Autoantibody-dependent and autoantibody-independent roles for B cells in systemic lupus erythematosus: past, present, and future

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Abstract

It has long been known that B cells produce autoantibodies and, thereby, contribute to the pathogenesis of many autoimmune diseases. Systemic lupus erythematosus (SLE), a prototypic systemic autoimmune disorder, is characterized by high circulating autoantibody titers and immune-complex deposition that can trigger inflammatory damage in multiple organs/organ systems. Although the interest in B cells in SLE has historically focused on their autoantibody production, we now appreciate that B cells have multiple autoantibody-independent roles in SLE as well. B cells can efficiently present antigen and activate T cells, they can augment T cell activation through co-stimulatory interactions, and they can produce numerous cytokines which affect inflammation, lymphogenesis, and immune regulation. Not surprisingly, B cells have become attractive therapeutic targets in SLE. With these points in mind, this review will focus on the autoantibody-dependent and autoantibody-independent roles for B cells in SLE and on therapeutic approaches that target B cells.

Keywords

Antigen presentation; Autoantibodies; B cells; Co-stimulation; Cytokines; Systemic Lupus Erythematosus

Introduction

The production of autoantibodies is a hallmark feature of many autoimmune diseases, including systemic lupus erythematosus (SLE). As the producers of autoantibodies, B cells have been ascribed a major and culpable role in SLE pathogenesis. Indeed, for the greater part of the last half-century, autoantibody production was thought to be the predominant, if not sole, role for B cells in SLE. We now appreciate that whereas autoantibody production in SLE is an exclusive B cell function, B cell function in SLE is not exclusive to autoantibody production. Several clinical observations and evidence from animal models have shed light on the pathogenicity of autoantibodies and on multiple antibody-*independent* roles of B cells in SLE, thereby broadening the pathogenic spectrum of B cells and bringing about a therapeutic focusing on *B cells* rather than on just autoantibodies. This paper will review past observations regarding autoantibodies and their association with SLE, present and recent research on autoantibody-independent roles of B cells, and future potential treatment options that target B cells in SLE.

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The past: Autoantibodies as the primary pathogenic element in SLE

SLE, arguably the prototypic systemic autoimmune disorder, is characterized by high circulating autoantibody titers, dysregulation among T, B, and myeloid cell compartments, and immune-complex deposition that triggers inflammatory damage in multiple organs/organ systems, including the skin, hematopoietic and lymphoreticular organs, joints, lungs, cardiovascular structures, nervous system, and kidneys. Although the clinical and laboratory manifestations of SLE are highly protean and display a vast degree of heterogeneity, development of circulating autoantibodies is essentially ubiquitous. Consequently, autoantibodies have historically provided diagnostic and prognostic criteria and have served as biomarkers of disease activity.

Among the panoply of autoantibodies found in SLE patients, several have substantial clinical importance (Figure 1). For example, anti-dsDNA and anti-Sm antibodies are highly specific for SLE and, thereby, are diagnostically highly valuable; anti-ribosomal P antibodies point to an increased risk of neuropsychiatric disease; anti-cardiolipin antibodies are associated with an increased risk of intravascular thrombosis; anti-Ro (SS-A) antibodies in mothers are linked with the development of congenital heart block in their newborns; and anti-RNP antibodies identify those patients with mixed connective tissue disease [1–4].

Among these autoantibodies, anti-dsDNA antibodies have been the most extensively studied since their first identification in SLE sera [5–6]. Multiple clinical association studies have correlated elevated anti-dsDNA levels with reduced survival or increased damage [7–12]. The value of anti-dsDNA titers in SLE nephritis is especially great, in that these antibodies have been correlated with development of nephritis [13–16] and progression to end-stage renal disease [17–18], and they have served as well as predictors of renal flares [12,19–20].

The notion of a central role for autoantibodies in SLE pathogenesis received a great boost from the identification of highly informative murine SLE models. The first such model resulted from the mating of New Zealand Black (NZB) and New Zealand White (NZW) mice [21]. In contrast to either parental strain, (NZBxNZW)F1 mice develop many of the traits of human disease, including circulating IgG autoantibodies to ssDNA, dsDNA, histones, and phospholipids as well as fatal, diffuse, proliferative glomerulonephritis [22]. Similar to human SLE, (NZBxNZW)F1 female mice are disproportionately affected, and estrogens increase disease severity [23]. In these mice, high circulating titers of anti-dsDNA autoantibodies develop by 4–5 months of age and lead to progressive Ig deposition in the glomeruli [24–25]. By 6 months of age, histological glomerulonephritis develops, followed shortly thereafter by development of proteinuria, with 50% mortality by 8–9 months of age [24].

A similar progression from serological autoimmunity to renal pathology to clinical disease was observed in MRL/MpJ-Fas^{lpr} (MRL/lpr) mice which genetically greatly differ from (NZBxNZW)F1 mice. MRL/lpr mice express a mutant Fas receptor (CD95), resulting in defective apoptosis of activated lymphocytes and consequent lymphadenopathy and splenomegaly [26–27]. By 2–3 months of age, these mice develop high serum titers of SLE-associated autoantibodies, including anti-dsDNA, anti-histone, anti-Sm, anti-Ro (SS-A), and anti-La (SS-B) autoantibodies [22,28]. Development of glomerulonephritis occurs even sooner in MRL/lpr mice than in (NZBxNZW)F1 mice, with the former experiencing 50% mortality by 5–6 months of age.

Although it fell short of irrefutable proof, the reproducible progression in at least two genetically disparate murine SLE models from serological autoimmunity to histological end-organ (kidney) pathology to clinical disease provisionally supported a vital pathogenic role for the autoantibodies and lent considerable credibility to the "autoantibody" school of thought. Further support came from the successful elution of anti-dsDNA antibodies from diseased

kidneys in both murine and human SLE, again consistent with a pathogenic role for these autoantibodies in SLE nephritis [24,29–32].

A more compelling and direct connection between anti-dsDNA antibodies and development of disease came from *ex vivo* studies. Murine and human anti-DNA IgG were applied to isolated perfused rat kidneys. Monoclonal anti-DNA antibodies derived from (NZBxNZW)F1 mice and polyclonal anti-DNA IgG obtained from SLE nephritis patients each bound to rat glomeruli and induced proteinuria [33]. Moreover, adoptive transfer of monoclonal anti-DNA antibodies derived from MRL/lpr mice into non-autoimmune mice documented the ability of these antibodies to interact directly with distinct glomerular and vascular antigens and promote nephritis [30,34–35]. Indeed, similar results were obtained following transplantation of IgG anti-DNA-secreting hybridomas derived from SLE patients into severe combined immunodeficiency (SCID) mice. Three of the five antibodies tested were detected in recipient kidneys; one bound exclusively in the glomeruli, and two bound to nuclei in the kidneys and other organs. Proteinuria developed in these mice which was associated with the ability of the antibodies to bind to the kidneys either extracellularly or intranuclearly [36]. Taken together, these results all pointed to a vital pathogenic role for autoantibodies in SLE.

The present: SLE pathogenesis beyond autoantibodies

As is so often the case in science (and life, in general), "conventional wisdom" becomes less and less "wise" with passing time and the accrual of new information. Whereas some SLE autoantibodies do correlate with disease activity and are sufficient to cause renal pathology (at least in animal models), a disjunction between serology and disease activity has frequently been noted in both human and murine SLE, and some experimental observations question the extent to which autoantibodies are even necessary for disease development.

In terms of clinical observations, clinical disease activity frequently does not correlate with serological activity. In an SLE cohort of 180 patients, approximately 10% displayed serological activity with no active disease. Furthermore, about half of these serologically active patients did not develop disease flares over a 17-year follow-up period [37]. The converse has also been observed; i.e., patients with clinically active disease despite "serological quiescence," in ~12% of a 514-patient SLE cohort [38]. This uncoupling of clinical disease from serological autoimmunity was also appreciated in a study of 127 SLE patients with nephritis and 206 SLE patients without nephritis. Of the patients with nephritis (confirmed by renal biopsy), 32% did not have detectable circulating anti-dsDNA antibodies. Conversely ~50% of the SLE patients without nephritis did harbor circulating anti-dsDNA antibodies [14]. Indeed, elimination of autoantibodies by plasmapheresis was unsuccessful in a controlled clinical trial [39], and treatment of some SLE patients with rituximab (to deplete B cells) has resulted in substantial clinical improvement despite no meaningful changes in anti-dsDNA levels [40].

Studies in murine SLE have also demonstrated a disjunction between the presence of autoantibodies (in the serum or kidney) and development of disease. (NZBxNZW)F1 mice transgenic for Ig μ heavy chain have a restricted B cell repertoire. Despite development of high titers of autoantibodies, glomerulonephritis and mortality in these mice are markedly reduced in comparison to (NZBxNZW)F1 wild-type controls [41]. Among congenic Fas-intact MRL mice that differ at the H-2 region (H-$2^{k/k}$, the MRL mouse wild-type genotype; H-$2^{b/b}$, derived from the non-autoimmune C57BL/6 mouse; or H-$2^{k/b}$ heterozygotes), development of disease features, including kidney pathology and mortality, are very similar despite disparate levels of circulating autoantibodies [42].

Work on the New Zealand Mixed (NZM) recombinant inbred strains derived from (NZBxNZW)F1 mice [43] has extended these observations. NZM mice deficient in STAT6, a transcription factor which promotes Th2 responses, display marked reductions in kidney

disease and mortality despite the presence of high levels of anti-dsDNA antibodies [44]. Moreover, NZM mice deficient in B cell activating factor belonging to the TNF family (BAFF; also commonly known as BLyS [b lymphocyte stimulator]), a vital B cell survival and differentiation factor, develop high titers of SLE-associated autoantibodies (despite the marked reduction in B cells) and glomerular IgG deposition with time but demonstrate greatly attenuated clinical disease (severe proteinuria and mortality) [45].

One could argue that the observations above do not necessarily point to an uncoupling between autoantibodies and development of disease. Multiple investigations have shown that only a subset of autoantibodies has nephritogenic properties; IgG subclass and binding capacities play significant roles in the autoantibodies' effects [30,33,46–48]. Thus, the high titers of autoantibodies in SLE-prone hosts with only mild or absent disease might be explained by invoking a paucity of nephritogenic autoantibodies. Nevertheless, other studies have demonstrated that disease can develop in the complete absence of autoantibodies, but not in the absence of B cells, calling into question the obligatory role of autoantibodies in (murine) SLE and challenging the paradigm that B cells in SLE function exclusively (or even primarily) to generate autoantibodies.

On the one hand, B cell-deficient MRL/lpr, Fas-intact MRL, and NZM mice each are completely protected from development of SLE as assessed by either pathological or clinical criteria [49–50, Jacob CO, unpublished data]. On the other hand, disease development proceeds despite limited autoantibody production, as long as functionally intact B cells are present. SLE-prone NZM 2328 and NZM 2410 mice deficient in STAT4, a transcription factor that drives Th1 responses, develop accelerated disease and mortality despite harboring reduced anti-dsDNA antibody levels in comparison to those in wild-type NZM controls [44,51].

More striking and definitive was the development of SLE-like disease in MRL/lpr mice that were completely deficient in circulating autoantibodies [52]. These MRL/lpr mice expressed a mutant transgene (denoted as mIgM Tg) that permitted expression of surface Ig but did not permit secretion of Ig. Thus, these mIgM.MRL/lpr mice harbored B cells that, in principle, were functionally normal other than their inability to secrete Ig. In contrast to B cell-deficient MRL/lpr mice which were resistant to disease development, mIgM.MRL/lpr mice developed interstitial nephritis and vasculitis, resulting in accelerated mortality (albeit to a lesser extent than in wild-type MRL/lpr mice), conclusively documenting an indispensable autoantibody-independent role for B cells in the MRL/lpr model of SLE.

This conclusion leads us to analyze candidate autoantibody-independent roles of B cells in SLE. These include: 1) activation of T cells through presentation of autoantigens; 2) co-stimulation of T cells; and 3) production of pro-inflammatory and/or regulatory cytokines (Figure 2).

Antigen presentation and T cell activation

Many different experimental approaches taken by many different laboratories have documented the ability of normal B cells to serve as efficient antigen presenters to T cells [53–57]. Importantly, B cells can process and present autoantigens to naive T cells, resulting in primed autoreactive T cells [58–59]. Of considerable consequence for SLE pathogenesis, B cells were shown to process and present specific SLE-associated autoantigens to T cells and to initiate autoimmune T cell responses [60]. Of note, highly autoreactive B cells accumulate in both murine and human SLE [61–63]. For example, in MRL/lpr mice, B cells specific for self IgG or DNA/histone predominate [61] and become important antigen-presenting cells for autoreactive T cells. These activated autoreactive T cells then can trigger a cascade of events leading to disease, including (but not limited to) their providing help to B cells in autoantibody production [52,64].

Indeed, B cells play a pivotal part in spontaneous T cell activation and expansion in the MRL/lpr and (NZBxNZW)F1 SLE murine models. In Ig μ Tg (NZBxNZW)F1 mice, a restricted B cell repertoire results in markedly reduced numbers of activated T cells [41]. B cell deficiency in MRL/lpr mice prevents the spontaneous activation and expansion of CD44+ CD62L− activated memory T cells, a subset of CD4+ cells that massively expands and accumulates in MRL/lpr mice (but not in non-autoimmune mice) [64]. In NZM 2328 mice, this cell population produces inflammatory cytokines, such as IL-17, and correlates closely with disease progression [65]. Thus, B cells appear to be vital for the activation of pathogenic T cells in SLE.

Co-stimulation of T cells

B cells not only can present antigen to T cells but can greatly affect the extent of T cell activation by virtue of a number of co-stimulatory interactions. In the context of B cell presentation of antigen to naive T cells, T cell surface CD28 will engage B cell surface CD80 (B7-1) and CD86 (B7-2), amplifying T cell activation, proliferation, and cytokine production. Upon activation, T cell surface expression of CTLA-4 (CD152), a homologue of CD28, is up-regulated. CTLA-4 binds to CD80 and CD86 with much higher avidity than does CD28 and leads to down-regulation of the ongoing T cell responses [66]. Indeed, blocking CD28/B7 interactions or activating CTLA-4 signaling can result in immunosuppression, with implications for the treatment of autoimmune diseases [67]. Such approach has been studied in murine SLE and is under investigation for human SLE [68–69].

Important co-stimulation of T cells by B cells also is effected through ligation of B cell surface CD40 with T cell surface CD154 (CD40L). Although many different cell types express CD40, it has been shown that in the absence of other APCs, B cells can prime naive CD4+ cells *in vivo* through CD40-CD154 engagement [70]. Other studies have demonstrated that CD40-CD154 interactions influence T cell priming, T cell–mediated effector functions, and promote the production of Th2 type cytokines [71–74]. Of crucial significance are the simultaneous reciprocal effects on the B cell, which include important signals for B cell activation, proliferation, Ig production, and isotype switching along with germinal center, memory B cell, and antibody-secreting plasma cell formation [75–77]. Additionally, CD40-CD154 engagement promotes cytokine production by B cells in both BCR–dependent and –independent manners [78].

The consequences of CD40-CD154 interaction are highly relevant to murine and human SLE. CD154-deficient MRL/lpr mice develop neither elevated levels of anti-dsDNA antibodies nor proliferative glomerulonephritis, and these mice harbor lower numbers of activated memory T cells compared to those harbored by CD154-intact MRL/lpr controls [79]. Along these lines, blockade of CD40-CD154 interaction via treatment with anti-CD154 monoclonal antibody (mAb) delayed disease onset and reduced levels of anti-dsDNA antibodies in (NZBxNZW)F1 mice. In addition, B cell activation and the numbers of IgG anti-dsDNA-secreting B cells were also reduced, and activation and transition of naïve T cells to memory T cells was inhibited [80].

In humans, genetic studies permit one to speculate that polymorphisms within CD40 may affect ultimate B cell function and/or T cell function with ramifications for SLE. The gene for CD40 is located in the region 20q11–13 which has been linked with SLE in three independent investigations of three ethnic groups [81–83]. Although a direct 7-SNP-analysis of the CD40 gene in over 400 European-Caucasians showed no association with SLE [84], a more recent study in 230 SLE families of the chromosome 20q13.1 region provided evidence of association with SNPs in and around the CD40 locus [85].

On the CD154 side of the equation, studies have shown increased numbers of CD154+ T cells in patients with active SLE [86–87]. Compared with healthy controls, SLE patients have higher levels of soluble CD154 which can mediate B cell activation [75,88]. These findings, together with observations in the murine SLE models, have prompted evaluation of CD40-CD154 blockade in SLE patients.

Five patients with SLE nephritis participated in an open-label study of a humanized CD154 mAb. A brief period of treatment with this agent reduced the percentage of IgG anti-DNA antibody-producing B cells [89]. However, in a phase 2 randomized, double-blind, placebo-controlled trial of 85 SLE patients with humanized anti-CD154 mAb (IDEC-131), neither improvement in disease activity nor changes in serum levels of complement or anti-dsDNA antibodies were appreciated in comparison to placebo-treated controls [90]. In an open-label trial, twenty-eight patients with active SLE nephritis were scheduled to receive a different humanized anti-CD154 mAb (BG9588), but the trial was terminated early due to thromboembolic events in two patients. Among the 18 patients in whom efficacy could be evaluated, a reduction in serum anti-dsDNA levels was noted, and two of the patients reached the primary endpoint of a 50% reduction in proteinuria without worsening of renal function [91]. Of interest, down-regulation of CD154 was noted to precede remission of SLE nephritis in an open-label trial of B cell depletion therapy [92], consistent with the notion that T cell activation is inhibited in the absence of B cells.

B cell cytokine production

In addition to their function as antigen-presenting cells and co-stimulators, B cells importantly contribute to immune responses in general through cytokine production. As mentioned above, one of the antibody-independent B cell functions resulting from CD40-CD154 interaction is the promotion of cytokine production by B cells. Duddy et al. [78] studied *ex vivo* human B cells and established a stimulation regimen that evaluated isolated or dual BCR- and CD40-mediated B cell responses. B cells stimulated by sequential B cell receptor engagement and CD40 ligation proliferate and secrete IL-6, TNFα, and lymphotoxin, which can act as autocrine growth and differentiation factors, serving to enhance immune responses. Exclusive CD40 stimulation, however, in the absence of specific antigen recognition, induces minimal pro-inflammatory cytokine production, but significant production of IL-10, which can have immunosuppressive effects (as discussed below).

Such cytokine production may be highly relevant to SLE disease pathogenesis, inasmuch as B cell-derived cytokines can exert paracrine effects on various cells: IFNγ, TNFα, IL-6, and GM-CSF on macrophage and/or follicular dendritic cell activation; IL-12, IFNγ, IFNα, and IL-2 on natural killer cell activation; IL-8, G-CSF, GM-CSF on the recruitment of inflammatory cells; and IL-1α, IL-1β, TNFα, GM-CSF, and IL-6 on T cell growth [93]. A few of these B cell-derived cytokines (which also are produced by various non-B cells) deserve particular mention, in as much as these cytokines are being evaluated as potential therapeutic targets.

One such cytokine is TNFα, which has an established role as an inflammatory mediator in a number of autoimmune diseases. Whereas TNF antagonists have been beneficial in rheumatoid arthritis and inflammatory bowel disease [94–95] and have anecdotally been successfully used in some SLE patients [96], their widespread utility in SLE remains debatable, inasmuch as complete inhibition of TNFα signaling might abrogate important immunoregulatory functions that try to keep the SLE process "in check" [65].

Two other cytokines warrant special mention. One is IFNα, whose contributory role to SLE pathogenesis has been well-documented [97–98]. Deletion of the IFNα receptor in NZM2328 mice leads to a delay in development of disease along with milder renal pathology [99], and results from a phase I clinical trial suggests that administration of a neutralizing mAb against

IFNα can ameliorate disease activity [100]. The other is IL-6, which stimulates B cell differentiation, maturation, immunoglobulin secretion as well as T cell functions [101]. Administration of anti-IL-6 mAb to (NZBxNZW)F1 mice prevents development of kidney disease [102], and an anti-IL6R mAb (tocilizumab) is undergoing clinical evaluation in human SLE [103]. For all these and other pro-inflammatory cytokines, their production by B cells may be especially important in the development of end-organ damage, such as in the kidney. Indeed, a recent report has documented that B cells of a non-antibody-secreting phenotype can infiltrate the kidneys of SLE nephritis patients [104].

As already mentioned, the capacity of B cells to stimulate T cells is a crucially important antibody-independent B cell function in SLE. In accordance with their cytokine-producing capability, B cells can differentiate into so-called effector Be1 and Be2 cells that secrete polarizing cytokines IFNγ and IL-4, respectively [105]. While the relevance for this specific mechanism has not yet been demonstrated in SLE, both Th1 and Th2 dysregulation have been associated with SLE.

Cytokine production by B cells lies at the heart of their ability to affect lymphoid tissue formation and neogenesis [106–107]. Defects in spleen dendritic cells [108], Peyer's patch organogenesis, and follicular dendritic cell organization are observed in the absence of B cells [109–110]. Additionally, transgenic mice expressing BLC (B lymphocyte chemoattractant, also called BCA-1) on pancreatic islet cells develop new lymph node-like structures, a phenomenon highly dependent on B cells [111]. Indeed, B cell production of lymphotoxin and TNFα is vitally important to germinal center formation and development of lymphoid tissue in general [112–114]. Moreover, in a number of autoimmune diseases, including SLE, dysregulated B-T interactions and local chronic immune responses can ensue following the formation of tertiary lymphoid tissues, the latter being directly affected by lymphotoxin [115].

In addition to producing pro-inflammatory, T cell-polarizing/activating, and lymphogenic cytokines, B cells also produce IL-10, a cytokine that inhibits pro-inflammatory cytokine production, antigen presentation by macrophages, and both Th1 and Th2 polarization [116]. Indeed, IL-10-producing "regulatory B cells" (Bregs) have been ascribed disease-modifying roles in a number of autoimmune conditions [117], including experimental autoimmune encephalomyelitis and inflammatory bowel disease [118–119]. Regarding SLE, adoptive transfer of IL-10-producing Bregs into MRL/lpr mice substantially reduced renal disease and improved survival. Additionally, these Bregs suppressed T cell proliferation and differentiation into Th1 cells, all in an IL-10-dependent manner [120].

The future: Targeting B cells – can we get rid of the bad ones while keeping the good ones?

Given that B cells contribute to SLE pathogenesis through a number of different mechanisms, the ideal B cell-directed treatment would entail selective inhibition of the "bad" B cells (or their "bad" activities) while preserving the "good" B cells and their "good" functions. Unfortunately, this is easier said than done. To date, B cell-targeted therapy has, in large measure, been global rather than specifically directed to the (presumed) pathogenic B cell subset(s). These approaches have included general B cell depletion through direct binding of surface molecules (e.g., CD20) or neutralizing growth factors (e.g., BAFF), by blocking B-T co-stimulation pathways (e.g., CD40-CD154), and by down-regulating BCR signaling through engaging inhibitory receptors on the B cell surface (Figure 3). Alternatively, focusing on the beneficial attributes of regulatory B cells might be an additional source of future treatments, perhaps through *in vivo* enrichment or *ex vivo* expansion followed by re-administration, as recently achieved in SLE mice [120].

Direct B cell depletion

The existence of regulatory B cells notwithstanding, the predominant effects (both autoantibody-dependent and autoantibody-independent) of B cells in SLE lead to promotion, rather than suppression, of disease. Accordingly, it stands to reason that B cell depletion should improve disease manifestations. To date, the most widely utilized clinical means of depleting B cells is through the targeting of CD20, a 33–37 kDa non-glycosylated tetraspan phosphoprotein which is specifically expressed on the surface of B cells but whose physiological function remains unknown [121]. A chimeric mouse-human mAb specific for CD20 (rituximab) was first approved by the FDA in 1997 to treat patients with non-Hodgkin's B cell lymphoma. Despite the absence of formal FDA approval of this drug for SLE, considerable experience with rituximab, both in the setting of clinical trials as well as in anecdotal "off-label" experience, has accrued in SLE. Anti-CD20 mAb binds surface-expressed CD20 (which is expressed exclusively on B cells from the pre-B cell stage until terminal plasma cell differentiation) and induces B cell lysis via apoptosis, antibody-dependent cell-mediated cytotoxicity, or complement-mediated cytotoxicity. Rituximab usually results in near-total B cell depletion in the peripheral blood within weeks of treatment [121].

Several "open-label" studies reported favorable outcomes in the treatment of various SLE manifestations. Among 18 pediatric SLE nephritis patients demonstrating resistance or toxicity to conventional regimens, treatment with rituximab improved clinical activity scores and renal function in 93% of them [122]. Among 17 adult SLE patients treated with graded doses of rituximab, 11 achieved full peripheral blood B cell depletion with attendant improvement in SLE disease activity, with 3 of these patients going into long-term complete remission [40]. Additional studies also pointed to clinical efficacy of the combination of rituximab + corticosteroids or rituximab + cyclophosphamide [123–127]. Thus, it was quite surprising (and disappointing) when results from the phase II/III EXPLORER study in SLE patients without nephritis [128] or the phase III LUNAR study in SLE patients with nephritis (http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=11947) failed to demonstrate any appreciable benefit from rituximab therapy. The reasons for these failures remain uncertain, but one component may be the elimination of immunoregulatory B cells [120].

In light of the uncertainties surrounding a CD20-based approach, an alternative strategy might be to target CD19, a 95 kDA glycoprotein member of the Ig superfamily that functions both as a co-stimulatory molecule and as a response modulator of basal and BCR-induced signaling [129]. CD19 expression through B cell ontogeny is somewhat broader than that of CD20, in that CD19 is expressed on early CD20- B cell precursors in the bone marrow and on some early plasma cells that have already lost their surface CD20 [130]. Due to the broader expression of CD19, greater B cell depletion might be realized with CD19-based therapies, but whether that actually would be clinically beneficial remains to be established.

B cell growth factors

Rather than directly targeting the B cell, one can target factors essential to B cell survival, such as BAFF. Constitutive overexpression of BAFF in BAFF-transgenic mice that otherwise are not autoimmune-prone leads to SLE-like features [131–133], and similar BAFF overexpression in mice with an autoimmune diathesis (but without overt SLE disease) promotes accelerated glomerulonephritis [134]. Circulating BAFF levels are elevated in murine SLE [131], and treatment of SLE-prone mice with BAFF antagonists ameliorates disease [131,135–137]. Since circulating BAFF levels are also elevated in human SLE [138–139], it stands to reason that therapeutic targeting of BAFF could be beneficial not just in murine SLE but in the human counterpart as well. Indeed, therapeutic targeting of BAFF in SLE is especially appealing, inasmuch as in vivo studies in mice have suggested that survival of autoreactive B cells is more

dependent upon BAFF than is survival of non-autoreactive B cells [140–141]. If this differential dependence upon BAFF is recapitulated in humans, then therapeutic neutralization of BAFF in SLE patients could lead to preferential elimination of autoreactive (pathogenic) B cells with sparing of non-autoreactive (non-pathogenic) B cells, an outcome not predicted for more global B cell depletion with rituximab (or other anti-CD20 mAb).

Elevated numbers of circulating plasma cells have been positively correlated with SLE disease activity [142] and, therefore, their neutralization could be therapeutic. Accordingly, another theoretical advantage to targeting BAFF rather than CD20 is that plasmablasts and plasma cells (representing the major "factories" of autoantibodies) express BAFF receptors and, as such, are sensitive to BAFF depletion [143]. In contrast, by the time B cells have differentiated into plasmablasts or plasma cells, surface CD20 has been lost, rendering these cells insensitive to rituximab.

With these considerations in mind, investigators have embarked on clinical trials in human SLE with BAFF neutralizers. The greatest experience to date with BAFF antagonists has accrued with belimumab, a fully human IgG1λ mAb that binds and neutralizes soluble BAFF [144]. Although a 52-week, randomized, double-blind, placebo-controlled phase-II trial of belimumab in SLE failed to meet its primary endpoints of clinical efficacy when the entire SLE cohort (n = 449) was considered, significantly reduced disease activity was demonstrable in the ~70% of patients who were "seropositive" (ANA titer ≥1:80 and/or positive for anti-dsDNA antibodies) at entry [145], raising the hope that belimumab may be clinically efficacious in a substantial subset of SLE patients. Indeed, a recent press release of the first of two separate large phase-III trials (n ≥ 810 in each) of belimumab in "seropositive" SLE patients has touted the statistically significant efficacy of belimumab (http://www.hgsi.com/latest/human-genome-sciences-and-glaxosmithkline-announce-positive-phase-3-study-results-for-benl-2.html).

Related agents (atacicept, BR3-Fc, AMG 623) are also being tested in SLE clinical trials, but none of these agents have yet completed phase II, so meaningful information regarding their efficacy is still pending.

Targeting auto-reactive B cells

The above treatments act indiscriminately, targeting both potentially autoreactive and non-autoreactive (i.e., "normal") B cells. An attractive line of therapy would involve specifically targeting autoreactive B cells while sparing non-autoreactive ones from elimination. The so-called tolerance-generating biological agent ("tolerogen"), abetimus sodium, consists of four double-stranded DNA epitopes attached to a non-immunogenic polyethylene glycol platform. It is intended to target potentially autoreactive B cells that express surface Ig receptor specific for dsDNA. By cross-linking those anti-dsDNA receptors, the pharmacologic agent can induce apoptosis or anergy, thereby either eliminating the B cell or inhibiting the production of anti-dsDNA antibodies. Additionally, abetimus sodium can form rapidly-cleared soluble complexes with circulating anti-dsDNA antibodies. Although in an animal model of SLE abetimus sodium lowered autoantibody levels, improved renal function, and increased survival [146], the agent met with very limited success in a number of controlled trials for human SLE [147–149] and is no longer being developed for human SLE.

B cell inhibitory receptors

In principle, what therapeutically is ultimately sought through a B cell-targeting approach is the abrogation of the function of pathogenic B cells. This does not necessarily require physical elimination of those B cells. Thus, engagement of inhibitory receptors on the B cell surface may functionally suffice and not lead to some of the potential problems associated with B cell

deficiency. One such target is CD22, a 135 kDA type-1 transmembrane sialoglycoprotein of the Ig superfamily that can regulate signal transduction [150–151]. Indeed, loss of CD22 signaling in mice results in production of high-affinity autoantibodies [151], so augmenting CD22 signaling in human SLE could be efficacious.

To that end, the anti-CD22 mAb epratuzumab has been tested. This agent primarily leads to a modulation of B cell function, although modest B cell depletion does ensue [152]. In a SLE phase II trial of epratuzumab, total disease scores decreased by ≥50% in all 14 patients at some point during the study, and 77% of patients demonstrated ≥50% decreases at 6 weeks. Multi-center, randomized phase III trails are ongoing.

Another potential target for B cell silencing, and one that has recently been associated with SLE directly, is the FcγRIIb inhibitory receptor. FcγRIIb-deficient mice develop autoantibodies and autoimmune glomerulonephritis in a strain-dependent fashion, and restoration of proper receptor expression on B cells in SLE-prone mice prevents autoimmunity [153–154]. In humans, functionally important FcγRIIb polymorphisms are associated with SLE, and decreased FcγRIIb expression has been observed on memory B cells in SLE patients with active disease [155–156]. Accordingly, increasing the signaling through FcγRIIb could be therapeutically beneficial in SLE. A non-depleting anti-CD19 mAb genetically engineered to have high affinity for FcγRIIb has been generated [157] and is currently undergoing pre-clinical evaluation.

Concluding Remarks

B cells have long been implicated in the pathogenesis of SLE by virtue of their production of autoantibodies. Observations of clinical discordance between serological activity and disease activity as well as compelling evidence from animal models have resulted in a paradigm shift regarding the exact, but obligatory, role of B cells in disease pathogenesis. It is now established that aside from autoantibody production, B cells are involved in a number of pathological mechanisms in SLE, and they, therefore, serve as important targets of new therapies. To this end, it remains to be seen if the recent clinical trials of B cell-targeted therapies will ultimately yield new efficacious and safe therapeutic agents. Chicago Cubs' fans may have to wait another 100 years for a World Series championship, but SLE patients should not have to wait another 50 years for better treatments!

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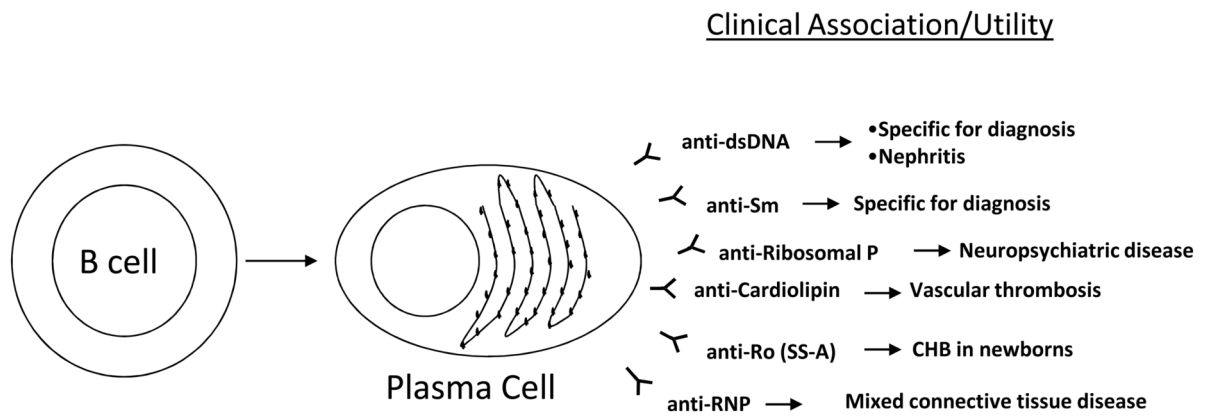# Autoantibody Production in SLE

Figure 1.
B cells produce a variety of autoantibodies in SLE. The relevant utility and clinical associations of those autoantibodies are enumerated.

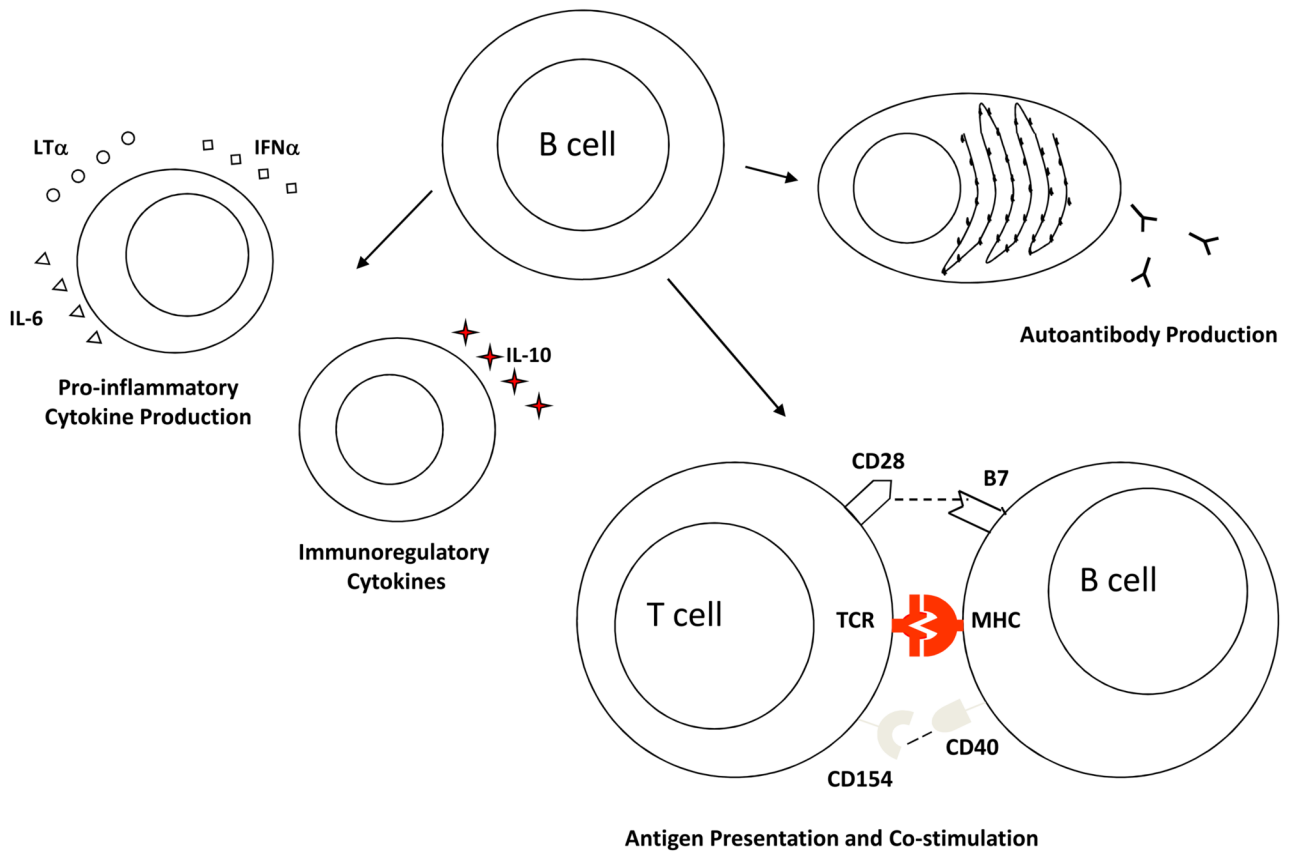**Multiple B Cell Functions in SLE Pathogenesis**

Figure 2.
B cells have multiple functions in SLE pathogenesis, including proinflammatory and immunoregulatory cytokine production, antigen presentation to and co-stimulation of T cells, and autoantibody production.
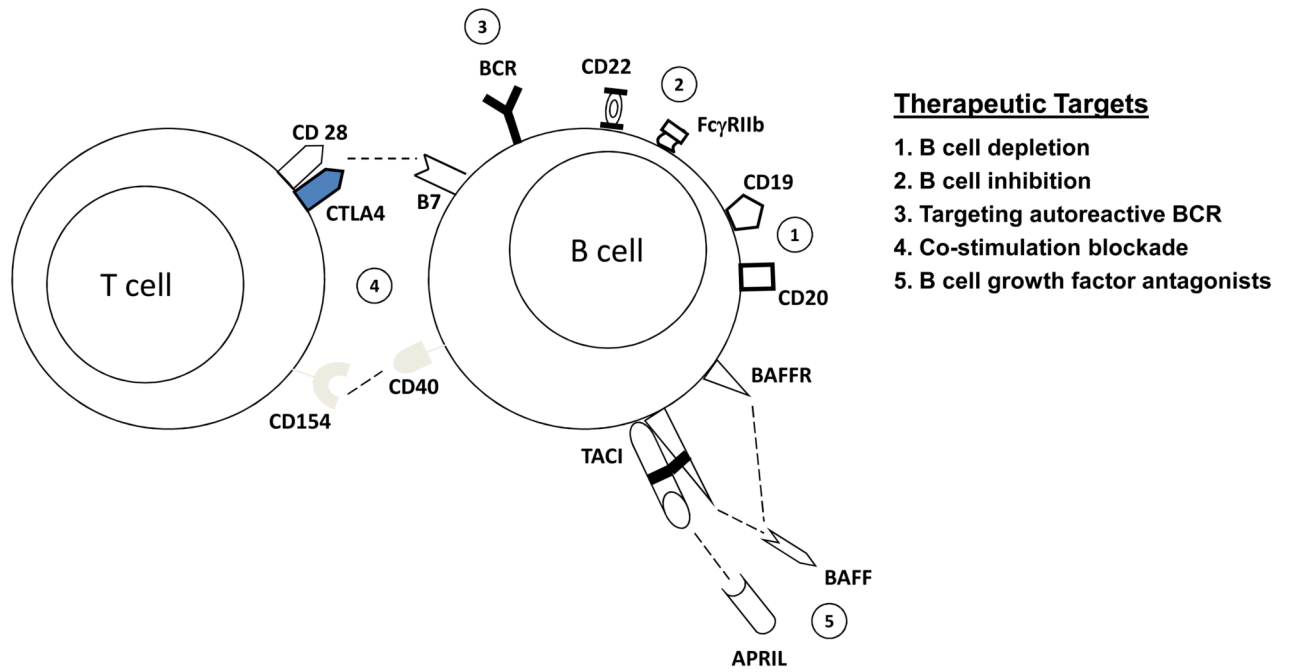
Therapeutic B Cell Targeting

Figure 3.
In light of the numerous functions of B cells in SLE, a number of therapeutic strategies have been developed in an attempt to target directly or indirectly B cells and their effects.

Table 1

B cell-related SLE therapeutics

Agent	Target	Mechanism	Status
Rituximab	CD20	Direct B cell depletion	Phase III
Ocrelizumab	CD20	Direct B cell depletion	Phase III
MDX-1342	CD19	Direct B cell depletion	Preclinical
Belimumab	BAFF	Depletion of B cell survival factor	Phase III
Atacicept	BAFF, APRIL	Depletion of B cell survival factors	Phase II-III
BR3-Fc	BAFF	Depletion of B cell survival factor	Phase II
AMG623	BAFF	Depletion of B cell survival factor	Phase I completed
BG9588	CD154	Co-stimulation blockade	Studies Terminated (during Phase II)
Abetimus	BCR/anti-DNA Ab	Tolerance induction	Studies Terminated (during phase III)
Epratuzumab	CD22	B cell inhibition	Phase III
XmAb5871	CD19/FcγRIIb	B cell inhibition	Preclinical