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Treatment Advances in Systemic Lupus Erythematosus: A Literature Review

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ABSTRACT

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with diverse clinical presentations, ranging from mild to severe, life-threatening organ involvement. Advances in understanding its multifaceted etiology—encompassing genetic, epigenetic, hormonal, and environmental factors—have shed light on key immunological pathways involved in disease pathogenesis. The roles of innate and adaptive immune responses, including dysregulated B and T cells, cytokines, and chemokines, have been elucidated, with interferon signaling emerging as a critical player. The introduction of novel therapeutic strategies, including monoclonal antibodies, Chimer Antigen Receptor T-cell therapy, and hematopoietic stem cell transplantation, reflects the evolving landscape of lupus management. Precision medicine and immunometabolism research offer promising avenues for tailoring treatment plans to individual patients, improving outcomes, and minimizing adverse effects. Despite significant progress, further studies are essential to refine therapeutic approaches, enhance disease remission rates, and explore potential curative solutions.

Keywords: SLE, treatment, INF gamma, antibodies, autoimmune, epigenetic, innate immune response, adaptive immune response, cytokines, multi-organ, immunosuppressive, MHC, self-antigens, immunomodulation, chemokines, lymphocytes, CAR T cells, hematopoietic stem cell transplant

1. Introduction

Systemic lupus erythematosus (SLE) is a complex inflammatory illness where multiple organ systems are impacted. Genetic, epigenetic, environmental, and ecological variables all contribute to its etiology. Both innate and adaptive immunological responses are triggered in SLE, which results in autoreactive B cells being activated by T cells and immune complexes accumulating in organs. This sets off an autoimmune cascade, which may present as either an extensive systemic illness or would present in the involvement of specific organs only. The clinical presentation is incredibly varied, from minor, self-limiting symptoms to severe, potentially fatal organ damage[1].

Due to high-throughput technology advancements, autoantibodies implicated in important SLE pathways have been identified. Significant variables have been found to include endogenous retroelements, interferon-induced proteins, cytokines, extracellular receptors, and functional autoantibodies that target DNase1L3. Studies have also shown that colonic IgA to nuclear antigens and mitochondria may be triggers, and that gut permeability and SLE are related. Furthermore, proliferative lupus nephritis has been linked to autoantibodies such as dsDNA, C1q, Sm, and ribosomal P. Additionally, distinct Ro52 species overexpressed in SLE neutrophils provide additional information on the illness's underlying processes[2].

This disease is driven by a complex etiology as well as a hereditary predisposition. With a focus on the biological role of IFN-α, research has progressively correlated SLE to the interferon (IFN) gene signature. However, new data shows that IFN-γ plays a vital -but sometimes underappreciated- aspect of the illness. Interestingly, high levels of IFN-γ have been detected in individuals even before a formal diagnosis of SLE was made, preceding the appearance of autoantibodies and the expression of IFN-α. Even though IFN-α and IFN-γ have similar effects, SLE is mostly linked to IFN-α production early on in the disease process, which may mask the roles of IFN-γ. In order to offer a more comprehensive knowledge of the effect on illness pathophysiology, research aims to investigate the function of IFN-γ in SLE[3].

In addition to the multi-organ involvement associated with SLE, the disease encompasses complicated relationships with incidents or pre-existing comorbidities. The loss of physiological reserve due to accumulating health deficiencies over time is known as frailty. In a newly developed SLE-specific frailty index (SLICC-FI), it was revealed that patients with SLE deemed as frail suffered a significantly higher mortality risk than SLE patients who were not frail[3]. A large-scale study conducted in China revealed that the risk of developing leukemia and bladder malignancies in patients with SLE is significantly higher when compared to patients with other autoimmune diseases[3]. It is often difficult to diagnose SLE due the difficulty of differentiating between SLE flare-ups and possible infections. This is due to intrinsic immunologic degradation and the side effects of immunosuppressive medications; SLE patients are susceptible to infections due to humoral and cellular immunodeficiency[4]. It's critical in day-to-day clinical treatment to distinguish between true infections and SLE flare-ups and recognize that some patients experience a worsening of SLE due to infection. This implies that active SLE and infection can coexist[4]. Therefore, prompt and accurate diagnosis and tailored management strategies are essential to improving outcomes for SLE patients. Furthermore, a deeper look into the etiology and pathogenesis of SLE is essential for guiding current treatment strategies and therapeutic advancements. In this review, the aim is to address key subtopics related to systemic lupus erythematosus, including its etiology, epidemiology, pathogenesis, treatment guidelines, and some of the new advancements in its treatments.

2. Etiology and Epidemiology of Systemic Lupus Erythematosus

2.1 ETIOLOGY

The autoimmune disorder comprises a wide spectrum of conditions characterized by the immune system's loss of tolerance to self-antigens, leading to tissue damage and chronic inflammation. Its etiology is multifactorial, with genetic, environmental, hormonal, and immunological involvement[5]. It is the genetic susceptibility that plays a decisive role, and several specific loci have been identified as associated with SLE, particularly in the region of the major histocompatibility complex (MHC), which is on chromosome 6[6]. Specifically, the risk for onset of the disease is associated with HLA-DR2 and HLA-DR3 alleles[7]. Moreover, genetic polymorphisms in genes with a role in complement proteins (C1q, C2, C4), cytokines, and signaling molecules (STAT4, IRF5, PTPN22) further lead to uncontrolled immune activation[8]. Familial aggregation and twin studies emphasize the heritable nature of SLE, with the concordance rates in monozygotic twins between 25-50% and 5% in dizygotic twins[5]. Environmental factors also play an essential role in the pathogenesis of SLE. UV radiation causes nucleus death (apoptosis), which leads to the accumulation of nuclear antigens that could act as autoantigenic[9]. Infections (e.g., Epstein-Barr virus (EBV) were also capable of triggering autoimmunity via molecular mimicry and aberrant immune response[9]. Some medications, such as hydralazine, procainamide, and isoniazid, can cause drug-induced lupus in some genetically predisposed patients[9].

The higher prevalence of SLE in females (especially in reproductive ages) indicates a hormonal effect[10]. Estrogens facilitate B-cell activation and autoantibody production, while androgens seem protective and partly explain the lower incidence in males[10]. Variability of hormones, particularly during pregnancy and postpartum, are also associated with disease exacerbation[10]. A key feature of SLE is immune dysregulation mediated by loss of tolerance to self-antigens and generation of autoantibodies , including anti-nuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA). [7] Dysregulation of this response results from defects within both the arms of the immune response, including aberrant T-cell activation, impaired functioning of regulatory T-cells, and hyperactivity of B-cells[11]. Additionally, complement deficiencies make immune complex and apoptotic debris clearance from the circulation even more limited, aggravating autoimmune processes[11]. Recent findings suggest that aberrant

epigenetic modifications, including DNA hypomethylation, histone modification, and non-coding RNA regulation, also play a crucial role in the development of SLE[11]. These changes modify emission without changing the underlying DNA sequence, increasing immune cell activation and autoantibody production. Epigenetic changes are possibly a consequence of environmental exposures, suggesting a connection between external triggers and genetic susceptibility[11]. The development and progression of SLE results from a multifactoral combination comprising of genetic predisposition, environmental triggers, hormonal influences, and epigenetic modifications.

2.2 EPIDEMIOLOGY

It is known that SLE affects women compared to men at a 9:1 ratio. It tends to affect women that are in their early reproductive ages which is from around the age of 20 to the age of 30[12]. However, in the male population that it affects, the larger cases tend to be within the ages of 45-60 years[13]. Additionally, the fact that SLE affects women more than men can be attributed to the role of steroid hormones. Hormones such as testosterone, estrogen, and progesterone have been known to impact the T helper 1/T helper 2 cytokine balance[13]. For instance, progesterone causes T helper 2 polarization associated with an increase in the number of cytokines like IL-10 and IL-6[13].

Furthermore, pregnancy is a major contributing factor to the progression of SLE, and many patients tend to report flares during pregnancy, which also occurs because pregnancy causes an increase in the amount of T helper 2 cytokines in the body, and the autoantibodies generated play a role in the development of this disease[13]. In terms of geographical differences in the communities of people affected by SLE, patients who are of Black, Hispanic, and Asian origins tend to have a higher number of cases, whereas patients who are White tend to have a comparatively lower incidence of this autoimmune disease.[1] Furthermore, the mortality rates of SLE are around 2-3 times higher in comparison to the population not affected by this disease, and 2 of the main contributors to mortality due to SLE tend to be infection and cardiovascular diseases[14].

3. Current Guidelines

3.1 DIAGNOSIS

A new criteria has been suggested by European League Against Rheumatism and the American College of Rheumatology (EULAR/ACR) that the level of ANA antibodies be measured initially as a screening test since it has been estimated that 95 percent of SLE patients are ANA positive and 98 percent of patients will have ANA and/or anti-dsDNA antibodies[15]. After the screening test, a scoring system has been suggested for the classification of patients. The score system requires ten points to confirm the classification with each group of symptoms having its own weight, which ranges from 2 to 10 points. The most common symptoms to be affected by SLE include discoid rash, photosensitivity, oral ulcers, non-erosive arthritis, serositis, renal disorder and CNS symptoms. Additionally, the EULAR/ACR criteria added new symptoms such as alopecia and fever[16].

3.2 TREATMENT GOALS

The main goals in the treatment plan for patients with SLE are to prevent organ damage from active lupus, such as damage to the kidneys and nervous system, manage the patient's pain and fatigue, and balance the use of immunosuppressants and immunomodulators to prevent autoimmunity. Another goal is to minimize co-occurring symptoms that may be caused by the treatment, especially atherosclerosis, renal symptoms, and neurological symptoms, which are known to be the main causes of death in SLE patients. One recommended method is to ensure patients adhere to treatments that maximise the efficacy of immunomodulators such as hydroxychloroquine and vitamin D. It is also recommended to avoid the prolonged use of steroid drugs such as >6 mg of the drug prednisone[17].

3.3 CURRENT DRUGS IN USE

It is known that SLE can lead to multiple organ damage. Therefore, it is important to consider the differentials before prescribing any medications to possible SLE patients, especially those drugs that can cause adverse effects. Some of the effects include acute and subacute renal and neurological symptoms. They are known causes of death in the SLE population[15]. In terms of first-line treatment, Hydroxychloroquine is recommended at a target dose of 5 mg/kg real body weight/day, with consideration to the individual's risk of developing flares and retinal toxicity. Additionally, glucocorticoids are also used as a bridging therapy during active disease at $\leq$ 5 mg per day, with withdrawal when it is not required. The withdrawal is done by tapering the dose, to prevent side effects like osteoporosis and Cushing's syndrome. Immunosuppressive drugs like methotrexate and azathioprine or biologic agents like belimumab and anifrolumab can also be considered when tapering the glucocorticoid dose to help reduce inflammation and prevent flares. For active lupus nephritis, anchor drugs like glucocorticoids, mycophenolate, or low-dose intravenous cyclophosphamide are used. They may be used together with belimumab or calcineurin inhibitors like voclosporin and tacrolimus as add-on therapy. There are also specific guidelines for each organ affected like cutaneous, neuropsychiatric, and hematological signs, which are some of the symptoms caused by SLE. It is important to employ the use of preventative measures such as infection prevention, which is done via the use of vaccinations, prophylactic antibiotics, ACE inhibitors for proteinuria, statins, and lifestyle changes. Additional preventative measures include kidney protection, and strategies to minimize the risks of cardiovascular disease and osteoporosis[18]. While many drugs options can be prescribed to patients with SLE, they are all given for symptom management and not for curative purposes.

4. Pathogenesis

4.1 EVIDENCE OF T CELLS AND CHEMOKINES

There is an association between SLE and other diseases that progress from SLE like lupus nephritis which predominantly affects the kidney. The pathogenesis mainly involves immune dysregulation and it is thought that T cells play a huge part in this[19]. T cells are part of the adaptive immune system and their abnormality can cause autoimmune conditions like SLE. Abnormal immune function causes a lack of T cell regulation causing SLE and

this is due to T cells and their subsets having failure of self-tolerance[19]. T cells have different subsets especially the helper T cell and each subset has a different function in regulating the immune system. Along with T cells, it is also shown that chemokines play a role in SLE causing further complications and creating inflammation. Chemokines are low molecular weight cytokines and their function is to attract immune cells to the site of their action[20]. Chemokines within the body help with the regulation of the immune system and it is observed that in SLE, chemokines are affected during its pathogenesis. The mechanism of chemokines involves binding to G protein receptors on the target cells and this allows the movement of immune cells to its particular site of requirement[20]. Chemokines work to regulate the immune system by signal transduction using receptors located on the surface of the cells to the site where there's inflammation or where chemokines are necessary and upon binding to the receptor, the chemokines will recruit cells that are needed for its action.

Studies have shown that CD4+, CD8+, double negative t cells (DNT cells), and other t cell subsets are involved in the pathogenesis of SLE. These T cell subsets are mainly a part of CD4+ cell, because CD4+ cells can be presented as 5 different forms or subsets such as TH1, TH2, TH17, Treg and TFH cells[19]. Each of these T cells and the various subsets present abnormally in SLE and certain symptoms of SLE are associated with specific T cells.

For example, subset of CD4+ such as TH17 is associated with the disease lupus nephritis (complication of SLE). It is also shown that deficiency of Treg cells aids in disease formation and this is a characteristic of SLE[19]. Treg cells regulate the immune system and usually suppress t cells that have a failure of self-tolerance. Since Treg cells are deficient, these abnormal t cells undergo autoreactivity and lead to the formation of SLE. Along with T cells, the contribution of chemokines is also involved in the pathophysiology of this disease. Ghafouri's et al. focuses on specific chemokines such as CCL2, CCL3, CCL4, CXCL12 and many more, showing their abnormalities and significance in SLE. CCL2 (monocyte chemoattractant protein 1) is found to attract monocytes, memory t cells and dendritic cells to the area of action where it attaches to the receptors CCR2 and CCR4[20]. CCl2 is found in high amounts in manifestations of lupus nephritis and this can be used as a marker to compare with normal cases. Other chemokines like CCL3 (macrophage inflammatory protein 1-alpha) are also shown to be elevated in patients with SLE and causes inflammatory response by attracting cells and interactions with CCR1, CCR4 and CCR5[20]. Overall, it is understood that SLE disrupts the immune system and during its pathogenesis, immune cells like T cells and chemokines are affected and present abnormally in these patients.

4.2 INVOLVEMENT OF INTERFERON AND B CELLS

Development of clinical SLE is most times a combination of genetic and environmental predisposition[21]. The dysregulation of the innate and adaptive immune system is a hallmark of the pathogenesis giving rise to circulating auto-antibodies. These auto-antibodies form an antigen-antibody complex and settle in the circulatory system (blood vessels), resulting in multi-organ damage[1]. Recently, the involvement of IFN-1 has also been considered a pivotal mediator of the disease and has led to the recognition of the significant role of the innate immune system in the pathogenesis and autoimmunity of SLE[21]. Overexpression of Toll-like receptors is a common trigger for the increase in IFN-1 production, and hence for disease progression. A study done in mice with a deficiency of toll-like receptors proved to be preventative against SLE, pointing to its significant involvement in the disease[1]. The production of IFN-1 can also be enhanced by retinoic acid inducible gene 1, melanoma differentiation associated protein 5 (MDA5). These molecules are triggered by nucleic acids or bacterial products like peptidoglycan[21].

Type 1 IFN bind to receptors like the IFNa and form a heterodimeric complex that initiates intracellular signalling via kinases that phosphorylate signal transducers and activator proteins STAT 1 and STAT 2 which then associate with IRF7 and 9 to form a complex known as ISGF3. This complex moves to the nucleus, where it increases the transcription of IFN-sensitive response elements, producing proteins that lead to the inflammatory process and progression of the disease[22]. B cells respond to antigens via generation of antibodies. The activation of Toll-Like Receptors in B cells plays a role in breaking immune tolerance. Transitional B cells are highly responsive to the stimulation by these receptors, resulting in the formation of marginal zone B cells, a highly characteristic feature of SLE. Increased production of cytokines like BAFF is also known to disrupt B cell tolerance, leading to an amplified generation of autoantibodies such as anti-dsDNA, anti-cardiolipin, anti-histone, etc[21].

4.3 RECENT FINDINGS IN PATHOGENESIS

Prior to recent developments and studies into SLE, the pathogenesis of SLE was thought to be caused by a combination of genetic and environmental factors resulting in impaired immune function and response[22]. The exact pathophysiology of SLE is difficult to determine due to its multifaceted nature, however, a few potential areas of therapeutic interest will be discussed below.

Recent studies explored the involvement of innate and adaptive immunity in the progression of SLE. One such finding is the involvement of dendritic cells (DCs) in autoreactive T and B cells[1]. These autoreactive immune cells produce autoantibodies, which cause end-organ damage; thus, understanding the mechanism underlying this process is of therapeutic importance. Teichmann et al.'s findings suggest that the severity of SLE is greatly reduced in the absence of DCs, but the specific cause for this is complex is not yet fully understood[23]. It is hypothesized that DCs promote T cell, B cell, and plasmablast (pDC) proliferation with antibody production, resulting in extrafollicular and germinal centre responses in SLE[22]. Similarly, neutrophils and interferons play a vital role. When neutrophils die, they can release neutrophil extracellular traps (NETs), which contain a large amount of DNA. These NETs typically aid in bacterial entrapment and death, but they are overexpressed in SLE patients. NET DNA is resistant to nuclease breakdown, thus serving as an autoantigen for pDC activation and subsequent IFN release[22]. IFNs can also help in DC maturation and autoreactive T cell activation, resulting in a feed-forward process that can

exacerbate chronic inflammation and cause additional tissue damage. Although it is uncertain if NETs are required for the development of disease in SLE, further study into IFN-blocking therapies can be beneficial.

Choi et al. argue that dysregulated T follicular helper (Tfh) cells play a critical role in SLE by driving autoreactive B cell maturation, differentiation, and autoantibody production in both germinal centres and extrafollicular settings in mice[22]. Despite studies confirming the participation of Tfh cells in human SLE being very sparse, an increase in the circulating Tfh (cTfh) cell population in individuals with acute SLE has been documented[1]. These Tfh-mediated B cell responses rely largely on CD154-CD40 interactions. While targeting CD154-CD40 interactions has the potential to reduce anti-dsDNA levels, the associated risks require additional therapeutic refinement. Nonetheless, recognising Tfh-driven pathways offer crucial insights toward designing novel treatments for SLE. Furthermore, the role of various autoantibodies, such as anti-nuclear and anti-dsDNA, in the pathogenesis of SLE is well established. However, a subset of patients were recently discovered to have elevated IgE autoantibodies, which is peculiar and suggests that targeting basophils, which are activated by IgE autoantibodies, may be advantageous for treatment with further study[22].

Immunometabolism, a recently founded concept associated with the pathophysiology of SLE describes how various types of immune cells have distinct metabolic requirements and hence, have unique metabolic processes. Mitochondria, which play an essential function in metabolic regulation, were discovered to be dysregulated in SLE with an increased mitochondrial mass observed in T cells and memory B cells of afflicted patients[24]. Beyond metabolism, it was found to play a key role in signaling innate and adaptive immunity via the release of mitochondrial ROS. In SLE, excess mitochondrial ROS is generated, leading to oxidative stress which induces intractable apoptosis, resulting in cell debris accumulation, which triggers immunological activation and culminates tissue destruction[24]. Further exploration into metabolic modulation using trans-omics, which is an integrated approach that brings together data from many "omics" domains (e.g., genomics, transcriptomics, proteomics, metabolomics, and others) has the potential to reveal the precise pathophysiology underlying SLE and hence contribute to the discovery of novel therapeutic regimens.

5. New Treatment Advancements in Systemic Lupus Erythematosus

5.1 EXPLORING USING OTHER MEDICATIONS

As plasma cells are known to make the pathogenic antibodies for SLE targeting plasma cells thus monoclonal antibodies can be potentially an effective treatment[25]. The current two that are suggested are daratumumab - an anti-CD38 - and elotuzumab - targets SLAMF7. Both of these drugs would lead to the depletion of plasma cells in the body, thus, decreasing SLE symptoms. The therapy paradigm for SLE has altered dramatically in recent years, with an emphasis on more focused and efficient approaches. Particularly for lupus nephritis, the European League Against Rheumatism (EULAR) has revised its recommendations to take into account new information on therapeutic approaches, such as the use of multitargeted treatments and alternate glucocorticoid regimens. An important turning point in the treatment of this complicated autoimmune illness has been reached with the approval of the first biological therapy for SLE[26]. One significant change in perspective in the treatment of SLE is the move toward biologics and small molecule inhibitors. While non-specific immunosuppression has been the mainstay of traditional therapy, new research has produced small compounds and monoclonal antibodies that specifically target the immunological processes implicated in SLE. The goal of this focused strategy is to increase effectiveness while reducing the negative effects of traditional treatments[27]. For instance, treatments that alter B and T lymphocyte activity or block particular cytokines are now being investigated in clinical trials and have shown encouraging outcomes in controlling disease activity and averting flare-ups[27]. Furthermore, cutting-edge studies have demonstrated the possibility of renin-angiotensin system (RAS) targeting as a unique therapeutic approach. Research conducted on animal models have demonstrated that altering the RAS's protective arm could lessen SLE-related disorders without depending on conventional immunosuppressive methods. For patients, especially those susceptible to the negative consequences of chronic immunosuppression, this strategy creates new opportunities for medication development that could provide safer substitutes[28].

5.2 CELL-BASED THERAPIES

5.2.1 Aryl Hydrocarbon Receptor-JUN Axis

A recent publication discovered that aryl hydrocarbon receptor (AHR) can be utilized with the help of CRISPR in treating SLE. AHR is a negative regulator of CXCL13 production, where CXCL13 is a chemoattractant for B cells produced by T cells. This induces the pathogenicity of SLE due to the recruitment of B cells. The study noted that patients with SLE have increased expression of PD-1^{+}/ICOS CXCL13^{+} T cells and decreased expression of CD96^{hi}IL-22 T cells. AHR works with JUN from the AP-1 family to eliminate the differentiation of T cells that produce CXCL13 and upregulate the IL-22 T cells. Therefore, this would not only decrease the recruitment of B cells, but also the lymphoid aggregation in inflamed tissues[29]. However, the paper did not clarify the potential side effects of using this treatment method.

5.2.2 Chimer Antigen Receptor T-cells

While Chimer Antigen Receptor (CAR) T cell therapy has been utilized in cancer treatment, introducing it to SLE treatment might also be of benefit. Anti-CD19 CAR T cell therapy has shown therapeutic remission in patients with no major clinical adverse effects and eliminates anti-DNA antibodies. However, long-term effects remain unknown, therefore, it is suggested to perform a long-term study that can shed light on these possible adverse effects[21].

5.2.3 Hematopoietic Stem Cell Transplantation

Hematopoietic Stem Cell (HSC) transplantation has been employed in multiple diseases and disorders, therefore, using it in SLE would not be unexpected. While it has been used for life-threatening situations, a paper suggests that incorporating it into the treatment plan early on can be a protective factor against organ failure. The aim is to replace the self-reactive T cells, B cells and plasma cells with normal cells. The study has stated that those who

responded to the therapy had mortality rates was less than 5% and there were no notable adverse effects experienced[21]. While it is promising to have minimal adverse effects, it is also important to study the possible long-term effects of HSC transplantation on patients with SLE.

6. Conclusion

Systemic Lupus Erythematosus is a complex autoimmune disease that continues to pose a challenge to researchers and clinicians alike. Key elements that contribute to the onset and progression of the disease, including genetic predisposition, hormonal influences, and environmental triggers, have been clarified by advances in understanding its etiology, pathogenesis, and epidemiological patterns. Recent findings, such as abnormalities in T and B cell activity, interferon signaling, and chemokine-mediated inflammatory processes, highlight the critical roles of immune dysregulation. The incorporation of cutting-edge therapeutic strategies, such as hematopoietic stem cell transplantation, CAR T-cell therapies, and biologics that target particular immune pathways, emphasizes how SLE management is continuously evolving. These developments present encouraging paths toward lowering disease activity, avoiding organ damage, and enhancing the quality of life for patients. Additionally, the investigation of precision medicine and immunometabolism represents a significant move toward personalized treatment plans with the goal of increasing therapeutic effectiveness while reducing side effects. Further understanding of the molecular causes of SLE is encouraged with the use of high-throughput technologies and creative research approaches. Together with thorough clinical trials, this advancement could improve existing treatment models and eventually lead to the development of cures for this complicated autoimmune condition.

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References:

1. Ma A, H C, J M, et al. An Overview of Systemic Lupus Erythematosus (SLE) Pathogenesis, Classification, and Management. *PubMed*. Published online 2022. Accessed January 15, 2025. https://pubmed.ncbi.nlm.nih.gov/36407159/
2. Gómez-Bañuelos E, Fava A, Andrade F. An update on autoantibodies in systemic lupus erythematosus. *Curr Opin Rheumatol*. 2023;35(2):61-67. doi:10.1097/BOR.0000000000000922
3. Liu W, Zhang S, Wang J. IFN-γ, should not be ignored in SLE. *Front Immunol*. 2022;13:954706. doi:10.3389/fimmu.2022.954706
4. Sawada T, Fujimori D, Yamamoto Y. Systemic lupus erythematosus and immunodeficiency. *Immunol Med*. 2019;42(1):1-9. doi:10.1080/25785826.2019.1628466
5. Akhil A, Bansal R, Anupam K, Tandon A, Bhatnagar A. Systemic lupus erythematosus: latest insight into etiopathogenesis. *Rheumatol Int*. 2023;43(8):1381-1393. doi:10.1007/s00296-023-05346-x
6. Webber D, Cao J, Dominguez D, et al. Association of systemic lupus erythematosus (SLE) genetic susceptibility loci with lupus nephritis in childhood-onset and adult-onset SLE. *Rheumatology*. 2020;59(1):90-98. doi:10.1093/rheumatology/kez220
7. Ortíz-Fernández L, Martín J, Alarcón-Riquelme ME. A Summary on the Genetics of Systemic Lupus Erythematosus, Rheumatoid Arthritis, Systemic Sclerosis, and Sjögren's Syndrome. *Clin Rev Allergy Immunol*. 2022;64(3):392-411. doi:10.1007/s12016-022-08951-z
8. Javinani A, Ashraf-Ganjouei A, Aslani S, Jamshidi A, Mahmoudi M. Exploring the etiopathogenesis of systemic lupus erythematosus: a genetic perspective. *Immunogenetics*. 2019;71(4):283-297. doi:10.1007/s00251-019-01103-2
9. C C, D Z, E E, et al. Environment and systemic lupus erythematosus. *PubMed*. Accessed January 15, 2025. https://pubmed.ncbi.nlm.nih.gov/38743446/
10. Kim JW, Kim HA, Suh CH, Jung JY. Frontiers | Sex hormones affect the pathogenesis and clinical characteristics of systemic lupus erythematosus. doi:10.3389/fmed.2022.906475
11. Y A, T M. Epigenetic Dysregulation in the Pathogenesis of Systemic Lupus Erythematosus. *PubMed*. Published online 2024. Accessed January 15, 2025. https://pubmed.ncbi.nlm.nih.gov/38256093/
12. Ce W, Tb N. The unexplained female predominance of systemic lupus erythematosus: clues from genetic and cytokine studies. *PubMed*. Accessed January 15, 2025. https://pubmed.ncbi.nlm.nih.gov/20063186/
13. The influence of reproductive hormones on systemic lupus erythematosus. Accessed January 15, 2025. https://www.explorationpub.com/Journals/ei/Article/100355
14. Mrw B, C D, T F, et al. Global epidemiology of systemic lupus erythematosus. *PubMed*. Accessed January 15, 2025. https://pubmed.ncbi.nlm.nih.gov/34345022/
15. C G, Mb AA, M G, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. *PubMed*. Published online 2018. Accessed January 16, 2025. https://pubmed.ncbi.nlm.nih.gov/29029350/
16. M A, N L, Sr J. New Criteria for Lupus. *PubMed*. Published online 2020. Accessed January 16, 2025. https://pubmed.ncbi.nlm.nih.gov/32405775/
17. A F, M P. Systemic lupus erythematosus: Diagnosis and clinical management. *PubMed*. Accessed January 16, 2025. https://pubmed.ncbi.nlm.nih.gov/30448290/
18. A F, M K, J A, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *PubMed*. Published online 2024. Accessed January 16, 2025. https://pubmed.ncbi.nlm.nih.gov/37827694/
19. Li H, Boulougoura A, Endo Y, Tsokos GC. Abnormalities of T cells in systemic lupus erythematosus: new insights in pathogenesis and therapeutic strategies. *J Autoimmun*. 2022;132:102870. doi:10.1016/j.jaut.2022.102870
20. Ghafouri-Fard S, Shahir M, Taheri M, Salimi A. A review on the role of chemokines in the pathogenesis of systemic lupus erythematosus. *Cytokine*. 2021;146:155640. doi:10.1016/j.cyto.2021.155640
21. Accapezzato D, Caccavale R, Paroli MP, et al. Advances in the Pathogenesis and Treatment of Systemic Lupus Erythematosus. *Int J Mol Sci*. 2023;24(7):6578. doi:10.3390/ijms24076578
22. Choi J, Kim ST, Craft J. The pathogenesis of systemic lupus erythematosus—an update. *Curr Opin Immunol*. 2012;24(6):651-657. doi:10.1016/j.coi.2012.10.004
23. Teichmann LL, Ols ML, Kashgarian M, Reizis B, Kaplan DH, Shlomchik MJ. Dendritic Cells in Lupus Are Not Required for Activation of T and B Cells but Promote Their Expansion, Resulting in Tissue Damage. Accessed January 16, 2025. https://www.cell.com/immunity/abstract/S1074-7613(10)00455-3
24. Takeshima Y, Iwasaki Y, Fujio K, Yamamoto K. Metabolism as a key regulator in the pathogenesis of systemic lupus erythematosus. *Semin Arthritis Rheum*. 2019;48(6):1142-1145. doi:10.1016/j.semarthrit.2019.04.006
25. Malkiel S, Barlev AN, Atisha-Fregoso Y, Suurmond J, Diamond B. Frontiers | Plasma Cell Differentiation Pathways in Systemic Lupus Erythematosus. doi:10.3389/fimmu.2018.00427
26. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *scite.ai*. Accessed January 4, 2025. https://scite.ai/reports/2019-update-of-the-eular-vJKjAkW
27. Vukelic M, Li Y, Kyttaris VC. Novel Treatments in Lupus. *Front Immunol*. 2018;9:2658. doi:10.3389/fimmu.2018.02658
28. M S, N D, C H, Ke R. Targeting the Protective Arm of the Renin-Angiotensin System to Reduce Systemic Lupus Erythematosus Related Pathologies in MRL -lpr Mice. *PubMed*. Published online 2020. Accessed January 4, 2025. https://pubmed.ncbi.nlm.nih.gov/32793221/
29. Law C, Wacleche VS, Cao Y, et al. Interferon subverts an AHR–JUN axis to promote CXCL13+ T cells in lupus. *Nature*. 2024;631(8022):857-866.

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