Current Science
CS 5 (3), 2354-2378 (2025)
Received 20 Feb 2025 | **Revised 18 March** 2025 | **Accepted 12 April**. 2025 | **Online Available 16 May** 2025
https://doi.org/ 10.52845/CS/2025-5-3-25

Current Science

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OPEN ACCESS

ISSN(O)2795-8639

Original Article

Research Progress on the Pathogenic Mechanism and Molecular Drug Development of Systemic Lupus Erythematosus

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Abstract:
Systemic lupus erythematosus (SLE) is a chronic, multi-organ, systemic autoimmune disease that predominantly affects women of childbearing age and can lead to damage in multiple organs. The immune system's equilibrium is upset in SLE patients, which leads to immune cells attacking healthy tissues and impairing cells' capacity to eliminate apoptotic materials. Consequently, the body accumulates nuclear antigens, which facilitates the production of antinuclear antibodies by B cells. Immune complexes are created when nuclear antigens and antinuclear antibodies interact. These immune complexes travel throughout the body with the blood flow, depositing in various organs, causing inflammation in different areas, excessively activating the complement system, and impacting multiple organs. One of the serious and relatively common complications that can arise is lupus nephritis. Since SLE affects many organs and nearly all body systems with recurrent episodes over a patient's lifetime, it causes significant suffering for those affected. Moreover, due to its complex mechanism and the difficulty in treatment, SLE is known as the "incurable cancer", and currently, molecular drugs still cannot provide a radical cure. Regarding the drug treatment of SLE, immunosuppressants, non-steroidal anti-inflammatory drugs, glucocorticoid drugs, and biological agents are still the mainstays at present. This article will start from the pathogenesis of SLE to introduce the application of drugs for SLE and summarize the development process of drugs for this disease in recent years.

Keywords: Systemic Lupus Erythematosus; Pathogenic Mechanism; Molecular Drug; Autoantibodies; Immune System.

Introduction

Globally, the incidence rate of systemic lupus erythematosus (SLE) is highest in the United States, while the total number of SLE patients in China ranks first globally and the incidence rate ranks second.[1-3] Due to differences in demographics, environmental exposures, and socioeconomic factors, the reported global incidence and prevalence of SLE vary significantly.[4] Black, Hispanic, and Asian populations experience SLE more severely, with higher incidence and prevalence rates compared to the white population.[5, 6] Several studies from North America, Europe and Asia have shown that the prevalence of SLE has gradually increased over time.[7-9] From the incomplete statistics of international data, it has always been observed that women are more affected by SLE than men.[4] In most studies, cardiovascular disease and infection are reported as the leading causes of death among SLE patients.[10]

The traditional treatment method is to administer hormones and immunosuppressants according to the specific conditions of patients and the degree of disease activity to relieve the disease condition and reduce inflammation and the degree of involvement of various organs of patients. However, the long-term use of steroid drugs will bring many inevitable pains to patients, including central obesity, osteoporosis, avascular necrosis of bone, and infections.[11] In recent years, there has been new progress in the research on targeted treatment of SLE. Targeted treatment has been favored by people and has also become a major focus of research. Starting from targeted therapy, drugs can be classified according to their mechanisms of action into targeted therapies for B cells, targeted therapies for cytokines and chemokines, targeted therapies for regulatory T cells, and targeted therapies for immune cells.[12] Currently, among B-cell targeted drugs, belimumab, voclosporin, and anifromulab have been marketed and are SLE treatment methods approved by the FDA.[13] The immune system in the human body is sophisticated and complex, and the research on the mechanism of SLE is still being explored. It is generally accepted by the public that the inflammatory response occurs and further expands due to the interaction of innate immunity and adaptive immunity.[12] Among these, dendritic cells (DC), regulatory T cells (Treg), cytokines, and chemokines are all crucial components of the immune system. Innate immunity and adaptive immunity are linked by the DC signaling pathway, which acts as a link between the two immune systems. Furthermore, Treg is crucial for controlling B cell-mediated humoral immunity and T cell development.[14-16]

2. Pathogenesis of SLE

Genetic and environmental factors, including ultraviolet radiation, gender, infections, drugs, and chemicals, all trigger abnormal immune responses, resulting in an imbalance in the immunoregulation of B cells and T cells in patients, an increase in antibodies, deposition of immune complexes, activation of the complement system, induction of inflammation, and ultimately leading to damage to the functions of multiple organs (Figure 1).

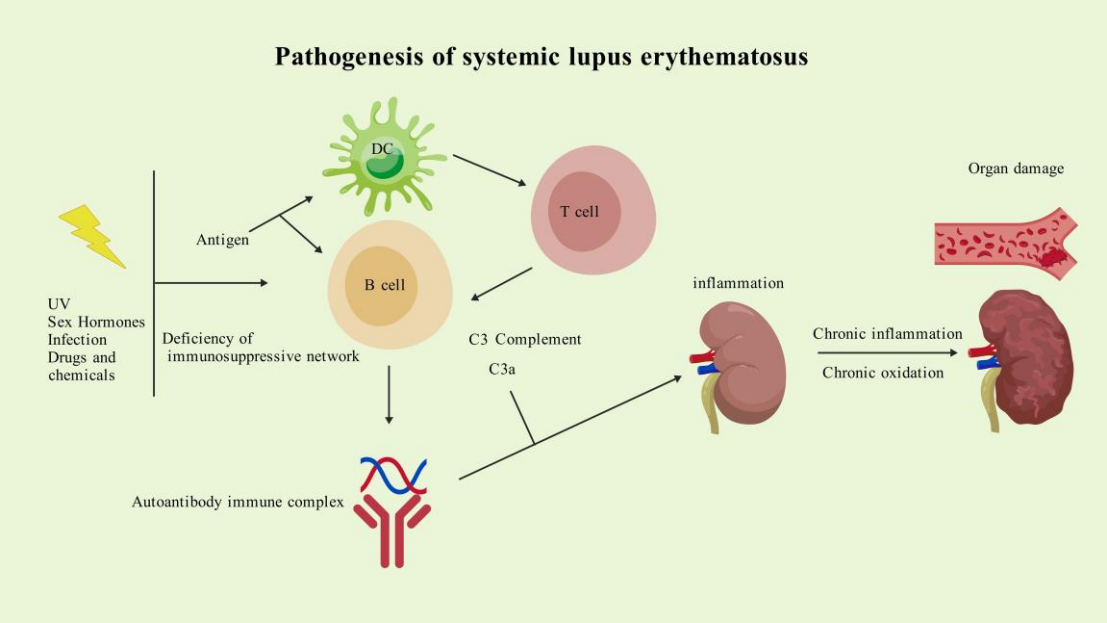

Figure 1. Pathogenic Mechanism of SLE: Genetic and environmental factors, such as ultraviolet radiation, gender, infections, drugs, and chemicals. Created with BioGDP.com.[17]

2.1 Genetic Factors

Studies have shown that SLE has a certain degree of heredity. Patients with SLE carry multiple genes related to the onset of SLE, and more than 50 such genes have been identified so far.[18] The human leukocyte antigen (HLA) genes, especially loci such as HLA-DR3 and HLA-DR15, are closely associated with the susceptibility to SLE. In patients, the frequencies of these genes are much higher than those in the normal population.[19, 20] These HLA class II molecules

play a crucial role in the process of antigen presentation. They can present self-antigens to T cells, thereby initiating an autoimmune response. If an individual carries a specific HLA class II genotype, it may cause abnormalities in the antigen presentation process and increase the risk of activation of autoreactive T cells.[21] SLE pathogenesis involves a number of non-HLA genes in addition to HLA genes. The development of SLE, for instance, is linked to deficits in the complement C1q, C2, and C4 genes.[22] To remove immunological complexes, apoptotic cells, etc., the complement system is crucial. Immune complexes and apoptotic cells can't be efficiently removed when complement gene deficits exist. When these chemicals build up in the body, they can cause an autoimmune reaction and lead to SLE.[23] For instance, self-antigen exposure results from the inability of people with C1q loss to routinely eliminate apoptotic cells, which activates the immune system and raises the risk of developing SLE.[24]

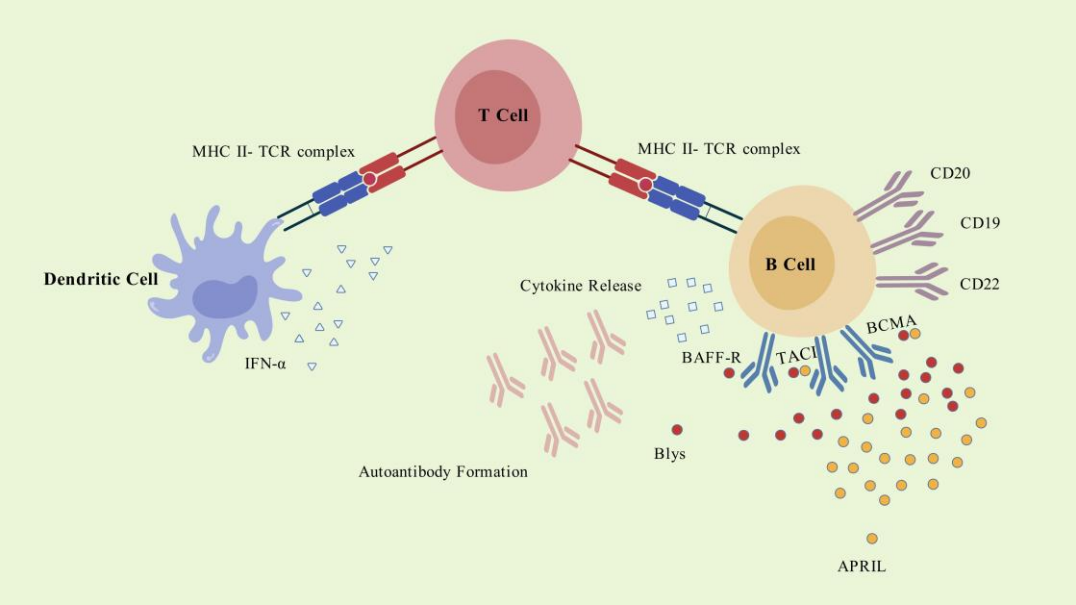

Figure 2. The Role of Immune Cells in SLE: B cells and T cells interact with each other by presenting antigens, releasing cytokines, and forming autoantibodies, which subsequently leads to the deposition of immune complexes, triggering inflammation, and further affecting multiple systems, resulting in SLE. APRIL: A Proliferation-Inducing Ligand, BLyS: B Lymphocyte Stimulator, BAFF-R: BLyS Receptor, TACI: Transmembrane Activator and Calcium Modulator and Cyclophilin Ligand Interactor, BCMA: B Cell Maturity Antigen. BLyS targets all three receptors, while APRIL targets the latter two receptors. INFα: Interferon α, TCR: T Cell Receptor, MHCII: Major Histocompatibility Complex Class II. Created with BioGDP.com.[17]

2.2 Immunological Factors

2.2.1 Immune Cells, Cytokines and Receptors

The body's immune system, which carries out immunological responses and immune functions, is crucial. The two primary lymphocyte types, B and T cells, are essential for immunological defense, immune surveillance, and immune homeostasis, among other functions.[25, 26]

(1) B cells secrete cytokines, and B cells are activated to produce antibodies.

The functional diversity of B cells makes them one of the core participants in immune responses. Their role is not limited to humoral immunity but is also closely related to cellular immunity and overall immune regulation. In a normal immune system, the anti-inflammatory and pro-inflammatory factors secreted by B cells maintain a stable balance for a long time. However, in an immunologically abnormal environment, B cells over-secrete inflammatory factors, causing the balance to be broken and inflammation to occur or intensify.[27]

Interleukin-6 (IL-6), interleukin-10 (IL-10), α tumor necrosis factor (TNF-α), α interferon (IFN-α), lymphotoxin, and other substances secreted by B cells can cause further inflammation.[28] IL-6

plays a crucial function in the start and improvement of the immune response and can encourage the growth and differentiation of T and B cells. Given its anti-inflammatory and immunosuppressive properties, IL-10 can control the strength of the immune response and keep an overabundance of it from harming the body.[29] TNF-α participates in the regulation of inflammatory responses and processes such as apoptosis.

The abnormal activation of B cells can lead to the production of a large number of autoantibodies. In patients with SLE, B cells can be activated through multiple pathways. For instance, the abnormal signaling pathway of the B cell receptor (BCR) enhances the recognition and response of B cells to self-antigens.[30] When B cells recognize self-antigens, with the assistance of cytokines such as interleukin-4 (IL-4) and interleukin-21 (IL-21) secreted by T cells, B cells can proliferate and differentiate into plasma cells to produce a large number of autoantibodies, such as antinuclear antibodies (ANA), anti-double-stranded DNA (ds-DNA) antibodies, etc. These autoantibodies combine with self-antigens to form immune complexes, which are deposited in tissue organs, triggering inflammatory reactions and tissue damage.[31] ANA is the symbolic autoantibody of SLE, and almost all SLE patients are positive.[32] ANA targets DNA, RNA, histones, ribonucleoproteins, and other elements found in the cell nucleus.[33] Its production mechanism is related to multiple factors, such as the abnormal activation of B cells and the abnormal exposure of self-antigens. Anti-ds-DNA antibodies have a relatively high specificity for SLE, and their titer is closely related to the activity of the disease.[34] Activating the complement system and causing inflammatory reactions that result in glomerulonephritis, skin erythema, and other conditions, anti-ds-DNA antibodies can combine with free double-stranded DNA in the body to form immune complexes that are deposited on the walls of small blood vessels, basement membranes, etc. in tissues like the kidneys and skin. Conversely, they stimulate platelets, which in turn stimulate antigen-presenting cells, thus raising the level of anti-DNA antibodies that worsen the health condition.[35-37]

In addition, patients with SLE can also produce various autoantibodies such as anti-Smith antibodies (Sm), anti-ribosomal P protein antibodies, and anti-phospholipid antibodies.[38] Antiphospholipid antibodies, for instance, can influence the pulmonary system's expression of antiphospholipid syndrome and cause thrombosis and repeated miscarriages.[39, 40]

Research has shown a strong correlation between the onset of SLE and aberrant regulatory B cell (Breg) function.[41] By releasing inhibitory factors like IL-10, breg cells aid in the suppression of autoimmune reactions and inflammation.[42] Furthermore, IL-10 has the ability to promote regulatory T cell development.[43] This indicates that multiple components of the immune system play important roles in the pathogenesis of SLE. In patients with SLE, Breg has the ability to negatively regulate the immune response, specifically manifested as a positive correlation between the percentage of Breg cells and the disease activity level, that is, the SLEDAI value.[44]

(2) Imbalance of T Cell Subpopulations

T cells play an important role in the immune responses within patients with SLE and are at the core of inflammatory reactions. T cells assist B cells in producing ds-DNA and themselves produce interleukin-17 (IL-17) and other cytokines, which help to amplify the inflammatory response.[45] Different types of T cell subpopulations play different roles in immune responses, driving the progress of immune reactions.[46]

Helper T cells (Th1) release interferon-γ (IFN-γ), interleukin-12 (IL-12), and TNF-α, promoting the occurrence of inflammatory reactions. Meanwhile, helper T cells (Th2) have an anti-inflammatory effect, secreting IL-4, IL-6, and IL-10 which are different from the cytokines released by Th1 cells and can effectively inhibit the occurrence of inflammation.[47] Helper T cells (Th17) can secrete pro-inflammatory factors such as IL-17 to promote the occurrence of inflammation, causing autoimmunity, while regulatory T cells (Treg) inhibit excessive immune responses and maintain immune tolerance.[48] Abnormal functions of Treg cells will lead to a weakened immunosuppressive effect. It is generally believed in this field that Treg cells inhibit autoreactive T cells by mediating the lysis of target cells and secreting

inhibitory cytokines (such as IL-10 and TGF-β).[49] In patients with SLE, the expression of Forkhead box protein P3 (Foxp3) in Treg cells in peripheral blood is decreased. Foxp3 is a key transcription factor for Treg cells to exert their immunosuppressive function.[50] The decreased expression of Foxp3 will affect the immunosuppressive function of Treg cells, making autoreactive T cells unable to be effectively inhibited, thus promoting the development of the disease.[51]

In SLE patients, the imbalance between follicular helper T cells (Tfh) and peripheral helper T cells (Tph) is a prominent characteristic.[52, 53] Among them, TFH assists B cells within lymphoid follicles,[54] while TPH helps B cells in the inflamed peripheral tissues.[55] TFH and TPH produce CXCL13, which can bind to the B cell chemokine receptor CXCR5.[56] The Aryl hydrocarbon Receptor (AHR) is an effective negative regulator of CXCL13 production in human CD4+ T cells. AHR works in concert with the AP-1 family member JUN to block the differentiation of CXCL13+ Tph cells and promote the formation of IL-22+ Th22 cells.[57] In summary, this leads to abnormal cellular immunity, the recruitment of B cells, and the formation of lymphoid aggregates in inflamed tissues.[58]

Under normal physiological conditions, there is a balance among T cell subpopulations, and they secrete cytokines to jointly maintain the internal immune environment. Therefore, Th1/Th2 and Th17/Treg are the key evaluation indicators for whether the T cell subpopulations maintain a balance. In patients with SLE, the number of Th17 cells increases or their functions are hyperactive, while the number of Treg cells decreases or their functions are impaired.[59]

(3) Monocytes

Monocytes are a type of white blood cell and are derived from hematopoietic stem cells in the bone marrow.[60] They circulate in the blood and possess powerful phagocytic functions, being able to phagocytose foreign or self-substances such as pathogens and apoptotic cells.[61, 62] Monocytes express multiple receptors on their surfaces, including pattern recognition receptors such as Toll-like receptors (Toll-like receptors), etc. These receptors can recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), thereby initiating an immune response.[63, 64] Furthermore, monocytes can also secrete a variety of cytokines and chemokines, such as interleukin-1 (IL-1), TNF-α, monocyte chemotactic protein 1 (MCP-1), etc. These factors play an important role in the process of inflammation and immune regulation.[65] In patients with SLE, especially during the active stage of the disease, the number of monocytes in the blood often shows abnormalities. Some studies have indicated that the peripheral blood monocyte count in SLE patients may increase.[66] This variation in the quantity could be linked to the stimulation of inflammatory agents and the modification of the bone marrow hematopoietic milieu. The inflammatory response can be made worse by the elevated monocytes.[67]

In individuals with SLE, monocytes exhibit a different pattern of cytokine release. Anti-inflammatory substances may be secreted less frequently, whereas pro-inflammatory molecules like TNF-α and IL-1 may be oversecreted.[68] This state of unbalanced cytokine release will foster an environment that is favorable to the ongoing occurrence and progression of autoimmune reactions, aggravating tissue damage and inflammation and accelerating the course of SLE.[69]

Following their uptake of self-antigens, monocytes use the MHC-II class molecules (such as HLA-DR) on their surface to present the antigens to T cells.[70] T cells that were initially in an immunotolerant condition are able to recognize self-antigens, activate, and develop into effector T cells because of the aberrant activation and phenotypic alterations of monocytes in SLE patients. In addition to attacking self-tissues and contributing to the immune response, these autoreactive T cells cause a number of pathological alterations in SLE.[71]

(4) Neutrophils

Neutrophil extracellular traps (NETs) are created when neutrophils are triggered by outside stimuli.[72] Double-stranded DNA (ds-DNA), histones, citrullinated peptides, myeloperoxidase (MPO) and other substances released by neutrophils are pre-sent in NETs, and these substances are regarded as antigens in the

adaptive immune system, which may thus sustain SLE.[73] Furthermore, by forming immunological complexes, neutrophils can cause tissue damage and trigger inflammatory reactions.[74]

In SLE patients, there are abnormalities in neutrophils, including impaired phagocytosis, increased aggregation, and accelerated cell death.[75] In SLE patients, the autoantibodies and interferon-α present in the serum induce neutrophil ferroptosis by enhancing the binding of the transcriptional repressor CREMα to the promoter of glutathione peroxidase 4 (Gpx4, a key regulator of ferroptosis), leading to the suppression of Gpx4 expression and subsequent increase in lipid reactive oxygen species (lipid-ROS).[76] After neutrophils die, the subsequent debris cannot be cleared, providing a stable source of self-antigens for the onset and spread of the disease.[77]

(5) Interferon (IFN)

IFN-I is a potent candidate for mediating many histone modifications, which can be regarded as indicators of the priming or training of IFN-induced immune system cells upon subsequent activation signals, as well as the impact of environmental triggers on the development of SLE autoimmunity and inflammation.[78] Activation of the IFN-I pathway or the development of lupus autoantibodies may serve as initiating events, potentially influenced by specific genetic risk factors.[79] Studies have shown that individuals with a high IFN-I score are more likely to progress to SLE than those with a low IFN-I score.[80] IFN-I signatures have been observed in 60%-85% of patients and are widely expressed across cell types, with an increased number of IFN-I-induced gene transcripts observed in monocytes compared to lymphocytes, exhibiting a relatively persistent expression even in the case of non-active disease.[81]

(6) Toll-like receptors (TLRs)

TLRs are a type of crucial pattern recognition receptor (PRR) in the immune system that can initiate innate immune responses by recognizing pathogen-associated molecular patterns (PAMPs).[82] Activated plasmacytoid dendritic cells (pDCs) express high levels of Toll-like receptor 7 (TLR7) and Toll-like receptor 9 (TLR9), and secrete large amounts of type I and type III interferons (IFN).[83]

TLR7 is an important member of the TLR family that recognizes exogenous single-stranded RNA (ssRNA) to activate downstream innate signaling pathways. The activation of the single-stranded RNA receptor TLR7 induces the production of pro-inflammatory cytokines and type I interferon (IFN-I).[84, 85] In some female SLE patients, the expression of TLR7 from both X chromosomes has been observed, particularly in B cells and pDCs. Another X chromosome-encoded gene, TASL, can be expressed from both X chromosomes and enhances signaling downstream of TLR7.[86-88] This is considered to be related to the increased susceptibility of females to SLE.

Long non-coding RNAs (lncRNAs) possess diverse sequences, flexible structures, and widespread distribution, and in recent years, they have been proven to play important roles in inflammation.[89, 90] A TLR7-binding lncRNA, Lnc-Atg16l1, can bind to activated TLR7 and enhance the TLR7/8 signaling pathway and inflammation by promoting the interaction between TLR7 and MyD88.[91]

TLR9 can recognize self-DNA and plays a role in the pathogenesis of SLE.[92] TLR9 can recognize pathogenic nucleic acids and endogenous nucleic acids in endosomes.[93] Endosomal TLRs require the chaperone protein UNC93B1 for stability and to ensure transport from the endoplasmic reticulum (ER) to the Golgi apparatus and eventually to endolysosomes.[94] S-palmitoylation is a reversible post-translational modification.[95] Palmitoyl-protein thioesterase 1 (PPT1) regulates systemic autoimmunity by removing S-palmitoylation of TLR9 in lysosomes; PPT1 promotes the secretion of IFN-α by plasmacytoid dendritic cells (pDCs) and TNF by macrophages. Additionally, the protein acyltransferase DHHC3 palmitoylates TLR9 in the Golgi apparatus and regulates the transport of TLR9 to endosomes. Subsequent depalmitoylation by PPT1 facilitates the release of TLR9 from UNC93B1.[96]

2.2.2 Deposition of Immune Complexes and Inflammatory Reactions

The circulating autoantibodies combine with antigens to form immune complexes. Numerous inflammatory mediators, including C3a and C5a, are produced by these immune complexes, which also deposit in tissues and activate the complement system. They attract inflammatory

cells such as neutrophils and macrophages to gather at the affected sites, where they release substances like lysosomal enzymes and reactive oxygen species, causing tissue damage.[97, 98]

2.2.3 Biomarker

Biomarkers play a crucial role in various aspects of the management of SLE, including diagnosis, prognosis assessment, and treatment monitoring. Traditional diagnostic methods for SLE often rely on a combination of clinical symptoms, physical examinations, and laboratory tests. However, the clinical manifestations of SLE are diverse and can mimic other diseases, making accurate diagnosis challenging. Biomarkers provide objective and specific indicators that aid in the early and accurate diagnosis of SLE.[99] For example, ANA is highly prevalent in SLE patients. Although ANA positivity is not specific to SLE, it serves as an important initial screening biomarker. High-titer ANA, combined with other specific autoantibodies such as anti-dsDNA antibodies and Sm antibodies, significantly increases the likelihood of SLE diagnosis. Anti-dsDNA antibodies are particularly specific to SLE and are closely associated with disease activity, especially in cases of lupus nephritis. The presence and titer changes of these antibodies can help clinicians distinguish SLE from other autoimmune diseases and initiate appropriate treatment in a timely manner. Prognosis Biomarkers also play a vital role in predicting the prognosis of SLE patients. They can provide valuable information about the potential course of the disease, the likelihood of developing severe complications, and the overall long-term outcome. For instance, elevated levels of certain cytokines, such as IL-6 and TNF-α, have been associated with more severe disease activity and a higher risk of organ damage in SLE patients.[100] High levels of these cytokines are often correlated with the development of lupus nephritis, cardiovascular disease, and other serious complications. Additionally, the presence of specific autoantibodies, such as anti-phospholipid antibodies, can predict an increased risk of thrombosis and pregnancy complications in SLE patients.[101] By identifying these biomarkers early in the disease course, clinicians can better stratify patients according to their risk of poor prognosis and implement more aggressive preventive and treatment strategies. During SLE treatment, changes in biomarker levels can reflect the response of the disease to treatment. For example, reduced titers of anti-dsDNA antibodies are often associated with a positive response to treatment and reduced disease activity. Conversely, elevated levels of anti-dsDNA antibodies may indicate a sudden onset of disease or treatment failure.[102] Similarly, changes in the levels of inflammatory cytokines can also be used to monitor treatment efficacy. If the levels of IL-6 and TNF-α decrease after treatment, it suggests that the treatment is effectively suppressing inflammation.[103] Biomarkers can also help clinicians identify patients who may be at risk of developing treatment-related side effects. For example, monitoring lipid levels and blood pressure in patients receiving JAK inhibitors can help detect early signs of metabolic and cardiovascular complications, allowing for timely intervention and adjustment of the treatment plan.[104] In conclusion, biomarkers are of great significance in the diagnosis, prognosis assessment, and treatment monitoring of SLE. The continuous discovery and validation of new biomarkers, as well as the improvement of existing biomarker-based diagnostic and monitoring methods, will contribute to more accurate and personalized management of SLE patients, ultimately improving their treatment outcomes and quality of life.

2.3 Environmental Factors

2.3.1 Infections

Viral infections may be related to the onset of SLE. In particular, Epstein-Barr virus (EBV) infection is considered to be associated with the onset of SLE.[105] EBV can induce B cell proliferation and antibody production, and change the function and phenotype of B cells. During the infection process, EBV can activate B cells, causing them to produce autoantibodies. Meanwhile, EBV infection may also affect the function of T cells and interfere with the normal immune regulatory mechanism.[106] In addition, bacterial infections may also play a role in the onset of SLE.[107] For instance, the lipopolysaccharide (LPS) component of the cell wall of certain Gram-negative bacteria can activate the immune system and stimulate macrophages to secrete cytokines such as IL-1 and interleukin-11 (IL-11), and these cytokines may participate in the inflammatory process of SLE.[108]

2.3.2 Ultraviolet Radiation

Ultraviolet (UV) radiation is one of the important environmental factors for the onset and exacerbation of SLE.[109] UV irradiation can induce apoptosis of skin cells, ex-posing intracellular self-antigens such as Ro/SSA and La/SSB.[110] These self-antigens can be taken up by antigen-presenting cells and presented to T cells, activating the autoimmune response.[111] Moreover, UV irradiation can also induce skin cells to produce various cytokines such as IL-6 and TNF-α, and these cytokines can promote the inflammatory response and further exacerbate the autoimmune damage. Therefore, in patients with SLE, symptoms such as aggravated skin erythema and intensified joint pain often occur after prolonged sun exposure.[112]

2.3.3 Drugs and Chemical Substances

Drug use can result in drug-induced lupus erythematosus (DILE). The ANA titer is elevated, and the symptoms resemble those of clinical SLE. The immunological traits and clinical symptoms go away after stopping the medicine.[113]

I. Anti-arrhythmic Drugs. Procainamide is a classic drug that can induce SLE. Long-term use of procainamide can cause the production of antinuclear antibodies (ANA) in patients. The incidence rate of its inducing SLE is about 20%. Patients may experience symptoms such as fever, joint pain, rash, and pleurisy, which are similar to those of idiopathic SLE.[114] The mechanism may be related to the fact that the drug changes the structure of self-antigens or the immune regulatory function, resulting in an abnormal immune response of the immune system to self-tissues.

II. Antihypertensive Drugs. Additionally, hydralazine can cause a condition similar to SLE. Among patients using hydralazine, about 5-10% will be ANA positive, and some patients will subsequently develop clinical SLE.[115] By altering intracellular metabolic processes, altering DNA methylation patterns, exposing self-antigens, or altering immune cell function, hydralazine may disrupt immunological tolerance. A potential explanation for the pathophysiology of DILE may perhaps be the accelerated development of neutrophil extracellular traps (NET) brought on by procainamide and hydralazine.[116]

III. TNF-α Inhibitors. Studies have found that TNF-α inhibitors can induce ANA and ds-DNA during application, that is, they exhibit symptoms similar to those of lupus-like symptoms.[117] However, the impact they cause is only on the skin, joints, etc. throughout the body, rarely involving the central nervous system (CNS), kidneys, etc. And after drug withdrawal, the titer of relevant antibodies decreases and the symptoms disappear. Therefore, when judging the relationship between TNF-α inhibitors and DILE, careful consideration is required.[118]

3. Progress in Drug Research and Treatment

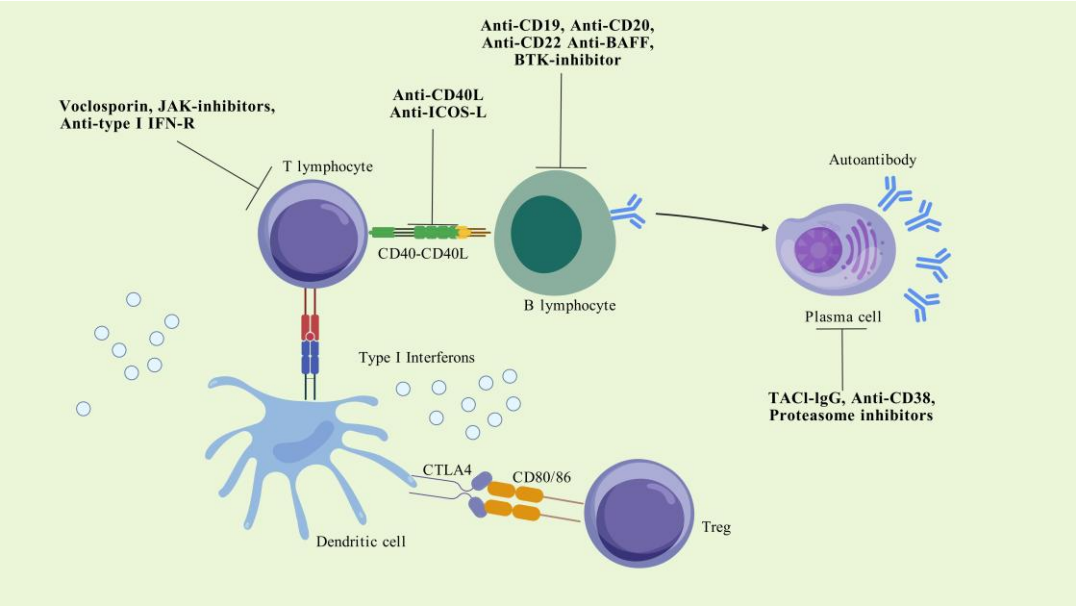

Figure 3. Therapeutic Targets for SLE: This figure illustrate several targets for the treatment of SLE. BDCA2: Blood Dendritic Cell Antigen 2; BTK: Bruton's Tyrosine Kinase; ICOS-L: Inducible T Cell

Costimulatory Ligand; JAK: Janus Kinase; TACI: Transmembrane Activator and Calcium Modulator and Cyclophilins Ligand Interactor; Type I IFN-R: Type I Interferon Receptor. Created with BioGDP.com.[17]

3.1 New Therapeutic Drugs and Progress

3.1.1 Targeting B Cells

(1) Monoclonal Antibodies Targeting BlyS (B Lymphocyte Stimulator). Belimumab suppresses BlyS, which lowers the body's autoimmune response and autoreactive B cell survival and differentiation.[119] Multiple clinical studies have shown that the combination of Belimumab with standard treatment can significantly reduce the disease activity of patients with SLE, decrease the dosage of hormones, and have good safety, especially for patients who do not respond well to traditional treatments.[120]

(2) Targeting BlyS and APRIL (A Proliferation-Inducing Ligand). Telitacicept is a fusion protein that more efficiently inhibits B cell activation and proliferation.[121] Telitacicept has demonstrated good efficacy in clinical trials, can greatly improve the patient's condition, and has a beneficial effect on lowering proteinuria, disease activity, and other symptoms, offering SLE patients a new therapy alternative.[122]

(3) Anti-CD22 Monoclonal Antibodies. Epratuzumab, a humanized monoclonal antibody that primarily targets CD22, binds to the extracellular segment of the CD22 molecule, causing CD22 to internalize and phosphorylate the intracellular segment. This inhibits BCR activation, suppresses B cell proliferation in SLE patients, and has an immunosuppressive effect by preventing the production of pro-inflammatory factors like IL-6 and TNF-α.[123]

(4) Anti-CD20 Monoclonal Antibodies. Rituximab, a human-mouse chimeric antibody that targets CD20, reduces CD20-positive B cells by complement-dependent cellular cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and other mechanisms.[124]

(5) Chimeric Antigen Receptor T Cell (CAR-T) Therapy. CAR-T therapy, as an emerging and powerful cellular immunotherapy, has shown potential application prospects in the field of SLE treatment.[125] CAR-T cells are constructed by recombining a single-chain antibody fragment (scFv) that recognizes tumor-associated antigens or autoimmune-related targets, a transmembrane region, and an intracellular signal activation domain (such as the CD3ζ chain, etc.) into a chimeric antigen receptor (CAR) through genetic engineering technology.[126] Then, the CAR gene is transduced into the patient's own T cells, enabling the T cells to acquire the ability to specifically recognize the target antigen. These modified CAR-T cells can identify and attach to the target cell's surface antigen after being reintroduced into the patient's body, which triggers the T cells' ability to kill the target cell.[127] The generation of autoantibodies and aberrant B cell activation are important pathogenic connections in SLE. As a result, B cell-related antigens are now among the primary targets of CAR-T treatment.**Error! Reference source not found.** The majority of mature B cells, for instance, express CD19 and CD20 on their surface. The treatment of SLE has drawn interest due to CAR-T cell therapy that targets CD19 or CD20.[128, 129] By depleting abnormally activated B cells, the production of autoantibodies can be reduced, thereby alleviating the symptoms of the disease.[130] Furthermore, certain other chemicals that are involved in immune cell activation or regulation are also being investigated. For instance, studies are also being conducted on cytokine receptors that are crucial for autoimmune reactions as targets for CAR-T treatment.[131] Besides directly killing target B cells, CAR-T cells also exert a series of regulatory effects on the immune system.[132] CAR-T cells have the ability to control the cytokine environment and influence the interaction between B cells and T cells during the therapy of SLE. For instance, by reducing the antigen presentation and co-stimulatory signals from B cells to T cells, the functional state of T cells can be adjusted, reducing the secretion of pro-inflammatory cytokines and increasing the production of anti-inflammatory cytokines, thereby reshaping the balance of the immune system.[131] Although CAR-T therapy has been widely applied in recent years, there are some adverse reactions, such as cytokine release syndrome (CRS) and neurotoxicity.[133] Among these are hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome

(MAS). A serious inflammatory, feverish, and cytopenia side effect of CAR-T cell therapy for hematological malignancies is called MAS/HLH.[134] In summary, CAR-T cell treatment has a wide range of potential applications in autoimmune illnesses, enabling patients to experience sustained drug-free remission. It still has a lot of obstacles to overcome, though.[135] First, the long-term safety of CAR-T therapy needs to be further evaluated, including the impact on the long-term function of the immune system and potential late-onset adverse reactions.[136] Second, future research will concentrate on how to better pick targets and optimize the design of the CAR structure to increase efficacy and decrease adverse responses.[137]

3.1.2 Targeting T Cells

Abatacept (ABA): A regulator of T cell costimulatory signals, is a fusion protein composed of cytotoxic T lymphocyte antigen-4 (CTLA-4) and the Fc segment of an IgG antibody. It selectively modulates CD80/CD86 required for the full activation of T cells, blocks the transmission of T cell costimulatory signals, inhibits T cell activation, and thereby suppresses inflammatory and immune responses.[138, 139]

3.1.3 Targeting Inflammatory Cytokines.

IL-6 Antagonists: Tocilizumab is a humanized anti-IL-6 receptor monoclonal antibody. It can competitively inhibit the binding of IL-6 to membrane-bound and soluble IL-6 receptors, thereby blocking IL-6-mediated signal transduction and suppressing downstream inflammatory reactions.[140]

IFN-α Receptor Antagonists: Anifrolumab is a monoclonal antibody that targets type I interferon receptor 1 (IFNAR1).[141] By binding to IFNAR1, it inhibits IFN-α-mediated immune responses by blocking the IFN-α signaling pathway.[142] In clinical studies, Anifrolumab significantly reduced the disease activity of patients with SLE, and it has been approved for the treatment of patients with moderate to severe SLE.[143]

3.1.4 Small Molecule Targeted Drugs.

JAK Inhibitors: The JAK-STAT signaling pathway plays a crucial role in the activation and proliferation of immune cells.[144] Tofacitinib and other JAK inhibitors have demonstrated some promise in studies on the management of SLE. By blocking this signaling route, they can lower inflammation and control immunological responses. Currently, some studies are exploring the optimal dosage and efficacy of their use in the treatment of SLE.[145]

BTK Inhibitors: Bruton's tyrosine kinase (BTK) plays an important role in the signal transduction of B cells.[146] BTK inhibitors are being studied for the treatment of SLE. Preliminary studies have shown that they can reduce the activation of B cells and the production of autoantibodies, and are expected to become new targeted drugs for treatment.[147]

Although emerging treatment methods such as CAR-T cell therapy and JAK inhibitors have brought new hope to patients with SLE, they also have significant limitations that cannot be ignored.[148] CAR-T cell therapy, which has achieved remarkable success in the treatment of some hematological malignancies, has also been explored as a potential treatment option for SLE.[149] However, its application in SLE faces several challenges. Firstly, the target antigens for CAR-T cell therapy in SLE are not as well-defined as in cancer. In SLE, the disease is caused by a complex immune dysregulation involving multiple cell types and pathways, making it difficult to identify a single, specific target antigen. The lack of a clear target antigen may lead to off-target effects, where the CAR T cells attack normal cells and tissues, causing severe side effects. Secondly, the cost of CAR-T cell therapy is extremely high. The process of manufacturing personalized CAR-T cells is complex and time-consuming, requiring advanced laboratory facilities and highly skilled personnel.[150] This high cost makes it inaccessible to many patients, especially those from low-income or resource-limited regions. Moreover, the long-term safety of CAR-T cell therapy in SLE is still uncertain.[151] Since the immune system of SLE patients is already dysregulated, the introduction of genetically modified T cells may disrupt the immune balance further and lead to unforeseen complications in the long run.[149] JAK inhibitors, which target the Janus kinase signaling pathway and can suppress the activation of multiple cytokines involved in the pathogenesis of SLE, have shown some therapeutic effects in clinical trials.[152] However, they also have several

limitations. One of the main concerns is the increased risk of infections. By inhibiting the JAK signaling pathway, these drugs can suppress the normal immune response, making patients more susceptible to various infections, including bacterial, viral, and fungal infections.[153] In some cases, these infections can be severe and even life-threatening. Another limitation is the potential for adverse effects on lipid metabolism and blood pressure. Long-term use of JAK inhibitors has been associated with an increase in lipid levels and blood pressure, which may increase the risk of cardiovascular diseases in SLE patients. Additionally, not all patients respond equally well to JAK inhibitors. Some patients may experience only a partial response or no response at all, and the factors that predict treatment response are not fully understood. This makes it difficult for clinicians to select the most appropriate patients for JAK inhibitor therapy.[154] In conclusion, while CAR-T cell therapy and JAK inhibitors represent promising emerging treatment options for SLE, their limitations need to be carefully considered. Further research is needed to address these challenges, improve the safety and efficacy of these therapies, and optimize their application in the treatment of SLE.

3.2 Drug Resistance and Relapse

In the long-term treatment of SLE, drug resistance and relapse are major challenges that seriously affect treatment effectiveness and patients' quality of life.[155] As patients receive various drug treatments over a long period of time, especially traditional immunosuppressants and some newly developed molecular drugs, immune cells in the body may gradually adapt and develop drug resistance mechanisms.[156] For instance, the continuous use of corticosteroids, which are commonly used in SLE treatment to suppress inflammation, often leads to drug resistance in many patients. Human cells can alter their signaling pathways in response to long-term corticosteroid exposure, reducing the drug's ability to bind to target receptors and exert its anti-inflammatory effects.[157] Similarly, for targeted drugs such as belimumab, although it has shown efficacy in reducing the number of autoreactive B cells, some patients may develop resistance over time.[119] This could be due to the emergence of alternative survival pathways in B cells that are not affected by BLyS blockade, allowing these autoreactive B cells to continue proliferating and producing autoantibodies. [158]

Relapse of SLE is another major obstacle in long-term disease management. Even after achieving remission through treatment, a significant proportion of patients still experience disease flares.[159] Due to the complex interplay of genetic, environmental, and immune factors in SLE, it is difficult to completely eliminate the underlying pathogenic mechanisms. Environmental factors such as stress, infection, and exposure to ultraviolet radiation can trigger the reactivation of the immune system, leading to symptom recurrence.[79] Additionally, the immune abnormalities in SLE patients, such as the persistent presence of autoreactive T cells and B cells, provide fertile ground for disease relapse. Even when the disease is in remission, these abnormal immune cells can be reactivated under certain conditions, initiating a new round of inflammation and tissue damage.[160, 161]

The challenges of drug resistance and relapse in SLE not only increase the physical and psychological burden on patients but also complicate the treatment process. Patients may need to switch to different medications or increase dosages, which can lead to more severe side effects.[162] Moreover, disease relapses can cause cumulative damage to various organs and tissues, gradually reducing the patient's quality of life and increasing the risk of death.[163] Therefore, addressing drug resistance and relapse is crucial for improving the long-term management of SLE. Future research should focus on understanding the mechanisms of drug resistance and relapse, developing new strategies to prevent or overcome these issues, and optimizing treatment regimens to achieve better long-term outcomes.

Table 1. Progress of targeted therapy for SLE

Category	Drug	Mechanism	Application
Glucocorticoid	Prednisone[166]	Prednisone can effectively inhibit the synthesis and release of various inflammatory mediators.	Prednisone can relieve skin damage, reduce joint inflammation, and also has a certain protective effect on the kidneys

			and other organs, reducing the deposition of immune complex in the kidneys.
	Methylprednisolone[167]	1 By inhibiting phospholipase A2 (PLA2), it reduces the production of inflammatory mediators. 2 Inhibit the production of various cytokines. 3 It has inhibitory effects on both T lymphocytes and B lymphocytes.	High-dose Methylprednisolone pulse therapy can rapidly control inflammation, save the patient's life, and maintain the function of vital organs.
Antimalarial drug	Hydroxychloroquine(HCQ)[168]	1 HCQ can alter the activity of lysosomal enzymes, inhibit cellular phagocytosis and antigen presentation, and reduce inflammatory responses. 2 HCQ can suppress the activation and proliferation of T lymphocytes, lower autoantibody levels, and mitigate autoimmune responses.	Hydroxychloroquine can alleviate joint inflammation and improve joint function in patients with SLE. It is used as an adjuvant therapy in combination with glucocorticoids and immunosuppressants for the treatment of lupus nephritis.
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Aspirin[169]	Cyclooxygenase (COX) catalyzes the conversion of arachidonic acid into inflammatory mediators, and aspirin irreversibly inhibits COX-1 and COX-2 and reduces prostaglandin synthesis, thereby reducing inflammatory response and pain.	Aspirin can be used in patients with mild SLE, especially when the symptoms are primarily related to joints and muscles.
	Ibuprofen[170]	Ibuprofen inhibits both COX-1 and COX-2, reducing the production of inflammatory mediators. Its action is relatively selective, and it stimulates the gastrointestinal tract less than some other non-steroidal anti-inflammatory drugs.	Ibuprofen is suitable for SLE patients with low-grade fever, and mild to moderate joint and muscle pain.
Immunosuppressant	Cyclophosphamide[171]	1 In the cell cycle, cyclophosphamide can inhibit lymphocytes from entering the S phase from the G1 phase, thereby blocking lymphocyte proliferation. 2 Additionally, cyclophosphamide can reduce the accumulation of inflammatory cells at the site of inflammation.	1 In the treatment of lupus nephritis, the combination of cyclophosphamide and glucocorticoids can significantly improve patients' renal survival rate and long-term survival rate. 2 For neuropsychiatric lupus, it can alleviate inflammatory reactions in the brain and improve patients' psychiatric symptoms and neurological functions.
	Mycophenolate mofetil[172]	1 Mycophenolate mofetil can reduce lymphocyte proliferation and decrease the production of autoantibodies. 2 Mycophenolate mofetil can	1 Mycophenolate mofetil can reduce proteinuria and improve renal function in patients with lupus nephritis. 2 It can alleviate symptoms such as skin erythema and scaling in patients with

		inhibit the aggregation of inflammatory cells at the site of inflammation and reduce the release of inflammatory cytokines.	skin involvement. 3 Mycophenolate mofetil can reduce the destruction of blood cells by autoimmune reactions and increase blood cell counts.
	Azathioprine[173]	Azathioprine is metabolized in the body as 6-mercaptopurine (6-MP). 6-MP inhibits key enzymes in purine synthesis, thereby interfering with DNA and RNA synthesis. This interference with nucleic acid synthesis leads to inhibition of lymphocyte proliferation.	1 Azathioprine combined with glucocorticoids can effectively improve the condition of patients with lupus nephritis. 2 It can reduce the destruction of blood cells by autoimmune reactions. 3 Azathioprine can alleviate cerebral inflammatory reactions to a certain extent.
Monoclonal antibody targeting BlyS (B Lymphocyte Stimulator)	Belimumab[119, 120]	Belimumab inhibits BLyS, reduces the survival and differentiation of autoreactive B cells, and decreases autoimmune responses.	Belimumab has been approved by the Food and Drug Administration (FDA) and The Center for Drug Evaluation of the National Medical Products Administration of China (CDE).
Monoclonal antibody targeted against BlyS and APRIL.	Telitacicept[121]	Telitacicept blocks the activation and proliferation of B cells.	CDE has approved telitacicept for the treatment of SLE patients with a score of 8 or above.
Anti-CD22 monoclonal antibody	Epratuzumab[123]	Epratuzumab inhibits the activation of BCR, suppresses the proliferation of B cells, and inhibit pro-inflammatory factors.	Epratuzumab failed to replicate the success of Phase II in Phase III clinical trials.
Anti-CD20 monoclonal antibody	Rituximab[124]	Rituximab depletes CD20-positive B cells through antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and other mechanisms.	Rituximab is often used in combination with other medications such as glucocorticoids and immunosuppressants for the treatment of SLE, reducing the dosage and adverse reactions of single drugs.
Therapeutic drugs targeting CD19/CD20/BCMA(CAR-T)	Remegen Olunxian Injection[125-127]	Remegen Olunxian Injection achieves deep depletion of B cells by precisely targeting the CD19 antigen on the surface of B cells, thereby reducing autoimmune responses and improving patients' symptoms.	Clinical trials in Chinese adult patients with active SLE have shown that Remegen Olunxian Injection can help patients achieve a state of low disease activity, with continued improvement in disease activity and clinical symptoms.
T-cell costimulatory signal modulator	Abatacept (ABA) [138, 139]	Abatacept regulates CD80/CD86, blocks the transmission of T cell co-stimulatory signals, and inhibits T cell activation.	There have been no clinical trials conducted domestically, but an evaluation of the efficacy and safety of ABA treatment was conducted in Madrid, Spain. The results demonstrated that ABA has a significant improving effect on lupus disease activity.

IL-6 antagonist	Tocilizumab[140]	Tocilizumab competitively inhibits the binding of IL-6 to both membrane-bound and soluble IL-6 receptors, thereby blocking IL-6-mediated signal transduction and inflammatory responses.	The results of Phase I clinical trials showed that after treatment with Tocilizumab, there was a significant improvement in disease activity and a dose-related decrease in absolute neutrophil count.
IFN-α receptor antagonist	Anifrolumab[141-143]	Anifrolumab binds to IFNAR1, blocking the IFN-α signaling pathway and inhibiting IFN-α-mediated immune responses.	CDE has approved the clinical trial application for anifrolumab injection, intended for the development and use in moderate to severe active SLE.
JAK inhibitor	Tofacitinib[144]	Tofacitinib inhibits JAK1, JAK3, and tyrosine kinase 2 (TYK2).	Tofacitinib has been used clinically to treat SLE and has shown certain efficacy and safety, and it has certain advantages in treating joint pain related to SLE.
	Baricitinib[174]	Baricitinib is a selective JAK1 and JAK2 inhibitor.	Baricitinib, when combined with other medications (such as glucocorticoids), may improve patients' disease activity, but more large-scale clinical trials are needed to clarify its long-term efficacy and safety.
BTK inhibitor	Ibrutinib[175]	BTK inhibitors reduce the activation of B cells and the production of autoantibodies.	In human clinical trials of Ibrutinib, small-scale studies have shown that some patients experienced a reduction in disease activity after treatment. However, some safety issues have arisen during the clinical trials.
	Fenebrutinib[146, 147]		In Phase II clinical trials, Fenebrutinib did not achieve a statistically significant difference in efficacy compared to the placebo group, but it demonstrated significant pharmacodynamic effects and had acceptable safety.

4 Conclusions

SLE is an autoimmune illness, and its exact pathophysiology is yet unknown.[164] The ratios of several T lymphocyte subsets, including Th1/Th2 and Th17/Treg, are unbalanced in SLE patients due to genetic, environmental, and medication variables. Immune complexes are deposited, B cells are overactivated, and pro-inflammatory cytokines such IL-6, IL-12, IL-17, TNF-α and IFN-γ are present in higher concentrations.[47] Additionally, SLE treatment medications are always changing. The advancement of science has given patients greater hope, as evidenced by the substantial advancements made in improving efficacy and lowering adverse reactions in both new and traditional medications with severe side effects.[165] In order to enhance the long-term prognosis of patients and lower treatment costs so that more patients can benefit, more research is still required to refine the new drug's treatment regimen. Comprehensive studies of the pathophysiology of SLE will continue to spur the creative creation of medicinal medications in the future.

Author Contributions: Conceptualization, S.L., M.N., W.J. and C.Q.; investigations, M.N., P.Z., J.B., Z.M. and H.D.; writing—original draft preparation, S.L. M.N. and W.J.; writing—review and editing, S.L. and C.Q.; project administration, S.L. and C.Q.; funding acquisition, S.L., W.J. and

C.Q. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Open project of Jiangsu Key Laboratory of Laboratory Medicine (JSKLM-Y-2024-002), the Science and Technology Project of Changzhou Health Committee for Young Talents (QN202204), Changzhou sci & Tech program (CJ20235020), State Key Laboratory of Analytical Chemistry for Life Science (SKLACLS2315), the Natural Science Foundation of the Jiangsu Higher Education Institution of China (22KJB150019).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created, or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

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