HHS Public Access

Author manuscript

Annu Rev Cell Dev Biol. Author manuscript; available in PMC 2022 October 12.

Published in final edited form as:

Annu Rev Cell Dev Biol. 2019 October 06; 35: 337–356. doi:10.1146/annurev-cellbio-100617-062518.

Non-Antibody Secreting Functions of B Cells and Their Contribution to Autoimmune Disease

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Abstract

B cells play multiple important roles in the pathophysiology of autoimmune disease. Beyond producing pathogenic autoantibodies, B cells can act as antigen presenting cells and producers of cytokines, including both pro-inflammatory and anti-inflammatory cytokines. Here we review our current understanding of the non-antibody-secreting roles that B cells may play during development of autoimmunity, as learned primarily from reductionist preclinical models. Attention is also given to concepts emerging from clinical studies using B cell depletion therapy, which shed light on the roles of these mechanisms in human autoimmune disease.

Keywords

B cells; T cells; autoimmune; antigen presentation; cytokine; B cell depletion

1 B CELLS IN AUTOIMMUNITY

B cells play multiple important roles in the pathophysiology of autoimmune disease. Historically, the main focus of studies of these functions has been on their role as producers of autoantibodies. Autoantibodies can contribute to autoimmune disease in several ways. Tissue deposition after binding autoantigen, can cause tissue destruction in a complement- or IgG Fc receptor-dependent manner. For example, autoantigen-autoantibody immune complexes accumulation in kidneys causing glomerular nephritis in systemic lupus erythematosus (SLE). Autoantibody binding can also interfere with physiological processes by blocking protein function, e.g. anti- acetylcholine receptor antibodies in myasthenia gravis. Acting indirectly, autoantibodies can influence autoreactive T cell responses by Fc receptor-mediated uptake of immune complexes and subsequent antigen presentation by antigen presenting cells (APCs) such as macrophages and dendritic cells (DCs). Finally, binding of immune complexes to Fc receptors also causes the release of inflammatory mediators and contributes to the recruitment of inflammatory cells (reviewed in (Guilliams et al 2014, Ludwig et al 2017)).

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A growing body of work suggests that antibody-independent B cell functions also play an important role in the development of autoimmune disease. B cells can act as antigen presenting cells and producers of cytokines, including both pro-inflammatory and anti-inflammatory cytokines. Studies of preclinical models suggest that these non-antibody-producing functions play an important role in certain autoimmune responses. The relevance of these functions has gained traction after the publication of several landmark papers that described clinical trials that found B cell depletion therapy (initially Rituximab, an anti-CD20 treatment) to be efficacious in the treatment of autoimmune diseases, including those considered to be mainly T cell-mediated (Edwards et al 2004, Hauser et al 2008, Pescovitz et al 2009). While the efficacy of rituximab correlates with B cell depletion, the correlation of rituximab efficacy with reduction of autoantibody levels is less clear, suggesting alternative roles for B cells beyond autoantibody production (Cambridge et al 2006, Looney et al 2004). Here we review current understanding of the non-antibody secreting roles that B cells may play during development of autoimmunity, as learned primarily from reductionist preclinical models. Attention is also given to concepts emerging from clinical studies using B cell depletion therapy, which shed light on the roles of these mechanisms in human autoimmune disease.

2. AUTOREACTIVE B CELLS IN THE PERIPHERY

In the periphery, autoreactive B cells can display a variety of phenotypes. The origins, specificity and developmental path of these B cells affect their functional characteristics (more extensively reviewed in (Getahun et al 2016b, Nemazee 2017)). Briefly, the majority of autoreactive B cells are generated by initial VDJ rearrangement early during B cell development (Wardemann et al 2003). As many as 70% of newly produced B cells in human bone marrow appear autoreactive. Central tolerance mechanisms such as receptor editing and clonal deletion purge autoreactive B cells that bind self-antigen with high avidity, while autoreactive B cells that bind self-antigen with intermediate avidity become anergic (a state of unresponsiveness), continue development and persist, albeit with a shorter half-life, in the periphery. As discussed below, while anergic B cells do not mount antibody responses, it is less clear whether they are capable of successful antigen presentation to T cells. Autoreactive B cells that, due to low antigen receptor affinity and/or low ambient antigen concentration, fail to perceive their cognate antigen, develop normally and are essentially ignorant. These cells can participate in immune responses to exogenous immunogens, and can thus be found in all B cell compartments. B cells bearing polyreactive antigen receptors that are self-reactive are found in the anergic compartment, but can also be found in the marginal zone B cell population in the spleen and in the innate-like B-1 cell population in the peritoneal cavity (Mannoor et al 2013). These cells may participate in autoimmune responses. Finally, autoreactive B cells can be generated de novo during the process of somatic hypermutation in germinal center reactions (reviewed in (Brink & Phan 2018)). The germinal center reaction with its dynamic B-T cell interactions has been implicated in promoting both pathogenic T cell responses and pathogenic class-switched autoantibody responses.

3. B CELLS AS ANTIGEN PRESENTATION CELLS

B cell presentation of antigen is an integral event in T cell-dependent antibody responses. Upon uptake by the B cell receptor (BCR), antigen is processed and presented in association with MHC class II molecules to solicit cognate help from antigen-specific CD4 T cells. Delivery of cognate help may require that T cells be primed initially by “professional” antigen presenting cells (APC), such as dendritic cells (DCs) and macrophages. Even though B cells can bind, process and present antigen at very low concentrations, by virtue of their antigen receptors (Rock et al 1984), whether B cells can directly prime CD4 T cells *in vivo* has been controversial. Many of the experimental systems used to examine this question have limitations that make it difficult to draw definitive conclusions. However, there is a strong case that B cells influence the magnitude and nature of T cell responses.

3.1. Antigen Presentation by Non-Autoreactive B Cells

Early work using avian and murine models suggested that B cells cannot prime, and may even tolerize T cells (Fuchs & Matzinger 1992, Lassila et al 1988). The notion of tolerization of T cells by antigen presenting B cells was further supported by *in vivo* studies using Fab fragments to target antigen to B cells. Presentation of antigen by B cells that were retained in the resting state by targeting Fab as antigen to IgD or targeting to non-activating B cell membrane proteins (Eynon & Parker 1992, Morris et al 1994b), resulted in T cell tolerance. However, targeting surface Ig on B cells with $F(ab')_2$ fragments resulted in T cell activation, demonstrating a requirement for activation of B cells and resultant upregulation of costimulatory molecules (see below) to convert tolerogenic APCs to activating APCs (Eynon & Parker 1992, Monroe & Cambier 1983, Morris et al 1994a).

To directly study interactions between antigen-reactive B and T cells, several groups used a co-adoptive transfer approach employing antigen receptor transgenic B and T cells to enable tracking of antigen-specific lymphocytes. These studies confirmed that antigen stimulation of B cells results in upregulation of costimulatory molecules, as well as T cell activation and proliferation, and that these T cells, in turn, facilitated antibody responses of these B cells (Constant 1999, Townsend & Goodnow 1998). However, involvement of other APCs was not formally excluded.

Initial studies of the sufficiency of non-B cell APC to support T cell activation using B cell-deficient $\mu MT^{-/-}$ mice gave conflicting results. Some studies reported no defects in CD4 T cell priming (Epstein et al 1995) after immunization, while others found reduced or impaired priming to several but not all protein antigens tested (Constant et al 1995). To avoid potential confounding effects due to changes in lymphoid architecture and cell migration, observed in $\mu MT^{-/-}$ mice, more recent studies have used chimeric mice to address this question. In mice in which all B cells are MHC class II deficient, but most non-B cells are MHC class II sufficient, immunization leads to reduced CD4 T cell responses, suggesting a role for B cell in the maintenance or amplification of T cell responses (Crawford et al 2006). These results agree with B cell depletion studies that also revealed reduced CD4 T cell responses upon immunization (Bouaziz et al 2007) and with earlier studies that claimed that antigen presenting B cells stimulate antigen experienced T cells (Ronchese & Hausmann 1993).

3.2. The Antigen Presentation Capacity of Autoreactive B Cells

The antigen presentation capacity of B cell populations enriched in autoreactive B cells has been studied extensively. However, while as a whole these populations were often superior in their ability to activate T cells, whether the autoreactive B cells within these population behave similarly has not been proven. Marginal zone B cells express higher levels of costimulatory molecules than do follicular B cells both at basal state and after activation, and evoke better T cell responses in vitro and in vivo (Attanavanich & Kearney 2004). Similarly, a B1-like B cell subpopulation expanded in lupus patients expresses more costimulatory molecules and has higher T cell stimulatory activity than do follicular B cells (Griffin & Rothstein 2011). B1 cells have also been reported to preferentially promote inflammatory (Th1/Th17) T cell responses (Zhong et al 2007). Another B cell population associated with disease development in several lupus models and enriched in autoreactive B cells, age-associated B cells (ABCs) (Rubtsova et al 2017), reside primarily at B-T cell borders and have elevated expression of MHC class II and costimulatory molecules. When loaded with antigen these B cells evoke stronger T cell responses than follicular B cells both in vitro and in vivo (Rubtsov et al 2015).

The largest pool of anergic autoreactive B cells in the periphery reside in the classically defined T3 compartment (Merrell et al 2006, Teague et al 2007). Work on several models of B cell anergy, makes clear that self-peptides derived from the autoantigen to which the cell's BCR react are presented on the cell's MHC class II molecules (Aviszus et al 2012, Kendall et al 2013, Seo et al 2002, Townsend & Goodnow 1998). However, B-T cell interactions are not productive because of a lack of costimulatory molecule expression (Eris et al 1994, Ho et al 1994). In support of this concept, transgenic overexpression of CD86 in vivo (Rathmell et al 1998), or addition of a stimulating anti-CD28 antibody in vitro (Ho et al 1994) can facilitate T cell responses. Similarly, acute loss of the ability to maintain B cell unresponsiveness, due to induced genetic ablation of inhibitory signaling molecules, results in CD86 upregulation and functional B-T cell interaction ((Getahun et al 2016a); and A. Getahun & J.C. Cambier, unpublished data). Interestingly, recent studies suggest that high avidity cross-reactivity with exogenous antigen can overcome anergy, causing autoreactive B cells to participate in germinal center reactions, and mutate away from self-reactivity (Burnett et al 2018, Sabouri et al 2014). While the role of T cells in that model is unclear, these findings support the notion that autoreactive B cells can present antigen when anergy is overcome and can, under these circumstances, productively interact with T cells.

Whether anergic autoreactive B cells can initiate autoreactive T cell responses remains unclear. In most of the studies mentioned above, experimental systems were used in which the T cells were not autoreactive, and were thus not subject to tolerance mechanisms. The relationship between B cell tolerance and T cell tolerance is reciprocal under normal physiological circumstances. B cell anergy is thought to be the result of self-antigen stimulation (signal 1) without T cell help (signal 2), and autoreactive T cells are either removed from the repertoire by negative selection during development or maintained in a tolerant state by peripheral mechanisms such as regulatory T cells and T cell anergy. Presentation of self-peptides by naive or anergic B cells induces both T cell unresponsiveness (anergy) (Murray et al 2013) and induction of Tregs (Morlacchi et al

2011). The additional signals involved in determining the outcome of such interactions are still unclear, but lack of co-stimulation would be expected to induce T cell anergy.

If tolerance is broken on either side, autoreactive B-T cell interactions can become productive again. In Aire-deficient mice, autoreactive T cells do not undergo negative selection, and escape of autoreactive T cell to the periphery leads to multi-organ autoinflammatory disease. Autoreactive B cells contribute to this state, as most organs are not affected in animals that are both B cell and Aire deficient. Serum transfer experiments suggest that this B cell function is not mediated by autoantibody, but rather is due to a reduction in T cell priming/expansion because of lack of antigen presentation by B cells (Gavanescu et al 2008). Loss of Tregs, due to foxp3 deficiency, also leads to autoinflammatory disease. B cells also play an important role in this pathophysiology, but mainly by production of autoantibody (Aschermann et al 2013). However, other studies suggest that dysregulation of regulatory T cells may enable B cells to activate autoreactive T cells (Zhang et al 2017). A loss of Tregs can also result in an inability to induce or maintain B cell anergy (Leonardo et al 2012). As we see in section 3.3, a B cell intrinsic loss of tolerance can be enough to lead to autoreactive T cell activation as well.

3.3 The Role of B Cell-Mediated Antigen Presentation in Preclinical Models of Autoimmune Disease

Evidence from preclinical models of three autoimmune diseases: SLE, multiple sclerosis (MS) and type 1 diabetes (T1D), indicate that B cells can shape autoreactive T cell responses and in some cases are sufficient to induce autoreactive T cell responses. However, depending on the disease model used the relative contribution of B cells as APCs differs. While this variability could be interpreted as a weakness of these models, it provides insight regarding the diversity of pathological pathways that can lead to the same autoimmune disease and the roles that B cells can play in such pathways.

3.3.1 Murine models of systemic lupus erythematosus.—An example of the ability of autoreactive B cells to initiate autoreactive T cell responses and autoimmune disease is a model developed by Rawlings and colleagues in which the disease driver is Wiskott-Aldrich syndrome (WAS) protein deficiency. In this model all B cells are WAS deficient, while the majority (>80%) of the non-B cells are WAS sufficient. These mice develop severe autoimmunity, which is characterized by spontaneous germinal center formation, T cell activation, production of class-switched autoantibodies and SLE-like pathology. This process is dependent on CD4 T cells and on B cell intrinsic Toll-like receptor (TLR) engagement (Becker-Herman et al 2011). While TLR-mediated signals are essential to autoreactive B cell activation, antigen presentation by B cells is required for the observed T cell activation, germinal center responses and class-switched autoantibody responses (Jackson et al 2016). When in these experiments the same approach was used with the addition of B cell deficiency of MHC class II, no T cell activation was seen. While, strictly speaking, the design of this experiment does not exclude the possibility that other APCs are involved in the priming of these T cells, the complete absence of an increase in T cell activation in mice that lack MHC class II only on their B cells demonstrates the importance of B cell- mediated antigen presentation for pathology.

Other SLE models support a role for B cells in promoting activation of pathogenic CD4 T cells. B cells from lupus-prone B6.NZM2410.Sle1.Sle2.Sle3 mice promote both T cell differentiation into follicular T helper cells and expansion of inflammatory (Th1/Th17) T cells in concert with other APCs (Choi et al 2018). Similarly, in the MRL.Faslpr mouse model B cells are required for development of lupus-like disease, in addition to their role as autoantibody producers. B cell deficient MRL.Faslpr mice do not develop disease (Shlomchik et al 1994) and have reduced CD4 T cell activation (Chan & Shlomchik 1998). Since MRL.Faslpr mice in which B cells cannot secrete antibodies develop many of the SLE features, including T cell activation and renal disease (Chan et al 1999), B cells likely support disease development by antigen presentation. DC are reportedly dispensable for T cells activation (Teichmann et al 2010) in this model, supporting a role for B cells as APC. To directly test the requirement for B cell-mediated antigen presentation, B cell lineage-specific genetic ablation of MHC class II was done on the MRL.Faslpr background. Unfortunately, the penetrance of deletion was not 100%, leaving a considerable population (~15%) of MHC positive B cells. Nonetheless these mice had a reduced number of activated T cells, fewer extrafollicular T helper cells and decreased pathology, further supporting the idea that B cells play an important role in activating autoreactive T cells in this model (Giles et al 2015).

3.3.2 Murine models of multiple sclerosis—Preclinical models of MS paint a more complex picture regarding B cell contribution to development of autoimmunity. Experimental autoimmune encephalomyelitis (EAE) is a model for MS in which transient neuroinflammation is induced by immunization with either recombinant myelin oligodendrocyte glycoprotein (MOG), or a peptide thereof, with adjuvant. While whole protein-based protocols have a higher dependence on B cells (Lyons et al 1999, Svensson et al 2002) than do peptide-based protocols, the latter clearly reveal immunomodulatory roles of B cells (Wolf et al 1996).

The strongest evidence that B cells promote T cell activation in EAE development can be found in models in which recombinant human MOG is used to induce disease. In this case development is fully B cell dependent. As indicated by requirements that B cells must express MHCII for animals to develop disease, B cells must be required for B cell presentation of MOG (Molnarfi et al 2013). Antibody transfer only partly restores disease phenotype, suggesting that the absence of disease is not only due to an absence of the cognate B-T interaction required for antibody responses, but also due to B cell-mediated activation of pathogenic T cells. In agreement with this, anti-MOG BCR transgenic mice that can not produce antibodies develop disease normally (Molnarfi et al 2013), and disease severity correlates with the number of MOG specific B cells present.

Other studies using similar immunization protocols in mice in which MHC class II expression was restricted to specific lineages, suggest that both DCs and antigen-specific B cells must express MHC class II for optimal T cell activation and EAE development, while neither suffices independently (Parker Harp et al 2015). After the initial priming by non-B cells, antigen presentation by B cells is sufficient to promote activation and proliferation of encephalitogenic CD4 T cells (Parker Harp et al 2018), including in the central nervous system where B cells promote the accumulation of encephalitogenic CD4 T cells and

inflammatory cytokine production by these T cells (Pierson et al 2014). During these later stages of disease there may also be a role for autoantibodies in promoting T cell activation, possibly via Fc receptor mediated antigen presentation by other APCs (Abdul-Majid et al 2002, Flach et al 2016).

3.3.3. Murine models of diabetes—Non-obese diabetic (NOD) mice develop spontaneous T1D. B cells play an important role in this model as NOD mice deficient in B cells do not develop diabetes (Serreze et al 1996). Although autoantibody production is indicative of increased risk of disease development, the degree to which (anti-insulin) autoantibodies play a role in diabetes is not completely clear. Transfer of immunoglobulin from overtly diabetic NOD mice did not reconstitute diabetes in B cell deficient mice (Serreze et al 1998) suggesting a minor role for autoantibodies in pathology. Other studies suggest that autoantibodies against islet antigen can promote disease (Silva et al 2011) and that Fc receptor expression on non-B cell APCs contributes to disease, suggesting a role for immune complex-induced antigen presentation (Inoue et al 2007).

Direct evidence that suggests that B cell act as APCs in T1D comes from chimeric NOD mice in which only the B cell compartment is MHC class II deficient. These mice are protected from disease development (Noorchashm et al 1999), although, due to their inability to mount T cell-dependent antibody responses, antibody mediated contributions cannot be excluded. Interestingly, chimeric NOD mice in which only the B cell compartment is MHC class I deficient are also largely protected from disease development, suggesting a role for B cells in cross-presenting and activating diabetogenic CD8 T cell responses as well (Marino et al 2012).

B cell participation in diabetes is also dependent on antigen specificity. When the B cell repertoire of NOD mice is enriched for B cells with reactivity to pancreatic self-antigens, specifically insulin (Hulbert et al 2001) or peripherin (Leeth et al 2016), these mice develop disease more rapidly than do wild-type NOD mice. Alternatively, mice lacking islet-reactive B cells are protected from disease development (Hulbert et al 2001, Silveira et al 2002). Especially since mice expressing transgenic B cell receptor for islet antigens are unable to class switch to IgG isotypes, the accelerated disease is likely due to B cell-mediated antigen presentation. In agreement with this, insulin-binding cells in VH125 NOD mice (mice with insulin-specific heavy chain only transgenes that have a 1-2% insulin binding B cell population) lose tolerance, accumulate in the pancreatic lymph nodes and pancreas, and express elevated levels of costimulatory molecules prior to development of disease symptoms (Smith et al 2018). In another variant of the 125 model the VH125 heavy chain variable region was knocked into the endogenous IgH locus, allowing insulin reactive B cells to participate in germinal center reactions. Interestingly, when these B cells were tested for their ability to present antigen to diabetogenic T cell clones recognizing different insulin-derived peptides, germinal center cells presented a broader repertoire of peptides than other B cell populations from the same animal (Wan et al 2016). Taken together these data suggest that B cells play a role as APCs in diabetes and contribute to both activation and diversification of T cell responses.

3.4. Evidence of B cell APC Function in Humans.

While clinical data from patients undergoing B cell depletion treatment do not provide much insight into the roles of B cells during the initiation phase of autoimmune disease and such data are restricted to analysis of peripheral blood cells, it does allow insight into the roles of B cells during later stages of disease. Similarities between clinical data and the preclinical data described above strengthen the case for a role of B cells in shaping T cell responses during autoimmunity in humans.

Following B cell depletion therapy, reductions are seen in total peripheral blood and tissue CD4 T cell numbers (see Cross et al 2006, Piccio et al 2010, Sentis et al 2017). Similar reductions are seen in the numbers of circulating T_{FH} cells (Audia et al 2017, Xu et al 2013, Zhao et al 2014) and splenic T_{FH} cells. The percentage of circulating activated T cells is also reduced (Tamimoto et al 2008), suggesting that B cells play a role in the activation and expansion of T cells during disease. It is not clear whether the reduction of T cells in sites such as neural tissue reflects a recruitment problem or a lack of local T cell expansion. A recent report shows that in MS antigen presentation by memory B cells promotes activation and proliferation of brain-homing CD4 T cells (Jelcic et al 2018), suggesting that B cells may contribute to both processes.

Another emerging theme is the resetting of the CD4 T cell compartment following B cell depletion. There is a shift from an oligoclonal repertoire to a more normal polyclonal repertoire of T cell receptors (Stasi et al 2007) and there is also a restoration of the balance between naive and memory T cells, namely a shift toward a more naive population of T cells (Sentis et al 2017). A reduction of proinflammatory Th1/Th17 responses has been observed following B cell depletion (Bar-Or et al 2010) along with increases in Treg numbers (Zhao et al 2014).

Collectively these data suggest that B cells participate in the activation and recruitment of autoreactive T cells in humans, consistent with findings from B cell depletion studies in mouse models (Bouaziz et al 2007, Monson et al 2011, Xiu et al 2008).

4. CYTOKINE PRODUCTION BY B CELLS

Early in vitro studies established that B cells can be stimulated to produce cytokines, including pro-inflammatory cytokines such as TNFα, IFNγ, and IL-12 and regulatory cytokines such as IL-6 and IL-10 (reviewed in (Lund & Randall 2010)). It has subsequently become apparent that cytokine production by B cells plays an important role in vivo in shaping immune responses, including autoimmune responses. Cytokine production can initiate T cell polarization, amplify cytokine responses, or suppress immune responses. All three scenarios appear to occur during autoimmune disease in preclinical models and patients.

4.1 Induction of Cytokine Production by B Cells

An important advance in our understanding of B-T cell interactions in the context of cytokine production came from Francis Lund’s lab. These investigators showed that like T cells, B cells can differentiate into different populations of effector B cells, initially referred

to as Be1 and Be2 cells, that produce distinct cytokine profiles. Be1 produces IFNγ and IL-12 and can also secrete IL-10, TNFα, and IL-6; Be2 produces IL-2, IL-4, and IL-13 and can also secrete IL-10, TNFα and IL-6. The presence of specific Th1 or Th2 cytokines (or T cells) at the time of B cell activation by antigen determines the differentiation of B cells into Be1 or Be2 cells, respectively (Harris et al 2000). Be2 cells are dependent on IL4R signaling. At least in vitro, Be2 cells do not differentiate into antibody-forming cells (Harris et al 2005b). Be1 cells, in contrast, are dependent on IFNγR signaling and T-bet expression, and differentiate into antibody forming cells (Harris et al 2005a). Both cell types have an amplifying function. For example, Th1 T cells polarize B cells toward the Be1 phenotype, and B cell-derived IFNγ can promote further Th1 polarization. While in most cases T cells produce more cytokine than do B cells, under certain pathological conditions B cells are the main contributor to certain cytokine (e.g. IL-6) responses (Tsantikos et al 2010).

Polarized B cells impose polarity on naive T cells (Harris et al 2000). In the context of autoimmunity, autoantigens that contain TLR ligands or other PAMPs could be expected to provoke cytokine responses from B cells, such responses may influence the B cells' subsequent cognate interactions with T cells. B cells can produce cytokines such as IL-6, IL-10, IFNγ and type I IFN after exposure to specific TLR ligands (Barr et al 2007, Green et al 2009). To explore this further, the Marshak-Rothstein lab used an in vitro system in which AM14 rheumatoid factor-specific B cells are exposed to immune complexes containing different DNA or RNA autoantigens. Combined BCR and TLR ligation activated these ignorant autoreactive B cells (Leadbetter et al 2002). DNA-containing immune complexes induced IL-2 production by these B cells, in a TLR9 dependent manner. Interestingly simultaneous exposure to TLR9 ligands and anti-IgM led to the production of IL6, IL10 and IL12 by the same B cells, while these cytokines were not produced in response to DNA-containing immune complexes suggesting that different rules may apply to BCR-mediated TLR-ligand uptake (Busconi et al 2007). RNA-containing immune complexes provoked responses in a TLR3 or TLR7 dependent manner, depending on the RNA structure. TLR3 dependent RNA-immune complexes could induce IL6 responses, while TLR7-dependent RNA-immune complexes required type I IFN to be present to produce IL6 (Green et al 2012). More work is needed to determine how these innate stimuli influence cytokine polarization of B cells. Given the association of infections with the development of certain autoimmune diseases, infections may be of particular interest, as they induce proinflammatory cytokine production by B cells (Bermejo et al 2013, Menard et al 2007).

4.2 Cytokine-Producing B Cells in Autoimmune Disease

Longitudinal studies have revealed elevated systemic levels of cytokines in autoimmune patients prior to the appearance of autoantibodies and clinical manifestations. In SLE patients, elevated systemic IL4, IL-5, IL-6 levels, temporally followed by elevated IFNγ levels, precede autoantibody production (Lu et al 2016). In rheumatoid arthritis (RA) patients, less clear correlations are seen, but multiple cytokines including IL-1, IL-6 and IL-12 appear years before disease onset. Of note, IL-6 precedes the appearance of anti-cyclic citrullinated peptide antibodies (Deane et al 2010).

Since many cell types can produce cytokines, it is difficult to define the contribution of B cell derived cytokines in most settings, especially since B cells can also promote T cell production of cytokines (Takemura et al 2001). By using genetic approaches, compelling evidence has emerged from preclinical models, supported by some clinical data, that B cell production of both proinflammatory and anti-inflammatory cytokines plays a significant role in the etiology of autoimmune disease.

4.2.1 Proinflammatory cytokine production by B cells in disease models—

Best defined in the context of autoimmunity is the role of B cells in the production of IL-6. IL-6 is a pleiotropic cytokine with proinflammatory properties and can promote autoreactive immune responses in several ways. IL-6 promotes (auto)antibody responses by inducing IL21 production by T cells (Dienz et al 2009), which in turn promotes B cell responses; and IL-6 (with IL21) also promotes T follicular helper cell differentiation by promoting BCL-6 expression (Nurieva et al 2009). IL-6 additionally promotes Th17 differentiation in concert with TGFβ (Bettelli et al 2006, Veldhoen et al 2006) and in concert with IL-1 and IL-23 (Ghoreschi et al 2010). Th17 cells play an important role in several autoinflammatory diseases.

B cells have been identified as major producers of IL-6 in several autoimmune disease models (Arkatkar et al 2017, Barr et al 2012, de Valle et al 2016, Tsantikos et al 2010), and in each case deletion of IL-6 prevented or ameliorated disease. The importance of IL-6 production by B cells in T_{FH} and antibody responses has been best demonstrated in the chimeric WAS-deficiency model. While chimeric mice in which B cells were WAS deficient developed spontaneous germinal centers, class-switched autoantibody, and lupus-like disease, mice in which WAS-deficient B cells were also deficient in IL-6 did not. IL-6 production by B cells was required for T cell activation, T_{FH} differentiation and subsequent germinal center formation, and disease development in this model (Arkatkar et al 2017). There are indications that similar sequential events are at play in other models. In the Yaa TLR7 driven lupus-like disease model, mice have increased serum IL6 levels that correlate with autoantibody responses. B cells are the major producers of IL6 in this model and IL6 deficiency delays disease, and this is correlated with reduced Th cell activation and IL21 production (Jain et al 2016).

Evidence also suggests that the pathogenic effects of B cell-derived IL-6 can be due to polarization of T cell responses toward Th17. In EAE models, B cell restricted IL-6 deficiency ameliorated disease development, which was associated with a reduction in IL17 producing T cells (Barr et al 2012, Molnarfi et al 2013). A recent study suggested that of all the IL-6 producing cells, DCs are unique in their ability to induce Th17 cells, and this induction requires trans-presentation of IL-6 on IL-6R during cognate interactions with T cells (Heink et al 2017). This study used a MOG peptide-induced EAE model, that is not B cell dependent. In a B cell-dependent EAE model, deficiency of either MHC class II or IL-6 in B cells resulted in severely reduced clinical manifestations and in a decrease in IL-17-producing T cells (Molnarfi et al 2013). It remains to be seen whether this trans-presentation mechanism applies to B cells as well, but B cells in autoimmune individuals express high levels of IL-6R (Nagafuchi et al 1993).

The contribution of B cell production of other cytokines, such as IFNγ, to autoimmunity is less understood. While in two lupus models significant production of IFNγ by B cells was observed, INFγR expression by B cells and INFγR signaling are required for autoreactive germinal center formation, autoantibody production and systemic autoimmunity (Domeier et al 2016, Jackson et al 2016). IFNγ production by B cells is dispensable, suggesting that it is not an autocrine effect or that other sources can compensate (Jackson et al 2016). In contrast, in a proteoglycan-induced arthritis model, B cell restricted IFNγ deficiency protects against disease development, and is associated with an increase in Treg cells, suggesting that B cell derived IFNγ inhibits Treg differentiation (Olalekan et al 2015).

4.2.2 Clinical evidence of proinflammatory cytokine production by B cells—

B cell depletion in autoimmune patients can lead to changes in cytokine profiles, some of which can be traced to B cell cytokine production by ex vivo analysis. Normalization of elevated circulating T_{FH} cell frequencies has been observed following B cell depletion therapy in autoimmune patients (Xu et al 2013, Zhao et al 2017). Elevated serum levels of IL-6 and IL-21, which are associated with T_{FH} differentiation, are also normalized in these patients after B cell depletion therapy. Evidence that B cell production of IL-6 may be responsible for this increase T_{FH} cell numbers comes from ex vivo cultures with PBMCs, in which B cells were shown to promote T_{FH} differentiation by producing IL6 and direct cell contact (Zhao et al 2017). B cells from MS patients directly assayed for IL-6 production produced more IL-6 than health controls following re-stimulation. Twelve months after B cell depletion therapy, IL-6 production by B cells had normalized to that of healthy controls. This decrease in IL-6 production correlated with a decrease in IL-17 production by PBMCs from these patients (Barr et al 2012), suggesting that, as observed in preclinical models, B cell derived IL-6 promotes Th17 responses (Barr et al 2012, Molnarfi et al 2013). Similarly, in RA patients rituximab treatment reduces the number of Th17 T cells in synovial tissue, which is associated with better clinical outcome, but does not affect Th1 cells or Treg numbers (van de Veerdonk et al 2011). Analysis of cytokine production by autoantigen-reactive B cells (myelin basic protein) in MS patients, revealed a higher frequency of IL-6 and TNFα producing cells in MS patients that was associated with increased disease severity (Nielsen et al 2016). The effects of B cell derived cytokines can reach beyond T cells. Another group found that in MS patients, there is an increase in a population of proinflammatory cytokine producing B cells, which, in addition to producing IL-6 and TNFα, produce GM-CSF. In vitro experiments showed that B cells produce GM-CSF which activates myeloid cells, and B cell depletion therapy is associated with a decrease in GM-CSF producing B cells and a decrease in myeloid cell proinflammatory responses (Li et al 2015), suggesting that B cells are directly involved in that aspect of autoinflammation as well.

4.2.3 Anti-inflammatory cytokine production by B cells in preclinical models

—The first indication that B cells may have immune-modulatory functions in autoimmunity beyond autoantibody production came from a series of studies using the MOG-peptide model of EAE (Fillatreau et al 2002, Wolf et al 1996). In the absence of B cells, more severe disease that did not resolve was observed. B cells that can produce IL-10 were required for disease resolution. These B cells developed during disease and upon transfer significantly

reduced disease development in recipients (Fillatreau et al 2002). Early studies in a collagen induced arthritis (CIA) model further supported the notion that B cells could be induced to have immunosuppressive abilities. Adoptive transfer of B cells isolated from arthritic mice, which had been re-stimulated in vitro with anti-CD40 and antigen, inhibited the induction of CIA in recipient mice in an IL-10 dependent manner (Mauri et al 2003).

Since the original work in these models, multiple B cell populations have been shown to have regulatory function (extensively reviewed in (Mauri & Menon 2017)). These include but are not limited to CD19+ TIM+ B cells (Ding et al 2011), CD1hi CD5+ B (B10) cell (Yanaba et al 2008) and CD138+CD44hi plasmablasts (Matsumoto et al 2014) in mice. In humans regulatory B cells (Bregs) include CD24hi CD27+ (B10) cells (Iwata et al 2011), CD19+ CD24+ CD38hi B cells (Blair et al 2010) and CD27int CD38hi plasmablasts (Matsumoto et al 2014).

Most of the suppressive effects of Bregs are attributed to IL-10 production. Only a small proportion of cells in each of these subpopulations actually express IL-10 and have suppressive activity. IL-10 inhibits Th1 and Th17 responses (Blair et al 2010, Mauri et al 2003, Yoshizaki et al 2012) and promotes Treg development and activity (Flores-Borja et al 2013, Watanabe et al 2010). IL-10 directly promotes Treg differentiation (Hsu et al 2015) and activity (Chaudhry et al 2011). IL-10 is not the only immunosuppressive cytokine produced by Bregs. IgM+CD138 plasma blasts can also produce IL-35, which dampens Th1 and Th17 responses (Shen et al 2014, Wang et al 2014). Other IL-10-independent suppression mechanisms include CD1d-dependent polarization of iNKT cells into iNKT cells with suppressive capacity (Oleinika et al 2018). In addition, in an EAE model a population of PD-L1^{hi} B cells was identified that has immunosuppressive abilities, which could directly suppress T_{FH} responses by PD-L1 and PD-1 interactions (Khan et al 2015).

A number of signals promote B cell differentiation into Bregs in human and mouse. These include antigen stimulation, CD40 ligation, TLR ligands, and cytokines (Blair et al 2010, Menon et al 2016, Yanaba et al 2009, Yoshizaki et al 2012). Different Breg populations appear to have different signaling requirements. IL-10 producing CD1d^{hi}CD5^{+} maturation requires IL21, CD40 interaction and cognate T cell interactions (Yoshizaki et al 2012). TIM-1 positive Bregs become activated and produce IL-10 after TIM-1 binding to apoptotic cells (Xiao et al 2015).

Effects of B cell depletion therapy suggest a temporal dependence of Breg function in autoimmune responses. For example, in MOG peptide-induced EAE, IL-10 producing CD1d^{hi}CD5^{+} B cells limit disease severity during onset and thus B cell depletion when these cells are active worsens disease. In contrast, once disease is established, B cell depletion has a beneficial effect, reducing CD4 T cell responses and CNS infiltration (Matsushita et al 2008). Similar observations were made in an SLE model (Haas et al 2010). Different populations of regulatory cells may act at different times during disease progression. In the case of MOG peptide-induced EAE, the same group suggested that Tregs attenuate the late-phase of the disease (Matsushita et al 2010). Others have described a role for IL-10 producing plasma blasts in attenuating the late-phase of the disease during MOG peptide-induced EAE (Matsumoto et al 2014). These observations suggest that different

populations of Bregs may control different phases of disease. Plasma cells are less sensitive to B cell depletion therapy, so the positive effects observed (Matsushita et al 2008) by depletion of T cell-activating B cells, would likely have occurred in the presence of IL-10 producing plasma blasts. Tregs important during the late phase of disease may induce the second population of Bregs. Tregs can produce IL-35 (Collison et al 2007) which promote the development of IL-10 and IL-35 producing Bregs (Wang et al 2014).

4.2.4 Clinical evidence of anti-inflammatory cytokine production by B cells.

—Several lines of evidence suggest that in humans Bregs play a similar role in maintaining immune tolerance. Reduced numbers of IL-10+ B cells are found in peripheral blood of T1D patients (Kleffel et al 2015), SLE patients (Blair et al 2010), RA patients (Flores-Borja et al 2013), and systemic sclerosis patients (Aravena et al 2017) and in children with a range of autoimmune diseases (Kalampokis et al 2017). In autoimmune patientsa not only a reduction in number of Bregs but also dysregulation of Breg function has been observed. In bullous pemphigoid patients, $CD19^{+}CD24^{hi}CD27^{+}$ Bregs lack suppressive functions and instead produce proinflammatory cytokines such as TNFα and IFNγ (Liu et al 2018). In SLE patients, reduced CD1d expression by Bregs and a resultant decrease in iNKT cells numbers and activation have been observed (Bosma et al 2012). In vitro findings suggest that this decreased CD1d expression may be due to the presence of elevated IFNα serum levels, which are often seen in SLE patients. Elevated IFNα has also been implicated in causing reduced numbers of Bregs in SLE patients. In healthy individuals plasmacytoid dendritric cells (pDC) promote CD19+ CD24+ CD38hi Breg differentiation in an IFN-α dependent manner, while Bregs, in turn, restrain IFN-α production by pDCs in an IL-10 dependent manner. This balance is disrupted in SLE patients, leading to an overproduction of IFN-α which inhibits Breg differentiation (Menon et al 2016).

The efficacy of B cell depletion therapy appears to correlate with its ability to restore Breg function. While a decrease in peripheral B cell numbers is observed in those treated with rituximab, clinical benefit correlates with a change in B cell compartment composition toward a more naive phenotype with a restored Breg population (Adlowitz et al 2015, Colliou et al 2013). Similarly, functional defects, such as reduced CD1d expression and dysregulated interactions between Bregs and pDCs observed in SLE patients are normalized following B cell depletion therapy in patients that benefit clinically from these treatments (Bosma et al 2012, Menon et al 2016).

5. B CELL-TARGETED THERAPY IN AUTOIMMUNITY

While B cell depletion therapy has shown efficacy in the treatment of several autoimmune diseases, there is room for improvement. For example, one anticipated effect of long-term B cell deficiency is an increase in susceptibility to infections. Also, depletion of B cells with regulatory functions may be undesirable. As our understanding of the nuances of B cell involvement during autoimmunity evolves, the challenge will be to modulate B cell behavior in a more targeted manner. While much remains to be done, early studies suggest that achieving this goal could be possible. For example, in a scleroderma model treatment BAFF-antagonist is efficacious, apparently acting by reducing disease-promoting IL6-producing B cells while sparing protective IL10-producing B cell (Matsushita et al 2018). Therapies

targeting B cells in an antigen-specific manner are also under development. Treatment with multivalent soluble autoantigen multimers (hyaluronic acid polymer with covalently linked MOG) prevented autoimmune disease in an EAE model (Hartwell et al 2018). In vitro these compounds induce an anergic state in antigen-specific B cells. The extent to which B cells are anergized in vivo by this treatment remains to be determined. Global induction of B cell anergy by targeting the BCR with anti-CD79 antibodies alleviated CIA disease (Hardy et al 2014), suggesting that induction of B cell anergy is a viable therapeutic approach for modulating disease development. Another self-antigen targeted approach that shows promise is the development of Tregs with chimeric receptors containing extracellular self-antigen and anmintracellular T cell signaling component to target Tregs to autoreactive B cells. Initial studies showed that these Tregs could suppress antigen-specific autoantibody responses. It remains to be seen whether this approach works by deleting these self-antigen reactive B cells or whether functional reprogramming is involved (Zhang et al 2018).

6. CONCLUDING REMARKS

B cells play functional roles in addition to producing antibodies. As described above, reductionist models have demonstrated a need for B cells to shape autoreactive T cell responses and to influence the cytokine milieu. Remaining issues include the visualization and interrogation of the cognate interactions between autoreactive B cells and autoreactive T cells, and how these interactions are influenced by tolerance mechanisms in both cells. With the development of new techniques that allow for in vivo analysis of cell-cell interactions and single cell analysis of endogenous responses, without the need for enrichment using BCR and TCR transgenesis, these questions are within reach. The greatest challenge will be to determine whether the rules of engagement observed in murine systems apply to developing autoimmune responses in humans. This will not be an easy task. Longitudinal studies of at-risk individuals, e.g first degree relatives, combined with new and powerful techniques for single cell analysis and labeling of antigen-specific B cells, will hopefully begin to provide insight into the role of B cells in establishing human autoimmune disease. Finally, as discussed above, targeted silencing of autoreactive B cells may increase the efficacy of therapy while reducing the risk associated with depletion of the entire compartment.

Acknowledgements

The authors would like to apologize to all colleagues whose work was not cited due to limited space. This work was supported by grants from the National Institutes of Health (DP3DK110845, R21AI124488, R01AI124487)

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