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Genetics of systemic lupus erythematosus: immune responses and end organ resistance to damage

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Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disorder. Considerable progress has been made to delineate the genetic control of this complex disorder. In this review, selected aspects of human and mouse genetics related to SLE are reviewed with emphasis on genes that contribute to both innate and adaptive immunity and to genes that contribute directly to susceptibility to end organ damage. It is concluded that the interactions among these two major pathways will provide further insight into the pathogenesis of SLE. An interactive model of the two major pathways is proposed without emphasis on the importance of breaking tolerance to autoantigens.

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Systemic lupus erythematosus (SLE) is considered to be a prototype of systemic autoimmune disorder. It is characterized by the presence of autoantibodies with complex specificities and protean clinical presentations at the initial diagnosis and relapses [1]. Both genetic and environmental factors play significant roles in its pathogenesis. The high heritability of human SLE and a higher disease concordance rate in monozygotic twins support a strong genetic contribution to the development of SLE [2•]. Most genetic studies have focused on genes affecting immune responsiveness. End organ responses to immune effectors have rarely been considered. In this review, the recent advances in the genetics of SLE will be reviewed. Emphasis will be made on the recent observation that end organ resistance to damage may be crucial to the clinical manifestation of SLE.

Overview of human SLE genetics

The initial approaches, including linkage analysis and candidate gene association studies, identified and confirmed a limited number of SLE-associated loci (e.g. HLA-*DR2/DR3*). The genome-wide association study (GWAS) approach to screen hundreds of thousands of single nucleotide polymorphisms (SNPs) across the genome in a hypothesis-free manner has advanced our understanding of genetic basis of SLE. Since 2007, eight GWAS in SLE (four in European-derived [3–6] and four in Asian populations [7•,8–10]) and subsequent meta-analysis and large-scale replication studies have revealed a growing number of risk loci exceeding the genome-wide significance level ($P < 5 \times 10^{-8}$). Fine mapping and functional characterization of GWAS signals have localized candidate causative variants, identification of target gene(s) directly influenced by the associated variants and elucidation of pathogenic mechanisms to understand how SLE susceptibility genes affect disease risk. Few of disease-associated variants affect gene coding sequences altering functions of the encoded proteins, whereas most fall in the noncoding regions regulating gene expression through transcriptional and/or posttranscriptional mechanisms. The majority of the established SLE susceptibility genes encode products involved in innate and adaptive immunity, particularly the three key immunological pathways contributing to the pathogenesis of SLE: firstly, clearance of apoptotic cells and immune complexes (ICs); secondly, activation of toll-like receptor (TLR), type I interferon (IFN) and NF-κB signaling; and finally, multiple dysfunctions in T/B cell signaling (Table 1). Two recent reviews have appeared to deal with gene-function studies in SLE genetics [11,12]. Only selected areas of interest will be discussed.

SLE susceptibility genes in innate immune responses

Clearance of apoptotic cells and ICs

Inefficient clearance of apoptotic cells and ICs that may result in autoantigens accumulation promote initiation and maintenance of autoimmune responses in SLE.

Deficiencies or polymorphisms in genes encoding components required for this process confer susceptibility to SLE (reviewed in [13]). For example, *ITGAM* encodes the α-chain of $\alpha_M\beta_2$ integrin that functions in phagocytosis of complement-coated particles and ICs as well as regulation of leukocyte apoptosis, adhesion and migration via interaction with a range of ligands. The SLE-associated missense *ITGAM* variant confers impaired phagocytosis of complement-opsonized targets by monocytes, neutrophils and macrophages, which might alter IC clearance and deposition, resulting in tissue damage [14]. This is supported by the finding that patients carrying the *ITGAM* risk variant show an increased risk in development of lupus nephritis [15,16].

Type I IFN pathway

Dysregulation of type I IFN is considered as one of the central drivers of SLE pathogenesis. More than half of the identified SLE susceptibility genes encode proteins that can be directly or indirectly linked to this pathway. TLRs (e.g. TLR7) or other cytosolic sensors (e.g. IFIH1) is a major trigger of type I IFN production in SLE.

Table 1

SLE-associated genes in the disease pathways[a]

Function	Position	Gene	OR	Population
Innate immune response				
Clearance of apoptotic cells and Immune Complexes	1p36	*C1Q*	Rare, complete deficiency	
	1q23	*FCGR2A*	1.3–1.4	EU,EA,AA,AS
		FCGR3A	1.2–1.5	EU,AA
		FCGR2B	1.3–2.5	AS
		FCGR3B	1.7–2.3	EU,AA
	3p21.31	*TREX1*	Rare mutation	
	6p21.3	*C4A/4B, C2*	Rare, complete deficiency	
	12p13	*C1R/C1S*	Rare, complete deficiency	
	16p13.3	*DNASE1*	Rare mutation	
	6q21	*ATG5*	1.2–1.3	EU,AS
	16p11.2	*ITGAM*	1.3–2.1	EA,EU,AA,AS,HS
Type I IFN pathway	2q24	*IFIH1*	1.1–1.4	EA,AA
	2q32	*STAT4*	1.4–1.8	EU,EA,AS,HS,AA
	5q34	*miR146a*	1.2–1.3	AS
	7q32	*IRF5*	1.3–1.9	EU,EA,AA,AS,HS
	11p15	*IRF7*	1.3–2.0	EU,EA,AA,AS
	12q24.32	*SLC15A4*	1.1–1.3	EA,AS
	16q24	*IRF8*	1.2–1.3	EU,EA
	19p13	*TYK2*	1.3	EA
	Xp22	*TLR7*	1.2–2.3	AS,EA,AA,HS
NFκB pathway	5q33.1	*TNIP1*	1.2–1.4	EA,AS
	6q23	*TNFAIP3*	1.7–2.3	EU,EA,AS
	22q11.21	*UBE2L3*	1.2–1.4	EU,EA,AS
	Xq28	*IRAK1*	1.1–1.6	EA,AS,AA,HS
Adaptive immune response				
Antigen presentation T & B cell signaling	6p21.3	*HLA region*	1.5–2.5	EU, AS
	1p13.2	*PTPN22*	1.4–2.4	EU,HS
	1q25	*TNFSF4*	1.2–1.5	EU,EA,AS,AA,HS
	1q31-q32	*IL10*	1.2–1.3	EU,EA
	2p25-p24	*RASGRP3*	1.2–1.4	AS,EU
	3q13	*CD80*	1.3	AS
	4q21	*AFF1*	1.2	AS
	4q24	*BANK1*	1.2–1.4	EU,EA,AS,AA
	4q26-q27	*IL21*	1.1–1.6	EA,AA
	6q21	*PRDM1*	1.2	EA
	7p12.2	*IKZF1*	1.2–1.4	EU, AS
	8p23	*BLK*	1.2–1.6	EU,EA,AS,AA
	8q13	*LYN*	1.2–1.3	EU
	10q21	*ARID5B*	1.2	AS
	11p13	*PDHX/CD44*	1.2–1.4	EA,AA,AS
	11q23.3	*ETS1*	1.2–1.4	AS,EU
	13q13	*ELF1*	1.3	AS
	15q24.1	*CSK*	1.3	EU
	16p11.2	*PRKCB*	1.2	AS
	17q21	*IKZF3*	1.2–1.9	EU,AA