MINI-REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Zinc Finger Proteins and the Risk of Systemic Lupus Erythromatosus

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Received: 18. 6. 2025

Revised: 7. 7. 2025

Accepted: 10. 7. 2025

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by autoantibody production and damage across multiple organ systems. It is highly variable and commonly affects women of reproductive age. Key features include overproduction of autoantibodies, large immune complexes, dysregulated immune/inflammatory pathways, and widespread tissue damage. SLE predominantly affects women (9:1 female: male ratio) aged 15–44. Zinc finger proteins (ZNFs) are DNA-binding transcription regulators. Emerging genetic studies show that single-nucleotide polymorphisms (SNPs) in ZNF-coding genes, including ZNF-76, are associated with autoimmune susceptibility. Lower serum ZNF-76 expression has been linked to higher risk of SLE.

Keywords: Systemic lupus erythematosus; zinc finger proteins; autoimmune disease.

1. Introduction

Autoimmune diseases develop when the immune system turns against normal body tissue. There are over 80 recognized types and possibly more than 100. Genetic predisposition is often assessed via family history, followed by diagnostic tests such as blood antibody assays, imaging, and sometimes biopsies. Early detection and management can reduce disease progression **(Angum et al., 2020)**. SLE is a global chronic autoimmune condition affecting multiple organs. It results from interactions among genetics, environment, and hormones **(Fava & Petri, 2019)**.

Global adult incidence of SLE averages 7.31 per 100,000 person-years, with total new cases around 380,000 annually. It disproportionately affects Black, Hispanic, and Asian populations, with higher rates than in White populations **(Barber et al., 2021; Tian et al., 2023)**. In the U.S., incidence estimates range from 3.7 to 49 per 100,000, depending on population **(Ungprasert et al., 2017; Li et al., 2020)**.

In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) updated the 1997 ACR classification by stating that biopsy-confirmed SLE nephritis (per ISN/RPS 2003) with antinuclear antibodies (ANA) or anti-dsDNA positivity is enough for diagnosis—enhancing accuracy and inclusivity **(Kudose et al., 2019)**.

ZNFs are transcription regulators with crucial roles in gene expression. Genetic studies have linked SNPs in ZNF genes, particularly five polymorphisms in ZNF-76 (rs10947540,

rs9394289, rs2267663, rs1894650, rs9366883), to increased SLE risk **(Qi et al., 2023)**.

2. Definition and prevalence of SLE

The term “lupus” (Latin for “wolf”) dates to the 13th century, describing rash appearance **(Felten et al., 2022)**. SLE involves aberrant immune activity and diverse clinical manifestations. It is more common among African American women and ethnic minorities. In the U.S., African American women face three- to fourfold higher rates of SLE than White women **(Ameer et al., 2022)**.

Environmental factors contribute to SLE risk, but mechanisms remain incompletely understood **(Monteiro et al., 2022)**. Diagnosis and treatment are complicated by genetic and phenotypic heterogeneity. Lupus nephritis is a frequent organ manifestation requiring tailored strategies. Managing pregnancy in SLE patients needs a multidisciplinary approach **(Rees et al., 2017)**. Women aged 15–44 are most affected, with female-to-male ratios up to 13:1; in children and the elderly, the ratio drops to 2:1 **(Fava & Petri, 2019)**.

Systemic lupus erythematosus prevalence and incidence vary globally due to differences in demographics, environment, socioeconomic status, and study methodologies. Data are particularly limited for Africa and Australia. Accurate epidemiological assessment is critical for understanding disease burden and improving outcomes. SLE mortality remains two to three times higher than in the general population **(Barber et al., 2021)**.

3. Pathogenesis of SLE

SLE is a heterogeneous autoimmune disease. Key mechanisms include autoantibody overproduction, immune complex deposition, elevated inflammatory responses, and tissue damage **(Yang et al., 2019)**. Genetic, environmental, and epigenetic factors interact, leading to altered gene expression **(Karrar & Cunninghame-Graham, 2018; Justiz Vaillant et al., 2023)**.

3.1. Genetic Susceptibility

Over 90 SLE susceptibility loci have been identified via GWAS, many involving multiple additive SNPs. Rare monogenic SLE variants also exist **(Ghodke-Puranik et al., 2024)**. Among 730 associated SNPs, 484 are in coding regions and only 21 change amino acids—indicating gene regulation plays a major role **(Laurynenka et al., 2021)**. Common risk genes cluster in pathways for lymphocyte signaling, interferon type I, and immune complex clearance **(Armstrong et al., 2014)**.

3.2. T and B Cell Signaling

Susceptibility genes affecting T/B cell signaling include HLA-DR2/DR3 (antigen presentation), PTPN22 (tyrosine phosphatase), CSK, BANK1, and transcription factors like ETS1, IKZF1-3, RAG1/2, FAS, SHOC2, KRAS **(Al-Mayouf et al., 2011; Ameer et al. 2022)**.

3.2.1. T Cell Role

T cells produce pro-inflammatory cytokines, drive autoantibody production by B cells, and harbor autoreactive memory cells. T follicular helper (Tfh) cells support germinal center reactions and IL-21–mediated B cell differentiation **(Nakayamada & Tanaka, 2021)**. Tfh expansion, triggered by RNA-containing immune complexes via TLR7, correlates with elevated autoantibodies in SLE **(Suárez-Fueyo et al., 2016; Tsokos et al., 2016)**.

Regulatory T cells (Tregs) maintain self-tolerance; their function is impaired in SLE due to low IL-2 and AP-1, contributing to elevated IL-17 and inflammation **(Giang & La Cava, 2016; Ameer et al., 2022)**.

3.2.3. B Cell Role

B cells generate autoantibodies via BCR, TLR, and BAFF signaling pathways. TLR9 stimulation promotes autoreactive marginal zone B cells, and high BAFF correlates with increased anti-dsDNA, anti-histone, and anti-cardiolipin levels **(Tsokos et al., 2016; Karrar & Cunninghame-Graham, 2018)**. Variants in CSK gene increase BCR-mediated activation and IgM levels **(Manjarrez-Orduño et al., 2012)**. Dysregulated BAFF and BCR signals disrupt tolerance and promote autoantibody production **(Möckel et al., 2021)**.

3.3. Impaired Apoptotic Clearance

Defective clearance of apoptotic debris exposes self-antigens and enhances immune activation. Key

phagocytes expressing TAM receptors (Tyro-3, Axl, Mer) are dysfunctional in SLE (**Pagani et al., 2020; Ameer et al., 2022**).

3.4. Environmental Factors

Exposure to silica, smoking, oral contraceptives, ultraviolet B (UVB) radiation, medications, and the Epstein–Barr virus (EBV) is linked to SLE. These factors may trigger inflammation, oxidative stress, and epigenetic changes in susceptible individuals **(Pan et al., 2019)**.

Smoking introduces oxidative stress and DNA damage, raising SLE risk (smoker OR ~1.5 in meta-analysis) **(Ameer et al., 2022)**.

UVB induces reactive oxygen species, cytokines (TNF-α, IL-1, IL-6, IFN-α), chemokines (CCL5, CCL20, CCL22), and adhesion molecules. It also causes DNA hypomethylation in $CD4^+$ T cells and impairs apoptotic debris clearance **(Achtman & Werth, 2015; Pan et al., 2019)**.

4. Clinical features of patients with SLE

Fatigue affects 67–90% of SLE patients and significantly reduces quality of life **(Jolly et al., 2019; Kawka et al., 2021)**. Other symptoms range from skin rash to severe organ damage including heart, lung, and kidney involvement **(Merola et al., 2014; Bendstrup et al., 2024)**.

- **Cardiovascular:** Myocardial, endocardial, and pericardial damage occur; pericarditis is the most common cardiac feature **(Gu et al., 2019)**.

- **Cutaneous:** Cutaneous lupus presents in multiple forms: discoid, subacute, acute, and rare variants **(Stull et al., 2023)**.

- **Gastrointestinal:** Manifestations include lupus enteritis, ulcers, ileus, and thrombotic events such as Budd-Chiari syndrome **(Fawzy et al., 2016)**.

- **Musculoskeletal:** Arthritis and arthralgia are reported in 80–90% of patients, often affecting small joints symmetrically. Severe cases can involve hip avascular necrosis **(Mahmoud et al., 2017; Ameer et al., 2022)**.

- **Pulmonary:** Common issues are pleuritis, pulmonary hypertension, lupus pneumonitis, diffuse alveolar haemorrhage, and interstitial lung disease **(Bendstrup et al., 2024)**.

- **Renal:** Lupus nephritis affects ~50% of patients, often early. Symptoms include proteinuria, hematuria, hypertension, edema, and renal impairment. Renal biopsy is classified into 6 ISN/RPS patterns. Inflammatory cytokines and immune complex deposition drive pathology **(Mahajan et al., 2020)**.

5. Biochemical diagnosis of SLE

Biomarkers are crucial for diagnosis, monitoring disease activity, and assessing responses. Due to the complexity of SLE, multiple biomarkers offer better coverage than any single test **(Ameer et al., 2022)**.

5.1. Antinuclear Antibodies (ANA)

ANA are highly sensitive (95–97%) but low specificity (~20%). A negative ANA reduces the likelihood of SLE, but a positive result is not definitive **(Pisetsky et al., 2019)**.

5.2. Complement (C3, C4) Levels

Hypocomplementemia—low C3, C4, or CH50—is included in SLICC (2012) and EULAR/ACR (2019) criteria. Low levels in both C3 and C4 carry greater diagnostic weight. Up to 89% of individuals have low complement at diagnosis **(Johnson et al., 2020; Pons-Estel et al., 2020; Chung et al., 2022)**.

5.3. Anti-dsDNA Antibodies

Anti-dsDNA has high specificity (~96%) for SLE and is weighted heavily in classification criteria. It is strongly associated with active nephritis. Sensitivity ranges from 52–70% and levels fluctuate with disease activity **(Fu et al., 2015; Justiz Vaillant et al., 2023)**.

5.4. Anti-Smith (Sm) Antibodies

Anti-Sm is detected in 5–30% of SLE patients depending on ethnicity and method. It is highly specific (~99%) and often appears early. Anti-Sm and anti-RNP antibodies are found together in 20–

30% of cases and are key classification markers **(Petri et al., 2012; Van Beers & Schreurs, 2022)**.

5.5. Urinary Biomarkers

Urine protein/creatinine ratio and 24-hour protein excretion remain standard for lupus nephritis. Experimental urinary biomarkers—chemokines, cytokines, adhesion molecules—show promise but lack formal validation and clinical approval **(Aragón et al., 2020)**.

6. Zinc Finger Proteins (ZNF) and systemic lupus erythematosus

Zinc finger proteins are abundant DNA-binding proteins involved in transcription, DNA repair, signaling, and protein degradation. SNPs in ZNF genes are associated with autoimmune diseases like rheumatoid arthritis, Crohn's disease, Graves' disease, alopecia areata, and asthma **(Haritunians et al., 2011; Wu et al., 2014; Cassandri et al., 2017)**.

Recent studies on Egyptian populations highlight ZNF-76 rs10947540 as a susceptibility factor for rheumatoid arthritis **(Fouda et al., 2025)**. In SLE, GWAS identified 28 SNPs associated with increased risk; five are located in ZNF76, including rs10947540. ZNF-76 acts as a transcriptional repressor by inhibiting p53 via interaction with TATA-binding protein. Altered ZNF-76 may contribute to p53-mediated SLE pathogenesis **(Yang et al., 2020; Qi et al., 2021)**. Case-control studies support the link between ZNF-76 rs10947540 and increased SLE susceptibility **(Ali Assar et al., 2024; Ahmed et al., 2025)**.

7. Conclusion

Systemic lupus erythematosus is a multifaceted systemic autoimmune disorder marked by antinuclear autoantibodies, immune-complex deposition, and organ damage. Genetic and transcriptomic studies have identified gene signatures associated with disease severity and risk. Notably, decreased serum ZNF-76 expression and specific ZNF-76 polymorphisms (e.g. rs10947540) associate with increased susceptibility to SLE in certain populations—suggesting avenues for personalized risk assessment and therapeutic targeting.

Conflict of interest

None of the authors declare any conflicts of interest

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