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Role of B cells in Systemic Lupus Erythematosus and Rheumatoid Arthritis

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Summary

B cell tolerance to many self-proteins is actively maintained by either purging self-reactive B receptors through clonal deletion and receptor editing, or by functional silencing known as anergy. However, these processes are clearly incomplete as B cell-driven autoimmune diseases still occur. The significance of B cells in two such diseases, rheumatoid arthritis and systemic lupus erythematosus, is highlighted by the ameliorative effects of B cell depletion. It remains to be determined, however, whether the key role of the B cell in autoimmune disease is autoantibody production or another antibody-independent function.

Introduction

In this article, we discuss current studies regarding B cell tolerance and what accounts for its disruption in disease states, as well as promising therapies for autoreactive B cell control. For a more extensive review, including thoughtful discourse of earlier pioneering studies, please see [1]. Here, we emphasize work done in the past two years in both human and mouse models with a focus on systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), where B cells play a dominant role and are being targeted in treatment.

Control of autoreactive B cells in healthy mice and people

Following receptor rearrangement, roughly 50% of immature B cells exhibit autoreactivity, which in healthy individuals is reduced to 6–20% of mature B cells [2]. Multiple mechanisms for controlling autoreactive cells in healthy mice have been revealed using immunoglobulin (Ig) transgenes (Tgs), including clonal deletion, receptor editing, and anergy (Figure 1) [1,3]. Importantly, some of the mechanisms of B cell tolerance illustrated using Tg models have also been shown to operate within a wild-type B cell repertoire [4].

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An autoreactive B cell's fate appears to be dictated by several features of the self-antigen (Ag), including valency and physiological context, as well as by features of the B cell receptor (BCR) itself, such as affinity. Unfortunately, in most cases involving disease-associated Ags, it remains difficult to identify the *bona fide* nature of the *in vivo* self-Ag, thus making attempts to correlate affinity with B cell fate suspect. Importantly, this is not such a concern with the AM14 model where the self-Ag (IgG_{2a} of the IgH^a allotype) can be easily manipulated. In this case, activation of rheumatoid factor (RF)-specific B cells was definitively shown to be Ag-driven [5].

In support of the role of B cell affinity, two different Ig Tg models on the K/BxN background have been used to track high- and low-affinity B cells to the self-Ag glucose-6-phosphate isomerase (GPI) (Figure 2). Similar to some anti-DNA models, high-affinity, anti-GPI B cells undergo either developmental arrest or receptor editing [6]. In contrast, low-affinity, anti-GPI B cells are present in the periphery and proliferate and secrete autoantibody upon receipt of T cell help *in vitro* or *in vivo* [7]. However, unlike the anti-IgG2a B cells in AM14 mice, the anti-GPI B cells do not appear to be clonally ignorant in non-autoimmune mice, as GPI autoantigen was detected bound to their BCR, and anti-GPI B cells in the marginal zone (MZ) were activated and spontaneously secreted Ig.

Activation of autoreactive B cells in disease

An inability to maintain control of autoreactive B cells can lead to autoimmune disease. Clinical evidence suggests that one breach in RA and SLE may stem from a defect in eliminating autoreactive B cells before they enter the mature B cell pool [8,9]. Likewise, Ig Tg models have shown that both anti-chromatin B cells and RF B cells are activated in autoimmune settings. Possible mechanisms to account for this activation are alterations in the T cell compartment, such that effective T cell help is available [10], or changes in the availability of self-Ag [1].

There are several described means by which T cells can lead to the activation of autoreactive B cells. In the BXD2 model, in which mice develop autoantibody-dependent arthritis and glomerulonephritis, it has been proposed that "autoreactive" germinal centers (GCs) develop as a direct result of IL-17-secreting T helper cells (Th17) [11]. However, in autoimmune Sanroque mice, impaired negative regulation of ICOS leads to a profound increase of T follicular helper cells that are thought to drive GC reactions [12]. There is no evidence for the involvement of Th17 cells in this model. Finally, studies using Fas/FasL-deficient mice suggest another scenario whereby CD4⁺ effector cells resistant to regulatory T cell activity accumulate and trigger autoantibody production [13].

Features of SLE-autoantigens themselves may promote a breakdown in B cell tolerance [14]. Marshak-Rothstein and colleagues have demonstrated that lupus-associated B cells, specifically those targeting nucleic-acid containing autoantigens, can be uniquely activated through the synergistic engagement of BCRs and toll-like receptors (TLRs). This paradigm, first developed using RF B cells, has been extended to include some (but not all) anti-DNA cells [14,15].

Defects in Fcγ receptors, key regulators of both innate and adaptive immunity, may also lead to aberrant B cell activation. Of particular interest is the inhibitory Fc receptor FcγRIIb. In mice, FcγRIIb deficiency leads to a spontaneous lupus-like disease and renders normally resistant strains susceptible to collagen-induced arthritis (CIA) [16]. In contrast, FcγRIIb overexpression specifically in B cells reduces both CIA and SLE [16,17]. In patients with SLE, specific transmembrane and promoter polymorphisms of FcγRIIb correlate with disease in certain ethnic groups [16]. Recent data suggests that FcγRIIb may be involved in regulating plasma cells. Murine bone marrow plasma cells (PCs) express FcγRIIb and can be triggered

in vitro to undergo apoptosis after engagement by immune complexes; however, PCs from lupus-susceptible mice lacking FcγRIIb were protected from apoptosis [18]. In addition, memory and plasma B cells from active SLE patients fail to upregulate FcγRIIb expression [19,20], but how this relates to previously described polymorphisms has not yet been determined.

Outcome of B cell activation

Once B cells are activated, they may differentiate into short-lived PCs or participate in a GC reaction from which memory B cells and long-lived PCs emerge (Figure 3). The signals dictating these distinct outcomes are still being defined, as are ways in which autoreactive B cells may be triggered to differentiate. Importantly, autoreactive antibody-secreting cells have been isolated from both short- and long-lived PC pools in SLE mice [21]. In other studies, while the provision of T cell help *in vivo* induced autoantibodies, there was no evidence of B cell memory formation or long-lived PC induction, as was also the case in a spontaneous model for autoreactive B cell activation [1,10,22].

In the RF model, B cells that were clonally ignorant on a non-autoimmune background differentiated into PCs on an autoimmune background or when provided with an appropriate antigen (anti-chromatin antibodies) [5]. Most interestingly, the generation of somatically mutated Igs did not proceed through the classic GC reaction but rather occurred at extrafollicular sites that may lack censoring mechanisms present in typical GCs [1]. This localization may be a general feature of autoreactive B cells that have co-engaged BCRs and TLRs or may reflect the T-independent nature of some autoreactive B cell responses [1]. Other mouse models, as well as SLE patients, do however suggest a role for GCs in the production of autoantibodies. Sanz and colleagues have clearly shown that a population of autoreactive B cells, normally excluded from GC reactions in healthy people, participates in these reactions in SLE patients [23].

Role of B cells in pathology

B cells most likely play several roles in the development and maintenance of RA and SLE, including the secretion of pathogenic antibodies (Abs) and cytokines (both inflammatory and inhibitory) and/or the activation of T cells. Several autoantibodies are associated with RA in humans and mice, including RF, anti-collagen type II, anti-GPI, and more recently, anti-cyclic citrullinated peptide (CCP) Abs [24–27]. The latter class of Abs is specific to a post-translational protein modification that is prevalent during joint inflammation in RA, and B cells secreting anti-CCP Abs have been detected in the synovial fluid of RA patients [28–30]. While the role of autoantibodies in disease pathogenesis in humans is unclear, the presence of RF and anti-CCP autoantibodies is a useful tool in the diagnosis of RA, and their serum titers are predictive of eventual disease severity [31,32]. Likewise, the direct role of SLE autoantibodies in pathology has been hard to establish, and the literature is replete with examples highlighting the uncoupling of autoantibody production from pathology [1].

Unlike in human RA, the pathogenic potential of autoantibodies is well-characterized in mouse RA models [25]. In the K/BxN model of RA, anti-GPI antibodies are both necessary and sufficient for arthritis induction [26,33]. Similarly, anti-collagen antibodies induce arthritis in the CIA model [24]. Interestingly, antibodies to CCP also arise early in disease in the CIA model, and while not sufficient to induce arthritis, they do worsen disease when injected in combination with a suboptimal dose of anti-collagen Abs [34].

B cells may also activate or exacerbate autoimmune responses via Ab-independent functions. Ag-specific B cells act as important antigen presenting cells (APCs) for Ag-specific T cells in SLE models [1]. Additionally, in both the CIA and proteoglycan-induced arthritis models, T

cell responses were significantly reduced in the absence of B cells, despite the presence of other professional APC populations [35,36]. Furthermore, B cells are essential for directing the formation of and activating T cells within ectopic lymphoid structures in the synovium of RA patients [37].

There is good evidence that B cell-produced cytokines can be key regulators of autoimmunity [38,39]. B cells from arthritic mice secrete cytokines associated with inflammatory responses, including TNF α and IL-6 [38]. Conversely, B cells have been implicated as playing a negative regulatory role in autoimmune responses in CIA [40]. These B regulatory cells secrete IL-10 and TGF β , similar to their regulatory T cell counterparts [41]. This protective effect was attributed to transitional type 2 marginal zone precursor (MZP) cells, as transfer of MZP cells, but not other B cell subsets, was able to prevent disease induction and ameliorate established arthritis [42].

Targets for immune intervention

B cell depletion therapy

Perhaps the best evidence for the importance of B cells in autoimmunity comes from the clinical effectiveness of B cell depletion therapy using rituximab, a chimeric monoclonal Ab against human CD20 [43]. Addition of rituximab to the RA treatment regimen led to reduced autoantibody levels and clinical improvement in the majority of patients, with some showing a complete resolution of inflammation [43]. Similarly, rituximab treatment improved clinical symptoms in patients with relapsing remitting multiple sclerosis, including a reduction in inflammatory brain lesions [44]. Several open clinical trials have suggested that rituximab can greatly improve SLE symptoms; however, in contrast to RA, B cell depletion in SLE patients was highly variable and led to a broad spectrum of clinical responses [45,46]. Furthermore, the extent of reconstitution after B cell depletion was more variable than that reported in RA [46].

Similarly in mice, B cell depletion studies have revealed that B cell subsets are differentially sensitive to anti-CD20. In particular, MZ B cells are relatively resistant, most likely as a consequence of their location in the spleen [47]. While B cell depletion is effective in several mouse models of arthritis [48,49], B cells from SLE mouse models are more resistant to depletion, as was observed in some SLE patients [50].

Rituximab specifically targets immature, naive, and memory B cells, but not PCs, which lack CD20 expression [51]. Therefore, the success of CD20 depletion may lie with affecting the APC function or cytokine production of B cells, in addition to diminishing the precursors of plasmablasts and/or short-lived PCs. In support of this, B cell depletion resulted in impaired T cell activation and clonal expansion both in response to model antigens, and in the CIA and proteoglycan-induced models of autoimmune arthritis [48,49].

Because current treatments for SLE and RA, including anti-CD20, do not efficiently target long-lived PCs, additional strategies are needed. One possible approach uses the proteasome inhibitor bortezomib [52], which induces cell death by activating the terminal unfolded protein response and results in the depletion of both short- and long-lived PCs. Interestingly, while GC B cells were also affected by bortezomib treatment, MZ B cells were not. Most significantly, bortezomib prevented lupus-like disease in two different mouse models of SLE [52].

B cell survival factors

Other attractive targets for immune intervention are the TNF family ligands BLyS (B lymphocyte stimulator) and APRIL (a proliferation-inducing ligand). Roughly 50% of SLE

patients have elevated serum levels of BLyS, and mice that over-express BLyS develop SLE-associated autoantibodies [53]. Anergic B cells have a greater requirement for BLyS and thus may be selectively targeted by a BLyS antagonist [54,55]. Conversely, increasing serum levels of BLyS, or decreasing the number of competing B cells, thereby making more BLyS available, relaxes negative selection such that more anergic B cells are now found in the mature B cell pool [56].

Importantly, unlike other B cell subsets, memory B cells do not require BLyS or APRIL for survival [57]. Thus they would likely be spared by strategies that reduce BLyS or APRIL *in vivo*, which in turn may be beneficial in that recall responses to pathogens and vaccines would be preserved. At the same time, autoreactive memory B cells would also persist but the consequences of this are not known [58,59].

Conclusions

Studies regarding the control of autoreactive B cells in health and the corresponding loss of control in disease have suggested several possible mechanisms of breakdown, including a defect in negative B cell selection while entering the mature cell pool, changes in the availability of T cell help, alterations in the nature of self-antigen, or alterations in inhibitory molecules such as FcγRIIb which may render B cells resistant to apoptosis or more susceptible to activation. For SLE- and RA-associated autoantigens, the unique co-ligation of the BCR and TLRs may further facilitate autoreactive B cell activation.

While B cells clearly play an important role in SLE and RA, the nature of their predominant contribution to pathogenesis – secretion of pathogenic Abs and/or cytokines, or APC function – is still being defined. Whatever the major contribution of B cells is, the ameliorative effects of B cell depletion therapies such as rituximab and bortezomib are promising. Alternative targets for reducing or eliminating the B cell pool in autoimmune patients may be B cell survival factors such as BLyS or APRIL. Potential complications in these therapies involve the differential susceptibility of certain B cell subsets to depletion, as well as the variability in efficacy in different diseases. This variability could prove beneficial, however, as it may enable tailoring the form of therapy to the specific condition.

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Figure 1. Autoreactive B cell fates

Ig tgs have revealed several mechanisms for B cell tolerance in healthy mice, including clonal deletion (elimination of the cell carrying the autoreactive BCR), receptor editing (elimination or dilution of the autoreactive BCR by additional Ig rearrangements), and anergy (functional compromise as a consequence of encountering Ag without additional stimulations). In addition, some autoreactive B cells are in a state of clonal ignorance (no apparent effect on the B cell in the presence of Ag).

Figure 2. Anti-GPI autoreactive B cells

High affinity anti-GPI B cells are tolerized, primarily by receptor editing, with a minor population retaining their autoreactive receptor and showing characteristics of anergy [6]. In contrast, low affinity anti-GPI cells are not tolerized, but exist in two functionally distinct compartments. The majority are found in the marginal zone and are spontaneously activated and secrete autoantibody, while the remainder are naive and in the follicle until they receive T cell help [7].

Figure 3. B cell differentiation

Upon activation, B cells differentiate into either short-lived PCs or enter the germinal center reaction where they undergo somatic hypermutation and affinity maturation. B cells that survive the selection process in the GC then further mature into either memory B cells or long-lived PCs.