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Pathogenesis of Childhood Onset Systemic Lupus Erythematosus

Edy Novery, Yulia Iriani, Krisna Murti*, Subandrate
Universitas Sriwijaya, Indonesia
Email: edy.novery@fk.unsri.ac.id, yuliairiani@fk.unsri.ac.id, krisna.arinafril@unsri.ac.id*, subandrate@unsri.ac.id

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease characterized by immune dysregulation and inflammation affecting multiple organs and tissues. Its pathogenesis is complex and multifactorial, involving interactions among genetic susceptibility, environmental triggers, and abnormalities in innate and adaptive immune responses that contribute to autoantibody production and tissue damage. Understanding these pathogenic mechanisms is essential for elucidating disease progression, clinical manifestations, and outcomes, particularly in pediatric patients. This review aimed to summarize the existing literature on the pathogenesis of childhood-onset systemic lupus erythematosus (cSLE). A literature search was conducted using PubMed, Embase, the Cochrane Library, and Google Scholar, and relevant publications were synthesized through a narrative review. The findings indicated that cSLE develops through interactions among genetic predisposition, environmental influences, and immune system dysfunction. Key pathogenic mechanisms include the loss of immune tolerance, dysregulated apoptosis, impaired clearance of apoptotic cellular debris, and abnormal activation of innate and adaptive immune cells, particularly T and B lymphocytes. These abnormalities promote the production of autoantibodies and the formation of immune complexes, which contribute to complement activation, inflammatory cytokine release, and subsequent tissue and organ injury. Childhood-onset SLE frequently exhibits a more severe clinical phenotype and greater disease activity than adult-onset SLE, with genetic factors playing a particularly prominent role in early disease development. Genetic susceptibility, together with environmental triggers, contributes to persistent immune activation and the dysregulation of proinflammatory signaling pathways, including type I interferon responses. These interconnected processes sustain systemic inflammation and promote damage to target organs. In conclusion, the pathogenesis of cSLE involves complex interactions among genetic susceptibility, defective immune tolerance, impaired apoptotic cell clearance, complement dysregulation, cytokine-mediated inflammation, and autoantibody production. A comprehensive understanding of these mechanisms may facilitate the identification of molecular biomarkers and the development of more targeted therapeutic strategies for pediatric patients with SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that affects multiple organs and tissues (Hedrich et al., 2017). SLE is characterized by the production of autoantibodies against self-antigens, resulting in the formation of immune complexes that can trigger inflammatory responses and cause tissue damage (Harry et al., 2018; Hedrich et al., 2017). The disease exhibits heterogeneous clinical manifestations, depending on the organs involved, the severity of immune dysregulation, and individual patient characteristics (Puengpipattrakul et al., 2023).

Systemic lupus erythematosus can develop at any age, affecting both adults and children (Puengpipattrakul et al., 2023). Childhood-onset systemic lupus erythematosus (cSLE) exhibits distinctive clinical characteristics, including heterogeneous manifestations, higher disease activity, and an increased risk of severe organ involvement compared with adult-onset SLE (Brunner et al., 2008; Bundhun et al., 2017; Smith et al., 2019). Although SLE affects both males and females, its incidence is substantially higher among females, particularly during the reproductive years (Kim et al., 2022). Approximately 20% of SLE cases develop during childhood or adolescence (Dai et al., 2025; Puengpipattrakul et al., 2023).

The reported prevalence of SLE varies across geographic regions and populations, partly reflecting differences in disease surveillance, diagnostic recognition, and population characteristics (Alexander et al., 2025; Barber et al., 2023; Hasan et al., 2022; Mattioli et al., 2025). The global prevalence of SLE has been estimated to range from 15.87 to 108.92 cases per 100,000 individuals (Tian et al., 2023). In the United States, the reported prevalence of pediatric SLE ranges from approximately 9.73 to 24 cases per 100,000 children (Valenzuela-Almada et al., 2022). In Brazil, the overall prevalence of SLE has been reported at approximately 8.7 cases per 100,000 individuals, with pediatric-onset cases accounting for an estimated 10–20% of cases. In Taiwan, the reported prevalence of childhood-onset SLE ranges from 4.8 to 8.1 cases per 100,000 individuals (Wu et al., 2022). These epidemiological variations highlight the importance of considering geographic, demographic, and methodological differences when interpreting disease prevalence.

The pathogenesis of SLE involves complex interactions among genetic susceptibility, environmental triggers, hormonal influences, and immune system dysregulation (Ahmed et al., 2025; Sestan et al., 2023). Both innate and adaptive immune responses contribute to disease development, with T and B lymphocytes playing central roles in the loss of immune tolerance and the production of pathogenic autoantibodies. Cytokines, complement proteins, and other immune mediators participate in interconnected inflammatory pathways that contribute to tissue injury and organ dysfunction (Dai et al., 2025). Understanding these mechanisms is particularly important in pediatric SLE, given its frequently aggressive clinical course and substantial potential for long-term organ damage. Therefore, this literature review aimed to comprehensively examine the pathogenesis of childhood-onset SLE and its implications for disease progression, clinical manifestations, and patient outcomes.

METHOD

This study employed a narrative literature review approach to examine the pathogenesis of childhood-onset systemic lupus erythematosus (cSLE). A literature search was conducted

using PubMed, Embase, the Cochrane Library, and Google Scholar to identify relevant scientific publications addressing the molecular and immunological mechanisms underlying cSLE. The retrieved articles were screened for relevance to the research objectives, particularly their examination of genetic susceptibility, environmental triggers, immune dysregulation, loss of immune tolerance, abnormalities in apoptosis and apoptotic cell clearance, complement and cytokine pathways, and autoantibody production. Publications addressing these pathogenic mechanisms in pediatric populations were prioritized for inclusion.

The selected literature was analyzed using a descriptive narrative synthesis. Relevant findings were identified, categorized, and synthesized according to the major pathogenic mechanisms involved in cSLE. The analysis focused on the interactions among genetic predisposition, environmental influences, innate and adaptive immune dysregulation, autoantibody formation, and inflammatory pathways contributing to tissue and organ damage. The synthesized findings were organized thematically to provide a comprehensive understanding of the interconnected molecular and immunological processes underlying the development and progression of childhood-onset SLE.

RESULTS AND DISCUSSION

Patogenesis

The pathogenesis of LES is a complex mechanism. This pathogenesis involves various mechanisms from both the innate immune system and the adinfective immune system (Dai et al., 2025). The role of dendritic cells as part of the innate immune system in capturing antigens from cells that undergo apoptosis. These cells will then act as presenting cell antigens (APCs). These APC cells then activate B cells that differentiate into plasma cells to produce antibodies (autoantibodies). The antibodies formed will attack the antigens that come from the self which eventually causes an advanced inflammatory process due to the response of the formation of antigen-antibody complexes. The role of the innate and adaptive immune systems plays a key role and is related to each other in the pathogenesis of LES (Dai et al., 2025; Liu et al., 2022).

The etiopathology of LES is not yet known for sure, it is suspected to involve a complex and multifactorial interaction between genetic variation and environmental factors. Genetic factors are thought to play an important role in the predisposition of the disease. The interaction between sex, hormonal status and environmental factors affects the susceptibility and clinical expression of LES disease. This condition causes disorders (dysregulation) of the immune system which are aggravated by the above conditions. This complex mechanism will involve both T lymphocytes and B lymphocytes. This mechanism also begins with immune tolerance failure, apoptosis disorders, clearance mechanisms, and ends with the formation of autoantibodies (Liu et al., 2022; Mok & Lau, 2003).

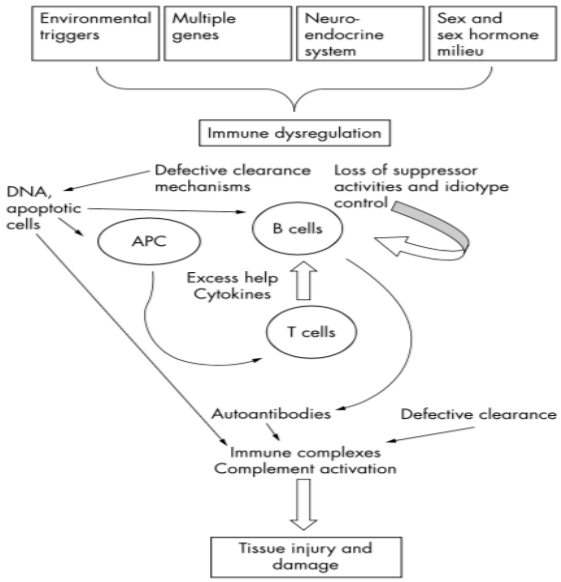


Figure 1. Pathogenesis of LES (Mok & Lau, 2003)

Immune Tolerance Failure

Immune tolerance failure is the main cause of the development of autoimmune diseases. This condition occurs when the control mechanisms to prevent the immune system from being damaged or malfunctioning do not work as they should, so that autoimmune diseases develop in an individual. The main mechanisms of immune tolerance failure, are divided into two main mechanisms (Li et al., 2022).

Central Tolerance Failure

This mechanism occurs during the development of lymphocytes in lymphoid organs. The maturation process of B lymphocytes occurs in the bone marrow, while T lymphocytes occur in the thymus. Lymphocytes that recognize high-affinity antigens are destroyed through the process of apoptosis. If this process fails, high-affinity lymphocytes that are hyperactive (autoreactive) will be released into the peripheral circulation. This is known as the negative selection mechanism (Li et al., 2022; Yu et al., 2018).

Peripheral Tolerance Failure

If autoreactive lymphocytes escape into the tissues, the body will have a second defense mechanism that occurs in the periphery. Lymphocytes that recognize antigens in the absence of a costimulator signal (danger signal) should become unresponsive or experience an anti-energy state. If this defense system fails, this mechanism will keep immune cells active and reactive that can attack against self-antigens. This failure can also occur when regulatory T cells suppress an excessive immune response. If the number or function of regulatory T cells decreases, then this mechanism will cause it to fail to suppress attacks that occur against self-antigens. This mechanism is known as peripheral tolerance failure (Yu et al., 2018).

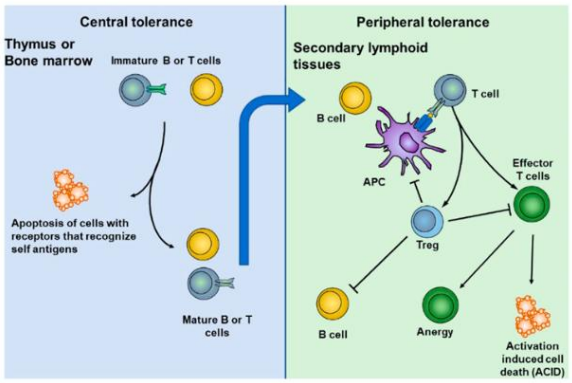


Figure 2. Immune Tolerance Failure (Yu et al., 2018)

Apoptosis Dysregulation and Clearance Mechanisms

Apoptosis is a normal process in cell regeneration, old or damaged cells will be programmed to die or destroy on their own. This happens so as not to harm the individual's body. In LES disease, there will be an increase in the rate of apoptosis. Apoptosis will result in an increase in the number of cells (such as lymphocytes and keratinocytes) that undergo cell death, so that a lot of nucleic acid material is released by the dead cell. In other conditions, mutations also play a role, mutations in certain genes, such as the FS-7-associated surface antigen (FAS) gene, which regulates cell death. This causes the elimination of T lymphocytes to be ineffective, so that immune cells that should have died remain alive and cause tissue damage (Mahajan et al., 2016).

In general, in most cases, LES experiences a mutation in complements. This will affect complement pathways (C) such as C1q, C1r, C1s, C2, C4A and C4B. This pathway will cause inflammation and immune activation through mechanisms that are not yet known for sure. A single mutation in a gene that can cause C1q deficiency will increase the risk of LES by more than 90%, and C4 complement deficiency also increases the risk of LES. Disruption of the clearance mechanism of antigen-antibody complexes results in the accumulation of these antigen-antibody complexes in peripheral tissues, triggering local inflammatory reactions, cytokine release, and immune cell infiltration. This sequence of pathways is at the core of the general pathogenicity of LES (Clavarino et al., 2025; Mahajan et al., 2016).

Complement Pathways and Cytokines

Systemic lupus erythematosus causes the immune system to become hyperactive and invade healthy tissues through a mechanism of autoantibody formation involving complex pathways including complement pathways and cytokines. This condition results in partial organ damage that will be irreversible as the main result of the inflammatory process that occurs. Systemic lupus erythematosus is characterized by the activation of B lymphocyte cells that form an antibody as a key process of an autoimmune disease. This process, in addition to producing antibodies, also produces cytokines, which can serve as biomarkers and predictors of disease activity (Chen et al., 2025; Richter et al., 2023).

Complement pathways play an important role in the pathogenesis of LES. The role of complements is very complex, as they can be protective and when their numbers decrease they exacerbate disease activity. The duality of this complement role in LES and in particular the classical pathway is very special. The complement pathway plays an important role in the

clearance mechanism of cell aopthosis and the elimination of antigen-antibody complexes (Richter et al., 2023).

An overactive complement system can cause excessive inflammation and tissue damage, while hypoactivation of complement can disrupt the clearance mechanism of apoptotic waste and antigen-antibody complexes, thereby promoting the occurrence of autoimmune diseases. Systemic lupus erythematosus in children can be found in hereditary deficiencies in the classical complement pathway (C1q, C3, C4), which increases the high risk of developing LES. Activation of the classical pathway in people with LES causes an increase in the consumption of C3 and C4 proteins. C3 and C4 proteins will settle in the tissues, especially the kidneys, so that C3 and C4 levels are found to decrease in blood tests. Therefore, complements are involved in the inflammation of LES, but complement deficiency itself will trigger the development of LES (Clavarino et al., 2025; Richter et al., 2023).

Once autoantigen recognition and alarm signalling are received, the innate immune response will play a role in the production of type I interferon (IFN-1), primarily by plasmacytoid dendritic cells (pDC). The cell dendritic will act as an APC so that it will then lead to the activation of the adaptive immune system and end up with the formation of autoantibodies (Zhang et al., 2009). Antigen-antibody complexes that settle in the tissue will activate complement. The cleansing of the antigen-antibody complex will be played by complement with the formation of a membrane attack complex (MAC) in an effort to destroy the antigen-antibody complex. It will also stimulate the activation of other immune cells and then cause tissue inflammatory processes and end up with damage to various organs. In addition, this complement pathway will bind to complement receptors involving CR3, CR4, and CR2 (CD21) which will enhance the pathogenic process by facilitating the presentation of the antigen by dendritic cells and culminate in the differentiation of B cells into plasma cells which ends in the formation of antibodies (Chen et al., 2025; Richter et al., 2023).

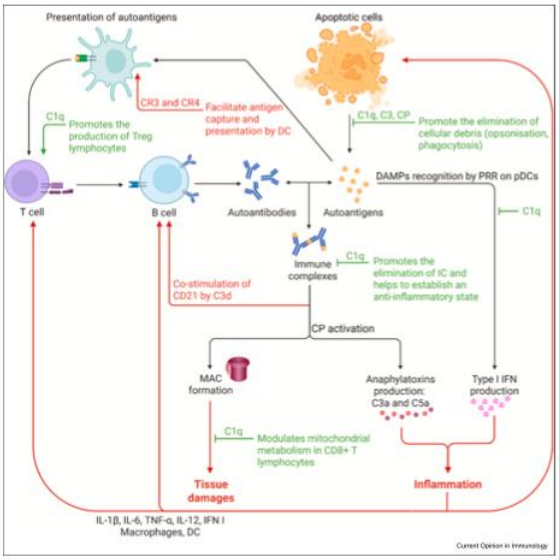


Figure 3. The Role of Complement in the Process Inflammatory (Clavarino et al., 2025)

Interleukin 17 (IL-17) contributes to the pathogenesis of LES. High serum levels of IL-17 are positively correlated in LES patients and are associated with higher and increased LES (Systemic Lupus Erythematosus Disease Activity Index/SLEDAI) disease activity index scores in LES patients (Izati et al., 2020). Increased levels of IL-17 in serum and increased number of cells producing IL-17 occur in most pediatric LES. In addition, higher levels of IL-17 are found in LES with the involvement of certain organs such as the skin, lungs, and kidneys. This suggests that IL-17 plays an important role in tissue damage in people with LES (Izati et al., 2020; Zhang et al., 2009).

The IL-23/IL-17 axis has an important role in the pathogenesis of LES. Active dendritic cells (DC) will produce inflammatory cytokines such as IL-6 and IL-23, stimulating Th-17 cells to produce IL-17. In addition, because IL-17 and IL-23 play a role in LES with renal involvement, which we know as lupus nephritis (Izati et al., 2020; Zhang et al., 2009). A 2009 study concluded that IL-17 is directly involved in the inflammatory process of the kidneys in people with LES, and is used as a marker in assessing the prognosis of lupus nephritis. This study explicitly suggests that the IL-23/IL-17 axis plays an important role in the pathogenesis of LES. Both cytokines may be useful as biomarkers for assessing the prognosis of LES with renal involvement (Zhang et al., 2009).

Another cytokine that plays a role is interleukin 12 (IL-12). This interleukin has various important roles in the immune system. Interleukin-12 is produced by dendritic cells and macrophages. Interleukin 12 as a bridging between the innate and adaptive immune systems. Interleukin-12 is a pro-inflammatory cytokine that induces the differentiation of naïve T-helper (Th) cells into Th-1 cells (Larosa et al., 2019).

Interleukin-12 induces various cytotoxic pathways and cytotoxic mediator expression by increasing the production of interferon gamma (IFN-□). The role of IL-12 can also activate natural killer (NK) cells and be involved in the formation of cytotoxic T lymphocytes. Interferon gamma induced by IL-12 is essential in the development of various autoimmune diseases including LES. IL-12 levels were found to be higher in people with LES and positively correlated with disease activity and negatively correlated with C3 complement levels (Larosa et al., 2019; Paradowska-Gorycka et al., 2016).

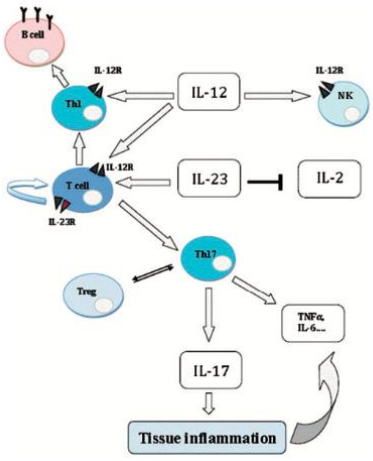


Figure 4. The role of IL-12 and IL-17 on Tissue Inflammation in LES (Larosa et al., 2019)

Autoantibody Production

In LES patients, there is a disruption of the clearance mechanism for cells that undergo apoptosis. In LES patients, autoantibodies are formed against nucleic acid components (antigen-antibody complexes) which are the most important contributors to the development of LES disease. This complex mechanism is accompanied by various mechanisms such as loss of immune tolerance, increased antigenic load, excessive expression of T cells, disruption of B cell suppression and the switch of immune response from T helper 1 (Th-1) to T helper 2 (Th-2) which causes hyperactivity of B cells and produces antibodies that are pathogenic to the components of the individual's body itself. The antibodies that are formed are antibodies to nucleic acids so that the target of the antigen is any nucleated cell that produces nucleic acids that can be dispersed in various organ systems (Pagkopoulou et al., 2025).

In addition to nucleic acids, the antibodies formed are directed at self molecules found in the cytoplasm, cell surface, and also at dissolved molecules such as IgG and coagulation factors. Anti-nuclear antibodies (ANA) are the most common antibodies found in people with LES (more than 95%). Anti-double stranded DNA (anti-dsDNA) and Anti-Smith (anti-Sm) are antibodies specific to LES, so the immunological component is included in the classification criteria of LES (Koga et al., 2021; Pagkopoulou et al., 2025).

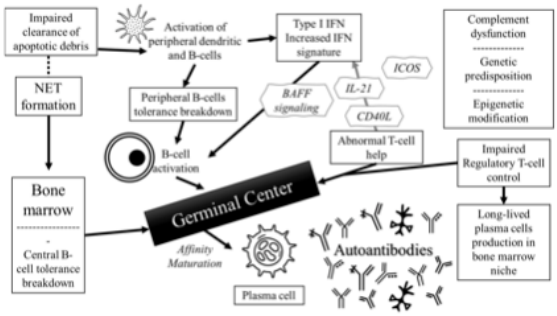


Figure 5. Autoantibody Production (Pagkopoulou et al., 2025)

CONCLUSION

Childhood-onset systemic lupus erythematosus (cSLE) is a complex, multisystem autoimmune disease that frequently exhibits a more aggressive clinical course and greater disease activity than adult-onset SLE. Pediatric SLE is characterized by distinctive clinical manifestations, molecular abnormalities, and patterns of disease progression. Genetic susceptibility plays a particularly prominent role in its pathogenesis, especially in patients with early disease onset. Impaired clearance of apoptotic cellular debris contributes to the accumulation of nuclear autoantigens, including DNA and RNA-associated components, which promote immune dysregulation and the loss of immunological tolerance. Interactions among genetic predisposition, hormonal influences, particularly estrogen signaling, and environmental triggers further contribute to autoreactive lymphocyte activation, autoantibody production, and immune complex formation. These processes stimulate proinflammatory cytokine signaling, including type I interferon pathways, leading to persistent systemic inflammation and subsequent tissue and organ damage. Collectively, these interconnected molecular and immunological mechanisms contribute to the development, clinical heterogeneity, and progression of childhood-onset SLE.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

The author is responsible for all stages of the research, including the conceptualization of the research, the preparation of the methodology, the search and selection of the literature, the analysis of data, the interpretation of the results, the preparation of the manuscript, and the final revision of the article. The author has read and approved the final version of the manuscript for publication.

GENERATIVE AI STATEMENT

The author states that Generative Artificial Intelligence (AI) is not used to produce research data, conduct scientific analysis, or replace the author's intellectual contribution in the preparation of this manuscript. When used in the manuscript preparation process, AI is only used to a limited extent to help improve the language and writing structure. The author remains fully responsible for the accuracy, integrity, and final content of the manuscript.

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