Pathogenesis of systemic lupus erythematosus: risks, mechanisms and therapeutic targets

Mary K Crow

ABSTRACT
Research elucidating the pathogenesis of systemic lupus erythematosus (SLE) has defined two critical families of mediators, type I interferon (IFN-I) and autoantibodies targeting nucleic acids and nucleic acid-binding proteins, as fundamental contributors to the disease. On the fertile background of significant genetic risk, a triggering stimulus, perhaps microbial, induces IFN-I, autoantibody production or most likely both. When innate and adaptive immune system cells are engaged and collaborate in the autoimmune response, clinical SLE can develop. This review describes recent data from genetic analyses of patients with SLE, along with current studies of innate and adaptive immune function that contribute to sustained IFN-I pathway activation, immune activation and autoantibody production, generation of inflammatory mediators and tissue damage. The goal of these studies is to understand disease mechanisms, identify therapeutic targets and stimulate development of therapeutics that can achieve improved outcomes for patients.

INTRODUCTION
Systemic lupus erythematosus (SLE) remains one of medicine’s most challenging yet informative diseases, characterised by systemic and organ-targeted clinical manifestations and extensive immune system dysfunction. In SLE, skin, joints, kidneys, cardiovascular system and central nervous system (CNS) can all be involved, with each patient demonstrating a distinct pattern of disease. The systemic nature of SLE reflects the widely distributed alterations in immune system activity that result in autoimmunity targeting nucleic acids and their associated proteins, as well as tissue-damaging inflammation. In managing patients with SLE and their associated comorbidities, a comprehensive approach is required, incorporating most aspects of internal medicine. To achieve the most efficacious and safe treatments for patients with SLE, researchers aspire to a deeper understanding of the mechanisms that account for lupus pathogenesis.

The diversity of clinical manifestations and the multiple molecular pathways implicated in patients diagnosed with SLE have raised the possibility that lupus represents many diseases rather than variable presentations of one disease. While research will ultimately inform the characterisation of SLE, there is rationale for viewing lupus as a disorder attributable to immune system mediators that represent common denominators across most patients, specifically type I interferon (IFN-I) and characteristic autoantibodies. Individual patients may preferentially engage one or another feature of the immune system to generate those products, and organ vulnerabilities will influence clinical presentation, but the common pathogenic mediators serve to define the unifying features of SLE. This admittedly selective review of mechanisms relevant to the pathogenesis of SLE will highlight the genetic variations that establish risk and the activation of the IFN-I system and generation of autoimmunity that are arguably the prerequisites for lupus disease.

HISTORICAL CONTEXT
Current understanding of SLE pathogenesis dates to Hargraves’ 1948 description of the lupus erythematosus (LE) cell, representing cell nuclei engulfed by phagocytic neutrophils after interaction with patient plasma. The ingested material was nuclear chromatin and was stained for depolymerised DNA, similar to material that might be generated by ultraviolet (UV) radiation or nitrogen mustard. The gamma globulin fraction of plasma contained the required patient-derived factor. Holman et al, among others, suggested that the factor might be an autoantibody specific for DNA, although data from Schett et al later supported specificity for the histone H1 component of chromatin. Harvey reported LE cell formation by plasma from 82% of patients with SLE, with a remarkably low false-positive rate. The antinuclear antibody (ANA) assay reflects at least one feature of the LE cell mechanism, the presence of autoantibodies reactive with cell nuclei. It is notable that while the ANA assay is not specific for SLE, the recently published European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for SLE require a positive ANA, supporting the fundamental contribution of ANAs to the disease. Extending that immune system-focused framework to consider the genetic and societal risks and triggers, the drivers of immune system activation, and the tissue and organ vulnerabilities that support accumulation of damage can broaden our view of opportunities to enhance both treatment and preventative approaches for care of patients with SLE.

RISKS AND TRIGGERS
Socioeconomic determinants
SLE occurs more than twice as often in African-American (AA) women as in those of European (EA) descent, and lupus is also more prevalent among Hispanics and Asians. In fact, with increasing ethnic diversity in the USA, the incidence and prevalence of SLE are increasing. The relative contributions of socioeconomic inequities and genetic factors to increased prevalence and disease severity can be difficult to dissect as lupus preferentially
impacts the poor and disadvantaged.\textsuperscript{13} Low income has been associated with a high organ damage score, but the rate of accrual of organ damage is greater in AA patients with SLE than in Caucasians, even when controlling for socioeconomic factors.\textsuperscript{14 15} The negative effects of low socioeconomic status go beyond the implications of inadequate financial resources and access to healthcare to include factors related to poor housing, environmental toxins, stress and limitations related to social networks.\textsuperscript{16–18} Death certificate data from the National Centre for Health Statistics Multiple Cause of Death database covering 2003–2013 showed that mortality was highest and age at death was lowest among AA patients with lupus regardless of socioeconomic status, while age at death was highest among low-income rural white patients, suggesting that genetic features associated with ancestry or race-related cultural factors may be more impactful than socioeconomic factors as determinants of lupus-related mortality.\textsuperscript{19} How social and cultural factors interact genetic susceptibility to increase risk of development of SLE and poor outcomes remains an area for additional study.\textsuperscript{20}

### Common genetic variants
Marion and Postlethwaite described the complexity and heterogeneity of SLE as driven by the ‘stochastic execution of a complex inherited program’.\textsuperscript{21} The classic experiments in lupus mice of Eisenberg, Cohen and colleagues, showing development of lupus-specific anti-Smith (Sm) autoantibodies in only 25% of genetically identical lupus mice maintained in a common environment, support the view that the risk of autoimmunity is under genetic control, but chance is also a factor in expression of disease.\textsuperscript{22} A study from Taiwan assessed information from the country’s healthcare system and estimated that 44% of the risk of developing SLE can be attributed to heritable factors, with 30.3% of risk attributable to non-shared environmental factors.\textsuperscript{23} In the same study, the relative risk of developing SLE in twin children of patients with SLE was 316, supporting the high relevance of genetic factors to risk of SLE.

Disease-associated genetic variants confer readiness for both IFN-\textit{I} pathway activation and generation of pathogenic autoantibodies. Among the gene transcripts demonstrating intrinsic basal variability among healthy individuals and influencing the homeostatic set point of the immune system are the IFN-\textit{I}-stimulated genes, consistent with variably robust immune responses to virus infection across the population and the risks they confer for development of SLE.\textsuperscript{24} The major histocompatibility complex (MHC) class II genes also show high intrinsic variability in expression among healthy individuals, and studies of immune function among those expressing the B8-DR3 ancestral haplotype, a profile associated with risk for SLE, describe alterations in T-cell responses similar to those seen in SLE.\textsuperscript{25–26} In vitro-stimulated mononuclear cells from healthy B8-DR3-positive individuals have reduced interleukin (IL)-2 production, a deficiency characteristic of patients with lupus.\textsuperscript{27–28}

### Figure 1
A broad view of the pathogenesis of SLE. As SLE is an immune-mediated disease, research and identification of therapeutic targets have focused on elucidation of the relevant immune cells and mediators and the alterations in immune function that contribute to autoimmunity and inflammation in SLE. The scope of research with potential to favourably impact approaches to patient management should encompass studies of the societal, genetic and environmental risks that contribute to susceptibility of an individual to develop SLE. Additionally, identification and characterisation of the molecular drivers of immune system activation, particularly those that involve stimulatory nucleic acids, may lead to interventions that prevent autoimmunity or at least prevent progression to clinical disease. Finally, studies of the genetic, cellular and molecular mechanisms that contribute to target organ vulnerability to immune mediators, or alternatively, organ resistance to inflammation, may provide insights and management approaches that limit accumulation of damage. See text for discussion. IFN, interferon; pDC, plasmacytoid dendritic cell; SLE, systemic lupus erythematosus.
Risk of development of SLE can be attributed to combinations of common variants, each with a small impact on disease risk, rare mutations with high penetrance and substantial impact on risk, and combinations of common variants and rare mutations. The experimental approaches used to identify common genetic variants with statistical significance for association with a lupus diagnosis have primarily been based on genome-wide association studies (GWAS) using platforms identifying single-nucleotide polymorphisms (SNPs). One major effort used the Immunochip platform that includes risk SNPs identified mostly in Caucasian subjects with other autoimmune diseases. That study and others have identified more than 150 common genetic variants, most in regulatory rather than coding regions, that show a statistical association with a diagnosis of SLE. Only a small number of risk variants confer changes in protein sequence, as is the case for an Fc receptor. Data suggest that the impact of accumulated genetic risk is non-linear, with the effect of some alleles greater when the total genetic risk load is high. Immunochip data have been used to generate Genetic Risk Scores (GRS), weighted based on OR, that associate with earlier accumulation of anti-double-stranded(ds)DNA and anti-cardiolipin autoantibodies in patients in the highest compared with lowest quartile for GRS. Another study used genome-wide SNP data from EA and Chinese cohorts to define a GRS and showed an association with early onset of disease and lupus nephritis. Relevant to the extreme skewing of SLE to women, calculation of a cumulative GRS for men versus women showed a significantly higher score for men. These recent studies suggest that aggregation of data from disease-associated SNPs, reflecting multiple molecular pathways, may provide an indication of potential for developing SLE.

Studies confirm that extended haplotypes in the MHC, in addition to broadly distributed SNPs, are strongly associated with a diagnosis of SLE in EA, Asian and AA ancestries. The complement locus, in the MHC class III region, is of particular interest in view of the important role of the classical pathway in clearing potentially pathogenic immune complexes. Among patients with SLE, Sjogren’s syndrome and healthy donors, those with fewer copies of C4 genes have increased risk, with C4A having a greater impact than C4B, and its gene copy number greater in men than in women. Data from mouse studies support the conclusion that C4A is particularly efficient at mediating self-antigen clearance. Recent detailed analyses of the MHC in patients with SLE and healthy subjects provide important insights regarding mechanisms of immune dysfunction in those bearing risk alleles. The peak MHC association signal for AA patients is targeted to a narrow region, with the most significant risk SNP rs9271413 in a region of the class II locus between DRB1 and DQA1 in the study led by Hanscombe et al. The same risk SNP was identified by the Wakeland group in lupus patients of EA ancestry. For AAs and EAs, there are additional independent MHC contributions to risk of disease. The identified human leucocyte antigen (HLA) risk haplotype is HLA-DRB1*03:01—HLA-DQA1*05:01—HLA-DQB1*02:01 (DR3) in those of EA descent and HLA-DRB1*15:03—HLA-DQA1*01:02—HLA-DQB1*06:02 (DR2) in the AAs, similar to observations in other studies. Associations of B*08:01 as well as low C4 copy number with anti-Ro autoantibody are noted in EA patients.

In view of the critical role played by the protein products of HLA genes in presentation of peptide antigens to T cells and the functional significance of the encoded class II amino acids, SNP data were analysed to prioritise a model that would best explain the obtained SLE association data. The HLA allele model, defining a broad haplotype, provided a superior fit compared with the genetic variants that modify amino acids in cell surface DR or DQ molecules for both EA and AA patient groups, suggesting that preferential binding of an antigenic peptide to the MHC class II antigen-binding site might not be the most consequential influence of the relevant MHC associations on development of SLE. However, an analysis of Immunochip data did identify several common amino acids in the peptide-binding site of DRB1, particularly alanine 71, an important peptide-binding site in patients with rheumatoid arthritis, among

Figure 2 Strong SLE association signals across the extended MHC region. The most significant genetic markers for association with a diagnosis of SLE for (A) European and (B) AA patients with SLE are indicated, along with the relevant p values. A black dot identifies the most significant marker for each patient group. The peak of association for Europeans is in the class III region, although there is broad association across the MHC. For AAs, the most significant SNP is located in a narrow stretch of the MHC class II region between DRB1 and DQA1. Adapted from Hanscombe et al., AA, African-American; MHC, major histocompatibility complex; SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphism.
those patients with SLE with a risk haplotype, and Molineros et al showed MHC class II peptide associations with particular autoantibody specificities.\textsuperscript{30-49} Significant progress in illuminating the immunopathogenetic consequences of MHC risk haplotypes, and additional risk variants in non-coding genomic regions, has been achieved by the Wakeland group based on targeted deep sequencing and extensive analysis of 28 GWAS-identified risk loci. The general principle arising from their analysis, with important consequences for understanding lupus pathogenesis, is that a risk SNP often tags a so-called super-enhancer that regulates level of expression across a number of genes in that haplotype. Risk haplotypes can impact binding of transcription factors, such as CCCTC-binding factor (CTCF) or IFN-regulatory factor 4 (IRF4), a critical protein that regulates B-cell differentiation and level of transcription of HLA class II molecules on dendritic cells.\textsuperscript{34-53} Therefore, a risk haplotype can increase transcription and expression of at least several genes, promoting broad immune system activation, and, in the case of the MHC risk haplotype, can increase expression of DR and DQ molecules, augmenting presentation of many antigens and subsequent T-cell activation.

Specific SNPs have pointed to molecular pathways, mechanisms and therapeutic targets that underlie disease pathogenesis (table 1). A meta-analysis expanded the documented lupus-associated genetic loci based on analysis of more than 10 000 newly genotyped SLE cases, more than 180 000 controls and existing datasets from east Asian cohorts, with only 3.6% representing coding variants.\textsuperscript{37-44} A transancestral analysis identified quantitative trait loci in EA and AA individuals, with EA risk genes enriched in functions related to the innate immune response, while AA-associated genes were enriched in pathways related to T-cell and B-cell activation and cellular stress.\textsuperscript{55} Of the SNP-predicted genes shared between the two ancestries, 67% were differentially expressed between SLE and controls, including the interferon (IFN)-stimulated and pattern recognition receptor transcripts, emphasising the strong link between genetic risk and activation of the IFN-I pathway. A synthesis of GWAS data by Sandling et al concluded that T-cell differentiation pathways are influenced by loci in the HLA locus, and innate immune system activation is reflected in genetic associations with the JAK–STAT pathway and loci near the IFN-kappa gene.\textsuperscript{56} Among the mechanisms informed by GWAS data, gene products involved in the toll-like receptor (TLR) 7 pathway and IFN-I are prominent.\textsuperscript{57} Lupus-associated SNPs that identify genes or genomic regions relevant to setting a threshold for signalling in lymphocytes, and several that contribute to impaired apoptotic and necrotic cell clearance, identify additional relevant mechanisms (table 1).\textsuperscript{58} In general, the SLE-associated variants impact signalling and regulatory pathways involved in innate or adaptive immune system functions, with the IFN-I pathway, NF-kB pathway and T-cell and B-cell activation and differentiation particularly affected.

### Monogenic and oligogenic variants

The current view of SLE risk favours common risk variants accounting for most of its heritability; however, rare mutations can have sufficiently severe impact to cause SLE.\textsuperscript{34-35} Rarely, mutations occur in the early complement component gene C1q, with high penetrance (about 90%), presence of anti-dsDNA antibodies, severe disease and onset often in childhood.\textsuperscript{59-63} C2 deficiency is the most common complement-related association with SLE and is linked with the HLA-DR2 haplotype. C4 deficiency can occur based on the C4A*Q0 (null) allele, also encoded in the MHC.\textsuperscript{62-64} Recent data support a contribution to risk of SLE for

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<thead>
<tr>
<th>Table 1</th>
<th>Selected SLE-associated common genetic variants that inform molecular pathways involved in lupus pathogenesis</th>
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<tbody>
<tr>
<td><strong>Molecular mechanisms informed by common genetic variants</strong></td>
<td><strong>Selected relevant genes</strong></td>
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<tr>
<td>DNA damage/repair and autophagy</td>
<td>ATG5</td>
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<td>T-cell and B-cell activation and signalling</td>
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Continued
complement deficiency based on heterozygous partial C2 gene deletion in the setting of low C4 copy number.66 The mechanisms impacted by complement deficiency may be multiple, with impaired removal of cell debris, apoptotic material or nucleic acid-containing immune complexes most important and contributing to augmented activation of endosomal TLRs and production of IFN-I.65 C1q deficiency also affects the functions of CD87 T cells.65 66 Mutations in genes encoding enzymes that degrade DNA also contribute to activation of nucleic acid sensors and development of SLE.67 Deficiency in DNASE1, a serum nuclease, has occasionally been described in children with SLE.67 68 Mutations in DNASE1L3, encoding an enzyme responsible for degradation of chromatin in apoptotic cell-derived microparticles, have been documented in childhood SLE in association with anti-dsDNA autoantibodies.69–71 DNASE2 primarily functions intracellularly, and its deficiency is associated with activation of molecular pathways initiated by cytosolic and endosomal TLR DNA sensors.72–75

Rare lupus-like disorders, such as Aicardi-Goutieres syndrome (AGS), can be considered ‘extreme phenotypes’ and hold important lessons for understanding potential pathogenic mechanisms. AGS, characterised by neurological disease and skin lesions accompanied by high levels of IFN-I and autoantibodies, is attributable to a mutation in one of several genes encoding proteins that regulate or degrade endogenous nucleic acids.76 TREX1 encodes a DNase that degrades DNA in the setting of DNA damage. Insufficient availability or function of TREX1 allows accumulation of ligands that drive activation of cyclic GMP-AMP synthase and STING-dependent induction of IFN-I.4 46 SAMHD1 regulates levels of deoxynucleoside triphosphates, and mutations associated with AGS can lead to impaired DNA repair as well as the potential for reverse transcription of endogenous genomic repeat elements.77 RNaseH2 removes RNAs that have been inappropriately retained in DNA, and its deficiency can cause DNA damage, sensitivity to UV irradiation, accumulation of DNA:RNA hybrids with so-called R-loops, and activation of the IFN-I pathway.78 A similar function is mediated by adenosine deaminase, RNA specific (ADAR1) that performs editing of double-stranded RNA.79 While the noted variants result in deficiencies in control of potentially stimulatory self-nucleic acids, gain of function mutations in IFI1H1, encoding MDA5, can contribute to STING-dependent production of IFN-β.80 Additional reports of monogenic lupus implicated mutations in the DNMT3A gene, mediating DNA methylation, and the gene encoding FAS, a T cell surface molecule that induces apoptosis. Mutations in protein kinase C delta (PRKCD) are reported, mediating apoptosis in the setting of DNA damage and a component of the mitochondrial cell death pathway triggered by ionising radiation and with a role in B cell tolerance.81 82 Considering the functional roles of the genes implicated in many cases of monogenic lupus, the mechanisms impacted involve early drivers of immune dysregulation and autoimmunity, particularly the nucleic acid stimuli that activate an innate immune response and production of IFN-I. While monogenic forms of lupus are uncommon, data from whole exome sequencing enrich the Gwas data and are characterising patients in whom one parent contributes common risk variants and the other parent is heterozygous for a mutation in a gene associated with monogenic lupus.82 83 Almlof et al provided data from 71 patients with SLE and identified very rare missense and nonsense mutations in genes associated with monogenic SLE, such as C1qR.83 Among others identified were genes associated with impaired regulation or degradation of endogenous nucleic acids, including DNASEI1L3, DNASE1 and RNASEH2A, again pointing to the significant contribution of alterations in nucleic acid regulation in the pathogenesis of SLE.83

In addition to gene mutations that promote activation of nucleic acid-sensing cytosolic receptors, others can alter generation of reactive oxygen species. A mutation in the neutrophil cytosolic factor 1 (NCF1) gene (Arg90His) results in impaired function of the protein, a component of the nicotinamide adenine dinucleotide phosphate oxidase complex 2 (NOX2). The mutation can alter effectorcytosis, the process through which apoptotic cells are phagocytosed and is associated with increased IFN-I.84–87

Identification of genomic loci and mutations associated with a diagnosis of SLE point to mechanisms central to lupus pathogenesis. In addition, insights regarding allele-related differences with broad impact on immune system activation, particularly those encoded in the MHC, may suggest novel approaches to identifying those at risk of SLE as well as productive approaches to therapy.84 85 Understanding how an individual’s genetic endowment establishes the immune system precursors and prerequisites for development of autoimmunity might be elucidated through studies of haematopoietic stem cells, with a recent study demonstrating alterations that skew those precursors towards myelopoiesis, consistent with the abundant expression of IFN-I-induced gene transcripts in myeloid cells as well as the growing recognition of a contribution of neutrophils to disease pathogenesis.

Environmental triggers

In addition to genetic factors that establish an at-risk immune system set point for development of autoimmunity, environmental factors (along with chance) appear to be necessary for initiation of immune system activation (table 2). Some triggers, such as UV light and drugs that mediate DNA damage or modify DNA methylation, may generate stimulatory self-nucleic acids, while other stressors or mediators of oxidative DNA modification may augment the stimulatory properties of those nucleic acids.86 Beyond those factors, potential microbial triggers of autoimmunity are of great interest. Herpes viruses, particularly Epstein-Barr virus (EBV), affect innate and adaptive immune responses, and epidemiological studies have supported an association between EBV infection and development of SLE.87–89 EBV can induce mitochondrial stress, and EBV DNA directly induces IFN-I production by plasmacytoid dendritic cells (pDCs)
in a TLR9-dependent manner, a response that can be blocked by chloroquine.91,94 EBV-encoded small RNAs, termed EBERs, have been postulated to activate cytotoxic sensors and induce IFN-β.95 In addition to induction of IFN-β by EBV in the setting of acute infection, EBV reactivation can induce B-cell proliferation, and anti-EBV-early antigen IgG has been associated with activation of the IFN-β pathway.96 A proposed mechanism by which EBV infection might promote development of SLE is based on SLE genomic risk loci being occupied by EBV nuclear antigen 2 (EBNA2), with the genomic architecture of many of those loci rewired by EBNA2.97,98 The potential for other viruses to serve as triggers for autoimmunity in the at-risk individual is demonstrated by the reports of typical lupus autoantibodies developing in the setting of infection with SARS-CoV-2.99-101

Growing interest in the role of the microbiome in the pathogenesis of autoimmune diseases is reflected in studies relevant to SLE, with murine lupus models supporting a contribution of microbial products to increased gut permeability and studies in patients with SLE, suggesting that microbial antigens can drive production of autoantibodies through a molecular mimicry mechanism.102-104 Translocation of a gut microbe, Enterococcus gallinarum, to liver induced autoimmunity in mice with susceptible genetic backgrounds, such as those with a TLR7 duplication, was associated with autoantibodies specific for dsDNA and Sm, and that microbe was also found in human liver biopsy tissue from patients with SLE.105-106 A potential contribution of TLR7 to impaired barrier integrity, and translocation of bacteria through the gut is supported by data from additional murine models.107 Dominance of certain bacterial strains is associated with lupus nephritis as well as increased disease activity, and staph and strep bacteria, dominating in a large study from Japan, are associated with enrichment of specific metabolites in those patients.108,109 Additional research will be required to gain understanding of whether gut microbes are primary drivers of lupus autoimmunity, as might occur through molecular mimicry, or whether the noted observations reflect secondary alterations in gut permeability due to inflammation.110 Recent reviews have addressed these and other candidate environmental triggers conferring risk of SLE or SLE flare, with many listed in table 2.111-113

### Epigenetic modifications

Modifications to chromatin can reflect the impact of the environment on readiness for gene transcription and can result in a ‘trained’ or primed immune response. Those environmental stimuli can be exogenous to the individual, for example, UV light exposure, but can also include endogenous stimuli. Assessment of differentially methylated CpG sites throughout the genome has been useful in identifying regions of active chromatin, often associated with gene transcription, and demethylation of IFN-I-stimulated gene loci has been confirmed in several studies.114-118 These results are consistent with transcriptome data, with IFN-I-regulated genes showing the most significant difference between patients and control subjects and some representing genes previously identified as lupus risk genes.119-122 An interesting analysis of genome methylation in monozygotic twins discordant for SLE identified genes that might be influenced by environmental factors, whether exogenous or endogenous. Among those, only absent in melanoma 2 (AIM2) is a well-recognised IFN-I-regulated gene.122 The AIM2 protein antagonises sensing of cytosolic dsDNA and AIM2-deficient mice produce excessive IFN-β.123 A study of genome demethylation in isolated neutrophils demonstrated an association of sorting nexin 18 (SNX18), encoding a protein that mediates endosomal trafficking and autophagosome formation, with changes in disease activity, and a CpG site in the GALNT18 gene, encoding N-acetylgalactosaminyltransferase 18, was associated with active nephritis. Hypomethylation of polymorphic sites in TREML4 and IL6 was also noted, identifying genes that are involved in augmenting signalling through TLR7 in the case of TREML4 or as a biomarker of lupus nephritis for IL-6.116,124,125 An miRNA, miR-18a, that regulates TNF-α, the gene encoding NFκB regulator A20, was hypomethylated in SLE CD4+ T cells.126 Assay for transposase-accessible chromatin sequencing has been used to identify genomic locations of histone modification associated with gene regulatory regions, with patients with SLE showing a unique epigenetic signature.127-131 IFN-1 is a strong candidate for mediating many of those histone modifications which can be viewed as indicators of IFN-induced priming or training of the immune system cells for augmented response when presented with a subsequent activating signal as well as measures of the impact of environmental triggers on development of autoimmunity and inflammation in SLE.123

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**Table 2 Candidate environmental risk factors for development of SLE or SLE flare**

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<th>Candidate environmental trigger</th>
<th>Examples</th>
<th>Potential pathogenic mechanisms</th>
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<tr>
<td>Ultraviolet light</td>
<td>UV-B radiation</td>
<td>Induction of apoptosis</td>
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<td>Induction of ROS and IFN-I</td>
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<td>Expression of genomic retroelements</td>
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<td>Inhaled exposures</td>
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For all indicated factors and potential mechanisms, additional research is required to support and define a role in SLE pathogenesis.
POTENTIAL DRIVERS OF IMMUNE SYSTEM ACTIVATION

While genetic risk and microbial or other environmental factors establish fertile ground for development of SLE, specific drivers of immune system activation are required to initiate production of IFN-I and self-antigen-specific autoantibodies. Characterisation of those drivers is an area of research ripe for attention. It is possible that either IFN-I pathway activation or development of lupus autoantibodies may serve as an initial event, likely influenced by the specific genetic risk factors at play. For example, an individual with several risk variants supportive of IFN-I production might generate high IFN-I levels following a virus infection or in the setting of DNA damage or a transient expression of genomic retroelements. An individual with a particular MHC risk allele might be more likely to effectively activate a T-cell response, engage a molecular mimicry process and generate anti-Ro antibodies following an infection. Yet both mediators may be necessary for development of clinical SLE. Among women with anti-Ro and/or anti-La autoantibodies, those with clinical manifestations of SLE or SS were significantly more likely to have increased serum levels of IFN-I, highlighting some common mechanisms between the two systemic autoimmune diseases.128 In a study of development of clinical SLE over 12 months in patients who were ANA positive and showed one clinical manifestation of SLE, those with a high IFN-I score were more likely to go on to classifiable SLE than those with a low IFN-I score.129 Among the candidate drivers of immune activation are products of DNA damage or inadequate regulation or degradation of genome-derived nucleic acids, such as DNA:RNA hybrids and their associated R loops, DNA or RNA derived from long interspersed nuclear element 1 (LINE1) or human endogenous retrovirus (HERV) sequences, or mitochondria-derived DNA or RNA, particularly when modified by oxidative stress (figure 1).130–141 Nucleotide excision repair, a mechanism to remove cyclobutene pyrimidine dimers induced by UV light, is less efficient in patients with SLE.142 Cells from patients with RNASEH2 mutations have shown formation of cyclobutene pyrimidine dimers after UV exposure, potentially priming for an IFN-I response when stimulated by nucleic acids or UV irradiation.143 Any number of candidate nucleic acid drivers may be relevant in an at-risk individual and initiate innate immune activation and IFN-I production.

ALTERED IMMUNOREGULATION

Transcriptional networks activated in SLE

Based on technologies that identify mRNA transcripts, studies of SLE blood and tissue have mapped core molecular pathways involved in most patients with SLE.144 Particularly striking is the IFN-I signature that was identified in peripheral blood cells from patients with SLE and comprises highly correlated expression of hundreds of gene transcripts induced by IFN-I.145–147 The IFN-I signature is observed in 60%–85% of patients and is broadly expressed across cell types, although increased numbers of IFN-I-induced gene transcripts are observed in monocytes compared with lymphocytes, with relatively sustained expression, even in the setting of inactive disease.148 Additional transcription factors associated with granulocytes, plasma cells and cell cycle are seen in many patients, along with decreased expression of a natural killer/T regulatory (Treg) cell signature.146 149 150 Among patients of different ancestry, there is a predominance of signatures dependent on genetic background, highlighting the need to consider ancestry of healthy control subjects when investigating lupus transcripts.151 Gene signatures in AA patients are particularly influenced by B-cell transcripts, while those of EA patients are more strongly influenced by myeloid transcripts. Multiple datasets with associated clinical and serological data are particularly valuable and support the observation that anti-ribonucleoprotein (RNP) autoantibodies, in the presence or absence of anti-dsDNA autoantibodies, are strongly associated with the IFN-I signature, with increased numbers of other ribonucleoprotein-targeted autoantibodies (eg, anti-Sm, anti-Ro and anti-La) also associated with the IFN-I pathway.152–154 Those autoantibodies are a particular feature of AA patients, suggesting that further investigation of their antigen targets and genetic variants impacting B-cell differentiation may be a path towards understanding the contribution of IFN-I to autoimmunity.151 152 Studies of transcriptional programmes, including those using single-cell RNA sequencing, are beginning to define patient subsets with characteristic clinical features, such as those with a dominant neutrophil signature associating with lupus nephritis.149 153–157 Additionally, combining transcriptome and genetic variant data can elucidate the genomic basis for activation of particular molecular pathways.15 138

Innate immune activation

Genetic variants relevant to the IFN-I pathway facilitate innate immune system activation in at-risk patients (table 1).159–162 Additional genetic associations point to immune system regulation by the cytosolic nucleic acid sensors and the inflammasome, with variants in TNFAP3, encoding A20, promoting activation of the NFκB pathway. TLR7 is a focal point for innate immune system activation and IFN-I production in SLE and represents a promising therapeutic target (figure 3). A recent report of a gain-of-function mutation in TLR7 in a girl with SLE supports interest in that gene and pathway.163 TLR7 and TLR8, the former expressed in pDCs and B cells and the latter in monocytes, are encoded on the X chromosome, and X chromosome inactivation and the function of XIST, mediating that process, may be altered in patients with SLE.164–168 While the responsible mechanisms require further study, expression of TLR7 from both X chromosomes has been observed in some women with SLE, particularly in B cells and pDCs. Another X chromosome-encoded gene, TSLR1, can be expressed from both X chromosomes and augment signalling downstream of TLR7.169–171 A variant of UNC93B1 confers increased association of TLR7 with its RNA ligand, and IRAK1 (also X-encoded) and IRF5 variants can augment TLR7 signalling. Taking these observations together, there is growing support for the TLR7 pathway contributing to the striking female predominance of SLE. Candidate TLR7 ligands also represent important pathogenic mediators in SLE. Immune complexes containing RNA, particularly those composed of U or hY RNAs and associated autoantibodies, including anti-RNP, anti-Sm, anti-Ro and anti-La, can be delivered to the TLR7 and TLR8 endosomal compartments via Fc receptors and activate those pathways, resulting in abundant production of IFN-I by pDCs or TNF by patrolling monocytes.172–174 Additional candidates for activation of an innate immune response focus on cytosolic sensors and their DNA or RNA ligands. Exosomes derived from apoptotic endothelial cells may be enriched in U1 RNA and its associated proteins, along with genomic retroelements with potential to activate the STING pathway.175 About 15% of patients with SLE show activated 2’3’-cyclic GMP-AMP in the DNA-sensing pathway, and its expression correlates with IFN-I-stimulated gene expression.176 Neutrophils, particularly low-density granulocytes, and neutrophil products, including neutrophil extracellular traps (NETs), remain a potential source of stimulatory nucleic acid and...
innate immune system activation. NETs can activate and damage vascular endothelial cells, are candidates for driving inflammation in kidneys of patients with lupus nephritis and promote small vessel vasculopathy. Serum NET levels are elevated in patients with lupus nephritis and correlate with proteinuria, and blood and tissues contain increased NETs in association with IL-33, a member of the IL-1 cytokine family, in active lupus. Neutrophil defensins also contribute to induction of IFN-I by NETs. IFN-I has protean effects on most components of the immune system, with those relevant to SLE reviewed by us previously. Additionally, recent data link IFN-I to DNA damage and B-cell differentiation. SLE B cells demonstrate increased IFN-I-dependent expression of ATR, encoding a serine threonine kinase that signals DNA damage and can promote DNA recombination. Interestingly, an inhibitor of ATR reduced formation of plasmablasts. In general, the sustained production of IFN-I acts as an immune adjuvant to promote generalised immune system activation and particularly contributes to B-cell differentiation and production of proinflammatory chemokines. Elevated serum concentrations of IFN-I as measured by a high-sensitivity assay may have important clinical implications, as high levels in patients with SLE in remission were associated with shorter time to relapse. In addition, genetic variants encoding components of the IFN-I signalling pathway, such as TYK2, currently studied as a therapeutic target of deucravancitinib, may identify patients with particularly robust responses to IFN-I.

While increased production of IFN-I in patients with SLE is most notable, monocytes, macrophages and lymphocytes secrete a panoply of soluble products, including tumour necrosis factor (TNF), IL-1, IL-6, IL-10, IL-12 and B-cell activating factor (BAFF), with many likely to contribute to immune system activation as well as B-cell survival and differentiation in the case of BAFF. Of those, only BAFF, inhibited by belimumab, has proven success as a therapeutic target. IL-6 levels are increased in active SLE, but efficacy of a monoclonal anti-IL-6 antibody was similar to placebo in a phase II trial. Although TNF levels may be elevated in patients with active disease, controlled trials of TNF antagonists in SLE are limited and their use has been associated with exacerbations of lupus disease activity.

Adaptive immune activation

T-cell depletion studies in murine models and studies of the phenotype and function of CD4+ T cells in blood and tissue of patients with SLE support the role of those cells in lupus pathogenesis. Production of most pathogenic IgG lupus autoantibodies requires T-cell help and somatic hypermutation, a T-cell-dependent process that occurs in the context of germinal centre reactions. In view of the important role of T cells in conferring antigen specificity to the immune response, identifying the self-antigen specificity of T cells in patients with lupus might allow identification of the most relevant antigens driving lupus autoimmunity. Only recently has preferential expansion of CD4+ T cells responsive to splicesome proteins, Ro/SSA or La/SSB antigens demonstrated their enrichment among T cells with activated phenotype (CD154/CD40 ligand+ and CD69+) and intracellular interferon gamma (IFN-γ). Lymph-associated genetic variants likely contribute to augmented production of that cytokine, with a STAT4 risk allele associated with increased IL-12-induced IFN-γ production in SLE T cells. Recent studies are fine-tuning the definition of the T cells that are most relevant to provision of help for B-cell differentiation, with T follicular helper (Tfh) cells and T peripheral helper (Tph) cells now viewed as most active in that regard. Dysregulation of the IFN-I pathway contributes to the development of Tph cells, and type III IFN (IFN-lambda) may collaborate with IFN-I to drive expansion of those cells. The role of CD8+ T cells in SLE is gaining interest. Their cell numbers are increased in early lupus and are present in the interstitium of kidneys from patients with nephritis. The contribution of IFN-I to mechanisms of lupus pathogenesis may involve both CD4+ and CD8+ T cells, with IFN-I-stimulated genes expressed in both subsets, Tfh support for pathogenic B cell responses dependent on IFN-I in a STAT4-dependent manner, and IFN-I promoting altered mitochondrial function and lupus-like functional impairment in CD8+ T cells.
In patients with lupus nephritis, autoantigen-specific T cells are enriched in patient urine, supporting the relevance of the same self-antigens targeted by lupus autoantibodies. Soluble mediators present in urine may represent useful biomarkers of disease activity. Activated leucocyte cell adhesion molecule, expressed on renal structural cells and serving as a ligand for T cell CD6, is significantly increased in urine from patients with active lupus nephritis, along with IL-16, another candidate biomarker of nephritis activity. A number of therapeutic approaches are directed at either amplifying the number and activity of Treg cells or inhibiting the interaction of Th cells with their partner B cells. Promising data are coming from studies of low-dose IL-2 therapy as well as inhibitors of CD40L.

Autoantibodies, particularly those complexed with nucleic acids in the form of immune complexes, are essential mediators of tissue inflammation and damage in patients with SLE. A conclusion supported by the apparent induction of remission by anti-CD19 CAR T-cell therapy in several patients with severe SLE. Lupus autoantibodies are also recognised to have immunomodulatory function, inducing IFN-γ and other inflammatory mediators. Defining the nature of the B cells that differentiate into autoantibody-producing cells and the cell-mediated and soluble factors that drive their differentiation continues to be an area of active investigation, with high importance for identification of therapeutic targets. To what degree alterations in generation of the antibody repertoire and central B-cell tolerance mechanisms contribute to autoimmunity in patients with SLE remains of interest. Most elusive have been studies of lupus bone marrow, the site of central B-cell tolerance. Tantalising data suggest that IFN-I produced in lupus bone marrow, perhaps driven by neutrophils, might be particularly important in altering tolerance mechanisms. Cell-intrinsic production of IFN-β in mesenchymal stem cells from bone marrow of patients with lupus raises the possibility that endogenous nucleic acid drivers of IFN-I might represent an ‘upstream’ event contributing to altered B-cell tolerance. These observations echo data showing expression of IFN-β in some circulating B cells from patients with SLE. Type I transitional B cells are enriched in autoreactive surface immunoglobulin receptors and express a phenotype and gene expression profile distinct from healthy donor cells. In SLE, those cells are increased but show decreased expression of CD19, a surface receptor important for B-cell receptor signalling, as well as CD21, also called CR2, a receptor for the C3d complement component and EBV. Those B cells are impaired in their response to TLR9 signalling, at least in part due to deficient CD19. A striking increase in IFN-I-stimulated gene transcripts has been documented in bone marrow B cells and in the recent emigrants, suggesting a link between increased production of IFN-I and altered B-cell differentiation. IFN-I might increase the threshold for BCR signalling in B-cell precursors, impairing tolerance mechanisms that depend on deletion of self-reactive cells.

Recent studies have characterised a B-cell subset that undergoes differentiation to produce autoantibodies. Often called age-associated B cells (ABCs) based on their identification in aged mice, detailed studies have defined the phenotype of these cells in patients with SLE and are working to understand the stimuli and receptor systems that drive their development. An agreed-upon feature of the ABCs is the expression of the transcription factor T-bet, and most studies describe expression of CD11c, an integrin typically expressed on myeloid cells. ABCs proliferate in response to TLR7 activation but not to cross-linking of the B cell receptor, a feature that differentiates them from most B cells, and they are supported by T cell-derived IL-21. Consistent with important roles for IFN-I and signalling through TLR7, pDCs and RNA-containing immune complexes generate B cells with the double negative CD27− IgD− B-cell phenotype characteristic of ABCs. A more fine-tuned description of the most relevant B cells in patients with SLE was recently reported, with the CXC53 ‘CD19hi’ phenotype most consistent with plasmablast frequencies. The relevance of this line of investigation is that it is defining the cell surface features as well as required stimuli that characterise those B cells that go on to produce lupus autoantibodies, thereby defining potential therapeutic targets.
Figure 5  Insights into pathogenic mechanisms identify therapeutic targets. (A) Inhibition of the IFN-I system is being addressed therapeutically, through approaches aimed at digesting stimulatory RNA-containing complexes, inhibiting or eliminating pDCs, inhibition of the TLR7 pathway signalling, blockade of IFNAR and inhibition of JAK1/TYK2 signalling. In addition, consideration should be given to therapeutic approaches that inhibit or eliminate long-lived plasma cells, as those cells are likely to produce the autoantibodies that form RNA-containing immune complexes and effectively deliver stimulatory RNA to endosomal TLR7. (B) Inhibition of components of the adaptive immune response represent rational therapeutic targets for treatment of patients with SLE. Inhibition of Th cell differentiation through inhibition of IL-12 signalling and expansion of Tregs might rebalance T-cell subsets to limit immune activation. Inhibition of ICOS or CD40L might reduce T cell-dependent B-cell activation and differentiation. Several approaches to direct (CD19 or CD20-directed therapies, BTK inhibition) or indirect (BAFF inhibitor) inhibition of B-cell differentiation can limit disease activity. Novel approaches such as CD19-CAR T cells that efficiently eliminate CD19+ B cells may prove effective. Targeting long-lived plasma cells is challenging but is being pursued with targeted therapies such as anti-CD38 and anti-BCMA antibodies. Effective control of disease may require therapeutic inhibition of components of both innate and adaptive immune systems, as with iberdomide, an inhibitor of the Ikaros and Aiolos transcription factors, although such approaches are accompanied by challenging toxicities. Therapeutics are indicated in bold. BAFF, B-cell activating factor; IFN, interferon; IL, interleukin; pDC, plasmacytoid dendritic cell; SLE, systemic lupus erythematosus; TLR, toll-like receptor; Treg, T regulatory.
As nicely described in recent reviews, plasmablasts and long-lived plasma cells may have distinct roles in the production of lupus autoantibodies.\(^\text{220-222}\) Plasmablasts are expanded and readily detected in the peripheral blood of active lupus patients and are a source of anti-dsDNA autoantibodies.\(^\text{221}\) The frequency of those cells can fluctuate over time in relation to disease activity, as levels of anti-dsDNA autoantibodies fluctuate, often prior to or at the time of flares of nephritis.\(^\text{224}\) What is not well understood is how their specificity for DNA is determined. Most plasmablasts express cell surface CD19, an important feature that may facilitate depletion by therapies such as anti-CD19 chimeric antigen receptor (CAR) T cells. In contrast, most long-lived plasma cells, thought to be a source of autoantibodies specific for extractable nuclear antigens (eg, anti-Sm and anti-RNP), do not express CD19 and so would be refractory to therapies targeting that molecule. Those plasma cells may be sustained for long periods of time, consistent with the relatively stable levels of autoantibodies specific for RNA-binding proteins observed in many patients.\(^\text{220}\) Therapies specific for CD38 or BCMA, both expressed on long-lived plasma cells, may be required to deplete the cells producing those antibodies.\(^\text{225}\) In addition to expansion of B-cell subsets that differentiate into autoantibody-producing cells, patients with SLE have a deficiency in innate-like B cells with a CD27\(^+\)IgD\(^-\) phenotype that produce natural IgM antibodies that contribute to clearance of apoptotic cells. Those protective IgM antibodies as well as IL-10 produced by those cells are decreased in patients with SLE.\(^\text{226}\)

The specific targets of the autoimmune response in SLE include intracellular and intranuclear particles that include nucleic acid and nucleic acid-binding proteins.\(^\text{227,228}\) Autoantibodies targeting some particles, such as the hy-RNA-containing Ro particle, are shared by patients with other systemic autoimmune diseases and often occur prior to a classifiable diagnosis of SLE. The U1-RNA-containing spliceosome and its Sm and RNP proteins are specific targets of the autoimmune response in SLE and are likely to hold important clues to drivers of autoimmunity in SLE.\(^\text{229}\) Dissecting the environmental and genetic factors that support development of an immune response targeting those lupus-specific self-antigens, with molecular mimicry a potential mechanism, is likely to reveal fundamental insights into SLE.

**TARGET ORGAN VULNERABILITY VERSUS RESILIENCE**

Lupus nephritis is understood to depend on deposition of autoantibodies, often in the form of immune complexes, in renal glomeruli, accompanied by complement activation and recruitment of neutrophils. Supporting that concept, a recent study comparing determinants of lupus nephritis among patients with SLE identified anti-dsDNA antibodies as the strongest predictor of lupus nephritis, although assessment of a panel of gene transcripts has potential for differentiating those patients who do and do not have active nephritis.\(^\text{230}\) As noted, NETs have been implicated in the pathology of lupus nephritis, with data supporting impaired degradation of NETs and contributions of NET-associated antimicrobial defensins to immune activation, potentially resulting in local production of IFN-\(\gamma\) and damage to renal vasculature or tubules.\(^\text{178,182,231}\) Efforts to access and potentially NET-supporting impaired degradation of NETs and contributions of those insights are achieved, we are left with considerable understanding of the contributions of innate and adaptive immune system cells, mediators and pathways to lupus pathogenesis and identification of rational therapeutic targets for current drug development (figure 5A,B). Particularly informative will be lessons gleaned from responder analyses and investigations of associated biologic mechanisms impacted by immunomodulatory agents tested in patients with SLE. One tentative conclusion from recent studies is that agents that modulate both IFN-\(\gamma\) pathway and production of autoantibodies, as was seen in a recent analysis of patients responsive to the agent ibudomid, promoting degradation of the transcription factor Aiolos, may be most effective in achieving clinical efficacy.\(^\text{242}\) Alternatively, combination therapies that together target both innate and adaptive immune system mechanisms may be required to achieve sustained remission. As knowledge grows, new targets will be identified, along with anticipation for improved outcomes for patients.

**Contributors** MKC is responsible for all planning, literature review and writing of this article.

**Funding** MKC is supported by the Benjamin M. Rosen Chair in Immunology and Inflammation Research.

**Competing interests** MKC is an associate editor of Annals of the Rheumatic Diseases. She has consulting relationships with AMPEL BioSolutions, Astra Zeneca, Bristol Myers Squibb, Glaxo Smith Kline and Lilly, and holds a research grant from Gilead Sciences.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Commissioned; externally peer reviewed.
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