Published in final edited form as:
Curr Opin Immunol. 2012 December ; 24(6): 651–657. doi:10.1016/j.coi.2012.10.004.

The Pathogenesis of Systemic Lupus Erythematosus – An Update

Jinyoung Choi[1,*], **Sang Taek Kim**[1,*], and **Joe Craft**[1,2]

[1]Department of Internal Medicine (Rheumatology), Yale School of Medicine, New Haven, CT 06520

[2]Department of Immunobiology, Yale School of Medicine, New Haven, CT 06520

Summary

Systemic lupus erythematosus (SLE, lupus) is characterized by a global loss of self-tolerance with activation of autoreactive T and B cells leading to production of pathogenic autoantibodies and tissue injury. Innate immune mechanisms are necessary for the aberrant adaptive immune responses in SLE. Recent advances in basic and clinical biology have shed new light on disease mechanisms in lupus, with this review discussing the recent studies that offer valuable insights into disease-specific therapeutic targets.

Introduction

Systemic lupus erythematosus (SLE, or lupus) is a systemic autoimmune disease with multiorgan inflammation. SLE is characterized by production of pathogenic autoantibodies directed against nucleic acids and their binding proteins, reflecting a global loss of self-tolerance (reviewed in [1]). The loss of tolerance with subsequent immune dysregulation is a consequence of genetic factors, in the setting of environmental triggers and stochastic events, with recent studies implicating over 30 genetic loci in disease pathogenesis (for recent reviews, see [2-5].

Aberrant innate immune responses play a significant role in the pathogenesis of SLE, contributing both to tissue injury via release of inflammatory cytokines as well as to aberrant activation of autoreactive T and B cells, with the latter leading to pathogenic autoantibody production and resultant end-organ injury (reviewed in [6]) (Figure). Autoantigenic nucleic acids and their binding proteins are required for self-antigen specific activation of autoreactive lymphocytes. Autoantigens complexed with their cognate autoantibodies also directly contribute to activation of innate immune cells via Fc receptor (FcR)-mediated uptake of complexes (or in the case of autoreactive B cells, initial engagement of the B cell antigen receptor by autoantigens *per se*), with the nucleic acid component of these complexes upon endosomal trafficking engaging intracellular Toll-like receptors (TLRs) with subsequent innate and B cell activation.

Contact: Joe Craft, joseph.craft@yale.edu, Telephone (203) 785-7063, FAX (203) 785-5415.
*These authors contributed equally.

This review will focus upon recently dissected biologic events that provide insight into disease pathogenesis in three major areas, dysregulation of innate and adaptive immune responses in SLE, and the role of autoantibodies in triggering end-organ injury (Figure). We will necessarily, in the interest of space, focus upon studies that offer new paradigmatic insights into pathogenic events.

Innate immunity in SLE

Dendritic cells (DCs) play a central role in adaptive immunity by activating B and T cells, with the presumption that they are similarly required for the activation of autoreactive T and B cells. But their precise involvement in autoimmunity, and the effects of their selective subsets in autoreactive lymphocyte activation, are less clearly understood. A recent study addressed this question by adapting a DC-depletion model (CD11c-diptheria toxin A; CD11c-DTA) to the widely used MRL.*Fas*^{lpr} mouse model of lupus [7]. These mice offered the unique opportunity to study the natural onset and progression of disease in lupus-prone animals in the absence of DCs, with the demonstration that the latter are crucial in regulating the magnitude of spontaneously arising systemic autoimmunity in that DC-deficient mice exhibited less severe disease than DC-intact controls. In particular, expansion of T cells and plasmablasts with autoantibody production depended on DCs, indicating their previously unrecognized role in promoting extrafollicular (EF) humoral responses in SLE. Previous work by the same group and others has shown that EF sites in murine lupus are critical for continued activation of and autoantibody production by short-lived plasmablasts [8,9] (more about this later; see Adaptive Immunity in SLE), with their activation dependent upon autoreactive B cell receptor (BCR) and subsequent TLR engagement by lupus autoantigens [10] [11]. Although the role of EF responses in promoting human SLE is unknown, in part due to the general lack of access of lymphoid tissues from patients, the finding of increased numbers of circulating plasmablasts in patients with active SLE suggests such responses may be operative [12,13]. DC promotion of plasmablast function in EF sites is appealing, given the role of BAFF in B cell survival with myeloid cells potentially potent producers of this and other soluble and contact-dependent factors that promote B cell maturation [14].

Other data suggesting that DCs can initiate EF humoral responses comes from slightly older intravital imaging studies, revealing engagement of the B cell receptor by DC-associated antigen, with B cell activation EF occurring before entry into B cell follicles [15]. More recent work links DCs to EF B cell maturation with the finding that a splenic DC subset found in the marginal zone, those expressing the DC-inhibitory receptor 2 (DCIR2), has the unique capacity to initiate T-cell dependent extrafollicular B cell responses [16]. Although the implications of these findings for SLE are uncertain at this time, it is clear that further exploration of the role of DC-driven T and B cell maturation in EF sites as well as in germinal center (GC) responses in SLE is warranted, with DCs a tempting therapeutic target in SLE.

In lupus-prone CD11c-DTA animals, both conventional DC (cDC) and plasmacytoid DC (pDC) are efficiently depleted, underscoring the potential role of both subsets in disease. Depletion of the latter with disease amelioration recalls earlier findings that these cells produce large amounts of type I interferons (IFNs) in response to nucleic acid-containing immune complexes [17,18], with an increase in this cytokine paralleling activity and severity of SLE in humans [19]. Recent studies support this idea with the finding that interferon regulatory factors (IRFs), including IRF5, are strongly associated with higher serum IFNα levels or IFNa signaling and autoantibody titers in patients with SLE [20](for review, see [21]. Thus, blockade of IFNs is an appealing therapeutic strategy in SLE [22], with early results demonstrating some promise [23-25].

New work has now provided a pathogenic link between the heightened IFN production in SLE and dysregulation of another innate immune cell, the neutrophil. Activation of the latter has long been found in SLE, including in association with accelerated vascular disease [26,27]; however, the precise role of neutrophils in global disease pathogenesis has been less clear. Activated neutrophils die in a unique process, NETosis that is distinct from necrosis and apoptosis [28]. Dying neutrophils extrude a large amount of DNA in the form of web-like structures (neutrophil extracellular traps, NETs) that are associated with antimicrobial cationic peptides LL37 (also known as calthelicidin) and that promote bacteria entrapment and efficient killing [28]. Immune complexes of autoantibodies and nucleic acids, abundantly circulating in the plasma of patients with SLE, engage TLRs in neutrophils after FcR-mediated uptake with resultant activation and death by NETosis. NET DNA is protected from nuclease degradation and is available as an autoantigen for TLR-directed pDC activation and IFN release [29,30]. The latter cytokines further prime additional neutrophils for NETosis while also aiding cDC maturation with subsequent autoreactive T cell activation [17](reviewed in [6]). These findings indicate a feed forward loop among cytokines and neutrophils, resulting in adaptive immune cell activation that amplifies chronic inflammation with resultant tissue damage. Although it is crucial to determine whether this amplification mechanism operates *in vivo* and whether NET formation is required for disease progression, these data add weight to the argument that blockade of interferon and/or TLR signaling may be therapeutically beneficial in SLE [6,31].

Dissection of immune-complex driven production of IFNs by pDCs has also shed light on the role of glucocorticoids in the treatment of SLE. These drugs are widely used to treat autoimmune diseases and are a mainstay for induction of disease remission and maintenance in SLE via inhibition of the transcription factor NFκB [32], with subsequent pDC death and consequently reduced IFN production. Yet, lupus patients often require higher therapeutic doses of steroids to relieve inflammatory symptoms than other related conditions, such as rheumatoid arthritis, with toxic side effects including immune suppression, weight gain, and osteoporosis. Recent work has demonstrated how the therapeutic potency of glucocorticoids may be dampened in SLE via disease-associated resistance to their immune modulatory effects [33]. Engagement of TLR7 and 9 after endosomal uptake of nucleic acid containing immune complexes promotes pDC survival and IFN production via activation of NFκB, overcoming the glucocorticoid inhibitory effect. In addition to providing novel insights into the mechanisms whereby autoantibody-immune complexes amplify inflammation and induce drug resistance in SLE [10], this work further suggests TLR7/9 targeting may be importantly therapeutically in SLE, in addition to providing a means to utilize lower, and therefore less toxic, doses of glucocorticoids.

Adaptive Immunity in SLE

Given the roles of autoantibodies and B cells in disease pathogenesis [14,34], a number of studies have been devoted to analysis of the function of autoreactive B and T cells in SLE (for reviews, see [35,36]). B cell tolerance is defective at several levels in SLE, including both abnormalities in central and peripheral selection responsible for removal of self-reactive immature B cells [37-39]. Aberrant tolerance, combined with enhanced BCR [40], TLR [41], and BAFF receptor signaling operative in lupus (reviewed in [42]) ultimately promotes activation and survival of autoreactive B cells. CD4 T cells are critical players in the pathogenesis of lupus as they regulate B cell responses and also infiltrate target tissues with effector function, leading to tissue damage (reviewed in [43]), with genetically determined defects in tolerance regulation and receptor signaling also contributing to their activation.

The combined T and B cell abnormalities in SLE result in production of pathogenic autoantibodies. The latter are high-affinity, somatically mutated, and Ig-switched, supporting the idea that they are the product of GC responses [44-46], with defects in GC selection operative in human SLE [37,47]. Autoreactive B cells differentiate into pathogenic memory and plasma cells via the GC response [37], with lupus nephritis patients exhibiting abnormalities in the peripheral B cell compartment with increased autoantibody titers that can be attributed to intensive GC activity [47].

Although the role of B cells in disease promotion in lupus has been well established [48], the precise nature of the CD4 T cells that promote autoreactive B cell maturation has been less clear. New data suggest that follicular helper T (Tfh) cells [49,50], which reside in GCs and provide essential signals for B cell maturation and Ig production after immunization with thymus-dependent antigens, are crucial to the pathogenesis of lupus in mice. Dysregulation of Tfh cells that promote B cell differentiation in GCs is associated with the development of SLE in the Roquin$^{san/san}$ mouse model [51]. In addition, abundant Tfh-like cells are located outside the GC where they support EF B cell differentiation in mouse models of SLE [52,53], with this site an important one for maturation of plasmablasts that contribute to the ongoing pathogenic production of autoantibodes in murine SLE models [9,54] as outlined above (Innate Immunity in SLE). Although data supporting the involvement of Tfh cells in human SLE remains relatively limited, expansion of a circulating Tfh (cTfh) cell population in patients with active SLE has been reported [55,56], with such expansion and dysregulation also occurring in patients with other systemic autoimmune disease [57]. Reassessment of past clinical trials in light of this newer data provides valuable insights into the potential involvement of Tfh cells in the pathogenesis of human lupus [58]. Treatment of lupus nephritis patients with anti-CD40L antibodies caused disappearance of circulating CD38^{bright} plasma cells with decrease in anti-dsDNA titers, indicating these autoantibodies are a product of CD154-CD40 interactions, likely arising via the Tfh-driven GC response [47]. In murine lupus, at least, Tfh-like cells in the EF focus also express CD40L that is critical for B cell maturation [52,59]; thus, blockade of CD154-CD40 would likely also diminish EF plasmablast maturation. While anti-CD154 therapy in humans resulted in unexpected thromboembolic events, most likely a consequence of Fc-receptor mediated platelet activation [60], such data nonetheless establish a role for Tfh cells in SLE pathogenesis, providing crucial insights into the role of effectors of Tfh cell function as potential therapeutic targets in disease [61].

Autoantibodies as Initiators of Tissue Injury in SLE

The kidney is a primary site of tissue injury in murine and human lupus. Nephritis results from glomerular deposition of immune complexes of autoantibodies and autoantigens, with engagement of FcRs on immune cells along with complement fixation [62]. These effector mechanisms initiate infiltration and activation of tissue-infiltrating macrophages that promote the inflammatory response with resultant tissue injury [63,64]. The contributions of autoantibody isotypes to tissue injury in the kidney has not been well understood, although those associated with Th1 responses are thought to predominate in the human and murine diseases [65-67]. More recent data has shown that a subset of SLE patients have high titers of circulating IgE autoantibodies, without associated allergy [68], raising the question that Th2 cytokines (IL-4) or IgE *per se* contributes to lupus nephritis. Recent analysis of mice deficient in the Src family tyrosine kinase Lyn, a defect that leads to intrinsic B cell hyperactivation with autoantibody production and subsequent mild immune-complex nephritis, supports this notion [69]. These lupus-prone mice contain elevated serum titers of IL-4 with immune complexes containing IgE autoantibodies capable of basophil activation with promotion of tissue injury. Of particular relevance, this study also found that patients with SLE had both serum IgE autoantibodies and activated circulating basophils that could

migrate to the spleens and lymph nodes [69]. If these mechanisms are operative in human lupus nephritis, targeting basophils may effective in those patients with high concentrations of IgE antinuclear antibodies [68].

As autoantibodies are critical for the pathogenesis of SLE and resultant tissue injury, B cell depletion is an attractive therapeutic option in disease. Early studies in lupus-prone mice revealed that B cells are absolutely essential for disease induction [48] via both autoantibody-dependent and –independent pathways [70], suggesting a role for B cell depletion as a remittive agent. Indeed, targeting CD20, which is expressed on almost all lineages of B cells except early pro B cells and plasmablast and plasma cells, is therapeutically beneficial in murine lupus [71,72], albeit at high doses as elevated plasma antibody levels in disease block FcR-mediated uptake and elimination of anti-CD20 coated B cells [73]. Rituximab, an anti-human CD20 monoclonal antibody, has now been shown to have clinical benefits in almost 200 off-label trials in autoimmune diseases [74]; however, results of two randomized clinical trials in lupus were disappointing. In the Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial, 257 patients with moderate SLE without renal involvement were randomized to treatment with rituximab or placebo, in both cases with background immunosuppressant therapy and steroids. After 52 weeks of therapy, rituximab-treated patients did not show significant improvement in disease activity compared to the placebo (background immunosuppressant therapy) group [75]. A second randomized controlled study, The LUpus Nephritis Assessment With Rituximab Study (LUNAR) trial, compared therapy with rituximab plus standard therapy for lupus nephritis, mycophenolate mofetil and steroids, to standard therapy alone [76]. After one year of treatment, the addition of rituximab did not result in enhanced clinical effectiveness over standard therapy, although benefits were present with subset analyses. Why did these trials not show substantive clinical benefit in light of the data from murine studies and observational data in humans supporting the efficacy of B cell depletion in lupus? Questions have been raised about both trial design and clinical outcome measures [36]. Thus, while disappointing, the results of these two studies have not scuttled the idea that targeting B cells in SLE may be therapeutically beneficial. Indeed, therapy with belimumab, a fully humanized monoclonal antibody directed against B-lymphocyte stimulator (BLyS), proved beneficial in recent clinical trials. Upon binding to its receptors, TACI, BAFF-R, and B cell maturation antigen (BCMA), BLyS activates signals for B cell survival and maturation. Circulating levels of *BLyS* mRNA and BLyS are elevated in lupus patients and are correlated with disease activity [77,78], with the belimumab effect primarily mediated by depletion of recently formed, rather than memory, B cells or long-lived plasma cells [79]. Two large, randomized controlled trials involving more than 800 SLE patients treated with intravenous belimumab or placebo have recently been completed (BLISS-52, BLISS-76) [80,81]. At 52 weeks follow up in both trials, patients who received belimumab had improvement of lupus activity and serological parameters with less disease progression compared to patients in the placebo group, with comparable, typically mild, adverse events. While these clinical benefits were lost at 76 weeks of follow up for reasons that are unclear, belimumab was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of autoantibody-positive adult patients with active SLE who are receiving standard therapies.

Conclusions

The pathogenic mechanisms that lead to the clinical lupus phenotype are becoming clear, with genetic predisposition in the setting of environmental and/or stochastic triggers leading to innate immune system activation associated with pathological T-B cell collaboration and subsequent inflammation and tissue injury. These interactions are critical to understand, as their interruption is important therapeutically, as demonstrated by clinical studies in patients.

Since there have been, and will undoubtedly continue to be, therapeutic toxicities or failures along the way, efforts to refine the mechanistic basis of these aberrant immune interactions are necessary. Their dissection offers a means to better understand disease biology and to maintain the pipeline of disease targets and ultimately that of therapeutic agents.

Acknowledgments

This work was supported in part by NIH grants AR40072, AR44076, AI075157, and AR053495, and by the Alliance for Lupus Research. S. Kim was supported by a Research Scientist Development Award from the American College of Rheumatology Research and Education Foundation.

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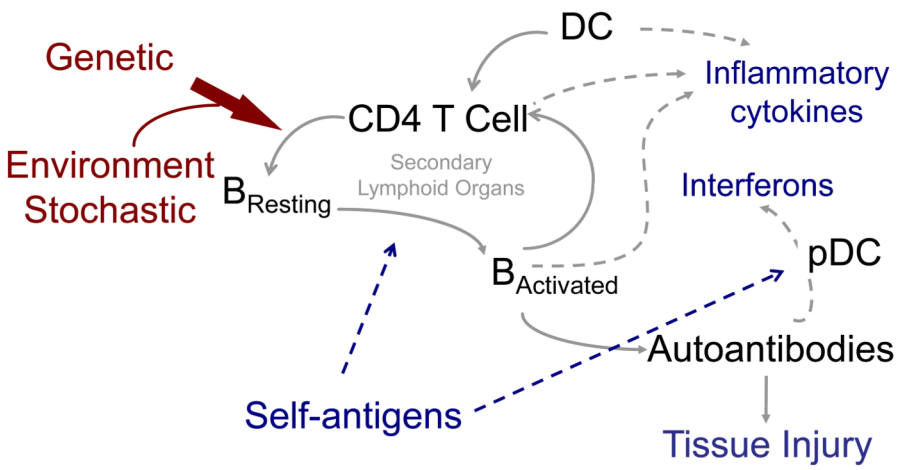
Highlights

- Innate effectors are critical for the lupus phenotype
- Aberrant adaptive immune responses promote disease progression in SLE
- Dissection of pathogenic events in SLE offers new therapeutic targets in SLE



1. . Mechanism of autoantibody production and tissue injury in lupus: A paradigm

Self-antigen dependent activation of autoreactive B cells and CD4 T cells in secondary lymphoid organs, leads to production of pathogenic autoantibodies that, along with inflammatory cytokines, promotes tissue injury in lupus. Antigen-presenting dendritic cells are necessary for adaptive immune cell activation, and contribute to inflammatory cytokine production. Autoantibodies in complexes with autoantibodies contribute to innate immune cell activation and cytokine production. Genetic predisposition is a requisite for aberrant immune system acivation, in the setting of environmental and stochastic events. Abbreviations: DC, dendritic cells; pDC, plasmacytoid dendritic cells.