data become accessible. Although individual heterogeneity is important for understanding disease mechanisms more thoroughly, the real progress in this field will potentially depend on how effectively findings from clinical, molecular and digital domains can be integrated and inform clinical decisions. Bringing these different layers together is what transforms isolated findings into a more meaningful insight, providing a more flexible and comprehensive way of understanding not only illness-related pathomechanisms but also how disease activity changes over time and how patients respond to treatment[6,71].

Although precision medicine holds great promise, the population-wide implementation of this approach in everyday rheumatology still faces major difficulties owing to the requirement of time, specialized infrastructure and substantial financial resources, which are not always provided in routine care. However, this challenge also raises a more practical consideration of the need for every patient to receive personalized treatment. At present, the combination of novel therapeutics and the T2T strategy already enables many individuals to achieve remission, demonstrating the strength of a structured, standardized approach[72]. What the D2T framework adds is not a rejection of standardization but its refinement, by helping to identify those patients who do not follow the usual trajectory and who might genuinely benefit from deeper, mechanism-based evaluation. In this way, D2T bridges the gap between population level strategies and individual precision, ensuring that personalization is applied to those patients who need it most, rather than as a universal expectation.

Conclusion

Although T2T provides a focused and structured approach to the management of RA, failure to reach the predefined treatment goals despite appropriate adherence to the guideline-recommended algorithm might indicate a more complex, D2T disease trajectory. Recognizing contributing factors can substantially improve the quality of disease management and long-term outcomes. Bringing the D2T perspective into T2T practice, especially in the early phase of the disease with a broader perspective, can help to avoid unnecessary treatment escalation, consequently reducing the risk of overtreatment and supporting more personalized, appropriate care. The D2T framework, perhaps unintentionally, has opened the door to the possibility of personalized medicine in RA. Overall, these insights suggest that uniform success requires individualized understanding, not by replacing the T2T approach, but by evolving it towards a flexible, patient-centred model.

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Perspective

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Neurodevelopmental comorbidities in juvenile systemic autoimmune and autoinflammatory diseases

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Abstract

Neurodevelopmental disorders affect a substantial proportion of children and represent a major public health challenge worldwide. Emerging evidence highlights complex interactions among genetic, environmental and immune factors — particularly during the critical window of neurodevelopmental vulnerability. These insights raise the possibility that children with juvenile systemic autoimmune and autoinflammatory diseases are at an increased risk of developing neurodevelopmental disorders. Early onset and delayed treatment of these autoimmune and autoinflammatory diseases seem to increase this vulnerability. Growing awareness of these associations is transforming paediatric rheumatology, highlighting the need for early screening, multidisciplinary management, and personalized interventions that target both inflammatory disease and neurodevelopment. International research collaborations, biomarker discovery and long-term follow-up are crucial for closing knowledge gaps and subsequently advancing care and outcomes. Recognizing and tackling neurodevelopmental disorders as frequent comorbidities of juvenile systemic autoimmune and autoinflammatory diseases is vital for improving educational attainment, psychosocial wellbeing and lifelong quality of life in children with chronic inflammatory conditions.

Sections

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Introduction

Neurodevelopmental disorders (NDDs), such as autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), specific learning disorders, intellectual disability and developmental coordination disorder are major public health challenges, affecting 10% of children worldwide[1]. These disorders are shaped by a complex interplay of genetic and environmental factors, encompassing immunological triggers. Strikingly, emerging evidence suggests that the immune system not only defends against pathogens but also has a critical role in neurodevelopment[2]. Despite breakthroughs since the 2000s, the mechanistic interaction between physiological brain development and immunity remains incompletely understood and is an active area of investigation[3]. New mechanistic studies reveal that immune mediators, including cytokines[4] and activated microglia[5], have essential physiological roles in neuronal migration, synaptic pruning, axonal pathfinding and myelination[6–10] (Table 1). Conversely, neurons and glial cells express immune-related receptors and can influence systemic immune responses[11,12]. Thus, early-life immune dysregulation might disrupt these tightly regulated processes, potentially resulting in neurodevelopmental alterations[13], positioning immune dysregulation as an important risk factor for NDDs[13]. Consequently, the interaction between systemic immune system activation and neurodevelopment is an area of growing interest in paediatric rheumatology.

Juvenile systemic autoimmune and autoinflammatory diseases are characterized by recurrent or chronic systemic inflammation and, in some cases, specific neuroinflammatory involvement[14,15] (Supplementary Table 1). Against this backdrop, awareness is growing that children with systemic autoimmune or autoinflammatory diseases face increased neurodevelopmental vulnerability. Clinical observations, supported by recent epidemiological studies in the early 2020s, have documented a higher prevalence of NDDs in this population than in the general paediatric population[16]. However, substantial variability across these diseases (driven by differences in age at onset, systemic disease severity and timing of treatment) continue to hinder definitive conclusions and the formulation of evidence-based follow-up and treatment strategies. Nevertheless, this emerging knowledge underscores the need to integrate neurodevelopmental considerations into future clinical guidelines.

Paediatric rheumatologists must now integrate the nuances of these associations into their daily practice for several key reasons. First, advances in neuroimmunology (over three decades) have clearly demonstrated that systemic inflammation and neuroinflammation can affect brain maturation and connectivity[17], providing plausible biological pathways linking juvenile systemic autoimmune and autoinflammatory diseases to NDDs — particularly in the case of chronic neuroinflammation or systemic immune dysregulation. Second,

Table 1 | Role of immune factors in neurodevelopment and associated juvenile autoimmune and autoinflammatory diseases

Immune mediator	Receptor expression	Effects on cells	Effects on synapse	Associated diseases	Refs.
IL-1β	IL-1β receptor expressed on astrocytes, neurons and microglia	Promotes astrocytosis and disrupts BBB development; promotes neuronal differentiation, migration and neurite outgrowth; enhances pruning by microglia	Inhibits synaptic plasticity; promotes NMDA receptor-mediated excitatory signalling	Inflammasomopathies and systemic JIA	118–123
IL-6	IL-6 receptor expressed on astrocytes, neurons and microglia	Promotes the differentiation and proliferation of neural stem cells	Alters cortical layering and increases glutamatergic neurotransmission and brain connectivity	Inflammasomopathies, systemic JIA, DADA2 and Behçet disease	48,124,125
IL-17A	IL-17A receptor expressed on astrocytes, neurons, microglia and neural stem cells	Promotes microglial activation	Increases the frequency of excitatory postsynaptic signalling	Inflammasomopathies and CRMO	8,45, 126–128
IL-18	IL-18 receptor expressed on astrocytes, neurons and microglia	Not reported	Not reported	Inflammasomopathies and systemic JIA	129
TNF	TNF receptor expressed on astrocytes, neurons, microglia and oligodendrocytes	Inhibits cortical migration, neurite elongation and neurite branching; promotes microglial activation	Inhibits synaptic plasticity and GABA signalling; promotes AMPA and NMDA excitatory signalling	Relopathies, JIA and DADA2	130–133
IFNα	IFNα receptor expressed on astrocytes, neurons, microglia, oligodendrocytes and neural stem cells	Promotes microglial activation	Promotes synaptic pruning	Type I interferonopathies, juvenile SLE, DADA2 and JDM	134–136
IFNγ	IFNγ receptor expressed on astrocytes, neurons, microglia and oligodendrocytes	Promotes neurite outgrowth; promotes stimulation and differentiation of neural stem cells	Reduces brain connectivity; increases GABA activity	MAS associated with systemic JIA or juvenile SLE	6,137–142
Complement	Complement receptors expressed on astrocytes, neurons, microglia and oligodendrocytes	Inhibits neuron migration; inhibits proliferation of neural stem cells (via C3aR); promotes proliferation and differentiation of neural stem cells (via C5aR1)	Promotes prenatal and postnatal synaptic pruning	Juvenile SLE and type I interferonopathies	143–146

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BBB, blood–brain barrier; CRMO, chronic recurrent multifocal osteomyelitis; DADA2, deficiency of adenosine deaminase 2; GABA, γ-aminobutyric acid; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MAS, macrophagic activation syndrome; NMDA, *N*-methyl-D-aspartate; SLE, systemic lupus erythematosus.

retrospective epidemiological studies have shown a higher-than-expected prevalence of NDDs (including ADHD, autism spectrum disorder and specific learning disorders) in children with systemic autoimmune and autoinflammatory diseases[16]. Third, early identification through systematic screening is crucial to improving outcomes. Finally, multidisciplinary, coordinated management of NDDs in children with chronic inflammatory conditions is essential for optimizing educational and psychosocial trajectories[18].

In this Perspective, we examine the mechanisms by which the immune system influences neurodevelopment, incorporating clinical data relevant to juvenile systemic autoimmune and autoinflammatory diseases. We also explore the latest data on the prevalence of NDDs in these conditions, discuss relevant protective and risk factors, and outline practical strategies for intervention. Finally, we propose future research priorities aimed at closing knowledge gaps and informing approaches to mitigate the NDD risk in this patient population.

Immune crosstalk in neurodevelopmental disorders

NDDs are a heterogeneous group of childhood-onset conditions characterized by impairments in cognition, communication, behaviour and motor function[1]. The most common diagnostic categories, ranked by prevalence, include specific learning disorders (8% of children), developmental coordination disorder (5%), ADHD (5%), autism spectrum disorder (1–2%) and intellectual disability (1–2%)[1]. Notably, most children present with comorbidities that overlap between these categories[19]. Although greater awareness, improved diagnostic accuracy and wider screening have increased case detection, epidemiological studies suggest that the incidence of NDD continues to rise independently of these factors[20]. From a societal perspective, the growing prevalence of NDDs is a notable global health concern[21]. Indeed, these conditions are now among the leading causes of disability-adjusted life years in children and adolescents, resulting in a range of consequences for educational attainment, employment, mental health and quality of life[22,23]. The economic burden of NDDs is substantial, encompassing direct medical costs, such as specialized care, therapeutic interventions and long-term support, as well as indirect costs including loss of work abilities, caregiver burden and reduced incomes[18]. Despite improved recognition of NDDs, access to early diagnostic services and interventions remain uneven among patients, particularly for children with co-occurring medical conditions[24,25].

The aetiology of NDDs reflects a complex interplay of gene and environment factors[26]. Twin and family studies consistently demonstrate high heritability[27], whereas large-scale genetic studies reveal polygenic architectures involving hundreds of common and rare variants that converge on neurodevelopmental and synaptic pathways[28,29]. Notably, several of these genetic variants involve immune-related genes, including those involved in cytokine signalling (such as *IL1R1* and *IL6R*), the major histocompatibility complex and microglial regulation[30], suggesting shared genetic vulnerabilities between NDDs and immune-mediated disorders. Nevertheless, genetic predisposition alone cannot fully explain the observed phenotypic diversity, underscoring the importance of external influences.

Environmental events, particularly those occurring during sensitive stages of development such as the prenatal and perinatal periods, are now recognized as important contributors[31]. Indeed, prenatal factors such as maternal infections, metabolic disorders (such as gestational diabetes and obesity) and advanced parental age have all been associated with an increased risk of NDDs[32]. Furthermore, perinatal factors, such as prematurity, intrauterine growth retardation and neonatal complications (including hypoxia and sepsis) further increase the risk of NDD occurrence, especially in genetically predisposed individuals[32,33]. Among these environmental triggers, immune-mediated factors are of particular importance. Indeed, the intricate interplay between the immune and nervous systems starts in the early stages of fetal development and continues for several years after birth, shaping the development and function of the brain during a critical window of neurodevelopmental vulnerability (Fig. 1).

First, during the prenatal period, maternal immune activation in pregnancy is associated with an increased risk of NDDs in offspring[34,35]. In particular, epidemiological studies have extensively demonstrated that maternal immune activation — induced by maternal infections or maternal immune-mediated disorders — increases the risk of NDD in offspring[36–39]. Animal models have replicated these findings using viral or bacterial mimetics[40,41], showing that maternal immune activation induces an intrauterine pro-inflammatory environment characterized by elevated levels of cytokines, particularly IL-6[42,43] and IL-17A[44]. Notably, IL-17A can cross the placenta, bind to fetal cortical neurons[45] and disrupt brain proteostasis[46], brain maturation[47] and connectivity[48], ultimately leading to NDD-like phenotypes.

Second, during the perinatal period, prematurity (defined as any birth before 37 weeks of gestation) affects around 10% of newborns worldwide, and remains the leading cause of childhood morbidity and long-term health complications in children under 5 years of age[49,50]. Prematurity is strongly associated with an increased risk of NDDs. Large epidemiological studies have shown that the more premature a child is at birth, the greater the risk of developing an NDD[51]. This association cannot be explained solely by genetic factors, but seems to be directly linked to inflammatory processes triggered by prematurity that affect the developing brain. Both experimental and clinical studies in the context of prematurity have revealed elevated systemic and cerebral pro-inflammatory cytokines[52], along with microglial activation[53], which could impair neuronal migration, synaptogenesis and myelination[54], and ultimately could lead to altered brain connectivity and function[55–57]. Accordingly, preterm infants often exhibit markers of systemic and central nervous system inflammation, which correlate with long-term outcomes of NDDs[58].

Third, although the early postnatal period represents a major window for brain development, risk factors for NDDs during this timeline have only recently gained attention. Synaptogenesis and synaptic pruning are among the most frequently studied processes shaping postnatal brain development. Pruning is a physiological mechanism in which microglia have a central role by engulfing and eliminating weak or unnecessary synapses through phagocytosis, thereby supporting neural plasticity[59]. This process is tightly modulated by immune signalling pathways, including the complement system[60,61] and various cytokines[62,63]. Thus, chronic activation of microglia might result in abnormal synaptic refinement and induce NDD development[64]. Interestingly, adverse childhood events have also been associated with an increased incidence of NDD[65]. This association could partly be explained by adverse childhood event-induced hyperactivation of the hypothalamic–pituitary–adrenal stress axis, resulting in cortisol dysregulation and chronic systemic inflammation[66,67]. Notably, adverse childhood events are also linked to a higher incidence of various autoimmune diseases later in life[68,69]. Consequently, several studies have found an association between early childhood infections and increased incidence of NDDs[70–72]. Given that systemic autoimmune and autoinflammatory diseases induce immune-mediated flares or

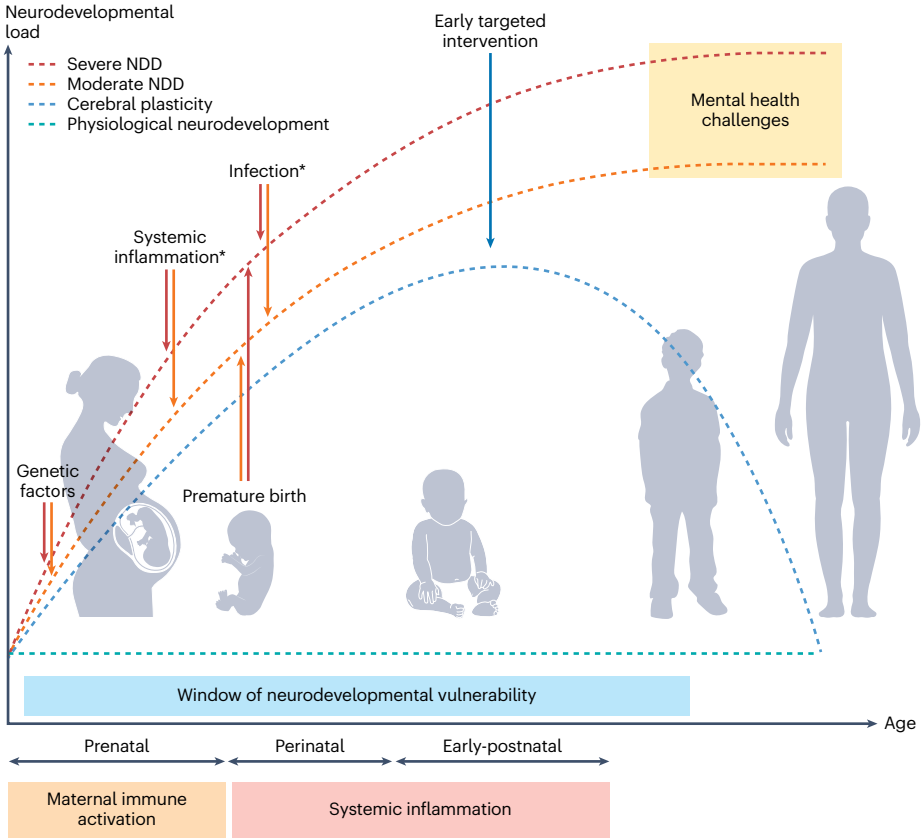

Fig. 1 | Immune influences on critical stages of neurodevelopment. The immune system could modify neurodevelopment at critical stages of brain maturation, contributing to neurodevelopmental disorders (NDDs). Orange and red arrows represent multiple-hit factors that increase neurodevelopmental load in patients with juvenile systemic autoimmune and autoinflammatory diseases, including genetic predisposition, maternal or patient infections, premature birth and systemic inflammation. The green dotted line represents the physiological neurodevelopmental trajectory; the blue dotted curve indicates cerebral plasticity; the orange and red dotted curves depict moderate and severe NDD trajectories, respectively. The blue arrow denotes an early targeted intervention, such as inflammatory disease-modifying treatment, specific psychiatric medication (for example, psychostimulants) and NDD-targeted management (including speech therapy, motor rehabilitation or remediation, psychoeducation programmes and school environment adaptations). *Infection and systemic inflammation can occur repeatedly throughout development. For instance, infections can arise in utero as well as postnatally, and systemic inflammation can also be present before or after birth and recur across multiple episodes.

chronic inflammation in early childhood, these conditions might interfere with normal brain development. Collectively, these mechanistic insights underscore the importance of adopting a neurodevelopmental approach in paediatric rheumatology.

Clinical correlations

Emerging evidence suggests that, beyond conditions directly characterized by neuroinflammation, several autoimmune and autoinflammatory diseases are associated with an increased prevalence of NDDs compared with the general population. These observations emphasize the unmet need to identify specific at-risk subgroups and clarify contributing risk factors, as well implement systematic NDD screening alongside standardized care pathways in routine paediatric rheumatology practice.

Prevalence of neurodevelopmental disorders

Neuroinflammation has been documented in juvenile systemic autoimmune and autoinflammatory diseases and might induce developmental delay or inflammatory neuropsychiatric features[15,73]. Indeed, central nervous system inflammation has been reported in several autoinflammatory diseases, such as type I interferonopathies[14,15] — Aicardi–Goutières syndrome being a classic example — and NLRP3-related disorders[74], including chronic infantile neurological cutaneous and articular syndrome. Similar findings have also been observed in autoimmune diseases, such as juvenile neuropsychiatric systemic lupus erythematosus[14,15,74,75] (Supplementary Table 1). Despite evidence of neuroinflammation and reported neuropsychiatric features in autoimmune and autoinflammatory disease, studies specifically investigating NDD comorbidities in juvenile patients remain scarce (Table 2).

In autoinflammatory diseases, pooled analyses suggest that the prevalence of cognitive impairment and development delay is approximately 13% and 7%, respectively, compared with 1–2% for intellectual disability in the general population[76]. Most studies have focused on familial Mediterranean fever (FMF), reporting increased features of inattention and hyperactivity[77,78]. Overall, the prevalence of ADHD comorbidity has been estimated at around 30% of patients[79,80], representing a sixfold increase compared with the general population[81]. One study further reported developmental delay in 32% of patients with FMF (compared with 1–2% in the general population), along with ADHD in 27.9% and specific learning disorders in 24% of patients, compared with 5% and 8%, respectively, in the general population[79,82]. Importantly, the presence of comorbid NDD is linked to poorer adherence to FMF treatment, emphasizing the need for early screening and management[79,80].

Research on NDDs in juvenile autoimmune diseases is limited. In juvenile systemic lupus erythematosus, studies report cognitive impairment in 40–60% of patients[83–86], with language and mathematics being the most affected learning domains[85,86]. These cognitive features — although not strictly NDDs — are observed in up to 82% of patients with acute, active juvenile neuropsychiatric systemic lupus erythematosus and persist for 12 months after disease onset, even when the disease becomes inactive[73]. This persistence is associated with higher Systemic Lupus International Collaborating Clinics (SLICC)/ACR

Table 2 | Neurodevelopmental disorders in juvenile autoimmune and autoinflammatory diseases

Study	Region	Disease	Number	Age (years)	Assessment	Key findings	Notes
Al-Mayouf et al.[76]	10 Arab centres	SAIDs (pooled)	144	Median 2.5 (range 0.1–13)	ADDI	Cognitive impairment (13% of patients) and developmental delay (7% of patients)	Pooled diseases: CRMO (34 patients), LACC1 (23 patients), PFAPA (18 patients), EOS (14 patients), CAPS (12 patients), TRAPS (12 patients), MKD (12 patients), Majeed syndrome (6 patients) and others (CANDLE, PAPA, Blau syndrome, SIFD, undifferentiated: 13 patients)
Özer et al.[78]	Turkey	FMF	52	Mean 11.8±2.8	CNS vital signs	Patients demonstrated impairment in complex attention, verbal or visual memory, executive function and processing speed when compared with healthy individuals	Mean disease duration: 5.58±2.9 years
Durcan et al.[77]	Turkey	FMF	271	NA	SDQ	Increased symptoms of inattention or hyperactivity symptoms when compared with healthy individuals	Symptoms more severe when disease onset occurred before 6 years of age
Lavi et al.[80]	Israel	FMF	124	NA	DSM-5	ADHD diagnosed in 32.8% of patients (risk four to six times higher)	ADHD associated with poor adherence to treatment
Biro et al.[79]	Israel	FMF	111	Mean 11.6±4.7	Clinical interview	Developmental delay (32.4% of patients), ADHD (27.9% of patients) and learning disabilites (24.3% of patients)	ADHD (OR 2.59) and learning disabilities (OR 2.7) associated with poor adherence
Papero et al.[83]	USA	Juvenile SLE	21	Mean 15.8	Neuropsychological evaluation	Lower cognitive status compared with patients with juvenile rheumatoid arthritis	Mean disease duration of 2.4 years; longer disease duration associated with lower cognitive status
dos Santos et al.[86]	Brazil	Juvenile SLE	36	Mean 15.4±4.7	WISC III and WAIS III	Cognitive impairment in 58% of patients, most commonly affecting verbal abilities	Mean age onset: 11.2±2 years
Frittoli et al.[85]	Brazil	Juvenile SLE	41	Mean 14.5±2.84	ACR criteria	Cognitive dysfunction in 41.5% of patients, mainly affecting mathematical performance	Not applicable
Aliyev et al.[84]	Turkey	Juvenile SLE	34	Median 17 (range 12–21)	WISC-IV	Lower perceptual reasoning index compared with healthy indivduals	Not applicable
Feldmann et al.[88]	Germany	Systemic JIA	31	Mean 12.5±4.3	WISC	No significant difference in intelligence quotient, memory and learning, attention and fine motor scores	Mean disease duration: 6.2±3.5 years
Ward et al.[89]	USA	JIA	68	Mean 8.6±1.9	Wechsler Intelligence Scale	No significant differences in cognitive outcomes	Subtypes: oligoarticular (32 patients), polyarticular (23 patients), systemic (7 patients) and others (6 patients)
Granjon et al.[90]	France	JIA	21	Mean 11.01±3.3	Raven's Progressive Matrices and NEPSY-II	No significant differences in cognitive outcomes	Subtypes: oligoarticular (7 patients), polyarticular (8 patients) and enthesitis-related (6 patients); mean disease duration: 4.82±2.69 years
Kyllönen et al.[92]	Finland	JIA	4180	Mean 8.3±4.8	ICD-10	Increased childhood behavioural and emotional disorders (OR 1.47–1.91) and disorders of psychological development (OR 1.17–1.80) when compared with healthy individuals	Early childhood onset associated with higher rates of behavioural disorders; trend for higher comorbitity in female patients
Haşlak et al.[93]	Turkey	JIA	459	Median 2.9 (1.5–21)	Clinical interview	ADHD diagnosed in 7.6% of patients	Subtypes: oligoarticular (222 patients), polyarticular (74 patients), systemic (57 patients), enthesitis-related (79 patients) and psoriatic (27 patients)

Table 2 (continued) | Neurodevelopmental disorders in juvenile autoimmune and autoinflammatory diseases

Study	Region	Disease	Number	Age (years)	Assessment	Key findings	Notes
Lupini et al.[94]	USA	JIA	365	Not reported	Clinical interview	Increased frequency of ADHD (OR 1.9) compared with children with T1D	Not applicable
Tezer et al.[91]	Turkey	JIA	79	Range 8–17	CNS vital signs	Significant cognitive deficits observed compared with healthy individuals	All JIA subtypes except oligoarthritis associated with an increased risk of neurocognitive impairments

ADDI, Autoinflammatory Disease Damage Index; ADHD, attention deficit hyperactivity disorder; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPS, cryopyrin-associated periodic syndromes; CNS, central nervous system; CRMO, chronic recurrent multifocal osteomyelitis; EOS, early-onset sarcoidosis; FMF, familial Mediterranean fever; ICD, International Classification of Diseases; JIA, juvenile idiopathic arthritis; LACC1, LACC1-mediated monogenic disorder; MKD, mevalonate kinase deficiency; NA, not available; NEPSY, A Developmental Neuropsychological Assessment; OR, odds ratio; PAPA, pyogenic arthritis, pyoderma gangrenosum; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; SAIDs, systemic autoinflammatory diseases; SDQ, Strengths and Difficulties Questionnaire; SIFD, sideroblastic anaemia with B cell immunodeficiency, periodic fevers and developmental delay; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; TRAPS, TNF-receptor-associated periodic syndrome; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale.

damage index scores compared with patients with juvenile systemic lupus erythematosus without neuropsychiatric involvement[87]. The underlying mechanisms remain unclear; persistent low-grade neuroinflammation might have a role, but general systemic activity, even in the absence of underlying neuroinflammation, could contribute to these cognitive features.

The literature on juvenile idiopathic arthritis (JIA) and NDDs remains inconsistent. Although some studies report no difference in NDD prevalence compared with the general population[88–90], others describe increased cognitive deficits[91] or a modest elevation in overall risk of NDDs (odds ratio 1.17–1.81)[92]. Notably, ADHD seems more frequent among patients with JIA, with prevalence estimates ranging from 7.5 to 9%, compared with 5% in the general population[93–96]. These discrepancies might reflect heterogeneity in systemic inflammation across subgroups of JIA and point to additional risk factors that modulate the interplay between juvenile autoimmune and autoinflammatory diseases and neurodevelopmental outcomes.

Finally, data on the prevalence and systematic characterization of NDDs in conditions such as periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome, mevalonate kinase deficiency or other rarer juvenile systemic autoinflammatory diseases are lacking. Furthermore, severe autoinflammatory diseases that can cause central nervous system sequelae are often associated with severe and global neurodevelopmental delay, making dimensional evaluation of specific NDD phenotypes particularly challenging[97].

Risk factors for neurodevelopmental disorders

The premise that inflammation directly alters brain development suggests that the subtype of autoimmune or autoinflammatory disease could modulate the onset of NDDs. JIA provides a relevant clinical paradigm to explore this hypothesis. JIA encompasses several distinct clinical forms. The classification of JIA has evolved over time, and currently includes various major subtypes: systemic JIA (Still's disease), rheumatoid factor-positive polyarticular JIA, ANA-positive oligoarticular JIA, enthesitis-related or spondylitis-related arthritis and other unclassified JIA[98,99]. This heterogeneity reflects different pathophysiological mechanisms, disease courses and prognosis. Notably, oligoarticular JIA, which is characterized by minimal systemic inflammation, has not been associated with an increased risk of NDD compared with other JIA subtypes[16,91]. This observation supports the hypothesis that a threshold level of inflammation might be necessary to perturb normal brain development. However, other confounding factors could contribute to this association, including variations in systemic inflammatory burden, chronic pain[100], sleep disturbances, psychosocial stressors or treatment-related adverse effects, especially corticosteroid exposure[101].

The timing of inflammation onset might affect neurodevelopmental trajectories by coinciding with periods of heightened developmental vulnerability. For example, FMF beginning before 6 years of age has been associated with more severe ADHD features than FMF beginning after this age[77]. Across juvenile systemic autoimmune and autoinflammatory diseases, onset before 3.5 years is associated with an ADHD prevalence of 45% (a ninefold increase compared with the general population), whereas onset between 3.5 and 11 years was associated with a prevalence of 26% (a fivefold increase)[16]. Onset after 11 years was associated with a similar prevalence to the general population[16]. However, these results, derived from retrospective epidemiological studies, require prospective validation to mitigate bias. If a critical window of immune vulnerability does exist, timely medical intervention could reduce the impact of inflammation on neurodevelopment. Indeed, in early-onset autoimmune or autoinflammatory diseases (before the age of 11), the sooner the disease-modifying treatment is started the better: ADHD prevalence was 20% among patients treated within 2 months of disease onset, compared with 45% when treatment was delayed[16]. These observations suggest that early treatment might attenuate the neurodevelopmental consequences of systemic inflammation, paving the way for preventive treatment. However, delayed treatment might also reflect greater disease severity, diagnostic delay or health-system disparities. Thus, prospective studies are needed to more accurately assess these potential risk factors.

Beyond the direct effects of inflammation intensity and timing, external factors could also modulate the impact of autoinflammatory or autoimmune disease on neurodevelopment. Perinatal events are among the most well-established risk factors for NDDs. For example, the combination of low birthweight (defined as below the 10th percentile) and a systemic autoimmune or autoinflammatory disease was associated with ADHD onset with 71% accuracy[102]. These findings suggest that low birth parameters predispose the brain to neurodevelopmental vulnerability, with systemic inflammation acting as a secondary trigger for clinical manifestation. Evidence also points to gender bias: whereas NDDs are generally more prevalent in boys in the general population, girls seem disproportionately affected in the context of systemic autoimmune or autoinflammatory disease[95]. Genetic, hormonal or sociocultural factors could be involved and are

worth further investigation[103,104]. Of course, the relative contribution of each above factor requires clarification through additional studies.

Screening and management of neurodevelopmental disorders

Given the high prevalence and notable impact of NDDs — often reported by parents and caregivers — we advocate for systematic screening in children with systemic autoimmune or autoinflammatory diseases (Fig. 2). Screening should follow a structured sequential approach, beginning with guided questions during routine outpatient visits and the use of validated questionnaires that are easy to administer, with more in-depth evaluations by specialists being undertaken when necessary.

Initial screening should begin with careful assessment of family medical history (particularly for NDDs), and repeated inquiries about developmental milestones such as timing of first words (typically around 12 months) and first steps (usually between 12 and 18 months). Clinicians should also pay close attention to reports of delays, regressions of previous acquired skills or early difficulties with pre-reading, writing and fine motor skills. Subsequent steps in paediatric rheumatology clinics should include vigilance for any school-related learning difficulty and the use of brief (5–15 min), standardized questionnaires,

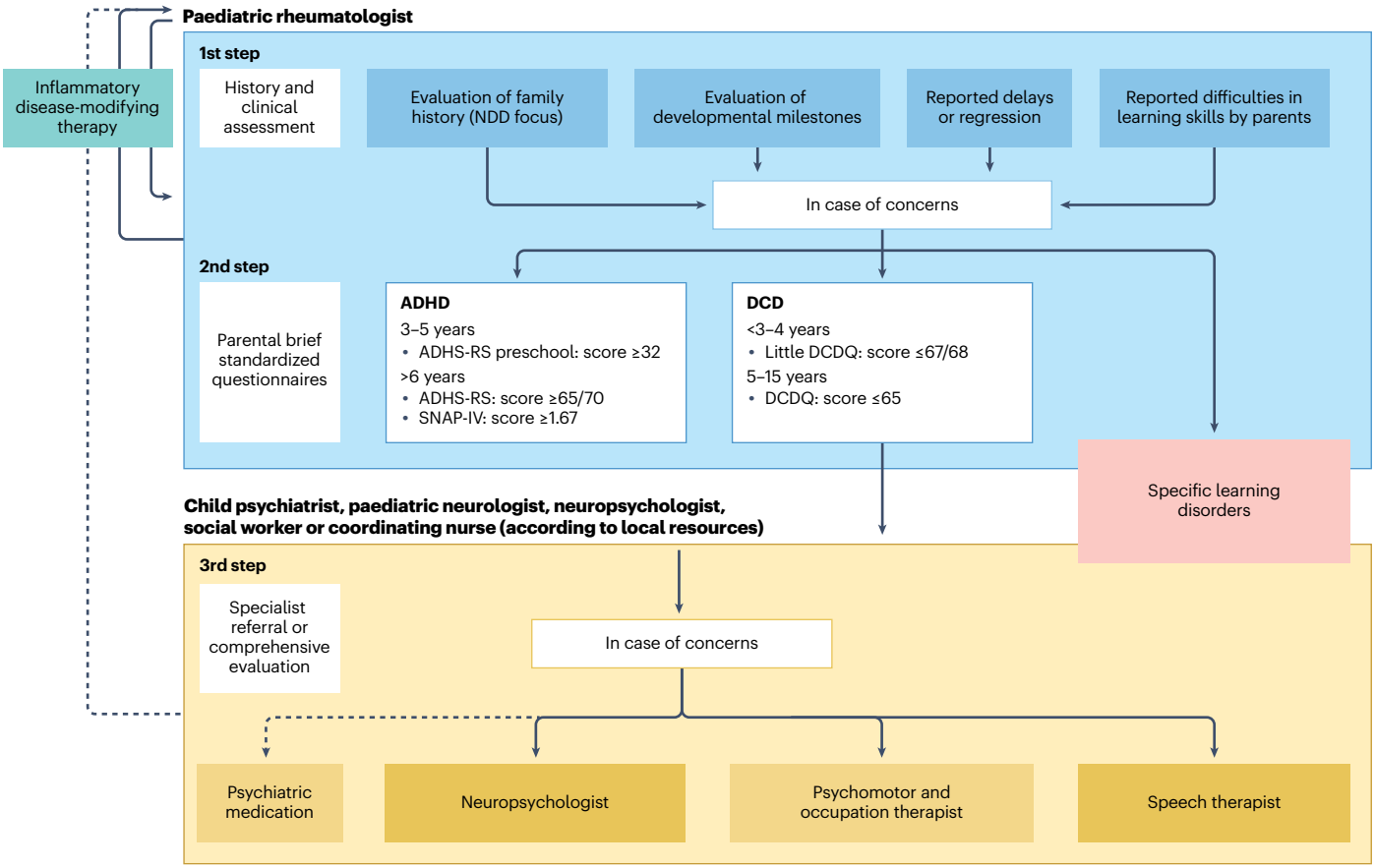

Fig. 2 | Stepwise multidisciplinary screening and care for neurodevelopmental disorders in juvenile systemic autoimmune and autoinflammatory diseases. Early detection of neurodevelopmental disorders (NDDs) in juvenile systemic autoimmune and autoinflammatory diseases requires a structured process that integrates clinical assessment, standardized screening tools and specialist evaluation. In particular, clinicians should assess for the most frequent NDDs in this patient population: attention deficit hyperactivity disorder (ADHD), developmental coordination disorder (DCD) and specific learning disorders. 1st step: initial history and clinical assessment: screening should begin with a thorough evaluation of the patient's family medical history and detailed inquiries about developmental milestones, paying close attention to reports of delays, regressions and difficulties in learning skills. If concerns arise during the clinical interview, proceed to step two. 2nd step: standardized questionnaires: parents or caregivers complete brief age-specific and sex-specific questionnaires with validated cut-off scores. For ADHD: ADHD-Rating Scale (ADHD-RS) preschool version (3–5 years old), ADHD-RS (>5 years old) or SNAP-IV. For developmental coordination disorder: Little Developmental Coordination Disorder Questionnaire (DCDQ) (3–4 years old) or DCDQ (>5 years old). The scores in the figure suggest the need for further investigations. 3rd step: specialist referral or comprehensive evaluation. If questionnaires or parental reports raise concerns, refer to specialists, such as child psychiatrists or neurologists. These specialists coordinate neuropsychological testing (for example, Wechsler Intelligence Scale for Children) to assess cognitive domains. Low working memory and processing speed might indicate ADHD, whereas verbal subtests can reveal language impairment. Speech therapists evaluate oral and written language development and provide targeted interventions. Psychomotor or occupational therapists assess motor coordination, praxis and graphomotor skills, and might provide remediation. Thus, the child psychiatrist or neurologist establishes the diagnosis, coordinates and supervises interventions, provides parental psychoeducation, adapts the school environment and, if necessary, initiates ADHD medication. The paediatric rheumatologist should initiate inflammatory disease-modifying therapy whenever stabilization of the underlying autoimmune or autoinflammatory disease is required, including to optimize neurodevelopmental trajectories.

adapted to age, that are easy to administer and largely free of charge. These tools can be subsequently completed by parents to facilitate early identification of potential NDDs (particularly ADHD and developmental coordination disorder; Fig. 2). For preschool aged children (3–5 years), the ADHD-Rating Scale (ADHD-RS) Preschool is commonly used, whereas for older children, ADHD-RS[105] and SNAP-IV[106] are widely applied. For the ADHD-RS, scores above the 93rd percentile are considered suspicious and indicate the need for further clinical evaluation. For the SNAP-IV, the suggested cut-off averages are 1.78 for inattention, 1.44 for hyperactivity or impulsivity and 1.67 for combined ADHD. The ADHD-RS and its preschool version are proprietary instruments that usually need to be purchased or accessed via an institution; however, these questionnaires are quick to complete (5–10 min). By contrast, the SNAP-IV is freely available online, designed for parents and teachers, takes 10–15 minutes to complete and offers an easy-to-use scoring system. For motor difficulties, the Developmental Coordination Disorder Questionnaire (DCDQ)[107] and its version for children aged 3–4 years (the Little DCDQ)[108] are widely used parent-report instruments that have been validated for children aged 5–15 years, with age-specific and gender-specific cut-off scores. Completion takes 10–15 minutes and the questionnaire is free of charge.

If the results of the above questionnaires or parental reports raise any concerns — whether global or specific — the next step is a comprehensive diagnostic evaluation. Ideally, this assessment should be conducted by a psychiatrist or paediatric neurologist. However, it might be adapted to local resources and involve neuropsychologists, coordinating nurses and social workers. These professionals can also help to coordinate communication with various partners. This stage provides an opportunity to discuss the prescription of psychiatric medication (such as psychostimulant) for ADHD, when appropriate. But above all, this step can determine whether referral to additional specialists is warranted, including neuropsychologists, psychomotor or occupational therapists and speech therapists, who can refine the diagnosis and offer targeted management strategies for NDDs (Fig. 2).

This multidisciplinary, stepwise approach ensures that preliminary screening during routine clinics leads to timely and targeted specialist intervention, optimizing both neurodevelopmental and systemic disease outcomes, while supporting stabilization of the underlying autoimmune or autoinflammatory condition. Therefore, we advocate for routine, proactive and repeated assessment of NDDs as an essential part of global comprehensive paediatric rheumatology care. Although such multidisciplinary management represents an ideal standard, we acknowledge the practical challenges posed by limited clinician time, resource constraints and limited access to specialists such as child psychiatrists and neuropsychologists — particularly in rural settings. To overcome these barriers, we urge paediatric rheumatologists to prioritize building and strengthening multidisciplinary networks with any available local NDD specialists, mirroring the successful efforts made over the past decade to integrate mental health into holistic paediatric rheumatology care[109–112].

Future directions and research priorities

As the intersection between systemic immunity and neurodevelopment emerges as a critical frontier in both clinical practice and scientific research, reshaping the paediatric rheumatology agenda becomes imperative. Future research and routine practice should therefore address several critical priorities, ranging from epidemiological surveillance and translational biomarker discovery to the development of multidisciplinary preventive and therapeutic strategies.

Glossary

Attention deficit hyperactivity disorder
(ADHD). A neurodevelopmental disorder characterized by persistent patterns of inattention, hyperactivity and impulsivity that are inconsistent with developmental stage or age.

Autism spectrum disorder
A spectrum of neurodevelopmental disorders characterized by atypical social communication, restricted interests and repetitive behaviours.

Developmental coordination disorder
(DCD). A neurodevelopmental disorder characterized by considerable difficulties in acquiring and executing motor skills, which leads to clumsiness and problems with daily activities.

Intellectual disability
A neurodevelopmental disorder characterized by substantial limitations in intellectual functioning and adaptive behaviours, affecting reasoning, learning and everyday life skills.

Microglia
Specialized immune cells within the central nervous system that remove cellular debris and help to shape neural circuits during development.

Neurodevelopment
The longitudinal process through which the brain and nervous system grow, organize and mature from early life into adolescence, shaping learning and behaviour.

Neurodevelopmental disorders
(NDDs). A large spectrum of disorders that disrupt the development of the brain, appearing in early childhood and affecting personal, social, academic or occupational functioning.

Specific learning disorders
Neurodevelopmental disorders that cause difficulties in acquiring and applying skills such as reading, writing and mathematics, despite having an average level of intelligence.

Synaptic pruning
A brain process involving the elimination of extra synapses, enhancing neural efficiency and supporting learning during development.

Awareness and clinical integration

The first and most immediate priority is to address neurodevelopmental risk in paediatric rheumatology. On a clinical level, achieving this goal requires a paradigm shift: systematic screening, ongoing monitoring and tailored support for neurodevelopment must become standard components of care, especially for early-onset autoimmune and autoinflammatory diseases. Paediatric rheumatologists should receive routine training to identify early signs of NDDs and to evaluate developmental trajectories and functioning across cognitive, language, motor and social–emotional domains. Additionally, strong collaboration between rheumatology, paediatric neurology and psychiatry is essential to ensure targeted, multidisciplinary interventions. Awareness campaigns should also target families: clear communication about potential neurodevelopmental vulnerabilities could lead to the earlier detection of subtle changes, as well as foster greater caregiver commitment to monitoring and recommended interventions.

Global registries and longitudinal studies

Most epidemiological studies on NDD and juvenile systemic autoimmune and autoinflammatory diseases originate from single-centre retrospective studies, which are prone to sampling bias and consequently have limited extrapolations. Furthermore, many of these studies have

been conducted in specific regions, particularly the Mediterranean basin, making it challenging to extrapolate findings to populations with different genetic, social or health care contexts. Therefore, the establishment of prospective international disease registries that explicitly include criteria for assessing neurodevelopment is an urgent research priority. These registries should be designed collaboratively by international consortia and patient associations to harmonized diagnostic definitions, standardized cognitive and behavioural assessment protocols, and consistent collection of essential demographics, pathological and developmental data — including key developmental milestones, neuropsychiatric features and educational outcomes. Tracking neurodevelopmental trajectories prospectively in children and adolescents with these diseases would enable accurate estimation of incidence and progression and help to identify high-risk clinical subgroups and additional predisposing factors. This approach would also help to clarify how interventions, such as treatment timing or disease control, influence outcomes and allow exploration of critical windows of vulnerability and resilience.

Translational research and biomarker development

Current clinical assessment tools for NDDs rely primarily on behavioural and psychometric tests, which, although essential for diagnosis, fail to capture the underlying biological–pathological mechanisms. Critical gaps remain in the availability of accessible, reliable biomarkers that can serve as early indicators of neuroinflammation or disturbed neurodevelopment in children with systemic autoimmune or autoinflammatory diseases. Promising approaches involve integrating advanced neuroimaging techniques — such as functional MRI and PET-MRI[113,114] — with peripheral and cerebrospinal fluid biomarker detection using high-dimensional inflammatory profiling[115]. Particular emphasis should be placed on identifying 'at-risk' molecular signatures to enable risk stratification, personalized monitoring and potentially preventive intervention with targeted therapies. Deep phenotyping studies that integrate multi-omics platforms with clinical and developmental endpoints are needed to unravel causal links between immune dysregulation and brain development in the context of juvenile systemic autoimmune and autoinflammatory diseases. To generate translationally relevant mechanistic insights, animal and in vitro models of systemic rheumatic diseases should include neurocognitive and behavioural phenotyping. In parallel, investigating the underlying genetic causes of monogenic autoimmune or autoinflammatory diseases might also reveal direct or indirect pathways connecting systemic inflammation with NDD development, as well as pathophysiological pathways that are completely unrelated to the immune system[14].

Long-term psychiatric outcomes and follow-up

A growing body of evidence suggests that NDDs often precede mental health challenges later in life, including anxiety disorders and depression, as well as schizophrenia and bipolar disorder[116]. In children with systemic autoimmune or autoinflammatory diseases, prolonged systemic inflammation — compounded by chronic illness, stress and the potential consequences of treatments — might exacerbate this risk (Fig. 1). Long-term, prospective cohort studies that follow patients from early childhood into adulthood are thus critical in mapping neurodevelopmental trajectories alongside psychiatric morbidity, educational attainment, social integration and quality of life. Such research should identify periods of increased vulnerability and clarify the role of cumulative disease burden and disease flares. Expanding the scope of follow-up will highlight opportunities for preventive strategies and enable timely mental health support at all stages of development, particularly at the most opportune moments.

Targeted interventions: windows of opportunity

Identifying therapeutic windows of opportunity during which targeted interventions could alter lifelong neurodevelopmental prognosis represents one of the most actionable future directions. Clarifying when and for which patients disease-modifying treatment confers the greatest neuroprotective benefit is essential. Additionally, research should focus on personalized interventions, including both pharmacological approaches (such as targeted anti-cytokine therapies, immunomodulation and psychiatric medication, for example, psychostimulants), as well as supportive approaches (including multidisciplinary neuropsychological interventions, speech and language therapy, occupational therapy and cognitive training) (Fig. 1). Another emerging area of research is the use of tissue-targeted or cell-targeted therapies that leverage advances in nanomedicine or biologic engineering to selectively modulate immune activity within the central nervous system or developmental niches[117]. Such precision approaches minimize off-target effects while optimizing neuroprotective efficacy.

Conclusions

The interplay between systemic immunity and NDD, particularly in the context of juvenile systemic autoimmune and autoinflammatory diseases, is reshaping the priorities of paediatric rheumatology. Clinical and epidemiological evidence consistently shows that children with these diseases experience higher rates of NDDs, influenced by factors such as disease subtype, age of onset, sex and perinatal history. Timing and effectiveness of disease-modifying treatments seem critical, suggesting that early intervention could substantially reduce the risk of subsequent NDD development. Given the profound medical, educational and psychosocial consequences of undiagnosed or delayed management of such conditions, integrating systematic neurodevelopmental screening into routine paediatric rheumatology practice is now essential. We advocate for a multidisciplinary, stepwise approach to assessment, ensuring timely identification and personalized management of affected children. Future advances depend on closing several knowledge and practice gaps by raising awareness among clinicians, patients, families and caregivers, developing prospective international registries, pursuing translational research and refining personalized therapeutic interventions. Ultimately, acknowledging and addressing neurodevelopmental dimensions of juvenile systemic autoimmune and autoinflammatory diseases are both a scientific imperative and a central component of holistic, patient-centred care, essential for optimizing outcomes for this vulnerable population.

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