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Autoimmunity and organ damage in systemic lupus erythematosus

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Abstract

Impressive progress has been made over the last several years toward understanding how almost every aspect of the immune system contributes to the expression of systemic autoimmunity. In parallel, studies have shed light on the mechanisms that contribute to organ inflammation and damage. New approaches that address the complicated interaction between genetic variants, epigenetic processes, sex and the environment promise to enlighten the multitude of pathways that lead to what is clinically defined as systemic lupus erythematosus. It is expected that each patient owns a unique ‘interactome’, which will dictate specific treatment.

It took almost 100 years to realize that lupus erythematosus, which was initially thought to be a skin entity, is a systemic disease that spares no organ and that an aberrant autoimmune response is involved in its pathogenesis. The involvement of vital organs and tissues such as the brain, blood and the kidney in most patients, the vast majority of whom are women of childbearing age, impels efforts to develop diagnostic tools and effective therapeutics. The prevalence ranges from 20 to 150 cases per 100,000 people and appears to be increasing as the disease is recognized more readily and survival rates improve. In the United States, people of African, Hispanic or Asian ancestry, as compared to those of other racial or ethnic groups, tend to have an increased prevalence of systemic lupus erythematosus (SLE) and greater involvement of vital organs. The 10-year survival rate has increased significantly over the last 50 years to more than 70%, mostly because of greater awareness of the disease, the extensive and wiser use of immunosuppressive drugs and a more efficient treatment of infections, the major cause of death^{1–3}.

Although low levels of autoreactivity and autoimmunity are necessary for lymphocyte selection and, in general, for the regulation of the immune system, in certain individuals, autoimmunity advances through multiple pathways (reviewed in ref. ⁴) and leads to organ inflammation and damage. The diverse mechanisms do not contribute equally to the expression of disease in all patients with SLE, as will be discussed below. It appears that the

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clinical heterogeneity of the disease is matched by the multiple pathogenic processes, which justifies the call for the development of personalized medicine (Fig. 1).

Genes and genetics

Over the past two decades, extensive genome-wide association studies and meta-analyses have identified close to 150 new SLE risk loci across multiple ancestries^{5,6}. Extensive use of exome sequencing has revealed an increasing number of monogenic cases of SLE, listed in ref. ⁷. Interestingly, several of the risk loci span multiple autoimmune diseases^{8,9}, stipulating disease commonality. Functional studies of shared loci may eventually help reclassify autoimmune diseases according to shared pathways, along with clinical characteristics. Detailed lists of gene variants have been published, and a limited number is listed in Table 1, along with evidence supporting involvement in disease pathogenesis. Several variants have been linked genetically, some with supporting biology, to pathogenic mechanisms and specific clinical manifestations, pointing strongly to the heterogeneity of the disease. Several genes linked to the immune response are regulated through long-distance chromatin interactions^{10,11}. Studies addressing long-distance interactions between gene variants in SLE are still missing, but, with the advent of new technologies, such studies will emerge.

Better understanding of the epigenome is needed to understand how it supplements the genetic contribution to the disease. Decreased DNA methylation of certain genes in SLE T cells has been recognized and has been attributed to poor function of the CpG remethylating enzyme DNMT1. For example, hypomethylation of *TNFSF5*, located on the X chromosome, results in increased CD40-ligand (CD40L) expression in T cells from women, and hypomethylation of *II10* increases interleukin (IL)-10 production. Yet methylation of genes in SLE is more complicated and does not follow a unidirectional pattern. For example, the *CD8* locus is methylated in T cells from patients with SLE, resulting in the generation of CD3+CD4⁻CD8⁻ T cells, whereas the *II2* locus is hypermethylated, resulting in low production of IL-2 (reviewed in ref. ¹²). Delivery of a demethylating agent specifically to either CD4⁺ or CD8⁺ cells in lupus-prone mice suppresses disease expression by enhancing the expression of FoxP3 and sustaining the expression of CD8¹³.

In SLE T cells, the cyclic AMP response element modifier (CREM α) binds to various regulatory elements within the *CD8* cluster and recruits histone modifiers, including DNMT3a and the histone methyltransferase G9a, causing stable silencing of *CD8A* and *CD8B*¹⁴. A similar process takes place in the *II2* locus, resulting in decreased IL-2 production¹⁵. In contrast, STAT3 recruitment to *II10* regulatory regions mediates the recruitment of histone acetyltransferase p300, resulting in enhanced gene expression¹⁶.

A large number of microRNAs are suspected to control at least one-third of human mRNA stability and translation, and, reasonably, they have been studied in SLE. A limited list is presented in Table 2. MicroRNA serum concentrations may serve as disease biomarkers¹⁷, and the development of antagomirs, used to silence endogenous microRNAs, may help to control the disease.

The contribution of epigenetic modifications to the expression of the disease complements the genetic susceptibility. Better understanding of the biochemical processes involved should offer unique opportunities to develop new therapeutics, and in a personalized manner.

Environment

Approximately a third of monozygotic twins are clinically concordant for SLE, which signifies the importance of environmental factors in the expression of the disease. The environment, including ultraviolet (UV) light, and cross-reactivity between self-antigens and molecules defined by viruses and other pathogens is important in the pathogenesis of SLE. Microbes, including innocuous commensal organisms that colonize the gut, skin, nasal cavities and the vagina, may trigger and sustain autoimmune inflammation in genetically susceptible hosts. Microbiota have been amply shown to shape the immune response, including the development of T helper type 1 (T_H1), T_H2 and regulatory T (T_{reg}) cells and have been implicated in several autoimmune diseases¹⁸.

Cross-reactivity between bacterial species and autoantigens has been long claimed to contribute to the expression of disease in susceptible individuals. The bacterium *Propionibacterium propionicum*, which encodes an ortholog of the RNA-binding protein Ro60, was found in cutaneous lesions of patients with subcutaneous lupus erythematosus and was shown to stimulate memory T cells from patients with SLE¹⁹, suggesting a direct involvement of pathogens in T cell proliferation and the production of autoantibodies.

Segmented filamentous bacteria induce intestinal IL-17-producing T_H17 cells²⁰, and gut microbiota drive autoimmune arthritis by promoting the generation of follicular helper T (T_{FH}) cells²¹. Microbiota apparently use Toll-like receptor (TLR) signaling because *TNFAIP3* (A20)-deficient mice, which develop autoimmunity, fail to do so when MyD88 (a central TLR signaling molecule) is genetically deleted, or the mice are treated with antibiotics²². Microbiota translocate from the gut to the mesenteric lymph nodes, spleen²³ and the liver and induce T_H17 and T_{FH} cells as well as innate immune pathways, including the plasmacytoid dendritic cell (pDC)-type I interferon (IFN α / β) axis. Interestingly, certain microbiota can be found in the liver of patients with SLE or autoimmune hepatitis²⁴. Microbiota contribute to disease expression through a number of mechanisms, including molecular mimicry, engagement of the innate immune response and the propagation of proinflammatory T_H17 cells. Accordingly, better understanding of the role of microbiota in the expression of SLE should reveal simple approaches for controlling autoimmunity through dietary changes or changing the distribution of microbiota in the gut and elsewhere.

Sex

Despite the fact that more than 90% of the people affected with SLE are women, we still do not have a clear understanding of the causative mechanisms. It is well known that people with XXX (Klinefelter syndrome) are prone to SLE and that epigenetic changes in certain pathogenic genes (for example, *TNFSF5*, encoding CD40L) contribute to disease expression. Also, six SLE susceptibility loci map to the X chromosome, four of which

(*TLR7*, *TMEM187*, *IRAK1* (MyD88-interacting kinase) and the IFN- α -inducible *CXorf21*) can escape X-chromosome inactivation²⁵.

Estrogen alters the thresholds for B cell apoptosis and activation, and estrogen receptor α contributes to T cell-mediated autoimmune inflammation by promoting T cell activation, and it also promotes lupus in NZB \times NZW F₁ mice. At the molecular level, estrogen upregulates CREM α expression, which is known to control the expression of *Il2* and *Il17* (reviewed in ref. ²⁶). Gene expression analysis revealed a female-biased autoimmunity-related network driven by the transcription factor VGLL3 that is linked with autoimmune diseases, including SLE, Sjogren's syndrome and scleroderma²⁷. While we still do not understand why women represent the vast majority of people with SLE, new evidence points to distinct molecular processes and the probable activation of X-chromosome-defined genes that are genetically linked to SLE.

Innate immune cell disturbances

Genetic and epigenetic factors contribute directly to alter cells of both the innate and adaptive immune responses. It is probable that certain immune aberrations may elicit others. Studies in mice and humans are still limited because of the reductionist approaches that are needed to understand the contribution of each abnormality to the expression of the disease. It will require artificial intelligence approaches to understand the sequence of events in any given patient. Such knowledge will be necessary for the application of precision treatment protocols.

Neutrophils in patients with SLE display an increased capacity to form neutrophil extracellular traps (NETosis) that harbor autoantigens, including chromatin, dsDNA and granular proteins. In patients with SLE, NETs are poorly cleared and stimulate pDCs to produce type I IFN through TLR9 stimulation²⁸. Endothelin-1 and hypoxia-inducible factor-1 α appear to mediate the expression of the stress-response protein REDD1, which drives the formation of NETs in SLE. NETs are decorated with tissue factor and IL-17 and are abundant in discoid skin lesions and in the kidneys of patients with SLE²⁹. Further, splenic neutrophils localized in the perimarginal zone can induce immunoglobulin (Ig) class switching, somatic hypermutation and antibody production by activating marginal zone B cells. Interestingly, patients who are neutropenic have fewer and less mutated marginal zone B cells and less preimmune Ig specific for T-independent antigens, suggesting neutrophils generate an additional level of innate immunity in the antibacterial defense³⁰.

DCs link innate and adaptive immune responses and have been identified in the expression of SLE, as their uncontrolled activation may drive autoimmunity³¹. Although the numbers are decreased in the periphery, they are found activated in the inflamed tissues, producing inflammatory cytokines and helping T and B cells. Immune complexes containing RNA induce OX40-ligand expression by conventional SLE DCs. Subsequently, they drive the differentiation of naive and memory CD4⁺ T cells into T_{FH} cells, which are able to help B cells³² and impair T_{reg} function³³. Conventional DCs in SLE instruct the differentiation of IgG and IgA plasmablasts and contribute to the formation of ectopic lymphoid structures³⁴.

pDCs are distinguished from conventional DCs by morphology and cell surface markers and are similarly low in the periphery, probably because they lodge in inflamed areas. Triggered by TLR7/9 agonists, they produce IFN type I³⁵ to contribute to disease expression, and duplication of *TLR7* promotes disease³⁶. Specific depletion of pDCs in mice reduces disease manifestations such as autoantibody production, glomerulonephritis and expression of IFN-inducible genes³⁷. At the clinical level, targeting of pDCs with a BDCA2 antibody ameliorates skin disease in patients with SLE³⁸, while chronic triggering of pDCs through TLR7 and TLR9 renders pDCs resistant to inhibition of the NF- κ B pathway and leads to steroid resistance³⁹.

Marginal zone macrophages surrounding the splenic follicles are crucial for the efficient clearance of apoptotic cells and for the induction of tolerance to autoantigens. Phagocytosis of apoptotic cells by splenic marginal zone macrophages requires the megakaryoblastic leukemia 1 transcriptional coactivator-mediated mechanosensing pathway⁴⁰. The production of type I IFN by macrophages in response to TLR7 engagement is enabled by the TREML4 receptor expressed on myeloid cells, and macrophages from *Trem4*^{-/-} mice are hyporesponsive to TLR7 agonists, while TREML4-deficient MRL-*lpr* lupus-prone mice display decreased autoimmunity and nephritis⁴¹. It should also be noted that IFN type I and tumor necrosis factor (TNF) cooperate to promote an inflammatory signature in monocytes, and such cooperation also occurs in monocytes from patients with SLE⁴².

Type I IFN, which affects multiple components of the immune system, has been demonstrated to contribute to the pathogenesis of adult and pediatric SLE⁴³ and to reflect disease activity (reviewed in detail in ref. ⁴⁴). Yet type I IFN alone may not be sufficient to cause disease expression⁴⁵ and, in some murine strains, may even be beneficial⁴⁶.

Proper processing of apoptotic material involves the activation of the transcription factor aryl hydrocarbon receptor (AhR) following engagement of TLR9, which leads to a series of events that suppress inflammation, including the production of IL-10. Deletion of *AhR* in myeloid cells causes autoimmunity, and its transcription signature correlates with disease activity in mice and humans⁴⁷. This observation may explain why TLR9 has a protective effect against autoimmunity.

Platelets are activated in patients and mice with SLE through a number of mechanisms, including the action of immune complexes and contact with injured endothelial cells, and they display a type I IFN signature⁴⁸. Once activated, platelets express and release CD40L and modulate adaptive immunity by activating antigen-presenting cells, including DCs. Platelets interact with pDCs in patients to increase the secretion of type I IFN by triggering TLR9 and TLR7⁴⁹. Understanding of the contribution of platelets may reveal adjuvant tools for the treatment of SLE.

Autoreactive IgE causes basophils to home to lymph nodes, promote T_H2 cell differentiation and enhance the production of self-reactive antibodies that cause lupus-like nephritis in mice lacking the protein tyrosine kinase Lyn. Patients with SLE with elevated concentrations of self-reactive IgEs and activated basophils have increased disease activity and active lupus nephritis⁵⁰.

Studies in mice have shown, in a definitive manner, the roles of neutrophils, basophils, pDCs, TLR activation and IFN type I production in the expression of SLE. Several of these contribute directly to organ damage, whereas others instruct, directly or indirectly, the aberrations of the adaptive immune response. The diversity of the involved pathways underlines the wide clinical spectrum of the disease, and it is quite possible that each cellular element contributes to the expression of disease, to varying degrees.

Lymphocyte disturbances in SLE

B cells in SLE have been reviewed extensively⁵¹⁻⁵³. Loss of B cell tolerance at distinct check points has explained the production of autoantibodies. B cell antigen receptor (BCR)-sequencing studies in children with SLE suggested that defects at distinct checkpoints in early B cell development accounted for autoantibody production⁵⁴. Although autoimmunity results from the failure of tolerance checkpoints, there is evidence that it may arise from the expansion of existing autoreactive cells⁵⁵.

Age-associated B cells (which include IgD⁻CD27⁻ and CD21^{lo} B cells) have been detected in human autoimmune disorders, including SLE. Their expansion is controlled by the transcription factor IRF5, variants of which are linked to SLE, through IL-21 expression and unique landscape remodeling⁵⁶. In mice, age-associated B cells are expanded in the absence of GTPase regulatory proteins (DEF6 and SWAP70), and DEF6 variants have been identified as conferring increased susceptibility to SLE⁵⁷.

The SLE molecular signature in B cells appears to become established during the resting naive phase and is dominated by the enrichment of accessible chromatin motifs for the transcription factors AP-1 and EGR⁵⁸, which is facilitated by, probably among other factors, IFN- γ ⁵⁹. B cells that lack IgD and CD27 are known to be expanded in patients with SLE and to produce autoantibodies. These cells are hyperresponsive to TLR7 agonists and IL-21, lack the TLR regulator TRAF5⁶⁰ and have features of freshly activated naive B cells⁶¹.

Although allergic reactions are not more frequent in people with SLE as compared to normal subjects, IgE antibodies specific for dsDNA are present in the sera of patients with SLE. These IgE antibodies bind to the high-affinity Fc γ RI receptor for IgE, can activate pDCs and transfer DNA to TLR9 in phagosomes. This activation results in the secretion of substantial amounts of IFN- α ⁶².

T cells are key players in promoting the autoimmune response by providing help to B cells and by activating antigen-presenting cells through cytokine release and direct cellular contact. Additionally, they infiltrate tissues and promote local inflammation. Autoreactive CD4⁺ T cells are presumed to respond to nucleosomal antigens and, in particular, to peptides derived from histones⁶³. An interesting T cell subset of unknown pathogenic importance was recorded in patients with SLE and multiple sclerosis (CXCR3⁺CD38⁺CD39⁺PD-1⁺HLA-DR⁺CD161⁺KLRG1⁻CD28⁺OX40⁺), which differs from T_{FH} cells and was first recognized in the gut of patients with celiac disease by virtue of binding gluten⁶⁴.

T_{FH} cells promote B cell function and evolve from CD4⁺ T cells in the presence of IL-6, IL-21 and inducible T cell costimulatory (ICOS)⁶⁵. ICOS deficiency protects MRL-*lpr* mice

from disease⁶⁶. A CD4⁺ cell subset that resembles T_{FH} cells is expanded in the peripheral blood of patients with active SLE⁶⁵. The ATP-gated ionotropic P2X7 receptor restricts the expansion of aberrant T_{FH} cells, but T_{FH} cells from patients with SLE are resistant to P2X7-mediated inhibition of cytokine-driven expansion, pointing to a signaling defect⁶⁷. CXCR5⁻ CXCR3⁺PD-1⁺ helper T cells, different from T_{FH} cells, are present in the periphery and in kidney tissues of people with SLE, and provide help to B cells by producing IL-10 and succinate⁶⁸.

CD8⁺ T cell cytotoxic responses are decreased in SLE and contribute to increased rates of infection⁷. A CD8⁺CD38⁺ T cell population is expanded in the peripheral blood of patients with SLE. CD8⁺CD38⁺ T cells display decreased production of granzymes and perforin and reduced cytotoxic capacity, and patients with SLE, for whom this population is expanded, experience infections more frequently. CD38, a marker of T cell exhaustion, is an ectonucleotidase that degrades NAD and, through the histone methyltransferase EZH2, suppresses the expression of cytotoxicity-related molecules⁶⁹. Specific inhibitors of CD38-mediated NAD degradation ameliorate age-related metabolic dysfunction and may be of use in restoring CD8⁺ T cell cytotoxic activity in people with SLE⁷⁰. Although exhaustion, defined by the levels of expression of molecules, has been argued to be desirable in autoimmunity⁷¹, it is important to understand the metabolic processes involved in further detail.

T_{reg} cells are characterized by constitutive expression of the transcription factor FoxP3 and high expression of the high-avidity IL-2 receptor α chain (CD25); in humans, some activated T effector (T_{eff}) cells also transiently express this molecule. The number of Treg cells is reduced during the early phases of the disease, whereas the CD45RA⁻FoxP3^{lo} non-T_{reg} cell population is increased in active SLE⁷². The realization that T_{reg} cells have higher affinity receptors for IL-2 and, therefore, stronger IL-2 receptor (IL-2R)-mediated signaling than T_{eff} cells, suggested that administration of IL-2 at a lower dose than that used for T_{eff} cells should promote T_{reg} cell expansion and function. Administration of low-dose IL-2 to lupus-prone mice expanded the population of T_{reg} cells and shrank the pool of CD3⁺CD4⁻CD8⁻ IL-17-producing T cells⁷³, which are known to contribute to the development of lupus nephritis⁷⁴. Low-dose IL-2 administered to people with SLE has been reported⁷⁵ to produce clinical benefit. A caveat to the apparent success of low-dose IL-2 is evidence that the IL-2-IL-2R-p-STAT5 signaling pathway in SLE T cells is compromised⁷⁶. IL-2 has the potential to reverse several pathogenic processes involved in the development of SLE, including poor T_{reg} cell function, increased IL-17 production, increased T_{FH} cell activity and the expansion of the population of CD4⁻CD8⁻ T cells⁷⁷. The demonstration that T_{reg} cells contribute to tissue repair⁷⁸ and the possibility that T_{reg} cells are limited in the kidneys of patients with lupus nephritis⁷⁹ encourage the consideration of approaches that enrich T_{reg} cells in the kidneys or other tissues.

The phenotype and function of T cells isolated from patients with SLE has been extensively studied in the search for clues to explain the pathogenesis of the disease and in an attempt to identify molecules that can serve as biomarkers and/or therapeutic targets⁸⁰. These studies have revealed that, in the context of SLE, T cell function is severely compromised as a result of a large number of signaling aberrations that distort gene expression profiles and skew the

cellular immune response toward a proinflammatory type (reviewed in refs. ^{80,81}). In brief, CD3-mediated T cell signaling is abnormal in people with SLE, and this is followed by aberrant expression of kinases, phosphatases, transcription factors, chemokine receptors and adhesion molecules and the production of chemokines and proinflammatory cytokines (Fig. 2).

Metabolic abnormalities have been recognized in people with SLE and in lupus-prone mice and have been linked to abnormal T cell function. SLE T cells display increased oxidative stress, as indicated by the depletion of glutathione (via NADPH loss), metabolic checkpoint kinase complex mTORC1, glycolysis and glutaminolysis. Inhibition of increased mTORC1, glycolysis or glutaminolysis mitigates disease in lupus-prone mice (reviewed in ref. ⁸²).

Lupus nephritis

The kidney is involved in more than half of patients with SLE and contributes significantly to morbidity. The contribution of autoantibodies with a number of reactivities and of immune complexes in the expression of kidney inflammation has been reviewed extensively over the years. Their role in instigating injury is considered to be mediated through the activation of the complement system, which accounts for the inflammatory response⁸³. Podocytes express increased amounts of the serine/threonine kinase CaMK4, which, through a distinct series of biochemical events, causes injury, and cell-targeted inhibition of CaMK4 in podocytes averts the deposition of immune complexes and nephritis⁸⁴. These findings signify the importance of resident cells in the initiation and propagation of kidney inflammation.

T cell migration to the kidney is important in the development of lupus-like nephritis⁸⁵. MRL-*lpr* mice that lack TCR $\alpha\beta$ do not develop lupus nephritis⁸⁶. Although kidney-infiltrating cells were thought to be exhausted⁸⁷, clonally expanded CD4⁺ and CD8⁺ T cells with memory effector cell markers are present in the kidneys of lupus nephritis. CD8⁺ T cells are present in all biopsy samples and were found to adhere to the Bowman's capsule and to infiltrate the tubular epithelium⁸⁸ and contribute to kidney damage. IL-17-producing T cells have been found within kidney cell infiltrates of patients with lupus nephritis⁷⁴, and IL-17 is important for the development of lupus nephritis⁸⁹. T_{FH} cells are present in the kidneys in close association with B cells in people with lupus nephritis, suggesting that they may provide help to them⁹⁰. Intrarenal B cells form germinal center-like structures produce antibodies to vimentin, which is a dominant target in human lupus tubulointerstitial nephritis⁹¹. Application of deep convolutional neural network methodology in specimens from patients with lupus nephritis enabled cell-distance mapping, which confirmed that DCs present antigen to CD4⁺ T cells⁹². Understanding the cellular architectures of in situ immunity in lupus nephritis should expand our understanding of the involved pathogenic processes.

Intrarenal macrophages have been considered important in the development of lupus nephritis (reviewed in ref. ⁹³). Analyses of macrophage and DC infiltrates in murine lupus nephritis have shown considerable heterogeneity. Monocytes are located around glomeruli and adjacent to tubules and peritubular capillaries in the renal interstitium and derive from

the expanded circulating Gr1lo monocyte population⁹⁴. Brief ischemia accelerates the infiltration of Ly6Chi inflammatory macrophages into the kidneys of MRL-*lpr* mice⁹⁵. DCs also infiltrate the kidneys in people with lupus nephritis, probably propagating local adaptive immune responses. Myeloid DC infiltration is associated with the accumulation of lymphoid aggregates in the kidneys⁹⁴. The identification of anti-inflammatory monocytes in the kidneys of patients with lupus nephritis⁹⁶ is especially important in considering prohealing rather than immunosuppressive therapeutic approaches. Lastly, CD43^{hi}CD11c⁺F4/80^{lo}MHC-II⁻ patrolling monocytes, which are known to orchestrate experimental kidney inflammation⁹⁷, are present in the kidneys of patients with lupus nephritis and lupus-prone mice. Their function depends on TNFAIP3-interacting protein 1 (also referred to as ABIN1) and its absence promotes lupus nephritis in a TLR-dependent manner⁹⁸.

Single-cell RNA sequencing of kidney and skin biopsy material from patients with lupus nephritis revealed type I IFN⁻response signatures in tubular cells and keratinocytes. Also, high IFN response and fibrotic signatures in tubular cells were associated with failure to respond to treatment⁹⁹. Recent single-cell RNA sequencing of kidney samples from people with lupus nephritis revealed 21 subsets of disease-active leukocytes, including multiple populations of myeloid cells, T cells, natural killer cells and B cells, that demonstrated both pro-inflammatory responses and inflammation-resolving responses. Also, evidence of activated B cells and of progressive stages of monocyte differentiation were detected in the kidney. A clear IFN type I response was observed in most cells. Two chemokine receptors, CXCR4 and CX3CR1, were broadly expressed, implying they may have central roles in cell trafficking¹⁰⁰. Similar studies that investigate resident kidney cells in parallel may reveal how the invasion of inflammatory cells alters the gene expression landscape and the function of kidney cells.

Nephritis can develop independently of systemic autoimmunity. Mice lacking ABIN1 develop glomerulonephritis and autoimmunity, both of which depend on TLR signaling, but ABIN1-deficient *Rag1*^{-/-} and *C3*^{-/-} mice develop glomerulonephritis without autoimmunity⁹⁸. Similarly, B6.*Nr4a1.Sle1.yaa* mice, which have a duplication of the *Tlr7* locus, lack patrolling monocytes and are prone to developing autoimmunity, do not develop glomerulonephritis but display ample evidence of systemic autoimmunity⁹⁸. A lack of association between autoimmunity and kidney damage has been previously suggested by studies of congenic lupus-prone NZM2328 strains¹⁰¹. The notion that the two processes are independent explains why certain patients with lupus nephritis develop end-stage renal disease despite heavy treatment with immunosuppressive drugs, while many people with systemic autoimmunity never develop clinical renal disease.

There are a multitude of mechanisms that are involved in the expression of lupus nephritis, including immune complexes, complement, infiltrating proinflammatory T cells and antibody-producing B cells, and monocytes and the inherent processes of resident cells account for the majority of the clinical heterogeneity of lupus nephritis and for the variable response to drugs and biologics. Understanding the dominant operative mechanism in each patient is the only way to develop personalized medicine.

Central nervous system (CNS) SLE

The central nervous system is involved frequently in people and mice with SLE. The clinical manifestations are quite diverse, apparently reflecting numerous immune and local pathogenic processes¹⁰². So far, antibody-mediated neuronal injury, microglial cell activation and infiltrating T cells are involved in the expression of brain injury. Antibodies that recognize double-stranded DNA can cross-react with the NR2A and NR2B subunits of the *N*-methyl-D-aspartate receptor and cause neuronal death, primarily via increased neuronal calcium influx, which mimics glutamate excitotoxicity¹⁰³. Transfer of these antibodies to normal mice¹⁰⁴ or immunization with the NMDAR-derived DWEYS pentapeptide¹⁰⁵ causes neuropsychiatric disease.

Within the brain, resident microglia are the predominant immune cells of the CNS and are potent cytokine producers. It appears that neuronal injury is followed by microglial activation, which involves the activation of the angiotensin-converting enzyme. Blockade of microglial activation with an angiotensin-converting enzyme inhibitor limits neuronal injury¹⁰⁶, offering another treatment option.

Lymphocytes and other immune cells are probably important in the expression of CNS disease. Tertiary lymphoid structures are present in the choroid plexus of lupus-prone mice and people with SLE¹⁰⁶, and lymphocytes apparently enter the brain parenchyma, but their nature and function have not been studied. The recent reports on the presence of T cells in the brains of people with autism¹⁰⁷ and Alzheimer's disease¹⁰⁸ call for more attention on the role of T cells in brain tissue injury.

Cutaneous lupus

Four of the eleven American College of Rheumatology–established criteria for the classification of the disease involve skin manifestations that exposure to sun may elicit or worsen. UV light–induced skin inflammation depends on the production of the cytokine CSF-1 by keratinocytes, which in turn recruits and activates monocytes, which enhance apoptosis of keratinocytes¹⁰⁹. Dying keratinocytes release autoantigens, including Ro60 (Ro antibodies have long been linked to cutaneous lupus), which may propagate the autoimmune response. Mice and humans deficient in the complement protein C1q are known to have a defect in the clearance of apoptotic material and have lupus-like skin manifestations¹¹⁰. C1q-coated apoptotic cells are engulfed by DCs, macrophages and endothelial cells through binding the receptor SCARF1 on the surface of these cells. SCARF1-deficient mice develop lupus-like disease¹¹¹.

T_H17 cells, which are present in skin biopsy material, may contribute to the inflammatory process¹¹². pDCs have the unique capacity to rapidly produce huge amounts of IFN- α upon recognition of viral RNA and DNA through TLR7 and TLR9 or through other pathogen recognition receptors that are present in skin lesions¹¹³. The development of skin lesions depends on FasL expressed on infiltrating T_H1 cells recognizing cognate antigen and on TLR7 in the absence of TLR9, revealing a complex regulation of skin inflammation in lupus. pDCs and IFN- α have been shown to be abundant in skin lesions¹¹⁴.

The importance of TNF in the expression of skin lesions has been shown in experiments in which lupus IgG was injected into the skin of various genetically modified mice. In brief, monocytes but not lymphocytes or Ig were required for the induction of skin inflammation (reviewed in ref. ¹¹⁵). Although TNF was required, only TNF receptor type I and not II trimerization was needed for the induction of inflammation. While blockade of IL-17 may have value in the treatment of patients with skin lupus, it is unclear whether TNF receptor trimerization inhibitors may have any value, particularly given that TNF blockade may lead to autoimmune manifestations.

Cardiovascular disease in SLE

Patients with SLE, and particularly those with oxidized LDL and β 2-glycoprotein I, have a 2-fold increased risk for cardiovascular disease¹¹⁶. Multiple mechanisms have been found to contribute to the expression of vascular damage. Type I IFN has been shown to inhibit the production of endothelial nitric oxide synthase and to cause endothelial damage¹¹⁷. Low-density granulocytes damage the vasculature because of their increased propensity for NETosis and promote vascular leakage and endothelial-to-mesenchymal transition through the degradation of vascular endothelial cadherin¹¹⁸. CCR5⁺T-bet⁺FoxP3⁺ CD4⁺ effector T cells are present in atherosclerotic plaques¹¹⁹. Invariant natural killer T cells, however, were recently claimed to interact with monocytes and promote an atheroprotective effect¹²⁰.

Whereas inflammation promotes atherosclerosis, it has been demonstrated that atherogenic hyperlipidemia promotes autoimmune T_H17 cell responses in vivo¹²¹. An atherogenic environment induces the production of IL-27 by DCs in a TLR4-dependent manner, which in turn triggers the differentiation of CXCR3⁺ T_{FH} cells, which are increased in mice⁶⁶ and patients with SLE¹²², while inhibiting the differentiation of follicular regulatory T cells¹²³.

Prospects and needs

Amazing progress has been made over the last few years due to increased funding from various sources and the recruitment of skilled researchers from various sections of immunology and other fields of medicine, including nephrology, dermatology and cardiology, and other areas of science, including advanced molecular biology and bioinformatics. As this Review briefly summarizes, every cellular, molecular and biochemical aspect of the immune system contributes somehow to the expression of the disease. In humans it is obviously difficult to assign the time of entry for each recorded abnormality in the pathogenesis of the disease and classify it as either primary or secondary. Lupus-prone mice and engineered mice, in which one suspected molecule is deleted, overexpressed or structurally altered, invariably demonstrate that each molecule is able and sufficient to cause autoimmunity, reflecting a 'house of cards' effect, rather than what actually happens in people with SLE. While the complete understanding of each pathway, be it cellular or molecular, is of enormous significance, more important is the need to master technology to identify which pathway is the driver in each individual person with SLE.

The list of failing clinical trials keeps expanding and has been regularly updated, but there has been no effort to change the approach to clinical trials in a radical manner¹. It is

unfortunate, although unavoidable, that we define the disease using diverse classification criteria. There is no doubt that each biologic helps some people with SLE, mostly because that pathway is central to the expression of the disease in the responding group of patients, but this is not sufficient. There are two solutions: administer to each patient with SLE multiple drugs/biologics in the hope that a greater number will experience clinical benefit, or identify the driving pathway in each patient and treat her accordingly. A corollary to the first approach is to administer biologics that correct multiple pathways.

The expanding use of whole-exome sequencing along with genome-wide association studies has increased the number of patients with monogenic lupus, which will most probably continue to increase. For these patients, besides treatment with drugs to control manifestations, there is the possibility, with advancing technologies, of talking about a cure. Although still early, it is important to identify patients in whom two or a few gene variants contribute to the expression of the disease (oligogenic patients). New technologies should be adapted by investigators in the field to study how individual single nucleotide polymorphisms (SNPs) interact with remote genes or their variants to enable autoimmune pathology¹²⁴.

The expanding use of single-cell sequencing will help to identify previously unknown functional immune cell subsets that may be upstream in immune system dysregulation and could offer new targets for treatment. Single-cell sequencing of involved tissues may reveal more features of the invading immune cells and, more importantly, that local resident cells have both previously unrecognized functions¹⁰⁰ and the ability to produce molecules that cause organ destruction.

It is unfathomable that, although practically all patients are women (9 or more in 10), we know very little of what lies behind this. The X chromosome packs numerous genes involved in the immune response, and it appears that improper inactivation may perturb the immune balance in favor of autoimmunity¹²⁵. Are there master regulators encoded by genes of the X chromosome that commandeer all that has been reported for SLE? Do these genes need to be expressed in a homozygous fashion through unleashing the inactive allele? In the same line of thinking, the study of the epigenome is still nascent in SLE.

Studies of the involved organs, including skin, the kidney and the brain, have revealed local processes that are responsible for tissue damage. Without ignoring the role of the autoimmune response in instigating organ damage, it is possible that the local inflammatory processes proceed independently with little or no outside input. Better understanding of these processes should open new approaches to disease treatment.

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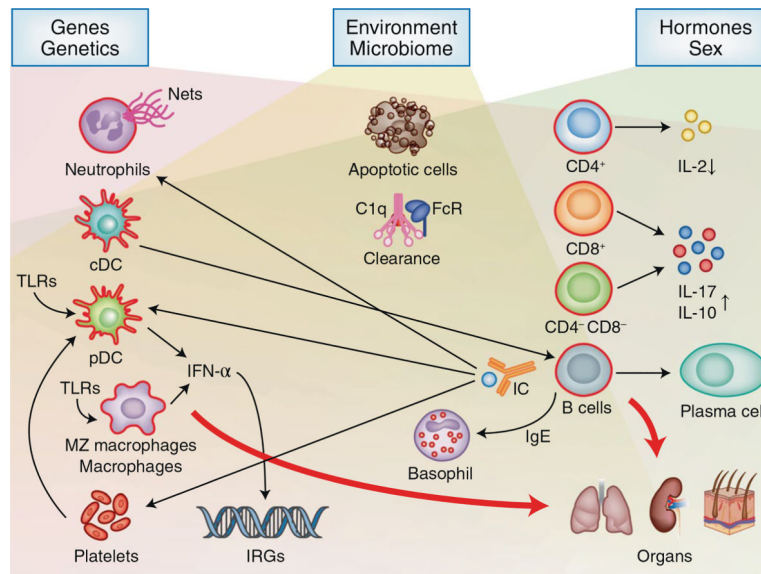


Fig. 1 |. The pathogenetic landscape of SLE.

Genetic, environmental and hormonal factors act on various elements of the innate and adaptive immune responses. Gene copy variants (for example, *C4* and *FCR*) and SNPs influence the expression of many genes involved in the immune response as well as in the control of organ damage (for example, *APOLI* and *KLK*). Environmental factors, including UV light, drugs and products of the microbiome, alter T and B cell responses and the functions of innate cells by stimulating TLRs. Hormones and genes defined by the X chromosome contribute to disease expression by altering the function of lymphocytes and of cells of the innate immune response. The involved factors lead eventually to loss of tolerance of B and T cells to autoantigens, which are present in abundance because of both increased rates of apoptosis and defects in mechanisms responsible for their clearance. The T cell response to antigen is aberrant in and late signaling events (Fig. 2) and results in misbalanced levels of cytokines, including decreased IL-2 and increased IL-17 production. T cells, through distinct pathways, also acquire a greater ability to invade tissues and contribute to the inflammatory response. B cells, in response to cognate and non-cognate (cytokines) interactions with T cells, produce antibodies. Antibodies enter tissues directly or in the form of immune complexes (IC), which contribute to tissue inflammation. Cells of the innate immune response, under the influence of the involved pathogenic factors, produce cytokines (including IFN- α) or, through the direct interaction with lymphocytes, contribute significantly to the inflammatory organ-damaging response. The clinical heterogeneity of the disease is highly correlated with the multitude of the pathways that lead to organ injury. Although several pathways operate in each individual, the relative contribution of each pathway varies from person to person. Finally, local factors dictate which organ will be afflicted by the autoinflammatory response.

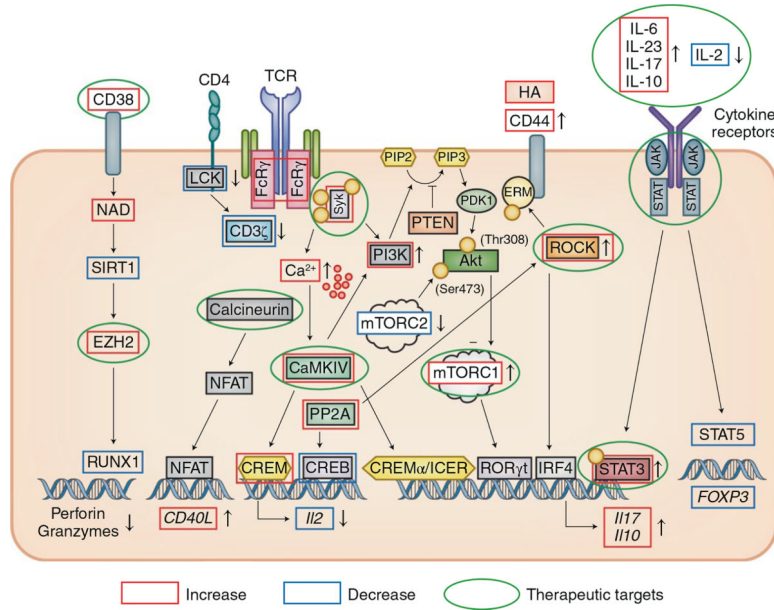


Fig. 2 | T cell early and late signaling aberrations in T cells from patients with SLE.

Engagement of the CD3 complex either by autoantigen or circulating CD3/TCR antibodies results in an increased intracytoplasmic calcium response. The CD3 complex is rewired, with the CD3 ζ chain replaced with the FcR γ chain, which recruits the kinase Syk. The calcium-requiring kinase CaMKIV enhances the binding of CREM α /ICER to the *Il2* and *Il17* or *Il10* promoters to suppress and enhance their expression, respectively. Calcineurin also dephosphorylates the transcription factor NFAT, which binds to the promoter of *CD40L* and increases its expression. Phosphatase PP2A is increased in T cells with diverse effects: in Treg cells, it dephosphorylates mTORC1 and promotes Treg cell function and, in effector T cells, it enhances the binding of IRF4 to the *Il17* promoter and it dephosphorylates p-CREB. PP2A also promotes ROCK activity, which phosphorylates ERM, which in turn enhances the ability of CD44 to bind its ligand hyaluronic acid (HA, expressed in the kidney and other tissues). IL-2 signaling is defective with decreased amounts of p-STAT5, whereas IL-6 signaling is increased with increased binding of p-STAT3 to the *Il17* promoter. An increased proportion of CD8⁺ T cells express the ectonucleotidase CD38, which suppresses the level of NAD and the activity of the deacetylase SIRT1, which in turn enhances the activity of the histone methyltransferase EZH2. As indicated by the green circles, a number of the molecules have been considered as therapeutic targets: Syk, ROCK, calcineurin, EZH2, IL-17, IL-23, JAK and mTOR as well as IL-2, which can be replenished with low doses.

Table 1 |

Select gene variants linked to SLE and suggested function

Gene	Function	Ref.
<i>IRF5</i> (promoter variants)	Increased expression, which leads to induction of proinflammatory cytokines and the definition of an inflammatory macrophage phenotype	126
<i>IRF7</i> (single SNP)	Increased production of type I IFN by DCs	127
<i>STAT4</i>	Binds the transcription factor HMGAI1; shared with rheumatoid arthritis	128
<i>STAT1</i>	Increased binding to a variant of the transcription factor ETS1	129
<i>PRDMI</i>	Linked to increased production of IL-6 and cathepsin S (needed for loading peptides into MHC-II)	16,17
<i>IKZF1</i>	Involved in the expression of <i>C/EBP</i> and five type I IFN-response genes	130
Fc receptor genes	Clearance of apoptotic cells and immune complexes; antibody-mediated cell cytotoxicity	131
<i>C1q, C4</i>	Clearance of apoptotic cells; negative immune selection	132
<i>C4</i>	Decreased number of copy variants is linked to SLE	133
<i>FCGR3B</i>	Decreased number of copy variants is linked to SLE	134
<i>NCF1</i>	Decreased number of copies predispose to, whereas increased protects against, SLE	135
<i>ITGAM</i>	Impaired phagocytosis of complement-opsonized targets in monocytes, neutrophils and macrophages	136
<i>NCF2</i>	Essential to LC3-associated phagocytosis	137
<i>ATG5, PRKCD, NCF1</i>	Essential for autophagy	137
<i>TLR7</i>	Increased IFN- α production	
<i>TNFAIP3</i>	Encodes the deubiquitinating enzyme A20, which is involved in the termination of NF- κ B signaling; A20-deficient mice develop severe autoinflammatory disease	138,139
<i>PTPN22</i>	Expansion of effector and memory T cells and increased production of IFN- γ , TNF and GM-CSF	140
Major histocompatibility antigens		
<i>HLA-DR2</i> and <i>HLA-DR3</i>	Contributes to SLE in Europeans	134
<i>HLA-DRB1*15:01</i> and <i>HLA-DQB1*6:02</i>	Contributes to SLE in Asians	141
<i>HLA-DR3</i> and <i>HLA-DR15</i>	Contributes to SLE across all ancestries	6
<i>BANK1</i> and <i>BLK</i>	Interaction between the SLE-associated variants	142

Gene	Function	Ref.
<i>IgG1</i>	A knockin mouse with a patient-identified IgG1 SNP developed lupus	143
<i>APOLL1</i>	Linked to lupus nephritis	144
<i>VGLL3</i>	Sex-biased transcription factor	27

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Table 2 |

MicroRNAs control aspects of the immune response and organ damage in SLE

MicroRNA	Function	Ref.
miR-146a	Regulates the innate immune response	145
miR-125a	Regulates the anti-inflammatory response	146
miR-155	Controls the expression of SH2-domain-containing inositol 5'-phosphatase 1 (SHIP1), which is important in B cell activation; miR155 ^{-/-} Fas ^{lpr} mice have decreased autoimmunity and nephritis	147
miR-148a	Impairs B cell tolerance by suppressing the expression of the autoimmune suppressor Gadd45a, the tumor suppressor PTEN and the proapoptotic protein Bim, which promotes the survival of immature B cells after engagement of the B cell antigen receptor	148
miR-23b	Suppresses IL-17-associated autoimmune inflammation by targeting TAB2, TAB3 and IKK α mRNA	149
miR-17[sim]92	Promotes T _{FH} cell differentiation; promotes DC activation through the microRNA let-7c and BLIMP-1	150 151
miR-150	Promotes renal fibrosis in lupus nephritis by downregulating expression of SOCS1	152