

Cytokines in Systemic Lupus Erythematosus: Their Role in Pathogenesis of Disease and Possible Therapeutic Opportunities

Leili Tahernia,¹ Shideh Namazi,² Nima Rezaei,^{2,3,4,*} and Vahid Ziaee^{5,6}

¹Children's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, IR Iran

²Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, IR Iran

³Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, IR Iran

⁴Network of Immunity in Infection, Malignancy and Autoimmunity, Universal Scientific Education and Research Network, Tehran, IR Iran

⁵Pediatric Rheumatology Research Group, Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, IR Iran

⁶Department of Pediatrics, Tehran University of Medical Sciences, Tehran, IR Iran

*Corresponding author: Nima Rezaei, Research Center for Immunodeficiencies, Children's Medical Center, Dr Gharib St., Keshavarz Blvd., Tehran, IR Iran. E-mail: rezaei_nima@tums.ac.ir

Received 2016 February 29; Revised 2016 March 15; Accepted 2016 April 09.

Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that may involve several organs. The disease is characterized by a recurring pattern of remission and flare. Immunologic factors seem to have important roles in the pathogenesis of SLE. Several studies revealed that cytokines are important in pathogenesis of this disorder. These cytokines include B-cell activating factor (BAFF), tumor necrosis factor (TNF), interferon (IFN), interleukin (IL)-23, IL-17, IL-10, IL-6 and IL-21. In this article, the role of cytokines and their encoding genes are described and therapeutic applications have been discussed briefly.

Keywords: Systemic Lupus Erythematosus, SLE, Pathogenesis, Immunologic Factors, Cytokines

1. Context

Lupus erythematosus is a group of autoimmune diseases that are characterized with vascular and connective tissue inflammation. All organs can be influenced in lupus yet kidneys, heart, nervous system and joints are the most affected organs in the systemic type and skin is affected in all groups (1, 2). Systemic lupus erythematosus (SLE) is more common in female (female/male: 9/1) adult population but it is not common in children and about 20% of patients are children below 15 years of age. The female to male ratio in children is 2-6 to 1 and in elderly population is 3 - 8 to 1 (3).

It seems the main contributing factor to this disease is the breakdown of body's tolerance towards autoantigens and subsequently, the rise of antibodies against the nucleus and cells (4, 5).

Overall, this disorder can be classified in four groups:

- Discoid lupus
- Systemic lupus erythematosus
- Drug induced lupus
- Neonatal lupus

2. Pathogenesis

Once cellular apoptosis is started with stimulating factors such as ultraviolet or autonomous mechanisms, the expression of acid nucleic auto-antigens increases and this subsequently, triggers a self-immune response.

Once the cells are damaged, antimicrobial peptides, such as LL37 and NET, are released and bind to immune complexes. These immune complexes are made of nucleic acid and antibodies. Therefore, they cannot be removed by macrophage and dendritic cells. However, these immune complexes are removed from the B-cell surface through FCYRIIA receptor and are entered into the cytoplasm through the endocytosis. Next, they bind to toll-like receptor 7/9 on the surface of the endosome.

This process causes the production of interferon- α by plasmacytoid dendritic cells. In addition, a small amount of autoantibodies are produced by cells. The generated interferon- α activates the myeloid dendritic cells.

After activation, the tolerance towards the body's antigen is broken, therefore, these dendritic cells present their antigens to CD4+ T-cells and activate them.

T-cell helps autoreactive B cells through binding to CD40/CD40L and production of interleukin (IL)-21, so this cell can generate autoantibodies. During the activation of DC cell, pro-inflammatory cytokines such as Tumor Necro-

sis Factor (TNF)- α , IL-6, B cell activating factors are produced. These cytokines influence B-cells, which cause the production of additional antibodies (6-18).

3. Important Factors in Pathogenesis of Systemic Lupus Erythematosus

Various factors are important in the pathogenesis of SLE, which can be divided to three major groups. All these factors cause breakdown in body's tolerance by stimulating immunologic response toward nucleic antigens. These factors are a) Environmental factors, b) Immunological factors and c) Genetic factors (19-21), that are explained in detail below.

3.1. Environmental Factors

Several environmental factors are considered as stimulating factors in pathogenesis of SLE. They include ultraviolet (UV), demethylating drugs, infections, intracellular viruses, virus-like factors and sexual hormones, but ultraviolet can also exacerbate SLE. Ultraviolet increases DNA breakdown on skin and leads to subsequent production of immune complex containing nucleic acid (men with SLE are less sensitive to light) (19, 21, 22).

Epstein Bar virus (EBV) enters B-cells and induces secretion of Interferon- α (IFN- α) by plasmacytoid dendritic cells, so it is considered as a potential factor in pathogenesis of SLE (20).

More than 100 drugs have been proposed to cause a form of SLE, which is called drug-Induced lupus (DIL). Drug-induced lupus pathogenesis is not completely understood, but it seems genetic factors play an important role. The most important medications are procainamide and hydralazine. These drugs change gene expression in CD40 T-cells by blocking DNA methylation and overexpression of leukocyte function dependent antigen (LFA-1); thus, they increase auto-reactivity in body cells (20).

Hormones are other environmental factors in stimulation of SLE. Hormones, such as estrogen and prolactin can cause autoimmune response by inducing maturation in auto-reactive B-cells with high affinity (19-24).

Exposure to chemical factors like cigarettes and trichloroethylene is another important environmental factor in SLE pathogenesis (25, 26).

3.2. Immunologic Factors

Inflammation and vascular endothelium irregularities including vascular damage, vasculitis and IC deposit are the main pathologies in SLE. Organ and tissue damage in SLE are due to unusual immune responses in the body. In healthy individuals, immunologic responses are triggered

only by infectious factors and foreign bodies. In SLE, there is immune system imbalance due to the body's response against autoantigens. This causes a breakdown in body's tolerance and stimulates auto-reactive T and B cells (21).

3.2.1. Auto-Antibodies

Central immunologic disorder in lupus is the formation of antibodies against innate antigens such as cytoplasmic and nucleic materials. These antibodies are named auto-antibodies. Two of these antibodies are classified in the lupus diagnostic criteria. These are anti-ds DNA and anti-sm antibodies. Anti DsDNA binds to back-bone nucleic acid parameters, while antibody level is changed based on the stage of disease activity and time. This titer is utilized in measurement of disease activity. Smith antigen is made of RNA (which is rich in uracil) and a number of Ribonucleoproteins (snRNP). These small nucleic snRNP have a role in RNA processing. Anti-Sm connects to central proteins in snRNP. Unlike anti-ds DNA, anti-sm level is constant throughout the disease period, so it can be used in SLE diagnosis (21, 27).

Moreover, there are a number of other antibodies involved in lupus, which are produced and identified in other autoimmune disorders. Anti-Ro antibody and anti-Lo antibody can be found in Sjogren syndrome and rheumatoid arthritis as well as lupus. These antibodies are related to neonatal lupus syndrome and subacute cutaneous lupus. Anti-phospholipid Ab, lupus anticoagulant Ab and coagulation system are related to anti phospholipid syndrome. This syndrome is characterized by venous and arterial thrombosis, fetus abortion and thrombocytopenia (21).

3.2.2. Immune Responses Disorders

Inappropriate activation of B cell, T cell and monocyte division is another feature in lupus. Auto antigens released from apoptotic cells are collected by APC and B cells. They are presented by MHC molecules to T lymphocytes. T lymphocytes help the release of auto antibodies by B cell stimulation. Moreover, B cell and T cell interaction by means of CD40/CD40 L signal produces IL10 and IL6 cytokines. These cytokines have a role in further activation of B cell and antibodies formation. In lupus, B cell polyclonal activation leads to an increase in auto antibodies production by distinction to plasma cells and long half-life pathogenic memory cells. Auto-antibodies production results in immune complex formation, which deposits in tissue due to no clearance. These immune complexes lead to activation of cells and complement cascade (13, 21).

3.2.3. Apoptosis in Systemic Lupus Erythematosus

Although, apoptosis rates in SLE increase yet, the underlying cause is not known. As a result of apoptosis, antigens and cells content are released. Naturally, apoptotic substances are cleared by phagocytic cells, but as mentioned before, lupus patients are unable to perform immune complexes clearance. Furthermore, FC receptor mediated phagocytosis of IgG (FCGR2A and FCGR3B) by monocytes and macrophage are impaired in SLE. This is a result of polymorphisms and copy number variations in receptor genes, respectively. On the other hand, defects in the initial components of classical complement pathway, C1q, C2 and C4 lead to a decrease in IC and apoptotic cells clearance (21). C1q connects directly to apoptotic cells, without presence of its receptors on phagocytic cells. In addition, C1q inhibits production of IFN- α from dendritic plasmoid cells (17).

3.2.4. Cytokine Cascade in Systemic Lupus Erythematosus

Cytokines are mediators, which are produced by immune cells specially T cell and other cells involved in immune responses. These cytokines can have inhibitory or excitatory roles according to T cell subgroups. Imbalance between Th1/Th2 cytokines is another important issue in SLE. There are paradoxical data about superiority in responses by Th1 or Th2, yet a rise in Th2 responses is obvious in SLE. Recent studies have highlighted the role of Th1 in pathogenesis of SLE (2, 28-34).

The most important Th1 and Th2 cytokines related to pathogenesis of SLE include TNF- α , IFN- α and IL12, and IL4, IL10, IL6 related to Th2 related to Th1, respectively. Moreover, some innate immune cytokines such as Proliferation Inducing Ligand (APRIL) and B-cell activating factor (BAFF) produced by APC cells (such as monocyte, macrophage and dendritic cells) are important in pathogenesis of SLE through proliferation of B cells (2, 28-34).

B cell activating factor (BAFF) and Proliferation Inducing Ligand (APRIL): BAFF and APRIL are two cytokines from the TNF family. The role of BAFF/APRIL system is not well understood in pathogenesis of SLE. The serum level of these cytokines increases in SLE. Some studies reported that there is a relationship between plasma level of BAFF and disease activity; yet, some studies claimed no relationship between them, which is totally against the first opinion, so it requires more assessments. Studies on transgenic rats demonstrated that BAFF over-expression leads to a T-cell independent lupus-like disease (30, 32, 35-38).

Increase in serum level of APRIL has been reported in the active phase of SLE and it has been suggested as a disease activity marker of SLE. It has been accompanied by an increase of IL-17 and IFN- γ . This association may be due to the role of Th17 helper in activation of SLE (39, 40).

Tumor necrosis factor (TNF)- α : TNF- α plasma level and its soluble receptor increase in SLE. They are related to disease activity. Besides, TNF- α is shown in mesangial cells in lupus nephritis. According to rat models, TNF is able to have both beneficial and deleterious effects. Tumor necrosis factor- α causes increase in autoantibodies and SLE exacerbation by inducing other pro-inflammatory cytokines, such as IL1 and IL6 (deleterious effect). It decreases production of IFN- α from plasmacytoid dendritic cells. It has been observed that treatment with anti-TNF antibodies in rheumatoid arthritis leads to a rise in lupus incidence. When treatments with these medications are discontinued, lupus symptoms are resolved (beneficial effects) (30, 32, 37, 41, 42). Although our recent study did not show any significant association between the gene encoding TNF- α and SLE, particular IL1 gene variants seem to affect individual susceptibility to juvenile-onset SLE (43).

Interferon (IFN)- α : Plasma level of IFN- α is increased in SLE. It is positively related to disease activity and antibody production. The role of IFN- α in pathogenesis of lupus was documented when it was used in the treatment of malignancies (such as Kaposi sarcoma) and viral infections (like hepatitis C and papilloma-virus). Interferon- α induces a lupus-like syndrome in these patients, which was undistinguishable from lupus disease. In addition, lupus symptoms disappeared when treatment with TNF- α was stopped. Moreover, interferon (type 1) gene expression increases in peripheral blood monocytes and involved organs. The pathologic role of this cytokine was verified by studying lupus rat models without IFN- α/β receptors; studies showed that disease severity incidence decrease in most rat models but not all of them (12, 18, 30, 32, 37, 44).

Interferon (IFN)- γ : IFN- γ is classified as TH1 cell cytokine. Rise in IFN- γ level in SLE was reported recently. It is involved in lupus pathogenesis by BAFF production. Interferon- γ is also related to disease activity. Genetic level of Th, mRNA (copy factor in TH1 differentiation) and IFN- γ are higher in patients with lupus in comparison with the control group. Patients with lupus nephritis demonstrate a dominant TH1 phenotype by IFN- γ over expression in peripheral blood and glomerulus. This phenotype is related to renal damage severity. Moreover, the role of IFN- γ in pathogenesis of SLE was proved by studying rat models with induced occurrence of fatal lupus. Autoantibodies production and glomerulonephritis incidence declines by omitting IFN- γ receptor (32, 45, 46).

Interleukin (IL) 23 / IL17: IL17 is a heterodimer cytokine. It includes an exclusive sub-unit, P19, and a common sub-unit with IL-12 naming P40. The IL23 is an important factor in pathogenesis of autoimmune diseases. Its abnormality was reported recently in SLE as well. There is an increase in mRNA expression of P40 and P19 sub-units in PBMC lupus

patients, between those that are not treated medically in comparison with lupus patients that are treated with immunosuppressive drugs. It is also higher in patients with active lupus compared to inactive lupus, so IL23 can be a good marker in SLE improvement. Interleukin-23 is able to stimulate T CD4 to produce IL17 and IFN- γ . These cytokines are effective in SLE progression. Lupus nephritis clinical and pathologic signs are decreased in MRL/LPV rate due to IL23 receptor defects. It seems that IL23 is an essential component in renal disease (32, 46).

Interleukin-17, which is known as IL17A, is a pro-inflammatory cytokine with an important role in inflammation regulation. Six types of IL17 have been identified, from IL17A to IL17F. These interleukins are homologues in structure. Increase in serum level of IL17 is reported in lupus. Interleukin-17 significantly induces B-cell proliferation and antibodies production with BAFF (30, 32, 37, 46).

Interleukin-10: Plasma level of IL10 increases in SLE and is related to disease activity. The role of IL10 in SLE is complicated. It stimulates activity, proliferation and disparity in B-cells. It also decreases apoptosis in auto-reactive B-cells in germinal center by mean of Bcl-2 expression. Therefore, it increases autoantibodies production. Interleukin-10 injection in adoptive transfer lupus rats increases renal disease whereas treatment with monoclonal antibodies against IL10 in the same rats inhibits disease occurrence. Previous studies have indicated the role of IL10 in pathogenesis of lupus (32, 37, 38, 46, 47). Meanwhile our recent study showed lack of association between IL10 and juvenile-onset SLE (48).

Interleukin-6: Similar to many systemic inflammatory diseases, plasma level of IL6 increases in SLE. Interleukin-6 is important in pathogenesis of SLE in two ways: on one hand, it affects B-cells and stimulates their proliferation and distinction to plasma cells, as a result, it escalates antibody production from plasma cells. On the other hand, it affects T-cells and differentiates it to TH17 by IL23 and TGF- β . Interleukin-6 regulates differentiation to TREG T-cell by suppression of Fox P3 (30, 32, 37, 46).

Interleukin-4: Although the role of IL4 in autoimmunity is well understood, there are a few studies on the role of IL4 in SLE. Renal immunoglobulin deposition was inhibited in IL-4 deficiency (49). It seems the role of IL4 in SLE is dependent on genetic background. Some studies showed that IL4 gene polymorphisms might be involved in the etiology and susceptibility of SLE (50, 51). We showed in our recent study on JSLE patients that IL-4 gene variants are associated with JSLE and might have a role in the pathophysiology of disease (50). An association between polymorphisms of interleukin-4 gene and discoid rash was reported in Chinese patients with SLE (52).

Interleukin-21: Plasma level of IL21 increases in SLE

patients. There is a relationship between polymorphism changes in cytokines encoding genes and lupus. Interleukin-21 is produced from follicular T helpers. It triggers differentiation and evolution in T helpers and stimulates antibody production in auto-reactive B cells in germinal centers. According to a study on San Roque rats, mutation in Roquin protein (a E3 ligase from ring-finger protein family, which encodes RC3hL gene) leads to an increase in ICOS expression (inducible-T cell co-stimulator and IL21 production). They cause a lupus-like disease. Roquin protein is a regulating factor in T helpers' differentiation. T helpers are important in germinal center response in spleen and increasing B cell response to antigens. San Roque mutation is a hypermorphic allele, which is produced by a point mutation in Roq protected domain. It causes Roquin impaired function. Rch31 san/san rats with G57BL/6 genetics have a systemic lupus-like autoimmune disease. This disease produces a germinal center in spleen and increases T helpers and dsDNA antibodies and immunoglobulins in plasma. The result is pre-pubertal death in the majority of rats.

T helpers in Rch31 san/san rats express high levels of ICOS. This results in involuntary production of Gc in the spleen. Roquin has a key role in mRNA Icos expression in T cells by binding to (3'-UTR) mRNA (3'-untranslated region). Defect in Rc3hl function leads to an increase in ICOS and mRNA stability in T helper CD4. As a result, a high level of ICOS is expressed at T cell levels. They interact with auto-reactive B cells and induce autoimmune response. There is a decrease in lupus incidence in knock out rats due to lack of IL2 receptors. These two studies demonstrate the role of IL21 in SLE pathogenesis (32, 53).

3.2.5. Cytokines Role in Systemic Lupus Erythematosus Treatment

We discussed on a number cytokines, which were important in the pathogenesis of lupus. There are some biological factors against these cytokines. These biological factors are being used to treat SLE (Table 1).

3.2.6. Proliferation Inducing Ligand (APRIL) and B-cell activating factor (BAFF) Inhibitors

- Belimumab: Belimumab is the first biological drug approved for the treatment of lupus. It is a recombinant monoclonal IgG1 antibody. It connects to BAFF and prohibits BAFF binding to its receptors (33, 54-57).

- Atacept: It is a chimeric protein that inhibits both BAFF and APRIL. It is more effective than Belimumab. This molecule is made of the FC part of antibody and extracellular domain of TACI (33, 54-56).

It should be noted that BAFF has three receptors, TAC-I, BCMA and BR3. B-cell activating factor connects to all three

Table 1. Biological Agents in the Treatment of Systemic Lupus Erythematosus, Target Points and Mechanism of Action

Drug name	Target	Clinical Trial Phase	Mechanism of Action
Belimumab	BAFF	1 - 3	Connects to BAFF and prohibits BAFF binding to its receptors
Atacicept	BAFF and APRIL	2 - 3	Inhibits both BAFF and APRIL and inhibits B cell activation
Sifalimumab	IFN- α	1 - 2	Reduces IFN- α plasma level
Rontalizumab	IFN- α	1 - 2	Declines IFN-related gene expression
NNC 0152-0000-0001	IFN- α	1	Suppression of IFN type I
IFN-α Kinoid	IFN- α	1 - 2	Suppression of IFN type I
Anti-IFN-γ(AMG 811)	IFN- γ	1	Reduces IFN- δ level
Rituximab	CD20	1 -	Antibody against CD20 marker, which induces CD20 B cell apoptosis
Epratuzumab	CD22	1 - 3	B cell apoptosis
Tocilizumab	IL-6 Receptor	1 - 2	Inhibits IL6 binding to its both receptors

Abbreviations: APRIL, proliferation inducing ligand; BAFF, B cell activating factor; SLE, systemic lupus erythematosus; IL, Interleukin; IFN, Interferon.

receptors and stimulates B cell and antibody production. While, APRIL binds only to TAC-I and BCMA receptors. When BAFF is inhibited alone, APRIL stimulates B cell and antibody production by connecting to these receptors (33).

- Rituximab: This is a chimeric monoclonal antibody against CD20 marker, which induces CD20 B cell apoptosis. It is not effective against plasma cells without CD20 marker (54, 56).

- Epratuzumab: A human monoclonal antibody against CD22 marker on B cells, which reduces cell antibody and antibody production (54, 56).

- Tocilizumab: A human monoclonal antibody against IL6 receptors, which inhibits IL6 binding to its both receptors (54, 56).

3.2.7. Monoclonal Antibody Against Interferon - α Include

- Sifalimumab (MEDI-545): This medication reduces IFN- α plasma level dose-dependently (33, 54, 55).

- Rontalizumab: It declines IFN-related gene expression dependently (33).

- Anti IFN-gamma (AMG 811): is a human monoclonal antibody, which reduces IFN- δ level dose dependently (33).

- NNC 0152-0000-0001 (33)

- IFN- α kinoid (IFN α vaccine) (33)

3.3. Genetic Factors

There are some evidences of genetic underlying factors in SLE pathogenesis. The risk for lupus is higher between siblings compared to unrelated people. Moreover, inheritance (> 66%) and disease similarity (20 - 40%) between identical twins are higher in comparison with non-identical twins. All these facts demonstrate a genetic base for lupus. According to a Genome-Wide Association Study

(GWAS) there are lots of genes involved in the pathogenesis of SLE such as HLA-DR, PTPN 22, STAT4, IRF5, BLK OX40L FC δ R IIA, BANK 1-IRAK-1, TNF AIP3, C2, C4, CD19 and IT GAM. These genes are involved in three biological processes: (41)

- Immune complex processing

- TLR message transport

- Message transport in lymphocytes

In this part, we explain some important genetic factors in SLE pathogenesis.

3.3.1. HLA Polymorphisms

First genomic region reported for SLE was MHC. This region is about 7.6 mb. It is located on chromosome 6 and classified in three major groups, which are class I, II and III. Class I and II are HLA proteins that are located in plasma proteins. Their main role is antigen presentation. HLA class III includes proteins that are involved in encoding some cytokines and complement cascade. Among HLA class-II alleles, HLA-DR2, DR3 are the most related genes to SLE in the Caucasian population; these alleles can increase the risk of SLE by two to three folds. There are also HLA-DQ and DR that are linked to lupus autoantibodies (58).

Class II: There are a number of genes in the MHC region that are not in the HLC family, but are related to SLE. In class II, we have TAPI and TAPII genes (transporter ATP-binding protein) (41, 58).

Class III: In class III, we have TNF- α , Super killer Vivaldic activity 2 (SKIV 2L) and cAMP natural killer (CREBL-1). These activate natural killer cells through the cytosols. We also have NOTCH-4 and MSH-5 in this class. GWAS study on European women showed that MSH5 is the most related gene to SLE. However, further researches are necessary to determine MSH5 or a related gene as a risk factor for SLE

(41, 58).

Class I: In this class, there are genes including MIC-B and 2H2 (G-Protein coupled receptor, olfactory receptor-2) that can activate natural killer cells through the cytosoles (41, 58).

3.3.2. Complement Genes

It is known that this regulation in complement cascade enhances SLE symptoms; for example, subjects that have a homozygote mutation in C19 gene usually present lupus with skin presentations and acute glomerulonephritis. However, subjects that have mutations in C2 and C4 genes, usually have a mild presentation of lupus that affects small joints and skin. Mutations in c2 are common and mutations in C4 are rare (1/10000 and less than 1/10000, respectively) (41, 58).

Two main forms of C4 genes, which are C4a and C4b are created as a result of copy number variations. These two forms are highly associated with SLE. Yong and colleague showed that in the European population, the number of these copy number variations (CNV) in C2 gene is variable, between two and six (it is about 0 to 5 for C4a and 0 to 4 CNV for C4b). This study demonstrated that a decrease in number of CNV in C4 gene is associated with increase in risk of SLE, while the higher number of CNV in C4 gene is a protective factor for SLE. It seems that elimination of immune complexes (IC) is important in this process. Indeed, lower CNV is correlated with less IC elimination (41, 58).

3.3.3. FC δ RIIA and FC δ RIIA Genes

These two genes are involved in SLE pathogenesis. These genes encode receptors that are critical in elimination of immune complexes binding to IgG. F17 6 v mutation is highly frequent in SLE patients. This mutation happens in FC δ RIIA gene with low affinity. Subjects with V/V genotype have high affinity for IgG1 and IgG3. H131R alleles in FC δ RIIA with low affinity for IgG are more common in African-American patients with lupus. Homozygote H/H people have higher affinity for IgG2 compared to subjects with RR genotype (41).

It has also been shown that the lower rate of CNV in FC δ RIIB gene is positively correlated with higher risk of SLE, for example subjects that don't have a CNV in their FC δ RIIB gene are at higher risk of SLE development. It has been suggested that decreases in IC elimination rate are important in this process (41, 58).

3.3.4. Genes Dependent on IFN-Type I

The production of IFN type I is induced by immune complexes (that contain nucleic acid) and message transporting through TLR endosomal receptors (TLR7/9). Recent

GWAS studies have identified several genes that are important in SLE pathogenesis. These genes appear to encode factors that regulate expression of IFN type I, including IRF5, IRAK-1 and TNAIP3. Once immune complexes connect to TLR endosomal receptors, IRAK-1 activates and induces IFN regulating factor (IRF5). Ultimately, the result is expression of IFN type I. A number of polymorphisms in IRAK1 and IRF5 are known in expression of these genes that result in the over-expression of IFN-type I. Furthermore, the SNP (rs2004640) located inside the IRF5 gene has the strongest association with lupus. TNFAIP3 gene suppresses the expression of IRAK-1. Therefore, it modulates the expression of IFN-type I. It has been identified that mutation in this gene can increase the production of these cytokines and finally, causes SLE in subjects (41, 58).

3.3.5. PIPN22

PIP22 is a tyrosine phosphatase that is located in the short arm of chromosome 1. This gene is expressed in lymphoid cells. It encodes a phosphatase enzyme that is called LYP. LYP is a potent suppressor of T cells activation. It has a molecular weight of 105 KDa. On the N-terminal, there is a catalytic phosphatase site, which is similar to other tyrosine non-phosphatase receptors. Also at the end of the protein, there are 200 amino acids that generate four motifs enrich in proline, these are called P1-P4.

The P1 motif binds to SH3 tyrosine kinase CSK, which blocks signal transduction from T cells. Among the SNPs identified on PIPN22, only SNP rs2476601 appears to be associated with SLE. This SNP causes C (cytosine) to T (thymidine) mutation (5). Subsequently, it causes an amino-acid change from arginine to tryptophan (W) on codon number 620. This codon is on the P1 motif. This mutation increases phosphatase activity of LYP and decreases binding of LYP to CSK binding cells. LYP 620W also suppresses signal transduction from T cell receptors more effectively compared to LYP 620R. Therefore, this mutation causes dysregulation in the negative selection process and decreases the rate of elimination of auto-reactive T cells during thymus selection.

This mutation can suppress the activity of regulatory T cell and subsequently increase the immunological reaction towards auto-antigens. Nonetheless, more studies are required to identify the mechanism that this mutation causes. This mutation is highly frequent in European people and less frequent in people from Asia and Africa. However, it appears that this mutation has stronger association with SLE in Mexican children compared to adults from Europe.

Other GWAS studies have shown an interaction between this gene and other genes like BLK and BANK-1 in SLE pathogenesis. BLK affects B cell tolerance and also affects

the activity of mature B cells. Bank-1 changes the activity of B cell and ultimately causes SLE. In addition, there is a relationship between SNP and lupus nephritis (41).

3.3.6. STAT-4

One haplotype on the third interon of STAT-4 gene has been introduced to be associated with SLE. This haplotype was identified through a study in SLE patients from North America, Sudan and three additional independent studies also confirmed the findings of this original study. These studies also showed that this haplotype can increase the risk of rheumatoid arthritis as well as SLE. These findings have been replicated in studies on other ethnic groups (41, 59).

4. Conclusions

Lupus appears to be a chronic systemic autoimmune disease and considerably heterogeneous in terms of clinical symptoms. The main cause of this disease is still unknown. However, numerous studies indicate that lupus is a result of interaction between environmental, immunological and genetic factors. These interactions breakdown body tolerance towards endogenous antigens and cause abnormal immunologic response to healthy tissue, resulting in tissue damage. A number of studies have been conducted on patients with SLE and animal models of this disease. These studies indicate that over expression of a number of cytokines is important in the pathogenesis of SLE. Over expression of inflammatory cytokines increases the proliferation of auto reactive B cells and results in higher production of autoantibodies. Numerous genetic factors, that are involved in processing of immune complex, signal transduction from TLR (for the production of IFN type I) and signal transduction from lymphocytes are considerable in SLE pathogenesis.

References

1. Fu SM, Deshmukh US, Gaskin F. Pathogenesis of systemic lupus erythematosus revisited 2011: end organ resistance to damage, autoantibody initiation and diversification, and HLA-DR. *J Autoimmun.* 2011;**37**(2):104–12. doi: [10.1016/j.jaut.2011.05.004](https://doi.org/10.1016/j.jaut.2011.05.004). [PubMed: [21632208](https://pubmed.ncbi.nlm.nih.gov/21632208/)].
2. Namazi S, Ziaee V, Rezaei N. The role of cytokines in systemic lupus erythematosus: review article [in Persian]. *Tehran Univ Med.* 2015;**73**(6):3997–404.
3. Lisnevskaja L, Murphy G, Isenberg D. Systemic lupus erythematosus. *Lancet.* 2014;**384**(9957):1878–88. doi: [10.1016/S0140-6736\(14\)60128-8](https://doi.org/10.1016/S0140-6736(14)60128-8). [PubMed: [24881804](https://pubmed.ncbi.nlm.nih.gov/24881804/)].
4. Tobon GJ, Izquierdo JH, Canas CA. B lymphocytes: development, tolerance, and their role in autoimmunity-focus on systemic lupus erythematosus. *Autoimmune Dis.* 2013;**2013**:827254. doi: [10.1155/2013/827254](https://doi.org/10.1155/2013/827254). [PubMed: [24187614](https://pubmed.ncbi.nlm.nih.gov/24187614/)].
5. Ahearn JM, Liu CC, Kao AH, Manzi S. Biomarkers for systemic lupus erythematosus. *Transl Res.* 2012;**159**(4):326–42. doi: [10.1016/j.trsl.2012.01.021](https://doi.org/10.1016/j.trsl.2012.01.021). [PubMed: [22424435](https://pubmed.ncbi.nlm.nih.gov/22424435/)].
6. Rottman JB, Willis CR. Mouse models of systemic lupus erythematosus reveal a complex pathogenesis. *Vet Pathol.* 2010;**47**(4):664–76. doi: [10.1177/0300985810370005](https://doi.org/10.1177/0300985810370005). [PubMed: [20448279](https://pubmed.ncbi.nlm.nih.gov/20448279/)].
7. Liu Y, Yin H, Zhao M, Lu Q. TLR2 and TLR4 in autoimmune diseases: a comprehensive review. *Clin Rev Allergy Immunol.* 2014;**47**(2):136–47. doi: [10.1007/s12016-013-8402-y](https://doi.org/10.1007/s12016-013-8402-y). [PubMed: [24352680](https://pubmed.ncbi.nlm.nih.gov/24352680/)].
8. Rullo OJ, Tsao BP. Recent insights into the genetic basis of systemic lupus erythematosus. *Ann Rheum Dis.* 2013;**72** Suppl 2:56–61. doi: [10.1136/annrheumdis-2012-202351](https://doi.org/10.1136/annrheumdis-2012-202351). [PubMed: [23253915](https://pubmed.ncbi.nlm.nih.gov/23253915/)].
9. Darrah E, Andrade F. NETs: the missing link between cell death and systemic autoimmune diseases?. *Front Immunol.* 2012;**3**:428. doi: [10.3389/fimmu.2012.00428](https://doi.org/10.3389/fimmu.2012.00428). [PubMed: [2335928](https://pubmed.ncbi.nlm.nih.gov/2335928/)].
10. Aringer M, Gunther C, Lee-Kirsch MA. Innate immune processes in lupus erythematosus. *Clin Immunol.* 2013;**147**(3):216–22. doi: [10.1016/j.clim.2012.11.012](https://doi.org/10.1016/j.clim.2012.11.012). [PubMed: [23290784](https://pubmed.ncbi.nlm.nih.gov/23290784/)].
11. Lewis JE, Fu SM, Gaskin F. Autoimmunity, end organ damage, and the origin of autoantibodies and autoreactive T cells in systemic lupus erythematosus. *Discov Med.* 2013;**15**(81):85–92. [PubMed: [23449110](https://pubmed.ncbi.nlm.nih.gov/23449110/)].
12. Shrivastav M, Niewold TB. Nucleic Acid sensors and type I interferon production in systemic lupus erythematosus. *Front Immunol.* 2013;**4**:319. doi: [10.3389/fimmu.2013.00319](https://doi.org/10.3389/fimmu.2013.00319). [PubMed: [24109483](https://pubmed.ncbi.nlm.nih.gov/24109483/)].
13. Fortuna G, Brennan MT. Systemic lupus erythematosus: epidemiology, pathophysiology, manifestations, and management. *Dent Clin North Am.* 2013;**57**(4):631–55. doi: [10.1016/j.cden.2013.06.003](https://doi.org/10.1016/j.cden.2013.06.003). [PubMed: [24034070](https://pubmed.ncbi.nlm.nih.gov/24034070/)].
14. Conti G, Coppo R, Amore A. Pathogenesis of systemic lupus erythematosus (LES) [in Italian]. *G Ital Nefrol.* 2012;**29** Suppl 54:S84–90. [PubMed: [22388837](https://pubmed.ncbi.nlm.nih.gov/22388837/)].
15. Chan VS, Nie YJ, Shen N, Yan S, Mok MY, Lau CS. Distinct roles of myeloid and plasmacytoid dendritic cells in systemic lupus erythematosus. *Autoimmun Rev.* 2012;**11**(12):890–7. doi: [10.1016/j.autrev.2012.03.004](https://doi.org/10.1016/j.autrev.2012.03.004). [PubMed: [22503660](https://pubmed.ncbi.nlm.nih.gov/22503660/)].
16. Choi J, Kim ST, Craft J. The pathogenesis of systemic lupus erythematosus—an update. *Curr Opin Immunol.* 2012;**24**(6):651–7. doi: [10.1016/j.coi.2012.10.004](https://doi.org/10.1016/j.coi.2012.10.004). [PubMed: [23131610](https://pubmed.ncbi.nlm.nih.gov/23131610/)].
17. Sturfelt G, Truedsson L. Complement in the immunopathogenesis of rheumatic disease. *Nat Rev Rheumatol.* 2012;**8**(8):458–68. doi: [10.1038/nrrheum.2012.75](https://doi.org/10.1038/nrrheum.2012.75). [PubMed: [22664835](https://pubmed.ncbi.nlm.nih.gov/22664835/)].
18. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med.* 2011;**365**(22):2110–21. doi: [10.1056/NEJMr1100359](https://doi.org/10.1056/NEJMr1100359). [PubMed: [22129255](https://pubmed.ncbi.nlm.nih.gov/22129255/)].
19. Mak A, Tay SH. Environmental factors, toxicants and systemic lupus erythematosus. *Int J Mol Sci.* 2014;**15**(9):16043–56. doi: [10.3390/ijms150916043](https://doi.org/10.3390/ijms150916043). [PubMed: [25216337](https://pubmed.ncbi.nlm.nih.gov/25216337/)].
20. Bertias G, Cervera R, Boumpas DT. Systemic Lupus Erythematosus: Pathogenesis and Clinical Features. In: Wilhelmus J, Bijlsma J, editors. *Eular Textbook on Rheumatic Diseases*. Switzerland: Eular; 2012. pp. 476–505.
21. Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. *J Clin Pathol.* 2003;**56**(7):481–90. [PubMed: [12835292](https://pubmed.ncbi.nlm.nih.gov/12835292/)].
22. Zandman-Goddard G, Solomon M, Rosman Z, Peeva E, Shoenfeld Y. Environment and lupus-related diseases. *Lupus.* 2012;**21**(3):241–50. doi: [10.1177/0961203311426568](https://doi.org/10.1177/0961203311426568). [PubMed: [22065092](https://pubmed.ncbi.nlm.nih.gov/22065092/)].
23. Wahren-Herlenius M, Dorner T. Immunopathogenic mechanisms of systemic autoimmune disease. *Lancet.* 2013;**382**(9894):819–31. doi: [10.1016/S0140-6736\(13\)60954-X](https://doi.org/10.1016/S0140-6736(13)60954-X). [PubMed: [23993191](https://pubmed.ncbi.nlm.nih.gov/23993191/)].
24. Nielsen CT. Circulating microparticles in systemic Lupus Erythematosus. *Dan Med J.* 2012;**59**(11):B4548. [PubMed: [23171755](https://pubmed.ncbi.nlm.nih.gov/23171755/)].
25. Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS. Smoking and use of hair treatments in relation to risk of developing systemic lupus erythematosus. *J Rheumatol.* 2001;**28**(12):2653–6. [PubMed: [11764212](https://pubmed.ncbi.nlm.nih.gov/11764212/)].
26. Cooper G, Gilbert K, Greidinger E, James J, Pfau J, Reinlib L, et al. Recent advances and opportunities in research on lupus: environmental influences and mechanisms of disease. *Cien Saude Colet.* 2009;**14**(5):1865–76. [PubMed: [19851599](https://pubmed.ncbi.nlm.nih.gov/19851599/)].

27. Pisetsky DS. The immunopathogenesis and immunopathology of systemic lupus erythematosus. In: Schur PH, Massarotti EM, editors. *Lupus erythematosus: clinical evaluation and treatment*. New York: Springer; 2012. pp. 13–26.
28. Su DL, Lu ZM, Shen MN, Li X, Sun LY. Roles of pro- and anti-inflammatory cytokines in the pathogenesis of SLE. *J Biomed Biotechnol*. 2012;2012:347141. doi: [10.1155/2012/347141](https://doi.org/10.1155/2012/347141). [PubMed: 22500087].
29. Lee HM, Sugino H, Nishimoto N. Cytokine networks in systemic lupus erythematosus. *J Biomed Biotechnol*. 2010;2010:676284. doi: [10.1155/2010/676284](https://doi.org/10.1155/2010/676284). [PubMed: 20414360].
30. Yap DY, Lai KN. The role of cytokines in the pathogenesis of systemic lupus erythematosus - from bench to bedside. *Nephrology (Carlton)*. 2013;18(4):243–55. doi: [10.1111/nep.12047](https://doi.org/10.1111/nep.12047). [PubMed: 23452295].
31. Apostolidis SA, Lieberman LA, Kis-Toth K, Crispin JC, Tsokos GC. The dysregulation of cytokine networks in systemic lupus erythematosus. *J Interferon Cytokine Res*. 2011;31(10):769–79. doi: [10.1089/jir.2011.0029](https://doi.org/10.1089/jir.2011.0029). [PubMed: 21877904].
32. Davis LS, Hutcherson J, Mohan C. The role of cytokines in the pathogenesis and treatment of systemic lupus erythematosus. *J Interferon Cytokine Res*. 2011;31(10):781–9. doi: [10.1089/jir.2011.0047](https://doi.org/10.1089/jir.2011.0047). [PubMed: 21787222].
33. Ronnblom L, Elkon KB. Cytokines as therapeutic targets in SLE. *Nat Rev Rheumatol*. 2010;6(6):339–47. doi: [10.1038/nrrheum.2010.64](https://doi.org/10.1038/nrrheum.2010.64). [PubMed: 20440285].
34. Perl A. Systems biology of lupus: mapping the impact of genomic and environmental factors on gene expression signatures, cellular signaling, metabolic pathways, hormonal and cytokine imbalance, and selecting targets for treatment. *Autoimmunity*. 2010;43(1):32–47. doi: [10.3109/08916930903374774](https://doi.org/10.3109/08916930903374774). [PubMed: 20001421].
35. Scholz JL, Oropallo MA, Sindhava V, Goenka R, Cancro MP. The role of B lymphocyte stimulator in B cell biology: implications for the treatment of lupus. *Lupus*. 2013;22(4):350–60. doi: [10.1177/0961203312469453](https://doi.org/10.1177/0961203312469453). [PubMed: 23553778].
36. Vincent FB, Saulep-Easton D, Figgitt WA, Fairfax KA, Mackay F. The BAFF/APRIL system: emerging functions beyond B cell biology and autoimmunity. *Cytokine Growth Factor Rev*. 2013;24(3):203–15. doi: [10.1016/j.cytogfr.2013.04.003](https://doi.org/10.1016/j.cytogfr.2013.04.003). [PubMed: 23684423].
37. Karageorgas TP, Tseronis DD, Mavragani CP. Activation of type I interferon pathway in systemic lupus erythematosus: association with distinct clinical phenotypes. *J Biomed Biotechnol*. 2011;2011:273907. doi: [10.1155/2011/273907](https://doi.org/10.1155/2011/273907). [PubMed: 22162633].
38. Vincent FB, Morand EF, Schneider P, Mackay F. The BAFF/APRIL system in SLE pathogenesis. *Nat Rev Rheumatol*. 2014;10(6):365–73. doi: [10.1038/nrrheum.2014.33](https://doi.org/10.1038/nrrheum.2014.33). [PubMed: 24614588].
39. Boghdadi G, Elewa EA. Increased serum APRIL differentially correlates with distinct cytokine profiles and disease activity in systemic lupus erythematosus patients. *Rheumatol Int*. 2014;34(9):1217–23. doi: [10.1007/s00296-014-3020-4](https://doi.org/10.1007/s00296-014-3020-4). [PubMed: 24748505].
40. Eilertsen GO, Nossent JC. APRIL levels strongly correlate with IL-17 in systemic lupus erythematosus. *Lupus*. 2014;23(13):1383–91. doi: [10.1177/0961203314543914](https://doi.org/10.1177/0961203314543914). [PubMed: 25057039].
41. Connolly JJ, Hakonarson H. Role of cytokines in systemic lupus erythematosus: recent progress from GWAS and sequencing. *J Biomed Biotechnol*. 2012;2012:798924. doi: [10.1155/2012/798924](https://doi.org/10.1155/2012/798924). [PubMed: 22654485].
42. Postal M, Appenzeller S. The role of Tumor Necrosis Factor-alpha (TNF-alpha) in the pathogenesis of systemic lupus erythematosus. *Cytokine*. 2011;56(3):537–43. doi: [10.1016/j.cyto.2011.08.026](https://doi.org/10.1016/j.cyto.2011.08.026). [PubMed: 21907587].
43. Ziaee V, Tahghighi F, Moradinejad MH, Harsini S, Mahmoudi M, Rezaei A, et al. Interleukin-6, interleukin-1 gene cluster and interleukin-1 receptor polymorphisms in Iranian patients with juvenile systemic lupus erythematosus. *Eur Cytokine Netw*. 2014;25(2):35–40. doi: [10.1684/ecn.2014.0352](https://doi.org/10.1684/ecn.2014.0352). [PubMed: 25109676].
44. Ronnblom L. The type I interferon system in the etiopathogenesis of autoimmune diseases. *Ups J Med Sci*. 2011;116(4):227–37. doi: [10.3109/03009734.2011.624649](https://doi.org/10.3109/03009734.2011.624649). [PubMed: 22066971].
45. Frieri M. Accelerated atherosclerosis in systemic lupus erythematosus: role of proinflammatory cytokines and therapeutic approaches. *Curr Allergy Asthma Rep*. 2012;12(1):25–32. doi: [10.1007/s11882-011-0236-1](https://doi.org/10.1007/s11882-011-0236-1). [PubMed: 22113625].
46. Iwata Y, Furuichi K, Kaneko S, Wada T. The role of cytokine in the lupus nephritis. *J Biomed Biotechnol*. 2011;2011:594809. doi: [10.1155/2011/594809](https://doi.org/10.1155/2011/594809). [PubMed: 22028590].
47. Okamoto A, Fujio K, Okamura T, Yamamoto K. Regulatory T-cell-associated cytokines in systemic lupus erythematosus. *J Biomed Biotechnol*. 2011;2011:463412. doi: [10.1155/2011/463412](https://doi.org/10.1155/2011/463412). [PubMed: 22219657].
48. Rezaei A, Ziaee V, Sharabian FT, Harsini S, Mahmoudi M, Soltani S, et al. Lack of association between interleukin-10, transforming growth factor-beta gene polymorphisms and juvenile-onset systemic lupus erythematosus. *Clin Rheumatol*. 2015;34(6):1059–64. doi: [10.1007/s10067-015-2877-2](https://doi.org/10.1007/s10067-015-2877-2). [PubMed: 25633651].
49. Deocharan B, Marambio P, Edelman M, Putterman C. Differential effects of interleukin-4 in peptide induced autoimmunity. *Clin Immunol*. 2003;108(2):80–8. [PubMed: 12921753].
50. Mahmoudi M, Tahghighi F, Ziaee V, Harsini S, Rezaei A, Soltani S, et al. Interleukin-4 single nucleotide polymorphisms in juvenile systemic lupus erythematosus. *Int J Immunogenet*. 2014;41(6):512–7. doi: [10.1111/iji.12152](https://doi.org/10.1111/iji.12152). [PubMed: 25320043].
51. Yu HH, Liu PH, Lin YC, Chen WJ, Lee JH, Wang LC, et al. Interleukin 4 and STAT6 gene polymorphisms are associated with systemic lupus erythematosus in Chinese patients. *Lupus*. 2010;19(10):1219–28. doi: [10.1177/0961203310371152](https://doi.org/10.1177/0961203310371152). [PubMed: 20530519].
52. Wu MC, Huang CM, Tsai JJ, Chen HY, Tsai FJ. Polymorphisms of the interleukin-4 gene in chinese patients with systemic lupus erythematosus in Taiwan. *Lupus*. 2003;12(1):21–5. [PubMed: 12587822].
53. Sarra M, Monteleone G. Interleukin-21: a new mediator of inflammation in systemic lupus erythematosus. *J Biomed Biotechnol*. 2010;2010:294582. doi: [10.1155/2010/294582](https://doi.org/10.1155/2010/294582). [PubMed: 20652041].
54. Rajadhyaksha AG, Mehra S, Nadkar MY. Biologics in SLE: the current status. *J Assoc Physicians India*. 2013;61(4):262–7. [PubMed: 24482965].
55. Jordan N, Lutalo PM, D'Cruz DP. Novel therapeutic agents in clinical development for systemic lupus erythematosus. *BMC Med*. 2013;11:120. doi: [10.1186/1741-7015-11-120](https://doi.org/10.1186/1741-7015-11-120). [PubMed: 23642011].
56. van Vollenhoven RF, Parodis I, Levitsky A. Biologics in SLE: towards new approaches. *Best Pract Res Clin Rheumatol*. 2013;27(3):341–9. doi: [10.1016/j.berh.2013.07.006](https://doi.org/10.1016/j.berh.2013.07.006). [PubMed: 24238691].
57. Stohl W. Therapeutic targeting of the BAFF/APRIL axis in systemic lupus erythematosus. *Expert Opin Ther Targets*. 2014;18(4):473–89. doi: [10.1517/14728222.2014.888415](https://doi.org/10.1517/14728222.2014.888415). [PubMed: 24521424].
58. Relle M, Schwarting A. Role of MHC-linked susceptibility genes in the pathogenesis of human and murine lupus. *Clin Dev Immunol*. 2012;2012:584374. doi: [10.1155/2012/584374](https://doi.org/10.1155/2012/584374). [PubMed: 22761632].
59. Tiffin N, Adeyemo A, Okpechi I. A diverse array of genetic factors contribute to the pathogenesis of systemic lupus erythematosus. *Orphanet J Rare Dis*. 2013;8:2. doi: [10.1186/1750-1172-8-2](https://doi.org/10.1186/1750-1172-8-2). [PubMed: 23289717].