Editorial introductions

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editors for this issue.

SECTION EDITORS

Kenneth Saag

Kenneth Saag, MD, MSc, is *Jane Knight Lowe* Professor of Medicine, Division of Clinical Immunology and Rheumatology, at the University of Alabama at Birmingham (UAB) in Birmingham, Alabama, USA and Professor of Epidemiology, at the UAB School of Public Health.

Dr Saag is a native of Chicago, and following studies in engineering at the University of Michigan, USA, he returned to Chicago for medical school and Internal Medicine Residency at Northwestern University, USA. He then traveled to the University of Iowa, USA, for his rheumatology and epidemiology training and remained on the faculty there until moving to UAB in 1998.

Dr Saag is the founding Director of the Agency for Health Care Research and Quality Deep South Center for Education and Research on Therapeutics, the UAB Center of Research Translation in Gout and Hyperuricemia, and the UAB Outcomes Research Center. He also serves as a Vice Chair for the UAB Department of Medicine. He has published over 300 peer reviewed manuscripts; has also authored more than 100 reviews, editorials, and book chapters. Recently he published the first edition of the clinical handbook *Diagnosis and Management of Osteoporosis*.

Dr Saag is the Secretary of the American College of Rheumatology (ACR) and Past President of the Board of Trustees of the National Osteoporosis Foundation.

George C. Tsokos

Dr George C. Tsokos, MD is Professor of Medicine at Harvard Medical School and Chief, Rheumatology Division, Beth Israel Deaconess Medical Center in Boston, USA. He trained in Rheumatology at the National Institutes of Health, USA. He has served various leadership positions including President of the Clinical Immunology Society, Chair of the Council of the University of Athens and Member or Chair of multiple federal study sections and Editor or Member of editorial boards of scientific journals.

Dr Tsokos holds a MERIT Award from the National Institutes of Health and has received several prestigious awards including the Kirkland, Howley, Evelyn Hess awards and the Distinguished Basic Investigator Award from the American College of Rheumatology, the Lupus Insight Award, the Carol Nachman International Prize in Rheumatology and the Marian Ropes Physician Achievement Award. Dr Tsokos' laboratory has opened and led the field of molecular abnormalities on immune cells in patients with SLE and identified previously unknown pathways which have served as the basis for novel treatments which are currently in various phases of development.

A scoping review of the epidemiology of systemic sclerosis and its organ manifestations: 2018–2024

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Purpose of review
Updates from large, observational cohorts and new statistical techniques have resulted in new data on the epidemiology of systemic sclerosis (SSc). This scoping review uses data from 2018 to 2024 to describe the current understanding of the epidemiology of SSc and several of its organ- manifestations.

Recent findings
Our review identified new estimates for the global incidence and prevalence of SSc (1.4–8.6 per 100 000 person-years and 17.6–18.9 per 100 000 individuals, respectively). Mortality rates remain high, though mortality at younger ages has decreased. interstitial lung disease and pulmonary arterial hypertension remain the most common causes of death for patients with SSc. Literature on gastrointestinal (GI) manifestations of SSc was scarce, and we identified significant heterogeneity in results. Furthermore, data on the epidemiology of racial, ethnic and sex-based disparities was lacking.

Summary
New techniques for the evaluation of the epidemiology of SSc highlight the high morbidity and mortality of SSc, and a growing prevalence rate compared with prior eras. Further research is needed to address notable heterogeneity in the reporting of epidemiological data and understudied disease manifestations, including GI disease and health disparities in disease outcomes.

Keywords
epidemiology, incidence, mortality, prevalence, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis, inflammation and vasculopathy. SSc is a rare disease that can affect multiple organ systems, and as such, comprehensively describing the epidemiology of SSc is challenging. Prior reviews of the epidemiology of SSc relied on small cohorts by necessity [1–3]. However, multiple large cohorts initiated in the 2000s, including the European Scleroderma Trials and Research Group (EUSTAR), the Australian Scleroderma Cohort study (ASCS) and Canadian Scleroderma Research Group (CSRG) have now collected longitudinal data for nearly 20 years, resulting in more updated and thorough epidemiological data. Additionally, newer statistical methods for evaluating the epidemiology of rare diseases have now been applied to SSc [4▪▪]. This study utilizes data from this transformation in the breadth and depth of epidemiological data, along with newer studies from regions where such detailed epidemiological data is not available, to describe the current understanding of SSc.

Large, population-based studies have found that the incidence of autoimmune disease in general is increasing [5▪▪]. Yet, SSc remains a rare and heterogeneous disease. Consequently, those same challenges faced by prior epidemiological reviews of SSc apply here. The incidence and prevalence of SSc vary greatly depending on patient factors, including geographic region, autoantibody profile, age of disease onset, timing of disease, ethnicity, sex and environmental exposure [6–8]. Likewise, organ specific manifestations vary across patient demographics [6,9]. Even risk factors for the development

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KEY POINTS

- New data from high quality cohort studies employing novel statistical methods have led to more reliable epidemiological data in systemic sclerosis.
- Interstitial lung disease and pulmonary arterial hypertension carry the highest risk for mortality among all the organ manifestations of systemic sclerosis.
- Although patients with diffuse cutaneous systemic sclerosis tend to have more severe disease courses, patients with limited cutaneous systemic sclerosis can have severe, progressive organ manifestations, most notably interstitial lung disease, which warrant close monitoring and therapeutic intervention
- Gastrointestinal tract involvement is highly prevalent in systemic sclerosis, but remains an understudied topic of epidemiological research.
- There are limited data on the epidemiology of disparities in systemic sclerosis, including those based on race, ethnicity and sex.

of SSc and its outcomes are highly disparate depending on patient and environmental factors [9,10].

We therefore present a scoping review of the epidemiology of SSc. In contrast to systematic reviews, scoping reviews typically 'examine the extent, range and nature of research activity,' rather than answer a specific research question [11]. The purpose of this study is to describe the scope of the most recent epidemiology of SSc and its severe organ-specific manifestations, including skin disease, interstitial lung disease (ILD), pulmonary hypertension/pulmonary arterial hypertension (PAH), gastrointestinal (GI) disease, Raynaud's phenomenon (RP) and scleroderma renal crisis (SRC).

METHODS

To create a scoping review evaluating updated literature on the epidemiology of SSc and its clinical manifestations, a search was created by a librarian (R.J.). The search included anything that discussed the epidemiology of SSc in humans dating back to 2018, written in English. Searches were conducted in PubMed, Embase (Elsevier), and Web of Science Core Collection. Terms related to epidemiology were combined with terms related to SSc (see exact search strategies in Supplement 1, Supplemental Digital Content, http://links.lww.com/COR/A61). Searches were conducted on May 2, 2024. Endnote was used for de-duplication, and resulted were added to JBI SUMARI for screening and data extraction.

Titles and abstracts were screened independently by two reviewers (S.D.G. and J.Y.L.) for relevance and quality. Inclusion criteria included any reference to epidemiology, SSc, SSc-ILD, SSc-PAH, SSc-GI disease, SSc-SRC and/or SSc-RP. Any paper that did not include original data or did not present prior data in a systematic methodology was excluded. Articles that did not reach consensus were screened by a third reviewer (ERV) until consensus was reached. This process was repeated for a full-text review of all articles, after which data was synthesized by a single reviewer (SDG).

RESULTS

Study selection

Our search yielded 2512 citations that met inclusion criteria. After exclusion based on title and abstract review, followed by full text review and article appraisal, we identified 101 articles for inclusion in our study. A complete PRISMA diagram of our exclusion process can be found in Fig. 1. Supplement 2, Supplemental Digital Content, http://links.lww.com/COR/A61 includes a full list of all articles identified in our review.

Incidence and prevalence

In studies published from 2018–2024, the overall incidence and prevalence of SSc varied drastically depending on geographic region and sex. The total global incidence of SSc based on data from all continents was estimated at 1.4–8.6 per 100 000 person-years depending on methodology of estimation used in two studies [4▪▪,7]. In the same two studies, the global pooled prevalence was estimated at 17.6–18.9 per 100 000 individuals [4▪▪,7]. Of studies that reported trends over time, SSc incidence increased in European studies, remained stable in one study from the United States, and decreased slightly in a single study from Thailand [5▪▪,12–16]; whereas, SSc prevalence increased across all studies and geographic regions in the present literature review [12,17,18]. Figure 2a and b illustrates the prevalence and incidence, respectively, of SSc by geographic region. The incidence of total SSc per continent ranged from 0.2 per 100 000 person-years in Africa to 2.0 per 100 000 person-years in the North America [7]. The lowest prevalence of SSc by continent was found in Asia at 6.8 per 100 000 individuals [7]; however, there was significant heterogeneity in methodology and estimates between studies and the reporting metrics also varied. For example, prevalence studies in South Korea and Japan identified the prevalence of SSc at 77.7 cases per million

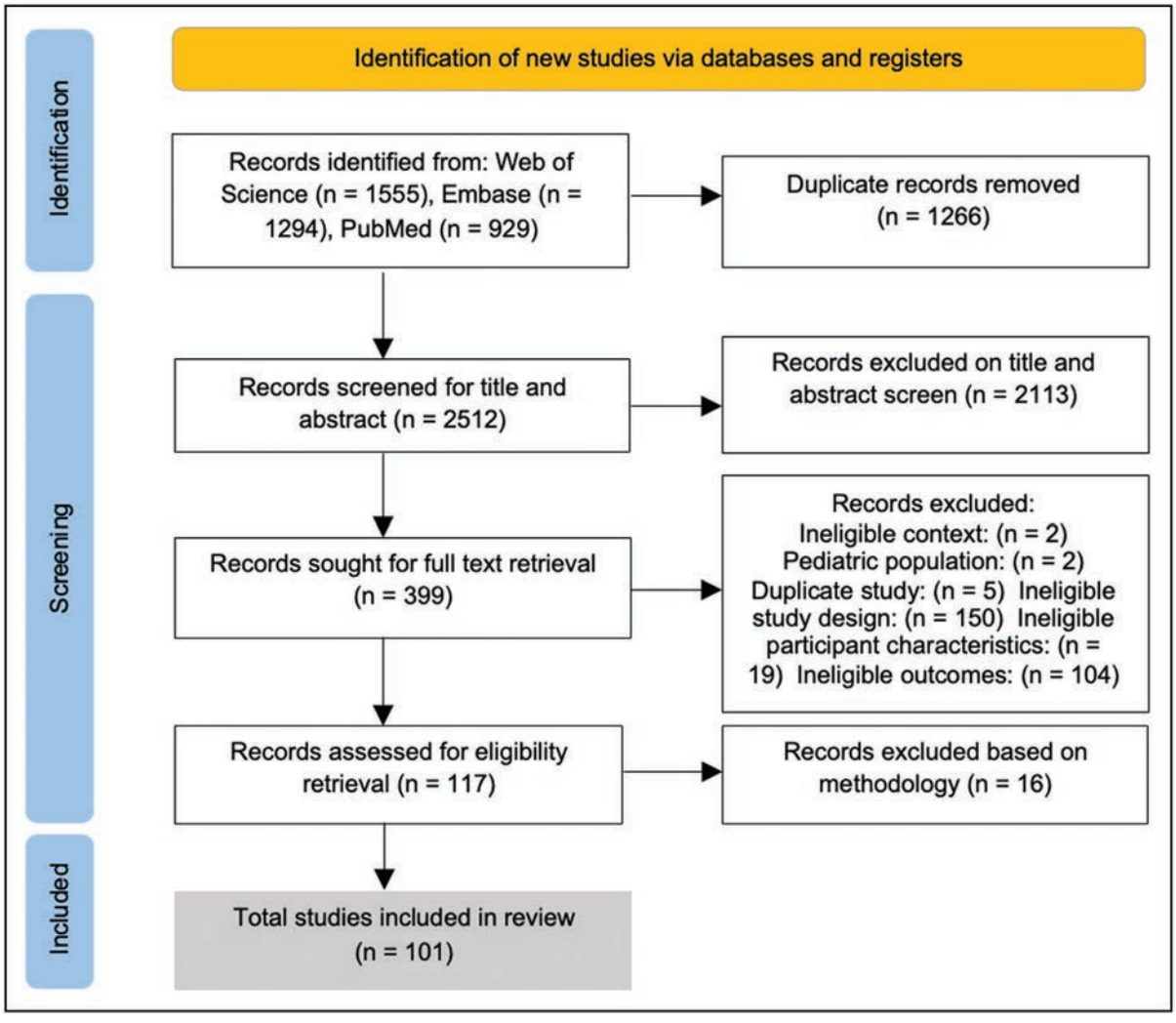

FIGURE 1. PRISMA diagram of records included and excluded in final review.

individuals and 37.0 cases per 100 000 individuals, respectively [19,20].

The global pooled incidence of SSc based on data from all continents in females was reported at 2.3–14.2 per 100 000 person-years compared to 0.5–3.2 per 100 000 person-years in males [4▪▪,7]. The global pooled prevalence of SSc in females was identified as 28.0–31.2 per 100 000 females [4▪▪,7]. In comparison, the global pooled prevalence of SSc in males was 6.0–6.8 per 100 000 individuals [4▪▪,7].

Mortality

Mortality from SSc remains high, though in the past 50 years mortality at younger ages has decreased [21]. In a meta-analysis of mortality in SSc from 1964 to 2005, the 5- and 10-year survival from time of diagnosis was 74.9% and 62.5%, respectively [22]. Overall 5- and 10-year survival for SSc identified in this study ranged from 64.5–94% and 44.9–87.8%, respectively [23–25]. But survival varied drastically between geographic regions. The leading causes of death in SSc were PAH and ILD [26]. Factors associated with progression of disease and mortality across studies included the presence of PAH, ILD, SRC, RP, malabsorption, later age at onset of disease, dcSSc, esophageal involvement and Scl-70 seropositivity [24–30]. Studies evaluating sex differences in mortality in SSc showed conflicting results, though a trend toward men having higher mortality rates was observed [18,31,32].

Clinical and autoantibody profiles

The most common autoantibodies identified across the spectrum of SSc included anti-Scl-70 antibody (also known as antitopoisomerase I), but there was wide variation in the prevalence of this antibody driven largely by differences in the makeup of cutaneous subtypes of each cohort (7.3–80.8% of patients

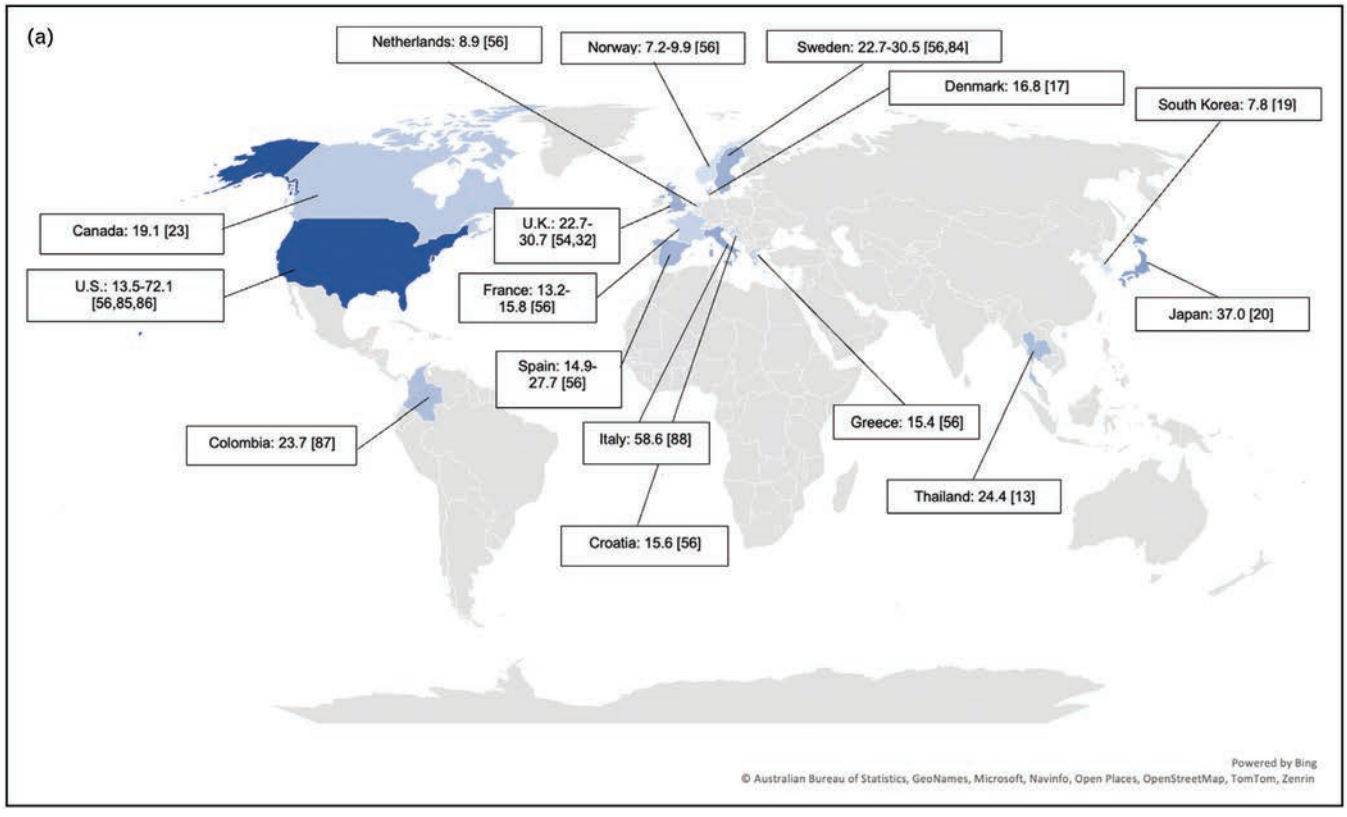

FIGURE 2. (a) Map of typical estimates of prevalence of SSc globally by country (all data reported as prevalence per 100 000 individuals). Data from countries where prevalence was reported as a subsection or region of the country, as opposed to the country as a whole, are not reported here when other estimates were available. In instances where prevalence was reported over multiple time periods, the most recent time period was selected. Data from Tian *et al.* was excluded from regional prevalence estimates because data was estimated based on a Bayesian hierarchical linear mixed model rather than observation (image made using Microsoft Excel). (b) Map of typical estimates of incidence of SSc globally by country (all data reported as incidence per 100 000 person-years). Data from countries where prevalence was reported as a subsection or region of the country, as opposed to the country as a whole, are not reported here when other estimates were available. In instances where prevalence was reported over multiple time periods, the most recent time period was selected. Data from Tian *et al.* was excluded from regional incidence estimates because data was estimated based on a Bayesian hierarchical linear mixed model rather than observation. SSc, systemic sclerosis.

depending on cohort) [14,28]. The anticentromere antibody also varied in prevalence (2.1–73%) [16,26]. The anti-RNA-polymerase III antibody was reported in 2–12.5% of patients, although the cohort reporting that 12.5% of patients had anti-RNA-polymerase III positivity excluded early and very early SSc patients [6,33]. Patients with dcSSc routinely had statistically significantly higher rates of anti-Scl-70 autoantibodies [24,28,34–37], whereas patients with lcSSc had significantly higher rates of anticentromere autoantibodies [24,34,35]. Autoantibodies also varied by organ specific manifestations of SSc, as described below.

Of the organ manifestations evaluated in this study, ILD was seen in 13.4–85.5% of patients in cohorts larger than 100 patients [25,38], PAH was observed in 6.4–21.6% of patients [25,26,39], RP was seen in 59.5–100% of patients depending on time of disease course [28,40,41], gastrointestinal (GI) disease varied depending on area of involvement from 10.6% [gastric antral vascular ectasia (GAVE)] – 89.2% (reflux esophagitis) [42,43], and SRC was seen in 0.8–6.2% of patients (see Fig. 3) [12,44]. There was significant heterogeneity in how clinical characteristics were defined, most notably in ILD and PAH. In ILD, the diagnosis was sometimes based on ICD codes, whereas in other cases was based on HRCT or pulmonary function test (PFT) findings. In pulmonary hypertension, the terms 'pulmonary hypertension' and 'pulmonary arterial hypertension' were often unclearly defined and may have been used interchangeably. Due to limitations in the scope of this review, we were unable to evaluate all clinical manifestations associated with SSc, including telangiectasias, calcinosis and cardiac involvement.

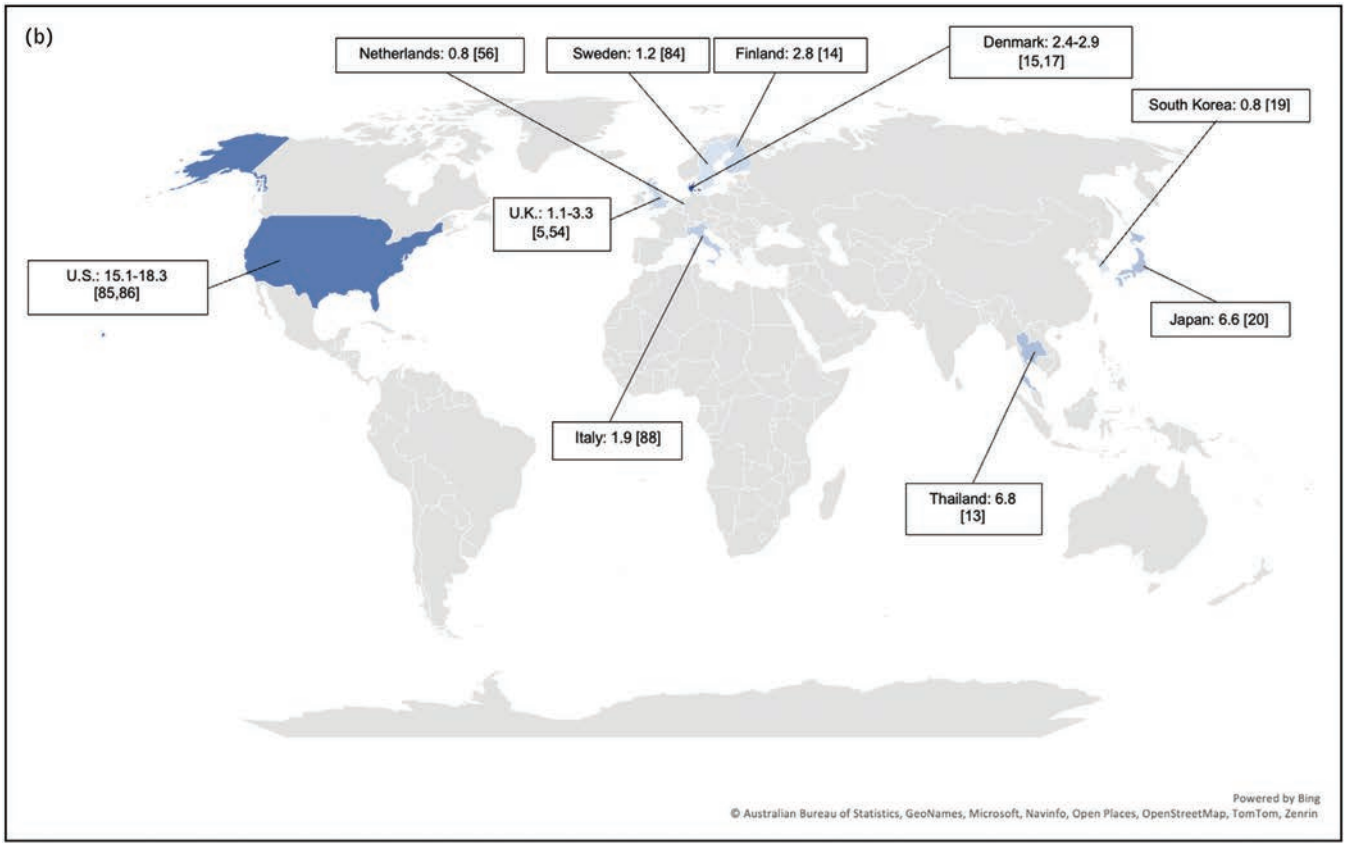

FIGURE 2. Continued.

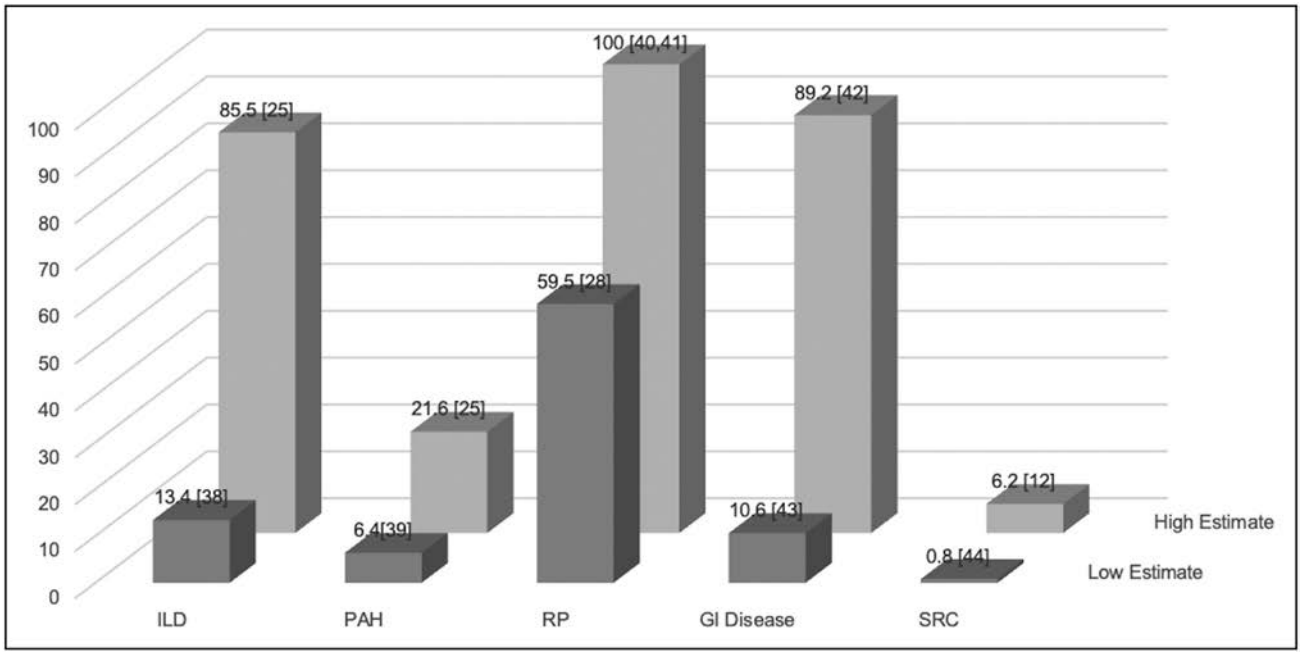

FIGURE 3. Range of estimates of prevalence of specific organ manifestations of SSc (all data reported as frequency of patients with organ manifestation out of all SSc patients). SSc, systemic sclerosis.

Disparities in disease distribution and outcomes

Few studies explicitly evaluated racial or ethnic disparities in the epidemiology of SSc. One study identified a higher overall risk of mortality in Asian SSc patients in Northern California [27]. Another study evaluated the prevalence of SSc in Native Americans as compared to non-Native Americans in the American Southwest. In that study, the prevalence of SSc in Native Americans was 40.0 per 100 000 individuals, compared to 17.1 per 100 000 in non-Native Americans [45].

Multiple studies found no significant difference in short term survival across race and ethnicity in SSc patients [9,45,46]. One study noted Black patients were more likely to have severe disease manifestations compared to White patients [47]. Moore *et al.* found an increased unadjusted hazard ratio of 2.061 [95% confidence interval (CI): 1.232–3.449, $P=0.006$] for death in African-American patients with SSc compared to non-African-American patients [48]. Similarly, Rodriguez-Pla *et al.* found the highest age-adjusted mortality rates in Black or African-American SSc patients (5.703 per million) and American Indian or Alaskan Native SSc patients (5.047 per million) compared to White (3.766 per million) and Asian or Pacific Islander (1.952 per million) SSc patients [49].

Environmental factors

Several studies evaluated environmental triggers of SSc with varying degrees of success. Individuals exposed to respirable silica were noted to have a higher incidence rate ratio for SSc compared to unexposed controls [50]. When adjusting for age, sex, smoking status and disease duration, SSc patients exposed to silica did not have a significantly increased mortality rate compared to SSc patients without silica exposure [51]. Other possible environmental triggers, including infectious agents, cigarette smoking and exposure to organic solvents showed conflicting evidence or no significant association with the development of SSc [10,52].

Timing to disease onset and clinical progression

The mean age at onset of symptoms in SSc is variable but was found in studies to range from 35.6 years to 52 years [6,53]. Studies that reported the age of onset of disease also noted large confidence intervals, indicating that the disease can present at nearly any age [6,28,36,53]. The average time between development of RP and first disease manifestation or diagnosis ranged from 0.8 to 3.8 years [29,40,44]. However, SSc can develop at any time after the onset of RP, and the diagnosis of SSc was made >20 years after the onset of RP in 6.3% of patients in one cohort [54].

Cutaneous disease in lcSSc patients with minimal skin involvement at baseline typically does not progress significantly from baseline [34]. Importantly, however, organ manifestations of SSc can progress in both lcSSc and dcSSc. ILD and digital ulcers, in particular, were identified as progressive in both cutaneous subtypes of SSc [34].

Systemic sclerosis-interstitial lung disease

We identified a total of 25 papers with a focus on SSc-ILD, more than any other complication of the disease. SSc-ILD is found in 13.4–85.5% of patients with SSc, depending on geographic region and method of diagnosis [25,38,55,56]. Five-year survival in SSc-ILD ranges from 44.4% to 92.8%, with higher survival likely related to confirmation of no concomitant pulmonary hypertension [23,57]. However, patients with stable FVCs typically survive longer with a 5-year survival of 85 [58]. When combined with emphysema or pulmonary hypertension, SSc-ILD carries even higher mortality [57,59]. Three-year progression of ILD occurred in nearly 40% of untreated patients, highlighting the importance of prompt treatment initiation [60▪]. This is further emphasized by the fact that even patients with a limited extent of radiological fibrosis (<10% on HRCT) had significantly decreased survival compared to controls with no fibrosis on HRCT [58].

ILD can develop at nearly any point in the disease course of SSc. In 35.3% of cases, ILD preceded the diagnosis of SSc; whereas in 74.5% of patients ILD was diagnosed within 3 years of SSc diagnosis [17]. The radiographic patterns most commonly identified in SSc-ILD include nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP), observed in 34.2–84.2% and 15.7–44.7% of patients, respectively [40,41]. Anti-Scl-70 antibody seropositivity is strongly associated with development of ILD, whereas anticentromere and anti-U3 ribonucleoprotein are protective against the development of ILD [55,61]. Multiple studies identified risk factors for death or disease progression in SSc-ILD, which included dcSSc, extent of lung fibrosis, age, male sex, pulmonary hypertension and exertional dyspnea [62–65].

Pulmonary hypertension and pulmonary arterial hypertension

As noted above, the terms 'pulmonary hypertension' and 'pulmonary arterial hypertension' were

not clearly defined in multiple studies. The incidence of pulmonary hypertension in SSc patients was 6.1 per 100 person-years and occurred in up 17.8–38.1% of patients with SSc and 31.2% of patients with SSc-ILD [36,41,66–68]. PAH occurs in 6.4%-21.6% of SSc patients, which is the highest prevalence amongst connective tissue diseases (CTDs) [25,26,39,69]. Pulmonary hypertension, including PAH, has the highest risk of mortality amongst organ-specific manifestations of SSc, and is especially deadly when seen in combination with ILD [70,71]. The 1-, 3-, and 5-year transplant-free survival rates for patients reported in a single study with PAH are 83.7%, 59.1%, and 41.1%, respectively [70]. Factors associated with worse outcomes in PAH include concomitant ILD, reduced DLCO, New York Heart Association (NYHA) class III-IV heart disease and age [70,72].

Gastrointestinal involvement

SSc can affect the GI tract at nearly any point in the disease course, and a general lack objective diagnostic testing for specific GI manifestations exists. As a result, data on GI disease is heterogenous and sparse. In particular, lower GI symptoms, including diarrhea, constipation and fecal incontinence lack prevalence data. Overall, up to 86.9% of patients experience esophageal disease, including reflux symptoms and esophageal dysphagia, while up to 30.6% of patients experience disease that affects the stomach [35]. Small intestinal bacterial overgrowth (SIBO) was identified in 39.9% of patients in a meta-analysis and is highly associated with disease duration [73▪,74]. GAVE was found in 10.6% of patients and associated with dcSSc and RNA polymerase III antibody seropositivity, but was not associated with worse survival [43]. Severe GI disease, however, was found to have a higher risk for all-cause mortality in SSc [75]. In particular, esophageal symptoms, including GERD, dysphagia and esophageal dysmotility were highly prevalent in SSc patients [76–78].

Scleroderma renal crisis

Whereas SRC was previously a leading cause of death in SSc patients, this is no longer the case. Its prevalence amongst all cutaneous subtypes of SSc patients ranges from 0.8%-6.2% of patients, depending on cohort composition [12,44]. SRC is significantly more common in dcSSc compared to lcSSc [24,26,34,35]. Risk factors for the development of SRC include glucocorticoid exposure, male sex, and cardiac involvement of SSc [79,80]. Although it is infrequent, when it does occur it is a significant risk factor for death [26,28]. In a recent meta-analysis, the frequency of progression to any renal replacement therapy for SRC was reported as 66.7%, and the need for permanent renal replacement therapy in SRC was reported as 35.4% [81].

Raynaud phenomenon

We identified significant discrepancies in the prevalence of RP amongst patients with SSc. Multiple studies noted 100% of patients with RP [36,40,41]. However, some studies noted a prevalence of RP as low as 59.5% [28]. These discrepancies often occurred due to the timing of when patient symptoms were recorded for a study in a patient's disease course, but the timing of the disease course was not clearly specified in all studies. Two studies evaluated a cohort of patients with very early diagnosis of SSc (VEDOSS), to assess which patients with RP are likely to develop SSc. One study identified ANA negativity as protective against the development of SSc in this population, whereas SSc antibody positivity in combination with puffy fingers strongly predicted progression to SSc [82]. Ferri *et al.* found that digital ulcers, certain nailfold capillaroscopy findings, esophageal symptoms and cardio-pulmonary symptoms were more common in the definite SSc group compared to the VEDOSS group [83]. Additionally, patients with $\leq$ 1 year between onset of RP and SSc diagnosis had less favorable outcomes [83].

DISCUSSION

We identified several key themes through our scoping review of the last 5 years of literature on the epidemiology of scleroderma. ILD and PAH carry the most morbidity and mortality, and likely as a result, are the most well studied complications of SSc. Conversely, GI disease is understudied but is still associated with poor outcomes. We also noted that although patients with dcSSc often have worse outcomes than patients with lcSSc, patients with lcSSc can still have progressive disease. Finally, despite significant health disparities across the field of rheumatology, there is still a dearth of research on the epidemiology of racial disparities in SSc.

ILD and PAH (in combination or individually), continue to be the most severe complications of SSc and contribute most to overall mortality in the disease [23,70,71]. Most importantly, studies show that even patients with mild ILD can progress, and that if untreated, there is a high likelihood for disease progression [58,60▪]. Our study highlights the need for continued vigilance, aggressive monitoring and prompt treatment of ILD and PAH. Given ILD and PAH can be found in both cutaneous forms of SSc, recommendations for the screening and treatment of ILD and PAH should extend to all patients with SSc.

Table 1. Unmet needs and recommendations for further epidemiological research in SSc

Unmet need	Recommendation for further epidemiological research
Heterogeneous methodologies	Develop standardized methods for the reporting of the epidemiology of SSc and its organ-specific manifestations.
Limited understanding of healthcare disparities	Describe disparities in the distribution, organ-specific manifestations and survival of underrepresented patient populations.
Lack of data on epidemiology of GI disease manifestations	Understand the distribution of GI disease in SSc and its effects on mortality.
Minimal research on differences between cutaneous subtypes of SSc	Further analyze differences in disease characteristics distinct to dcSSc and lcSSc.

GI, gastrointestinal; SSc, systemic sclerosis.

Our study found that GI disease remains an understudied disease manifestation. Despite its overall high prevalence, there is limited research describing GI complications of SSc, especially including GAVE, SIBO, diarrhea, constipation and fecal incontinence. The data that does exist suggest that severe GI manifestations of SSc lead to poor outcomes [75]. Research is needed on both the epidemiology of GI disease in SSc, as well as for the development of GI-directed therapies.

We found that both dcSSc and lcSSc can have severe disease courses. Although dcSSc was associated with higher mortality rates overall, lcSSc was found to be associated with increased mortality compared to the general population. ILD and PAH were also found in high percentages in the lcSSc population [34].

We noted significant disparities in the epidemiology of SSc, including those based on race, ethnicity and sex. Despite these important findings, there was an overall paucity of available literature studying how disparities contribute to differential disease manifestations and mortality. Future research on the epidemiology of SSc would benefit from attention to disparities and lesser studied organ-specific manifestations.

The most notable limitation of our study is that there is significant heterogeneity in research on the epidemiology of scleroderma. This is, in part, due to differences in disease distribution based on regionality and sex. However, this heterogeneity is also due to a lack of consensus on reporting of data, clinical definitions, and appropriate statistical analysis.

CONCLUSION

SSc remains a rare disease, but its severe outcomes and protean manifestations make it an important topic of continued epidemiological research. Despite a growing body of literature on its epidemiology, topics such as health disparities in SSc and GI manifestations of the disease remain understudied (see Table 1 for a complete list of unmet needs in SSc epidemiology research). Future studies should seek to standardize reporting of the epidemiology of SSc and its complications. Our updated scoping review highlights the need for continued research across the spectrum of populations and SSc disease manifestations.

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Conflicts of interest

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R.J. – none.
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Epidemiology of systemic vasculitis

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Purpose of review
Ongoing research contributes to our understanding of the epidemiology of vasculitis and its outcomes across the globe. This review aims to summarize important research studies published on this topic in the last 18 months.

Recent findings
The implementation of rapid referral systems and use of large vessel imaging have improved the diagnosis of giant cell arteritis. A population-based study in immunoglobulin G4-related disease provides incidence and prevalence estimates for the United States for the first time. Recently published data supported viral infectious triggers for Kawasaki disease and immunoglobulin A vasculitis. Population studies in antineutrophil cytoplasmic antibody associated vasculitis report an increase in the incidence of eosinophilic granulomatosis with polyangiitis and have provided further insights into the burden of cardiovascular disease in these patients. Data on Behçet's disease continues to show increased all-cause mortality and need for better treatment strategies.

Summary
Recent literature highlights the heterogeneity of the epidemiology of vasculitis in different parts of the world as well as associated outcomes, comorbidities, and potential triggers. Thought new classification criteria are being employed in some forms of vasculitis, standardization of case identification remains an unmet need in multiple other forms of vasculitis.

Keywords
antineutrophil cytoplasmic antibody associated vasculitis, Behçet's disease, epidemiology, giant cell arteritis, immunoglobulin G4-related disease, Kawasaki disease

INTRODUCTION

The primary systemic vasculitides represent a group of heterogeneous diseases characterized by vessel wall inflammation leading to end-organ damage [1]. Growing knowledge of the epidemiology of these conditions contributes to the knowledge and treatment of patients living with vasculitis. This review summarizes studies on the epidemiology of vasculitis published during the last 18 months (Table 1) including studies investigating their mortality, morbidity, and environmental/infectious triggers (Table 2).

LARGE VESSEL VASCULITIS

Giant cell arteritis

The incidence, prevalence, and clinical characteristics of giant cell arteritis (GCA) vary depending on the population being studied, case definition, and study design [2]. Recent studies incorporate large vessel imaging for case identification, allowing for increased recognition of the subset of patients with large-vessel GCA (LV-GCA). A recent study from Spain using the national ARTESER (ARTEritis by Sociedad Española de Reumatología) registry [3], estimated an incidence of GCA of 7.42 (95% confidence interval [CI] 6.57–8.27) per 100 000 persons age ≥50 between 2013 and 2019. The case definition included having at least one of the following: a positive temporal artery biopsy, positive vascular imaging, expert rheumatologist diagnosis, meeting

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KEY POINTS

- Recent studies reporting on the epidemiology of giant cell arteritis (GCA) evidence the role of imaging and fast-track mechanisms in the detection of patients with GCA, including the detection of patients with large vessel vasculitis.
- The first US epidemiologic study on immunoglobulin G4 (IgG4)-RD reported an incidence of 1.39 per 100 000 person-years in 2019, with an estimated point prevalence of 5.3 per 100 000 persons.
- A Danish registry study showed that patients with granulomatosis with polyangiitis and microscopic polyangiitis, compared to controls, had an increased risk of cardiovascular disease within the 12 months preceding diagnosis (hazard ratio 3.05, 95% confidence interval 2.48–3.75), with this risk being highest in the immediate, 1-month period, and remaining elevated during the 12-month period.
- Epidemiological studies utilization large populations databases from the UK, South Korea, and Japan, have shown increase in the prevalence of eosinophilic granulomatosis with polyangiitis.
- Studies on Kawasaki disease and immunoglobulin A vasculitis continue to support the role of viral and bacterial infections in the pathogenesis of these conditions.

three of five 1990 American College of Rheumatology (ACR) criteria [4]. Notably, the incidence of GCA was very consistent for geography and season.

While the high incidence of GCA in Scandinavian countries is well established [2], more recent estimates provide further information regarding disease characteristics. A population-based study from Western Norway between 2013 and 2020 estimated an incidence of 20.7 [95% confidence interval (CI) 18.2–23.5] GCA cases per 100 000 persons age ≥50 years [5]. Only patients who fulfilled the ACR 1990 or ACR/European Alliance of Associations of Rheumatology (EULAR) 2022 criteria [6] were included in this study. Interestingly, rising incidence of noncranial GCA was noted, potentially reflecting increased use of diagnostic imaging to detect large vessel inflammation. Another epidemiologic study from Norfolk, United Kingdom (UK) between 2011 and 2020 showed that the 2022 ACR/EULAR criteria, compared to the ACR 1990 criteria, did not lead to significantly higher rates of GCA [7▪▪]. The incidence of GCA per 100 000 person-years of age ≥50 years was 9.84 (95% CI 8.64–11.16) using the 2022 criteria compared to 9.16 (95% CI 8–10.43) using the 1990 criteria. The incidence of GCA increased from 6.8 (95% CI 4.0–10.9) in 2016 to 18.3 (95% CI 13.5–24.3) in 2019, after the introduction of fast-track ultrasound pathway for diagnosis in 2017, with a later decline during the COVID-19 pandemic of 11.3 (95% CI 7.6–11.3) in 2020. These findings highlight the significance of disease detection and the clinical care pathways that allow for enhanced recognition and diagnosis. Finally, a recent epidemiological study comparing the rates of GCA development in the Melanoma Inquiry in Southern Sweden (MISS) prospective cohort, did not report any association between the risk of GCA and moderate to high sun exposure during a mean follow-up of 14 years (Table 2) [8].

With the increasing use of vascular imaging, the significance of subclinical GCA (i.e., no symptoms attributed to vascular manifestations) in polymyalgia rheumatica (PMR) is a topic of current debate [9,10]. A meta-analysis including 556 patients from 13 cohorts between 1965 and 2020 estimated that 23% (95% CI 14-36, $I^2 = 84\%$) of patients with PMR had subclinical GCA, using any screening method. The pooled prevalence for the 7 studies that utilized PET/CT was 29% (95% CI 13–53, $I^2 = 85\%$) [11▪]. A cross-sectional multicenter study of 347 patients with a new diagnosis of PMR without signs or symptoms of concomitant GCA identified 22.8% of patients with subclinical GCA [12]. Ultrasound evaluation in this study included evaluation of the temporal superficial, common carotid, subclavian, and axillary arteries, and defined subclinical GCA by at least one halo sign. Vascular involvement in subclinical GCA was predominantly extracranial. While these studies raise concern about subclinical GCA in a subset of patients with PMR, the implications of these findings remain unclear. A prospective case–control study of 150 patients with PMR, including 50 with subclinical GCA as defined by at least one halo sign on vascular ultrasound, reported an increased risk of relapse among subclinical GCA patients (62% vs. 16%, $P < 0.001$) [13]. However, another study of 337 patients with PMR that utilized F-FDG PET or PET/CT to identify subclinical GCA in 9% of patients, did not report any difference in the risk of relapse [hazard ratio (HR) 0.82, 95% CI 0.50–1.36] [14]. Limitations of these studies include lack of blinding, selection bias, and different definitions. Further prospective studies are needed to understand the prevalence and significance of subclinical GCA in patients with PMR.

Takayasu arteritis

In contrast to GCA, Takayasu arteritis (TAK) is more prevalent in Asia with lower rates reported in European countries [15]. A recent epidemiological study from Norfolk, UK [7▪▪] estimated the incidence of

Table 1. Epidemiological studies reporting prevalence and incidence of primary systemic vasculitides

Study (publication year)	Country	Dates	Case identification	Incidence and prevalence estimates
Large vessel vasculitis; giant cell arteritis and Takayasu arteritis				
Fernández-Lozano *et al.* (2024) [3]	Spain	2013–2019	Medical record review	GCA: 7.42 (95% CI 6.57–8.27) per 100 000 people age >50 (Incidence)
Skaug *et al.* (2023) [5]	Norway	2013–2020	Medical record review	GCA: 20.7 (95% CI 18.2–23.5) per 100 000 people age >50 (incidence)
Mukhtyar *et al.* (2023) [7▪▪]	UK	2011–2020	Medical record review	GCA: 9.16 (95% CI 8–10.43) per 100 000 people age >50 using 1990 criteria (incidence) GCA: 9.84 (95% CI 8.64–11.16) per 100 000 people age >50 using 2022 criteria (Incidence) TKA: 0.28 (95% CI 0.15–0.47) per 10 000 people using 1990 criteria (Incidence) TKA: 0.04 (95% CI 0.00–0.14) per 100 000 using 2022 criteria (incidence)
Medium vessel vasculitis; Kawasaki disease and Polyarteritis Nodosa				
Sakai-Bizmark *et al.* (2024) [20]	USA	2016–2020	National claims database	KD: 6.51 and 5.38 per 100 000 pediatric population during the prepandemic and pandemic periods respectively. (hospitalization rate)
Lin *et al.* (2024) [21]	Taiwan	2020	National claims database	KD: 2.41, 2.67 and 2.60 per 100 000 person-months age <6 years old in April, May, June 2020 (Incidence)
Jin Oh *et al.* (2024) [22]	South Korea	2012–2020	National claims database	KD: 238.9, 230, 141.2 per 100 000 age <5 years old in 2018, 2019, and 2020, respectively (Incidence)
Kawazoe *et al.* (2024) [28▪]	Japan	2020	National hospital survey	PAN: 1.74 per 100 000 in 2020 (prevalence)
Variable vessel vasculitis; IgG4-RD and Behcet disease				
Suárez-Amorín *et al.* (2023) [30]	Spain	1999–2018	Medical record review	Behçet: 0.492 per 100 000 people. (incidence) 10.41 per 100 000 in 2018 (prevalence)
Wallace *et al.* (2023) [34▪▪]	USA	2009–2021	Commercial claims database	IgG4-RD: 0.78 to 1.29 per 100 000 person-years in 2015 and 2019. (incidence)
Small vessel vasculitis; ANCA vasculitis and IgA vasculitis				
Benavides-Villanueva *et al.* (2024) [39]	Spain	2020–2023	Medical record review	GPA: 0.56 (95% CI 0.39–0.73) per 100 000 people MPA: 0.59 (95% CI 0.4–0.78) per 100 000 people Unclassified: 0.18 (95% CI 0.11–0.26) per 100 000 people (Incidence)
Rubenstein *et al.* (2024) [43▪]	France	2018	Medical record review	GPA: 0.48 (95% CI 0.35–0.64) per 100 000 people MPA: 0.39 (95% CI 0.28–0.53) per 100 000 people EGPA: 0.16 (95% CI 0.09–0.26) per 100 000 people (prevalence)
Hwee *et al.* (2024) [45▪▪]	UK	2005–2019	National claims database	EGPA: 0.23 (95% CI 0.16–0.34) to 0.4 (95% CI 0.29–0.54) per 100 000 person-years (incidence) EGPA: 2.27 (95% CI 2–2.57) in 2005, 4.56 (95% CI 4.21–4.94) in 2019 per 100 000 person-years respectively (prevalence)
Lee *et al.* (2024) [46]	South Korea	2007–2018	National claims database	EGPA: 0.11 (95% CI 0.08–0.14) in 2007 to 0.16 (95% CI 0.12–0.19 in 2017 per 100 000 people (incidence) EGPA: 0.11 in 2017 to 1.12 in 2018 per 100 000 people (prevalence)
Sada *et al.* (2024) [47]	Japan	2005–2020	Commercial claims database	EGPA: 0.42 (95% CI 0.01–2.34) in 2005, 5.86 (95% CI 5.32–6.45) in 2020 (prevalence)

CI, confidence interval; EGPA, eosinophilic granulomatosis with polyangiitis; GCA, giant cell arteritis; IgG4-RD, IgG4-related disease; KD, Kawasaki disease; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa; TKA, Takayasu arteritis.

Table 2. Epidemiological studies reporting mortality, morbidity, and environmental/infectious triggers associated with primary systemic vasculitides

Vasculitis, study (publication year)	Country, years	Case identification	Variable of interest	Main results
GCA Gisslander *et al.* (2023) [8]	Sweden, 2000–2019	Regional claims database	Association between moderate or high sun exposure and GCA risk adjusted for diabetes, hyperlipidemia, hypertension, smoking, obesity.	Women with moderate or high sun exposure compared to women who indicated they avoided sun exposure: (HR 1.2, 95% CI 0.9–1.6)
KD Marutani *et al.* (2024) [24▪]	Japan, 2020–2021	Medical record review	Comparison of the prevalence of viral infections between KD patients and controls	Human rhinovirus/enterovirus: (KD: 34.5%, Controls: 21.1%, $P=0.004$). Parainfluenza virus 3: (KD: 4.7%, Controls: 1.6%, $P=0.037$). Respiratory syncytial virus: (KD: 6.1%, Controls: 1.4%, $P=0.002$).
KD Yanai *et al.* (2024) [25]	Japan, 2011–2014	Medical record review	Association between maternal blood heavy metal concentrations (divided into four quartiles based on concentration levels: Q1-Q4) and KD risk during the first three years of birth.	Mercury: OR 1.29, (95% CI 0.82–2.03). Cadmium: OR 0.99, (95% CI 0.63–1.58). Lead: OR 0.84, (95% CI 0.52–1.34). Selenium: OR 1.17, (95% CI 0.70–1.94). Manganese: OR 0.70, (95% CI 0.44–1.11). Q4 compared with Q1.
BD Choi et. al. (2024) [31▪]	Korea, 2002–2020	National claims database	Cause-specific mortality rate compared to the general population	Malignancy: HR 1.96, (95% CI 1.30–2.98). Cardiovascular: HR 2.68, (95% CI 1.45–4.97). Gastrointestinal: HR 3.50, (95% CI 1.35–9.07). Respiratory disease: HR 5.00, (95% CI 1.34–18.62). Infection: HR 3.33, (95% CI 1.02–10.92). Neurological: HR 1.58, (95% CI 1.06–2.35). Genitourinary disease: HR 2.20, (95% CI 1.43–3.37).
AAV Moiseev *et al.* (2023) [48▪]	Multinational, NR	International disease registry	Frequency and risk factors of CVD in patients with AAV	Frequency of CVD, (n = 2286); Any CVE 10.7%, MI 8.1, Stroke 3.2%, MI and Stroke 0.6%, Death from any cause 19.9%. Significant risk factors for CVD in the multivariate model; Smoking: HR 1.98, (95% CI 1.48–2.64). Age of onset 55–65 years: HR 2.93, (95% CI 1.99–4.31). Pulmonary disease: HR 1.50, (95% CI 1.09–2.06). Kidney disease: HR 3.02 (95% CI 2.08–4.37). Chinese origin: HR 4.24 (95% CI 3.07–5.85).
AAV Nygaard *et al.* (2024) [49▪▪]	Denmark, 1996–2021	National claims database	Risk of any cardiovascular outcome and MACE disease prior to diagnosis of AAV compared to age and sex matched controls	Within 12 months preceding the diagnosis date, Any cardiovascular outcome: HR 3.05, (95% CI, 2.48–3.75). MACE: HR 1.98, (95% CI 1.39–2.82). Within 1 month preceding the diagnosis date, Any cardiovascular outcome: HR 10.73, (95% CI 7.05–16.32). MACE: HR 5.78, (95% CI 2.67–12.52).
IgAV Maisons *et al.* (2023) [50]	France, 2010–2022	National disease database	Seasonal variations in IgAV incidence	Autumn months: (OR 1.65, 95% CI, 1.45–1.87), for children. (OR 1.28, 95% CI, 1.06–1.53) for adults. Winter months: (OR 1.52, 95% CI, 1.34–1.73), for children. (OR 1.42, 95% CI 1.17–1.71) for adults.
IgAV Felix *et al.* (2024) [51▪]	France, 2015–2023	National claims database	Association of seasonal pathogens and NPI with IgAV incidence during the COVID-19 pandemic	The change in the incidence of IgAV: NPI implementation, March 2020 (-53.6%, 95% CI -66.6–40.6%), NPI lifting, April 2021 (37.2%, 95% CI 28–46.3%). Estimated percentage of seasonal pathogen related IgAV: S. pneumonia, (37.3, 95% CI, 22.3–52.3). S. pyogenes, (25.6, 95% CI, 16.7–34.4).
IgAV Park *et al.* (2024) [52]	South Korea, 2016–2019	National claims database	Association of virus prevalence and subsequent incidence of IgA vasculitis 1 and 2 months later in children and adults. A significant association was defined as ($P=< 0.05$) on Granger causality testing between positive detection rates of virus and IgA vasculitis incidence at specific time points.	Significant associations at both 1- and 2-month time point in both adults and children: Bocavirus, Human Metapneumovirus, Human Parainfluenza virus. Selective associations with children or adults at 1- or 2- month time point: Human Respiratory Syncytial Virus, Norovirus, Respiratory Adenovirus, Rotavirus No association: Astrovirus, Coronavirus, Enteric Adenovirus, Influenza and Rhinovirus.

AAV, antineutrophil cytoplasmic antibodies vasculitis; BD, Behçet's disease; CI, confidence interval; CVD, cardiovascular events; GCA, giant cell arteritis; HR, hazard ratio; IgAV, IgA vasculitis; KD, Kawasaki disease; MACE, major adverse cardiovascular events; NPI, nonpharmaceutical interventions; NR, not reported; OR, odds ratio.

TAK between 2011 and 2020 showing an incidence rate of 0.28 (95% CI 0.15–0.47) per 10 000 according to the 1990 ACR criteria [16] and 0.04 (95% CI 0.00–0.14) per 100 000 according to the ACR/EULAR 2022 criteria [17]. Four out of thirteen patients initially classified as TAK were reclassified as GCA and nine were unclassified large vessel vasculitis due to age <60 years. These findings underscore the importance of advancing classification criteria, as our clinical understanding of disease develops, to accurately capture the burden due to TAK in the population.

MEDIUM VESSEL VASCULITIS

Kawasaki disease

Kawasaki disease (KD) is a medium vessel vasculitis predominantly affecting the pediatric population and is a leading cause of acquired cardiac disease in children of developed countries [18]. Higher incidences of KD have historically been reported in Asian countries, such as Japan, where an annual incidence of 371 cases per 100 000 children under the age of 5 was reported in 2019 [19]. Given previously reported associations with infectious triggers, several groups have sought to understand the impact of the COVID-19 pandemic on the occurrence of KD. Interestingly, a decrease in KD incidence has been reported since the pandemic. In the United States, an observational study of a national inpatient database showed decreased KD hospitalization rates from the prepandemic to pandemic periods (65.1–53.8 per 1 million children, respectively) [20]. The largest decreases in hospitalization were seen for patients 1–4 years old, compared to other age groups. In Taiwan, the observed incidences of KD during April, May, and June 2020 were approximately 51–52% reduced for each month, compared to the predicted incidence from previous years [21]. Similarly, an almost two-fold reduction in incidence was reported from 2019 to 2020 in South Korea [22]. In one Denmark hospital, an initial uptick in KD cases was seen during the first six months of the pandemic followed by an absence of cases during the following year [23]. Hypotheses for these observed changes included the replacement of KD by the clinically similar but distinct multisystem inflammatory syndrome in children linked to acute SARS-CoV-2, or the decrease in exposure to other infectious agents and potential triggers for KD resulting from isolation precautions.

Infectious triggers were recently analyzed in a Japanese study of KD and control patients who had respiratory panel polymerase chain reaction testing [24▪]. Of 2460 patients who underwent respiratory panel testing, 175 were identified as KD cases, with the remainder serving as controls. Several pathogens, including human rhinovirus/enterovirus, parainfluenza virus, and respiratory syncytial virus, were more frequent in the KD case group (Table 2). Interestingly, cases of RSV in non-KD patients at the study institution peaked in April 2021 and were later followed by a peak in RSV-positive KD cases in May 2021. This 4-week delay between infectious and associated KD peak may suggest that the immune response to the virus, rather than the viral inoculation itself, triggers the onset of KD in some patients.

Beyond infectious triggers, there are efforts to understand environmental factors that may influence KD risk. A Japanese group investigated a possible effect of maternal heavy metal exposure in a national, prospective cohort study in approximately 85 000 mother-child pairs, but found no significant association between maternal blood heavy metal concentrations and KD during the first three years of birth [25]. Previous proposed environmental triggers have included tropospheric wind patterns, inhaled pollutants, early childhood microbe exposure, and population density [26].

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a necrotizing, medium vessel vasculitis with a wide breadth of clinical presentation, from skin-limited disease to multiorgan failure. The lack of updated classification criteria and the changes in epidemiology, resulting from a decrease in cases of hepatitis B and C virus, highlight the need for updated epidemiological data on PAN [27]. A nationwide study in Japan estimated the number of patients with PAN by randomly surveying 4172 of 15 652 hospitals [28▪]. From 2235 hospital responses and using an estimate calculation, 22,00 patients with PAN were approximated. When applied to the population of Japan as of 2020, the authors calculated a prevalence of 17.4 PAN cases per 1 million people. Although differences in methodology limit the comparison to other studies, this prevalence is higher than what has previously been reported in Spain, the UK, and Germany but lower than reported in France, Sweden, and Australia.

VARIABLE VESSEL VASCULITIS

Behçet's disease

Recent epidemiological studies have contributed to our understanding of the disease burden of Behçet's disease (BD). A multicenter hospital-based study from the Cantabria region in Northern Spain estimated the incidence of BD, according to the 1990

International Study Group (ISG) criteria [29], at 0.49 per 100 000 individuals and a prevalence of 10.1 per 100 000 [30]. A population-based study using the Korea National Health Insurance Service compared mortality rates between patients with BD and the general population. During a mean follow-up of 11.9 years, patients with BD had an excess mortality compared to the general population (HR 1.28, 95% CI 1.20–1.38) [31▪], with the highest mortality risk during the first year after diagnosis (HR 2.66, 95% CI 2.09–3.40). Differences in cause-specific mortalities were also reported (Table 2).

Immunoglobulin G4 related disease

IgG4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory disease with potential manifestations in nearly every organ system [32]. The first US epidemiologic study that used a validated algorithm [33] to identify IgG4-RD showed that the overall incidence increased from 0.78 in 2015 to 1.39 in 2019 per 100 000 person-years [34▪▪]. The point prevalence was estimated at 5.3 per 100 000 persons. IgG4-RD was associated with significant excess mortality compared to the general population with a HR of 2.51 (95% CI 1.76–3.56). The incidence and prevalence of IgG4-RD are comparable to ANCA-associated vasculitis (AAV) [35], indicating a need for increased awareness.

SMALL VESSEL VASCULITIS

Antineutrophil cytoplasmic antibody-associated vasculitis

AAV encompasses a group of three small vessel vasculitides – granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). New 2022 ACR/EULAR classification criteria are available for AAV [36–38]. A study from Northern Spain from 2000 to 2023 reported the annual combined incidence of GPA/MPA to be 13.4 (95% CI 10.0–16.8) per 1 000 000 inhabitants per year, with a very slight male predominance [39]. The individual incidence of GPA was 5.6 (95% CI 3.9–7.3), MPA was 5.9 (95% CI 4.0–7.8), and unclassified vasculitis was 1.8 (95% 1.1–2.6) per 1 million inhabitants per year. The incidence of GPA/MPA appeared to be increasing gradually over time. The pooled prevalence of GPA/MPA was 184.7 cases (95% CI: 181–188) per 1 million individuals. Incidence in this study was higher than a previous analysis in Southern Spain but lower than that of many Northern European countries, posing continued questions about the possible influence of a north-south geographic gradient risk for AAV within Europe [40–42]. A study in Southern France used multimodal case detection and the 2022 ACR/EULAR classification criteria to determine a pooled (GPA, MPA, and EGPA) AAV prevalence of 128 (95% CI: 107–152) per 1 million inhabitants [43▪]. Prevalence of GPA and MPA were each estimated to be 54 cases (95% 41–70), with EGPA estimated at 20 cases (95% CI: 12–31) per 1 million people. In a stratified by the geographic origin of individuals, the prevalence of AAV was significantly higher amongst individuals of non-European origin (primarily North African) compared to those of European origin (238 vs. 119 cases per million, $P = 0.001$). This difference was observed only in patients with MPA (141 vs. 47 cases per million, $P < 0.0001$). Although these findings should be interpreted with caution given a small sample size ($n = 31$) of non-European patients, a lower frequency of GPA in African American patients has been previously reported [44].

The epidemiology of EGPA is often underreported. In 2024, a retrospective study of EGPA using longitudinal medical records of UK primary care practices reported an increase in the prevalence of EGPA from 22.7 (95% CI 20–25.7) cases in 2005 to 45.6 (95% CI 42.1–49.4) cases per 1 million people in 2019 [45▪▪]. From 2006 to 2019, the incidence varied from 2.3 (95% CI 1.6–3.4) to 4.0 (95% CI 2.9–5.4) cases per 1 million people per year. An 11-fold increase in EGPA prevalence (1.1 per 1 million in 2007 to 11.2 per 1 million in 2018) was observed in a recent national South Korean retrospective study [46]. In Japan, the crude prevalence of EGPA has also increased drastically from 4.2 (95% CI 0.1–23.4) cases per 1 million people in 2005 to 58.6 (95% CI 53.2–64.5) in 2020 [47]. The changes may be attributed to updates in classification criteria, methodological differences, and/or improved disease management leading to longer survival time.

The potential risk for accelerated atherosclerosis and cardiovascular disease (CVD) is an area of increasing interest. A recent multinational group, including sites in the European Union (EU), China, Russia, Turkey, the UK, and the United States, collected retrospective data on CVD, defined as myocardial infarction (MI), cerebrovascular accident (CVA), or both, from 2286 AAV patients at tertiary vasculitis centers [48▪]. A total of 245 (10.7%) patients experienced a CVD, including MI in 185 (6.1%), CVA in 74 (3.2%), and both MI and CVA in 14 (0.6%) patients. Median time from AAV onset to CVD was 17.5 months, with no difference in the risk of CVD between the first, second, and third years of AAV follow-up. CVD rates were higher in the Chinese (24.2%) and UK (9.7%) cohorts. Multivariate Cox regression analysis identified age $\geq$55 years,

smoking, Chinese origin, and pulmonary or kidney disease as significant risk factors for CVD.

A Danish registry study from 1996 to 2021 examined the risk of CVD preceding a diagnosis of GPA/MPA using comparison to age- and sex-matched controls [49▪▪]. CVD, defined in this study as ischemic heart disease, acute MI/percutaneous coronary intervention/coronary artery bypass graft surgery, coronary angiogram, heart failure, venous thromboembolism, atrial fibrillation, ischemic stroke, pericarditis, and/or ventricular arrhythmias/ICD implantations/cardiac arrest, within the 12 months preceding diagnosis was higher in patients with GPA/MPA compared to controls (HR 3.05, 95% CI 2.48–3.75). Risk of CVD was highest in the immediate, 1-month period, before AAV diagnosis (HR 10.73, 95% CI 7.05–16.32), and the risk of major adverse cardiovascular events remained elevated during the 12-month period. Risk for individual CVD components is shown in Table 2. This study represents one of the first major ventures in characterizing the risk of CVD preceding AAV diagnosis, conjuring interesting hypotheses about the role of subclinical inflammation and CVD risk.

Immunoglobulin A vasculitis

IgA vasculitis (IgAV) is an immune complex-mediated small vessel vasculitis that is predominant in the pediatric population but can also occur in adults. Infection has been proposed to play a role in the pathogenesis of IgAV and disease spikes have been reported in the fall and winter months of Western countries. These seasonal spikes were demonstrated in a post-COVID-19 pandemic French retrospective registry for both children and adults [50], though cases in children declined [odds ratio (OR) 0.62, 0.47–0.81] during the pandemic period. Another French hospital database study sought to investigate a connection between the resurgence of certain infectious microbes after COVID-19 precautions were lifted and spikes in IgAV [51▪]. The incidence of IgAV decreased during the COVID-19 pandemic followed by an increase correlating with the introduction and subsequent removal of social distancing and masking mandates, suggesting a link between changes in circulating pathogens such as *S. pneumoniae* and *S. pyogenes* with IgAV incidence (Table 2). Finally, a recent study from South Korea examined associations between 11 respiratory and gastrointestinal viral infections on IgAV rates between 2016 and 2019, showing associations between certain viruses before IgA case spikes (Table 2) [52]. These studies corroborate a potential role for preceding viral or bacterial infections in the pathogenesis of IgA vasculitis.

CONCLUSION

Recent studies on the epidemiology of vasculitides continue to expand our understanding of these conditions and highlight possible geographic differences. It is important to acknowledge methodological differences between studies, which therefore limit the interpretation and comparison of their results. Studies providing better epidemiological data on comorbidities and potential environmental exposures will provide information to improve the care of patients with vasculitis and advance our knowledge of factors influencing disease.

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Conflicts of interest

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Epidemiology of myositis

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Purpose of review
This review aims to synthesize recent developments in the epidemiology of idiopathic inflammatory myopathies (IIMs), focusing on incidence, prevalence, disease classification, and clinical outcomes.

Recent findings
IIM is a rare group of autoimmune diseases characterized by muscle weakness and systemic involvement, with incidence rates ranging from 0.2 to 2 cases per 100 000 person-years. The role of myositis-specific autoantibodies (MSAs) in stratifying disease risk and prognosis is increasingly recognized, such as in anti-MDA5 positive DM, which is associated with a high risk of rapidly progressive interstitial lung disease. Furthermore, patients with IIM exhibit elevated risks of comorbidities, including cardiovascular disease and malignancy.

Summary
IIM diseases are complex disorders with significant health impacts, necessitating enhanced awareness and research. Improved classification and understanding of MSAs are crucial for earlier diagnosis and tailored therapeutic strategies. Continued epidemiological research is essential to elucidate underlying mechanisms and inform future interventions, ultimately aiming to enhance the quality of life and clinical outcomes for affected patients.

Keywords
dermatomyositis, epidemiology, immune mediated necrotizing myopathy, myositis, polymyositis

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs), or autoimmune inflammatory myopathies, are a diverse group of rare autoimmune diseases primarily affecting skeletal muscle but also involving other organ systems such as the skin, joints, lungs, heart, and gastrointestinal tract. IIM most often presents with sub-acute or chronically progressive, symmetric proximal muscle weakness, pain, and fatigue. But patients can develop a wide range of extra-muscular manifestations, making diagnosis challenging in some cases. IIM is rare, with an incidence rate of 0.2–2 cases per 100 000 person-years and a prevalence of 2–25 cases per 100 000 people [1–3]. In comparison, rheumatoid arthritis has an incidence of 13–37 per 100 000 person-years and a prevalence of 0.2–0.5% [4], while systemic lupus erythematosus (SLE) has an incidence of 23.2 per 100 000 person-years and a prevalence of 241 per 100 000 people [5]. Despite its rarity, IIM is associated with a significant negative impact on patients' mortality, morbidity, and healthcare utilization. Therefore, there is a pressing need for novel strategies and interventions to improve clinical outcomes for these patients.

Adult IIM can be divided into five main clinicopathologically distinct subtypes: dermatomyositis, polymyositis, immune mediated necrotizing myositis (IMNM), inclusion body myositis (IBM), and antisynthetase syndrome (ASyS) [2]. It is beyond the scope of this review to address pediatric IIM, like juvenile dermatomyositis (JDM). Additional work on this important patient population is urgently needed. The 2017 EULAR/ACR IIM classification criteria incorporate serological, clinical, and histopathologic data, reflecting newer understanding of IIM sub-types compared to prior IIM classification criteria, such as the Bohan and Peter criteria [6–8]. Myositis-specific antibodies (MSAs), for example, have become increasingly critical in establishing the diagnosis of IIM, identifying clinically important disease sub-types, and determining risk of particular

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KEY POINTS

- IIM is a rare group of autoimmune diseases characterized by muscle weakness and systemic involvement, with incidence rates ranging from 0.2 to 2 cases per 100 000 person-years.
- The role of myositis-specific autoantibodies (MSAs) in stratifying disease risk and prognosis is increasingly recognized.
- Patients with IIM exhibit elevated risks of comorbidities, including cardiovascular disease and malignancy.
- Continued epidemiological research is essential to elucidate underlying mechanisms and inform future interventions, ultimately aiming to enhance the quality of life and clinical outcomes for affected patients.

extra-muscular manifestations and probable outcomes [1,6].

This review aims to provide a rigorous and focused synthesis of recent developments in the understanding of IIM epidemiology, with a particular emphasis on incidence and prevalence, disease classification, and clinical outcomes.

Dermatomyositis

Dermatomyositis is characterized by unique skin lesions alongside a diverse array of systemic manifestations, including muscular, joint, and pulmonary involvement. The subset of dermatomyositis without muscle involvement is referred to as clinically amyopathic dermatomyositis (CADM). The distinct pathognomonic cutaneous findings of dermatomyositis include violaceous papules and macules overlying the extensor surfaces of joints (Gottron's papules and sign), heliotrope rash, V-sign, and shawl sign [1,9▪].

The age and sex-adjusted overall incidence of dermatomyositis from a population-based study of Olmsted County, Minnesota, USA, is 1.1 per 100 000 person-years, translating to 2858 new cases annually in the U.S. [10▪▪]. The incidence of dermatomyositis increases with age, peaking at 3.2 per 100 000 person-years in individuals aged 80 years and older, and is higher among women 1.9 per 100,000 person-years than men. The overall prevalence of dermatomyositis in the same cohort was found to be 13 per 100 000 person-years and 20 per 100 000 person-years among females. CADM had an incidence and prevalence of 0.5 and 7.0 per 100 000 person-years, respectively [10▪▪]. The mean (SD) yearly age and sex-adjusted incidence for dermatomyositis in a retrospective nationwide cohort study of US veterans was 1.0 (0.4) per 100 000 persons [11]. The age-adjusted incidence of dermatomyositis was estimated as 1.2 per 1 000 000 person-years in the first systemic review of IIM epidemiology in Africa [12], and dermatomyositis was the most prevalent (41%) IIM subtype in a cohort study from Oman with prevalence rate of 2.2 per 100 000 people [13].

MSAs are instrumental to diagnosis, risk stratification, and prediction of disease related complications [14]. Dermatomyositis-associated MSAs, in the order of decreasing prevalence in the MYONET registry, include anti-Mi-2, anti-TIF1γ, anti-MDA5, anti-SAE, and anti-NXP2 [3,15]. Of MSAs, the anti-TIF1γ-antibody, followed by the anti-NXP-antibody, has the strongest association with increased cancer risk [16▪▪]. Autoantibodies against cell division cycle and apoptosis regulator 1(CCAR1-antibodies) may be associated with lower cancer risk in anti-TIF1γ-Ab-positive dermatomyositis [17▪,18]. Anti-MDA5 Ab-positive dermatomyositis is typically amyopathic and is often complicated by rapidly progressive interstitial lung disease (RP-ILD). This form of dermatomyositis is more common in East-Asian populations, especially among women [14,15,19▪,20]. Anti-NXP2-Ab-positive dermatomyositis is a less common subtype of dermatomyositis that is often characterized by prominent muscle disease, calcinosis, and dysphagia [1].

Polymyositis

Polymyositis is characterized by proximal, symmetric muscle weakness without any cutaneous involvement. Polymyositis was historically regarded as a common form of IIM; however, its prevalence in more recent studies has declined as many patients previously diagnosed with polymyositis are now diagnosed instead with other conditions, such as IBM, IMNM, or ASyS [21]. There are no autoantibodies specific to polymyositis, and a thorough evaluation to rule out other mimicking diagnoses is crucial. Further research is needed to help clarify the true prevalence and incidence of polymyositis using newer classification criteria, such as the 2017 EULAR/ACR criteria.

Inclusion body myositis

IBM is the most common IIM subtype among individuals over age 50 years [2]. IBM typically presents with gradually progressive, asymmetric proximal muscle weakness particularly involving the quadriceps and/or finger flexors, and it may go to cause dysphagia or respiratory compromise [22,23]. While IBM has often been considered a disease that predominantly affects older, white men [2,3,24▪], a

recent analysis of IBM patients in the Johns Hopkins Myositis Center Registry noted a significant number of females, Black, and younger individuals [24▪]. Black, compared to non-Black, patients experienced significant proximal muscle weakness but less dysphagia. Women and those with onset before age 50 were more likely initially to be misdiagnosed with polymyositis. Additionally, women, compared to men, were more likely to develop dysphagia [24▪]. Autoantibodies to cytosolic 5′-nucleotidase (cN1a) are often observed in IBM and can aid in making the diagnosis [24▪,25▪].

In a recent population-based study in Olmsted County, Minnesota, USA, the incidence of IBM, based on the European Neuromuscular Center (ENMC) 2013 criteria, was 0.32–1.22 per 100 000 person-years, with a prevalence of 182 per million in individuals aged 50 years or older [26]. In a population-based study of western Sweden, IBM prevalence was 0.12 per 100 000 people and incidence was 0.012 per 100 000 person-years [25▪]. Key revisions to the 2024 ENMC IBM diagnostic criteria include decreasing the age cutoff for a common presentation of IBM from 50 to 45 years and anticN1a Ab positivity as supporting evidence of IBM [23]. These revised criteria will likely lead to higher estimates of IBM prevalence and incidence than have been previously observed.

Antisynthetase syndrome

This IIM subtype is characterized by the serologic presence of antiaminoacyl transfer RNA synthetase (ARS) antibodies, inflammatory myopathy, interstitial lung disease (ILD), arthritis, Raynaud's phenomenon, and 'mechanic's hands' [9▪]. ARS antibodies account for 25–35% of all myositis-specific antibodies and include anti-Jo1 (the most commonly reported ARS antibody), -PL7, -PL12, -EJ, -OJ, -KS, -Zo, and -Ha [27].

The prevalence and incidence of ASyS remains poorly characterized. Among MYONET registry participants, ASyS was one of the most common IIM, accounting for 17% of cases, following dermatomyositis (31%) and polymyositis (27%)[28]. Data on ASyS incidence and prevalence from non-European and North American populations are more limited. In a systemic review of IIM in Africa, the frequency of ASyS was 2.9% [12]. The mean (± SD) age of onset of ASyS is approximately 45 to 55 ± 15 years, and ASyS is more common among women than men [9▪,27,29,30,31▪▪].

Individual ARS antibodies are associated with increased risk of particular ASyS clinical manifestations. Isolated arthritis is associated with anti-Jo1 Ab positivity, isolated ILD with anti-EJ, myositis with anti-OJ, and Gottron's sign with anti-PL7 [27]. Anti-Ro52 positivity is associated with ILD, which can be rapidly progressing and confer an increased mortality [27]. Cutaneous manifestations in ASyS can overlap with those of dermatomyositis, but the presence of mechanic's hands, ILD, and rarely cardiac involvement can help differentiate ASyS with DM-like cutaneous feature from true dermatomyositis [9▪]. A recent large retrospective cohort study identified three distinct endotypes in ASyS patients using unsupervised clustering analysis based on clinical presentation and laboratory parameters: the rapidly progressing RP-ILD cluster, the DM-like cluster, and the arthritis cluster [31▪▪]. The RP-ILD cluster (23.7%) was characterized by severe lung disease, with 93% in this cluster developing RP-ILD and 70% experiencing acute respiratory failure. Other symptoms more commonly seen in the RP-ILD compared to other clusters were fever, dyspnea, and elevated CRP and ESR. The dermatomyositis-like cluster (14.5%) experienced heliotrope and Gottron's rashes, prominent muscle weakness, and increased prevalence of anti-PL7 antibodies positivity. The arthritis cluster (61.8%) primarily displayed arthritis/arthralgia and mechanic's hands and experienced the lowest risk of RP-ILD [31▪▪]. Interestingly, ARS profile was not a statistically significant factor identified by the machine learning algorithm used in generating these three unique ASyS endotypes.

Immune-mediated necrotizing myositis

IMNM is a rarer IIM subtype characterized by subacute, severe proximal muscle weakness, and markedly elevated serum CK levels [32]. IMNM can be further subclassified by antisignal recognition particle (anti-SRP) or anti3-hydroxy-3-methylglutaryl-coA reductase (anti-HMGCR) antibody positivity status, and a seronegative subclass also exists [32]. Anti-HGCR myopathy has been linked to statin exposure but can also occur in individuals with no known statin exposure [33,34]. Patients with anti-SRP myopathy have an increased risk of more severe muscle weakness and respiratory muscle involvement than anti-HMGCR or seronegative IMNM [32]. Extra-muscular manifestations of IMNM are rare. But cardiac involvement and ILD have been reported in anti-SRP myopathy [32,35]; and cutaneous manifestations (dermatomyositis-like rash) and Raynaud's phenomenon anti-HMGCR myopathy [32,34,36–38]. IMNM has a higher prevalence among women than men, and while the mean age of onset is between 40 and 65 years, it can occur at any age [3,32,39▪,40,41].

The total incidence of anti-HMGCR myopathy in Olmsted County, Minnesota, USA, was 0.83 per 100 000 person-years and prevalence was 1.85 per

100 000 people [40]. Among statin-exposed Americans, Native Americans compared to other racial/ethnic groups, had an approximately 150-fold increased prevalence of anti-HMGCR IMNM [42]. In recent UK, Spanish, and Australian cohorts, anti-HMGCR IMNM incidence ranged from 0.9 to 6.0 per million [34,41]. In New Zealand, the overall incidence of anti-HMGCR IMNM was 4.0 per 100 000 persons per year, with twice the incidence among those over 40 years old and five-fold increased incidence among those of Polynesian ancestry [39▪].

DISEASE OUTCOMES

ALthough IIM diseases are rare, they have a profound impact on both quality of life and life expectancy. High mortality rates in IIM stem from its association with ILD, malignancy, and cardiovascular disease (CVD). Understanding these outcomes is crucial for improving care strategies and enhancing the quality of life for individuals living with IIM.

Health-related quality of life

Certain comorbidities are common in IIM and contribute significantly to adverse outcomes, including end-organ damage and reduced patient productivity and well being. Individuals with IIM report poorer HRQoL and well being compared to the general population [43▪▪]. IIM disease activity and well being are inversely associated [44], but further research is needed to disentangle these complex and multifactorial relationships. For example, IIM patients with advanced age, multimorbidity, and mental health conditions are at particularly increased risk of worse physical function [43▪▪,45,46]. Patients with IIM may also face financial strain from medical expenses, caregiving, and/or physical disabilities [47,48]. Thus, physicians should seek out opportunities to personalize treatment plans and help mitigate adverse impacts of IIM on patients HRQoL.

Cardiovascular

IIM patients have significantly elevated cardiovascular risk compared to the general population, and cardiovascular disease is a significant cause of increased mortality in these patients [49,50▪]. This increased cardiovascular risk in IIM patients is driven not only by traditional cardiovascular risk factors, such as older age, male sex, dyslipidemia, hypertension, and smoking, but also likely by the chronic inflammation of IIM disease activity [51▪]. In polymyositis and dermatomyositis, the risk of adverse cardiovascular events is increased during the first five years after diagnosis compared during years 5 to 10 (relative risk of 3.51), suggesting that systemic inflammation related to IIM-disease activity may be a key determinant of this increased cardiovascular risk [52]. The risk of adverse cardiovascular events was approximately 2.5 times higher in polymyositis and dermatomyositis compared to other IIM subtypes, and men have 43% higher risk than women [52]. The prevalence of myocardial involvement in a single-center retrospective cohort of anti-MDA5 DM/CADM patients was 16%, with ventricular wall dyskinesia being the most common manifestation [53]. Cardiac involvement of IMNM is controversial and mostly reported in anti-SRP antibody myopathy [54]. A Chinese retrospective cohort study reported 50% prevalence of cardiac involvement in anti-SRP antibody-positive IMNM, where arrhythmia and ECG evidence of myocardial ischemia were the most common manifestations [54]. Cardiac involvement in anti-HMGCR and seronegative IMNM appears uncommon, but has been documented in case reports [54]. Future research is needed to advance understanding of the relationships of racial and ethnic diversity, genetic ancestry, socioeconomic status, and sex and gender with cardiovascular risk in IIM.

Malignancy

Patients with IIM are at an increased risk of malignancy, and this risk is greatest in dermatomyositis and specifically dermatomyositis with anti-TIF1γ or anti-NXP2 antibody positivity [55]. In a retrospective analysis of the Johns Hopkins Myositis Cohort, anti-TIF1γ antibodies were strongly associated with contemporaneous cancer, particularly breast and ovarian [56▪▪]. Cancers were also common in patients with anti-Mi2, anti-SAE, and anti-NXP2 antibodies. However, those with anti-HMGCR, anti-MDA5, and antisynthetase antibodies had cancer rates similar to those of the general population [56▪▪]. In a single-center study from China, the pooled prevalence of cancer in anti-TIF1γ dermatomyositis patients was 41%, with lung (23%), breast (17%), and gastric cancer (9%) reported most commonly [18]. In a retrospective analysis from Japan, the standard incidence rate (SIR) for early phase malignancy (malignancy diagnosis within 3 years of IIM onset) was highest among anti-TIF1γ compared to anti-ARS, anti-MDA5, and anti-Mi2 [55] positive patients. Anti-MDA5 dermatomyositis was associated with higher SIR of late phase malignancy (malignancy diagnosis within 4–10 years of IIM onset), suggesting longer duration cancer screening may be appropriate in these patients [16▪▪,55]. The International Myositis Assessment and Clinical

Studies Group (IMACS) recently published cancer screening guidelines for IIM patients [16▪▪], which is an important step in improving outcomes for these patients. However, when these guidelines were retrospectively applied to a dermatomyositis cohort, 90% were identified as intermediate or high-risk, and would thus be recommended to receive more comprehensive cancer screening evaluations (e.g. CT imaging) [57▪]. Thus, additional studies, including cost-effectiveness analyses, should continue to refine cancer screening practices in IIM and improve outcomes for these patients.

Clinical factors associated with heightened risk of malignancy in IIM patients include advanced age, male sex, smoking history, skin necrosis, dysphagia, rapid-onset myositis, low lymphocytic infiltration in muscle biopsies, elevated inflammatory markers, and obesity [18,58]. While anti-TIF1γ antibodies-positivity is associated with increased malignancy risk, recent data suggest certain anti-TIF1γ patients may have lower malignancy risk than others based on additional auto-antibody profiles. For example, autoantibodies against the cell division cycle and apoptosis regulator 1 (CCAR1) were found to be linked with decreased cancer prevalence in anti-TIF1γ-positive dermatomyositis patients [17▪]. Additionally, anti-TIF1γ dermatomyositis patients with compared to those without anti-Sp4 antibody positivity have lower cancer rates [59].

Pulmonary manifestations

The subtypes of IIM that are strongly associated with ILD include polymyositis, dermatomyositis, and ASyS [60]. ILD was the common manifestation (96.6%) in a Chinese cohort [31▪▪] and frequently reported in patients with ant-Jo1, -PL12, -PL7, and -EJ antibody positive patients [9▪,27,30,31▪▪]. Screening for ILD is warranted for patients with anti-MDA-5 dermatomyositis, ASyS, or overlap antibodies (e.g. PM-Scl, Ku, Ro52) as the presence of these autoantibodies are associated with heightened ILD risk [61]. RP-ILD is a severe and often fatal complication of anti-MDA5 dermatomyositis, with over 60% mortality within six months [20,62]. In another Chinese cohort, around 40% of anti-MDA5 dermatomyositis patients develop RP-ILD [62]. Various clinical factors are likely associated with mortality from RP-ILD in anti-MDA5 dermatomyositis, including older age, male sex, poorer baseline pulmonary function, lymphocytopenia, high serum ferritin or CRP levels, anti-Ro52 antibody positivity, and severity of ILD at the time of diagnosis [14,20,62]. However, clinician's ability to predict which anti-MDA5 dermatomyositis patients will or will not develop RP-ILD remains very limited. In recent studies, elevated plasma levels of secreted phosphoprotein 1 (SPP1) [63] and specific polymorphisms in the *WDFY4* gene [62] may be associated with RP-ILD risk in anti-MDA5-DM, and if these relationships are replicated in additional studies, these biomarkers may be useful in improving RP-ILD risk stratification efforts in these patients.

CONCLUSION

IIM encompasses a varied spectrum of clinical disease that leads to significant adverse health impacts for patients. Recent advancements in the understanding of IIM epidemiology, in particular the use of specific MSAs to help risk-stratify patients, has improved clinicians' ability to identify important clinical phenotypes and in turn to improve patient outcomes. Future work should build on this recent progress to close key knowledge gaps concerning the complex relationships between environmental (e.g. comorbidities, social determinants of health) and genetic risk factors for IIM incidence and disease progression; and should continue to incorporate increasingly diverse (e.g. racial/ethnic, SES) patient populations. Multidisciplinary approaches leveraging novel causal inference and genetic epidemiologic methods may be especially helpful in further disentangling these relationships and identifying opportunities for therapeutic intervention.

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Conflicts of interest

There are no conflicts of interest.

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Releasing our model T – chimeric antigen receptor (CAR) T-cells for autoimmune indications

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Purpose of review
This review provides an update on the rapidly growing field of engineered cellular therapies for autoimmune disorders, primarily focusing on clinical experience and correlative studies with chimeric antigen receptor (CAR) T-cells.

Recent findings
To date, two case series describing treatment with CAR T-cell therapy for systemic lupus erythematosus (SLE) suggest that drug-free remission can be sustained in patients with previously treatment-refractory disease. The outcomes of these studies are similar, despite the use of different CAR constructs and lymphodepletion regimens. Although it is not yet clear whether the patients described have truly been cured, the majority of remissions have remained durable up to last follow-up at 1–2 years from treatment. Meanwhile, mechanistic studies are providing a window into how transient B-cell depletion mediates lasting benefit. With the encouraging data in SLE, CAR T-cells and other novel B-cell-depleting agents (e.g. bispecific T-cell engagers) are now being evaluated as treatment for other autoimmune conditions, with the goal of durable response.

Summary
Recent reports highlight cellular therapies as a promising strategy for patients with treatment-refractory autoimmune conditions; however, there is still limited experience, and better insight into this therapeutic approach is expected to emerge rapidly.

Keywords
bispecific antibody, chimeric antigen receptor, systemic lupus erythematosus

INTRODUCTION

Chimeric antigen receptor (CAR) T-cells are an exciting new avenue of treatment for autoimmune disease, offering the potential to induce immune tolerance and potentially cure disease. These T cells are genetically engineered to express a receptor combining the cell surface antigen recognition domain of an antibody with the intracellular signaling machinery of a T-cell receptor [1]. CD19-targeted CAR T-cells have been transformative for treating refractory B-cell leukemias and lymphomas. Although life-threatening toxicities of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and immune effector cell-associated hemophagocytic lymphocytic histiocytosis-like syndrome (IEC-HS) emerged in the treatment of patients with malignant disease, the diagnosis, grading, and management of these toxicities are now well understood, making it possible to expand this strategy to other patient populations. Following a seminal study from Germany in which five patients with refractory systemic lupus erythematosus (SLE) achieved drug-free remission [2▪], interest in cellular therapies for rheumatic conditions has blossomed. There are dozens of academic and industry-sponsored trials opening across the globe (Supplementary Table 1, http://links.lww.com/COR/A60). In this review, we provide an overview of the status of CAR T-cell therapies for autoimmune disease, focusing on clinical experience in SLE, mechanisms of action, expanding indications, parallel approaches using bispecific T-cell engagers (BiTEs), and safety considerations.

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KEY POINTS

- B-cell-targeted CAR T-cells may induce remission in patients with treatment refractory autoimmune disease.
- Mechanisms of action of CD19 CAR T-cells are multifaceted, and durability of response beyond CAR-T persistence may be attributed to remodeling of the B-cell compartment.
- Bispecific T-cell enagagers may provide an off-the-shelf strategy to accomplish similar B-cell compartment remodeling, but whether they can induce and sustain drug-free remission is yet to be established.
- The safety signal of CAR T-cells in autoimmune disease has been reassuring thus far, but too few patients have been treated to establish the frequency of rare events.

SYSTEMIC LUPUS ERYTHEMATOSUS CLINICAL EXPERIENCE

The initial success of CD19 CAR T-cells in the German SLE cohort led to widespread enthusiasm for this approach. However, key questions include whether these results can be replicated in larger and independent cohorts, whether clinical remission off medication will be durable, whether serious adverse events will emerge with more patients treated, and if the same lymphodepleting regimen used in oncologic indications is needed in patients with autoimmunity. Although these questions will be addressed by ongoing, industry-sponsored trials, two recent academic studies provide some insights.

The first study, by Müller *et al.* [3▪], is a subsequent report of the original German cohort, now including eight patients with SLE with 6–29 months of follow-up. Patients were 15–32 years of age at diagnosis and had 1–20 years of disease duration prior to CAR T-cell treatment. All had proliferative lupus nephritis (class III or IV ± V). The median baseline SLE Disease Activity Index SLE Disease Activity Index (SLEDAI)-2K score was 13. Patients received lymphodepleting chemotherapy with fludarabine and cyclophosphamide prior to CAR T-cell infusion. All achieved 'Definition of Remission in SLE' (DORIS) criteria (see Table 1 for disease activity definitions) by 6 months and were in drug-free remission. Two individual case reports of CD19 CAR T-cell therapy in SLE have also been published, including an adult with refractory thrombocytopenia (nonrenal indication) and an adolescent on dialysis from chronic kidney disease, both of whom achieved an objective clinical response [4,5].

Complementing the CD19 CAR T-cell data, a phase I study of autologous CAR T-cell therapy for SLE was completed in China (Wang *et al.*). For this study, the CAR construct included CARs targeting both BCMA (plasma cell marker) and CD19 [6▪▪]. Thirteen patients were included, with 6–46 months of follow-up. The first two patients had concomitant diffuse large B-cell lymphoma. The remaining 11 patients were 14–26 years of age at SLE diagnosis, with 1–21 years of disease duration prior to CAR T-cell therapy. As with the German cohort, all had lupus nephritis (class III or IV ± class V; one isolated class V). The median baseline SLEDAI-2K score for patients with SLE alone was 10. Lymphodepletion prior to CAR-T infusion was with cyclophosphamide alone. One patient with SLE-related marrow suppression received half the target dose, did not experience a durable remission, and was re-treated after a second apheresis but again relapsed and was suspected to have anti-CAR antibodies. Nine of 13 patients met DORIS criteria [7], and 12 of 13 achieved Lupus Low Disease Activity State (LLDAS) criteria [8] off immune

Table 1. Indices used to assess disease response to chimeric antigen receptor-T-cell therapy

Composite disease activity indices/definitions of low disease activity
Systemic lupus erythematosus
DORIS – Clinical SLEDAI = 0; Physician Global Assessment <0.5 (0–3); may be on antimalarials, low-dose glucocorticoids (prednisone ≤5 mg/day), and/or stable immunosuppressives
LLDAS – SLEDAI-2K ≤4, with no activity in major organ systems or new features of SLE activity; Physician Global Assessment ≤1 (0–3), prednisone (or equivalent) dose ≤7.5 mg/day, and well tolerated standard maintenance doses of immunosuppressive drugs
Idiopathic inflammatory myositis
ACR-EULAR major response – total improvement score ≥60 in adult DM/PM, based on improvement scores in six domains
Systemic sclerosis
EUSTAR-Activity Index – disease activity score with worsening skin (+1.5), digital ulceration (+1.5), mRSS >18 (+1.5) or < 18 (mRSS score × 0.084), tendon friction rub (+2.25), CRP >1 mg/dl (+2.25), and DLCO <70% predicted (+1) that sum to total score out of 10
Rheumatoid arthritis
DAS-28-CRP – disease activity score that includes tender and swollen joint counts, patient global assessment score, and CRP; a score of >4.6 corresponds to high disease activity, whereas <2.6 is considered to be remission

ACR-EULAR, American College of Rheumatology-European Alliance of Associations for Rheumatology; CRP, C-reactive protein; DAS-28-CRP, Disease Activity Score 28-CRP; DLCO, diffusing capacity for carbon monoxide; DM, dermatomyositis; DORIS, Definition of Remission in SLE; EUSTAR, European Scleroderma Trials and Research group; LLDAS, Lupus Low Disease Activity State; mRSS, modified Rodnan Skin Score; PM, polymyositis; SLEDAI, SLE Disease Activity Index.

Table 2. Summary of case series of chimeric antigen receptor-T-cell therapy in systemic lupus erythematosus

	Group size	Median age at CAR-T	Median SLEDAI	Prior RTX	Prior Cy	CAR	CAR-T-cell dose	Lymphodepletion	Response	AEs
Müller *et al.*	8 (1 male)	23.5 (range 18–38)	13	4/8	5/8	CD19	1×10^6 cells/kg	Flu (25 mg/m^2/day × 3 days) Cy (1000 mg/m^2)	8/8 achieved drug-free remission	CRS (grade 1) No ICANS 1 UTI, 1 URI, 1 PNA
Wang *et al.*	13 (3 males)	29 (range 16–46)[a]	10[a]	0/13	8/13	CD19 BCMA[b]	3×10^6 cells/kg	Cy (300 mg/m^2) × 3 days	9/13 achieved drug-free remission	CRS (grade 1) No ICANS 1 UTI 3 URI requiring hospitalization

AE, adverse events; CRS, cytokine release syndrome; Cy, cyclophosphamide; Flu, fludarabine; ICANS, immune effector cell-associated neurotoxicity syndrome; PNA, pneumonia; RTX, rituximab; SLEDAI, SLE Disease Activity Index; URI, upper respiratory tract infection; UTI, urinary tract infection.
[a]For patients with SLE alone (no concomitant lymphoma).
[b]Targets cells that contain BCMA or CD19; construct also included IL-15/IL-15 sushi domain.

suppressive medications. Three patients with significant baseline proteinuria/chronic kidney disease met LLDAS but not DORIS criteria.

Similarities between these case series include treatment of patients mostly in their 20–30s, all with treatment refractory disease. Taken together, most patients achieved and maintained drug-free remission (4 with >2 years follow-up) with a favorable treatment-related toxicity profile (Table 2). Finally, Wang *et al.* show that clinical response may be achieved with less lymphodepletion than used for malignant indications, although this requires confirmation in larger studies.

MECHANISMS OF ACTION

In the treatment of B-cell malignancies with CD19 CAR T-cells, durability of response is linked to persistence of CAR T-cells, which can be inferred by prolonged B-cell aplasia [9▪]. Curiously, in the studies described above, B-cells were rapidly eliminated but repopulated 2–4 months later, some (but not all) autoantibodies normalized, and most patients sustained remission without additional medication. These findings raise key mechanistic questions. Why are CD19 CAR T-cells more effective in some patients than other B-cell-targeting agents like rituximab? If plasma cells are CD19-negative, why do we see reduction in many autoantibodies after CD19 CAR T-cell therapy? If SLE is marked by broad immune dysregulation [10], why should targeting the B-cell compartment alone permit drug free remission? Lastly, what is the mechanism of durability of response?

The answer to the first question is the least elusive – rituximab leads to incomplete B-cell depletion, particularly in the tissues, and misses the CD20-negative plasmablast population [11▪]. This has recently been shown in a comparison of lymph node tissue depletion of CD19+ cells in five patients with autoimmunity treated with CD19 CAR T-cells vs. five patients treated with rituximab. Biopsies were obtained during periods of complete peripheral B-cell depletion. CD19+ and CD20+ B-cells were fully eliminated from lymph node tissues after CD19 CAR T-cell therapy but not after rituximab [12▪]. Post-CAR-T biopsies in three patients with SLE showed CD19+-cell depletion in additional organs including the kidney. Of note, obinutuzumab, an anti-CD20 monoclonal antibody glycoengineered to facilitate antibody-dependent cellular killing, showed improved B-cell depletion and renal response rates compared with rituximab-treated historical controls with proliferative lupus nephritis (compare NOBILITY to LUNAR trials), suggesting that potentiated antibody-mediated cellular cytotoxicity itself may achieve deeper B-cell depletion [13,14].

Understanding autoantibody depletion after CAR T-cell therapy is more nuanced. In a recent study, phage immunoprecipitation sequencing was used to study the autoantibody profiles of healthy individuals as well as those with malignancy pre- and post- CAR T-cell therapy [15▪]. The investigators found that even healthy individuals make autoantibodies, creating a molecular fingerprint termed the 'autoreactome', which is stable over time. When the autoreactome of patients with malignancy was analyzed in the context of different CAR T-cell therapies, it was minimally impacted by CD19 CAR T-cells but dramatically influenced by BCMA CAR T-cells. To reconcile these data with the clinical response of patients with SLE to CD19 CAR T-cell therapy [3▪], the authors postulate that CD19+ cells may be a source of some pathogenic autoantibodies and/or have additional pathogenic functions beyond autoantibody production. Indeed, a recent review highlights that autoantibodies arise from three sources – activated, switched memory B-cells (CD19+), short-lived plasmablasts (CD19+), and long-lived plasma cells (BCMA+), with different autoantibodies deriving more prominently from different sources [11▪]. Changes in autoantibodies

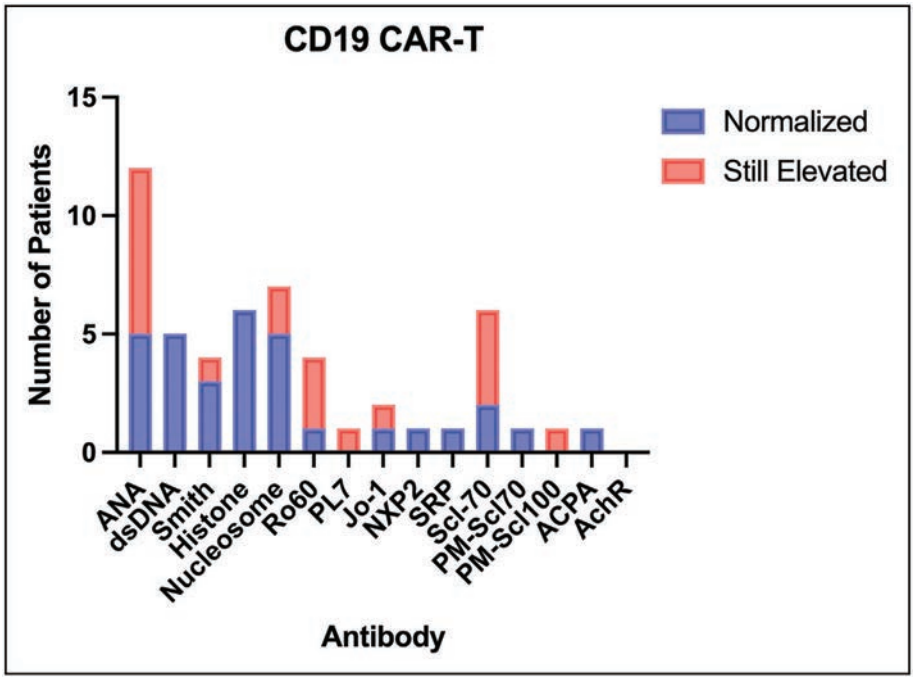

FIGURE 1. Normalization of autoantibodies after chimeric antigen receptor T-cell treatment. The scale reflects the fraction of patients initially with elevated levels of a given autoantibody who had normal levels post CAR T-cell treatment. Reductions without normalization are not captured [3▪,19▪,20]. CAR-T, chimeric antigen receptor-T cell.

after CD19 CAR T-cell therapy from the limited number of reported cases are summarized in Fig. 1. However, these findings are qualified in that autoantibody levels often track poorly with clinical disease.

In terms of B-cell compartment targeting, increasing data suggest widespread consequences of CD19 targeting in SLE. Wilhelm *et al.* [16▪▪] performed deep immune profiling following CD19 CAR T-cell therapy in patients with SLE using single-cell RNA-seq and TCR-seq. The general composition of the monocyte and T-cell compartments was largely unchanged, as was the TCR repertoire. However, there was a significant reduction in the interferon signature in these compartments, supporting a model in which B-cells contribute to interferon signaling through production of antibodies and subsequent immune complexes that are recognized by innate signaling mechanisms in other cell types. B-cells also secrete cytokines, serve as antigen-presenting cells, and contribute to the germinal center niche in lymph nodes [11▪]. Indeed, lymph node biopsies of patients treated with CD19 CAR T-cells show disrupted follicular dendritic cell networks and fewer T-follicular helper cells. It has been postulated that follicular dendritic cells may acquire CD19 from B-cells through trogocytosis, making them an additional CD19 CAR T-cell target [12▪]. These multifaceted mechanisms related to CD19+ cell targeting are depicted in Fig. 2.

Lastly, while follow-up has been less than 5 years for all reported cases, maintenance of remission after peripheral B-cell re-population suggests a 'reset' of this compartment. As described in the original Mackensen *et al.* article [2▪], profiling of B-cells before and after treatment shows reduction of memory B-cells, an increase of naive and transitional B-cells, and a concomitant shift in B-cell receptor clones that produce IgA and IgG to distinct clones that produce IgD and IgM [16▪▪].

EXPANDING INDICATIONS

Given the promising data in SLE, CAR T-cells are now being evaluated in additional autoimmune conditions, particularly those characterized by autoantibody production and established use of B-cell-targeted therapies. These include systemic sclerosis (SSc), idiopathic inflammatory myositis (IIM), rheumatoid arthritis, ANCA-associated vasculitis (AAV), myasthenia gravis, and neuromyelitis optica spectrum disorder.

In the same study by Müller *et al.* [3▪], three patients with IIM and four patients with SSc were described. They were older than those treated for SLE and had shorter average disease duration prior

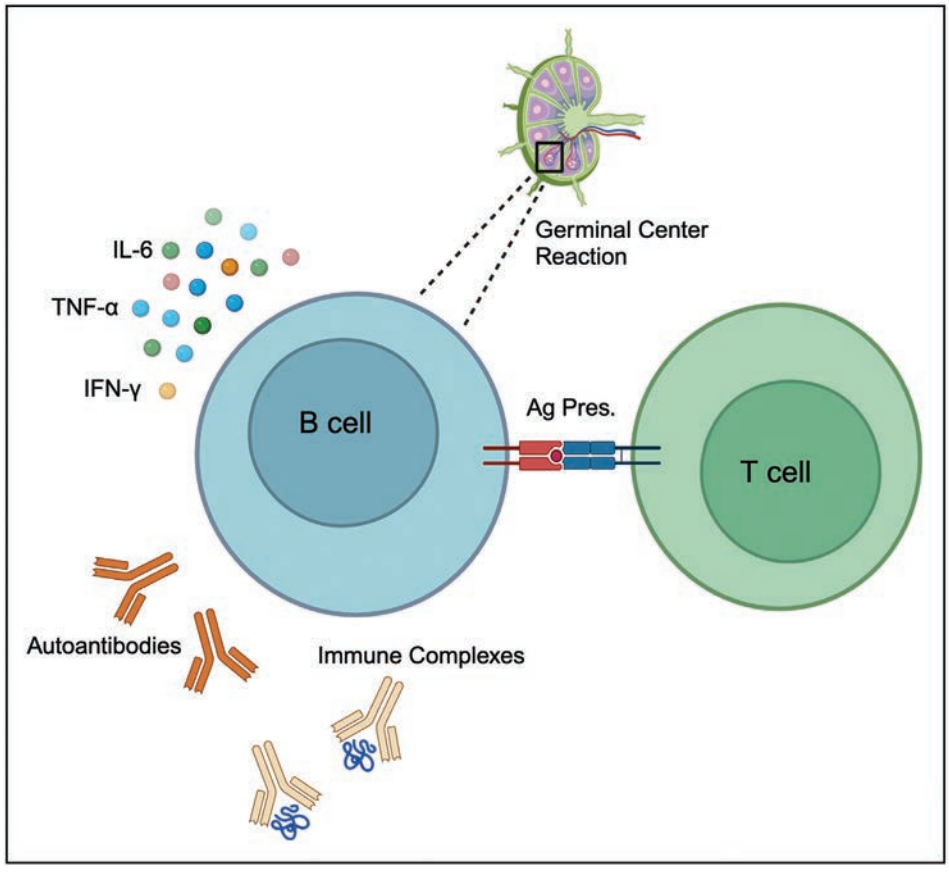

FIGURE 2. The multifaceted contribution of B-cells in lupus. Activated B-cells secrete inflammatory cytokines and produce autoantibodies. These antibodies can bind nucleic acids to form immune complexes that can be internalized by monocytes and dendritic cells (not shown), resulting in inflammatory signaling. Immune complexes may also deposit in tissues and result in direct tissue damage after complement fixation. B-cells are also antigen-presenting cells and contribute to the normal architecture of the germinal center in lymph nodes. Created using Biorender.com.

to CAR T-cell treatment. All patients had interstitial lung disease, although patients with IIM also had active myositis and patients with SSc had active skin disease. After CD19 CAR T-cell treatment, all patients with IIM had normalization of creatine kinase (CK) and manual muscle test 8 (MMT-8) scores and achieved an ACR-EULAR Major Clinical Response [17]. The three patients with SSc that had more than 6 months of follow-up all had an improvement in their modified Rodnan skin score (mRSS; median 9 point decrease) and a median decrease in the EUSTAR-Activity Index [18] of 4.2. As with SLE, these patients remained off all immunosuppressive agents at last follow-up.

Experience in treating IIM and SSc was recently expanded by Wang *et al.* [19▪] who used an allogeneic CD19 CAR T-cell platform to treat one patient with IIM and two patients with SSc, with 6 months of follow-up. CAR T-cells made from healthy donors were CRISPR-Cas9 edited to knock out *HLA-A, HLA-B*, and *CIITA* to prevent host rejection of CAR T-cells and *TRAC* to prevent graft-vs.-host disease. Allogeneic CD19 CAR T-cells led to rapid B-cell depletion that lasted 2–3 months. There was no CRS or graft-vs.-host disease. The patient with IIM had SRP antibody-positive necrotizing myopathy of 10 years duration. Three months following CAR T treatment, her CK levels decreased from 2295 to 234 U/l and her MMT-8 improved from 75 to 145/150. SRP antibody levels became undetectable, and muscle necrosis on baseline biopsy was mostly resolved by 6 months. The two patients with SSc were Scl-70 antibody-positive and had multisystem disease. Following treatment, both mRSS scores decreased by 20 points, with reduction of TGF-β expression in biopsied skin. In one patient with significant ILD at baseline, there was improvement in chest imaging and reduction of KL-6 antigen by 6 months, although forced vital capacity was largely unchanged. Scl-70 antibodies reduced in both patients, although started to rebound in one patient by month 6 following CAR T-cell infusion. As with prior studies, other

immunosuppression had been stopped prior to CAR-T infusion except for low-dose glucocorticoids.

In terms of rheumatoid arthritis, there is one report of autologous CD19 CAR T-cell therapy in a female individual with comorbid myasthenia gravis [20]. CAR T-cell therapy led to rapid improvement in both myasthenia gravis and RA symptoms (DAS-28-CRP 4 → 1) with normalization of anticitrullinated peptide antibodies. For more on CAR T-cells in neurologic disorders, the reader is directed to additional reports [21–24]. Lastly, while there are no clinical cases of using CD19 CAR T-cells in patients with AAV, a proof-of-concept study in an MPO+ AAV mouse model led to protection from necrotizing crescentic glomerulonephritis [25], and open trials will determine whether this disease is similarly responsive.

ALTERNATIVE STRATEGIES: BISPECIFIC T-CELL ENGAGERS

The dramatic clinical response to CAR T-cells has raised the possibility of using BiTEs, which bind CD3 and a cell-specific antigen to promote elimination of target cells by endogenous T cells. Advantages to this strategy include that it is off-the-shelf, does not require lymphodepleting chemotherapy, and has no risk of insertional mutagenesis. However, unlike CAR T-cells, BiTE-based therapies have not typically been curative when used for malignant conditions.

In the last year, BiTEs have started to be evaluated in autoimmune disease. In one case series, blinatumomab (CD3 × CD19) was provided to six patients with refractory RA [26▪▪]. The median number of prior failed therapies was seven, all of which were discontinued 3 weeks prior to blinatumomab, save for background methotrexate. Blinatumomab was given as a continuous infusion over 5 days with a second cycle 1 week later [27]. Abatacept was started as a maintenance agent at week 16. Treatment led to peripheral depletion of CD19+ cells, and, to a lesser extent, T cells, which were 'consumed' during T-cell engagement. The median tender joint count decreased from 9.0 to 0.5, and mean DAS-28-CRP improved from 4.72 to 2.28 at 3 months, correlating with improvements in sonographic assessment of synovitis. Synovial biopsies pretreatment and posttreatment in two of three patients showed undetectable staining for CD19, suggesting blinatumomab at least partially reached the tissues. Interestingly, the single patient with incomplete synovial tissue depletion flared at month 3. As with CAR T-cell therapy, the B-cell compartment showed remodeling with reduction in memory B-cells and an increase in naive B-cells.

In two additional letters, five patients were treated with step-up doses of subcutaneous teclistamab, a bispecific antibody (CD3 × BMCA) targeting plasma cells [28,29]. Each patient had a different autoimmune disease and had failed more than five prior therapies. Prior immune suppression was weaned or discontinued prior to start. All patients showed clinical improvement, although the follow-up period is insufficient to comment on long-term remission.

Overall, these studies suggest alternative immunotherapy approaches can promote clinical improvement in patients with treatment-refractory disease, although relative efficacy compared with CAR T-cells is not established.

SAFETY CONSIDERATIONS

Whether the adverse events experienced by patients treated with CAR T-cell or BiTE therapy for autoimmune disease will be the same as those treated for malignancy is unknown. Both strategies carry theoretical risks of the inflammatory side effects of CRS and ICANS. More recently, toxicities of IEC-HS [30] (resembling HLH) and immune effector cell-associated hematotoxicity (ICAHT) [31] have been described. In addition, less commonly identified toxicities will likely continue to emerge [32]. In malignancy, the underlying disease burden and rate of in-vivo expansion and persistence of CAR T-cells are some determinants of toxicity. Thus far, CRS after CAR T-cell therapy for autoimmune disease has been low grade [3▪,6▪▪], and ICANS has been rare [33]. Early (<30 days post-CAR-T) hematopoietic toxicity has been reported, although details are unknown [6▪▪]. In a propensity-matched study, adult patients with and without a history of autoimmune disease treated for lymphoma with CD19 CAR T-cells ($n = 58$ in each group) showed similar rates of CRS and ICANS, suggesting a history of autoimmunity does not increase baseline risk for adverse events [34▪].

Another consideration is the risk for infection. In the described literature for CAR T-cells and BiTEs in autoimmune disease, several patients had upper respiratory tract and urinary tract infections after treatment [6▪▪,9▪,26▪▪,29]. Progressive multifocal leukoencephalopathy (PML) due to JC virus reactivation is a rare side effect of other B-cell-targeting agents like rituximab. In adults receiving CD19 CAR T-cells for malignancy, the reported incidence of PML is 0.9 cases per 1000 [35]. As patients with autoimmune disease appear to have much shorter CAR-T persistence relative to those with malignancy, disease-specific risk for PML remains to be established.

Finally, in the last year, risk of secondary malignancy after CAR T-cell therapy has emerged, resulting in a new FDA boxed warning. Since the first clinical gene therapy trials in which viral vectors were used for gene insertion, insertional mutagenesis has been a known potential toxicity [36] leading to the requirement for 15-year follow-up [37]. However, analysis of large cohorts of CAR T-cell recipients suggests the risk of lymphoma arising from genetically modified T cells is low, with secondary malignancies more likely to result from preexisting somatic mutations and clonal hematopoiesis in patients with a history of primary malignancy [38▪▪,39,40]. Clonal hematopoiesis has also been described in autoimmunity and is a developing area of research [41–43], although shorter CAR T-cell persistence may also protect against this complication. In the future, introducing CARs using non-integrating viruses or mRNA-based methods [22,44], or switching to BiTEs, may avoid the risk of insertional mutagenesis altogether.

CONCLUSION

In conclusion, there is growing evidence that B-cell-targeting CAR T-cell therapy can achieve drug-free remission in patients with treatment-refractory lupus and other autoimmune diseases. As the number of published cases is still small, the durability of response and patient-specific factors that predict outcome and toxicity remain to be determined. We anticipate that results from several industry-sponsored trials will address these issues, creating a path for expansion to pediatric patients. In parallel, further exploration of BiTEs for autoimmune disease is also anticipated. The cellular therapy field is growing rapidly, and there are several strategies that were not discussed in depth in this article. These include allogeneic, off-the-shelf products and CAR-based therapies relying on alternative cell sources such as natural killer cells [45▪] and regulatory T cells [46–48]. This collective and exciting progress is made possible by a close collaboration between oncologists and rheumatologists who share a determination to bring curative therapies to patients with autoimmune disease.

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Conflicts of interest

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- ▪ of special interest
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Pathogenesis of psoriatic arthritis: new insights from a bone marrow perspective

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Purpose of review
Psoriatic arthritis is an immune-mediated disease that primarily affects the skin and joints. It falls under the umbrella term of rheumatic diseases, which describes a group of closely related yet distinct disorders with many common underlying molecular pathways. Despite the distinct clinical manifestation of each disorder, the shared therapeutic strategies attest to the commonality of cellular and molecular underpinnings. Herein we provide a concise yet comprehensive overview of the interleukin (IL)-23/IL-17 axis and its involvement in mechanistic pathways leading to the pathogenesis of this dual skin and joint clinical manifestation which is characteristic of psoriatic arthritis and other rheumatic diseases.

Recent findings
The interconnection between activated innate immune cells and adaptive immunity has transformed current thinking to include other organs such as the bone marrow as potential tissue of disease origin. A plethora of animal models and genetic studies converge on the critical role of IL-23/IL-17 axis, and highlight the importance of myeloid cell activation as common pathways between autoinflammatory and autoimmune diseases and chronic inflammation. These findings underscore the intricate immune mechanisms involved in inflammatory arthritis and highlight molecular mechanisms in disease pathogenesis.

Summary
These insights pave the way for the development of novel diagnostic and therapeutic strategies, with a focus on translating these findings into improved clinical practice.

Keywords
bone marrow, interleukin 17, interleukin 23, myeloid cells, psoriatic arthritis

INTRODUCTION

Psoriatic arthritis (PsA), an extra-cutaneous feature of psoriasis (PsO), primarily involves the small joints of the hands including distal interphalangeal (DIP), proximal interphalangeal (PIP), and metatarsal phalangeal (MP) joints that may eventually lead to the sausage fingers. In adults, it can present after the clinical manifestations of PsO and affects both males and females almost indiscriminately [1]. It affects up to 30% of people with psoriasis and 0.10–0.25% of the adult general population [2]. Understanding the pathogenesis of PsA remains a challenge due to the complex interplay of diverse tissues and tissue-specific immune responses that occur simultaneously. This complexity is further compounded by varied clinical presentations, unpredictable progression, and heterogeneous responses to treatment. Moreover, the intricate interaction between the immune system and various factors like genetic susceptibility, biomechanical stress, environmental stressors, epigenetic changes, and microbiome dysbiosis complicates the formulation of definitive diagnostic markers and therapeutics. Therefore, it's timely and appropriate to investigate the cellular and molecular mechanisms of disease pathogenesis.

In most adult patients, PsA occurs first in the skin and then progresses to the joints [3]. A prospective study found that the annual incidence rate of PsA was 2.7 cases (95% confidence interval 2.1–3.6) per 100 psoriasis patients [4]. Consequently, genetic studies on PsA are usually compared to psoriasis. However, it is worth noting that some of those studies will be confounded by phenotype misclassification due to the presence of unidentified

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KEY POINTS

- Recent advances in clinical and experimental imaging highlight the bone marrow as a critical tissue of disease pathogenesis.
- Animal models that concurrently exhibit skin and joint inflammation have been instrumental to elucidate the importance of bone marrow involvement, myelopoiesis and the interleukin (IL)-23/IL-17 axis in the pathogenesis of psoriatic arthritis.
- These findings pave the way for the development of novel diagnostic and therapeutic strategies, with a focus on translating these insights into improved clinical practice.

PsA patients within the psoriasis study groups. Moreover, in pediatric patients' disease can occur in the joints first and then followed by inflammation of the skin [5]. Hence, data from animal models with functional significance may be critical in elucidating pathogenetic mechanisms.

INSIGHTS FROM ANIMAL MODELS

Animal models have been extensively used to study inflammatory arthritis, but in most commonly used models such as collagen-induced arthritis, collagen-antibody induced arthritis, or serum transfer arthritis KBxN only joint inflammation occurred. On the contrary, in animal models of skin inflammation such as the imiquimod model [6] and tape striping model [7] skin inflammation was studied in the absence of arthritis. An important animal model that showed dual characteristics of skin and joint inflammation was the SKG mouse. In that model, a point mutation in the ZAP-70 gene, yielded reduced T-cell receptor (TCR) signaling that causes severe synovitis with progression of synoviocyte proliferation, pannus-eroded adjacent cartilage and subchondral bone along with infiltration of inflammatory cells in the skin, depicting the features of chronic arthritis with skin inflammation [8]. However, as the inflammation occurs in the joints and then progresses to extra-articular manifestations that include dermatitis it was considered more of a model that resemble rheumatoid arthritis and not PsA.

In PsA, several alleles of human leukocyte antigen (HLA), present in the genetic region of the major histocompatibility complex (MHC) on chromosome 6, are responsible for the synovial and cutaneous manifestations and the heterogeneous clinical manifestation of the disease [9,10]. Therefore, the HLA-B27 model, which has introduced the B27 and human β2-microglobulin genes into rats, is considered to more closely resemble the human disease [11]. Further studies revealed that HLA-B27 is prone to misfold in the endoplasmic reticulum resulting in activated unfolded protein response (UPR) of bone marrow macrophages [12]. Cytokine production by bone marrow macrophages analyzed in the presence or absence of UPR-induction or HLA-B27 upregulation revealed an increased expression of IL-23 associated with Th17 activation and robust upregulation of IL-17 [13▪▪].

The role of IL-23 in the pathogenesis of skin inflammation was highlighted when it was demonstrated that direct intradermal administration of IL-23 in mouse skin initiates a cascade of events resulting in erythema, mixed dermal infiltrate, and epidermal hyperplasia associated with parakeratosis [14]. Interestingly, gene transfer of IL-23, which recapitulates more closely the human condition where elevated IL-23 is detected in the circulation and not just the skin, demonstrated an increased myeloproliferative bone marrow with increased activation of bone resorbing osteoclasts leading to erosive arthritis [15▪,16]. Both the skin and bone phenotype observed in these two IL-23-induced animal models were independent of IL-17. Furthermore, highlighting the significance of IL-23 as driver of skin inflammation and subsequent arthritis has been manifested in the K-23 mouse model which showed that mice expressing increased levels of IL-23 in the skin develop PS and PsA, including dactylitis, enthesitis and joint destruction. Of note, the skin abnormalities preceded development of enthesitis, dactylitis, and bone destruction, depicting skin inflammation as the initiator of joint inflammation [17].

Another model that closely resembles PsA is the in vivo gene transfer model of IL-17A [18]. In this model, overexpression of IL-17A leads to a myeloproliferative bone marrow which results in skin inflammation over time, but no spontaneous arthritis is observed. However, there is an increased expression of osteoclast precursors which express the receptor activator of nuclear factor kappa beta (RANK) and c-fms receptor and these result in exacerbated responses during collagen-induced arthritis and in ex-vivo osteoclastogenesis assays accounting for a more erosive phenotype. Similarly, adoptive transfer of bone marrow derived neutrophils from IL-17A gene transfer mice is sufficient to transfer skin inflammation in naïve mice resulting in resulting in erythema, mixed dermal infiltrate, and epidermal hyperplasia associated with parakeratosis similar to the IL-23 local injections [19].

Another important model is the transmembrane TNF (tmTNF) which results in osteoproliferative joint inflammation with synovitis, enthesitis and osteitis, but even after extensive histological analysis

of extra articular sites revealed no inflammation or other pathology in skin, colon, and intestine of 100-day-old *tmTNF tg* mice [20]. Although there are undoubtedly other notable animal models to reflect the complex features of human PsA the aforementioned models are sufficient to highlight the importance of the IL-23/IL-17 axis in this disease. One question that remains unsolved is which tissue is responsible for the pathogenesis of PsA. Although the clinical manifestation is predominantly in the skin and joints other organs are also involved. This type of disease manifestation has transformed current thinking to include other organs such as the bone marrow or the gut as potential tissues of disease origin.

BONE MARROW

These transgenic mice have highlighted that disease manifestation can occur in either order (skin to joint or joint to skin). More importantly it has highlighted the importance of bone marrow as a potential origin tissue of the disease. Indeed, transfer of the inflammatory disease of HLA-B27 transgenic rats is achieved by bone marrow engraftment similar to the aforementioned adoptive transfer of bone marrow neutrophils from IL-17A gene transfer mice which is sufficient to transfer skin inflammation [19,21▪▪]. In fact, early studies have shown that the bone marrow microenvironment is critical in the initiation of PsA as multiple reports have demonstrated transmission of PsA through bone marrow transplantation [22–24]. Recent clinical data resulting from diagnostic use of MRI has demonstrated that bone marrow edema and osteitis is an early feature of the disease even without demonstrable enthesitis and thus place the bone marrow involvement as either the first sign of local inflammation or is secondary to articular and periarticular inflammation [25]. Imaging in experimental animal models of arthritis has also been fundamentally instrumental in delineating the pathogenic mechanisms in the bone marrow. Light-sheet microscopy imaging in cleared bones has revealed the increase of transcortical vessels in the bone marrow which are created by bone resorbing osteoclasts [26▪▪]. These bone resorbing osteoclasts carve out canaliculi which are layered by $CD31^+$ endothelial cells and allow the egress of neutrophils from the bone marrow to the circulation. Since osteoclasts differentiate from bone marrow macrophages which are activated in most of the aforementioned animal models, these observations strongly support that the activation of myeloid cells in the bone marrow may be critical in the pathogenesis of PsA. These observations are in keeping with the activation of bone marrow macrophages in the HLA-B27 rat model, the activation of osteoclast precursors and neutrophils in the IL-23 and IL-17A gene transfer models. Hematopoietic stem and progenitor cells also have the ability to sense peripheral inflammation and adapt a myeloproliferative phenotype to meet the increased demands in response to infection or other stimuli [27]. Such adaptations however can lead to unwanted effects including increased differentiation of osteoclast progenitors leading to pathological bone destruction and increased neutrophil egress leading to the accumulation of neutrophils in the skin and the formation of neutrophil exudates in the skin commonly known as Munro's microabscesses. In keeping with myeloid activation CLEC5A/MDL-1 which is expressed exclusively on myeloid cells and is a major PU.1 transcriptional target during myeloid differentiation regulating a number of myeloid-dependent immune and inflammatory responses including differentiation, activation and recruitment of myeloid cells during inflammation is also critical for PsA [28,29]. Specifically, IL-23 induces CLEC5A/MDL-1 expression and activation leading to NFATc1 regulation of osteoclast differentiation genes and its deletion attenuates bone loss in inflammatory arthritis [30,31]. Similarly, IL-23 gene transfer in mice leads to the expansion of a myeloid $IL\text{-}17A^+$ $CLEC5A/MDL1^+$ neutrophil subset in the bone marrow which migrates to the skin to evoke epidermal hyperplasia, acanthosis, parakeratosis, and Munro's microabscesses [32]. Genetic ablation of CLEC5A/MDL-1 prevents IL-23-induced bone loss and skin inflammation depicting CLEC5A/MDL-1 is critical for the dual pathology observed in PsA [32]. The implications of bone marrow in PsA are not only related with the pathogenesis but also with the development of chronic inflammation and persistent inflammatory flares and relapse following discontinuation of therapy due to epigenetic regulation of inflammatory memory as recently reviewed [33]. This inflammatory memory which can be the result of cytokine stimulation and/or immunoreceptor activation can explain the subclinical residual synovitis that persists in RA and PsA patients in remission [34,35]. (Fig. 1).

Interplay of Innate and adaptive immunity in psoriatic arthritis

The close interaction of innate and adaptive immune cells is responsible for the development as well as maintenance of psoriatic disease [36]. In genetically predisposed individuals, certain environmental factors (such as dysbiosis, biomechanical stress, smoking, and obesity) can trigger an immune-inflammatory response. Locally, these factors activate Toll-like

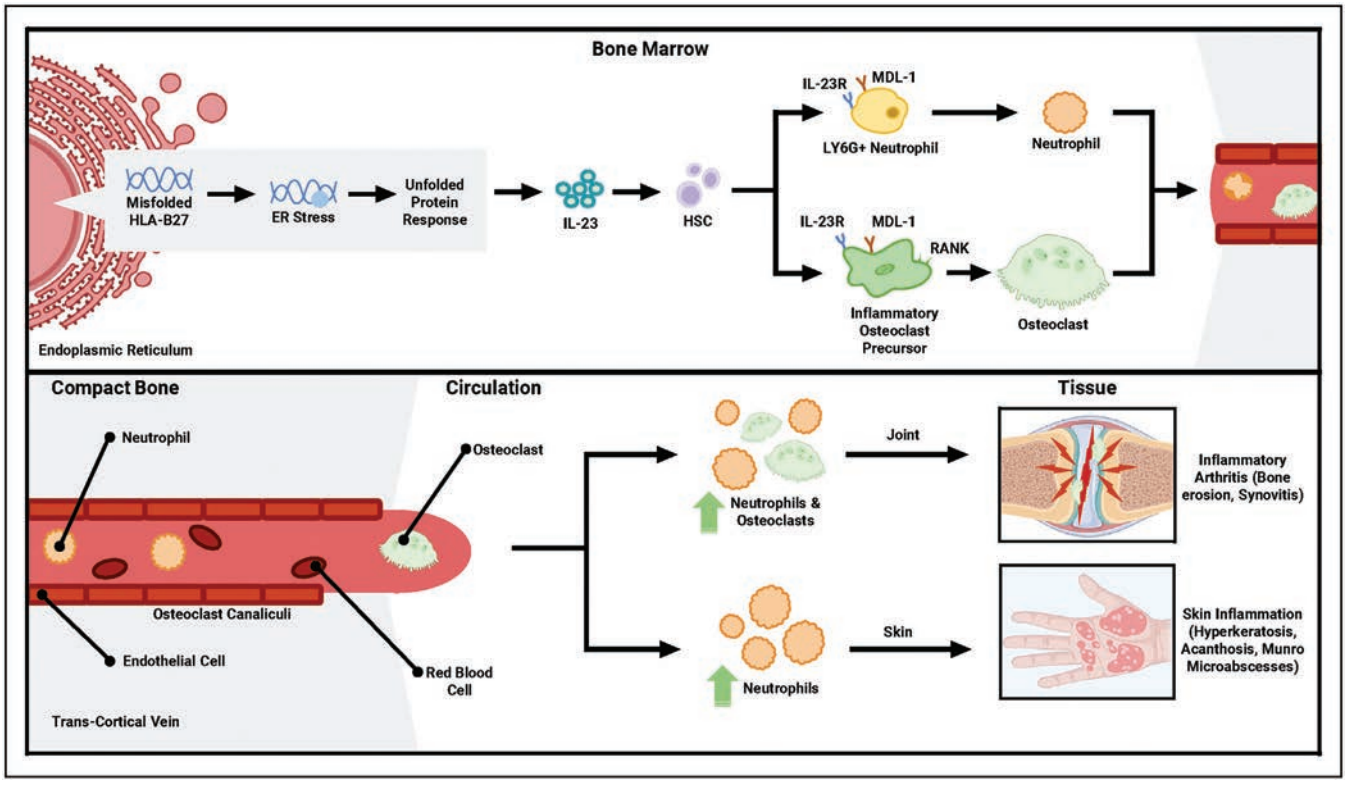

FIGURE 1. Bone marrow involvement in PsA pathogenesis. Schematic cartoon representation of events in the bone marrow leading to increased IL-23 expression following unfolded protein response which expands hematopoietic stem cells (HSC's), leading to MDL-1/CLEC5A+ osteoclast and neutrophil precursors which egress to the circulation and accumulate in the skin and joints of PsA patients causing PsA related pathology. PsA, psoriatic arthritis.

receptors (TLRs) type 2 on antigen-presenting cells (APCs), including monocytes, dendritic cells (DCs), and macrophages. This activation leads to the release of inflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor (TNF), IL-17, and IL-23 [37]. In lymph nodes and local tissue, APCs activate the T lymphocytes causing cytokines release that perpetuates innate and adaptive immune system. IL-6 and TGFß facilitate the differentiation of naïve T cells into T cell subset 17 (Th-17) and induce the expression of IL-23R that facilitates the response of IL-23 [38].

A study by Raemdonck *et al.* on TLR-7 binding to macrophages suggested their role in the cross-regulation of T cells, providing an interesting insight into the skin and joint immunopathogenic changes. They observed that an increased TLR-7 activity in PsA leads to the development of glycolytic macrophage cells that promote Th-17 polarization. TLR-7 ligands such as microRNA-29 (miR-29) and microRNA Let-7b (miR-Let7b) were significantly elevated in PsA synovial fluid (SF). Dermal administration of miR-Let7b in low-grade arthritic mice resulted in earlier onset and more severe disease. In this study, skin miR-Let7b expression promoted dermal accumulation of $CD3^+$T cells and $CD68^+$ macrophages, reflected by increased biomarkers of these cell types that activate inflammation and osteoclastogenesis [39]. In addition to this, circulating innate lymphoid cells (ILC's) which are found in different distributions across mucosal sites and produce various cytokines were detected at higher levels in patients with PsA compared to healthy individuals [40]. Among these ILC subsets the ILC-3 subset which is activated by IL-23 and produces IL-17 and IL-22 were found to be increased in the blood and synovial fluid of patients with PsA [40,41]. Overall IL-23 stimulates immunoreceptors in myeloid cells as well as the more studied αβ T cells, γδ T cells and ILCs to produce IL-17, IL-22, TNF, and other cytokines contributing to ongoing inflammatory pathways that sustain persistent inflammation highlighting the dominance of IL-23/IL-17 axis in the pathology of PsA [42].

An additional mechanism of sustained inflammation is observed via defects in T regulatory cells (Tregs), which are critical in suppressing inflammation and thus maintaining self-tolerance and preventing autoimmunity [43]. Indeed, the pathogenic conversion of $Foxp3^+$ T cells into Th17 cells is an

established mechanism of autoimmune arthritis pathogenesis [44]. Loss of immune tolerance by defects in immune suppression can be systemic or even local as recently observed in another study whereby Tregs derived from synovial fluid of PsA patients have a distinct phenotype with intermediate expression of Foxp3, that showed upregulation of CD161 and RORγt and increased production of IL-17 cytokines as compared to the circulatory Tregs [45]. Loss of immunosuppression in specific tissues may be a pathogenic trigger for skin and joint inflammation in inflammatory arthritis, however, how this inflammation is transferred to other tissues remains elusive. Along with Tregs, circulatory $CD8^+$ T cells and neutrophils have both been implicated in spreading the disease as these cells circulate between the blood, skin, and lymph nodes, including non-cutaneous distal lymph nodes, and contribute to systemic immune responses [46,47].

In addition to Th17 cells $CD8^+$ cells have previously been detected to produce IL-17 and IL-22, which are involved in the pathogenesis of psoriasis [48]. More recently, it was demonstrated that in peripheral blood of PsA patients there was an increase in IL-17A and IL-22 coproducing $CD8^+$ T cells, compared to healthy controls. A unique population of $CD8^+CCR10^+$ T cells, were enriched in PsA, differentiated PsA from psoriasis. These effector memory cells expressed high levels of the DNAX accessory molecule 1, skin-homing receptors CCR4 and cutaneous lymphocyte antigen. These $CD8^+CCR10^+$ T cells lacked cytotoxic potential and displayed an overall regulatory function suggesting a unique role of these cells in the pathogenesis of PsA [47]. DNA methylation patterns in $CD8^+$ T cells cells discern psoriasis from psoriatic arthritis and correlate with cutaneous disease activity and may serve as potential biomarkers to diagnose as well as differentiate PsA from psoriasis [49]. Finally, an enrichment of associated variants to markers of open chromatin in $CD8^+$ memory primary T cells was also described [50]. The enhanced circulation of such $CD8^+$ cells may indicate an additional possible mechanism of maintaining the systemic chronic inflammation which contributes to the development of PsA [51].

CLOSING REMARKS AND CONCLUSION

The multiorgan systemic inflammation observed in PsA is commonly observed in autoimmunity and can originate from multiple tissues. Recent research has demonstrated specific changes in the gut microbiota associated with PsA and the potential mechanisms through which they contribute to disease pathogenesis highlighting the significance of the gut-bone-axis [52,53]. The human microbiome, particularly the gut microbiome, is essential in maintaining health and disease states. Dysbiosis, or imbalance in the microbiome, has been implicated in psoriasis and PsA. Studies have shown that gut microbiota is necessary for disease initiation in the genetically susceptible animal models of PsA where again the role of Th17 and the IL-23/IL-17 axis is pivotal [54,55]. Although the pathogenesis of PsA remains elusive, the recent studies reviewed herein have provided significant insights into the complex interplay of genetic, immunological, and environmental factors that contribute to the disease. These recent updates not only enhance our understanding of the multiple mechanisms involved in the pathogenesis of PsA but also pave the way for the development of novel diagnostic and therapeutic strategies. Future research should continue to explore these promising areas, with a focus on translating these findings into clinical practice to improve the lives of individuals living with PsA.

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Conflicts of interest

The author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Recent advances in immunometabolism in rheumatic diseases

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Purpose of review
Aberrant autoreactive innate and adaptive immune responses cause systemic autoimmune diseases. Autoimmunity has been linked to abnormal metabolic states, and immunometabolism has emerged as a critical field in understanding the pathogenesis of rheumatic diseases. We aimed to explore the latest research on metabolic reprogramming in various immune cell types, including T cells, B cells, neutrophils, dendritic cells, monocytes, and macrophages, in the context of rheumatic diseases.

Recent findings
Each immune cell utilizes preferred metabolic pathways, and the cell activation dramatically modifies metabolic status. The inhibition of these pathways alters cell survival, differentiation, proliferation, and cytokine production – all of which contribute to rheumatic disease progression.

Summary
Targeting metabolic pathways or introducing anti-inflammatory metabolites, such as itaconate, could be novel therapeutic strategies for rheumatic diseases. Further research should focus on strategies for translating basic research findings to bedside applications.

Keywords
immune cells, immunometabolism, metabolite, rheumatic disease

INTRODUCTION

Immunometabolism, the study of cellular metabolism within immune cells, has emerged as a critical field in understanding the pathogenesis of rheumatic diseases. Recent advances have revealed that metabolic reprogramming plays a pivotal role in shaping immune cell function, activation, and differentiation [1]. This metabolic adaptation is not solely a consequence of cellular activation but actively drives immune responses and contributes to persistent inflammation and tissue damage [2].

We aimed to provide a comprehensive overview of the latest research on immunometabolism in the various immune cell types implicated in rheumatic diseases; particularly, how metabolic pathways in immune cells are altered in these conditions, and how these changes impact disease pathogenesis. Furthermore, we highlight the therapeutic potential of targeting metabolic pathways as novel therapeutic strategies in rheumatic diseases.

T-CELL METABOLISM

T-cell metabolism significantly impacts activation, differentiation, and effector functions, especially in autoimmune diseases. In their naive state, T cells primarily rely on oxidative phosphorylation (OXPHOS) to efficiently meet energy demands. However, upon activation through antigen recognition via the T-cell receptor, T cells undergo a metabolic shift from OXPHOS to aerobic glycolysis [3]. This shift, similar to the 'Warburg effect' in cancer cells, supports the rapid proliferation and biosynthetic needs of activated T cells by providing ATP and necessary metabolic intermediates for nucleotide and amino acid synthesis [4]. The increased glucose uptake is facilitated by upregulation of glucose transporters (GLUTs) such as GLUT1, driven by signaling pathways, including phosphatidylinositol 3'-kinase (PI3K)/Akt and mechanistic

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KEY POINTS

- Metabolic reprogramming in immune cells plays a pivotal role in the pathogenesis of rheumatic diseases by shaping immune cell function and promoting inflammation.
- Targeting specific metabolic pathways in T cells, such as glycolysis, offers potential therapeutic strategies for autoimmune diseases like systemic lupus erythematosus.
- Modulating metabolism in other immune cells, including B cells, neutrophils, dendritic cells, monocytes, and macrophages, may provide novel avenues for treating rheumatic diseases.
- Future therapies targeting cell metabolism may restore immune balance in rheumatic diseases while minimizing adverse effects.

target of rapamycin (mTOR) [5,6]. These pathways enhance GLUT1 trafficking to the cell surface, increasing glucose availability to sustain increased glycolysis.

Hypoxia-inducible factor 1α (HIF-1α) is crucial in this metabolic shift by promoting glycolytic gene expression under hypoxic conditions. Several glycolytic enzymes have been identified as potential direct targets of HIF1α [4]. Moreover, high levels of HIF1α expression are regulated by mTOR [7]. Emerging evidence suggests that mitochondrial dysfunction in T cells reportedly facilitates redox stress, preventing the proteasomal degradation of HIF-1α, thereby promoting glycolytic reprogramming and driving precursor T cells towards terminal exhaustion [8].

The importance of pyruvate dehydrogenase (PDH) in T-cell activation and function has been increasingly recognized. PDH is crucial for histone acetylation and transcriptional reprogramming by producing extramitochondrial acetyl-CoA. PDH can translocate to the nucleus and associate with chromatin-remodeling complexes, linking metabolic and histone-modifying enzymes in regulating T-cell activation [9]. Recent study revealed that glutarate, a metabolite derived from tryptophan catabolism within T cells, reportedly regulates T-cell differentiation both through α-ketoglutarate-dependent dioxygenase inhibition, and through direct regulation of T-cell metabolism via glutarylation of the PDH E2 subunit [10].

Effector T-cell subsets exhibit distinct metabolic profiles essential for differentiation and function. T helper (Th) 1, Th17, and T-follicular helper (Tfh) cells require glycolysis for differentiation, whereas glycolysis deprivation promotes regulatory T-cell (Treg) differentiation [3]. Peripheral Tregs rely on the mevalonate pathway and glycolysis-derived end products to synthesize fatty acids, which are essential for their proliferation and function [3]. De novo fatty acid synthesis plays a crucial role in Th17-cell differentiation. A T-cell deficiency in acetyl-CoA carboxylase 1 (ACC1) inhibits Th17 cell differentiation while enhancing the generation of Tregs [11]. The mTOR complex 1 (mTORC1)-signaling pathway is vital for promoting glycolysis in Th1 and Th17 cells by inducing HIF-1α [3]. Contrastingly, combined mTORC1–mTORC2 activity is necessary for Th2 and Tfh-cell differentiation [12]. PDH kinase 1 (PDHK1) also regulates Th17 cell development by controlling pyruvate conversion pathways [13].

Regarding T-cell metabolism function as it relates to autoimmune diseases, systemic lupus erythematosus (SLE) T cells exhibit enhanced glycolytic activity compared with healthy controls [3]. Calcium/calmodulin-dependent protein kinase IV (CaMK4) promotes GLUT1 expression and increases pyruvate kinase muscle isozyme 2 (PKM2) activity in SLE T cells, enhancing aerobic glycolysis and inducing differentiation into Th1 and Th17 cells [14,15]. Inhibition of PKM2, one of the final rate-limiting enzymes in glycolysis, ameliorates experimental autoimmune encephalomyelitis (EAE) [15,16]. Furthermore, PKM2-mediated glycolysis is linked to increased Tfh cells in patients with SLE and lupus-prone mice [17]. TEPP-46, which reduces invasion of dimeric PKM2 into the nucleus, can reduce glycolysis, inhibit Tfh-cell differentiation, and alleviate inflammatory damage in lupus-prone mice [17]. The rate-limiting glycolysis enzyme 6-phosphofructokinase platelet type (PFKP) is also reportedly a key regulator of Treg metabolism and function in systemic autoimmunity [18]. CaMK4 was found to phosphorylate PFKP, enhancing its enzymatic activity and promoting aerobic glycolysis in Tregs. This leads to impaired Treg differentiation, stability, and immunosuppressive function [18].

The transcription factor CREMα and its short variant 'inducible cAMP early repressor' (ICER) regulate key enzymes involved in glucose and glutamine metabolism, which are essential for T-cell function and differentiation [19]. ICER controls the expression of PDH phosphatase catalytic subunit 2, altering the activity of the PDH kinase and pyruvate metabolism in lupus T cells [20]. Additionally, ICER promotes the transcription of glutaminase 1, the initial enzyme in glutaminolysis, which is critical for Th17-cell differentiation. In mouse models, inhibition of glutaminase 1 reportedly reduces Th17-cell differentiation and lupus disease [21]. Furthermore, the conversion of glutamate to α-ketoglutarate by glutamate oxaloacetate transaminase 1 is another important step in

this pathway, and its inhibition suppresses Th17-cell differentiation [22].

Rab4A, a small GTPase, has been identified as important in T-cell metabolism and autoimmune pathogenesis. It controls CD98 receptor recycling and kynurenine-sensitive mTOR activation, which promotes mitochondrial accumulation and enhanced tricarboxylic acid (TCA) and pentose phosphate pathway (PPP) fluxing [23▪]. These effects favor CD4 T-cell proliferation and immune dysregulation, enhancing autoantibody production and glomerulonephritis in lupus-prone mice [23▪].

Iron metabolism has also emerged as a crucial factor in T-cell function, particularly concerning the transferrin receptor (CD71) in SLE. Elevated CD71 expression in SLE T cells is linked to increased intracellular iron, impairing mitochondrial function and mTORC1 signaling [24]. Blocking CD71 can reduce iron levels, normalize T-cell activation, and improve mitochondrial function, highlighting CD71 as a potential therapeutic target for SLE [24].

A novel finding reveals that CD38 influences T-cell metabolism by altering lipid composition on the cell membrane, particularly through the conversion of GM3 to GM2 gangliosides, which enhances calcium flux via the PLC11-IP3 pathway [25]. This alteration leads to endoplasmic reticulum stress and suppresses interleukin (IL)-2 production, suggesting CD38 as a potential therapeutic target in SLE [25].

Interestingly, itaconate, an immunomodulatory metabolite, inhibits Th17-cell differentiation while promoting Treg differentiation through metabolic and epigenetic changes [27]. Itaconate suppresses glycolysis and oxidative phosphorylation in T cells, leading to decreased levels of key metabolites crucial for chromatin accessibility and transcription factor binding [26▪▪]. This results in reduced RORγt binding at the Il17a promoter in Th17 cells and increased Foxp3 expression in Tregs. Itaconate-treated Th17 cells can ameliorate disease activity in an EAE model [26▪▪]. In a separate study, an itaconic acid derivative displayed beneficial roles in attenuating immune dysregulation and organ damage in lupus-prone mice [27].

By targeting specific pathways such as mTOR, HIF-1α, or PKM2 or using immunomodulatory metabolites like itaconate, influencing T-cell metabolism selectively to restore immune balance while preserving essential functions may be possible. The complex molecular interplay within T cells (Fig. 1) provides a rich landscape for developing novel therapeutic strategies in autoimmune diseases.

B-CELL METABOLISM

B cells are pivotal in adaptive immunity, primarily tasked with antigen presentation to T cells and the production of pathogen-specific antibodies and cytokines. However, autoreactive B cells can contribute to autoimmune diseases by generating autoantibodies and pro-inflammatory cytokines, thereby disrupting immune regulation [28].

Activated B cells undergo metabolic reprogramming, characterized by increased glycolysis and OXPHOS compared with naive B cells [29]. This metabolic shift is crucial for B-cell activation and function. Activated B cells exhibit increased glucose uptake and lactate production, whereas resting B cells maintain metabolic quiescence through signaling molecules such as tumor necrosis factor (TNF)-receptor-associated factor 3 (TRAF3) and glycogen synthase kinase 3 (GSK3) [28]. Inhibition of glycolysis, mitochondrial respiration, or cytosolic acetyl-CoA synthesis reduces the proliferation and survival of activated B cells [28]. Key factors such as mTORC1, c-Myc, and protein kinase Cβ are essential for B-cell activation [28]. Upon antigen exposure, B cells form germinal centers with the help of Tfh cells [30]. During this process, random mutations are introduced into the B-cell antigen receptor to increase diversity. GC B cells consume more glucose than naive B cells and have heightened expression of glycolysis-associated genes [30].

The expression of HIF-1α, which drives glycolysis, is also enhanced in germinal center B cells [28]. The serine/threonine phosphatase PP2A is required for germinal center formation and purine/pyrimidine metabolism [31]. B cells exit the germinal center and differentiate into memory B cells or plasma cells. Plasma cells produce large amounts of antibodies, requiring more glucose and amino acids than naive B cells. Glucose is used for energy generation and antibody glycosylation, while OXPHOS is necessary for antibody secretion in plasma cells [29].

Dysregulated immunometabolism can promote autoimmune diseases by disrupting self-tolerance mechanisms. Elevated BAFF levels in patients with SLE enhance glycolysis through the PI3K/AKT/mTOR pathway, promoting autoreactive B-cell survival [32,33]. TRAF3 deficiency leads to increased glycolysis and mitochondrial respiration, contributing to autoimmune disease development by promoting B-cell hyperactivation [34]. Recent studies have explored the metabolic demands of activated B cells in lupus rely on glucose oxidation for survival [35]. In lupus-prone mice, inhibiting glycolysis with 2-deoxyglucose (2-DG) selectively reduces pathogenic B and germinal center B cells without affecting Tfh cells [35]. Thus, targeting glycolysis in BCMA-expressing B cells could be a novel therapeutic strategy for lupus.

Short-chain fatty acids regulate B-cell differentiation and antibody production through histone

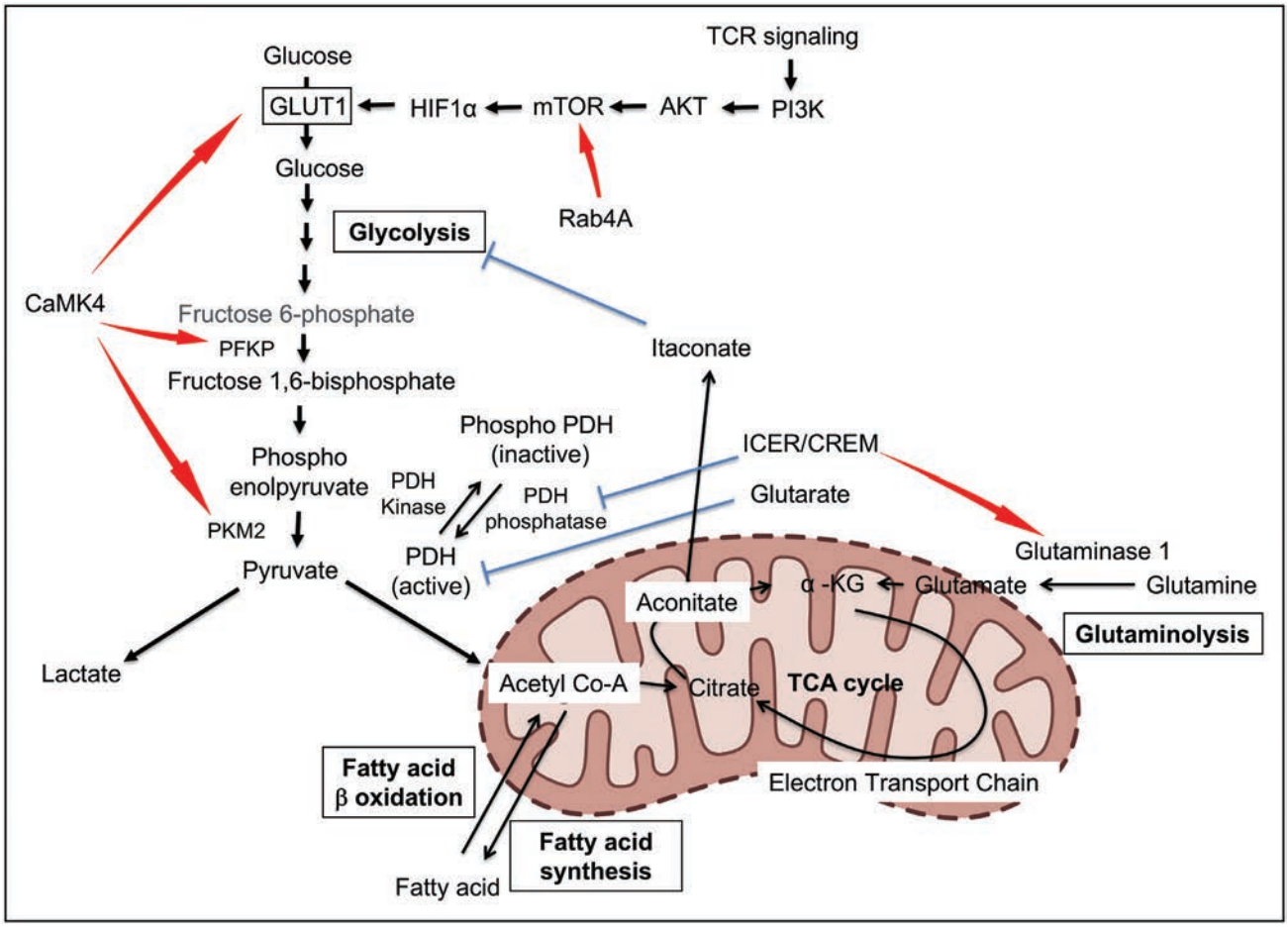

FIGURE 1. Comprehensive overview of cellular metabolism imbalance in T cells. Increased activity of mTOR and HIF1α promotes glycolysis. Increased CaMK4 and ICER/CREM expressions are observed in Th17 cells. CaMK4 increases enzymatic activity of GLUT1, PFKP, and PKM2, thereby enhancing glycolysis. ICER promotes glutaminase 1 expression and increases glutaminolysis in Th17 cells. ICER also downregulates PDH phosphatase catalytic subunit 2, preventing PDH activation in Th17 cells. Itaconate modulates T-cell differentiation by suppressing glycolysis and oxidative phosphorylation, leading to reduced Th17 cells and enhanced Treg differentiation. Rab4A regulates T-cell metabolism by controlling kynurenine-sensitive mTOR activation, promoting mitochondrial function and metabolic flux. Glutarate regulates T-cell differentiation via glutarylation of the PDH E2 subunit. α-KG, α-ketoglutarate; CaMK4, calcium/calmodulin-dependent protein kinase IV; CREM, cAMP response element modulator; HIF1α; hypoxia-inducible factor 1 alpha, ICER, inducible cAMP early repressor; mTOR, mammalian target of rapamycin; PDH, pyruvate dehydrogenase; PKM2, pyruvate kinase muscle isozyme 2; TCA cycle, tricarboxylic acid cycle.

deacetylase inhibition and miRNA expression. Long-chain fatty acids act as ligands for PPAR-γ, influencing gene expression related to lipid metabolism [36]. Oxysterols regulate cholesterol homeostasis via liver X receptors, affecting B-cell differentiation and antibody production. Sphingosine 1-phosphate (S1P) guides B-cell migration through receptor-mediated signaling pathways [36].

Monocarboxylate transporter 1 (MCT1) is important in pyruvate metabolism for antibody class-switch recombination (CSR) through H3K27 acetylation [37]. MCT1 deficiency in B cells impairs IgG production because of disrupted CSR and reduced GCB cells. Mechanistically, MCT1 maintains pyruvate levels necessary for AID transcription via H3K27 acetylation [37].

Thioredoxin (Trx), a redox protein highly expressed in regulatory B cells (Bregs), regulates their differentiation and function by maintaining mitochondrial electron transport and homeostatic levels of reactive oxygen species (ROS) [38]. Trx inhibition leads to mitochondrial membrane depolarization and increased ROS levels, impairing Breg function [38].

Thus, B-cell metabolism is a key regulator of immune responses, with implications for both normal immune function and autoimmune disease. Future research focusing on the metabolic networks

in B cells may unlock new avenues for immunomodulatory therapies and personalized treatment approaches in autoimmune diseases.

NEUTROPHIL METABOLISM

Neutrophils are the most abundant leukocytes in human blood. Neutrophils, especially low-density granulocytes, use a particular form of cell death called 'NETosis' by releasing neutrophil extracellular traps (NETs) and DNA, which act as a self-antigen [39]. Although NET formation is important for homeostatic, antimicrobial, and procoagulant function, it is involved in autoimmune diseases, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, SLE, and antiphospholipid syndrome [40]. Glycolysis is one of the main pathways used for energy production during NET formation [41]. Inhibition of glycolysis or PPP inhibits the release of phorbol-12-myristate-13-acetate-induced NETs [42,43]. C5a is requisite for the pathogenesis of ANCA-associated vasculitis [44]. S1P acts as a downstream effector molecule of C5a and enhances neutrophil activation [45]. A S1P receptor modulator, FTY720, ameliorated experimental anti-myeloperoxidase-ANCA-associated vasculitis by increasing fatty acid oxidation [45]. Similarly, a pan-inhibitor of the inhibitors of apoptosis proteins dampened neutrophil activation [46]. However, this inhibitory effect was abolished by gene silencing or pharmacological inhibition of fatty acid oxidation [46]. Thus, cell metabolism can be a therapeutic target in neutrophil-related autoimmune diseases. However, as the data on neutrophil metabolism in autoimmune diseases are scarce, further studies are needed.

DENDRITIC CELL METABOLISM

Conventional dendritic cells (cDCs) are involved in the development and activation of self-reactive pathogenic T cells. Resting cDCs are characterized by a catabolic metabolic state, continuously breaking down fatty acids and glutamine [47▪▪]. Upon activation, cDCs switch to aerobic glycolysis, glycogen metabolism, and fatty acid synthesis to further stimulate T-cell activation. Stimulation with a toll-like receptor (TLR) agonist rapidly enhances mTORC1 activation, leading to increased glycolysis and fatty acid synthesis [48,49]. Consistent with Th17, itaconate decreases glycolysis and suppresses myeloid dendritic cell (mDC) maturation [50]. Interestingly, lactate, produced by activated cDCs and other immune cells, boosts the expression of NADH dehydrogenase (ubiquinone)-1α subcomplex 4-like 2 (NDUFA4L2) through a mechanism mediated by HIF-1α [47▪▪]. NDUFA4L2 limits the production of mitochondrial ROS in cDCs that regulate pathogenic autoimmune T cells in central nervous system autoimmunity [47▪▪]. These data suggest that lactate provides a negative feedback signal to suppress abnormal immune activation.

Plasmacytoid dendritic cells (pDCs) are type I interferon (IFN)-producing cells involving viral infection and autoimmunity. In pDCs, AMP-activated protein kinase is strongly implicated as a driver of metabolic reprogramming after activation via TLR7/9. Mitochondrial oxygen consumption was elevated and mitochondrial inhibitors reportedly abrogate IFNα production [51]. However, glycolysis is not essential during pDC activation and IFNα production [51]. The differences in cell metabolism between mDC and pDC are very interesting.

MONOCYTE AND MACROPHAGE METABOLISM

Cell metabolism in monocytes and macrophages is less studied in rheumatic diseases. Rapamycin, an mTOR inhibitor, reduces type I IFN production in monocytes from patients with SLE [52]. Fumarate hydratase inhibition increases IFNβ production in macrophages [53]. Indeed, macrophages from patients with SLE have decreased levels of fumarate hydratase [39]. Type I IFN boosts the expression of Irg1, which produces itaconate. Itaconate creates a negative feedback loop and reduces the type I IFN response [54]. Itaconate ameliorates several autoimmune models, including rheumatoid arthritis, SLE, multiple sclerosis, and autoimmune hepatitis [26▪▪,27,50,55]. Notably, glucocorticoids, the therapeutic mainstay for many autoimmune diseases, increase and sustain itaconate production and inhibit the inflammatory response in macrophages [56]. The genetic deficiency in Irg1 interferes with the anti-inflammatory effects of glucocorticoids and abrogates their beneficial effects for the lipopolysaccharide-induced lung inflammation model [56]. As itaconate has antimicrobial and antiviral effects, it could be a novel therapeutic agent for autoimmune diseases without promoting increased susceptibility to infections.

CONCLUSION

Recent studies have demonstrated the importance of immunometabolism in rheumatic diseases. Targeting these abnormalities in the metabolic pathways or adding anti-inflammatory metabolites could benefit rheumatic disease treatment. However, further research should focus on the heterogeneity of immunometabolism in each rheumatic

disease, drug delivery to reduce side effects, and strategies for translating these findings to clinical trials. We believe that the treatments targeting cell metabolism can help improve patient care in rheumatic diseases.

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Conflicts of interest

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REVIEW

OPEN

Genetic and epigenetic factors shape phenotypes and outcomes in systemic lupus erythematosus – focus on juvenile-onset systemic lupus erythematosus

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Purpose of review
Systemic lupus erythematosus (SLE) is a severe autoimmune/inflammatory disease. Patients with juvenile disease-onset and those of non-European ancestry are most severely affected. While the exact pathophysiology remains unknown, common and rare gene variants in the context of environmental exposure and epigenetic alterations are involved. This manuscript summarizes the current understanding of genetic and epigenetic contributors to SLE risk, manifestations and outcomes.

Recent findings
Though SLE is a mechanistically complex disease, we are beginning to understand the impact of rare and common gene variants on disease expression and associated outcomes. Recent *trans*-ancestral and multigenerational studies suggest that differential genetic and environmental impacts shape phenotypic variability between age-groups and ancestries. High genetic burden associates with young age at disease-onset, organ involvement, and severity. Additional epigenetic impact contributes to disease-onset and severity, including SLE-phenotypes caused by rare single gene variants. Studies aiming to identify predictors of organ involvement and disease outcomes promise future patient stratification towards individualized treatment and care.

Summary
An improved understanding of genetic variation and epigenetic marks explain phenotypic differences between age-groups and ancestries, promising their future exploitation for diagnostic, prognostic and therapeutic considerations.

Keywords
childhood, epigenetic, genetic, juvenile, systemic lupus erythematosus

BACKGROUND

Systemic lupus erythematosus (SLE) is a chronic autoimmune/inflammatory disease with significant morbidity and mortality [1,2]. Severity and disease outcomes vary between ancestries and age-groups with non-European and pediatric patients being most severely affected [3–6]. Although the exact pathophysiology of SLE remains unclear, the importance of genetic factors has been established [3,7,8] with increased risk of SLE in twins and siblings of those with SLE [9,10]. While genetic factors increase the risk for SLE significant genetic variability and environmentally mediated factors may explain phenotypic differences between patients, ancestries and age-groups [11].

Differences in disease presentation and progression between adult- (aSLE) and juvenile-onset (j)SLE

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KEY POINTS

- Systemic lupus erythematosus (SLE) is a severe and mechanistically complex systemic autoimmune/inflammatory disease with a strong genetic component;
- Increased genetic burden contributes to early disease-onset, increased incidences among non-European ancestries, and more severe phenotypes;
- Because rare and common variants affect the same genes/pathways, the study of rare high effect-size variants informs the understanding of more common forms of SLE;
- Epigenetic signatures contribute to disease expression and phenotypes in genetically predisposed individuals, promising their potential as disease biomarker and/or treatment target.

patients may be caused by variable composition of inherited and acquired factors. Notably, compared to aSLE, an increased prevalence of common and rare genetic variants has been reported in jSLE, and increased genetic burden may result in early disease expression and more severe phenotypes [11–13,14▪]. However, even within this relatively small group of patients with monogenic risk variants, phenotypic variability exists. Thus, additional genetic and acquired (epigenetic) factors emerged as disease-modifying factors that may be used as predictive markers [15▪,16].

COMMON VARIANTS

For most people with SLE, it is a complex polygenic disease. Hundreds of SLE-associated single nucleotide polymorphisms (SNPs) have been identified from genome wide association studies (GWAS) primarily including adult participants [17–19]. While individual SNPs and extended haplotypes increase an individual's risk for SLE, their impact on gene function does not sufficiently explain disease expression. As a result, SNPs only explain a fraction of the heritability of SLE [20–22]. Because of the relatively low impact of SLE-associated SNPs on gene function, polygenic risk scores (PRSs) have been proposed to estimate risk [23] and account for 30–73% of SLE heritability [24,25▪▪]. Missing heritability is due to several factors, including: (a) Limitations in estimating epigenetic changes, gene:gene and gene:environment interactions; (b) Missed ancestry-specific alleles through relative under-representation of non-European ancestries; (c) rare SLE-associated variants are not captured by GWAS, but may be more prevalent among jSLE when compared to aSLE patients [1,2,11,20,21,24,25▪▪].

While GWAS have improved our understanding of SLE genetics, available studies have limitations. Population stratification, or confounding by genetic ancestry, was frequently addressed by restriction to European participants [26]. This is a particular challenge when aiming to understand a disease that is more prevalent and severe among non-European populations [6,27]. In recent years, *meta*-GWAS in stratified ancestral populations [18,28,29,30▪▪] and *trans*-ancestral GWAS [17,19,25▪▪,30▪▪,31] demonstrated shared and distinct SLE risk loci across global populations. A *trans*-ancestral *meta*-GWAS of European-American (Cases/controls: 6748/11 516), African-American (2970/2452) and Hispanic-American (1872/2016) SLE patients identified 22 shared risk loci, which included 11 previously unidentified regions [17]. *Meta*-GWAS of East-Asian (6707/16 047) and European (28 662/43 408) populations identified 79 SLE risk loci shared between populations, with 9 loci showing ancestry differential effects [25▪▪]. Continued expansion of historically underrepresented global populations will result in the identification of currently unknown SLE-associated variants.

The human leukocyte antigen (HLA) system on chromosome 6 is the most polymorphic region of the genome [32] and has strong associations with immune-mediated diseases. It was the first genetic region associated with SLE [33–35] and demonstrates some of the strongest associations with SLE risk [17–19,25▪▪]. A study across 11 autoimmune/inflammatory phenotypes, accessing whole exome sequencing (WES) data from UK biobank participants, identified more HLA risk alleles in SLE when compared to other immune-mediated diseases [36▪▪]. However, there are likely still HLA alleles and extended haplotypes to be discovered.

Although most GWAS studies were performed in aSLE cohorts, risk alleles identified are also relevant in jSLE. Several studies have reported an inverse association between the number of risk alleles and age at diagnosis [12,17,37▪▪,38]. Because risk alleles and PRS burden associate with disease severity, increased genetic burden in children may also contribute to more severe phenotypes [4,12,37▪▪,38]. A recent study testing associations between SLE risk alleles and age at diagnosis identified and intronic region of *CCDC113* to be associated with young age at diagnosis [39]. The study also completed the first GWAS of jSLE (Cases/controls: European: 199/3671; East-Asian: 556/409) identifying two SLE-associated regions on chromosome 6 mapping to a *TSBP1-AS1* intron and *HLA-DQA1* (previously associated with aSLE).

Another limitation of GWAS relates to the prediction of impact of SNPs and/or extended haplotypes

on gene function. Recently, innovative analytical models have been applied to datasets, identifying previously not appreciated SLE-associated variants [40]. A multiancestral study of SLE GWAS cohorts, including participants of East-Asian (cases/controls: 5877/188 558), European (14 355/505 956) and Admixed-American (1393/2327) ancestries, performed multitrait analyses using summary statistics from 13 other autoimmune/inflammatory diseases [40]. Authors confirmed 79 and identified 27 "novel" SLE risk loci. Lastly, transcriptome-wide analyses and cell type enrichment using gene expression prediction identified an additional 22 risk loci. Developments are not limited to the association of genetic variability with disease risk; pathway prediction and computational drug repurposing may also predict future therapeutic interventions [40].

A central aim of genetic studies is associating genetic variability with clinical manifestations, complications, and disease outcomes. Across studies, detailed clinical information is frequently lacking, limiting the ability to predict genotype: phenotype associations. A recent North American study involving children and adults with SLE observed an association between 39 non-HLA SNPs [odds ratio (OR) = 1.26; 95% confidence interval (CI):1.09–1.46; $P = 0.0006$] and lupus nephritis (LN), which was strongest among children of European ancestry when compared to aSLE patients or children of non-European ancestry [41▪]. A Taiwanese study observed associations between a combination of 27 SLE-associated SNPs and LN onset at younger ages [38]. A study in 319 jSLE patients from the UK identified 10 type I interferon (IFN)-related jSLE quantitative trait loci to be associated with young age at disease-onset (*IRAK1*, *TLR7*, *IFIH1*, *STAT4*, *TYK2*, *IRF8*), global disease activity (*IFIH1*, *STAT4*, *IRF8*), and/or mucocutaneous involvement (*TLR7*, *IFIH1*) [42] (Table 1). Studies linking SLE-associated osteonecrosis with SLE risk alleles yielded variable results. A GWAS involving 636 SLE patients with steroid-associated osteonecrosis (95 588 controls, Japanese Biobank) identified previously not know risk loci, namely *MIR4293/MIR1265* (OR = 1.99), *TRIM49* (Tripartite Motif Containing 49)*/NAALAD2* (N-acetylated alpha-linked acidic dipeptidase-2) (OR = 1.65) and *MYO16* (Myosin-16) (OR = 3.91) [43]. Another GWAS in a multiancestral cohort of children and adults with SLE (71/940 with osteonecrosis) identified an intronic variant in *WIPF1* (WAS/WASL interacting protein family member 1) to be associated with increased osteonecrosis risk that remained after accounting for corticosteroid exposure [44]. Studies highlight the need for structured investigation of the genetic contribution to specific manifestations and promise a deeper understanding of genetic factors shaping clinical heterogeneity in SLE.

The combined consideration of risk alleles in polygenic risk scores (PRS) can increase predictive ability for disease expression and associated phenotypes [24,25▪▪]. Their accuracy and predictive value depend on the degree of genetic divergence between discovery and validation cohorts [26,45]. Early studies demonstrated differences in SLE-PRS distributions by ancestry, with people of Amerindian, South-Asian, East-Asian and African heritage exhibiting higher SLE-PRS when compared to Europeans [19]. Studies of SLE-PRS derived from large European cohorts demonstrated area under the receiver operating characteristic (ROC) curves (AUC) of 0.72 (95% CI: 0.69–0.74) [37▪▪]. Similarly, when PRSs are trained and tested in Chinese cohorts, SLE-PRS AUC reach 0.76 (95% CI: 0.74–0.78) [25▪▪]. As expected, the performance of European-derived SLE-PRSs in Chinese cohorts were modest (AUC: 0.62; 95% CI: 0.60–0.64) [25▪▪], emphasizing the importance of ancestral matching between discovery and test populations.

RARE VARIANTS

The importance of rare high effect-size variants was first reported in the 1970s in the context of the complement system [46]. Although "monogenic SLE" is rare in human populations, variants commonly affect the same genes and pathways that exhibit common SLE-associated variants (Table 1) [3,11,12,14▪,47]. Through their high effect-size, rare variants shaped the current understanding of SLE pathogenesis [3] and facilitated the recognition that excessive IFN production plays a key role in SLE [3,48,49]. Increased accessibility allowed single centers and consortia to execute studies using whole exome or whole genome sequencing. As a result, rare variants have been reported in 3.5–15% of jSLE patients in different cohorts worldwide [13,14▪,50]. The true prevalence of "monogenic SLE" across age-groups and ancestries, however, cannot be estimated accurately.

Although we are just beginning to fully understand the genetic architecture of SLE, some key pathways have emerged (Table 2):

Genetic variants in the complement pathway remain some of the most prevalent variants reported in SLE [13,14▪,46,51]. Early-onset SLE or lupus-like phenotypes have been associated with the deficiency of complement factors, including C1q, C1r, C1s, C2, C3, C4A, and C4B [51–55]. Complement regulates important immune processes, and the loss of clearing apoptotic debris contributes to autoantibody formation and IFN expression [3,49].

Table 1. ¡SLE-associated common SNPs in genes also associated with "monogenic SLE"

Gene context	rsid	Chr	Pos (hg19)	AlleleA	AlleleB	Variant annotation	OR (95% CI)	*P*-value	References
BANK1	rs4637409	4q24	102 753,408 (hg19)	C		intronic	0.84 (0.80–0.87)	1.45×10^{-17}	[17]
BLK	rs2061831	8p23	11 339,882 (hg19)	G		regulatory region	1.31 (1.25–1.37)	1.46×10^{-40}	[17]
IFIH1	rs1990760	2	163 124,051 (hg19)	C	T	missense	1.11 (1.07, 1.11)	1.8210^{-7}	[149]
	rs11891191	2	162 267,194 (hg38)	C	T	3'UTR variant (*9C>T)	N/A	Disease-onset: 0.006; Activity: 0.005 (Female 0.01; non-European 0.01); Mucocutaneous: 0.003 (Female 0.008; non-European 0.01)*	[42]
	rs1990760	2	162 267,541 (hg38)	C	T	missense	In linkage disequilibrium with rs3747517	Disease-onset: 2×10^{-12}; Activity: 0.006 (Male 0.001); Mucocutaneous: 0.008 (Female 0.006)*	
	rs3747517	2	162 272,314 (hg38)	C	T	missense	In linkage disequilibrium with rs1990760	Disease-onset: 2×10^{-15}	
IRAK1	rs1059702	X	154 018,741 (hg38)	A	G	missense	N/A	Disease-onset: 0.006; Age: 0.002 (non-European 0.0002)*	[42]
RNASEH2C	rs1308020	11	65 497,558 (hg19)	G	A	intergenic	0.87 (0.84, 0.87)	1.28×10^{-9}	[150]
TNFAIP3	rs2230926	6	138 196,066 (hg19)	T	G	missense	1.88 (1.74, 1.88)	7.34×10^{-59}	[151]
TNIP1	rs10036748	5	150 458,146 (hg19)	C	T	intronic	1.28 (1.23, 1.28)	5.65×10^{-33}	[17,151]
TLR7	rs4830478	X	12 900,169 (hg19)	A		regulatory region	1.136 (1.09–1.18)	2×10^{-9}	[18]
	rs3853839	X	12 887,911 (hg38)	C	G	3'UTR variant (*881C>G)	N/A	Disease-onset: $<10^{-15}$; Mucocutaneous: 0.004 (Female 0.01; European 0.03)*	[42]

CI, 95% confidence interval; N/A, not available; OR, odds ratio.
* Spearmen's rho based on targeted panel-sequencing approach [14▪].

Table 2. Genes associated with "monogenic SLE"

Gene symbol	Gene name	Gene function	Functional impact	Reference
ACP5	Acid Phosphatase 5, Tartrate Resistant	Acid phosphatase	LoF	[152]
ADAR1	Adenosine Deaminase RNA Specific	RNA processing	LoF	[153]
ADA2	Adenosine Deaminase 2	Degrades extracellular adenosine	LoF	[154]
BANK	B Cell Scaffold Protein With Ankyrin Repeats 1	B cell receptor signaling	LoF	[155]
BLK	BLK Proto-oncogene, Src Family Tyrosine Kinase	B cell receptor signaling, B cell development	LoF	[155]
C1QA	Complement C1QA	Complement	LoF	[156,157]
C1QB	Complement C1QB	Complement	LoF	[158]
C1QC	Complement C1QC	Complement	LoF	[158]
C1R	Complement C1r	Complement	LoF	[159]
C1S	Complement C1Qs	Complement	LoF	[160]
C2	Complement C2	Complement	LoF	[54]
C4A	Complement C4A	Complement	LoF	[161,162]
C4B	Complement C4B	Complement	LoF	[161,163]
CYBB	Cytochrome b-245 β chain	Oxidase in phagocytes	LoF	[164]
DDX58	DEAD Box Polypeptide 58 (RIG-I)	dsRNA sensor	GoF	[70,165,166]
DNASE1	Deoxyribonuclease 1	DNA clearance	LoF	[167]
DNASE1L3	Deoxyribonuclease 1 like 3	DNA clearance	LoF	[61]
DNASEII	Deoxyribonuclease 2	DNA clearance	LoF	[58]
FAS (TNFRSF6)	Fas cell surface death receptor	Apoptosis	LoF	[168,169]
FASL	Fas Ligand	Apoptosis	LoF	[170]
IFIH1(MDA5)	Interferon Induced with helicase C	RNA sensor	GoF	[165,171]
ISG15	ISG15 ubiquitin-like modifier	Negative regulation of Type I IFN	LoF	[172]
KRAS	KRAS Proto-oncogene, GTPase	RAS/MAPK signaling	LoF	[173]
LYN	LYN Proto-oncogene, Src family tyrosine kinase	Regulates inhibitory signaling in B cells and myeloid cells	LoF	[174]
MAN2B1	Mannosidase αclass 2B member 1	Carbohydrate metabolism	LoF	[90]
NEIL3	Nei Like DNA Glycosylase 3	Glycosylase which initiates base excision repair	LoF	[175]
PEPD	Peptidase D	Collagen degradation	LoF	[176]
PRKCD	Protein kinase C δ	Serine/threonine kinase	LoF	[76,177]
PSMA3	Proteasome 20S Subunit α3	Proteasome	LoF	[178]
PSMB4	Proteasome 20S Subunit β4	Proteasome	LoF	[178]
PSMB8	Proteasome 20S Subunit β8	Proteasome	LoF	[178]
PSMB9	Proteasome 20S Subunit β9	Proteasome	LoF	[178]
PSMB10	Proteasome 20S Subunit β10	Proteasome	LoF	[178]
PTPN2	Protein tyrosine phosphatase, nonreceptor type 2	Negative regulator of JAK/STAT	LoF	[81]

Table 2 (*Continued*)

Gene symbol	Gene name	Gene function	Functional impact	Reference
PTPN11	Protein tyrosine phosphatase, nonreceptor type 11	RAS/MAPK signaling	LoF	[179]
RELA	RELA Proto-Oncogene, NF-KB subunit	NF-KB signaling	LoF	[180]
RAG2	Recombination activating 2	V(D)J Recombination	LoF	[181]
RNASEH2A	Ribonuclease H2 Subunit A	RNA processing	LoF	[153]
RNASEH2B	Ribonuclease H2 Subunit B	RNA processing	LoF	[153]
RNASEH2C	Ribonuclease H2 Subunit C	RNA processing	LoF	[158]
SAT1	Spermidine/Spermine N1-Acetyltransferase 1	Polyamine metabolism	LoF	[88]
SAMHD1	SAM and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1	Deoxyribonucleoside triphosphatase, inhibits reverse transcription	LoF	[66]
SHOC2	SHOC2, leucine rich repeat scaffold protein	RAS/MAPK signaling	LoF	[182]
SLC7A7	Solute carrier family 7 member 7	Cationic amino acid transporter	LoF	[183–186]
SOCS1	Suppressor Of Cytokine Signaling 1	Negative regulator of JAK/STAT	LoF	[82]
TLR7	Toll-like receptor 7	TLR signaling	GoF	[74▪▪,75,76]
TMEM173 (STING1)	Transmembrane protein 173	Detects cytosolic nucleic acids	GoF	[89]
TREX1	Three prime repair exonuclease 1	DNA clearance	LoF	[90]
TNFAIP3	TNFα Induced Protein 3	NF-KB signaling	LoF	[91]
TNIP1	TNFAIP3 Interacting Protein 1	NF-KB signaling	LoF	[92,187]
UNC93B1	Unc-93 Homolog B1	TLR signaling	LoF	[77]

GOF, gain-of-function; LOF, loss-of-function.

Defects in nucleic acid sensing and processing, either by abnormal clearance or enhanced sensing can trigger IFN expression, inflammation and autoimmunity [3,49]. SLE-like phenotypes were reported in patients with variants in Deoxyribonuclease (DNAse) enzymes that play an important role in innate antiviral responses. Deficiency of DNAse-1 (*DNASE1*), a cytoplasmic endonuclease degrading dsDNA [56], and lysosomal DNAse-2 (*DNASE2*) deficiency were reported in early-onset SLE patients who may exhibit "atypical" clinical features, such as neonatal pancytopenia, polyarthritis and cholestasis [57▪▪,58]. Loss-of-function variants affecting the 3'-5' exonuclease *TREX1* (*DNAse3*) were reported in familial chilblain lupus, early-onset SLE, and in Aicardi-Goutières syndrome (AGS) [48,59]. Recently, transmission disequilibrium testing confirmed that jSLE patients are enriched in rare variants, and identified rare variants in a diverse jSLE cohort, including loss-of-function in *HNRNPUL2*, encoding for the Heterogeneous Nuclear Ribonucleoprotein U Like 2, that plays a key role in double-stranded DNA repair [60▪]. Lastly, loss-of-function variants in *DNASE1L3*, an extracellular serum DNAse, were reported in six families [61]. DNAse-1L3 is responsible for extracellular dsDNA clearance. Its loss results in extracellular accumulation of immunogenic DNA (e.g. from neutrophil NETs), their recognition by innate toll-like receptors (TLRs) and IFN production that amplifies damage and extracellular DNA accumulation [62].

Disruption of RNA sensing has been linked with SLE. Variants in *RNASEH2A*, *RNASEH2B*, and *RNASEH2C*, encoding for the heterotrimeric RNAseH2 ribonuclease complex, were reported in SLE and AGS [63]. RNAseH2 processes RNA/DNA hybrids, a complex found during endogenous retrovirus transposition, in R-loops, and long interspersed nuclear elements (LINE-1) that trigger autoimmunity [64,65]. The innate antiviral SAMHD1 protein recognizes single-stranded (ss)RNA, ssDNA and self-dsDNA.

Monogenic SLE, AGS, and increased IFN expression were reported in patients with *SAMDH1* loss-of-function variants [14▪,66–68]. The retinoic-acid-inducible-gene-I/RIG-I (*DDX58*) encodes for a cytosolic RNA sensor that activates mitochondrial antiviral signaling protein (MAVS) to induce IFNs and other inflammatory cytokines. Gain-of-function variants in *DDX58* were reported in Singleton-Merton syndrome [69], SLE and LN [70].

Innate endosomal toll-like receptors (TLRs 3,7,8,9) are important IFN activators [71]. Especially the importance of the lysosomal ssRNA sensor TLR-7 has been highlighted in SLE [72,73]. Recently, a *de novo TLR7* gain-of-function variant was discovered in a jSLE patient, enhancing TLR-7 activation through guanosine and cGMP [74▪▪]. This was validated by additional reports of gain-of-function variants in *TLR7* in additional patients, highlighting neuroinflammation as an important clinical feature of this genotype [75,76]. The critical role of TLR-7 in SLE was further demonstrated by missense variants in *UNC93B1*, encoding for a chaperone protein that binds TLRs in the endoplasmic reticulum, guides them to endo-lysosomes, and modulates TLR-7 responses to self-nucleic acid [77]. Loss-of-function impairs TLR-7 regulation, resulting in pro-inflammatory cytokine (including IFN) expression and systemic autoimmunity [77,78▪▪,79,80]. As TLRs are partially redundant and/or complementary, it appears likely that SLE-associated variants will also be detected in other endosomal TLRs.

Defective regulation of JAK/STAT signaling in jSLE has recently been highlighted by the identification of 6 "novel" loss-of-function variants in the Tyrosine-protein phosphatase nonreceptor type 2 encoding gene *PTPN2* [81]. PTPN2 regulates the JAK/STAT pathway through dephosphorylation of JAK and STAT proteins to prevent prolonged activity. SLE-associated variants contribute to elevated IL-2, type I and II IFN levels, immunodeficiency and autoimmunity [81]. These observations underscore the importance of negative regulation of JAK/STAT signaling to retain immune balance that was previously highlighted by early-onset autoimmunity associated with suppressor of cytokine signaling-(SOCS)1 haploinsufficiency [82].

Dysregulated NF-κB signaling was recently linked with SLE phenotypes. Heterozygous variants in *RELA* were reported in patients with early-onset SLE, where modified RelA/p65 proteins spontaneously localize to the nucleus, leading to a lower activation threshold of the NF-κB and elevated IFN expression [83]. Patients with loss-of-function variants in *TNFAIP3* encoding for the A20 chaperone protein in the NF-κB pathway demonstrate the connection of this pathway to autoimmunity. Loss of A20 function (also referred to as haploinsufficiency A20/HA20) associates with clinically variable phenotypes, including Behçet's disease, SLE, and JIA [14▪,84].

Abnormalities in immune cell signaling and metabolism – a variant in the serine/threonine protein kinase Cδ (*PRKCD*) was reported in three siblings with SLE [85], and subsequently validated in another, consanguineous, family [86]. Recently, siblings with jSLE and immunodeficiency were reported to have compound heterozygous variants in *PRKCD* [87▪]. The reduction in PKCδ activity leads to deficient B cell apoptosis and increased B cell proliferation [85]. A recent study described two families with X-linked recessive loss-of-function variants in *SAT1* [88], encoding for the Spermidine/spermine N1-acetyltransferase 1 (SSAT1) enzyme. SSAT1 regulates polyamines catabolism and is most highly expressed in neutrophils. Polyamines bind DNA and change its conformation from *B*-DNA to *Z*-DNA, which may trigger autoimmunity. Neutrophils from mice carrying SAT1 loss-of-function variants are more likely to produce neutrophil NETs. This adds to the body of previous studies reporting rare variants in genes coding for metabolic proteins such as *PEPD* (encoding for prolidase) and *MAND2B1* (mannosidase-alpha class-2B member-1) in patients with jSLE [89,90].

Somatic, nongermline variants may affect individual cell-lines and can be missed in currently used sequencing approaches. In SLE, reports on resulting mosaicism are mostly limited to aneuploidy syndromes that also increase the risk SLE development, including Klinefelter (47XXY) [91,92] and Triple X (47XXX) syndromes [93]. Recently, a patient with jSLE-like disease and mosaic tetrasomy affecting 9p24.3q12 (including the IFN cluster) was reported, which may contribute to increased IFN expression [94].

Moreover, heterozygous somatic mutations have been reported in the *NRAS* proto-oncogene (c.38A>G/p.G13C) of 4 jSLE patients that associate with reduced interactions of the GTPase NRAS with BCL-2 (B-cell lymphoma 2). Subsequently reduced apoptosis likely contributes to SLE-like disease with a lymphoproliferative phenotype [95], resembling clinical phenotypes observed in patients with Autoimmune Lymphoproliferative syndrome (ALPS) [96,97].

Mosaics affecting immune cell subsets have previously been reported in monogenic autoinflammatory diseases, namely cryopyrin-associated periodic syndrome (CAPS) [98–101], where mosaicism can result in untypically late disease-onset through clonal expansion [102]. Thus, somatic variants affecting abovementioned genes may also contribute to SLE and should move into the focus of future research.

Phenotypic variability in "monogenic SLE" has been reported. Results from WES/WGS in SLE cohorts suggests interplay between rare and common variants that alter disease phenotypes. The UK Biobank provides WES data from 454 787 participants (95% European) [103]. A recent study focusing on immune-mediated diseases including SLE suggested contributions from both common and rare variants to diseases, as well as pleiotropy across immune-mediated diseases [104▪]. While this highlights the functional convergence of common and rare variant associations with SLE, it does not necessarily explain disease discordance in genetically identical monozygotic twins [105]. Thus, additional acquired (namely epigenetic) events may be involved [15▪,105].

EPIGENETIC CONTRIBUTION

Epigenetic mechanisms control gene expression through re-arrangement of nucleosomes and variable chromatin accessibility in a tissue-specific manner [7,8,16,106]. The addition of a methyl-group to the 5' carbon position within cytidine-guanosine dinucleotides reduces recruitment of the transcriptional complex to regulatory regions [16,107]. Posttranslational histone modifications result in "opening" or "closure" of chromatin through changing electric charge [107,108]. Noncoding (nc)RNAs include long ncRNAs, that modulate chromatin conformation and control interactions between core promoters and distal regulatory elements [109], and micro-(mi)RNAs [107] that control the stability and integrity of mRNA [110]. Epigenetic marks change during cell and tissue differentiation, are heritable but reversible. They are susceptible to hormonal impact (e.g., estrogens) and environmental exposure (e.g. to infections, diet, medications) [7,106]. Thus, epigenetic marks are interesting candidates in the search for disease biomarkers and therapeutic targets across age-groups [3,111].

DNA methylation, the most studied epigenetic mechanism, contributes to variable genotype:phenotype correlations in inflammatory disease, including SLE [7,15▪,106,112]. DNA methylation profiles in immune cells have been linked with altered receptor/ligand interactions, transcription factor signaling and cytokine expression. Hypomethylation of the *CD70* promoter in $CD4^+$ T cells from aSLE patients results in increased co-stimulatory CD70 surface expression and B cell stimulation [8,113–116] which was, however, not confirmed in PBMCs (Peripheral Blood Mononuclear Cells) from jSLE patients [115].

The lymphocyte-specific Lck tyrosine kinase is essential for the activation and function of naïve and effector T cells [117]. Hypomethylation of the *LCK* gene in $CD4^+$T cells may therefore contribute to pathological T cell activation in jSLE [118,119]. The SLE-associated effector T cell phenotype may be favored further through inhibition of the transcription factor FOXP3 (Forkhead Box P3) that is essential for the development and function of regulatory T cells (Treg) [120–128]. Increased *FOXP3* methylation in jSLE likely impacts on its expression [129]. The signal transducer and activator of transcription (STAT) transcription factor family is controlled by balanced activity of Janus kinases (JAK) and suppressor of cytokine signaling (SOCS) family members. STAT transcription factors play a key role in multiple aspects of immune responses and effector T cell biology [130]. In PBMCs from jSLE patients, hypomethylation of the *JAK2* and hypermethylation of the *SOCS3* promoters contribute to imbalanced gene expression, increased IFN expression and immune activation [131]. Furthermore, epigenetic dysregulation of IFN-associated genes has been linked with their increased expression in PBMCs, $CD4^+$/$CD8^+$ T cells, $CD19^+$ B cells, and $CD16^+$ neutrophils from SLE patients [15▪,108,113,118,132]. Notably, several Differentially Methylated Positions (DMPs) between jSLE patients and controls are shared between immune cell subsets and affect IFN signaling [118]. One of these shared genes, *IFI44L*, is hypomethylated in adult [133–135] and pediatric patients [136]. Oligoadenylate synthetases (OAS)1 and 2 are IFN-induced genes involved in the innate antiviral response [137,138]. Hypomethylation of *OAS1* and *OAS2* and upregulated gene expression in $CD8^+$ T cells and neutrophils associate with jSLE [118]. Furthermore, IFN dysregulation has been linked with LINE-1 that comprises 17–21% of the human genome and is involved in genome (in-)stability and evolution [139,140]. Hypomethylation of *LINE1* associates with IFN-regulated gene expression in autoimmune diseases, including SLE [140] where it associates with disease activity (in jSLE) [113].

Recently, phenotypic variation (severity of neurodevelopmental involvement) among AGS patients sharing the same genotype (*RNASEH2B* p.A177T) was linked with distinct DNA methylation profiles in PBMCs. Notably, DMPs associated with genes involved in IFN signaling associated with disease severity [15▪]. Thus, IFN-associated DNA methylation profiles may allow the prediction of disease activity and future patient stratification towards individualized treatment and care in patients with rare genetic forms of SLE/SLE-like disease and "classical" SLE.

Posttranslational histone modifications and the associated "histone code" are even more complex and incompletely understood, especially in children. However, genes affected by histone

dysregulation in SLE (at least partially) overlap with pathologically methylated genes [3,106].

The IFN-induced transcriptional regulator interferon regulatory factor 5 (IRF5) plays a role in amplifying inflammation through pro-inflammatory cytokine expression [141]. Its transcription is controlled by histone acetylation, and the histone deacetylase inhibitor Trichostatin A reduces its expression, promising therapeutic considerations [40].

STAT5 controls the balance between Treg and effector Th17 cells [142]. In $CD4^+$ T cells, the transcription factor cAMP Responsive Element Modulator (CREM)α recruits to the *Dual Specificity Protein Phosphatase (DUSP)4* promoter, which results in co-recruitment of the histone acetyltransferase p300, epigenetic "opening" and increased DUSP-4 expression [128,143]. This results in DUSP-4-mediated STAT5 de-phosphorylation and imbalanced STAT3/STAT5 signaling, favoring IL-17A and reducing IL-2 expression, hallmarks of SLE T cells [128,144] (Fig. 1). Because CREMα is induced by estrogen receptor signaling, this mechanism may contribute to the female predominance and phenotypical differences between pre and postpubertal SLE patients [5,145].

Lastly, in addition to functional impairment of enzymatic activity, mutations in *RNASEH2B* affect its interaction with the chromatin silencing complex (CoREST) that, among others, comprises HDAC2 and Lysine-Specific Histone Demethylase (KDM)1A. This suggests coordination between histone modifications and the degradation of RNA:DNA hybrids and its dysregulation in SLE [146].

Dysregulated expression of miRNAs is associated with DNA methylation and histone modifications [147,148]. Recent studies highlight the involvement of altered miRNA expression in the dysregulation of innate and damage-associated pathways, effector and regulatory T cell function in jSLE. Associations with organ involvement and/or disease activity and damage promise potential as future markers of disease activity and progression (Table 3).

CONCLUSION

SLE is a patho-mechanistically complex autoimmune/inflammatory disease. Though most studies have been performed in aSLE cohorts of European ancestry, we are beginning to understand genetic and environmental impacts that shape phenotypic differences between age-groups and ancestries. Genetic predisposition is necessary to develop disease, and genetic burden defines the age at disease-onset. First attempts to predict organ involvement and disease outcomes promise potential for future patient stratification towards individualized treatment and care. While rare variants with high effect size only affect a minority of SLE patients across age-groups, they transformed the understanding of more common forms of SLE. Phenotypic variability among patients with "monogenic SLE" underscores a role for additional common variants and epigenetic variability. A better

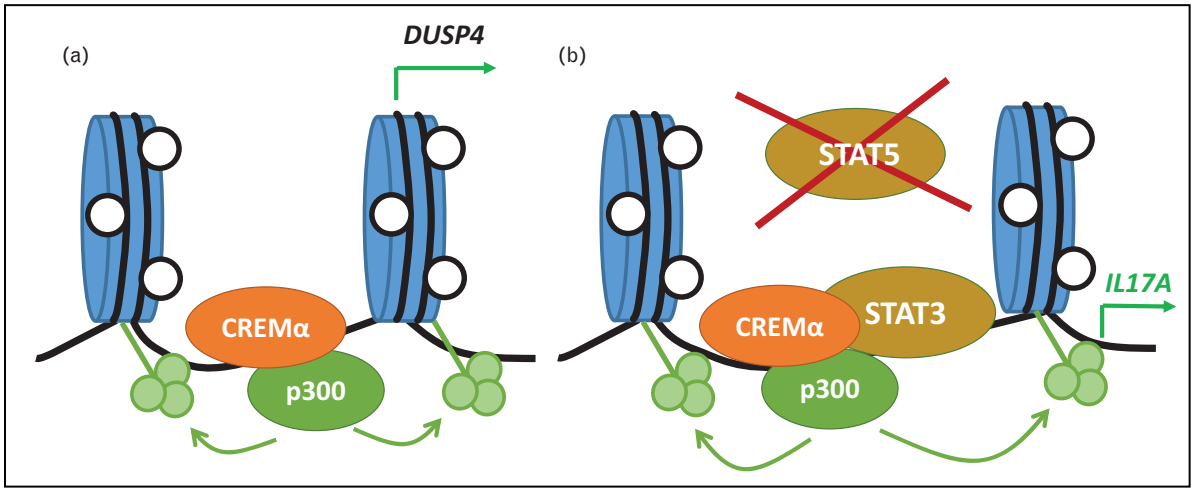

FIGURE 1. The transcription factor CREMα instructs epigenetic remodeling in T cells from SLE patients. (a) CREMα recruits to the *DUSP4* proximal promoter where it instructs histone acetylation (green circles) through co-recruitment of the histone acetyltransferase p300. Resulting epigenetic opening allows for the expression of the protein dual specificity protein phosphatase (DUSP)4. (b) At the same time, CREMα recruits to regulatory elements along the *IL17* cluster where it instructs DNA demethylation (open circles) and histone acetylation (green circles) through p300. Increased expression of DUSP4 (from a) results in an imbalance between phosphorylated STAT3 and STAT5, favoring STAT3 signaling. This results in increased recruitment of STAT3 alongside CREMα, both trans-activators of IL-17 transcription.

Table 3. Micro-RNAs associated with jSLE and other systemic autoimmune/inflammatory diseases (may be incomplete)

miRNA							
Up-regulated	**Down-regulated**	**Cell type/ tissue**	**mRNA target(s)**	**Function(s)**	**Proposed biomarker potential**	**jSLE context**	**Additional inflammatory diseases context**
	MiRNA-155	PBMCs	$PP2A_C$ and IL-2	Forced expression of miRNA-155 decreases relative expression of PP2Ac and increases IL-2 release in c PBMCs *in vitro*. Ex vivo expression of PP2AC mRNA correlates with SLEDAI scores. Patients with SLE exhibit increased activity of the PP2A catalytic subunit resulting in decreased IL-2 production in T cells [188].	MiRNA-155 inversely correlates with SLEDAI scores, proteinuria and correlated with total leukocyte counts.	[189]	RA [190], LSc [191], SjS [192], MS [193], JIA [194]
MiRNA-146a		Plasma (circulating exosomal miRNA)	TNF Receptor Associated Factor 6 (TRAF6)	Circulating exosomal miRNA-146a may inhibit lupus-induced inflammation through down-regulation of TRAF6 and regulate IFN production.	MiRNA-146a inversely correlates with SLEDAI-2K, antidouble stranded DNA and urine protein creatine.	[195]	RA, SLE, IBD, MS, psoriasis, GD, GO, SjS, T1D, AS, SSc, DM, BD, DM [196]
	MiRNA-125a	Plasma	Unknown	MiRNA-125a expression negatively associated with IL-17 levels, which may contribute to Th17 phenotype in SLE.	MiRNA-125a inversely correlates with SLEDAI-2K, SLICC scores, ESR and proteinuria.	[197]	RA [198], SLE [199], GD [200], HD [200]
	MiRNA-145	Renal vascular cells	Unknown	The expression of miRNA-145 is linked to the degree of renal vascular lesions (RVL) in lupus nephritis (LN). MiRNA-145 is negatively regulated by PDGF-BB. PDGF-BB-induced proliferation and migration of human vascular smooth muscle cells (HVSMC) is inhibited by miRNA-145. MiRNA-145 may promote apoptosis of HVSMCs and play a role in vascular injury.	MiRNA-145 may allow noninvasive monitoring of vascular lesions (negative correlation) in juvenile lupus nephritis patients.	[201]	SLE [202], MS [203], SSc [204], CD [205]
	MiRNA-9–5p	PBMCs	NFKB1	MiRNA-9-5p and miRNA-125b-5p are downregulation in jSLE patients when compared to controls. NFKB1 expression is downregulated and TRAF6 is upregulated in jSLE patients when compared to the healthy controls.	Both miRNAs may be markers of the disease, but no differences were observed between active and inactive jSLE.	[206]	MS [207], T1D [208], SLE [209]
	MiRNA-125b-5p		TRAF6			[207]	Psoriasis [210], SLE [211], RA [212]
	MiRNA-200a	Serum	Unknown	Serum levels of miR-200a are lower in jSLE patients as compared to healthy participants.	Disease activity: MiRNA-200a negatively correlates with SLEDAI ($r=-0.425$), ESR ($r=-0.284$), CRP ($r=-0.338$), BUN ($r=-0.263$) and Scr ($r=-0.345$), while it positively correlates with C3 ($r=0.631$), C4 ($r=0.524$) and ALB ($r=0.394$). Diagnostic for SLE: AUC 0.8379 (cut-off value = 2.225, sensitivity = 70%, specificity = 70%). Diagnostic for LN: AUC 0.7619 (cut-off value = 2.005, sensitivity = 80%, specificity = 76%)	[213]	MS [214]

ALB, albumin; AS, ankylosing spondylitis; BD, Behçet's disease, BUN, blood urea nitrogen; CD, Crohn disease; CRP, C-reactive protein; DM, dermatomyositis; ESR, erythrocyte sedimentation rate; GD, Graves ' disease; GO, Graves' ophthalmopathy (orbidopathy); HD, Hashimoto disease; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; LN, lupus nephritis; LSc, localised scleroderma; MS, multiple sclerosis; MS, multiple sclerosis; PDGF-BB, platelet derived growth factor BB; RA, rheumatoid arthritis; scr, serum creatinine; SjS, primary Sjogren syndrome; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index.SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; SLICC, 2012 Systemic Lupus Collaborating Clinics classification criteria for SLE; SSc, systemic sclerosis; T1D, type 1 diabetes mellitus.

understanding of epigenetic marks will allow their inclusion in diagnostic, prognostic and therapeutic considerations.

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