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Systemic lupus erythematosus—messages from experimental models

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of autoreactive T cells and autoantibodies that can affect virtually every organ system. The most severe clinical manifestations include immune complex-mediated glomerulonephritis, arthritis, vasculitis, cerebritis, pericarditis, cytopenias and serositis [1]. The diversity of clinical manifestations and disease phenotype, together with limited access to patient tissues, has made the study of human lupus difficult. However, the availability of a number of animal models for SLE has allowed us to make significant progress towards understanding the pathogenetic mechanisms contributing to disease development, and developing therapeutic strategies that specifically target the critical immune cells that are involved. This review will summarize some of the findings in the experimental murine models for SLE that have led to our current understanding of the pathogenetic mechanisms involved in the development of the disease in humans.

Experimental models for systemic lupus nephritis

Spontaneous models

Initial efforts to identify pathogenetic mechanisms in SLE utilized murine models that spontaneously developed syndromes resembling human lupus. The serological and clinical characteristics of these models are summarized in Table 1.

One of the first autoimmune models, the New Zealand black (NZB) mouse, was found to develop a spontaneous autoimmune disease resembling haemolytic anaemia, and only rarely, glomerulonephritis [2]. However, this strain does share some immunological features in common with SLE patients, including abnormal B-cell tolerance [3], intrinsic B-cell hyperproliferation and immunoglobulin production [4–6], loss of suppressor cell function [7], and defective apoptosis of resting B cells [8]. Also, like human lupus, there is a genetic component contributing to NZB disease, and linkage studies have identified several chromosomal loci associated with nephritis and autoantibody production [9].

When the NZB mice are crossed with either the New Zealand White (NZW) or the Swiss-Webster (SWR) strains, the female F_1 progeny, referred to as B/W or SNF_1, respectively, develop a lethal accelerated glomerulonephritis, due to the deposition of immune complexes, including anti-DNA Ig [4, 17–20]. Since B/W and SNF_1 disease resemble human lupus very closely, in both the immunological features of the disease and increased incidence of disease in females, studies in these models may identify the critical factors contributing to the development of human SLE. Some of the immunological features that are observed in the NZB mice, such as a loss of suppressor cell function and polyclonal B-cell activation, are similarly seen in their B/W and SNF_1 offspring [6, 7, 21, 22]. Genetic loci associated with susceptibility to renal disease have been identified. Carlsten and Tarkowski [23] mated B/W mice ($H2^{d,z}$) with the NZB parent ($H2^{d}$) and found that B/W mice with the $H2^{d,d}$ haplotype, relative to their d,z siblings, had increased survival, decreased renal disease, and decreased levels of serum IgG + M and IgG against ss- and dsDNA, demonstrating a role for the major histocompatibility complex (MHC) in the development of the disease. However, the importance of class II MHC genes for lupus susceptibility was questioned recently by the results of studies in mice transgenic for E^{z} [24] or A^{z} [25] genes, which showed that production of autoantibodies was not linked with inheritance of the transgenes. Non-MHC loci from NZB or NZW mice have also been linked to various lupus traits, such as nephritis and autoantibody production. For instance, the *Nba1* locus on chromosome 4 has been associated with nephritis, as has the *Nba2* locus on chromosome 1. The same region of chromosome 1 also contains the *Sle1* and *Lbw-7* loci, and all three are linked to the production of autoantibodies, particularly IgG antibodies reactive with chromatin [9, 26–28]. Recently, this region in humans, specifically 1q41-q42, showed evidence of linkage with SLE, including the production of anti-chromatin antibodies [29]. Thus, important susceptibility genes for autoimmunity appear to be conserved between mice and humans [30], supporting approaches to look for candidate human SLE-associated genes based on mouse studies.

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TABLE 1. Murine models of SLE

	Mean survival (weeks)	Clinically relevant autoantibodies	Sensitivity to exogenous sex hormones	Clinical features
NZB	Males: 67 Females: 63	Anti-erythrocyte Anti-ssDNA Anti-dsDNA(low) NTA	None	Haemolytic anaemia Mild glomerulonephritis
(NZB × NZW)F_1 (B/W)	Males: 58 Females: 35	Anti-dsDNA NTA	Oestrogens accelerate; androgens protect	Severe glomerulonephritis
(SWR × NZB)F_1 (SNF_1)	Males: 64 Females: 29	Anti-dsDNA Anti-ssDNA	Oestrogens accelerate	Severe glomerulonephritis
MRL/*lpr*	Males: 22 Females: 20	Anti-dsDNA Anti-Sm RF	Controversial; oestrogens may slightly accelerate disease	Severe glomerulonephritis, synovitis, polyarteritis lymphadenopathy, etc.
MRL/+	Males: 98 Females: 73	Anti-Sm	Controversial	Late-onset glomerulonephritis
BXSB/MP	Males: 20 Females: 68	Anti-ssDNA Anti-dsDNA Anti-erythrocyte	None	Severe glomerulonephritis, haemolytic anaemia, lymphadenopathy, vasculitis
Motheaten	Males: 3.2 Females: 3.2	Anti-ssDNA Anti-dsDNA	Not tested	Severe glomerulonephritis, pneumonitis, alopecia
Viable motheaten	Males: 10 Females: 10			

NTA, natural thymotoxic antibody; RF, rheumatoid factor.
Sources: [10–16]; M. L. Stoll, unpublished data.

Several other murine models that spontaneously develop a lupus-like syndrome are also available. However, in these models, genes have been identified that secondarily accelerate lupus. The MRL/Mp-+/+ (MRL/+) and MRL/Lp-*lpr*/*lpr* (MRL/*lpr*) autoimmune models differ phenotypically by the development of early onset autoimmunity in the MRL/*lpr* mice, attributable to a single gene, *lpr* [11], which was later found to code for the Fas receptor for apoptosis [31]. This finding stimulated intensive interest in a possible role for the Fas protein in human lupus, but the results, as discussed below, have been ambiguous. When crossed on to different backgrounds, the *lpr* gene causes a variety of clinical and serological abnormalities, with most strains developing some degree of autoantibody production and lymphoproliferation, mainly consisting of CD3+ CD4− CD8− B220+ T cells [12, 32], but not the severe renal disease observed in the MRL/*lpr* strain [11]. This finding and others [33, 34], suggests that MRL background genes also play a role in the development of lupus. Interestingly, in MRL/*lpr* mice, there is less evidence for an MHC association with the disease, as selective matings have revealed that the disease occurs with other MHC haplotypes [24]. Recently, several additional chromosomal loci have been discovered that, independent of Fas expression, conferred increased susceptibility to autoantibody production and vasculitis [35].

A unique feature of the BXSB/Mp strain is that disease onset occurs at a much earlier age in males compared with females [11, 36]. This trait was mapped to one or more genes on the Y chromosome, and was not associated with male reproductive hormones, as castration of pre-pubertal males did not significantly affect disease outcome [36]. This as yet unidentified gene has been designated *Yaa* (Y chromosome-linked autoimmune acceleration). As with the *lpr* gene [11, 12], the phenotype of male mice bearing the *Yaa* gene also depends on background genes; for instance, C57BL/6 males to whom the Yaa chromosome was transferred did not develop autoimmunity [37]. Using backcrosses of the lupus-prone (NZW × C57B1/6.Yaa)F_1 males with the wild-type C57B1/6 strain, Santiago and coworkers [38] detected loci on three separate autosomal chromosomes that contributed to the disease, supporting the requirement of additional contributory genes besides *Yaa* in the development of autoimmunity in BXSB mice.

Mice that are homozygous for mutations at the 'motheaten' locus (me) and the allelic variant 'motheaten viable' (me^v) develop a severe combined syndrome with profound systemic autoimmunity characterized by abnormalities in natural killer cell function and differentiation, as well as macrophage/monocyte morphology and function. The mutation is located in the gene for protein tyrosine phosphatase 1C (PTP1-c), also known as haematopoietic cell phosphatase (HCP), an enzyme involved in multiple signalling pathways in B- and T-cell haematopoiesis [39]. However, recently it was reported that the presence of T and B cells was not required for the motheaten phenotype, except for autoantibody production, calling into question the use of this strain as a paradigm for human autoimmune disease [14].

Induced models

C3H [40] and Balb/c mice [41] have been reported to develop a lupus-like syndrome when injected at 2 months of age with an antibody bearing the 16/6 idiotype, which is frequently detected in humans with SLE [42, 43].

Antibodies reactive with ss- and dsDNA, as well as the 16/6 idiotype are produced, and the mice ultimately develop a lethal glomerulonephritis. T cells that induced production of the 16/6 idiotype in an MHC-restricted manner were found to be involved [44, 45]. In other studies, T cells which inhibited *in vivo* production of Ig bearing the 16/6 idiotype and inhibited disease development in mice immunized with the 16/6 idiotype were identified [46]. Thus, these studies appear to support a role for idiotypic network interactions in autoimmunity. However, it has been difficult for other laboratories to reproduce this model [47], with environmental factors in specific laboratories speculated to be responsible, as has been shown in the murine models for collagen arthritis [47], diabetes [48] and multiple sclerosis [49].

In selected parent $\rightarrow F_1$ combinations, graft-*vs*-host disease (GVHD) can be induced by injection of parental lymphocytes into adult non-irradiated F_1 hybrids, for example, $(C57BL/10 \times DBA/2)F_1$ mice injected with DBA/2 cells. The disease is characterized by a chronic autoimmune syndrome resembling human SLE, with hypergammaglobulinaemia, production of IgG antibodies to a variety of autoantigens, as well as antibody-mediated glomerulonephritis [50, 51]. T_H2-type cells from the donor appear to participate in the pathogenetic process, acting on host F_1 B cells, perhaps through the production of interleukin-4 (IL-4) and IL-5 [52, 53].

When some strains of mice are injected with pristane, a branched alkane routinely used to prime mice for hybridoma implantation, SLE-like changes in the glomerulus, with deposition of immunoglobulin and complement, are observed. Autoantibodies are produced that react with ssDNA and histones, but not dsDNA [54]. The genetic background, particularly at H-2, influences serology in this model; anti-DNA autoantibodies are produced in Balb/c mice ($H\text{-}2^d$) with pristane immunization, while SJL mice ($H\text{-}2^s$) produce antinuclear ribonucleoprotein antibodies [54].

Transgenic and knockout models

Transgenic and knockout models for specific genes that have been proposed to have a role in the pathogenesis of autoimmunity permit direct testing of their significance in disease. These genes include those for cytokines, T cell or Ig receptors, MHC, or co-stimulatory molecules. However, these new animal models for disease are limited by the assumptions that they make regarding the importance of a specific gene in disease pathogenesis. Thus, the results of studies using these mice must be validated by observations in spontaneous murine models and human disease. Examples of some of the 'knockout' mice currently under study include transforming growth factor-beta (TGF-β1)$-/-$ mice, which develop serum antibodies that are reactive with dsDNA, ssDNA and the Sm ribonucleoprotein, resulting in Ig glomerular deposits [55]. Autoimmune disease also occurs in mice with deleted IL-2 [56] and IL-10 [57], CTLA-4 [58], and T cell receptor (TCR) genes [59]. In contrast, autoimmune mice deficient in CD4 [60] or terminal deoxynucleotidyl transferase (TdT) [61] show diminished autoimmunity. Polymorphisms in some human genes have been linked to SLE, and studies in mice deficient in these genes have provided insight into their role in disease pathogenesis. One example is the human IgG receptor (FcγR) genes, particularly FcγRIIa and FcγRIIIa [62–64]. Polymorphisms in these genes may be important risk factors for SLE nephritis, and differences in clinical manifestations could result from the genetically determined ability to bind and clear immune complexes. Moreover, studies in murine models suggest that FcγR receptors are necessary for nephritis, in addition to the formation of immune complexes. Clynes *et al.* [65] crossed B/W mice with a knockout strain lacking FcγRI and FcγRIII receptors ($\gamma-/-$). These mice developed anti-DNA antibodies, and immune complexes were deposited in the glomeruli. However, inflammatory nephritis and renal failure did not occur, even though complement was deposited, indicating a requirement for FcγR in disease initiation. Studies in animal models have also clarified the mechanism by which C1q deficiency contributes to the development of autoimmunity. C1q deficiency has been associated with lupus in over 90% of the known occurrences of this deficiency, and defects in C1q are found in lupus patients [66]. These observations suggested that C1q plays a role in protecting against the development of SLE [67], and this hypothesis was tested in C1q-deficient mice (*C1qa* $-/-$). These mice developed significant titres of autoantibodies, and 25% of them had glomerulonephritis associated with immune complex deposition, and multiple apoptotic cell bodies, implying either that increased apoptosis and/or a defect in the clearance of apoptotic cells contributed to the development of autoimmunity. Cells undergoing apoptosis produce subcellular structures (blebs), containing nuclear and cytoplasmic constituents, and thus may be the source of antigen driving the production of autoantibodies in SLE [68, 69]. The data in C1q-deficient mice suggest that one way that C1q may protect from SLE is by binding to and promoting the clearance of apoptotic cells, thus removing the autoantigenic stimulus.

Transgenic models include mice transgenic for human *BCL2*, an oncogene that promotes cell survival; these mice develop a disease characterized by the production of autoantibodies and kidney disease, and lymphocytic infiltration of arteries and solid organs [70]. Transgenic mice expressing interferon-γ (IFN-γ) in the epidermis produced autoantibodies reactive with dsDNA and histones, and further, the levels of these antibodies were higher in females *vs* males, as is found in human SLE [71]. Mice transgenic for autoantibody heavy chain genes show that autoantibody-producing B cells and autoreactive T cells are strictly regulated in non-autoimmune mice [72, 73].

Immunopathogenesis of SLE

A number of immunological abnormalities have been noted in both lupus patients and murine models. An essential component of murine lupus is autoreactive

B cells, which are found at relatively higher numbers, and are substantially activated, compared with non-autoimmune mice [22, 74]. These B cells produce a variety of autoantibodies [75–79], including antibodies to dsDNA, which are virtually diagnostic of lupus, as they are both highly sensitive and specific for the disease [76], and in general correlate with nephritis in human lupus patients [76, 77, 80]. This has led to the hypothesis that DNA may be the eliciting antigen in SLE [81–83]. On the other hand, in both humans and mice, the correlation between nephritis and anti-DNA antibody levels is not universal [77], and the polyreactivity of many anti-DNA antibodies further undermines this relationship [84]. In addition, numerous investigators have observed that modulation of disease outcome in murine lupus need not have a corresponding effect on the levels of anti-DNA antibodies [13, 85–89]. Moreover, the existence of somatically mutated and class-switched anti-DNA immunoglobulins is highly indicative of T-cell help (see, for example [90]). Furthermore, DNA has been shown to be poorly immunogenic in laboratory animals, even those predisposed to autoimmunity [91, 92], reviewed in [93]. Still, the relevance of anti-DNA antibodies to the pathogenetic process in SLE is clearly evident in studies using LPJ-394, a synthetic immunomodulant that selectively targets B cells producing anti-dsDNA antibodies [94]. In BXSB mice, treatment with LPJ-394 led to a reduction in serum levels of anti-DNA antibodies, reduced proteinuria, and increased survival [94], and similar reductions in anti-dsDNA antibody levels have been noted in SLE patients receiving LPJ-394 therapy [95].

Although the exact mechanisms involved in the pathogenesis of lupus nephritis are as yet unclear, there has been general agreement that disease is mediated by glomerular deposition of autoantibodies as immune complexes formed *in situ* or by direct binding of the antibodies to an intrinsic renal antigen or a self-antigen deposited in the kidney [96]. This deposited immunoglobulin then induces renal injury primarily through complement fixation, and recruitment and activation of inflammatory mediators [97]. However, a recent study suggested that the production of autoantibodies was not required for renal disease; MRL/MpJ-Fas*lpr* (MRL/*lpr*) mice that expressed a mutant transgene that did not permit secretion of circulating Ig still developed renal disease, suggesting that Ig-expressing B cells might also participate in the disease process either as antigen-presenting cells or as part of the local inflammatory process [98].

Evidence from studies of newly diagnosed lupus patients who also have an acute Epstein–Barr virus (EBV) infection have implicated this virus in the pathogenesis of lupus [99–101]. Work in mice has corroborated these findings; a peptide from the Sm RNP (PPPGMRPP) was found to be similar to a peptide from the Epstein–Barr nuclear antigen (EBVNA) (PPPGRRP) with the latter peptide reacting with lupus autoantibodies, but not antibodies from EBV-infected individuals who did not have autoimmune disease [102]. Immunization of normal rabbits and certain inbred mouse strains with the EBVNA peptide by James *et al.* [103, 104], resulted in the production of antibodies that cross-reacted with the Sm peptide, and clinical disease. These studies suggested that autoimmune disease might develop as a result of B- and T-cell responses to a particular antigen, such as EBV, that diversify over time, so that eventually antibodies may also be directed against host proteins, such as Sm. This autoreactivity can potentially spread to other epitopes within the cross-reactive protein and even to other proteins, a concept known as epitope spreading (reviewed in [105–107]). However, this effect has not always been seen by other investigators; attempts to reproduce it independently have found limited epitope spreading but not autoimmune disease [108]. These data again illustrate the difficulties that may be encountered in reproducing and interpreting results in some animal models.

T cells, particularly $\alpha\beta$ CD4+ cells, are considered to be essential for the development of lupus, by inducing isotype switching and affinity maturation [109–112]. The derivation of $\alpha\beta$ CD4+ T-helper cell lines from mice that are capable of inducing lupus nephritis *in vivo* [13, 113, 114], as well as the beneficial effects of therapeutic strategies targeting T cells, like neonatal thymectomy [115], and the treatment of mice [116] and humans with SLE with anti-CD4 antibody [117] (reviewed in [118]) further support the role of $\alpha\beta$ CD4+ cells in disease pathogenesis. The importance of CD4+ T cells in disease was also clearly supported by the finding that anti-dsDNA antibody production was decreased in CD4-deficient MRL/*lpr* mice. However, they did eventually develop moderate nephritis [60]. One way that T cells mediate their effect may be via increased production of cytokines; in some models like GVHD, and in lupus patients, a T_H2 pattern of cytokine production is observed [119], while in others, for example, NZB/NZW and MRL/*lpr* mice, the pattern is more complex, with increases seen in IL-4, IL-6 and IL-10 [120]. Deficient production of IL-6, tumour necrosis factor-α (TNF-α), IL-1 and IL-12 has also been noted [121, 122]. Nakajima *et al.* [123] observed clinical improvement with the administration of IL-4, whereas others have seen improvement with TNF-α [124, 125]. In non-autoimmune mice, transgenic expression of IL-4 results in autoantibody production and immune complex glomerulonephritis [126]. However, disease is ameliorated in (NZB $\times$ C57BL/6.*Yaa*)F_1 transgenic mice overexpressing IL-4 in B cells [127]. CD4+ T cells have also been proposed to cause renal damage directly, since they may be found in the interstitium and glomeruli of kidneys from SLE patients [128] and mice with nephritis (Silvin *et al.*, in preparation). Finally, $\gamma\delta$ T cells may play a role, through their ability to regulate both $\alpha\beta$ T-cell and B-cell autoreactivity [129–131].

Recent studies from the B/W model have attempted to reconcile the observations that autoantibody production is associated with polyclonal B- and T-cell activation, but the autoantibodies appear to result from specific antigen-driven responses [132, 133]. These studies tested

the hypothesis that self-peptides derived from the VH region of anti-DNA antibodies were ligands for autoreactive T cells. In support of this, it was noted that some of these peptides increased the production of IgG anti-DNA antibodies *in vitro* [134], immunization with these peptides accelerated autoantibody production and nephritis [135, 136], and adoptive transfer of T-cell clones reactive with these peptides accelerated nephritis [136]. Finally, immune tolerance induction to three of these peptides in pre-nephritic B/W mice delayed the development of IgG anti-DNA antibodies and significantly improved survival [137]. Multiple mechanisms might contribute to the ability of these peptides to propagate an autoimmune response, including reciprocal activation of T and B cells by autoantibodies leading to the continuous recruitment of neo-autoreactive T helper cells, and pathogenic autoimmunity in a genetically predisposed individual [134]. We have obtained similar results in the SNF_1 cross. Initially, we found that modulation of the production of IgG expressing a pathogenic idiotype associated with nephritis, $Id^{LN}F_1+$, by anti-idiotypic antibody or Id-reactive T-cell clones, altered the time of disease onset [13, 87, 138, 139]. We identified a peptide derived from a pathogenic $Id^{LN}F_1+$ antibody that stimulated these T-cell clones, and found that it was structurally similar to one of the peptides relevant in B/W disease [135–137], as each contained a triple basic amino acid motif, KXKXK. Recently, a peptide with the same motif derived from a natural autoantibody was also shown to modulate B/W disease [140]. Since T cells from patients with SLE may also be activated by VH peptides [141], similar mechanisms are likely to be critical to the development of human lupus and therapeutic regimens using autoantibodies or peptide determinants derived from them as tolerogens might therefore be useful in the treatment of human SLE. In support of this, treatment of MRL/*lpr* mice with dsDNA–anti-dsDNA immune complexes increased their survival, perhaps due to anti-idiotypic regulation of pathogenic antibody production [142]. Furthermore, an idiotypic vaccine that was derived from an anti-dsDNA antibody from MRL/*lpr* mice, 3E10, showed some protective effects in murine lupus, and was found to stabilize disease activity in some lupus patients [143].

Another feature of the pathogenic autoantibodies of SNF_1 mice and other murine SLE models is that they are cationic, suggesting that immune complexes containing these antibodies may initiate lupus nephritis by binding to negatively charged proteoglycans in the glomerular basement membrane [110, 144–146]. B cells producing these antibodies most likely process and present DNA complexed with cationic protein, such as histones, to pathogenic T cells that are specific for nucleosomal antigen(s) presented by either $I\text{-}A^d$ or $I\text{-}A^q$. These T helper clones can then provide help to B cells which produce autoantibodies to ssDNA, dsDNA and histones [147, 148], thus nucleosome-specific T helper cells play an important role in initiating and sustaining the production of pathogenic antinuclear antibody production in murine [147, 149] and human lupus [150, 151]. In further support for the role of nucleosomes as the target of autoreactive T cells in the development of lupus nephritis, tolerogenic therapy with nucleosome-derived peptides was recently found not only to delay the onset of nephritis in pre-nephritic SNF_1 mice, but was also effective in halting the progression of established disease [152].

Studies in the SNF_1 model have also established the importance of the contact-dependent, cognate interaction between pathogenic T helper and B cells in lupus nephritis. Antibody to CD40L (gp39), which transduces a co-stimulatory signal required for B-cell growth and differentiation, prevented pathogenic T helper clones and primary cells from inducing the production of autoantibodies by syngeneic B cells [153]. Treatment of SNF_1 mice with antibody to CD40L prior to the expression of elevated levels of IgG autoantibodies delayed the development of lupus nephritis [153], and was also found to be beneficial for the treatment of established disease [154]. Since disease mechanisms in SNF_1 mice and lupus patients are similar, and increased expression of CD40L has been noted in SLE patient T cells [155, 156], it is highly likely that anti-CD40L therapy will be effective for human lupus, and recruitment of patients for clinical trials is now under way [157]. However, other data examining the role of CD40–CD40L interactions in CD40L-deficient *lpr*/*lpr* mice suggested that this interaction was not an absolute requirement for class switching and that the production of IgG autoantibodies may arise by both CD40L-dependent and -independent pathways, although renal disease appears to be CD40L-dependent [158]. Studies in murine models have also shown that blocking other co-stimulatory interactions such as CTLA-4/B7, may be a useful therapeutic approach for SLE. In B/W mice, administration of murine CTLA-4Ig blocked autoantibody production, suppressed nephritis, and increased survival [159], and clinical trials in SLE patients are planned [160].

As discussed above, the *lpr* gene of MRL/*lpr* mice was found to encode for an apoptosis signalling receptor [31], suggesting that abnormalities in lymphocyte apoptosis might play a role in the development of lupus (reviewed in [161]). Supporting data include: (1) increased levels of soluble Fas in the serum of human lupus patients [162, 163]; and (2) the association of a rare lupus-like autoimmune condition with the absence of Fas [164]. On the other hand, the initial study associating high soluble Fas (sFas) levels with SLE looked at a very small group of patients, and only six of 10 had high sFas levels [162]. Later studies confirmed that elevated levels of sFas were not consistently found in lupus patients and do not correlate with disease activity [165, 166]. Furthermore, some investigators have found normal or high levels of Fas expression on lymphocytes derived from lupus patients [167] and increased levels of *in vitro* apoptosis in patients with SLE [168]. However, while MRL/*lpr* disease is largely associated with deficient apoptosis *in vivo* [31], apoptosis among lymphoid cells *in vitro* is increased [169]. Thus,

the role of sFas in SLE requires further study, with the data suggesting that perhaps a subgroup of SLE patients may have structural Fas or Fas ligand (FasL) defects, that contribute to their disease.

Conclusion

Contributions to the development of SLE in humans include multiple genetic factors such as intrinsic immunological abnormalities, MHC genes, sex hormones, and environmental factors such as infectious agents, among others, with a complex network involved in its regulation. Although no single murine model for the disease encompasses all of these factors, we are fortunate that each of these models possesses many of the features of human SLE, enabling investigators to address specifically the relevance of contributory agents and identify specific immunoregulatory defects that may predispose to the disease. In addition, the use of murine models facilitates the development and testing of immunotherapies that may specifically downregulate the pathogenic immune processes without the use of immunosuppressive agents.

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