B Cell Repertoire Changes in Mouse Models of Aging

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Abstract

Changes in the antibody repertoire are a well-established feature of immunosenescence. These reflect an aggregate of age-associated alterations in the generation, numbers, and proportions of B cell subsets, as well as the homeostatic and

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selective processes governing them. A basic understanding of these relationships, coupled with integrated assessments of how they change with age, should reveal mechanisms underlying the immunosenescent phenotype. Mouse models provide powerful tools for these analyses, allowing controlled manipulation of key genetic, cellular, and microenvironmental factors. Here we summarize current understanding of how primary and antigen-experienced murine B cell repertoires are established, as well as how they shift with age.

Keywords
Age-associated B cells · Homeostasis · Repertoire · B lymphopoiesis

Introduction

Immunosenescence, the progressive dysregulation of immune function with age, reflects a mosaic of genetic, epigenetic, and microenvironmental changes (Aspinall and Andrew 2000; Aw et al. 2007; Franceschi et al. 1998; Ginaldi et al. 2001; Gruver et al. 2007; Malaguarnera et al. 2001; Mishto et al. 2003; Mocchegiani and Malavolta 2004; Pawelec 2003; Pawelec et al. 1999, 2006; Stout and Suttles 2005). This complexity confounds minimal explanations of the overall phenomenon and underscores the need to exploit systems whereby defined factors can be deliberately manipulated. Accordingly, mouse model systems, which have been refined as immunologic experimental tools, have yielded significant insights into the underlying mechanistic relationships.

Altered clonotype repertoires are a consistent feature of immunosenescence. This is anecdotally evident from the shifts in immune responsiveness, increased autoimmunity, and clonal expansions that accompany age and is corroborated through empirical evidence in human and animal models. For example, both the frequency and clonotypic composition of hapten- and virus-specific primary B cells change with age (Lu and Cerny 2002; Nicoletti et al. 1991, 1993, Nicoletti and Cerny 1991; Riley et al. 1989; Zharhary and Klinman 1983, 1986a, b); and nearly all laboratory mouse strains display an age-associated appearance of autoantibodies (Eaton-Bassiri et al. 2000; Erikson et al. 1998). Most observations addressing these age-associated repertoire shifts are based on assessments at single time points. While these can *identify* repertoire changes, the underlying mechanisms resist interrogation via such static sampling approaches, because lymphocytes comprise multiple, dynamic populations under stringent selective and homeostatic controls.

Lymphocyte dynamics involve the continuous generation and loss of cells, such that relatively constant numbers are maintained. Thus, the overall stability of lymphocyte numbers disguises underlying and ongoing cellular and molecular processes. For example, commitment rates to the B lineage per se, as well as the entrance rates and lifespan of B cells in different functional subsets, can vary. Further, these compartments not only play differing immunological roles but also can interact with and impact one another's behavior. Finally, selective events based on B cell receptor (BCR) specificity, innate ligand responsiveness, and homeostatic factors

underlie this dynamically changing landscape. Accordingly, effective interrogation of repertoire changes – including those associated with advancing age – requires simultaneous, longitudinal assessments of lymphocyte generation, homeostasis, and selection.

The size, proportions, and dynamics of nearly all progenitor and mature B lineage subsets shift with age in the mouse, so overall changes in clonotype frequency and composition likely reflect the aggregate of these shifts. Understanding age-associated repertoire changes therefore requires an appreciation of the molecular and cellular mechanisms governing primary and antigen-experienced repertoires. Herein, we review currently accepted notions about the identity and relationships of B lineage subsets and their progenitors, emphasizing the selective and homeostatic processes impacting repertoire composition. With this as background, age-associated changes in these parameters and their potential relationship to repertoire shifts in primary and antigen-experienced B cell subsets are discussed. A schematic summary of these overall changes is provided in Fig. 1.

Primary Repertoire Development

Lineage Commitment and Developing Bone Marrow B Cell Subsets

In adults, B cells are generated in the bone marrow (BM), where pluripotent hematopoietic stem cells (HSCs) give rise to multipotent progenitor (MPPs) that initiate lymphoid-restricted gene expression. This yields common lymphoid progenitors (CLPs) (Kee and Paige 1995), a population enriched for B lineage-specified precursors that subsequently become committed to the B lineage (Allman and Miller 2003). Several microRNAs (miRNAs), epigenetic modifiers, transcription factors, and cytokine receptors comprise a regulatory network for B lineage specification and commitment (Busslinger 2004; Kee et al. 2000; Medina and Singh 2005; Morrison et al. 1998; Nutt et al. 1999; Singh and Pongubala 2006) (also see Frasca et al., this volume). For example, Ikaros is expressed in all hematopoietic lineages and controls the emergence of lymphoid progenitors (Koipally et al. 1999; Ng et al. 2007); the proto-oncogene PU.1 is critical for both myeloid and lymphoid differentiation (Singh et al. 1999); and the transcriptional repressor Bcl11A is essential for normal B and T cell development (Liu et al. 2003). The E protein family members E2A and EBF coordinately activate the expression of B cell-specific genes, especially those governing pre-BCR production and function (Kee and Murre 1998; Kee et al. 2000; O'Riordan and Grosschedl 1999; Singh et al. 2005), and also regulate Pax-5 (Schebesta et al. 2002), a key mediator that activates B lineage-specific genes and represses genes associated with other lineages (Busslinger 2004; Busslinger and Urbanek 1995). IL-7/IL-7R is a key cytokine axis for early B lineage development, promoting both survival and differentiation (Allman and Miller 2003). Complex interplay between cell intrinsic and extrinsic signals characterizes the regulation of these transcriptional systems (DeKoter et al. 2002; Medina and Singh 2005; Singh et al. 2005).

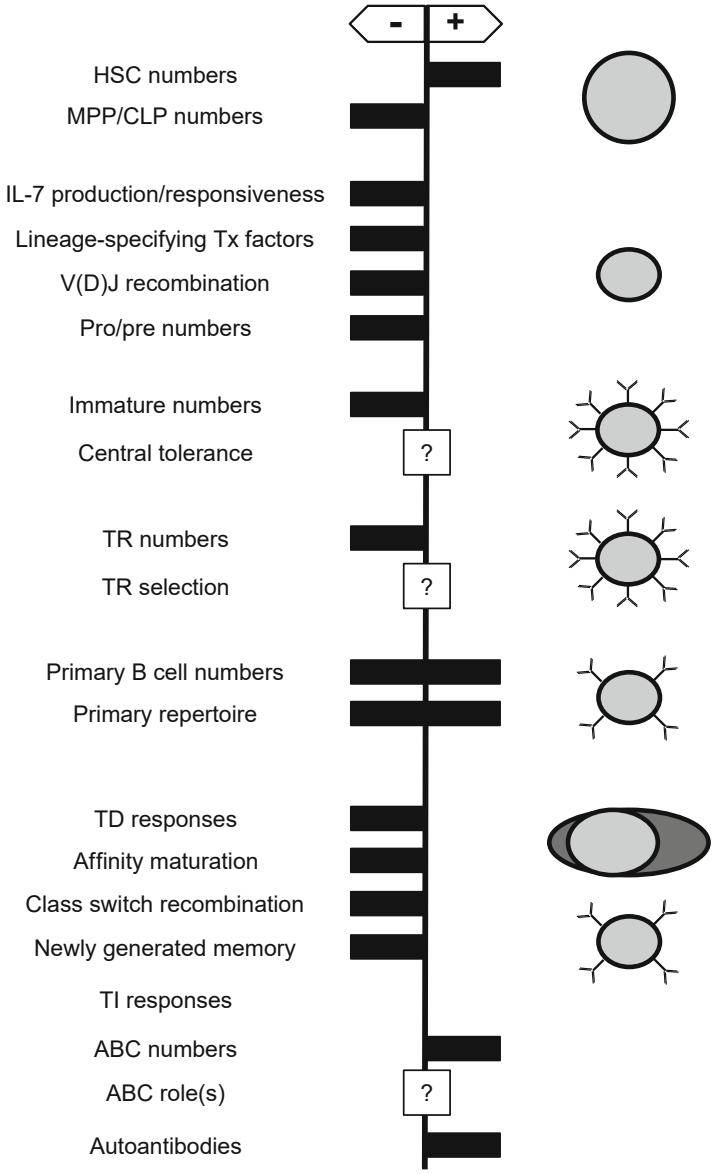

Fig. 1 Changes in B cell traits with age. Major B cell subsets are shown to the right with characteristic traits and/or processes to the left. Bars indicate changes in aged mice compared to young adults. Bars left of center denote age-associated reductions, while bars right of center indicate age-associated increases. Disparate or mixed results are indicated as bidirectional bars, and currently unexplored characteristics are signified by a central question mark

An emerging area of interest involves the interaction between transcription factors and miRNAs in the regulation of B lymphocyte development and differentiation (de Yebenes et al. 2013). One example involves the miRNA cluster mirn23a,

which acts at the MPP stage – possibly together with PU.1 – to enhance myelopoiesis at the expense of B lymphopoiesis (Kurkewich et al. 2016).

Although these transcriptional and signaling events occur prior to antigen receptor gene rearrangement, they can nonetheless influence repertoire composition in several ways. First, they dictate the rate of lineage commitment, thus impacting B cell production rates and shifting downstream homeostatic demands. Second, they will influence the rate and specificity of key intracellular events, thus coloring the likelihood and nature of heavy and light chain gene rearrangements.

Subsequent to lineage commitment, B cell differentiative stages are characterized according to surface markers and Ig gene rearrangement status (Hardy et al. 1991; Hardy and Hayakawa 1991, 2001; Melchers et al. 1989; Osmond 1990; Osmond and Park 1987; Rolnik and Melchers 1991). In the pro-B stage, cells rearrange their Ig heavy chain genes (Fuxa et al. 2004; Zhang et al. 2006). This is followed by surface Ig heavy chain expression with surrogate light chain and BCR signaling molecules, delineating onset of the pre-B cell stage. Surface pre-BCR expression and signaling are required for transit from the pro- to pre-B cell stage (Jumaa et al. 1999; Melchers 1997; Melchers et al. 1994; Osmond et al. 1998; Reth 1991; Reth et al. 1987; Tsubata and Reth 1990; Tsubata et al. 1992) and result in a proliferative burst characteristic of the large pre-B cell compartment. Light chain gene rearrangement during the late pre-B cell stage leads to the expression of a complete BCR, defining the immature (IMM) bone marrow B cell. Once in the IMM subset, cells either die or exit the bone marrow to complete maturation (Allman et al. 1992, 1993).

Peripheral Maturation and Pre-immune B Cell Subsets

Recent marrow émigrés are termed transitional (TR) B cells (Loder et al. 1999) and can be further divided into subsets termed T1, T2, and T3 (Allman et al. 2001). While historically viewed as a linear progression from the IMM marrow stage through the successive TR compartments, it now appears that branched, asynchronous models for transit into and through these subsets are more likely (Allman et al. 2004; Mehr et al. 2003; Shahaf et al. 2004; Srivastava et al. 2005). Cells that successfully complete TR differentiation enter the mature peripheral B cell pools.

Mature follicular (FO) B cells, a subset of the so-called B2 lineage, encompass the majority (>80%) of peripheral B lymphocytes in the circulation, lymph nodes, and spleen and are the progenitors of both primary antibody-forming cells and memory B cells. The FO B cell subset has a diverse BCR repertoire arising from Ig gene combinatorial diversity and functions primarily in immune surveillance and responses to T cell-dependent (TD) antigens. Additional subsets of mature B2 lineage B cells include marginal zone (MZ) B cells, which are phenotypically, functionally, and anatomically distinct from FO B cells and play a major role in responses to T cell-independent (TI) antigens. In peritoneal and pleural cavities, the B1 lineage predominates (reviewed in Hayakawa and Hardy 2000). B1 B cells appear first in ontogeny and are, at least in part, maintained by self-renewal (Hardy and Hayakawa 2001; Hardy et al. 1984; Hayakawa et al. 1997). The MZ and B1 subsets have restricted BCR repertoires and share several functional attributes, particularly

participation in TI immune responses (Kearney 2005; Lopes-Carvalho et al. 2005; Lopes-Carvalho and Kearney 2004; Martin and Kearney 2002). The derivation of B1 B cells, though distinct from the other B cell subsets, is not yet entirely clear (Allman et al. 2001; Berland and Wortis 2002; Hayakawa and Hardy 2000; Hayakawa et al. 2000; Lopes-Carvalho et al. 2005; Montecino-Rodriguez and Dorshkind 2006; Wortis and Berland 2001). However, in the context of age-associated repertoire shifts, it is noteworthy that while production from BM B2 progenitors predominates in young adults, this wanes in aged mice. Therefore, if B1 progenitors are stable and distinct from B2 progenitors, the B1 lineage may wax with advancing age, thus altering the combined B cell repertoire (Baumgarth 2016; Holodick and Rothstein 2015; Montecino-Rodriguez and Dorshkind 2006; Montecino-Rodriguez et al. 2006).

Selection and Homeostasis Among Emerging and Primary B Cells

Although they occur before complete BCR expression and perforce cannot be specificity-driven, heavy and light chain gene rearrangement processes, as well as heavy chain selection at the pre-BCR stage, will influence the incipient B cell repertoire. For example, only heavy chains with structural characteristics affording surrogate light chain pairing are selected for further differentiation (Martin et al. 2003; Melchers et al. 2000). In addition, heavy and light chain gene rearrangement processes rely on multiple factors, including the expression of appropriate enzyme and targeting complexes, accessibility and marking of heavy and light chain loci, and the activity of DNA damage resistance and repair systems (for reviews, see Feeney et al. 2004; Johnson et al. 2003; Jung et al. 2006; Mostoslavsky et al. 2003; Murre 2005; Schatz et al. 1992; Schlissel 2003, 2004; Schlissel and Stanhope-Baker 1997).

The interaction of homeostasis and selection powerfully impacts all B cell subsets subsequent to BCR expression, directly determining repertoire composition. A critical notion emerging from appreciation of this interplay is that events acting upstream of mature B lymphocyte pools can impact downstream populations. Since advancing age is accompanied by substantial shifts in both B cell generation and the success rate of IMM and TR differentiation, distinguishing primary lesions from homeostatic compensation is critical to a mechanistic understanding of age-related changes (Cancro 2005; Miller and Cancro 2007; Quinn et al. 2005).

Stringent specificity-based selection occurs at the IMM stage, where high-avidity interactions yield secondary Ig gene rearrangements or death (Casellas et al. 2001; Chen et al. 1995; Gay et al. 1993; Nemazee et al. 1991; Nemazee and Weigert 2000; Nossal and Pike 1975; Nossal 1983; Pelanda et al. 1997; Prak et al. 1994; Prak and Weigert 1995; Tiegs et al. 1993). These central tolerance mechanisms result in the loss of ~90% of all IMM cells formed (Allman et al. 1993; Osmond 1991). While it is possible that the IMM pool is governed by homeostatic mechanisms to preserve its size, this remains speculative and does not seem tied to BCR-mediated negative selection. Instead, BCR signal strength is the major, if not sole, determinant of survival at the IMM stage.

Specificity-based selection continues to act on newly formed cells that exit the marrow to join TR pools. Whereas high-avidity BCR interactions lead to cell death, a lack of minimal BCR signaling precludes maturation and entrance to mature peripheral pools (Cancro and Kearney 2004; Clarke and McCray 1993; Forsdyke 2005; Hayakawa et al. 1999; Martin and Kearney 2000; Wang and Clarke 2004). While BM-negative selection depends on BCR signal strength (and is therefore cell intrinsic), the likelihood that a given cell completes TR differentiation to join a mature B cell subset is based on both BCR signal strength and the availability of B lymphocyte stimulator (BLyS, also termed BAFF). BLyS is the limiting resource for which TR, FO, and MZ B cells compete (reviewed in Cancro 2004; Miller et al. 2006). Through this competitive mechanism, steady-state numbers of mature B cells are governed by ambient BLyS levels that vary the proportion of TR cells completing maturation, as well as the lifespan of FO and MZ B cells (Harless et al. 2001; Hsu et al. 2002). This connection between BCR specificity and fitness for interclonal competition indicates that BLyS availability, within the context of the emerging clonotypic cohort, will determine thresholds for TR selection. This relationship has recently been confirmed in several transgenic systems (Hondowicz et al. 2007; Lesley et al. 2004; Thien et al. 2004).

The relationship between BLyS availability, antigen receptor specificity/signal strength, and TR selective stringency makes several implications relevant to age-associated changes in the primary repertoire. First it implies that BCR- and BLyS-mediated signals must be integrated, likely via cross talk between intracellular signaling systems and transcriptional regulators such as PI3 kinase and NF-kB (Stadanlick and Cancro 2006; Stadanlick et al. 2008). Although the molecular details remain the subject of intense research, age-associated perturbations of any of these systems may influence primary repertoire diversity. Moreover, decreased B cell generation rates in BM – a feature of the aging immune system – might permit a broader array of clonotypes, including autoreactive cells, to enter peripheral pools as competition wanes (Miller et al. 2006).

Antigen-Experienced Pools

Establishing and Maintaining Antigen-Experienced Subsets

Antigen-experienced subsets contain the descendants of primary B cells recruited into immune responses and thus include activated cells themselves, as well as the resulting effector and memory pools. Humoral immune responses are generally characterized as T-dependent (TD) or T-independent (TI), depending on their requirement for cognate T cell help. In general, proteins engender TD responses, reflecting the requisite for MHC class II-restricted antigen presentation that affords delivery of costimulation. These responses primarily involve FO B cells and typically lead to long-term humoral immunity. A key characteristic of TD responses is the formation of germinal centers (GCs), where proliferating B cells undergo class-switch recombination, as well as the somatic hypermutation and affinity-based selection processes

that culminate in cells producing high-affinity antibody (McHeyzer-Williams et al. 2001). In contrast, TI responses do not require cognate help, although T cell-derived cytokines may promote limited isotype switching (Borisova 2006). TI responses elicit little if any memory, lack substantial hypermutation or affinity maturation, and consist predominantly of IgM. Two classes of TI antigens exist: TI-1 responses are induced via pattern recognition receptors such as Toll-like receptors (TLRs) (Shih et al. 2002), and TI-2 responses are generated by antigens with densely repeating epitopes. Both TI-1 and TI-2 responses preferentially arise from B1 and MZ B cells (Martin et al. 2001). Whether this reflects intrinsic bias in the pre-immune repertoires of these cells or more extensive expression of pattern recognition receptors (Hsu et al. 2006; Martin et al. 2001) – both of which are empirically observed – remains debated.

Antigen activation yields a series of short-lived cells, which are detectable for only days or weeks following antigen challenge, as well as several subsets of long-lived cells, which persist for months or years (Bortnick and Allman 2013; Manz et al. 1997; Schittek and Rajewsky 1990; Treml et al. 2006). During TD responses, antigen-activated B cells become either GC B cells or short-lived plasma cells (PC), in a differentiation decision dictated by BCR affinity (Paus et al. 2006). Short-lived PC arise in the first few days of an immune response, congregating at the T/B cell interface and extrafollicular regions of secondary lymphoid organs (McHeyzer-Williams et al. 2001). The critical relationship between BCR repertoire and recruitment into long-lived pools has been revealed using transgenic systems (Dal Porto et al. 1998, 2002). For example, B cells with low initial affinity for antigen can participate in GC reactions when higher affinity competition is eliminated, suggesting that initial repertoire can shape the pool of antigen-reactive B cells that ultimately succeed and contribute to immune responses. Long-lived antigen-experienced populations include a group of long-lived PC, as well as a separate group termed memory B cells, both of which reside primarily in the bone marrow (Manz and Radbruch 2002; McHeyzer-Williams and McHeyzer-Williams 2005). The delineation of these groups based on surface markers is debated; however, a clear functional difference is that long-lived PC secrete antibody, while memory B cells do not (Arce et al. 2004; Driver et al. 2001; Manz et al. 2002; McHeyzer-Williams and McHeyzer-Williams 2005; McHeyzer-Williams et al. 1991, 1993, 2000). The lineal relationships between various antigen-experienced subsets are unclear. For example, whether long-lived populations are generated from cells within the generally short-lived populations, and/or differentiate from distinct progenitors through a separate selective mechanism, is debated.

A novel B cell subset termed age-associated B cells (ABCs) was first reported by the Cancro and Marrack groups in 2011 (Hao et al. 2011; Rubtsov et al. 2011). Although various phenotyping schemes have been applied to detect ABCs, a uniformly applied distinguishing feature is expression of the transcription factor T-bet. ABCs accumulate steadily with age in various tissues including the spleen and are variably found in the blood. Interestingly, ABCs seem to accumulate more rapidly in females and become detectable much earlier in mouse models of humoral autoimmunity. Irradiation-reconstitution experiments initially indicated that ABCs are not naïve cells generated by aged bone marrow, but instead result from extensively

divided FO B cells, suggesting that they represent antigen-experienced cells that gradually accumulate as a function of lifelong antigenic experiences (Hao et al. 2011). This notion is supported by recent reports showing that they appear and persist in influenza infection (Naradikian et al. 2016b) and that they are somatically mutated and require cognate help for their formation (Russell Knode et al. 2017). Further clues as to ABC origin suggest that they arise in B cell responses to antigens that contain TLR ligands and engender particular T cell cytokine polarization, notably IFN-gamma and IL21 (Naradikian et al. 2016a, b). Together, these observations indicate ABCs are a memory B cell subset specific for intracellular pathogens and/or endogenous microbiota; they may accumulate as a consequence of chronic infection or as the result of ongoing responses to nucleic acid-containing self-antigens in an autoimmune context (Naradikian et al. 2016a; Rubtsova et al. 2015).

Homeostasis in Antigen-Experienced Subsets

The concept of a biological niche for naïve B cells is well established, with the BLyS/BR3 ligand/receptor axis playing a central role. In contrast, knowledge of factors governing the size and composition of antigen-experienced B cell subsets is more limited. As with naïve pools, interplay between homeostasis and selection seems likely in the establishment and maintenance of antigen-experienced subsets. Multiple steps in the generation of effector and memory B cells rely on selective decisions. These include the relationship between BCR affinity and recruitment into the extrafollicular PC pool versus the GC (Paus et al. 2006), affinity maturation per se, as well as commitment to long-lived PC versus memory B cells (Angelin-Duclos et al. 2000; Fairfax et al. 2007) and the timing of GC exit (Weisel et al. 2016).

Homeostatic controls, while evident in antigen-experienced pools, also remain poorly understood. While neither short-term effectors nor long-lived antigen-experienced populations compete with primary B cells for survival, the trophic factors and relationships are only now being explored. Recent evidence suggests that additional BLyS family receptors or ligands, such as TACI, BCMA, and APRIL, likely play a role (Goenka et al. 2014b; Oropallo et al. 2011). In support of this idea, TACI is associated with activated B cells and regulates some TI immune responses (Treml et al. 2006; von Bulow et al. 2001), whereas BCMA is required for survival of long-lived PC in BM, possibly mediated through APRIL elaborated by stromal cells (Belnoue et al. 2008; Huard et al. 2008; O'Connor et al. 2004). TACI expressed on FO B cells partitions BLyS outside the GC, while BLyS produced by T follicular helper cells is required for correct affinity maturation (Goenka et al. 2014a). Further, ongoing immune responses appear to create temporary homeostatic niches for short-lived populations while leading to little change in long-term protective memory pools (Radbruch et al. 2006). Long-lived bone marrow PC survival is competitive (Manz and Radbruch 2002; Manz et al. 1997, 2002), possibly involving cell extrinsic stromal factors as well as FcγRIIb expression (Xiang et al. 2007). While antigen re-exposure is presumably key, the molecular and cellular bases for the remarkable maintenance and durability of some humoral responses remain elusive.

For example, long-lived bone marrow PC are resistant to radiation and other agents that disrupt lymphocyte activation or proliferation; and antibody responses to certain viral infections or vaccine regimens in humans have half-lives estimated at 50 to thousands of years, although the frequency of circulating memory B cells may or may not correlate with serum antibody titer (Amanna et al. 2007).

Age-Associated Changes in Progenitor and Primary Pools

An extensive literature demonstrates that the primary repertoire shifts with age. For example, the phosphorylcholine-specific repertoire shifts from one predominated by the T15 clonotype to a more diverse pool (Nicoletti and Cerny 1991; Nicoletti et al. 1993; Riley et al. 1989; Zharhary and Klinman 1986b). On the other hand, overall diversity in the primary pool is not altered extensively, as assessed by fine specificity analyses (Nicoletti and Cerny 1991; Zharhary and Klinman 1984). Nonetheless, it is well established that subset representation in central and peripheral lymphoid organs shifts with age; and clonal expansions in both the B and T cell pools suggest that some specificities can be inordinately expanded. Understanding the basis for these changes requires considering all events likely to impact repertoire generation, selection, and maintenance. These include changes in the size and behavior of generative pools, as well as changes in the primary pools themselves.

B Cell Generative Rate and Subsets Change with Age

Age-associated changes in B lineage development include reductions in precursor frequencies, lowered expression of critical regulatory genes, diminished pro- and pre-B cell numbers, and dampened responsiveness to differentiation cues (Frasca et al. 2003, 2004b; Johnson et al. 2002; Labrie et al. 2004; Miller and Allman 2003; Riley et al. 1989; Sherwood et al. 1998; Stephan et al. 1996, 1998; Van der Put et al. 2004). Together, these observations indicate overall diminution of B cell generation and throughput.

The impact of aging is first manifested in HSCs and CLPs. Somewhat paradoxically, while HSC numbers are maintained and possibly expanded in aged mice (Zediak et al. 2007), the MPP/ELP and CLP pools are reduced (Allman and Miller 2005a; Miller and Allman 2003, 2005). Although the basis for this remains unclear, correlations with age-associated reductions in stromal IL-7 production (Stephan et al. 1998), as well as reduced expression of E2A and EBF and genes they control, may contribute (Frasca et al. 2003, 2004b; Sherwood et al. 2000; Van der Put et al. 2003, 2004). As might be expected from these changes in upstream pools, pro-B cell numbers are reduced, with an even greater proportional reduction in pre-B cell numbers (Allman and Miller 2005b; Quinn et al. 2005; Riley et al. 1991). This decline in part reflects reduced IL-7-mediated proliferation at the pro- to pre-B cell

transition (Monroe and Allman 2004; Stephan et al. 1997). Hormonal changes may be another important extrinsic factor, since pregnancies delay the age-associated reduction in BM B cell production (Barrat et al. 1999).

The dynamics of developing B cells also change with age. In vivo BrdU labeling studies (Johnson et al. 2002; Kline et al. 1999; Labrie et al. 2004) showed reductions in successful pro- to pre-B cell transit, yielding a fourfold drop in pre-B cell numbers and a corresponding decrease in the IMM B cell generation rate. However, the throughput of pre-B cells increased, so a twofold greater proportion of pre-B cells enter the IMM pool. In addition, residency within the IMM pool is longer. Together, these apparent compensatory features result in an IMM pool that is only about twofold smaller than in young adults.

Dynamics and Proportions of Peripheral Subsets Change with Age

Reflecting the upstream reductions in IMM B cell numbers, TR pools are reduced in throughput and size; however, because residency time is extended, TR cell numbers are not significantly reduced. Similarly, the FO pool's turnover rate is reduced in aged mice (Johnson et al. 2002; Kline et al. 1999; Quinn et al. 2005), so FO pool size is maintained in the face of reduced marrow production. Despite this fairly stable overall size, B cell clonal expansions are more prevalent in aged mice (Ben-Yehuda et al. 1998; Weksler 2000; Weksler and Szabo 2000). In contrast, the MZ and B1 pools are unaffected or even enlarged in aged mice, but this may vary by strain (Allman and Miller 2005b; Quinn et al. 2005; Weksler 2000).

Whether the homeostatic mechanisms controlling primary B cell numbers change with age has not been extensively interrogated, but ABCs have provided key clues, as there is recent evidence that they have a profound effect on B cell generation and homeostasis in aged mice (Ratliff et al. 2013). By 18–22 months of age, ABCs comprise a significant proportion of the peripheral B cell pool and continue to accumulate in murine bone marrow and spleen – at the expense of follicular-like (bone marrow) and splenic follicular B cells – to 27–29 months. Furthermore, TNF-alpha secretion by ABCs contributes to an inflammatory bone marrow environment, which in turn leads to a reduction in B lymphopoiesis. In earlier studies (Keren et al. 2011a, b), B cell depletion in aged (20–24 months) mice restored B lymphopoiesis and led to shifts in the peripheral B cell repertoire, further supporting the notion of a feedback mechanism that regulates lymphopoiesis (Osmond et al. 1981). ABCs express BR3 and bind BLyS, but do not appear to require it for persistence (Hao et al. 2011), suggesting they may occupy a separate niche and no longer compete for space with the more numerous (in youth) mature naïve pools.

There is additional evidence that homeostatic mechanisms shift with age. For example, in young adults, emerging cells expressing high levels of the BLyS receptor, TACI, are selected during TR differentiation. This process is dampened in aged mice, allowing cells with lower TACI levels to join the mature FO pool

(Quinn et al. 2005). In addition, FO B cells from aged mice more effectively capture BLyS-mediated survival signals in vitro, although the underlying mechanism is unclear. These observations suggest a model whereby selection at the marrow-periphery interface is relaxed in aged mice; yet competition among mature follicular or marginal zone B cells may be more severe, reflecting lifelong selection for optimally fit clonotypes (Cancro et al. 1998; Quinn et al. 2005).

Developing and Primary Repertoires Change with Age

Alterations in the BM preselection repertoire might be expected, given the numerous age-associated changes in cytokine and transcription factors, many of which are involved in Ig gene rearrangement (Frasca et al. 2004b; Labrie et al. 2004; Sherwood et al. 1998, 2000; Stephan et al. 1998). There is a correlation between the age-associated reduction of pre-B cell numbers and reduced RAG gene expression, V(D)J recombinase activity, and V to (D)J rearrangement (Labrie et al. 2004; Szabo et al. 1999, 2003). Evidence for age-associated, intrinsic shifts in V gene segment use are suggested by studies showing an increased frequency of phosphorylcholine-responsive cells arising from sIg^- BM cells in aged BALB/c mice (Zharhary and Klinman 1986b). These increases included clonotypes bearing VhS107 (T15) as well as other Vh segments.

The interplay of intrinsic and microenvironmental changes in aged BM could affect the preselection repertoire in several ways. Shifts in heavy chain allele choice at the pre-BCR stage or in light chain choice at the pre-B stage could alter repertoire composition. Decreased pre-B cell production may mean that fewer B cells of different clonotypes are generated. However, this effect may be at least partially offset if extended residency time in the IMM stage affords greater opportunity for receptor editing or Vh gene replacement. Finally, the existence of multiple B differentiation lineages whose Vh gene preferences differ and whose dominance varies with age might underlie some of these observations.

There is ample evidence for age-associated shifts in the primary repertoire, but whether these act to generally expand or contract diversity is uncertain. The phosphorylcholine-specific response in young BALB/c and B6 mice is dominated by VhS107/VK22 gene segments, whereas aged mice use a broader range of Vh and VK segments (Nicoletti et al. 1991; Nicoletti and Cerny 1991). Moreover, phosphorylcholine-binding monoclonal antibodies generated from aged mice show greater polyreactivity. In contrast, while the frequency of NP-responsive cells is about twofold lower in aged mice, there is no accompanying change in repertoire diversity or clonotype distribution (Zharhary and Klinman 1986a); and repertoire diversity to influenza hemagglutinin is similar in aged and young mice (Zharhary and Klinman 1984). Finally, the autoreconstituting repertoire that emerges after irradiation – or drug-induced lymphopenia – is truncated in aged mice, when assessed by CDR3 length heterogeneity (Li et al. 2001).

Immune Responses and Antigen-Experienced Pools Change with Age

Some age-related changes in immune responses may be related to shifts in the preselection or primary repertoires, while others may be the result of alterations that are observed as or after responding cells have encountered antigen. Immune responses in aged mice sometimes – but not always – involve reduced antibody production and/or antibody of lower affinity in comparison to young mice; however, overall diversity of the responding repertoire is retained or enhanced. Consistent with these observations, ABCs from 22-month-old mice have a heterogeneous repertoire that is comparable to the repertoire of FO B cells from the same animals, yet ABCs display significant somatic hypermutation (Russell Knode et al. 2017). Short-lived PC responses and pools are normal to increase in aged individuals, whereas long-lived PC and memory cell numbers are reduced. All of this suggests that the antigen-experienced repertoire is different in quality and possibly quantity in aged mice.

Extensive age-associated changes have been reported in TD immune responses. These include impaired GC formation and kinetics, defective cellular interactions, and deficiencies in somatic hypermutation (SHM) and affinity maturation (reviewed in Zheng et al. 1997). The antibody response to NP-CGG in aged B6 mice is impaired in terms of primary response kinetics and the amount of antibody produced; moreover, the average affinity of NP-binding antibodies is about sixfold lower than in young mice (Miller and Kelsoe 1995). Although GCs form in aged mice, their number and size are significantly reduced, their kinetics are delayed, and there is little or no somatic hypermutation. In apparent contrast, some experimental systems suggest that somatic hypermutation yields increased diversity of serum Igs in aged mice (Williams et al. 2000). These different results are not necessarily contradictory, as SHM may occur even when B cells are activated outside of GCs (Weller et al. 2004; William et al. 2002). Microenvironment may play an important role: Peyer's patch GC B cells from aged B6D2F1 mice were similar in frequency and activation phenotype to those observed in young mice yet showed higher somatic mutation frequencies (Rogerson et al. 2003).

Cellular interactions are also altered with age (Goidl et al. 1976; Song et al. 1997; Yang et al. 1996). T cell intrinsic changes may account for some of this; for example, a decrease in IL-2 production with age leads to reduced CD40L expression as well as a general CD4+ T cell population shift away from the naïve phenotype and toward either a memory or a regulatory phenotype (Haynes et al. 2002). Another example involves the impairment of antigen-specific, fully mature T follicular helper cell differentiation in aged mice, contributing to the reduced antibody production observed in flu infection (Lefebvre et al. 2016). The proportion of antigen-responsive B cells to DNP-specific stimulation is decreased in aged mice, and T cells from aged mice can downregulate B cell responsiveness (Zharhary 1986; Zharhary and Klinman 1983). In an Igh^b *scid* chimera system with donor lymphocytes from

young or aged mice, where the primary response to NP is highly restricted to the use of Vh186.2/lambda-1 gene segments, aged donor helper T cells – but not aged B cells – are less effective at inducing GC formation and shift Vh gene segment use away from Vh186.2 to include higher proportions of others, particularly C1H4 (Yang et al. 1996). In addition, somatic hypermutation in GC B cells was reduced in frequency with aged donor T or B cells. Thus, both germline repertoire use and SHM are likely altered in aged mice; and immunosenescence likely results from changes in both B and T cell compartments.

Class-switch recombination also appears impaired in aged mice (Frasca et al. 2004a, 2005, 2007). B cells from old BALB/c mice stimulated in vitro with optimal levels of CD40L and IL-4 display a reduced ability to isotype switch (Frasca et al. 2007). Defects in isotype switching as well as SHM are associated with an age-related downregulation of E47, which leads to reduced expression of the activation-induced cytidine deaminase (AID) (Blomberg and Frasca 2013; Frasca et al. 2005).

Mirroring the spectrum of observations in primary repertoire analyses, whether age impacts the magnitude or diversity of antibody responses, varies, depending on the model antigen employed as well as the strain of mice studied. For example, the magnitude of the antibody response to *S. pneumoniae* vaccine and TNP-BA differs in B6 and BALB/c mice, indicating a role for genetic factors in the immune response (Nicoletti and Cerny 1991). However, the clonotypic diversity of the response to both antigens and to phosphorylcholine is greater in aged mice of both strains (Nicoletti et al. 1991; Nicoletti and Cerny 1991). In contrast, both primary and secondary responses to DNP-BGG are reduced in aged mice (Goidl et al. 1976; Weksler et al. 1978). A study of the IgM component of the primary response to TNP-KLH shows that the peak IgM response is delayed in aged mice but the spectrum and affinity of antibodies are similar to those seen in young animals (Zharhary et al. 1977).

Several studies have shown decreased affinity or avidity of antibodies produced by aged mice in TD responses, in some cases along with evidence for a role for altered T cell responses (Doria et al. 1978; Goidl et al. 1976; Nicoletti et al. 1993; Weksler et al. 1978; Zharhary et al. 1977). When mixtures of phosphorylcholine-specific antibodies from young or aged donor mice are injected into recipients that subsequently receive a lethal dose of *S. pneumoniae*, only antibodies from young donors allowed survival (Nicoletti et al. 1993). Moreover, the average affinity of antibodies from aged donors is lower than that of young donors for free PC hapten (Nicoletti et al. 1993). Thus, the efficacy of antibodies produced by aged mice may be quite different from those produced by young mice. In accord with this overall picture, aged mice challenged with NP-CGG show a higher antigen-forming cell (AFC) response than young mice, but smaller and fewer GCs (Han et al. 2003). Most of the AFC in old mice were low-affinity IgM producers, and the number of high-affinity AFC was half that of young controls. There were significantly fewer AFC in BM of aged mice following immunization, and reconstitution experiments demonstrated that aged BM was defective in supporting AFC. Thus, the spleen may prove the primary source of the antibody response in aged mice, in contrast to BM in young

mice. This shift in AFC location could reflect several potential age-related defects in the B cell response including potential BM homing problems, an altered antigen-specific precursor frequency, reduced capacity for AFCs in the bone marrow environment, or a combination of these and other factors. Due to the unclear relationship between naïve B cells and long-lived plasma cell generation, it is difficult to determine whether impaired humoral immunity in the aged mice is due to a failure to generate cells capable of seeding the bone marrow and becoming PC memory or if the defect is downstream. It has been proposed that long-lived PC occupy a highly specialized, tightly regulated niche, and it is possible that this niche is unable to support the entrance of newly formed long-lived PC in old mice, due to intensive competition for survival factors (Radbruch et al. 2006).

Only a few studies have addressed TI responses in aged mice. Zharhary et al. (1977) made a direct comparison of the IgM response following immunization with TD versus TI forms of the TNP hapten. While the peak IgM response was delayed in aged mice for the TD antigen, there was no delay for the TI antigen. Similarly, Weksler et al. (1978) reports that TI responses are generally less impaired than TD responses in aged mice. It is tempting to speculate that because TI responses are largely B cell intrinsic, they will be less severely impacted by age-related changes in T cell function. Moreover, TI responses may be further preserved by the age-associated persistence of MZ and B1 cells (Quinn et al. 2005), which are largely responsible for antibody production to TI antigens. Thus, the comparative resilience of TI responses may increasingly impact repertoire composition with advancing age.

Perhaps the largest age-associated change in BCR repertoire results from the increased prominence of ABCs at the expense of FO B cells. ABCs are key players in the reduced B lymphopoiesis observed in aged mice, acting as pro-inflammatory cells that contribute to an unfavorable bone marrow microenvironment, which in turn may lead to shifts in BCR diversity (Ratliff et al. 2013, 2015; Riley 2013). Based on current evidence, ABCs are antigen-experienced B cells that may arise from both TD and TI responses – in particular, to antigens that engage both the BCR and endosomal nucleic acid sensors, such as viruses and self-antigens (Rubtsov et al. 2011; Rubtsova et al. 2015). It is not yet known whether ABCs participate effectively or at all in adaptive responses to novel pathogens or in recall responses.

Summary and Perspective

Assessing the nature and basis for repertoire changes is a first-order consideration in our understanding of immunosenescence. Multiple processes appear to act in concert to alter the B cell repertoire with age. These include reduced B cell generation, shifts in V gene choice, and altered subset dynamics and selection overlaid with compensatory homeostatic mechanisms. Murine model systems are attractive routes to interrogate the underlying mechanisms, not only because of their substantial similarities to age-associated shifts in human immune responsiveness but also because they provide an opportunity to approach basic questions experimentally. Some important questions include further elucidation of the “B cell feedback”

mechanism's effects on B lymphopoiesis and bone marrow output repertoire, whether the stringency of central or TR tolerance changes with age, and how B cell repertoire shifts and impaired immune responses in aged individuals are linked.

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