



Age-associated B cells in autoimmune diseases

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Abstract

Age-associated B cells (ABCs) are a transcriptionally and functionally unique B cell population. In addition to arising with age and following infection, ABCs are expanded during autoimmune disease, including those with systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis. The exact nature of how ABCs impact disease remains unclear. Here, we review what is known regarding ABC development and distribution during diseases including systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis. We discuss possible mechanisms by which ABCs could contribute to disease, including the production of cytokines and autoantibodies or stimulation of T cells. Finally, we speculate on how ABCs might act as mediators between sex, infection, and autoimmune disease, and discuss avenues for further research.

Keywords Age-associated B cell · T-bet B cell · Atypical B cell · Systemic lupus erythematosus · Multiple sclerosis

Introduction

Autoimmune disease occurs when self-tolerance mechanisms fail, and autoreactive lymphocytes and antibodies proliferate and target self-antigen. Examples of autoimmune disease can be identified in almost every organ and the resulting site and presentation of disease varies widely. The etiology of autoimmune disease is complex and incompletely understood, although there are known genetic and environmental contributors to disease. Additional insight into the mechanisms that drive autoimmunity is being revealed; however, the precise cause of disease, as well as curative treatments, remains elusive.

It is clear that B cells actively participate in pathogenicity of autoimmune disease. Particularly, the efficacy of B cell-depleting therapies, such as the anti-CD20 therapy, Rituximab, makes clear the pathogenic role of the B cell population [1–3]. Surprisingly, the success of B cell depletion therapy is not due to the elimination of autoreactive antibodies, as plasma cell numbers are maintained during treatment [4–7]. Although B cell depletion provides evidence that B

cells are involved in the progression of various autoimmune diseases, the manner of their involvement is not completely clear. B cells are a highly heterogeneous population, and while the success of these therapies demonstrates that B cells contribute pathogenically, it is also known that certain B cell subsets can act in a regulatory manner and alleviate disease [8, 9].

Age-associated B cells (ABCs), a unique population of memory B cells, appear in both individuals with autoimmune disease and in vivo models of autoimmunity. ABCs, identified by expression of T-bet, CD11c, CD11b, and lack of CD21, were initially shown to increase during both aging and autoimmunity [10, 11]. It was then shown that ABCs also expand in a number of intracellular infections [12–14] and during transplant rejection [15]. ABCs are a class-switched, antigen-specific memory population that display a distinct transcriptional program from other B cell subsets [16, 17]. Single-cell RNA sequencing demonstrates that ABCs differentially express an array of genes compared to other B cell subsets, including those encoding transcription factors, cytokines, signaling molecules, and proteins related to motility and metabolism [18]. There is increasing evidence that ABCs play a role in autoimmune disease, though the mechanisms by which they promote disease are not fully elucidated. Possible mechanisms include the production of autoantibodies and inflammatory cytokines and/or the presentation of antigen to and stimulation of T cells. Understanding the role ABCs play in autoimmune disease

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may lend valuable insight into the initiation and progression of disease.

In this review, we describe what is currently known about the role of ABCs in various autoimmune diseases and models of autoimmunity. ABC differentiation, anatomic localization, and activation and responsiveness are discussed. We describe the current evidence regarding possible mechanisms of ABC contribution to autoimmune disease. Finally, we discuss how ABCs in the contexts of age, infection, and autoimmune disease might interrelate, and describe avenues for further research in defining ABC involvement in autoimmune disease.

Frequency of ABCs is increased during autoimmunity

In addition to expanding during aging and infection, ABCs accrue in numerous autoimmune diseases and mouse models of autoimmunity (Table 1). Here, we consider ABCs to be T-bet⁺, CD21^{low}, CD11c⁺, CD11b⁺ B cells, or combinations thereof. The markers that define ABCs are not consistent in the literature and those termed atypical, double negative

2, and CD21^{low} B cells are likely similar populations to ABCs. Additionally, these identification strategies also have a degree of overlap with non-ABC B cell populations. For instance, a proportion of CD21⁻ cells might be transitional B cells or CD11b⁺ might include the B1 population. The current ABC classification requires refinement both to differentiate the population from non-ABC subsets and to better understand heterogeneity within the ABC population. For instance, different ABC markers might associate with variable stages of differentiation or represent plasticity or heterogeneity within the ABC sub-population. A common characteristic of the ABC population is their elevated frequency during autoimmune disease.

There are numerous examples of ABCs in the context of autoimmune disease. The peripheral blood of people with systemic lupus erythematosus (SLE) exhibits elevated proportions of ABCs compared to healthy individuals [19–23]. While ABCs account for roughly 1% of the circulating B cell population in healthy donors, ABC proportions can increase to over 5% in individuals with SLE [17]. ABC frequency correlates with disease; individuals with active SLE display increased ABCs compared to individuals with quiescent disease [19, 23]. People with multiple

Table 1 ABCs are expanded in various autoimmune diseases

Disease or disease model	Species	Markers and references
Systemic lupus erythematosus (SLE)	Human	CD19 ⁺ CD21 ^{lo} [19] CD19 ⁺ T-bet ⁺ [20] CD19 ⁺ CD11c ⁺ T-bet ⁺ [21] CD19 ⁺ T-bet ^{hi} CXCR5 ^{mes} CD11c ^{hi} [22] CD27 ⁻ IgD ⁻ CXCR5 ⁻ CD11c ⁺ [23]
Multiple sclerosis (MS)	Human	CD19 ⁺ CD21 ^{lo} [24] CD19 ⁺ CD20 ⁺ CD11c ⁺ CD21 ⁻ [25] CD19 ⁺ T-bet ⁺ [26]
Rheumatoid arthritis (RA)	Human	CD19 ⁺ CD11c ⁺ CD21 ⁻ [11]
Sjögren's syndrome (SS)	Human	CD19 ⁺ CD27 ⁻ CD21 ^{lo} [27] CD19 ⁺ CD27 ⁻ CD38 ^{lo} CD21 ^{lo} [28]
Axial spondyloarthritis	Human	CD19 ⁺ CD27 ⁻ CD38 ^{lo} CD21 ^{lo} [28]
Scleroderma	Human	CD19 ⁺ CD11c ⁺ CD21 ⁻ [11]
Malarial autoimmune anemia	Human	B220 ⁺ CD11b ⁺ T-bet ⁺ [29]
Common variable immunodeficiency (CVID) with autoimmune complications	Human	CD19 ⁺ CD21 ^{lo} [30, 31] CD19 ⁺ CD38 ^{low} CD21 ^{low} [32]
Crohn's disease	Human	CD19 ⁺ T-bet ⁺ [33]
SLE—MER ^{-/-}	Mouse	CD19 ⁺ CD11c ⁺ CD11b ⁺ [11] CD19 ⁺ CD11c ⁺ B220 ⁺ [34]
SLE—NZBxWF1	Mouse	CD19 ⁺ CD11c ⁺ CD11b ⁺ [11]
SLE—Chronic graft-versus-host disease	Mouse	CD19 ⁺ CD11c ⁺ [21]
SLE—B6.SLE1.2.3	Mouse	CD19 ⁺ T-bet ⁺ [35]
SLE—Cutaneous lupus erythematosus	Humanized mouse	B220 ⁺ CD11b ⁺ T-bet ⁺ [36]
Systemic autoimmunity—PTPN22 knock-in	Mouse	CD19 ⁺ CD11c ⁺ CD11b ⁺ [37]
MS—experimental autoimmune encephalomyelitis (EAE)	Mouse	CD19 ⁺ CD11c ⁺ T-bet ⁺ [25]
RA—Collagen-induced arthritis	Mouse	CD19 ⁺ CD11c ⁺ T-bet ⁺ [38]
Experimental autoimmune hepatitis	Mouse	CD19 ⁺ CD11b ⁺ [39]

sclerosis (MS), rheumatoid arthritis (RA), Sjögren’s syndrome (SS), and axial spondylarthritis display increased proportions of circulating ABCs [11, 24, 27, 28]. ABC frequency is increased in people with secondary autoimmune manifestations, including those with CVID with autoimmune diseases and autoimmune anemia during malaria [29–32]. Finally, ABC expansion can be observed in the peripheral blood of individuals with scleroderma and Crohn’s disease [11, 33], diseases that display auto-inflammatory characteristics. While there is strong correlation with ABC frequency and autoimmune disease, the verdict on causation is still out.

Given the various instances of ABC expansion in autoimmune disease, it appears that the presence of this subset could have important implications in disease. In vivo models are a critical tool for understanding the mechanistic relationship between ABCs and autoimmunity, and elevated proportions and numbers of ABCs are observed in various models (Table 1). Multiple mouse models for SLE demonstrate expanded levels of ABCs [11, 21, 34–37]. Similarly, ABCs are increased in the experimental autoimmune encephalomyelitis (EAE) model of MS [25], the collagen-induced arthritis model of RA [38], and a model for autoimmune hepatitis [39]. ABCs expand with age regardless of disease status, though autoimmune-prone

mice exhibit elevated ABC proportions earlier in life compared to age-matched wild type mice [11].

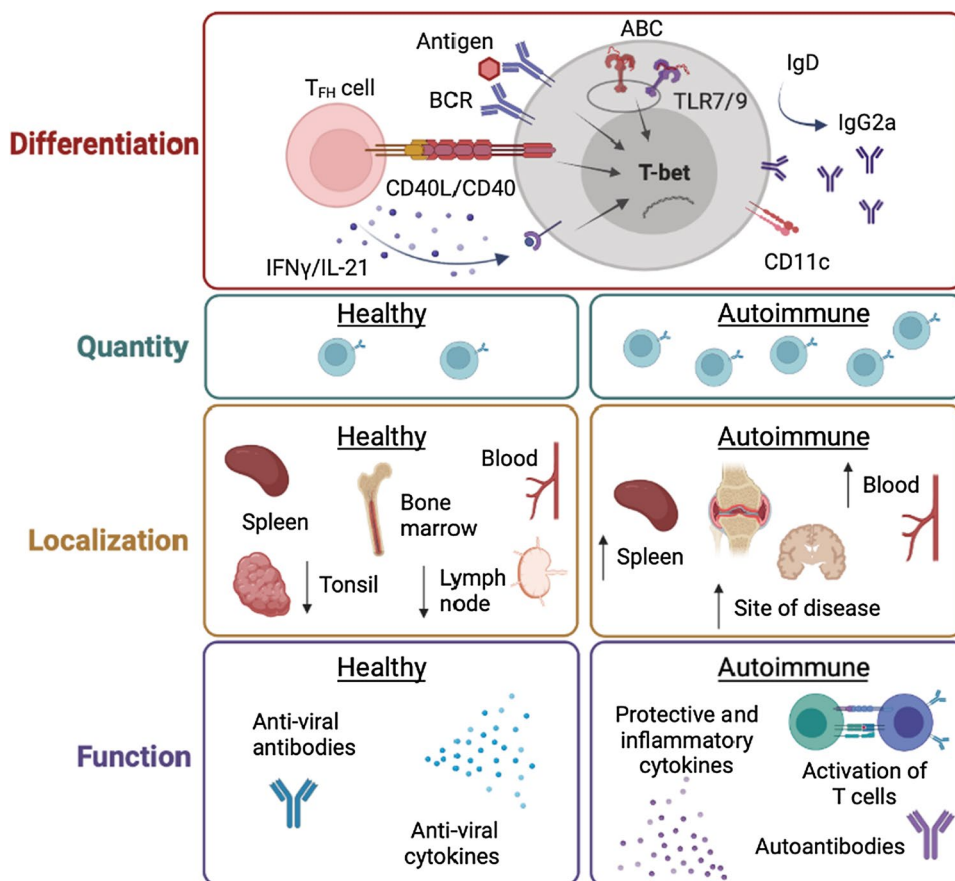
While mouse models cannot fully recapitulate human disease, they can provide important insights into the mechanisms by which ABCs contribute to disease. In mouse models, samples are not limited to peripheral blood, and the constraints of the availability of donors can be circumvented. ABCs have primarily been examined in the peripheral blood of people with autoimmune diseases due to relative ease of access, though chemokine analyses and in vivo models demonstrate that ABCs display unique localization and trafficking patterns.

Anatomic distribution of ABCs

The localization of ABCs is unique from that of other B cell subsets and is dependent on disease state (Fig. 1). In non-autoimmune settings, ABCs are detected in the spleen, peripheral blood, and bone marrow, though are rare in lymph nodes and tonsils [17]. The spleen appears to act as the primary ABC reservoir following viral infection [17, 40]. There is evidence that ABCs persist long-term in the marginal zone, where they are primed to initiate secondary germinal centres [41].

Fig. 1 Age-associated B cells in health versus autoimmune disease

Age-associated B cells (ABCs) differentiate from a combination of signals that include BCR stimulation and TLR7/9 engagement, in addition to CD40, IFN γ , and IL-21 signals, likely provided by T follicular helper cells. During times of health, ABCs are maintained at low levels in the spleen, bone marrow, and circulation, and are nearly undetectable in tonsil and lymph nodes. During autoimmune disease, ABC quantity is increased, and ABCs circulate and are present at the site of disease. ABCs produce anti-viral antibodies and cytokines in healthy individuals during viral infection. During autoimmune disease, ABCs produce both protective and inflammatory cytokines, stimulate T cells, and produce autoantibodies.



During ongoing inflammation, ABCs exit the spleen and circulate. The ABC frequency in the peripheral blood is elevated during both infection and autoimmunity [11, 19–21, 24, 25, 27, 28, 30, 31, 33, 40, 42]. The circulating ABCs may be migrating to the site of disease, as ABCs also increase in abundance at sites of inflammation. For instance, ABCs are found within kidney allografts of transplant recipients [15] and in the nasal tissue of individuals with rhinovirus infection [43]. During autoimmunity, ABCs also appear increased in the diseased tissue. Individuals with MS display greater proportions of ABCs in the cerebral spinal fluid than in paired peripheral blood samples [24]. Similarly, in the MS model EAE, higher numbers of ABCs are present in the central nervous system compared to naïve mice [25] and ABCs are increased in the liver during experimental autoimmune hepatitis [39]. In a humanized mouse model of cutaneous lupus erythematosus, wherein peripheral blood mononuclear cells (PBMCs) from lupus patients are engrafted into irradiated mice, ABCs are found within diseased skin lesions [36].

The pattern of chemokine receptors expressed by ABCs aligns with observations that ABCs localize to the site of disease. The inflammatory chemokine receptor CXCR3, generally absent on circulating B cells [44], displays increased expression on ABCs from those with axial spondyloarthritis [28] and MS [26], likely facilitating their migration to the site of disease [45]. Further, T-bet and CXCR3 expression on B cells is correlated in individuals with MS and in the collagen-induced arthritis (CIA) model of arthritis [46, 47]. Migration assays demonstrate that CXCR3 expression facilitates B cell migration [47], including across brain endothelial cell layers [46]; CXCR3 expression on ABCs in people with MS therefore may enhance their capacity to cross the blood–brain barrier and home to the diseased tissue. CXCR6 expression, implicated in extra lymphatic homing, is elevated on ABCs compared to total B cells in individuals with SLE [19].

In contrast to the spleen, circulation, and site of disease, ABCs appear largely absent from secondary lymphoid organs at steady state and during autoimmunity. In mice with collagen-induced arthritis, ABCs are found at low frequency in the inguinal lymph nodes [38]. ABCs display lower expression of CXCR5, a chemokine receptor that facilitates migration to lymph nodes, compared to follicular and marginal zone B cells [10]. In individuals with SLE, ABCs do not express CXCR4 [48], a chemokine receptor that facilitates extra lymphatic migration [49].

ABCs are found at various anatomical sites, though appear to preferentially localize to the spleen and site of inflammation. The differences in frequency of ABCs between the various compartments indicate that homeostasis is not maintained and is dependent on disease state. Localization is not the only respect in which ABCs are unique from

other B cell populations; the differentiation and activation requirements of ABCs also demonstrate their distinctiveness.

ABC origin and differentiation

ABC differentiation requires a combination of innate sensor stimulation in the context of a certain cytokine milieu. ABCs are stimulated to differentiate following the engagement of toll-like receptors 7 or 9 (TLR7/9), the B cell receptor (BCR), and exposure to cytokines including IFN γ and IL-21 (Fig. 1). ABCs continuously differentiate from peripheral B cell populations, in contrast to derivation from bone marrow precursors, as evidenced by their slower reconstitution compared to the follicular and marginal zone B cell compartments following irradiation [10]. Engagement of the nucleic acid sensors TLR7 or 9 is required for ABC differentiation from peripheral B cells [50]. TLR7/9 can be stimulated by microbial infections or endogenous components, including cellular debris or chromatin. Recently, a gain-of-function variant that results in amplified TLR7 signaling has been shown to drive expansion of ABCs and result in lupus development [51]. Engagement of TLR7/9 is critical but not solely sufficient for the appearance of ABCs; subsequent IFN γ and/or IL-21 exposure is required for ABC differentiation from follicular B cells and is CD40-dependent. IL-4 negatively regulates IL-21-induced ABC differentiation, though it does not affect the IFN γ -dependent pathway [50]. T follicular helper cells are critical for the development of ABCs, likely due to their provision of cytokines and stimulation of CD40 [41, 52]. Individuals with mutations in genes which affect signaling of IL-21, CD40, or IFN γ display low proportions of ABCs in their peripheral blood, highlighting the important roles of these signaling pathways in ABC accumulation [53]. ABCs appear to be driven to accumulate by the same cytokine milieu during infection and autoimmune disease [50, 54]. BCR stimulation is an additional signal that stimulates the generation of ABCs; when BCR stimulation is coupled with TLR7/9 stimulation, the ABC response is magnified [10]. The combination of antigen and CpG/IFN γ stimulation resulted in high T-bet expression in human tonsil B cells [55]. ABC accumulation is negatively regulated by the Early Growth Response 2/3 transcription factors, and it appears that ABCs largely circumvent this tolerance checkpoint during autoimmune disease [56].

As a part of their generation ABCs class switch to IgG, primarily IgG1 (humans) or IgG2a/c (mice) [11, 42, 57]. This aligns with the critical role for T-bet, a primary marker of ABCs, in class switching to IgG2a [58, 59]. Whether this class switching occurs within or outside of a germinal center is incompletely understood. Class switching and affinity maturation can happen within or outside of the germinal center response [60–62] and B cells that persist indefinitely

can arise intra- or extra-follicularly [63]. Current evidence indicates that ABCs can arise from both within and outside of germinal centers, though likely predominantly arise extra-follicularly. Immunofluorescence staining has shown ABCs to be located both within and outside of the germinal center [16, 17, 64]. However, ABCs precede the development of germinal centers during viral infection and fate-tracking showed ABC formation without germinal center entrance [41]. ABCs also display lower levels of somatic hypermutation compared to memory and germinal center B cells [16, 48]. The reliance of Bcl-6, a critical regulator of the germinal center reaction, on ABC development is unclear, with conflicting reports [41, 52]. It is likely that ABCs predominantly arise from within a germinal center, though their differentiation pathway may differ between contexts.

A requirement of the transcription factor T-bet, often used to define ABCs, for the appearance of ABCs is unclear. CD11c expression is not downstream of T-bet [50] and mice with a B cell-specific T-bet deletion display a significant but not complete loss of CD11c-expressing B cells [35, 38]. The CD11c⁺ B cells that do arise in these mice appear to be functional ABCs that display a similar phenotype to T-bet⁺ ABCs [65], although there is a loss of IgG2a class switching in the absence of T-bet [52]. It is clear that ABC differentiation results from a combination of signals that are unique from other B cell subsets.

ABC activation and survival

ABCs also display unique activation and survival requirements. Unlike follicular and marginal zone B cells, ABCs do not rely on BAFF for survival [10, 66]. ABCs also do not proliferate upon CD40 stimulation, are hypo-responsive to BCR stimulation alone, and exhibit lower survival compared to follicular B cells [10, 31]. Further unlike other B cell types, ABCs respond more readily to TLR7 and TLR9 stimulation and secrete antibody in response to TLR rather than BCR activation [10, 23]. Some have proposed that ABCs may be anergic due to their lack of responsiveness to BCR and CD40 stimulation [27]; however, it is well documented that ABC stimulation by TLR7/9 agonists poses a robust response to BCR stimulation [10]. It is possible that ABCs are activated by viral particles which antagonize TLR as well as exhibit Ig specific antigens rather than single molecular structures. Another unique aspect that has lent people to believe ABCs are hypo-responsive is their requirement for antigens to be membrane bound, and lack of responsiveness to soluble antigen [67]. ABCs differ clearly from other B cell subsets in their responsiveness to activation signals. Better understanding of the signals controlling ABC activation may help to elucidate their roles in immune dysregulation.

Mechanisms of ABC contribution to autoimmunity

ABCs have the capacity to contribute to autoimmune disease through a variety of mechanisms, including through the presentation of antigen, production of autoantibodies or cytokines, or initiation of germinal center development. These possible mechanisms of contribution are not mutually exclusive, and ABCs could contribute in multiple and different manners depending on the context.

Autoantibodies

A likely way in which ABCs contribute to autoimmunity is through the production of autoantibodies. ABCs from individuals with SS produce antibodies specific to various self-antigens including rheumatoid factor (IgG), double stranded DNA, and lipopolysaccharide [27]. During malaria anemia, following pathogen stimulation of TLR9, ABCs are a major producer of autoantibodies responsible for the loss of erythrocytes [29]. ABCs at the site of disease produce IgG2a in a model of lupus characterized by skin lesions [36]. In a model of SLE ABCs produce more antichromatin IgG2a than non-ABC B cells, and depleting or knocking out ABCs results in a loss of antichromatin IgG and IgG2a [21, 35]. Murine splenic B cells differentiated into ABC-like cells through stimulation of lipopolysaccharide in the presence of IL-21 and TLR7 were responsible for the production of total IgG including IgG2a/b and IgG3 [21]. During SLE, higher proportions of ABCs positively correlate with levels of autoantibodies [11, 21, 23]. A murine model for SLE also highlighted the importance of TLR7 in the production of autoantibodies, as inhibition of TLR7 resulted in decreased autoantibody production [68]. While autoantibody production often contributes to autoimmune pathogenesis, it is not always required for the development of disease. In the MS disease model EAE, knocking out the ABC population does not alter the serum levels of myelin-specific IgG2a/c [40].

In addition to the production of antibodies, ABCs might also play a role in the germinal center response, which is critical for production of autoreactive B cell clones. T-bet expression in B cells is critical for the formation of spontaneous germinal centers in a model of SLE [35]. Coinciding with reduction of germinal center formation, T-bet deletion in B cells reduced the levels of kidney damage and mortality in this model [35]. It is likely that ABCs contribute in part to the development and exacerbation of autoimmune disease through the production of autoantibodies, and they may also facilitate germinal center development which result in autoreactive clones.

Cytokines

The production of cytokines is another likely mechanism by which ABCs contribute to disease. ABCs express a distinct cytokine profile from other B cells. The expression of numerous cytokines is increased on ABCs, including IFN γ , TNF, IL-17, IL-10, and IL-4, compared to other B cell subsets [10, 25, 69, 70]. While the ABC cytokine profile has primarily been characterized during aging and viral infection, there are a few studies that indicate that ABCs display a distinct profile during autoimmune disease. In individuals with Crohn's disease, ABCs in the gut display increased expression of IFN γ and IL-6 compared to other B cells, and expression is further elevated during active disease [33]. ABCs in EAE mice display increased IL-17A compared to other B cells and ABCs in non-EAE mice [12]. It appears that ABCs also express regulatory cytokines. Splenic ABCs in EAE mice display increased expression of regulatory IL-10 [12], known to attenuate neuroinflammation [71]. ABC production of IL-10 is higher than other B cell subsets during experimental autoimmune hepatitis [39] and a T-bet expressing marginal zone B cell population expresses high levels of IL-10 during CIA [47]. Together, these findings indicate that cytokines produced by ABCs might contribute to disease in both pathogenic and protective manners.

In addition to the direct effects of cytokines, ABC cytokine production can influence the makeup of the B cell population. ABCs can reduce the proliferation of pro-B cells through TNF-mediated apoptosis [69], which is not shared by follicular B cells despite evidence of significant TNF production by these cells [72]. Follicular B cells in fact, are able to counteract the ABC-mediated apoptosis of pro-B cells through IL-10 production [69]. ABCs are therefore able to influence the total B cell population in unique cytokine dependent ways.

How ABC cytokine production is induced and maintained during disease deserves further investigation. More research is needed to determine how the cytokine profile is changed during different phases of disease and the expression between lymphoid organs and site of disease. It is clear that ABCs are capable of substantial cytokine production that could contribute to disease in various manners.

T cell help

Activation of inflammatory T cells is another possible mechanism by which ABCs contribute to autoimmune disease. ABCs are able to form stable interactions with T cells and act as antigen-presenting cells [66]. Follicular B cells display largely even distribution throughout follicles, though ABCs more frequently localize in T cell or B/T cell border zones of the spleen [66]. Increased expression of CCR7 facilitates the migration of ABCs to the T cell zone, and ABCs display

increased chemotaxis responsiveness, assessed by transwell migration assays, to the T cell zone chemokines CCL21 and CCL19 [66]. Once in the T cell zone, ABCs are able to form stable interactions with T cells and are more effective antigen presenters than follicular B cells *in vivo* [66]. ABCs also display elevated expression of costimulatory molecules, including CD80 and CD86, compared to follicular B cells [10, 11, 23].

There is evidence that ABCs stimulate pathogenic T cells during autoimmune disease. ABCs from autoimmune-prone mice are more efficient antigen-presenting cells than follicular B cells *in vivo* [66]. In Crohn's disease, ABCs are important mediators of T cell cytokine expression; CD4⁺ T cells co-cultured with ABCs display increased IFN γ expression compared to those cultured with non-ABC B cells [33]. Individuals with Crohn's disease that harbor higher frequencies of ABCs also exhibited increased Th1 infiltration into the gut compared to those with lower ABC frequencies [33]. In a model of SLE, mice without ABCs displayed reduced expression of T cell activation markers and IFN γ [35]. Conversely, CD11b⁺ B cells isolated from mice with experimental autoimmune hepatitis impaired the proliferation and IFN γ production of CD4⁺ T cells [39], highlighting that the mechanisms of ABC contribution likely vary between diseases. It is apparent that ABCs can influence and activate T cells through robust antigen presentation capabilities as shown both by *in vitro* and *in vivo* studies. Their ability to activate T cells in this manner may be important for the role of T cells in autoimmune disease.

ABCs and tolerance

The success of B cell therapies highlights the pathogenic role of B cells in disease [73], though subsets of B cells also act in a protective manner during autoimmune disease [74]. There is evidence that ABCs in certain contexts, or a subset of the ABC population, might promote tolerance. ABCs express elevated Fas compared to follicular B cells at steady state [11]. Fas, via its interaction with Fas ligand, plays a critical role in the maintenance of immune tolerance [75]. During autoimmune disease, circulating ABCs display elevated Fas expression compared to non-ABC B cells, including in people with SLE, SS, and CVID with autoimmune complications [19, 27, 31]. In alignment with these results, our group has observed that EAE results in increased expression of inhibitory receptors PD1, PDL1, and CTLA4 on ABCs [25]. Collectively, these findings indicate that autoimmunity may drive an increase in inhibitory receptor expression on ABCs.

It is not clear if the expression of inhibitory receptors, or the secretion of regulatory IL-10 as described above, allow for ABCs to contribute in a protective manner during disease. Mice without ABCs develop exacerbated EAE

disease, suggesting a protective function of ABCs [25]. During CIA, a T-bet expressing marginal zone B cell population is elevated during the remission phase of disease, compared to active disease [47]. This finding indicates that these cells may be acting in a manner to mitigate disease, though how this innate-like population relates to ABCs is unclear. Conversely, multiple SLE models support a pathogenic role for ABCs [21, 35]. It appears that ABCs have the capacity to contribute in both protective and pathogenic manners via a variety of mechanisms, depending on the disease context. Delineating between B cell populations that contribute to versus protect from disease may allow for the development of more targeted and efficacious therapies.

Discussion

How do ABCs differ between the contexts of autoimmune disease, aging, and infection?

Thus far ABCs have primarily been examined separately in the three contexts in which they have been implicated: infection, autoimmunity, and aging. However, these occurrences are often overlapping and intertwined. If the ABC population displays related transcriptional profiles and exerts similar functions in these different contexts remains largely unexplored, and there is value in additional side-by-side comparisons of the ABC population. One group has pursued a comparison of the ABC transcriptional profile in individuals with malaria versus those with HIV using single cell RNA sequencing [18]. They found that the ABCs display a heterogeneous transcriptional profile within individuals and disease groups, and that the ABC profiles of those with malaria and HIV were comparable [18]. Alternately, our group has demonstrated ABCs take on distinct phenotypes in mice infected with gammaherpesvirus 68 versus those induced for EAE [25]. In particular, gammaherpesvirus 68 infection leads to an upregulation of IFN γ , while EAE upregulates IL-17A expression on ABCs, and inhibitory receptor expression is downregulated during gammaherpesvirus 68 infection and upregulated on ABCs during EAE [25]. These results demonstrate that infection and autoimmunity can drive ABCs to take on distinct phenotypes.

In addition to phenotypic differences, there is evidence that ABCs display unique functionalities between contexts. While ABCs are required for germinal center formation in a model of SLE, they are dispensable for germinal center development following immunization with Chicken Gamma Globulin [35], highlighting the distinct functional roles of ABCs depending on context. Further studies to expand on the similarities and differences between ABCs in various contexts will be important; transcriptional characterization, deep ABC phenotyping by mass cytometry, and clonal

repertoire analysis would be valuable. Comparison of the ABC population between individuals, and using mouse models, during various infections, autoimmune diseases, and over different ages, will help to elucidate the ways in which this population contributes to these different, often concurrent, circumstances.

Do ABCs contribute to the female sex bias in autoimmune disease?

There is a preponderance of females affected by autoimmune diseases, with females accounting for over 75% of those with autoimmune disease [76]. It has previously been suggested that ABCs might contribute to the observed female sex bias in autoimmunity [77]. ABCs display a female sex bias during aging, with similar proportions of ABCs during youth and adolescence, though increasing in proportion with age more so in females than males [11]. Recently, it has been reported that ABC frequency during viral infection and autoimmunity is increased in females more so than males in adolescent mice, demonstrating that the sex bias is not restricted to aging [25, 40, 48]. The preferential ABC accumulation in females may be due to the dominant role of TLR7 stimulation in their development; TLR7 is X-linked and partially escapes X-chromosome inactivation, leading to its overexpression in females [78]. This increased availability of TLR7 might foster ABC differentiation females. In support of unbalanced TLR7 expression resulting in the ABC sex bias, it was recently shown that duplication of *Tlr7* in males overrides the observed female sex bias of ABCs in a model of SLE [48]. Given the strong correlation of sex biases in both autoimmune disease and ABC frequency, ABCs may be an important factor in our understanding of autoimmune etiology. Further investigation of the ABC population in males versus females during infection and disease is necessary to determine if the sex bias extends beyond frequency and results in distinct functional capacities in the ABC population between sexes.

Are ABCs mediators between viral infection and autoimmune disease?

A history of viral infection is a well-established contributing factor to autoimmune disease. Intriguingly, nearly all of the diseases in which ABCs are known to accumulate are associated with a history of Epstein-Barr virus infection, including SLE, MS, RA, and SS [79–86]. Current understanding of how Epstein-Barr virus contributes to autoimmune disease is limited, though a variety of possible mechanisms have been suggested [87]. Our group postulates that ABCs act as a mediating link between Epstein-Barr virus infection and disease. Previously, we have used a murine

analog of Epstein-Barr virus, gammaherpesvirus 68, to demonstrate that latent infection results in more severe disease in EAE and collagen-induced arthritis [38, 88]. Recently, we demonstrated that ABCs remain elevated and continue to express TNF and IFN γ long-term during latent gammaherpesvirus 68 infection [40]. Therefore, we suggest that latent Epstein-Barr virus infection might stimulate the continued activation of the ABC population, poisoning them to contribute pathogenically at the onset of autoimmune disease. In support of this, we find that ABCs are required for gammaherpesvirus 68-exacerbation of EAE and collagen-induced arthritis; mice with a B cell-specific T-bet deletion do not develop the increase in disease severity with latent infection [25, 38]. Additionally, it has also been shown that hepatitis C virus infection results in ABC-like cells producing rheumatoid factor-type autoantibodies [89]. ABCs also expand in the presence of viral infections that have not been associated with autoimmune disease, such as murine CMV [57], influenza [17], HIV [16, 42], and SARS-CoV-2 [90]. An important avenue for further research is elucidating the mechanism(s) by which virus-induced ABCs might contribute to autoimmune disease. It is possible that the efficacy of B cell depletion therapies can be partially explained by their depletion of Epstein-Barr virus-infected B cells and/or the pathogenic ABC population.

How do current therapeutics impact the ABC population?

B cell depletion therapy is highly efficacious and a commonly used treatment in various autoimmune diseases [73]. Rituximab, a monoclonal antibody that binds to the B cell surface marker CD20 and targets those cells for destruction, is regularly used clinically to treat autoimmune disease [91, 92]. It is currently unknown if ABCs are effectively depleted by Rituximab. In some individuals with RA or SS, ABCs expressed higher levels of CD20 than other B cell subsets, indicating that they may indeed be effectively targeted [11, 27]. However, therapeutics which more specifically target ABCs might be of value, as CD20-expressing protective B cell types are inevitably depleted by Rituximab. Unfortunately, as of yet, a unique antigen on the surface of ABCs that might be used to target their destruction is yet to be identified. The ABC profile in people with autoimmune diseases receiving B cell depletion therapies should be characterized, both to determine if ABCs are effectively depleted and, if so, to examine their reconstitution profile. There is substantial evidence that the B cell subsets that reconstitute following B cell depletion are correlated with clinical course in both MS and RA and it has been suggested that monitoring of the reconstitution profile might allow for personalization of treatment regimens [2, 93, 94]. The reconstitution profile of ABCs, both the quantity of returning ABCs and

their phenotypic and functional characteristics, and association with disease, should be investigated.

ABCs play an essential role in anti-viral immune responses and are required to eliminate certain infections. However, a consequence of their accumulation is likely the ability to contribute to autoimmune disease. The precise mechanism(s) by which ABCs function during autoimmune diseases requires additional delineation, though it is clear that the ABC population can exert various functional capacities, including the production of cytokines and autoantibodies and the stimulation of T cells. There are many features of ABC biology still to be investigated, including heterogeneity in the ABC population both within and between individuals and disease states and the relative contributions of ABCs at various anatomical locations. It is an exciting time to be studying ABCs, with many areas of ongoing intense investigations that will hopefully aid in better understanding this unique population and its role in autoimmune pathogenesis.

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Declarations

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