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AGE-RELATED FACTORS THAT AFFECT B CELL RESPONSES TO VACCINATION IN MICE AND HUMANS

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Abstract

Aging significantly changes the ability to respond to vaccinations and infections. In this review, we summarize published results on age-relared changes in the response to infection with the influenza virus and on the factors known to increase influenza risk infection leading to organ failure and death. We also summarize how aging affects the response to the influenza vaccine with a special focus on B cells, which have been shown to be less responsive in the elderly. We show the cellular and molecular mechanisms contributing to the dysfunctional immune response of the elderly to the vaccine against influenza. These include a defective interaction of helper T cells (CD4+) with B cells in Germinal Centers, changes in the microenvironment, and the generation of immune cells with a senescence-associated phenotype. Finally, we discuss the effects of aging on metabolic pathways and we show how metabolic complications associated with aging lead to immune dysfunction.

Keywords

Aging; B cells; T cells; vaccine responses; immunometabolism

1| The impact of aging on humoral immunity to vaccination

1.1. Aging and influenza infection

Aging induces a progressive reduction of immune function (immunosenescence). Humoral immune responses are impaired by aging, and elderly individuals become more prone to viral and bacterial infections[1,2]. Hospitalization following infection with the influenza virus

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CONFLICT OF INTEREST:
None

is higher in the elderly than in younger individuals and this represents a significant contributor to the reduction in function and development of disability[1].

The Centers for Disease Control and Prevention (CDC) performs evaluations of influenza infections and associated hospitalizations through the Influenza Hospitalization Surveillance Network (FluSurv-NET), which covers approximately 27 million people, representing the 9% of the U.S. population (https://www.cdc.gov/mmwr/volumes/68/wr/mm6824a3.htm). Data from the 2018–2019 season have shown that, similar to previous seasons, hospitalization rates were higher among individuals >65 years of age and older, who accounted for a large percentage (almost 50%) of reported hospitalizations due to influenza infection. Among all influenza-associated hospitalizations, 95% were associated with influenza A virus, 4% with influenza B virus and only few with influenza A and B virus coinfection. Among those with influenza A virus, almost 50% were with the A/H3N2. The A/H3N2 virus, since its introduction in 1968, has undergone genetic and antigenic changes leading to several seasonal epidemics[3]. A/H3N2 is the most common subtype affecting elderly individuals[4], leading to the highest hospitalization rates and death[5].

Influenza infection is controlled by an initial antibody response needed to allow the development of T cell-mediated immune responses. With regards to T cells, CD8+ T cells are more effective than CD4+ T cells in terms of ability to clear virus[6–9]. Infection induces local pulmonary inflammation and then influenza-specific CD8+ T cell immune responses, which are needed for the clearance of influenza virus[10–13]. Viral clearance occurs through killing of infected pulmonary cells via mechanisms mediated by perforin[13], Fas[13], and/or TRAIL[14].

Not only age, but also other factors increase the risk of influenza infection leading to organ failure and death. These include chronic lung and cardiac disease, metabolic disease, immunosuppression, obesity, and neuromuscular disorders[15]. Frailty is a measure of decrease in health and physical function, and increase in vulnerability. Frailty is a significant predictor of health outcomes and is another risk factor for influenza infection[16]. Frailty has been shown to be associated with an overall increased mortality risk and decline in functional status among older adults. Importantly, influenza infection and associated complications have been correlated with frailty in hospitalized elderly individuals[7,17,18].

1.2. Aging and influenza vaccination

Although antiviral drugs are effective in protecting from influenza infection, vaccination is still the best way to prevent infection with the influenza virus[19]. Due to the increase in the aging world population, prevention of infection in the elderly represents an important public health concern. The influenza vaccine induces initially specific antiviral B and T cells that result in protective humoral and cellular immune responses, respectively[20]. The antibody response to the vaccine represents the initial line of protection from subsequent infection. However, age-related decreases in humoral immune responses have been reported and these are responsible for reduced responses of the elderly to vaccination[1,2,21–26]. Not only the production but also the time of duration of protective humoral and cellular immune responses following vaccination decrease with age[27]. Older adults (≥65 years of age) account for more than 90% of seasonal influenza-related deaths and hospitalizations. For

this reason, yearly influenza vaccination is strongly recommended for these vulnerable individuals to protect them from infection and associated complications. Vaccination has been shown to significantly reduce disease burden and transmission of the infection to individuals living within the community.

In general, young individuals have more robust antibody responses as compared to elderly individuals when vaccinated for the first time, but after subsequent vaccinations the difference between the two age groups is reduced, suggesting the importance of previous vaccination and/or infection[28]. Repeated vaccinations with the same vaccine results in a significant increase in specific antibodies and serum titers in both young and elderly individuals[29]. However, influenza vaccine-specific antibodies do not reliably persist year-round in older adults, suggesting that alternative vaccination protocols providing better clinical benefits are needed[30]. Elderly individuals who have been vaccinated, however, can still become infected with severe additional complications that lead to hospitalization, catastrophic disability, deterioration of underlying medical conditions and death[1,22,25]. But there is evidence that those immunized have a less severe illness.

Several causes have been described as factors determining the limited success of influenza vaccination among elderly adults. In addition to age, history of previous vaccinations, individual's genetic background, and chronic underlying conditions may compromise the capacity of older adults to generate protective responses after influenza vaccination[31,32].

Seasonal influenza vaccines aim to produce high affinity neutralizing antibodies that protect from infection. Antibody responses are the gold standard to measure influenza vaccine-specific protective responses. This is significantly decreased in the elderly, in part due to decreased generation of specific protective antibodies[4,20,33–36], switched memory B cells[34,35,37–39] and long-lived plasma cells[40,41]. The majority of high affinity neutralizing antibodies are specific for the head domain of the strain-specific viral hemagglutinin (HA) molecule but some may also be directed toward the more conserved HA stalk region[42–44]. These high affinity antibodies are generated following many rounds of somatic hypermutation (SHM) of the immunoglobulin (Ig) variable regions genes in Germinal Centers (GCs)[45]. The GC is a microstructure that develops in secondary lymphoid tissue during an immune response and is responsible for the generation of plasma cells that secrete specific antibodies as well as memory B cells. The generation of a robust GC response is critical for the production of high affinity antibodies, since this is where SHM and affinity maturation of Ig genes occurs[46]. Age-associated defects in the ability to generate high affinity antibodies in response to influenza vaccination have been reported in both mice[47–49] and humans[50,51], and has been correlated with age-related dysfunctional innate and adaptive immune cells.

The reduced response of the elderly to influenza vaccination has been associated with the age-decrease in T cell function[27,52,53], decreases in naïve T cells and parallel increases in memory/effector T cells[54], loss of CD28 expression[55], and increased cytomegalovirus (CMV) seropositivity[56]. In most studies, CMV-positive individuals that are ≥60 years of age, as compared to age-matched CMV-negative individuals, have lower influenza vaccine-specific antibody responses[57–60], and this is associated with increased frequencies of

senescent CD4+ T cells with a terminally-differentiated phenotype (CD45RA+CCR7-CD27-CD28-). These cells produce significant amounts of IL-10[7], a cytokine known to suppress the activation of cytotoxic T lymphocytes and to down-regulate the expression of costimulatory molecules on antigen-presenting cells[61]. High IL-10, together with reduced IFN-γ production, also reduces the generation of memory T cells in response to influenza vaccination[7,62].

A recent study has shown that human effector memory CD8+ T cells, known to increase in frequency in the blood of elderly individuals, include two different subsets characterized by low and high expression of the IL-7Rα receptor[63]. The two subsets show different expression of effector molecules, transcription factors, and DNA methylation profiles, with the IL-7Rα^{low} subset expressing high levels of perforin, granzyme B, IFN-γ, TNF-α and the senescence-associated marker CD57, and being highly cytotoxic and pro-inflammatory. This subset was also characterized by increased expression of the chemokine receptors CX3CR1 and CXCR1[64,65]. It was found that elderly individuals who are responders to the influenza vaccine have increased frequencies of the IL-7Rα^{low} subset as compared to elderly non-responders. The authors speculate that the increased expression of chemokine receptors may have induced a faster migration of these cells to the sites of vaccine injection where they may have been responsible for higher secretion of pro-inflammatory cytokines and better immune responses through the release of cytotoxic mediators[63].

B cells also undergo profound age-related changes. These include a redistribution of B cell subsets in the peripheral blood with significant increased frequencies and numbers of pro-inflammatory B cells; decreases in the expression of molecules involved in Ig class switch recombination (CSR) and SHM, two processes leading to the generation of high affinity protective antibodies, as well as GC formation; and decreases in repertoire diversity. In vitro experiments have characterized age-defects in B cells and shown that mitogen-stimulated human B cells from elderly individuals have decreased expression of activation-induced cytidine deaminase (AID), the enzyme that regulates CSR and SHM, and secrete less IgG as compared to those from young individuals. Influenza vaccine-specific antibody responses are reduced in the elderly, mainly due to intrinsic defects in B cells but also to defects in antigen presentation and T cell help. AID is a B cell biomarker of antibody responses which 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 novel pandemic (p)H1N1 influenza vaccine[34,51,66,67].

As opposed to serum antibodies, memory B cells generated in response to the influenza vaccine are maintained in aged humans[68], suggesting an intrinsic defect of memory B cells to differentiate into plasma cells. The generation of vaccine-specific antibody responses is negatively associated with inflammation, measured by serum TNF-α[69]. Human B cells isolated from the peripheral blood of elderly people express higher levels of TNF-α mRNA than those from young individuals. B cell intrinsic TNF-α positively correlates with serum TNF-α and both negatively correlate with B cell function, measured by AID. Only memory B cell subsets express TNF-α mRNA and more in elderly than in young individuals[70].

Age-related decreases in immune responses of dendritic cells (DCs) and monocytes include a reduced recruitment and function, such as reduced TLR-induced cytokine production, phagocytosis, granule release and microbial activity. Myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) from elderly individuals secrete significantly less pro-inflammatory cytokines such as TNF-α, IL-6 and IL-12 (p40) in response to the stimulation with TLR agonists and these defects have been correlated with low responses to the influenza vaccine[71]. Classical monocytes (CD14+CD16-) are induced after influenza vaccination in both young and elderly individuals[72], but those from older individuals secrete less TNF-α and IL-6, and more IL-10, after in vivo stimulation with the vaccine[73]. This cytokine secretion profile is associated with the reduced production of influenza vaccine-specific antibodies in elderly individuals[72].

2 | The impact of the aged / senescent environment on the humoral response to vaccination

While age impacts the B cell response to the influenza vaccine in both human and mouse models, most mechanistic insights have come from the examination of what occurs in mice and it is well documented that the B cell response to vaccination in aged mice is different and less good than that in young mice. The major causes of the age-associated decrease in vaccine responses are summarized in Fig. 1.

The secretion of high affinity antibodies depends on the efficient interaction of antigen-specific B cells and CD4 T helper (Th) cells within the GC. One of the critical components necessary for a robust GC response is the proper differentiation of CD4 T cells. Naïve CD4 T cells can differentiate into various helper subsets such as Th1, Th2, Th9, Th17, T follicular helper (Tfh), and regulatory T cells (Treg) following antigenic stimulation by DCs in the presence of environmental cytokines[74]. Each of these subsets has a distinct role in an immune response, which has been tailored for the situation prompting the response: for example, IL-4 induces the generation of Th2 cells which are effective at clearing parasites such as helminth worms, while IL-12 and IFN-γ induce the generation of Th1 cells which are effective at clearing intracellular pathogens such as viruses. Important for this discussion, Tfh cells are vital for a robust GC response and high affinity antibody production from the GC cannot proceed in the absence of Tfh[75].

2.1. Impact of the aged environment

With aging, there are reduced levels of the chemokine CXCL13, a B cell chemoattractant chemokine 13 in the B cell follicles[76,77] and since this chemokine is important for the proper trafficking of CD4 Tfh cells to the B cell follicle during an immune response[78], the CD4 T cell help available to B cells declines with age. In addition, the aged environment also impairs naïve CD4 T cell differentiation into Tfh cells by an unknown mechanism, so that there are fewer T cells available to help a B cell response[76]. Important for this discussion are T follicular regulatory cells (Tfr), which can be generated *de novo* from Foxp3+ natural regulatory T cells (Treg)[79]. These Tfr can work to limit B cell help, B cell responses and germinal center formation, thus reducing the robustness of an ongoing humoral response[79,80]. The critical factor during a GC response which determines the magnitude of

the antibody response is the ratio of Tfh:Tfr[81,82]. Importantly, more Tfr cells accumulate in old versus young mice[83], ultimately resulting in fewer GC B cells and reduced high affinity antibody production following vaccination of aged mice. It is also noteworthy that not only is the Tfh:Tfr ratio impacted by aging, other CD4 T cell subsets that are infrequent in young mice, such as activated regulatory T cells, exhausted and cytotoxic subsets, co-emerge in old mice[84].

Adoptive transfer experiments performed in mice have shown that the aged environment plays a crucial role in many of these age-related changes in humoral immunity. When young donor CD4 T cells are transferred into old immunized hosts, the young donor T cells do not differentiate to a Tfh phenotype as readily as they do in young hosts[76]. In addition, TGF-β in the aged environment promotes the expression of the transcription factor forkhead box P3 (FOXP3) in the responding Tfh cells, thus driving them to differentiate to Tfr, which further limits the humoral response[85]. The end result of fewer Tfh cells and more Tfr cells is that there are fewer and smaller germinal centers in the aged hosts receiving young T cells when compared to young hosts. This reduced germinal center formation can then result in less affinity maturation of antibodies and induction of an overall less protective humoral response.

2.2. How senescence can impact the humoral response

What is different about the aging environment that can drive these age-related differences in CD4 T cell differentiation and negatively impact the humoral response to vaccination? One of the main differences between young and aged individuals lies in the presence of the senescent cells in the aged tissue microenvironment. Aging increases the number of cells characterized by a senescent phenotype[86] and this can have a dramatic impact both systemically and in local tissues. A senescent cell is defined by cell cycle arrest and the inability to proliferate upon stimulation with a mitogenic challenge, which can occur in response to various cellular stresses. A variety of different stressors have been shown to induce senescence. These include telomeric and non telomeric DNA damage, such as telomere shortening after several cell divisions (replicative senescence), oxidative stress, mitochondrial deterioration, and oncogene expression[87]. While there is not a single identifying biomarker for senescence, some of the most common ones include expression of senescence-associated beta-galactosidase, elevated expression of $p16^{INK4A}$, hypophosphorylated retinoblastoma protein, telomere damage, senescence associated heterochromatic foci, and several soluble factors that constitute the senescence associated secretory phenotype (SASP)[88]. The SASP is especially important in vivo since it is composed of soluble factors that can become systemic including cytokines, chemokines, bradykines, prostenoids, micro RNAs (miRNA), and damage associated molecular pattern proteins (DAMPs)[89–91]. One of the key factors in senescence is that while a senescent cell does undergo cell cycle arrest, it can still be transcriptionally active and secrete numerous inflammatory molecules of the SASP. When the SASP factors are released by senescent cells, they can impact cells within the local tissue and/or systemically, as well as cells of the immune system. This point is particularly important since cytokines and chemokines are two of the main components of the SASP and have the potential to impact the function of innate and adaptive immune cells. The cytokines that are often components of the SASP include

IL-6, IL-8, IL-1α, TGF-β and GM-CSF[92]. TGF-β is of special importance in this list since it is one of the main inducers of CD4 T cell differentiation, inducing a Treg phenotype characterized by FOXP3 expression[93]. These induced Tregs (iTregs), much like thymus generated Tregs, can act to constrain an adaptive immune response and limit antibody production[94] and Treg populations have been shown to be increased with both murine[95–98] and human[99,100] aging. IL-6 is another SASP component that plays an important role in CD4 T cell differentiation. It is involved in generation of both Tfh and Th17 subsets[101,102] and, in fact, Th17 cells and IL-17 production by CD4 T cells is elevated with aging[103–105]. Thus, CD4 T cells that undergo differentiation within a senescent environment are likely to produce T helper subsets that are distinct from those generated in a young non-senescent environment and this has the potential to impact the adaptive immune response in older individuals.

Also, the chemokines CXCL1 (GROα), CXCL2 (GROβ), CCL2 (MCP-1), CCL5 (RANTES), CCL20 (MIP-3α) and CCL26 (eotaxin-3) can be notable components of the SASP[92]. These chemokines can act to enhance inflammation, trafficking and recruitment of cells of the innate and/or adaptive immune systems, thus contributing to age-related inflammation both locally and systemically. This is especially problematic when senescent cells develop in organs like the lungs and recruit responding T cells to an inflammatory environment where their differentiation program may not be similar to what occurs in a young, non-inflammatory environment.

2.3. B cell senescence

In addition to the senescent environment impacting the generation of robust humoral responses, B cells themselves can begin to exhibit senescent traits in older individuals. In mice, percentages and numbers of splenic B cells are maintained with age but there is a shift in the proportions of the different B cell subsets, characterized by increasing numbers of age-associated B Cells (ABCs), at the expense of the Follicular (FO) B cell subset, so that the total number of splenic B cells does not change significantly[106–108]. In humans, conversely, B cell percentages and numbers are significantly and progressively decreased with age[109–113] and there is also a shift in the proportions of the different B cell subsets with a decrease in the percentage of switched memory B cells, no change in IgM memory and a significant increase in the percentage of naïve and the subset called Double Negative (DN) B cells[70,110]. DN B cells have been shown to be similar to mouse ABCs, generated from conventional mature B cell subsets (naïve in humans, FO in mice) after in vivo or in vitro stimulation with TLRs. These cells have previously been called late/exhausted memory or tissuelike memory B cells, and they represent the most pro-inflammatory B cell subset, which has been reported to be also increased in the blood of patients with autoimmune[114–116] and infectious diseases[117–119]. These observations have suggested that DN B cells may accumulate in vivo in inflammatory conditions and in the presence of chronic stimulation with self antigens or viral/parasitic antigens, and may secrete autoimmune or protective antibodies, respectively. This occurs in autoimmune diseases in which B cells are chronically exposed to self antigens and in infectious diseases in which B cells are continuously exposed to and stimulated by viral or parasitic antigens, as it occurs in HIV or malaria, respectively. In both examples, DN B cells represent a terminally

differentiated B cell subset that has undergone class switch in response to chronic stimulation and cannot be restimulated in vivo and/or in vitro.

DN B cells are transcriptionally and metabolically active and secrete several pro-inflammatory factors such as cytokines (TNF-α, IL-6), chemokines (IL-8) and micro-RNAs (microRNA-16, 155, 93), which are all components of the SASP[70]. DN B cells are therefore able to sustain and propagate systemic inflammation[70]. DN B cells show no proliferation and antibody secretion in response to "new" antigens (influenza vaccine), even in individuals previously vaccinated, but they secrete autoimmune antibodies in both mice[120] and humans[121]. They do so because they express the membrane phenotype CD95+CD21-CD11c + and they also spontaneously express the transcription factor T-bet, both associated with autoimmunity[110,121]. The frequency of this B cell population in the blood is negatively correlated with induction of a protective response following influenza vaccination. As opposed to human DN, mouse ABCs have specificity for a live influenza virus (A/PR8/34) and this occurs only in mice infected and not in naïve mice. Similar to human DN B cells, mouse ABCs do not have specificity for the influenza vaccine. The influenza-specific ABC response is non-follicular and helper T cell-independent, but requires the presence of the virus. Influenza-specific ABCs differentiate into specific antibody-secreting cells, some of which home to bone marrow and lungs, and persist for long periods of time after infection (>4 weeks), suggesting their role in providing significant protection[122].

3 | changes in B cell metabolism WITH AGE

3.1. Introduction to immunometabolism

Metabolism and immunity have been considered for a long time to be two independent systems, with the metabolism regulating transformation and assimilation of nutrients and the immune system regulating innate and adaptive immune responses against pathogens and vaccines. Ongoing research however shows that these two systems work together controlling the individual's response to stress. Metabolic studies represent a rapidly emerging and evolving field of research. Lymphocyte metabolism is now recognized as a crucial regulator of cellular homeostasis and function[123].

Effector cell function is intrinsically linked to cellular metabolism and it has been shown, at least for T cells[124,125] and macrophages[126,127], that several metabolic enzymes and their regulators can also have a direct effect on the regulation of cell function. Cell activation is critically supported by metabolic shifts that produce energy for cell activation and differentiation, suggesting the exciting possibility that cell function in various conditions could be regulated by an intervention targeting cell's metabolism.

The major pathways utilized to generate energy are: 1) glycolysis, in which glucose is incompletely oxidized in the cytosol (anaerobic glycolysis), producing lactate as the final product. It is fast but energy inefficient; 2) oxidative phosphorylation (OXPHOS) in which carbon substrates such as glucose-derived pyruvate, Fatty Acids (FAs) and glutamine are oxidized in the mitochondria to generate ATP; 3) the pentose phosphate pathway, know to produce NADPH upon a shunt of glycolysis, a crucial pathway for the maintenance of cell redox balance and nucleotides. In general, glycolysis is used by cells involved in robust

proliferation and secretion because it provides the biosynthetic precursors needed for nucleotide, amino acid, lipid synthesis [reviewed in[128]]. Intermediates of the glycolytic pathway provide carbon that provides energy for several biosynthetic pathways. Therefore, glycolysis provides all the components needed for proliferation and the synthesis of effector molecules. A better understanding of fuel utilization by immune cells from both mice and humans has gained significant support by extracellular flux analysis, which measures oxygen consumption rates (OCR) and extra-cellular acidification rates (ECAR), as indicators of OXPHOS or anaerobic glycolysis, respectively.

Studies conducted on T cells have shown that resting T cells are quiescent and require almost exclusively the production of adenosine triphosphate (ATP) for basal cell functions[129]. After stimulation, T cells enter the cell cycle, rapidly divide and require both ATP and biosynthetic precursors to support proliferation[129–131]. Memory T cells no longer need to proliferate and therefore decrease their glycolytic metabolism[132]. The transition of T cells from oxidative to glycolytic and vice versa has been shown to regulate not only cell survival but also the expansion of antigen-specific T cell clones and the competitive selection of high-affinity clones[133,134].

It is not known if changes in the metabolic requirements of lymphocytes during immune responses are uniform, or if different stimuli induce different metabolic pathways to drive specific cell functions. In a pro-inflammatory microenvironment, activated CD4+ T cells differentiate into Th1 and Th17 cells, whereas in an anti-inflammatory microenvironment T regulatory (T_{REG}) cells prevail[135,136]. Th1 and Th17 CD4+ T cells express high Glut1 levels and activate glycolysis, whereas T_{REG} express lower levels of Glut1 and rely on OXPHOS and lipid oxidation. Metabolic analysis of CD4+ and CD8+ human T cells has shown that CD4+ T cells have larger mitochondria than CD8+ T cells and almost exclusively engage in OXPHOS to support their effector function. Conversely, CD8+ T cells are more glycolytic, leading to higher proliferation and faster growth[137]. Moreover, human CD8+ EMRA (Effector Memory reacquiring the RA marker) T cells, the subset with pro-inflammatory characteristics that increase with age, and have dysfunctional mitochondrial function but CD4+EMRA T cells have more functional mitochondria able to generate the energy requirements for function[138].

Macrophage M1 and M2 subsets also show different patterns, with inflammatory M1 macrophages being mainly glycolytic, whereas anti-inflammatory M2 macrophages use lipid oxidation[139].

3.2. Metabolic requirements of B cell responses

As opposed to T cells, B cell metabolic requirements for effective cell function have not been thoroughly investigated. It is not well known how metabolic requirements of B cells change after stimulation. Also the metabolic requirements of protective versus autoimmune antibody responses are not well known.

Similar to other immune cells, unstimulated B cells use glucose and fatty acids as sources of energy. B cells stimulated through the B cell receptor (BCR) in both mice and humans upregulate the expression of the glucose transporter Glut1 and primarily activate glycolysis

and to a lesser extent OXPHOS to support their demands of energy for antibody production[140,141]. Published studies have shown that up-regulated expression of Glut1 depends on the activation of mechanisms dependent on the cell cycle regulator c-Myc and phosphatidylinositol-3-OH kinase (PI3K)[141,142]. Glycolytic inhibition or deletion of Glut1 significantly inhibits B cell proliferation and antibody secretion both in vivo and in vitro, suggesting that the importance of glucose transporters in the metabolic reprogramming of cells undergoing proliferation and antibody production.

In the absence of a second co-stimulatory signal, B cells are unable to perform glycolysis and OXPHOS and die, as a consequence of mitochondrial dysfunction resulting from accumulation of intracellular calcium through calcium response-activated calcium channels. The presence of T cells providing a second signal, or the simulation with TLR agonists, prevents cell death, suggesting that BCR signaling activates a metabolic program that controls survival or cell death, depending on the presence or absence of a second signal, respectively[140]. Using RNA-based next-generation sequencing (RNA-seq) to measure changes in the expression of genes encoding enzymes associated with cellular metabolism, it was found that the key glycolytic enzymes hexokinase 2 (HK2) and lactate dehydrogenase (LDHA) were up-regulated, consistent with the increase in glycolysis, whereas genes encoding subunits of the enzyme pyruvate dehydrogenase (PDHX), which catalyzes pyruvate to acetyl CoA, were less up-regulated, confirming that in response to BCR stimulation B cells primarily activate glycolysis and to a lesser extent OXPHOS[140].

Metabolic reprogramming is suppressed in anergic B cells. However, B cells chronically exposed to high levels of BAFF show enhanced and more rapid metabolic reprogramming in response to TLR4 stimulation, with glycolysis being increased rapidly and OXPHOS also increased, but at a slower rate[141]. These results suggest that failure to induce tolerance redirects B cells to a program that is essential for the secretion of (autoimmune) antibodies.

3.3. Age-associated metabolic changes

Aging is associated with several metabolic changes such as enhanced insulin resistance[143,144], reduced mitochondrial function[145,146] and dysregulated nutrient uptake[147]. Each of the nine hallmarks of aging (genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication) is associated with metabolic dysfunction and it has been shown that both hyper-nutrition and sedentary lifestyle can accelerate aging and can have catastrophic metabolic consequences[148]. Similarly, seven pillars of aging were put forward by the Geroscience Interest Group (GSIG) and also include metabolism and inflammation (metabolism, macromolecular damage, epigenetics, inflammation, adaptation to stress, proteostasis, stem cells and regeneration). A study that has systemically integrated in vivo phenotyping with gene expression, biochemical analysis, and metabolomics was performed in young and old mice. Results have allowed the identification of a metabolic footprint of aging, based on altered metabolites in the plasma of young and old mice, that can be used as biomarkers of aging and healthspan[149]. Many of these plasma metabolites have been positively associated with inflammaging[150–153], the chronic inflammatory status of the elderly[154], and negatively

associated with immune function[155–157]. Although several studies have investigated how plasma metabolites fuel inflammaging and vice versa, very few studies have investigated mouse and human metabolic changes in immune cells.

3.3.1. Age-dependent changes in mouse B cell metabolism—One of the few published studies on age-related changes in B cell metabolic pathways has shown that aging induces defects in glucose-induced energy production, leading to decreased OXPHOS. In this study, antibody-secreting cells (ASCs) from the bone marrow of young and old mice were analyzed and whole genome expression arrays were performed[158]. Results showed different expression of 1500 genes involved in both immune and metabolic regulation of cell function. The age-dependent reduction in OXPHOS was associated with decreased expression of both PDHX and LDHA genes, indicating that ASCs from old mice preferentially activate glycolysis rather than OXPHOS for energy production. The activation of glycolysis, moreover, was associated with increased levels of reactive oxygen species (ROS), suggesting higher levels of oxidative stress in ASCs from old as compared to those from young mice. These results provide a metabolic-associated mechanism to support the age-associated increase of ROS with aging, responsible for higher chromosomal instability and DNA mutations, as previously shown[159]. ROS are produced in the cell and in multiple cellular organelles [mitochondria, peroxisomes, endoplasmic reticulum (ER)] in response to stress. Genes regulating mitochondrial respiratory chain proteins known to affect mitochondrial morphology[160] were found higher in ASCs from old versus young mice. Genes regulating peroxisome assembly and size[161], peroxisome metabolism[162] and peroxisome receptors for acyl-CoA esters[163] were also found up-regulated in ASCs from old versus young mice.

B cells infiltrate the obese adipose tissue (AT), recruited by chemokines secreted by the adipocytes and by the immune cells that have infiltrated the AT, for which they express the corresponding receptors[106,164]. A recent publication in mice has shown that aging induces the expansion of AT resident B cells that are highly inflammatory, and their expansion is dependent on the activation of the NLRP3 inflammasome, likely due to AT-associated metabolic and mitochondria dysfunction and increased production of mitochondrial ROS[165,166]. Inhibition of Nlrp3 activation by blocking IL-1 signaling, or intra-AT removal of B cells with anti-CD20 antibodies, inhibits the NLRP3-dependent B cell accumulation and rescues the metabolic dysfunction of the aging AT[164]. These results demonstrate that the NLRP3 inflammasome, a major regulator of inflammaging and age-associated metabolic disorders, may be effectively targeted to reduce AT inflammation and associated complications.

3.3.2. Age-dependent changes in human B cell metabolism—Studies in humans have also shown different expression of metabolic markers in peripheral B cells from young and elderly individuals[167]. In particular, it was found that blood-derived ASCs from elderly individuals had higher mitochondrial mass and mitochondrial ROS and lower Sirtuin1 (SIRT1), an anti-inflammatory marker involved in DNA damage responses and cell metabolism[168]. SIRT1 levels were higher in ASCs from both young and elderly individuals that responded better to vaccination producing higher amounts of H1N1- and H3N2-specific

IgG antibodies. SIRT1 is an anti-aging and anti-inflammatory molecule known to protect from viral infections, including influenza virus infection. When naïve B cells were isolated from the peripheral blood of young and elderly individuals and analyzed by Seahorse to measure OXPHOS by OCR and glycolysis by ECAR, unstimulated B cells from young individuals were found to be higher in both meaures as compared to B cells from elderly individuals. After culture with polyclonal stimuli, both OXPHOS and glycolysis increased as compared to unstimulated B cells and significant defects in OXPHOS, and mild defects in glycolysis, were observed in B cells from elderly versus young individuals. Transcriptome analyses showed additional defects in one-carbon metabolism, a pathway that makes one-carbon moiety (methyl group) available for nucleotide synthesis and methylation[169].

A mitochondrial signature of young and old influenza vaccine responders has identified genes and proteins controlling mitochondrial biogenesis and OXPHOS[170]. Briefly, OXPHOS pathways and crucial genes involved in cellular respiration, mitochondrial DNA transcription and regulation, and heme biosynthesis were found up-regulated in vaccine responders, the majority of which were young. Although this study was performed on PBMCs and therefore it is not known which cell type is responsible for the activation of OXPHOS pathways, it represents the first genome-wide transcriptional analysis of age-associated metabolic measures performed before and after influenza vaccination, showing the crucial role of mitochondrial pathways in human vaccine responses.

We recently compared frequencies and metabolic requirements of DN B cells in the blood of healthy individuals of different ages and in the blood and in the AT of individuals with obesity. Our published results[121] confirmed that DN B cell frequencies significantly increase in the blood of elderly versus young individuals, as we have previously reported[70,110]. Our initial observation on obese individuals was also confirmed as we showed that the frequencies of DN B cells were increased in the blood of obese versus lean young individuals, suggesting that obesity, similar to aging, induces higher frequencies of these pro-inflammatory B cells. In the immune B cell fraction of the AT, DN frequencies are the highest and we observed that some individuals had percentages as high as 50% of the total B cell pool. As to their metabolic requirements, we showed that DN B cells from young individuals show only basal activation levels of OXPHOS, aerobic glycolysis and fatty acid oxidation, whereas DN B cells from elderly and obese individuals show higher activation levels of OXPHOS and glycolysis to support their function. DN B cells from the AT have the highest levels of activation of metabolic pathways as they enroll in OXPHOS, glycolysis and fatty acid oxidation. When we measured the spontaneous secretion of antibodies specific for autoantigens that increase with age, such as dsDNA and MDA (malondealdehyde) in DN and naïve B cells, we found that DN B cells make dsDNA- and MDA-specific autoantibodies whereas naïve do not[121]. MDA is a marker of oxidative stress and product of lipid peroxidation[171], both of which increase with age. Anti-MDA antibodies are also present in the serum of patients with lupus systemic erythematosus[172]. We also found that DN B cells, but not naïve B cells, make autoantibodies specific for AT-derived antigens, in agreement with the observation that fat mass increases with age in humans[173]. The secretion of these autoantibodies occurs without any exogenous stimulation. Therefore, the increased glucose consumption and the activation of OXPHOS, glycolysis and fatty acid oxidation

pathways that we observed in AT DN cells is needed to support their function, i.e. the production of autoimmune antibodies.

DN B cells from the AT are also highly oxidative, and express the highest levels of intracellular ROS as compared to DN B cells from the blood from young and elderly lean individuals and from obese individuals. ROS is a marker of oxidative stress which is sensed by cellular anti-stress proteins such as AMPK (5'-AMP activated kinase) and Sestrin 1, able to reduce both stress and cell death. DN B cells show the highest levels of activated AMPK (phospho-AMPK) and Sestrin 1. AMPK is an enzyme able to sense nutrient changes and is a key metabolic regulator expressed in all mammalian cells[174]. The metabolic advantage of DN B cells in the AT, as compared to DN B cells from the blood drives their increased survival in the hostile pro-inflammatory milieu of the AT. Our results altogether highlight the impact of stress sensing pathways on DN B cell survival and also highlight possible mechanisms leading to the secretion of autoimmune antibodies. Further understanding of the regulation of these metabolic pathways is needed to provide new directions to control the secretion of autoimmune antibodies during aging, obesity and other inflammatory conditions.

CONCLUSIONS

The response to infection and vaccination is dramatically influenced by aging. Since older adults are often targeted for vaccination, this is an important clinical issue. B cells and humoral immunity are crucial components of the immune response and the generation of protective antibodies is the basis for most vaccinations, including influenza vaccines. Aging significantly changes B cell responses including alterations in B cell subpopulations, metabolism and differentiation following vaccination. In addition, B cell extrinsic factors, including the aging senescent environment, also have a negative impact on the generation of a robust humoral response. All of these factors must be considered in order to develop improved strategies for production of novel vaccines for older adults.

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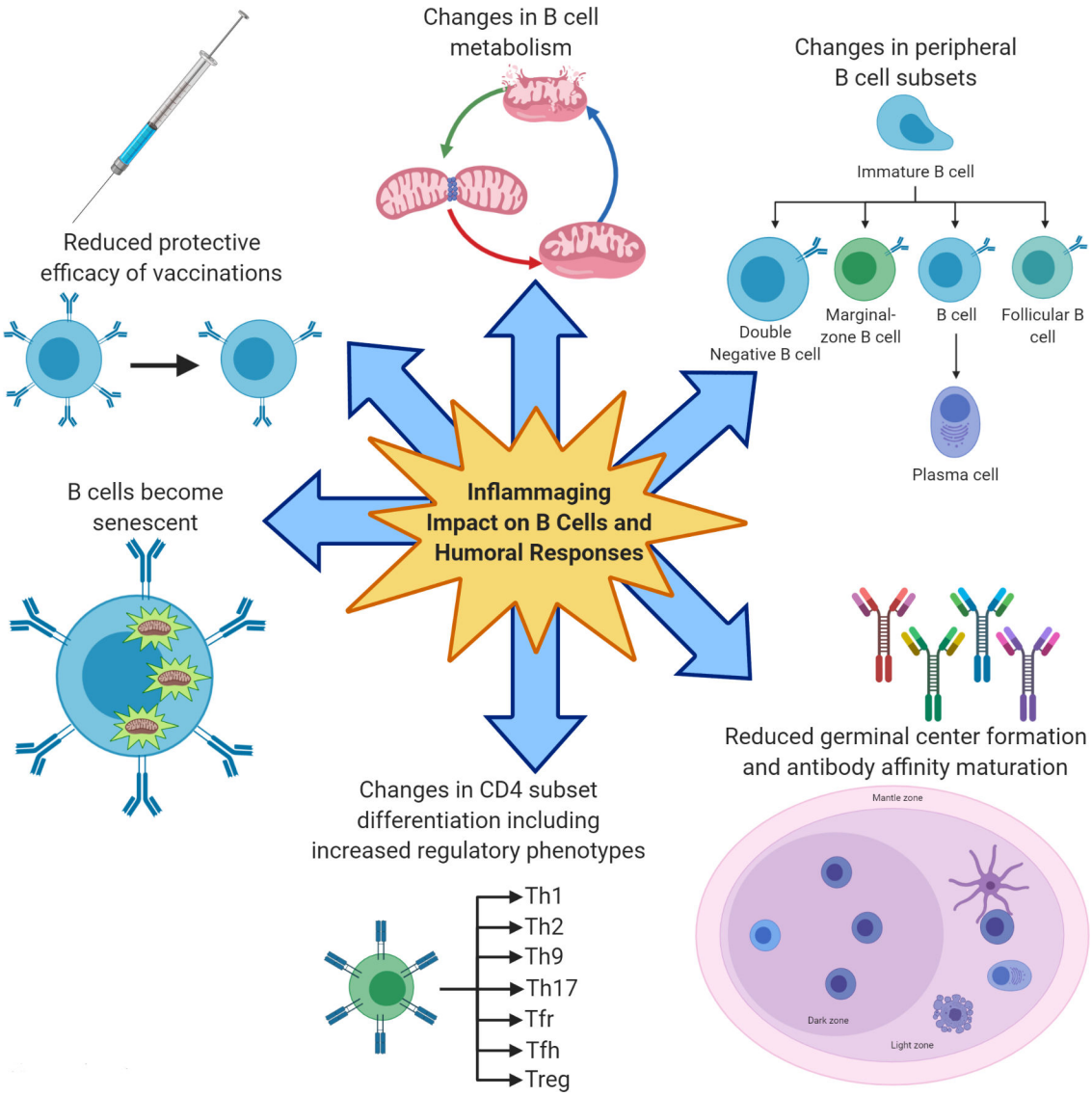

Figure 1. B cell intrinsic and extrinsic factors responsible for reduced vaccine-specific humoral immunity with age.

Reduced humoral responses of aged mice and humans to vaccination are associated with increased inflammaging, the chronic low grade inflammatory status of old age. Inflammaging induces B cell senescence and redistribution of the circulating B cell subsets with an increase in the pro-inflammatory B cell subset called Double Negative, and also impairs the differentiation of naïve CD4+ T cells into effector Tfh cells in the GC leading to changes in the relative proportions of CD4+ subsets with an increase in regulatory subsets. Changes in B cell metabolism with aging also occur and these lead to immune dysfunction.