Published in final edited form as:
Curr Opin Immunol. 2009 August ; 21(4): 425–430. doi:10.1016/j.coi.2009.06.001.

Effects of aging on B cell function

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Summary of recent advances

Ability to make an optimal immune response to vaccines and infectious agents declines with age in humans and animal models. Recent advances have shown intrinsic B cell defects in aged mice and humans, including decreases in Ig class switch recombination (CSR), activation-induced cytidine deaminase (AID), and E47 transcription factor. Effects on somatic hypermutation (SHM) have been varied depending on the system studied. Increase of AID in mice has shown improved CSR but not SHM. The reported microarray analysis of human B cell subsets may now be used to delineate B cell defects with aging and all the advances presented should lead to selecting agents for improved immune response in the elderly.

Introduction

B, T and cells of the innate immune system have previously been implicated in a suboptimal immune response in aged humans and mice, but clarity concerning the importance of intrinsic B cell contributions to this decline and precise molecular biomarkers for B cell deficiencies with age have only recently been elucitated. Herein we review recent contributions in this area as well as others relating to specific B cell deficiencies with age and summarize key classic reports in light of these new findings. The significance of these findings is that they offer specific biological markers to measure the quality of the humoral immune response and as well should lead to protocols to directly improve these and the immune response in the elderly as well as potentially in other immunocompromized individuals.

High affinity antibodies are produced as a consequence of affinity maturation processes which occur in the germinal centers (GC) of B cell follicles [1]. During GC reactions, many activated B cells undergo apoptosis and only a minority survive and differentiate into centroblasts that undergo clonal expansion in the dark zone of the GC. During proliferation, the process of somatic hypermutation (SHM) introduces base-pair changes into the V region of the rearranged genes encoding the IgV of the heavy and light chains. Centroblasts then differentiate into centrocytes and move to the light zone, where the B cell receptor, with the help from T cells and follicular dendritic cells, is selected for improved binding to the antigen. Newly generated centrocytes that produce an unfavourable antibody undergo apoptosis and are removed. A subset of centrocytes undergoes Ig class switch recombination (CSR), a DNA recombination mechanism through which the heavy chain class of the antibody produced by an activated B cell changes from IgM and IgD to either IgG, IgA or IgE. The process occurs within GCs, but also outside of GCs in both T cell-dependent (TD) and T cell-independent (TI) responses [2,

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3]. Antigen-selected centrocytes eventually differentiate into memory B cells which can either differentiate into plasmablasts, or remain as non-secreting precursors for antigen recall [4]. The short-lived plasmablasts migrate to the bone marrow, where they differentiate into long-lived plasma cells and provide humoral antibody. Plasmablasts and plasma cells are maintained for long periods of time and compete for space in distict “survival niches” formed by stromal elements [5]. Thus, humoral antibody results from competition between newly generated plasmablasts and plasma cells [5].

Aging decreases humoral responses

The changes in the humoral immune response with age are both qualitative and quantitative, as affinity, specificity and class of antibody produced are changed. A progressive decline in both the number and the size of GCs has been reported [6], as evaluated by immunohistochemistry and flow cytometry using monoclonal antibodies specific for peanut agglutinin (PNA) and GL-7 [6] or PNA and CD38 [7] (see Table 1). The impairment in GC reactions occurring during aging results from not only T cell and follicular dendritic cell (FDC) defects but also intrinsic B cell defects, e.g. in decreased SHM of Ig genes. This results in decreased antibody affinity maturation as well as diminished recirculating antibody-secreting plasma cells in the bone marrow [8]. In adoptive transfer experiments, plasma cells producing both low and high affinity antibodies as a consequence of a recent antigenic stimulation were found to be significantly diminished in the bone marrow of old as compared to young mice [9].

The effects of age on antibody affinity maturation are controversial and results obtained by different groups are conflicting. When the IgH V region genes from GC B cell populations were sequenced, SHM was found to be reduced in splenic GCs [10] or increased in Peyer’s patch GCs, and especially in IgM, [11] of aged mice, and the reduction was attributed to defective T cell help to B cells *in vivo* [7]. The reduced SHM could occur by less costimulation (via CD40, CD80, and CD86) or less cytokine stimulation from CD4 T cells. However, when adoptive hosts receiving young T cells and aged B cells were tested, they also exhibited a reduced capacity to hypermutate antibody genes, suggesting a deficiency in the B cell compartment as well [12]. CD4 T cells from old mice have been shown to produce less IL-2, proliferate and differentiate poorly upon antigen stimulation [13], and show reduced CD40 ligand expression, crucial for cognate B/T interaction [7]. The production of other cytokines is also altered in old age (Th1-derived cytokines are increased and Th2-derived cytokines are decreased) [14,15], thus contributing to reduced vaccine efficacy (as well as increased inflammation).

Studies in humans are also conflicting, showing no change (at least in productive V genes) in SHM with age in GCs of the spleen but a decrease in GCs of Peyer’s patches [16], suggesting that these variations in antibody affinity mainly reflect differences in the way that the antibodies are selected, although perturbations in SHM machinery can also be a possible mechanism. These authors have also more recently shown a decrease in SHM in peripheral blood B cells with age [17*]. In tonsils, the extent of SHM was found unchanged or even increased into the eighth decade of life [18]. These apparent discrepancies may be re-evaluated by considering whether the B cell population being measured is newly challenged with antigen, in which case defects in SHM might be seen with increased age, or whether persistent/increased SHM (e.g. in the tonsil) may reflect accumulation of SHM upon repeated antigenic stimulation.

Specific antibody responses are impaired in aged mice and humans

Aging in mice is associated with a decreased production of precursor B cells in the bone marrow [19–21], which also likely reflects decrease in precursor/stem cells with age [22,23]. However, the population of mature splenic B cells is maintained, in part, in aged mice because of their

increased life-span [24*]. This seems to occur because the peripheral pool is filled with B cells that are long-lived at least in part as a consequence of specificity for, and chronic stimulation by, environmental antigens [25], and also because the number of B cells secreting antibodies to autoantigens increases with age [26]. In contrast with mouse B cells, human peripheral B cell percentages and numbers significantly decrease with age [27–29**]. There is one other report [30] and a review [31] showing that memory B cell percentages increase not significantly with age, but the majority favor a decrease.

The absolute numbers of human B cell precursors in the bone marrow have been shown to decline [32] or not decline [33] with age. The percentage of peripheral blood naïve B cells is increased and their absolute numbers remain unchanged in old individuals [28,29**]. Both human naïve and IgM memory B cells show defects in CSR [29**]. Therefore switch memory cells are deficient in number and function (for CSR), whereas naïve cells are deficient only functionally. Similarly, in the human tonsil, naive B cells have been shown to increase with age [18]. The percentage of IgM memory B cells are not significantly decreased but the absolute numbers are (a result of decreased total B cells with age) [29**]. The reduction in IgM cells has been suggested to cause reduced specific antibody titers in elderly individuals vaccinated against pneumococcal polysaccharides and to *Streptococcus pneumoniae* infection [28]. The reduction in TI responses with age is less severe than that of TD responses and mimics the same differences seen in mice [28,34] and below). Very recent molecular characterization of B cell subsets by the Tangye laboratory [35*] should allow better analysis of human B cell deficits with age in the future.

The antibodies generated in old mice are less protective compared to the antibodies generated in young mice [36]. Age-associated alterations in B cell repertoire expression have also been reported, old mice showing a shift in antibody repertoire from non-self to self-recognition and from high to low affinities [37,38]. A skewing of V-gene usage has also been reported [39]. In old mice the immune response to influenza has less IgG than that in young mice. It was shown that young mice had mostly IgG1 plasma cells producing high affinity antibody after immunization, whereas aged mice had predominantly IgM plasma cells [9]. The total number of anti-dinitrophenyl (DNP) plaque-forming cells generated in the spleen of old mice immunized with the TD antigen DNP-bovine gamma globulin, have been reported to be only 15% of that observed in young mice [40], whereas old mice immunized with the TI antigen DNP-Ficoll were able to make as many plaque-forming cells as young mice did, confirming results obtained with other TI antigens, such as type III pneumococcal polysaccharide (SIII) and LPS [41].

Although antigen-specific antibody responses decline in old mice, total levels of serum antibodies are increased in mice [42] and humans [29**,43]. These results may be explained as the initial antigenic stimulation is defective in aged B cells. The accumulation in the sera of IgG may come from plasmablasts secreting antibodies of suboptimal quality both in affinity and polyclonality, or from normal or increased numbers of Ig-secreting cells present in lymphoid organs, including mucosal tissues. We cannot yet exclude differences in B cell homing and recirculation processes with age, but others have also shown defects in Peyer's patch B cell function, SHM [16] and CSR [11], with age.

Molecular mechanisms for the reduced activity of B cells in aged mice and humans

The inability of B cells from old individuals to respond to vaccination is due to a defect in the molecular events leading to the production of secondary isotypes by CSR. In this process, activation-induced cytidine deaminase (AID) is required [44,45]. AID initiates CSR by deamination of cytidine residues in S regions, thus creating uracils, and the resulting

mismatches are recognized by specific enzymes and excised, leading to DNA double strand breaks [44,46]. AID is also necessary for SHM [44,45]. E2A activity is necessary for CSR because the E47 transcription factor has been shown to be important in transcriptional regulation of *Aicda*, the gene encoding AID [47,48].

We have previously shown that *in vitro* stimulated splenic B cells from old mice are deficient in the production of multiple class switch isotypes and CSR [49]. Our preliminary data indicate that stimulated follicular naïve splenic B cells are impaired in aged mice for CSR. This occurs concomitant with decreased induction of E47 and AID. Others have shown no difference between young and old B cells in AID levels [50], but this could be due to a different time of measuring AID (48 h *versus* 4–5 days in our study) [49]. Although B cells may suffer from a lack of adequate T cell help in aging, as we have discussed above, we have demonstrated that intrinsic changes in B cells also occur and have a significant impact on antibody production. The mechanism for the age-related decrease in E47 levels in old splenic B cells is mRNA stability [51] (see model, Fig. 1). E47 protein degradation rates are comparable in young *versus* aged B cells, in contrast with bone marrow-derived IL-7-expanded pro-B/early pre-B cells [52]. The stability of E47 mRNA is regulated at least in part by the p38 MAPK signal transduction cascade, which phosphorylates a protein, tristetraprolin (TTP), that interacts with the adenylate/uridylate-rich elements (ARE) in the 3′ untranslated region (UTR) of many mRNAs modifying their stability [53*]. We have found that tristetraprolin (TTP), a physiological regulator of mRNA expression and stability, is involved in the degradation of the E47 mRNA [54**]. TTP mRNA and protein levels are higher in stimulated splenic B cells from old mice as compared with young mice. Inhibition of the p38 MAPK signaling pathway significantly reduces TTP protein phosphorylation in B cells. Old B cells in response to LPS make less phosphorylated p38 MAPK [54**] and therefore, as would be expected, make less phosphorylated TTP. This leads to an increase in the amount of TTP bound to the 3′-UTRs of E47 (and inflammatory cytokines, e.g. TNF-α) and therefore decreased E47 mRNA stability in old B cells. We hypothesize that the increase in inflammatory cytokines [15] seen in aging feeds back to increase degradation of inflammatory cytokine mRNAs in aged B cells and as a side effect E47 and B cell function is decreased in aged mice and humans. Our preliminary data show that TNF-α-stimulated splenic B cells from old mice are impaired in their ability to induce AID and CSR to IgA.

We have recently extended our studies on murine B cells to human B cells to investigate whether aging also affects CSR, E47 and AID expression in B cells isolated from the peripheral blood of human subjects. Elderly humans have fewer percentages of CD19+ total B cells, switch memory B cells, and increased percentages of naïve B cells. They also have less E47, AID and Igγ1 circle transcripts [29**].

As AID had previously been shown to be necessary for both CSR and SHM, we would have predicted defects in both of these with aging. We have directly shown defects in CSR in mice and human subjects. Data from others on SHM in aging are less clear as discussed above but this may also reflect more dependence of CSR, as compared with SHM, on AID levels, as the Nussenzweig and Papavasiliou laboratories have recently shown increase of AID in mouse models elevates CSR but SHM is not changed [55*,56*].

Conclusions

Results in mice and humans provide a possible molecular mechanism for a B cell intrinsic defect in the humoral immune response with aging. Although there are defects in T cells as well as in B cells during aging, these results suggest that improving the aged immune response will likely require methods to directly improve the function of B cells as well as T cells in elderly individuals.

Acknowledgments

This work is supported by NIH AG-23717 and AG28586 (BBB).

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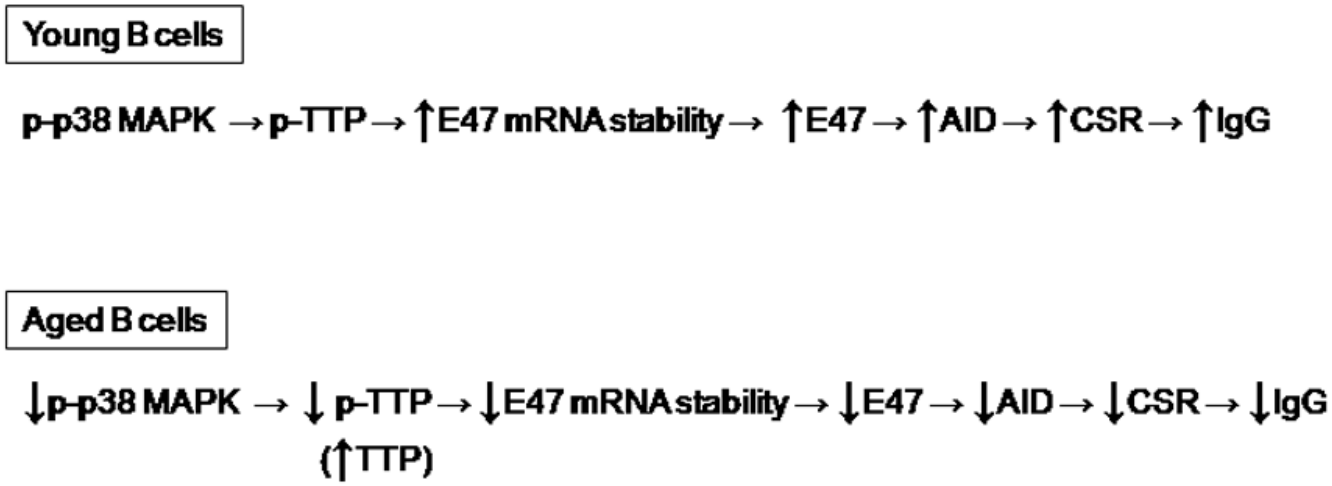

Fig. 1. Mechanism for decreased CSR in aged activated B cells

The details of this model have been determined in activated B cells from mice [34,49,51,54], but human activated B cells also share the components following and including E47 mRNA stability [29]. Activated B cells from old subjects have less IgG, CSR, AID and E47 than those from young subjects. The molecular mechanism for this is that E47 mRNA stability is lower in B cells from older mice/humans and in mice this reflects more TTP and less phosphorylated TTP in old cells binding to the 3′UTR of E47 mRNA and causing its degradation. Less phospho-p38 MAPK generates this pathway in old B cells.

Table 1

Age-related changes in B cells in mice and humans

Parameter	Mice (> 18 months)	Humans (> 65 years)
Bone marrow B cell progenitors	decreased [19–21]	decreased [32]
		unchanged [33]
B cell numbers	unchanged [24]	reduced [27–29]
Peripheral blood naïve B cells (CD19+IgD+CD27−) Peripheral blood naïve B cells (CD19+CD27−IgG−IgA−)	nd	increased % and unchanged number [28] increased % and unchanged number [29]
Tonsil naïve B cells (IgD+CD38−CD27−)	nd	increased % [18]
Peripheral blood total memory B cells (CD19+CD27+)	nd	increased % (not significantly) [30]
Peripheral blood IgM memory B cells (CD19+IgD+CD27+)	nd	unchanged % and decreased number [28]
Peripheral blood IgM memory B cells (CD19+CD27+IgG−IgA−)	nd	unchanged % and decreased number [29]
Peripheral blood switch memory B cells (CD19+IgG+IgA+)	nd	Decreased % and number [29]
GCs	decreased in number and size [6,7]	decreased % of IgD−CD38+CD27− B cells in tonsil [18]
CSR	decreased [34,49]	decreased [28,29]
SHM	reduced in splenic GCs [10] increased for IgM in Peyer's patch GCs [11]	unchanged in splenic GCs [16] decreased in Peyer's patch GCs [16] decreased in peripheral B cells [17] unchanged or increased in tonsil [18]
In vitro IgG	decreased [34,49]	decreased [29]
Serum IgG	increased [42]	increased [29]
Serum IgM,G,A		increased [43]
Plasma cells	decreased after immunization with TD antigens [40] unchanged after immunization with TI antigens [41]	nd

nd, not done; CSR, class switch recombination; GCs, germinal centers; SHM, somatic hypermutation