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. 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. 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. 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. 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
(GWA) studies in 2008. 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. 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. Another field of extensive studies is how epigenetic DNA modifications contribute to SLE.

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. 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. Several of the SLE risk variants are associated with increased type I IFN activity in serum of SLE patients. 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. Second, SNPs often exert their effect in a cell-type-specific and context-dependent manner, 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. 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.

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. 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. 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.

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. 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.

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. In contrast to these data, no association between STAT4 genotype and STAT1 protein levels was found in peripheral blood B cells from SLE patients, 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.\(^\text{42,55}\) In terms of protein levels in monocytes, no differences in STAT1 were seen in unstimulated SLE monocytes.\(^\text{51}\) 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.\(^\text{56}\) 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.\(^\text{57,58}\) IRF5 was initially identified as an SLE risk loci in a candidate gene study in 2005,\(^\text{22}\) and additive effects of IRF5 and STAT4 risk variants were later demonstrated.\(^\text{58,59}\) GWAS and fine-mapping studies have identified at least two independent association signals in IRF5.\(^\text{60-62}\) 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).\(^\text{62}\) Risk variants in both regions are associated with increased IRF5 mRNA levels in immune cells from SLE patients and LCLs.\(^\text{60-63}\) Candidate mechanisms for the transcriptional regulation include altered binding of the transcription factors Sp1 and ZBTB3 to promoter risk variants,\(^\text{62,63}\) 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.\(^\text{64}\) Other potential mechanisms of the IRF5 risk variants include differential splicing,\(^\text{60}\) altered polyadenylation affecting mRNA stability\(^\text{61}\) and altered DNA methylation level of a CpG site (cg04864179) in the IRF5 promoter.\(^\text{36}\)

Studies of protein levels show increased IRF5 levels in SLE monocytes carrying risk variants.\(^\text{65}\) 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.\(^\text{66}\) 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.
from neutrophils were found in IRF5 risk carriers. 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.

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. 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. 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. 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. The absent effect in adult B cells may reflect a power issue but can also suggest that the SLE risk variant exerts 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, 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. 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.

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. 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. The reduced phosphorylation of IRF5 resulted in an impaired suppression of TLR7/8-induced IFNβ expression. In keeping with increased type I IFN expression, SLE patients carrying these rare BLK variants have a stronger IFN signature. 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 IFNβ 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.

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

Genetic variants in BANK1 are associated with SLE. BANK1 encodes a scaffold protein that binds to BLK, and a genetic epistatic interaction between risk polymorphisms in BANK1 and BLK has been demonstrated. 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. 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. 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.

BANK1 participates in the MyD88-TRAF6-signalling complex that is important for TLR signalling and type I IFN production. 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. 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. There are three independent genetic signals in TNFAIP3 associated with SLE susceptibility. 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. Based on long-range chromosomal interactions, a possible effect on IFNGR1 and IL20RA mRNA expression has also been suggested by the TT > A allele.

A coding variant in the de-ubiquitinase domain (DUB) of A20 (Phe127Cys) is also associated with SLE susceptibility. 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.
(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. In neutrophils from SLE patients, the Phe127Cys risk allele was associated with increased histone H3 citrullination and increased NET formation in response to PMA. Moreover, the presence of anti-cyclic citrullinated peptide autoantibodies of the IgG subtype was enriched in these patients. 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. 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. 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. 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. 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. Mice homozygous for the protective TYK2 variant of Pro1124Ala (corresponding to the human Pro1104Ala) were shown to have a diminished Th17 skewing in vitro, which was probably related to a decreased IL-23 receptor response. Notably, whereas homozygous protective Pro1124Ala mice were completely protected from developing disease in the experimental autoimmune encephalomyelitis model of multiple sclerosis, no protection was seen in two murine lupus models (BM12 T cell adoptive transfer or Wiskott-Aldrich deficient B cell bone marrow chimera model).

**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). In addition to the missense variant, reduced copy numbers of NCF1 is also associated with SLE. 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. Mutations in NCF1 cause chronic granulomatous disease, which is a primary immune deficiency that can present with lupus-like symptoms.

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. ROS have previously been shown to block immune complex-induced type I IFN production by pDCs. In line with these data, patients carrying the NCF1-339 risk variant have a stronger IFN signature. These patients are also diagnosed at a younger age and are more likely to have anti-phospholipid antibodies and a secondary anti-phospholipid syndrome.

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.

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. Such risk scores can identify patients at increased risk for renal disorders, cardiovascular events and decreased survival. 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.

ORCID

Niklas Hagberg https://orcid.org/0000-0003-2064-2716
Christian Lundtoft https://orcid.org/0000-0001-5872-4253

REFERENCES

1. Bengtsson AA, Rönnblom L. Systemic lupus erythematosus: still a challenge for physicians. J Intern Med. 2017;281:52-64.
2. Björk M, Dahlström O, Wetterö J, Sjöwall C. Quality of life and acquired organ damage are intimately related to activity limitations in patients with systemic lupus erythematosus. BMC Musculoskelet Disord. 2015;16:188.
3. Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum. 2006;54:2550-2557.
4. Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63:3918-3930.
5. Chen L, Morris DL, Vyse TJ. Genetic advances in systemic lupus erythematosus: an update. Curr Opin Rheumatol. 2017;29:423-433.
6. Baechler EC, Batliwalla FM, Karypis G, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci U S A. 2003;100:2610-2615.
7. Rodero MP, Decalf J, Bondet V, et al. Detection of interferon alpha protein reveals differential levels and cellular sources in disease. J Exp Med. 2017;214:1547-1555.
8. Leffler J, Bengtsson AA, Blom AM. The complement system in systemic lupus erythematosus: an update. Ann Rheum Dis. 2014;73:1601-1606.
9. Emilen W, Niebur J, Kadera R. Accelerated in vitro apoptosis of lymphocytes from patients with systemic lupus erythematosus. J Immunol. 1994;152:3685-3692.
10. Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR. Impaired phagocytosis of apoptotic cell material by...
monocyte-derived macrophages from patients with systemic lupus erythematosus. *Arthritis Rheum*. 1998;41:1241-1250.

11. Lövgren T, Eloranta ML, Bäve U, Alm GV, Rönnblom L. Induction of interferon-alpha production in plasmacytoid dendritic cells by immune complexes containing nucleic acid released by necrotic or late apoptotic cells and lupus IgG. *Arthritis Rheum*. 2004;50:1861-1872.

12. Bäve U, Magnusson M, Eloranta ML, Perers A, Alm GV, Rönnblom L. Fc gamma RIIa is expressed on natural IFN-alpha-producing cells (plasmacytoid dendritic cells) and is required for the IFN-alpha production induced by apoptotic cells combined with lupus IgG. *J Immunol*. 2003;171:3296-3302.

13. Means TK, Latz E, Hayashi F, Murali MR, Golenbock DT, Luster AD. Human lupus autoantibody-DNA complexes activate DCs through cooperation of CD32 and TLR9. *J Clin Invest*. 2005;115:407-417.

14. Lande R, Ganguly D, Facchinetti V, et al. Neutrophils activate plasmacytoid dendritic cells by releasing self-DNA-peptide complexes in systemic lupus erythematosus. *Sci Transl Med*. 2011;3:73ra19.

15. Garcia-Romo GS, Caielli S, Vega B, et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Sci Transl Med*. 2011;3:73ra20.

16. Crow MK, Rönnblom L. Type I interferons in host defence and inflammatory diseases. *Lupus Sci Med*. 2019;6:e000336.

17. Morand EF, Furie R, Tanaka Y, et al. Trial of anifrolumab in active systemic lupus erythematosus. *N Engl J Med*. 2020;382:211-221.

18. Kuo CF, Grainge MJ, Valdes AM, et al. Familial aggregation of systemic lupus erythematosus and coaggregation of autoimmune diseases in affected families. *JAMA Intern Med*. 2015;175:1518-1526.

19. Rodero MP, Crow YJ. Type I interferon-mediated monogenic autoinflammation: the type I interferonopathies, a conceptual overview. *J Exp Med*. 2016;213:2527-2538.

20. Costa-Reis P, Sullivan KE. Monogenic lupus: it’s all new!. *Curr Opin Immunol*. 2017;49:87-95.

21. Kyogoku C, Langefeld CD, Ortman WA, et al. Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE. *Am J Hum Genet*. 2004;75:504-507.

22. Sigurdsson S, Nordmark G, Göring HH, et al. Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. *Curr Opin Immunol*. 2012;24:530-537.

23. Remmers EF, Plenge RM, Lee AT, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. *Hum Mol Genet*. 2008;17:8391-8396.

24. Kariuki SN, Crow MK. Association of the IRF5 risk haplotype with high type I IFN factor alpha levels in patients with lupus. *Arthritis Rheum*. 2010;62:553-561.

25. Niewold TB, Kelly JA, Flesch MH, Espinoza LR, Harley JB, Crow MK. Association of the IRF5 risk haplotype with high serum interferon-alpha activity in systemic lupus erythematosus patients. *Arthritis Rheum*. 2008;58:2481-2487.

26. Salloum R, Franke BS, Kariuki SN, et al. Genetic variation at the IRF7/PHRF1 locus is associated with autoantibody profile and serum interferon-alpha activity in lupus patients. *Arthritis Rheum*. 2010;62:553-561.

27. Raj P, Rai E, Song R, et al. Regulatory polymorphisms modulate the expression of HLA class II molecules and promote autoimmunity. *Elife*. 2016;5:e12089.
43. Dimas AS, Deutsch S, Stranger BE, et al. Common regulatory variation impacts gene expression in a cell type-dependent manner. Science. 2009;325:1246-1250.

44. Fairfax BP, Humburg P, Makino S, et al. Innate immune activity conditions the effect of regulatory variants upon monocyte gene expression. Science. 2014;343:1246949.

45. Lee MN, Ye C, Villani AC, et al. Common genetic variants modulate pathogen-sensing responses in human dendritic cells. Science. 2014;343:1246980.

46. Ding J, Orozco G. Identification of rheumatoid arthritis causal genes using functional genomics. Scand J Immunol. 2019;89:e12753.

47. Taylor KE, Remmers EF, Lee AT, et al. Specificity of the STAT4 genetic association for severe disease manifestations of systemic lupus erythematosus. PLoS Genet. 2008;4:e1000084.

48. Sigurdsson S, Nordmark G, Garnier S, et al. A risk haplotype of STAT4 for systemic lupus erythematosus is over-expressed, correlates with anti-dsDNA and shows additive effects with two risk alleles of IRF5. Hum Mol Genet. 2008;17:2868-2876.

49. Svennungsson E, Gustafsson J, Leonard D, et al. A STAT4 risk allele is associated with ischaemic cerebrovascular events and anti-phospholipid antibodies in systemic lupus erythematosus. Ann Rheum Dis. 2010;69:834-840.

50. Bolin K, Sandling JK, Zickert A, et al. Association of STAT4 polymorphism with severe renal insufficiency in lupus nephritis. PLoS One. 2013;8:e84450.

51. Hagberg N, Joelsson M, Leonard D, et al. The STAT4 SLE risk allele rs7574865[T] is associated with increased IL-12-induced IFN-gamma production in T cells from patients with SLE. Ann Rheum Dis. 2018;77:1070-1077.

52. Kariuki SN, Kirou KA, MacDermott EJ, Barillas-Arias L, Crow MK, Niewold TB. Cutting edge: autoimmune disease risk variant of STAT4 confers increased sensitivity to IFN-alpha in lupus patients in vivo. J Immunol. 2009;182:34-38.

53. Hagberg N, Rönnblom L. Interferon-alpha enhances the IL-12-induced STAT4 activation selectively in carriers of the STAT4 SLE risk allele rs7574865[T]. Ann Rheum Dis. 2019;78:429-431.

54. Patel ZH, Lu X, Miller D, et al. A plausibly causal functional lupus-associated risk variant in the STAT1-STAT4 locus. Hum Mol Genet. 2018;27:2392-2404.

55. Kim-Hellmuth S, Bechheim M, Putz B, et al. Genetic regulatory effects modified by immune activation contribute to autoimmune disease associations. Nat Commun. 2017;8:266.

56. Hasni S, Gupta S, Davis MA, et al. 183 A phase 1B/2A trial of tofacitinib, an oral janus kinase inhibitor, in systemic lupus erythematosus. Lupus Sci Med. 2019;6:A139.

57. Barnes BJ, Moore PA, Pitha PM. Virus-specific activation of a novel interferon regulatory factor, IRF-5, results in the induction of distinct interferon alpha genes. J Biol Chem. 2001;276:23382-23390.

58. Takaoka A, Yanai H, Kondo S, et al. Integral role of IRF-5 in the gene induction programme activated by Toll-like receptors. Nature. 2005;434:243-249.

59. Abelson AK, Delgado-Vega AM, Kozyrev SV, et al. STAT4 associates with systemic lupus erythematous through two independent effects that correlate with gene expression and act additively with IRF5 to increase risk. Ann Rheum Dis. 2009;68:1746-1753.

60. Graham RR, Kozyrev SV, Baechler EC, et al. A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. Nat Genet. 2006;38:550-555.

61. Graham RR, Kyogoku C, Sigurdsson S, et al. Three functional variants of IFN regulatory factor 5 (IRF5) define risk and protective haplotypes for human lupus. Proc Natl Acad Sci U S A. 2007;104:6758-6763.

62. Kottyan LC, Zoller EE, Bene J, et al. The IRF5-TNPO3 association with systemic lupus erythematosus has two components that other autoimmune disorders variably share. Hum Mol Genet. 2015;24:582-596.

63. Sigurdsson S, Göring HH, Kristjansdottir G, et al. Comprehensive evaluation of the genetic variants of interferon regulatory factor 5 (IRF5) reveals a novel 5 bp length polymorphism as strong risk factor for systemic lupus erythematosus. Hum Mol Genet. 2008;17:872-881.

64. Thynn HN, Chen XF, Hu WX, et al. An allele-specific functional SNP associated with two systemic autoimmune diseases modulates IRF5 expression by long-range chromatin loop formation. J Invest Dermatol. 2020;140(2):348-360.

65. Feng D, Stone RC, Eloranta ML, et al. Genetic variants and disease-associated factors contribute to enhanced interferon regulatory factor 5 expression in blood cells of patients with systemic lupus erythematosus. Arthritis Rheum. 2010;62:562-573.

66. Li D, Matta B, Song S, et al. IRF5 genetic risk variants drive myeloid-specific IRF5 hyperactivation and presymptomatic SLE. JCI Insight. 2020;5:e124020.

67. Hedl M, Abraham C. IRF5 risk polymorphisms contribute to interindividual variance in pattern recognition receptor-mediated cytokine secretion in human monocyte-derived cells. J Immunol. 2012;188:5348-5356.

68. Mentlein L, Thorlacius GE, Meneghel L, et al. The rheumatic disease-associated FAM167A-BLK locus encodes DIORA-1, a novel disordered protein expressed highly in bronchial epithelium and alveolar macrophages. Clin Exp Immunol. 2018;193:167-177.

69. Agrawi LA, Mentlein L, Meneghel L, et al. Clinical associations and expression pattern of the autoimmunity susceptibility factor DIORA-1 in patients with primary Sjogren’s syndrome. Ann Rheum Dis. 2018;77:1840-1842.

70. Ge B, Pokholok DK, Kwan T, et al. Global patterns of cis variation in human cells revealed by high-density allelic expression analysis. Nat Genet. 2009;41:1216-1222.

71. Simpfendorfer KR, Olsson LM, Manjarrez Orduño N, et al. The autoimmunity-associated BLK haplotype exhibits cis-regulatory effects on mRNA and protein expression that are prominently observed in B cells early in development. Hum Mol Genet. 2012;21:3918-3925.

72. Wu YY, Georg I, Diaz-Barreiro A, et al. Concordance of increased B cell subset and lupus phenotypes in mice and humans is dependant on BLK expression levels. J Immunol. 2015;194:5692-5702.

73. Simpfendorfer KR, Armstead BE, Shih A, et al. Autoimmune disease-associated haplotypes of BLK exhibit lowered thresholds for B cell activation and expansion of Ig class-switched B cells. Arthritis Rheumatol. 2015;67:2866-2876.

74. Delgado-Vega AM, Dozmorov MG, Quiros MB, et al. Fine mapping and conditional analysis identify a new mutation in the autoimmune disease-associated FAM167A-BLK locus encoding DIORA-1, a novel disordered protein expressed highly in bronchial epithelium and alveolar macrophages. Clin Exp Immunol. 2018;193:167-177.

75. Diaz-Barreiro A, Bernal-Quiros M, Georg I, Maranon C, Alarcon-Riquelme ME, Castillejo-Lopez C. The SLE variant Ala71Thr of the BLK protein.
BANK1 through impairment of the SH3 domain function. *Genes Immun*. 2016;17:128-138.

76. Jiang SH, Athanasopoulos V, Ellyard JL, et al. Functional rare and low frequency variants in BLK and BANK1 contribute to human lupus. *Nat Commun*. 2019;10:2201.

77. Castillejo-Lopez C, Delgado-Vega AM, Wojcik J, et al. Genetic and physical interaction of the B-cell systemic lupus erythematosus-associated genes BANK1 and BLK. *Ann Rheum Dis*. 2012;71:136-142.

78. Guo L, Deshmukh H, Lu R, et al. Replication of the BANK1 genetic association with systemic lupus erythematosus in a European-derived population. *Genes Immun*. 2009;10:531-538.

79. Kozyrev SV, Bernal-Quiros M, Alarcon-Riquelme ME, Castillejo-Lopez C. The dual effect of the lupus-associated polymorphism rs10516487 on BANK1 gene expression and protein localization. *Genes Immun*. 2012;13:129-138.

80. Dam EM, Habib T, Chen J, et al. The BANK1 SLE-risk variants are associated with alterations in peripheral B cell signaling and development in humans. *Clin Immunol*. 2016;173:171-180.

81. Kawai T, Sato S, Ishii KJ, et al. Interferon-alpha induction through Toll-like receptor involves a direct interaction of IRF7 with MyD88 and TRAF6. *Nat Immunol*. 2004;5:1061-1068.

82. Georg I, Diaz-Barreiro A, Morell M, Pey AL, Alarcon-Riquelme ME. BANK1 interacts with TRAF6 and MyD88 in innate immune signaling in B cells. *Cell Mol Immunol*. 2019.

83. Ma A, Malynn BA. A20: linking a complex regulator of ubiquitylation to immunity and human disease. *Nat Rev Immunol*. 2012;12:774-785.

84. Musone SL, Taylor KE, Lu TT, et al. Multiple polymorphisms in the TNFAIP3 region are independently associated with systemic lupus erythematosus. *Nat Genet*. 2008;40:1062-1064.

85. Adrianto I, Wen F, Templeton A, et al. Association of a functional variant downstream of TNFAIP3 with systemic lupus erythematosus. *Nat Genet*. 2011;43:253-258.

86. Wang S, Wen F, Wiley GB, Kinter MT, Gaffney PM. An enhancer element harboring variants associated with systemic lupus erythematosus engages the TNFAIP3 promoter to influence A20 expression. *PLoS Genet*. 2013;9:e1003750.

87. Odqvist L, Jevnikar Z, Riise R, et al. Genetic variations in A20 DUB domain provide a genetic link to citrullination and neutrophil extracellular traps in systemic lupus erythematosus. *Ann Rheum Dis*. 2019;78:1363-1370.

88. Dendrou CA, Cortes A, Shipman L, et al. Resolving TYK2 locus genotype-to-phenotype differences in autoimmunity. *Sci Transl Med*. 2016;8:363ra149.

89. Zhao J, Ma J, Deng Y, et al. A missense variant in NCF1 is associated with susceptibility to multiple autoimmune diseases. *Nat Genet*. 2017;49:433-437.

90. Gorman JA, Hundhausen C, Kinsman M, et al. The TYK2-P1104A autoimmune protective variant limits coordinate signals required to generate specialized T cell subsets. *Front Immunol*. 2019;10:44.

91. Holmdahl R, Sareila O, Olsson LM, Backdahl L, Wing K. Ncf1 polymorphism reveals oxidative regulation of autoimmune chronic inflammation. *Immunol Rev*. 2016;269:228-247.

92. Reid S, Alexsson A, Frodlund M, et al. High genetic risk score is associated with early disease onset, damage accrual and decreased survival in systemic lupus erythematosus. *Ann Rheum Dis*. 2020;79:363-369.

93. Chen L, Wang YF, Liu L, et al. Genome-wide assessment of genetic risk for systemic lupus erythematosus and disease severity. *Hum Mol Genet*. 2020. https://doi.org/10.1093/hmg/ddaa030

94. Webber D, Cao J, Dominguez D, et al. Association of systemic lupus erythematosus (SLE) genetic susceptibility loci with lupus nephritis in childhood-onset and adult-onset SLE. *Rheumatology (Oxford)*. 2020;59:90-98.

How to cite this article: Hagberg N, Lundtoft C, Rönblom L. Immunogenetics in systemic lupus erythematosus: Transitioning from genetic associations to cellular effects. *Scand J Immunol*. 2020;92:e12894. https://doi.org/10.1111/sji.12894