Immunogenetics of Systemic Lupus Erythematosus: A Comprehensive Review

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Summary

Our understanding of the genetic basis of systemic lupus erythematosus has progressed rapidly in recent years. While many genetic polymorphisms have been associated with disease susceptibility, the next major step involves integrating these genetic polymorphisms into the molecular mechanisms and cellular immunology of the human disease. In this review, we summarize some recent work in this area, including the genetics of the type I IFN response in SLE, including polygenic and monogenic factors, as well as epigenetic influences. Contributions of both HLA and non-HLA polymorphisms to the complex genetics of SLE are reviewed. We also review recent reports of specific gene deficits leading to monogenic SLE-like syndromes. The molecular functions of common SLE-risk variants are reviewed in depth, including regulatory variations in promoter and enhancer elements and coding-change polymorphisms, and studies which are beginning to define the molecular and cellular functions of these polymorphisms in the immune system. We discuss epigenetic influences on lupus, with an emphasis on micro-RNA expression and binding, as well as epigenetic modifications that regulate the expression levels of various genes involved in SLE pathogenesis and the ways epigenetic marks modify SLE susceptibility genes. The work summarized in this review provides a fascinating window into the biology and molecular mechanisms of human SLE. Understanding the functional mechanisms of causal genetic variants underlying the human disease greatly facilitates our ability to translate genetic associations toward personalized care, and may identify new therapeutic targets relevant to human SLE disease mechanisms.

Keywords

systemic lupus erythematosus; genetics; interferon; autoimmune diseases

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1. Introduction

Systemic lupus erythematosus (SLE) is a severe, chronic autoimmune disorder characterized by involvement of multiple organ systems, loss of tolerance to self-antigens and dysregulated interferon responses. It is a highly heterogeneous condition, and different patients exhibit different combinations of symptoms and laboratory features. Humoral autoimmunity is a distinctive feature of SLE and many patients have circulating autoantibodies directed against double stranded DNA (anti-ds-DNA) and/or small nuclear RNA-binding proteins (such as anti-Ro, anti-La, anti-Sm, and anti-RNP). The pathogenesis of SLE is multifactorial, and the irreversible breakdown in immunologic self-tolerance which characterizes the disease can be attributed to the interplay among multiple genetic risk factors and environmental influences. Incidence of SLE is highest in women particularly during the childbearing years (female: male ratio 9:1) however, individuals of all ages, genders, and ancestral backgrounds are susceptible [1, 2]. SLE occurrence is four times higher in African-Americans as compared to European-Americans [3] and various studies have exhibited both genetic and immunologic differences among SLE patients from these ancestral backgrounds [4–7]. Familial aggregation and monozygotic twin studies strongly support the idea of genetic predisposition to SLE. Familial aggregation studies have demonstrated that siblings of SLE patients have greater relative risk for the disease, with sibling risk ratio (λs) as high as 29 compared with the general population [8] . Likewise, there is approximately ten-fold higher risk for SLE in monozygotic twins than in dizygotic twins [9, 10], while first degree relatives of patients with SLE have a 20-fold increased risk of developing SLE as compared with the healthy population [3, 11]. Within the families with multiple affected members, the SLE occurrence does not usually follow a classical Mendelian inheritance pattern. In the majority of cases, genetic susceptibility of SLE follows the common disease-common variant assumption, with polygenic inheritance of multiple alleles with a modest effect size (odds ratios for disease between 1.15 and 2.5) that combine to result in overall genetic risk. While the etiology of most SLE cases appears to be complex genetically, a few cases SLE and SLE-like disorders can be attributed to highly penetrant rare mutations which will be discussed in detail subsequently.

Numerous genome wide association studies (GWAS) have been performed in patients with SLE across various ethnic populations, and currently more than 40 common risk loci have been definitively linked to SLE susceptibility in case-control genetic studies [12, 13]. As expected, the strongest association signal among the common genetic variants obtained from HLA region, while many other non-HLA SLE susceptibility loci are located within or near genes with functional relevance in the immune system. In addition, number novel genetic loci have been associated with SLE susceptibility that may or may not function within immune system pathways and have no known previous relationship to the pathogenesis of SLE. Examining the list of genes associated with SLE, there is a remarkable over-representation of genes involved in type I interferon (IFN) signaling, production, and response [13, 14]. Interferon alpha (IFN-α) is a type I interferon classically involved in viral defense which has the potential to break self-tolerance by activating antigen-presenting cells after the uptake of self-material [15], and is central to the pathogenesis of SLE [16]. IFN-α can be synthesized by many cells in response to viral infection, but plasmacytoid dendritic

cells (pDCs) play a specialized role in the production of IFN-α [17]. Circulating IFN-α levels are high in SLE patients [18] and this high IFN phenotype is heritable within SLE families with a complex or polygenic pattern of inheritance [11]. These data suggest that high serum IFN-α is a heritable risk factor for SLE [11]. Also, some individuals treated with recombinant IFN-α have developed de novo SLE, which typically improves when the IFN is discontinued [19, 20]. Many of the genetic polymorphisms associated with SLE susceptibility have been shown to contribute to high IFN levels in human SLE patients [21–23]. These data support the idea that gain-of-function polymorphisms in the IFN pathway are a common pathogenic mechanism in SLE. Additionally, number novel genetic loci have been identified that have an effect on IFN-α levels in SLE patients, supporting the genetic nature of the IFN dysregulation observed in SLE [24–28]. Collectively these data strongly support the causative role of this heritable molecular subphenotype in SLE etiology and pathogenesis. In this review, we will discuss polygenic and monogenic influences on type I IFN. In addition to type I IFN-related genes, genes related to other immune system functions such as B- and T- cell signaling, clearance of dead cellular debris, and cytokine signaling make up a large portion of the genetic loci associated with SLE. In this review, we will discuss polygenic and monogenic influences on type I IFN, as well as the functional significance of some of the other SLE-associated polymorphisms located in immune system genes. These immunogenetic data provide novel insights into the molecular pathogenesis of human SLE. Figure 1 illustrates these major pathways and cell types which are involved in human SLE, and the genes discussed in the review are shown in the cell type in which they are presumed to function.

2. Human leukocyte antigen (HLA) complex in SLE

The classical HLA complex (also referred to as major histocompatibility locus [MHC]) is the most gene-dense region of the genome, encoding more than 200 genes in a 3.6 Mb region on 6p21.3. Many of these genes function in the immune system. The HLA region is subdivided into the telomeric class I region and the centomeric class II and class III regions. The class I and II regions encode highly polymorphic classical HLA genes (HLA-A, -B, -C, -DR, -DQ, -DP) that process and present peptides for T cell recognition and involved in transplant compatibility, and the class III region encodes a variety of important immune system genes (such as C2, C4A, C4B, TNF-α, lymphotoxin–α, heat shock proteins, and CFB). Association between HLA variants and SLE is extensively explored and till today all SLE GWAS in different ethnic populations demonstrated the HLA region as the prominent strongest predictor of genetic risk [13]. Among these HLA regions, genes in class II are dominantly represented as SLE susceptibility loci. Previous studies of the HLA region in SLE have shown that HLA-DRB1 (DRB1*1501 and DRB1*0301) is a robustly associated with SLE [29, 30]. Recent GWAS studies in European and Asian population have further confirmed these associations [13, 31, 32]. Given the importance of the HLA class II molecules in T cell dependent antibody responses, the close association between class II alleles (specifically HLA-DR and HLA-DQ alleles) with autoantibody subsets in SLE patients seems to make sense [29]. A study comparing anti–dsDNA negative SLE cases to healthy controls demonstrated a significant association for a SNP, rs2301271, 9 kb downstream from HLA-DQA2 [33], and a strong association was observed between anti-

dsDNA and HLA-DR3 at rs2187668, further supporting the importance of the HLA region in determining autoantibody responses. Similarly, a recent largest SLE sub-phenotype genetic association study demonstrated *HLA-DRB1*03:01* not only just influence SLE susceptibility but is also associated with anti-Ro and anti-La autoantibody production [34]. Furthermore, the role of SLE-associated HLA Class II alleles in initiating SLE-relevant autoantibody responses has been shown in humanized mice expressing the HLA-DR3 transgene but not other DR or DQ alleles [35]. An HLA class III gene, super viralicidic activity 2-like (SKIV2L) encoding RNA helicase SKI2W enzyme, was identified as a SLE susceptibility risk gene independent of class II loci [36]. Also, the rs3131379 SNP in MSH5 (HLA class III locus) demonstrated association in a GWAS study [37]. It seems likely given the complexity of the region and the high density of immune system genes, that the multiple association signals reported to date could represent multiple independent risk factors. A recent study using high-density SNP screening of the MHC region supports this idea, reporting multiple independent loci associated with SLE, including HLA-DRB1*0301, DRB1*1401, DRB1*1501 and the DQB2 alleles, CREBL1, MICB and OR2H2 [22]. Together these studies highlight the essential influence of HLA genes in SLE pathogenesis.

3. Polygenic Influences on type I IFN

3.1. IFN Regulatory Factors

Interferon regulatory factors (IRFs) are classically involved in inducing IFN-α and IFN-induced genes downstream of Toll-like receptor (TLR) activation. Additionally they play prominent role in cytokine secretion, cellular apoptosis, immune cell development, tumor suppression, and cell activation and differentiation [38, 39]. Interestingly, genetic variations in three of the nine IRFs (IRF5, IRF7, and IRF8) have been linked to SLE susceptibility, supporting a key role for this family of proteins in SLE pathogenesis. Studies in several different ethnic groups have confirmed IRF5 as a risk locus for SLE, and its association with increased circulating IFN-α levels [22, 40]. Four main functional variants in IRF5 have been reported, a promoter polymorphism which alters binding affinity at the promoter, one at rs2004640 which creates an alternate splice site (exon 1B) in the untranslated first exon, another is a 30-bp in-frame insertion/deletion in exon 6, and the third is a 3'UTR polymorphism which creates an alternate polyadenylation site resulting in shorter and more stable mRNA. It has been demonstrated that these four variants combine to form a SLE risk haplotype in individuals of European ancestry [41] and these various IRF5 haplotypes are also associated with the formation of anti-Ro, anti-La, and anti-dsDNA autoantibodies [42]. As IRF5 activates IFN production, these variants may pose a risk due to their ability to produce excess IFN. Studies on IRF5 in human SLE cohorts have shown that the risk variant predisposes to greater serum IFN-α, supporting the idea that the risk haplotype is a gain-of-function variant [22]. The same risk variant has been associated with autoantibody formation in SLE patients and in healthy individuals, and most of the risk of SLE related to IRF5 genotype is found within the autoantibody positive, high IFN group of patients [42, 43]. IRF7 is another IRF family member which also interacts with the MyD88 adaptor protein downstream of TLR signaling, and is phosphorylated and activated following TLR engagement [38]. Genetic variants in the IRF7 locus have been associated with SLE in various studies [37, 44, 45]. Several SNPs in the IRF7 region were shown to correlate with

IFN levels and autoantibody profiles in SLE patients of various ancestral backgrounds [46]. A recent study on human dendritic cells demonstrated a cis-expression quantitative loci (eQTL) SNP located within the SLE-associated haplotype is not only associated with IRF7 expression but also confers the trans-eQTL effect on type I IFN response regulation in activated but not unstimulated dendritic cells [47]. This supports the previous human studies that indicate IRF7 variants are associated with greater IFN-α in circulation. IRF8 has no direct interaction with MyD88, but it does appear to play a role in the TLR pathway as dendritic cells lacking IRF8 do not produce inflammatory cytokines in response to TLR9 ligand [48]. IRF8 deficiency in humans results in an immunodeficiency characterized by the loss of monocytes and dendritic cells, indicating its role in monocyte and dendritic cell development [49]. Genetic variants in the IRF8 gene region are associated with susceptibility to both SLE and multiple sclerosis (MS) [50, 51]. Type I IFN plays a contrasting role in MS and SLE, as while IFN-α is increased and thought to be causal in SLE, type I IFN levels are lower in patients with MS than in healthy controls [38], and recombinant human IFN-β is used as a treatment for MS. A study investigating whether IRF8 alleles were associated with type I IFN levels or serologic profiles in SLE and MS revealed that MS-associated allele downstream of IRF8 (rs17445836G) was associated with decreased activity of the type I IFN pathway in these two different autoimmune diseases and was associated with anti-dsDNA antibodies and increased IRF8 in B cells in the patients with SLE [52]. Taken together, these data support a role for IRF8 variants in modulating type I IFN and humoral autoimmunity in multiple autoimmune conditions.

3.2. STAT4

STAT4 encodes the signal transducer and activator of transcription 4 protein (STAT4) which plays an important role in downstream responses to type I IFN and other cytokines. Functionally, activation and phosphorylation of STAT4 is induced by IL-12, IL-23, and IFN-α which then promotes Th1 as well as Th17 responses [53]. Both candidate gene association studies and multiple GWAS studies using populations from European or Asian ancestry have demonstrated a robust association between SLE and *STAT4* [13]. In SLE patients, the risk variant for *STAT4* (rs7574865) was associated with increased sensitivity to IFN-α signaling, as evident from its simultaneous association with both lower serum IFN-α activity and greater IFN-α-induced gene expression in PBMCs [21]. Interestingly, the same risk variant was also associated with a more severe SLE phenotype characterized by a higher frequency of nephritis and the presence of anti-dsDNA antibodies [54].

3.3. IFIH1

IFIH1 is an innate immune receptor located in the cytosol which senses dsRNA and promotes IRF3 and 7 phosphorylation, activating transcription of antiviral genes and type I IFN production. Based on the studies in SLE and other various autoimmune conditions it has been proposed that a common coding change variant in IFIH1 (rs1990760, A946T) leads to increased expression and gain-of-function in IFIH1 and subsequent predisposition to human autoimmune disease [13]. This risk variant was also modulated IFN-α-induced gene expression in peripheral blood cells in anti-dsDNA positive SLE patients, and was associated with the production of anti-dsDNA antibodies [55]. Recently, a large-scale multi-ancestral admixture mapping genetic screen revealed three independently associated variants

in the IFIH1 gene (one intronic and two missense variants). These variants were associated with increased apoptosis and elevated expression of inflammation-related genes, as well as autoantibody production [56].

3.4. OPN

Osteopontin (OPN, encoded by the *SPP1* gene) is overexpressed in humans with SLE and has been involved in the development of murine lupus [57, 58]. A number of studies have linked genetic variants in OPN with SLE susceptibility, clinical manifestations of SLE; and high IFN levels in SLE affected males and young-onset female lupus patients [13, 59]. OPN interacts with the MyD88 adaptor protein downstream of TLR ligation, and is an important molecule for IFN-α production in plasmacytoid dendritic cells (pDCs), thus supporting its role in SLE pathogenesis [60].

4. Monogenic Causes of SLE and SLE-like high-IFN syndromes

4.1. Monogenic deficiencies in SLE

4.1.1. Complement deficiency—Relatively rare primary complement defects such as complete deficiency of the early components of classical complement pathway genes (C1q, C1r/s, C2, C4A and C4B) are strongly associated with increased susceptibility to SLE [61–64]. The occurrence of a lupus-like syndrome or SLE has been demonstrated in 90% of homozygous C1q deficient cases, in more than 50% of cases with C1s/C1r deficiencies, in 10 to 30% of C2 deficient cases (more often a deletion in intron 6 that leads to a premature stop codon in exon 7 resulting in failure to synthesize the protein), and in 75% of C4-deficient cases [65]. Complement is essential for opsonization and clearance of autoantibody-containing immune complexes and clearing apoptotic cells. Interestingly, complement also plays a role in T and B cell activation and complement deficiency may disrupt the balance of lymphoid cell activation. Deficiencies of the classical complement component pathway are likely to affect SLE pathogenesis by decreasing clearance of apoptotic cell debris and immune complexes (IC), resulting in increased self-antigen availability, and dysregulated IC-related TLR signaling or IC induced cytokines such as IFN-α [65]. The genes for complement components C2 and C4 are in linkage disequilibrium with MHC polymorphisms, and these genes are hypothesized to contribute independently to the risk of SLE [66].

4.1.2. Apoptosis defects—Several lines of evidence indicate that abnormalities in the apoptosis (programmed cell death) contribute to the development of SLE, as the elimination of autoreactive T or B cells is impaired in this disease [67]. In addition, it appears that increased lymphocyte apoptosis and delayed clearance of phagocyte-mediated apoptotic cells as evident in SLE patients could contribute to B-cell hyperactivity and subsequent autoantibody production [68]. The accelerated apoptosis of circulating cells observed in SLE patients could serve as a major source of autoantigens in the form of apoptotic blebs and debris [68]. The role of FAS-mediated apoptosis in immunity and elimination of autoreactive lymphocytes are clear [69]. Defects in FAS and FASL provided one of the first murine models of SLE, the MRL/lpr mouse [70]. The monogenic human condition autoimmune lymphoproliferatve syndrome (ALPS) results from FAS or FASL defects, and

this condition shares some features of SLE such as lymphadenopathy, positive anti-nuclear antibodies (ANA), autoimmune cytopenias, and sometimes organ system inflammation [71]. However, the role of FAS and FASL gene polymorphisms in the etiology of SLE has been inconclusive [72]. Studies in SLE patients indicated that FAS may be involved in the defective apoptosis of T cells and resistance to the FAS-mediated apoptosis in these cells [69, 73, 74]. Other studies have observed that polymorphisms in FAS and FASL genes could alter their basal expression [75] and thus have been suggested to play important roles in pathogenesis of SLE [72, 74, 76] .

4.1.3. DNASE1/DNASE1L3—Deoxyribonuclease I (DNase I, encoded by *DNASE1*) is specific endonuclease essential during apoptosis. Decreased DNase I activity may result in increased risk of antinucleosome antibody production, a cardinal feature of SLE. Various studies have reported a link between low DNase I activity and the development of murine or human SLE [77, 78]. Two unrelated cases of juvenile SLE exhibiting very high levels of antinucleosomal antibodies were reported with a mutation in exon 2 of DNAse type 1 [79], however this mutation has not been confirmed in other patient populations. Recently, study of seven consanguineous families with multiple SLE affected children by linkage analysis and exome sequencing identified loss-of-function mutations in *DNASE1L3* as a monogenic cause of an SLE-like syndrome [80]. A strict Mendelian autosomal recessive pattern of association was observed between this mutation and SLE. Clinically, the affected individuals presented with hallmarks of SLE such as ANA, anti-dsDNA autoantibodies, anti-neutrophil cytoplasmic antibodies (ANCA) and hypocomplementemia [80]. It is possible that these DNASE mutations facilitate an SLE-like phenotype via inappropriate accumulation of DNA which can then become a neo-antigen and form inflammatory immune complexes with anti-dsDNA antibodies.

4.1.4. PRKCD—Recently, in another study on consanguineous family with three siblings affected with SLE was reported in which the affected individuals all had homozygous inactivating mutations in *PRKCD* gene [81]. *PRKCD* encodes protein kinase C δ (PKCδ), which has been implicated in the control of cell proliferation, apoptosis, and B-cell signaling [82, 83]. The identified missense mutation of PRKCD (G510S) resulted in reduced expression and activity of the encoded protein PKCδ, leading to resistance to B cell receptor- and calcium-dependent apoptosis and increased B cell proliferation. B cells from the patients carrying PRKCD mutations demonstrated hyperproliferative responses to stimulation through the BCR, CD40 and TLR9 signaling pathways [81]. Phenotypically, the affected siblings had anti-dsDNA antibodies, nephritis and hypocomplementemia without hypergammaglobulinemia [81].

4.2 Monogenic influences on IFN: SLE-like interferonopathies

4.2.1 TREX1—TREX1, also called, DNAse type III, is the main 3'-5'DNA exonuclease enzyme that proofreads DNA polymerase, also functioning as a DNA degrading enzyme in granzyme-A-mediated apoptosis and as a cytosolic DNA sensor [84]. *TREX1* deficiency impairs DNA damage repair, leading to the intracellular accumulation of endogenous DNA. This defective DNA clearance stimulates systemic autoimmunity by inducing TLR-independent IFN-α production. *TREX1* mutations in humans lead to Aicardi-Goutieres

syndrome (AGS), which shares several features with SLE. This gene is also commonly mutated in SLE [85], as missense variants in TREX1 were observed in 0.5 to 2.7% SLE patients but were nearly absent in healthy controls indicating TREX1 mutations are the most frequent form of monogenic lupus [86, 87]. The *TREX1-SLE* association supports the importance of defective clearance of DNA in activation of innate immunity and the development of SLE.

4.2.2 STING—TLR-independent cytosolic DNA-sensing pathways that signal via stimulator of interferon genes (STING; also known as "TMEM173," "MPYS," "MITA," and "ERIS") mediate immunity to pathogens and also promote autoimmune pathology [88]. STING activates host defense by induction of IFN-β through a well-characterized pathway involving TBK1 and interferon regulatory factor 3 (IRF3) [88] and the production of the NF-κB-driven cytokines TNF-α and IL-6 [89]. STING deficiency ameliorates the autoimmune phenotype of TREX1-deficient mice, as the loss of STING reduces the overproduction of IFN and chronic inflammation [90]. Supporting this idea, gain-of-function mutations in *TMEM173*, gene encoding STING, were recently reported in subjects with a monogenic condition characterized by high IFN levels and vascular and pulmonary inflammation [91, 92]. Loss-of-function polymorphisms for STING are also known, however they have not yet been linked to any human diseases [93].

4.2.3 SAMHD1—SAMHD1 also known as Aicardi- Goutières syndrome type 5 (AGS5), is a putative nuclease encoded by the *SAMHD1/ AGS5* gene that is upregulated in response to viral infections and may have a regulatory role in immune system and cerebral vascular homeostasis [94–97]. Similar to TREX1, mutations in SAMHD1 including biallelic null alleles as well as missense mutations have been associated with Aicardi-Goutieres syndrome. At least 16 different mutations in the *SAMHD1* gene have been reported in patients with Aicardi-Goutieres syndrome [98–101]. These mutations result in loss-of-function of the SAMHD1 protein. However, how this protein dysfunction leads to immune system abnormalities, inflammatory damage to the brain and skin, and other characteristics of this syndrome is still unknown. Circulating IFN-α is increased in these patients, even though the molecular mechanism by which SAMHD1 deficiency causes IFN overproduction is not known.

4.2.4 TRAP—The acid phosphatase 5 (ACP5) gene encodes tartrate-resistant acid phosphatase (TRAP). Deficiency of the ACP5 gene has been associated with an immuno-osseous dysplasia called spondyloenchondrodysplasia (SPENCD). SPENCD has been regarded primarily as a skeletal dysplasia, but patients with this disease also demonstrates a high frequency of autoimmune phenotypes, including SLE, hemolytic anemia, Sjogren's syndrome, inflammatory myosis, hypothyroidism and thrombocytopenia [102, 103]. It has been identified that loss-of-function mutations in the *ACP5* gene are causal of the disease resulting in elevated serum IFN activity and an IFN signature in SPENCD patients, and [102, 103]. TRAP is expressed in bone and in immune cells, including osteoclasts and dendritic cells. Since OPN is a recognized substrate for osteoclast-derived TRAP and is dephosphorylated by TRAP [104], it is possible that in the absence of TRAP in pDC, OPN would remain phosphorylated and persistently activate IFN-α via TLR9/MyD88 [103]. This

hypothesis is supported by the observation that SPENCD patients have higher urinary levels of phosphorylated OPN as compared with controls, suggesting that TRAP is responsible for dephosphorylating OPN, and that this function is defective in patients with SPENCD [103]. Interestingly, as noted above genetic polymorphisms in the *SPP1* gene have been associated with SLE susceptibility, and patients carrying *SPP1* risk alleles have elevated IFN-α activity and increased OPN protein levels [59, 105]. These data would suggest that in humans TRAP deficiency may result in over-active OPN and type I IFN, and it is possible that this may be particularly important in those patients with *SPP1* risk alleles.

5 Regulatory variants associated with SLE susceptibility

5.1 TNFAIP3 and TNIP1

The tumor necrosis factor alpha inducible protein 3 (*TNFAIP3*) gene, encodes the ubiquitin-modifying enzyme A20, a critical regulator of NF-κB activity downstream of tumor necrosis factor alpha (TNFα), TLRs, and interleukin 1 receptor [106]. TNFAIP3 limits inflammatory signals by diminishing NF-κB signaling. Variants near *TNFAIP3* have been associated with susceptibility to multiple polygenic autoimmune disorders including SLE, rheumatoid arthritis, and others [107]. Presumably these autoimmune disease associated variants would be loss-of-function, reducing the ability of TNFAIP3 to limit inflammation. A number of independent genetic associations between SLE and various SNPs spanning the TNFAIP3 region have been reported [108–110]. These include a common coding-change variant in exon 3 (rs2230926), as well as a coding-change variant in the deubiquitination domain that reduces the enzymatic function of TNFAIP3 [111]. Another study further characterized the TNFAIP3 risk haplotype by fine mapping and genomic re-sequencing in multiple world populations, and found a TT>A polymorphic dinucleotide (deletion T followed by a T to A transversion) far downstream of the TNFAIP3 gene as top polymorphism accounting for association between TNFAIP3 and SLE in European ancestry [112]. This polymorphism lies within a long-range enhancer element that binds NF-κB and SATB1, enabling physical interaction of this enhancer with the TNFAIP3 promoter through long-range DNA looping. Impaired binding of NF-κB to the TT>A risk alleles or knockdown of SATB1 expression by shRNA inhibits the looping interaction resulting in reduced A20 expression [113], and the reduced A20 expression would lead to impaired control over inflammatory signaling pathways. TNFAIP3-interacting protein 1 (*TNIP1*) is another gene that is involved in limiting inflammatory NF-κB signaling, and variants in this gene have also been associated with SLE susceptibility [114, 115]. The risk haplotypes of *TNIP1* result in decreased expression of TNIP1 mRNA [115], consistent with the idea that the SLE-risk variant reduces the effect of the immunosuppressive TNIP1 gene product. When an inactive form of the protein encoded by *TNIP1* (ABIN1) is knocked into mice, an immune complex nephritis that resembles lupus nephritis develops [116]. The results for both TNFAIP3 and TNIP1 indicate the importance of NF-κB pathway regulation in the pathogenesis of SLE. Figure 2 shows the proposed molecular mechanisms of these genes as well as others discussed in this review in a schematic diagram.

5.2 BLK

BLK encodes a B lymphocyte specific tyrosine kinase, a member of the Src family of kinases that functions in intracellular signaling and regulates cell proliferation and differentiation. A GWAS carried out in the European population revealed that two different BLK SNPs were associated with SLE. One of these polymorphisms was located within the intergenic region of *FAM167A* and *BLK* and was associated with reduced expression of *BLK* but increased expression of *FAM167A* in SLE patients [37, 117] . Association of BLK polymorphisms with SLE was later confirmed in Asian ancestry as well [31]. Recently, using trans-population fine mapping and sequencing, the SLE-associated interval in the BLK promoter has have been refined to two variations [118]. The first is a common SNP (rs922483) in the proximal BLK promoter that causes decreased promoter activity and modulation in alternative promoter usage, and the second is a tri-allelic variant (rs1382568) in the upstream alternative BLK promoter that results in altered promoter activity in B progenitor cell lines [118]. This study identifies regulatory variations near the BLK gene that modulate the transcription of *BLK* in B cells, which would presumably alter immune responses and thus contribute to SLE pathogenesis.

5.3 ETS1 and PRDM1

ETS1 is a member of the ETS family of transcription factors that acts as a negative regulator of B cells and T-helper-17 cell differentiation by inhibiting the function of PR domain zinc finger protein 1 (encoded by *PRDM1*, also known as *BLIMP1*) [119, 120]. PRDM1 functions as repressor of IFN-β gene expression, and is an important factor in B cell development. GWAS studies in European and Asian populations have demonstrated that *PRDM1* is a risk locus for SLE [13]. A recent study has also shown that *ETS1* is an SLE susceptibility locus in Asian populations, and this was then also later replicated in European populations [121]. The risk variant identified in these studies was located in the 3' UTR region of the gene (rs1128334), and has been associated with decreased *ETS1* expression levels in PBMCs from healthy individuals [31]. Decreased expression of this suppressive gene would be expected to result in increased immune system activation. Murine models support this idea, as *ETS1*-deficient mice developed a lupus-like disease distinguished by high titers of autoantibodies and local complement activation [122]. A multi-ancestral fine-mapping study spanning ETS1 loci examined the functional mechanism of ETS1 variants on the basis of their likelihood of affecting transcription factor binding, miRNA binding, or chromatin state [123]. They observed that the ETS1 risk allele rs6590330 caused enhanced binding of pSTAT1 and decreased ETS1 expression [123].

5.4 IKZF1

DNA-binding protein Ikaros (encoded by *IKZF1*) is a lymphoid-restricted zinc finger transcription factor that controls lymphocyte differentiation and proliferation, as well as self-tolerance through regulation of B-cell receptor signaling [124]. IKZF1 was established as a novel susceptibility gene for SLE GWAS in Chinese Han population and has been replicated in a Europena population [13, 121]. The risk allele of IKZF1 SNP rs4917014 was associated with correlated with lower expression levels of IKZF1 mRNA in PBMCs from SLE patients [125]. Additionally, expression quantitative trait locus (eQTL) studies of IKZF1 showed that

this same risk allele also affected the expression of multiple genes in trans such as C1QB and five type I interferon response genes [126]. This study supported both cis and trans transcriptional influences from this IKZF1 SNP, supporting a regulatory role for this polymorphism in SLE.

6 Coding-change polymorphisms

6.1 PTPN22

Tyrosine-protein phosphatase nonreceptor type 22 (PTPN22) is a lymphoid specific phosphatase that controls antigen receptor signal transduction in both T and B lymphocytes [127]. Two functional variants of the PTPN22 gene have been identified— one is a nonsynonymous variant rs2476601 (arg620trp) that increases the risk of SLE, as well as multiple other autoimmune diseases [128]. A loss of function PTPN22 variant (Arg263Gln) reduces the phosphatase activity of PTPN22, and has been associated with protection against SLE in European population [129]. PTPN22 is expressed in most leukocytes, and studies of the coding change polymorphism have documented numerous alterations in the cellular immune system related to these polymorphisms, and it's likely that the role of this gene in SLE is complex. Roles for the PTPN22 risk alleles in effector T cell and regulatory T cell development have been supported [130]. A study in SLE patients has suggested a link between PTPN22 and innate cytokine production, as the SLE patients who carry the common coding-change risk allele for PTPN22 had higher serum IFN-α activity and lower serum tumor necrosis factor (TNF) levels [131]. Recent work with PTPN22 in model systems also supports a role for PTPN22 in TLR responses and type I IFN production [132]. The common PTPN22 risk allele has also been associated with anti-dsDNA autoantibody production in SLE [33], and abnormalities in the B cell compartment such as expansion of transitional and anergic B cells [133], and decreased removal of autoreactive B cells [134].

6.2 ILT3

Immunoglobulin-like transcript 3 receptor (ILT3) is an immunosuppressive surface receptor that is induced by type I IFNs, and thus could represent a negative feedback pathway regulating type I IFNs in vivo. ILT3 is expressed on dendritic cells and monocyte/ macrophage lineage cells [135]. ILT3 expression has been examined in multiple sclerosis patients who were being treated with type I IFN in the form of recombinant IFN-β, and increased ILT3 expression was observed in patients who were responding to treatment [136]. ILT3 polymorphisms have been examined in SLE in a candidate gene study in which coding-change polymorphisms that were likely to alter protein folding were prioritized [26]. The rs11540761 coding-change SNP in the extracellular region of ILT3 was correlated with decreased cell surface expression of ILT3 on circulating MDCs and to a lesser extent PDCs in these patients. The rs1048801 SNP changes an amino acid on the cytoplasmic portion of the ILT3 receptor, and this polymorphism was not associated with a change in expression of ILT3 on dendritic cells but was associated with increased serum levels of TNF-α. Both these loss-of-function polymorphisms were significantly and independently linked with increased levels of serum type I IFN activity in SLE patients, supporting the idea that loss of this suppressive receptor results in decreased control of type I IFN responses in SLE.

7 Epigenetic influences on SLE pathogenesis

Though the recent advances in genetic association studies have identified many SLE predisposing genes, we are not able to fully account for SLE susceptibility with these genetic variations, and epigenetics may account for some of this unexplained heritability. Furthermore, the incomplete disease concordance rates in monozygotic twin studies in SLE would suggest epigenetic influences to SLE development. Studies examining methylation in monozygotic twins discordant for SLE have demonstrated significant differences in these discordant pairs [137]. Differences in epigenetic modifications such as DNA methylation, histone modifications (acetylation, ubiquitination, phosphorylation and citrullination of histone tails) and noncoding RNA, can impact the expression and function of genes involved in SLE pathogenesis.

7.1 Effect of DNA hypomethylation and histone modification changes on type I IFN and SLE pathogenesis

Within DNA, methylation usually occurs at CpG islands sites by methyltransferases that lead to inducive or suppressive effects on gene expression. In SLE patients, DNA from T cells is hypomethylated at multiple sites, which can lead to upregulated expression pro-inflammatory molecules [138]. Various factors like ultraviolet light, SLE-inducing drugs, aging, and altered expression of certain microRNAs can promote DNA hypomethylation [138]. Studies have shown that various methylation-sensitive genes that functionally contribute to SLE development are overexpressed in SLE CD4+ T cells, for example CD11A, perforin, CD70, and CD40L [139]. A recent genome-wide DNA methylation analysis comparing SLE patients and healthy controls demonstrated significant hypomethylation of type I IFN-regulated genes in SLE CD4+ T cells, CD19+ B cells and CD14+ monocytes [140, 141]. Given that type I IFN is increased in the circulation of many SLE patients, it is not clear how much of the epigenetic change in circulating T cells is induced by type I IFN signaling vs. some intrinsic hypomethylation in SLE patient cells. Supporting the idea that some of the changes might be intrinsic, a study in human T cells from healthy individuals with or without the SLE-risk MECP2-IRAK1 haplotype demonstrated lupus-associated variant in the MECP2/IRAK1 locus leads to an increased levels of a specific MECP2 transcript isoform in stimulated T cells and further showed a similar hypomethylation of IFN-regulated genes, providing evidence for a genetic–epigenetic interaction associated with SLE-risk variants [142].

Different combinations of histone modifications can affect DNA replication, transcription and chromatin structure [143], and alterations in histone modifications leading to abnormal gene expressions likely contribute to SLE pathogenesis [12]. For example, a study demonstrated significantly increased H4 acetylation (H4ac) in monocytes from SLE patients, as well as increased expression of genes involved in the type I IFN pathway [144]. Additionally, studies examining epigenetic information in Epstein–Barr virus-transformed lymphoblastoid cell lines exhibited an enrichment of active histone marks in the promoters of SLE and RA susceptibility genes [145, 146]. These studies support the idea that epigenetic methylation marks modulate the genetic variations implicated in SLE and autoimmune disease.

7.2 Influences of microRNAs on type I IFN and SLE pathogenesis

MicroRNAs (miRNAs) are endogenous small non-coding RNA molecules which function in RNA silencing and post-transcriptional regulation of gene expression by binding to specific target messenger RNA (mRNA) transcripts and promoting their degradation/destabilization and/or translational inhibition [147]. Recent studies support a critical role for miRNAs in the function of both innate and adaptive immunity, and miRNA alterations have been associated with autoimmune diseases such as SLE, RA, and Sjogren's syndrome [148, 149]. It has been observed that several miRNAs play essential role in negative regulation of innate immune responses. For example miR-146a can inhibit type I IFN production by targeting multiple key molecules in the innate signaling pathway such as TLR7, RIG-I pathway [150, 151]. This miRNA also suppresses NFκB activation and related cytokine production by acting on signaling adaptor proteins the TNF receptor-associated family (TRAF)-6 and IL-1 receptor-associated kinase (IRAK)-1 [152]. Another miRNA miR-155/miR-155* was shown to influence regulation of type I interferon production in pDCs [153].

MiRNA expression profiling studies in PBMCs, plasma and different tissues from SLE patients has discovered distinct miRNA signatures as compared with healthy individuals demonstrating association of miRNAs dysregulation with disease activity, organ system involvement, and autoantibody profiles, indicating a possible role for miRNAs as biomarkers in SLE patients [148, 154]. Of the particular interest are studies which have investigated the functional impact of SLE-associated genetic polymorphisms upon miRNA expression or binding. An SLE-risk allele has been reported in the *miR146a* miRNA. This miRNA is a negative regulator of the IFN pathway, and a promoter variant (rs57095329) was linked to decreased expression of miR-146a [155]. This promoter polymorphism results in reduced protein-binding affinity for the transcription factor ETS1 (also note genetic variants in ETS1 described above), which causes lower levels of miR-146a expression [155]. Alteration of miRNA binding sites in target mRNA represents another mechanism by which inherited genetic variation can impact the ability of miRNAs to regulate gene expression. Some SLE-associated SNPs have been identified that introduce or abolish miRNA binding sites. An SLE associated SNP in the *SPI1* gene is in complete linkage with a functional SNP in the 3′ UTR region of this gene (rs1057233) that alters the target sequence of microRNA miR-569 [156]. This genetic variation disrupts the miR-569 binding site, resulting in an increase in *SPI1* mRNA level which could contribute to SLE development [156]. A TLR7 SLE-risk allele provides another example of genetic variation altering miRNA binding. The SLE risk allele of TLR7 (rs3853839) is common across multiple ancestral backgrounds, and demonstrates an allelic effect on TLR7 expression [157]. This risk allele results in altered binding of miRNA-3148 and slower degradation of the TLR7 transcript [157]. These studies illustrate how genetic variations that impact miRNA binding sites impact transcript abundance, and subsequently alter immune cells contributing to SLE pathogenesis.

8 Conclusions

In summary, this review illustrates the wide diversity of molecular genetic mechanisms involved in SLE pathogenesis. This is illustrated in both the large number of immune cell

types involved in both innate and adaptive immunity (Figure 1), as well as the large diversity in the genetic mechanisms by which these polymorphisms impact the molecular biology of SLE (Figure 2). The work summarized in this review represents a critical area of SLE research which allows for a fascinating window into human SLE pathogenesis. By understanding the functional mechanisms of causal genetic variants underlying the human disease, we will be able to understand the molecular pathogenesis of SLE in humans. This will facilitate our ability to translate genetic associations toward personalized care, and may help us use existing medications in a way that is more directed at pathogenic factors which are relevant for a particular individual, and new therapeutic targets may also emerge as the molecular mechanisms of human SLE are more fully understood.

Acknowledgments

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Highlights

- Genetic risk factors for lupus differ somewhat between world populations

- Multiple genes contribute to type I interferon dysregulation in lupus

- Lupus-risk genes function via a wide range of molecular and immunologic mechanisms

- Micro-RNAs and methylation changes also contribute to the lupus disease process
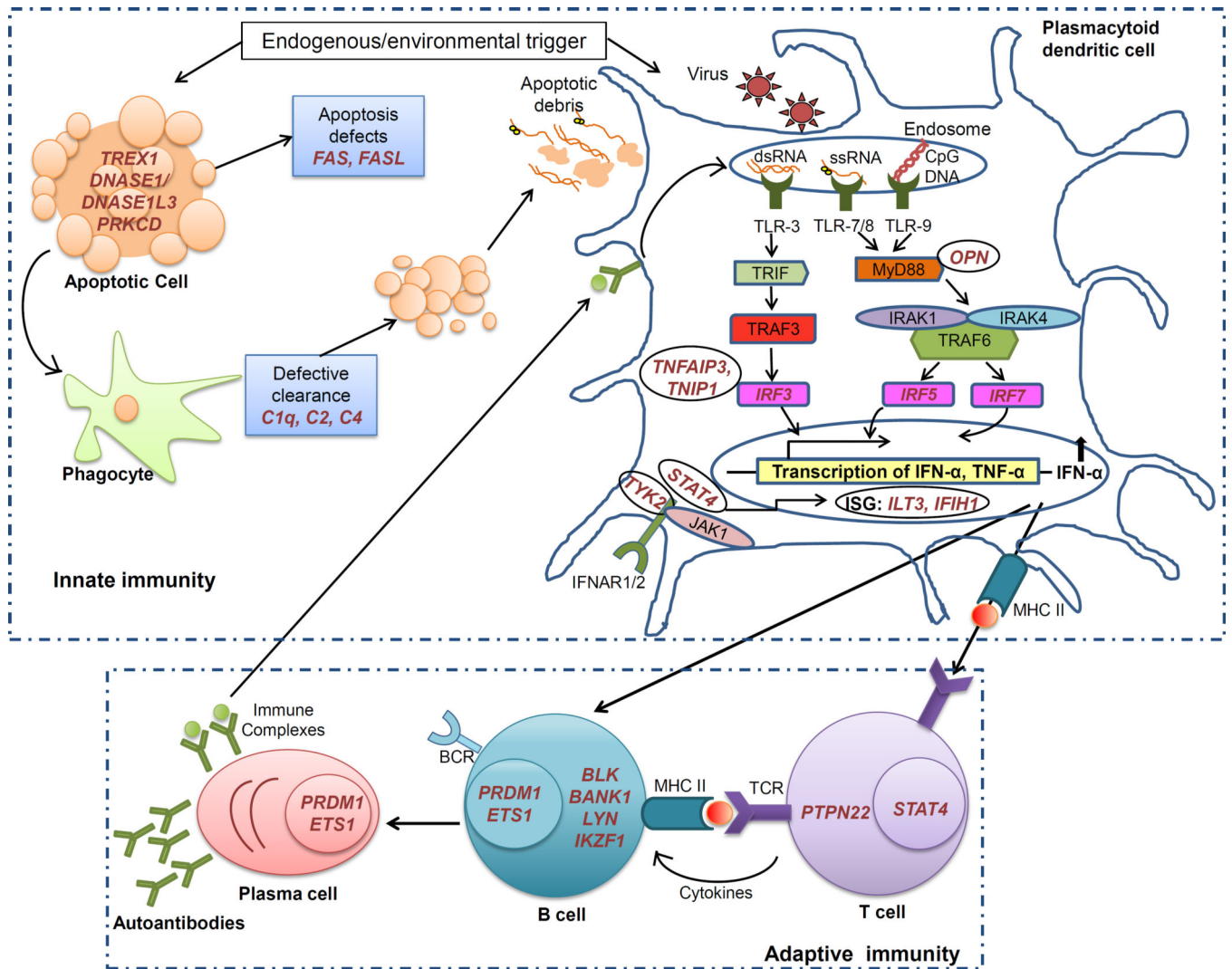
Figure 1. Proposed cellular location for gene products described in the review

Major pathways and cell types involved in SLE, with SLE-risk genes shown in the cell type in which they are presumed to function. Panel A shows genes that influence different cell types involved in innate immune response, while panel B shows genes that impact various cell types involved in adaptive immune response.
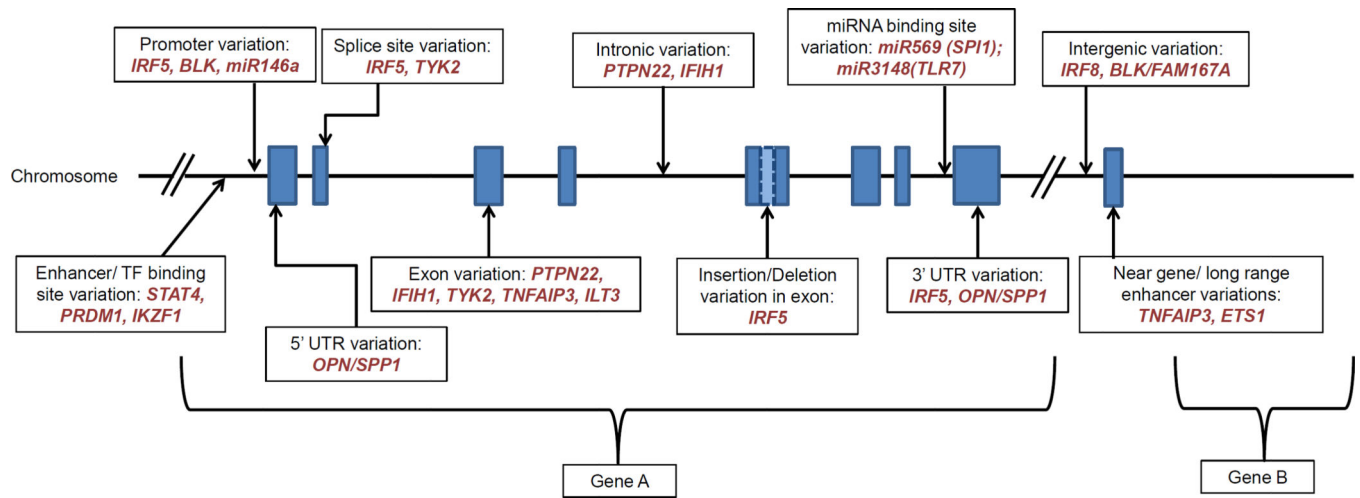
Figure 2.
Schematic showing a generalized gene diagram, with proposed location of functional variants in known regulatory regions, exons, splice sites, introns and intergenic sites discussed in this review. The actual SLE associated variants are located in various regions throughout the genome.