New Cells in Old Mice: The ABCs of Humoral Immunosenescence

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Abstract: Dampened humoral immune responses and increased propensity for autoimmune and inflammatory diseases are hallmarks of aging. Here, we summarize recent progress in understanding how aging affects humoral immunity, focusing on the discovery of a phenotypically and functionally unique B cell subset in aged mice, its potential role in immunosenescence, and its relationship to increased inflammation and autoimmunity.

Keywords: Age, B cell homeostasis, function.

OVERVIEW

Aging is a complex process characterized by functional declines in multiple physiologic systems. Age-related alterations in the immune system, a spectrum of changes that are *in toto* termed "immunosenescence," yield enhanced susceptibility to infectious diseases, increased propensity for inflammatory responses and autoantibody production, and consequently, increased morbidity and mortality [1-14]. Understanding the mechanisms through which age-associated phenomena yield the overall immunosenescent phenotype presents a fundamental and challenging biological problem. Multiple factors contribute to this general deterioration of immune activity, encompassing both cell-intrinsic changes and alterations in lymphoid organ microenvironments. In particular, determining how age-associated changes result in modified homeostatic relationships among steady-state lymphocyte pools, and how this in turn impacts the initiation and quality of adaptive immune responses, may provide the keys to effective prophylaxis and intervention. In this review, we briefly summarize global shifts in humoral immune responsiveness that emerge with age, followed by a detailed consideration of changes in the genesis and homeostasis of B lymphocyte populations. Finally, we focus on a recently described B lineage subset that emerges with age [15,16], and discuss how the shifting palette of functional B cell subsets may contribute to the global landscape of immunosenescence.

AGING ALTERS HUMORAL IMMUNE RESPONSES

Protective humoral immunity requires maintaining both naïve and antigen-experienced B cell subsets that respond robustly to pathogens, yet maintain self-tolerance. Multiple studies have revealed that, in contrast to healthy young adults, aged individuals display blunted humoral responses to both new and previously encountered antigens, as well as increases in autoantibody levels [4,7,11,13,17-19]. Accordingly, studies over the last several decades have interrogated the basis for this array of features. Table **I** summarizes some of the changes in B cell development, dynamics and function that have been revealed by these efforts.

Early work focused primarily upon whether the frequency or clonal composition of responsive B cells changes in aged individuals, as well as whether hallmarks of effective humoral immune responses are altered. Examinations of how aging influences responding B cell frequencies, using model antigens in mice, have yielded mixed results. For example, aged mice have decreased frequencies of B cells responsive to some antigens, such as the haptens 2,4-dinitrophenyl (DNP) [20] and (4-hydroxy-3-nitrophenyl)acetyl (NP) [21]. In contrast, the frequencies of B cells for other antigens are either unchanged, or, in some cases, increased with age [22-24]. More detailed analyses of clonal composition have led to the notion that while some specificities are maintained within the aged B cell repertoire, the relative representation of particular IgVH gene families shifts, and the responsive repertoire is relatively reduced in overall clonotypic diversity. Moreover, these shifts have been implicated in qualitative changes to antibodies produced against newly encountered antigens [25-27]. These changes in repertoire diversity and composition reflect multiple underlying mechanisms. For example, truncation of the responsive repertoire is partly explained by so-called B cell clonal expansions that emerge at the expense of more diverse naïve B cell populations [28,29]. Furthermore, shifts in key features of developing B cells and their production rates (discussed below) may yield skewed generation or selection of naïve B cell clonotypes [30-32].

In addition to changes in the composition of naïve B cell pools per se, a substantial literature indicates that B lineage-extrinsic components act in concert to yield overall dulled humoral responses. For example, both CD4+ and CD8+ T cells in aged mice display reduced responsiveness to encounters with novel Ag [33], and the effectiveness with which CD4+ T cells provide cognate help diminishes with age

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Table I. Age-associated Changes in B Cell Subsets and Compartments

	Bone Marrow	Periphery (Spleen)
Cell-intrinsic	Myeloid skewing of HSC [83] Reduced E47, E2A in pro-B and pre-B cells [84,105,106] Reduced IL-7R levels [40] Shifts in Vh repertoire [30,107]	Repertoire shifts [22,25-27,97] Increased autoreactivity Reduced E47, AID [84,105,108,109]
Micro-environmental	Reduced HSC niche capacity [31,85] Reduced IL-7 production [86] Architectural changes [110]; possible link to homing of PCs	Architectural changes linked to homing deficiencies of TR, MZ B cells [110]
Homeostatic	Reduced numbers and proportion of pro-B and pre-B cells [31,41,111] Slowed turnover of IMM B Decreased throughput of pre-B cells	Constant mature B cell numbers Decreased mature B cell turnover, hence increased lifespan [87,112] Increased number and proportion of ABCs [15,16]
Immune responses	Fewer GCs and PCs following T-dependent immunization [108,113-115] Defects in T helper function [33-35] No change in PCs following T-independent immunization [116] Increased prevalence of chronically activated B cells [117] Increased prevalence of PCs secreting autoantibodies [117-120] Impaired class switching [109,121]	

[34,35]. In addition, aging detrimentally impacts the ability of follicular dendritic cells (FDC) to participate in germinal center (GC) reactions [36,37]. Analogously, age-associated alterations in B cell functional attributes may exert *trans* effects on T cells *via* altered cytokine secretion and antigen presentation properties.

Taken together, these findings suggest that the causes of depressed humoral immunity in aging are complex, and likely involve a B cell-intrinsic loss of responsiveness and alterations in antigen receptor diversity, as well as reduced stromal and accessory cell support. With this in mind, research has focused on understanding the basis for these multifaceted defects, thus fostering detailed analyses of how developing and mature B cell populations change with age.

AGING IMPACTS B LYMPHOCYTE GENERATION, SELECTION, AND HOMEOSTASIS

Altered hematopoiesis is a consistent feature of aging, marked by increased rates of myeloid cell production and reduced rates of both T and B lymphocyte production [33, 38-42]. A brief synopsis of B cell differentiation is provided here, in order to highlight aspects that shift with age. Detailed reviews of this process are available elsewhere [43-45].

In adults, B cells are continuously generated from bone marrow (BM) hematopoietic stem cells (HSC) that give rise to intermediates with increasingly restricted lineage alternatives. Multipotent progenitors (MPPs) derived from HSC have an equal ability to differentiate into myeloid and lymphoid lineages [45]. MPPs may differentiate into B lymphocyte-specified progenitors that, through the upregulation of key proteins and cytokine receptors, become committed to the B lineage as pro-B cells. The transcription factors E2A, Early B cell Factor (EBF), and Pax-5 are crucial for B lineage commitment [44]. These proteins are necessary for activating genes such as RAG and for regulating VDJ recombination, and thus B cell antigen receptor (BCR) formation [46-49]. Furthermore, these transcription factors upregulate the expression of receptors requisite for B cell survival and subsequent differentiative cues, such as the interleukin-7 receptor (IL-7R) [50]. Successive rearrangements at the immunoglobulin (Ig) heavy and light chain loci during the pro- and pre-B cell stages yield differentiation into IgM+ immature (IMM) B cells [51]. IMM B cells exit the BM and migrate to the spleen to complete maturation as transitional (TR) B cells [52-57]. Following TR differentiation, these newly formed B cells enter one of two mature peripheral B cell pools defined by both function and anatomical location: the splenic marginal zone (MZ) or the splenic or lymph node follicle (FO).

In addition to a knowledge of these differentiative events and subsets, appreciating the influence of selection and competition in shaping B cell pools is fundamental to understanding the overall impact of age-related changes. Indeed, stringent selection and competition, based on both BCR specificity and homeostatic demands, occurs among emerging and mature B cells. Thus, avid BCR ligation among IMM B cells in the BM leads to receptor editing or cell death [58]. This is largely a B cell intrinsic process in which the BCR signaling thresholds for selection cannot be modified by extrinsic factors. About 90% of all IMM B cells are lost to these so-called central tolerance mechanisms. Once the surviving IMM B cells exit the BM, they continue to undergo selection based on BCR specificity during the TR stages

[59]. During TR selection, sustained or strong BCR signals yield death or inactivation [55, 60-64]. In addition, TR B cells must also receive a minimal, or so-called "tonic", BCR signal to successfully complete differentiation [65-69]. Thus, only those TR B cells whose BCR signal strengths fall between the thresholds for these negative and positive selection processes persist. Under normal circumstances, only about 30% of TR cells survive to join the mature preimmune pools [56, 57, 70]. Within mature peripheral pools, the requisite for tonic BCR signals remains.

Because B cells are continuously produced, each subset exists at a dynamic steady state, whose magnitude is dictated by the rate at which new cells are generated and by cellular lifespan. Thus, the rate of influx from the TR pool, coupled with the longevity of FO and MZ B cells, determines steady state mature B cell numbers. B lymphocyte stimulator (BLyS, also termed BAFF), governs mature B cell homeostasis through interactions with BLyS Receptor 3 (BR3, also termed BAFFR, reviewed in [71]), which is initially expressed in the early TR stages [72]. Unlike selection at the IMM stage, the range of acceptable BCR signal strengths affording survival in the TR, FO, and MZ subsets is plastic, and can be varied by the availability of BLyS. Thus, the lack of BLyS/BR3 signaling leads to profound reductions in FO and MZ compartments [73,74] due to failed TR differentiation and shortened mature B cell lifespan [75]. Conversely, elevated BLyS levels increase the proportion of TR B cells completing maturation and extend the lifespan of FO and MZ B cells [72], thereby enlarging the mature pools and raising the likelihood that potentially autoreactive B cells survive TR differentiation [76].

Changes in the magnitude, kinetics, and behavior of virtually all B cell generative compartments are observed with advancing age. This reflects cell-intrinsic changes among key lymphocyte progenitors and B cell differentiation intermediates, as well as alterations in the capacity of the BM to support B cell differentiation. The numbers of hematopoietic stem cells (HSCs) remain constant or actually increase with age in mice [77,78]. However, a combination of cell-intrinsic and microenvironmental factors are thought to result in age-associated changes in gene expression (transcription factors and cell surface proteins) [77,79], reduced expansion (self-renewal) potential [80], reduced homing efficiency [81], engraftment potential [82], and myeloid skewed differentiation [83]. The existence of an intrinsic, genetically controlled "program" that leads to shifted HSC potential during aging has been postulated [80], but whether observed genetic changes are a cause or an effect of HSC aging is not known.

With age, the steady-state numbers of B lineage differentiative intermediates change. Initial studies reported a 2- to 4-fold drop in the numbers of pre-B cells, suggesting that diminished B lymphopoiesis reflects a block at the pro- to pre-B cell step [41]. However, subsequent analyses have revealed that reductions are detectable in the earliest B lineage specified subsets [38]. Importantly, the proportional drop is greatest at the pre-B stage, suggesting that with age, there are differential effects on the molecular interactions mediating transit through successive stages of B cell development. Indeed, E47, a key component of the transcription factor E2A, is decreased in aged pro- and pre-B cells [84]. The loss of E47 expression is likely due to post-transcriptional regulation, as mRNA levels are similar in young and old mice. RAG levels are also decreased in aged pro-B cells, resulting in a decrease in VDJ recombination and thus a decrease in successful pro- to pre-B cell differentiation [31]. Furthermore, there is an intrinsic decrease in the ability of pro-B cells to respond to IL-7 [40]. In sum, aging is clearly accompanied by B cell-intrinsic defects that hinder their development. The BM microenvironment also changes with age, contributing to the reduced rates of B cell genesis. For example, changes to endothelial cells reduce the capacity of the BM to create HSC-specific niches [85], and B cell progenitors are affected by decreased secretion of requisite IL-7 from BM stromal cells [86].

Despite age-associated reductions in BM output, the steady-state numbers of mature B cells remain relatively constant in mice [87]. Conflicting evidence exists as to whether circulating B cell numbers in humans similarly remain constant or instead decrease (see [88] for review). This leads to the question of how peripheral lymphocyte numbers are maintained in the face of reduced input, as well as whether the mechanisms responsible for preserving these peripheral lymphoid niches is related to blunted humoral responsiveness and autoimmunity. Indeed, multiple laboratories have demonstrated altered turnover and throughput rates in IMM, TR, and mature B cell subsets of aged individuals compared to young adults, suggesting altered homeostatic demands that might lead to shifts in selection, competition, and survival. These possibilities raise the question of whether novel B cell subsets arise with age and, if so, how they are related to previously reported changes in B cell homeostasis and function, as well as the overall immunosenescent phenotype.

A PHENOTYPICALLY AND FUNCTIONALLY DISTINCT B CELL SUBSET ACCUMULATES WITH AGE

A mature B cell subset that emerges with age, termed age-associated B cells (ABCs), has recently been reported by two groups. Hao *et al*. define ABCs as CD21/35- CD23- CD19+ B cells which respond poorly to adaptive and most innate stimuli *in vitro*, and may directly or indirectly foster aberrant responses by secreting inflammatory cytokines and/or negative regulatory cytokines, and also by engendering Th17 differentiation [15]. Rubtsov *et al*. define ABCs as CD11c+CD11b+CD19+ B cells that may play a direct role in autoimmunity *via* secretion of autoantibodies [16]. Strengthening this potential relationship with autoimmunity, they found that ABCs emerge at very early ages in autoimmune-prone mice, and reported phenotypically similar cells in female rheumatoid arthritis patients [16]. A comparison of the ABCs characterized by each research team is provided in Table **II**. Based upon the numerous similarities, it is likely that the ABCs reported by each group are related and overlapping subsets. In both cases, ABCs accumulate with age, are more prevalent in female mice, and rely upon TLR signaling to expand. Moreover, in both cases, stimulated ABCs exhibit functional attributes associated with innate immunity,

inflammatory responses, and/or autoimmunity. These general features are schematized in Fig. (**1**). In the discussion that follows, we treat ABCs as a singular subset for the sake of clarity.

The gradual emergence and persistence of this previously unappreciated, functionally novel subset raises several questions. First, what are the progenitor pools for ABCs, and what drives their generation? Second, are ABCs connected to homeostatic changes seen with advancing age, either in terms of their generation, or in terms of *trans* effects upon the remaining FO and MZ cells? Third, do ABCs either directly or indirectly alter the quality of immune responses, thus contributing to the increased susceptibility to infection inflammatory processes and autoantibody production that accompany aging? Finally, considering these factors in aggregate, might approaches targeting ABCs or their downstream effects help revitalize immune responses or amelio-

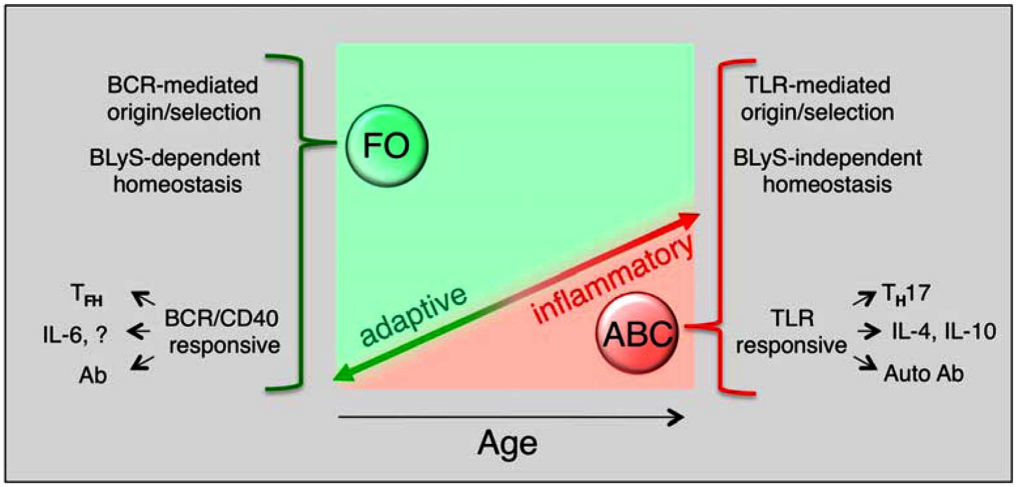

Fig. (1). Schematic of ABC accumulation and impact with age. With increasing age, the proportion of ABCs (shaded red) increases, at the expense of FO and MZ subsets (shaded green). The functional attributes of ABCs differ from FO B cells. Whereas FO B cells respond to BCR crosslinking, ABCs do not, and instead respond only to TLR-driven signals. In addition, ABCs are independent of the cytokine BLyS, while FO B cells require BLyS signaling for continued survival. The effector functions of ABCs, in terms of antigen presentation, cytokine secretion, and T cell polarization also differ.

Table II. Properties of Age-associated B Cells

		Hao *et al.* [15]	**Rubtsov *et al.* [16]**
Surface marker phenotype	Defining markers	CD21- CD23-	CD11b+ CD11c+
	B lineage markers	CD19+ B220+ IgMlo IgDlo	CD19+ B220+ IgM+/- IgDlo
	Other markers	CD11b+/- CD5- CXCR5lo CXCR4+	CD11b+ CD5+ VCAM-1+
	Activation markers	MHC II+ CD86lo	MHC II+ CD86lo CD138+
Origin/Features	Gender predominance	Female > male	Female > male
	Anatomic distribution	Spleen, BM, blood	Spleen, blood (BM N.D.)
	Transcription factors	Pax5+ Blimp-1+	Pax5+ Blimp-1+
	Generation/progenitors	TLR-driven/FO	TLR-driven/?
Activating stimuli	Anti-IgM ± anti-CD40	No	N.D.
	TLR 7	Yes, modest augmented by anti-IgM	Yes, robust
	TLR 9	Yes, robust augmented by anti-IgM	N.D.
Functional properties	Autoantibody production	Undetectable anti-dsDNA	Yes, anti-chromatin
	Cytokine production	High IL-4, IL-10	N.D.
	Antigen presentation	Yes, skews CD4+ T cells to Th17	N.D.

+/- indicates presence of some cells that are + and some that are –
N.D.: not done

rate age-associated disease susceptibilities in the elderly?

ABCs ORIGINATE FROM MATURE B CELL PROGENITORS *VIA* TLR-MEDIATED PROCESSES

The near-absence of cells with the ABC-defining phenotype in young adult mice raises the question of how ABCs arise. Autoreconstitution studies indicate that ABCs are not simply the product of B cell generation in aged BM, because their frequency and number in sublethally irradiated aged mice are extremely low after 12 weeks, despite full reconstitution of all other developmental and primary B cell subsets [15]. Instead, there is strong evidence that Toll-like receptor (TLR) signaling plays a critical role in the generation of ABCs from pre-existing mature B cell progenitors. Both aged and young FO B cells acquire the ABC phenotype upon TLR9 stimulation *in vitro* [15]. Moreover, TLR7 and MyD88 signaling are required for ABC development, as aged TLR7 or MyD88 knockout mice fail to accumulate ABCs [16]. Finally, 30 days after adoptive transfer into replete hosts, a very small proportion of the donor FO B cells acquire characteristics of ABCs after extensive division. Thus, FO B cells are the likely progenitors of ABCs, though MZ and/or TR progenitors cannot be ruled out; and chronic TLR signaling is apparently required to drive expansion and differentiation to the ABC phenotype. It remains to be seen whether all FO B cells have the potential to differentiate into ABCs, such that stochastic mechanisms limit the numbers that acquire full ABC character; or if instead, ABCs are derived from a particular subset of clones within the FO pool. Accordingly, determining whether ABCs display clonotypic bias congruent with B cell clonal expansions might prove informative in terms of both their origin and driving forces. For example, MZ and B1 subsets display clear clonotypic biases that might be evident if they serve as ABC progenitors [89-92]. Alternatively, only B cells with BCRs that bind antigens associated with TLR7 and TLR9 ligands might be responsible for the accumulation of ABCs, regardless of subset. These possibilities are not mutually exclusive, and should prove approachable with current technologies that allow detailed repertoire and specificity analyses in aged B cell pools [29].

THE INTERACTION OF ABCs WITH BLyS: IMPLICATIONS FOR B CELL HOMEOSTASIS

Regardless of exact origin, determining how the continuously enlarging ABC subset impacts homeostasis of other B cell subsets is key to understanding their overall impact. Given the central role of BLyS in determining the set point for primary B cell numbers, it is striking that despite similar BLyS receptor levels and BLyS binding capacity, ABCs do not depend upon BLyS for survival. This is evidenced by their robust survival and lack of BLyS dependence compared to FO and MZ B cells *in vitro*, as well as their persistence following *in vivo* BLyS blockade [15]. Thus, the molecular basis for BLyS-independent ABC survival, as well as how their consumption of BLyS impacts the selection and dynamics of BLyS dependent pre-immune pools, demands further exploration.

BLyS signaling through BR3 provides survival signals through non-canonical NF-κB activation and "crosstalk" with multiple downstream elements of tonic BCR signaling [93-95], yielding survival through upregulation of anti-apoptotic members of the Bcl-2 family [72] and metabolic mediators [96]. Thus the BLyS independence of ABCs may reflect a myriad of factors, including altered BR3 or BCR signals, compensatory signaling and crosstalk from TLRs, or other, as yet unknown stimuli that mimic these pathways. One clue to this puzzle may be the observation that BCR ligation acts synergistically with TLR9 signals in ABC activation, whereas BCR stimulation alone has no effect on ABCs [15]. This implies that BCR signaling is fundamentally different in ABCs, inasmuch as it can deliver or modify signals in the context of TLR driven downstream elements, but mediates neither the proliferation- nor death-inducing events associated with BCR ligation in FO and MZ cells.

Apart from the molecular mechanisms underlying BLyS independence, this physiological property implies that a profound shift in B cell homeostasis occurs with advancing age: the mature B cell niche is increasingly populated by cells that do not depend on BLyS for survival yet consume BLyS effectively – thus limiting BLyS availability to other mature subsets. The question of whether ABCs show exceptional cellular lifespan, as well as whether they act as "supercompetitors" in the pre-immune B cell niche, remains to be addressed. Indeed, slowed turnover of the overall mature, pre-immune B cell pool has been well-established through *in vivo* labeling studies [87]. Inasmuch as these prior studies analyzed mature splenic B cells in aggregate, it is tempting to speculate that ABCs may contribute disproportionately to these protracted kinetics. Alternatively, because ABCs will increasingly usurp available BLyS, both FO and MZ B cells may themselves be more stringently selected. This would yield a situation in which only the strongest homeostatic competitors, which are longer lived, would remain in the FO and MZ pools. Indeed, the observation that FO B cells from aged mice show improved survival *in vitro* compared to those from young mice is consistent with the notion that only the "most fit" FO B cells persist in the presence of ABCs.

An increased incidence of B-cell clonal expansions accompanies age in both mice and humans. This has led to the suggestion that genetic changes coupled with selection processes underlie the "evolution" of persistent B-cell clonal expansions [28,97]. The establishment of ABCs from chronically stimulated and expanded FO and MZ progenitors would be consistent with this hypothesis, as such alterations might free ABCs from BLyS-tuned selection processes.

DO ABCs INFLUENCE IMMUNE RESPONSIVENESS AND TOLERANCE?

The growing presence of ABCs, coupled with their novel functional attributes, prompts consideration of their contributions to the features of immunosenescence. In general, ABCs could contribute to age-associated declines in humoral responsiveness and propensity for chronic inflammation or autoantibody production either directly, based on their distinct activation requisites; or through *trans* effects mediated

by their proinflammatory and regulatory cytokine production and antigen presentation capacities. There is suggestive evidence for each of these possibilities.

Unlike FO B cells, which respond to BCR ligation and costimulation *in vitro*, ABCs instead respond to TLR9 and/or TLR7 stimuli, particularly in combination with BCR ligation [15,16]. This resistance to classically T-dependent modes of activation, coupled with a reliance on TLR stimulation, might limit the quality of ABC responses to the short-lived extrafollicular effectors characteristic of T-independent antigens. Moreover, TLRs are commonly associated with skewing towards inflammatory responses [98]. Thus, steadily increasing numbers of ABCs may yield more prominent innate-like immune responses, characterized by low affinity antibody and inflammatory processes, instead of GC initiation, affinity maturation, and memory B cell differentiation.

In addition to such direct effects on humoral responses, ABCs likely exert *trans* effects through their secretion of regulatory and inflammatory cytokines, as well as their antigen presentation abilities. Following *in vitro* stimulation, ABCs produce regulatory cytokines, such as IL-10 [15], that have been shown to inhibit adaptive immunity [99]. Moreover, they also secrete inflammatory cytokines that can further alter response quality. Interestingly, ABCs preferentially skew activated CD4+ T cells to a Th17 fate compared to presentation mediated by young FO B cells, aged FO B cells, or dendritic cells [15]. Thus, during initial antigen encounter, ABCs may foster Th17 differentiation at the expense of T follicular helper generation, again thwarting GC formation, affinity maturation, and memory cell formation.

These properties are equally relevant to the potential role for ABCs in autoimmunity. Thus, TLR7 and TLR9 are well-established factors in autoantibody secretion and autoimmune disease development [100,101]. Indeed, following TLR7 activation *in vitro*, ABCs produce anti-chromatin antibody, directly implicating ABCs in the increased autoantibody titers observed in aged mice [16]. Similarly, Th17 cells secrete a range of cytokines that exacerbate inflammatory/autoimmune diseases [102,103]. Thus, ABC-mediated antigen presentation may contribute to a broader susceptibility background in aged individuals that includes elevated proinflammatory cytokines and shifts in T cell-associated immune responses [14,18,19,102,104]. Together, these attributes suggest that frank humoral autoimmune disease, which often emerges in young or middle aged adults, might be associated with premature accretion of ABC. The early accumulation of ABCs observed by Rubtsov *et al.* in autoimmune prone mice, as well as in middle-aged RA and scleroderma patients, is consistent with this possibility[16].

ARE ABCs TARGETS FOR INTERVENTION?

It is tempting to speculate that approaches either targeting ABCs per se, or leveraging their functional characteristics to advantage, might be useful in either rejuvenating immune responses or changing the course of inflammatory or autoimmune diseases. For example, vaccine efficacy might be improved through the design of antigen/adjuvant systems that stimulate both the TLR and BCR receptors of ABCs. If ABCs promote Th17 responses in aged individuals, then ablating ABCs might help to reduce the likelihood or progression of inflammatory/autoimmune disorders. While these are tantalizing conjectures, a deeper understanding of the origins, attributes, and functional consequences of ABCs is clearly required before specific targets can be identified or evaluated.

SUMMARY

B cell generation, subset composition, diversity, and function are altered with age. A previously unappreciated mature B cell subset that accumulates with age has recently been identified. Cells of this age-associated B cell (ABC) subset are phenotypically distinct from other mature subsets, and appear to favor innate, inflammatory immune responses. The accumulation of the ABC subset may bias the immune system toward increased propensity for inflammatory or autoimmune responses, and/or impaired "classical" responses that generate robust plasma cell production and memory. Important aspects of the ABC subset that await further investigation include the identification of progenitors, requisites for persistence, and possible alterations in BCR- and TLR-mediated signaling, as well as a determination of their precise role in autoimmunity. Finally, while it is tempting to speculate that ABC-targeted approaches might improve some aspects of immunosenescence, further understanding of their origins and functional attributes is required before such possibilities can be critically evaluated.

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CONFLICT OF INTEREST

None declared.

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