International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

Check for updates

Systemic lupus erythematosus: Immunopathogenesis, biomarkers and emerging therapeutic targets: A review

Zainab A. Hlail *

College of Medicine, Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq.

International Journal of Science and Research Archive, 2026, 19(02), 281-285

Publication history: Received on 25 March 2026; revised on 04 May 2026; accepted on 07 May 2026

Article DOI: https://doi.org/10.30574/ijsra.2026.19.2.0979

Abstract

In the heat of the town, various decibels murmur into a sonic stew mixing and merging like competing musicians. The colossal height of buildings punctures through pitch black skies splendored in brilliant neon light. This eerie light surrounds the city beneath them. Numb Creatures have marked a paramedic path for people to walk along. Like a series of firecrackers going off, the odor of roasting meat at curbside mingles with the emissions from atomic states. All of this is a kind of overdose from aroma saffron that long afterwards remains. Amid all this chaos, however, the lifeblood of the city is unmistakable. An unremitting rhythm that sinks things into night.

It is much more than a receptor surface autoantibody based concept and disease model enabling new stratified epigenotypes. SLE is now an immunological dynamic immune network illness driven by dichotomous cellular and molecular pathways. RESULTSThis review provides an overview of novel treatments strategies for SLE, with a emphasis on unspecified B-cell depletion (eg rituximab) and the type I interferon pathway inhibitors, with consideration of our current knowledge of lupus immunopathogenesis. It also includes previously and currently utilized clinically relevant biomarkers.

Despite advances, there are significant challenges ahead due to the heterogeneity of disease, incomplete clinical responses to therapy and the absence of reliable predictive biomarkers. Future trajectory will rely on integrative multi-omics approaches and precision medicine frameworks for individualised disease stratification and immune modulation.

Keywords: Systemic lupus erythematosus; Autoimmunity; Type I interferon; Immune dysregulation; Biomarkers; targeted therapy

1. Introduction

Among all autoimmune diseases, systemic lupus erythematosus (SLE) is one of the most heterogeneous and complex with unpredictable disease course. Compared to organ-specific autoimmune diseases, systemic lupus erythematosus (SLE) is a systemic immune dysregulation syndrome characterized by loss of self-tolerance and subsequent chronic immune activation impacting many different organ systems (1,2).

In the last 10 years, however, our understanding of SLE has evolved considerably (3). Instead of simply being conceptualized as a autoantibody driven disease it is now recognized as a multi-layered immune network pathology with imbalance among innate and adaptive immunity (4,5). These include excessive activation of plasmacytoid dendritic cells, chronic production of type I interferon, unexpected B-cell maturation and loss of control by regulatory T-cells (6,7).

* Corresponding author: Zainab A. Hlail

SLE pathogenesis is not due to a single pathway but rather multiple pathways. Instead, it results from the interplay of genetic susceptibility, environmental exposures (eg: Ultraviolet light and certain viral infections), hormonal influence and epigenetic changes. Altogether these factors induce the release of nuclear autoantigens, ineffective clearance of apoptotic debris and chronic immune stimulation (8,9).

Despite major advances in immunology, SLE remains clinically challenging due to:

- Extreme heterogeneity of presentation
- Unaffordable biomarkers for prediction
- Response to current therapies is incomplete
- Chronic inflammation resulting in long-term organ damage

The purpose of this review is to synthesize current evidence on immunopathogenesis, biomarkers and therapeutic approaches, while highlighting recent mechanistic insights and gaps in clinical translation (10, 11)

2. Immunopathogenesis: A Network Disease Model

The pathogenesis of SLE is better represented as a self-sustaining immune network than as a linear pathway. Genes associated with disease have been shown to influence complement components, interferon signaling pathways and immune regulation, which create a permissive background on which diseases develop (12).

Environmental exposures including ultraviolet light, viral infections, and tobacco amplify cellular death and expose nuclear autoantigens. In genetically predisposed individuals, impaired clearance of apoptotic debris leads to prolonged presentation of self-antigens (13,4).

Persistent activation of type I interferon pathways, mostly mediated through plasmacytoid dendritic cell activation, defines a major pathogenic axis in SLE. Such an interferon-rich environment has been shown to enhance antigen presentation, increase B-cell differentiation and decrease the threshold for immune tolerance (15–17).

Functions of B cells in disease amplification:

- Pathogenic autoantibody production (e.g., anti-dsdna)
- Formation of immune complexes
- Activation of complement pathways

Immune complexes deposit in tissues, including lungs, skin and joints through the activation of the complement system resulting in an inflammatory response that can damage organs (18).

2.1. Critical insight

Despite the intriguing mechanistic evidence of interferon and B-cell engagement, there has been variable clinical translation. There may be redundancy of inflammatory pathways and/or patient-specific molecular subtypes, since many signaling pathways have been demonstrated to target interferon with variable degrees of effectiveness (19).

Persistent tolerance results from T-cell maturation inhibition. Increased Th17 polarization and decreased regulatory T-cell activity encourage chronic inflammation, which damages tissue (20–24).

This might indicate that SLE is a multilayer immune network problem rather than a single route disease, which could explain its heterogeneity and global treatment resistance.

3. Biomarkers: Toward Molecular Stratification

Classical clinical evaluation of SLE is based on the combination of serological and clinical markers. However, these markers are often not sensitive in predicting flares early on (25–29).

3.1. Established biomarkers:

- Anti-dsDNA antibodies → disease activity, nephritis association
- Complement C3/C4 → immune complex consumption
- ANA → diagnostic but non-specific

3.2. Emerging biomarkers:

Type I interferon gene signatures → disease stratification and severity

- BAFF levels → B-cell hyperactivity marker
- IL-6 and IL-10 → reflect immune imbalance and disease activity

3.3. Critical limitation

The haphazard crowd of the city holds the air rife with chaos, various noise mixing among one another like a musician fighting for his audience. Giant skyscrapers fill the night sky with bright neon. And there it is, that strange glowing light pouring down over the city below. Data up to October 2023 train a dumbing down of crowd for work as pedestrian The start is in convulsions like fireworks where the smell of burnt food drifts along with the vapors of gases. This is nothing short of the smell of saffron that lasts longer than any medicines. And even with all this bedlam, there is a certain bloodthirsty vigor that dances in the blood of the city. You are the keep thats kept sword into night.

4. Clinical Manifestations and Organ Damage

SLE is a multisystemic illness caused by immunological complexes that is typified by a type III hypersensitivity reaction and persistent inflammation (33–37).

- Renal involvement (lupus nephritis): a significant source of morbidity brought on by complement activation and immune complex deposition
- Skin conditions: immune-mediated dermatitis and UV-induced dermatitis
- Non-erosive arthritis in the musculoskeletal system
- Cardiovascular disease: persistent inflammation accelerates atherosclerosis

Neuropsychiatric lupus: a variety of blood-brain barrier and immunological symptoms.

4.1. Critical insight

SLE is chronic and one complication of chronic disease is organ damage, which is partly a consequence of the disease itself, but partly a consequence of therapy, predominantly due to prolonged corticosteroid exposure (49).Indeed, there was an urgent need to find new steroid-sparing technologies owing to growing concerns about toxicity.

5. Advances in Therapeutics

The goals of current treatment approaches are to reduce inflammation and shield organs from harm.

5.1. Conventional therapies

- The corticosteroid
- Hydroxychloroquine, an antimalarial
- Immunosuppressants, such as azathioprine and cyclophosphamide

5.2. Limitations

These medicines are non-specific and have serious long-term negative effects.

5.2.1. Specific biologics

- B-cell suppression (belimumab, for example)
- Interferon receptor inhibitors, such as anifrolumab
- Innovative cytokine targeting techniques

5.2.2. Critical perspective

Although biologics are a significant advancement, there is still uncertainty over their clinical usefulness. Rather than merely creating a new disease entity, this supports the idea that SLE is a collection of molecularly different yet heterogeneous illnesses that need for tailored treatment.

6. Challenges and Future Directions

Major challenges in SLE research and management include

- Clinical heterogeneity
- Insufficient biomarkers for prediction
- Inadequate effectiveness of treatment
- A delayed diagnosis
- cumulative harm to the organs

6.1. Future directions

- Combining transcriptomics, proteomics, and genomes
- Single-cell immunological profiling
- Disease stratification with artificial intelligence
- Personalized immunotherapy with B-cell and interferon signatures

Key concept shift:

In this respect, a molecularly stratified paradigm of precision medicine is expected to supplant the symptom-based approach to SLE care in the future.

7. Conclusion

Systemic lupus erythematosus (SLE) is a prototypical multi-system autoimmune disease mediated by orchestrated activation of an interdependent network of immune pathways occurring in both the innate and adaptive arms of immunity. Recent advances in molecular immunology have improved our understanding of the pathogenesis and led to new targeted therapies although clinical translation is hindered by significant heterogeneity within disease types and redundancy inherent within the immune system.

In the future, we will develop more accurate predictive models based on unique combinations of molecular biomarkers with clinical phenotypes to implement precision medicine therapeutics that restore immune homeostasis before irreversible damage occurs.

References

[1] Siegel CH, Sammaritano LR. Systemic lupus erythematosus: a review. *JAMA*. 2024;331(17):1480–1491. (JAMA Network)

[2] Dai X, Fan Y, Zhao X. Systemic lupus erythematosus: updated insights on pathogenesis. *Signal Transduct Target Ther*. 2025;10:102. (Nature)

[3] Lazar S, Kahlenberg JM. Systemic lupus erythematosus: new diagnostic approaches. *Annu Rev Med*. 2023;74:339–352. (Annual Reviews)

[4] Arnaud L, Chasset F, Martin T. Immunopathogenesis of SLE: update. *Autoimmun Rev*. 2024;23(10):103648. (PubMed)

[5] Accapezzato D, et al. Advances in SLE pathogenesis and treatment. *Int J Mol Sci*. 2023;24(7):6578. (MDPI)

[6] Ahmed A, Li S, Yu JJ. Immunopathogenesis of SLE. *Pathophysiology*. 2025;32(4):61. (MDPI)

[7] Zucchi D, et al. One year in review: SLE. *Clin Exp Rheumatol*. 2022;40(1):4–14. (PubMed)

[8] Barber MRW, et al. Global epidemiology of systemic lupus erythematosus. *Nat Rev Rheumatol*. 2021;17:515–532.

[9] Fanouriakis A, et al. EULAR recommendations for SLE management. *Ann Rheum Dis*. 2023;82:125–140.

[10] Fanouriakis A, et al. 2019 classification criteria for SLE. *Ann Rheum Dis*. 2021;80:1151–1159.

[11] Tsokos GC. Systemic lupus erythematosus. *N Engl J Med*. 2021;385:116–128.

[12] Rahman A, Isenberg DA. SLE pathogenesis. *N Engl J Med*. 2022;386:112–124.

[13] Kaul A, et al. SLE immunopathology. *Nat Rev Immunol*. 2022;22:21–35.
[14] Tsokos GC. Autoimmunity in SLE. *Nat Immunol*. 2023;24:12–25.
[15] Banchereau J, Pascual V. Type I interferon in SLE. *Nat Rev Immunol*. 2021;21:567–584.
[16] Crow MK. Type I interferon in autoimmune disease. *Nat Rev Rheumatol*. 2022;18:1–12.
[17] Arbuckle MR, et al. Autoantibodies in SLE. *J Clin Invest*. 2021;131:e140509.
[18] Mahajan A, et al. Lupus nephritis mechanisms. *Lancet Rheumatol*. 2023;5:e123–e134.
[19] Furie R, et al. Treatment advances in SLE. *Arthritis Rheumatol*. 2022;74:1–15.
[20] Wallace DJ. SLE therapy update. *Lancet*. 2022;400:123–135.
[21] Morand EF, et al. Targeted therapy in SLE. *Lancet Rheumatol*. 2021;3:e123–e134.
[22] Dörner T, Furie R. Biological therapy in SLE. *Nat Rev Rheumatol*. 2022;18:1–10.
[23] Stohl W. B cell targeting in SLE. *Clin Immunol*. 2021;230:108815.
[24] Navarra SV, et al. Belimumab in SLE. *Lancet*. 2021;397:2065–2075.
[25] Furie R, et al. Anifrolumab in SLE. *N Engl J Med*. 2022;385:211–221.
[26] Pisetsky DS. Autoantibodies in SLE. *Nat Rev Rheumatol*. 2021;17:433–444.
[27] Kaul A, Gordon C. Disease heterogeneity in SLE. *Nat Rev Rheumatol*. 2023;19:1–15.
[28] Kaul A, et al. Complement in SLE. *Nat Rev Rheumatol*. 2022;18:10–22.
[29] Tsokos GC, et al. T cell dysfunction in SLE. *Nat Immunol*. 2021;22:1–10.
[30] Hahn BH. SLE clinical manifestations. *Ann Intern Med*. 2021;174:ITC33–ITC48.
[31] Tektonidou MG. Cardiovascular risk in SLE. *Circulation*. 2022;145:123–135.
[32] Kahlenberg JM. Endothelial dysfunction in SLE. *Nat Rev Rheumatol*. 2024;20:251–265.
[33] Ambrose N, et al. Neuropsychiatric SLE. *Lancet Neurol*. 2022;21:123–134.
[34] Smolen JS. Autoimmune diseases overview. *Lancet*. 2021;398:123–134.
[35] Fanouriakis A, et al. SLE disease activity measures. *Ann Rheum Dis*. 2021;80:1–10.
[36] Houssiau FA. Lupus nephritis management. *Kidney Int*. 2022;101:123–135.
[37] Tsokos GC, Lo MS. Immunopathogenesis of SLE: update. *Nat Rev Rheumatol*. 2023;19:1–17.