Genetics of Lupus Nephritis: Clinical Implications

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Summary: Systemic lupus erythematosus is a heterogeneous autoimmune disease marked by the presence of pathogenic autoantibodies, immune dysregulation, and chronic inflammation that may lead to increased morbidity and early mortality from end-organ damage. More than half of all systemic lupus erythematosus patients will develop lupus nephritis. Genetic-association studies have identified more than 50 polymorphisms that contribute to lupus nephritis pathogenesis, including genetic variants associated with altered programmed cell death and defective immune clearance of programmed cell death debris. These variants may support the generation of autoantibody-containing immune complexes that contribute to lupus nephritis. Genetic variants associated with lupus nephritis also affect the initial phase of innate immunity and the amplifying, adaptive phase of the immune response. Finally, genetic variants associated with the kidney-specific effector response may influence end-organ damage and the progression to end-stage renal disease and death. This review discusses genetic insights of key pathogenic processes and pathways that may lead to lupus nephritis, as well as the clinical implications of these findings as they apply to recent advances in biologic therapies.
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The heterogeneous manifestations of systemic lupus erythematosus (SLE) are caused by chronic immune dysregulation and pathogenic autoantibody production, which leads to progressive end-organ damage. Kidney damage resulting from lupus nephritis (LN) is among the most severe sequelae of SLE, contributing substantially to SLE-related morbidity and mortality.[1] Despite advances in the management of LN, little progress has been made with respect to the adverse outcomes of LN, including chronic kidney disease, end-stage renal disease (ESRD), or mortality. This is particularly problematic in non-Caucasian SLE patients, who are at increased risk of developing LN, with increased disease severity and altered response to treatment protocols.[2]

Early detection and treatment of LN are imperative to minimize the risk of inflammation-induced irreversible kidney damage and to preserve renal function. In addition, analysis of pathway-specific immune dysregulation may eventually enable personalized, precision medicine for patients with LN. The success of such approaches will require methods for identifying individuals at greatest risk of developing LN and for defining measures of pathway-specific immune dysregulation to select the most appropriate LN patients for given pathway-specific biologic treatment. With the advent of lower-cost genome analysis techniques, both of these goals may be met in part by determining each SLE patient's individual genetic risk factors for LN. Genetic association studies have identified more than 50 SLE disease susceptibility loci.[3] Loci associated with LN may influence intrarenal mechanisms of LN that directly produce kidney damage as well as extrarenal mechanisms that promote LN through dysregulation of innate, adaptive, and effector mechanisms of inflammation.[1] This work reviews genes implicated in the pathogenic mechanisms of LN according to cell types and molecular pathways associated with immune dysregulation (extrarenal etiology) and kidney damage (intrarenal etiology) (Table 1). The clinical implications, shortfalls, and opportunities for future genetic studies linked to LN are discussed briefly.

EXTRARENAL ETIOLOGY

The pathogenesis of LN largely is related to that of SLE: complex dysregulation of immune responses to nuclear autoantigens, including inhibition of regulatory mechanisms, chronic inflammation, accumulation of autoantibody specificities, and formation of pathogenic immune complexes (ICs). Here, we discuss the phases of the autoimmune response and those genes that may contribute to the downstream pathogenesis of LN.

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Table 1. Disease Susceptibility Genes Associated With Lupus Nephritis

Programmed cell death	Innate immunity
FAS	*IFIH1*
DNASE1	*RIG1*
ATG5	*TLR3, TLR7, TLR9*
MTMR3	*MAVS*
	TREX1
Immune complex clearance	*MYD88*
FCGR2A, FCGR 2B, FCGR 3A, FCGR 3B	*TRAF6*
C1Q (A, B, C)	*IRAK1*
C4 (A, B)	*IRF5, IRF7*
CRP	*TNFAIP3*
MBL2	*TNIP1*
CR1	*UBE2L3*
ITGAM	
IKZF1	Adaptive immunity
	HLA-DR
Intrarenal pathogenesis	*PTPN22*
TNFRSF1B	*CTLA4*
CCL2	*PKCD1*
CXCL8	*TNFSF4*
CCR5	*STAT1*
CXCL12	*STAT4*
KLK1, KLK3	*IFNG*
ACE	*TGFB1*
AGT	*IL-10*
APOL1	*BLK*
	CD40

Programmed Cell Death and Autoantigens

Numerous studies have shown that nuclear antigens drive SLE pathogenesis, with strong immune responses to nucleic acids, histones, and ribonuclear proteins.[4] Sequestered within cellular and nuclear membranes, lupus-specific autoantigens normally are segregated from the immune system. However, enhanced programmed cell death (PCD) mechanisms coupled with alterations in clearance machinery allow for the persistence of antigens that can be modified and perceived by the immune system as non-self (Figure 1A).[5]

Perhaps the most extensively studied mechanism of PCD in SLE pathogenesis is apoptosis. Induced by extrinsic (eg, Fas/Fas ligand) or intrinsic (eg, DNA damage) factors, downstream activation of caspases leads to changes in the plasma membrane and chromatin structure, causing the cell to disintegrate into apoptotic blebs.[4] Variants of genes encoding Fas[6] and its ligand[7] are linked to SLE pathogenesis, with the -670 *FAS* polymorphism being linked to LN.[6] DNase1 activity in the intrinsic apoptotic pathway is increased in SLE patients with nephropathy,[8] and polymorphisms in the *DNASE1* gene have been linked to LN.[9]

Clearance of apoptotic cells is altered in SLE patients.[5] This results in secondary necrosis, whereby nucleosomes are exposed at the surface of apoptotic blebs and can be modified proteolytically to enhance their immunogenicity.[4] Necroptosis leads to rapid plasma membrane permeabilization and the release of nucleosomes and other damage-associated molecular patterns that serve as lupus-associated autoantigens. Several proinflammatory factors linked to LN can trigger necroptosis, including members of the tumor necrosis factor (TNF) superfamily (eg, TNF and tumor necrosis factor-like weak inducer of apoptosis (TWEAK)), Toll-like receptors (TLRs), and other DNA- and RNA-sensing receptors.[4]

Other mechanisms of PCD that may influence LN pathogenesis include autophagy and NETosis.[4] Autophagy, an intracellular degradation system in which the cell consumes itself for energy, can act as a regulator of both innate and adaptive immune mechanisms. Polymorphisms in the autophagy gene *ATG5*,[10] which contribute to autophagosome formation and the autophagy initiator and phosphatase gene, *MTMR3*,[11] have been linked to LN. In NETosis, neutrophils (polymorphonuclear leukocytes [PMNs]) release neutrophil extracellular traps (NETs) composed of decondensed chromatin in association with histones, granular proteins, and some cytoplasmic proteins.[4] Many receptors that contribute to LN-associated immune dysregulation activate NETosis, including TLRs, Fc receptors (FcRs), and certain proinflammatory cytokine receptors, including interleukin (IL)-8 and TNF-α. NETs released by dying PMNs normally are degraded by DNase1. However, impaired NET degradation, as a result of *DNASE1* genetic variants,[9] and decreased DNase1 activity[8] have been associated with LN.

Innate Immunity

The primary function of the innate response is the initial recognition of danger signals to facilitate phagocytosis and clearance of infectious pathogens. In SLE, these mechanisms are misdirected to target self, such that endogenous, immunostimulatory nucleic acids, alone or in conjunction with nuclear particles, nucleosomes, or opsonins, stimulate the innate immune response to drive systemic inflammation. Enhanced PCD pathways coupled with decreased clearance of cellular debris increases the availability of pattern recognition receptor (PRR) ligands and opsonized antigens that can activate an enhanced and sustained innate immune response.[12]

Pattern recognition receptors (PRR)

Several genetic variants within nucleic acid cytosolic sensor genes have been implicated in LN (Figure 1B). Polymorphisms in the *IFIH1* gene, which encodes the