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Review Article

Genetic and Immunological Underpinnings of Systemic Lupus Erythematosus: Bridging Molecular Insights with Clinical Translation

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ABSTRACT

Systemic Lupus Erythematosus (SLE) is a multifactorial autoimmune disorder characterized by a breakdown in immune tolerance, leading to chronic inflammation and multiorgan damage. The pathogenesis of SLE involves complex interactions between genetic susceptibility, hormonal influences, environmental triggers, and immune system dysregulation. Advances in high-throughput genomics, transcriptomics, and immune profiling have significantly enhanced our understanding of the molecular underpinnings of SLE, identifying over 90 risk loci involved in antigen presentation, lymphocyte activation, interferon signalling, and apoptotic cell clearance. Notably, dysregulation of T and B cell subsets, hyperactive type I interferon responses, and defective clearance of apoptotic debris represent key immunopathogenic events. This review critically synthesizes recent insights into the genetic and immunological architecture of SLE, highlighting the role of monogenic variants, ethnic-specific risk factors, and epigenetic modulators. A selective assessment of 122 peer-reviewed publications, published from 2019 to 2025, was performed utilizing databases such as PubMed, Scopus, Web of Science, and Google Scholar. Only novel studies and thorough investigations were included. The review also explores translational implications, including the emergence of targeted therapies such as anti-BAFF agents, interferon pathway inhibitors, and JAK-STAT modulators. Furthermore, we discuss the promise of biomarker-guided precision medicine in overcoming therapeutic heterogeneity and improving patient outcomes. By bridging molecular insights with clinical application, this review underscores the importance of integrative, patient-tailored approaches to redefine the diagnosis, stratification, and management of SLE in the era of systems medicine.

Keywords: Autoimmunity, Immunogenetics, Precision Medicine, SLE, Type I Interferon.

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a multifaceted, quintessential autoimmune disorder characterized by a breakdown of immunological tolerance, the generation of autoantibodies, and the accumulation of immune complexes in tissues, resulting in persistent inflammation and organ impairment.[1] SLE clinically presents with diverse symptoms impacting the integumentary, musculoskeletal, renal, central neurological, and hematologic systems.[2] This phenotypic variety illustrates the multifaceted nature of its pathophysiology, involving complex interactions among genetic, hormonal, environmental, and immunological variables.[3] A notable epidemiological characteristic of SLE is its pronounced female preponderance, with a female-to-male ratio approaching 13:1 during reproductive years. This gap underscores the potential regulatory functions of sex hormones, especially estrogens and suggests the involvement of X-linked gene control in disease vulnerability.[4,5] In addition to its complex biology, SLE has a significant worldwide disease burden and enormous healthcare consumption. SLE is associated with elevated morbidity and mortality rates, with global prevalence estimates varying from 17 to 70 per 100,000 individuals with notable geographical discrepancies.[6] Higher frequency and severity observed in populations of African, Asian, and Hispanic descent.[7] These differences highlight the impact of ancestry-specific genetic risk factors and reinforce the necessity for increased representation in SLE research.[8] In the last twenty years, Genome-Wide Association Studies (GWAS) and candidate gene analyses have discovered more than 90 susceptibility loci for SLE.[9] This encompasses genes associated with antigen presentation (e.g., HLA-DRB1, DQA1, DQB1), lymphocyte activation (e.g., STAT4, PTPN22, BANK1, BLK), interferon signalling (e.g., IRF5, IRF7, IFIH1), and apoptotic cell clearance (e.g., DNASE1,

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TREX1, C1q). These loci converge on critical immunopathogenic pathways that facilitate autoimmunity, systemic inflammation, and tissue damage. The findings have elucidated the molecular foundation of SLE and identified prospective biomarkers and treatment targets.[10,11] Notwithstanding these advancements, conventional therapies such as corticosteroids, antimalarials, and broad-spectrum immunosuppressants continue to be inadequate owing to their nonspecificity and considerable side effects. The advent of biologics, including belimumab (anti-BAFF) and anifrolumab (anti-IFNAR1), signifies a significant advancement in precision medicine.[12,13] Nonetheless, categorizing individuals according to molecular endotypes to enhance therapy efficacy continues to pose a significant problem.[14] Although this burden is significant, substantial clinical requirements remain unaddressed. These requirements encompass diagnostic delays, inadequate predictors of flare activity, and the lack of precise biomarkers for early organ damage.[15,16] Significant mechanistic gaps persist in our comprehension of the interplay between genetic susceptibility, environmental stimuli, and immune dysregulation in the onset and persistence of disease. This review offers a complete and integrative examination of the genetic and immunological factors associated with SLE, in contrast to prior reviews that predominantly emphasize either genetic or clinical components. Focus is directed towards essential molecular pathways such as lymphocyte dysregulation, interferon signalling, and apoptotic clearance and their significance for biomarker development and focused therapy approaches. This study seeks to facilitate the progression of personalized strategies in the therapy of SLE by integrating molecular knowledge with clinical translation.

METHODOLOGY

A comprehensive literature review was performed utilizing databases including PubMed, Scopus, Web of Science, and Google Scholar. The search methodology incorporated Medical Subject Headings (MeSH) alongside relevant free-text terms, including "Systemic Lupus Erythematosus", "SLE", "immunogenetics", "autoimmunity," "precision medicine", "Lupus", and "Lupus Nephritis". The inclusion criteria employed original research articles, systematic and comprehensive reviews and meta-analysis published in English language, within 2019 to 2025. The articles encompassing human studies, validated animal models and translational research that primarily focused on mechanistic, genetic and immunological insights into SLE are selected. Non peer reviewed publication, articles published other than English language, conference abstracts, case reports, editorials and commentaries, letters to the editor are the main exclusion criteria. Studies that are devoid of genetic, mechanistic and immunological relevance are also excluded. The gathered data were rigorously assessed to encapsulate genetic determinants, immunological dysregulation, and treatment progressions in SLE. Finally, this comprehensive review was developed through a meticulous analysis of 140 peer reviewed articles offering a comprehensive understanding of association of genetic and immunological factors in SLE.

Genetic Architecture of SLE

SLE is a polygenic autoimmune disease characterized by a significant hereditary component, as demonstrated by familial clustering, twin studies, and population-based genetic investigations.[17] The genetic structure of SLE includes prevalent variants with moderate impact sizes and rare, high-penetrance alterations. Progress in GWAS, fine-mapping, and omics has revealed more than 90 loci related with SLE, highlighting the role of genes in antigen presentation, lymphocyte activation, interferon signalling, and apoptotic cell clearance.[18] These loci influence both susceptibility and the phenotypic variability seen in clinical symptoms, encompassing organ-specific involvement and autoantibody patterns.[19] The complex genetic underpinnings of SLE can be summarized in Table 1 across key loci, signalling pathways, and cellular mechanisms.

HLA Loci and Antigen Presentation

Significant genetic connections in SLE have regularly been identified within the Major Histocompatibility Complex (MHC) area on chromosome 6, particularly with HLA class II genes, including HLA-DRB1, DQA1, and DQB1. These genes encode components crucial for antigen presentation to CD4+ T cells, a fundamental mechanism in beginning adaptive immunological responses.[20,21] Alleles like HLA-DRB103:01 and DRB115:01 are prevalent in SLE patients and correlate with an increased risk for the generation of particular autoantibodies, including anti-Ro and anti-dsDNA. Detailed mapping of this region has shown several independent signals, indicating intricate haplotypic relationships. Furthermore, HLA polymorphisms affect thymic selection, peripheral tolerance, and epitope binding affinity, therefore altering T cell autoreactivity.[22,23] The genetic structure of the MHC is influenced by significant linkage disequilibrium, complicating the identification of causal variants; however, functional annotation through peptide binding assays and expression Quantitative Trait Loci (eQTL) studies has started to elucidate the immunological effects of these alleles.[24] The HLA class I and II molecules not only influence T cell repertoire during thymic selection but also regulate immune responses through peptide presentation in the periphery.[25] Figure 1 presents a comparative diagram of endogenous (MHC-I) and exogenous (MHC-II) antigen presentation pathways, emphasizing the involvement of certain T cell subsets ($CD8^+$ and $CD4^+$) in antigen recognition and immune regulation. In SLE, modifications in these pathways result in the emergence of nuclear autoantigens and the disruption of self-tolerance.

Non-HLA Genetic Variants

Although the HLA region is the predominant locus, various non-HLA genes also influence disease vulnerability via different

immunological processes.[26] Variations in transcription factors like STAT4 and IRF5 affect cytokine synthesis and T cell differentiation. STAT4 polymorphisms correlate with augmented IL-12 signalling and a bias towards Th1 and Th17 responses, hence leading to proinflammatory cytokine profiles.[27] PTPN22 encodes a tyrosine phosphatase that adversely modulates T Cell Receptor (TCR) signalling and its R620W variation results in loss of function, extends the lifespan of autoreactive T cells.[28] B cell signalling is similarly disrupted by variations in genes such as BANK1 and BLK, which elevate B Cell Receptor (BCR) signalling thresholds, leading to a loss of tolerance and the production of autoantibodies.[29] Polymorphisms in genes associated with immune complex management (FCGR2A, FCGR3B) and nucleic acid detection (IFIH1, IRF7) further substantiate a multifaceted disruption of immunological homeostasis in SLE. TYK2, a member of the Janus kinase family, regulates type I Interferon (IFN-I) receptor signalling, establishing a genetic connection to the interferon signature frequently seen in patients.[30,31]

Rare Variants and Monogenic SLE

A subset of patients, who frequently arrive as children, carry uncommon, high-penetrance mutations that result in monogenic forms of SLE, in contrast to the polygenic risk expressed by common variants. These cases underscore critical pathways whose disruption is adequate to induce lupus-like disease.[32] Mutations in TREX1, a DNA exonuclease, and DNASE1/DNASE1L3, which degrade extracellular DNA, lead to the buildup of endogenous nucleic acids that activate intracellular pattern recognition receptors, including TLR9 and STING.[33] Deficiencies in complement components, such as C1q, C2, and C4, hinder the clearance of immune complexes and apoptotic debris, creating a pro-inflammatory environment that promotes autoimmunity.[34] The monogenic variants of SLE provide mechanistic insight and imply that even sporadic instances may possess subclinical abnormalities in analogous pathways.[35] Although, few monogenic variants directly cause SLE, certain mutations in the interferon pathway promote SLE-like conditions, such as interferonopathies, rather than classical SLE.[36]

Ethnic and Population-Specific Variants

The frequency and influence of genetic variations differ significantly among ethnic groups, illustrating population-specific selection pressures and genetic drift.[37] The ITGAM gene, which encodes CD11b (a complement receptor crucial for phagocytosis), exhibits a more pronounced correlation in persons of African and Hispanic descent. Likewise, variations in the TNFSF13B gene (which encodes BAFF) and PRDM1 have been emphasized in Asian cultures.[38,39] These variations possess clinical significance, perhaps elucidating racial disparities in the severity of SLE and therapy results.[40] The historical under-representation of non-European populations in genomic investigations has constrained the usefulness of genetic discoveries. Recent initiatives in trans-ancestral Genome-Wide Association Studies (GWAS) and admixture mapping are effectively tackling this disparity.[41] The susceptibility, severity, and genetic architecture of SLE are substantially influenced by ethnic differences.[42] Higher prevalence, severe manifestations including lupus nephritis, poor renal outcomes, and higher mortality are exhibited by the individuals of African ancestry, probably due to population-specific high-risk alleles such as ITGAM (CD11b) and APOL1 variants.[43] Higher frequencies of TNFSF13B (BAFF) and PRDM1 variants are being exhibited by Asian populations, which leads to heightened antibody production and multisystem involvement. Earlier onset, aggressive renal disease, and risk alleles such as Native American-driven HLA and complement pathway variants are frequently seen in Latino groups.[44,45] On the other hand, populations from European heritage typically exhibit moderate phenotypes and have relatively fewer higher-risk genes.[46] These ethnic-specific genetic signatures collectively illustrate the observed heterogeneity in disease severity, treatment responses, and chronic outcomes across populations.

Functional Consequences of Risk Alleles

A substantial fraction of disease-related SNPs is located in non-coding areas, indicating a regulatory rather than a structural function.[47] Functional genomics methodologies, including as eQTL mapping, ATAC-seq, and CRISPR-Cas9 genome editing, have been essential in clarifying the effects of these polymorphisms. Risk alleles adjacent to IRF5 and TNFAIP3 affect gene expression by altering enhancer activity or transcription factor binding.[48,49] Chromatin conformation analyses demonstrate that certain risk loci establish three-dimensional connections with distant promoters, hence influencing long-range regulation mechanisms. These findings underscore the significance of epigenomic context in the interpretation of GWAS data and propose possible targets for therapeutic intervention.[50]

T Cell Dysregulation in SLE

SLE T cells exhibit sustained activation, marked by modified signalling pathways, epigenetic changes, and a disproportionate ratio of effector to regulatory subsets.[51] A defining characteristic is the proliferation of pro-inflammatory T helper (Th) cell subsets, especially Th1 and Th17, to the detriment of immunosuppressive regulatory T cells (Tregs). These alterations underpin the persistent systemic inflammation and organ-specific autoimmunity evident in SLE.[52] To summarize the major T cell abnormalities contributing to SLE pathogenesis, the key signalling defects, functional alterations, and clinical implications are presented in Table 2.

Aberrant T Cell Activation and Signalling

In SLE, T cells demonstrate a diminished activation threshold resulting from impairments in proximal T Cell Receptor (TCR) signalling. The hyperactivation of SLE T cells is induced by

amplified TCR and co-stimulatory signalling.[53] Significant signalling components including CD3ζ are downregulated, accompanied by compensatory overexpression of the Fc Receptor γ chain (FcRγ), which recruits Syk in lieu of ZAP70, hence biasing TCR signalling towards hyper responsiveness.[54] This leads to increased calcium influx and persistent activation of Nuclear Factor of Activated T cells (NFAT) and Extracellular signal-Regulated Kinase (ERK) pathways, facilitating inflammatory cytokine production and extended T cell survival.[55] Figure 2 illustrates that signalling via the TCR complex, CD28, and IL-2 receptor activates downstream molecules such as ZAP70, LAT, PI3K, and the JAK/STAT and MAPK pathways. The pathways converge on transcription factors including NF-κB, AP-1, and STAT5, which jointly enhance effector function, survival, and inflammatory gene expression in autoreactive T cells. Dysregulation at several points in this pathway is associated with defective regulatory T cell induction and chronic inflammation.[56,57]

Effector T Cell Imbalance: Th1 and Th17 Dominance

Increased expression of transcription factors T-bet and RORγt facilitates differentiation into Th1 and Th17 lineages, respectively.[58] Th1 cells secrete IFN-γ, which amplifies macrophage activation and MHC expression, whereas Th17 cells release IL-17, IL-21, and IL-22, facilitating neutrophil recruitment, tissue inflammation, and B cell assistance.[59] The genetic variation STAT4, frequently linked to SLE, promotes IL-12-mediated Th1 polarization and IL-23-dependent Th17 growth, thereby connecting genetic susceptibility to effector T cell differentiation.[60] Th17 responses have been specifically associated with lupus nephritis and neuropsychiatric symptoms.[61]

Regulatory T Cell Dysfunction

FoxP3+ CD4+ Tregs, which typically inhibit autoreactive T cell responses, exhibit both quantitative and functional deficiencies in patients with SLE.[62] Research has indicated diminished expression of FoxP3 and IL-2 receptor α (CD25), coupled with resistance to IL-2 signalling attributed to impaired STAT5 phosphorylation.[63] Furthermore, the inflammatory cytokine environment, abundant in IL-6 and IFN-α, undermines the Treg phenotype, promoting its transformation into pathogenic Th17 or T follicular helper (Tfh)-like cells. The overall consequence is a reduction in peripheral tolerance and an intensification of autoimmunity.[64,65]

Co-stimulatory and Co-inhibitory Pathways

Deviant co-stimulation further exacerbates T cell dysregulation. The CD28-CD80/CD86 and ICOS-ICOSL pathways are excessively active in SLE, promoting T cell proliferation and cytokine production.[66] The connections between CD40 and CD40L (CD154) are essential and the overexpression of CD40L on SLE CD4+ T cells enhances B cell activation, immunoglobulin class switching, and germinal center development. Clinical trials focusing on CD40L have shown effectiveness but were discontinued due to thrombotic consequences, underscoring the necessity for safer modulation approaches.[67] In contrast, co-inhibitory receptors like CTLA-4 and PD-1 are downregulated or malfunctioning, reducing the T cell exhaustion and anergy pathways that typically limit autoreactivity.[68]

T follicular helper (Tfh) and peripheral helper (Tph) Cells

Tfh cells, characterized by the expression of CXCR5, Bcl6, and IL-21, are proliferated in SLE and are associated with autoantibody levels and disease severity.[69] These cells localize

Table 1: Key Genetic Variants, Pathways, and Immune Dysregulation in SLE.

Category	Key Genes/Pathways	Mechanism/Effect	Clinical Relevance	References
Genetic Architecture	>90 loci	Polygenic, affect immunity, autoantibody patterns	Susceptibility, phenotypic variability	17-19
HLA Loci	HLA-DRB1, DQA1, DQB1	Antigen presentation, thymic selection, T cell autoreactivity	Autoantibody production, organ-specific involvement	20-25
Non-HLA Variants	STAT4, IRF5, PTPN22, BANK1, BLK, TYK2	Th1/Th17 bias, altered TCR/BCR signalling, IFN signature	Proinflammatory profile, autoantibody generation	26-31
Rare / Monogenic Variants	TREX1, DNASE1/DNASE1L3, C1q/C2/C4	Nucleic acid accumulation, impaired immune clearance	Early-onset lupus, severe phenotypes	32-35
Ethnic Variants	ITGAM, TNFSF13B, PRDM1	Population-specific allele frequency	Racial differences in disease severity & therapy response	36-40
Functional Effects of SNPs	IRF5, TNFAIP3	Regulatory SNPs, altered enhancer/transcription factor binding	Targets for therapeutic intervention	41-44

to germinal centers and offer essential assistance to B cells via IL-21 and CD40L signalling.[70] A newly recognized subtype, Tph cells (CXCR5– PD-1hi ICOS+), has analogous helper roles in inflamed peripheral organs and is prevalent in lupus nephritis. The pathogenic T cell subsets serve as promising therapeutic targets, as demonstrated by current trials of IL-21 and ICOS inhibitors.[71]

Epigenetic and Metabolic Regulation of T Cells

Epigenetic reprogramming reinforces T cell abnormalities in SLE. Global DNA hypomethylation in SLE T cells results in the upregulation of proinflammatory genes, including CD70 and perforin.[72] Histone changes and modified microRNA expression (e.g., miR-21, miR-146a) additionally influence T cell activity.[73] SLE T cells exhibit metabolic reprogramming characterized by enhanced glycolysis and mitochondrial hyperpolarization, which facilitate the formation of Reactive Oxygen Species (ROS) and confer resistance to cell death.[74] Recent research suggests that epigenetic modifications in SLE can occur both pre-emptively, increasing susceptibility, as well as secondary to chronic inflammation, indicating a reciprocal rather than purely coincidental association.[75]

B Cell Hyperactivity and Autoantibody Production

B cells have a complex involvement in the pathogenesis of SLE, contributing through autoantibody generation, antigen presentation, cytokine release, and modulation of T cell responses.[76] The B cell compartment in SLE is marked by a disruption of central and peripheral tolerance mechanisms, proliferation of autoreactive clones, and abnormal differentiation into plasmablasts and long-lived plasma cells. These disruptions arise from internal anomalies in B cell signalling and external signals from the inflammatory surroundings.[77] The key processes underlying B cell hyperactivity and autoantibody production in SLE are summarized in the Table 2.

Breakdown of B Cell Tolerance and Repertoire Skewing

Under physiological settings, autoreactive B lymphocytes are either eliminated or rendered anergic during their formation in the bone marrow (central tolerance) or in the peripheral tissues (peripheral tolerance).[78] In SLE, these regulatory checkpoints are impaired, permitting the persistence and activation of B lymphocytes that target nuclear antigens, including double-stranded DNA, histones, and ribonucleoproteins.[79] Single-cell BCR sequencing has demonstrated heightened clonality and somatic hypermutation in autoreactive clones, indicating active Germinal Centre (GC) responses and antigen-driven selection.[80]

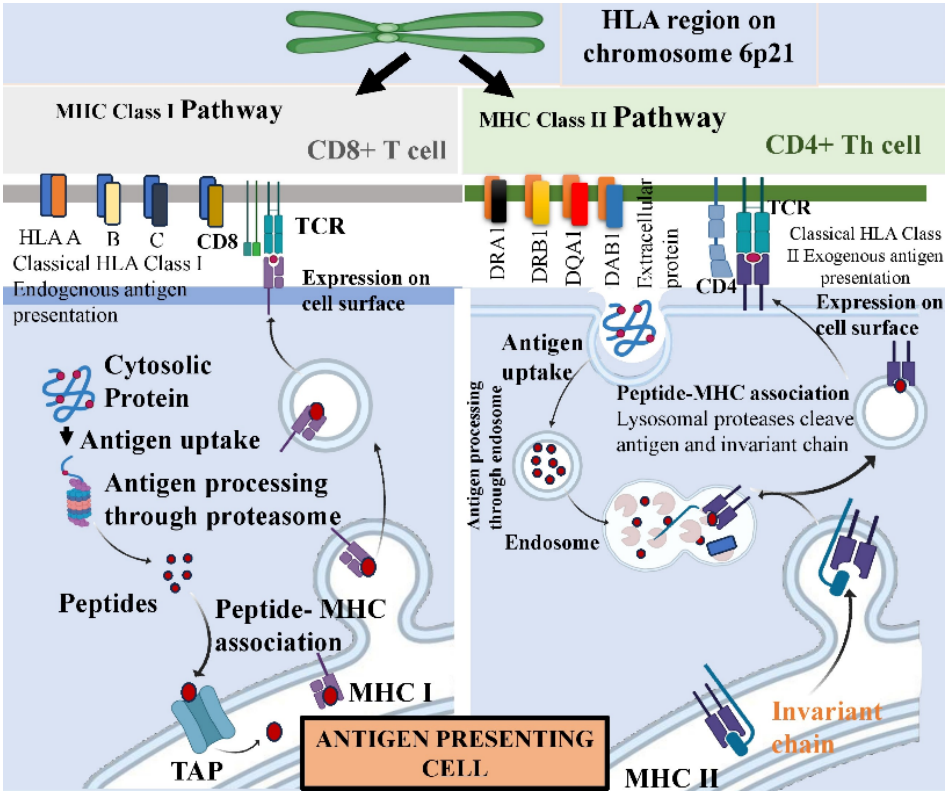

Figure 1: Schematic representation of MHC class I and II antigen presentation pathways. Diagram created using resources from Freepik (www.freepik.com) and Bioicons (CC BY 4.0, https://bioicons.com/). It shows endogenous (left) and exogenous (right) antigen processing and presentation by HLA molecules, which are central to T cell activation and autoimmunity in SLE.

Table 2: Mechanistic Overview of T Cell and B Cell Abnormalities and their Clinical Consequences in SLE.

Category / Process	Key Genes / Pathways	Mechanism / Effect	Clinical Relevance	References
T Cell Dysregulation	Th1/Th17, Tregs	Persistent activation, effector/ regulatory imbalance	Chronic inflammation, organ autoimmunity	45-46
Aberrant T Cell Signalling	CD3ζ↓, FcRγ↑, ZAP70, NFAT, ERK	Hyperresponsive TCR signalling, ↑ Ca^{2+} influx	Sustained cytokine production, prolonged T cell survival	47-51
Effector T Cell Imbalance	T-bet, RORγt, STAT4	Th1 → IFN-γ, Th17 → IL-17/21/22	Lupus nephritis, neuropsychiatric SLE	52-55
Regulatory T Cell Defects	FoxP3, CD25, STAT5	Treg quantitative/functional deficiency, IL-2 resistance	Loss of tolerance, enhanced autoimmunity	56-59
Co-stimulatory / Inhibitory Pathways	CD28, ICOS, CD40L, CTLA-4, PD-1	Overactive co-stimulation, downregulated co-inhibition	Enhanced T/B activation, poor autoreactive suppression	60-62
Tfh / Tph Cell Expansion	CXCR5, Bcl6, IL-21, PD-1, ICOS	Tfh → B-cell help, Tph → peripheral helper activity	Correlates with autoantibody titers & disease severity	63-65
Epigenetic & Metabolic Reprogramming	DNA hypomethylation, miR-21/146a, glycolysis ↑, mitochondrial hyperpolarization	Epigenetic rewiring, ROS ↑; apoptosis resistance	Maintains T cell hyperactivity, chronic inflammation	66-68
B Cell Tolerance Breakdown	Central & peripheral tolerance checkpoints	Loss of negative selection → autoreactive B cells persist	Autoantibody generation, systemic involvement	69-73
BAFF Overexpression	BAFF/BAFF-R signalling	Prolonged survival of autoreactive B cells & plasma cells	Therapeutic target (e.g., belimumab)	74-75
BCR & TLR Dysregulation	BCR + TLR7/9 → MyD88, IRF5, NF-κB	Autoantibody production, class switching, plasmablast expansion	Exacerbation of SLE flares & systemic damage	76-79
Germinal Center / Extrafollicular Response	Tfh IL-21, CD40L; extrafollicular plasmablasts	High-affinity IgG autoantibodies, rapid plasmablast bursts	Predicts active disease & lupus nephritis	80-82
Cytokine Imbalance	IL-6, TNF-α, lymphotoxin ↑; IL-10 ↓	Promotes Th17/Tfh polarization, weak regulation	Drives multi-organ inflammation	83-85
Autoantibody Specificities	Anti-dsDNA, anti-Sm, anti-RNP	Immune complex deposition	Nephritis, neuro/CV manifestations	86-88

BAFF Overexpression and B Cell Survival

B cell activating factor (BAFF, or BLyS), a member of the TNF family, is significantly increased in SLE and enhances the survival of autoreactive transitional and naïve B cells.[81] Elevated BAFF levels preserve low-affinity autoreactive clones that would otherwise face deletion, therefore augmenting the population of autoreactive B cells. The BAFF/BAFF-R axis is essential for the survival of class-switched memory B cells and plasma cells, providing the basis for BAFF-targeted drugs.[82]

Dysregulated BCR and TLR Signalling

Engagement of B Cell Receptors (BCR) by self-antigens, especially when associated with nucleic acids, synergizes with Toll-like receptor (TLR) 7 and 9 signalling to promote activation.[83] TLR7 and TLR9, situated in endolysosomal compartments, detect RNA and DNA, respectively, resulting in MyD88-dependent activation of the IRF5 and NF-κB pathways. These signals facilitate B cell proliferation, differentiation, and class change. TLR7 overexpression is significantly correlated with increased generation of anti-RNA antibodies and has been linked to SLE-susceptible mice models (e.g., Yaa locus).[84] The activation of

autoreactive B cells in SLE relies not only on the B Cell Receptor (BCR) but also on endosomal nucleic acid sensors, including TLR7 and TLR9, which detect self-RNA and DNA complexes.[85] Figure 3 delineates the convergence of these signals and their subsequent activation of the MyD88, TRAF6, IRF5, and NF-κB pathways. Genetic variations in BANK1, BLK, and TNFAIP3 enhance this signalling, leading to extended B cell survival, plasma cell differentiation, and the synthesis of high-affinity autoantibodies.[86]

Germinal Center and Extrafollicular B Cell Responses

Autoreactive B lymphocytes can experience somatic hypermutation and affinity maturation in germinal centres, facilitated by Tfh cells.[87] Increased concentrations of Tfh-derived IL-21 and CD40L maintain germinal centre responses, facilitating the production of high-affinity IgG autoantibodies, including anti-dsDNA and anti-Sm.[88] Concurrently, extrafollicular responses are gaining recognition in SLE, where stimulated B cells swiftly develop into plasmablasts outside of structured follicles. Extrafollicular plasmablasts exhibit markers including CD11c and T-bet, and are prevalent in patients with active illness.[89]

B Cell Cytokine Production and Immune Modulation

In addition to autoantibody secretion, B cells in SLE play a role in immunological dysregulation via cytokine synthesis. Activated B cells secrete IL-6, TNF-α, and lymphotoxin-α, facilitating inflammation and aiding Th17 and Tfh polarization.[90,91] IL-10, producing regulatory B cells (Bregs), which typically inhibit T cell activation and inflammatory responses, are both quantitatively and functionally impaired in SLE, intensifying immunological activation.[92]

Autoantibody Specificities and Pathogenic Roles

SLE is defined by a diverse spectrum of autoantibodies that target nuclear, cytoplasmic, and cell surface antigens. Anti-dsDNA, anti-Sm, and anti-RNP are regarded as diagnostic markers that correspond with disease activity and specific organ involvement.[93] For instance, anti-dsDNA antibodies create immunological complexes that accumulate in the glomeruli, instigating complement activation and nephritis.[94] Certain autoantibodies exhibit cross reactivity with neuronal or vascular antigens, hence leading to neuropsychiatric and cardiovascular symptoms.[95]

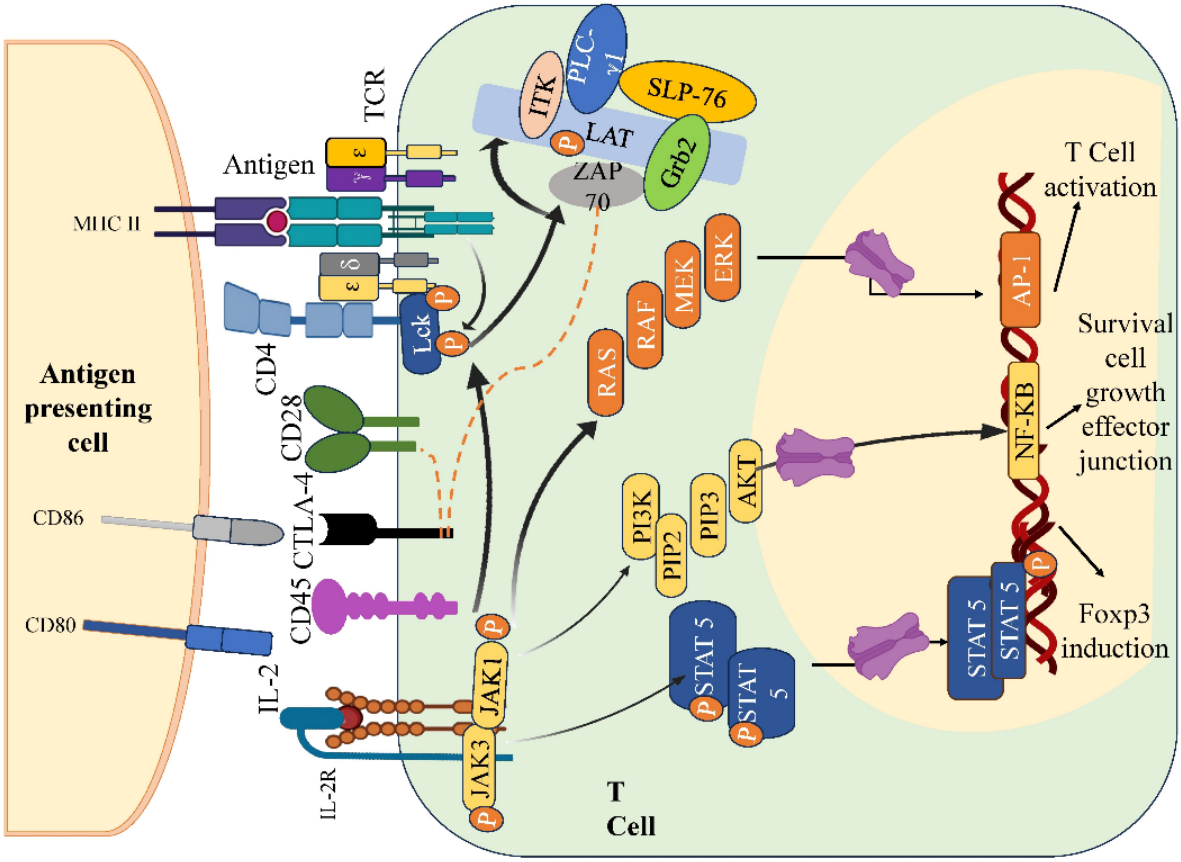

Figure 2: Illustration of T cell receptor and co-stimulatory signalling cascades involved in SLE. Diagram created using resources from Freepik (www.freepik.com) and Bioicons (CC BY 4.0, https://bioicons.com/). Signalling events downstream of TCR-CD3 and CD28 engagement activate transcription factors (NF-κB, AP-1, STAT5) that regulate T cell activation and survival.

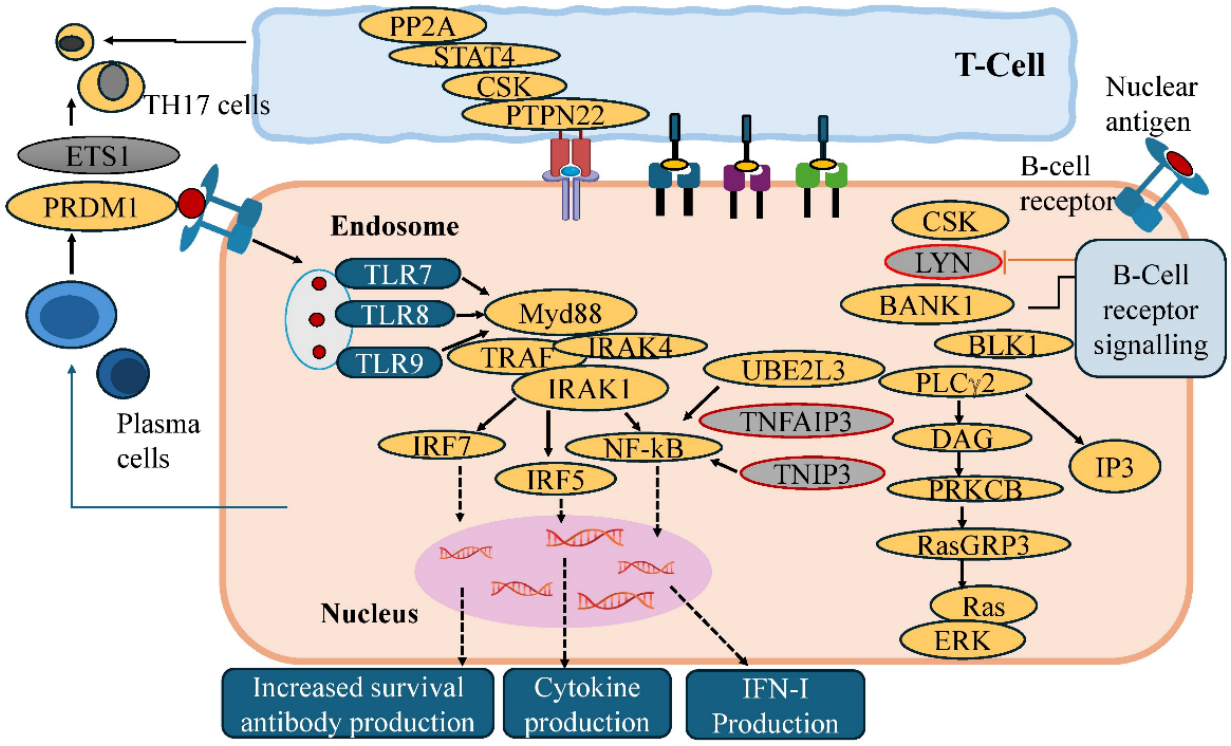

Figure 3: Pathogenic B cell signalling pathways in SLE. Diagram created using resources from Freepik (www.freepik.com) and Bioicons (CC BY 4.0, https://bioicons.com/). It highlights roles for BCR, TLRs, and key signalling molecules (e.g., IRF5, TRAF6, BANK1) in autoantibody production and B cell survival.

Type I Interferon Signature: Driver of Innate Dysregulation in SLE

The IFN-I pathway, particularly IFN-α is a major mechanistic and therapeutic axis in SLE, merging genetic predisposition with immunological activation.[96] The heightened expression of Interferon-Stimulated Genes (ISGs), referred to as the "interferon signature," is prevalent in most patients and correlates with disease activity, especially in lupus nephritis and skin manifestations.[97] Plasmacytoid Dendritic Cells (pDCs) are principal producers of IFN-α in SLE, activated by Toll-like receptors TLR7 and TLR9 by immune complexes that contain nucleic acids and autoantibodies.[98] This activates MyD88 mediated signalling and facilitates the nuclear translocation of IRF5 and IRF7, so initiating the transcription of IFN-α. Genetic variations in IRF5, IRF7, and TLR7 are associated with heightened IFN responses and elevated disease risk.[99] IFN-α exerts its effects by binding to the interferon-alpha receptor (IFNAR), thereby activating the JAK-STAT pathway specifically JAK1, TYK2, STAT1, and STAT2, which then induces ISG production. These genes govern antigen presentation, B cell activation, T cell polarisation, and facilitate chronic inflammation.[100] In conjunction with plasmacytoid dendritic cells, innate sensors such as IFIH1 (MDA5) and the cGAS-STING pathway identify self-nucleic acids, enhancing the interferon loop, which is further intensified by the inadequate removal of apoptotic debris resulting from complement or nuclease deficits.[101] Clinically, IFN-I activity serves as both a biomarker and an effector of disease severity, and therapeutic targeting of this pathway is now achievable.[102]

Impaired Apoptotic Cell Clearance: Source of Autoantigens in SLE

A primary deficiency in SLE is the inadequate removal of apoptotic and necrotic cells, leading to the accumulation of nuclear debris that acts as a continual supply of autoantigens.[103] This impaired clearance arises from intrinsic phagocyte malfunction and deficits in essential nucleases like DNASE1 and TREX1, responsible for degrading extracellular DNA.[104] The accumulation of uncleared apoptotic debris facilitates the generation of nucleic acid-containing immune complexes that stimulate plasmacytoid dendritic cells through TLR7 and TLR9, hence augmenting type I IFN production and sustaining immunological activation.[105] The complement system components, including as C1q, C4, and C2, are crucial for tagging apoptotic cells for elimination, and genetic abnormalities in these molecules represent major monogenic risk factors for SLE.[106] The accumulation of cellular debris fosters a pro-inflammatory milieu, enhances epitope dissemination, and stimulates chronic autoantibody synthesis. Immune complexes accumulate in organs, triggering complement activation and attracting inflammatory cells, resulting in organ damage typical of lupus nephritis and cutaneous lupus.[107] Concentrating on the mechanisms associated with apoptotic cell recognition and removal, such as enhancing complement activity or restoring nuclease function, may offer therapeutic avenues to alleviate the underlying autoimmunity in SLE.[108] The buildup of apoptotic

debris and immune complexes in SLE triggers a series of inflammatory responses. These complexes are identified by Fc receptors (e.g., FCGR2A/3B) and nucleic acid-sensing TLRs in innate immune cells,[109] as seen in Figure 4. These initiates complement activation and signalling via MyD88, TRAF6, and IRF5/7, leading to substantial type I IFN generation and further enhancement of the autoimmune response. Renal resident cells also engage in this cycle, contributing to tissue-specific pathologies, including lupus nephritis.[110]

Hormonal and Environmental Influences

The significant female predominance in SLE, especially during reproductive years, underscores the influence of sex hormones on illness susceptibility and pathogenesis.[111] Oestrogens augment immunological response by upregulating IFN-I production, elevating TLR7 expression on B cells and dendritic cells, and facilitating B cell survival and class switching, promoting the survival of autoreactive clones and enhances autoantibody synthesis.[112] Conversely, androgens induce immunosuppressive effects by downregulating proinflammatory cytokines and enhancing regulatory T cell activity, providing partial protection in males.[113] Progesterone exhibits a multifaceted role, possessing both pro-inflammatory and anti-inflammatory effects that are contingent upon its concentration and the immunological environment.[114] Hormonal variations during menstruation, pregnancy, and menopause may affect disease exacerbations, with immunological modulation during pregnancy frequently intensifying SLE activity, especially in women with active disease at conception.[115] Environmental exposures serve as significant catalysts in genetically predisposed individuals. Ultraviolet (UV) radiation triggers keratinocyte death, resulting in heightened release of nuclear autoantigens and subsequent immunological activation. Ultraviolet radiation also increases the expression of proinflammatory cytokines and adhesion molecules in the skin, contributing to SLE-specific dermal lesions.[116] Viral infections, especially Epstein-Barr Virus (EBV), have been associated with molecular mimicry and the proliferation of autoreactive B cells. Smoking induces oxidative stress, causes DNA damage, promotes proinflammatory cytokine production, and alters DNA methylation patterns.[117] These environmental factors collectively facilitate epigenetic remodelling and dysregulated innate immune activation, exacerbating the loss of tolerance in SLE.[75]

Therapeutic Landscape and Precision Targeting in SLE

The treatment of SLE is swiftly transitioning from empirical immunosuppression to molecularly targeted therapies based on an understanding of disease mechanisms.[118] Conventional therapy, such as glucocorticoids, hydroxychloroquine, and cytotoxic medicines like mycophenolate mofetil and cyclophosphamide, are essential yet constrained by nonspecific effects, toxicity, and inconsistent efficacy among patient subgroups.[119] The emergence of precision immunomodulation has resulted in the creation and authorization of biologics and small-molecule inhibitors that

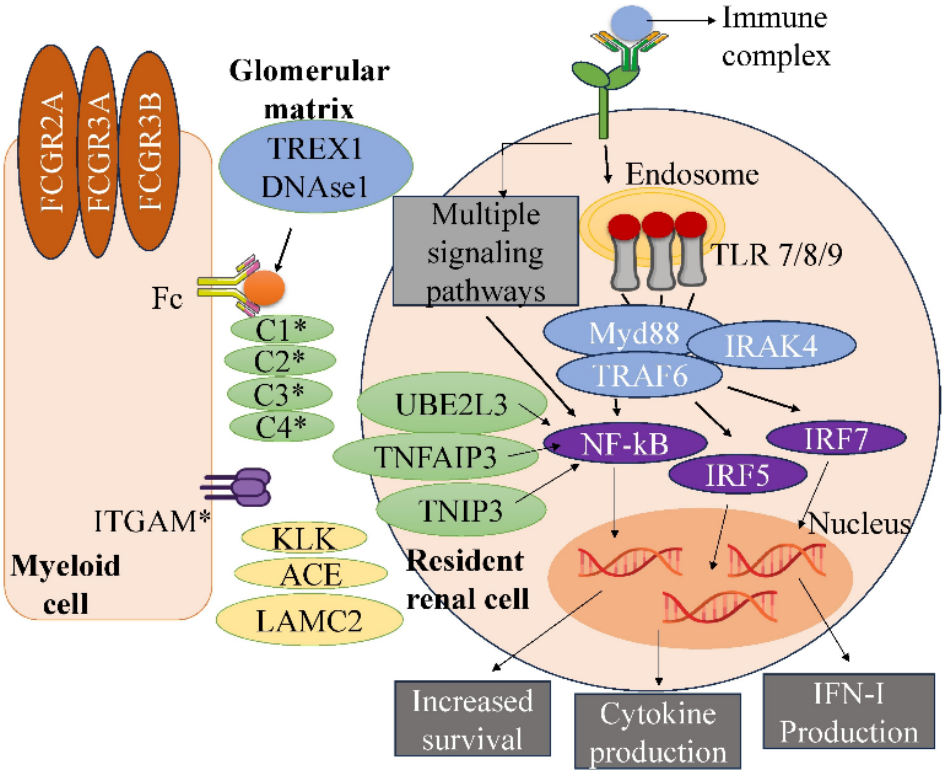

Figure 4: Immune complex deposition and innate immune activation in lupus nephritis. Diagram created using resources from Freepik (www.freepik.com) and Bioicons (CC BY 4.0, https://bioicons.com/). Fc receptors, complement components, and intracellular DNA/RNA sensors (e.g., TLR9) activate proinflammatory pathways in resident renal cells.

Table 3: Approved and Emerging Therapies for SLE: Mechanism of Action and Target Population and Limitations.

Drug	Mechanism of Action	Target Pathway	Indication/Population	Limitations	References
Hydroxychloroquine	TLR inhibition, immunomodulation	Innate immunity	All SLE patients	Retinopathy risk, slow onset, insufficient for severe SLE	132
Belimumab	Anti-BAFF antibody	B cell survival	Active, seropositive SLE	Limited in severe LN, high cost, delayed effect	133
Rituximab	Anti-CD20 B cell depletion	B cell elimination	Refractory or off-label in LN	Variable response, infection risk, off-label use	134
Anifrolumab	IFNAR blockade	Type I IFN signalling	Moderate to severe non-renal SLE	Viral infection risk, limited LN data, costly	135
Voclosporin	Calcineurin inhibition	T cell signalling	Lupus nephritis	Nephrotoxicity, hypertension, requires monitoring	136
Baricitinib	JAK1/2 inhibition	Cytokine signalling	Investigational	Infection risk, long-term safety unclear	137
Obinutuzumab	Type II anti-CD20 antibody	B cell depletion	Clinical trials	Infusion reactions, infection risk, limited data	138
BTK inhibitors	BCR signal inhibition	B cell activation	Preclinical/early trials	Limited data, unknown long-term safety	139

directly address critical immunopathogenic pathways in SLE. B cell targeted treatments are among the most clinically proven and commonly utilized strategies.[120] Belimumab, a monoclonal antibody that targets the B cell activating Factor (BAFF), is authorized for the treatment of autoantibody-positive SLE and has been effective in diminishing disease activity and flare incidence, especially in patients exhibiting elevated serologic activity.[121] Rituximab, an anti-CD20 monoclonal antibody, is not officially sanctioned for SLE due to ambiguous results in randomized studies; however, it has demonstrated efficacy in refractory instances, particularly in lupus nephritis and hematologic complications.[122] Obinutuzumab, a glycoengineered anti-CD20 antibody with enhanced antibody-dependent cellular cytotoxicity, is undergoing advanced clinical assessment.[123] Atacicept, which inhibits both BAFF and APRIL, has demonstrated biological efficacy but necessitates additional safety validation.[124] Focusing on IFN-I signalling has become a logical strategy due to the widespread presence of the interferon signature in SLE patients. Anifrolumab, a monoclonal antibody that inhibits the type I IFN receptor subunit IFNAR1, was recently approved following its demonstrated efficacy in diminishing overall disease activity, skin involvement, and corticosteroid utilization.[125] Alternative medicines, such as sifalimumab and rontalizumab, directly target IFN-α and have had inconsistent efficacy, potentially due to inadequate inhibition of broader interferon pathways.[126] Inhibitors of the JAK-STAT pathway present a compelling strategy owing to their capacity to regulate several proinflammatory cytokines, such as IFN-I, IL-6, and IL-23. Baricitinib (a JAK1/2 inhibitor) and deucravacitinib (a TYK2 inhibitor) are now being studied and have demonstrated initial effectiveness in alleviating illness symptoms while maintaining acceptable safety profiles.[127] Ongoing strategies in development encompass Bruton's tyrosine kinase (BTK) inhibitors, which interfere with B cell receptor and Fc receptor-mediated activation of B cells and myeloid cells, as well as agents that target co-stimulatory molecules, including CD40L and ICOSL, designed to eliminate pathogenic T-B cell interactions.[128] Dapirolizumab pegol, an anti-CD40L antibody, has advanced through early-phase trials demonstrating promising immunological benefits and tolerability. These therapeutic advancements coincide with a growing focus on biomarker-guided treatment selection.[129] Molecular stratification utilizing IFN gene signature status, BAFF serum concentrations,

plasmablast frequency, and immune cell transcriptomics is being established to select probable responders and mitigate undesirable effects.[130] Polygenic risk scores, single-cell immunological profiling, and the integration of patient-specific genomic, epigenetic, and proteomic data may ultimately facilitate real-time treatment decision-making.[131] Table 3 illustrates that the growing assortment of sanctioned and experimental medicines signifies a shift towards mechanism-based therapy in SLE along with its limitations. This precision medicine strategy not only aims to enhance outcomes and quality of life but also deepens our comprehension of SLE heterogeneity, therapeutic efficacy, and resistance.

Translational Implications and Future Directions

The future of SLE research depends on integrating high-resolution genetic data with clinical applications to facilitate dynamic, patient-specific disease management. The emphasis should transition from reiterating established immunological pathways to discovering real-time disease trajectories through integrative, longitudinal methodologies. Innovative instruments including single-cell atlases, spatial omics, and organ-specific immune profiling provide the capacity to reveal context-dependent disease determinants and treatment weaknesses.[110] Advancements in artificial intelligence and machine learning can derive clinically relevant patterns from intricate omics datasets, facilitating early diagnosis, disease classification, and personalized treatment selection.[50] These computational frameworks must be integrated into standard care to enhance therapy timing, dosing, and combination tactics. Practical application necessitates both biomarker identification and validation among varied populations. This encompasses the integration of patient-reported outcomes, digital health surveillance, and socioeconomic factors influencing care. Equitable precision medicine in SLE will depend on ethical data sharing, inclusive clinical trials, and infrastructure that facilitates adaptive learning healthcare systems. Ultimately, advancing from static classification systems to a dynamic, systems medicine approach could revolutionize SLE management from generalized suppression to proactive, tailored intervention enhancing both survival rates and quality of life.[107]

CONCLUSION

SLE is a multifaceted autoimmune disorder influenced by genetic, epigenetic, hormonal, and environmental variables, leading to a variety of clinical manifestations. Progress in immunogenomics, transcriptomics, and cellular profiling has elucidated critical pathways including compromised apoptotic clearance, dysregulated interferon signalling, and hyperactive lymphocytes. These findings have resulted in the creation of pathway-specific treatments, including BAFF inhibitors, anti-IFNAR medicines, and JAK inhibitors. Nonetheless, treatment results are variable owing to patient diversity and insufficient biomarker incorporation. The advent of systems-level and precision medicine methodologies presents a promising avenue, facilitating molecular stratification and personalized treatment options. Future research should prioritize longitudinal cohort studies, the integration of multi-omics data, and inclusive clinical trials to enhance illness prediction and treatment response. Ultimately, integrating mechanistic knowledge with clinical application will be crucial for evolving SLE treatment from broad immunosuppression to targeted, individualized interventions that enhance outcomes and quality of life.

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ABBREVIATIONS

ACE: Angiotensin-converting enzyme; **AP-1:** Activator protein 1; **ATAC-seq:** Assay for transposase-accessible chromatin using sequencing; **BAFF:** B-cell activating factor; **BANK1:** B-cell scaffold protein with ankyrin repeats 1; **BCR:** B-cell receptor; **BLK:** B-lymphocyte kinase; **BTK:** Bruton's tyrosine kinase; **C1:** Complement component 1; **C2:** Complement component 2; **C3:** Complement component 3; **C4:** Complement component 4; **CD:** Cluster of differentiation; **CRISPR:** Clustered regularly interspaced short palindromic repeats; **CSK:** C-Src tyrosine kinase; **DAB1:** MHC class II DA beta 1; **DNA:** Deoxyribonucleic acid; **DNASE1:** Deoxyribonuclease 1; **dsDNA:** Double-stranded DNA; **DQA1:** HLA class II DQ alpha 1; **DRA1:** HLA class II DR alpha 1; **DRB1:** HLA class II DR beta 1; **eQTL:** Expression quantitative trait loci; **ERK:** Extracellular signal-regulated kinase; **ETS1:** E26 transformation-specific transcription factor 1; **FCGR2A:** Fc gamma receptor IIA; **FCGR3A:** Fc gamma receptor IIIA; **FCGR3B:** Fc gamma receptor IIIB; **FCGR:** Fc gamma receptor; **FOXP3:** Forkhead box P3; **GWAS:** Genome-wide association studies; **HLA:** Human leukocyte antigen; **ICOSL:** Inducible T cell costimulator ligand; **IFIH1:** Interferon induced with helicase C domain 1; **IFN:** Interferon; **IFN-I:** Type I interferon; **IFNAR:** Interferon alpha/beta receptor; **IL:** Interleukin; **IRAK1:** Interleukin-1 receptor-associated kinase 1; **IRAK4:** Interleukin-1 receptor-associated kinase 4; **IRF:** Interferon regulatory factor; **IRF5:** Interferon regulatory factor 5; **IRF7:** Interferon regulatory factor 7; **ITGAM:** Integrin subunit alpha M; JAK**:** Janus kinase; **KLK:** Kallikrein; **LAMC2:** Laminin subunit gamma 2; **LAT:** Linker for activation of T cells; **LCK:** Lymphocyte-specific protein tyrosine kinase; **LN:** Lupus nephritis; **LYN:** Lck/Yes-related novel protein tyrosine kinase; **MHC:** Major histocompatibility complex; **MYD88:** Myeloid differentiation primary response protein 88; **NETs:** Neutrophil extracellular traps; **NF-κB:** Nuclear factor kappa-light-chain-enhancer of activated B cells; **PLCγ2:** Phospholipase C gamma 2; **PP2A:** Protein phosphatase 2A; **PRDM1:** PR domain zinc finger protein 1; **PRKCB:** Protein kinase C beta; **PTPN22:** Protein tyrosine phosphatase non-receptor

type 22; **RASGRP3:** Ras guanine nucleotide releasing protein 3; **RNA:** Ribonucleic acid; **SLE:** Systemic lupus erythematosus; **SLP-76:** SH2 domain-containing leukocyte protein of 76 kDa; **SNP:** Single nucleotide polymorphism; **STAT:** Signal transducer and activator of transcription; **STING:** Stimulator of interferon genes; **TCR:** T cell receptor; **TH:** T helper cell; **TLR:** Toll-like receptor; **TNFAIP3:** Tumor necrosis factor alpha-induced protein 3 (A20); **TNIP3:** TNFAIP3-interacting protein 3; **TRAF6:** TNF receptor-associated factor 6; **TREX1:** Three prime repair exonuclease 1; **TYK2:** Tyrosine kinase 2; **UBE2L3:** Ubiquitin-conjugating enzyme E2 L3; **ZAP-70:** Zeta-chain-associated protein kinase 70.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: R.G. and P.C., Resources: R.G., G.H.K., B.K., Data Collection: R.G., G.H.K., P.S. and J.M., Validation: P.C., C.K., Original Draft Preparation: R.G., Writing - Review & Editing: R.G. and P.C.

SUMMARY

This study examines the genetic and immunological foundations of SLE, emphasizing its complex characteristics that encompass more than 90 susceptibility loci. These loci influence essential pathways including antigen presentation, lymphocyte activation, IFN-I signalling, and apoptotic cell clearance. The research examines prevalent polygenic risks and infrequent monogenic variations, as well as ethnicity-specific genetic variables that contribute to illness heterogeneity. Principal immunopathogenic characteristics encompass T and B cell dysregulation, an amplified interferon response, and impaired elimination of apoptotic debris. Hormonal factors and environmental stimuli, such as UV exposure and infections, additionally increase illness risk. Progress in genetics and immune profiling has resulted in tailored medicines, including anti-BAFF and IFNAR inhibitors, as well as JAK-STAT modulators. This study underscores precision medicine methodologies, promoting biomarker-based, personalized treatment solutions. Integrating molecular insights with clinical applications is crucial for enhancing outcomes and customizing therapies in the context of personalized SLE care.

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