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REVIEW

Chance, genetics, and the heterogeneity of disease and pathogenesis in systemic lupus erythematosus

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Abstract Systemic lupus erythematosus (SLE) is a remarkably complex and heterogeneous systemic autoimmune disease. Disease complexity within individuals and heterogeneity among individuals, even genetically identical individuals, is driven by stochastic execution of a complex inherited program. Genome-wide association studies (GWAS) have progressively improved understanding of which genes are most critical to the potential for SLE and provided illuminating insight about the immune mechanisms that are engaged in SLE. What initiates expression of the genetic program to cause SLE within an individual and how that program is initiated remains poorly understood. If we extrapolate from all of the different experimental mouse models for SLE, we can begin to appreciate why SLE is so heterogeneous and consequently why prediction of disease outcome is so difficult. In this review, we critically evaluate extrinsic versus intrinsic cellular functions in the clearance and elimination of cellular debris and how dysfunction in that system may promote autoimmunity to nuclear antigens. We also examine several mouse models genetically prone to SLE either because of natural inheritance or inheritance of induced mutations to illustrate how different immune mechanisms may initiate autoimmunity and affect disease pathogenesis. Finally, we describe the heterogeneity of disease manifestations in SLE and discuss the mechanisms of disease pathogenesis with emphasis on glomerulonephritis. Particular attention is given to discussion of how anti-DNA autoantibody initiates experimental lupus nephritis (LN) in mice.

Keywords Systemic lupus erythematosus · Autoimmunity · Glomerulonephritis · Autoantibody · Pathogenesis · Immune tolerance

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For most autoimmune diseases, we know more about the middle and end stages of the disease than the beginning. Lupus, systemic lupus erythematosus (SLE), is not different in that respect. SLE is the prototypic systemic autoimmune disease [1]. We are developing an understanding of how the potential for SLE is inherited and many genetic susceptibility loci that may contribute to SLE have been identified, but we are still in the very early stages of understanding how the identified susceptibility loci combine to produce disease phenotypes in SLE. More importantly, we do not know how the genetic program inherent within the inherited susceptibility genes is initiated to cause SLE nor what events or stimuli initiate the program. The heterogeneity of disease presentation in SLE further complicates understanding of how SLE is initiated. Virtually all organ systems of the body are potential targets for damage by the disease processes of SLE. Just what determines in a given individual with SLE which organs will be targeted is poorly understood and is an important area for future research. The plethora of autoantibodies that occurs in many individuals with SLE is thought to be the main drivers of organ damage or altered cellular function in the disease [2]. Established criteria for clinical diagnosis of SLE have been modified and updated to better reflect clinical presentation in patients and improvements in diagnostic tools and capabilities [3–7]. The published criteria include most, if not all, pathologic manifestations of SLE. A more recent guideline has been published specifically for diagnosis and management of glomerulonephritis

in SLE, lupus nephritis (LN) [8]. Although there are more deaths due to cardiovascular disease in SLE patients, renal disease had the highest standardized mortality ratio (SMR) among patients in a very large, multicenter international cohort [9]. SMR was calculated as the ratio of deaths observed to deaths expected by cause for calendar-year periods and accounting for gender and age. Since patients are diagnosed with SLE after onset of clinical symptoms and because clinical symptoms can be so heterogeneous, there has been minimal opportunity to understand how SLE is initiated within individual patients or why disease phenotypes are so variable. This review will highlight current knowledge regarding the etiopathogenesis of damage to major target organs in SLE.

SLE

Autoimmunity in SLE is a consequence of the progressive innate immune stimulation of antigen-selective, adaptive immune responses to autoantigens [10–13]. The products of the autoimmune response are autoantibodies primarily, but not exclusively [2], to a variety of nuclear antigens including DNA, RNA, ribonuclear proteins, and histones [14] Pathogenic manifestations of lupus can encompass many tissues and organs and may include but are not limited to inflammation in the skin, joints, and other connective tissues; vasculitis; glomerular and interstitial nephritis; cardiopulmonary inflammation; central and peripheral nervous system inflammation; and thrombocytopenia [3, 15]. SLE is more prevalent in women than men with an estimated prevalence of 1/1,000 among American women above the age of 17 [16]. SLE also has an unequal prevalence depending upon race and ethnicity being more prevalent [17, 18] and with worse disease severity [19, 20] among African Americans, Asian, and Hispanic individuals. The frequency of lupus among female children below age 17 is estimated to be as high as 1/400 for non-Caucasian Americans [21]. The disease is generally more severe at onset in children than in adults [22, 23].

Mouse models for SLE

There are several experimental mouse models for SLE [24, 25]. All of the mouse models of spontaneous SLE share the phenotypes of antinuclear and anti-DNA autoantibody production and glomerulonephritis [1]. Similar to SLE in humans, multiple susceptibility loci may contribute to SLE in mice [26]. The first identified autoimmune mouse model was NZB and its F_1 hybrid with NZW, NZY, or NZC [27]. Autoimmunity in (NZB × NZW)F_1 (B/W) mice most closely resembles SLE in humans [26, 28] with female gender bias, complex genetic associations including major histocompatibility complex (MHC)-linked and non-linked loci [29–33], antinuclear and anti-DNA autoantibody [24], and lupus-like glomerulonephritis [28]. NZM, derived by inbreeding progeny of unintended backcross of B/W with NZW, have similar complex inheritance of SLE as B/W but are homozygous [25, 34]. Genetic susceptibility to SLE in MRL$^{lpr/lpr}$ and BXSB^{Yaa} is primarily the result of a single mutation *lpr* that affects Fas expression in MRL and an X chromosome translocation *Yaa* that duplicates a region that includes the *tlr7* gene in BXSB [35]. B/W and other lupus-susceptible mice have been invaluable as experimental models to test hypotheses related to disease pathogenesis in SLE.

Genetics and stochasticity in SLE

At the Fourth International Congress of Immunology (Toronto, 1986), Dr. C. Garrison Fathman opened his presentation on autoimmunity in type I diabetes with the statement that "Autoimmunity is a combination of genetics and bad luck." The statement was and continues to be astute and accurate. Most autoimmune diseases have significant linkages to one or more genetic loci. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) are exceptions in which autoimmune disease is linked to mutations in single genes, *foxp3* for IPEX [36, 37] and *aire* for APECED [38–40]. SLE has a strong heritable component, estimated to be approximately 66 % [41, 42], with rates of concordance between 20 and 40 % in monozygotic twins and from 2 to 5 % in dizygotic twins or siblings [41, 43, 44]. The sibling recurrence risk ratio in SLE patients is 29-fold higher than in the general population [41], and the higher concordance among monozygotic than dizygotic twins [44] indicates the importance of susceptibility inheritance. Genome-wide association (GWA) and gene mapping studies have identified approximately 30 susceptibility loci for SLE [42, 45, 46]. Individually, each locus has relatively modest risk association, *odds ratio* (OR)<2.5, and together account for only 15 % or less of the estimated genetic heritability of SLE [47, 48]. What accounts for the "missing heritability" for SLE is unknown or at least unresolved but may include epigenetic factors, other risk factors, or the likely possibility that the "SLE phenotype" is a collection of several distinct and rare subtypes [48, 49]. Penetrance for most identified risk loci is low, and as noted above, concordance is relatively low for monozygotic twins. Monozygotic twins receive the same genetic "hand," but "luck" clearly influences outcome as the genetic hand is played. Similarly, MRL$^{lpr/lpr}$ mice are genetically homogeneous. All develop SLE, but only 25 % produce the anti-Sm autoantibody [50]. No C57 BL/6$^{lpr/lpr}$ mice produce anti-Sm. Anti-Sm in MRL$^{lpr/lpr}$ is independent of gender, age, parentage, and environment. The potential to produce anti-Sm autoantibody is genetically determined, but anti-Sm production in the 25 % of MRL$^{lpr/lpr}$ that produce the autoantibody is determined by chance. Epistatic interactions among

susceptibility loci have been identified [51–55], most notably between HLA and *CTLA4*, although again with relatively modest risk, OR<2. Low concordance and penetrance among susceptibility loci for SLE are consistent with stochastic expression of multiple susceptibility genes [1] and epigenetic effects on susceptibility gene expression [56, 57]. Low concordance has also been cited as indication for an environmental stimulus to initiate autoimmunity in SLE, which would also be manifested as a stochastic effect on disease susceptibility [41, 44, 58].

Exceptions to low penetrance for susceptibility loci in SLE are genes that encode early complement components [42], particularly C1q [59, 60], and TREX1, a gene that encodes a nuclease important in the degradation of cytosolic DNA [61]. Mutations in C1q [59] and TREX1 [62] are rare, but both are strong risk factors for lupus (OR=10 and 25, respectively). Mutations that inhibit function of those genes initiate autoimmunity and SLE without a requirement for "bad luck" other than inheriting a bad C1q or TREX1 gene. Although there have been fewer genetic studies in pediatric lupus patients with concomitantly much less data, the risk and confirmed loci are similar to those in adults [63]. Inherited deficiencies in early complement components present the highest risk and, when present, account for the earlier disease manifestation in children [59].

MHC

Genetic risk for SLE is associated with inheritance of MHC class II and class III loci [49]. Within MHC class II, HLA-DRB1 haplotypes DBR1*1501 and DBR1*0301 confer the strongest MHC class II association with SLE [64, 65]. The MHC class III locus contains genes encoding complement components and other proteins, single nucleotide polymorphisms (SNP) for which GWA has established linkage to SLE. These include the early complement components C1q, C4, C1r/s, C2, and C3 [66–68], the MutS homolog 5 (MSH5), super viralicidic activity 2-like (SKIV2L), integrin alpha m (ITGAM, CD11b), integrin beta chain beta 2 (ITGB2, CD18), and Fcγ receptor (FcγR) genes [69–75]. The phenotypic contributions of complement, ITGAM, and FcγR are discussed in more detail below. MSH5 is important in immunoglobulin (Ig) class switch recombination [76], meiosis, and DNA mismatch repair [76]. The phenotypic contribution of SKIV2L is less understood.

Type I IFN

As found in other autoimmune diseases such as systemic sclerosis, type 1 diabetes, rheumatoid arthritis, psoriasis, Sjogren's syndrome, and dermatomyositis, over half of patients with SLE exhibit a type I interferon (IFN)-inducible gene signature in their peripheral blood leukocytes [77–82]. As it turns out, close to half of the genetic susceptibility loci found to be associated with SLE are involved in type I IFN production or downstream signaling [83]. Type I IFNs that consist of 13 IFN-α isotypes, IFN-β, IFN-ε, IFN-κ, and IFN-ω, are major mediators of inflammation and the innate immune response. Plasmacytoid dendritic cells (pDCs) produce IFN in response to cell membrane or endosomal signaling when innate immune receptors, including toll like receptors (TLR) 3, 7, 8, and 9, are engaged by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) or when specialized receptors, such as RIG-I or IFIH1, are engaged by intracellular RNA and DNA [84]. The IFNAR1/2 receptor when engaged by type I IFN initiates a signaling cascade through the Janus-activated protein kinases (JAK), JAK1 and TYK2, which regulate a myriad of downstream genes [83, 85, 86]. Many of these downstream genes are likely involved in SLE pathogenesis by affecting expression of chemokines, facilitating monocyte and DC maturation, activating autoreactive T and B cells, promoting autoantibody secretion from differentiated, autoreactive plasma cells, and by facilitating apoptosis of immune cells [86]. The importance of the type I IFN signature in SLE pathogenesis is supported by the observation that those patients with endogenous anti-IFNα autoantibodies tend to have lower serum type I IFN levels, reduced activation of type I IFN pathways, and lower SLE disease activity scores [87].

Other cytokines and cytokine signaling

Although members of the tumor necrosis α (TNF-α) family have been associated with SLE, the role of TNFα specifically is still to be determined. TNF ligand superfamily 4 (TNFSF4) polymorphism confers susceptibility to SLE [88]. The TNFSF4 receptor is expressed mainly on activated antigen-presenting cells (APCs) and activated $CD4^+$ T cells, and increased expression of TNFSF4 may enhance interactions with APCs or by modulating T cell activation [88–90]. B/W mice inherit a dominant TNF-α allele from NZW $H\text{-}2^z$ that results in reduced TNF-α [91]. Recombinant TNF-α replacement therapy induces a significant delay in LN in B/W mice. Associations between interleukin (IL)-10 [92–94], IL-1 signaling [95], IL-21 [96], and inducible T cell co-stimulator (ICOS) [97] and susceptibility to SLE have also been identified.

Genetic risk and intrinsic versus extrinsic problems in disposal of cellular debris

The highest risk associations for SLE are in genes that control disposal and degradation of apoptotic cells and cellular debris, C1q [59, 60] and TREX1 [62, 98]. TREX1 is a negative

regulator of the type I interferon-stimulatory DNA (ISD) response [99]. TREX1 deletion in mice results in the accumulation of endogenous retroelement DNA, ISD-dependent IFN production, inflammation, and autoimmunity. C1q binds apoptotic cells and particles and facilitates their degradation and removal [60, 100, 101]. C1q is a complex of three polypeptides, A, B, and C, encoded by genes within chromosomal region 1p34.1 to 1p36.3 [102]. C1q deficiency may be caused by nonsense or missense mutations in A, B, or C with no identified preference [59]. Mice made genetically deficient in either C1q [60] or DNaseI [103] accumulate apoptotic cells and nuclear debris and develop SLE-like autoimmunity including LN. Similarly, mutant mice that lack functional Tyro 3 family member Mer also have defective phagocytosis and clearance of apoptotic cells and also develop SLE-like autoimmunity [104].

Circulating monocytes and macrophages from SLE patients exhibit a reduced capacity for eliminating apoptotic cells [105, 106]. What is not clear is whether that observed phagocytic defect is intrinsic to phagocytic cells or extrinsic from the effects of chronic inflammation on phagocytic cells in SLE patients. Peritoneal macrophages but not bone marrow-derived macrophages in B/W mice have phagocytic defects similar to those in phagocytes from SLE patients [107, 108]. Those results indicated that the phagocytic defect in circulating or peripheral tissue macrophages in B/W mice is extrinsic and related to autoimmunity in the mice and not intrinsic to the macrophages. The latter is relevant to understand whether phagocytic defects and poor elimination of apoptotic cells contribute to initiation of SLE early in disease pathogenesis, "cause," or simply reflect the cumulative effects of autoimmunity and ongoing chronic inflammation, "effect." Whether cause or effect, reduced phagocytosis and elimination of apoptotic, necroptotic, NETotic, or necrotic debris would exacerbate autoantibody production and disease progression.

Izui et al. were the first to realize that inflammatory stimuli such as lipopolysaccharide (LPS) could induce release of circulating DNA, formation of circulating DNA–anti-DNA complexes, and glomerulonephritis [109–111]. Immune complexes of antinuclear autoantibodies and remnants of secondary necrosis from poorly phagocytosed apoptotic cells augment inflammatory cytokine release ex vivo in phagocytic cells from SLE patients [112] likely as a result of increased signaling from FcγR and TLR. That enhanced ability to phagocytose cellular debris from secondary necrosis contrasts with the inherited susceptibility locus in ITGAM, CD11b. An inherited polymorphism in ITGAM is a susceptibility locus for SLE although with modest individual risk [74, 75]. Monocytes/macrophages and neutrophils from individuals homozygous [113] or heterozygous [114] for the susceptibility allele have reduced iC3b-dependent phagocytosis by complement receptor 3 (CR3). The reduced phagocytic function of CR3 encoded by the susceptible allele is consistent with the association of susceptibility in SLE with reduced potential to eliminate apoptotic cells and cellular debris. The modest single risk for SLE associated with ITGAM implies that other intrinsic and/or extrinsic factors must operate with ITGAM to affect disease.

As noted above, the rather low penetrance and low concordance for most inherited susceptibility loci have been interpreted as indication for the necessary contribution of environmental factors for autoimmunity and disease in SLE [41, 44, 58]. At least in B/W and other mice genetically predisposed to SLE, initiation of spontaneous autoimmunity is independent of an identified external innate or adaptive immune stimulus [1]. Mice not genetically prone to autoimmunity and homozygous for an induced null mutation in the inhibitory FcγRIIb develop SLE-like autoimmunity including glomerulonephritis [115]. The elimination of a critical regulatory pathway for inhibiting B cell activation results in SLE-like autoimmunity in an otherwise normal background. Sanroque mice produce anti-DNA autoantibody and develop LN [116]. Sanroque mice are homozygous for an induced mutation in the roquin ubiquitin ligase gene *Rc3h1* [117]. Sanroque mice have spontaneous T follicular helper cell (T_{FH}) expansion and germinal center (GC) formation. $Lyn^{-/-}$ mice have defective B cell signaling and development with reduced B cell numbers, more rapid turnover, and abnormal response to T-independent (TI) and T-dependent (TD) antigens [118–120]. As $Lyn^{-/-}$ mice age, they develop autoantibodies and lupus-like autoimmune disease. Lyn function is not required to initiate B cell receptor-dependent activation but is essential for tolerance and negative regulation including FcγRIIb [121]. $Cd22^{-/-}$ mice have a similar B cell phenotype to $Lyn^{-/-}$ [122]. Chronic graft-versus-host (GVH) disease in mice produces SLE-like autoimmunity including selective production of antinuclear autoantibodies, including anti-DNA autoantibody, and glomerulonephritis [123–125]. The intensive, chronic T cell stimulation in GVH stimulates normally tolerant autoreactive B cells to produce autoantibodies. Intraperitoneal pristane injection of mice not genetically predisposed to autoimmunity induces chronic inflammation, autoantibody production, including anti-DNA, and lupus-like disease [126]. The mechanism for autoantibody production in that experimental system is not understood but is likely due to chronic stimulation of mononuclear cells, particularly Ly6C-positive monocytes, and type I interferon production [127]. Mice from strains not genetically predisposed to autoimmunity produce IgG anti-DNA antibody with glomerular immune deposits and proteinuria when immunized with DNA-peptide complexes, but the induced autoantibody production is not sustained [128, 129].

Eilat and Wabl [130] have introduced a new and interesting hypothesis for the role of endogenous retroviral elements in the induction of autoimmunity in B/W and other autoimmune mice. Their hypothesis derives from the experimental effects of an antiretroviral drug on disease progression in B/W mice [131]. The hypothesis predicts that intracellular replication and accumulation of retroviral DNA and RNA stimulate IFN

production and the creation of neo-epitopes to which T cells are not tolerant. The hypothesis is consistent with SLE susceptibility associated with TREX1 deficiency discussed above and the function of nucleic acid sensing TLR7 and 9 in B cell activation [11, 132].

Tolerance and self-reactivity

Whether good versus bad luck in SLE reveals itself as random environmental influence, inherited [133] or stochastic epigenetic regulation, or other stochastic genetic events remains largely unknown. The immune system has evolved recognition and sensing capabilities to maximize pathogen detection at the risk of self-reactivity [134]. For example, a surprising percentage of Ig heavy and light chain variable regions genes in the mouse primary B cell repertoire encode anti-DNA antibodies [13, 135]. That potential for self-reactivity must be and normally is restrained [134]. Any genetic [115, 116], innate immune [126, 136], or adaptive immune [123, 124, 128, 129] disruption of the regulatory balance and control of self-reactivity can initiate autoimmunity. If the activation is sustained or progressive, the acute autoimmunity can become chronic and produce autoimmune disease.

Autoantibodies and autoimmune B cell activation

Disease phenotypes in SLE are highly pleomorphic [3, 4, 15, 137] due to the heterogeneity of molecular and cellular dysregulation of immune function [138]. The most frequent immune aberration, common to human and mouse SLE, is antinuclear autoantibody production. Antinuclear autoantibodies in human and mouse SLE may include antibodies reactive to DNA; chromatin; nucleosomes; histones; non-histone DNA-binding proteins; and ribonuclear proteins (RNP), Sm, U1-RNP, Ro/SSA, and La/SSB [14] with reactivity or cross-reactivity to phospholipids [139, 140]. Reactivity to double-stranded DNA (dsDNA) and the Sm ribonuclear protein antigen are generally specific for SLE [3]. Immune pathogenesis in human [141–143] and mouse [24] SLE is most correlated with autoantibody production to native DNA (dsDNA), although most anti-dsDNA monoclonal antibodies (mAbs) also bind chromatin and nucleosomes [135, 144].

How autoreactive B cell activation and anti-DNA autoantibody production are initiated and what initiates the activation is still basically unknown. What is known is that autoreactive B cells undergo clonally selective specificity maturation and class switching to IgG driven by specificity for DNA or other nuclear antigens within GC [12, 13, 145]. Initiation of the autoimmune response depends upon innate immune signaling primarily through TLR7 and 9 on B cells and APCs [11, 132]. IFN production by APCs, particularly pDC, is a consistent and critical mechanism in the innate immune-dependent initiation of inflammation and T and B cell activation [146–148]. The IgG autoimmune antibody response, including IgG anti-DNA, is CD4 T cell-dependent [149], although determination of which CD4 T cell subsets are necessary for autoantibody production is somewhat confusing and seems mostly to depend upon the experimental system or autoimmune mouse model. T_{FH} seem to be the most critical T cell subset because of their critical role in the GC response [116, 150].

Sanroque mice (roquin$^{san/san}$) are a mutant strain with spontaneously expanded T_{FH} and GC [117]. Sanroque mice develop lupus-like autoimmunity including anti-DNA autoantibody production and glomerulonephritis. The roquin$^{san/san}$ mutation disrupts an ICOS repressor resulting in excessive co-stimulation of T_{FH} and IL-21 production. GC formation and autoantibody production were independent of T_H1, T_H2, and T_H17 [116]. Interestingly, T_{FH} and GC expansion requires T cell signaling but is independent of IL-21. The results with sanroque mice contrast with other results implicating a necessity for IL-17 and/or T_H17 in immune and autoimmune GC formation [151, 152]. Spontaneous GC formation and pathogenic autoantibody production in BXD2 mice were dependent upon IL-17 signaling through the IL-17 receptor [152]. The effect of IL-17 may be to promote B cell retention in GC to promote autoreactive B cell activation [150]. GWA has identified genetic associations between IL-21 [96] and ICOS [97] with susceptibility to SLE in humans.

Disease pathogenesis

Disease pathogenesis in SLE is manifested as systemic acute and chronic inflammation that affects many organ systems, although to varying degrees within individual SLE patients [3, 4, 15, 137]. The major cause of mortality in adult SLE is myocardial infarction consequent to premature atherosclerosis and coronary heart disease [15], although renal end-stage disease has the highest SMR in SLE [9]. Interestingly, even though the most recognized pathology related to SLE in B/W mice is glomerulonephritis [28], atherosclerotic lesions and myocardial infarction were described in early reports of pathology in those and other hybrids with NZB [27]. LN is also a severe life-threatening disease manifestation of SLE in both adults [153, 154] and children [155], generally being more severe at disease onset in children [22, 23]. The following sections will discuss the mechanisms of tissue damage for different manifestations of disease pathogenesis.

Lupus nephritis

Glomerulonephritis in human [142, 156–158] and mouse [24, 159] SLE has long been associated with glomerular immune

deposits of IgG autoantibody to DNA. Glomerular lesions in affected kidneys contain both subendothelial and subepithelial complexes of chromatin, IgG anti-DNA antibody, and complement [160–162]. The glomerular immune complexes induce leukocyte infiltration and accumulation and initiate a tissue destructive chronic inflammation. The role for B cells that secrete anti-DNA autoantibodies is obvious, and the antibodies in LN are discussed in detail below. T cells, monocytes and macrophages, dendritic cells, and neutrophils also contribute to glomerular inflammation, but their function is more heterogeneous and varies within different experimental systems and mouse models of SLE. Common to all of the experimental systems and mouse models for LN is antibody that binds DNA and/or chromatin except one. mIgM.MRL/MpJ-*Fas*^{lpr} mice have surface Ig receptor-positive B cells, but the B cells cannot secrete Ig [163]. Those mice are autoimmune and develop a B cell-dependent interstitial nephritis. The most prominent immunohistology of the interstitial nephritis in mIgM.MRL/MpJ-*Fas*^{lpr} mice was T cell infiltration. Although different from the diffuse proliferative nephritis in wild-type (wt) MRL-*Fas*^{lpr} and other mice that develop spontaneous LN, the phenotype of mIgM.MRL/MpJ-*Fas*^{lpr} mice provides insight about kidney pathogenesis in LN unrelated to anti-DNA autoantibody. In contrast to the mIgM.MRL/MpJ-*Fas*^{lpr} mice, F2 mice homozygous for *Fas*^{lpr} and a J_H deletion (JhD) with ~50 % genetic contribution from MRL/MpJ had no kidney pathology [164]. JhD homozygous mutant mice lacked B cells from birth. The JhD mutant mice indicated the requirement for B cells for kidney pathology in mIgM.MRL/MpJ-*Fas*^{lpr} mice.

FcγR

Mice with homozygous null mutation of the FcγR chain have reduced cell surface expression of FcγRI, III, and IV, no signaling capability through the receptors, and consequently defective FcγR-dependent activation and phagocytic function among cells that normally express activating cell surface FcγR [165, 166]. When the $\gamma^{-/-}$ mutation was backcrossed into NZB and NZW to create NZB.$\gamma^{-/-}$ and NZW.$\gamma^{+/-}$ that were mated to create F_1, the B/W $\gamma^{-/-}$ were autoimmune with similar anti-DNA autoantibody titers as wt B/W [167]. In contrast to wt B/W, however, $\gamma^{-/-}$ B/W had attenuated LN including reduced glomerulonephritis, reduced proteinuria, and prolonged survival. These results were profound in their implication that FcγR-dependent rather than complement-dependent activation of inflammatory effector cells is more important for glomerular inflammation in LN. On the other hand, mice with a homozygous null mutation of the inhibitory FcγRIIB developed spontaneous autoimmunity including anti-DNA autoantibody production and glomerulonephritis depending upon genetic background. All of the results with FcγR mutations in mice are consistent with genetic linkages between SLE susceptibility and FcγR loci [46]. Complement activation may be important for glomerular recruitment of leukocytes [168] that initiate and accelerate glomerulonephritis [169]. Activated complement components also induce increased FcγR expression on neutrophils and monocytes making them more susceptible to activation by immune complexes via FcγR [168, 170, 171]. Early complement components and activating FcγR are both important in SLE susceptibility for their roles in removing and eliminating necrotic and apoptotic cells and cellular debris [46, 172].

Mesangial cells

In vitro experiments have implicated mesangial cells for promoting inflammation in LN through FcγR or innate immune, TLR stimulation [173–176], or direct binding by nephritogenic anti-DNA autoantibody [177]. The results are controversial if not contradictory and difficult to reconcile with in vivo genetic results. Until activated by IFNγ to express activating FcγRI, IIA, and IIIA, mesangial cells only expressed inhibitory FcγRIIB [173, 178]. This result would imply that IgG immune complexes should inhibit not promote proinflammatory cytokine expression by normal mesangial cells. Mesangial cells also do not express TLR 7, 8, and 9 but do express TLR 1–6 [179]. In the absence of TLR9 [132, 180], it is unclear how DNA or nucleosomes would activate mesangial cells in the absence of mononuclear or myeloid cells [176].

The most insightful results about the role for mesangial cells in LN were obtained with B/W bone marrow chimeric mice [181]. Only mice chimeric for B/W $\gamma^{+/+}$ bone marrow cells but not B/W $\gamma^{-/-}$ bone marrow cells developed glomerulonephritis, even though both had equivalent glomerular IgG deposits. B/W $\gamma^{-/-}$ bone marrow chimeric mice had no myeloid or mononuclear cellular infiltrates that would have been expected if FcγR^{+} mesangial cells produced chemokines and cytokines in response to the glomerular immune complexes. Together, the above results indicate that signaling through activating FcγR on resident myeloid and mononuclear cells initiate glomerulonephritis in SLE. Complement's role in LN is in recruiting leukocytes and accelerating their response to glomerular IgG deposits [168, 169].

T cells

The role for T cells in glomerular pathogenesis in SLE is complicated. Part of the difficulty is in distinguishing whether the accumulation of activated T cells in inflamed glomeruli or tubular interstitium is cause or effect. Interstitial T cell infiltration in MRL/MpJ-*Fas*^{lpr} mice is discussed above. In human SLE patients [182] and B/W

[183] and NZM2328 mice [184], LN has been correlated with glomerular IL-18 and IFNγ indicative of T_H1 infiltration. In both cases, T_H1 were likely more important for progression than initiation of glomerular pathogenesis. The discovery of IL-17 and T_H17 and their role in inflammation and autoimmune disease [185] has yielded a new perspective for disease development in SLE [186]. The requirement for IL-17 signaling for autoimmunity in BXD2 [152] described above is an excellent example.

Fcγr2b$^{-/-}$*.Traf3ip2*$^{-/-}$ mice also present an insightful if not intriguing example for the role of IL-17 in LN. *Fcγr2b*$^{-/-}$*.Traf3ip2*$^{-/-}$ mice lack the inhibitory FcγRIIB but also lack the CIKS/ACT1 adaptor required for signaling by all IL-17 cytokines through the IL-17 receptor [187]. These mice produce IgG anti-DNA with glomerular IgG deposits like *Fcγr2b*$^{-/-}$ mice but have attenuated glomerular disease and increased survival. *Fcγr2b*$^{-/-}$*.il17a*$^{-/-}$ mice had a similar phenotype to *Fcγr2b*$^{-/-}$*.Traf3ip2*$^{-/-}$ mice. Unlike the BXD2 mice, loss of IL-17a or IL-17 receptor signaling did not diminish autoantibody production or GC formation in *Fcγr2b*$^{-/-}$*.il17a*$^{-/-}$ mice and only partially reduced GC in *Fcγr2b*$^{-/-}$*.Traf3ip2*$^{-/-}$ mice. Recruitment of inflammatory cells, particularly neutrophils, was reduced in both *Fcγr2b*$^{-/-}$*. Traf3ip2*$^{-/-}$ and *Fcγr2b*$^{-/-}$*.il17a*$^{-/-}$ mice.

Anti-DNA antibody specificity and lupus nephritis

The strongest immunological and serological correlate for glomerulonephritis in SLE is IgG autoantibody to dsDNA [141, 143]. Glomerular lesions consist of fibrinoid, electron dense subendothelial and subepithelial deposits of complexes of IgG anti-DNA, chromatin, and complement [142, 160–162, 188]. Nevertheless, a subset of SLE patients [154, 189–192] and anti-DNA antibody VH and VL transgenic B/W mice [193–195] produce anti-dsDNA similarly to patients with LN or wt B/W, respectively, but do not develop LN. Serum IgG anti-dsDNA may precede LN by several years in serologically positive clinically quiescent patients (SPCQ), and the transgenic B/W live well beyond a year with no signs of LN. As such, the transgenic B/W are reasonable models for SPCQ in SLE patients. Ebling and Hahn had observed that eluted IgG anti-DNA were limited to a subset of total serum IgG anti-DNA [188]. The restricted subset was limited to anti-DNA IgG with relatively high pI. Krishnan et al. [144] passively induced LN in non-autoimmune mice by injecting anti-DNA mAbs or mAb-producing hybridomas. Only mAbs that also bound cross-reactively to basement membrane matrix antigens in vitro bound to glomerular basement membrane (GBM) or mesangial matrix (MM) in vivo and induced proteinuria. Binding in glomeruli by the mAbs was independent of DNA, chromatin, or nucleosomes. Non-GBM-binding mAbs had similar or even higher relative affinity for dsDNA and chromatin as the GBM-binding mAbs [144]. The 3H9 mAb, from which the 3H9, VH, and VL transgenic B/W [193] were derived, does not bind basement membrane matrix antigens or GBM and does not induce passive LN [144, 196]. The subset of anti-DNA IgG in glomerular eluates isolated by Ebling and Hahn [188] likely included antibodies that bound directly to GBM or MM. The pioneering work of Madaio and colleagues [197–199] and Eilat and colleagues [200] had already demonstrated that anti-DNA mAbs may bind directly to glomerular antigens independently of DNA and initiate LN. The experiments of Krishnan et al. [144] demonstrated that only GBM-binding anti-dsDNA bound in glomeruli when co-injected with non-GBM-binding anti-dsDNA. The conclusion from these results is that binding to DNA, chromatin, or nucleosomes alone is neither necessary nor sufficient for anti-DNA IgG to initiate glomerular binding and LN. The stochastic processes of somatic recombination and somatic hypermutation determine antibody specificity, and at least for B/W mice, only about 20 % of individual anti-DNA antibodies could be expected to initiate glomerular binding and LN [144]. These stochastic processes may contribute to SPCQ in SLE patients and the variation in onset of LN in B/W and other autoimmune mice.

An alternative conclusion to the above suggests that anti-DNA autoantibody may only bind to chromatin on GBM or in MM and is based upon morphologic data from nephritic kidneys [201, 202] or kidneys perfused with nucleosome-anti-DNA complexes [203]. Essentially, the proposed mechanism requires histone-dependent binding of nucleosomes to GBM or MM. Izui et al. [204] had earlier demonstrated that both ssDNA and dsDNA bound GBM in vitro. In those experiments, ssDNA bound more efficiently. Although intuitively appealing, the proposed mechanism is inconsistent with the known structure of nucleosomes [205] and chromatin [206] and their physical chemical properties [207]. The highly negatively charged nucleosomes are unlikely to promote interaction with the negatively charged GBM [208, 209]. Nucleosomes may bind to individual GBM components on a laboratory sensor chip [210], but nucleosomes do not bind to GB or other areas of the kidney in vivo in either humans [211] or mice [212]. In the aforementioned experiments above, nucleosomes were only bound to GBM in the presence of anti-DNA antibody [201] or when the perfused immune complexes were prepared with high antibody excess. Under such conditions, excess antibody in the complexes may be able to bind directly to GBM [144]. The morphologic data [201, 202] are also consistent with direct GBM and MM-binding of anti-dsDNA antibody. GBM or MM-bound antibody may bind to extracellular chromatin and increase the size of glomerular immune complexes [144, 213, 214]. The morphologic data may reflect the middle to end stages of glomerular IgG deposition [142, 160–162] but not the initiating event.

Accumulating results in mice and humans indicate at least an indirect role for neutrophil extracellular traps (NETs) and NETosis in SLE. Since Radic and Marion recently reviewed that topic in this series [213], no further discussion will be included here. It is important to note, however, that recent experiments in MRL$^{lpr/lpr}$ *nox2*$^{-/-}$ mice that are defective for NETosis and NET release from neutrophils have even worse SLE disease symptoms than MRL$^{lpr/lpr}$ Nox2 sufficient mice [215]. NETosis by neutrophils is at least not required for SLE in MRL$^{lpr/lpr}$ mice. Important to note, however, DNA extracellular traps can be formed without NADPH oxidase and by innate immune cells other than neutrophils [216].

The mechanistic pattern for lupus nephritis that emerges from the above mouse models is likely as follows (Fig. 1):

1. The stochastic generation, activation, and antigen selection of DNA-reactive B cells will eventually yield an IgG anti-DNA that cross-reacts with relatively high affinity to GBM and/or MM antigens.
2. IgG anti-DNA binds directly to cross-reactive GBM or MM antigens [144] and activates complement and resident hematopoietic cells expressing activating FcγR [167, 181].
3. Chromatin [202], apoptotic bodies [217], and/or microparticles [218] released by necrosis or inflammation-induced NETosis, necroptosis, or apoptosis may bind to GBM-bound IgG anti-DNA to produce progressively larger immune complexes [219]. Cytokines and chemokines produced by activated leukocytes [220], including IL-17 [187] and IL-12 [182], recruit more cellular infiltration by myeloid cells, monocytes, and T cells.

The initial binding of IgG anti-DNA and small immune complexes to GBM will likely be reversible and represents the rate-limiting step for initiation of LN [144]. The above process will establish a feed-forward, progressive accumulation of IgG and immune complexes, inflammatory cells, and mediators that eventually destroy glomerular and tubular structure and function.

Skin

The skin is a target of tissue damage in several different forms of lupus erythematosus (LE). Ultraviolet radiation (UVR) from sun exposure has been implicated in triggering onset and/or exacerbation of the cutaneous lesions of LE by several possible mechanisms. The term "cutaneous lupus erythematosus" (CLE) encompasses several conditions that share histologic features of hyperkeratosis, follicular plugging, and inflammation of adnexal structures [221]. Major groups include acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), chronic cutaneous lupus erythematosus, and intermittent cutaneous lupus erythematosus (ICLE) [222]. Chronic CLE is further subdivided into discoid lupus erythematosus (DLE) and chilblain LE with the former being triggered by UVR with cold and humidity acting as a trigger for the latter [222]. The patient with CLE may follow a classical course in which LE remains confined to the skin or can develop other organ involvement to become SLE. The reverse can also occur in which initially there is no skin involvement in SLE with one form of CLE appearing later in the course of the disease.

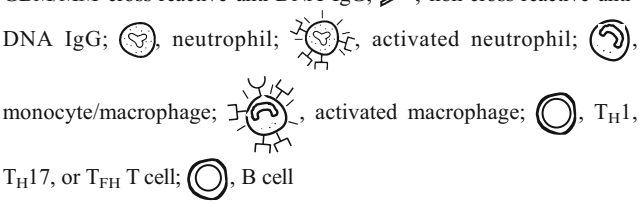
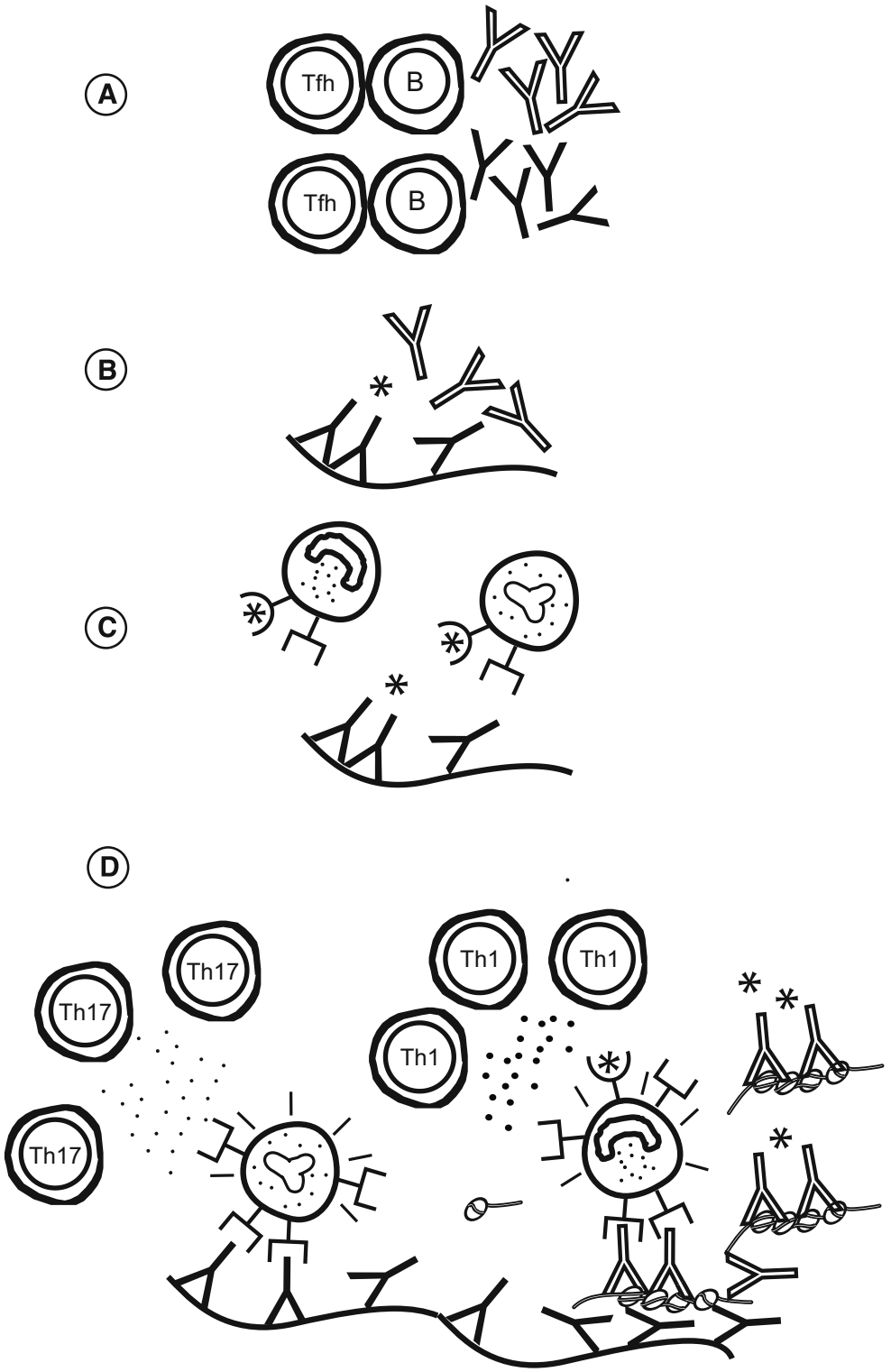


Fig. 1 GBM/MM-binding anti-dsDNA initiates glomerulonephritis in SLE. **a** Activated T_{FH} activate DNA-reactive and stimulated B cells to produce IgG anti-dsDNA autoantibody. **b** IgG anti-dsDNA binds directly to GBM or MM cross-reactive antigen(s). **c** Resident neutrophils and monocytes/macrophages are activated by FcγR and complement. **d** GBM/MM-bound anti-dsDNA can bind to extracellular chromatin, apoptotic bodies, microparticles, or DNA extracellular traps. The large GBM/MM-bound immune complexes activate more complement and activating FcγR-expressing neutrophils and monocyte/macrophages. Chemokines and cytokines released by activated leukocytes attract and activate T_H1 and T_H17 CD4 T cells. This process establishes a progressive, feed-forward mechanism to sustain chronic inflammation that eventually destroys glomerular structure and function.

The cellular infiltrates in CLE include $CD8^+$ cytotoxic and $CD4^+$ T effector cells, $CD68^+$ macrophages, pDCs, and $V\alpha24^+$ $V\beta11^+$ invariant natural killer T cells (iNKT) [223–225]. Inflammation-promoting cytokines, including IL-1β, IL-17, IL-18, TNFα, IFNγ, and high-mobility group box 1 (HMGB1) protein, are present in CLE lesional skin and can stimulate production of chemokines and expression of adhesion molecules (intracellular adhesion molecule-1 (ICAM-1) and E-selectin) to promote leukocyte influx [226–232]. IL-17A is positively correlated with expression of IFN-α and antiviral myxovirus A protein (MxA) in all subtypes of CLE [233].

Exposure to UVR-A and UVR-B can induce apoptosis of keratinocytes and is associated with c-Jun N-terminal kinase (JNK) that facilitates induced nitric acid synthase (iNOS) production [234–237]. Increased iNOS leads to increased production of nitric oxide (NO) that may counter UVR-A-induced apoptosis by increasing Bcl-2 expression and reducing Bax protein in endothelial cells [238]. Compared to skin of normal individuals in which iNOS expression is upregulated within 2 days after UVR, iNOS in CLE patients appears 72 h after UVR exposure that would allow apoptosis of keratinocytes to proceed unopposed within the first 72 h after UVR exposure [238–240]. Apoptotic keratinocytes in turn



may become a source for innate and subsequent adaptive immune cell activation [112, 136]. Recent experiments in mice demonstrated that repeated epicutaneous stimulation with the TLR-7 agonist imiquimod not only induced a lupus-like systemic autoimmune disease but also increased skin photosensitivity to UVR-B light [241]. In those experiments, systemic autoimmunity and photosensitivity were dependent upon pDC. These results are important because they implicate the skin as a potential primary organ for TLR-7 dependent initiation of SLE.

Lungs

Some form of pulmonary inflammation occurs in 50–70 % of patients with SLE [242–244]. Pleuritis is the most common and occurs with or without pleural effusions [245]. Etiology and pathogenesis of pleuritis and pleural effusions in SLE patients is unknown. Other less common pulmonary involvement includes bronchiolitis obliterans, interstitial lung disease, shrinking lung syndrome, pulmonary arterial hypertension, diffuse alveolar hemorrhage, vasculitis, pulmonary nodules, and diaphragmatic weakness [242, 245, 246]. Although the cause of diffuse alveolar hemorrhage (DAH) in SLE has not been completely elucidated, immune-mediated damage of small blood vessels and alveolar space is suspected. There are three different histologic patterns of tissue damage that include pulmonary capillaritis, diffuse alveolar damage, and bland pulmonary hemorrhage [242, 246–255]. Patients with DAH often have lupus nephritis, high titers of anti-DNA antibody, hypocomplementemia, and anemia [242, 248, 256]. Pulmonary embolism, often associated with antiphospholipid syndrome, is increased in patients with SLE [247]. Pulmonary arterial hypertension not secondary to pulmonary emboli or cardiac disease is uncommon, and its cause and pathogenesis are unknown.

Interstitial lung disease (ILD) most commonly has the nonspecific interstitial pneumonia (NSIP) pattern and can occur with desquamative interstitial pneumonitis but only rarely in non-smoking SLE patients [257]. The cause of ILD in SLE, as in other conditions, is unknown. In SLE patients, ILD can develop with no previous lung disease or after lupus pneumonitis, in which there are deposits of IgG and C3 within alveolar septa, diffuse alveolar inflammation associated with hyaline membranes, and alveolar hemorrhage [258, 259].

Cardiovascular system

The pericardium may be involved in up to 100 % of SLE patients with involvement consisting of an acute pericarditis often associated with pleurisy and pleural effusions and pericardial effusion that rarely progresses to cardiac tamponade or constrictive pericarditis [260–264]. The pericardial effusion is exudative having a straw-colored appearance with a high leukocyte count that is predominantly neutrophilic [265]. In rare cases, the pericardial effusion may be hemorrhagic [266]. Antinuclear and anti-DNA antibodies, low complement, and immune complexes are commonly found in the pericardial fluid [267].

The myocardium is involved with myocarditis in up to 40–50 % of patients with SLE, based on autopsy reports [268], but clinically significant myocarditis is less common (from 10 to 14 %) [269–271]. Histologic examination reveals widespread deposition of Ig and complement in myocardial blood vessel walls and within muscle bundles that may or may not be associated with inflammatory plasma cell and lymphocyte infiltrates [268]. Fibrinoid deposits and hematoxylin bodies occur, and patchy myocardial fibrosis is seen in SLE patients with myocarditis who have been treated with corticosteroids [272]. Several different antibody specificities have been associated with lupus myocarditis including anti-RNP occurring with coexistence of skeletal myositis, anti-Ro antibodies, and antimyocardial antibodies, although their involvement in pathogenesis of the myocarditis is not yet proven. The association between neonatal and newborn congenital heart block and maternal SLE is well established [273]. Congenital heart block is strongly correlated with the presence of autoantibodies to SSA/Ro and SSB/La in both mothers' and infants' sera [274–277]. Infants acquire the autoantibodies transplacentally. The association between anti-SSA/Ro52 autoantibody and congenital heart block may be related to cross-reactivity of the autoantibody with the 5-HT4 serotoninergic receptor [278].

Valvular abnormalities detected by transesophageal echocardiography have been reported in up to 61 % of patients with SLE [279]. In that study, 43 % of patients had valvular vegetations, and 50 % had thickening of mitral and aortic valves. Libman-Sacks endocarditis, atypical verrucous endocarditis, is the term used to describe the atypical sterile verrucous lesions of the valves and mural endocardium originally described in the SLE patients. Such lesions were later also found in patients without SLE but with antiphospholipid antibodies [280, 281]. The active Libman-Sacks lesions have accumulations of fibrin clumps, lymphocytes, and plasma cells that upon healing are converted to dense vascularized fibrous tissue with an absence of calcification [272]. Ig and complement are found deposited often throughout the valve leaflet inside and outside of the verrucae [282]. In patients with antiphospholipid syndrome, anti-β2-glycoprotein antibodies are deposited in the verrucae [283].

Patients with SLE are at increased risk for accelerated atherosclerosis that cannot be explained entirely by traditional atherosclerosis risk factors [284]. While it is still undetermined what the cause(s) of the accelerated atherosclerosis in SLE are, attention has focused on the autoimmune and inflammatory state typical of SLE. Monocytes and T cells are recruited to nascent plaques in arterial walls where monocytes secrete monocyte chemotactic protein-1 (MCP-1), IL-6, and TNFα, while the Th1 $CD4^+$ cells produce IFNγ, known to be proinflammatory and atherogenic [284]. Macrophages phagocytose oxidized low-density lipoprotein (oxLDL) to become foam cells. The foam cells contribute to plaque accumulation that is then followed by fibrosis from the extracellular matrix produced by arterial smooth muscle cells [284]. Contributions to accelerated atherosclerosis in SLE might include the presence of IgG anti-oxLDL antibodies and anti-apoA-I antibodies, the latter negating the atheroprotective properties of apoA-I and high-density lipoprotein (HDL) [285, 286].

Vasculitis

Vasculitis is reported to occur in as many as 40 % of patients with SLE [287–289]. Although typically small vessels are involved, medium- and large-sized vessels can also be involved in the vasculitis of SLE [288, 290, 291]. Small vessel involvement is typically that of leukocytoclastic vasculitis while medium-sized involvement shows a necrotizing or polyarteritis nodosum pathology [291, 292]. The spectrum of organs exhibiting vasculitis in SLE includes, most commonly, the skin, but also kidneys, coronary, brain, mesentery, gallbladder, and urinary bladder blood vessels [287, 288, 292–296].

The pathophysiologic mechanism of lupus vasculitis is thought to be secondary to immune complex deposition. Studies using human umbilical cord endothelial cells exposed to IgG immune complexes from lupus sera showed that the immune complexes upregulated endothelial cell expression of the receptor for advanced glycation end products (RAGE) and upregulated expression of ICAM1, vascular cell adhesion molecule-1 (VCAM-1), IL-8, IL-6, TNFα, and MCP-1 [297]. That study also implicated endothelial cell signaling via the HMGB1-RAGE axis to be critical for the lupus immune complex effect in activation of NF-κB p65, ICAM-1, VCAM-1, chemokines, and cytokines [297].

Nervous system

Nervous system involvement has long been recognized as a major feature of SLE and includes a wide spectrum of presentations with varying clinical severity and to different degrees among different patients. There can be involvement of the central nervous system (CNS) and/or the peripheral nervous system (PNS). The term "neuropsychiatric lupus" is used to encompass both neurologic, e.g., stroke, headaches, seizures, myasthenia gravis, demyelinating syndrome, myelopathy, Guillain-Barre syndrome, polyneuropathy, cranial neuropathy, and aseptic meningitis, and psychiatric syndromes, e.g., acute confusional state, anxiety disorders, mood disorder, severe depression, psychosis, and cognitive dysfunction [298]. The incidence of neuropsychiatric lupus reported in the literature varies widely due to the lack of standardized diagnostic criteria [299]. The current mechanistic scenario, although not proven, purposes that certain autoantibodies, with or without complement activation and proinflammatory cytokine proliferation, orchestrate nervous system damage through different processes including immune complex deposition, thrombosis, vasculopathy, and inflammation that result in neurodegeneration [300]. Cerebral atrophy is a common finding on imaging of brains of SLE patients, and significant correlations have been reported between brain atrophy and cerebral dysfunction. Severe cognitive impairment is present in SLE patients in association with reduction in white and gray matter [301, 302]. Brain vasculature in SLE patients with neuropsychiatric involvement displays abnormalities including ischemic infarcts and hemorrhages, narrowing or occlusion of small arteries and veins, and varying degrees of cerebral hypoperfusion [303–308].

Studies measuring neurometabolites underscore the presence of neurodegeneration in neuropsychiatric lupus [309]. *N*-acetylaspartate (NAA), a biomarker of axonal integrity usually present at high levels in normal axons and neurons, is reduced in normal appearing white matter (NAWM), gray matter (GM), and brain lesions in patients with neuropsychiatric lupus [304, 309, 310]. In addition, levels of glial fibrillary protein and neurofilament triplet protein are elevated in cerebrospinal fluid (CSF) of patients with neuropsychiatric lupus and brain involvement, suggesting ongoing neuronal and astrocytic damage [311]. Plasminogen inhibitor activator-1 (PAI-1) and D-dimer levels have been reported to be elevated in patients with increased CSF glial fibrillary acidic protein, neurofilament triplet protein, and tau protein [312]. This result suggests that abnormal fibrinolysis may also be contributing to neuronal and astrocyte damage.

A large array of autoantibodies has been detected in serum or CSF of patients with SLE and has been implicated to various extents in the pathogenesis of neuropsychiatric lupus. These are listed in Table 1 [309]. A subset of anti-DNA autoantibodies may cross-react with the NR2A and NR2B polypeptides of the *N*-methyl-D-aspartate (NMDA) receptor [325–327]. NMDA-binding anti-DNA antibodies caused neuronal damage only after the blood–brain barrier (BBB) was compromised by LPS-induced inflammation in mice [327]. Neuronal dysfunction caused by the combination of NMDA-binding antibody and LPS-induced BBB damage was accompanied by poor memory function in

Table 1 Autoantibodies potentially implicated in nervous system involvement in SLE

Antibody	Reference
NMDA cross-reactive anti-DNA	[327]
Anti-NMDA receptor	[313]
Anti-microtubule-associated protein 2	[314]
Anti-α tubulin	[315]
Anti-ganglioside(s)	[316]
Anti-glial fibrillary acidic protein	[317]
Anti-phospholipid	[318]
Anti-ribosomal P protein	[319]
Anti-endothelial cell	[320]
Anti-intermediate neurofilament α internexin	[321]
Anti-triosephosphate isomerase	[322]
Anti-Smith small nuclear ribonucleoproteins	[323]
Anti-histones	[324]

experimentally treated mice. Mice producing NMDA-binding antibody but without BBB damage showed no signs of memory loss or neuronal dysfunction. These results with NMDA cross-reacting antibodies have important implications for the role of autoantibody in CNS lupus in human SLE.

There is evidence of neuroinflammation in brains of patients with SLE, since levels of soluble VCAM-1, soluble ICAM-1, soluble L-selectin, IL-6, IL-8, IL-10, IFNγ, and TNFα are elevated in CSF of patients with neuropsychiatric lupus [311, 328–336]. The role of complement in patients with neuropsychiatric SLE is unknown, but studies in lupus prone MRL^{lpr} mice demonstrate evidence of complement activation contributing to neuronal apoptosis, CNS inflammation, and BBB damage [337–343]. Correlative studies show that levels of serum or CSF matrix metalloproteinase-9 are higher in SLE patients with neuropsychiatric than in SLE patients without CNS involvement [334, 344].

Hematological system

Some form of hematologic disorder is observed in most patients with active SLE. The disorder(s) take the form of anemia, neutropenia, thrombocytopenia, and/or lymphopenia. Anemia can be due to the anemia of chronic disease, arising from suppressed erythropoiesis secondary to chronic inflammation, anti-erythropoietin autoantibodies, autoimmune hemolytic anemia induced by anti-erythrocyte autoantibody and complement, pure red cell aplasia induced by antibodies to erythropoietin or bone marrow erythroblasts, or aplastic anemia secondary to antibodies to bone marrow precursor cells [345, 346]. Lymphocytes in SLE with leukopenia have reduced expression of CD55 and CD59 that renders the lymphocytes susceptible to lysis by complement [347, 348]. The cause of neutropenia is unknown but is associated with anti-neutrophil antibodies and increased levels of TNF-related apoptosis-inducing ligand (TRAIL) that could increase neutrophil apoptosis [349]. Thrombocytopenia is observed in up to 30 % of patients with SLE and is thought to develop as a result of platelet destruction by antiphospholipid antibodies. Anti-thrombopoietin receptor C-Mpl and anti-CD154 antibodies may also play roles in thrombocytopenia but remains to be proven [350]. In addition to immune thrombocytopenia (ITP) described above, there is also increased incidence of thrombotic thrombocytopenic purpura (TTP) in which there is increased platelet consumption from platelet aggregation and thrombosis. Severe cases of ITP are associated with ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) deficiency or anti-ADAMTS13 antibody that induces platelet aggregation and thrombosis [351].

Summary and conclusions

Several major points emerge from this review. One, genetic disruption of any one of the normal mechanisms that regulate self-tolerance will cause autoimmunity to DNA and LN. This outcome is no doubt a consequence of the innate immune commitment to use nucleic acids as "pathogen danger signals" and a promiscuous, DNA-reactive B cell repertoire. Two, SLE is remarkably heterogeneous with respect to inheritance, genetic susceptibility, and disease phenotype. Clearly, genetic heterogeneity affects phenotypic heterogeneity among different individuals and racial and ethnic subpopulations. Phenotypic heterogeneity in the presence of identical genotypes, monozygotic twins and inbred mice, indicates that the genetic program for SLE is initiated and executed stochastically. Three, very little is known about what exactly initiates SLE in either mice or humans. Most of the receptors and signaling molecules and pathways have been identified, but what actually sets autoimmune activation in motion is unknown. Even in the well-defined mouse genetic models, B/W, MRL^{lpr}, BXSB, BXD2, FcγRIIB$^{-/-}$, and Sanroque, the initiating event leading to the well described and understood autoimmune phenotype is not understood. For example, in mice from all of those strains, DNA-reactive B cells are stimulated or activated to produce anti-DNA autoantibody. The activation is selective and Ig-receptor-dependent. The stimulus is believed to be DNA in the form of chromatin, microparticles, apoptotic bodies, or cellular debris, but the origin of the stimulus is unknown. Four, disease manifestation in SLE is heterogeneous. Both the heterogeneity of disease and the inability to know how and when autoimmunity is initiated make prognosis and therapy such a challenge for SLE. Future longitudinal studies that undertake very broad, inclusive evaluations of as many phenotypic parameters as possible will be necessary. The studies should include evaluation of the circulating proteome and RNA expression in circulating cells. If those studies can include patients prior to disease onset or at least in the very early stages of autoimmunity, the results will almost for sure produce new and useful insight for future diagnostic and therapeutic development.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Kotzin BL (1996) Systemic lupus erythematosus. Cell 85(3):303–306
2. Sherer Y, Gorstein A, Fritzler MJ, Shoenfeld Y (2004) Autoantibody explosion in systemic lupus erythematosus: more than 100 different antibodies found in SLE patients. Semin Arthritis Rheum 34(2):501–537
3. Guidelines ACoRAHCoSLE (1999) Guidelines for referral and management of systemic lupus erythematosus in adults. Arthritis Rheum 42(9):1785–1796
4. Hochberg MC (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40(9):1725. doi:10.1002/1529-0131(199709)40:9<1725::AID-ART29>3.0.CO;2-Y
5. Stoll T, Seifert B, Isenberg DA (1996) SLICC/ACR Damage Index is valid, and renal and pulmonary organ scores are predictors of severe outcome in patients with systemic lupus erythematosus. Br J Rheumatol 35(3):248–254
6. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25(11):1271–1277
7. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, Bruce IN, Isenberg D, Wallace DJ, Nived O, Sturfelt G, Ramsey-Goldman R, Bae SC, Hanly JG, Sanchez-Guerrero J, Clarke A, Aranow C, Manzi S, Urowitz M, Gladman D, Kalunian K, Costner M, Werth VP, Zoma A, Bernatsky S, Ruiz-Irastorza G, Khamashta MA, Jacobsen S, Buyon JP, Maddison P, Dooley MA, van Vollenhoven RF, Ginzler E, Stoll T, Peschken C, Jorizzo JL, Callen JP, Lim SS, Fessler BJ, Inanc M, Kamen DL, Rahman A, Steinsson K, Franks AG Jr, Sigler L, Hameed S, Fang H, Pham N, Brey R, Weisman MH, McGwin G Jr, Magder LS (2012) Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 64(8):2677–2686. doi:10.1002/art.34473
8. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, Karpouzas GA, Merrill JT, Wallace DJ, Yazdany J, Ramsey-Goldman R, Singh K, Khalighi M, Choi SI, Gogia M, Kafaja S, Kamgar M, Lau C, Martin WJ, Parikh S, Peng J, Rastogi A, Chen W, Grossman JM, American College of R (2012) American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 64(6):797–808. doi:10.1002/acr.21664
9. Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, Urowitz M, Fortin PR, Petri M, Barr S, Gordon C, Bae SC, Isenberg D, Zoma A, Aranow C, Dooley MA, Nived O, Sturfelt G, Steinsson K, Alarcon G, Senecal JL, Zummer M, Hanly J, Ensworth S, Pope J, Edworthy S, Rahman A, Sibley J, El-Gabalawy H, McCarthy T, St Pierre Y, Clarke A, Ramsey-Goldman R (2006) Mortality in systemic lupus erythematosus. Arthritis Rheum 54(8):2550–2557. doi:10.1002/art.21955
10. Christensen SR, Kashgarian M, Alexopoulou L, Flavell RA, Akira S, Shlomchik MJ (2005) Toll-like receptor 9 controls anti-DNA autoantibody production in murine lupus. J Exp Med 202(2):321–331. doi:10.1084/jem.20050338
11. Christensen SR, Shupe J, Nickerson K, Kashgarian M, Flavell RA, Shlomchik MJ (2006) Toll-like receptor 7 and TLR9 dictate autoantibody specificity and have opposing inflammatory and regulatory roles in a murine model of lupus. Immunity 25(3):417–428
12. Shlomchik M, Mascelli M, Shan H, Radic MZ, Pisetsky D, Marshak-Rothstein A, Weigert M (1990) Anti-DNA antibodies from autoimmune mice arise by clonal expansion and somatic mutation. J Exp Med 171:265–297
13. Tillman DM, Jou NT, Hill RJ, Marion TN (1992) Both IgM and IgG anti-DNA antibodies are the products of clonally selective B cell stimulation in (NZB x NZW)F1 mice. J Exp Med 176(3):761–779
14. Tan EM (1989) Antinuclear antibodies: diagnostic markers for autoimmune diseases and probes for cell biology. Adv Immunol 44:93–151
15. Petri M (2006) Systemic lupus erythematosus: 2006 update. J Clin Rheumatol 12(1):37–40. doi:10.1097/01.rhu.0000200420.67262.04
16. Ward MM (2004) Prevalence of physician-diagnosed systemic lupus erythematosus in the United States: results from the third national health and nutrition examination survey. J Womens Health (Larchmt) 13(6):713–718. doi:10.1089/1540999041783208
17. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, Liang MH, Kremers HM, Mayes MD, Merkel PA, Pillemer SR, Reveille JD, Stone JH, National Arthritis Data W (2008) Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I Arthritis Rheum 58(1):15–25. doi:10.1002/art.23177
18. McCarty DJ, Manzi S, Medsger TA Jr, Ramsey-Goldman R, LaPorte RE, Kwoh CK (1995) Incidence of systemic lupus erythematosus. Race and gender differences. Arthritis Rheum 38(9):1260–1270
19. Contreras G, Lenz O, Pardo V, Borja E, Cely C, Iqbal K, Nahar N, de La Cuesta C, Hurtado A, Fornoni A, Beltran-Garcia L, Asif A, Young L, Diego J, Zachariah M, Smith-Norwood B (2006) Outcomes in African Americans and Hispanics with lupus nephritis. Kidney Int 69(10):1846–1851. doi:10.1038/sj.ki.5000243
20. Franco C, Yoo W, Franco D, Xu Z (2010) Predictors of end stage renal disease in African Americans with lupus nephritis. Bull NYU Hosp Jt Dis 68(4):251–256
21. Klein-Gitelman MS (2011) Pediatric systemic lupus erythematosus. Medscape Reference. http://emedicine.medscape.com/article/1008066-overview-a0101.
22. Tucker LB, Menon S, Schaller JG, Isenberg DA (1995) Adult- and childhood-onset systemic lupus erythematosus: a comparison of onset, clinical features, serology, and outcome. Br J Rheumatol 34(9):866–872
23. Brunner HI, Huggins J, Klein-Gitelman MS (2011) Pediatric SLE—towards a comprehensive management plan. Nat Rev Rheumatol 7(4):225–233. doi:10.1038/nrrheum.2011.15
24. Andrews BS, Eisenberg RA, Theofilopoulos AN, Izui S, Wilson CB, McConahey PJ, Murphy ED, Roths JB, Dixon FJ (1978) Spontaneous murine lupus-like syndromes. Clinical and immunopathological manifestations in several strains. J Exp Med 148(5):1198–1215
25. Rudofsky UH, Evans BD, Balaban SL, Mottironi VD, Gabrielsen AE (1993) Differences in expression of lupus nephritis in New Zealand mixed H-2z homozygous inbred strains of mice derived from New Zealand black and New Zealand white mice. Origins and initial characterization. Lab Invest 68(4):419–426
26. Wakeland EK, Liu K, Graham RR, Behrens TW (2001) Delineating the genetic basis of systemic lupus erythematosus. Immunity 15(3):397–408
27. Howie JB, Helyer BJ (1968) The immunology and pathology of NZB mice. Adv Immunol 9:215–266
28. Helyer BJ, Howie JB (1963) Renal disease associated with positive lupus erythematosus tests in a cross-bred strain of mice. Nature 197:197
29. Drake CG, Babcock SK, Palmer E, Kotzin BL (1994) Genetic analysis of the NZB contribution to lupus-like autoimmune disease in (NZB x NZW)F1 mice. Proc Natl Acad Sci U S A 91(9):4062–4066
30. Knight JG, Adams DD (1978) Three genes for lupus nephritis in NZB x NZW mice. J Exp Med 147:1653–1660

31. Kono DH, Burlingame RW, Owens DG, Kuramochi A, Balderas RS, Balomenos D, Theofilopoulos AN (1994) Lupus susceptibility loci in New Zealand mice. Proc Natl Acad Sci U S A 91(21):10168–10172
32. Kotzin BL, Palmer E (1987) The contribution of NZW genes to lupus-like disease in (NZB x NZW)F_1 mice. J Exp Med 165:1237–1251
33. Morel L, Wakeland EK (1998) Susceptibility to lupus nephritis in the NZB/W model system. Curr Opin Immunol 10(6):718–725
34. Morel L, Rudofsky UH, Longmate JA, Schiffenbauer J, Wakeland EK (1994) Polygenic control of susceptibility to murine systemic lupus erythematosus. Immunity 1(3):219–229
35. Perry D, Sang A, Yin Y, Zheng YY, Morel L (2011) Murine models of systemic lupus erythematosus. J Biomed Biotechnol 2011: 271694. doi:10.1155/2011/271694
36. Wildin RS, Ramsdell F, Peake J, Faravelli F, Casanova JL, Buist N, Levy-Lahad E, Mazzella M, Goulet O, Perroni L, Bricarelli FD, Byrne G, McEuen M, Proll S, Appleby M, Brunkow ME (2001) X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. Nat Genet 27(1):18–20. doi:10.1038/83707
37. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, Ochs HD (2001) The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 27(1):20–21. doi:10.1038/83713
38. Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, Krohn KJ, Lalioti MD, Mullis PE, Antonarakis SE, Kawasaki K, Asakawa S, Ito F, Shimizu N (1997) Positional cloning of the APECED gene. Nat Genet 17(4): 393–398. doi:10.1038/ng1297-393
39. Finnish-German AC (1997) An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. Nat Genet 17(4):399–403. doi:10.1038/ng1297-399
40. Ahonen P (1985) Autoimmune polyendocrinopathy–candidosis–ectodermal dystrophy (APECED): autosomal recessive inheritance. Clin Genet 27(6):535–542
41. Alarcon-Segovia D, Alarcon-Riquelme ME, Cardiel MH, Caeiro F, Massardo L, Villa AR, Pons-Estel BA, Grupo Latinoamericano de Estudio del Lupus E (2005) Familial aggregation of systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in 1,177 lupus patients from the GLADEL cohort. Arthritis Rheum 52(4):1138–1147. doi:10.1002/art.20999
42. Harley IT, Kaufman KM, Langefeld CD, Harley JB, Kelly JA (2009) Genetic susceptibility to SLE: new insights from fine mapping and genome-wide association studies. Nat Rev Genet 10(5): 285–290. doi:10.1038/nrg2571
43. Block SR, Winfield JB, Lockshin MD, D'Angelo WA, Christian CL (1975) Studies of twins with systemic lupus erythematosus. A review of the literature and presentation of 12 additional sets. Am J Med 59(4):533–552
44. Deapen D, Escalante A, Weinrib L, Horwitz D, Bachman B, Roy-Burman P, Walker A, Mack TM (1992) A revised estimate of twin concordance in systemic lupus erythematosus. Arthritis Rheum 35(3):311–318
45. Boackle SA (2013) Advances in lupus genetics. Curr Opin Rheumatol 25(5):561–568. doi:10.1097/BOR.0b013e328363eb4e
46. Deng Y, Tsao BP (2010) Genetic susceptibility to systemic lupus erythematosus in the genomic era. Nat Rev Rheumatol 6(12):683–692. doi:10.1038/nrrheum.2010.176
47. So HC, Gui AH, Cherny SS, Sham PC (2011) Evaluating the heritability explained by known susceptibility variants: a survey of ten complex diseases. Genet Epidemiol 35(5):310–317. doi:10.1002/gepi.20579
48. Vaughn SE, Kottyan LC, Munroe ME, Harley JB (2012) Genetic susceptibility to lupus: the biological basis of genetic risk found in B cell signaling pathways. J Leukoc Biol 92(3):577–591. doi:10.1189/jlb.0212095
49. Connolly JJ, Hakonarson H (2012) Role of cytokines in systemic lupus erythematosus: recent progress from GWAS and sequencing. J Biomed Biotechnol 2012:798924. doi:10.1155/2012/798924
50. Eisenberg RA, Craven SY, Warren RW, Cohen PL (1987) Stochastic control of anti-Sm autoantibodies in MRL/Mp-lpr/lpr mice. J Clin Invest 80(3):691–697
51. Gray-McGuire C, Moser KL, Gaffney PM, Kelly J, Yu H, Olson JM, Jedrey CM, Jacobs KB, Kimberly RP, Neas BR, Rich SS, Behrens TW, Harley JB (2000) Genome scan of human systemic lupus erythematosus by regression modeling: evidence of linkage and epistasis at 4p16-15.2. Am J Hum Genet 67(6):1460–1469. doi:10.1086/316891
52. Hughes T, Adler A, Kelly JA, Kaufman KM, Williams AH, Langefeld CD, Brown EE, Alarcon GS, Kimberly RP, Edberg JC, Ramsey-Goldman R, Petri M, Boackle SA, Stevens AM, Reveille JD, Sanchez E, Martin J, Niewold TB, Vila LM, Scofield RH, Gilkeson GS, Gaffney PM, Criswell LA, Moser KL, Merrill JT, Jacob CO, Tsao BP, James JA, Vyse TJ, Alarcon-Riquelme ME, Network B, Harley JB, Richardson BC, Sawalha AH (2012) Evidence for gene-gene epistatic interactions among susceptibility loci for systemic lupus erythematosus. Arthritis Rheum 64(2):485–492. doi:10.1002/art.33354
53. Castillejo-Lopez C, Delgado-Vega AM, Wojcik J, Kozyrev SV, Thavathiru E, Wu YY, Sanchez E, Pollmann D, Lopez-Egido JR, Fineschi S, Dominguez N, Lu R, James JA, Merrill JT, Kelly JA, Kaufman KM, Moser KL, Gilkeson G, Frostegard J, Pons-Estel BA, D'Alfonso S, Witte T, Callejas JL, Harley JB, Gaffney PM, Martin J, Guthridge JM, Alarcon-Riquelme ME (2012) Genetic and physical interaction of the B-cell systemic lupus erythematosus-associated genes BANK1 and BLK. Ann Rheum Dis 71(1):136–142. doi:10.1136/annrheumdis-2011-200085
54. Dang J, Shan S, Li J, Zhao H, Xin Q, Liu Y, Bian X, Liu Q (2014) Gene-gene interactions of IRF5, STAT4, IKZF1 and ETS1 in systemic lupus erythematosus. Tissue Antigens 83(6):401–408. doi:10.1111/tan.12349
55. Leng RX, Wang W, Cen H, Zhou M, Feng CC, Zhu Y, Yang XK, Yang M, Zhai Y, Li BZ, Wang XS, Li R, Chen GM, Chen H, Pan HF, Ye DQ (2012) Gene-gene and gene-sex epistatic interactions of MiR146a, IRF5, IKZF1, ETS1 and IL21 in systemic lupus erythematosus. PLoS ONE 7(12):e51090. doi:10.1371/journal.pone.0051090
56. Javierre BM, Fernandez AF, Richter J, Al-Shahrour F, Martin-Subero JI, Rodriguez-Ubreva J, Berdasco M, Fraga MF, O'Hanlon TP, Rider LG, Jacinto FV, Lopez-Longo FJ, Dopazo J, Forn M, Peinado MA, Carreno L, Sawalha AH, Harley JB, Siebert R, Esteller M, Miller FW, Ballestar E (2010) Changes in the pattern of DNA methylation associate with twin discordance in systemic lupus erythematosus. Genome Res 20(2):170–179. doi:10.1101/gr.100289.109
57. Ballestar E, Esteller M, Richardson BC (2006) The epigenetic face of systemic lupus erythematosus. J Immunol 176(12):7143–7147
58. James JA, Kaufman KM, Farris AD, Taylor-Albert E, Lehman TJ, Harley JB (1997) An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. J Clin Invest 100(12):3019–3026. doi:10.1172/JCI119856
59. Botto M, Walport MJ (2002) C1q, autoimmunity and apoptosis. Immunobiology 205(4–5):395–406. doi:10.1078/0171-2985-00141
60. Botto M, Dell'Agnola C, Bygrave AE, Thompson EM, Cook HT, Petry F, Loos M, Pandolfi PP, Walport MJ (1998) Homozygous C1q

deficiency causes glomerulonephritis associated with multiple apoptotic bodies. Nat Genet 19(1):56–59. doi:10.1038/ng0598-56
61. Mazur DJ, Perrino FW (1999) Identification and expression of the TREX1 and TREX2 cDNA sequences encoding mammalian 3′→5′ exonucleases. J Biol Chem 274(28):19655–19660
62. Lee-Kirsch MA, Gong M, Chowdhury D, Senenko L, Engel K, Lee YA, de Silva U, Bailey SL, Witte T, Vyse TJ, Kere J, Pfeiffer C, Harvey S, Wong A, Koskenmies S, Hummel O, Rohde K, Schmidt RE, Dominiczak AF, Gahr M, Hollis T, Perrino FW, Lieberman J, Hubner N (2007) Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 are associated with systemic lupus erythematosus. Nat Genet 39(9):1065–1067. doi:10.1038/ng2091
63. Shaw EA, Stevens AM (2008) Are pediatric autoimmune diseases primarily genetic diseases? Curr Opin Rheumatol 20(5):589–594. doi:10.1097/BOR.0b013e328307f283
64. Hashimoto H, Tsuda H, Matsumoto T, Nasu H, Takasaki Y, Shokawa Y, Hirose S, Terasaki PI, Iwaki Y (1985) HLA antigens associated with systemic lupus erythematosus in Japan. J Rheumatol 12(5):919–923
65. Yuan YJ, Luo XB, Shen N (2010) Current advances in lupus genetic and genomic studies in Asia. Lupus 19(12):1374–1383. doi:10.1177/0961203310376639
66. Arason GJ, Jorgensen GH, Ludviksson BR (2010) Primary immunodeficiency and autoimmunity: lessons from human diseases. Scand J Immunol 71(5):317–328. doi:10.1111/j.1365-3083.2010.02386.x
67. Pickering MC, Botto M, Taylor PR, Lachmann PJ, Walport MJ (2000) Systemic lupus erythematosus, complement deficiency, and apoptosis. Adv Immunol 76:227–324
68. Sullivan KE (1998) Complement deficiency and autoimmunity. Curr Opin Pediatr 10(6):600–606
69. Luo BH, Carman CV, Springer TA (2007) Structural basis of integrin regulation and signaling. Annu Rev Immunol 25:619–647. doi:10.1146/annurev.immunol.25.022106.141618
70. Marnell L, Mold C, Du Clos TW (2005) C-reactive protein: ligands, receptors and role in inflammation. Clin Immunol 117(2):104–111. doi:10.1016/j.clim.2005.08.004
71. Fernando MM, Stevens CR, Sabeti PC, Walsh EC, McWhinnie AJ, Shah A, Green T, Rioux JD, Vyse TJ (2007) Identification of two independent risk factors for lupus within the MHC in United Kingdom families. PLoS Genet 3(11):e192. doi:10.1371/journal.pgen.0030192
72. Chung SA, Taylor KE, Graham RR, Nititham J, Lee AT, Ortmann WA, Jacob CO, Alarcon-Riquelme ME, Tsao BP, Harley JB, Gaffney PM, Moser KL, Petri M, Demirci FY, Kamboh MI, Manzi S, Gregersen PK, Langefeld CD, Behrens TW, Criswell LA (2011) Differential genetic associations for systemic lupus erythematosus based on anti-dsDNA autoantibody production. PLoS Genet 7(3):e1001323. doi:10.1371/journal.pgen.1001323
73. Yang W, Shen N, Ye DQ, Liu Q, Zhang Y, Qian XX, Hirankarn N, Ying D, Pan HF, Mok CC, Chan TM, Wong RW, Lee KW, Mok MY, Wong SN, Leung AM, Li XP, Avihingsanon Y, Wong CM, Lee TL, Ho MH, Lee PP, Chang YK, Li PH, Li RJ, Zhang L, Wong WH, Ng IO, Lau CS, Sham PC, Lau YL (2010) Genome-wide association study in Asian populations identifies variants in ETS1 and WDFY4 associated with systemic lupus erythematosus. PLoS Genet 6(2):e1000841. doi:10.1371/journal.pgen.1000841
74. Harley JB, Alarcon-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, Moser KL, Tsao BP, Vyse TJ, Langefeld CD, Nath SK, Guthridge JM, Cobb BL, Mirel DB, Marion MC, Williams AH, Divers J, Wang W, Frank SG, Namjou B, Gabriel SB, Lee AT, Gregersen PK, Behrens TW, Taylor KE, Fernando M, Zidovetzki R, Gaffney PM, Edberg JC, Rioux JD, Ojwang JO, James JA, Merrill JT, Gilkeson GS, Seldin MF, Yin H, Baechler EC, Li QZ, Wakeland EK, Bruner GR, Kaufman KM, Kelly JA (2008) Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet 40(2):204–210. doi:10.1038/ng.81
75. Hom G, Graham RR, Modrek B, Taylor KE, Ortmann W, Garnier S, Lee AT, Chung SA, Ferreira RC, Pant PV, Ballinger DG, Kosoy R, Demirci FY, Kamboh MI, Kao AH, Tian C, Gunnarsson I, Bengtsson AA, Rantapaa-Dahlqvist S, Petri M, Manzi S, Seldin MF, Ronnblom L, Syvanen AC, Criswell LA, Gregersen PK, Behrens TW (2008) Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX. N Engl J Med 358(9):900–909. doi:10.1056/NEJMoa0707865
76. Sekine H, Ferreira RC, Pan-Hammarstrom Q, Graham RR, Ziemba B, de Vries SS, Liu J, Hippen K, Koeuth T, Ortmann W, Iwahori A, Elliott MK, Offer S, Skon C, Du L, Novitzke J, Lee AT, Zhao N, Tompkins JD, Altshuler D, Gregersen PK, Cunningham-Rundles C, Harris RS, Her C, Nelson DL, Hammarstrom L, Gilkeson GS, Behrens TW (2007) Role for Msh5 in the regulation of Ig class switch recombination. Proc Natl Acad Sci U S A 104(17):7193–7198. doi:10.1073/pnas.0700815104
77. Emamian ES, Leon JM, Lessard CJ, Grandits M, Baechler EC, Gaffney PM, Segal B, Rhodus NL, Moser KL (2009) Peripheral blood gene expression profiling in Sjogren's syndrome. Genes and Immunity 10(4):285–296. doi:10.1038/gene.2009.20
78. Greenberg SA, Pinkus JL, Pinkus GS, Burleson T, Sanoudou D, Tawil R, Barohn RJ, Saperstein DS, Briemberg HR, Ericsson M, Park P, Amato AA (2005) Interferon-alpha/beta-mediated innate immune mechanisms in dermatomyositis. Ann Neurol 57(5):664–678. doi:10.1002/ana.20464
79. Baechler EC, Bauer JW, Slattery CA, Ortmann WA, Espe KJ, Novitzke J, Ytterberg SR, Gregersen PK, Behrens TW, Reed AM (2007) An interferon signature in the peripheral blood of dermatomyositis patients is associated with disease activity. Mol Med 13(1–2):59–68. doi:10.2119/2006-00085.Baechler
80. Braunstein I, Klein R, Okawa J, Werth VP (2012) The interferon-regulated gene signature is elevated in subacute cutaneous lupus erythematosus and discoid lupus erythematosus and correlates with the cutaneous lupus area and severity index score. Br J Dermatol 166(5):971–975. doi:10.1111/j.1365-2133.2012.10825.x
81. Irvine KM, Gallego P, An X, Best SE, Thomas G, Wells C, Harris M, Cotterill A, Thomas R (2012) Peripheral blood monocyte gene expression profile clinically stratifies patients with recent-onset type 1 diabetes. Diabetes 61(5):1281–1290. doi:10.2337/db11-1549
82. Baechler EC, Batliwalla FM, Karypis G, Gaffney PM, Ortmann WA, Espe KJ, Shark KB, Grande WJ, Hughes KM, Kapur V, Gregersen PK, Behrens TW (2003) Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci U S A 100(5):2610–2615. doi:10.1073/pnas.0337679100
83. Bronson PG, Chaivorapol C, Ortmann W, Behrens TW, Graham RR (2012) The genetics of type I interferon in systemic lupus erythematosus. Curr Opin Immunol 24(5):530–537. doi:10.1016/j.coi.2012.07.008
84. Tang D, Kang R, Coyne CB, Zeh HJ, Lotze MT (2012) PAMPs and DAMPs: signal 0s that spur autophagy and immunity. Immunol Rev 249(1):158–175. doi:10.1111/j.1600-065X.2012.01146.x
85. Platanias LC (2005) Mechanisms of type-I- and type-II-interferon-mediated signalling. Nat Rev Immunol 5(5):375–386. doi:10.1038/nri1604
86. Stark GR, Darnell JE Jr (2012) The JAK-STAT pathway at twenty. Immunity 36(4):503–514. doi:10.1016/j.immuni.2012.03.013
87. Morimoto AM, Flesher DT, Yang J, Wolslegel K, Wang X, Brady A, Abbas AR, Quarmby V, Wakshull E, Richardson B, Townsend MJ, Behrens TW (2011) Association of endogenous anti-interferon-alpha autoantibodies with decreased interferon-pathway and disease activity in patients with

systemic lupus erythematosus. Arthritis Rheum 63(8):2407–2415. doi:10.1002/art.30399
88. Cunninghame Graham DS, Graham RR, Manku H, Wong AK, Whittaker JC, Gaffney PM, Moser KL, Rioux JD, Altshuler D, Behrens TW, Vyse TJ (2008) Polymorphism at the TNF superfamily gene TNFSF4 confers susceptibility to systemic lupus erythematosus. Nat Genet 40(1):83–89. doi:10.1038/ng.2007.47
89. Ohshima Y, Tanaka Y, Tozawa H, Takahashi Y, Maliszewski C, Delespesse G (1997) Expression and function of OX40 ligand on human dendritic cells. J Immunol 159(8):3838–3848
90. Latza U, Durkop H, Schnittger S, Ringeling J, Eitelbach F, Hummel M, Fonatsch C, Stein H (1994) The human OX40 homolog: cDNA structure, expression and chromosomal assignment of the ACT35 antigen. Eur J Immunol 24(3):677–683. doi:10.1002/eji.1830240329
91. Jacob CO, McDevitt HO (1988) Tumour necrosis factor-alpha in murine autoimmune 'lupus' nephritis. Nature 331(6154):356–358. doi:10.1038/331356a0
92. Chong WP, Ip WK, Wong WH, Lau CS, Chan TM, Lau YL (2004) Association of interleukin-10 promoter polymorphisms with systemic lupus erythematosus. Genes and Immunity 5(6):484–492. doi:10.1038/sj.gene.6364119
93. Eskdale J, Gallagher G, Verweij CL, Keijsers V, Westendorp RG, Huizinga TW (1998) Interleukin 10 secretion in relation to human IL-10 locus haplotypes. Proc Natl Acad Sci U S A 95(16):9465–9470
94. Lazarus M, Hajeer AH, Turner D, Sinnott P, Worthington J, Ollier WE, Hutchinson IV (1997) Genetic variation in the interleukin 10 gene promoter and systemic lupus erythematosus. J Rheumatol 24(12):2314–2317
95. Sawalha AH, Webb R, Han S, Kelly JA, Kaufman KM, Kimberly RP, Alarcon-Riquelme ME, James JA, Vyse TJ, Gilkeson GS, Choi CB, Scofield RH, Bae SC, Nath SK, Harley JB (2008) Common variants within MECP2 confer risk of systemic lupus erythematosus. PLoS ONE 3(3):e1727. doi:10.1371/journal.pone.0001727
96. Hughes T, Kim-Howard X, Kelly JA, Kaufman KM, Langefeld CD, Ziegler J, Sanchez E, Kimberly RP, Edberg JC, Ramsey-Goldman R, Petri M, Reveille JD, Martin J, Brown EE, Vila LM, Alarcon GS, James JA, Gilkeson GS, Moser KL, Gaffney PM, Merrill JT, Vyse TJ, Alarcon-Riquelme ME, Network B, Nath SK, Harley JB, Sawalha AH (2011) Fine-mapping and transethnic genotyping establish IL2/IL21 genetic association with lupus and localize this genetic effect to IL21. Arthritis Rheum 63(6):1689–1697. doi:10.1002/art.30320
97. Cunninghame Graham DS, Wong AK, McHugh NJ, Whittaker JC, Vyse TJ (2006) Evidence for unique association signals in SLE at the CD28-CTLA4-ICOS locus in a family-based study. Hum Mol Genet 15(21):3195–3205. doi:10.1093/hmg/ddl395
98. Namjou B, Kothari PH, Kelly JA, Glenn SB, Ojwang JO, Adler A, Alarcon-Riquelme ME, Gallant CJ, Boackle SA, Criswell LA, Kimberly RP, Brown E, Edberg J, Stevens AM, Jacob CO, Tsao BP, Gilkeson GS, Kamen DL, Merrill JT, Petri M, Goldman RR, Vila LM, Anaya JM, Niewold TB, Martin J, Pons-Estel BA, Sabio JM, Callejas JL, Vyse TJ, Bae SC, Perrino FW, Freedman BI, Scofield RH, Moser KL, Gaffney PM, James JA, Langefeld CD, Kaufman KM, Harley JB, Atkinson JP (2011) Evaluation of the TREX1 gene in a large multi-ancestral lupus cohort. Genes Immun 12(4):270–279. doi:10.1038/gene.2010.73
99. Bhoj VG, Chen ZJ (2008) Linking retroelements to autoimmunity. Cell 134(4):569–571. doi:10.1016/j.cell.2008.08.010
100. Gaipl US, Beyer TD, Heyder P, Kuenkele S, Bottcher A, Voll RE, Kalden JR, Herrmann M (2004) Cooperation between C1q and DNase I in the clearance of necrotic cell-derived chromatin. Arthritis Rheum 50(2):640–649. doi:10.1002/art.20034
101. Korb LC, Ahearn JM (1997) C1q binds directly and specifically to surface blebs of apoptotic human keratinocytes: complement deficiency and systemic lupus erythematosus revisited. J Immunol 158(10):4525–4528
102. Sellar GC, Cockburn D, Reid KB (1992) Localization of the gene cluster encoding the A, B, and C chains of human C1q to 1p34.1-1p36.3. Immunogenetics 35(3):214–216
103. Napirei M, Karsunky H, Zevnik B, Stephan H, Mannherz HG, Moroy T (2000) Features of systemic lupus erythematosus in Dnase1-deficient mice. Nat Genet 25(2):177–181
104. Scott RS, McMahon EJ, Pop SM, Reap EA, Caricchio R, Cohen PL, Earp HS, Matsushima GK (2001) Phagocytosis and clearance of apoptotic cells is mediated by MER. Nature 411(6834):207–211
105. Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR (1998) Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. Arthritis Rheum 41(7):1241–1250. doi:10.1002/1529-0131(199807)41:7<1241::AID-ART15>3.0.CO;2-H
106. Baumann I, Kolowos W, Voll RE, Manger B, Gaipl U, Neuhuber WL, Kirchner T, Kalden JR, Herrmann M (2002) Impaired uptake of apoptotic cells into tingible body macrophages in germinal centers of patients with systemic lupus erythematosus. Arthritis Rheum 46(1):191–201. doi:10.1002/1529-0131(200201)46:1<191::AID-ART10027>3.0.CO;2-K
107. Russell PJ, Steinberg AD (1983) Studies of peritoneal macrophage function in mice with systemic lupus erythematosus: depressed phagocytosis of opsonized sheep erythrocytes in vitro. Clin Immunol Immunopathol 27(3):387–402
108. Russell PJ, Cameron FH (1986) Studies of macrophage function in murine systemic lupus erythematosus. 3. The nature, anatomical location, and reversibility of the phagocytic defect. J Leukoc Biol 39(1):49–62
109. Fournie GJ, Izui S, Lambert PH, Conte JJ (1976) Genesis and pathogenicity of anti-DNA antibodies. Adv Nephrol Necker Hosp 6:47–61
110. Izui S, Kobayakawa T, Zryd MJ, Louis J, Lambert PH (1977) Mechanism for induction of anti-DNA antibodies by bacterial lipopolysaccharides in mice; II. Correlation between anti-DNA induction and polyclonal antibody formation by various polyclonal B lymphocyte activators. J Immunol 119(6):2157–2162
111. Izui S, Lambert PH, Fournie GJ, Turler H, Miescher PA (1977) Features of systemic lupus erythematosus in mice injected with bacterial lipopolysaccharides: identification of circulating DNA and renal localization of DNA-anti-DNA complexes. J Exp Med 145(5):1115–1130
112. Munoz LE, Janko C, Grossmayer GE, Frey B, Voll RE, Kern P, Kalden JR, Schett G, Fietkau R, Herrmann M, Gaipl US (2009) Remnants of secondarily necrotic cells fuel inflammation in systemic lupus erythematosus. Arthritis Rheum 60(6):1733–1742. doi:10.1002/art.24535
113. Rhodes B, Furnrohr BG, Roberts AL, Tzircotis G, Schett G, Spector TD, Vyse TJ (2012) The rs1143679 (R77H) lupus associated variant of ITGAM (CD11b) impairs complement receptor 3 mediated functions in human monocytes. Ann Rheum Dis 71(12):2028–2034. doi:10.1136/annrheumdis-2012-201390
114. Fossati-Jimack L, Ling GS, Cortini A, Szajna M, Malik TH, McDonald JU, Pickering MC, Cook HT, Taylor PR, Botto M (2013) Phagocytosis is the main CR3-mediated function affected by the lupus-associated variant of CD11b in human myeloid cells. PLoS ONE 8(2):e57082. doi:10.1371/journal.pone.0057082
115. Bolland S, Ravetch JV (2000) Spontaneous autoimmune disease in Fc(gamma)RIIB-deficient mice results from strain-specific epistasis. Immunity 13(2):277–285

116. Linterman MA, Rigby RJ, Wong RK, Yu D, Brink R, Cannons JL, Schwartzberg PL, Cook MC, Walters GD, Vinuesa CG (2009) Follicular helper T cells are required for systemic autoimmunity. J Exp Med 206(3):561–576. doi:10.1084/jem.20081886
117. Vinuesa CG, Cook MC, Angelucci C, Athanasopoulos V, Rui L, Hill KM, Yu D, Domaschenz H, Whittle B, Lambe T, Roberts IS, Copley RR, Bell JI, Cornall RJ, Goodnow CC (2005) A RING-type ubiquitin ligase family member required to repress follicular helper T cells and autoimmunity. Nature 435(7041):452–458
118. Chan VW, Meng F, Soriano P, DeFranco AL, Lowell CA (1997) Characterization of the B lymphocyte populations in Lyn-deficient mice and the role of Lyn in signal initiation and down-regulation. Immunity 7(1):69–81
119. Hibbs ML, Tarlinton DM, Armes J, Grail D, Hodgson G, Maglitto R, Stacker SA, Dunn AR (1995) Multiple defects in the immune system of Lyn-deficient mice, culminating in autoimmune disease. Cell 83(2):301–311
120. Nishizumi H, Taniuchi I, Yamanashi Y, Kitamura D, Ilic D, Mori S, Watanabe T, Yamamoto T (1995) Impaired proliferation of peripheral B cells and indication of autoimmune disease in lyn-deficient mice. Immunity 3(5):549–560
121. Cornall RJ, Cyster JG, Hibbs ML, Dunn AR, Otipoby KL, Clark EA, Goodnow CC (1998) Polygenic autoimmune traits: Lyn, CD22, and SHP-1 are limiting elements of a biochemical pathway regulating BCR signaling and selection. Immunity 8(4):497–508
122. O'Keefe TL, Williams GT, Batista FD, Neuberger MS (1999) Deficiency in CD22, a B cell-specific inhibitory receptor, is sufficient to predispose to development of high affinity autoantibodies. J Exp Med 189(8):1307–1313
123. Portanova JP, Claman HN, Kotzin BL (1985) Autoimmunization in murine graft-vs-host disease. I. Selective production of antibodies to histones and DNA. J Immunol 135(6):3850–3856
124. Gleichmann E, Van Elven EH, Van der Veen JP (1982) A systemic lupus erythematosus (SLE)-like disease in mice induced by abnormal T-B cell cooperation. Preferential formation of autoantibodies characteristic of SLE. Eur J Immunol 12(2):152–159. doi:10.1002/eji.1830120210
125. Morris SC, Cheek RL, Cohen PL, Eisenberg RA (1990) Autoantibodies in chronic graft versus host result from cognate T-B interactions. J Exp Med 171(2):503–517
126. Satoh M, Reeves WH (1994) Induction of lupus-associated autoantibodies in BALB/c mice by intraperitoneal injection of pristane. J Exp Med 180(6):2341–2346
127. Lee PY, Weinstein JS, Nacionales DC, Scumpia PO, Li Y, Butfiloski E, van Rooijen N, Moldawer L, Satoh M, Reeves WH (2008) A novel type I IFN-producing cell subset in murine lupus. J Immunol 180(7):5101–5108
128. Desai DD, Marion TN (2000) Induction of anti-DNA antibody with DNA-peptide complexes. Int Immunol 12(11):1569–1578
129. Desai DD, Krishnan MR, Swindle JT, Marion TN (1993) Antigen-specific induction of antibodies against native mammalian DNA in nonautoimmune mice. J Immunol 151(3):1614–1626
130. Eilat D, Wabl M (2012) B cell tolerance and positive selection in lupus. J Immunol 189(2):503–509. doi:10.4049/jimmunol.1200848
131. Beck-Engeser GB, Eilat D, Harrer T, Jack HM, Wabl M (2009) Early onset of autoimmune disease by the retroviral integrase inhibitor raltegravir. Proc Natl Acad Sci U S A 106(49):20865–20870. doi:10.1073/pnas.0908074106
132. Leadbetter EA, Rifkin IR, Hohlbaum AM, Beaudette BC, Shlomchik MJ, Marshak-Rothstein A (2002) Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. Nature 416(6881):603–607
133. Webb R, Wren JD, Jeffries M, Kelly JA, Kaufman KM, Tang Y, Frank MB, Merrill J, Kimberly RP, Edberg JC, Ramsey-Goldman R, Petri M, Reveille JD, Alarcon GS, Vila LM, Alarcon-Riquelme ME, James JA, Vyse TJ, Moser KL, Gaffney PM, Gilkeson GS, Harley JB, Sawalha AH (2009) Variants within MECP2, a key transcription regulator, are associated with increased susceptibility to lupus and differential gene expression in patients with systemic lupus erythematosus. Arthritis Rheum 60(4):1076–1084. doi:10.1002/art.24360
134. Goodnow CC (1996) Balancing immunity and tolerance: deleting and tuning lymphocyte repertoires. Proc Natl Acad Sci U S A 93(6):2264–2271
135. Krishnan MR, Marion TN (1998) Comparison of the frequencies of arginines in heavy chain CDR3 of antibodies expressed in the primary B-cell repertoires of autoimmune-prone and normal mice. Scand J Immunol 48(3):223–232
136. Christensen SR, Shlomchik MJ (2007) Regulation of lupus-related autoantibody production and clinical disease by Toll-like receptors. Semin Immunol 19(1):11–23
137. Lam GK, Petri M (2005) Assessment of systemic lupus erythematosus. Clin Exp Rheumatol 23(5 Suppl 39):S120–S132
138. Rahman A, Isenberg DA (2008) Systemic lupus erythematosus. N Engl J Med 358(9):929–939. doi:10.1056/NEJMra071297
139. Hasselaar P, Derksen RH, Blokzijl L, de Groot PG (1990) Crossreactivity of antibodies directed against cardiolipin, DNA, endothelial cells and blood platelets. Thromb Haemost 63(2):169–173
140. Lafer EM, Rauch J, Andrzejewski C Jr, Mudd D, Furie B, Furie B, Schwartz RS, Stollar BD (1981) Polyspecific monoclonal lupus autoantibodies reactive with both polynucleotides and phospholipids. J Exp Med 153(4):897–909
141. Manson JJ, Ma A, Rogers P, Mason LJ, Berden JH, van der Vlag J, D'Cruz DP, Isenberg DA, Rahman A (2009) Relationship between anti-dsDNA, anti-nucleosome and anti-alpha-actinin antibodies and markers of renal disease in patients with lupus nephritis: a prospective longitudinal study. Arthritis Res Ther 11(5):R154. doi:10.1186/ar2831
142. Koffler D, Schur PH, Kunkel HG (1967) Immunological studies concerning the nephritis of systemic lupus erythematosus. J Exp Med 126(4):607–624
143. Isenberg DA (1997) Autoantibodies: markers of disease or pathogenic? Ann N Y Acad Sci 823:256–262
144. Krishnan MR, Wang C, Marion TN (2012) Anti-DNA autoantibodies initiate experimental lupus nephritis by binding directly to the glomerular basement membrane in mice. Kidney Int 82(2):184–192. doi:10.1038/ki.2011.484
145. Marion TN, Krishnan MR, Steeves MA, Desai DD (2003) Affinity maturation and autoimmunity to DNA. Curr Dir Autoimmun 6:123–153
146. Crow MK (2007) Type I interferon in systemic lupus erythematosus. Curr Top Microbiol Immunol 316:359–386
147. Banchereau J, Pascual V (2006) Type I interferon in systemic lupus erythematosus and other autoimmune diseases. Immunity 25(3):383–392. doi:10.1016/j.immuni.2006.08.010
148. Pascual V, Banchereau J, Palucka AK (2003) The central role of dendritic cells and interferon-alpha in SLE. Curr Opin Rheumatol 15(5):548–556
149. Wofsy D, Seaman WE (1985) Successful treatment of autoimmunity in NZB/NZW F1 mice with monoclonal antibody to L3T4. J Exp Med 161(2):378–391
150. Vinuesa CG, Linterman MA, Goodnow CC, Randall KL (2010) T cells and follicular dendritic cells in germinal center B-cell formation and selection. Immunol Rev 237(1):72–89. doi:10.1111/j.1600-065X.2010.00937.x
151. Patakas A, Benson RA, Withers DR, Conigliaro P, McInnes IB, Brewer JM, Garside P (2012) Th17 effector cells support B cell responses outside of germinal centres. PLoS ONE 7(11):e49715. doi:10.1371/journal.pone.0049715

152. Hsu HC, Yang P, Wang J, Wu Q, Myers R, Chen J, Yi J, Guentert T, Tousson A, Stanus AL, Le TV, Lorenz RG, Xu H, Kolls JK, Carter RH, Chaplin DD, Williams RW, Mountz JD (2008) Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice. Nat Immunol 9(2):166–175. doi:10.1038/ni1552
153. Hochberg MC, Petri M (1993) Clinical features of systemic lupus erythematosus. Curr Opin Rheumatol 5(5):575–586
154. Isenberg DA, Manson JJ, Ehrenstein MR, Rahman A (2007) Fifty years of anti-ds DNA antibodies: are we approaching journey's end? Rheumatology (Oxford) 46(7):1052–1056. doi:10.1093/rheumatology/kem112
155. Papadimitraki ED, Isenberg DA (2009) Childhood- and adult-onset lupus: an update of similarities and differences. Expert Rev Clin Immunol 5(4):391–403. doi:10.1586/eci.09.29
156. Mellors RC, Ortega LG, Holman HR (1957) Role of gamma globulins in pathogenesis of renal lesions in systemic lupus erythematosus and chronic membranous glomerulonephritis, with an observation on the lupus erythematosus cell reaction. J Exp Med 106(2):191–202
157. Freedman P, Markowitz AS (1962) Isolation of antibody-like gamma-globulin from lupus glomeruli. Br Med J 1(5286):1175–1178
158. Krishnan C, Kaplan MH (1967) Immunopathologic studies of systemic lupus erythematosus. II. Antinuclear reaction of gamma-globulin eluted from homogenates and isolated glomeruli of kidneys from patients with lupus nephritis. J Clin Invest 46(4):569–579. doi:10.1172/JCI105558
159. Aarons I (1964) Renal immunofluorescence in Nzb-Nzw mice. Nature 203:1080–1081. doi:10.1038/2031080a0
160. Channing AA, Kasuga T, Horowitz RE, Dubois EL, Demopoulos HB (1965) An ultrastructural study of spontaneous lupus nephritis in the NZB-BL-NZW mouse. Am J Pathol 47(4):677–694
161. Farquhar MG, Vernier RL, Good RA (1957) An electron microscope study of the glomerulus in nephrosis, glomerulonephritis, and lupus erythematosus. J Exp Med 106(5):649–660
162. Kalaaji M, Mortensen E, Jorgensen L, Olsen R, Rekvig OP (2006) Nephritogenic lupus antibodies recognize glomerular basement membrane-associated chromatin fragments released from apoptotic intraglomerular cells. Am J Pathol 168(6):1779–1792. doi:10.2353/ajpath.2006.051329
163. Chan OT, Hannum LG, Haberman AM, Madaio MP, Shlomchik MJ (1999) A novel mouse with B cells but lacking serum antibody reveals an antibody-independent role for B cells in murine lupus. J Exp Med 189(10):1639–1648
164. Shlomchik MJ, Madaio MP, Ni D, Trounstein M, Huszar D (1994) The role of B cells in lpr/lpr-induced autoimmunity. J Exp Med 180(4):1295–1306
165. Takai T, Li M, Sylvestre D, Clynes R, Ravetch JV (1994) FcR gamma chain deletion results in pleiotrophic effector cell defects. Cell 76(3):519–529
166. Nimmerjahn F, Bruhns P, Horiuchi K, Ravetch JV (2005) FcgammaRIV: a novel FcR with distinct IgG subclass specificity. Immunity 23(1):41–51. doi:10.1016/j.immuni.2005.05.010
167. Clynes R, Dumitru C, Ravetch JV (1998) Uncoupling of immune complex formation and kidney damage in autoimmune glomerulonephritis. Science 279(5353):1052–1054. doi:10.1126/science.279.5353.1052
168. Godau J, Heller T, Hawlisch H, Trappe M, Howells E, Best J, Zwirner J, Verbeek JS, Hogarth PM, Gerard C, Van Rooijen N, Klos A, Gessner JE, Kohl J (2004) C5a initiates the inflammatory cascade in immune complex peritonitis. J Immunol 173(5):3437–3445
169. Wang Y, Hu Q, Madri JA, Rollins SA, Chodera A, Matis LA (1996) Amelioration of lupus-like autoimmune disease in NZB/WF1 mice after treatment with a blocking monoclonal antibody specific for complement component C5. Proc Natl Acad Sci U S A 93(16):8563–8568
170. Shushakova N, Skokowa J, Schulman J, Baumann U, Zwirner J, Schmidt RE, Gessner JE (2002) C5a anaphylatoxin is a major regulator of activating versus inhibitory FcgammaRs in immune complex-induced lung disease. J Clin Invest 110(12):1823–1830. doi:10.1172/JCI16577
171. Skokowa J, Ali SR, Felda O, Kumar V, Konrad S, Shushakova N, Schmidt RE, Piekorz RP, Nurnberg B, Spicher K, Birnbaumer L, Zwirner J, Claassens JW, Verbeek JS, van Rooijen N, Kohl J, Gessner JE (2005) Macrophages induce the inflammatory response in the pulmonary Arthus reaction through G alpha i2 activation that controls C5aR and Fc receptor cooperation. J Immunol 174(5):3041–3050
172. Walport MJ (2000) Lupus, DNase and defective disposal of cellular debris. Nat Genet 25(2):135–136. doi:10.1038/75963
173. Uciechowski P, Schwarz M, Gessner JE, Schmidt RE, Resch K, Radeke HH (1998) IFN-gamma induces the high-affinity Fc receptor I for IgG (CD64) on human glomerular mesangial cells. Eur J Immunol 28(9):2928–2935
174. Morcos M, Hansch GM, Schonermark M, Ellwanger S, Harle M, Heckl-Ostreicher B (1994) Human glomerular mesangial cells express CD16 and may be stimulated via this receptor. Kidney Int 46(6):1627–1634
175. Lopez-Armada MJ, Gomez-Guerrero C, Egido J (1996) Receptors for immune complexes activate gene expression and synthesis of matrix proteins in cultured rat and human mesangial cells: role of TGF-beta. J Immunol 157(5):2136–2142
176. Kanapathippillai P, Hedberg A, Fenton CG, Fenton KA (2013) Nucleosomes contribute to increase mesangial cell chemokine expression during the development of lupus nephritis. Cytokine 62(2):244–252. doi:10.1016/j.cyto.2013.03.016
177. Qing X, Zavadil J, Crosby MB, Hogarth MP, Hahn BH, Mohan C, Gilkeson GS, Bottinger EP, Putterman C (2006) Nephritogenic anti-DNA antibodies regulate gene expression in MRL/lpr mouse glomerular mesangial cells. Arthritis Rheum 54(7):2198–2210. doi:10.1002/art.21934
178. Radeke HH, Janssen-Graalfs I, Sowa EN, Chouchakova N, Skokowa J, Loscher F, Schmidt RE, Heeringa P, Gessner JE (2002) Opposite regulation of type II and III receptors for immunoglobulin G in mouse glomerular mesangial cells and in the induction of anti-glomerular basement membrane (GBM) nephritis. J Biol Chem 277(30):27535–27544. doi:10.1074/jbc.M200419200
179. Patole PS, Pawar RD, Lech M, Zecher D, Schmidt H, Segerer S, Ellwart A, Henger A, Kretzler M, Anders HJ (2006) Expression and regulation of Toll-like receptors in lupus-like immune complex glomerulonephritis of MRL-Fas(lpr) mice. Nephrol Dial Transplant 21(11):3062–3073. doi:10.1093/ndt/gfl336
180. Hemmi H, Takeuchi O, Kawai T, Kaisho T, Sato S, Sanjo H, Matsumoto M, Hoshino K, Wagner H, Takeda K, Akira S (2000) A Toll-like receptor recognizes bacterial DNA. Nature 408(6813):740–745
181. Bergtold A, Gavhane A, D'Agati V, Madaio M, Clynes R (2006) FcR-bearing myeloid cells are responsible for triggering murine lupus nephritis. J Immunol 177(10):7287–7295
182. Calvani N, Richards HB, Tucci M, Pannarale G, Silvestris F (2004) Up-regulation of IL-18 and predominance of a Th1 immune response is a hallmark of lupus nephritis. Clin Exp Immunol 138(1):171–178. doi:10.1111/j.1365-2249.2004.02588.x
183. Jacob CO, van der Meide PH, McDevitt HO (1987) In vivo treatment of (NZB X NZW)F1 lupus-like nephritis with monoclonal antibody to gamma interferon. J Exp Med 166(3):798–803
184. Bagavant H, Deshmukh US, Wang H, Ly T, Fu SM (2006) Role for nephritogenic T cells in lupus glomerulonephritis: progression to renal failure is accompanied by T cell

activation and expansion in regional lymph nodes. J Immunol 177(11):8258–8265
185. Harrington LE, Mangan PR, Weaver CT (2006) Expanding the effector CD4 T-cell repertoire: the Th17 lineage. Curr Opin Immunol 18(3):349–356. doi:10.1016/j.coi.2006.03.017
186. Nalbandian A, Crispin JC, Tsokos GC (2009) Interleukin-17 and systemic lupus erythematosus: current concepts. Clin Exp Immunol 157(2):209–215. doi:10.1111/j.1365-2249.2009.03944.x
187. Pisitkun P, Ha HL, Wang H, Claudio E, Tivy CC, Zhou H, Mayadas TN, Illei GG, Siebenlist U (2012) Interleukin-17 cytokines are critical in development of fatal lupus glomerulonephritis. Immunity 37(6):1104–1115. doi:10.1016/j.immuni.2012.08.014
188. Ebling F, Hahn BH (1980) Restricted subpopulations of DNA antibodies in kidneys of mice with systemic lupus. Comparison of antibodies in serum and renal eluates. Arthritis Rheum 23(4):392–403
189. Gladman DD, Urowitz MB, Keystone EC (1979) Serologically active clinically quiescent systemic lupus erythematosus: a discordance between clinical and serological features. Am J Med 66:210–215
190. Madaio MP (1999) The role of autoantibodies in the pathogenesis of lupus nephritis. Semin Nephrol 19(1):48–56
191. Ng KP, Manson JJ, Rahman A, Isenberg DA (2006) Association of antinucleosome antibodies with disease flare in serologically active clinically quiescent patients with systemic lupus erythematosus. Arthritis Rheum 55(6):900–904. doi:10.1002/art.22356
192. Swaak AJ, Aarden LA, Statius van Eps LW, Feltkamp TE (1979) Anti-dsDNA and complement profiles as prognostic guides in systemic lupus erythematosus. Arthritis Rheum 22(3):226–235
193. Steeves MA, Marion TN (2004) Tolerance to DNA in (NZB x NZW)F1 mice that inherit an anti-DNA V(H) as a conventional micro H chain transgene but not as a V(H) knock-in transgene. J Immunol 172(11):6568–6577
194. Friedmann D, Yachimovich N, Mostoslavsky G, Pewzner-Jung Y, Ben-Yehuda A, Rajewsky K, Eilat D (1999) Production of high affinity autoantibodies in autoimmune New Zealand Black/New Zealand white F1 mice targeted with an anti-DNA heavy chain. J Immunol 162(8):4406–4416
195. Wellmann U, Letz M, Schneider A, Amann K, Winkler TH (2001) An Ig mu-heavy chain transgene inhibits systemic lupus erythematosus immunopathology in autoimmune (NZB x NZW)F1 mice. Int Immunol 13(12):1461–1469
196. Gilkeson GS, Bernstein K, Pippen AM, Clarke SH, Marion T, Pisetsky DS, Ruiz P, Lefkowith JB (1995) The influence of variable-region somatic mutations on the specificity and pathogenicity of murine monoclonal anti-DNA antibodies. Clin Immunol Immunopathol 76(1 Pt 1):59–67. doi:10.1006/clin.1995.1088
197. Madaio MP, Carlson J, Cataldo J, Ucci A, Migliorini P, Pankewycz O (1987) Murine monoclonal anti-DNA antibodies bind directly to glomerular antigens and form immune deposits. J Immunol 138(9):2883–2889
198. Pankewycz OG, Migliorini P, Madaio MP (1987) Polyreactive autoantibodies are nephritogenic in murine lupus nephritis. J Immunol 139(10):3287–3294
199. Sabbaga J, Line SR, Potocnjak P, Madaio MP (1989) A murine nephritogenic monoclonal anti-DNA autoantibody binds directly to mouse laminin, the major non-collagenous protein component of the glomerular basement membrane. Eur J Immunol 19(1):137–143. doi:10.1002/eji.1830190122
200. Raz E, Brezis M, Rosenmann E, Eilat D (1989) Anti-DNA antibodies bind directly to renal antigens and induce kidney dysfunction in the isolated perfused rat kidney. J Immunol 142(9):3076–3082
201. Kalaaji M, Fenton KA, Mortensen ES, Olsen R, Sturfelt G, Alm P, Rekvig OP (2007) Glomerular apoptotic nucleosomes are central target structures for nephritogenic antibodies in human SLE nephritis. Kidney Int 71(7):664–672. doi:10.1038/sj.ki.5002133
202. Fenton KA, Tommeras B, Marion TN, Rekvig OP (2010) Pure anti-dsDNA mAbs need chromatin structures to promote glomerular mesangial deposits in BALB/c mice. Autoimmunity 43(2):179–188. doi:10.3109/08916930903305633
203. Kramers C, Hylkema MN, van Bruggen MC, van de Lagemaat R, Dijkman HB, Assmann KJ, Smeenk RJ, Berden JH (1994) Anti-nucleosome antibodies complexed to nucleosomal antigens show anti-DNA reactivity and bind to rat glomerular basement membrane in vivo. J Clin Invest 94(2):568–577. doi:10.1172/JCI117371
204. Izui S, Lambert PH, Miescher PA (1976) In vitro demonstration of a particular affinity of glomerular basement membrane and collagen for DNA. A possible basis for a local formation of DNA-anti-DNA complexes in systemic lupus erythematosus. J Exp Med 144(2):428–443
205. Luger K, Mader AW, Richmond RK, Sargent DF, Richmond TJ (1997) Crystal structure of the nucleosome core particle at 2.8 A resolution. Nature 389(6648):251–260. doi:10.1038/38444
206. Schalch T, Duda S, Sargent DF, Richmond TJ (2005) X-ray structure of a tetranucleosome and its implications for the chromatin fibre. Nature 436(7047):138–141. doi:10.1038/nature03686
207. Materese CK, Savelyev A, Papoian GA (2009) Counterion atmosphere and hydration patterns near a nucleosome core particle. J Am Chem Soc 131(41):15005–15013. doi:10.1021/ja905376q
208. Caulfield JP, Farquhar MG (1976) Distribution of annionic sites in glomerular basement membranes: their possible role in filtration and attachment. Proc Natl Acad Sci U S A 73(5):1646–1650
209. Kanwar YS, Farquhar MG (1979) Anionic sites in the glomerular basement membrane. In vivo and in vitro localization to the laminae rarae by cationic probes. J Cell Biol 81(1):137–153
210. Mjelle JE, Rekvig OP, Fenton KA (2007) Nucleosomes possess a high affinity for glomerular laminin and collagen IV and bind nephritogenic antibodies in murine lupus-like nephritis. Ann Rheum Dis 66(12):1661–1668. doi:10.1136/ard.2007.070482
211. Rumore P, Muralidhar B, Lin M, Lai C, Steinman CR (1992) Haemodialysis as a model for studying endogenous plasma DNA: oligonucleosome-like structure and clearance. Clin Exp Immunol 90(1):56–62
212. Gauthier VJ, Tyler LN, Mannik M (1996) Blood clearance kinetics and liver uptake of mononucleosomes in mice. J Immunol 156(3):1151–1156
213. Radic M, Marion TN (2013) Neutrophil extracellular chromatin traps connect innate immune response to autoimmunity. Semin Immunopathol 35(4):465–480. doi:10.1007/s00281-013-0376-6
214. Agodoa LY, Gauthier VJ, Mannik M (1985) Antibody localization in the glomerular basement membrane may precede in situ immune deposit formation in rat glomeruli. J Immunol 134(2):880–884
215. Campbell AM, Kashgarian M, Shlomchik MJ (2012) NADPH oxidase inhibits the pathogenesis of systemic lupus erythematosus. Sci Transl Med 4(157):157ra141. doi:10.1126/scitranslmed.3004801
216. Morshed M, Hlushchuk R, Simon D, Walls AF, Obata-Ninomiya K, Karasuyama H, Djonov V, Eggel A, Kaufmann T, Simon HU, Yousefi S (2014) NADPH oxidase-independent formation of extracellular DNA traps by basophils. J Immunol. doi:10.4049/jimmunol.1303418
217. Cline AM, Radic MZ (2004) Murine lupus autoantibodies identify distinct subsets of apoptotic bodies. Autoimmunity 37(2):85–93
218. Ullal AJ, Pisetsky DS (2013) The role of microparticles in the generation of immune complexes in murine lupus. Clin Immunol 146(1):1–9. doi:10.1016/j.clim.2012.10.004
219. Gauthier VJ, Mannik M, Striker GE (1982) Effect of cationized antibodies in performed immune complexes on deposition and persistence in renal glomeruli. J Exp Med 156(3):766–777
220. Schiffer L, Bethunaickan R, Ramanujam M, Huang W, Schiffer M, Tao H, Madaio MP, Bottinger EP, Davidson A (2008) Activated renal macrophages are markers of disease onset and disease remission in lupus nephritis. J Immunol 180(3):1938–1947

221. Hansen CB, Dahle KW (2012) Cutaneous lupus erythematosus. Dermatol Ther 25(2):99–111. doi:10.1111/j.1529-8019.2012.01508.x
222. Oke V, Wahren-Herlenius M (2013) Cutaneous lupus erythematosus: clinical aspects and molecular pathogenesis. J Intern Med 273(6):544–554. doi:10.1111/joim.12057
223. Flier J, Boorsma DM, van Beek PJ, Nieboer C, Stoof TJ, Willemze R, Tensen CP (2001) Differential expression of CXCR3 targeting chemokines CXCL10, CXCL9, and CXCL11 in different types of skin inflammation. J Pathol 194(4):398–405
224. Wenzel J, Zahn S, Mikus S, Wiechert A, Bieber T, Tuting T (2007) The expression pattern of interferon-inducible proteins reflects the characteristic histological distribution of infiltrating immune cells in different cutaneous lupus erythematosus subsets. Br J Dermatol 157(4):752–757. doi:10.1111/j.1365-2133.2007.08137.x
225. Hofmann SC, Bosma A, Bruckner-Tuderman L, Vukmanovic-Stejic M, Jury EC, Isenberg DA, Mauri C (2013) Invariant natural killer T cells are enriched at the site of cutaneous inflammation in lupus erythematosus. J Dermatol Sci 71(1):22–28. doi:10.1016/j.jdermsci.2013.04.012
226. Popovic K, Ek M, Espinosa A, Padyukov L, Harris HE, Wahren-Herlenius M, Nyberg F (2005) Increased expression of the novel proinflammatory cytokine high mobility group box chromosomal protein 1 in skin lesions of patients with lupus erythematosus. Arthritis Rheum 52(11):3639–3645. doi:10.1002/art.21398
227. Wittmann M, Macdonald A, Renne J (2009) IL-18 and skin inflammation. Autoimmun Rev 9(1):45–48. doi:10.1016/j.autrev.2009.03.003
228. Tanasescu C, Balanescu E, Balanescu P, Olteanu R, Badea C, Grancea C, Vagu C, Bleotu C, Ardeleanu C, Georgescu A (2010) IL-17 in cutaneous lupus erythematosus. Eur J Intern Med 21(3):202–207. doi:10.1016/j.ejim.2010.03.004
229. Zahn S, Rehkamper C, Kummerer BM, Ferring-Schmidt S, Bieber T, Tuting T, Wenzel J (2011) Evidence for a pathophysiological role of keratinocyte-derived type III interferon (IFN-lambda) in cutaneous lupus erythematosus. J Invest Dermatol 131(1):133–140. doi:10.1038/jid.2010.244
230. Maverakis E, Miyamura Y, Bowen MP, Correa G, Ono Y, Goodarzi H (2010) Light, including ultraviolet. J Autoimmun 34(3):J247–J257. doi:10.1016/j.jaut.2009.11.011
231. Bennion SD, Norris DA (1997) Ultraviolet light modulation of autoantigens, epidermal cytokines and adhesion molecules as contributing factors of the pathogenesis of cutaneous LE. Lupus 6(2):181–192
232. Reefman E, Kuiper H, Limburg PC, Kallenberg CG, Bijl M (2008) Type I interferons are involved in the development of ultraviolet B-induced inflammatory skin lesions in systemic lupus erythaematosus patients. Ann Rheum Dis 67(1):11–18. doi:10.1136/ard.2007.070359
233. Oh SH, Roh HJ, Kwon JE, Lee SH, Kim JY, Choi HJ, Lim BJ (2011) Expression of interleukin-17 is correlated with interferon-alpha expression in cutaneous lesions of lupus erythematosus. Clin Exp Dermatol 36(5):512–520. doi:10.1111/j.1365-2230.2010.03996.x
234. Uehara T, Xi Peng X, Bennett B, Satoh Y, Friedman G, Currin R, Brenner DA, Lemasters J (2004) c-Jun N-terminal kinase mediates hepatic injury after rat liver transplantation. Transplantation 78(3):324–332
235. Uehara T, Bennett B, Sakata ST, Satoh Y, Bilter GK, Westwick JK, Brenner DA (2005) JNK mediates hepatic ischemia reperfusion injury. J Hepatol 42(6):850–859. doi:10.1016/j.jhep.2005.01.030
236. Caricchio R, McPhie L, Cohen PL (2003) Ultraviolet B radiation-induced cell death: critical role of ultraviolet dose in inflammation and lupus autoantigen redistribution. J Immunol 171(11):5778–5786
237. Korhonen R, Linker K, Pautz A, Forstermann U, Moilanen E, Kleinert H (2007) Post-transcriptional regulation of human inducible nitric-oxide synthase expression by the Jun N-terminal kinase. Mol Pharmacol 71(5):1427–1434. doi:10.1124/mol.106.033449
238. Suschek CV, Krischel V, Bruch-Gerharz D, Berendji D, Krutmann J, Kroncke KD, Kolb-Bachofen V (1999) Nitric oxide fully protects against UVA-induced apoptosis in tight correlation with Bcl-2 up-regulation. J Biol Chem 274(10):6130–6137
239. Kuhn A, Fehsel K, Lehmann P, Krutmann J, Ruzicka T, Kolb-Bachofen V (1998) Aberrant timing in epidermal expression of inducible nitric oxide synthase after UV irradiation in cutaneous lupus erythematosus. J Invest Dermatol 111(1):149–153. doi:10.1046/j.1523-1747.1998.00253.x
240. Belmont HM, Levartovsky D, Goel A, Amin A, Giorno R, Rediske J, Skovron ML, Abramson SB (1997) Increased nitric oxide production accompanied by the up-regulation of inducible nitric oxide synthase in vascular endothelium from patients with systemic lupus erythematosus. Arthritis Rheum 40(10):1810–1816. doi:10.1002/1529-0131(199710)40:10<1810::AID-ART13>3.0.CO;2-D
241. Yokogawa M, Takaishi M, Nakajima K, Kamijima R, Fujimoto C, Kataoka S, Terada Y, Sano S (2014) Epicutaneous application of toll-like receptor 7 agonists leads to systemic autoimmunity in wild-type mice: a new model of systemic lupus erythematosus. Arthritis & Rheumatol 66(3):694–706. doi:10.1002/art.38298
242. Zamora MR, Warner ML, Tuder R, Schwarz MI (1997) Diffuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival, and outcome. Medicine (Baltimore) 76(3):192–202
243. Hunninghake GW, Fauci AS (1979) Pulmonary involvement in the collagen vascular diseases. Am Rev Respir Dis 119(3):471–503
244. Emlen W (1993) Systemic lupus erythematosus and mixed connective tissue disease. Immunol Allergy Clin N Am 13(2):291–311
245. Santiago-Casas Y, Vila LM (2009) Pulmonary hemorrhage in patients with systemic lupus erythematosus. Curr Respir Med Rev 5(1):49–54. doi:10.2174/157339809787354065
246. Kamen DL, Strange C (2010) Pulmonary manifestations of systemic lupus erythematosus. Clin Chest Med 31(3):479–488. doi:10.1016/j.ccm.2010.05.001
247. Virdi RP, Bashir A, Shahzad G, Iqbal J, Mejia JO (2012) Diffuse alveolar hemorrhage: a rare life-threatening condition in systemic lupus erythematosus. Case Rep Pulmonol 2012:836017. doi:10.1155/2012/836017
248. Santos-Ocampo AS, Mandell BF, Fessler BJ (2000) Alveolar hemorrhage in systemic lupus erythematosus: presentation and management. Chest 118(4):1083–1090
249. Marino CT, Pertschuk LP (1981) Pulmonary hemorrhage in systemic lupus erythematosus. Arch Intern Med 141(2):201–203
250. Travis WD, Colby TV, Lombard C, Carpenter HA (1990) A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol 14(12):1112–1125
251. Hughson MD, He Z, Henegar J, McMurray R (2001) Alveolar hemorrhage and renal microangiopathy in systemic lupus erythematosus. Arch Pathol Lab Med 125(4):475–483. doi:10.1043/0003-9985(2001)125<0475:aharmi>2.0.co;2
252. Leatherman JW (1987) Immune alveolar hemorrhage. Chest 91(6):891–897
253. Myers JL, Katzenstein AA (1986) Microangiitis in lupus-induced pulmonary hemorrhage. Am J Clin Pathol 85(5):552–556
254. Schwab EP, Schumacher HR Jr, Freundlich B, Callegari PE (1993) Pulmonary alveolar hemorrhage in systemic lupus erythematosus. Semin Arthritis Rheum 23(1):8–15
255. Nellessen CM, Poge U, Brensing KA, Sauerbruch T, Klehr HU, Rabe C (2008) Diffuse alveolar haemorrhage in a systemic lupus erythematosus patient successfully treated with rituximab: a case report. Nephrol Dial Transplant 23(1):385–386. doi:10.1093/ndt/gfm701
256. Badsha H, Teh CL, Kong KO, Lian TY, Chng HH (2004) Pulmonary hemorrhage in systemic lupus erythematosus. Semin Arthritis Rheum 33(6):414–421

257. Esmaeilbeigi F, Juvet S, Hwang D, Mittoo S (2012) Desquamative interstitial pneumonitis in a patient with systemic lupus erythematosus. Can Respir J : J Can Thoracic Soc 19(1):50–52
258. Haupt HM, Moore GW, Hutchins GM (1981) The lung in systemic lupus erythematosus. Analysis of the pathologic changes in 120 patients. Am J Med 71(5):791–798
259. Matthay RA, Schwarz MI, Petty TL, Stanford RE, Gupta RC, Sahn SA, Steigerwald JC (1975) Pulmonary manifestations of systemic lupus erythematosus: review of twelve cases of acute lupus pneumonitis. Medicine (Baltimore) 54(5):397–409
260. Cervera R, Font J, Pare C, Azqueta M, Perez-Villa F, Lopez-Soto A, Ingelmo M (1992) Cardiac disease in systemic lupus erythematosus: prospective study of 70 patients. Ann Rheum Dis 51(2):156–159
261. Law WG, Thong BY, Lian TY, Kong KO, Chng HH (2005) Acute lupus myocarditis: clinical features and outcome of an oriental case series. Lupus 14(10):827–831
262. Nihoyannopoulos P, Gomez PM, Joshi J, Loizou S, Walport MJ, Oakley CM (1990) Cardiac abnormalities in systemic lupus erythematosus. Association with raised anticardiolipin antibodies. Circulation 82(2):369–375
263. Crozier IG, Li E, Milne MJ, Nicholls MG (1990) Cardiac involvement in systemic lupus erythematosus detected by echocardiography. Am J Cardiol 65(16):1145–1148
264. Sturfelt G, Eskilsson J, Nived O, Truedsson L, Valind S (1992) Cardiovascular disease in systemic lupus erythematosus. A study of 75 patients form a defined population. Medicine (Baltimore) 71(4): 216–223
265. Wolkove N, Frank H (1974) Lupus pericarditis. Can Med Assoc J 111(12):1331–1333
266. Castier MB, Albuquerque EM, Menezes ME, Klumb E, Albanesi Filho FM (2000) Cardiac tamponade in systemic lupus erythematosus. Report of four cases. Arq Bras Cardiol 75(5):446–448
267. Goldenber D (1973) Pericardial-fluid complement. Ann Intern Med 78(5):786
268. Doherty NE, Siegel RJ (1985) Cardiovascular manifestations of systemic lupus erythematosus. Am Heart J 110(6):1257–1265
269. Harvey AM, Shulman LE, Tumulty PA, Conley CL, Schoenrich EH (1954) Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. Medicine (Baltimore) 33(4):291–437
270. Badui E, Garcia-Rubi D, Robles E, Jimenez J, Juan L, Deleze M, Diaz A, Mintz G (1985) Cardiovascular manifestations in systemic lupus erythematosus. Prospective study of 100 patients. Angiology 36(7):431–441
271. Estes D, Christian CL (1971) The natural history of systemic lupus erythematosus by prospective analysis. Medicine (Baltimore) 50(2): 85–95
272. Bulkley BH, Roberts WC (1975) The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy. A study of 36 necropsy patients. Am J Med 58(2):243–264
273. Esscher E, Scott JS (1979) Congenital heart block and maternal systemic lupus erythematosus. Br Med J 1(6173):1235–1238
274. Buyon JP, Ben-Chetrit E, Karp S, Roubey RA, Pompeo L, Reeves WH, Tan EM, Winchester R (1989) Acquired congenital heart block. Pattern of maternal antibody response to biochemically defined antigens of the SSA/Ro-SSB/La system in neonatal lupus. J Clin Invest 84(2):627–634. doi:10.1172/JCI114208
275. Derksen RH, Meilof JF (1992) Anti-Ro/SS-A and anti-La/SS-B autoantibody levels in relation to systemic lupus erythematosus disease activity and congenital heart block. A longitudinal study comprising two consecutive pregnancies in a patient with systemic lupus erythematosus. Arthritis Rheum 35(8):953–959
276. Fritsch C, Hoebeke J, Dali H, Ricchiuti V, Isenberg DA, Meyer O, Muller S (2006) 52-kDa Ro/SSA epitopes preferentially recognized by antibodies from mothers of children with neonatal lupus and congenital heart block. Arthritis Res & Ther 8(1):R4. doi:10.1186/ar1848
277. Reed BR, Lee LA, Harmon C, Wolfe R, Wiggins J, Peebles C, Weston WL (1983) Autoantibodies to SS-A/Ro in infants with congenital heart block. J Pediatr 103(6):889–891
278. Eftekhari P, Salle L, Lezoualc'h F, Mialet J, Gastineau M, Briand JP, Isenberg DA, Fournie GJ, Argibay J, Fischmeister R, Muller S, Hoebeke J (2000) Anti-SSA/Ro52 autoantibodies blocking the cardiac 5-HT4 serotoninergic receptor could explain neonatal lupus congenital heart block. Eur J Immunol 30(10):2782–2790. doi:10.1002/1521-4141(200010)30:10<2782::AID-IMMU2782>3.0.CO;2-9
279. Roldan CA, Shively BK, Crawford MH (1996) An echocardiographic study of valvular heart disease associated with systemic lupus erythematosus. N Engl J Med 335(19):1424–1430. doi:10.1056/NEJM199611073351903
280. Libman E, Sacks B (1924) A hitherto undescribed form of valvular and mural endocarditis. Arch Intern Med 33(8):701–737. doi:10.1001/archinte.1924.00110300044002
281. D'Alton JG, Preston DN, Bormanis J, Green MS, Kraag GR (1985) Multiple transient ischemic attacks, lupus anticoagulant and verrucous endocarditis. Stroke 16(3):512–514
282. Bidani AK, Roberts JL, Schwartz MM, Lewis EJ (1980) Immunopathology of cardiac lesions in fatal systemic lupus erythematosus. Am J Med 69(6):849–858
283. Ziporen L, Goldberg I, Arad M, Hojnik M, Ordi-Ros J, Afek A, Blank M, Sandbank Y, Vilardell-Tarres M, de Torres I, Weinberger A, Asherson RA, Kopolovic Y, Shoenfeld Y (1996) Libman-Sacks endocarditis in the antiphospholipid syndrome: immunopathologic findings in deformed heart valves. Lupus 5(3):196–205
284. Skaggs BJ, Hahn BH, McMahon M (2012) Accelerated atherosclerosis in patients with SLE—mechanisms and management. Nat Rev Rheumatol 8(4):214–223. doi:10.1038/nrrheum.2012.14
285. Fesmire J, Wolfson-Reichlin M, Reichlin M (2010) Effects of autoimmune antibodies anti-lipoprotein lipase, anti-low density lipoprotein, and anti-oxidized low density lipoprotein on lipid metabolism and atherosclerosis in systemic lupus erythematosus. Rev Bras Reumatol 50(5):539–551
286. O'Neill SG, Giles I, Lambrianides A, Manson J, D'Cruz D, Schrieber L, March LM, Latchman DS, Isenberg DA, Rahman A (2010) Antibodies to apolipoprotein A-I, high-density lipoprotein, and C-reactive protein are associated with disease activity in patients with systemic lupus erythematosus. Arthritis Rheum 62(3): 845–854. doi:10.1002/art.27286
287. Cieslik P, Hrycek A, Klucinski P (2008) Vasculopathy and vasculitis in systemic lupus erythematosus. Pol Arch Med Wewn 118(1–2):57–63
288. Calamia KT, Balabanova M (2004) Vasculitis in systemic lupus erythematosis. Clin Dermatol 22(2):148–156. doi:10.1016/j.clindermatol.2003.12.022
289. Ramos-Casals M, Nardi N, Lagrutta M, Brito-Zeron P, Bove A, Delgado G, Cervera R, Ingelmo M, Font J (2006) Vasculitis in systemic lupus erythematosus: prevalence and clinical characteristics in 670 patients. Medicine (Baltimore) 85(2):95–104. doi:10.1097/01.md.0000216817.35937.70
290. Kumar N, Choudhary N, Agarwal G, Rizvi Y, Kaul B, Ahlawat R (2007) Extensive medium-vessel vasculitis with SLE: an unusual association. J Clin Rheumatol 13(3):140–142. doi:10.1097/RHU.0b013e318064e779
291. Matsumoto T, Kobayashi S, Shimizu H, Nakajima M, Watanabe S, Kitami N, Sato N, Abe H, Aoki Y, Hoshi T, Hashimoto H (2000) The liver in collagen diseases: pathologic study of 160 cases with particular reference to hepatic arteritis, primary biliary cirrhosis, autoimmune hepatitis and nodular regenerative hyperplasia of the liver. Liver 20(5):366–373
292. Swanepoel CR, Floyd A, Allison H, Learmonth GM, Cassidy MJ, Pascoe MD (1983) Acute acalculous cholecystitis complicating systemic lupus erythematosus: case report and review. Br Med J (Clin Res Ed) 286(6361):251–252

293. Yuan S, Ye Y, Chen D, Qiu Q, Zhan Z, Lian F, Li H, Liang L, Xu H, Yang X (2013) Lupus mesenteric vasculitis: clinical features and associated factors for the recurrence and prognosis of disease. Semin Arthritis Rheum. doi:10.1016/j.semarthrit.2013.11.005
294. Ashouri JF, Davis JL, Farkas A, Durack JC, Ramachandran R, Dall'Era M (2012) A young woman with systemic lupus erythematosus and extensive mesenteric vasculitis involving small and medium vessels. Arthritis Care Res (Hoboken) 64(12):1928–1933. doi:10.1002/acr.21833
295. Weisman MH, McDanald EC, Wilson CB (1981) Studies of the pathogenesis of interstitial cystitis, obstructive uropathy, and intestinal malabsorption in a patient with systemic lupus erythematosus. Am J Med 70(4):875–881
296. Geri G, Saadoun D, Guillevin R, Crozier S, Lubetzki C, Mokhtari K, Amoura Z, Wechsler B, Le Boutin D, Costedoat-Chalumeau N, Samson Y, Cacoub P (2014) Central nervous system angiitis: a series of 31 patients. Clin Rheumatol 33(1):105–110. doi:10.1007/s10067-013-2403-3
297. Sun W, Jiao Y, Cui B, Gao X, Xia Y, Zhao Y (2013) Immune complexes activate human endothelium involving the cell-signaling HMGB1-RAGE axis in the pathogenesis of lupus vasculitis. Lab Invest 93(6):626–638. doi:10.1038/labinvest.2013.61
298. Sciascia S, Bertolaccini ML, Baldovino S, Roccatello D, Khamashta MA, Sanna G (2013) Central nervous system involvement in systemic lupus erythematosus: overview on classification criteria. Autoimmun Rev 12(3):426–429. doi:10.1016/j.autrev.2012.08.014
299. Borowoy AM, Pope JE, Silverman E, Fortin PR, Pineau C, Smith CD, Arbillaga H, Gladman D, Urowitz M, Zummer M, Hudson M, Tucker L, Peschken C (2012) Neuropsychiatric lupus: the prevalence and autoantibody associations depend on the definition: results from the 1000 faces of lupus cohort. Semin Arthritis Rheum 42(2):179–185. doi:10.1016/j.semarthrit.2012.03.011
300. Levy DM, Ardoin SP, Schanberg LE (2009) Neurocognitive impairment in children and adolescents with systemic lupus erythematosus. Nat Clin Pract Rheumatol 5(2):106–114. doi:10.1038/ncprheum0988
301. Bosma GP, Middelkoop HA, Rood MJ, Bollen EL, Huizinga TW, van Buchem MA (2002) Association of global brain damage and clinical functioning in neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 46(10):2665–2672. doi:10.1002/art.10574
302. Appenzeller S, Bonilha L, Rio PA, Min Li L, Costallat LT, Cendes F (2007) Longitudinal analysis of gray and white matter loss in patients with systemic lupus erythematosus. Neuroimage 34(2):694–701. doi:10.1016/j.neuroimage.2006.09.029
303. Sibbitt WL Jr, Brooks WM, Kornfeld M, Hart BL, Bankhurst AD, Roldan CA (2010) Magnetic resonance imaging and brain histopathology in neuropsychiatric systemic lupus erythematosus. Semin Arthritis Rheum 40(1):32–52. doi:10.1016/j.semarthrit.2009.08.005
304. Sibbitt WL Jr, Sibbitt RR, Brooks WM (1999) Neuroimaging in neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 42(10):2026–2038. doi:10.1002/1529-0131(199910)42:10<2026::aid-anr2>3.0.co;2-j
305. Luyendijk J, Steens SC, Ouwendijk WJ, Steup-Beekman GM, Bollen EL, van der Grond J, Huizinga TW, Emmer BJ, van Buchem MA (2011) Neuropsychiatric systemic lupus erythematosus: lessons learned from magnetic resonance imaging. Arthritis Rheum 63(3):722–732. doi:10.1002/art.30157
306. Nobili F, Mignone A, Rossi E, Morbelli S, Piccardo A, Puppo F, Indiveri F, Sambuceti G, Rodriguez G (2006) Migraine during systemic lupus erythematosus: findings from brain single photon emission computed tomography. J Rheumatol 33(11):2184–2191
307. Zhang X, Zhu Z, Zhang F, Shu H, Li F, Dong Y (2005) Diagnostic value of single-photon-emission computed tomography in severe central nervous system involvement of systemic lupus erythematosus: a case–control study. Arthritis Rheum 53(6):845–849. doi:10.1002/art.21591
308. Appenzeller S, Amorim BJ, Ramos CD, Rio PA, de Etchebehere EC, Camargo EE, Cendes F, Costallat LT (2007) Voxel-based morphometry of brain SPECT can detect the presence of active central nervous system involvement in systemic lupus erythematosus. Rheumatology (Oxford) 46(3):467–472. doi:10.1093/rheumatology/kel255
309. Kapadia M, Sakic B (2011) Autoimmune and inflammatory mechanisms of CNS damage. Prog Neurobiol 95(3):301–333. doi:10.1016/j.pneurobio.2011.08.008
310. Axford JS, Howe FA, Heron C, Griffiths JR (2001) Sensitivity of quantitative (1)H magnetic resonance spectroscopy of the brain in detecting early neuronal damage in systemic lupus erythematosus. Ann Rheum Dis 60(2):106–111
311. Trysberg E, Nylen K, Rosengren LE, Tarkowski A (2003) Neuronal and astrocytic damage in systemic lupus erythematosus patients with central nervous system involvement. Arthritis Rheum 48(10):2881–2887. doi:10.1002/art.11279
312. Kwiecinski J, Klak M, Trysberg E, Blennow K, Tarkowski A, Jin T (2009) Relationship between elevated cerebrospinal fluid levels of plasminogen activator inhibitor 1 and neuronal destruction in patients with neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 60(7):2094–2101. doi:10.1002/art.24603
313. Gono T, Kawaguchi Y, Kaneko H, Nishimura K, Hanaoka M, Kataoka S, Okamoto Y, Katsumata Y, Yamanaka H (2011) Anti-NR2A antibody as a predictor for neuropsychiatric systemic lupus erythematosus. Rheumatology (Oxford) 50(9):1578–1585. doi:10.1093/rheumatology/keq408
314. Lefranc D, Launay D, Dubucquoi S, de Seze J, Dussart P, Vermersch M, Hachulla E, Hatron PY, Vermersch P, Mouthon L, Prin L (2007) Characterization of discriminant human brain antigenic targets in neuropsychiatric systemic lupus erythematosus using an immunoproteomic approach. Arthritis Rheum 56(10):3420–3432. doi:10.1002/art.22863
315. Ndhlovu M, Preuss BE, Dengjel J, Stevanovic S, Weiner SM, Klein R (2011) Identification of alpha-tubulin as an autoantigen recognized by sera from patients with neuropsychiatric systemic lupus erythematosus. Brain Behav Immun 25(2):279–285. doi:10.1016/j.bbi.2010.09.019
316. Galeazzi M, Annunziata P, Sebastiani GD, Bellisai F, Campanella V, Ferrara GB, Font J, Houssiau F, Passiu G, De Ramon GE, Fernandez-Nebro A, Bracci L, Scorza R, Puddu P, Jedryka-Goral A, Smolen J, Tincani A, Carcassi C, Morozzi G, Marcolongo R (2000) Anti-ganglioside antibodies in a large cohort of European patients with systemic lupus erythematosus: clinical, serological, and HLA class II gene associations. European Concerted Action on the Immunogenetics of SLE The Journal of rheumatology 27(1):135–141
317. Sanna G, Piga M, Terryberry JW, Peltz MT, Giagheddu S, Satta L, Ahmed A, Cauli A, Montaldo C, Passiu G, Peter JB, Shoenfeld Y, Mathieu A (2000) Central nervous system involvement in systemic lupus erythematosus: cerebral imaging and serological profile in patients with and without overt neuropsychiatric manifestations. Lupus 9(8):573–583
318. Afeltra A, Garzia P, Mitterhofer AP, Vadacca M, Galluzzo S, Del Porto F, Finamore L, Pascucci S, Gasparini M, Lagana B, Caccavo D, Ferri GM, Amoroso A, Francia A (2003) Neuropsychiatric lupus syndromes: relationship with antiphospholipid antibodies. Neurology 61(1):108–110
319. Hanly JG, Urowitz MB, Siannis F, Farewell V, Gordon C, Bae SC, Isenberg D, Dooley MA, Clarke A, Bernatsky S, Gladman D, Fortin PR, Manzi S, Steinsson K, Bruce IN, Ginzler E, Aranow C, Wallace DJ, Ramsey-Goldman R, van Vollenhoven R, Sturfelt G, Nived O, Sanchez-Guerrero J, Alarcon GS, Petri M, Khamashta M, Zoma A, Font J, Kalunian K, Douglas J, Qi Q, Thompson K, Merrill JT (2008) Autoantibodies and neuropsychiatric events at the time of systemic lupus erythematosus diagnosis: results from an

international inception cohort study. Arthritis Rheum 58(3):843–853. doi:10.1002/art.23218
320. Meroni PL, Tincani A, Sepp N, Raschi E, Testoni C, Corsini E, Cavazzana I, Pellegrini S, Salmaggi A (2003) Endothelium and the brain in CNS lupus. Lupus 12(12):919–928
321. Lu XY, Chen XX, Huang LD, Zhu CQ, Gu YY, Ye S (2010) Anti-alpha-internexin autoantibody from neuropsychiatric lupus induce cognitive damage via inhibiting axonal elongation and promote neuron apoptosis. PLoS ONE 5(6):e11124. doi:10.1371/journal.pone.0011124
322. Sasajima T, Watanabe H, Sato S, Sato Y, Ohira H (2006) Anti-triosephosphate isomerase antibodies in cerebrospinal fluid are associated with neuropsychiatric lupus. J Neuroimmunol 181(1–2):150–156. doi:10.1016/j.jneuroim.2006.09.003
323. Jurencak R, Fritzler M, Tyrrell P, Hiraki L, Benseler S, Silverman E (2009) Autoantibodies in pediatric systemic lupus erythematosus: ethnic grouping, cluster analysis, and clinical correlations. J Rheumatol 36(2):416–421. doi:10.3899/jrheum.080588
324. Sun XY, Shi J, Han L, Su Y, Li ZG (2008) Anti-histones antibodies in systemic lupus erythematosus: prevalence and frequency in neuropsychiatric lupus. J Clin Lab Anal 22(4):271–277. doi:10.1002/jcla.20248
325. Kowal C, Degiorgio LA, Lee JY, Edgar MA, Huerta PT, Volpe BT, Diamond B (2006) Human lupus autoantibodies against NMDA receptors mediate cognitive impairment. Proc Natl Acad Sci U S A 103(52):19854–19859. doi:10.1073/pnas.0608397104
326. Huerta PT, Kowal C, DeGiorgio LA, Volpe BT, Diamond B (2006) Immunity and behavior: antibodies alter emotion. Proc Natl Acad Sci U S A 103(3):678–683. doi:10.1073/pnas.0510055103
327. Kowal C, DeGiorgio LA, Nakaoka T, Hetherington H, Huerta PT, Diamond B, Volpe BT (2004) Cognition and immunity; antibody impairs memory. Immunity 21(2):179–188. doi:10.1016/j.immuni.2004.07.011
328. Baraczka K, Nekam K, Pozsonyi T, Jakab L, Szongoth M, Sesztak M (2001) Concentration of soluble adhesion molecules (sVCAM-1, sICAM-1 and sL-selectin) in the cerebrospinal fluid and serum of patients with multiple sclerosis and systemic lupus erythematosus with central nervous involvement. Neuroimmunomodulation 9(1):49–54
329. Baraczka K, Nekam K, Pozsonyi T, Szuts I, Ormos G (2004) Investigation of cytokine (tumor necrosis factor-alpha, interleukin-6, interleukin-10) concentrations in the cerebrospinal fluid of female patients with multiple sclerosis and systemic lupus erythematosus. Eur J Neurol 11(1):37–42
330. Katsumata Y, Harigai M, Kawaguchi Y, Fukasawa C, Soejima M, Takagi K, Tanaka M, Ichida H, Tochimoto A, Kanno T, Nishimura K, Kamatani N, Hara M (2007) Diagnostic reliability of cerebral spinal fluid tests for acute confusional state (delirium) in patients with systemic lupus erythematosus: interleukin 6 (IL-6), IL-8, interferon-alpha, IgG index, and Q-albumin. J Rheumatol 34(10):2010–2017
331. Trysberg E, Carlsten H, Tarkowski A (2000) Intrathecal cytokines in systemic lupus erythematosus with central nervous system involvement. Lupus 9(7):498–503
332. Fragoso-Loyo H, Richaud-Patin Y, Orozco-Narvaez A, Davila-Maldonado L, Atisha-Fregoso Y, Llorente L, Sanchez-Guerrero J (2007) Interleukin-6 and chemokines in the neuropsychiatric manifestations of systemic lupus erythematosus. Arthritis Rheum 56(4):1242–1250. doi:10.1002/art.22451
333. Svenungsson E, Andersson M, Brundin L, van Vollenhoven R, Khademi M, Tarkowski A, Greitz D, Dahlstrom M, Lundberg I, Klareskog L, Olsson T (2001) Increased levels of proinflammatory cytokines and nitric oxide metabolites in neuropsychiatric lupus erythematosus. Ann Rheum Dis 60(4):372–379
334. Trysberg E, Tarkowski A (2004) Cerebral inflammation and degeneration in systemic lupus erythematosus. Curr Opin Rheumatol 16(5):527–533
335. Tomita M, Holman BJ, Williams LS, Pang KC, Santoro TJ (2001) Cerebellar dysfunction is associated with overexpression of proinflammatory cytokine genes in lupus. J Neurosci Res 64(1):26–33
336. Mondal TK, Saha SK, Miller VM, Seegal RF, Lawrence DA (2008) Autoantibody-mediated neuroinflammation: pathogenesis of neuropsychiatric systemic lupus erythematosus in the NZM88 murine model. Brain Behav Immun 22(6):949–959. doi:10.1016/j.bbi.2008.01.013
337. Walport MJ (2002) Complement and systemic lupus erythematosus. Arthritis Res 4(Suppl 3):S279–S293
338. Jacob A, Hack B, Chiang E, Garcia JG, Quigg RJ, Alexander JJ (2010) C5a alters blood–brain barrier integrity in experimental lupus. FASEB J 24(6):1682–1688. doi:10.1096/fj.09-138834
339. Jacob A, Bao L, Brorson J, Quigg RJ, Alexander JJ (2010) C3aR inhibition reduces neurodegeneration in experimental lupus. Lupus 19(1):73–82. doi:10.1177/0961203309348978
340. Jacob A, Hack B, Bai T, Brorson JR, Quigg RJ, Alexander JJ (2010) Inhibition of C5a receptor alleviates experimental CNS lupus. J Neuroimmunol 221(1–2):46–52. doi:10.1016/j.jneuroim.2010.02.011
341. Alexander JJ, Jacob A, Bao L, Macdonald RL, Quigg RJ (2005) Complement-dependent apoptosis and inflammatory gene changes in murine lupus cerebritis. J Immunol 175(12):8312–8319
342. Alexander JJ, Bao L, Jacob A, Kraus DM, Holers VM, Quigg RJ (2003) Administration of the soluble complement inhibitor, Crry-Ig, reduces inflammation and aquaporin 4 expression in lupus cerebritis. Biochim Biophys Acta 1639(3):169–176
343. Alexander JJ, Jacob A, Vezina P, Sekine H, Gilkeson GS, Quigg RJ (2007) Absence of functional alternative complement pathway alleviates lupus cerebritis. Eur J Immunol 37(6):1691–1701. doi:10.1002/eji.200636638
344. Ainiala H, Hietaharju A, Dastidar P, Loukkola J, Lehtimaki T, Peltola J, Korpela M, Heinonen T, Nikkari ST (2004) Increased serum matrix metalloproteinase 9 levels in systemic lupus erythematosus patients with neuropsychiatric manifestations and brain magnetic resonance imaging abnormalities. Arthritis Rheum 50(3):858–865. doi:10.1002/art.20045
345. Voulgarelis M, Kokori SI, Ioannidis JP, Tzioufas AG, Kyriaki D, Moutsopoulos HM (2000) Anaemia in systemic lupus erythematosus: aetiological profile and the role of erythropoietin. Ann Rheum Dis 59(3):217–222
346. Schett G, Firbas U, Fureder W, Hiesberger H, Winkler S, Wachauer D, Koller M, Kapiotis S, Smolen J (2001) Decreased serum erythropoietin and its relation to anti-erythropoietin antibodies in anaemia of systemic lupus erythematosus. Rheumatology (Oxford) 40(4):424–431
347. Garcia-Valladares I, Atisha-Fregoso Y, Richaud-Patin Y, Jakez-Ocampo J, Soto-Vega E, Elias-Lopez D, Carrillo-Maravilla E, Cabiedes J, Ruiz-Arguelles A, Llorente L (2006) Diminished expression of complement regulatory proteins (CD55 and CD59) in lymphocytes from systemic lupus erythematosus patients with lymphopenia. Lupus 15(9):600–605
348. Ruiz-Arguelles A, Llorente L (2007) The role of complement regulatory proteins (CD55 and CD59) in the pathogenesis of autoimmune hemocytopenias. Autoimmun Rev 6(3):155–161. doi:10.1016/j.autrev.2006.09.008
349. Midgley A, McLaren Z, Moots RJ, Edwards SW, Beresford MW (2009) The role of neutrophil apoptosis in juvenile-onset systemic lupus erythematosus. Arthritis Rheum 60(8):2390–2401. doi:10.1002/art.24634
350. Hepburn AL, Narat S, Mason JC (2010) The management of peripheral blood cytopenias in systemic lupus erythematosus. Rheumatology (Oxford) 49(12):2243–2254. doi:10.1093/rheumatology/keq269
351. Enami T, Suzuki T, Ito S, Yoshimi A, Sugihara M, Mamura M, Hayashi T, Goto D, Matsumoto I, Tsutsumi A, Sumida T (2007) Successful treatment of refractory thrombotic thrombocytopenic purpura with cyclosporine and corticosteroids in a patient with systemic lupus erythematosus and antibodies to ADAMTS13. Intern Med 46(13):1033–1037