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Immunogenetics in systemic lupus erythematosus: Transitioning from genetic associations to cellular effects

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Abstract

Systemic lupus erythematosus (SLE) is a heterogeneous rheumatic autoimmune disease. Genetic studies have identified up to 100 SLE risk loci. Many of these encode proteins of importance in the immune system, but the cellular and molecular mechanisms underlying these associations are still elusive. In this review, we will highlight some of the SLE risk loci where mechanistic insights have been achieved recently by linking genetic risk polymorphisms to cellular or molecular phenotypes important for the disease process.

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is one of the most heterogeneous autoimmune diseases. The disease is characterized by the occurrence of a large number of different autoantibodies and inflammation in multiple organs.[1] The clinical picture varies from a mild disease with inflammation in skin and joints to a life-threatening condition with involvement of major organs such as the central nervous system. Consequently, patients with SLE experience a considerably reduced quality of life and increased mortality.[2,3] There is a lack of efficient drugs without severe adverse effects, and the complex clinical picture and the many different aberrations in the immune system have hampered the development of new therapies. In fact, a large number of drugs for SLE have failed in clinical trials and only one new drug have been approved for SLE during the last 60 years.[4] Thus, there is an urgent need for new therapies in SLE, but this requires detailed information of the various pathways involved in the disease process.

During the last decade, a better understanding of the different pro-inflammatory and regulatory pathways in SLE has been acquired. This is not only due to increased knowledge of the immune system and the different mechanisms leading to an autoimmune process, but also to a dramatic increase in the genetic information in SLE. Today, up to 100 risk loci for SLE have been reported and many of these are connected to pathways important for the immune system.[5] During the last years, there has been substantial progress in connecting disease-associated genetic variants to cellular

functions, but so far little of this knowledge has been translated into new therapeutic strategies. In the present review, we will discuss how different genetic variants associated with increased risk for SLE affect the function of different immune cells and how this knowledge can be used to stratify patients in different disease subsets, predict clinical manifestations and ultimately guide the clinician when selecting the optimal treatment.

2 | THE IMMUNE SYSTEM IN SLE

The heterogeneity of SLE patients is reflected in the large number of abnormalities found in the immune system of SLE patients, but the presence of autoantibodies to nuclear antigens and an activated type I interferon (IFN) system are hallmarks of the SLE pathology.[6,7] Partial or complete deficiencies in the early components of the complement cascade (C1q, C2 and C4), which facilitate clearance of apoptotic cells and immune complexes, are strongly associated with SLE susceptibility.[8] In general, patients with SLE have an increased apoptosis and reduced clearance of apoptotic material.[9,10] This imbalance results in an excess of nuclear antigens accessible to the immune system. Together with autoantibodies targeting DNA or RNA-binding proteins, nucleic acid-containing immune complexes are formed. These immune complexes trigger type I IFN production in plasmacytoid dendritic cells (pDCs) via activation of endosomal Toll-like receptor (TLR)7 and TLR9.[11-13] Another source of nucleic acid-containing autoantigens that triggers type I IFN production by pDCs are neutrophil extracellular traps (NETs), which are released by dying neutrophils in a process called NETosis.[14,15] The produced IFN act as an endogenous adjuvant that strongly activate several arms of the immune system. The maturation of dendritic cells into antigen-presenting cells together with activation, differentiation and increased survival of B cells and T cells in response to type I IFN can both lead to the break of tolerance and the perpetuation of an autoimmune response as summarized in Figure 1.[16] The pathogenic role of type I IFN is underscored by the recent successful phase 3 trial of the type I IFN receptor-blocking antibody anifrolumab.[17]

3 | THE GENETIC BACKGROUND TO SLE

The aetiology of SLE is complex and involves both genetic, epigenetic and environmental factors. Sibling and twin studies show that the genetic component of SLE is strong with an estimated heritability of >40%.[18] SLE is in principle a polygenic disease, but rare forms of monogenic SLE exist, such as complement-deficiencies or SLE-like phenotypes including interferonopathies.[8,19,20]

During the last two decades, genetic studies have provided extensive knowledge of the genetic basis for SLE. In the early 2000, small candidate gene studies successfully identified several common genetic risk variants (single nucleotide polymorphisms (SNPs)) for SLE.[21-23] The advances in technologies for genetic analysis led to the publication of four separate SLE genome-wide association

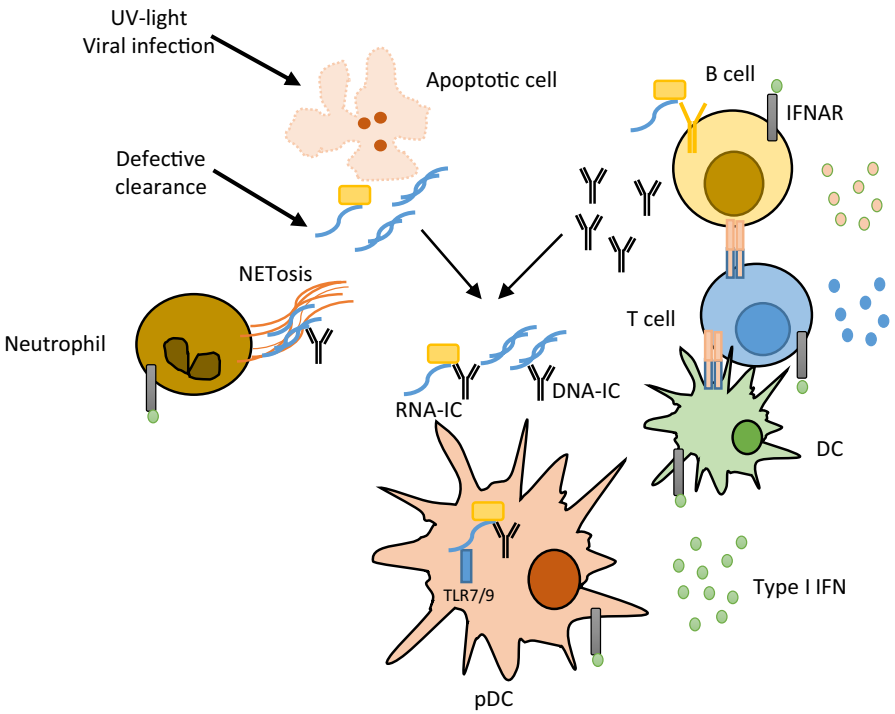

FIGURE 1 Immunologic aberrations contributing to the pathogenesis of SLE. Increased apoptosis together with a defective clearance and increased NETosis results in an excess of extracellular DNA or RNA-containing autoantigens. Together with autoantibodies, nucleic acid-containing immune complexes (ICs) are formed, which stimulate production of type I interferon (IFN) from plasmacytoid dendritic cells (pDCs) via endosomal Toll-like receptors 7 and 9 (TLR7/9). The produced IFN activates B cells to further autoantibody production and induce maturation of antigen-presenting dendritic cells (DCs) that activate T cells

(GWA) studies in 2008.[24-27] Later GWA studies have capitalized on increasing sample sizes, a denser genotyping and reference data set that allow for imputation of non-typed SNPs, and to date, there are up to 100 SLE risk loci reported.[5,28,29] In addition to these common genetic variants, whole-exome and whole-genome sequencing have begun to identify rare genetic SLE risk variants that are not captured in traditional GWA studies.[30-33] Another field of extensive studies is how epigenetic DNA modifications contribute to SLE.[34-36]

The majority of common genetic SLE risk variants are located in non-coding regions of the genome, and the effect size of each SNP is relatively small. Similar to other autoimmune diseases, the strongest associations are found in the HLA region.[29] In keeping with the immunologic findings, a large proportion of the SLE risk loci harbours genes connected to immune complex clearance, B and T cell activation and the type I IFN production or signalling.[37,38] Several of the SLE risk variants are associated with increased type I IFN activity in serum of SLE patients.[39-41] Yet, the molecular and cellular mechanisms underlying these findings are still poorly defined. Such studies have turned out to be more challenging than first anticipated for several reasons. First, due to linkage disequilibrium (LD) multiple SNPs may have a similar association signals. In regions with large LD-blocks encompassing several genes, it can thus be hard to identify the target gene of a disease-associated SNP. This is particularly true for the HLA region, which contains multiple independent SLE association signals spanning a very large number of genes.[42] Second, SNPs often exert their effect in a cell-type-specific and context-dependent manner,[43-46] and it is thus important to study the correct cell-type during the relevant activation state. The context dependency can also manifest in different effects in patient cells compared to cells from healthy individuals. Third, given the small effect sizes of disease-associated SNPs these studies require access to genotyped cells from a large number of individuals. In comparison to DNA used for the genetic studies, genotyped primary cells are a very limited resource that is much more complex to handle. Despite these challenges, there have been substantial progress in connecting disease-associated SNPs to cellular functions in recent years.

4 | CONNECTING GENETIC RISK VARIANTS TO CELLULAR FUNCTIONS

In this section, we will highlight some of the SLE risk loci, where genetic risk variants have been linked to alterations in immune cell functions in recent years.

4.1 | Signal transducer and activator of transcription 4 (STAT4)

STAT4 is a transcription factor that transduce signalling from the IL-12, IL-23 and type I IFN receptors. Several SNPs in LD in the third intron of *STAT4,* tagged by rs7574865, were initially described as SLE risk variants in a candidate gene study of a region previously associated with rheumatoid arthritis.[23] In addition to SLE itself, the *STAT4* risk allele is also associated with specific clinical manifestations including earlier age at diagnosis, presence of anti-dsDNA, ischaemic cerebrovascular disease, nephritis and severe renal insufficiency.[47-50]

Studies of immune cells from SLE patients revealed that, while basal levels of STAT4 protein was not affected by the *STAT4* risk allele, an enhanced induction of STAT4 protein was found in $CD8^+$ T cells from risk allele carriers following T cell receptor (TCR) activation. The increased levels of STAT4 resulted in increased levels of phosphorylated STAT4 (pSTAT4) and IFN-γ production following re-stimulation with IL-12.[51] Similarly, TCR-activated $CD8^+$ T cells from SLE patients carrying the *STAT4* risk allele had an enhanced IFN-α-induced pSTAT4 and a trend for increased pSTAT1.[51] This finding supports the hypothesis that *STAT4* risk allele carriers have an increased type I IFN receptor sensitivity, which was previously suggested based on the observation that SLE patients carrying the *STAT4* risk allele have increased expression of type I IFN induced genes, despite having lower levels of type I IFN serum activity.[52]

Contrasting the findings in SLE cells, a later study of immune cells from healthy donors found a decreased pSTAT4 and IFN-γ production in $CD8^+$ T cells from *STAT4* risk allele carriers following re-stimulation with IL-12.[53] The exact mechanism for this finding remains to be determined, but exogenously added IFN-α was shown to enhance the IL-12-induced pSTAT4 selectively in *STAT4* risk allele carriers. In support of a gene-environment interaction between type I IFN and the *STAT4* risk allele, it was also demonstrated that the effect of the *STAT4* risk allele in SLE patients was stronger in patients with detectable levels of IFN-α in plasma compared to patients without detectable levels of IFN-α.[53]

The gene encoding STAT1 is located adjacent to *STAT4*, and studies of lymphoblastoid cell lines (LCLs) generated from B cells of SLE patients found increased mRNA levels of *STAT1* in *STAT4* risk allele carriers. This effect was possibly mediated by allele-dependent binding of the transcription factor HMGA1 to rs11889341 located in the third intron of *STAT4*.[54] In contrast to these data, no association between *STAT4* genotype and STAT1 protein levels was found in peripheral blood B cells from SLE patients,[51] or healthy donors (unpublished data from 96 healthy individuals, $P = .35$).

This discrepancy likely reflects the different activation status of primary B cells and LCLs. In keeping with an activation-induced effect of the *STAT4* risk allele, rs11889341 also associates with *STAT1* mRNA levels in monocyte-derived macrophages and lipopolysaccharide (LPS) or muramyl dipeptide (MDP)-stimulated monocytes, but not in resting monocytes.[42,55] In terms of protein levels in monocytes, no differences in STAT1 were seen in unstimulated SLE monocytes.[51] The different effects of the *STAT4* risk allele are summarized in Figure 2, and together, these data highlight the context dependency of the *STAT4* risk allele.

The utility of using genetic information in the clinical setting is highlighted by a recent phase 1b/2a clinical trial of 30 patients treated with the Janus kinase (JAK) inhibitor tofacitinib, which stratified the patients by the *STAT4* risk allele rs7574865. In this study, a significant decrease in the IFN signature, levels of low-density granulocytes and NETs were identified exclusively in *STAT4* risk allele carriers.[56] This is an interesting example of how genetic stratification of patients may be used in clinical trials, and we anticipate that such an approach will be utilized in future clinical trials, and perhaps also in retrospective analysis of previous clinical trials.

4.2 | Interferon regulatory factor 5 (IRF5)

Interferon regulatory factor 5 is a transcription factor involved in MyD88-dependent activation of TLRs and the subsequent production of cytokines, including type I IFNs.[57,58] *IRF5* was initially identified as an SLE risk loci in a candidate gene study in 2005,[22] and additive effects of *IRF5* and *STAT4* risk variants were later demonstrated.[48,59] GWAS and fine-mapping studies have identified at least two independent association signals in *IRF5*.[60-62] One of them is located in the *IRF5* promoter region (tagged by rs4728142), whereas the other consists of a haplotype of 24 SNPs spanning both *IRF5* and the neighbouring gene *TNPO3* (transportin 3, tagged by rs12534421).[62] Risk variants in both regions are associated with increased *IRF5* mRNA levels in immune cells from SLE patients and LCLs.[60-63] Candidate mechanisms for the transcriptional regulation include altered binding of the transcription factors Sp1 and ZBTB3 to promoter risk variants,[62,63] and altered binding of the transcription factor EVI1 to an enhancer element in the promoter region of *TNPO3* that regulates *IRF5* mRNA expression via long-range chromatin interactions.[64] Other potential mechanisms of the *IRF5* risk variants include differential splicing,[60] altered polyadenylation affecting mRNA stability[61] and altered DNA methylation level of a CpG site (cg04864179) in the *IRF5* promoter.[36]

Studies of protein levels show increased IRF5 levels in SLE monocytes carrying risk variants.[65] A recent study of healthy donor cells found no differences in IRF5 protein levels between carriers of an *IRF5* risk haplotype relative to a protective haplotype. Instead, increased basal levels of nuclear localized (ie activated) IRF5 were detected in monocytes, pDCs and neutrophils from *IRF5* risk individuals.[66] Moreover, an increased frequency of pDCs in peripheral blood that produced elevated levels of type I IFN in response to TLR7/8 stimulation and increased spontaneous NETosis

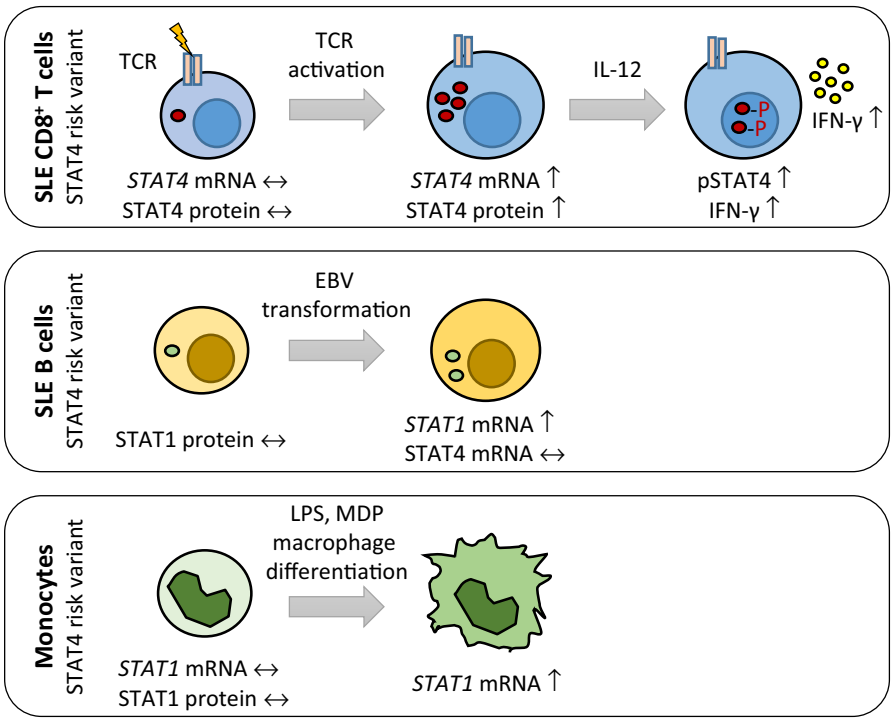

FIGURE 2 Cellular effects of genetic risk variants in *STAT4*. The effect of *STAT4* risk variants on *STAT4* and *STAT1* mRNA and protein expression in different immune cell types before and after in vitro activation, as indicated. Abbreviations: EBV, Epstein-Barr virus; IFN, interferon; LPS, lipopolysaccharide; MDP, muramyl dipeptide; pSTAT4, phosphorylated STAT4; TCR, T cell receptor

from neutrophils were found in *IRF5* risk carriers.[66] Another study in cells from healthy individuals demonstrated increased production of TNF-α following TLR and nucleotide-binding oligomerization domain-containing(NOD)2 receptor activation of monocyte-derived dendritic cells carrying the promoter *IRF5* risk alleles.[67]

Thus, the effects of *IRF5* risk variants are complex and the SLE risk probably involves several biological functional variants (Figure 3). In addition to the cell-type, context- and disease-dependent effects, another layer of complexity is added by the fact that functional rare variants in other SLE-associated genes affect IRF5 functions, which is described below.

4.3 | The B lymphocyte kinase (BLK)/Family with sequence similarity 167, member A (FAM167A) locus

Non-coding SNPs in the *BLK/FAM167A* locus are associated with SLE.[25] *BLK* encodes a Src tyrosine kinase involved in B cell receptor signalling, and *FAM167A* encodes a protein with unknown function expressed in B cells and the lung.[68,69] LCLs and primary B cells from healthy individuals carrying the SLE risk allele have decreased mRNA levels of *BLK,* whereas *FAM167A* mRNA levels are increased.[25,68,70] A study with a small number of healthy individuals reported decreased *BLK* mRNA and protein levels in naïve and transitional B cells from umbilical cord blood of risk allele carriers, but did not find a difference in adult peripheral blood B cells.[71] The absent effect in adult B cells may reflect a power issue but can also suggest that the SLE risk variant exert its effect particularly during early B cell development. *BLK* is expressed at considerably lower levels in T cells than in B cells, but a decreased expression of *BLK* is also seen in T cells from risk allele carriers,[71] raising the possibility that the effect is mediated by other cell types than B cells.

Healthy individuals carrying the *BLK* SLE risk allele rs2736340 have increased levels of anti-dsDNA in serum and an increased frequency of the B1-like cell subset that is involved in antibody response during an infection or vaccination.[72] B cells from carriers of a *BLK* risk haplotype for rheumatoid arthritis, which includes several SLE risk variants, were shown to have an enhanced response to B cell receptor cross-linking, as measured by induction of CD86 protein, phosphorylation of phospholipase C gamma 2 (PLCγ2) and SHP2, and an increased ability to induce T cell proliferation.[73]

In addition to the non-coding SLE risk variants, a low-frequency mutation (Ala71Thr) resulting in decreased protein levels of BLK through enhanced ubiquitin-mediated proteasomal degradation is also associated with SLE.[74,75] Moreover, several rare *BLK* missense variants (minor allele frequency

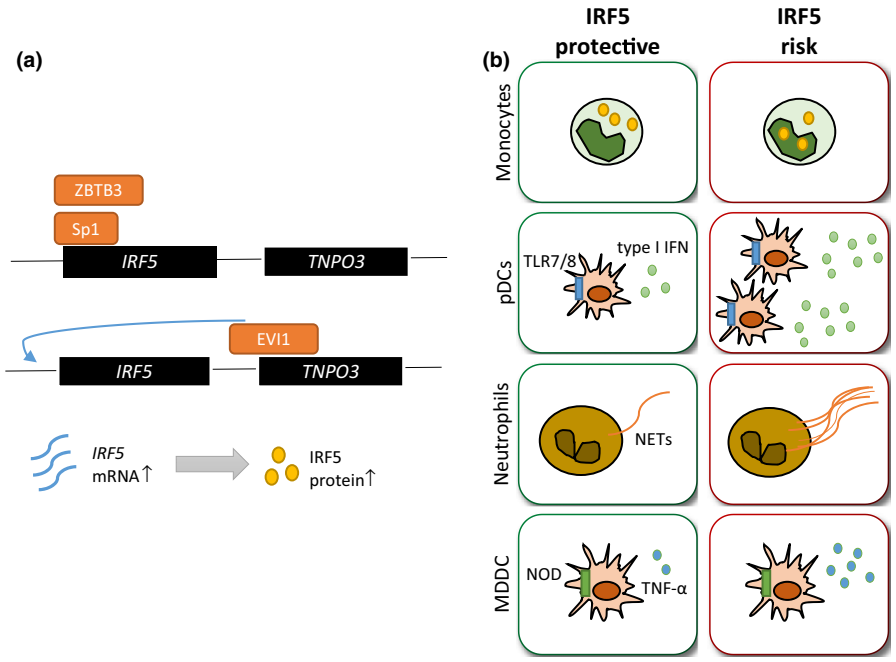

FIGURE 3 Transcriptional regulation and cellular effects of genetic risk variants in *IRF5*. A, Increased *IRF5* mRNA and protein levels in carriers of *IRF5* risk variants due to altered affinity for transcription factors in the promoter of *IRF5*, and in the promoter of *TNPO3* partaking in long-range chromatin interactions. B, Healthy individuals carrying an *IRF5* risk haplotype have increased levels of nuclear translocated IRF5 in monocytes, an increased frequency of plasmacytoid dendritic cells (pDC) that produce higher levels of type I interferon (IFN) in response to Toll-like receptor 7 or 8 (TLR7/8) stimulation, enhanced spontaneous NETosis by neutrophils, and an augmented production of TNF-α in monocyte-derived dendritic cells (MDCC) in response to nucleotide-binding oligomerization domain-like (NOD)-receptor activation

(MAF) <0.5%) with a reduced capacity to phosphorylate IRF5 were recently identified.[76] The reduced phosphorylation of IRF5 resulted in an impaired suppression of TLR7/8-induced *IFNb* expression. In keeping with increased type I IFN expression, SLE patients carrying these rare *BLK* variants have a stronger IFN signature.[76] Although, rare functional BLK missense variants were also identified in healthy individuals, the effects were not as strong as for the variants exclusively found in SLE patients, where five out of six variants conferred a >50% impaired *IFNb* repression. Further studies are needed to validate the importance of these rare risk variants in SLE pathology. An interesting question with possible implications for the incomplete penetrance seen for the rare BLK variants is whether their effect differs depending on if they are located on the same or on the opposite strand of the common SNPs that affects mRNA expression. The functional effects of *BLK* risk variants are summarized in Figure 4.

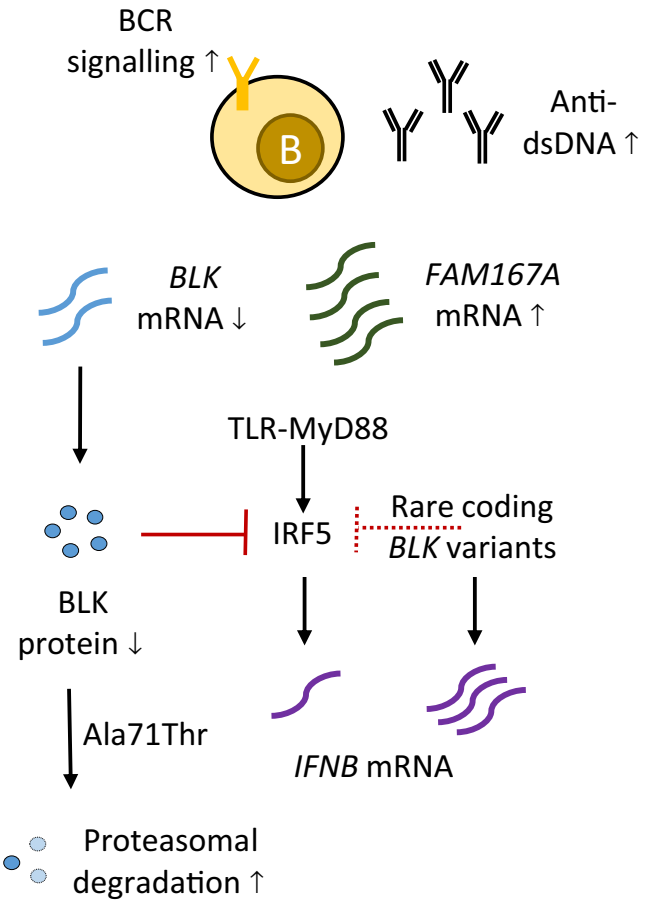

FIGURE 4 Effects of common and rare SLE risk variants in *BLK*. B cells carrying common SLE risk variants in *BLK* have reduced *BLK* mRNA and protein levels, whereas *FAM167A* mRNA levels are increased. The coding SLE risk variant Ala71Thr results in decreased BLK protein levels due to enhanced proteasomal degradation. Rare coding SLE-specific variants confer an impaired inhibition on IRF5-mediated IFN-β transcription. Patients carrying common SLE risk variants in *BLK* have increased levels of anti-dsDNA autoantibodies

4.4 | B cell scaffold protein with ankyrin repeats 1 (BANK1)

Genetic variants in *BANK1* are associated with SLE.[27] *BANK1* encodes a scaffold protein that binds to BLK, and a genetic epistatic interaction between risk polymorphisms in *BANK1* and *BLK* has been demonstrated.[77] Three *BANK1* SNPs are associated with SLE. Two of them are coding SNPs (Arg61His and Ala383Thr), whereas the third is located in a putative splice branch point.[27,78] *BANK1* is expressed as a full-length isoform, or an isoform which lacks the second exon (Δ2). The Arg61His SLE risk variant is associated with decreased levels of the Δ2 isoform and an altered subcellular distribution of BANK1.[79] A study of primary B cells from healthy donors showed an increased proportion of memory B cells and decreased B cell signalling in individuals carrying a *BANK1* SLE risk haplotype.[80]

BANK1 participates in the MyD88-TRAF6-signalling complex that is important for TLR signalling and type I IFN production.[81,82] A low-frequency coding *BANK1* variant (MAF < 2%) with impaired repression of TRAF6-mediated IRF5 nuclear localization and type I IFN production was recently identified.[76] Together with the rare *BLK* variants described above, these are two examples of how rare/low-frequency coding variants in previously SLE-associated genes affect the function of another SLE-associated gene, which ultimately results in increased type I IFN activation.

4.5 | TNF alpha induced protein 3 (TNFAIP3)

TNFAIP3 encodes the ubiquitin-editing enzyme A20 that restricts NF-κB signalling and prevents spontaneous inflammation.[83] There are three independent genetic signals in *TNFAIP3* associated with SLE susceptibility.[26,84] Fine mapping of the *TNFAIP3* locus identified a TT >A polymorphic dinucleotide (deletion of T followed by a T to A transversion) in an enhancer element downstream of the *TNFAIP3* promoter as a functional SLE risk variant. The TT >A allele have reduced binding of NF-κB, which results in reduced *TNFAIP3* mRNA and A20 protein expression in LCLs.[85,86] Based on long-range chromosomal interactions, a possible effect on *IFNGR1* and *IL20RA* mRNA expression has also been suggested by the TT >A allele.[46]

A coding variant in the de-ubiquitinase domain (DUB) of A20 (Phe127Cys) is also associated with SLE susceptibility.[26,84] An NF-κB independent role of Phe127Cys was suggested by the fact that CRISPR/Cas9-mediated knock-in of another DUB-inactivating mutation (Cys103Ala) in the human monocyte cell line U937 did not affect NF-κB signalling, but instead resulted in increased *PADI4* mRNA expression and protein levels.[87] Peptidyl arginine deiminase 4

(PADI4) is an enzyme involved in protein citrullination and NETosis. Increased mRNA expression and protein levels of PADI4 was also evident in primary immune cells from healthy individuals carrying the Phe127Cys DUB-domain risk allele.[87] In neutrophils from SLE patients, the Phe127Cys risk allele was associated with increased histone H3 citrullination and increased NET formation in response to PMA.[87] Moreover, the presence of anti-cyclic citrullinated peptide autoantibodies of the IgG subtype was enriched in these patients.[87] This is an informative example of how disease-associated SNPs can have completely different effects than first anticipated based on the genomic location. Moreover, these data raise the possibility that PADI4-inhibitors may have a therapeutic effect in SLE patients carrying the Phe127Cys risk allele. The effects of the *TNFAIP3* risk variants are summarized in Figure 5.

4.6 | Tyrosine Kinase 2 (TYK2)

Tyrosine Kinase 2 (TYK2) is an enzyme that transmits signals from multiple cytokine receptors (eg type I IFN, type III IFN, IL-12, IL-23, IL-10, IL-13 and the IL-6 receptors) through the phosphorylation of STAT molecules. A candidate gene study in 2005 identified genetic variants in *TYK2* that were protective for SLE.[22] Fine mapping of the *TYK2* locus shows that two haplotypes, tagged by two rare missenses SNPs (rs34536443 (Pro1104Ala) and rs12720356 (Ile684Ser or Ile684Thr), drive this association.[88] The Pro1104Ala mutation is located in the kinase domain of TYK2 and is also protective for several other autoimmune diseases including rheumatoid arthritis, psoriasis, type I diabetes, ankylosing spondylitis, inflammatory bowel disease and multiple sclerosis. Notably, Ile684Ser, which is located in the pseudokinase domain, is protective for rheumatoid arthritis, psoriasis and type I diabetes, but a risk variant for ankylosing spondylitis and inflammatory bowel disease. Together, these data suggest that the two TYK2 mutations have different biological functions.

Initial studies in LCLs showed that despite the fact that both coding variants impaired the catalytic activity of TYK2, reconstitution of TYK2-knock-out cell lines with the protective TYK2 variants rescued IFN-α-induced STAT signalling, suggesting that compensatory mechanisms from other JAK enzymes operate.[89] By CRISPR/Cas9-mediated editing of Pro1104Ala and Ile684Ser in HEK293T cells, it was later demonstrated that IFN-β-induced phosphorylation of TYK2 was impaired in cells carrying the protective allele of Pro1104Ala.[88] In studies of PBMCs from healthy individuals, the impaired STAT phosphorylation in carriers of the protective allele of Pro1104Ala was evident in response to IFN-α, IFN-β, IL-12 and IL-23, but not IL-6, IL-10 or IL-13.[88,90] Mice homozygous for the protective TYK2 variant of Pro1124Ala (corresponding to the human Pro1104Ala) where shown to have a diminished Th17 skewing in vitro, which was probably related to a decreased IL-23 receptor response.[90] Notably, whereas homozygous protective Pro1124Ala mice were completely protected from developing disease in the experimental autoimmune encephalomyelitis model of multiple sclerosis,[88,90] no protection was seen in two murine lupus models (BM12 T cell adoptive transfer or Wiskott-Aldrich deficient B cell bone marrow chimera model).[90]

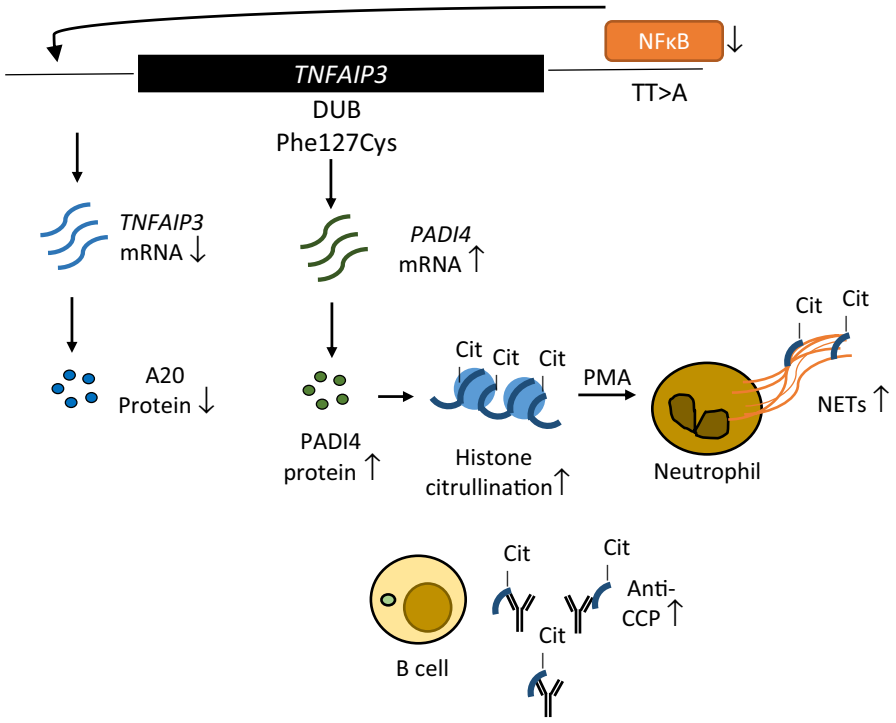

FIGURE 5 Effects of *TNFAIP3* SLE risk variants. The TT >A genetic risk variant impairs *TNFAIP3* mRNA expression via a reduced binding of NF-κB to an enhancer element involved in long-range DNA interaction with the *TNFAIP3* promoter. The coding variant Phe127Cys located in the de-ubiquitinase domain (DUB) confers increased *PADI4* mRNA and protein levels, resulting in increased citrullination (Cit) of histones and associates with increased NETosis and the presence of anti-cyclic citrullinated peptide (CCP) antibodies

Together, these data suggest that the protective *TYK2* variants exert their effect by diminishing the signalling from a large number of pro-inflammatory cytokines.

4.7 | Neutrophil cytosolic factor 1 (NCF1)

A strong SLE GWAS signal initially discovered within the *GTF2IRD1-GTF2I* intergenic region was later mapped to a missense variant in *NCF1* (Arg90His, also known as NCF1-339).[91,92] In addition to the missense variant, reduced copy numbers of *NCF1* is also associated with SLE.[91,92] *NCF1* encodes the NOX2 subunit of the phagocyte NADPH oxidase, which is central for the formation of reactive oxygen species and the subsequent oxidative burst and release of NETs.[93] Mutations in *NCF1* cause chronic granulomatous disease,[94] which is a primary immune deficiency that can present with lupus-like symptoms.[95]

Neutrophils from SLE patients carrying the NCF1-339 risk variant have a reduced extracellular NOX2-derived production of reactive oxygen species (ROS) and impaired NET formation.[92,96] ROS have previously been shown to block immune complex-induced type I IFN production by pDCs.[97] In line with these data, patients carrying the NCF1-339 risk variant have a stronger IFN signature.[96] These patients are also diagnosed at a younger age and are more likely to have anti-phospholipid antibodies and a secondary anti-phospholipid syndrome.[96]

In summary, the genetic associations of variants that confer a reduced ROS production add to the accumulating data that ROS have important immune regulatory functions that protect from autoimmunity.[98]

5 | SUMMARY

During the last years, we have gained an increased understanding of the cellular and molecular mechanisms underlying several of the genetic SLE risk variants. Many of the SNPs impact the type I IFN system, neutrophil function and B cell functions. The increasing knowledge of the functional effects of genetic risk variants may ultimately enable patient stratification into groups with similarly affected pathways based on genetics. Such information may be useful both in clinical trials and in choice of treatment in the clinical setting. Genetic information may also be used to predict how severe the disease will be and identify patients that have an increased risk for certain organ manifestations. The genetic information can be leveraged by the use of polygenetic risk scores that measures the cumulative effects of a large number of individual SLE risk variants.[99-101] Such risk scores can identify patients at increased risk for renal disorders, cardiovascular events and decreased survival.[99,100] With increasing knowledge about the cellular mechanisms of genetic risk variants, it may be possible to construct polygenic risk scores reflecting different immuno-cellular pathways and stratify patients according to these.

Although there has been a great progress in the understanding of the molecular mechanisms underlying genetic risk variants in recent years, the mechanisms for the majority of risk genes are still elusive. Future studies integrating genetics with single-cell transcriptomics, proteomics, metabolomics, microbiomics and other omics data will hopefully advance this field further and yield knowledge that in the end can be translated to the clinic.

CONFLICT OF INTERESTS

The authors have no financial disclosures.

AUTHOR CONTRIBUTIONS

NH, CL and LR wrote the paper and approved the final version of the manuscript.

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