# IMMUNOGENETICS OF LUPUS ERYTHEMATOSUS

*By*

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## ABSTRACT

*Kye words :* Lupus , Genetics, Association.

**Immunopathogenesis of SLE**

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease with a prevalence of approximately 1/2500 in European populations affecting mainly females (9 females:1 male) [1]. It's characterized by a plethora of immunological and laboratory abnormalities with multiple organ / tissue damage. Almost all of the key components in the immune system are involved in the disease pathogenesis which is largely still unclear [2] .

Deficiencies in the recognition and clearance of apoptotic cells by phagocytosis have been shown in patients with SLE [3,4]. Whether apoptosis itself is abnormal or merely an effect of environmental triggers, such as U.V. irradiation or viral infection, is less understood [5,6] .

During necrosis or apoptosis nuclear antigens are subjected to modifications which allow them to be rec-

ognized as non-self. Activation of TLR7 and TLR9 by self nucleic acids and immune complexes leads to the production of IFN-α and proinflammatory cytokines such as IL-6, TNF-? and IL-12 [7] .

IFN-α fosters autoimmunity by several mechanisms; It promotes dendritic cell maturation, the production of pro-inflammatory cytokines, stimulation of Thl pathways, B-cell activation , plasma cell differentiation and regulation of apoptosis [8]. In SLE the type IFNα can contribute to loss of tolerance and activation of autoreactive T and B cells with production of autoantibodies [9].

The expression of antinuclear antibodies (ANA) can be divided to three stages: antibody induction, maintenance and elimination. Antigens involved in the first two stages may not be the same. Indeed, there is evidence that viral and bacterial antigens can induce ANA production while self molecules may mediate antibody maintenance [10] .

However, recent studies by Schroeder et al 2013 [11], Detanico et al 2013 [12] argue that ANA arise predominantly from nonautoreactive B cells that are transformed into autoreactive cells by the process of somatic hypermutation , which is normally associated with affinity maturation during the germinal center reaction.

CD4 T cell differentiation is altered in SLE presented in the bias of TH1/TH2 balance to TH1 [13] and subsequently transcriptional factors T-bet /GATA3 to T-bet [14], and in the bias of TH17 / Treg to TH17 and subsequently transcriptional factors ROR?t/Foxp3 to RORαt [15,16]. Besides the role of follicular helper (TFH ) [17] in providing help to B cells allowing the formation of germinal center [18].

CD8 T cell function is impaired in peripheral blood T cells from patients with SLE. Double-negative T cells are also expanded and found within cellular infiltrates in kidney biopsies of patients with lupus nephritis with secretion of IL-1b and IL-17 [19] .

**SLE susceptibility genes**

Here we summarize the confirmed genetic risk loci placed in the context of major SLE disease pathways , where possible.

**1- Autoantigen generation, clearance & presentation related genes :**

**1.1- ATG5**

ATG5 which is a regulator of autophagy and apoptosis, was reported to be over-expression in SLE patients that may result in accelerated apoptosis [20] .

**1.2-GIMAP5**

Several studies have shown that GIMAP5 normally protects cells from apoptosis and that loss of GIMAP5 function results in decreased mitochondrial integrity with lymphocyte apoptosis and lymphopenia, the role of GIMAP5 in the pathogenesis of SLE was confirmed by Hellquist et al 2007[21] .

**1.3- FcγRs**

Reduced expression of FcγRIIb has been reported for memory B cells and plasma cells from SLE patients. Loss of FcγRIIB results in development of lupus-like symptoms in mice, with the development of autoantibodies and autoimmune glomerulonephritis. On the other hand, reduced function of the FcγRIIIB has been associated with impaired immune complex clearance and hence associated with disease susceptibility [7] .

**1.4-Complement**

Complement components facilitates clearance of immune complexes and apoptotic cells.So, their deficiency especially in the early components of the classical complement pathway, are associated with SLE. For example, C1q complete deficiency is associated with a 93% risk of SLE . Although related complete deficiencies of C4 or C2 are rare, they as well confer a high risk of developing SLE [22] .

**1.5- ITGAM**

ITGAM is a receptor for C3b fragment, and thereby shares in the uptake of complement-coated particles and the immune complexes clearance, suggesting that it might be relevant to SLE. Through genome wide association studies (GWASs) in European populations associations between SLE susceptibility and ITGAM have been reported [23,24] .

**1.6- HLA**

To date, all SLE GWAS in various populations have identified the HLA region as the strongest determinator of genetic risk [25]. HLA-DRB1 has been identified as a consistent association locus with SLE in different ethnic populations especially, the

DRB1*15:01 allele as well as DRB1*03:01 [22]

**2- Dendritic cell function and IFN signaling related genes :**

**2.1- IRF5, IRF7 and IRF8**

IRF5, IRF7 and IRF8 are members of the interferon regulatory factor family. They are a group of transcription factors that play a role in modulation of immune cell growth, differentiation, apoptosis and type I IFN signaling pathway. The associations between SLE risk and polymorphisms of these three gene have been identified in several association studies [26] . IRF5 is one of the most strongly associated SLE locus outside the MHC region [27] .

**2.2- TNFAIP3 and TNIP1**

TNFAIP3 and TNIP1 encode regulators of the NF-κB signaling pathway, hence indicating their potential roles in the pathogenesis of SLE. The association between the polymorphisms of TNFAIP3 and SLE were reported through several GWASs with the strongest association at rs2230926 [28] .

**2.3- ETS1 and ELF1**

ETS1 is a transcription factor that binds to IFN stimulated response elements (ISRE) and function as a negative regulator of the differentiation of Th17 cells and B cells as well as negative regulator of IFN-I induced transcription.[29]. ELF1 is a member of ETS family of transcription factors that has roles in T-cell development and function.(30). ETS1 and ELF1 have been identified as a SLE susceptibility loci in Asian populations [27,29] .

**2.4- IFIH1**

IFIH1 is an innate immune receptor for dsRNA that promotes IFN-I production when activated [28]. Rs1990760 in IFIH1 has been identified to increase the transcript levels of IFIH1 in SLE patients [31].

**2.5- TYK2**

Tyrosine kinase 2 (TYK2) is a member of the tyrosine kinase that is important for signaling by type I IFN ,also shares in the STAT signaling pathway and induction of Th1 cell differentiation upon antigen stimulation of dendritic cells. Variants in TYK2 with increased expression of type 1 IFN gene were reported to be associated with SLE [32] .

**2.6- UBE2L3**

UBE2L3 is involved in the degra-

dation of Toll-like receptors (TLR) that is widely expressed by lymphocytes[33]. GWASs in multiple populations confirmed the association of genetic variations in the UBE2L3 with SLE[27,31]

**2.7- PRKCB**

PRKCB is a member of the protein kinase C that is involved in B-cell receptor mediated NF-κB activation [34]. A GWAS performed in a Chinese Han population has identified a variant in PRKCB in association with SLE[35] .

**2.8- SLC15A4**

SLC15A4 is a member of the solute carrier superfamily of intrinsic membrane transporters. It is involved in Nod1-dependent NF-κB signaling[36]. SLC15A4 has been identified as a susceptibility locus for SLE through GWAS in a Chinese population [27]

**3- B cell function and signaling related genes :**

**3.1- BANK1, BLK and LYN**

BANK1 encodes for a B-cell-specific scaffold protein involved in B-cell receptor signaling. BLK encodes a non receptor tyrosine kinase that is involved in B-cell receptor signaling and B-cell development . Also, LYN encodes a tyrosine protein kinase, which has unique roles in B lymphocyte signaling. The three genes have been reported to be related to SLE [37] .

**3.2- IL-10**

IL-10 facilitates B cell proliferation, differentiation and antibody production. The polymorphisms in IL-10 were reported to be associated with SLE in several studies. Furthermore, Increased production of IL-10 by peripheral B cells and monocytes has been shown to correlate with disease activity in SLE patients [38] .

**3.3- RasGRP3**

RasGRP3 is a Ras activator expressed in numerous B-cell lines and endothelial cells. A variant of (rs13385731) at the RasGRP3 locus causes suppression of RasGRP3 and is associated with SLE in Chinese Han population [27] .

**3.4- NCF2**

Neutrophil cytosolic factor 2 is a critical cytosolic subunit of NADPH oxidase system. It plays a positive role in B-cell activation, resulting in increased autoantibody production [39]. In different populations, NCF2

was proven to be associated with increased SLE risk [40] .

**3.5- PRDM1**

PRDM1 is involved in B-cell differentiation and development [27] . Because of the role in B-cell differentiation, the variants that affect PRDM1 could allow the differentiation of plasma cell with more increase in B-cells activity and autoantibody production in SLE patients [41] .

**3.6- IKZF1**

IKZF1 encodes a transcription factor, associated with lymphocyte proliferation and differentiation, and regulation of B-cell receptor signaling[42]. Rs4917014 within IKZF1 was identified as a SLE susceptibility locus in a Chinese Han population [27], Reduced expression levels of IKZF1 in peripheral blood are also observed in SLE patients [29] .

**4- T cells function and signaling related genes :**

**4.1- STAT4**

STAT4 is a signaling molecule, in signal transduction by multiple cytokines receptors in T cells and monocytes as IL-17, IL-12, IL-23 and type I IFN, also it mediates the differentiation and proliferation of both T helper 1 (Th1) and Th17 cells which may help the development of autoimmune diseases . Several GWASs have identified STAT4 as a susceptible gene in SLE patients[41] .

**4.2- PTPN22**

PTPN22 ( Protein phosphatase nonreceptor type 22 ) encodes the lymphoid tyrosine phosphate protein, which interacts with cytoplasmic tyrosine kinase and thus inhibits T-cell activation and suppress T regulatory cells. The SNP rs2476601 in PTPN22 was reported to be associated with SLE [43,44] .

**4.3- TNFSF4**

TNFSF4 (also known as OX40L) is a co-stimulatory molecule on the surface of antigen-presenting cells (APCs), that binds to OX40 on activated CD4+and CD8+T cells. Their interaction has been shown in inhibition of the generation of IL-10-producing CD4+type 1 regulatory T cells as well as in the promotion of conventional T cells activation. A risk variant(rs2205960) upstream of TNFSF4 was identified in relation to SLE [45] .

**4.4- CD44 - PDHX**

Two intergenic SNPs located be-

tween PDHX and CD44 on 11p13, (rs2732552 and rs387619), were associated with SLE in a multiethnic study. PDHX encodes a subunit of the pyruvate dehydrogenase complex that is involved in the conversion of pyruvate to acetyl coenzyme A. CD44 encodes a cell-surface glycoprotein, which plays important roles in lymphocyte recirculation, homing, activation and apoptosis [26].

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