

# A brief insight into systemic lupus erythematosus pathogenesis

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## Abstract

Systemic lupus erythematosus is an autoimmune disease which afflicts many systems. The precise pathogenesis is still unclear, but strong evidences sustain a multifactorial mechanism, based on the interaction of various genetic, epigenetic, environment, hormonal and immune-regulatory factors. Nowadays, the research interest focuses on cellular and molecular alterations, as results of the complexity of apoptotic process and immune responses acting as initiators and leading to tissue injury. The paper points out on key pathogenic cells, molecules and processes involved in SLE pathogenesis, namely B and T lymphocytes, mast cells, apoptosis, complement system and oxidative stress.

**Keywords:** *systemic lupus erythematosus, pathogenesis, B/T lymphocytes, apoptosis, mast cells, complement system, oxidative stress*

## Epidemiologic landmarks

Systemic lupus erythematosus (SLE) is an autoimmune condition characterized by various clinical manifestations associated with the presence in 90% of cases of anti-nuclear auto-antibodies. Due to the complex pathogenic context, extremely well studied, mainly on murine models, SLE is regarded as "prototype" for the autoimmune pathology [1, 2]. Occurrence of tissue lesions as well as clinical symptoms is determined by genetic, epigenetic, environment, hormonal and immune-regulatory factors [1, 2].

The most afflicted category of population is that of young women, with a peak incidence between 15 and 40 years and a 6-10:1 female to male ratio. African-American, Latin and Asian individuals have a higher prevalence of SLE and multiorgan damage than other ethnic

groups [3, 4].

Renal impairment is recorded in 50-80% of juvenile lupus cases, without variations between ethnic groups, and in less than 30% of late SLE cases [5-10]. Renal damage may represent the first manifestation of SLE, however it is frequently diagnosed at 1-5 years from the onset of the disease; it may also arise at more than 5 years after initiation, in any moment of evolution [11, 12].

## Pathogenic mechanism

The main character in the pathogenic mechanism of SLE is the immune system [13, 14]. The above mentioned factors act either independently or jointly on the immune system, triggering the production of autoreactive B lymphocytes or abnormal types of activated T lymphocytes and of antigen presenting cells, with the consequent manufacture of auto-antibodies, immune complexes and cytokines, all these elements leading to installation of inflammation and,

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subsequently, of specific organ lesions [13-15].

Over-activation of immune system is especially promoted by genetic factors [16]. Genetic influences are often a cumulated effect of several genes, while rarely they rise due to presence of numerous nucleotide polymorphisms or to a single gene defect – resulting in an increased risk for SLE [16]. It is well ascertained the essential role played by genes responsible for immune regulation, HLA polymorphism, synthesis of IFN- $\alpha$ , complement proteins, receptors for immunoglobulins or Toll-like, cell-adhesion molecules, and molecules involved in lymphocyte activation (STAT4, BLK, PTPN22) [16].

Currently, researches on the pathogenic mechanism of SLE are focused on cellular and molecular alterations. The most recent theories target: (i) the role of apoptosis, through a defect in removal of cell debris resulted from apoptosis, which may become auto-antigens, (ii) the role of dendritic and T cells, abnormally activated by the afflux of autoantigens resulted from apoptosis, which produce excessive cytokines – in the circumstances of a disturbance in the mechanism of T lymphocytes regulation; (iii) the role of hyperactivated B lymphocytes [13, 14].

The resulted autoantibodies and immune complexes are important mediators required in the occurrence of tissue damage characteristic for morphologic lesions of SLE (such as lupus nephritis). Nevertheless, the immune complexes are insufficient to explain the sequences of pathogenic mechanism. The intervention of complement and cytokines is mandatory, since they are responsible for the amplification and maintenance of autoimmune processes.

The alternative pathway of complement system activation [17] and oxidative stress [18] are also considered noteworthy participants in SLE pathogenesis.

#### *B lymphocyte signaling*

Studies on murine models revealed abnormal signaling mechanisms through B lymphocytes, with the AKT/mTOR pathway playing an essential role [19, 20]. The gene

analysis of signaling molecules specific for B lymphocytes identified two inhibitor receptors, Lyn and CD22, which are critical in the regulation of B lymphocyte phenotype expressed in SLE. Additionally, Fc $\gamma$ RIIB is another inhibitor receptor with a key role in impeding the development of this phenotype [19].

#### *B lymphocyte tolerance*

The failure in B cell tolerance is considered another significant event in triggering the pathogenic mechanism of SLE. The central tolerance process takes place in bone marrow, the immature auto-reactive B lymphocytes being removed, mainly through interventions concentrated on their specific receptors [21, 22]. Approximately 55-75% of immature B cell receptors are auto-reactive, while normal tolerance mechanisms eliminates them from B lymphocyte repertoire [23]. B cells that surpass central tolerance will migrate into the spleen and will become mature cells. In this stage, the auto-reactive B lymphocytes are eliminated through peripheral tolerance mechanisms (deletion, anergy, follicular exclusion and clonal ignorance) [24]. Supplementary, recent study have shown that auto-reactive B lymphocytes originating in the germinal center of lymph nodes are tolerate if the auto-antigens (i.e. nucleoproteins released during apoptosis), are expressed in large quantities in the vicinity of the germinal center [25]. If B lymphocytes are antigen-independent, the tolerance mechanisms involve Toll-like receptors (TLR7 and TLR9) and dendritic cells [26, 27].

#### *T lymphocyte signaling*

Multiple anomalies have been identified in T lymphocytes signaling pathways in SLE patients [28]. Experimental studies on murine SLE models have shown that stimulation of T lymphocyte receptor (TCR) induces increased intracellular calcium levels in T cells. This is caused by levels of CD3 $\zeta$ , an extremely important component of TCR signaling pathway [29], which are compensated by the increased expression of analogues of Fc $\epsilon$ R $\gamma$  molecules [30]. Unlike CD3zeta, Fc $\epsilon$ R $\gamma$  does not bind the protein kinase associated with the zeta chain (ZAP $\zeta$ ), but conversely connects

with spleen tyrosin kinase (Syk), which results in the increase of calcium level after binding with TCR [31]. Inhibition of Syk leads to inhibition of the development of kidney disease hence anti-Syk therapy reduces levels of T lymphocytes and prolongs survival, despite the lack of effect on auto-antibodies production [32]. Therefore, the alteration of T lymphocyte signaling pathway determines the modification of intensity of autoimmune response and improvement of clinical symptomatology.

#### *Apoptosis*

Two defects of apoptosis are associated with SLE: (i) the failure of immune system cells to enter apoptosis program, due to defects in Fas pathway, which leads to production of auto-reactive lymphocytes, triggering initiation of pathogenic mechanism of SLE; (ii) the impairment of the removal for apoptotic debris causes inflammation, which implies activation of TLR7 and TLR9 pathway, leading to initiation of pathogenic mechanism of SLE [33].

#### *Mast cells*

Besides lymphocytes and macrophages, a significant number of mast cells contribute to the structure of the inflammatory infiltrate [34, 35]. The role of the mast cell in SLE pathogeny currently represents an interesting issue, due to the enormous potential to synthesize and release inflammatory factors [36]. However, there are no data which correlate the number of mast cells with SLE severity. On the other hand, recent experimental data substantiate the involvement of these cells in protective actions, as they intervene in tissue repair and remodeling processes following inflammation [37]. Unfortunately, reproducibility of these results was not possible [38], which makes the positive role of mast cells questionable.

#### *Complement system and oxidative stress*

Complement system ensures the balance between tissue protection and destruction,

through three known activation pathway (classic, alternative and lectin pathway). This dual role is manifested in SLE through protection achieved by clearance of immune complexes and apoptotic debris and destruction, which through its products, mediates the inflammatory process developed in the kidney and other target organs [17].

Specifically, in SLE the alternative pathway is preferentially activated, its selective inhibition being beneficial – probably due to positive effects of the activation of classic and lectin pathway [17, 39].

Concurrently, pathogenic mechanism of SLE involves also the critical intervention of oxidative stress, which has the potential to promote an autoimmune response. Assessment of oxidative stress may have prognostic value for the evolution of SLE [40]. Recent evidence indicates that the imbalance in oxidative stress, translated through increase of malondialdehyde (MDA) levels and decrease of natural antioxidants is a major event in progression of SLE [41-44]. Increased levels of MDA are correlated with intense activation of the alternative pathway of complement, both being in accordance with SLE activity [18, 39, 45, 46]. Moreover, it was proved that activation of alternative pathway of complement and presence of MDA represents major mediators for tissue inflammation in SLE progression [47].

Consequently, it is believed that inhibition of oxidative stress may represent a novel therapeutic approach in SLE, oriented both at the cellular as well as molecular level [48].

#### **Final remarks**

The understanding of the mechanism responsible for the pathogenesis of SLE requires a better knowledge of the intimate relationships developed between cells and molecules involved in apoptosis and immune responses.

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