B Cell Biology and Dysfunction in SLE

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Abstract

Systemic lupus erythematosus (SLE) is a complex disease characterized by the production of autoantibodies and clinical involvement in multiple organ systems. The immunological events triggering the onset of clinical manifestations have not yet been fully defined, but a central role for B cells in the pathogenesis of this disease has been brought to the fore in the last several years by work performed at multiple laboratories in both mice and humans. B cell defects that have been defined include abnormal expression or function of key signaling molecules, dysregulation of cytokines with key B cell effects, and perturbations in B cell developmental subsets. Many of these defects may contribute to or be reflective of abnormalities in B cell tolerance. Both antibodydependent and antibody-independent mechanisms of B cells are important in SLE. Thus, autoantibodies contribute to autoimmunity by multiple mechanisms, including immunecomplex mediated type III hypersensitivity reactions and type II antibody-dependent cytotoxicity, and by instructing innate immune cells to produce pathogenic cytokines, including IFNa, TNF, and IL-1. Autoantibody-independent B cell functions have been postulated to include antigen-presentation, T-cell activation and polarization, and dendritic cell (DC) modulation. Several of these functions are mediated by the ability of B cells to produce immuno-regulatory cytokines, chemokines, and lymphangiogenic growth factors and by their critical contribution to lymphoid tissue development and organization, including the development of ectopic tertiary lymphoid tissue. Given the large body of evidence implicating abnormalities in the B cell compartment in SLE,

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Correspondence: Jennifer H. Anolik, M.D., Ph.D., Box 695, 601 Elmwood Ave, Rochester, New York 14642; jennifer_anolik@ URMC.rochester.edu. there has been a recent therapeutic focus on developing interventions that target the *B* cell compartment by multiple mechanisms.

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with considerable heterogeneity in clinical manifestations and disease course, characterized by pathogenic autoantibody formation, immune complex deposition, and end organ damage. Although multiple immunologic abnormalities are important for the development and clinical expression of SLE, a growing body of evidence, most recently including the efficacy of B cell depletion therapy, supports the key role of the B cell in disease pathogenesis. It is important to be aware of the current state of knowledge regarding what is known about B cell dysfunction in SLE, the mechanisms contributing to loss of B cell tolerance, and the effector pathways by which B cells contribute to disease expression.

Abnormalities in B Cell Signaling Pathways

Three broad categories of defects that can lead to a lupus-like phenotype have been defined in the mouse and are instructive for thinking about B cell abnormalities in SLE. These defects may affect (1) B cell activation thresholds (e.g., FcR), (2) B cell longevity (e.g., BAFF transgenics), or (3) apoptotic cell/autoantigen processing (e.g., Mer knock-out). Although many alterations in B cell signaling or costimulatory molecules that may alter (1, activation thresholds) or (2, cell longevity) or both have been shown to lead to a lupus-like phenotype in the mouse, their relevance for human SLE and even spontaneous murine models of SLE is not well defined. Recently, Mohan and colleagues elucidated the mechanism by which the Sle1 susceptibility locus derived from lupusprone New Zealand Mixed (NZM2410) mice contributes to the development of autoimmunity. A gene within this locus encoding a member of the SLAM (signaling lymphocyte activation molecule) family was found to be highly expressed in immature B cells and altered in these lupus-prone mice in such a way as to impair signaling and impede antigen driven negative selection (B cell deletion, receptor revision, and anergy induction).¹ This suggests that some of the genes that contribute to lupus may function by down-regulating B cell receptor (BCR) signaling at the immature stage and impairing B cell tolerance.

In contrast, other B cell signaling defects may cause upregulated signaling, as exemplified by the loss of inhibitory Fc receptor function. Thus, FcyRIIb deficiency leads to a lupuslike phenotype in mice although with different penetrance, depending on the mouse strain.² Moreover, deficiency of the inhibitory FcyRIIb reduces the threshold for autoreactive B cell activation,³ and restoration of proper FcyRIIb expression on B cells in lupus-prone mice prevents the expansion and accumulation of autoantibody-producing plasma cells.4 These findings are even more meaningful given that polymorphisms in FcyRIIb are associated with human SLE and have a direct functional consequence on B cell signaling.^{5,6} Thus, a FcyRIIb membrane spanning Ile232 to Thr232 substitution, associated with lupus in Asian populations, caused decreased FcR lipid raft association and greater, more sustained calcium mobilization and downstream biochemical signaling events upon B cell receptor (BCR) engagement.⁵ Distinct FcR polymorphisms may be associated with lupus in different patient populations and could have differential effects on modifying BCR signaling. Moreover, other defects may lead to decreased expression of FcyRIIb, as recently demonstrated in human lupus memory B cells.⁶ Overall, Fc receptor polymorphisms are likely one of the many genetic modifiers in human lupus that may directly impact B cell signaling, with other examples including the decreased expression of the tyrosine kinase Lyn.⁷ Such alterations in B cell signaling proteins could explain earlier observations of increased calcium responses to BCR ligation in SLE B cells.8 Such defects are important, because they may contribute to the loss of peripheral B cell tolerance in SLE.

Alterations in B cell longevity also can lead to lupuslike phenotypes, as exemplified by transgenic expression of BAFF (B cell activator of the TNF family), a key cytokine that promotes B cell survival. These mice develop a lupuslike phenotype with excessive numbers of mature B cells, spontaneous GC (germinal center) reactions, autoantibodies, high PC (plasma cell) numbers, and Ig (immunoglobulin) deposition in the kidney.⁹ Moreover, lupus-prone mice have elevated levels of circulating BAFF; administration of soluble BAFF receptor ameliorates disease progression and improves survival.¹⁰ The importance of BAFF in human SLE has been demonstrated by the finding of elevated serum levels in SLE patients and the correlation with serum IgG and autoantibody levels.¹¹ Excessive BAFF may be another factor that promotes the survival of autoreactive B cells in the periphery.^{12,13}

The impaired clearance of apoptotic debris may also lead to SLE and may do so in part by providing large amounts of self-antigen and immune complexes that deliver stimulatory signals to autoreactive B cells. Several publications in recent years indicate that such apoptotic blebs and immune complexes contain ligands for Toll-like receptors (TLR), including RNA or DNA, which can provide costimulatory signals for autoreactive B cells.¹⁴⁻¹⁹ B cell self-stimulation may be magnified by increased sensitivity to TLR activation, as exemplified by the recently defined TLR7 duplication Yaa lupus susceptibility locus²⁰ and speculatively reproduced by TLR polymorphisms. Notably, plasmacytoid dendritic cells may also be activated by costimulation of TLRs and FcRs via immune complex binding, stimulating the secretion of large quantities of IFN- α ,²¹ a cytokine with important immunomodulatory functions that include activation and maturation of DCs and stimulation of both T and B cells.

Defective B Cell Tolerance in SLE

As SLE is characterized by the generation of large amounts of autoantibodies directed against chromatin and a variety of other self-antigens, the loss of B cell tolerance clearly plays a key role in the disease. However, it remains controversial whether such tolerance breakdown takes precedence over other immune abnormalities or, instead, is secondary to abnormal regulation by T cells and/or DCs. Recent evidence that the breakdown of B cell tolerance likely occurs very early in SLE and may precede or trigger other immune abnormalities is provided by the demonstration that SLE patients express ANAs (antinuclear antibodies) several years before the onset of clinical disease.²²

A great deal of additional evidence indicates that SLE is a disease characterized by defects in B cell tolerance and homeostasis.²³⁻²⁵ As demonstrated in animal models, B cell tolerance is established at multiple checkpoints throughout B cell development, both in the bone marrow and the periphery, and is enforced largely by negative selection (deletion, editing, or anergy) although positive selection and sequestration into the B1 and marginal zone (MZ) compartments has also been described.26 Recent work has demonstrated the role of the breakdown of peripheral tolerance mechanisms in SLE in both mice27 and humans.28,29 Thus, Sanz and coworkers have shown that an important tolerance checkpoint operates in healthy subjects to censor autoreactive (9G4) B cells in the mature naïve compartment, thereby preventing the expansion of these cells into the memory compartment,³⁰ a checkpoint recently corroborated by others³¹ and further shown by us to be faulty in SLE.29 Other work by Nussenzweig and associates has shown that 50% to 75% of newly produced human B cells are autoreactive and must be silenced by tolerance mechanisms.³² Key checkpoints to censor autoreactive B cell clones occur at the immature B cell stage in the BM (bone marrow) and the transition between new emigrant and mature B cells in the periphery, but with up to 20% of peripheral naïve B cells still reactive with nuclear antigens. Moreover, in a small number of SLE patients, peripheral checkpoints were found to be defective, with a further increase in autoreactivity within the mature naïve compartment.²⁸ The precise mechanisms of tolerance breakdown in human SLE remain to be defined.

Numerous studies in human SLE have documented significant abnormalities in B cell homeostasis that may be reflective of the loss of B cell tolerance and aberrant B cell activation. Such abnormalities include naïve B cell lymphopenia, increased transitional B cells, and an expansion of peripheral blood plasmablasts.33-35 Of note, the frequency and absolute number of plasmablasts in patients with SLE correlates with overall disease activity and autoantibody titers.³⁶ Moreover, IFN- α may contribute to naïve lymphopenia in SLE, given its known inhibition of B cell lymphopoiesis in the bone marrow.37 An association between naïve lymphopenia in SLE and VH4.34 encoded anti-i/anti-B cell antibodies has also been demonstrated.38 Of note, these antibodies preferentially bind a CD45/B220 glycoform expressed on naïve B cells and may induce lymphopenia through their reported lymphocytotoxic activity.

Contribution of Dysregulated B Cells to Disease Expression

B cells may theoretically participate in the immune dysregulation of SLE at multiple levels by: (1) serving as the precursors of antibody-secreting cells, (2) taking up and presenting autoantigens to T cells, (3) helping to regulate and organize inflammatory responses through cytokine and chemokine secretion (such as interleukin-10, interleukin-6, interferon- γ , and lymphotoxin- α), and (4) regulating other immune cells.24,39,40 Thus, autoantibodies contribute to autoimmunity by multiple mechanisms, including immune-complex mediated type III hypersensitivity reactions, type II antibodymediated cytotoxicity, and instructing innate immune cells to produce pathogenic cytokines, to include IFNa, TNF, and IL-1.41 The importance of antibody-independent functions for B cells was first demonstrated in murine SLE, where B cells have been found to be critical to the development of disease, even when they are unable to secrete autoantibodies. Thus, genetically B cell-deficient J_H knockout MRL/lpr lupus-prone mice have strikingly attenuated disease, with the expected absence of autoantibodies but also the surprising lack of T cell activation.42 Shlomchik and colleagues have used a novel approach to further elucidate the role of B cells in SLE by generating MRL/lpr mice that express a mutant transgene-encoding surface Ig that cannot be secreted. These mice have B cells, but no circulating Ig, yet develop T cell activation and nephritis.⁴⁰ This landmark study was the first to highlight that B cells can play a pathogenic role in lupus independent of serum autoantibody.

There has been much speculation about what the key autoantibody-independent functions of B cells are in SLE. A particularly novel function may be direct effects on lymphoid neogenesis through the production of LT α . The formation of tertiary or ectopic lymphoid tissue formation is a process that may lead to dysregulated B/T-cell interactions and local amplification of autoimmune responses in multiple autoimmune

diseases, including RA, Sjogren's syndrome, type I diabetes, multiple sclerosis, inflammatory bowel disease, Hashimoto's thyroiditis, and SLE.43,44 For example, recent reports suggest the importance of this process in human lupus nephritis.45 Moreover, B cells can produce numerous other cytokines and may do so in a polarized fashion, mimicking Th1/Th2 cells. So-called effector B cells (Be1 and Be2) can participate in feedback regulation of T helper cells,46 although the relevance of these mechanisms for SLE has yet to be demonstrated. Along similar lines, B cells play a key role in the recruitment of CXCR5+ follicular T helper (F_{TH}) cells to the germinal center.47 FTH cells provide critical assistance for follicular and germinal center B cells, inducing activation, differentiation, and antibody production. The influence of B cells on F_{TH} cells via ICOSL and OX40L costimulation may be important in SLE , as excessive activity of F_{TH} cells induces hyperactive GC, breakdown of B cell tolerance, autoantibody production, and a lupus-like phenotype.48 Another central autoantibodyindependent function of B cells is in the regulation of T cells through antigen presentation. This function can be mediated by antigen-specific B cells and also efficiently by rheumatoid factor producing B cells, which can present virtually any antigen owing to their ability to capture immune complexes.49 The activation of autoreactive T cells by activated B cells has been shown to play a role in murine lupus.^{25,50}

Therapeutic Targeting of the B Cell Compartment

Despite the provocative data summarized above, the role of B cells in human SLE disease pathogenesis and the relative importance of autoantibody dependent versus independent mechanisms have remained unclear. However, the contribution of B cells to ongoing disease activity in human SLE has recently been corroborated by studies of the effects of B cell depletion. A number of prospective open studies⁵¹⁻⁵³ and several retrospective cohort studies of rituximab in the treatment of SLE have reported favorable results, and phase III randomized controlled trials are underway. B cell depletion has the potential to induce disease amelioration by inhibiting autoantibody production, by interfering with other B cell pathogenic functions, or both. Given that disease-specific autoantibodies remain relatively stable at least in the shortterm, the importance of autoantibody independent roles of B cells in ongoing disease is highlighted. We have found that on longer follow-up, however, SLE patients with sustained clinical responses have normalization of autoantibodies.54 These patients also demonstrate a unique B cell reconstitution profile with dramatic transitional B cell expansions and a delay in memory B cell reconstitution, overall suggesting a de novo immune reconstitution without reemergence of autoimmunity. CD20 targeted B cell depletion also effectively normalizes the significant disturbances in peripheral B cell homeostasis discussed earlier, including naive lymphopenia, plasma cell expansions, and the expansion of autoreactive 9G4 memory B cells.55

Alternative approaches to B cell-targeted therapies are under investigation. It would be attractive to be able to specifically target autoreactive B cells. Tolerogens, synthetic molecules that bind to and extensively cross-link autoantibodies and may induce either anergy or deletion of B cells expressing the autoreactive B cell receptors, may fulfill this objective. LJP394, the first such B cell tolerogen developed and studied in human trials, has demonstrated limited efficacy in SLE.56 As an alternative to selective B cell depletion, therapies targeting co-stimulatory signaling pathways, including the CD40-CD40L pathway^{57,58} and the CD28-B7 pathway, are under investigation. Another approach is to interfere with critical B cell survival factors. A recently completed phase II trial of belimumab, an antibody against BAFF, has demonstrated promising activity, and additional agents antagonizing BAFF and the related cytokine APRIL are in various stages of development. Finally, targeting key signaling molecules that may be dysregulated in SLE is an important but challenging area of drug discovery for the future.

Conclusions

In summary, B cells in SLE display a number of defined abnormalities and participate in the autoimmune process in diverse ways. New approaches that target the B cell compartment in the treatment of SLE show great promise, not only for clinical treatment but also for further elucidation of disease pathogenesis.

Disclosure Statement

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