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AUTOANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS: FROM PATHOGENIC MECHANISMS TO BIOMARKERS AND TARGETED THERAPEUTIC STRATEGIES

Sangeen Khan[*1,2], Muhammad Umair[2], Muhammad Naveed[3], Jun Huang[4]

[1]*Guangzhou ChuangRui Health Scientific., Ltd, Guangdong Medical Valley, Nansha District, Guangdong, 511400, China*
[2]*Department of Microbiology and Immunology, School of Basic Medical Sciences, Zhengzhou University, Zhengzhou 450052, Henan, China*
[3]*Departments of Microbiology, Hazara university Mansehra, 21300.*
[4]*China Sino-French Hoffmann Institute, Department of Basic Medical Science, Guangzhou Medical University, Guangzhou, China*

[*1]sangeenmicrobiologist@gmail.com, [4]hj165@sina.com

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Abstract

Systemic Lupus Erythematosus (SLE) is a complex autoimmune condition marked by a breakdown in immune tolerance, leading to the production of autoantibodies against self-antigens. Disease progression is driven by these autoantibodies through immune complex formation, complement activation, and inflammatory responses, resulting in tissue damage and multi-organ involvement. Key autoantibodies including anti-dsDNA, anti-Sm, anti-Ro/SSA, anti-La/SSB, and anti-phospholipid antibodies not only contribute to disease pathogenesis but also serve as important biomarkers for diagnosis, prognosis, and monitoring disease activity. B-cell dysregulation, genetic susceptibility, epigenetic changes, and environmental factors have recently been recognized as key regulators of autoantibody production. While current therapies targeting immune cells and inflammatory pathways have improved SLE management, challenges such as disease heterogeneity, treatment resistance, and adverse effects persist. Advances in precision medicine, autoantibody profiling, and emerging therapies are opening new avenues for personalized care. This review summarizes the pathogenic mechanisms, clinical significance, and therapeutic potential of autoantibodies in SLE, with emphasis on their role in improving diagnosis and targeted treatment.

1. INTRODUCTION

1.1 Overview of Systemic Lupus Erythematosus (SLE)

Systemic Lupus Erythematosus (SLE) is a complex and heterogeneous autoimmune disorder in which immune tolerance is lost, leading to the activation of autoreactive immune cells and the production of autoantibodies against self-antigens. Immune complexes formed by these autoantibodies accumulate in various tissues, where they trigger inflammatory responses and cause progressive organ damage. Being a

systemic disease, SLE has the potential to affect multiple organs, including the skin, joints, kidneys, cardiovascular system, lungs, blood vessels, and central nervous system. As a result, a wide range of clinical manifestations is observed, spanning from mild symptoms such as fatigue, arthralgia, and skin rashes to severe, life-threatening complications such as lupus nephritis, cardiovascular disorders, and neuropsychiatric abnormalities [1].

The pathogenesis of SLE arises from a complex interplay of genetic susceptibility, hormonal regulation, environmental triggers, and immune dysregulation. More than 100 SLE-associated genetic loci, including HLA-DR, IRF5, STAT4, and BLK, have been identified through genome-wide association studies (GWAS), many of which are involved in regulating antigen presentation, interferon signaling, and lymphocyte activation. Genetic predisposition alone, however, is not sufficient to trigger disease development, suggesting that environmental and hormonal factors also act as important contributors. The influence of hormones, particularly estrogen, is highlighted by the notably higher prevalence of SLE in females (with a female-to-male ratio of approximately 9:1), as estrogen can enhance B-cell activation and promote autoantibody production. In addition, cellular stress and antigen release may be promoted by environmental factors such as ultraviolet (UV) radiation, infections, and certain medications, thereby initiating or exacerbating autoimmune responses [2,3].

Despite considerable progress in understanding the pathogenesis of SLE, diagnosis and treatment continue to pose challenges owing to disease heterogeneity and the absence of a definitive cure. Abnormal immune activation is mainly targeted by current therapeutic strategies, which aim to control inflammation, prevent disease flares, and reduce organ damage through the use of immunosuppressive agents, antimalarial drugs, and biologic therapies. However, the need for more targeted and personalized therapeutic approaches is underscored by variable treatment responses and the potential for adverse effects.

1.2 Role of Autoantibodies in Systemic Lupus Erythematosus

Autoantibodies represent a defining feature of autoimmune disorders, including systemic lupus erythematosus (SLE), and function as key mediators of immune-mediated tissue injury. A broad range of self-antigens, including nucleic acids, proteins, and cellular components, are recognized by these pathogenic antibodies, resulting in the disruption of immune tolerance and the activation of inflammatory pathways. In SLE, several autoantibodies are commonly detected, including anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm), anti-nuclear antibodies (ANA), and anti-ribonucleoprotein (anti-RNP), and these are associated with disease diagnosis, activity, and clinical manifestations. Tissue damage and disease progression are driven by these autoantibodies through mechanisms such as immune complex formation, complement activation, and inflammatory cell recruitment (Figure 1):

Immune Complex Formation: Immune complex formation with self-antigens represents the primary mechanism through which autoantibodies contribute to SLE pathogenesis. These complexes can deposit in various tissues, particularly the kidneys, skin, and blood vessels, where the complement system is activated and inflammatory cascades are initiated, leading to tissue injury. A classic example is lupus nephritis, in which glomerular inflammation and progressive renal damage are triggered by immune complex deposition within the glomeruli, representing one of the major causes of morbidity in SLE patients [4].

Direct Cellular Damage: Beyond immune complex-mediated injury, cellular or extracellular antigens can be directly targeted by certain autoantibodies, disrupting normal tissue function. For instance, components of the glomerular basement membrane can be cross-reacted with by anti-double-stranded DNA (anti-dsDNA) antibodies, promoting renal inflammation and contributing to kidney damage. This mechanism highlights the ability of autoantibodies to directly mediate organ-specific injury in systemic autoimmune diseases [5].

Cytokine Dysregulation: Immune signaling can also be influenced by autoantibodies through the modulation of cytokine production and inflammatory pathways. In SLE, the production of type I interferons (IFNs) central drivers of chronic inflammation and immune activation has been shown to be

stimulated by anti-dsDNA antibodies. This interaction further amplifies autoimmune responses and contributes to disease progression [6].

In addition to their pathogenic functions, valuable clinical biomarkers for diagnosis, disease monitoring, and prognosis are provided by autoantibodies. For instance, lupus nephritis and disease activity are strongly associated with elevated anti-dsDNA levels, whereas anti-Smith (anti-Sm) antibodies, despite their high specificity for SLE, are detected in only a smaller proportion of patients. Therefore, improving disease classification, patient stratification, and the development of targeted therapeutic strategies requires a clear understanding of the pathogenic and diagnostic roles of autoantibodies.

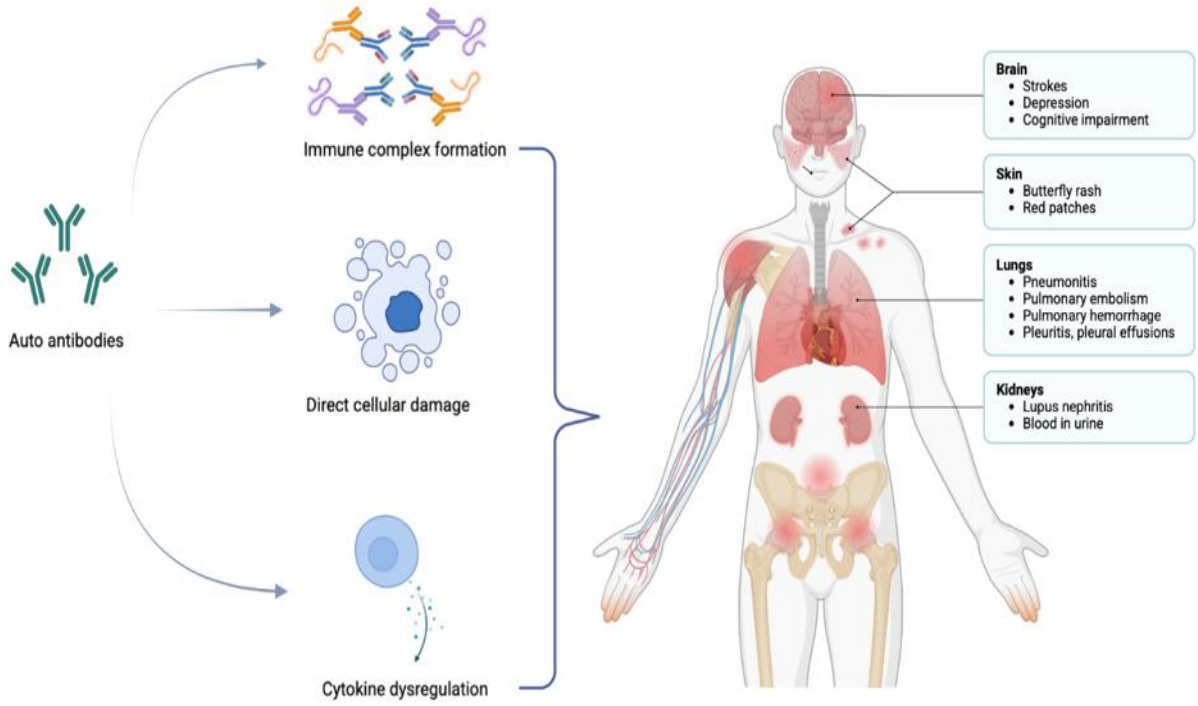


Figure 1: Mechanisms of tissue damage mediated by autoantibodies: (a) Immune complex formation (b) Direct cellular damage (c) Cytokine dysregulation.

1.3 Historical Evolution and Clinical Significance of Autoantibodies Discovery in SLE

Understanding of autoimmune pathogenesis has been fundamentally shaped by the discovery and characterization of autoantibodies in systemic lupus erythematosus (SLE), which has also contributed to improved disease diagnosis. A major breakthrough was achieved in 1948, when the lupus erythematosus (LE) cell phenomenon characterized by neutrophils containing engulfed nuclear material was identified by Hargraves and colleagues. The first evidence of abnormal immune recognition of nuclear components was provided by this observation, which later led to the identification of anti-nuclear antibodies (ANA), a marker that became key to diagnosing SLE. Further progress made in the 1950s led to the discovery of anti-double-stranded DNA (anti-dsDNA) antibodies, which were shown to have a strong association with disease activity and renal involvement, particularly in lupus nephritis [7].

With the advancement of immunological and molecular techniques, an expanding spectrum of An expanding spectrum of SLE-associated autoantibodies was identified with the advancement of immunological and molecular techniques. Among these, anti-Smith (anti-Sm) antibodies, discovered in the 1960s, were recognized as highly specific markers for SLE. The sensitivity and accuracy of autoantibody identification were further improved by the development of detection methods, including

immunofluorescence, enzyme-linked immunosorbent assay (ELISA), and multiplex-based platforms, enabling better disease classification and patient monitoring [8]. Beyond their diagnostic value, an understanding of disease mechanisms particularly the role of immune complex formation and complement activation in tissue injury has been significantly advanced by historical discoveries of SLE autoantibodies. These insights have guided the development of targeted therapeutic approaches aimed at modulating immune complex-mediated inflammation and improving clinical outcomes in SLE patients [9].

1.4 Scope and Objectives of the Review

A comprehensive overview of the current understanding of autoantibodies in SLE is provided by this review, with a particular focus on their pathogenic mechanisms, diagnostic significance, and therapeutic potential. How autoantibodies contribute to disease progression through key mechanisms, including immune complex formation, complement activation, and direct cellular injury is discussed. In addition, the clinical relevance of major SLE-associated autoantibodies, such as anti-dsDNA, anti-Sm, and anti-ribosomal P antibodies, is highlighted, particularly regarding their role in disease diagnosis, monitoring, and prediction of clinical outcomes [10].

Emerging therapeutic strategies aimed at reducing autoantibody production or limiting their pathogenic effects including B-cell-targeted therapies, type I interferon blockade, and complement inhibition are summarized in this review. Despite significant advances, several challenges remain, particularly in understanding the role of autoantibodies during early disease development and their potential application as biomarkers for predicting disease flares and therapeutic responses [11]. Finally, future research directions are discussed, including the development of improved diagnostic approaches and personalized treatment strategies. By integrating findings from basic immunology, clinical studies, and translational research, this review aims to provide new insights into SLE pathogenesis and to contribute to the advancement of more effective, patient-centered therapies [12].

2. Pathogenic Autoantibodies in SLE

2.1 Key Autoantibodies in SLE

2.1.1 Anti-dsDNA Antibodies

Anti-double-stranded DNA (anti-dsDNA) antibodies are among the most specific autoantibodies associated with SLE and are detected in approximately 60–70% of affected patients. Disease activity, particularly the development of lupus nephritis one of the most severe organ complications of SLE is strongly correlated with their presence. Renal injury is primarily driven by these antibodies through the formation of immune complexes with DNA, which accumulate in the glomerular basement membrane and activate the complement system, leading to inflammatory responses and progressive tissue damage [13].

In addition to immune complex-mediated effects, renal pathology can be directly promoted by anti-dsDNA antibodies through cross-reactivity with endogenous antigens, including α-actinin and laminin, further contributing to glomerular injury [14]. Moreover, apoptosis can be induced by their interaction with renal cells, such as mesangial cells and podocytes, disrupting cellular function and impairing the glomerular filtration barrier, ultimately accelerating the progression of lupus nephritis [15].

2.1.2 Anti-Smith (Anti-Sm) Antibodies

Anti-Smith (anti-Sm) antibodies are autoantibodies that target spliceosomal small nuclear ribonucleoproteins (snRNPs) and are regarded as highly specific biomarkers for SLE, despite being found in only about 20–30% of patients. Although their prevalence is relatively low, more severe disease manifestations, including neuropsychiatric involvement and renal complications, are linked to the presence of anti-Sm antibodies [16].

Although the precise pathogenic mechanisms of anti-Sm antibodies remain incompletely understood, emerging evidence suggests that tissue injury may be driven by these antibodies through immune complex formation, complement activation, and subsequent inflammatory responses. Their strong disease

specificity and association with clinical severity underscore their importance as both diagnostic markers and potential indicators of disease progression in SLE [17].

2.1.3 Anti-Ro/SSA and Anti-La/SSB Antibodies

Anti-Ro/SSA and anti-La/SSB antibodies are commonly detected in SLE and are also characteristic of other autoimmune conditions, particularly Sjögren's syndrome. Among these autoantibodies, cutaneous manifestations of SLE especially photosensitivity and subacute cutaneous lupus erythematosus (SCLE) are strongly associated with anti-Ro/SSA antibodies, reflecting their involvement in skin-directed autoimmune responses [18].

Beyond their role in maternal autoimmune disease, important clinical implications during pregnancy arise from anti-Ro/SSA antibodies, as they can cross the placenta and affect fetal tissues, potentially causing neonatal lupus manifestations such as congenital heart block and cutaneous lesions [19]. In comparison, anti-La/SSB antibodies are commonly detected alongside anti-Ro/SSA antibodies and are generally linked to a milder disease severity profile, although they offer additional diagnostic value in SLE and related autoimmune disorders. Antiphospholipid antibodies (aPLs), including lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein I antibodies, are frequently detected in SLE patients and play a central role in the pathogenesis of antiphospholipid syndrome (APS). These antibodies interfere with normal coagulation processes, promoting a hypercoagulable state that increases the risk of arterial and venous thrombosis [20].

2.1.4 Anti-Nuclear Antibodies (ANAs)

Anti-nuclear antibodies (ANAs) are among the most widely recognized serological markers of SLE and are detected in more than 95% of affected individuals. A broad spectrum of nuclear components, including histones, nucleosomes, and ribonucleoproteins, is recognized by these antibodies, reflecting the loss of immune tolerance against self-nuclear antigens. Although ANAs are not specific to SLE and can also be detected in other autoimmune conditions, their high sensitivity makes them an essential component of SLE diagnosis and clinical evaluation [21]. Beyond their diagnostic value, disease pathogenesis may be influenced by ANAs through the formation of immune complexes with nuclear antigens. These complexes can deposit in susceptible tissues, activate the complement cascade, and promote the recruitment of inflammatory cells, thereby sustaining chronic inflammation and contributing to tissue injury in SLE [22].

2.1.5 Anti-Phospholipid Antibodies

Anti-phospholipid antibodies (aPLs), including anti-cardiolipin antibodies and lupus anticoagulant, represent an important subset of autoantibodies linked to thrombotic events and pregnancy-related complications in patients with SLE. Phospholipid-binding proteins, particularly β2-glycoprotein I, are primarily targeted by these antibodies, which promote a pro-thrombotic state through the activation of endothelial cells, platelets, and monocytes [23]. This immune-mediated activation enhances coagulation pathways and contributes to vascular inflammation and thrombosis. The presence of aPLs is a key diagnostic feature of anti-phospholipid syndrome (APS), an autoimmune disorder marked by recurrent thrombosis and pregnancy complications. APS can occur as an independent condition (primary APS) or develop alongside SLE (secondary APS), further underscoring the clinical significance of aPL detection in autoimmune disease management [24].

2.2 Mechanisms of Autoantibody Mediated Tissue Damage in SLE

Multiple interconnected mechanisms, including immune complex formation, complement activation, and direct cellular injury, underlie the contribution of autoantibodies to SLE pathogenesis. Together, these processes drive chronic inflammation and progressive damage across various organs.

2.2.1 Immune Complex Formation and Deposition

A major mechanism of autoantibody-mediated injury in SLE involves the formation of immune complexes between autoantibodies and their corresponding self-antigens. Susceptible tissues, particularly the kidneys, skin, and blood vessels, can be infiltrated by these complexes, where complement activation

and the release of inflammatory cytokines and chemokines are triggered, resulting in tissue inflammation [25]. In lupus nephritis, persistent inflammatory responses are initiated by immune complex deposition within the glomeruli, leading to glomerular injury, fibrosis, and eventual renal dysfunction [26].

2.2.2 Complement Activation

Following immune complex deposition, the classical complement pathway is activated by autoantibodies, generating inflammatory mediators such as C3a and C5a and promoting the formation of the membrane attack complex (MAC). The recruitment and activation of immune cells, including neutrophils and macrophages, at sites of immune complex accumulation are enhanced by C3a and C5a. Meanwhile, direct membrane damage and cellular lysis are induced by MAC formation. Therefore, excessive complement activation serves as a major driver of inflammation and tissue injury in SLE, particularly in renal and cutaneous manifestations [27]. Interestingly, complement components also serve a protective function under normal physiological conditions by facilitating the clearance of apoptotic cells and immune complexes. However, when this system becomes deficient or dysregulated, autoimmunity and disease progression in SLE can paradoxically be promoted [28].

2.2.3 Direct Cellular Toxicity

In addition to immune complex-mediated mechanisms, target cells can be directly engaged by certain autoantibodies, disrupting cellular function. For example, renal cells, including mesangial cells and podocytes, can be bound by anti-dsDNA antibodies, inducing apoptosis and compromising the integrity of the glomerular filtration barrier [28]. Similarly, anti-ribosomal P antibodies have been implicated in neuropsychiatric lupus through their interaction with neuronal cells and their potential effects on neuronal function [29]. These findings highlight the ability of specific autoantibodies to induce organ-specific injury and contribute to the diverse clinical manifestations of SLE.

2.3 Organ Specific Effects of Autoantibodies in SLE

The clinical diversity of SLE is largely attributed to the ability of pathogenic autoantibodies to target different tissues and drive organ-specific inflammation. Depending on the target antigen and the organ affected, distinct clinical manifestations are produced by these autoantibodies through mechanisms involving immune complex deposition, complement activation, and direct cellular injury.

2.3.1 Lupus Nephritis

Lupus nephritis is one of the most severe complications of SLE, affecting approximately 40–60% of patients and representing a major cause of disease-associated morbidity. The development of lupus nephritis is strongly linked to anti-dsDNA and anti-nucleosome antibodies, which drive immune complex formation and complement activation within renal tissues [30]. Beyond immune complex-mediated injury, renal antigens can also be cross-reacted with by these antibodies, further amplifying inflammation and contributing to progressive kidney damage [31].

2.3.2 Cutaneous Manifestations

Cutaneous lupus erythematosus (CLE) is characterized by inflammatory skin lesions that are often triggered or worsened by ultraviolet (UV) exposure. Photosensitivity and subacute cutaneous lupus erythematosus (SCLE) are strongly associated with anti-Ro/SSA antibodies, suggesting their important role in skin-specific autoimmune responses [32]. Cutaneous injury may be promoted by these antibodies through the formation of immune complexes within the dermis, leading to complement activation and localized inflammatory responses [33].

2.3.3 Neuropsychiatric Lupus

Neuropsychiatric lupus (NPSLE) involves a broad spectrum of neurological and psychiatric manifestations caused by autoimmune-mediated damage to the nervous system. Anti-ribosomal P and anti-NMDA receptor antibodies have been implicated in NPSLE, although their precise pathogenic mechanisms remain under investigation [34]. According to current evidence, the central nervous system may be

accessed by these antibodies, which can interact with neuronal cells and induce inflammatory responses or neuronal damage, contributing to neurological dysfunction [35].

2.3.4 Hematologic Involvement

Hematological abnormalities are common manifestations of SLE and include thrombocytopenia, autoimmune hemolytic anemia, and thrombotic complications. Among these, thrombotic events are largely driven by anti-phospholipid antibodies through the induction of endothelial activation, enhanced platelet aggregation, and the creation of a pro-coagulant state [36]. This mechanism contributes to the increased risk of vascular complications observed in patients with SLE-associated anti-phospholipid syndrome.

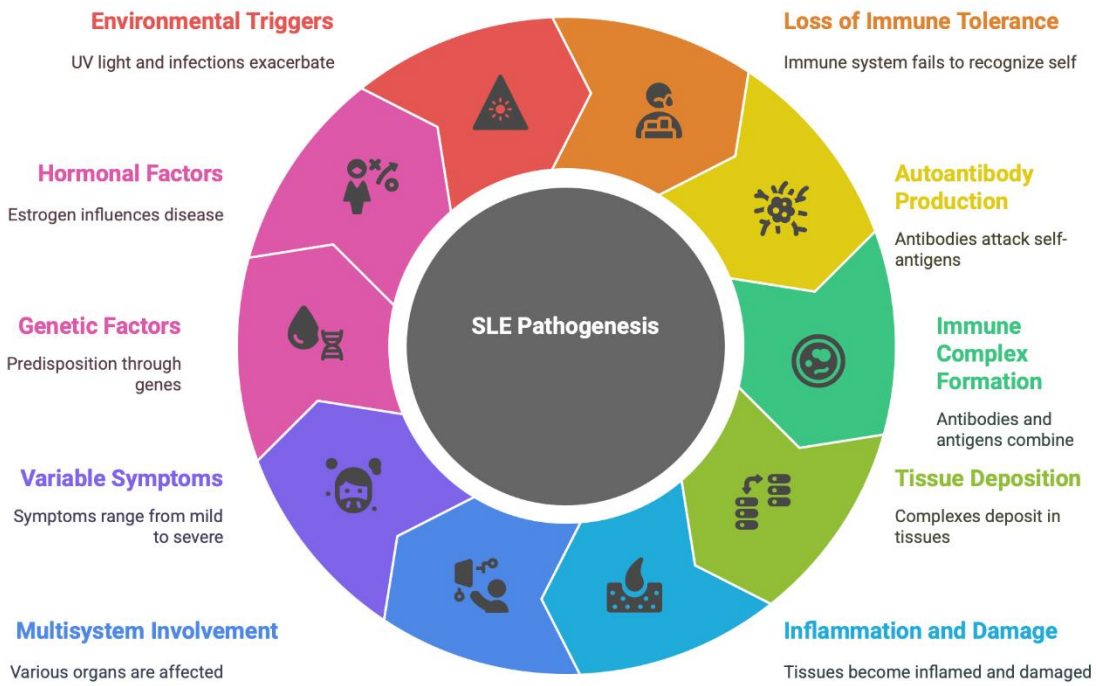


Figure 2: Pathogenesis of autoantibodies in Systemic Lupus Erythematosus.

3. Autoantibodies as Diagnostic and Prognostic Biomarkers in SLE

Systemic Lupus Erythematosus (SLE) is characterized by the presence of diverse autoantibodies that serve as valuable biomarkers for disease diagnosis, prognosis, and monitoring. Important information for distinguishing SLE from other autoimmune disorders and improving patient management is provided by these autoantibodies, owing to their varying levels of sensitivity, specificity, and clinical associations. This section discusses the clinical significance of major autoantibodies, along with recent advances in their detection and interpretation.

3.1 Diagnostic Biomarkers

Early detection of SLE is critically supported by autoantibodies, as they can appear before the onset of clinical symptoms and provide important clues for disease classification. However, their diagnostic value varies depending on the sensitivity and specificity of individual autoantibodies, making their interpretation alongside clinical findings essential.

3.1.1 Role of ANAs in SLE Diagnosis

Antinuclear antibodies (ANAs) are among the most sensitive biomarkers for SLE and are found in more than 95% of patients. A wide range of nuclear components, including DNA, histones, and ribonucleoproteins, is recognized by these antibodies, and their detection forms a key criterion for SLE classification [37]. The indirect immunofluorescence assay (IFA) using HEp-2 cells remains the gold-standard method for ANA detection, owing to its high sensitivity and its ability to distinguish between different staining patterns, including homogeneous, speckled, nucleolar, and cytoplasmic types. Additional diagnostic information can be gained from these patterns, as they often point to the presence of specific autoantibodies and their potential clinical relevance. For instance, homogeneous staining is typically linked to anti-dsDNA antibodies, while speckled patterns may point to anti-Sm or anti-RNP antibodies.

Despite their high sensitivity, ANAs lack disease specificity, as they can also be detected in other autoimmune diseases, infections, and even some healthy individuals, particularly with advancing age [38]. Therefore, combining ANA results with clinical manifestations and additional serological markers is essential for an accurate diagnosis. Diagnostic interpretation has further been shown to be improved by ANA staining patterns, particularly in patients presenting with ambiguous clinical features, as recent studies demonstrate [39]. Moreover, testing efficiency, consistency, and reliability in clinical settings have been enhanced by the development of automated ANA detection platforms, including multiplex immunoassays [40].

3.1.2 Diagnostic Value of Anti-dsDNA and Anti-Sm Antibodies

Anti-dsDNA and anti-Sm antibodies rank among the most clinically significant autoantibodies in SLE, owing to their high specificity and strong association with disease manifestations. Anti-dsDNA antibodies are found in approximately 60–70% of SLE patients and are closely linked to disease activity, particularly lupus nephritis. Several detection methods are used for anti-dsDNA measurement, including the Farr assay, enzyme-linked immunosorbent assay (ELISA), and chemiluminescence immunoassay (CLIA). While high specificity is offered by the Farr assay, its technical complexity limits widespread use, whereas greater sensitivity and higher-throughput analysis are provided by ELISA and CLIA [41].

Although anti-Sm antibodies are found in only 20–30% of SLE patients, their high specificity makes them an important serological hallmark of the disease. Recent efforts have focused on improving detection accuracy through advanced assays and recombinant antigen-based approaches [42]. Notably, improved detection of low-titer anti-dsDNA antibodies that might otherwise be missed by conventional techniques has been demonstrated using CLIA-based methods [43]. The importance of early identification of these antibodies in preventing long-term organ complications is further emphasized by studies in pediatric SLE [44]. In addition, diagnostic accuracy can be enhanced by combining anti-dsDNA and anti-Sm antibodies with other disease indicators, such as complement levels and clinical parameters, particularly in patients with atypical or incomplete disease presentations [45].

3.2 Prognostic Value of Autoantibodies in Diseases Activity and Organ Damage Prediction

Beyond their diagnostic utility, important prognostic information in SLE is offered by autoantibodies, as they reflect disease activity, predict clinical flares, and signal the risk of organ involvement. Tracking autoantibody levels and patterns over time can help identify patients at greater risk of complications and support the development of individualized treatment strategies.

3.2.1 Predicting Disease Flares

Disease flares are major contributors to SLE-related morbidity and mortality, making early prediction essential for effective disease management. Among various autoantibodies, disease exacerbations are strongly associated with anti-dsDNA antibodies, particularly in patients with lupus nephritis [46]. Clinical deterioration is often preceded by a rise in anti-dsDNA antibody titers, making them valuable indicators of impending disease activity. A significantly higher risk of experiencing flares has been shown by patients with rising anti-dsDNA levels, compared with those showing stable or declining antibody levels.

In addition to anti-dsDNA antibodies, organ-specific prognostic information is provided by other autoantibodies. Neuropsychiatric manifestations have been associated with anti-ribosomal P antibodies, whereas cutaneous and neonatal lupus manifestations are linked to anti-Ro/SSA and anti-La/SSB antibodies [47]. Simultaneous detection of multiple autoantibodies has been enabled by recent advances in multiplex antibody profiling, allowing a more comprehensive assessment of flare risk. Furthermore, potential for improving the accuracy of disease flare prediction has been shown through the integration of autoantibody profiles with clinical parameters using machine learning approaches [48,49].

3.2.2 Association with Organ Damage

The accumulation of irreversible organ damage is a major determinant of long-term outcomes in SLE, and specific autoantibody profiles can help identify patients at greater risk. Renal involvement is strongly associated with anti-dsDNA antibodies, which remain one of the most important predictors of lupus nephritis development and progression [50]. Similarly, vascular complications are driven by anti-phospholipid antibodies (aPLs), including anti-cardiolipin and anti-β2-glycoprotein I antibodies, which promote thrombosis and heighten cardiovascular risk in SLE patients [51].

Other autoantibodies have also been linked to specific organ manifestations. Neuropsychiatric complications, including psychosis and depression, are associated with anti-ribosomal P antibodies, while anti-C1q antibodies have emerged as potential biomarkers for renal flares and progression toward end-stage renal disease (ESRD) [52,53]. Recent studies suggest that risk stratification may be improved through comprehensive autoantibody profiling, which can help identify patients prone to severe organ involvement. For example, more aggressive renal disease requiring intensive immunosuppressive therapy has been associated with elevated anti-C1q levels [54]. Moreover, an increased risk of multi-organ damage has been linked to the simultaneous presence of multiple autoantibodies, including anti-dsDNA, anti-Sm, and anti-C1q, underscoring the importance of integrated serological assessment in SLE management [55].

3.3 Autoantibodies in Monitoring Disease Activity and Treatment Response

Accurate monitoring of disease activity remains essential for optimizing treatment strategies and improving long-term outcomes in patients with SLE. Among the available biomarkers, valuable insight into disease activity, treatment response, and the risk of progression is offered by autoantibody levels, particularly those of anti-dsDNA antibodies. Nevertheless, given the heterogeneous nature of SLE, their interpretation must be integrated with clinical findings and other laboratory parameters.

3.3.1 Correlation with SLE Disease Activity Index (SLEDAI)

The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) is a widely used clinical tool for evaluating disease activity in SLE. An association between elevated anti-dsDNA antibody levels and increased SLEDAI scores has been demonstrated by several studies, particularly in patients with active renal or hematological involvement. However, this relationship is not always consistent, as clinical stability may be maintained by some patients with high anti-dsDNA titers, whereas significant disease activity may be experienced by others with relatively low antibody levels.

To improve the accuracy of disease assessment, recent studies have focused on combining autoantibody measurements with additional biomarkers, such as complement components C3 and C4. For example, better predictive value for disease activity has been shown when anti-dsDNA levels are integrated with complement profiles, compared with relying on individual biomarkers alone [56]. Furthermore, potential for improving disease activity prediction and enhancing the clinical utility of SLEDAI assessment has been demonstrated by machine learning-based approaches that incorporate autoantibody profiles alongside clinical and laboratory parameters [57].

3.3.2 Autoantibody Titers and Treatment Response

Changes in autoantibody levels can also provide insights into therapeutic effectiveness and disease progression. Clinical improvement, particularly in lupus nephritis, is frequently associated with a decline in anti-dsDNA antibody levels following immunosuppressive treatment, whereas ongoing disease activity or an insufficient therapeutic response may be indicated by persistent or rising titers [58]. The importance

of autoantibody monitoring in treatment evaluation has been further highlighted by the development of targeted biologic therapies. For example, autoantibody production, including anti-dsDNA levels, has been shown to be reduced by belimumab a monoclonal antibody targeting B-cell activating factor (BAFF) which also decreases disease flare frequency in patients with active SLE [59]. Moreover, therapeutic selection and improved patient outcomes may be supported by integrating autoantibody profiles into personalized medicine approaches. Emerging treatment algorithms that incorporate serological markers aim to identify patients most likely to benefit from specific biologic therapies, supporting a more individualized approach to SLE management [60].

4. Molecular and Cellular Mechanisms Driving Autoantibody Production in SLE

Autoantibody production is a defining feature of SLE and stems from a complex interplay between immune dysregulation, genetic susceptibility, epigenetic alterations, and environmental influences. Central to this process is the breakdown of B-cell tolerance, which enables autoreactive B cells to survive, expand, and differentiate into antibody-producing cells. Deeper insights into the cellular and molecular pathways responsible for autoantibody generation have been provided by recent advances in immunology, revealing potential targets for therapeutic intervention. This section discusses the contribution of B-cell abnormalities, plasma cells, and T-cell interactions in sustaining autoimmune responses in SLE.

4.1 B-Cell Dysregulation in SLE

B cells act as central drivers of SLE pathogenesis owing to their capacity to generate pathogenic autoantibodies against self-antigens, including nuclear components such as double-stranded DNA and histones. Under normal conditions, autoreactive B cells are eliminated or kept in check by immune tolerance mechanisms; however, these regulatory processes are impaired in SLE, leading to persistent autoimmune activation. The expansion of autoreactive B-cell populations and continuous autoantibody production are promoted by dysregulated B-cell signaling, enhanced survival, and heightened responsiveness to cytokines (Figure 3). Furthermore, a self-amplifying inflammatory network that sustains disease progression is created by interactions between B cells, T cells, and other immune components [61].

4.1.1 Role of Plasma Cells and Memory B Cells

Long-lived plasma cells represent a major source of persistent autoantibody production in SLE. Residing within specialized bone marrow niches, these cells secrete autoantibodies continuously and remain relatively resistant to conventional immunosuppressive therapies, contributing to ongoing disease activity. Memory B cells, on the other hand, preserve immune memory and can rapidly differentiate into antibody-producing plasma cells once re-exposed to antigen, allowing autoimmune responses to persist even after the original trigger has been removed. Because of these features, both plasma cells and memory B cells stand out as important contributors to disease relapse and treatment resistance [62].

The importance of cytokines such as B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) in supporting the survival and differentiation of autoreactive B cells and plasma cells has been highlighted by recent studies. Increased disease activity and autoantibody production are associated with elevated BAFF levels in SLE patients. By interacting with their receptors on B cells, B-cell survival is enhanced and plasma cell differentiation is promoted by BAFF and APRIL, making them attractive therapeutic targets [63]. For example, clinical efficacy has been demonstrated by belimumab, a BAFF-neutralizing monoclonal antibody, which reduces autoantibody levels and lowers disease activity in SLE patients [64]. In addition, potential for eliminating long-lived plasma cells in experimental models has been shown by plasma cell-targeting approaches, such as anti-CD38 therapies [65]. Other cytokines, including IL-6 and IL-10, also contribute to plasma cell maintenance and autoantibody production, with plasma cell survival supported by IL-6 and B-cell differentiation into plasma cells promoted by IL-10 [66]. These findings underscore the importance of targeting cytokine networks to achieve more effective control over autoantibody-mediated inflammation.

4.1.2 T and B Cell Interactions

The interaction between T cells and B cells is essential for the generation of high-affinity autoantibodies. B-cell maturation, germinal center formation, and differentiation into plasma cells and memory B cells are promoted by follicular helper T cells (Tfh) a specialized subset of $CD4^+$ T cells—through critical signals delivered via co-stimulatory molecules and cytokines, particularly IL-21. In SLE, normal B-cell tolerance mechanisms are disrupted by the abnormal expansion and activation of Tfh cells, resulting in increased production of autoreactive antibodies [67].

Recent evidence indicates that Tfh–B-cell interactions are importantly regulated by immune checkpoint pathways, including inducible co-stimulator (ICOS) and programmed cell death protein-1 (PD-1). Enhanced B-cell activation and autoantibody production have been associated with increased ICOS expression on Tfh cells, whereas autoimmune responses have been reduced in experimental models through inhibition of ICOS signaling [68]. Similarly, excessive Tfh activity and sustained autoantibody generation in SLE may be driven by impaired PD-1 signaling [69].

Beyond Tfh cells, B-cell responses are also influenced by other T-cell subsets, including regulatory T cells (Tregs) and Th17 cells. Immune tolerance is maintained by Tregs through the suppression of autoreactive immune activation, and their dysfunction in SLE contributes to impaired control of autoreactive B cells. Conversely, inflammation is promoted by Th17 cells through IL-17 production, which also supports autoantibody generation. Therefore, therapeutic strategies aimed at restoring T-cell balance, such as enhancing Treg activity or blocking pathogenic Tfh-related pathways represent promising approaches for controlling autoantibody-mediated autoimmunity [70].

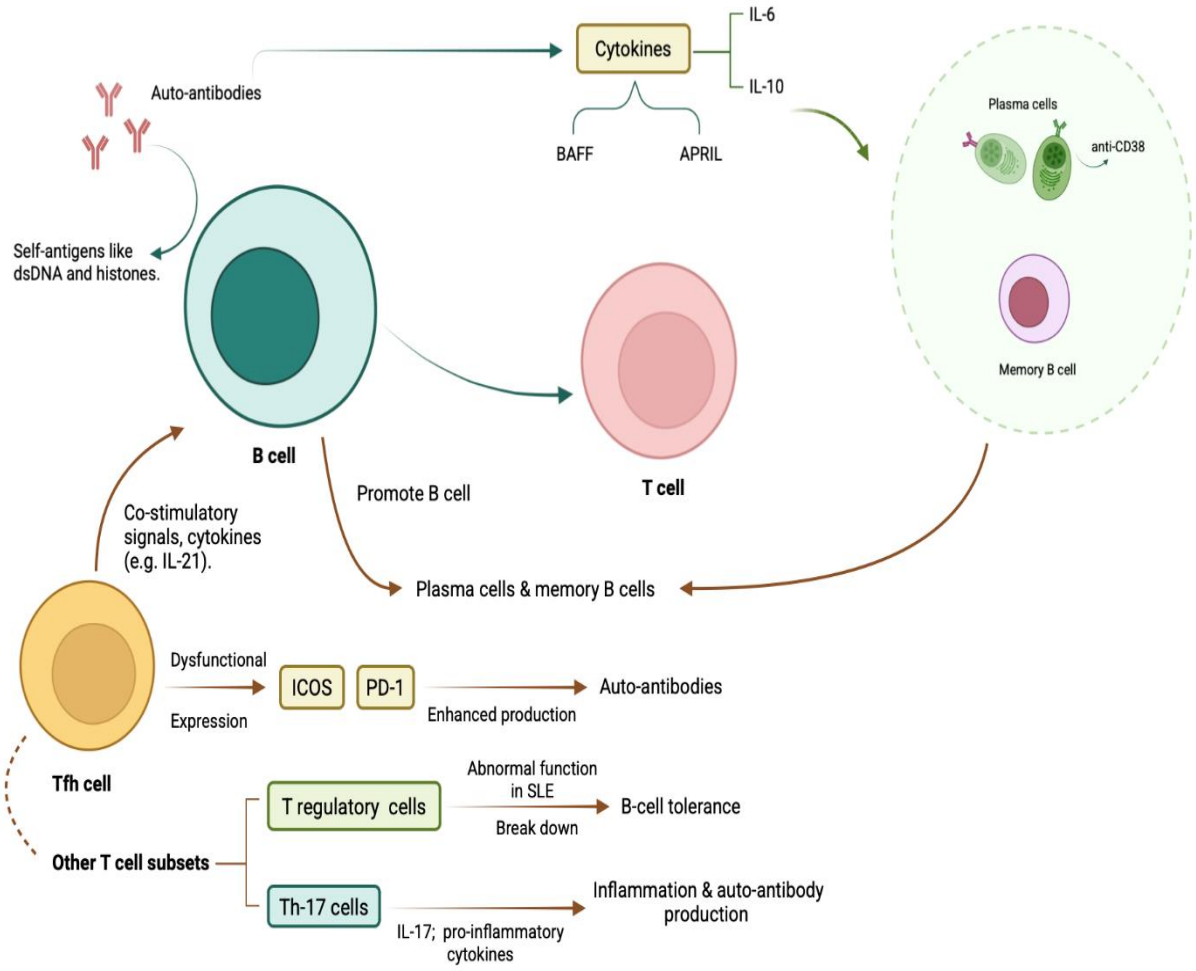


Figure 3: B-cells dysregulation in systemic lupus erythematosus.

4.2 Genetic and Epigenetic Mechanisms Regulating Autoantibody Production in SLE

The development of pathogenic autoantibodies in SLE is shaped by both genetic predisposition and epigenetic alterations that regulate immune cell function. The likelihood of autoimmune activation can be increased by genetic susceptibility factors, particularly those involved in antigen presentation and immune signaling, while B-cell responses and autoantibody production are further shaped by epigenetic modifications. The interaction between these factors provides an important link between inherited risk, environmental influences, and disease development.

4.2.1 HLA Associations

The human leukocyte antigen (HLA) region, particularly HLA class II genes such as HLA-DR and HLA-DQ, stands out as one of the strongest genetic contributors to SLE susceptibility and autoantibody generation. Immune responses are regulated by these molecules through the presentation of self-antigens to T cells, which can subsequently drive the activation and expansion of autoreactive B cells. Because of extensive genetic variation within the HLA region, an increased risk of developing SLE and producing characteristic autoantibodies is associated with specific alleles. For example, the generation of anti-dsDNA and anti-Sm antibodies, an important serological feature of SLE has been linked to HLA-DR3 and HLA-DR4 [71].

Multiple risk variants within and outside the HLA region that contribute to SLE susceptibility have further been identified through advances in genome-wide association studies (GWAS). Interferon signaling, immune activation, and B-cell responses have been implicated as being regulated by non-HLA genes, including IRF5, STAT4, and BLK, thereby influencing autoantibody production [72]. These findings highlight the importance of genetic background in shaping immune tolerance and determining individual susceptibility to autoimmune disease.

4.2.2 Epigenetic Modifications in B Cells

While genetic factors establish susceptibility to SLE, epigenetic modifications serve as dynamic regulators that shape immune cell behavior and disease progression. The expression of genes involved in B-cell activation, differentiation, and tolerance can be altered by changes in DNA methylation, histone modifications, and non-coding RNA expression. In SLE, increased expression of autoreactive genes has been associated with global DNA hypomethylation in B cells, promoting abnormal immune activation. These epigenetic changes can also be shaped by environmental triggers, such as infections and ultraviolet radiation, providing a mechanistic link between external factors and autoimmune responses.

For example, increased CD70 expression results from hypomethylation of the CD70 gene in B cells, enhancing T-cell co-stimulation and promoting autoantibody production [73]. Similarly, genes involved in B-cell differentiation and activation are regulated by histone modifications, including acetylation and methylation. Potential for reducing autoantibody production in preclinical studies has been shown through pharmacological inhibition of histone deacetylases (HDACs), suggesting possible therapeutic applications [74].

In addition, the regulation of B-cell responses is influenced by non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). For instance, B-cell activation is influenced by miR-155 through modulation of signaling pathways such as PI3K/AKT, while lncRNAs have been implicated in controlling B-cell differentiation and autoantibody synthesis [75]. Collectively, these findings demonstrate that epigenetic mechanisms play a critical role in sustaining autoimmune responses and represent promising targets for the development of novel SLE therapies.

4.3 Environmental Factors Driving Autoantibody Production in SLE

Environmental factors play a crucial role in triggering and amplifying autoantibody production, particularly in individuals with underlying genetic susceptibility. Autoimmune responses can be promoted by these external stimuli through the induction of epigenetic alterations, activation of innate immune pathways, and disruption of established mechanisms of immune tolerance (Figure 4). Understanding how environmental factors interact with genetic and immune abnormalities provides important insights into SLE initiation and disease progression.

4.3.1 Infections and Molecular Mimicry

Infectious agents are considered important contributors to autoantibody generation through mechanisms such as molecular mimicry, bystander activation, and epitope spreading. Molecular mimicry occurs when structural similarities are shared between microbial antigens and self-antigens, resulting in the activation of autoreactive immune cells. During infection, previously inactive autoreactive B cells can also be stimulated by inflammatory cytokines through bystander activation, while the autoimmune response is broadened by epitope spreading as additional self-antigens are targeted over time.

Several pathogens have been implicated in SLE development through these mechanisms. For example, Epstein–Barr virus (EBV) has been associated with SLE pathogenesis owing to similarities between EBV nuclear antigen-1 (EBNA-1) and the autoantigen Ro60, potentially promoting cross-reactive immune responses [76]. Similarly, the generation of anti-dsDNA antibodies through antigenic cross-reactivity has been linked to bacterial infections, including those caused by Streptococcus species [77]. Other viral infections, such as cytomegalovirus (CMV) and human endogenous retroviruses (HERVs), have also been proposed as potential contributors to autoimmune activation in SLE [78].

4.3.2 Ultraviolet Light and Autoantibody Induction

Ultraviolet (UV) radiation is one of the most well-established environmental triggers associated with SLE exacerbation and autoantibody production. Apoptosis of keratinocytes is induced by UV exposure, leading to the release of normally hidden nuclear antigens, including dsDNA and histones. Immune recognition is promoted by the increased availability of these self-antigens, facilitating the generation of autoantibodies. In addition, plasmacytoid dendritic cells (pDCs) are stimulated by UV radiation to produce type I interferons (IFNs), which enhance B-cell activation and sustain autoimmune responses [79].

Recent studies suggest that SLE development is also driven by UV-induced oxidative stress through alterations in epigenetic regulation within immune cells. For instance, DNA hypomethylation in B cells can be induced by UV exposure, resulting in increased expression of autoreactive genes and enhanced autoimmune activity [80,81]. Furthermore, the expression of regulatory microRNAs, including miR-155, may be influenced by UV radiation, which modulates B-cell activation and antibody production [82]. These findings highlight the complex interaction between environmental exposure, epigenetic regulation, and immune dysfunction in driving SLE pathogenesis.

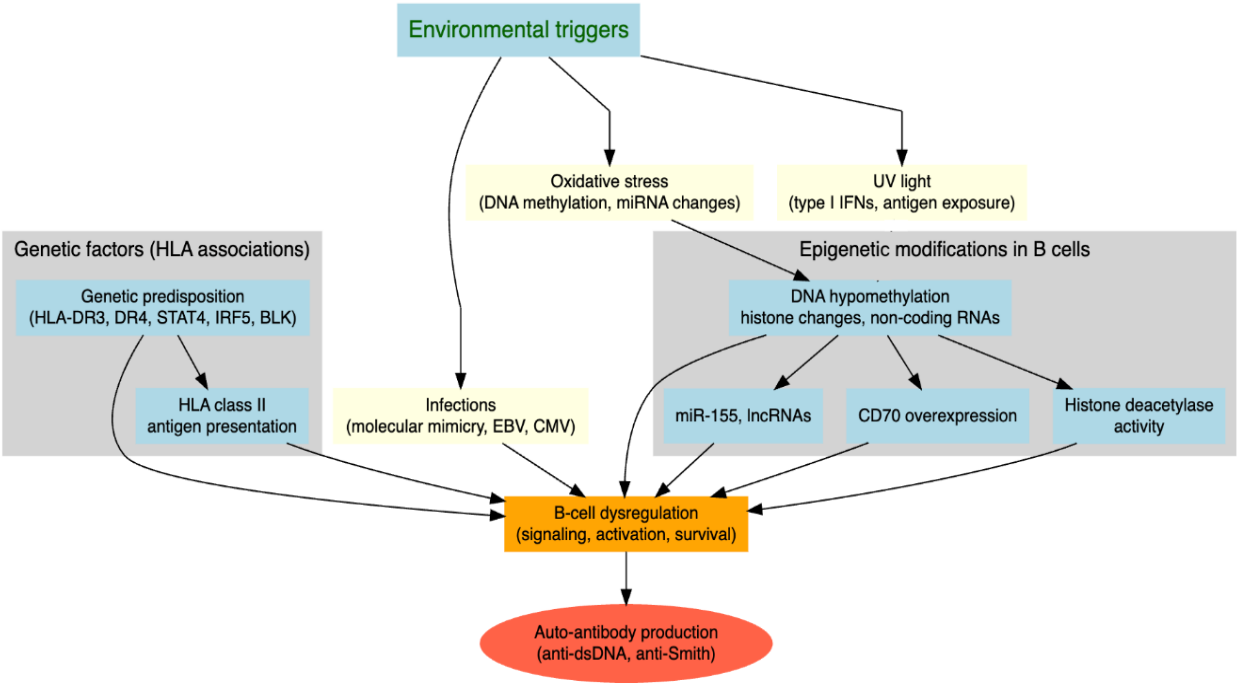


Figure 4: Environmental triggers in systemic lupus erythematosus: epigenetic modifications, innate immune activation, tolerance breakdown.

5. Therapeutic Targeting of Autoantibody Mediated Pathogenesis in SLE

Autoantibodies act as central drivers of SLE pathogenesis by forming immune complexes, activating inflammatory pathways, and promoting tissue injury. Therefore, therapeutic strategies have focused on reducing autoantibody production, eliminating autoantibody-producing cells, or suppressing downstream immune activation. However, major challenges in achieving durable disease control remain, owing to the heterogeneity of autoantibody profiles among patients and the potential risks associated with broad immunosuppression [83]. This section discusses current and emerging therapeutic approaches aimed at modulating autoantibody-mediated immune responses in SLE.

5.1 Current Therapies Targeting Autoantibody Production

Current therapeutic approaches for SLE primarily target immune cells involved in autoantibody generation, including B cells and plasma cells, or broadly suppress immune activation. Although outcomes have been improved by these strategies, particularly in severe manifestations such as lupus nephritis, the need for more selective and personalized therapies is highlighted by limitations including incomplete response, relapse, and treatment-related toxicity (Figure 5).

5.1.1 B-Cell Depletion

B cells play a central role in SLE pathogenesis by producing autoantibodies and regulating immune responses through antigen presentation and cytokine secretion. Consequently, B-cell depletion has become an important therapeutic strategy, leading to the development of monoclonal antibodies that target B-cell surface markers, particularly CD20.

Rituximab, a chimeric monoclonal antibody directed against CD20-expressing B cells, is the most extensively studied B-cell depletion therapy in SLE. B-cell elimination is induced by rituximab through antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis, achieved by binding to CD20 on pre-B and mature B cells. However, its efficacy in randomized clinical trials has been inconsistent. Primary endpoints were not met by the EXPLORER trial in non-

renal SLE or the LUNAR trial in lupus nephritis, potentially due to patient heterogeneity, trial design limitations, and the persistence of long-lived plasma cells that continue producing autoantibodies despite B-cell depletion [84,85].

Despite these findings, clinical benefits of rituximab have been demonstrated in real-world studies, particularly among patients with refractory SLE, lupus nephritis, neuropsychiatric lupus, and hematological manifestations. Reductions in disease activity scores, decreased corticosteroid requirements, and improved disease control have been observed clinically following rituximab treatment [86,87]. These findings underscore the importance of appropriate patient selection and individualized treatment strategies.

Other anti-CD20 therapies, including ocrelizumab and obinutuzumab, are being investigated as potential alternatives. Ocrelizumab is a humanized anti-CD20 antibody designed to reduce immunogenicity and enhance ADCC activity. Although improvements in renal parameters were demonstrated in studies of lupus nephritis, clinical development was limited by infection-related safety concerns [88]. Obinutuzumab, a glycoengineered anti-CD20 antibody, enhances B-cell killing through improved antibody binding and direct induction of cell death. Effective B-cell depletion and reduced autoantibody production in SLE models have been shown in preclinical studies, and its therapeutic potential is currently being evaluated in ongoing clinical trials [89].

Although significant therapeutic benefits are provided by B-cell depletion, its major limitation lies in the persistence of long-lived plasma cells, which lack CD20 expression and remain capable of producing pathogenic autoantibodies. Therefore, combination approaches targeting both B cells and plasma cells, including proteasome inhibitors or sequential depletion strategies, are being explored. Additionally, careful monitoring is required because of the risks of infection and hypogammaglobulinemia associated with prolonged B-cell depletion [90].

5.1.2 Plasma Cell Targeting

Long-lived plasma cells represent a major challenge in SLE treatment because autoantibodies are continuously produced by these cells, which remain resistant to conventional B-cell depletion therapies. Therefore, direct targeting of plasma cells has emerged as a promising therapeutic strategy.

Plasma cell apoptosis is induced by proteasome inhibitors, such as bortezomib, through disruption of protein degradation pathways, resulting in the accumulation of misfolded proteins and cellular stress. Reduced autoantibody levels and improved disease manifestations in SLE mouse models have been demonstrated by bortezomib in preclinical studies [91]. Furthermore, potential benefits in refractory SLE, including reductions in anti-dsDNA antibody levels and improved renal function among patients with lupus nephritis, have been shown in early clinical studies [92].

However, the clinical application of bortezomib is limited by adverse effects, including peripheral neuropathy, thrombocytopenia, and gastrointestinal toxicity. Current research is therefore focused on developing safer and more selective plasma cell-targeting approaches to improve therapeutic outcomes.

5.1.3 Immunosuppressive Agents

Broad immunosuppressive agents remain essential components of SLE management, particularly in patients with severe organ involvement. Immune activation is reduced by drugs such as mycophenolate mofetil (MMF), cyclophosphamide, and azathioprine through the inhibition of lymphocyte proliferation and the limitation of autoantibody production via different molecular mechanisms.

MMF and cyclophosphamide are widely used for lupus nephritis, with MMF often favored owing to its improved safety profile and lower risk of gonadal toxicity. In contrast, cyclophosphamide is generally reserved for severe or life-threatening disease because of its potential complications, including bone marrow suppression, infertility, and an increased risk of malignancy. Azathioprine is commonly used as a maintenance therapy to prevent disease relapse. However, increased risks of infection and systemic toxicity are associated with long-term use of these immunosuppressive agents, underscoring the need for more targeted treatment approaches.

Combination therapies, such as MMF combined with biologic agents like belimumab, have recently been explored to enhance therapeutic efficacy while reducing treatment-related complications [93,94]. These

advances reflect a shift toward precision-based approaches that aim to control autoantibody-driven inflammation while preserving immune function.

5.2 Emerging Targeted Therapies for Autoantibody Modulation in SLE

Recent advances in immunology have led to the development of targeted therapeutic strategies designed to specifically interfere with the pathways responsible for autoantibody generation, while minimizing broad immune suppression. These emerging approaches include cytokine blockade, restoration of immune tolerance, and advanced cellular and genetic therapies, offering new possibilities for more precise management of SLE.

5.2.1 Anti-Cytokine Therapies

Cytokines such as interleukin-6 (IL-6) and B-cell activating factor (BAFF) are essential regulators of B-cell survival, differentiation, and autoantibody production, making them attractive therapeutic targets in SLE. The differentiation of B cells into plasma cells is promoted by IL-6, which also supports the persistence of autoreactive B-cell populations, thereby contributing to sustained autoantibody production. Promising results have been shown in preclinical SLE models when IL-6 signaling is targeted with agents such as tocilizumab, reducing inflammatory responses and autoantibody levels. Improvements in disease activity have also been demonstrated in early clinical investigations; however, potential adverse effects, including infections and elevated liver enzymes, remain important considerations [95].

In contrast, greater clinical success in SLE treatment has been achieved through BAFF inhibition. BAFF is a critical survival factor for B cells, and its excessive production promotes the expansion of autoreactive B cells and increased autoantibody generation. Belimumab, a monoclonal antibody targeting BAFF, has been approved for SLE treatment and has been shown to reduce disease activity, flare frequency, and autoantibody levels, thereby improving long-term patient outcomes [96]. More recently, combination approaches targeting multiple cytokine pathways—such as the simultaneous inhibition of BAFF and IL-6 signaling—are being explored as potential strategies for patients with refractory disease who show inadequate responses to single-agent therapies [97].

5.2.2 Immune Tolerance Induction

Unlike conventional immunosuppressive therapies that broadly inhibit immune activity, immune tolerance-based approaches aim to restore normal self-recognition while preserving protective immune functions. These strategies include tolerogenic dendritic cells, antigen-specific peptide therapies, and low-dose interleukin-2 (IL-2) treatment to enhance regulatory T-cell (Treg) activity.

Immune tolerance is maintained in large part by Tregs, which suppress autoreactive B- and T-cell responses. In SLE, the breakdown of immune regulation and persistent autoantibody production are driven in part by impaired Treg function. Promise has been shown by low-dose IL-2 therapy, which selectively expands Treg populations and reduces autoimmune activity. Increased Treg numbers and improved disease control have been demonstrated in clinical studies of SLE patients receiving low-dose IL-2 treatment [98].

Additionally, peptide-based tolerance therapies that use disease-associated autoantigen fragments aim to retrain immune responses by reducing autoreactive T-cell activation and, in turn, limiting autoantibody production. Although these approaches remain under investigation, they represent a promising strategy for achieving long-lasting disease remission without resorting to generalized immunosuppression.

5.2.3 Gene Editing and CAR-T Cell Therapy

Advances in genetic engineering and cellular immunotherapy have introduced innovative approaches for targeting autoreactive immune cells in SLE. Technologies such as CRISPR-Cas9 gene editing and chimeric antigen receptor (CAR)-T cell therapy aim to eliminate pathogenic immune populations or restore immune tolerance at a molecular level.

CAR-T cell therapy involves genetically modifying T cells so that they express synthetic receptors capable of recognizing specific immune targets. In SLE, potential has been shown by CD19-targeted CAR-T cells, which effectively eliminate B cells, including autoreactive populations, and reduce autoantibody

production in preclinical models [99]. Similarly, the possibility of modifying genes involved in B-cell activation, immune regulation, and autoantibody synthesis is offered by CRISPR-Cas9 technology, providing a future avenue for highly personalized therapy.

Despite their promising potential, several challenges remain before these approaches can be widely applied, including off-target genetic effects, long-term safety concerns, immune-related complications, and high manufacturing costs. Continued optimization and clinical evaluation will be necessary to determine their feasibility and durability in SLE treatment.

5.3 Challenges and Future Perspectives in Autoantibody Targeted Therapy for SLE

Despite significant progress in developing therapies targeting autoantibody-driven mechanisms in SLE, several challenges continue to limit their effectiveness. Achieving durable and personalized treatment outcomes remains hindered by the complex heterogeneity of autoantibody responses among patients, together with the risk of excessive immune suppression. Addressing these challenges will require a better understanding of disease-specific immune profiles and the development of safer, precision-based therapeutic approaches.

5.3.1 Heterogeneity of Autoantibody Responses

A major challenge in SLE treatment is the considerable diversity of autoantibody profiles among patients. Although autoantibodies are a common feature of SLE, distinct patterns of autoantibody production, targeting different nuclear and cellular antigens, may be exhibited by individual patients. For example, anti-dsDNA antibodies associated with renal involvement are predominantly produced by some patients, whereas anti-Sm or anti-RNP antibodies linked to different clinical manifestations are exhibited by others. This variability is shaped by genetic susceptibility, environmental exposures, and epigenetic regulation, making disease progression and therapeutic responses difficult to predict [100].

Therefore, optimal benefits may not be provided for all patients by a single therapeutic approach. Patient-specific disease mechanisms may be identified, and more effective treatment selection enabled, through the integration of biomarker-based classification, autoantibody profiling, and personalized medicine approaches.

5.3.2 Risk of Immunosuppression

Another major limitation of autoantibody-targeted therapies is the risk of impaired immune defense caused by excessive immune suppression. Although disease activity can be effectively controlled by therapies that reduce B-cell activity or broadly suppress immune responses, susceptibility to infections and other complications may be increased by these same treatments. For example, hypogammaglobulinemia can be caused by B-cell depletion therapies such as rituximab, reducing protective antibody responses and increasing infection risk. Similarly, potential complications such as malignancy, bone marrow suppression, and organ toxicity are associated with the long-term use of immunosuppressive agents, including cyclophosphamide and azathioprine [101].

Achieving an optimal balance between controlling pathogenic autoimmunity and preserving normal immune function remains a critical challenge, particularly in patients with severe or treatment-resistant SLE. Improved therapeutic efficacy, alongside minimized adverse effects, is being pursued through emerging strategies, including combination therapies, targeted immune modulators, and biomarker-guided treatment approaches.

Overall, the treatment landscape of SLE has been significantly expanded by advances in autoantibody-targeted therapies, with approaches ranging from B-cell depletion and plasma cell targeting to cytokine inhibition, immune tolerance induction, and gene-based therapies. However, developing safer and more effective next-generation therapies will require overcoming patient-to-patient variability and reducing treatment-related risks. Improved strategies for achieving long-term disease control in SLE may be provided by future research integrating immunological profiling, precision medicine, and novel therapeutic platforms.

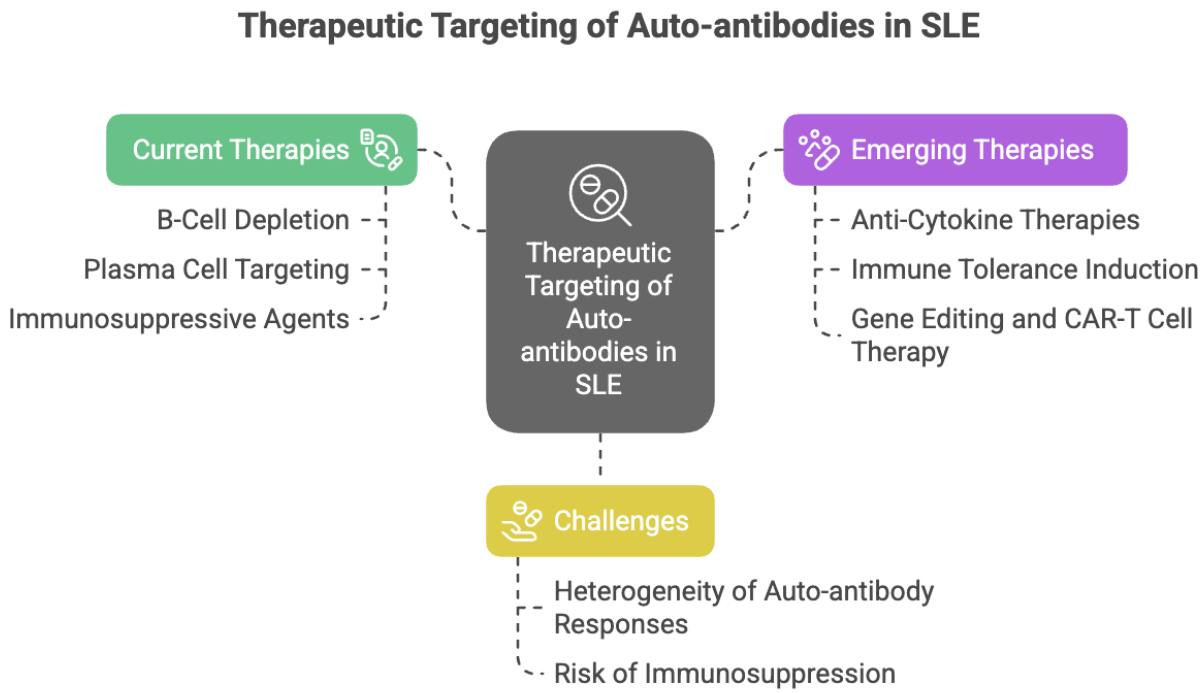


Figure 5: Therapeutic targeting of autoantibodies in systemic lupus erythematosus: workflow and strategies.

6. Multifunctional Roles of Autoantibodies in SLE

Although autoantibodies are widely recognized as major contributors to SLE pathogenesis, emerging evidence suggests that their functions extend beyond immune-mediated tissue damage. Depending on their specificity, concentration, and biological context, autoantibodies can participate in immune regulation, tissue repair, pregnancy-related complications, and disease-associated comorbidities. A more comprehensive view of autoantibody biology is offered by understanding these diverse roles, which may also reveal new therapeutic opportunities to selectively inhibit harmful responses while preserving beneficial immune functions.

6.1 Protective Roles of Auto-antibodies

Autoantibodies are traditionally considered harmful mediators of autoimmune diseases; however, immune homeostasis and tissue maintenance are supported by certain populations of autoantibodies. These beneficial functions challenge the notion that all autoantibodies are inherently pathogenic and highlight the importance of distinguishing protective responses from disease-driving ones.

6.1.1 Natural Autoantibodies and Immune Homeostasis

Natural autoantibodies (NAbs), primarily produced by B-1 cells and marginal zone B cells, are low-affinity, polyreactive antibodies encoded by germline genes. Unlike pathogenic autoantibodies, immune balance is supported by NAbs, which recognize and facilitate the clearance of apoptotic cells and cellular debris, thereby preventing the buildup of immunogenic self-components that could trigger autoimmune activation.

In SLE, impaired clearance of apoptotic material is a key factor contributing to autoantigen exposure and autoantibody formation. Therefore, immune tolerance may be helped by NAbs, which limit the availability of self-antigens and reduce the activation of autoreactive lymphocytes. Recent studies have

further shown that inflammation can be regulated by NAbs through the neutralization of pro-inflammatory cytokines, including IL-6 and TNF-α, thereby reducing tissue injury [102].
Moreover, intestinal immune regulation is supported by NAbs through their interaction with commensal microorganisms, which helps prevent bacterial translocation across the gut barrier. This function may be particularly relevant in SLE, where increased systemic inflammation is associated with alterations in microbiome composition and impaired intestinal barrier integrity [103].

6.1.2 Autoantibodies in Tissue Repair

Beyond immune regulation, tissue repair and regeneration following injury may be supported by certain autoantibodies. For example, despite their well-known association with thrombosis in SLE, anti-phospholipid antibodies (aPLs) have also been implicated in promoting endothelial cell proliferation and angiogenesis processes that are essential for vascular repair. However, pathological vascular remodeling and atherosclerosis may be promoted when these pathways are excessively activated [104].
Similarly, tissue remodeling may be supported by autoantibodies targeting extracellular matrix components, such as collagen and fibronectin, which can facilitate the removal of damaged structures and support extracellular matrix reconstruction. These repair-associated functions may influence recovery processes in organs affected by chronic inflammation, including the kidneys during lupus nephritis [105].

6.2 Autoantibodies in Pregnancy and Neonatal Lupus

Pregnancy in patients with SLE requires careful management, given the ability of specific maternal autoantibodies to cross the placenta and affect fetal development. Among these, neonatal lupus erythematosus (NLE) a condition marked by manifestations such as congenital heart block, cutaneous lesions, and hepatic abnormalities in newborns is strongly associated with anti-Ro/SSA and anti-La/SSB antibodies [106].
Mechanistically, fetal cardiac proteins can be bound by maternal anti-Ro/SSA and anti-La/SSB antibodies, which interfere with calcium signaling pathways in developing cardiomyocytes, resulting in inflammation and irreversible damage to the cardiac conduction system. A reduced incidence of neonatal lupus complications has been shown to result from early identification of at-risk pregnancies and preventive strategies, including hydroxychloroquine therapy [107].
In addition to neonatal complications, maternal pregnancy outcomes can be negatively influenced by SLE-associated autoantibodies. Thrombosis is promoted and placental function impaired in particular by anti-phospholipid antibodies, contributing to complications such as recurrent pregnancy loss, preeclampsia, and intrauterine growth restriction [108].

6.3 Autoantibodies in SLE associated comorbidities

The impact of autoantibodies in SLE extends beyond primary disease manifestations, contributing to the development of major comorbidities, particularly cardiovascular complications and increased susceptibility to infections.

6.3.1 Cardiovascular Disease

Cardiovascular disease remains one of the leading causes of morbidity and mortality among individuals with SLE. Endothelial dysfunction, inflammation, atherosclerosis, and thrombosis are all promoted by autoantibodies, especially anti-phospholipid antibodies and anti-oxidized low-density lipoprotein (anti-oxLDL) antibodies, contributing to cardiovascular complications [109]. Recent studies have also drawn attention to the role of anti-HSP60 antibodies in vascular disease. Heat shock proteins expressed on stressed endothelial cells are targeted by these antibodies, triggering inflammatory responses and driving plaque formation, thereby speeding up atherosclerotic processes in SLE patients [110].

6.3.2 Infections in SLE

Patients with SLE exhibit increased susceptibility to infections due to both disease-associated immune abnormalities and immunosuppressive treatments. Impaired host defense mechanisms may be directly contributed to by certain autoantibodies. For example, complement-mediated pathogen clearance can be

interfered with by antibodies targeting complement components such as C1q and C3, reducing effective immune protection [111].
Additionally, antiviral immunity may be compromised by anti-cytokine autoantibodies, including those directed against IFN-α, which disrupt cytokine signaling pathways and increase vulnerability to viral infections such as herpes zoster and cytomegalovirus [112]. Susceptibility to bacterial infections, particularly those caused by encapsulated organisms such as Streptococcus pneumoniae, may also be heightened by autoantibody-mediated impairment of opsonization and phagocytosis [113].

7. Future Perspectives and Emerging Strategies in Autoantibody Based Management of SLE

Despite significant progress in understanding autoantibody-driven mechanisms in SLE, several challenges remain, including disease heterogeneity, unpredictable treatment responses, and limitations of current diagnostic approaches. Earlier diagnosis, accurate disease prediction, and individualized therapeutic strategies will likely be enabled by future advances in SLE management, which will depend on integrating precision medicine, advanced biomarker discovery, and innovative technologies.

7.1 Precision Medicine in SLE

Precision medicine represents a paradigm shift in SLE treatment, moving away from generalized therapeutic approaches toward strategies tailored to individual molecular, genetic, and immunological profiles. Since substantial variability in clinical manifestations and immune abnormalities is exhibited by SLE patients, identifying patient-specific biomarkers, particularly autoantibody signatures, is essential for improving diagnosis, predicting disease outcomes, and selecting the most effective therapies (Figure 6).
New opportunities to integrate biological information from individual patients have been created by advances in genomics, proteomics, and computational biology. This approach may enable clinicians to identify distinct disease subgroups and develop targeted interventions that maximize therapeutic benefits while minimizing unnecessary immunosuppression.

7.1.1 Personalized Autoantibody Profiling

Personalized autoantibody profiling involves the comprehensive characterization of an individual's autoantibody repertoire to identify disease-associated patterns and predict clinical outcomes. Given the diverse autoantibody landscape of SLE, valuable insights into disease mechanisms may be provided by profiling these antibody signatures, helping guide patient-specific treatment decisions.
Simultaneous detection of multiple autoantibodies is enabled by high-throughput technologies, including protein microarrays and next-generation sequencing approaches, allowing the identification of antibody patterns associated with specific organ complications. For example, lupus nephritis is strongly associated with anti-dsDNA antibodies, whereas neuropsychiatric manifestations are linked to anti-ribosomal P antibodies. Furthermore, diagnostic accuracy, risk prediction, and treatment selection can be improved by combining autoantibody profiles with genetic and clinical information, ultimately supporting more personalized disease management [114].

7.1.2 Biomarker-Driven Clinical Trials

Traditional SLE clinical trials often face difficulties in demonstrating therapeutic efficacy due to patient heterogeneity and variable disease manifestations. A more effective approach is provided by biomarker-driven clinical trials, which stratify patients according to molecular characteristics, allowing therapies to be evaluated in populations most likely to benefit.
Autoantibodies have emerged as important biomarkers for patient selection and treatment monitoring. For example, anti-dsDNA levels have been investigated in trials evaluating B-cell-targeted therapies, including rituximab and belimumab, given their association with disease activity and treatment response. Drug development may be accelerated, trial variability reduced, and therapeutic outcomes improved by biomarker-guided approaches that focus on biologically defined patient groups.
The BILAG-Biomarker Index represents an example of integrating clinical features with biomarker information to improve treatment assessment and decision-making in SLE [115,116]. However, challenges remain, including the lack of standardized biomarker detection methods and the need to identify additional markers capable of accurately predicting therapeutic responses.

7.2 Novel Technologies for Autoantibody Detection

Recent technological advances have significantly improved the detection and characterization of autoantibodies, providing deeper insights into SLE immunopathogenesis. Enhanced sensitivity, specificity, and analytical capacity are offered by these emerging platforms, enabling a more comprehensive evaluation of complex autoimmune responses.

7.2.1 Multiplex Assays

Multiplex assay platforms represent a major advancement in autoantibody detection, enabling the simultaneous measurement of multiple antibodies from a single biological sample. Comprehensive profiling of autoantibody repertoires with improved efficiency and accuracy is allowed by technologies such as Luminex-based assays, ELISA arrays, and bead-based immunoassays. These approaches are particularly valuable in SLE because multiple autoantibody specificities are often exhibited by patients, and the combined antibody profile may provide more clinically relevant information than individual antibody measurements. Disease classification may be improved, patients at risk of specific organ complications identified, and personalized treatment strategies supported through multiplex profiling [117,118]. Despite these advantages, widespread clinical implementation requires further efforts toward assay standardization, data interpretation, and harmonization between different platforms.

7.2.2 Machine Learning for Autoantibody Pattern Recognition

The increasing availability of high-dimensional immunological datasets has created opportunities for applying machine learning (ML) approaches to SLE research. Unlike conventional statistical methods, complex patterns and relationships among autoantibody profiles, clinical features, genetic variations, and molecular signatures can be identified by ML algorithms.

In SLE, potential in predicting disease subtypes, identifying patient clusters, and forecasting treatment responses has been demonstrated by ML-based models. For example, autoantibody patterns were analyzed by Choi et al. (2023) using ML approaches, which identified distinct immune profiles associated with different disease trajectories [119]. Furthermore, predictive accuracy may be enhanced and clinical decision-making supported by integrating autoantibody data with cytokine profiles, imaging information, and clinical parameters [120,121].

However, several challenges must be addressed before ML can become a routine component of SLE management. These include the requirement for large and diverse datasets, standardized data collection methods, and improved interpretability of predictive models. Collaborative efforts between immunologists, clinicians, and computational scientists will be essential to translate ML-based discoveries into practical clinical applications.

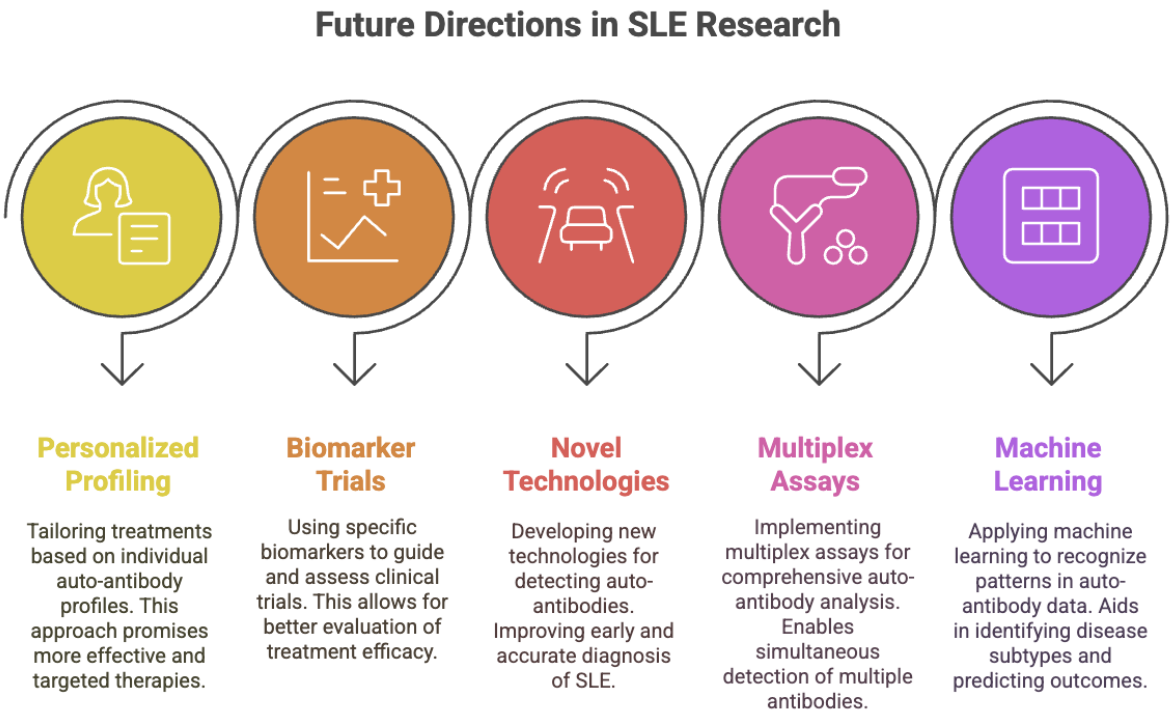


Figure 6: Future directions in SLE research: key emerging approaches.

8. Bridging current Knowledge Gaps Towards Improved SLE Management

Despite substantial progress in understanding SLE pathogenesis and treatment, several critical challenges remain. A major priority for future research is the establishment of larger, more diverse patient cohorts to validate genetic and epigenetic findings across different populations. Caucasian and Asian populations have largely been the focus of current studies, limiting the generalizability of discoveries to other ethnic groups. Developing globally applicable diagnostic and therapeutic strategies will require expanding research to include more diverse populations [122].

In addition, long-term longitudinal studies are needed to clarify how genetic, epigenetic, and immunological changes evolve throughout disease progression and influence treatment responses [123]. Improved biomarkers with greater sensitivity and specificity are also urgently required for early diagnosis, disease monitoring, and prediction of therapeutic outcomes. Although valuable clinical information is provided by existing biomarkers, including autoantibodies and complement components, their application remains limited by variability and insufficient standardization. Promising opportunities to identify novel biomarkers and uncover disease-associated cellular pathways with greater precision are offered by emerging technologies such as single-cell RNA sequencing, proteomics, and multi-omics approaches [124].

Future therapeutic development will also require strategies that address the complex and heterogeneous nature of SLE. Improved disease control while reducing relapse rates may be achieved through combination therapies that integrate biologic agents with conventional immunosuppressive drugs. Furthermore, a promising avenue for developing next-generation therapies is represented by targeting key signaling pathways involved in immune dysregulation, including the mTOR and JAK-STAT pathways [125].

Beyond immune pathways, recent studies have drawn attention to the emerging role of the gut microbiome in SLE development and progression. Immune imbalance may be contributed to by alterations in microbial composition and intestinal barrier function, which influence inflammatory responses and autoantibody production, suggesting that microbiome-based interventions could represent a future therapeutic strategy [126].

The integration of artificial intelligence (AI) and machine learning into SLE research provides additional opportunities to transform disease management. Complex biological datasets can be analyzed by these technologies, which can identify hidden patterns, predict disease trajectories, and support personalized treatment decisions. However, close collaboration between clinicians, immunologists, computational scientists, and data specialists will be required for successful implementation, to ensure accurate interpretation and clinical translation of these approaches [127].

Overall, the future of SLE research will depend on integrating diverse patient populations, advanced biomarker discovery, innovative therapeutic strategies, and computational technologies. Early diagnosis may be improved, precision-based treatment enabled, and long-term outcomes ultimately enhanced for individuals living with SLE worldwide through these multidisciplinary efforts.

9. Conclusion

Systemic Lupus Erythematosus (SLE) remains a complex and heterogeneous autoimmune disorder marked by diverse clinical manifestations and multi-organ involvement. Considerable progress has been made in understanding the immunological mechanisms driving SLE, particularly the role of autoantibodies in disease development, diagnosis, and treatment response, contributing to improved diagnostic strategies and targeted therapies aimed at controlling autoantibody-mediated inflammation. Despite these advances, effective management remains difficult given the disease's clinical diversity, unpredictable course, and variable treatment responses. Continued efforts in immunological profiling, biomarker discovery, and precision medicine will be key to overcoming these challenges and improving long-term outcomes for patients with SLE.

Data availability

No datasets were generated or analyzed during the current study.

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