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Review Article **Open Access**

Cytokines in systemic lupus erythematosus: their role in pathogenesis of disease and possible therapeutic opportunities

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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: cytokines, immunologic factors, pathogenesis, SLE, systemic lupus erythematosus.

Introduction

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 (Abs) 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.

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 (ICs). 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 these cells can generate autoantibodies. During the activation of dendritic cell, pro-inflammatory cytokines such as Tumor Necrosis Factor (TNF)-α, IL-6 and B cell activating

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factors are produced. These cytokines influence B cells, which cause the production of additional antibodies [6-18].

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 [9-12], that are explained in detail below.

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].

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].

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-dsDNA 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-dsDNA, 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].

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 antigen presenting cell (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/CD40L signal produces IL-10 and IL-6 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 tissues due to no clearance. These immune complexes lead to activation of cells and complement cascade [13, 21].

Apoptosis in systemic lupus erythematosus

Although apoptosis rates in SLE is increased 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 macrophages 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].

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 IL-12, for Th1, and IL-4, IL-10, IL-6 for Th2, 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 transgenetic 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 T Helper 17 (Th17) 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 IL-1 and IL-6 (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 IL-1 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. IFN-α role in pathogenesis of lupus was documented when using it in treatment of malignancies (such as Kaposi Sarcoma) and viral infections (like hepatitis C and papilloma-virus). IFN-α induced a lupus like syndrome in these patients, which was undistinguishable from lupus disease. In addition, lupus symptoms were disappeared when stopping 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 cytokines 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. Rising in IFN-γ level in SLE is reported recently. It is involved in lupus pathogenesis by BAFF production. IFN-γ is also related to disease activity. The level of IFN-γ mRNA and protein are higher in lupus patients 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 decline by omitting IFN-γ receptor [32, 45, 46].

Interleukin (IL) -23/IL-17*:* IL-17 is a heterodimer cytokine. It includes an exclusive sub-unite P19 and a common sub-unite with IL-12 naming P40. IL-23 is an important factor in pathogenesis of autoimmune diseases. Its abnormality is reported recently in SLE as well. There is an increase in mRNA expression of P40 and P19 sub-unites in PBMCs of lupus patients 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 IL-23 can be a good marker of SLE improvement. IL-23 is able to stimulate T CD4 to produce IL-17 and IFN-γ. These cytokines are effective in SLE progression. Lupus nephritis clinical and pathologic signs are decreased in MRL/LPV rate due to IL-23 receptor defects. It expresses that IL-23 is an essential component in renal disease [32, 46].

IL-17, which is known as IL-17A, is a pro-inflammatory cytokine with an important role in inflammation regulation. Six type of IL-17 are identified yet, from IL-17A to IL-17F. Theses interleukins are homologues in structure. Increase in serum level of IL-17 is reported in lupus. IL-17 induces B cell proliferation and antibodies production significantly with BAFF [30, 32, 37, 46].

IL-10: Plasma level of IL-10 increases in SLE and is related to disease activity. The role of IL-10 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. So, it increases autoantibodies production. IL-10 injection in the adoptive transfer lupus rats increases renal disease whereas treatment with monoclonal antibodies against IL-10 in the same rats inhibits disease occurrence. This studies prone the role of IL-10 in pathogenesis of lupus [32, 37, 38, 46, 47]. Meanwhile our recent study showed lack of association between IL-10 and juvenile-onset SLE [48].

IL-6: Similar to lots of systemic inflammatory diseases, plasma level of IL-6 increases in SLE. IL-6 is important in pathogenesis of SLE in two ways: In 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 them to TH-17 by IL-23 and TGF-β. IL-6 regulates differentiation to regulatory T cell by suppression of FoxP3 [30, 32, 37, 46].

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

IL-21: Plasma level of IL-21 increases in SLE patients. There is a relationship between polymorphism changes in cytokines encoding genes and lupus. IL-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 study on Sanroque rat, mutation in Roquin protein (a E3 ligase from ring-finger protein family which encodes Rc3h1 gene) leads to increase in ICOS expression (inducible T cell co-stimulator and IL-21 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. Sanroque mutation is a hypermorphic allele which is produced by a point mutation in Roq protected domain. It cause Roquin impaired function. Rc3h1 san/san rats with G57BL/6 genetic have a systemic lupus like autoimmune disease. It produces germinal center in spleen and increases T helpers and, dsDNA antibodies and immunoglobulins in plasma. The result is prepubertal death in majority of rats.

T helpers in Rc3h1 san/san rats express high levels of ICOS. This results in involuntary production of Gc in 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 increase in ICOS and mRNA stability in T helper CD4.As a result, a high level of ICOS expresses 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 IL-21 receptors. These two studies demonstrate the role of IL-21 in SLE pathogenesis [32, 53].

Cytokines role in systemic lupus erythematosus treatment

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

Table 1. Biological agents used 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 & APRIL	2-3	Inhibits both BAFF and APRIL and inhibit 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	1-3	Antibody against CD20 marker which induces CD20 B cell apoptosis
Epratuzumab	CD22	1-3	B cell apoptosis
Tocilizumab	IL-6 Receptor	1-2	Inhibits IL-6 binding to its both receptors

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

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].
- Atacicept: 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, TACI, BCMA and BR3. B cell activating factor connects to all three receptors and stimulates B cell and antibody production. While, APRIL binds only to TACI and BCMA receptors. When BAFF is inhibited alone, APRIL stimulates B cell and antibody production by connecting to these receptors [33].

- Rithuximab: 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].

Monoclonal antibodies against interferon-α include

- Sifalmumab (MEDI-545): This medication reduces IFN-α plasma level dose dependently [33, 54, 55].
- Rontalizumab: It declines IFN-related gene expression dose dependently [33].
- Anti IFN-gamma (AMG 811): is a human monoclonal antibody, which reduces IFN-γ level dose dependently [33].
- NNC 0152-0000-0001 [33]
- IFN-α kinoid (IFN-α vaccine) [33].

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 nonidentical 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, PTPN22, STAT4, IRF5, BLK OX4OL FCγRIIA, BANK1, IRAK1, TNFAIP3, C2, C4, CD19 and ITGAM. 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.

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. The main role of HLA class I and II proteins 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 and 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].

There are a number of genes in the MHC region that are not in the HLA family, but are related to SLE:

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 cytosole [41, 58].

Class II: In class II, we have TAPI and TAPII genes (transporter ATP-binding protein) [41, 58].

Class III: In this class, we have TNF-α, superkiller viralicidic activity 2-like (SKIV2L) and cAmp natural killer (CREBL-1). These activate natural killer cells through the cytosols. We also have NOTCH4 and MSH5 in this class. GWAS 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].

Complement genes

It is known that cytosole 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 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].

FCγRIIA and FCγRIIIA genes

These two genes are involved in SLE pathogenesis. They encode receptors that are critical in elimination of immune complexes binding to IgG. F176V mutation is highly frequent in SLE patients. This mutation happens in FCγRIIIA gene with low affinity. Subjects with V/V genotype have high affinity for IgG1 and IgG3. H131R alleles in FCγIIA 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 FCγRIIB gene is positively correlated with higher risk of SLE, for example subjects that don't have a CNV in their FCγRIIB 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].

Genes dependent on IFN type I

The production of IFN type I is induced by immune complexes (that contain nucleic acid) and massage transporting through TLR endosomic receptors (TLR7/9). Recent GWASs 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, IRAK1 and TNAIP3. Once immune complexes connect to TLR endosomic receptors, IRAK1 activates and induces IFN regulating factor (IRF5). Ultimately, the result is expression of IFN type I. A number of polymorphisms in IRAK1 and IRF5 genes are known 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 IRAK1. 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].

PIPN22

PIPN22 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 (tymidine) mutation [5]. Subsequently, it causes an amino-acid change from arginine (R) 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. LYP620W 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 GWASs have shown an interaction between this gene and other genes like BLK and BANK1 in SLE pathogenesis. BLK affects B cell tolerance and also affects the activity of mature B cells. Bank1 changes the activity of B cell and ultimately causes SLE. In addition, there is a relationship between SNP and lupus nephritis [41].

STAT4

One haplotype on the third interon of STAT4 gene has been introduced to be associated with SLE. This haplotype was identified through a study in SLE patients from North America and Sudan. Three additional independent studies also confirmed the findings of this original study. These studies 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].

Conclusion

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.

Conflict of interest

The authors declare no conflict of interest.

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