

REVIEW

Cellular and molecular pathogenesis of systemic lupus erythematosus: lessons from animal models

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Abstract

Systemic lupus erythematosus (SLE) is a complex disease characterized by the appearance of autoantibodies against nuclear antigens and the involvement of multiple organ systems, including the kidneys. The precise immunological events that trigger the onset of clinical manifestations of SLE are not yet well understood. However, research using various mouse strains of spontaneous and inducible lupus in the last two decades has provided insights into the role of the immune system in the pathogenesis of this disease. According to our present understanding, the immunological defects resulting in the development of SLE can be categorized into two phases: (a) systemic autoimmunity resulting in increased serum anti-nuclear and anti-glomerular autoantibodies and (b) immunological events that occur within the target organ and result in end organ damage. Aberrations in the innate as well as adaptive arms of the immune system both play an important role in the genesis and progression of lupus. Here, we will review the present understanding – as garnered from studying mouse models – about the roles of various immune cells in lupus pathogenesis.

Introduction

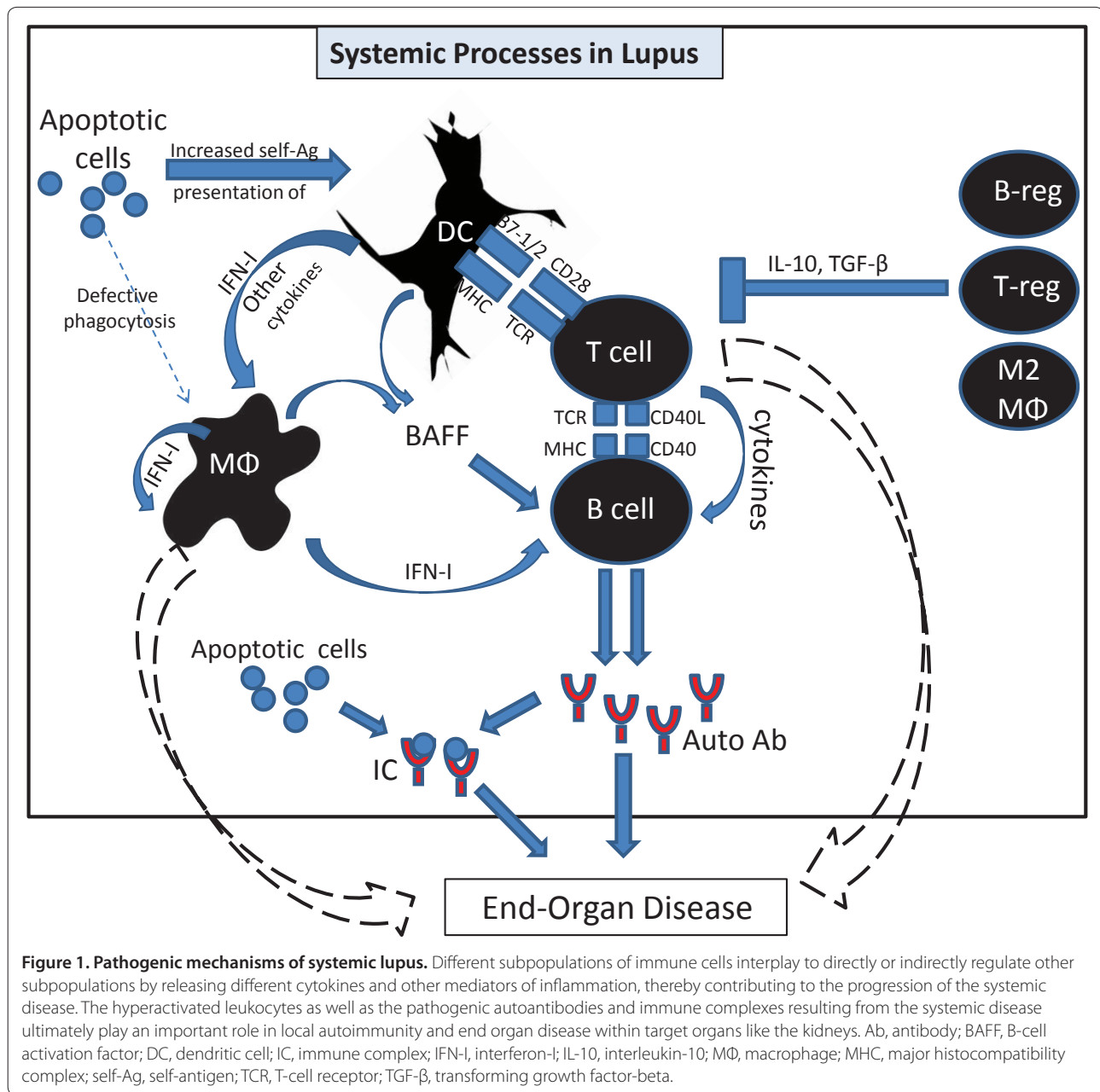
Our understanding of the pathogenesis mechanisms leading to lupus has been augmented by the analysis of several different murine models over the past four decades. Various mouse models of spontaneous lupus have been employed in an effort to understand the cellular and genetic mechanisms behind induction of systemic lupus erythematosus (SLE). The classic models of spontaneous lupus include the F1 hybrid of the New

Zealand Black (NZB) and New Zealand White (NZW) strains, called NZB/W F1, and its derivatives, such as NZM2328 and NZM2410, and the MRL/lpr and BXSB/Yaa strains. The goal of this review is to discuss the systemic and local immune responses – as learned from the studies employing various mouse model systems – that lead to the development of lupus. The cellular and molecular mechanisms that contribute to the pathogenesis of lupus are discussed in the following sections and are illustrated in Figure 1.

Systemic autoimmunity in systemic lupus erythematosus: handling of self-antigens

The presence of high titers of autoantibodies against nuclear antigens is the hallmark of SLE. Whereas there is little evidence to indicate whether self-antigens in SLE are aberrant in sequence or structure, there is evidence that the aberrant handling of self-antigens could facilitate lupus pathogenesis. Although apoptotic bodies are normally rapidly cleared with the help of the complement and other systems, defects in this clearance system could lead to the accumulation of apoptotic bodies and their prevalence in serum [1]. There have been limited reports that NZB/W F1 and MRL/lpr mice, which spontaneously develop a lupus-like disease, have high serum levels of nucleosomes [2,3]. Non-autoimmune C3H, BALB/c, and C57BL/6 mouse strains, when injected with apoptotic bodies, developed serum autoantibodies similar to those seen in SLE [4]. Although these studies warrant independent confirmation, they support the notion that apoptotic cells could harbor the immunogens responsible for anti-nuclear antibody formation. Moreover, mice with defects in genes that play an important role in the clearance of apoptotic bodies, like DNase I, serum amyloid protein P (SAP), sIgM, or tyrosine kinase c-mer, all develop SLE-like disease with elevated levels of anti-nuclear antibodies [5-8]. These data support the hypothesis that the inefficient clearance of apoptotic bodies could be one factor leading to the development of SLE. The important role of the complement system and FcR in the process of clearing apoptotic materials has also been recently documented. Thus, C1q-deficient mice exhibit impaired internalization of apoptotic cells by peritoneal macrophages

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and develop proliferative glomerulonephritis characterized by high levels of apoptotic cell bodies [9].

Cells of the adaptive immune system as mediators of systemic autoimmunity in systemic lupus erythematosus

B lymphocytes in systemic lupus erythematosus

Autoantibodies are major contributors to end organ damage as illustrated by the glomerulonephritis associated with anti-nuclear and anti-glomerular antibodies, congenital heart block associated with anti-Ro antibody, and thrombosis associated with anti-cardiolipin antibodies

[10]. However, B cells can contribute to SLE pathogenesis through additional pathways. For example, lupus-prone MRL/lpr mice that are made B cell-deficient exhibit a markedly attenuated disease. These mice have an absence of autoantibodies, as expected, but also display a dramatic lack in T-cell activation. This study, by Shlomchik and colleagues [11], implied an essential role for B cells, but not necessarily autoantibodies, in the pathogenesis of lupus [11]. In another study, Shlomchik and colleagues [12] used MRL/lpr mice expressing a mutant immunoglobulin (Ig) that cannot be secreted, thus essentially prohibiting autoantibody generation, and

showed that those mice still developed nephritis and vasculitis with associated T-cell activation. That study convincingly showed that B cells may contribute to the development of lupus in ways that are independent of autoantibodies. The additional role of B cells as antigen-presenting cells that mediate T-cell activation in lupus comes from MRL/lpr mice studies showing that B-cell deficiency leads to reduced CD4⁺ and CD8⁺ T-cell activation [13].

Besides secreting proinflammatory cytokines like interleukin-6 (IL-6) and interferon-gamma (IFN- γ), B cells may secrete IL-10, which has an anti-inflammatory function. Therefore, B cells that secrete IL-10 (or B10 cells) have been called regulatory B cells and were first reported in B10.PL mice in which IL-10-producing B cells were found to regulate the severity of experimental autoimmune encephalitis [14]. In murine lupus, IL-10 deficiency was found to contribute to more severe disease with an increase in Th1 cytokine levels [15]. A recent study using CD19^{-/-} NZB/W mice reported that B10 cells could induce expansion of regulatory T cells, a subset of T cells with immunosuppressive function [16]. However, data from human lupus reveal a different facet of IL-10. In the case of human SLE, studies suggest that IL-10 promotes rather than inhibits lupus [17]. A better understanding of the role of IL-10-producing B cells and the mechanism of action of IL-10 is required to explain the differences between the murine and human data.

Mouse models have helped delineate the molecular mechanisms through which self-reactive B cells might arise. *Sle1* is a lupus susceptibility locus derived from the NZM2410 mouse strain. Using *Sle1* congenic C57Bl6 mice, Kumar and colleagues [18] reported that the autoimmune-associated variant of the *Ly108* gene, a member of the SLAM family of immune cell receptors which lies within the *Sle1* locus, leads to loss of B-cell tolerance because of impaired negative selection of autoreactive B cells at the immature B-cell stage. On the other hand, increased B-cell signaling, especially in the case of mature peripheral B cells, has been implicated in the pathogenesis of humoral autoimmunity. Mice that are deficient in various inhibitory molecules that dampen B-cell receptor (BCR) signaling, such as SHP-1 [19], Lyn [20], or Fc γ RIIb [21], develop systemic autoimmunity. Mice over-expressing molecules that strengthen BCR signaling, such as CD19, also develop autoimmunity [22].

Recent studies have implicated a class of immune system receptors called Toll-like receptors (TLRs) in the synergistic activation of B cells by BCR and TLR signaling. Simultaneous engagement of BCRs that are specific for DNA by nuclear antigens that are abundant in apoptotic material and TLR9 on B cells causes activation of both BCR and TLR signaling pathways [23]. In the NZB/W and MRL/lpr mouse models of lupus, activation

of TLR9 with a synthetic DNA ligand causes accelerated nephritis with increased anti-DNA antibody levels [24]. On the other hand, TLR9-deficient autoimmune mouse models exhibit lower levels of anti-double-stranded DNA (anti-dsDNA) and anti-chromatin antibody [25]. Similarly, B cells possessing BCRs specific for RNA could be synergistically activated by BCR and TLR7 signaling [26]. These findings were supported by research in the BXSB mouse model of lupus. Duplication of the *TLR7* gene in the *Yaa* lupus susceptibility locus leads to increased gene dosage effects that contribute to the lupus-like phenotype seen in this model [27].

Defects that may lead to increased survival of autoreactive B cells have also been found to contribute to the development of autoimmunity. B-cell activation factor (BAFF) is a major B-cell survival factor that functions particularly at the transitional B-cell stage. BAFF transgenic mice develop a lupus-like disease with expansion of the peripheral B-cell pool and heightened production of autoantibodies [28]. Increased BAFF levels are thought to infringe the negative selection checkpoint at the T1 transitional stage, thereby allowing the survival and maturation of autoreactive B cells in the periphery and their participation in the germinal center reaction. These findings are supported by the observations that lupus-prone mice exhibit elevated serum BAFF levels and that administration of TACI-Ig, which acts as a soluble receptor for BAFF, is effective in treating murine lupus [29].

T lymphocytes in systemic lupus erythematosus

The obligatory role of T cells in lupus pathogenesis has been demonstrated by using several genetically engineered mouse models [30]. Lupus T cells are likely to contribute to disease through contact-dependent mechanisms (mediated by CD40L:CD40, OX40L:OX40, and so on) as well as released cytokines [30]. One important cytokine secreted by the Th1 cells is IFN- γ , which plays a pivotal role in the production of pathogenic isotypes of anti-nuclear autoantibodies in murine lupus models. Expression of IFN- γ in the skin of transgenic mice leads to the production of anti-DNA and anti-Sm autoantibodies [31]. A deficiency of IFN- γ in MRL/lpr and NZB/W lupus-prone mice leads to reduced anti-DNA antibody levels [32,33]. In support of these findings, blocking the IFN- γ receptor with monoclonal antibodies or soluble IFN- γ receptor reduces disease activity in lupus-prone mice [34,35].

CD4⁺ Th17 cells are a recently described CD4⁺ T-cell subset that appears to mediate pathogenesis in some lupus mouse models [36]. However, it has become clear that the contribution of Th17 cells to autoimmunity is far more complex, depending on the disease and mouse model [37]. Studies in patients with SLE or related diseases have demonstrated that Th17 cells may have a

role in disease development in some, but not all, patients [38]. Given the heterogeneity of the disease, it may be possible that Th17 cells play a role in lupus pathogenesis in a genetically defined subset of subjects or in particular end organ manifestations and that anti-IL-17 therapy may be helpful specifically in those patients. In addition, the regulatory T cell subset appears to modulate the breakdown of T-cell tolerance in lupus [39]. Clearly, we need to gain a better understanding of how pathogenic T cells (Th17 cells) and regulatory T cells, perhaps in yin-yang fashion, dictate disease activity in lupus.

Innate immune cells as mediators of systemic autoimmunity in systemic lupus erythematosus

The important role of the innate immune system in SLE pathogenesis has only recently been appreciated. Described below are the possible roles played by three key cell types in the innate immune system.

Monocytes/macrophages

Monocytes/macrophages from patients with lupus have been found to have a reduced capacity to phagocytose apoptotic materials [40], and their numbers were reduced in the inflammatory exudates from patients with SLE [41]. It was postulated, on the basis of those studies, that the defective phagocytosis of monocytes/macrophages contributed to inefficient clearing of apoptotic materials, leading to autoimmunity [42], a notion that is supported by mice lacking the myeloid cell receptors, Tyro3, Axl, and Mer receptor tyrosine kinases [43,44]. Whereas c-mer knockout mice exhibited increased anti-dsDNA autoantibody levels without any significant renal pathology [43], Tyro3/Axl/Mer triple-knockout mice exhibited high levels of autoantibodies along with multiple end organ involvement [44].

Monocytes/macrophages can contribute to disease in another important way: through the elaboration of pro-inflammatory cytokines and chemokines. This is illustrated by macrophages from B6.*Sle3* congenic mice, in which *Sle3* is a lupus susceptibility locus derived from the NZM2410 lupus-prone strain [45]. These murine studies showed that monocytes/macrophages in lupus probably have defects beyond abnormal phagocytosis and that these cells may take part in aberrant regulation of the immune system. A study by Kilmon and colleagues [46] demonstrated that macrophages regulate B-cell tolerance by secreting regulatory factors like IL-6 and CD40L and that macrophages from lupus-prone MRL/lpr mice are less capable of repressing Ig secretion coincident with reduced secretion of these repressive factors. Collectively, these findings implicate a more significant role for monocytes/macrophages in the pathogenesis of lupus, but further studies in patients with SLE are necessary to substantiate these findings.

Polymorphonuclear cells in systemic lupus erythematosus

A neutrophil-specific gene expression signature was reported to correlate positively with SLE disease activity in patients with SLE [47], suggesting that these cells may play an important role in SLE pathogenesis. The exact mechanism by which this occurs is not yet clear. However, a recent study demonstrated that neutrophil extracellular traps, which are networks of DNA, histones, and neutrophil proteins that function primarily to trap microorganisms, may be involved in SLE pathogenesis, possibly by generating autoantigens and serving as adjuvants [48]. The role of neutrophils in murine lupus, unlike that in human lupus, is poorly studied.

Dendritic cells in systemic lupus erythematosus

Studies in mouse models have been pivotal in determining the role that dendritic cells (DCs) play in the pathogenesis of lupus. One of the earliest findings implicating the putative role of DCs in the breakdown of tolerance was that transferring DCs from normal donor mice to normal recipient mice could cause loss of tolerance in the host, leading to the appearance of anti-DNA and anti-cardiolipin autoantibodies [49]. A study by Chen and colleagues [50] showed that mice with defective DC apoptosis accumulated large numbers of DCs and exhibited chronic lymphocyte activation and systemic autoimmunity.

Other studies using murine models have helped in identifying the genetic loci responsible for imparting the abnormal phenotypes seen in DCs from lupus-prone mice. One such locus is *Sle3*, which is a lupus susceptibility locus derived from the NZM2410 strain of lupus-prone mice. C57BL/6 (B6) mice congenic for *Sle3* develop moderate glomerulonephritis along with modest levels of anti-nuclear antibodies [51]. Moreover, the DCs from B6.*Sle3* congenics are less susceptible to apoptosis, have a more mature phenotype, and are more proinflammatory. They are also more efficient in stimulating T cells *in vitro* and eliciting autoantibodies *in vivo* compared with DCs from normal B6 mice [45]. These studies provided insights into genetic factors and immune mechanisms related to abnormal DC activation in murine lupus.

Studies have also shown that DCs play an important role in SLE pathogenesis by secreting potent proinflammatory cytokines, such as type I IFNs (IFN- α) [52]. Immune complexes (ICs) purified from sera of patients with SLE were found to stimulate plasmacytoid DCs (pDCs) to produce IFN- α [53]. Later studies revealed a possible role of TLRs as potent inducers of IFN- α production by activated pDCs in lupus. IFN- α secreted by activated pDCs was found to directly influence B cells to produce antibodies of the IgG subclass against soluble autoantigens in mice [54]. This cytokine also upregulated BAFF expression by monocytes and mature DCs, which

promotes both the survival of autoreactive B cells and their differentiation into plasmablasts [55]. Together, these reciprocal events lead to a pathogenic cycle, in which both the innate and adaptive immune systems cooperate and feedback upon each other, eventually leading to high titers of autoantibodies.

Local autoimmunity in systemic lupus erythematosus

SLE is an autoimmune disease that affects multiple organ systems, including the kidney, skin, heart, lung, and hematopoietic and nervous systems. As reviewed below and illustrated in Figure 1, the players mediating local autoimmunity and renal disease in lupus can be classified broadly as (a) ICs and infiltrating cells of hematological origin and (b) resident cells of the kidneys.

Role of immune complexes and infiltrating cells of hematological origin in lupus nephritis{Level 2 heading}

Anti-DNA and DNA ICs were the first ICs isolated from kidney elutes of patients with SLE and mouse models [56]. Intraperitoneal injection of human and murine anti-DNA antibodies was found to trigger lupus-like kidney disease [57], establishing a direct role of these antibodies in the pathogenesis of lupus nephritis. Similarly, transgenic overexpression of Ig anti-DNA antibodies in mouse models can lead to renal pathology similar to that seen in human lupus nephritis, highlighting a causal role for autoantibodies in the development of lupus nephritis [58].

Various mechanisms have been proposed to explain how anti-DNA antibodies may lead to renal disease in lupus [59]. Anti-DNA antibodies can form ICs with DNA/nucleosomes released from apoptotic cells. Eventually, ICs become deposited in the kidney, leading to the initiation of a local inflammatory response through FcγR- or complement-mediated mechanisms or both. Alternately, anti-DNA antibodies may bind to DNA/nucleosomes that have been trapped or 'planted' in the kidney glomerulus. A third mechanism suggests possible cross-reactivity between anti-DNA antibodies and local renal antigens like laminin, alpha-actinin, and heparan sulfate [60].

Other studies have shown that anti-DNA antibodies are not an absolute requirement for development of SLE. NZM2328.Lc4 mice exhibit lupus-like disease with glomerular IC deposits and eventually develop fatal lupus nephritis. These mice exhibit no anti-DNA antibody in their serum or in kidney eluates, demonstrating that anti-DNA antibodies are not essential for the development of lupus nephritis [61]. Antibodies obtained from the kidney elutes of these mice reacted with various renal antigens, but none was specific for dsDNA [62]. Another study eluted Igs from renal tissues obtained from patients with lupus at autopsy and screened the Igs against a panel

of 14 different antigens, which included dsDNA, chromatin, Sm, SSA, SSB, and histones [63]. These authors found that only 0.3% to 41.3% of total kidney-eluted IgG reacted with these antigens. Therefore, a vast majority of renal antibodies bind to yet-unknown antigens. In support of this idea, a study using a glomerular proteome array showed that serum from lupus mice and patients reacts with multiple nuclear and matrix-derived autoantigens [64].

Role of lymphoid cells in lupus nephritis

Lymphoid aggregates with T cells and B cells have been observed within the kidneys afflicted by lupus nephritis, although their intrarenal roles remain to be fully appreciated. T cells also play a major role in pathogenesis of SLE. Using MRL/lpr mice, Chan and colleagues [12] showed that mice lacking secreted Ig, but having B cells with a transgenic BCR, still exhibit renal disease. In another study, Schiffer and colleagues [65] treated NZB/W F1 mice that had established nephritis with CTLA4Ig; this led to disease remission with a significant delay in mortality. Using a transgenic mouse model system, Heymann and colleagues [66] demonstrated that both cytotoxic T (Tc) cells and Th cells have direct roles in glomerulonephritis. The authors used transgenic mice expressing the model antigens ovalbumin and hen egg lysozyme in glomerular epithelial cells called podocytes. Co-injection of ovalbumin-specific transgenic CD8⁺ Tc and CD4⁺ Th cells into these mice resulted in periglomerular mononuclear infiltrates and inflammation of parietal epithelial cells, similar to lesions frequently observed in human chronic glomerulonephritis. The ovalbumin-specific CD8⁺ Tc cells were found to be activated and expanded in the renal lymph nodes, and the activation of T cells in turn could be prevented by depletion of DCs. Crosstalk between tubulointerstitial DCs and Th cells resulted in intrarenal cytokine and chemokine production and in recruitment of more Tc cells, monocyte-derived DCs, and macrophages. That study was the first direct evidence that glomerular antigen-specific Tc and Th cells can induce glomerulonephritis in a process regulated by DCs. Although similar studies in the context of lupus nephritis are eagerly awaited, the above studies suggest that type IV hypersensitivity-driven mechanisms are likely to be important in mediating autoimmune nephritis.

Kidneys of nephritic NZM2328 mice show high levels of expression of Th1-type cytokines like IFN-γ and IL-12 [67]. Administration of IFN-γ, a Th1 cytokine, to NZB/W F1 mice exacerbates disease, whereas the deficiency of IFN-γ in MRL/lpr mice ameliorates nephritis [32,34]. Similarly, inhibition of IL-18, a cytokine that induces IFN-γ and other Th1 cytokines, was found to cause a significant reduction in lymphoproliferation and IFN-γ

production and resulted in a decrease in lupus nephritis [68]. These studies reinforce the concept that type IV hypersensitivity reactions may also contribute to lupus nephritis.

Other studies have shown a possible role for IL-4, a Th2-type cytokine, in glomerulosclerosis in which transgenic overexpression of IL-4 was found to facilitate glomerulosclerosis [69]. In various studies, IL-4 was found to have a direct effect on fibroblast proliferation, collagen gene expression, and collagen synthesis [70]. Moreover, inhibition of IL-4 signaling in various lupus-prone mouse models was found to protect mice from developing advanced nephritis in the presence of anti-DNA antibody and infiltrating inflammatory cells [32]. Therefore, IL-4 appears to play a pivotal role in the pathogenesis of glomerulosclerosis and chronic renal fibrosis in lupus by acting directly upon resident renal cells.

Role of myeloid cells in lupus nephritis

Infiltration of DCs in the glomeruli and tubulointerstitial spaces of the kidneys has been reported in various murine models of nephritis, including NZB/W F1 [67], anti-glomerular basement membrane (anti-GBM) [71], and mice engineered to express a foreign antigen on podocytes [66]. DCs may promote lupus nephritis by several mechanisms. One mechanism may be through migration of DCs to local lymph nodes and presentation of renal antigens to autoreactive lymphocytes in the local lymph nodes, thereby initiating an autoimmune response against renal autoantigens [72]. DCs may also secrete a variety of different proinflammatory and profibrotic cytokines like IL-6, IL-1, IL-18, IFN- α , tumor necrosis factor-alpha (TNF- α), and transforming growth factor-beta to promote renal inflammation and fibrosis [73]. Despite these possibilities, we do not currently understand the degree to which intrarenal DCs are important for lupus pathogenesis or the exact mechanisms through which they operate.

Similar to DCs, macrophages are recruited to the nephritic kidneys of patients with SLE and lupus-prone mice [74,75] and influence the progression of lupus nephritis. In a study using poly(I:C)-induced lupus nephritis in NZB/W mice, proliferative glomerulonephritis was found to be associated with renal-infiltrating macrophages and renal expression of IFN-inducible genes, matrix metalloproteinases (MMPs), and growth factors [76]. Glomerular crescent formation and renal MMP and growth factor expression were dependent on renal macrophages that expressed IL-10, MMPs, osteopontin, and various growth factors, including platelet-derived growth factor-C (PDGF-C) and heparin-binding epidermal growth factor-like growth factor (HB-EGF) [76]. These findings accord a potentially important role for macrophages as mediators of aggressive nephritis

in lupus by driving the expression of various cytokines and growth factors in the kidney. Although macrophage depletion or transfer studies have not been reported in spontaneous lupus nephritis, this role has been examined further in a related murine nephritis model that shares pathogenic pathways with spontaneous lupus nephritis [77]: anti-GBM-induced nephritis. In the latter model, depletion and adoptive transfer studies have demonstrated a critical role for macrophages in the pathogenesis of nephritis [78,79].

By implanting renal tubular epithelial cells genetically modified to produce colony-stimulating factor-1 (CSF-1) under the renal capsule of MRL/lpr mice, Kelley and colleagues [80] showed that CSF-1 and TNF- α released by tubular epithelial cells were responsible for promoting renal pathology by fostering macrophage accumulation. In a study using NZB/W lupus-prone mice, Schiffer and colleagues [75] identified an activated type II macrophage population as a key marker for proteinuria onset and disease remission and suggested that therapy for lupus nephritis include strategies that prevent both activation of monocytes and their migration to the kidney.

Neutrophils, another myeloid cell subtype, have also been shown to infiltrate nephritic kidneys and contribute to the pathogenesis of experimental nephritis [81], although their role in lupus nephritis is less well defined. Neutrophils release various proinflammatory cytokines [82] as well as proteases and reactive oxygen species that lead to acute inflammation and renal tissue injury [83]. Further studies in murine models are clearly warranted.

Role of resident renal cells in lupus nephritis

It is clear that many intrinsic renal cells, including podocytes and tubular epithelial cells, have the capacity to co-stimulate intrarenal T cells via ICAM-I, MHC-II, B-7, and/or CD40-mediated mechanisms [84-86] or by releasing pathogenic cytokines [87]. However, the extent to which these intrarenal co-stimulatory mechanisms and cytokines are operative in spontaneous lupus nephritis remains unknown. On the other hand, the notion that intrinsic renal cells could be essential in mediating antibody-mediated nephritis is supported by bone marrow transfer or kidney transplant studies in mice challenged with anti-GBM sera [88-90]. These studies have defined the roles of MHC-II, INF- α , and Fn14 expression on intrinsic renal cells in mediating nephritis. Overall, we have a very limited understanding of the role that intrinsic renal cells play in spontaneous lupus nephritis.

Conclusions

As discussed in this review, mouse models have proven to be indispensable for understanding the immunological and molecular basis of systemic autoimmunity in lupus.

However, it is becoming increasingly clear that local autoimmunity in target organs and the responses that target organs play are equally important in disease pathogenesis. Murine models are also proving to be instrumental in helping us unravel the intricate mechanisms that underlie the end organ responses in lupus, although the specific roles of various cell types warrant systematic investigation. Mouse models have also enhanced our understanding of the respective roles of various cells and molecules in the innate immune system and the interplay between the innate and adaptive immune systems in lupus pathogenesis. The challenge ahead is to better define the cellular and molecular players orchestrating lupus and to translate our improved understanding of lupus pathogenesis into better rationalized therapeutics targeting selected cells or molecules (or both) that facilitate lupus.

Autoimmune Basis of Rheumatic Diseases

This article is part of a series on *Systemic lupus erythematosus*, edited by David Pisetsky, which can be found online at <http://arthritis-research.com/series/lupus>

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Abbreviations

anti-dsDNA, anti-double-stranded DNA; BAFF, B-cell activation factor; BCR, B-cell receptor; CSF-1, colony-stimulating factor-1; DC, dendritic cell; GBM, glomerular basement membrane; IC, immune complex; IFN, interferon; Ig, immunoglobulin; IL, interleukin; MMP, matrix metalloproteinase; NZB, New Zealand Black; NZW, New Zealand White; pDC, plasmacytoid dendritic cell; SLE, systemic lupus erythematosus; Tc, cytotoxic T; TLR, Toll-like receptor; TNF- α , tumor necrosis factor-alpha.

Competing interests

The authors declare that they have no competing interests.

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