New insights into the immunopathogenesis of systemic lupus erythematosus

George C. Tsokos[1], Mindy S. Lo[2], Patricia Costa Reis[3] and Kathleen E. Sullivan[4]

Abstract | The aetiology of systemic lupus erythematosus (SLE) is multifactorial, and includes contributions from the environment, stochastic factors, and genetic susceptibility. Great gains have been made in understanding SLE through the use of genetic variant identification, mouse models, gene expression studies, and epigenetic analyses. Collectively, these studies support the concept that defective clearance of immune complexes and biological waste (such as apoptotic cells), neutrophil extracellular traps, nucleic acid sensing, lymphocyte signalling, and interferon production pathways are all central to loss of tolerance and tissue damage. Increased understanding of the pathogenesis of SLE is driving a renewed interest in targeted therapy, and researchers are now on the verge of developing targeted immunotherapy directed at treating either specific organ system involvement or specific subsets of patients with SLE. Accordingly, this Review places these insights within the context of our current understanding of the pathogenesis of SLE and highlights pathways that are ripe for therapeutic targeting.

[1]*Division of Rheumatology, Beth Israel Deaconess Medical Center, Harvard Medical School, 110 Francis Street, Boston, Massachusetts 02215, USA.*
[2]*Division of Immunology, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, Massachusetts 02115, USA.*
[3]*Department of Pediatrics, Lisbon Medical School, Lisbon University, Santa Maria Hospital, Avenida Professor Egas Moniz, 1649–035 Lisbon, Portugal.*
[4]*Division of Allergy and Immunology, The Children's Hospital of Philadelphia, The University of Pennsylvania Perelman School of Medicine, 3615 Civic Center Boulevard, Philadelphia, Pennsylvania 19104, USA.*

Correspondence to: K.E.S.
sullivak@mail.med.upenn.edu

doi:10.1038/nrrheum.2016.186
Published online 22 Nov 2016

Progress in understanding systemic lupus erythematosus (SLE) has been hampered by disease heterogeneity. Patients with SLE can present with diverse organ involvement as well as diverse autoantibodies. In fact, SLE probably represents several heterogeneous diseases that fall into a broad clinical phenotype of systemic autoimmunity. Many patients with SLE have mild disease, whereas others have a catastrophic presentation and life-threatening progression. Our current understanding of the factors that drive the different phenotypes in SLE is limited; however, in spite of an imperfect understanding of the pathogenesis of SLE, great progress has been made over the past 50 years and mortality is now only 10% within 10 years (compared with 50% within 3 years in the 1960s)[1]. Nevertheless, infections related to immune suppression, cardiovascular disease, and renal failure constitute a substantial burden, and medical costs and costs related to lost productivity are high[2].

The pathogenesis of SLE hinges on loss of tolerance and sustained autoantibody production (FIG. 1). Unlike self-limited autoantibody processes, such as autoimmune haemolytic anaemia, SLE is generally a lifelong condition. One of the key concepts in pathogenesis is an imbalance between apoptotic cell production and disposal of apoptotic material (FIG. 2). Nuclear antigens are typically not accessible to the immune system, but during the course of apoptosis the cell membrane forms blebs that pinch off from the cell and contain fragmented cellular material, including nuclear antigens[3]. Such apoptotic debris is normally cleared rapidly and would not be accessible to the immune system. In humans, approximately 1 billion neutrophils undergo apoptosis every day and increases in the apoptotic cell load can be generated by exposure to ultraviolet light, infections, and toxins, which are all known to be associated with SLE. Persistent apoptotic debris containing nucleic acids can stimulate an inflammatory response through the activation of nucleic acid recognition receptors, such as members of the Toll-like receptor (TLR) family[4]. Circulating apoptotic microparticles also prime neutrophils for extrusion of nuclear material, providing yet more antigen[5]. Nucleic acid recognition receptors control endogenous retroviruses, recognize viral pathogens, and defend against intracellular bacteria, and are strongly associated with type I interferon (IFN) production. Defects in these pathways are now strongly implicated in the pathogenesis of SLE, as both increasing disease susceptibility and directly causing monogenic forms of SLE (TABLES 1,2).

Type I IFNs and other cytokines promote B-cell differentiation and loss of tolerance. B cells can respond to nucleic acids through direct antigen recognition and via surface IgM receptors for proteins complexed with nucleic acids. Once autoantibodies have formed, B cells can also take up nucleic acids through Fc receptors and B-cell receptors recognizing Fc (rheumatoid factor)[6]. Once activated, these B cells mature, expand, and begin

Key points

- Our understanding of the pathogenesis of systemic lupus erythematosus (SLE) has changed rapidly over the past decade
- Refinements in our understanding over the past 3 years have led to the potential for precision targeting of therapeutic strategies
- Advances in epigenetic therapeutic agents and the manipulation of cells *ex vivo* have the potential to further improve patient care

to secrete more antibody, which enhances the adaptive immune response. T-cell and B-cell abnormalities have long been described in SLE and are thought to be central to the disease process. The autoantibodies identified in SLE are generally high-affinity, somatically mutated IgG, which suggests that they have arisen in germinal centres, where T cells provide help for class switching.

This framework for understanding SLE has been our model for the past ten years. It is founded on genetic data, *in vitro* analyses, and observations in mouse models. In this Review, we cover new insights that extend this model and offer the potential for novel therapeutic interventions in SLE. We discuss environmental and genetic factors that contribute to the risk of developing SLE, and examine how gene expression and regulation contributes to the phenotype of the disease and how these effects provide a window into the clinical features. Subsequent sections investigate mechanisms as we understand them from a cell biology perspective, and three examples of local tissue effects that can contribute to organ damage and modulate disease are also presented (FIG. 1).

Environmental risk factors

Imperfect disease concordance between monozygotic twins suggests that environmental factors influence the pathogenesis of SLE. Hormones and ultraviolet light have long been recognized as contributors to SLE[7,8]. Women comprise 90% of most SLE cohorts, and oestrogen and prolactin enhance immune responses through diverse mechanisms[9,10]. Ultraviolet light is thought to drive apoptosis, providing an immunologic stimulus. A possible connection between sunlight exposure and drug-induced lupus has also been identified. Ultraviolet light converts propranolol into a proinflammatory aryl hydrocarbon receptor ligand, possibly explaining its association with lupus-like disease[11].

Infections have been implicated in SLE for many years. Epstein–Barr virus and cytomegalovirus are considered to be SLE triggers[12], whereas *Helicobacter pylori*[13], hepatitis B virus[14], and parasite infections are thought to be protective[15]. One study found that herpes simplex virus type 2 transcripts were overexpressed in patients with systemic autoimmune diseases, although the role of immunosuppression in increased viral gene expression could not be eliminated[16]. Further data support a role for microorganisms in general. Lipopolysaccharide is a component of the cell wall of Gram-negative bacteria that can activate TLR4. Serum levels of lipopolysaccharide are increased in patients with SLE[17] and biomarkers of lipopolysaccharide engagement by TLR4, such as shedding of CD14, correlate with disease activity[18]. TLR4 activation promotes disease in mouse models of lupus[19]. Microbial stimulation of myeloid cells by TLRs is critical for antigen presentation to T cells[20]. These data suggest that chronic microbial translocation contributes to the pathogenesis of SLE. Bacterial biofilms represent another mechanism by which microorganisms interact with the immune system. Amyloid–DNA complexes, found in many biofilms, greatly increased the production of autoantibodies in lupus-prone mice[21]. At this point, the evidence seems clear that SLE is not uniformly caused by a single infection, but the role of bacteria and viruses generally in SLE represents an emerging area of study, and TLR antagonists are being evaluated as therapeutic agents.

The microbiome represents the collection of bacteria, viruses, and fungi that coexist on and in the human body. Collectively, microbial cells far outnumber human cells within the body and, while many were previously thought to be silent passengers, we now know that some can modulate the immune system[22]. Interest in the microbiome has grown exponentially, as it represents an attractive therapeutic target. In women with SLE, a lower *Firmicutes* to *Bacteroidetes* ratio was seen than in healthy individuals, even during times of remission[23]. In humans, microbiome studies are largely correlative, but mouse studies support a mechanistic role for the microbiome. Increased levels of *Bacteroidetes* were also seen in lupus-prone mice[24]. In a separate study, a manipulation that aimed to normalize the microbiome was beneficial in MRL/lpr mice[25]. The mechanism of the effect is not fully understood, but certain gut bacteria foster the development of regulatory T cells (T_{reg} cells)[26,27]. Developing the 'correct' (that is, healthy) microbiome might require neonatal exposure; one study found that development of antinuclear antibodies was dependent on bacterial colonization during the neonatal period in mice[28]. Although therapeutic alteration of the microbiome in humans has been limited to the setting of infections and inflammatory bowel disease, these studies represent an important proof of concept for the pursuit of additional studies in patients with SLE.

Genes and gene expression

One of the great advantages of pursuing genetic analyses in a highly heterogeneous disorder such as SLE is that it is otherwise difficult to understand which facets of disease represent susceptibility features, and which represent consequences of the disease.

Heritability of SLE and genetic studies

The heritability of SLE has long been recognized; a higher concordance rate in monozygotic twins than in dizygotic twins and the high sibling recurrence risk ratio support a strong heritability[29]. The major histocompatibility complex (MHC) was the first risk locus to be associated with SLE, and alleles within the MHC locus still confer the strongest genetic susceptibility for SLE in the general population today[30]. This seminal finding supports a disease process in which T cells play a central part, as their activation is dependent on MHC proteins (FIG. 2). In the past decade, numerous genome-wide

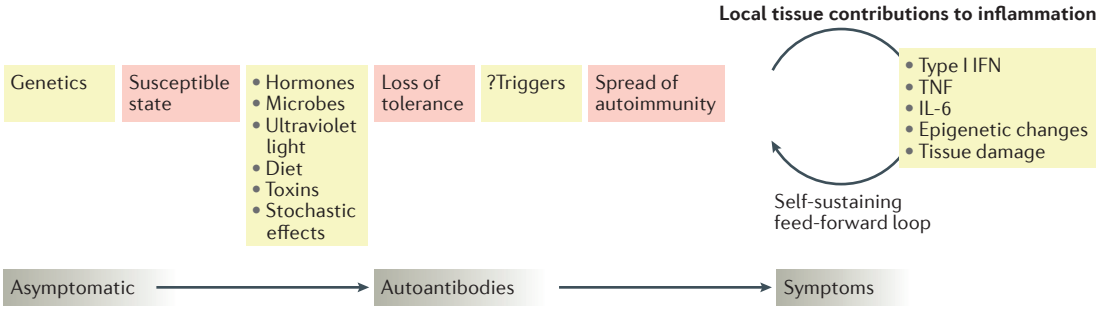

Figure 1 | **The current model of the pathogenesis of SLE.** The progression of systemic lupus erythematosus (SLE) can be divided into discrete stages. Environmental and genetic factors contribute to the development of disease. Triggers such as infection can elicit autoimmunity, but the elements that drive a sustained loss of tolerance and spreading of autoimmunity are poorly understood. Epigenetic changes, immune-complex deposition and autoantibody-mediated tissue damage can drive chronic inflammation and irreversible damage in end organs. IFN, interferon.

association studies (GWAS) have been performed and we now recognize over 40 loci that are confirmed to be associated with SLE[31]. Variants rarely lie in the coding exons, however, and most are instead thought to affect regulatory regions[32]. Regulatory risk variants may affect proximal genes or may act at a distance through chromosomal looping[33]; such variants might also have effects on multiple genes.

Genes associated with SLE are listed in TABLE 1. The overall genetic risks identified to date are limited, with each gene generally conferring a relative risk <2. The yet to be identified heritability could lie in rare variants that are individual to each kindred, or epigenetic effects. Most of the identified loci are associated with multiple autoimmune diseases[32,34]. The GWAS data have focused interest on three major cellular pathways, each influenced by many variants[35]: lymphocyte signalling, either within T cells or B cells; IFN signalling pathways involving either nucleic acid sensing or the production and response to IFNs; and clearance of immune complexes and other waste. Interestingly, a number of monogenic disorders are associated with an increased risk of developing SLE or a related phenotype (TABLE 2), and can be similarly categorized according to these same three pathophysiological pathways[36]. The key findings from these GWAS are identification of these three disease-associated pathways, variant sharing with other autoimmune diseases, and heterogeneity across populations and ethnic groups. Although GWAS have been criticized for failure to identify 'druggable' targets or major 'causative' variants, they have unquestionably moulded key concepts around the pathogenesis of SLE.

Epigenetic mechanisms in SLE

Genetics and genomics can be applied to evaluate heritable risks of disease. By contrast, epigenetics refers to the study of durable changes in gene expression that are not accompanied by alterations to the nucleotide sequence. Epigenetics is beginning to receive attention in the field of rheumatology. Epigenetic processes include DNA methylation, post-translational histone modifications, and noncoding RNAs that regulate gene expression.

DNA methylation was the first epigenetic change identified in patients with SLE. DNA methylation regulates gene expression by serving as a platform for repressive protein binding. Procainamide and other drugs known to induce lupus-like features are inhibitors of DNA methylation[37]. T cells from mice treated with these drugs are capable of inducing lupus in recipient mice[38]. These data not only clearly implicate the epigenome in SLE, but also highlight the central role of T cells. In humans, T cells from patients with active SLE have global DNA hypomethylation[39], especially those from patients with lupus nephritis[40]. The consequence of this hypomethylation is typically overexpression of genes, because DNA methylation is usually repressive. When examined on a genome-wide basis, IFN-stimulated genes (ISGs) were specifically hypomethylated in patients with SLE[40]. Further study revealed that, during a flare, naive $CD4^+$ T cells become primed for T_H2, T_H17, and T follicular helper (T_{FH}) cell immune responses through the activity of the chromatin-modifying enzyme histone–lysine *N*-methyltransferase EZH2 (REF. 41). Diet is known to influence DNA methylation, which may be one mechanism by which diet contributes to SLE susceptibility[42,43]. A further DNA modification is the formation of 5-hydroxymethylcytosine; levels of this modified form of cytosine are increased in T cells of patients with SLE and are also associated with increased gene expression[44].

Histones undergo a number of post-translational modifications that can serve as binding sites for proteins involved in regulation of gene expression. Histone modifications were initially studied in mouse models of lupus, in which treatment with histone deacetylase inhibitors improved disease features[45]. Furthermore, histone deacetylase 6 is overexpressed in MRL/lpr mice, and treatment directed at normalizing this enzyme improved the features of lupus[46,47]. The mechanisms by which these agents work is controversial, because these treatments seem to be highly immunosuppressive[48]. Nevertheless, these studies provide an important proof of principle that agents acting on epigenetic mechanisms could be useful in the treatment of human SLE. Our understanding of histone modifications in humans has been driven by two distinct approaches. In the first approach, total

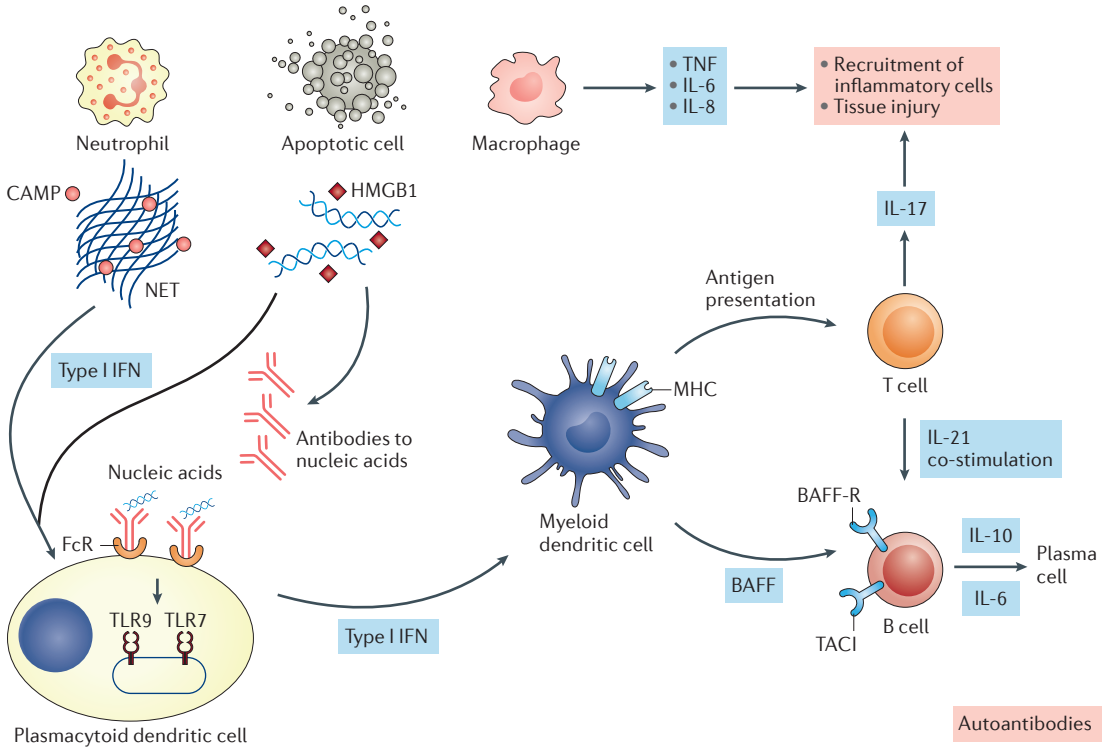

Figure 2 | **Cellular contributions to the development of SLE.** Neutrophils and apoptotic cells are at the apex of the cascade of pathogenetic mechanisms in systemic lupus erythematosus (SLE). They provide the critical ligands to drive expression of type I interferons (IFNs). Neutrophils represent a key inflammatory participant in organ damage; these cells also release neutrophil extracellular traps (NETs), a source of citrullinated peptide and nucleic acid antigens, via NETosis. Many cells produce type I IFNs, but plasmacytoid dendritic cells produce the highest levels of these cytokines. Apoptotic debris can also activate inflammatory cytokine expression which participates in the recruitment of cells into tissues. T cells and B cells both participate in autoreactivity, with B cells ultimately producing autoantibodies. T-cell production of IL-17 also contributes to organ infiltration by neutrophils. BAFF, B-cell activating factor; BAFF-R, BAFF receptor; CAMP, cathelicidin antimicrobial peptide; FcR, Fc receptor; MHC, major histocompatibility complex; TACI, transmembrane activator and cyclophilin ligand interactor; TLR, Toll-like receptor.

histone modifications were measured and shown to be aberrant in T cells from patients with SLE. These aberrations were corrected by treatment with mycophenolate mofetil[49]. The second approach utilized genome-wide analyses. In the initial analysis, histone H4 acetylation was shown to be globally increased in monocytes from patients with SLE[50]. This finding is consistent with those from DNA methylation studies[51] because both DNA hypomethylation and histone H4 hyperacetylation drive increased expression of target genes. Within the sites with increased H4 acetylation, potential binding sites for IFN regulatory factor 1 (IRF1) were identified, and IRF1 binding was directly shown to be increased in SLE[52]. IRF1 is a transcription factor downstream of type I IFN, which ties this finding of an altered epigenome back to the known influence of type I IFNs. Multiple histone modifications in enhancer regions were globally altered in SLE monocytes, which no doubt dictates altered cell behaviour[53]. Some histone modifications persist after stimulation, thereby 'bookmarking' genes for facilitated re-expression. This feature might contribute to disease chronicity[54,55]. One of the therapeutic efforts directed at the epigenome utilizes inhibitors of bromodomain-containing protein 4 (BRD4), a protein critical for enhancer function[56]. One such BRD4 inhibitor was demonstrated to be effective in a mouse model of lupus[57], again demonstrating the power of these genome-wide approaches to identify novel therapeutic targets.

MicroRNA regulation in SLE

MicroRNAs (miRNAs) target specific mRNAs for degradation and can regulate the abundance of multiple mRNAs[58]. Changes in miRNA expression have been identified in peripheral blood mononuclear cells and renal tissue from patients with SLE[59–61]. Plasma miRNAs can also be isolated and are presumed to be released from cells as a result of death, stress, or exocytosis[62]. Several of the miRNAs identified in patients with SLE seem to affect pathways that are central to the disease processes of SLE[61], such as TLR signalling and expression of ISGs[63]. Expression of miRNAs is very tissue-specific, and studies of miRNAs in kidney and peripheral blood samples from patients with SLE, have found none in either tissue[59,60]. Other data from human studies have implicated miR-30a in B cells, where this miRNA was thought to regulate expression of LYN, a critical signalling molecule[64]. In MRL/lpr mice, overexpression of miR-21 and miR-148a is responsible for the reduction in levels of

Table 1 | **GWAS-identified SLE susceptibility genes**

Pathway(s)	Loci implicated in SLE and other autoimmune diseases	Loci implicated only in SLE
Lymphocyte activation	*PTPN22*, *TNFSF4*, *IL10*, *SPRED2*, *STAT4*, *PXK*, *AFF1*, *IL12A*, *BANK1*, *TCF7*, *SKP1*, MHC genes, *IKZF1* and *IKZF3*, *BLK*, *ARID5B*, *CD44*, *LYN*, *ETS1*, *FLI1*, *SH2B3*, *CSK*, *ELF1*, *CIITA*, *ITGAM*, *TYK2*	*IKZF2*
IFN or Toll-like receptors	*IFIH1*, *PRDM1*, *UHRF1BP1*, *TNFAIP3*, *IRF5-TNPO3*, *IRF7* and *IRF8*, *SOCS1*, *PRKCB*, *UBE2L3*, *IRAK1*	None
Inflammation	*TNIP1*	None
Immune complex or waste clearance	*FCGR2A*, *FCGR2B*, *FCGR3B*, *ATG5*, *CLEC16A*	*NCF2*, *LYST*
Unknown	*ABHD6* (may be related to lymphocyte activation), *RAD51B* (may be related to IFN pathways), *MECP2* (may be related to IFN pathways), *RASGRP3*, *TMEM39A*, *PITG1*, *TNXB*, *JAZF1*, XKR6, *FAM167A–AS1*, *WDFY4*, unknown genes: rs1167796, rs463128, rs7186852, rs7197475	*SMG7* (may be related to interferon pathways), *DHCR7*, *NADSYN1*, *SLC15A4*, *PLD2*, *CXorf21*

GWAS, genome-wide association studies; IFN, interferon; MHC, major histocompatibility complex; SLE, systemic lupus erythematosus.

DNA methyltransferase 1 (DNMT1), an enzyme that creates epigenetic changes by DNA hypomethylation[65]. The influence of miRNAs was demonstrated when a transgenic mouse overexpressing miR-17-92 spontaneously developed lupus-like disease. The mechanism seemed to be diminished expression of T_{FH} cell regulators phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN and PH domain leucine-rich repeat-containing protein phosphatase 2 (REFS 66,67). Deficiency of miR-155 in MRL/lpr mice suppresses lupus, indicating that the effects of miRNAs are context-specific and site-specific, as would be expected[68]. In addition to studying the role of miRNAs in the pathogenesis of SLE, researchers are showing increasing enthusiasm for using these stable nucleic acids as biomarkers. For example, miR-21 regulates lymphocyte signalling, and levels of miR-21 in T cells correlate with SLE disease activity index (SLEDAI) scores[69]. The first miRNA-based therapeutic agent was approved in 2013 for the treatment of familial hypercholesterolaemia[70], and this field is likely to expand rapidly.

Differences in gene expression

Transcript abundance represents the final balance between active transcription and mRNA turnover, and integrates both transcript production and destruction effects. Levels of transcripts ultimately control cell activities. Early studies of gene expression were performed on peripheral blood mononuclear cells or whole blood and uniformly identified a set of ISGs[71–73]. Inflammatory and granulocyte signatures were also seen. These pivotal studies, now over ten years old, led to focused efforts on understanding the role of type I IFN and neutrophils. Gene expression has been examined in sorted cells from patients of varied ancestry[74]; ISGs could be identified in each cell population but the expression of specific genes varied dramatically between cell types, as well as between people of different ancestry[74]. This study is an important reminder that our current understanding of ethnic and population differences is disappointingly rudimentary. Array studies on human T cells have shown changes in gene expression related to disease activity and clinical presentation[75–77]. In oncology, arrays and other measures of gene expression are now routinely used to stratify patients' level of risk and direct therapy. Their use in rheumatology has been limited to research efforts, but a study utilizing advanced informatics found clear disease activity profiles[78]. Clinical use of gene expression for disease profiling could, therefore, become a reality in rheumatology clinics.

Apoptosis and nucleic acid sensors

Aberrant apoptotic cell clearance

The dysregulation of apoptosis and nuclear debris clearance that is characteristic of SLE contributes to an increase in autoantigen exposure[3]. The imbalance in apoptotic cell production and clearance is highly influenced by infection, ultraviolet light exposure, and cytokines. Accumulated apoptotic debris can trigger TLRs and nucleic acid sensors. Immune cells, including B cells, some T cells, dendritic cells (DCs), and macrophages, as well as nonimmune cells, such as epithelial cells and fibroblasts, express TLRs. Several pathways have evolved to prevent immune activation in response to endogenous cellular debris. Apoptotic cells become coated with complement component C1q, C-reactive protein, pentraxin 3, and serum amyloid P, which enhances phagocytosis without immune stimulation[79,80]. Additionally, DNase I contributes to degradation of chromatin[79]. Decreased DNase I activity has been described both in patients with SLE and in lupus-prone mice[81]. Characterization of the pathogenesis of monogenic forms of SLE has emphasized the role of aberrant apoptotic clearance. Sequencing analysis of seven consanguineous families with highly penetrant, autosomal recessive lupus-like disease identified inactivating mutations in *DNASE1L3* (REF. 82). Another family with a Mendelian pattern of SLE inheritance was found to carry loss-of-function mutations in *PRKCD*, which encodes the enzyme protein kinase Cδ[83]. This enzyme is activated in multiple apoptotic pathways. These rare monogenic diseases represent useful models of SLE because the disease process can be clearly defined. Although affected patients often have a phenotype that is not typical of classic SLE, they provide important insights.

Role of TLRs

Apoptotic cells are cleared largely by cells in the reticuloendothelial compartment. Clearance is generally silent but when the burden of apoptotic cells exceeds that which can be cleared, the apoptotic debris can elicit immune responses[84]. Mouse models have been instrumental in defining the role of TLRs in lupus; however, extrapolation of findings from these models to humans is controversial because not all features are consistent with our current understanding of SLE in humans. Nevertheless, in the analysis of specific pathways, mouse models of lupus offer great advantages. Collectively, they have provided confirmation of the importance of TLR trafficking.

Table 2 | **Monogenic causes of SLE and lupus-like disease**

Gene	Effect	Features	Pathway	Refs
C1QA, C1QB, C1QC	Complement C1 deficiency	Early-onset, severe SLE, infections; high penetrance*; AR	Immune complex and waste clearance	210,211
C1R, C1S	Complement C1 deficiency	Early-onset, severe SLE, infections; high penetrance; AR	Immune complex and waste clearance	212,213
C4A, C4B	Complement C4 deficiency	Early-onset, severe SLE, infections; high penetrance; AR	Immune complex and waste clearance	214
C2	Complement C2 deficiency	Infections, cutaneous disease; moderate penetrance; AR	Immune complex and waste clearance	215
C3	Complement C3 deficiency	Membranoproliferative glomerulonephritis; low penetrance; AR	Immune complex and waste clearance	216
CYBB	X-linked chronic granulomatous disease	Infections, chronic granulomatous disease; low penetrance; X-linked	Immune complex and waste clearance	217
PEPD	Xaa-Pro dipeptidase deficiency	Cutaneous ulcers; low penetrance; AR	Immune complex and waste clearance	218
MAN2B1	Lysosomal α-D-mannosidase (laman) deficiency	Hearing loss, dysostosis multiplex, progressive cognitive decline; low penetrance; AR	Lysosomal oligosaccharide catabolism	219
TREX1	Aicardi–Goutières syndrome 1	Basal ganglia calcification, brain atrophy, skin ulcers, fevers; high penetrance; AR or AD	Nucleic acid sensing; type I IFN	220,221
DNASE1	SLE	High penetrance; AD	Nucleic acid sensing	222
DNASE1L3	SLE 16	Early onset; high penetrance; AR	Nucleic acid sensing	82
SAMHD1	Aicardi–Goutières syndrome 5	Basal ganglia calcification, brain atrophy, skin ulcers, fevers; high penetrance; AR	Nucleic acid sensing; type I IFN	223
ACP5	Spondyloenchondrodysplasia with immune dysregulation	Spondyloenchondrodysplasia, vitiligo, growth retardation; low penetrance; AR	Nucleic acid sensing; type I IFN	224
RNASEH2A, RNASEH2B, RNASEH2C	Aicardi–Goutières syndrome 4, 2, and 3 respectively	Basal ganglia calcification, brain atrophy, skin ulcers, fevers; high penetrance; AR	Nucleic acid sensing; type I IFN	225
ADAR	Aicardi–Goutières syndrome 6	Basal ganglia calcification, brain atrophy, skin ulcers, fevers; high penetrance; AR or AD	Nucleic acid sensing; type I IFN	226
IFIH1	Aicardi–Goutières syndrome 7	Basal ganglia calcification, brain atrophy, skin ulcers, fevers; high penetrance; AD	Nucleic acid sensing; type I IFN	225
DDX58	Singleton–Merten syndrome 2	Dental loss, arterial calcification, joint contractures; high penetrance; AD	Nucleic acid sensing; type I IFN	227
TMEM173	STING-associated vasculopathy, infantile-onset	Skin ulcers, interstitial lung disease; low penetrance; AD	Nucleic acid sensing; type I IFN	228
ISG15	Immunodeficiency 38, with basal ganglia calcification	Mycobacteria, intracranial calcification; low penetrance; AR	Nucleic acid sensing; type I IFN	229
PSMB8	Nakajo syndrome	Fever, contractures, neutrophilic dermatitis; low penetrance; AR	Immune complex and waste clearance; type I IFN	230
FAS, FASLG	Autoimmune lymphoproliferative syndrome 1A and 1B, respectively	Autoimmune cytopenias, adenopathy; high penetrance; AD	Lymphocyte signalling	231–233
PRKCD	Autoimmune lymphoproliferative syndrome 3	Autoimmune cytopenias, adenopathy; moderate penetrance; AR	Lymphocyte signalling	83
PTPN11	Noonan syndrome 1	Short stature, cardiac anomalies; low penetrance; AD	Lymphocyte signalling	234
RAG1, RAG2	Several types of severe combined immune deficiency	Infections, granulomas; low penetrance; AR	Lymphocyte signalling	235,236

*Penetrance is indicted as a qualitative assessment of the percentage of people with the condition who have features of SLE.**AD, autosomal dominant;** AR, autosomal recessive; IFN, interferon; SLE, systemic lupus erythematosus.

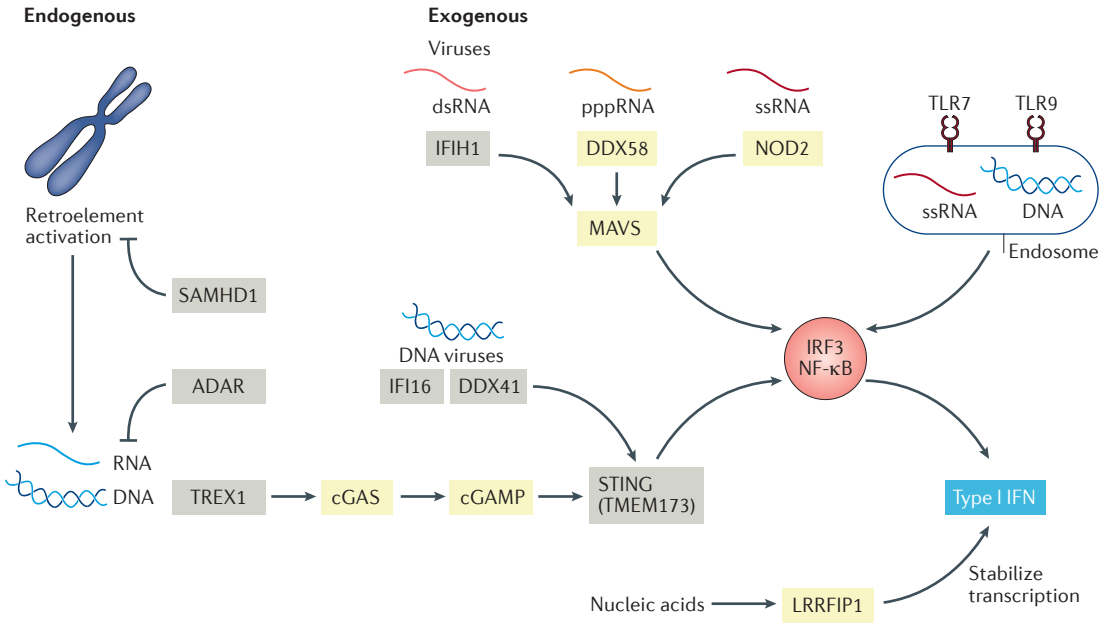

Figure 3 | **Nucleic acid sensors in SLE.** The importance of the immune response to nucleic acids in systemic lupus erythematosus (SLE) has been emphasized by data from mouse models and patients with monogenic diseases associated with defects in these pathways. Toll-like receptors (TLRs) are restricted to vesicles and primarily respond to endocytosed nucleic acids. Cytoplasmic sensors recognize endogenous nucleic acids as well as a myriad of viruses. Responses converge on two transcription factors, interferon regulatory factor 3 (IRF3) and nuclear factor-κB (NF-κB), which are responsible for the induction of type I interferon (IFN) expression as well as some inflammatory cytokines.

TLR3, TLR7, TLR8 and TLR9 reside in the endoplasmic reticulum. Transfer of TLRs to endosomes is regulated by the trafficking protein unc-93 homologue B1 (UNC93B1). The importance of intracellular trafficking cannot be overstated, as it represents a key regulatory strategy. In plasmacytoid DCs (pDCs), UNC93B1 sorts large complexes of DNA into early endosomes, where TLR9 and IRF7 drive a strong IFN response. Small monomeric DNA is sorted into late endosomes, where TLR9 and NF-κB drive a proinflammatory cytokine response[85]. Correct localization of TLRs limits their access to self-antigens[86]. In pristane-treated mice, TLR7 (which senses single-stranded RNA) was specifically required for the production of RNA-reactive autoantibodies and for the development of glomerulonephritis[87]. Data from studies of pharmacologic or genetic manipulation of TLR7 expression or function support a central role for TLR7 in inflammation, loss of tolerance, and type I IFN production[88–91].

The relationship of TLR9 to SLE is more complex than that of TLR7. TLR9 is a receptor for DNA containing unmethylated CpG sequence motifs. SLE patients with active disease had a higher number of TLR9-expressing B cells and monocytes than did patients with low disease activity, and levels of these cells correlated with levels of antibodies to double-stranded DNA (anti-dsDNA)[92]. In TLR9-deficient lupus-prone mice, the generation of anti-dsDNA and anti-chromatin autoantibodies was specifically inhibited, while levels of other autoantibodies (such as anti-Sm) were maintained or even increased[93]. However, in one lupus model, TLR9 deficiency exacerbated disease through a mechanism that might relate to competition with TLR7 for UNC93B1 (REF. 94). TLR3 and TLR8 also recognize RNA and limited data support a role for these additional receptors in susceptibility to SLE. These data have led to a model of SLE in which TLRs engage nucleic acids and drive a type I IFN response (FIG. 3).

Cytosolic nucleic acid sensors

Cytosolic nucleic acid sensors recognize viral infections and initiate defences focused on type I IFN production. These sensors can also detect endogenous ligands and elicit inflammation independent of infection. Signalling pathways for these sensors converge on stimulator of IFN genes protein (STING, encoded by *TMEM173*)[95]. Additional protection from the deleterious effects of endogenous nucleic acids comes from nucleases, which degrade nucleic acids. Three cytosolic RNA helicases have been identified: probable ATP-dependent RNA helicase DDX58, interferon-induced helicase C domain-containing protein 1 (IFIH1, also known as MDA5), and probable ATP-dependent RNA helicase DHX58 (also known as LGP2). These sensors act in the cytoplasm to complement the function of endosomal TLRs[96]. The cytosolic sensors activate both IFN and inflammatory cytokine production[96]. Variants in *IFIH1* have been linked to SLE[97]. Cytosolic DNA sensors also exist. All three main types of inflammasomes can respond to DNA; however, the process that drives these responses is not well understood (with the exception of the AIM2 inflammasome, which is activated by STING)[98]. Mouse models of lupus support a key role for this pathway in the aetiopathogenesis of SLE[99].

Here again, extraordinary insights have come from the study of rare monogenic disorders with a lupus-like phenotype in humans. Aicardi–Goutières syndrome has features that are reminiscent of a congenital infection; however, this syndrome is caused by gene defects that drive overproduction of type I IFN. Specifically, mutations in genes encoding cytosolic nucleic acid sensors or their regulators, such as *TREX1*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *ADAR*, or *IFIH1*, are all associated with this phenotype[100] (TABLE 2). The Aicardi–Goutières phenotype has a more prominent neurologic component than is typical of adult-onset SLE; however, autoantibodies are prolifically produced and some pathologic features overlap with those of SLE[100,101]. In addition, common variants in these same genes have been associated with SLE (TABLE 1).

Soluble mediators

Cytokines can contribute to susceptibility to SLE, but are more strongly implicated in loss of tolerance and end-organ effects (FIG. 1). Levels of many cytokines are elevated in SLE (such as TNF, IL-4, IL-6, and IL-10) and their main effects are the promotion of autoantibody production and inflammation (FIG. 4). Type I and type II IFNs have emerged as key cytokines in the pathogenesis of SLE (as well as other autoimmune diseases) and increases in their levels precede autoantibody development[102,103]. Upregulation of TNF can increase type I IFN expression[104,105]. IFNα, a type I IFN typically produced as part of the innate immune response to viral infection, has multiple effects consistent with known immunologic features of SLE, such as upregulation of B-cell activating factor (BAFF, also known as TNF ligand superfamily member 13B or BLyS), decreased T_{reg} cell function, and induction of plasma cells[106]. Transcripts of IFNα and ISGs have been detected in inflamed kidney and skin tissues from patients with SLE[107,108]. A direct pathogenic role for IFN in mouse models of lupus is also supported by studies in which exogenous administration of IFNα exacerbates disease[109,110]. Unfortunately, despite these compelling data, clinical trials of IFN inhibitors have been disappointing. Levels of two other cytokines, IL-18 and IL-38, are also increased in SLE. IL-18 is a potent proinflammatory cytokine produced via the inflammasome, and IL-38 is thought to be an anti-inflammatory cytokine with key regulatory functions[111,112].

Patients with SLE may also have an imbalanced T cell cytokine profile characterized by decreased IL-2 and increased IL-17 levels[113]. Production of IL-2 is impaired on multiple levels[114,115]. IL-2, in addition to being critical for T_{reg} cell development and function, is also necessary for restricting expression of IL-17. In SLE, IL-17 may mediate local tissue damage through the induction of inflammatory cytokines and chemokines, and by recruiting other immune cells. The differentiation of the T helper cell subset producing IL-17 (T_H17 cells) is dependent on IL-23, and an anti-IL-23 antibody ameliorated disease in one mouse model of lupus[116].

B-cell activation and autoantibody production are promoted in SLE by BAFF. Serum levels of BAFF are increased in patients with SLE and positively correlate with autoantibody titres[117]. Transgenic overexpression of BAFF in a mouse model of lupus exacerbated disease[118], emphasizing the role of this cytokine in supporting autoimmunity. BAFF is a critical factor for B-cell homeostasis and high BAFF levels might reduce the stringency of B-cell selection, allowing autoreactive clones to persist in the periphery[119]. Notably, B-cell-depletion therapy in patients with SLE is followed by an increase in BAFF levels, raising concern that the repopulating B cells could have a phenotype of increased autoreactivity[120]. BAFF thus represents an important therapeutic target; indeed, belimumab, an anti-BAFF monoclonal antibody, is the first drug to be approved for the treatment of SLE in more than 50 years[121]. BAFF-directed therapy has demonstrated clinical efficacy but the magnitude of the beneficial effect is modest, as has been true for B-cell-depleting approaches[122,123]. The message might be that narrowly targeted approaches in humans with established disease cannot reverse pathologic downstream processes that have

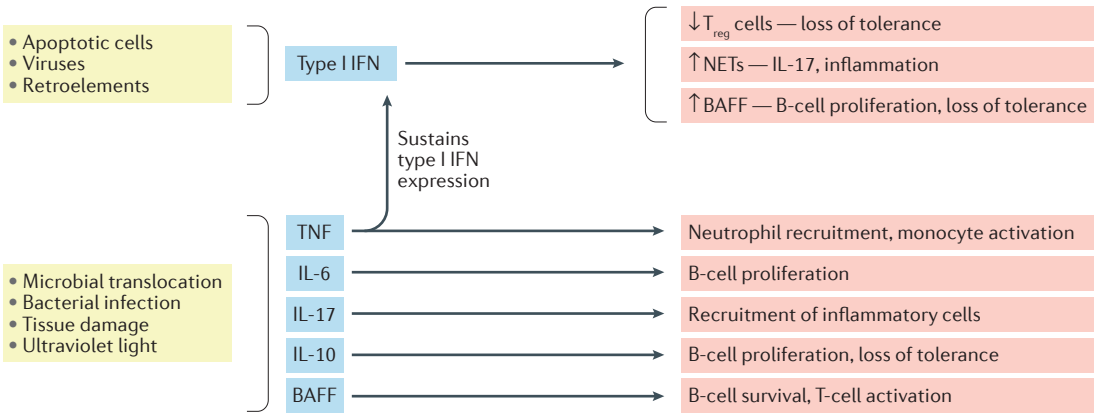

Figure 4 | **Cytokines implicated in SLE.** Various stimuli that have been epidemiologically associated with systemic lupus erythematosus (SLE) can drive cytokine expression. Collectively, the effects of this increased cytokine expression include both inflammation and loss of tolerance. BAFF, B-cell activating factor; IFN, interferon; NET, neutrophil extracellular trap; T_{reg} cell, regulatory T cell.

previously been initiated. Targeting of other cytokines is nonetheless a priority for the pharmaceutical industry because therapeutic monoclonal antibodies are an established pipeline.

Major cell types involved in SLE

Dendritic cells

Inappropriate or dysfunctional antigen presentation by DCs might promote the breakdown of T-cell and B-cell tolerance in SLE and other autoimmune diseases (FIG. 2). Patients with SLE show multiple DC abnormalities, including a reduced number of circulating conventional DCs, but increased numbers of pDCs[124]. The pDC subset is the primary cell type responsible for type I IFN secretion in response to nucleic acid, via TLR7 and TLR9. The pDCs take up immune complexes via FcγRIIa and access TLR7 and TLR9 in the endosomal compartment[125]. In SLE, conventional DCs promote autoreactivity rather than tolerance[126]. In turn, activated T cells also promote increased IFN production by pDCs[127]. Conventional DCs have been demonstrated to be critical for the development of lupus nephritis in a mouse model[128]. Thus, both types of DCs are thought to be pivotal to the disease process in SLE.

Myeloid cells

Neutrophils show several facets of dysregulation in SLE. Impaired phagocytosis by neutrophils in SLE has been described in multiple reports, and might contribute to the increased susceptibility to infection associated with this disease[129]. In one study, neutrophils from patients with SLE showed reduced production of reactive oxygen species (ROS), which correlated with disease severity and end-organ damage[130]. Patients with chronic granulomatous disease, in which ROS production is defective, have a high incidence of SLE[131,132] (TABLE 2). Increased levels of ISG products, autoantibodies, and glomerulonephritis have been described in a mouse model of chronic granulomatous disease, and lupus-prone mice deficient in ROS production also show an exacerbation of lupus-like disease[133,134]. Deficient ROS generation might alter the apoptotic pathway, which connects this finding to the recognized contribution of defective clearance of apoptotic cells to the pathogenesis of SLE. Immune complexes can drive the generation of mitochondrial ROS, and oxidized mitochondrial DNA can be highly immune-stimulatory, providing a feed-forward loop[135]. Neutrophils are short-lived and so represent the dominant cell type in the daily burden of apoptotic cells. Small changes in neutrophil apoptosis could markedly impact waste clearance. In an adoptive cell transfer model, neutrophils from mice with chronic granulomatous disease could drive autoantibody production in control (disease-free) recipient mice[136]. The converse was also true; apoptotic neutrophils from control animals were capable of driving autoantibody production when transferred to recipients with chronic granulomatous disease. This study provides direct mechanistic evidence for a central role of myeloid cells in SLE.

Patients with SLE have an abnormal subset of neutrophils (termed low-density granulocytes) with an increased propensity for NETosis[137]. NETosis is a mechanism of cell death that occurs in response to various stimuli, including infectious organisms and oxidative stress. NETosis involves the extrusion of chromatin and other nuclear, cytoplasmic, and granular material from the cell (FIG. 2). This extruded material, called neutrophil extracellular traps (NETs), contains proinflammatory cytokines, antimicrobial peptides, enzymes such as myeloperoxidase, and potentially antigenic citrullinated histones and dsDNA[138]. NETosis contributes to the type I IFN signature of SLE by stimulating IFN production by pDCs[137]. This effect occurs via TLR9 activation by DNA and anti-DNA antibodies in complex with NET-derived antimicrobial peptides such as cathelicidin antimicrobial peptide (also known as LL-37)[139,140]. In turn, type I IFN primes neutrophils for NET release in patients with SLE, suggesting a possible positive feedback loop. The extruded nuclear material from NETs represents a major source of the nuclear antigens that drive autoantibody development in SLE.

Monocytes from patients with SLE consistently have increased baseline expression of CC chemokine ligand 2 (CCL2, also known as monocyte chemoattractant protein 1 (MCP-1))[141]. MCP-1 is regulated by lipopolysaccharide and IFNs, and is important in regulation of cell migration. Monocyte infiltration into kidneys influences renal damage, and monocyte infiltration into blood vessels contributes to atherosclerosis, two key morbidities in SLE[142,143]. Renal macrophage infiltration is a particularly strong prognostic biomarker for progression of lupus nephritis[144]. Monocytes are, therefore, a pivotal cell type in organ damage. Monocyte-depletion therapy was attempted in one clinical trial, which did not demonstrate clinical effectiveness, but this approach did not deplete tissue macrophages, which are thought to be important drivers of end-organ damage in SLE[145].

T cells

T cells are thought to be central to the pathogenesis of SLE because of their association with MHC proteins, and because adoptive transfer of these cells confers lupus-like disease in some mouse models. Loss of T-cell tolerance is implied in autoimmune diseases. Conceptually, this loss of tolerance could happen centrally at the time of thymic education or peripherally; however, mouse models support the importance of defects in peripheral tolerance[146]. Deficient or defective T_{reg} cells have been identified both in mouse models and human studies[147]. GWAS have also identified defects in lymphocyte signalling that could centrally alter thymic deletion of autoreactive cells. Thus, multiple pathways exist by which T-cell tolerance could be defective in SLE. One of the first phenomena to be described was that of aberrant signalling through the T-cell receptor. This phenomenon is not cell-intrinsic, and can be induced in normal T cells by serum IgG from patients with SLE[148]. In T cells from patients with SLE, the CD3 ζ chain (which mediates signalling via tyrosine-protein kinase ZAP-70) is downregulated owing to increased mTOR activity, causing ZAP-70 to be replaced by FcRγ. FcRγ then pairs with tyrosine-protein kinase SYK rather than with ZAP-70, resulting in hyperactivation of the T-cell-receptor signalling pathway[149,150].

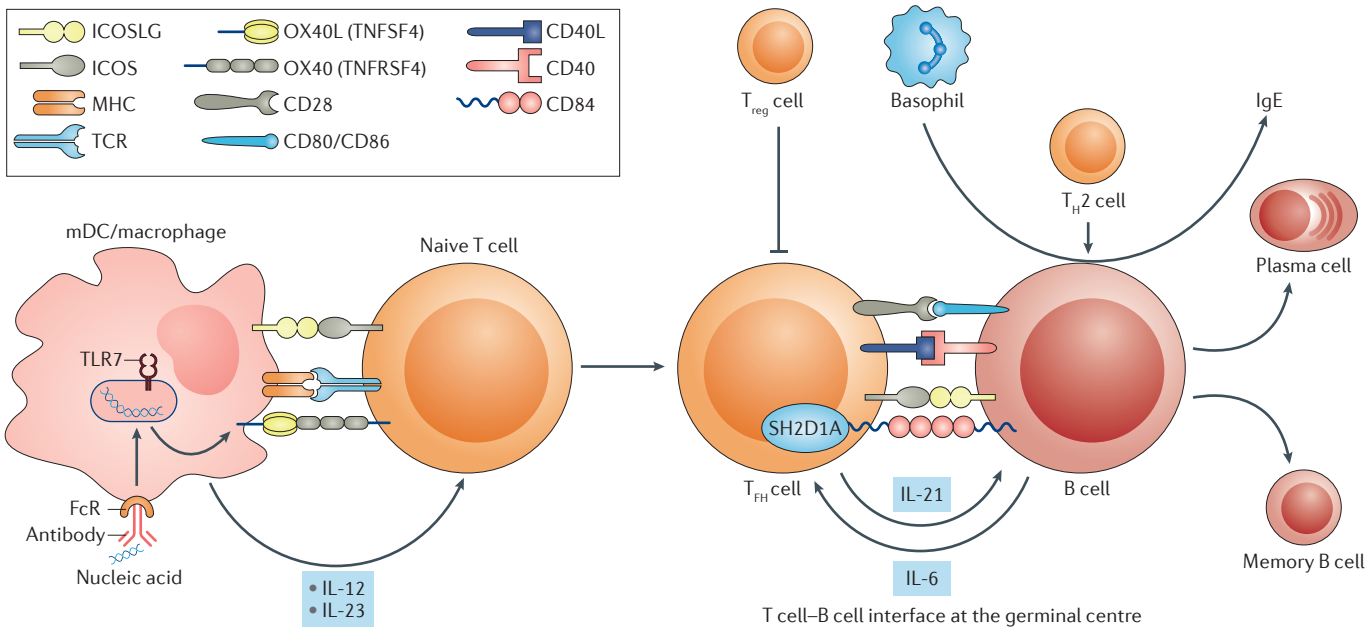

Figure 5 | **Involvement of B cells in SLE.** B cells are greatly influenced by the cytokine milieu and the type of T cell that derives from that cytokine milieu. In systemic lupus erythematosus (SLE), B cells interact with T follicular helper (T_{FH}) cells at the T cell–B cell interface in secondary lymphoid organs. The interaction revolves around engagement of cell-surface receptors and secretion of cytokines. FcR, Fc receptor; mDC, myeloid dendritic cell; MHC, major histocompatibility complex; TCR, T-cell receptor; T_H2, type 2 T helper cell; TLR, Toll-like receptor; T_{reg} cell, regulatory T cell.

Despite this hyperactivated phenotype, T-cell production of IL-2 is actually impaired. Expression of IL-2 in SLE T cells is compromised by decreased levels of the transcription factor AP-1 and suppression by cAMP-responsive element modulator (CREMα)[114,115]. Treatment with the mTOR inhibitor rapamycin *in vitro* reversed this effect, and mTOR inhibitor treatment *in vivo* has been clinically efficacious, supporting the importance of this pathway in SLE[151].

Patients with SLE also show altered T-cell subset populations. T_H17 cells are a subset of $CD4^+$ T cells found infiltrating the kidneys of patients with lupus nephritis, and in the skin lesions of patients with SLE[152]. Polarization to T_H17 involves changes to the epigenome that can be driven by microbial products[153]. Double-negative T cells ($CD4^-CD8^-$) seem to be the primary source of IL-17 in SLE[154]. Double-negative T cells are expanded in patients with SLE as well as in lupus-prone mice and are thought to contribute to loss of tolerance[155,156], as they also express IL-1β and IFNγ, and promote B-cell differentiation and antibody production.

T cells provide more than just signals for class switching. They represent a key checkpoint for autoreactive B cells in SLE. T-cell–B-cell interactions are a key focus of current SLE research because these interactions occur outside their usual locations, in secondary lymphoid organs, and are more transient than in healthy individuals, suggesting that the very essence of the interaction is pathologic[157,158]. These aberrant T-cell–B-cell interactions are also reflected in the somatic mutations seen in autoantibody gene segments[159]. Somatic mutations reflect both T cell help and germinal centre passage. T_{FH} cells specifically support B-cell differentiation by producing IL-21 and receptor engagement in the germinal centre (FIG. 5). Expansion of the T_{FH} cell subset has been described in several mouse models of lupus[160,161] and increased levels of T_{FH} cells correlate with increased disease activity and severity in patients with SLE[162–164]. T_{FH} cells can be seen within lymphoid aggregates in kidney biopsy samples from patients with active lupus nephritis, and activated T_{FH} cells correlate with autoantibody titres in these patients[165,166]. Emerging evidence suggests that the expansion of T_{FH} cells in SLE is directed by interaction with OX40 ligand (also known as TNF ligand superfamily member 4 (TNFSF4)), which is expressed on myeloid antigen-presenting cells[167]. In SLE, the expression of OX40 ligand on myeloid antigen-presenting cells is induced (via TLR7 activation) by circulating RNA-containing immune complexes[167] (FIG. 5). The pathologically expanded and activated T_{FH} cell compartment markedly affects B-cell differentiation. Enhanced antibody production and loss of tolerance are both expected in this setting.

T_{reg} cells have an important role in maintaining tolerance. Both T cells and B cells are subject to T_{reg} cell control. Normal development of T_{reg} cells (a subset of $CD4^+$ cells that inhibit and suppress autoreactive lymphocytes) is dependent on IL-2. Treatment of patients with SLE with low-dose IL-2 for 5 days caused a dramatic increase in peripheral blood $CD25^+FoxP3^+$ T_{reg} cells, although the clinical consequences of long-term IL-2 therapy have not yet been determined[168]. This study might be seen as an important proof of principle for *in vivo* T_{reg}-cell-directed therapy.

B cells and autoantibody production

Although SLE is a clinically heterogeneous disease, patients are near-universally characterized by the presence of autoantibodies, particularly those directed against nuclear antigens. Loss of tolerance and altered B-cell differentiation might be genetically determined, by variants present from birth or acquired as part of the disease process[169]. Activation of B cells through the TLR pathway promotes loss of tolerance. Mouse models have demonstrated that transitional B cells that have recently emigrated from bone marrow are susceptible to accelerated maturation by TLR9, which bypasses tolerance checkpoints[170]. Tolerance can also be broken by B-cell stimulation via cytokines; BAFF in particular has been implicated in this process. BAFF antagonism in mice clearly leads to improved self-tolerance, and conversely BAFF overexpression leads to autoimmunity[171–173]. Tolerance does not seem to be an all-or-nothing phenomenon, however. An elegant demonstration of the evolution of autoantibodies in SLE was performed using stored plasma from members of the armed forces. This study demonstrated progressive development of autoantibodies over the 5–8 years preceding onsert of the clinical manifestations of SLE[174]. Human studies have clearly implicated both environmental and genetic contributions in loss of tolerance. Early immature B cells show increased levels of polyreactivity and autoreactivity in SLE, possibly owing to a break in central B-cell tolerance that enables increased numbers of autoreactive clones to reach the periphery[175]. B-cell subsets are skewed to the more mature subsets, those poised to become antibody-secreting plasma cells[176]. In addition, IL-10-secreting B cells with regulatory capabilities show functional impairment in SLE[177,178]. These observations support the concept that B-cell development is aberrant in SLE.

B cells contribute to SLE through their responses to antigen, regulation of other cells, and autoantibody production. Autoantibodies contribute to SLE through the formation of immune complexes, direct agonist or antagonist action, and by interference with intracellular functions[179]. Immune complexes activate complement and, through binding Fc receptors, drive inflammation. A unique indirect mechanism of action occurs through binding of RNA. The 60 kDa SSA/Ro protein binds RNA, preferring Alu retroelement RNA. Anti-Ro antibodies deliver this Alu RNA to the endosomal compartment via Fc receptors, thereby activating TLRs[180]. Antibody production in patients with SLE in general seems to favour high-affinity versions, as even anti-influenza virus antibodies have higher affinity in patients with SLE than their counterparts in healthy controls do[181]. A previously unanticipated B-cell phenomenon is the production of pathologic IgE antibodies. IgE is typically associated with allergic responses, and little effort was made to characterize IgE in patients with SLE until researchers showed that half of SLE patients have IgE directed to dsDNA[182]. Levels of self-reactive IgE increase with increased disease activity in patients with SLE and the IgE immune complexes can stimulate type I IFN in pDCs[183]. High total IgE concentrations have also been described in patients with SLE[184], but even in the absence of high IgE levels, autoantibodies of the IgE isotype and dysregulated basophils have now been observed in both mouse models of lupus and patients with SLE[185]. High numbers of basophils in mouse models of lupus contribute to a T_H2 cell polarization[186]. Importantly, depletion of either IgE or basophils in mice with lupus led to diminished renal disease, supporting their mechanistic role in SLE[182,185–187] and providing support for a clinical trial of IgE-directed therapy.

Organ-specific disease features

New experiments highlight that loss of tolerance and tissue damage are two distinct processes. Autoimmunity and kidney damage in NZM2328 lupus-prone mice are controlled by variants in *Agnz1* and *Cgnz1*. Replacement of the pathologic *Cgnz1* allele with the normal allele did not affect the expression of autoimmunity, but prevented kidney failure[188]. In another example, when the *gld.apoE*$^{-/-}$ mouse (a lupus-prone mouse with profound atherosclerosis) was rendered IRF5-deficient, it was protected from autoimmunity but displayed increased numbers of atherosclerotic lesions[189]. Thus, tissue effects are regulated independently of tolerance. These local tissue effects, which are also independent of haematopoietic cell influence, are major contributors to end-organ damage in SLE. These effects have been best described for kidney, skin, and the central nervous system (CNS).

Nephritis

Among women with SLE, approximately 30–40% of those with European ancestry, and nearly 50% of those with Afro-Caribbean ancestry develop lupus nephritis, which is associated with substantial morbidity and mortality[190,191]. Central features are immune-complex deposition and cell proliferation. Anti-dsDNA antibodies crossreact with several renal cell types and are thought to be central to the nephritis process. GWAS identified a lupus-nephritis-associated variant near the gene encoding the platelet-derived growth factor (PDGF) receptor[192]. Expression of PDGF and its receptor is increased in kidney tissue from patients with SLE[193], and anti-PDGF antibodies inhibit mesangial cell proliferation in animal models[194].

HER2 (also known as ERBB2) is also overexpressed in lupus nephritis[61] and can be upregulated by IFNs and IRF1 (REF. 61). HER2 regulates miR-26a, which in turn regulates cell proliferation[195]. The HER2-miR-26a pathway may be of clinical interest because anti-HER2 agents have already been developed for breast cancer treatment. Mesangial cells are capable of producing IFNs, which may amplify local inflammatory processes[196], regulate HER2 expression, and inhibit renal progenitor cell differentiation into podocytes, which compromises healing. In turn, mesangial proliferation and podocyte function are controlled in SLE by local activity of calcium/calmodulin-dependent protein kinase type IV (CaMK IV)[197,198]. Treatment of MRL/lpr mice with a CaMK IV inhibitor decreased IFN production and ameliorated nephritis[199]. Local cytokine production is thought to amplify the cell infiltrate. In the MRL/lpr model, TNF and IFNγ are produced in glomeruli before active cellular infiltrate[200].

Thus, therapies that limit tissue damage by targeting renal parenchymal cells may also prove useful in the treatment of lupus nephritis.

Skin

Cutaneous involvement is common in SLE and skin can constitute the only organ affected. Skin lesions are seldom life-threatening, but represent an important source of morbidity in SLE. Different subsets of cutaneous lupus erythematosus (which have distinct natural histories) are classified as acute, subacute, discoid, and intermittent (lupus erythematosus tumidus). Ultraviolet light is a typical precipitant of an SLE flare as a result of keratinocyte apoptosis. Immune complexes can be seen in skin biopsies from patients with SLE (termed the 'lupus band') and this finding is in fact diagnostic of SLE.

Common autoantibodies seen in patients with cutaneous forms of SLE are anti-ribosomal P protein and anti-galectin-3. Antibodies to Ro52 (also known as TRIM21) are also found, and deficiency of Ro52 in mice induces a lupus-like skin disease[201]. Why the effects of Ro52 deficiency were localized to the skin is unclear, but Ro52 is highly expressed in inflamed skin[202], and this finding might reflect the role of Ro52 as a nucleic-acid-binding protein rather than as having a direct role in providing protection to the skin[203]. Cutaneous lesions in SLE might, therefore, reflect the presence of specific autoantibodies, but also seem to relate to the cutaneous-dominant expression of certain proteins.

CNS disease

CNS disease remains one of the most troubling and puzzling clinical features of SLE. A meta-analysis indicated that polymorphisms in genes associated with immune-complex clearance, such as *FCGR3A* and *FCGR3B* (encoding low affinity IgG Fc region receptors IIIa and IIIb (FcγRIIIa and FcγRIIIb)) and *ITGAM* (encoding integrin αM) are potential susceptibility genes for neuropsychiatric lupus[204]. Polymorphisms in *TREX1* (which encodes 3′ repair exonuclease 1, also known as DNase III), have also been associated with seizures in SLE[205].

Dysfunction of the blood–brain barrier enables immunoglobulins, cytokines, and immune cells to gain access to the brain tissue, and is a central mechanism of neuropsychiatric lupus. The complement system has a key role in disrupting the integrity of the blood–brain barrier. Treatment with a C5a receptor antagonist or a C5a antibody improved the function of the blood–brain barrier and decreased CNS inflammation in mouse models of lupus[206,207]. Complement inhibition also improved neuronal survival in these studies[206,207].

Autoantibodies, including antiphospholipid antibodies and those targeting ribosomal P peptides, the NMDA receptor, and matrix metalloproteinase-9, could participate in the pathogenesis of neuropsychiatric lupus through multiple mechanisms, including by directly causing neuronal cell death[208]. In MRL$^{lpr/lpr}$ mice, CNS disease was amplified by the cytokine TNF-related weak inducer of apoptosis (TWEAK, also known as TNF ligand superfamily member 12). Mice deficient in the TWEAK receptor had better cognition and integrity of the blood–brain barrier than their littermates[209]. These studies open the door for therapeutics for CNS disease, for which there is a critical unmet need.

Conclusions

Conventional therapy for SLE has utilized broad-based immunosuppression. Advances in our understanding of SLE pathogenesis, as described here, will enable the development of targeted therapies that may lead to individualized approaches to care. Many of the advances made over the past decade are driving interest in developing targeted therapeutics and repurposing of drugs. Cytokines, tolerance pathways, local tissue mediators, and epigenetic mechanisms show promise as novel targets in SLE.

1. Bernatsky, S. *et al.* Mortality in systemic lupus erythematosus. *Arthritis Rheum.* **54**, 2550–2557 (2006).
2. Zhu, T. Y., Tam, L. S. & Li, E. K. Cost-of-illness studies in systemic lupus erythematosus: a systematic review. *Arthritis Care Res. (Hoboken)* **63**, 751–760 (2011).
3. Casciola-Rosen, L. A., Anhalt, G. & Rosen, A. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. *J. Exp. Med.* **179**, 1317–1330 (1994).
4. Theofilopoulos, A. N., Kono, D. H., Beutler, B. & Baccala, R. Intracellular nucleic acid sensors and autoimmunity. *J. Interferon Cytokine Res.* **31**, 867–886 (2011).
5. Dieker, J. *et al.* Circulating apoptotic microparticles in systemic lupus erythematosus patients drive the activation of dendritic cell subsets and prime neutrophils for NETosis. *Arthritis Rheumatol.* **68**, 462–472 (2016).
6. Leadbetter, E. A. *et al.* Chromatin–IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature* **416**, 603–607 (2002).
7. Achtman, J. C. & Werth, V. P. Pathophysiology of cutaneous lupus erythematosus. *Arthritis Res. Ther.* **17**, 182 (2015).
8. Grimaldi, C. M. Sex and systemic lupus erythematosus: the role of the sex hormones estrogen and prolactin on the regulation of autoreactive B cells. *Curr. Opin. Rheumatol.* **18**, 456–461 (2006).
9. Shelly, S., Boaz, M. & Orbach, H. Prolactin and autoimmunity. *Autoimmun. Rev.* **11**, A465–A470 (2012).
10. Cunningham, M. & Gilkeson, G. Estrogen receptors in immunity and autoimmunity. *Clin. Rev. Allergy Immunol.* **40**, 66–73 (2011).
11. Dorgham, K. *et al.* Ultraviolet light converts propranolol, a nonselective β-blocker and potential lupus-inducing drug, into a proinflammatory AhR ligand. *Eur. J. Immunol.* **45**, 3174–3187 (2015).
12. Nelson, P., Rylance, P., Roden, D., Trela, M. & Tugnet, N. Viruses as potential pathogenic agents in systemic lupus erythematosus. *Lupus* **23**, 596–605 (2014).
13. Sawalha, A. H., Schmid, W. R., Binder, S. R., Bacino, D. K. & Harley, J. B. Association between systemic lupus erythematosus and *Helicobacter pylori* seronegativity. *J. Rheumatol.* **31**, 1546–1550 (2004).
14. Ram, M. *et al.* The putative protective role of hepatitis B virus (HBV) infection from autoimmune disorders. *Autoimmun. Rev.* **7**, 621–625 (2008).
15. Chen, M. *et al. Toxoplasma gondii* infection inhibits the development of lupus-like syndrome in autoimmune (New Zealand Black × New Zealand White) F_1 mice. *Int. Immunol.* **16**, 937–946 (2004).
16. Gan, L. *et al.* Gene expression profiles from disease discordant twins suggest shared antiviral pathways and viral exposures among multiple systemic autoimmune diseases. *PLoS ONE* **10**, e0142486 (2015).
17. Shi, L. *et al.* The SLE transcriptome exhibits evidence of chronic endotoxin exposure and has widespread dysregulation of non-coding and coding RNAs. *PLoS ONE* **9**, e93846 (2014).
18. Nockher, W. A., Wigand, R., Schoeppe, W. & Scherberich, J. E. Elevated levels of soluble CD14 in serum of patients with systemic lupus erythematosus. *Clin. Exp. Immunol.* **96**, 15–19 (1994).
19. Zhai, J. X. *et al.* PDTC attenuate LPS-induced kidney injury in systemic lupus erythematosus-prone MRL/lpr mice. *Mol. Biol. Rep.* **39**, 6763–6771 (2012).
20. Pasare, C. & Medzhitov, R. Toll-like receptors: linking innate and adaptive immunity. *Microbes Infect.* **6**, 1382–1387 (2004).
21. Gallo, P. M. *et al.* Amyloid-DNA composites of bacterial biofilms stimulate autoimmunity. *Immunity* **42**, 1171–1184 (2015).
22. Belkaid, Y. & Hand, T. W. Role of the microbiota in immunity and inflammation. *Cell* **157**, 121–141 (2014).
23. Hevia, A. *et al.* Intestinal dysbiosis associated with systemic lupus erythematosus. *mBio* **5**, e01548–e01514 (2014).
24. Johnson, B. M., Gaudreau, M. C., Al-Gadban, M. M., Gudi, R. & Vasu, C. Impact of dietary deviation on disease progression and gut microbiome composition in lupus-prone SNF_1 mice. *Clin. Exp. Immunol.* **181**, 323–337 (2015).
25. Zhang, H., Liao, X., Sparks, J. B. & Luo, X. M. Dynamics of gut microbiota in autoimmune lupus. *Appl. Environ. Microbiol.* **80**, 7551–7560 (2014).

26. Furusawa, Y. *et al.* Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* **504**, 446–450 (2013).
27. Arpaia, N. *et al.* Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* **504**, 451–455 (2013).
28. Van Praet, J. T. *et al.* Commensal microbiota influence systemic autoimmune responses. *EMBO J.* **34**, 466–474 (2015).
29. Alarcon-Segovia, D. *et al.* Familial aggregation of systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in 1,177 lupus patients from the GLADEL cohort. *Arthritis Rheum.* **52**, 1138–1147 (2005).
30. Morris, D. L. *et al.* Unraveling multiple MHC gene associations with systemic lupus erythematosus: model choice indicates a role for HLA alleles and non-HLA genes in Europeans. *Am. J. Hum. Genet.* **91**, 778–793 (2012).
31. Cui, Y., Sheng, Y. & Zhang, X. Genetic susceptibility to SLE: recent progress from GWAS. *J. Autoimmun.* **41**, 25–33 (2013).
32. Farh, K. K. *et al.* Genetic and epigenetic fine mapping of causal autoimmune disease variants. *Nature* **518**, 337–343 (2015).
33. Martin, P. *et al.* Capture Hi-C reveals novel candidate genes and complex long-range interactions with related autoimmune risk loci. *Nat. Commun.* **6**, 10069 (2015).
34. Li, Y. R. *et al.* Meta-analysis of shared genetic architecture across ten pediatric autoimmune diseases. *Nat. Med.* **21**, 1018–1027 (2015).
35. Harley, I. T., Kaufman, K. M., Langefeld, C. D., Harley, J. B. & Kelly, J. A. Genetic susceptibility to SLE: new insights from fine mapping and genome-wide association studies. *Nat. Rev. Genet.* **10**, 285–290 (2009).
36. Belot, A. & Cimaz, R. Monogenic forms of systemic lupus erythematosus: new insights into SLE pathogenesis. *Pediatr. Rheumatol. Online J.* **10**, 21 (2012).
37. Richardson, B. *et al.* Evidence for impaired T cell DNA methylation in systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum.* **33**, 1665–1673 (1990).
38. Richardson, B., Ray, D. & Yung, R. Murine models of lupus induced by hypomethylated T cells. *Methods Mol. Med.* **102**, 285–294 (2004).
39. Sawalha, A. H. *et al.* Defective T-cell ERK signaling induces interferon-regulated gene expression and overexpression of methylation-sensitive genes similar to lupus patients. *Genes Immun.* **9**, 368–378 (2008).
40. Coit, P. *et al.* Renal involvement in lupus is characterized by unique DNA methylation changes in naive CD4$^+$ T cells. *J. Autoimmun.* **61**, 29–35 (2015).
41. Coit, P. *et al.* Epigenetic reprogramming in naive CD4$^+$ T cells favoring T cell activation and non-T_H1 effector T cell immune response as an early event in lupus flares. *Arthritis Rheumatol.* **68**, 2200–2209 (2016).
42. Lim, U. & Song, M. A. Dietary and lifestyle factors of DNA methylation. *Methods Mol. Biol.* **863**, 359–376 (2012).
43. Cooney, C. A., Dave, A. A. & Wolff, G. L. Maternal methyl supplements in mice affect epigenetic variation and DNA methylation of offspring. *J. Nutr.* **132**, 2393S–2400S (2002).
44. Zhao, M. *et al.* Increased 5-hydroxymethylcytosine in CD4$^+$ T cells in systemic lupus erythematosus. *J. Autoimmun.* **69**, 64–73 (2016).
45. Mishra, N., Reilly, C. M., Brown, D. R., Ruiz, P. & Gilkeson, G. S. Histone deacetylase inhibitors modulate renal disease in the MRL-lpr/lpr mouse. *J. Clin. Invest.* **111**, 539–552 (2003).
46. Regna, N. L. *et al.* HDAC expression and activity is upregulated in diseased lupus-prone mice. *Int. Immunopharmacol.* **29**, 494–503 (2015).
47. Regna, N. L. *et al.* Specific HDAC6 inhibition by ACY-738 reduces SLE pathogenesis in NZB/W mice. *Clin. Immunol.* **162**, 58–73 (2016).
48. Skov, S. *et al.* Histone deacetylase inhibitors: a new class of immunosuppressors targeting a novel signal pathway essential for CD154 expression. *Blood* **101**, 1430–1438 (2003).
49. Yang, Y. *et al.* The effect of mycophenolic acid on epigenetic modifications in lupus CD4$^+$ T cells. *Clin. Immunol.* **158**, 67–76 (2015).
50. Zhang, Z., Song, L., Maurer, K., Petri, M. A. & Sullivan, K. E. Global H4 acetylation analysis by ChIP-chip in systemic lupus erythematosus monocytes. *Genes Immun.* **11**, 124–133 (2010).
51. Coit, P. *et al.* Genome-wide DNA methylation study suggests epigenetic accessibility and transcriptional poising of interferon-regulated genes in naive CD4$^+$ T cells from lupus patients. *J. Autoimmun.* **43**, 78–84 (2013).
52. Zhang, Z. *et al.* Interferon regulatory factor 1 marks activated genes and can induce target gene expression in systemic lupus erythematosus. *Arthritis Rheumatol.* **67**, 785–796 (2015).
53. Shi, L. *et al.* Monocyte enhancers are highly altered in systemic lupus erythematosus. *Epigenomics* **7**, 921–935 (2015).
54. Zhang, Z., Song, L., Maurer, K., Bagashev, A. & Sullivan, K. E. Monocyte polarization: the relationship of genome-wide changes in H4 acetylation with polarization. *Genes Immun.* **12**, 445–456 (2011).
55. Zhang, Z., Maurer, K., Perin, J. C., Song, L. & Sullivan, K. E. Cytokine-induced monocyte characteristics in SLE. *J. Biomed. Biotechnol.* **2010**, 507475 (2010).
56. Kanno, T. *et al.* BRD4 assists elongation of both coding and enhancer RNAs by interacting with acetylated histones. *Nat. Struct. Mol. Biol.* **21**, 1047–1057 (2014).
57. Wei, S., Sun, Y. & Sha, H. Therapeutic targeting of BET protein BRD4 delays murine lupus. *Int. Immunopharmacol.* **29**, 314–319 (2015).
58. Wu, L. & Belasco, J. G. Let me count the ways: mechanisms of gene regulation by miRNAs and siRNAs. *Mol. Cell* **29**, 1–7 (2008).
59. Dai, Y. *et al.* Microarray analysis of microRNA expression in peripheral blood cells of systemic lupus erythematosus patients. *Lupus* **16**, 939–946 (2007).
60. Dai, Y. *et al.* Comprehensive analysis of microRNA expression patterns in renal biopsies of lupus nephritis patients. *Rheumatol. Int.* **29**, 749–754 (2009).
61. Costa-Reis, P. *et al.* The role of microRNAs and human epidermal growth factor receptor 2 in proliferative lupus nephritis. *Arthritis Rheumatol.* **67**, 2415–2426 (2015).
62. Carlsen, A. L. *et al.* Circulating microRNA expression profiles associated with systemic lupus erythematosus. *Arthritis Rheum.* **65**, 1324–1334 (2013).
63. Yan, S., Yim, L. Y., Lu, L., Lau, C. S. & Chan, V. S. MicroRNA regulation in systemic lupus erythematosus pathogenesis. *Immune Netw.* **14**, 138–148 (2014).
64. Liu, Y. *et al.* MicroRNA-30a promotes B cell hyperactivity in patients with systemic lupus erythematosus by direct interaction with Lyn. *Arthritis Rheum.* **65**, 1603–1611 (2013).
65. Pan, W. *et al.* MicroRNA-21 and microRNA-148a contribute to DNA hypomethylation in lupus CD4$^+$ T cells by directly and indirectly targeting DNA methyltransferase 1. *J. Immunol.* **184**, 6773–6781 (2010).
66. Xiao, C. *et al.* Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes. *Nat. Immunol.* **9**, 405–414 (2008).
67. Kang, S. G. *et al.* MicroRNAs of the miR-17 approximately 92 family are critical regulators of T_{FH} differentiation. *Nat. Immunol.* **14**, 849–857 (2013).
68. Thai, T. H. *et al.* Deletion of microRNA-155 reduces autoantibody responses and alleviates lupus-like disease in the *Fas^{lpr}* mouse. *Proc. Natl Acad. Sci. USA* **110**, 20194–20199 (2013).
69. Stagakis, E. *et al.* Identification of novel microRNA signatures linked to human lupus disease activity and pathogenesis: miR-21 regulates aberrant T cell responses through regulation of *PDCD4* expression. *Ann. Rheum. Dis.* **70**, 1496–1506 (2011).
70. Hennessy, E. J. & Moore, K. J. Using microRNA as an alternative treatment for hyperlipidemia and cardiovascular disease: cardio-miRs in the pipeline. *J. Cardiovasc. Pharmacol.* **62**, 247–254 (2013).
71. Bennett, L. *et al.* Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J. Exp. Med.* **197**, 711–723 (2003).
72. Baechler, E. C. *et al.* Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc. Natl Acad. Sci. USA* **100**, 2610–2615 (2003).
73. Kirou, K. A. *et al.* Coordinate overexpression of interferon-α-induced genes in systemic lupus erythematosus. *Arthritis Rheum.* **50**, 3958–3967 (2004).
74. Sharma, S. *et al.* Widely divergent transcriptional patterns between SLE patients of different ancestral backgrounds in sorted immune cell populations. *J. Autoimmun.* **60**, 51–58 (2015).
75. Juang, Y. T. *et al.* A systemic lupus erythematosus gene expression array in disease diagnosis and classification: a preliminary report. *Lupus* **20**, 243–249 (2011).
76. Grammatikos, A. P. *et al.* A T cell gene expression panel for the diagnosis and monitoring of disease activity in patients with systemic lupus erythematosus. *Clin. Immunol.* **150**, 192–200 (2014).
77. Bradley, S. J., Suarez-Fueyo, A., Moss, D. R., Kyttaris, V. C. & Tsokos, G. C. T cell transcriptomes describe patient subtypes in systemic lupus erythematosus. *PLoS ONE* **10**, e0141171 (2015).
78. Banchereau, R. *et al.* Personalized immunomonitoring uncovers molecular networks that stratify lupus patients. *Cell* **165**, 551–565 (2016).
79. Gaipl, U. S. *et al.* Cooperation between C1q and DNase I in the clearance of necrotic cell-derived chromatin. *Arthritis Rheum.* **50**, 640–649 (2004).
80. Janko, C. *et al.* CRP/anti-CRP antibodies assembly on the surfaces of cell remnants switches their phagocytic clearance toward inflammation. *Front. Immunol.* **2**, 70 (2011).
81. Wilber, A., O'Connor, T. P., Lu, M. L., Karimi, A. & Schneider, M. C. Dnase1l3 deficiency in lupus-prone MRL and NZB/W F_1 mice. *Clin. Exp. Immunol.* **134**, 46–52 (2003).
82. Al-Mayouf, S. M. *et al.* Loss-of-function variant in *DNASE1L3* causes a familial form of systemic lupus erythematosus. *Nat. Genet.* **43**, 1186–1188 (2011).
83. Belot, A. *et al.* Protein kinase Cδ deficiency causes Mendelian systemic lupus erythematosus with B cell-defective apoptosis and hyperproliferation. *Arthritis Rheum.* **65**, 2161–2171 (2013).
84. Dieker, J. *et al.* Enhanced activation of dendritic cells by autologous apoptotic microvesicles in MRL/lpr mice. *Arthritis Res. Ther.* **17**, 103 (2015).
85. Honda, K. *et al.* Spatiotemporal regulation of MyD88–IRF-7 signalling for robust type-I interferon induction. *Nature* **434**, 1035–1040 (2005).
86. Barton, G. M., Kagan, J. C. & Medzhitov, R. Intracellular localization of Toll-like receptor 9 prevents recognition of self DNA but facilitates access to viral DNA. *Nat. Immunol.* **7**, 49–56 (2006).
87. Savarese, E. *et al.* Requirement of Toll-like receptor 7 for pristane-induced production of autoantibodies and development of murine lupus nephritis. *Arthritis Rheum.* **58**, 1107–1115 (2008).
88. Pawar, R. D. *et al.* Inhibition of Toll-like receptor-7 (TLR-7) or TLR-7 plus TLR-9 attenuates glomerulonephritis and lung injury in experimental lupus. *J. Am. Soc. Nephrol.* **18**, 1721–1731 (2007).
89. Pawar, R. D. *et al.* Toll-like receptor-7 modulates immune complex glomerulonephritis. *J. Am. Soc. Nephrol.* **17**, 141–149 (2006).
90. Subramanian, S. *et al.* A TLR7 translocation accelerates systemic autoimmunity in murine lupus. *Proc. Natl Acad. Sci. USA* **103**, 9970–9975 (2006).
91. Ramirez-Ortiz, Z. G. *et al.* The receptor TREML4 amplifies TLR7-mediated signaling during antiviral responses and autoimmunity. *Nat. Immunol.* **16**, 495–504 (2015).
92. Papadimitraki, E. D. *et al.* Expansion of Toll-like receptor 9-expressing B cells in active systemic lupus erythematosus: implications for the induction and maintenance of the autoimmune process. *Arthritis Rheum.* **54**, 3601–3611 (2006).
93. Christensen, S. R. *et al.* Toll-like receptor 9 controls anti-DNA autoantibody production in murine lupus. *J. Exp. Med.* **202**, 321–331 (2005).
94. Fukui, R. *et al.* Unc93B1 restricts systemic lethal inflammation by orchestrating Toll-like receptor 7 and 9 trafficking. *Immunity* **35**, 69–81 (2011).
95. Ishikawa, H. & Barber, G. N. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. *Nature* **455**, 674–678 (2008).
96. Schlee, M. & Hartmann, G. Discriminating self from non-self in nucleic acid sensing. *Nat. Rev. Immunol.* **16**, 566–580 (2016).
97. Molineros, J. E. *et al.* Admixture mapping in lupus identifies multiple functional variants within *IFIH1* associated with apoptosis, inflammation, and autoantibody production. *PLoS Genet.* **9**, e1003222 (2013).
98. Hornung, V. *et al.* AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. *Nature* **458**, 514–518 (2009).
99. Choubey, D. Interferon-inducible Ifi200-family genes as modifiers of lupus susceptibility. *Immunol. Lett.* **147**, 10–17 (2012).
100. Crow, Y. J. & Manel, N. Aicardi–Goutières syndrome and the type I interferonopathies. *Nat. Rev. Immunol.* **15**, 429–440 (2015).

101. Cuadrado, E. *et al.* Aicardi–Goutières syndrome harbours abundant systemic and brain-reactive autoantibodies. *Ann. Rheum. Dis.* **74**, 1931–1939 (2015).
102. Munroe, M. E. *et al.* Altered type II interferon precedes autoantibody accrual and elevated type I interferon activity prior to systemic lupus erythematosus classification. *Ann. Rheum. Dis.* **75**, 2014–2021 (2016).
103. Lu, R. *et al.* Dysregulation of innate and adaptive serum mediators precedes systemic lupus erythematosus classification and improves prognostic accuracy of autoantibodies. *J. Autoimmun.* **74**, 182–193 (2016).
104. Weckerle, C. E. *et al.* Large-scale analysis of tumor necrosis factor α levels in systemic lupus erythematosus. *Arthritis Rheum.* **64**, 2947–2952 (2012).
105. Yarilina, A., Park-Min, K. H., Antoniv, T., Hu, X. & Ivashkiv, L. B. TNF activates an IRF1-dependent autocrine loop leading to sustained expression of chemokines and STAT1-dependent type I interferon-response genes. *Nat. Immunol.* **9**, 378–387 (2008).
106. Liu, Z. & Davidson, A. IFNα inducible models of murine SLE. *Front. Immunol.* **4**, 306 (2013).
107. Castellano, G. *et al.* Local synthesis of interferon-α in lupus nephritis is associated with type I interferons signature and LMP7 induction in renal tubular epithelial cells. *Arthritis Res. Ther.* **17**, 72 (2015).
108. Farkas, L., Beiske, K., Lund-Johansen, F., Brandtzaeg, P. & Jahnsen, F. L. Plasmacytoid dendritic cells (natural interferon-α/β-producing cells) accumulate in cutaneous lupus erythematosus lesions. *Am. J. Pathol.* **159**, 237–243 (2001).
109. Fairhurst, A. M. *et al.* Systemic IFN-α drives kidney nephritis in B6.*Sle1 23* mice. *Eur. J. Immunol.* **38**, 1948–1960 (2008).
110. Liu, Z. *et al.* Interferon-α accelerates murine systemic lupus erythematosus in a T cell-dependent manner. *Arthritis Rheum.* **63**, 219–229 (2011).
111. Rudloff, I. *et al.* Brief report: interleukin-38 exerts antiinflammatory functions and is associated with disease activity in systemic lupus erythematosus. *Arthritis Rheumatol.* **67**, 3219–3225 (2015).
112. Wang, D., Drenker, M., Eiz-Vesper, B., Werfel, T. & Wittmann, M. Evidence for a pathogenetic role of interleukin-18 in cutaneous lupus erythematosus. *Arthritis Rheum.* **58**, 3205–3215 (2008).
113. Talaat, R. M., Mohamed, S. F., Bassyouni, I. H. & Raouf, A. A. $T_H1/T_H2/T_H17/T_{Reg}$ cytokine imbalance in systemic lupus erythematosus (SLE) patients: correlation with disease activity. *Cytokine* **72**, 146–153 (2015).
114. Kyttaris, V. C., Juang, Y. T., Tenbrock, K., Weinstein, A. & Tsokos, G. C. Cyclic adenosine 5′-monophosphate response element modulator is responsible for the decreased expression of c-*fos* and activator protein-1 binding in T cells from patients with systemic lupus erythematosus. *J. Immunol.* **173**, 3557–3563 (2004).
115. Solomou, E. E., Juang, Y. T., Gourley, M. F., Kammer, G. M. & Tsokos, G. C. Molecular basis of deficient IL-2 production in T cells from patients with systemic lupus erythematosus. *J. Immunol.* **166**, 4216–4222 (2001).
116. Kyttaris, V. C., Kampagianni, O. & Tsokos, G. C. Treatment with anti-interleukin 23 antibody ameliorates disease in lupus-prone mice. *Biomed. Res. Int.* **2013**, 861028 (2013).
117. Pers, J. O. *et al.* BAFF overexpression is associated with autoantibody production in autoimmune diseases. *Ann. NY Acad. Sci.* **1050**, 34–39 (2005).
118. Stohl, W. *et al.* BAFF overexpression and accelerated glomerular disease in mice with an incomplete genetic predisposition to systemic lupus erythematosus. *Arthritis Rheum.* **52**, 2080–2091 (2005).
119. Liu, Z. & Davidson, A. BAFF and selection of autoreactive B cells. *Trends Immunol.* **32**, 388–394 (2011).
120. Carter, L. M., Isenberg, D. A. & Ehrenstein, M. R. Elevated serum BAFF levels are associated with rising anti-double-stranded DNA antibody levels and disease flare following B cell depletion therapy in systemic lupus erythematosus. *Arthritis Rheum.* **65**, 2672–2679 (2013).
121. Ledford, H. After half-century's wait, approval paves path for new lupus drugs. *Nat. Med.* **17**, 400 (2011).
122. Furie, R. *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.* **63**, 3918–3930 (2011).
123. Navarra, S. V. *et al.* Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* **377**, 721–731 (2011).
124. Jin, O. *et al.* Systemic lupus erythematosus patients have increased number of circulating plasmacytoid dendritic cells, but decreased myeloid dendritic cells with deficient CD83 expression. *Lupus* **17**, 654–662 (2008).
125. Batteux, F., Palmer, P., Daeron, M., Weill, B. & Lebon, P. FcγRII (CD32)-dependent induction of interferon-α by serum from patients with lupus erythematosus. *Eur. Cytokine Netw.* **10**, 509–514 (1999).
126. Mozaffarian, N., Wiedeman, A. E. & Stevens, A. M. Active systemic lupus erythematosus is associated with failure of antigen-presenting cells to express programmed death ligand-1. *Rheumatology (Oxford)* **47**, 1335–1341 (2008).
127. Leonard, D. *et al.* Activated T cells enhance interferon-α production by plasmacytoid dendritic cells stimulated with RNA-containing immune complexes. *Ann. Rheum. Dis.* **75**, 1728–1734 (2015).
128. Celhar, T. *et al.* RNA sensing by conventional dendritic cells is central to the development of lupus nephritis. *Proc. Natl Acad. Sci. USA* **112**, E6195–E6204 (2015).
129. Wu, S. A. *et al.* Impaired phagocytosis and susceptibility to infection in pediatric-onset systemic lupus erythematosus. *Lupus* **22**, 279–288 (2013).
130. Bengtsson, A. A. *et al.* Low production of reactive oxygen species in granulocytes is associated with organ damage in systemic lupus erythematosus. *Arthritis Res. Ther.* **16**, R120 (2014).
131. De Ravin, S. S. *et al.* Chronic granulomatous disease as a risk factor for autoimmune disease. *J. Allergy Clin. Immunol.* **122**, 1097–1103 (2008).
132. Magnani, A. *et al.* Inflammatory manifestations in a single-center cohort of patients with chronic granulomatous disease. *J. Allergy Clin. Immunol.* **134**, 655–662 (2014).
133. Campbell, A. M., Kashgarian, M. & Shlomchik, M. J. NADPH oxidase inhibits the pathogenesis of systemic lupus erythematosus. *Sci. Transl Med.* **4**, 157ra141 (2012).
134. Kelkka, T. *et al.* Reactive oxygen species deficiency induces autoimmunity with type 1 interferon signature. *Antioxid. Redox Signal.* **21**, 2231–2245 (2014).
135. Lood, C. *et al.* Neutrophil extracellular traps enriched in oxidized mitochondrial DNA are interferogenic and contribute to lupus-like disease. *Nat. Med.* **22**, 146–153 (2016).
136. Sanford, A. N., Suriano, A. R., Herche, D., Dietzmann, K. & Sullivan, K. E. Abnormal apoptosis in chronic granulomatous disease and autoantibody production characteristic of lupus. *Rheumatology (Oxford)* **45**, 178–181 (2006).
137. Villanueva, E. *et al.* Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus. *J. Immunol.* **187**, 538–552 (2011).
138. Smith, C. K. & Kaplan, M. J. The role of neutrophils in the pathogenesis of systemic lupus erythematosus. *Curr. Opin. Rheumatol.* **27**, 448–453 (2015).
139. Garcia-Romo, G. S. *et al.* Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Sci. Transl Med.* **3**, 73ra20 (2011).
140. Lande, R. *et al.* Neutrophils activate plasmacytoid dendritic cells by releasing self-DNA-peptide complexes in systemic lupus erythematosus. *Sci. Transl Med.* **3**, 73ra19 (2011).
141. O'Gorman, W. E. *et al.* Single-cell systems-level analysis of human Toll-like receptor activation defines a chemokine signature in patients with systemic lupus erythematosus. *J. Allergy Clin. Immunol.* **136**, 1326–1336 (2015).
142. Hill, G. S. *et al.* Predictive power of the second renal biopsy in lupus nephritis: significance of macrophages. *Kidney Int.* **59**, 304–316 (2001).
143. Asanuma, Y. *et al.* Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N. Engl. J. Med.* **349**, 2407–2415 (2003).
144. Li, J., Liu, C. H., Xu, D. L. & Gao, B. Significance of CD163-positive macrophages in proliferative glomerulonephritis. *Am. J. Med. Sci.* **350**, 387–392 (2015).
145. Masek-Hammerman, K. *et al.* Monoclonal antibody against macrophage colony-stimulating factor suppresses circulating monocytes and tissue macrophage function but does not alter cell infiltration/activation in cutaneous lesions or clinical outcomes in patients with cutaneous lupus erythematosus. *Clin. Exp. Immunol.* **183**, 258–270 (2016).
146. Chen, Y., Cuda, C. & Morel, L. Genetic determination of T cell help in loss of tolerance to nuclear antigens. *J. Immunol.* **174**, 7692–7702 (2005).
147. Chavele, K. M. & Ehrenstein, M. R. Regulatory T-cells in systemic lupus erythematosus and rheumatoid arthritis. *FEBS Lett.* **585**, 3603–3610 (2011).
148. Juang, Y. T. *et al.* Systemic lupus erythematosus serum IgG increases CREM binding to the *IL-2* promoter and suppresses IL-2 production through CaMKIV. *J. Clin. Invest.* **115**, 996–1005 (2005).
149. Enyedy, E. J. *et al.* Fc ε receptor type I γ chain replaces the deficient T cell receptor ζ chain in T cells of patients with systemic lupus erythematosus. *Arthritis Rheum.* **44**, 1114–1121 (2001).
150. Liossis, S. N., Ding, X. Z., Dennis, G. J. & Tsokos, G. C. Altered pattern of TCR/CD3-mediated protein-tyrosyl phosphorylation in T cells from patients with systemic lupus erythematosus. Deficient expression of the T cell receptor ζ chain. *J. Clin. Invest.* **101**, 1448–1457 (1998).
151. Fernandez, D. R. *et al.* Activation of mammalian target of rapamycin controls the loss of TCRζ in lupus T cells through HRES-1/Rab4-regulated lysosomal degradation. *J. Immunol.* **182**, 2063–2073 (2009).
152. Crispin, J. C. *et al.* Expanded double negative T cells in patients with systemic lupus erythematosus produce IL-17 and infiltrate the kidneys. *J. Immunol.* **181**, 8761–8766 (2008).
153. Liu, Y. *et al.* Increased expression of TLR2 in $CD4^+$ T cells from SLE patients enhances immune reactivity and promotes IL-17 expression through histone modifications. *Eur. J. Immunol.* **45**, 2683–2693 (2015).
154. Apostolidis, S. A., Crispin, J. C. & Tsokos, G. C. IL-17-producing T cells in lupus nephritis. *Lupus* **20**, 120–124 (2011).
155. Crispin, J. C. & Tsokos, G. C. Human TCR-$\alpha\beta^+$ $CD4^-$ $CD8^-$ T cells can derive from $CD8^+$ T cells and display an inflammatory effector phenotype. *J. Immunol.* **183**, 4675–4681 (2009).
156. Shivakumar, S., Tsokos, G. C. & Datta, S. K. T cell receptor α/β expressing double-negative ($CD4^-/CD8^-$) and $CD4^+$ T helper cells in humans augment the production of pathogenic anti-DNA autoantibodies associated with lupus nephritis. *J. Immunol.* **143**, 103–112 (1989).
157. Mandik-Nayak, L. *et al.* $MRL^{-lpr/lpr}$ mice exhibit a defect in maintaining developmental arrest and follicular exclusion of anti-double-stranded DNA B cells. *J. Exp. Med.* **189**, 1799–1814 (1999).
158. Sinai, P. *et al.* T/B-cell interactions are more transient in response to weak stimuli in SLE-prone mice. *Eur. J. Immunol.* **44**, 3522–3531 (2014).
159. Mietzner, B. *et al.* Autoreactive IgG memory antibodies in patients with systemic lupus erythematosus arise from nonreactive and polyreactive precursors. *Proc. Natl Acad. Sci. USA* **105**, 9727–9732 (2008).
160. Keszei, M. *et al.* Expansion of an osteopontin-expressing T follicular helper cell subset correlates with autoimmunity in *B6.Sle1b* mice and is suppressed by the H1-isoform of the Slamf6 receptor. *FASEB J.* **27**, 3123–3131 (2013).
161. Yang, X. *et al.* T follicular helper cells mediate expansion of regulatory B cells via IL-21 in lupus-prone MRL/lpr mice. *PLoS ONE* **8**, e62855 (2013).
162. Choi, J. Y. *et al.* Circulating follicular helper-like T cells in systemic lupus erythematosus: association with disease activity. *Arthritis Rheumatol.* **67**, 988–999 (2015).
163. Szabo, K., Papp, G., Szanto, A., Tarr, T. & Zeher, M. A comprehensive investigation on the distribution of circulating follicular T helper cells and B cell subsets in primary Sjögren's syndrome and systemic lupus erythematosus. *Clin. Exp. Immunol.* (2015).
164. Le Coz, C. *et al.* Circulating T_{FH} subset distribution is strongly affected in lupus patients with an active disease. *PLoS ONE* **8**, e75319 (2013).
165. Liarski, V. M. *et al.* Cell distance mapping identifies functional T follicular helper cells in inflamed human renal tissue. *Sci. Transl Med.* **6**, 230ra46 (2014).
166. Simpson, N. *et al.* Expansion of circulating T cells resembling follicular helper T cells is a fixed phenotype that identifies a subset of severe systemic lupus erythematosus. *Arthritis Rheum.* **62**, 234–244 (2010).

167. Jacquemin, C. *et al.* OX40 ligand contributes to human lupus pathogenesis by promoting T follicular helper response. *Immunity* **42**, 1159–1170 (2015).
168. von Spee-Mayer, C. *et al.* Low-dose interleukin-2 selectively corrects regulatory T cell defects in patients with systemic lupus erythematosus. *Ann. Rheum. Dis.* (2015).
169. Dörner, T., Jacobi, A. M., Lee, J. & Lipsky, P. E. Abnormalities of B cell subsets in patients with systemic lupus erythematosus. *J. Immunol. Methods* **363**, 187–197 (2011).
170. Guerrier, T., Youinou, P., Pers, J. O. & Jamin, C. TLR9 drives the development of transitional B cells towards the marginal zone pathway and promotes autoimmunity. *J. Autoimmun.* **39**, 173–179 (2012).
171. Thien, M. *et al.* Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. *Immunity* **20**, 785–798 (2004).
172. Lesley, R. *et al.* Reduced competitiveness of autoantigen-engaged B cells due to increased dependence on BAFF. *Immunity* **20**, 441–453 (2004).
173. Mackay, F. *et al.* Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. *J. Exp. Med.* **190**, 1697–1710 (1999).
174. Arbuckle, M. R. *et al.* Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N. Engl. J. Med.* **349**, 1526–1533 (2003).
175. Wardemann, H. *et al.* Predominant autoantibody production by early human B cell precursors. *Science* **301**, 1374–1377 (2003).
176. Odendahl, M. *et al.* Disturbed peripheral B lymphocyte homeostasis in systemic lupus erythematosus. *J. Immunol.* **165**, 5970–5979 (2000).
177. Gao, N. *et al.* Impaired suppressive capacity of activation-induced regulatory B cells in systemic lupus erythematosus. *Arthritis Rheumatol.* **66**, 2849–2861 (2014).
178. Pillai, S., Mattoo, H. & Cariappa, A. B cells and autoimmunity. *Curr. Opin. Immunol.* **23**, 721–731 (2011).
179. Koscec, M. *et al.* Autoantibodies to ribosomal P proteins penetrate into live hepatocytes and cause cellular dysfunction in culture. *J. Immunol.* **159**, 2033–2041 (1997).
180. Hung, T. *et al.* The Ro60 autoantigen binds endogenous retroelements and regulates inflammatory gene expression. *Science* **350**, 455–459 (2015).
181. Kaur, K. *et al.* High affinity antibodies against influenza characterize the plasmablast response in SLE patients after vaccination. *PLoS ONE* **10**, e0125618 (2015).
182. Dema, B. *et al.* Autoreactive IgE is prevalent in systemic lupus erythematosus and is associated with increased disease activity and nephritis. *PLoS ONE* **9**, e90424 (2014).
183. Henault, J. *et al.* Self-reactive IgE exacerbates interferon responses associated with autoimmunity. *Nat. Immunol.* **17**, 196–203 (2016).
184. Liphaus, B. L., Jesus, A. A., Silva, C. A., Coutinho, A. & Carneiro-Sampaio, M. Increased IgE serum levels are unrelated to allergic and parasitic diseases in patients with juvenile systemic lupus erythematosus. *Clinics (São Paulo)* **67**, 1275–1280 (2012).
185. Charles, N., Hardwick, D., Daugas, E., Illei, G. G. & Rivera, J. Basophils and the T helper 2 environment can promote the development of lupus nephritis. *Nat. Med.* **16**, 701–707 (2010).
186. Charles, N. *et al.* Lyn kinase controls basophil GATA-3 transcription factor expression and induction of T_H2 cell differentiation. *Immunity* **30**, 533–543 (2009).
187. Dema, B. *et al.* Immunoglobulin E plays an immunoregulatory role in lupus. *J. Exp. Med.* **211**, 2159–2168 (2014).
188. Ge, Y. *et al. Cgnz1* allele confers kidney resistance to damage preventing progression of immune complex-mediated acute lupus glomerulonephritis. *J. Exp. Med.* **210**, 2387–2401 (2013).
189. Watkins, A. A. *et al.* IRF5 deficiency ameliorates lupus but promotes atherosclerosis and metabolic dysfunction in a mouse model of lupus-associated atherosclerosis. *J. Immunol.* **194**, 1467–1479 (2015).
190. Cervera, R. *et al.* Morbidity and mortality in systemic lupus erythematosus during a 5-year period. A multicenter prospective study of 1,000 patients. European Working Party on Systemic Lupus Erythematosus. *Medicine (Baltimore)* **78**, 167–175 (1999).
191. Flower, C., Hennis, A., Hambleton, I. R. & Nicholson, G. Lupus nephritis in an Afro-Caribbean population: renal indices and clinical outcomes. *Lupus* **15**, 689–694 (2006).
192. Chung, S. A. *et al.* Lupus nephritis susceptibility loci in women with systemic lupus erythematosus. *J. Am. Soc. Nephrol.* **25**, 2859–2870 (2014).
193. Matsuda, M. *et al.* Gene expression of PDGF and PDGF receptor in various forms of glomerulonephritis. *Am. J. Nephrol.* **17**, 25–31 (1997).
194. Ostendorf, T. *et al.* Antagonism of PDGF-D by human antibody CR002 prevents renal scarring in experimental glomerulonephritis. *J. Am. Soc. Nephrol.* **17**, 1054–1062 (2006).
195. Ichii, O. *et al.* Decreased miR-26a expression correlates with the progression of podocyte injury in autoimmune glomerulonephritis. *PLoS ONE* **9**, e110383 (2014).
196. Flur, K. *et al.* Viral RNA induces type I interferon-dependent cytokine release and cell death in mesangial cells via melanoma-differentiation-associated gene-5: implications for viral infection-associated glomerulonephritis. *Am. J. Pathol.* **175**, 2014–2022 (2009).
197. Ichinose, K. *et al.* Cutting edge: calcium/calmodulin-dependent protein kinase type IV is essential for mesangial cell proliferation and lupus nephritis. *J. Immunol.* **187**, 5500–5504 (2011).
198. Ichinose, K. *et al.* Lupus nephritis IgG induction of calcium/calmodulin-dependent kinase type IV expression in podocytes and alteration of their function. *Arthritis Rheumatol.* **68**, 944–952 (2016).
199. Ichinose, K., Juang, Y. T., Crispin, J. C., Kis-Toth, K. & Tsokos, G. C. Suppression of autoimmunity and organ pathology in lupus-prone mice upon inhibition of calcium/calmodulin-dependent protein kinase type IV. *Arthritis Rheum.* **63**, 523–529 (2011).
200. Tshilela, K. A. *et al.* Glomerular cytokine expression in murine lupus nephritis. *Clin. Exp. Nephrol.* **20**, 23–29 (2016).
201. Espinosa, A. *et al.* Loss of the lupus autoantigen Ro52/Trim21 induces tissue inflammation and systemic autoimmunity by disregulating the IL-23–T_H17 pathway. *J. Exp. Med.* **206**, 1661–1671 (2009).
202. Oke, V. *et al.* High Ro52 expression in spontaneous and UV-induced cutaneous inflammation. *J. Invest. Dermatol.* **129**, 2000–2010 (2009).
203. Fabini, G., Rutjes, S. A., Zimmermann, C., Pruijn, G. J. & Steiner, G. Analysis of the molecular composition of Ro ribonucleoprotein complexes: identification of novel Y RNA-binding proteins. *Eur. J. Biochem.* **267**, 2778–2789 (2000).
204. Ho, R. C. *et al.* Genetic variants that are associated with neuropsychiatric systemic lupus erythematosus. *J. Rheumatol.* **43**, 541–551 (2016).
205. Namjou, B. *et al.* Evaluation of the *TREX1* gene in a large multi-ancestral lupus cohort. *Genes Immun.* **12**, 270–279 (2011).
206. Jacob, A. *et al.* Inhibition of C5a receptor alleviates experimental CNS lupus. *J. Neuroimmunol.* **221**, 46–52 (2010).
207. Jacob, A. *et al.* C5a alters blood–brain barrier integrity in experimental lupus. *FASEB J.* **24**, 1682–1688 (2010).
208. Ho, R. C. *et al.* A meta-analysis of serum and cerebrospinal fluid autoantibodies in neuropsychiatric systemic lupus erythematosus. *Autoimmun. Rev.* **15**, 124–138 (2016).
209. Wen, J. *et al.* Neuropsychiatric disease in murine lupus is dependent on the TWEAK/Fn14 pathway. *J. Autoimmun.* **43**, 44–54 (2013).
210. Pondman, K. W., Stoop, J. W., Cormane, R. H. & Hannema, A. J. Abnormal C1 in a patient with systemic lupus erythematosus. *J. Immunol.* **101**, 811 (1968).
211. Kallel-Sellami, M. *et al.* Pediatric systemic lupus erythematosus with C1q deficiency. *Ann. NY Acad. Sci.* **1108**, 193–196 (2007).
212. Wu, Y. L., Brookshire, B. P., Verani, R. R., Arnett, F. C. & Yu, C. Y. Clinical presentations and molecular basis of complement C1r deficiency in a male African-American patient with systemic lupus erythematosus. *Lupus* **20**, 1126–1134 (2011).
213. Suzuki, Y., Ogura, Y., Otsubo, O., Akagi, K. & Fujita, T. Selective deficiency of C1s associated with a systemic lupus erythematosus-like syndrome. Report of a case. *Arthritis Rheum.* **35**, 576–579 (1992).
214. Kemp, M. E., Atkinson, J. P., Skanes, V. M., Levine, R. P. & Chaplin, D. D. Deletion of *C4A* genes in patients with systemic lupus erythematosus. *Arthritis Rheum.* **30**, 1015–1022 (1987).
215. Wahl, R. *et al.* C2 deficiency and a lupus erythematosus-like illness: family re-evaluation. *Ann. Intern. Med.* **90**, 717–718 (1979).
216. Pussell, B. A., Bourke, E., Nayef, M., Morris, S. & Peters, D. K. Complement deficiency and nephritis: a report of a family. *Lancet* **1**, 675–677 (1980).
217. Battersby, A. C., Cale, A. M., Goldblatt, D. & Gennery, A. R. Clinical manifestations of disease in X-linked carriers of chronic granulomatous disease. *J. Clin. Immunol.* **33**, 1276–1284 (2013).
218. Klar, A. *et al.* Prolidase deficiency: it looks like systemic lupus erythematosus but it is not. *Eur. J. Pediatr.* **169**, 727–732 (2010).
219. Urushihara, M. *et al.* Sisters with α-mannosidosis and systemic lupus erythematosus. *Eur. J. Pediatr.* **163**, 192–195 (2004).
220. Lee-Kirsch, M. A. *et al.* Familial chilblain lupus, a monogenic form of cutaneous lupus erythematosus, maps to chromosome 3p. *Am. J. Hum. Genet.* **79**, 731–737 (2006).
221. Rice, G. *et al.* Heterozygous mutations in *TREX1* cause familial chilblain lupus and dominant Aicardi–Goutières syndrome. *Am. J. Hum. Genet.* **80**, 811–815 (2007).
222. Yasutomo, K. *et al.* Mutation of *DNASE1* in people with systemic lupus erythematosus. *Nat. Genet.* **28**, 313–314 (2001).
223. Ramantani, G. *et al.* Aicardi–Goutières syndrome and systemic lupus erythematosus (SLE) in a 12-year-old boy with *SAMHD1* mutations. *J. Child Neurol.* **26**, 1425–1428 (2011).
224. Briggs, T. A. *et al.* Tartrate-resistant acid phosphatase deficiency causes a bone dysplasia with autoimmunity and a type I interferon expression signature. *Nat. Genet.* **43**, 127–131 (2011).
225. Crow, Y. J. *et al.* Characterization of human disease phenotypes associated with mutations in *TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR*, and *IFIH1*. *Am. J. Med. Genet. A* **167A**, 296–312 (2015).
226. Rice, G. I. *et al.* Mutations in *ADAR1* cause Aicardi–Goutières syndrome associated with a type I interferon signature. *Nat. Genet.* **44**, 1243–1248 (2012).
227. Jang, M. A. *et al.* Mutations in *DDX58*, which encodes RIG-I, cause atypical Singleton–Merten syndrome. *Am. J. Hum. Genet.* **96**, 266–274 (2015).
228. Liu, Y. *et al.* Activated STING in a vascular and pulmonary syndrome. *N. Engl. J. Med.* **371**, 507–518 (2014).
229. Zhang, X. *et al.* Human intracellular ISG15 prevents interferon-α/β over-amplification and auto-inflammation. *Nature* **517**, 89–93 (2015).
230. Brehm, A. *et al.* Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production. *J. Clin. Invest.* **125**, 4196–4211 (2015).
231. Wu, J. *et al.* Fas ligand mutation in a patient with systemic lupus erythematosus and lymphoproliferative disease. *J. Clin. Invest.* **98**, 1107–1113 (1996).
232. Xiang, N., Li, X. M., Wang, G. S., Tao, J. H. & Li, X. P. Association of *FAS* gene polymorphisms with systemic lupus erythematosus: a meta-analysis. *Mol. Biol. Rep.* **40**, 407–415 (2013).
233. Rieux-Laucat, F. *et al.* Mutations in *FAS* associated with human lymphoproliferative syndrome and autoimmunity. *Science* **268**, 1347–1349 (1995).
234. Bader-Meunier, B. *et al.* Are RASopathies new monogenic predisposing conditions to the development of systemic lupus erythematosus? Case report and systematic review of the literature. *Semin. Arthritis Rheum.* **43**, 217–219 (2013).
235. Chen, K. *et al.* Autoimmunity due to RAG deficiency and estimated disease incidence in *RAG1/2* mutations. *J. Allergy Clin. Immunol.* **133**, 880–882. e810 (2014).
236. Walter, J. E. *et al.* Impaired receptor editing and heterozygous *RAG2* mutation in a patient with systemic lupus erythematosus and erosive arthritis. *J. Allergy Clin. Immunol.* **135**, 272–273 (2014).

Author contributions

K.E.S. and P.C.R. reviewed and edited the manuscript before submission. G.C.T., M.S.L., and P.C.R. researched data for the article, wrote substantial sections of the manuscript, contributed substantially to discussions of the content, and reviewed the final draft.

Competing interests statement

The authors declare no competing interests.