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Genetics of Lupus Nephritis: Clinical Implications

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Abstract

Systemic lupus erythematosus (SLE) 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. Over half of all SLE patients will develop lupus nephritis. Genetic association studies have identified more than fifty polymorphisms that contribute to lupus nephritis pathogenesis, including genetic variants associated with altered programmed cell death (PCD) and defective immune clearance of PCD 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.

Keywords

SLE; lupus nephritis; genetics; immune response

Introduction

The heterogeneous manifestations of systemic lupus erythematosus (SLE) are caused by chronic immune dysregulation and pathogenic autoantibody production that leads to progressive end-organ damage. Kidney damage resulting from lupus nephritis (LN) is

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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 one day enable personalized, precision medicine for 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 a 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 over fifty SLE disease susceptibility loci.[3] Loci associated with LN may influence intra-renal mechanisms of LN that directly produce kidney damage as well as extra-renal 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 briefly discussed.

Extrarenal etiology

The pathogenesis of LN is largely 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 which may contribute to the downstream pathogenesis of LN.

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 are normally 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 (e.g. Fas/FasL) or intrinsic (e.g. 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, FasL,[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 proteolytically modified to enhance their immunogenicity.[4] Necroptosis leads to rapid plasma membrane permeabilization and the release of nucleosomes and other damage-associated molecular patterns (DAMPs) that serve as lupus-associated autoantigens. Several pro-inflammatory factors linked to LN can trigger necroptosis, including members of the tumor necrosis factor (TNF) superfamily (e.g. TNF and 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 where 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] that contributes to autophagosome formation and the autophagy initiator and phosphatase gene, *MTMR3*,[11] have been linked to LN. In NETosis, neutrophils (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, and certain pro-inflammatory cytokine receptors, including IL-8 and TNF-α. NETs released by dying PMNs are normally degraded by DNase1. However, impaired NET degradation, as the 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—Several genetic variants within nucleic acid cytosolic sensor genes have been implicated in LN (Figure 1B). Polymorphisms in the *IFIH1* gene, which encodes the dsRNA sensor MDA5, allow for more avid binding of RNA and increased baseline and ligand-induced type I IFN responses. SLE patients carrying *IFIH1* risk variants have enhanced responses to type I IFN and are more likely to develop anti-dsDNA antibodies that may contribute to LN.[13] Glomeruli of patients with LN exhibit enhanced expression of MDA5.[14] Both MDA5 and RIG-I, whose genetic variant is also associated with LN,[15] mediate downstream signaling via the adaptor molecule MAVS. The *MAVS* polymorphism most commonly found in African-American SLE patients has not yet been studied as a modifier of LN risk, but it could feasibly protect against LN because

patients with this polymorphism exhibit decreased levels of type I IFN and an absence of autoantibodies to RNA-binding proteins.[16] The DNA-specific exonuclease Trex1 inhibits pro-inflammatory responses driven by cytosolic dsDNA sensors. Some genetic variants of *TREX1* have been implicated in LN, while others are thought to protect against the development of anti-Ro and anti-dsDNA autoantibodies.[17]

Endogenous nuclear particles undergoing receptor-mediated endocytosis can reach endosomes and interact with endosomal TLRs (Figure 1C). Genetic variants of TLR3 (dsRNA), TLR7/8 (ssRNA), and TLR9 (DNA) have been associated with LN. Activation of TLR3 on antigen presenting cells (APCs) or renal mesangial cells can aggravate LN[15] by upregulating the expression of CXCL1/GROα to recruit PMNs to the site of inflammation, where they can contribute to renal injury.[18] TLR7/8[19] and TLR9[20] signal through MyD88,[21] TRAF6,[22] and IRAK1,[23,24] genetic variants of which may contribute to severe renal insufficiency in LN. In addition, signaling through particular TLR9 genetic variants has been linked to more severe renal disease at the time of LN presentation.[20]

Signaling through PRRs leads to type I IFN production through transcriptional activation of interferon regulatory factors (IRF), including IRF3, IRF5, and IRF7. *IRF5*[2,25,26] and *IRF7*[2,25] polymorphisms are associated with LN. Particular genetic variants of these IRFs are associated with the presence of anti-dsDNA[27] and increased type I IFN activity levels,[28] which may contribute to LN. In addition, signaling through the NFκB and MAPK pathways results in upregulation of co-stimulatory molecules and other pro-inflammatory mediators that can contribute to LN. Such pathways are regulated in part by ubiquitination and proteasomal degradation. *TNFAIP3*, which encodes the deubiquitinase A20, has shown strong genetic association with LN.[29] In SLE patients, downregulation of A20 allows for enhanced activity of transcription factors that promote inflammation and survival of autoreactive B cells.[29,30] A20 also contributes to the regulation of MAPK signaling, most notably through the *TNIP*-encoded A20-binding inhibitors of NF-κB (ABIN) proteins.[31] Dysregulation of NF-κB and MAPK pathways in SLE may be attributed to *TNIP1* genetic variants.[26,32] Another regulator of ubiquitin-mediated transcriptional control, *UBE2L3*, is also associated with LN.[33] In contrast to A20 and ABINs, UBE2L3 amplifies NF-κB activation via linear ubiquitination, promoting development of autoreactive B-lymphocytes into plasma cells that secrete autoantibodies capable of forming ICs, which may contribute to LN pathogenesis.[34,35]

Opsonin receptors—Like PRRs, opsonins also recognize nuclear antigens and cellular debris. IgG antibodies, complement, pentraxins, and collectins engage FcR and/or complement receptors (after interacting with complement components) to activate innate immunity and enhance phagocytosis. Genetic variants of opsonins and of their receptors have been associated with LN.[12] For example, nuclear antigens opsonized with IgG form ICs that contribute directly to renal pathology in LN, and both ICs and complement components have been found in glomerular biopsies from LN patients.[1] In the extra-renal space, IgG-opsonized nuclear antigens engage FcγRs to activate APCs and facilitate phagocytosis, which clears antigen and moves the immune response toward the adaptive phase. Polymorphisms and/or copy number variants in multiple FcγR subtype genes are associated with LN,[36–40] including *FCGR2A*, *FCGR2B*, *FCGR3A*, and *FCGR3B*.

The FcγRIIa R131 polymorphism is associated with LN across multiple ethnicities.[40–42] This polymorphism decreases binding affinity for IgG2, thereby reducing clearance of IgG2-containing ICs that contribute to LN pathogenesis, particularly in SLE patients who have C1q IgG2 responses.[43] The R131 polymorphism FcγRIIa also increases responsiveness to the pentraxin opsonin, C-reactive protein (CRP), allowing for increased intra-renal inflammation.[41] Impairment of the inhibitory receptor FcγRIIb supports the development of SLE by allowing unopposed FcγR signaling. A loss-of-function FcγRIIb variant, T232, excludes FcγRIIb from lipid rafts, leading to increased pro-inflammatory signaling.[37]

An LN-associated genetic variant of the FcγRIIIa receptor, *FCGR3A*-158V (also known as 176V/F when the leader sequence is included), increases binding affinity for IgG1, IgG3, and IgG4 relative to the non-risk allele.[44] In addition, patients who carry the 158V (176V) allele have increased CD25 expression, Ca^{2+} flux and NK cell activation.[44] Recent evidence from a multi-ethnic inception cohort of SLE patients demonstrated that LN patients carrying the high-binding *FCGR3A* V176 variant progressed more quickly to ESRD.[45] Two different allotypic variants of *FCGR3B*, NA1 and NA2, have been associated with LN.[36] The product of the NA1 allele shows higher binding for IgG1 and IgG3.[46] The NA1 and NA2 alleles may also affect interactions with other cell surface receptors, such as the β2-integrin, CD11b/CD18[46] (ITGAM), whose genetic variants have also been linked to LN.[26,47,48] Low copy number of *FCGR3A*[49] and *FCGR3B*[50] have also been linked to LN.

The complement system includes a series of proteins that opsonize antigens, irreparably damage membranes, and induce inflammatory responses through the three complement pathways: classical (C1q, CRP), alternative, and collectin (e.g. mannose binding lectin [MBL]). In addition, the complement system may affect the ability of innate immune cells to facilitate phagocytosis of nuclear antigens and PCD debris. LN has been genetically associated with the opsonin C1q, as well as complement proteins C2 and C4, and complement inhibitors, which affect the clearance of cellular debris after PCD.[51] Genetic variants of pentraxins, such as CRP,[36,41] and collectins, such as MBL,[52,53] also contribute to LN by disrupting complete clearance of autoantigens, enhancing inflammation, and increasing autoantibodies to C1q.

Multiple complement receptors have been genetically linked to LN. Perhaps the most frequently noted is CR3 (ITGAM/CD11b/Mac-1). The R77H, P1146S, and A858V variants of *ITGAM* decrease phagocytic clearance of antigens, alter leukocyte adhesion,[54,55] and decrease potentially inhibitory interactions with TLR7/8.[56] In addition to CR3, CR1 (CD35), CR2 (CD21), and CR4 (ITGAX subunit) have also been linked to LN. Reduced transcription and expression of the CR1 receptor is associated with the presence of anti-dsDNA responses and decreased clearance of ICs that contribute to renal pathology.[57] Genetic variants of the *CR2* receptor reduce protein expression through decreased transcription and alternative splicing, leading to decreased phagocytosis of apoptotic cells and decreased activation of the alternative complement pathway.[51]

Activation of FcRs or CR3/ITGAM leads to the secretion of innate cytokines, including type I IFN, which engages the IFNα receptor (IFNAR) (Figure 1D).[58] IFNAR activates NF-κB and MAPK pathways in addition to JAK-STAT pathway proteins[59] that are genetically

linked to LN. Of note are TYK2,[60] which binds to the IFNAR-JAK1-STAT4 complex. The gene encoding STAT4 is perhaps the most noted IFNAR-mediated signaling protein associated with LN.[2,25,26] LN is also genetically associated with *IKZF1*, which encodes the Ikaros family zinc finger 1 transcription factor that enhances STAT4 signaling.[61]

Adaptive Immunity

T-lymphocyte activation—T-lymphocytes are the coordinators of the adaptive immune response. Full T-lymphocyte activation requires: (i) presentation of antigen on the major histocompatibility complex (MHC) of an APC (macrophages, dendritic cells, or B-lymphocytes) to the T-cell receptor (TCR) on the T-lymphocyte, (ii) interactions of cognate co-stimulatory molecules between the APC and T-lymphocyte, and (iii) soluble mediator communication between the APC and T-lymphocyte to determine T-lymphocyte differentiation and downstream effector responses.[62] Genetic variants affecting all phases of T-lymphocyte activation have been associated with LN (Figure 2A).

First, the strongest SLE genetic associations to date have been in the MHC region. Two well-established SLE susceptibility loci, encoded by *HLA-DR2*[63,64] and *HLA-DR3*,[26,63] are associated with LN. In addition, a meta-analysis of 25 case-control LN studies suggested that HLA-DR15 increases risk of LN, while *HLA-DR4* and *HLA-DR11* might be protective.[64] The TCR complex is composed of many proteins, including TCRα, β, and ζ chains and CD3. Multiple studies have noted decreased TCRζ chain expression in SLE. Decreased TCRζ chain expression can be caused by a genetic variant in the 3′-UTR that also decreases downstream IL-2 expression and increases IFN-γ expression, which contributes to LN.[65] FcγRIII is also part of the TCRζ complex and amplifies TCR-mediated T-lymphocyte activation. As discussed above, genetic variants in *FCGR3A* are thought to contribute to altered cellular activation[44] and are associated with LN[36] and progression to ESRD.[45] Proximal TCR signaling events are regulated by protein tyrosine phosphatases, including *PTPN22-encoded* Lyp. Genetic variants of *PTPN22* are associated with LN, and C1858T (R620W) is thought to be a gain-of-function variant,[66,67] such that TCR-mediated IL-2 is decreased[67] while IFN-γ is increased and resistant to control by T-regulatory mechanisms (also see “B-lymphocyte activation”).[66]

Second, engagement of co-stimulatory molecules is required to prevent anergy, and co-stimulatory molecules are associated with SLE and LN. The classic co-stimulatory molecules are CD28 on the T-lymphocyte, engaged with B7 family members on the APC. Alternatively, engagement of B7 family members by CTLA-4 on the T-lymphocyte negatively regulates T-cell activation. Of particular interest are genetic variants in *CTLA4* that lead to decreased expression and potential dysregulation of T-lymphocyte pro-inflammatory signaling that may contribute to LN.[3] Genetic variants in *PDCD1*, which encodes the CD28 family member PD-1 expressed on T-lymphocytes, are associated with LN.[68] SLE patients harboring such variants display aberrant expression and negative regulatory function of PD-1 in T-lymphocyte activation.[69] Other co-stimulatory molecule partners include members of the TNF receptor (TNFR) superfamily. Genetic variants within the genes encoding APC-expressed CD40[70] and T-lymphocyte-expressed CD40L/CD154[71] result in altered receptor/ligand expression and cellular activation[71] and are associated with

LN.[70] Genetic variants within *TNFSF4* (OX40L, which activates OX40 on T-lymphocytes) are also associated with LN.[55,72] One of the strongest LN associations within *TNFSF4* is at the upstream variant rs2205960, where alternate alleles are present in the protective and risk haplotypes.[72] The risk haplotype is associated with increased OX40L expression, enhanced T-lymphocyte activation with decreased generation of IL-10 producing T-regulatory cells, and increased SLE disease activity with LN.[73]

Third, the presence of cytokines drives activation and differentiation of T-lymphocytes, and multiple cytokine-driven T-lymphocyte activation pathways are implicated in LN pathogenesis. Associated genetic variants have been identified in each of these pathways, including enhanced effector Th1, Th2, and Th17 pathways, attenuated T-regulatory (Treg) mechanisms, and augmented T-follicular helper (Tfh) cell mechanisms that select high-affinity, antibody-producing B cells for clonal expansion in germinal centers.[74] APC-secreted cytokines engage in receptor-mediated phosphorylation of STAT proteins, leading to activation of transcription master regulators that drive the differentiation of pathway-specific T-lymphocytes. In addition, many APC-secreted cytokines are altered during the innate autoimmune response that leads to LN.

The Th2 differentiation pathway is associated with LN and affects B-lymphocyte activation. Within this pathway, IL-4 drives both STAT6 phosphorylation that subsequently activates GATA-3 to drive Th2 differentiation, and STAT4 activation that leads to autoantibody production. Autoantibody-mediated pathology in LN is further supported by genetic variants within the T follicular helper differentiation pathway,[75,76] where IL-6 and IFN-γ[77] via STAT1[78] activate Tfh-differentiating Bcl-6. In low IL-2 conditions, as observed in SLE and LN, Bcl-6 is also activated by IL-12 via STAT4[26,55] (IL-12-STAT4 inhibits Bcl-6 in high IL-2 conditions).

In addition to autoantibody-mediated inflammation, Th17-mediated intra-renal cellular inflammation has been intimately linked to LN, and copy number variation of several genes encoding Th17-type cytokines is associated with SLE pathogenesis.[74] With respect to Th1 differentiation, as described above, genetic variants in proximal TCR signaling mediators may result in enhanced IFN-γ production, which contributes to LN pathogenesis. In the Th1 differentiation pathway, IL-12/IL-12 receptor interactions lead to STAT1→T-bet→IFN-γ production or STAT4→IFN-γ production, and components of these pathways are genetically linked to SLE and LN.[79] *STAT4* genetic variants associate with LN in multiple studies,[26,55] and the proximity of some variants in the *STAT1-STAT4* region implicates *STAT1* as well.[78] Finally, genetic variants within *IFNG* that lead to enhanced IFN-γ secretion[77] are also implicated in LN.

Under normal circumstances, activation of inflammatory pathways ultimately results in immune regulation through the differentiation of T regulatory cells. However, in SLE patients (and in LN), many regulatory mechanisms are impaired.[80] Two key soluble mediators which negatively regulate inflammation are genetically associated with LN. LN-associated variants of *TGFB1*[81] decrease TGFβ secretion and affect the number of circulating T regulatory cells. Polymorphisms in the *IL10* gene[82] that decrease IL-10

expression and loss-of-function *IL10R* variants[83] contribute to LN and higher SLICC damage scores.[84]

B-lymphocyte activation—B-lymphocytes act as both APC and effector cells, secreting both (auto)antibody and soluble mediators. Similar to TCR signaling in T-lymphocytes, B-lymphocytes are activated through the antigen-specific B-cell receptor (BCR) (Figure 2B). Genetic variants in the BCR complex and proximal signaling molecules are enriched in SLE patients and may contribute to LN.[85] Similar to the TCR, BCR proximal signaling events are controlled by src family protein tyrosine kinases (e.g. Csk, Lyn, and Blk) and protein tyrosine phosphatases (e.g. Lyp, encoded by *PTPN22*; see "T-lymphocyte activation"). The gain-of-function R620W variant of *PTPN22* results in Lyp that does not bind to Csk,[67] causing Csk to allow proximal BCR signaling and to mediate inhibitory phosphorylation of Lyn. The inhibitory phosphorylation of Lyn is amplified in SLE patients carrying a genetic variation of *CSK* that increases Csk expression, thus increasing BCR-mediated activation of mature B cells and higher plasma concentrations of total IgM in the periphery.[86] Genetic variants with *LYN* are also associated with SLE,[10,87] and patients carrying the risk allele more frequently carry the lupus-associated autoantibodies that contribute to LN.[87]

Lyn is a double-edged kinase, acting as both negative and positive regulator of the BCR signaling complex. Phosphorylation of the negative regulators FcγRIIb and CD22 by Lyn inhibits BCR signaling, yet Lyn positively amplifies BCR-mediated B-lymphocyte activation by phosphorylating the CD19/CD21 (CR2) signal transducing complex. Genetic variants in CD19 are associated with LN,[88] resulting in decreased expression in naïve B-lymphocytes, but increased expression in memory B-lymphocytes and the presence of lupus-associated autoantibodies.[88] The adaptor molecule BANK, encoded by *BANK1*, binds to Lyn and promotes Lyn-mediated tyrosine phosphorylation of the inositol triphosphate receptor, IP_3R, when BANK is bound to it, leading to BCR-induced calcium mobilization. Multiple functional genetic variants of *BANK1* are associated with SLE.[89,90] The *BANK1-61H* variant is thought to be protective, while the R61 variant results in protein isoforms that are able to self-multimerize without being phosphorylated by Syk, which may result in enhanced downstream, BCR-mediated calcium mobilization.[90] In addition to Lyn, BANK also binds Blk, acting through PLC-γ2 to convert phosphatidylinositol 4,5-bisphosphate into the second messenger inositol 1,4,5-trisphosphate (*IP3*) to trigger calcium release from the ER and subsequent entry of extracellular calcium. Genetic variants of *BLK* have been found to associate with LN across multiple ancestral backgrounds,[2,26] and two functional *BLK* promoter variants have been found to modulate transcription of BLK in B-lymphocytes via the use of alternative promoters in immature vs. mature B-lymphocytes.[91]

Stimulation of B-lymphocytes by co-receptors, such as the TNFR superfamily member CD40, or through TLR activation, synergizes with BCR signaling and leads to B-lymphocyte proliferation, cytokine production, antibody secretion, and isotype switching.[92] The P227A variant of CD40 has been shown to enhance transcriptional regulation of pro-inflammatory cytokine secretion and antibody production.[93] While a number of *CD40* variants affect receptor expression,[70] the P227A variant causes the normal CD40-inhibitory adaptor molecule, TRAF3, to become stimulatory and enhance transcriptional signaling pathways.[94] CD40 also positively regulates B-lymphocyte activation through the adaptor

molecule TRAF6, genetic variants of which are associated with LN.[22] CD40 synergizes with TLRs and the BCR to amplify B-lymphocyte activation.[93] Both the BCR and the IFN-α receptor[95] are able to rescue TLRs from post-activation TLR tolerance on B-lymphocytes, allowing them to further drive immune dysregulation associated with SLE and renal disease in LN. These findings suggest that genetic variants which affect negative regulators of B-lymphocyte activation and plasma cell differentiation allow B-lymphocytes to break tolerance, secrete autoantibodies that contribute to renal disease and exacerbate inflammation that causes kidney damage in LN.

Intrarenal etiology

The development and renal deposition of ICs in LN has been extensively studied, as renal deposits are found in almost all patients with SLE (Figure 3).[96] Recent studies indicate that ICs containing anti-nuclear autoantibodies interact with trapped nucleosomes in an antigen-specific manner, particularly in SLE patients with autoantibody specificities to nucleosome components, such as chromatin and dsDNA.[1] In addition, a large number of SLE patients carry anti-C1q antibodies, which are able to amplify pathogenic complement activation that results in renal damage when the autoantibodies interact with anti-C1q containing ICs.[1] Despite the presence of ICs, many SLE patients never develop clinical kidney disease, although they have histological evidence of intrarenal inflammation. Clinically silent nephritis suggests that the presence and/or deposition of ICs alone is not enough to drive the development of LN and that other pathological factors are involved.[97]

Increasing evidence implicates the TNFR superfamily in the pathogenesis of renal injury in LN by promoting inflammation, apoptosis, and the accumulation of extracellular matrix, which can reduce glomerular blood flow and damage the glomerular permeability barrier.[98] Inflammation associated with kidney damage in SLE results includes the production of TNF-α at the site of damage.[98] The TNF-α receptor TNFR1 is normally expressed within the glomeruli and by peritubular endothelial cells and is upregulated in response to renal injury in LN,[99] primarily associating with the soluble form of TNF-α.[100] The second TNF-α receptor, TNFR2, is not expressed in the kidney until inflammation has occurred, and it is the presence of TNFR2 that is essential for the development of glomerulonephritis.[101] Polymorphisms of TNFR2 are associated with LN.[102] TNFR2 associates with the membrane-bound form of TNF-α,[100] promoting the secretion of pro-inflammatory mediators. Perhaps the most promising TNFR superfamily member to contribute to LN is the recently identified ligand, TWEAK. TWEAK interacts with the Fn14 receptor, and expression of genes encoding TWEAK and Fn14 are upregulated in the glomerulus and tubulointerstitium of SLE patients with LN;[103] however it is unknown if genetic variants of *TNFSF12* (TWEAK) associate with LN.

Histopathological data from kidneys of SLE patients with LN suggest that the inflammation taking place within the kidney is a microcosm of systemic immune dysregulation, with the interaction between parenchymal cells and leukocytes determining the extent of renal damage.[1] APC, differentiated Th cells (Th1, Th2, Th3, and Tfh), and B-lymphocytes, as well as ectopic germinal centers, are all present within the LN kidney.[1] These cell types must be recruited to the inflamed kidney by chemokines, such as MCP-1/CCL2

(macrophages), [104] IL-8/CXCL8 (T-lymphocytes)[105] and CXCR5, which binds BCA-1/CXCL13 (B-lymphocytes),[106] all of which are associated with LN.

In addition to enhanced pro-inflammatory processes that lead to LN and kidney damage, renal protective mechanisms that prevent clinical LN in some SLE patients with ICs may be altered, enhancing the risk of developing LN that may be refractory to current treatment regimens and progress to ESRD. As discussed above, immune regulatory mechanisms are altered in SLE patients with LN, including at the genetic level. The chemokine SDF-1/CXCL12 recruits T-regulatory cells and polymorphisms within *CXCL12* are associated with LN,[107,108] and their effects may be enhanced by the down-regulation of SDF-1 by anti-dsDNA autoantibodies.[109] In addition, genetic variants in the Kallikrein genes, *KLK1* and *KLK3*, are associated with immune complex-mediated LN,[110] and delivery of the *Klk1* gene in mouse models of lupus-like disease downmodulates antibody-mediated glomerulonephritis.[111]

Genetic variants contributing to systemic co-morbidities may also contribute to the development and severity of LN. For example, hypertension has been associated with LN[112] and may be a risk factor for poor outcome.[113] Genetic variants within the *ACE* (encoding angiotensin-converting enzyme)[114] and *AGT* (encoding angiotensinogen)[115] genes confer greater susceptibility to the development and severity of LN. In addition, genetic variants in *APOL1* have been significantly linked to early development of LN and faster progression to ESRD, particularly in SLE patients of African descent.[116] Although the mechanism by which *APOL1* facilitates the progression of kidney disease has not been completely elucidated, there is some evidence to suggest that a second hit is required to induce renal disease.[117] For SLE patients, immune dysregulation of type I IFN responses and the presence of lupus-associated autoantibodies may provide the second hit required to damage podocytes, leading to the development of LN and progression to ESRD.[117]

Clinical Implications and Opportunities

Considerable advances have been made in our understanding of the genetic basis of SLE, and novel approaches and studies that explore the relationship between genetics, cellular function, and clinical sequelae are moving forward. Given the renewed interest in personalized, precision medicine, there is a strong push to use what we know about the presence of genetic variants and altered immune pathways to make treatment decisions for SLE patients on an individual basis.[118,119] The significant side effects associated with current immunosuppressants and the presence of LN in over half of SLE patients drive home the need for this initiative.

This approach to patient treatment is certainly not without its challenges.[118] In addition to cost considerations, there are considerations for the contribution of the identified genetic variations to altered immune pathways leading to LN, potential epistatic interactions of genes, current inability to predict the course of renal disease (which will most likely require genomic, proteomic, and clinical approaches), and the need for improved clinical study designs to permit development of targeted therapy. The good news is that other fields, such as oncology, are beginning to apply pharmacogenomic approaches to patient treatment with

some success, using genetic approaches to determine which patients will respond to a selected therapy.[120] We also have a treasure trove of recent and upcoming biologic therapies that address dysregulation of pathways that contribute to LN, and growing knowledge of LN-associated genetic risk variants may potentially inform the selection of particular therapies for SLE patients with LN or those who may be at increased genetic risk of developing LN, as outlined in Table 2.[121,122]

For example, utilizing B-lymphocyte depleting therapy with rituximab in refractory LN led to an excellent response in uncontrolled studies, even without the use of cyclophosphamide or steroids. In addition, the mechanism of action was not limited to B-lymphocyte depletion, but also increased the number of T regulatory cells.[123,124] In contrast, in the Lupus Nephritis Assessment with Rituximab (LUNAR) trial, rituximab therapy led to increased response rates and greater reductions in anti-dsDNA and C3/C4 levels, yet did not improve clinical outcomes after one year of treatment.[125] In addition to other factors, this disparity could be due to genetic differences that influence B-lymphocyte activation or other inflammatory mechanisms involved in LN. Because rituximab primarily acts by depleting CD20-positive B-lymphocytes, LN patients who carry genetic variants within B-lymphocyte activation pathways may benefit the most from rituximab therapy (Table 2). For LN patients (or SLE patients at increased genetic risk of developing LN) who carry genetic variants that influence LN pathogenesis through other mechanisms, rituximab therapy may be less than ideal or may require additional therapeutic modalities to block immune complex-independent mechanisms of LN pathogenesis. For example, patients with genetic risk variants impacting multiple inflammatory pathways and cell types may benefit from a broader spectrum biologic therapy, such as the retinoic acid receptor (RAR) target tamibarotene or the small molecule anti-inflammatory laquinimod.[122]

Personalized treatment could also benefit from genetic studies for other possible drug targets in LN, including BLyS (encoded by *TNFSF13B*) and TWEAK (encoded by *TNFSF12*). The BLyS inhibitor belimumab, the first drug approved for SLE in over 50 years, shows promise for reducing or sustaining disease activity levels, including the renal domain of the BILAG. Patients treated with belimumab showed increased levels of complement components with decreased levels of anti-dsDNA autoantibodies, but studies are needed to specifically evaluate the effects of belimumab treatment on LN.[126] Recent studies significantly associated LN with TWEAK, leading to the proof-of-concept Anti-TWEAK in Lupus Nephritis Patient Study (ATLAS), a double-blind controlled trial for patients with Class II and IV LN that is currently underway, with high expectations.[127]

While many genetic variants have been identified which associate with LN, there is still much work to be done. For example, a number of recent studies have identified proteomic biomarkers which are strongly associated with LN in SLE patients.[128] While certain chemokine family members, including MCP-1/CCL2,[104] IL-8/CXCL8,[105] and CXCR5[106] are encoded by genes with known variants associated with LN, others like TWEAK, BLyS, and APRIL have not been explored in detail for the presence of LN associated variants. Given the number of genetic variations in regions that encode proteins which regulate multiple signaling pathways (e.g. IRF/NFκB/MAPK) or regulate multiple receptors (e.g. TCR/BCR and TNFRs), studies addressing epistatic interactions of LN-associated gene

variants are warranted. Studies are also needed to determine which epigenetic changes affect expression of associated genes that lead to downstream cellular and clinical sequelae in LN.

On a larger scale, there is a need for opportunities to more adequately address what genetic mechanisms drive LN pathogenesis. Genome wide association studies (GWAS) that not only address SLE cases vs. healthy controls, but SLE patients with and without LN, as well as SLE patients with different classes of LN, would allow us to identify genes that are associated with this specific disease manifestation. Including non-SLE patients with nephritis will allow us to decipher the pathogenesis of autoimmune vs. non-autoimmune mediated renal injury. Alternatively, it is possible that some genes that drive non-autoimmune nephritis (e.g. possibly *TNFRSF1B* [TNFR2]), may be additionally altered as the result of lupus-associated immune dysregulation and thus contribute to the development of LN. At this time, genetics do not completely explain LN or SLE, and environmental or occupational exposure to a number of infectious and chemical agents may contribute to disease.[129] Evaluation of genetic-environmental interacts in the context of LN may provide additional insights into disease pathogenesis.

Building on pharmacogenomic studies in oncology, potential successes using immune pathway-specific biologic therapies in LN, and technological advances in cost-effective genetic screening, it may soon be feasible to sequence patients' DNA and apply this information to understanding immune system function and selecting ideal treatment. Improved clinical trial designs would also help move this approach forward, bringing the field closer to our goal of decreasing morbidity and mortality in SLE patients with LN.

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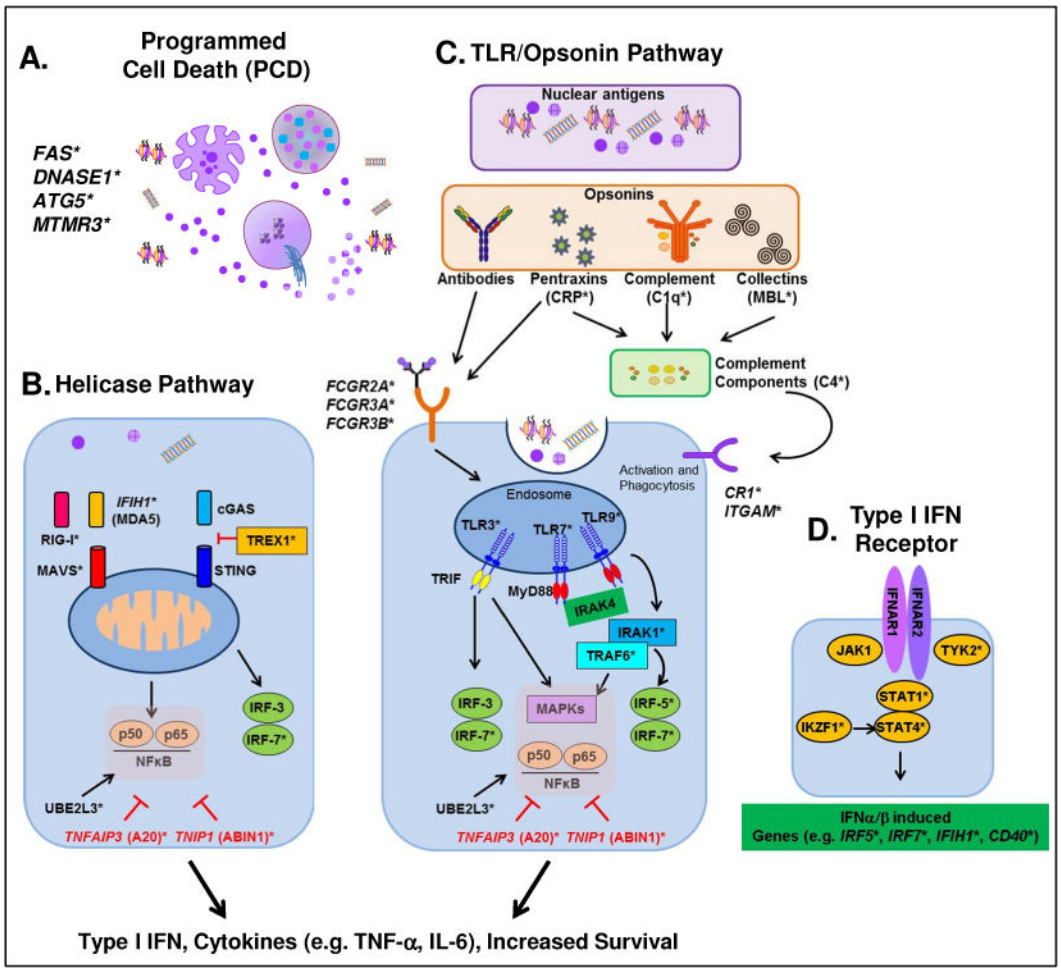

Figure 1.

Innate immunity processes contribute to lupus nephritis. **A**. Enhanced programmed cell death (PCD) coupled with decreased clearance of PCD debris results in the availability of nuclear autoantigens, including nucleosomes, nuclear particles, RNA, and DNA. **B.** Intracellular RNA (RIGI-I and MDA5) and DNA (cGAS) sensors interact with RNA, DNA, and nuclear particles. **C.** Nuclear antigens are opsonized by antibodies, complement, pentraxins, and/or collectins (the latter two then interact with complement components), which then interact with Fc (antibody) or complement (CR) receptors to bring antigens into phagocytic endosomes, where RNA and DNA can interact with the TLR receptors TLR3, TLR7 and TLR9, respectively. The helicase (**B**) and Opsonin/TLR (**C**) pathways result in prolonged immune cell survival and secretion of pro-inflammatory cytokines. These include Type I IFNs, which then engage the Type I IFN receptor (**D**). Activation of the Type I IFN receptor results in the production of transcription factors, cytokines, and receptors that prolong and amplify the immune response.

*Genes/molecules with genetic variants associated with lupus nephritis

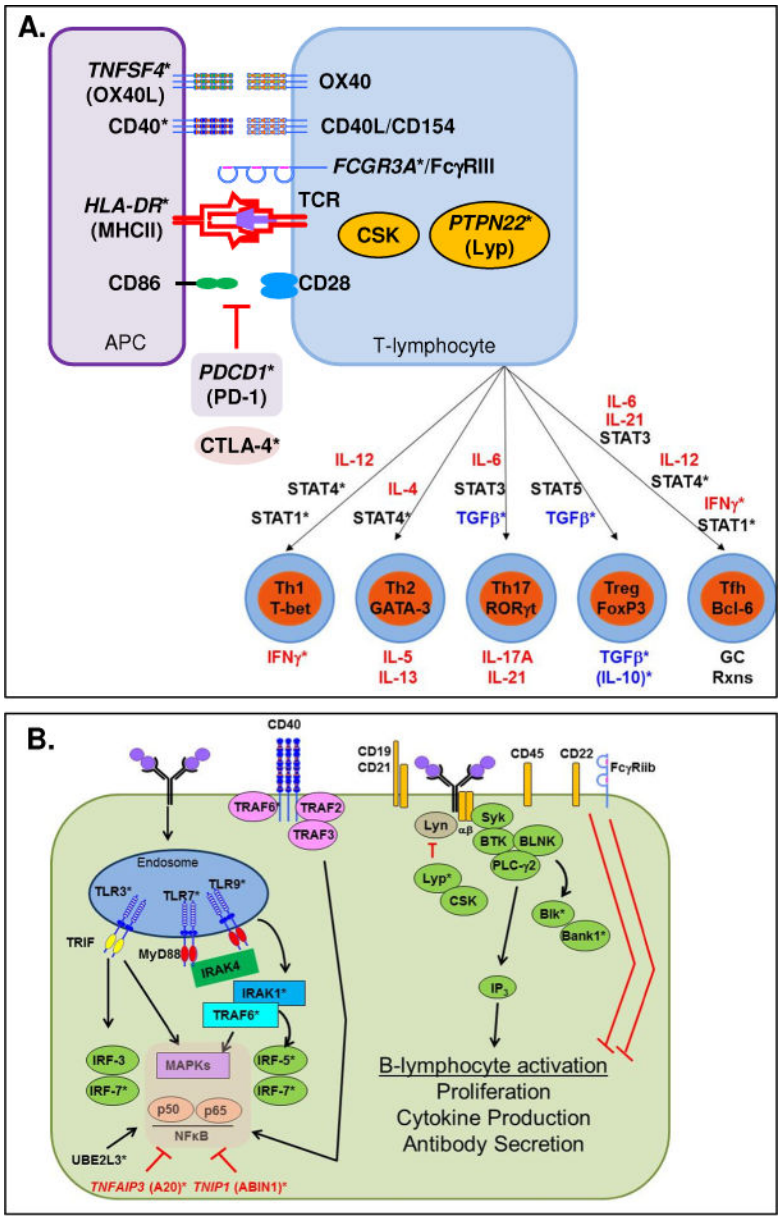

Figure 2.

Adaptive immunity processes contribute to lupus nephritis. **A.** T-lymphocyte activation. Nuclear antigens are phagocytosed, processed, and presented in the context of MHC by APC, which then interacts with the TCR on T-lymphocytes and activates downstream signaling events (Signal 1). Co-stimulatory molecules from the CD28 and TNFR families engage to prevent anergy and amplify the MHCII/TCR response in CD4 T-helper cells (Signal 2). Downstream signals lead to the secretion of cytokines (Signal 3), which then interact with transcriptional regulators to drive T-lymphocyte differentiation pathways. **B.** B-lymphocyte activation. Nuclear antigens stimulate the BCR, activating the BCR signaling complex that results in downstream signaling events. Co-stimulatory molecules, including CD40 and TLRs, synergize with the BCR to amplify B-lymphocyte activation.
*Genes/molecules with genetic variants associated with lupus nephritis

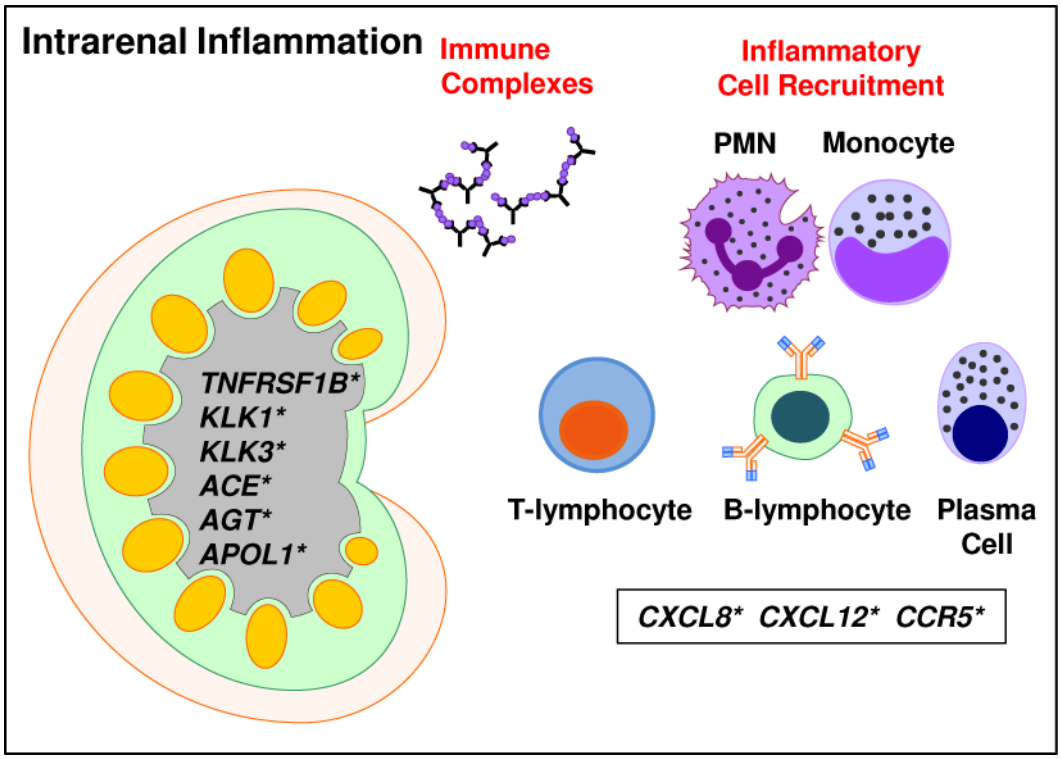

Figure 3.

Intrarenal inflammation contributes to lupus nephritis. Autoantibody-containing immune complexes become bound within the glomerulus, leading to inflammation that results in the recruitment of immune cells to the kidney, including PMNs, monocytes, T-lymphocytes, B-lymphocytes, and plasma cells. The immune cells further interact and amplify the immune response (see Figures 1–2). In addition, genetic variants in genes expressed in the kidney (including *TNFRSF1B*, *KLK1*, *KLK3*, *ACE*, *AGT*, and *APOL1*) may result in enhanced susceptibility to kidney damage and lupus nephritis.

*Genes/molecules with genetic variants associated with lupus nephritis

Table 1

Disease susceptibility genes associated with lupus nephritis

Programmed cell death (PCD)	**Innate Immunity**
FAS	IFIH1
DNASE1	RIG1
ATG5	TLR3, 7, 9
MTMR3	MAVS
	TREX1
Immune Complex Clearance	MYD88
FCGR2A, 2B, 3A, 3B	TRAF6
C1Q (A,B,C)	IRAK1
C4 (A,B)	IRF5, 7
CRP	TNFAIP3
MBL2	TNIP1
CR1	UBE2L3
ITGAM	
IKZF1	**Adaptive Immunity**
	HLA-DR
Intra-Renal Pathogenesis	PTPN22
TNFRSF1B	CTLA4
CCL2	PKCD1
CXCL8	TNFSF4
CCR5	STAT1
CXCL12	STAT4
KLK1, 3	IFNG
ACE	TGFB1
AGT	IL10
APOL1	BLK CD40

Table 2

Pathway-specific therapeutic strategies for lupus nephritis

Pathway	Biologic Therapy	Mechanism of Action	Potential Genes of Interest
Innate Immunity	Sifalimumab Rontazilumab MEDI-546	anti-IFNα monclonal antibody (human) anti-IFNα monclonal antibody (humanized) anti-IFNα receptor monclonal antibody (human)	*TYK2, STAT1, STAT4, IKZF1, IRF5, IRF7, IFIH1, CD40*
	Sirukumab Tocilizumab	anti-IL-6 monclonal antibody (human) anti-IL-6 receptor monclonal antibody (humanized); blocks IL-6 from binding sIL-6R and mIL-6R	*TNFAIP3, TNIP1, STAT1*
	Eculizumab	anti-complement component C5 (humanized); terminal complement inhibitor	*TNFAIP3, TNIP1*
	SM-101	Recombinant FcγRIIB (Inhibitory FCγR) agonist	*FCGR2B*
Adaptive Immunity: T-lymphocytes	Abatacept	Fc:CTLA-4 fusion protein; CD28-B7 blocker	*CTLA4*
	Rigerimod	Synthetic peptide; CD4 modulator	*HLA-DR*
Adaptive Immunity: B-lymphocytes	Rituximab Ocrelizumab	Anti-CD20 monoclonal antibody (chimeric mouse human); depletes B-lymphocytes Anti-CD20 monoclonal antibody (humanized); depletes B-lymphocytes	*CD40, TRAF6, PTPN22, BLK, BANK1*
	Epratuzumab	Anti-CD22 monclonal antibody (humanized); inhibits BCR signaling	*PTPN22*
	Belumimab Tabalumab Blisibimod	Anti-sBlyS monoclonal antibody (humanized); Anti-BlyS monoclonal antibody (human); neutralizes sBLyS and mBLyS Peptibody antagonist of BLyS; neutralizes sBLyS and mBLyS	*TNFSF13B, TNFRSF13B, TNFAIP3, TNIP1*
	Bortezomib	Proteasome inhibitor; depletes plasma cells	*TNFAIP3, TNIP1*
	Atacicept	Fc-TACI fusion protein; neutralizes BLyS and APRIL	*TNFRSF13B, TNFAIP3, TNIP1*
Tissue Injury and Inflammation	Laquinimod	Small molecule; anti-inflammatory	*MYD88, TNFAIP3, TNIP1, HLA-DR, CD40, STAT1, IFNG, CCR5*
	BIIB023	Anti-TWEAK monoclonal antibody (humanized)	*TNFSF12, TNFAIP3, TNIP1*
	Fresolimumab	Anti-TGFβ monclonal antibody (human); blocks fibrosis	*TGFB1*
	Tamibarotene	Small molecule; RAR agonist, anti-inflammatory	*MYD88, PTPN22, TNFAIP3, TNIP1, STAT1, IFNG, TGFB1*
	GSK-2586184	Small molecule; JAK inhibitor	*MYD88, HLA-DR, STAT1, IFNG, TGFB1*