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Pathological Mechanism and Targeted Drugs of Systemic Lupus Erythematosus

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Abstract. The abnormal activation of immune system leads to a chronic immune-mediated disease called systemic lupus erythematosus (SLE) in general that attacks the organs of human. In the past, clinical practice often involved treatment with glucocorticoids combined with immunosuppressants. However, many patients still fail to achieve a state of low lupus disease activity (LLDAS) and are also plagued by adverse reactions such as osteoporosis, infections, and premature ovarian failure. Therefore, there is an urgent need for safer treatment regimens with fewer side effects. In recent years, with the development of knowledge into the pathology of SLE, phenomena such as aberrant B cell activation and deregulation of type I interferon (IFN-α) have been observed., providing directions for targeted therapy. Through comparative literature analysis, this article reviews the latest progress in mechanism-related studies involving B cells and IFN-α in SLE, as well as the research and development of targeted drugs. It covers aspects such as B cell-targeted therapy (e.g., telitacicept), IFN-α blockade (e.g., anifrolumab), JAK inhibition (e.g., baricitinib), and IL-6 receptor antagonism (e.g., tocilizumab). It summarizes the mechanisms of action, treatment strategies, clinical applications, and limitations of various new targeted drugs, aiming to provide a reference for personalized management and treatment strategies for SLE.

Keywords: SLE, pathogenesis, targeted therapy, immunology

1. Introduction

Systemic lupus erythematosus is a significantly varied chronic immune-mediated condition in which immune system is abnormally activated, which results in the body's own organs being attacked, resulting in inflammation and dysfunction across multiple organ systems [1]. In the past, glucocorticoids combined with immunosuppressants were often used to treat the disease [1]. However, numerous people continue to be unable to attain the low disease activity state in lupus despite medication and are still correlated with adverse symptoms such as osteoporosis, infections, and premature ovarian failure. Therefore, a safer therapy alternative with fewer side effects is required.

Recently, detailed research regarding the pathogenesis of systemic lupus erythematosus have shown features such as disruption of IFN-α and aberrant B cell activation, providing potential directions for targeted therapy. Study has demonstrated that aberrant B cell activation results in an

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increase in memory cells and plasmablasts as well as aberrant inflammatory cytokine release, and excessive production of pathogenic autoantibodies [1]. Furthermore, in cases of IFN-α dysregulation, it affects patients' epigenetics and various immune cell functions [2]. By investigating targeted therapies for B cells and class I interferons, we expect to provide more targeted and personalized treatment plans for SLE, reduce side effects, and improve patients' long-term prognosis. This review provides an overview of articles related to mechanisms involving B cells and α interferons in SLE, along with recent research progress in targeted drug development. It uses comparative literature analysis to summarize the mechanisms, therapeutic strategies, clinical utility, and limitations of various new targeted drugs, aiming to provide references for personalized management and treatment strategies for SLE.

2. Pathogenesis of SLE

2.1. Genetic and environmental triggers

SLE arises from the interplay of genetic variants and environmental factors. More than 150 SLE-associated variations were found across ethnic groups by genome-wide association studies (GWAS), mostly seen in regulatory areas as opposed to coding ones. These variants affect pathways including type I interferon signaling, T/B lymphocyte activation and differentiation, and antigen presentation. Patients of African and European descent with SLE commonly carry combinations of HLA risk alleles (e.g., DR2, DR3), which enhance antigen presentation, disrupt immune tolerance, and activate autoimmunity [3]. Additionally, APOL1 gene variants in individuals of African descent may exacerbate immune dysregulation, which increases lupus nephritis risk [3]. Monogenic and oligogenic variants are more frequent in childhood SLE, often exhibiting higher pathogenicity. These variants are frequently associated with nuclease defects and complement deficiencies, which activate the IFN-α pathway and indirectly stimulate the immune system [4]. UV radiation and viral infections, such as Epstein-Barr Virus (EBV) DNA, are examples of environmental triggers, both of which are capable of inducing the IFN-α pathway via Toll-like receptor (TLR) activation. Drugs like isoniazid and procainamide can inhibit DNA methylation or induce neutrophil extracellular trap (NET) release. Chemical exposures (e.g., mercury, pesticides) stimulate aryl hydrocarbon receptor (AHR) signaling, which contributes to immune dysregulation and SLE development [4].

2.2. Immune system dysregulation

Immunological dysregulation in SLE includes abnormal activation of the adaptive and innate immune systems. A key feature in SLE pathogenesis is hyperactivation within the type I IFN signaling pathway. Massive IFN-α production results from RNA/DNA immune complexes activating plasmacytoid dendritic cells (pDCs) by intracellularly engaging TLR7/TLR9. B-cell development into plasma cells is encouraged by IFN-α, which upregulates antigen-presenting molecules, and establishes an IFN signature, and sustains immune system activation. Furthermore, SLE patients exhibit increased Neutrophil Extracellular Traps (NETs) formation by neutrophils with a decreased cleaning ability, which results in persistent immune stimulation [4]. In adaptive immunity, abnormal T and B cells functions are closely linked. Increased numbers of peripheral and follicular helper T cells further boost B-cell differentiation. B-cell clonal expansion is widespread, with double-negative and age-associated B cells critically involved. These B-cell subsets can be activated by TLR7/IFN-α signaling, differentiating into plasma cells and creating positive feedback loops with TLR7/TLR9 pathway activation [4].

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2.3. Pathogenic consequences

SLE pathogenesis is primarily driven by autoantibodies and immune complexes. Antinuclear antibodies (e.g., anti-dsDNA) bind to self-nucleic acids and deposit in tissues, triggering localized inflammation. NETs promote IL-33 (an IL-1 family cytokine) expression and exacerbate vasculitis. IFN-α activates glial cells and disrupts the blood-brain barrier, which contributes to neurological manifestations like epilepsy and cognitive impairment [4].

3. Targeted therapies of SLE

3.1. B-cell targeted therapies

Telitacicept, a fusion protein, targets both a ligand that induces proliferation and a factor that activates B cells. By blocking their binding to receptors (TACI, BCMA) on B cells, telitacicept reduces autoantibody production. It was approved in China in 2021 for treating SLE [5]. 249 individuals took part in a placebo-controlled, randomized, double-blind trial, and telitacicept (subcutaneously administered at doses of 80, 160, or 240 mg per week) in addition to conventional treatment was assessed. At week 48, patients receiving the corresponding telitacicept dosages had SRI-4 response rates of 71.0%, 68.3%, and 75.8%, versus 33.9% for those receiving placebo (all $p<0.001$). When telitacicept was compared to a placebo, it was also shown to decrease glucocorticoid usage and disease activity. Telitacicept had a safety profile comparable to that of a placebo, even if upper respiratory tract infections and injection site responses occurred. While effective, infection monitoring is warranted during telitacicept treatment.

3.2. IFN- α- targeted therapies

A completely human monoclonal antibody called anifrolumab prevents IFN-α from attaching to type I interferon receptor subunit 1 (IFNAR1), which is used to prevent downstream signaling and aberrant immune activation [6]. For 52 weeks, as part of the phase III TULIP-2 clinical trial, patients were randomized to undergo treatment with intravenous anifrolumab (300 mg) or placebo, delivered every four weeks. In comparison to the placebo group (32%), the anifrolumab group (48%) achieved the BICLA response ($P=0.001$) [7]. Anifrolumab also reduced skin disease severity and glucocorticoid doses. Safety data showed higher rates of bronchitis, herpes zoster, infusion reactions, upper respiratory tract infections, also including nasopharyngitis with anifrolumab versus placebo, whereas serious adverse event rates did not diverse significantly [6]. Patients with notable interferon-driven illness characteristics may benefit from early IFN signaling targeting.

3.3. JAK inhibitors

Baricitinib selectively inhibits Janus kinase 1/2, by inhibiting the signaling pathways of various pro-inflammatory cytokines, including type I interferons, implicated in SLE. During a 24-week worldwide phase II research, individuals with active SLE were randomly assigned baricitinib with 2 mg / 4 mg once daily, or a placebo added to standard therapy. By week 24, a greater percentage of patients in the 4-mg group attained an SLE Responder Index-4 response (64% vs 48%) and also remission in arthritis and rash (67% vs 53%) relative to the placebo group (both $P<0.05$) [8]. All groups had similar rates of adverse events, though the baricitinib treatment arms had a slightly increased risk of serious adverse events (SAEs); no deaths occurred. However, the results from the SLE-BRAVE studies did not demonstrate statistically significant benefits in SRI-4 over placebo [9].

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These findings suggest baricitinib may offer clinical benefits, particularly for cutaneous and musculoskeletal involvement, but efficacy may vary.

3.4. Other emerging targets

A chimeric monoclonal antibody called tocilizumab targets the interleukin-6 receptor, which is used to block IL-6-mediated inflammatory signaling relevant to SLE. 16 mild-to-moderate SLE patients were included in phase I open-label dose-escalation research in which they received intravenous tocilizumab with dosages of 2, 4, or 8 mg/kg every two weeks within 12 weeks, followed by an 8-week observation period. Dose-dependent reductions in absolute neutrophil counts occurred (median reductions: at 4 mg/kg, 38% and 8 mg/kg, 56%), with normalization of counts post-treatment [10]. Eight of fifteen evaluable patients achieved a ≥4-point decrease in modified SELENA-SLEDAI scores. Arthritis resolved or improved in all seven baseline cases. Both anti-dsDNA antibody levels and circulating plasma cell frequencies decreased by a median of 47%. Infusions were generally well-tolerated, with one withdrawal due to neutropenia and infections reported in 11 patients (not directly linked to neutropenia). These data suggest targeting IL-6 signaling can modulate autoantibody production and inflammation, however, still needs close monitoring.

4. Future perspectives

Recent insights into SLE pathogenesis have spurred the development of targeted therapies—including BAFF/APRIL blockade, IFN-α signaling inhibition, JAK pathway modulation, and IL-6 receptor antagonism—distinct from traditional immunosuppressants. While agents like belimumab and anifrolumab are approved, diverse clinical responses highlight the unmet need to move beyond conventional serologic markers towards advanced biomarkers (e.g., myxovirus resistance protein (MX1), reflecting type I interferon pathway activity). JAK inhibitors and IL-6 blockade offer additional options, particularly for patient refractory to standard therapies in cutaneous or musculoskeletal domains, though experience is largely limited to case series with scarce long-term safety data. Future research should prioritize combination strategies targeting multiple immune pathways, integrate pharmacogenomics for personalized dosing (precision medicine), and implement early intervention to prevent irreversible organ damage.

5. Conclusion

Systemic lupus erythematosus (SLE) treatment currently faces notable challenges, as traditional immunosuppressants often fail to achieve durable disease control and are accompanied by significant safety concerns, such as osteoporosis, infections, and premature ovarian failure, with many patients unable to reach a low disease activity state. Moreover, the heterogeneity in clinical responses further complicates effective management. The complexity and variability of the disease significantly increase the difficulty of treatment. Among the many organs and systems that systemic lupus erythematosus can affect are the kidneys, skin, cardiovascular, and neurological system. There are huge differences in symptom manifestations and the severity of organ involvement among different patients. However, advancements in targeted therapies have yielded substantial progress. B-cell targeted therapies, such as telitacicept, which blocks BAFF and APRIL to reduce autoantibody production, and IFN-α-targeted therapies like anifrolumab, which inhibits downstream signaling and aberrant immune activation, have emerged as effective options, with some already approved for clinical use. Additionally, JAK inhibitors like baricitinib, which block multiple pro-

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inflammatory cytokine pathways, and IL-6 receptor antagonists such as tocilizumab, which modulate autoantibody production and inflammation, have shown promise in addressing specific manifestations of the disease. These targeted approaches have brought positive impacts by providing safer alternatives with fewer side effects compared to traditional treatments, enabling more precise disease management, reducing reliance on glucocorticoids, and improving patients' long-term prognosis. Looking ahead, the development of targeted drugs for SLE will focus on personalized, biomarker-guided strategies to address the heterogeneity in clinical responses, moving beyond conventional serologic markers to advanced ones that reflect specific pathway activities. Combination regimens targeting multiple immune pathways and precision dosing strategies will also be prioritized to enhance therapeutic efficacy while minimizing toxicity, along with early intervention to prevent irreversible organ damage, ultimately aiming to provide more effective and tailored treatments for SLE patients.

References

[1] Dan Q, and You S. (2024) Current status of B-cell targeted therapy in systemic lupus erythematosus. Chin J New Drugs. 33, 785-791.
[2] Li J, Gao Q, and Shi H.(2025) The role of interferon-alpha in systemic lupus erythematosus and the progress of drug therapy. Clin Med J. 23, 13-17.
[3] Armstrong DL, Zidovetzki R, Alarcón-Riquelme ME, Tsao BP, Criswell LA, Kimberly RP, Harley JB, Sivils KL, Vyse TJ, Gaffney PM, Langefeld CD, and Jacob CO.(2014) GWAS identifies novel SLE susceptibility genes and explains the association of the HLA region. Genes Immun. 15, 347-354.
[4] Crow MK. (2023) Pathogenesis of systemic lupus erythematosus: Risks, mechanisms and therapeutic targets. Ann Rheum Dis. 82, 999-1012.
[5] Liu B, Zhao Y, Liu D, Li X, Ma Z and Yang Q. (2024) The Latest Progress in the Application of Telitacicept in Autoimmune Diseases. Drug Des Devel Ther. 18, 5811-5825.
[6] Loncharich MF and Robertson I. (2023) Anifrolumab in systemic lupus erythematosus. Drugs Today (Barc). 59(2), 53-61.
[7] Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, Bae S-C, Brohawn PZ, Pineda L, Berglind A and Tummala R; TULIP-2 Trial Investigators. (2019) Trial of Anifrolumab in Active Systemic Lupus Erythematosus. N Engl J Med. 382, 211-221.
[8] Wallace DJ, Furie RA, Tanaka Y, Kalunian KC, Mosca M, Petri MA, Dörner T, Cardiel MH, Bruce IN, Gomez E, Carmack T, DeLozier AM, Janes JM, Linnik MD, de Bono S, Silk ME and Hoffman RW.(2018) Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet. 392, 222-231.
[9] Yin J, Hou Y, Wang C and Qin C. (2025) Clinical outcomes of baricitinib in patients with systemic lupus erythematosus: Pooled analysis of SLE-BRAVE-I and SLE-BRAVE-II trials. PLoS One. 20, e0320179.
[10] Illei GG, Shirota Y, Yarboro CH, Daruwalla J, Tackey E, Takada K, Fleisher T, Balow JE and Lipsky PE. (2010) Tocilizumab in systemic lupus erythematosus: Data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum. 62, 542-552.