Molecular Aspects of Systemic Lupus Erythematosus

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Abstract. Systemic lupus erythematosus (SLE) is an autoimmune disease caused by combined genetic and environmental factors that change the normal pathways of human immunity. SLE is potentially fatal and carries significant morbidity. The SLE patient can inherit multiple predisposing genes. T The identified SLE genes generally affect activation of autoimmune responses, resulting in aggregation of immune complexes. In order to help diagnose SLE, specific disease index system is used. In this index system, a minimum of four categories must be met to diagnose a patient with SLE. Steroid medication for immunomodulation can result in various side effects in long term use. Therefore, further research is important not only for deeper understanding of SLE etiopathogenesis, mechanisms and diagnosis, but also for optimized or improved therapies.

Keywords: Systemic lupus erythematosus · Autoimmune disease · Etiopathogenesis

1 Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease caused by a combination of genetic and environmental factors. SLE susceptible gene can cause different mechanisms and disease manifestations [1]. SLE will dissipate the immune tolerance to nucleic acid-containing antigens that trigger the inflammation responses. Progressing disease can damage a number of organs, including the kidneys, cardiovascular system, skin, joints, and central nervous system. SLE is potentially fatal and can carry significant morbidity [2].

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SLE affects predominantly females, and its prevalence varies depending on geographic location and ethnicity [2]. The disease has extremely diverse clinical presentations. Some individuals display mild cutaneous or articular symptoms that do not need any major treatment and are controlled by a short period of low-dose steroids. In the other extreme, severe SLE of postpartum mothers can lead to organ failures and death in less than a week, despite treatment with immunosuppressive medications and high dose steroids [3].

2 Etiopathogenesis

Previous studies have established that the SLE pathogenesis alters three major immune pathways, by dissipation of adaptive immune tolerance, inducing defective clearance of apoptotic debris, and hyperactivating the innate immune system, especially in the Toll-like receptor (TLR) signalling and type I interferon (IFN) pathways [2].

Various genes can cause SLE susceptibility (Table 1), but the disease is due to a single gene in less than five percent of SLE patients. In most cases, multiple genes are involved, and usually at least four genes have been identified [4].

The SLE susceptibility genes that have been identified to date affect activation of autoimmune responses, resulting in aggregation of immune complexes [5]. Research also has found increased apoptosis and impaired phagocytosis in blood mononuclear cells of SLE patients [6, 7].

SLE gene variants can be classified by their effects on biological mechanisms. Some genes affect autoreactive lymphocytes, through reducing activation thresholds, enhancing antigen presentation of self-antigens, or accommodating the endurance of lymphocytes. Other SLE genes trigger immune response spontaneously or as a response of environmental factors. Some SLE susceptibility genes inhibit apoptosis mechanisms, triggering more inflammatory responses. Other susceptibility genes change immune cells activation by IgG immune complexes, resulting in tissue damage. Therefore, it was concluded that interplay of various susceptibility loci with environmental factors could affect SLE etiopathogenesis [8].

The first SLE genetic association discovered was the human leucocyte antigen (HLA) located in chromosome 6p21, housing approximately 200 genes, with most genes having their own immunological functions. Seven HLA Class II alleles were reported associated with SLE susceptibility. HLA-DR2 and HLA-DR3 were those most associated with SLE susceptibility in some ethnic populations [1, 4].

Precise mechanisms on how HLA-DR alleles cause SLE is not completely understood yet. The effect was presumed because of the influence of HLA-DR on the autoreactive T-cells through the presentation of molecular mimics [1].

Some SLE susceptibility genes, such as BANK1, are known to affect B cells function, causing failure in B cell tolerance. Three BANK1 SNPs are found associated with SLE disease. They are two non-synonymous substitutions in the inositol 1,4,5-triphosphaste receptor (IP3R) and ankyrin domains, rs10516487G>A in exon 2 encoding Arg61His and rs3733197G>A in exon 7 encoding Ala383Thr, and a noncoding SNP, rs17266594T>C, located in intron 1 of BANK1 at a putative splice branch point for exon 2 [10].

Table 1. Genes associated with SLE susceptibility [9]

	Gene associated with SLE
Lymphocyte signalling	BANK 1
	BLK
	CD80
	CSK
	ETS1
	HLA DR
	IL-10
	LYN
	PP2A
	PRDM1 (BLIMP1)
	PRKCB
	PTPN22
	RasGRP3
	STAT4
	TNFSF4 (OX40L)
Innate immune signalling	IFIH1
	IKZF1
	ILT3
	IRAK1
	IRF5
	IRF7
	IRF8
	TLR7
	TLR9
	TNFAIP3 (A20)
	TNIP3 (ABIN3)
	TYK2
	UBE2L3
Intra-renal signalling	ACE
	COL25A1
	KLK
	LAMC2

(*continued*)

Table 1. (*continued*)

	Gene associated with SLE
Immune complex clearance	ATG5
	DNAse1
	FCGR2A, 3A, 3B
	ITGAM
	TREX1

Autoantibody-producing B cells are activated with the help of T-cells via cytokines and co-stimulatory molecules. Primary signal from antigenic peptide by MHC and non-specific signal by co-stimulatory molecules' interaction start the activation of T-cells. The co-stimulatory molecules are CD28 on T cells with the B7 family B7-1 (CD80) and B7-2 (CD86) on antigen-presenting cells. The sCTLA-4 mRNA, which is expressed on non-stimulated T-cells, may hinder the interaction between B7 on antigen-presenting cells and mCTLA-4 on T-cells. As a result, a signal is sent to T-cells in order to trigger immune response. Meanwhile, there is a possibility sCTLA-4 to bind B7 on antigen presenting cells and therefore hinder with T-cell responses which is mediated by B7:CD28. sCD28 and sCTLA-4 have been found strongly associated with SLE patients, which suggests that sCD28 and sCTLA-4 have roles in T-cell activation [11].

Association of CSK with SLE has been identified to arise through the intronic polymorph of rs34933034. SLE has been associated with increased CSK expression and also with increased inhibitory phosphorylation of Lyn. In SLE patients with these susceptibility genes, B cell receptor (BCR)-mediated mature B cells activate and plasma IgM increases. The amount of transitional B cells is doubled in cord blood of SLE patients swith the susceptibility gene, suggesting that the Lyp-Csk complex increases disease occurrence by affecting B cell activation [12] (Table 2).

Lymphocytes express the Ets1 transcription factor, and studies have found ETS1 association with a number of autoimmune diseases. Of the polymorphisms of ETS1 identified in SLE patients, a SNP rs34846069 resides in the final exon of the gene, though without amino acid change (Asp440→Asp) [2].

The interferon-induced helicase C domain 1 (IFIH1) is located at chromosome 2 (2q24) and triggers IFN response, such as pro-inflammatory cytokines production and apoptosis. High levels of IFIH1 could enhance autoimmune response, thus contributing to disease progression by increasing the level of antinuclear autoantibodies. IFIH1 is responsible for activation of IFN-regulatory factors 3 and 7, NF-kB, and the rise of production of IFN. IFIH1 acts as a SLE activator because of its characteristic to recognizes dsRNA viruses. Viral infections may promote cellular injury and apoptosis, thus increasing autoantigens. Confirmed SNPs of IFIH1 include rs1990760 (A946T), associated with emergence of SLE through the risk allele A [13].

Angiotensin-converting enzyme (ACE) gene is located on long arm of chromosome 17. Polymorphisms occur with insertion or deletion of a 287 bp long Alu repeat sequence within intron 1. ACE increases the level of angiotensin II, which is a vasoactive peptide,

Table 2. SLE-associated genes with related SNPs according to disease phenotypes [1, 17]

Disease phenotypes	Definition	SLE associated gene with related SNPs
Skin manifestation	A rash on the face (cheeks and nose), often in a butterfly shape	VDR rs1168268 IL-6 174G/C FCGR2A rs1801274 ITGAM rs1143679
Serositis	Pleuritis or pericarditis	PTPN2 rs2542151 TRAF3IP2 rs33980500, rs13190932, and rs13196377
Kidney	Persistent protein or cellular casts in the urine	HLADR2, HLADR3 rs2187668 STAT4 rs7574865, rs11889341, rs7568275, and rs7582694 IRF5 rs2004640, rs2079197, and rs10488631 DNAse I Q222R TNFS4 rs2205960 ITGAM rs1143683, rs1143679 IRF7 rs4963128
Neurologic	Seizures or psychosis	TREX1 rs922075, rs6776700, rs6442123, rs2242150, and rs11797
Arthritis	Joint pain and swelling of two or more joints	ITGAM rs1143679 FGCR2A, FCGR3A VDR rs3890733 Mir146a rs2910164
Hematologic	Anemia, leukopenia, lymphopenia or thrombocytopenia	STK17A haplotype TAGTC IL-21 rs907715
Immunology	Positivity for anti-dsDNA, anti-Sm, or antiphospholipid antibodies	STAT4 rs7582694, rs7574865 C4 reduction TRAF3IP2 rs33980500 C3 reduction Mir146a rs2910164 Anti-dsDNA HLADR2, HLADR3 rs2187668 ITGAM rs1143679, rs9888739 IRF5 rsrs10488631 SSA/SSB IRF7 rs4963128 HCP5 rs3099855 HLADR3 rs2187668 HCP5 rs3099844

potent pro-inflammatory modulator, and growth factor. Angiotensin II stimulates the contraction of vascular smooth muscle cells and affects the proliferation of smooth muscle, monocyte adhesion, platelet adhesion and aggregation. Therefore, ACE gene insertion or deletion polymorphisms may contribute to SLE disease susceptibility in vasculitis and vascular changes [14].

The ITGAM gene is strongly associated with SLE susceptibility. ITGAM encodes for the CD11b chain of the Mac-1 integrin. The ITGAM polymorphism associated with SLE disease (rs1143679) results in substitution of arginine to histidine at position 77. This will lead to constraint of cell adhesion and integrin ligands mediation, phagocytosis and inflammatory cytokine production [15].

In SLE, the patient can inherit multiple susceptibility genes. The contribution of the SLE gene polymorphisms to the disease susceptibility is not yet fully understood. Gene interaction can be additive or epistatic. Epistatic gene interaction happens in human leukocyte antigen (HLA) and CTLA4, STAT4 and IRF5, ITGAM and IRF5, BLK and TNFSF4. SLE gene polymorphisms are involved in immunological response and hematologic mechanisms (HLA, ITGAM, STAT4, and IRF5). IL-10 and TNFS4 gene polymorphisms have been associated with SLE in several ethnicities. STAT4 is also associated with early onset and severe progression of the disease [16].

3 Epigenetics

Epigenetics refers to heritable gene conditions that do not result in DNA sequence change but entail change in the gene expression [18]. Epigenetic mechanisms for gene expression work through specific signalling to the target tissue. Changes in the molecular mechanism or epigenome result in disordered signalling molecules that are found in autoimmune diseases, including SLE. Deeper understanding of epigenetics in the SLE pathology and its mechanisms may help to find alternative SLE therapies [19].

One of the epigenetic mechanisms is DNA methylation, in which a methyl group is added to the 5′ carbon position of cytosine in cytosine-phosphate-guanosine (CpG) dinucleotides. Such mechanisms regulate RNA polymerases, transcription factors, and transcriptional co-activators. A change in DNA methylation patterns is one of the possible causes of SLE. Both two methylation patterns, i.e. increased and reduced DNA methylation, n can appear at the same time in a patient of an autoimmune disease [19].

DNA methylation reduction in SLE patients occurs in CD6, CREM promoter P1, ESR1, HERVs, IFI44L, IKZF4, IL4, IL6, IL10, IL13, IL17A, IL17F, IRF7, ITGAL, KIR2DL4, MX1, PP2A, PRF1, TNFSF5, and TNFSF7 genes. Increasing DNA methylation in SLE patients happens in CD8A, CD8B, IL2, FOXP3, NOTCH1, and NR3C1 genes [19].

Besides DNA methylation, histone protein modification also contributes to SLE occurrence. Histone protein concentrates to octamers. Complexes of histone octamers with 147 base pairs of genomic DNA are called nucleosomes. Post-transitional modifications happen to histone proteins which control the availability of transcriptional factors and gene expression. Histone modifications include methylation, acetylation, phosphorylation, and citrullination [19].

Histone modification happens also in TNF, through H3 acetylation resulting in increased gene expression, leading to increased monocyte maturation and pro-inflammatory cytokine expression in SLE patients. Histone modification also happens in IL10, through H3K18 acetylation resulting in increased gene expression and B cell activation in SLE patients.

4 Renal Involvement

One common SLE manifestation is renal involvement or lupus nephritis, which can appear in up to 60% of SLE patients. Renal involvement can appear early or later as SLE is progressing. SLE susceptibility genes associated with renal involvement include HLA-DR3 and DR-2.[1] The STAT4 gene polymorphism rs7574865 is associated significantly with manifestation of severe nephritis, and is generally more strongly associated with SLE when the patients are showing nephritis symptoms [1].

5 Diagnosis

Broad symptoms of SLE make SLE difficult to differentiate with other diseases with similar symptoms, making it challenging in diagnosis. A specific disease index system is used to help on SLE diagnosis. In this system, a minimum four category criteria must be met to diagnose patient with SLE disease. Among these four diagnostic markers, one must include a clinical trait and one an immunological trait. Because of the strong association of SLE with lupus nephritis, diagnosis often depends on the existence of histological evidence of lupus nephritis and also on the presence of anti-nuclear or anti-dsDNA antibodies [8].

6 Therapy

Steroid medication is used as SLE therapy, hoping for total immunomodulation as the result of the medication. However, long-term steroid use can cause various side effects. Hydrochloroquine which is an antimalarial medication is being used as a preventive medication in SLE patients. It has been hypothesized that hydrochloroquine raises the pH level in intracellular vesicles and as a result blocks innate activation through endocytic receptors such as TLRs. Monoclonal antibodies targeting IFN-I are still being studied as a form of SLE therapy. This is only expected to lessen symptoms, not to remove them, and therefore monoclonal antibody therapies for IFN blockage might not be successful in treating SLE patients with critical condition. BlyS-neutralizing antibody is a medication more recently approved by FDA. It targets the survival of B-cell, resulting in reduction of B cells and autoantibodies, to maintain normal levels of C3 and C4 in SLE patients [8].

Systemic lupus erythematosus (SLE) is a potentially fatal polygenic inheritable autoimmunity disease, mainly affecting the female gender, with a wide range of symptoms but often involving kidneys.

Since the first SLE associated (HLA) genes were detected in 1970, many more have been discovered to trigger SLE or modify its severity. Certain polymorphisms can change the normal pathways of such genes and further promote SLE. In addition, epigenetic DNA methylation and histone modification are also heritable conditions that can cause or affect SLE. Other contributing factors can be cellular injury and apoptosis by viral infections, leading to increased autoantigens after being recognised by SLE activator genes like IFIH1.

Due to the large number of potentially contributing hereditary and environmental factors, the symptoms of SLE show wide variation and require a systematic approach like SLE indexing to help in correct diagnosis.

Also because of the wide range of causative factors and resulting symptoms, there has been until recently limited success in developing new mitigating and therapeutic medications for SLE. The traditional countermeasure of steroids can have side effects in long term use, and hydrochloroquine is more suited as preventive medication. A more recent FDA-approved solution is a BlyS-neutralizing antibody that will reduce B-cells and autoantibodies in SLE patients. Nevertheless, further research into understanding the SLE mechanisms remains important, to cover the detailed impact and significance of the associated factors.

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