HHS Public Access

Author manuscript

Annu Rev Cell Dev Biol. Author manuscript; available in PMC 2021 April 22.

Published in final edited form as:

Annu Rev Cell Dev Biol. 2020 October 06; 36: 551–574. doi:10.1146/annurev-cellbio-011620-034148.

B Cell Immunosenescence

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Abstract

Innate and adaptive immune responses decline with age, leading to greater susceptibility to infectious diseases and reduced responses to vaccines. Diseases are more severe in old than in young individuals and have a greater impact on health outcomes such as morbidity, disability, and mortality. Aging is characterized by increased low-grade chronic inflammation, so-called inflammaging, that represents a link between changes in immune cells and a number of diseases and syndromes typical of old age. In this review we summarize current knowledge on age-associated changes in immune cells with special emphasis on B cells, which are more inflammatory and less responsive to infections and vaccines in the elderly. We highlight recent findings on factors and pathways contributing to inflammaging and how these lead to dysfunctional immune responses. We summarize recent published studies showing that adipose tissue, which increases in size with aging, contributes to inflammaging and dysregulated B cell function.

Keywords

aging; inflammation; B cells; vaccine responses; obesity

1. INTRODUCTION TO IMMUNE AGING

Aging is associated with defects in immunity and compromised responses to previously unencountered antigens and vaccines (reviewed in Frasca & Blomberg 2016). Humoral and cellular immune responses decrease in elderly individuals, leading to increased frequency and severity of infectious diseases and reduced protective effects of vaccination. Hospitalization due to infection is much more common in the elderly than in younger

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DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

individuals and is a major contributor to the development of disability in the elderly (Ferrucci et al. 1997).

Aging is also associated with the increased chronic, low-grade, systemic inflammation known as inflammaging (Franceschi et al. 2000), which contributes to metabolic dysfunction and the development of insulin resistance and represents a significant risk factor for morbidity and mortality of elderly individuals, as it is implicated in the pathogenesis of several debilitating chronic diseases of old age including type 2 diabetes mellitus (T2DM), osteoporosis, Alzheimer's disease, rheumatoid arthritis, and coronary heart disease. Inflammaging induces intrinsic inflammation in immune cells leading to both decreased protective responses against infections and decreased vaccine responses (Bryl et al. 2001, Frasca et al. 2014, Parish et al. 2009).

Decreased T cell function has been considered for many years to be the only contributor to immunosenescence. However, age-related defects in other components of the immune system also occur and contribute to the increased frequency and severity of infectious diseases in the elderly. In this review, we focus on B cell defects with aging (see Section 3), but we also summarize published results on the effects of age on T cells, antigen-presenting cells (APCs), natural killer (NK) cells, and neutrophils.

1.1. Aging-Related Changes in T Cells

Thymic involution plays a crucial role in T cell immunosenescence (Hirokawa & Makinodan 1975) and is responsible for reductions in circulating naive T cells, CD4 T cell receptor (TCR) excision circles, markers of thymic output, and TCR diversity in individuals more than 60 years of age (Naylor et al. 2005). However, the frequency of memory/effector T cells increases (Pawelec et al. 2002). A significant decrease in naive $CD8^+$ but not $CD4^+$ T cells has been reported, with the decrease in naive $CD8^+$ T cells not altered by cytomegalovirus (CMV) seropositivity. However, in CMV-seropositive individuals the decline in $CD4^+$ naive T cells was significantly decreased; these individuals also exhibited an absolute increase in the ratio of effector to effector memory $CD4^+$ and $CD8^+$ T cells with age (Wertheimer et al. 2014).

Aging is also associated with an increased frequency of a subset of $CD8^+$ T cells called memory T cells with a naive phenotype (T_{MNP}); these cells have the characteristics of a naive phenotype but also the capacity to secrete multiple factors [i.e., tumor necrosis factor-α (TNF-α), interferon002D03B3 (IFN-γ), granzyme B] in response to persistent viral antigens. T_{MNP} are transcriptionally different from memory and effector T cells. Their frequency and numbers significantly increase after infection with West Nile virus and influenza virus and are positively correlated with the severity of acute viral infection (Pulko et al. 2016).

T cells downregulate the expression of the CD28 molecule with age, and subsets of $CD4^+CD28^-$ and $CD8^+CD28^-$ T cells emerge (Vallejo 2005). The downregulation of CD28 expression due to chronic immune activation of human T cells is one of the signatures of replicative senescence and has been associated with impaired vaccine responses (Goronzy et al. 2001, Saurwein-Teissl et al. 2002).

Cytotoxicity of $CD8^+$ T cells also decreases with age (McElhaney et al. 2012), leading to reduced virus-specific killing of influenza virus in the lungs. This is due to a significant reduction in the frequency of cells that coexpress granzyme B and perforin (Thiery et al. 2011). This decline has been shown to predict not only increased risk of influenza illness (McElhaney et al. 2009) but also its severity in elderly individuals (Shahid et al. 2010). In addition, a decreased IFN-γ:interleukin-10 (IL-10) ratio in influenza-stimulated lymphocytes is associated with a reduced cytolytic capacity of the $CD8^+$ T cells that clear influenza virus from infected lungs (McElhaney et al. 2012).

1.2. Aging-Related Changes in Antigen-Presenting Cells

Dendritic cells (DCs) are professional APCs. Human DCs, classified as myeloid DCs (mDCs) or plasmacytoid DCs (pDCs), have distinct functional activities: mDCs produce IL-12 and induce helper T cell type 1 (Th1) and cytotoxic T lymphocyte (CTL) responses, whereas pDCs produce IFN-α/β in response to bacteria and viruses (Banchereau et al. 2000). Both mDCs and pDCs from elderly individuals are significantly impaired in their capacity to secrete TNF-α, IL-6, and IL-12 (p40) in response to Toll-like receptor (TLR) stimulation, and these defects have been associated with less effective responses to influenza vaccine (Panda et al. 2010).

An in-depth global analysis examined the impact of aging on classical ($CD14^+CD16^-$, which are 90% of circulating monocytes), intermediate ($CD14^+CD16^+$), and nonclassical ($CD14^{DIM}CD16^+$) monocytes. Classical monocytes produce low levels of reactive oxygen species (ROS) and high levels of reactive nitrogen species, IL-1β, and TNF-α, whereas $CD14^{DIM}CD16^+$ monocytes are involved in patrolling the vascular endothelium via CX3CR1-CX3CL1 interactions and produce TNF-α, IL-1β, and CCL3 in response to viruses and immune complexes via a proinflammatory TLR7/TLR8/MyD88/MEK pathway. Results have shown no age effects on unstimulated monocyte subsets; however, agonist-stimulated monocytes from elderly individuals showed reduced production of IFN-α, IFN-γ, IL-1β, CCL20, and CCL8 and higher expression of CX3CR1 (Metcalf et al. 2017).

A mechanism by which monocytes fuel inflammaging despite reduced secretion of proinflammatory cytokines has been proposed. In both mice and humans, high circulating levels of TNF-α due to inflammaging have been shown to induce premature egress of monocytes from the bone marrow. These immature monocytes, when stimulated with bacterial products in vivo, secrete high levels of TNF-α, thus contributing to inflammaging. At the same time, however, similar to what has been shown for T and B cells, TNF-α induces dysfunctional tissue-associated monocytes, leading to reduced bacterial clearance (Puchta et al. 2016).

1.3. Aging-Related Changes in Natural Killer Cells

NK cells are innate lymphoid cells (ILCs) that account for 15% of peripheral blood lymphocytes. NK cells are cytotoxic lymphocytes that share many features with ILC1, such as their capacity to produce IFN-γ, although they are developmentally distinct (Spits et al. 2016). Several NK cell subsets can be distinguished according to their differential expression of some phenotypical and functional markers. In the subset of

$CD56^{HIGH}CD16^{LOW}$ NK cells, the cells are more immature and secrete cytokines and chemokines, whereas the major NK cell subset $CD56^{DIM}CD16^{+}$ is made up of mature NK cells with high cytotoxic capacity after direct contact with tumor or virus-infected target cells (Cooper et al. 2001).

Aging induces a redistribution of NK cell subsets that is characterized by an increase in the number of mature NK cells with a significant reduction in the more immature NK cell subset that is probably due to the decreased production of bone marrow precursors in the elderly (Campos et al. 2014, Chidrawar et al. 2006). Both age and persistent CMV infection contribute to the NK cell phenotypical and functional changes observed in the elderly.

Aging also induces changes in NK cell functions including decreased NK cell proliferation in response to IL-2 stimulation (Borrego et al. 1999). Aging does not change total NK cell cytotoxicity, probably due to the increased frequencies of mature NK cells, but impairment of NK cell cytotoxicity on a per cell basis as a consequence of the decreased expression of activating receptors has been reported (Hazeldine et al. 2012). The decreased lytic activity of NK cells from the elderly has been attributed to a pronounced age-related decrease in the ability to generate inositol trisphosphate during spontaneous cytolytic activity against targets (Mariani et al. 1998). Human NK cells from healthy subjects over 90 years of age, however, are still able to secrete the chemotactic cytokines MIP-1α, Rantes, and IL-8 and can also effectively release these chemokines in response to IL-12 and IL-2, but their production remains lower than that observed in young subjects (Mariani et al. 2002).

1.4. Aging-Related Changes in Neutrophils

Neutrophils represent a frontline defense against bacterial and fungal pathogens. An age-related decrease in neutrophil function has been reported and accounts for the increased frequency of infection in the elderly. Briefly, the microbicidal activity of neutrophils from elderly individuals is significantly reduced by aging (Simell et al. 2011, Wenisch et al. 2000) due to impaired phagocytosis (Butcher et al. 2001, Wenisch et al. 2000), degranulation (McLaughlin et al. 1986), and ROS production (Fulop et al. 2004). Neutrophils from elderly individuals also show impaired migration in response to chemotactic stimuli, leading to delayed recruitment of neutrophils to the site of infection (Bartlett et al. 2016). Reduced neutrophil chemotaxis increases tissue damage and inflammation due to the release of proteases, such as neutrophil elastase, that help migration through the tissue (Cepinskas et al. 1999) but can significantly damage the tissue itself, inducing local inflammation (Sapey et al. 2014). Mechanisms for reduced migration have been identified that are associated with reduced signaling through phosphoinositide 3-kinase (PI3K), and inhibition of this pathway has been shown to improve neutrophil migration (Sapey et al. 2014).

Studies conducted in mice have shown that neutrophil extracellular trap (NET) formation is also impaired with age (Tseng et al. 2012). NETs are composed of nucleic acids and antimicrobials; they function to entrap pathogens and limit infection (Brinkmann et al. 2004). The age defect in NET formation is associated with bacteremia, explaining why elderly individuals are more susceptible to invasive bacterial disease following skin and soft tissue infection.

2. INFLAMMAGING

Inflammation is an evolutionarily conserved, acute, beneficial process characterized by the activation of immune and nonimmune mechanisms that protect the organism from harmful conditions such as bacterial, viral, and parasitic infections by eliminating pathogens and promoting repair. Acute inflammatory responses decrease with aging. Inflammaging, however, increases with age (Franceschi et al. 2000). Inflammaging (chronic inflammation) induces intrinsic inflammation in most immune cells, making them less responsive to infections and vaccines.

Not only cytokines but also acute phase proteins, such as C-reactive protein (CRP) and mannose-binding lectin, are markers of inflammaging. A review and meta-analysis (Soysal et al. 2016) revealed that frailty and prefrailty are associated with higher levels of inflammatory parameters, in particular IL-6 and CRP. Another recent study (Elisia et al. 2017) has evaluated endogenous and ex vivo–stimulated levels of 18 inflammatory markers and found significant increases with age in IL-12p70, CRP, and PGE_2, consistent with the concept of inflammaging, and a decrease in granulocyte colony-stimulating factor (G-CSF) in both men and women, whereas no effects were found for IL-1β, IFN-α, and TNF-α. These studies, showing a significant person-to-person variation in inflammatory measures in all age groups, strongly indicate the need for longitudinal tracking to better study age-dependent changes in the immune system.

To confirm these conclusions, a multi-omics approach has recently been used to evaluate the link between inflammaging and disease risk. The study (Alpert et al. 2019) performed high-throughput molecular profiling of adult individuals followed longitudinally. The parameters measured were whole-blood gene expression (the transcriptome), immune cytokines and chemokines (the immunome), and the frequencies of immune cell subsets such as CD4/CD8 T cells, B cells, and NK cells. The results allowed the construction of a high-dimensional trajectory of immune aging (IMM-AGE) that described the person’s immune status better than chronological age and accurately predicted all-cause mortality.

How inflammaging contributes to adverse health outcomes is largely unknown. It has been proposed that the balance of proinflammatory and anti-inflammatory responses in aging determines clinical outcomes in humans. Therefore, the identification of pathways controlling inflammaging across multiple systems is needed to design appropriate therapeutic interventions to reduce inflammaging and increase the health spans of elderly individuals.

Inflammaging is driven by several factors, including single-nucleotide polymorphisms (SNPs) in the promoter regions of proinflammatory genes, chronic stimulation of immune cells with viruses (e.g., CMV), changes in gut microbiome composition, and cellular senescence (reviewed in Frasca & Blomberg 2016). Recently, another mechanism for fueling inflammaging has been proposed called garbaging. Garbaging involves endogenous/self, misplaced, or altered molecules that are generated by damaged or dead cells and organelles (cell debris) and recognized by receptors of the innate immune system. Their production is

physiological and increases with age. However, their disposal by the proteasome is severely decreased by aging (Franceschi et al. 2017).

2.1. Single Nucleotide Polymorphisms and Inflammaging

SNPs on promoter regions of the proinflammatory genes for IL-6 and IFN-γ have been associated with inflammaging. The −174 G/C single-nucleotide polymorphism is a functional variant located in the promoter region of the gene for IL-6 that regulates the rate of gene transcription and serum IL-6 concentration. The GG genotype is associated in elderly men but not in women with increased IL-6 levels (Olivieri et al. 2002) and a higher risk of death after acute coronary syndrome (Antonicelli et al. 2005). In addition, a SNP in the promoter region of the gene for TNF-α (−308 G>A) has been shown to be a risk factor for death after acute coronary syndrome in elderly male patients (Antonicelli et al. 2005). The +874 A allele for the IFN-γ gene is associated with low IFN-γ production and is positively associated with longevity in male and female centenarians (Lio et al. 2002). This T/A polymorphism coincides with a putative NF-κB binding site, which is involved in the transcription of the human gene for IFN-γ and therefore could directly influence the level of IFN-γ (Pravica et al. 2000).

2.2. Cytomegalovirus and Inflammaging

CMV seropositivity is associated with inflammaging. CMV is a β-herpesvirus that infects from 40% to 70% of the human population; it is a persistent, latent, asymptomatic infection in healthy individuals but may cause severe disease in immunocompromised hosts (Freeman 2009). The reactivation of CMV is induced by proinflammatory mediators. CMV infection rapidly induces the translocation of NF-κB into the nucleus, the production of TNF-α, and the further activation of latent CMV, establishing a vicious loop with additional upregulation of the inflammatory response (Prosch et al. 1995). CMV is one of the main components of the immune risk phenotype that predicts less longevity in the very elderly (Wikby et al. 2006). CMV seropositivity is associated with changes in the immune profile of elderly individuals, including decreased numbers of naive cells and increased numbers of memory cells with a terminally differentiated and exhausted phenotype associated with the secretion of proinflammatory cytokines and chemokines. This occurs for T cells (Derhovanessian et al. 2014, Redeker et al. 2017), B cells (Frasca et al. 2015, Welten et al. 2016), and NK cells (Gumá et al. 2004, Lopez-Sejas et al. 2016) in both mice and humans.

2.3. Gut Microbiome and Inflammaging

The gut microbiome has also been linked to inflammaging. In general, microbial dysbiosis drives intestinal permeability and the translocation of bacterial components into the bloodstream, sustaining inflammaging, immune cell activation, and decreased immune responses (Thevaranjan et al. 2017). Increased gut permeability with age induces not only systemic but also lung inflammation and tissue damage as shown by increased levels of circulating bacterial toxins, leading to pulmonary endothelial damage.

A study of healthy adults (Schirmer et al. 2016) has shown that differences in the composition and function of the gut microbiome play important roles in the regulation of

cytokine production, specifically TNF-α and IFN-γ. However, other factors such as genetics and environmental factors also play important roles.

Studies conducted on Italian centenarians (99–104 years of age) (Biagi et al. 2010) have shown quantitative differences among the gut microbiota of centenarians and those of young and elderly individuals. In centenarians, strong correlations between increased facultative anaerobes (opportunistic proinflammatory bacteria) and plasma levels of IL-6 and IL-8 were found. Conversely, young and elderly individuals have microbial patterns characterized by several symbiotic species with anti-inflammatory properties. These results indicate that the fecal microbiota of centenarians is a partially compromised ecosystem that is expected to influence the immune system. However, despite their inflammatory status, centenarians have reached the extreme limit of human life span and have escaped and/or delayed inflammatory age-related diseases, suggesting that inflammaging may have been counterbalanced by other physiological events.

2.4. Cellular Senescence and Inflammaging

Cellular senescence is another significant contributor to inflammaging due to the acquisition of the senescence-associated secretory phenotype (SASP) by different cell types, including immune cells. The SASP is responsible for the secretion of proinflammatory chemokines, cytokines, growth factors, and matrix metalloproteinases (Campisi 2011). The age-dependent accumulation of senescent cells and their secretory products provides a favorable environment for the development of inflammation-based, age-related diseases.

How the SASP is acquired is not known, although it has been proposed that both intrinsic (telomeric and nontelomeric DNA damage, oxidative stress, and genomic or epigenomic damage) and extrinsic (chronic viral infections, gut dysbiosis, and pollution and industrial toxicants) factors are involved (reviewed in Furman et al. 2019). Briefly, genomic or epigenomic damage activates a DNA damage response that becomes chronic and leads to the activation of p38MAPK and protein kinase C, increased ROS production, and the expression of p16 tumor suppressor. The SASP is positively regulated by NF-κB and C/EBP-β, which are downstream of signaling cascades that control inflammatory cytokine gene expression. In addition, an early response to senescence-inducing stimuli is characterized by the increased expression of the gene for IL-1α; the resulting IL-1α then binds to its receptor, which in turn initiates a signaling cascade that ultimately activates NF-κB and leads to the secretion of inflammatory mediators (Orjalo et al. 2009).

3. B CELLS AND ANTIBODY RESPONSES ARE DECREASED IN THE AGED

Antibody responses are decreased with age in both mice and humans, leading to increased frequency and severity of infectious diseases and reduced protective effects of vaccination. Not only is the production of high-affinity protective antibodies decreased by age, but also the duration of protective immunity following immunization is shortened. The decreased ability of aged individuals to produce high-affinity protective antibodies against infectious agents likely results from combined defects in T cells, B cells, and other immune cells.

B cells undergo profound changes with age in both mice and humans. Aging decreases B cell differentiation in the bone marrow and the output of mature B cells; induces a redistribution of B cell subsets in the periphery with a significant increase in frequencies and numbers of proinflammatory B cells; decreases the expression of molecules involved in immunoglobulin (Ig) class-switch recombination (CSR) and somatic hypermutation (SHM), two processes leading to the generation of high-affinity protective antibodies as well as germinal center (GC) formation; and decreases repertoire diversity.

3.1. Effects of Age on B Cell Differentiation

Several studies have characterized B cell differentiation in the bone marrow of mice of different ages. The generation of B2 (conventional) B cells from bone marrow precursors is impaired in old mice, whereas B1 progenitors are retained in the bone marrow of old mice even when B2 progenitors are reduced (Alter-Wolf et al. 2009). These results have shown that reduced numbers of pro-B, pre-B, and immature B cell subsets are generated in the bone marrow of old versus young mice. The mechanisms involve a combination of cell-intrinsic changes as well as changes in the microenvironment. The bone marrow of old mice contains lower frequencies of common lymphoid progenitors (CLPs) (Miller & Allman 2003), and hematopoietic stem cells (HSCs) from old mice are biased to produce myeloid rather than lymphoid cells (Muller-Sieburg et al. 2012). Age-related changes in the bone marrow microenvironment include reductions in the stromal-derived cytokine IL-7 (Stephan et al. 1998), which is an important survival and proliferative factor for B-lineage precursors, leading to reduced recombination-activating gene (RAG) activity in pro-B cells and reduced size of the pro-B and pre-B cell pools (Labrie et al. 2004). Aging-related changes at the molecular level include decreased expression of the transcription factor E2A (Lescale et al. 2010, Riley et al. 2005), the pre-B cell receptor (BCR) surrogate light chain (Riley et al. 2005), and the transcription factor PAX5 (Anspach et al. 2001).

The bone marrow of old mice contains increased frequencies of the proinflammatory B cell subset called age-associated B cells (ABCs) that secrete significantly high amounts of TNF-α, which is shown to impair the generation of young pro-B cells (Ratliff et al. 2013). This finding suggests a possible contribution of bone marrow–resident ABCs to altered B cell development.

Studies in humans (Nuñez et al. 1996, Rossi et al. 2003) have shown that the frequencies of pro-B, pre-B, and immature B cells are not significantly changed in individuals from 24 to 88 years of age. In contrast, linear regression analysis of the percentage of B cell precursors in bone marrow samples from several patients with or without tumors showed a statistically significant decrease in B-lineage precursors with age (McKenna et al. 2001).

3.2. Effects of Age on Peripheral B Cell Subsets

In mice, the frequencies and numbers of splenic B cells are maintained with age, but there is a shift in the proportions of the different B cell subsets. The splenic B cell compartment of old mice is characterized by increasing numbers of ABCs, likely at the expense of the follicular (FO) B cell subset, so that the total number of splenic B cells does not change significantly (Frasca et al. 2017d, Hao et al. 2011, Ratliff et al. 2013). Two groups have

characterized the phenotype and function of ABCs and the mechanisms for their generation during aging. The first group (Hao et al. 2011) has shown that ABCs are refractory to BCR and CD40 stimulation, but they respond to TLR7/9 stimulation, proliferate, and secrete IgG, IL-10, and IL-4. The second group (Rubtsov et al. 2011), conversely, has shown that ABCs increase not only in the spleens of old female mice but also in young lupus-prone NZB/WF1 mice, and cells with a similar phenotype can also be detected in the peripheral blood of elderly women with autoimmune diseases. As ABCs secrete autoantibodies, their in vivo depletion leads to a reduction in the numbers of autoimmune antibodies, suggesting that the cells might have a direct role in the development of autoimmunity. ABCs are generated in vitro by FO B cells (Hao et al. 2011), and their generation requires MHC class II and CD40/CD40L interactions (Russell Knode et al. 2017). ABCs are also generated in vivo by viruses such as the influenza virus. The influenza-specific ABC response is nonfollicular and helper T cell independent but requires high viral dose and pathogen-recognition pathways. Influenza-specific ABCs differentiate into specific antibody-secreting cells, some of which relocate to the bone marrow and the lungs and persist for more than 4 weeks, suggesting they may provide significant protection (Swain et al. 2017).

In contrast to the other splenic B cell subsets, ABCs show significant SHM (Russell Knode et al. 2017). Their mutation frequency, however, is lower than that found in GC B cells after stimulation, suggesting that ABCs have undergone mild stimulation from endogenous antigens over time.

The peripheral B cell pool is regulated by competition for the survival factor BAFF/BLyS (Miller & Cancro 2007). BAFF and its receptors mediate peripheral B cell homeostasis. The size, dynamics, and behavior of the B cell subsets influenced by BAFF change with age (Miller & Cancro 2007), and enhanced BAFF responsiveness contributes to the decreased turnover rates of the aged B cell pool. FO B cells rely on BAFF/BLyS for survival, but ABCs do not, although they express BAFF/BLyS receptors and sequester this cytokine (Hao et al. 2011).

In humans, B cell percentages and numbers have been shown to significantly decrease with age (Ademokun et al. 2010; Frasca et al. 2008, 2016b, 2017c; Wikby et al. 2006), and there is a shift in the proportions of the different B cell subsets. Using anti-CD19, -CD27, and -IgD antibodies, it is possible to identify four major subsets: naive (IgD^+CD27^-), IgM or unswitched memory (IgD^+CD27^+), switched memory (IgD^-CD27^+), and double negative (DN) memory (IgD^-CD27^-) B cells. Aging induces a significant decrease in the percentage of switched memory B cells, no change in IgM memory, and a significant increase in the percentage of naive and DN B cells (Frasca et al. 2017b,c). In other reports, IgM memory B cells are reduced in the elderly, which is hypothesized to result in a predisposition to pneumococcal infection (Buffa et al. 2011, Shi et al. 2005).

Switched memory B cells, the cells responsible for driving rapid secondary antibody responses after reexposure to the same antigen, decrease in both frequencies and numbers with age, suggesting an intrinsic defect in the ability of such B cells to undergo class switch. Switched memory B cells are long-lived and quiescent; they carry somatically hypermutated

Ig V genes and are able to generate more rapid and robust responses than are naive B cells (reviewed in Frasca et al. 2011).

The B cell pool of elderly people, similar to old mice, has increased frequencies and numbers of a B cell subset that shares similar characteristics with murine ABCs. These ABC-like cells, DN B cells, have also been called late memory or tissue-like memory B cells. This is the most proinflammatory B cell subset, which has been reported to be increased in the blood of patients with autoimmune (Adlowitz et al. 2015, Claes et al. 2016, Wehr et al. 2004) and infectious (Chang et al. 2016, Illingworth et al. 2013, Moir et al. 2008) diseases. This suggests that these cells may expand in vivo in the presence of autoantigens or pathogen-derived antigens in the context of a favorable inflammatory microenvironment, leading to the production of autoimmune or protective antibodies, respectively. DN B cells are transcriptionally active and affect the microenvironment by secreting proinflammatory mediators that in turn sustain and propagate the inflammatory response (Frasca et al. 2017b). DN B cells do not proliferate and do not make antibodies to influenza antigens in previously vaccinated individuals, but they do secrete autoimmune antibodies (Frasca et al. 2019, Rubtsov et al. 2011), in agreement with their membrane phenotype ($CD95^+CD21^-CD11c^+$) and their spontaneous expression of the transcription factor T-bet (Frasca et al. 2017c, 2019). We have recently shown that DN B cells from elderly as compared with young individuals utilize higher amounts of glucose; upregulate oxidative phosphorylation, aerobic glycolysis, and fatty acid oxidation; and activate AMPK (5′-AMP-activated kinase) and Sestrin 1, which are both able to mitigate stress and cell death (Frasca et al. 2019). AMPK is the energy-sensing enzyme and key metabolic regulator ubiquitously expressed in mammalian cells (Ruderman & Prentki 2004). This metabolic advantage drives DN B cell survival and function (secretion of autoimmune antibodies) (Frasca et al. 2019).

In apparent contrast with these data, two groups have reported an increase in the percentage of total memory B cells ($CD19^+CD27^+$) in the aged (Colonna-Romano et al. 2003). This finding may reflect not only the maintenance of IgM memory B cells but also the increase in DN B cells observed with age.

3.3. Effects of Age on Antibody Production

Antibody responses and secretion of switched IgG represent the gold standard measure of protection from infections and vaccine efficacy. Mitogen-stimulated splenic B cells from old mice are deficient in the production of multiple class-switched isotypes and CSR (Frasca et al. 2004) due to decreased expression of E47 and activation-induced cytidine deaminase (AID), although no differences between AID levels in young and old B cells have been reported (Russell Knode et al. 2019). AID is the enzyme that induces DNA cleavage and therefore is required for both CSR and SHM of Ig genes (Muramatsu et al. 2000). These processes are crucial for the generation of high-affinity antibodies and robust humoral immunity. AID is not required for normal B cell development but is expressed by activated B cells, mainly in GCs of peripheral lymphoid organs (Stavnezer et al. 2008). SHM and CSR occur in GCs in response to both T cell-dependent and -independent stimuli.

The mechanism for the age-related decrease in the E47 level in old splenic B cells is mRNA stability (Frasca et al. 2005). The stability of E47 mRNA is regulated at least in part by the

p38 mitogen-activated protein kinase (MAPK) signal-transduction cascade, which phosphorylates a protein called tristetraprolin (TTP) that interacts with the adenylate/uridylate–rich elements in the 3′ untranslated region of many mRNAs to modify their stability (Stoecklin & Anderson 2006), thereby protecting the mRNA from degradation. In response to mitogen stimulation, old B cells make less phosphorylated p38 MAPK and TTP and have higher levels of E47 mRNA degradation (Frasca et al. 2007).

Similar to murine splenic B cells, mitogen-stimulated human B cells from elderly individuals have decreased expression of E47 and AID and secrete less IgG as compared with those from young individuals. Influenza vaccine–specific antibody responses are reduced in the elderly in part due to decreased generation of specific serum antibodies (Frasca et al. 2010, 2012, 2013b; McElhaney et al. 2013), switched memory B cells (Amanna et al. 2007; Frasca et al. 2010, 2012, 2013c; Sasaki et al. 2008), and long-lived plasma cells (Pritz et al. 2015, Sasaki et al. 2011). AID is a B cell biomarker that is not only associated with but also predicts the quality of the antibody response to the influenza vaccine, as it correlates with serum antibodies and with the generation of high-affinity antibodies specific for the pandemic (p)H1N1 influenza vaccine (Frasca et al. 2010, 2012, 2013b; Khurana et al. 2012).

Memory B cells are maintained in aged mice (Goenka et al. 2014) and humans (Frasca et al. 2016a), but the serum response is not, suggesting an intrinsic defect in the differentiation of plasma cells. One possible explanation for similar memory B cell responses despite lower levels of AID is that IgG^+ cells in old individuals could be positively selected and proliferate in response to repeated vaccines.

The ability to generate a vaccine-specific antibody response is negatively correlated with the level of serum TNF-α (Frasca et al. 2014). Human unstimulated B cells from elderly individuals make higher levels of TNF-α than do those from young individuals, a finding that positively correlates with serum TNF-α levels. These higher levels of serum and unstimulated B cell TNF-α negatively correlate with B cell function as measured by AID. Only memory B cells and especially DN B cells make TNF-α, and they seem to make more in elderly than in young individuals (Frasca et al. 2017b).

3.4. Effects of Age on Signal Transduction

Defects in cell activation and signal transduction occur with aging in B cells. Studies in mice have shown reduced proliferation in response to BCR engagement and reduced phosphorylation of both tyrosines and serines/threonines in B cells from old as compared with young mice; however, no aging effects were observed when B cells from old mice were stimulated with phorbol esters or anti-CD40 antibodies (Whisler et al. 1991). Age-related impairments in both cytosolic protein kinase C enzymatic activity and cytosolic Ca^{2+} concentration were also observed in stimulated B cells (Whisler et al. 1991).

In humans, it has recently been shown that the calcium/calmodulin–dependent protein kinase type IV (CaMKIV) is phosphorylated after in vitro stimulation of peripheral blood mononuclear cells from young individuals who have been vaccinated for influenza (Nakaya et al. 2011). Three days after vaccination, phospho-CaMKIV levels were found to be

inversely correlated with serum antibody titers, suggesting a possible role for CaMKIV in the regulation of antibody responses to the influenza vaccine. CaMKIV belongs to the family of calcium/calmodulin–dependent protein kinases that regulate Ca^{2+}-dependent cell function and inflammation through TNF-α production.

3.5. Effects of Age on B Cell Repertoire

The age-related decline in the output of B cells from the bone marrow of old mice as well as the homeostatic expansion of constitutively activated cells predicts reduced mature B cell diversity (Dunn-Walters & Ademokun 2010, Johnson et al. 2002). Murine B cells may be selected and accumulate with age based on their reactivity to both exogenous and self-antigens (Johnson et al. 2002), while antigen-inexperienced cells are gradually excluded from the peripheral repertoire with aging (Hao et al. 2011, Johnson et al. 2002, Rubtsov et al. 2011). In addition, a skewing process occurring in the bone marrow, as indicated by altered V_L and V_H usage, may account for the reduced B cell repertoire (Alter-Wolf et al. 2009).

In humans, several studies have investigated changes in the antibody repertoire with age (reviewed in Dunn-Walters & Ademokun 2010). The analysis of DNA samples from the peripheral blood of individuals from 19 to 94 years of age using spectratyping of the Ig V_H complementarity-determining region 3 (CDR3) has shown that some elderly individuals have a significant collapse in repertoire diversity; together with oligoclonal expansions, the extent of the loss of diversity correlates with frailty (Gibson et al. 2009). The hyperexpansions of plasma cells that yield monoclonal gammopathies of undetermined significance (MGUSs) and other monoclonal B cell expansions are also associated with age (Kyle & Rajkumar 2006).

Using spectratype analysis and high-throughput sequencing, another study (Martin et al. 2015) has shown that the B cell repertoire of elderly individuals shows evidence of nonspecific clonal expansions in the absence of antigenic challenge. This loss of specific B cell diversity correlates with poor health.

4. ANTIBODY RESPONSES TO VACCINES ARE DECREASED IN THE AGED

Vaccine efficacy decreases with age, resulting in higher morbidity and mortality in the elderly due to viral and bacterial infections even after vaccination as well as an increased societal burden. The age-related changes in the immune system outlined in Sections 1–3 lead to failures in the adaptive response to vaccines (Crooke et al. 2019). In this section we summarize experimental data that aging is linked to a higher severity of respiratory tract infections (RTIs). For the sake of space, we focus primarily on vaccines for influenza, *Streptococcus pneumoniae* (or pneumococcus), and respiratory syncytial virus (RSV), which represent major causes of morbidity and mortality in the United States.

4.1. Responses to Influenza Vaccine

Influenza is an acute RTI usually occurring as an epidemic during the winter months. Influenza vaccines provide moderate protection against influenza-associated hospitalizations among adults. In the elderly, however, they provide less protection, especially in seasons in which the vaccine and the circulating strains are antigenically variant (Rondy et al. 2017). In general, young individuals have more robust antibody responses than do elderly individuals to the first vaccination, but after subsequent vaccinations the difference between young and elderly individuals declines rapidly, suggesting the importance of prior vaccination and/or infection (Mosterín Höpping et al. 2016). Repeated vaccinations with a vaccine containing the same viral strains results in a significant increase in protective antibodies and titers in both young and elderly individuals (Andrews et al. 2015). Furthermore, evidence consistently shows that serum antibody responses following influenza vaccination do not reliably persist year-round in older adults, stressing the need for alternative vaccination strategies that could provide better clinical outcomes (Young et al. 2017). Once infection occurs, other immune defense mechanisms are needed to prevent serious complications from influenza infection.

Several factors have been described as determining the limited success of influenza vaccination among elderly adults. In addition to age, other host-related factors such as preexisting immunity, genetic polymorphisms, and the presence of chronic underlying conditions may compromise influenza vaccine responsiveness (Castrucci 2018, Dhakal & Klein 2019). Influenza infection and associated complications have been associated with frailty in hospitalized elderly individuals (Andrew et al. 2017, McElhaney et al. 2012, Yao et al. 2011).

For many years decreased T cell function has been considered to be the most significant contributor to decreased influenza vaccine responses in the elderly. Intrinsic B cell defects also have been found to contribute to lower influenza vaccine responses in elderly individuals (Frasca et al. 2012, 2013b,c, 2014) as well as in individuals in other risk groups (Frasca et al. 2013a, 2016b; Kobie et al. 2011). Recent studies have shown that the transcription factor PAX5, a master regulator of B cell differentiation, is reduced in mature B cells from elderly individuals and is associated with increased proinflammatory B cells, which are unable to respond to influenza vaccination (Nipper et al. 2018). In addition, defects in DCs from elderly individuals have been associated with low antibody response to the influenza vaccine (Panda et al. 2010).

Latent CMV infection is common in older adults and has been shown to accelerate aging of the immune system due to the induction of dysfunctional, terminally differentiated $CD8^+$ T cells (Derhovanessian et al. 2013). Although persistent CMV infection has been implicated in defective antibody responses to influenza vaccine with aging, some studies have shown negative CMV effects (Frasca et al. 2015, Haq et al. 2017) and others no effects (Furman et al. 2015). Recent data suggest that CMV status does not impact the response to vaccination but rather impairs cellular responses to influenza virus challenge. A meta-analysis and review (van den Berg et al. 2019) of 17 studies on the antibody response to influenza vaccination in association with CMV infection concluded that there is no unequivocal evidence that latent CMV infection affects the antibody response to vaccination. One

possible reason for this result is that CMV DNA (latent viral load) may be a better measure of current CMV status than serum IgG titers and therefore a stronger correlate of immunological burden (Merani et al. 2018).

Genetic changes in the antibody repertoire and epigenetic modifications during aging are also involved in the quality/effectiveness of the immune response to influenza vaccine in the elderly. Analysis of the human antibody repertoire performed in young and elderly individuals before and after influenza vaccination showed that over decades BCR repertoires become increasingly specialized but less plastic. In this study (de Bourcy et al. 2017), older subjects exhibited both a contracted naive repertoire and decreased intralineage diversification, suggesting that older B cells have a reduced ability to generate novel antibody responses and improve BCR specificities by SHM. A recent study (Gensous et al. 2018) of baseline whole-genome DNA methylation in peripheral blood mononuclear cells of responders and nonresponders to influenza vaccination of different ages identified possible age-related DNA methylation contributors to vaccine responsiveness. Epigenetic and transcriptomic profiles and humoral immune response outcomes in 50–74-year-old healthy recipients of the influenza vaccine showed that sites of methylation are associated with known differentiation-signaling and antigen-presentation pathways. A broad list of CpG sites showing associations with gene expression and vaccine-induced humoral immune outcomes was defined. Further studies of these epigenetic trends on larger independent cohorts are needed to identify epigenetic biomarkers that can predict vaccine efficacy.

Changes with age in plasmablasts, the transient population of B cells activated upon antigen exposure (Wrammert et al. 2008), also affect the response of the elderly to the influenza vaccine (Sasaki et al. 2011). Earlier research on plasmablast responses showed that the lower antibody response to influenza vaccination in the elderly is primarily due to reduced quantities of vaccine-specific antibodies rather than a reduction in antibody avidity or affinity. The authors of this study, Sasaki and colleagues (2011), also suggested that exposure history affects the cross-reactivity of vaccination-induced antibodies. In line with these findings, analyses of the clonal structure and mutation distribution of B cell repertoires have shown that elderly individuals had increased numbers of mutations in their repertoires before vaccination, suggesting that priming by previous infections or vaccinations may have occurred (Jiang et al. 2013). In contrast, as reported in Section 3.3, our published results (Khurana et al. 2012) have shown a significant decrease with age in the generation of high-affinity antibodies specific for the pandemic (p)H1N1 influenza vaccine, as measured by antibody-antigen complex dissociation rates using real time kinetics in surface plasmon resonance.

4.2. Responses to Pneumococcus Vaccine

Infection with the gram-positive bacteria *Streptococcus pneumoniae* (or pneumococcus), a common pathogen in the nasopharynx most often associated with pneumonia, represents a major cause of morbidity and mortality. The risk of infection is higher in the elderly, with people ≥65 years of age experiencing up to a fivefold increase in the incidence of and death due to pneumococcal community-acquired pneumonia relative to younger controls (Jain et al. 2015).

Before antibacterial treatments were available, more than 70% of patients hospitalized for pneumococcal pneumonia died of the infection, and mortality rates were higher in older adults (Austrian & Gold 1964). By the end of the twentieth century, mortality rates dropped to 20% in individuals ≥65 years of age and to 40% in those ≥85 years of age (Bennett et al. 1992, Breiman et al. 1990, Plouffe et al. 1996).

The incidence of pneumococcal pneumonia increases with the number of comorbidities (Shea et al. 2014), and inflammaging is also associated with increased susceptibility to pneumococcal infection, with higher disease severity and decreased survival in elderly as compared with young individuals (Antunes et al. 2002, Yende et al. 2005). Moreover, age-related changes in the upper respiratory tract (URT) microbiota have been suggested to contribute to *Streptococcus pneumoniae* colonization and its inefficient clearance, as shown by studies conducted in both mice (Thevaranjan et al. 2016) and humans (Whelan et al. 2014). The URT is colonized by several different species of pathogens and is continuously exposed to bacteria present in the environment, which survive in the nasal and oral cavities of older individuals due to the loss of resistance to colonization and altered immunity.

Although deaths and hospitalizations related to pneumonia have decreased substantially in the postvaccination era (Simonsen et al. 2011), older adults respond less effectively to pneumococcal vaccines and remain increasingly susceptible to pneumococcus infection, which can be explained by immunosenescence mechanisms (Krone et al. 2014). In addition to reduced B and T cell responses with aging, impaired functions of IgG antibodies, complement components, and neutrophils are involved in decreased opsonization, which is one of the most important immunological strategies against pneumococcal infection (Simell et al. 2011).

For adults ≥65 years of age, two vaccines are available: the 23-valent pneumococcal polysaccharide vaccine (PPV23) and the 13-valent pneumococcal conjugate vaccine (PCV13). PPV23 induces antibodies by a T cell–independent mechanism, resulting in short-lived responses; it is less immunogenic in elderly individuals than in younger controls, with decreased IgM opsonic activity and potency (Park & Nahm 2011). The reduction of switched memory B cells in the elderly has also been suggested as a cause of the lower response to the vaccine (Leggat et al. 2013). Data on the efficacy of PPV23 against community-acquired pneumonia is very heterogeneous, ranging from no effect to around 50% efficacy in many studies. These differences depend on important variations in study inclusion criteria and variations in the quality and focus of the studies (Van Buynder & Booy 2018), stressing the need to achieve a more effective direct vaccine in the older adult population.

In the PCV13 vaccine, bacterial polysaccharides are covalently conjugated to an immunogenic carrier protein, which induces a T cell–dependent immune response that in turn induces B cell memory. PCV13 is common in many pediatric immunization programs, and recent data from the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) study (Bonten et al. 2015) led to its licensing in several countries for older persons. PCV13 has a well-established immunogenicity and safety profile, but data are lacking on efficacy and effectiveness in adults (Marra & Vadlamudi 2019). Because few

countries have adopted PCV13 for routine adult immunization, future studies will provide better data to evaluate the effectiveness of PCV13 in this setting. In addition, implementation of two different vaccines administered under very specific schedules may be difficult, raising concerns about immunization adherence (Berical et al. 2016). Nevertheless, vaccines with a broader coverage and duration of protection are needed. Novel strategies should aim at improving the functionality of vaccine-induced antibodies in older people or targeting alternative molecules such as surface proteins or noncapsular antigens (Adler et al. 2017). A mucosal vaccine with an appropriate adjuvant would be an attractive strategy that is currently under investigation (Adler et al. 2017, Kataoka et al. 2017).

4.3. Responses to Respiratory Syncytial Virus Vaccine

The importance of RSV is increasingly recognized in hospitalized adults, mainly in those 65 years and older. Vaccines for the prevention of RSV infections are not yet available, and development efforts are made more difficult in the older population by age-associated decreases in immune responses.

RSV infection in elderly individuals causes great suffering due to hospitalization and death and is considered a social burden similar to that of seasonal influenza (Falsey et al. 2005, Haber 2018). The clinical manifestations of RSV infection are similar to those caused by other RTIs. Most of the studies published on hospitalizations due to RSV infections have been conducted in individuals ≥ 65 years of age, with at least 10% of cases due to acute respiratory illnesses following RSV infection. Elderly individuals with chronic obstructive pulmonary disease and/or congestive heart failure, cerebrovascular diseases, Alzheimer's disease, cancer, or T2DM have been shown to be at higher risk.

5. OBESITY AS A MECHANISM OF B CELL AGING

The increase in obesity rates is a worldwide concern. The prevalence of obesity varies in different US states, and in the United States as a whole is higher in African American and Hispanic adult individuals (Cent. Dis. Control Prev. 2018).

Obesity is associated with several chronic diseases of old age such as cardiovascular disease, T2DM, cancers, psoriasis, atherosclerosis, inflammatory bowel disease, and fatty liver disease (reviewed in Frasca & McElhaney 2019, Frasca et al. 2017a). An alarming problem is the decreased proportion of obese patients responding to vaccination (Frasca et al. 2016b, Ovsyannikova et al. 2014, Sheridan et al. 2012), which may further affect the outcome of infection and lead to significant health and economic consequences. Obesity is an inflammatory condition associated with chronic activation of the immune system, systemic inflammation, and immune dysfunction, similar to what has been observed during aging. Obesity induces attenuated antibody responses to the influenza vaccine, as we (Frasca et al. 2016b) and others (Sheridan et al. 2012) have shown, with young obese individuals showing responses similar to those of elderly lean individuals, suggesting that obesity accelerates age defects in B cells. This may be due to obesity-driven increased inflammaging and persistent immune activation. This represents an additional risk factor for the elderly, in which the prevalence of chronic disease as well as the occurrence of complications increases as compared with younger controls. Indeed, B cells from obese individuals show higher

expression of SASP markers, and their peripheral blood B cell pools are characterized by higher frequencies of the proinflammatory DN B cell subset, which is able to spontaneously secrete proinflammatory cytokines and chemokines as well as other markers of the SASP (Frasca et al. 2017b).

Obese adipose tissue (AT) is heavily infiltrated with B cells in both mice (Frasca et al. 2017d) and humans (Frasca et al. 2018), which we call AT-B cells. These AT-B cells are recruited by chemokines secreted by the adipocytes, for which they express the corresponding receptors (Frasca et al. 2018). A recent publication (Camell et al. 2019) has shown that aging in mice is associated with the expansion of a unique population of tissue-resident B cells localized in fat-associated lymphoid clusters. These B cells are proliferating and inflammatory, are transcriptionally distinct from splenic ABCs, and are expanded in female mice; their expansion is dependent on Nlrp3 inflammasome activation. Either inhibition of Nlrp3-dependent B cell accumulation by blocking IL-1 signaling or intra-AT removal of B cells with anti-CD20 antibodies was able to rescue the metabolic impairment of the aging AT. These results demonstrate that the Nlrp3 inflammasome, a major regulator of age-related inflammation and metabolic disorders, may be effectively targeted to reduce AT inflammation and the associated complications.

Our recently published results in humans (Frasca et al. 2018) have shown secretion of AT-specific IgG autoimmune antibodies in the obese subcutaneous AT. We have identified several mechanisms responsible for the release of self-antigens, the induction of class switch, and the production of autoimmune antibodies. These mechanisms include reduced oxygen availability in the obese AT (leading to hypoxia and reduced mitochondrial respiration), NK cell cytotoxicity, and DNA damage. All of these factors induce cell death and the release of additional intracellular content such as proinflammatory cytokines, protein antigens, cell-free DNA, and lipids. These molecules stimulate class switch and the secretion of autoimmune IgG antibodies that have been described to be pathogenic (Winer et al. 2011), as they may form immune complexes and activate the complement and Fc receptors on immune cells, leading to enhanced local inflammation, remodeling of the AT, impairment of adipocyte function and nutrient metabolism, and deterioration of obesity-associated conditions. This represents a novel mechanism by which DNA released from cells dying in the AT may attract immune cells expressing TLRs, which may propagate the inflammatory response, as recently shown in murine macrophages. AT-specific IgG antibodies are secreted in the human obese AT by AT-B cells that express mRNA for AID. These AT-B cells also express mRNA for the transcription factor T-bet and the membrane marker CD11c, which are both involved in the production of autoimmune IgG antibodies. AT-specific IgGs are also present in the plasma of obese individuals. We have recently characterized these antigenic specificities using immunoprecipitation and mass spectrometry (Frasca et al. 2020). We believe that these results, the first of their kind, are very important for the development of novel therapeutic strategies of intervention to control autoimmunity.

ACKNOWLEDGMENTS

This study was supported by National Institutes of Health grants R56 AG32576 (D.F. and B.B.B.), R56 AG059719 (D.F.), and R01 AG023717 (B.B.B.).

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