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Review

The immune system through the ages

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Abstract: The components of the immune system develop in utero and like a computer, some components are immediately functional (the innate components) but other components must learn the programs and details necessary to function (antigen adaptive components). Like other systems, including military and municipal, the innate and antigen specific components develop into an immune system that helps maintain and surveil the other body processes and systems for aberrations, provide surveillance and protection of the mucoepithelial borders and protection from microbial invasion. Inability, excesses, or errors in these processes cause disease. Aging of the immune system brings immunosenescence, inflammaging, more errors, and decreased surveillance which increases risk for new infections (e.g. COVID-19, influenza), recurrence of latent infections, cancer and autoimmune and inflammatory diseases. With greater understanding of the surveillance, effector and regulatory deficits upon aging, better therapies can be developed.

Keywords: immune system; aging; vaccines; autoimmunity; infections; inflammaging; immunosenescence

1. Introduction

The immune system undergoes many changes as individuals age from fetus to neonate to child to adult and older adult. As we age, we accumulate protections necessary to live in, and with the microbial world (including our own microbiome), but also necessary to deal with the challenges of our environment and bad habits (e.g. smog, smoking and over-eating) [1–8]. Like a computer, some

components are immediately functional, like the innate components, but other components must learn the programs and details necessary to function, the antigen-specific component. Like the development of a military for a new country, the immune system first builds an innate, militia-like system to protect the borders and provide a rapid response to the incursions of invaders. With maturity, an infrastructure develops that can coordinate, activate, and regulate a greater number of actors, with more sophisticated weapons and the ability to learn, remember and specifically target enemies. This is provided by the antigen-specific actions of B and T lymphocytes. Although a major priority for the immune system is to be able to combat an infectious challenge, the normal, every-day functions include self-management, surveillance for abnormal (tumor) cells and the means for their elimination, removal of cellular and molecular trash, facilitating the repair and renewal of cells and tissues, monitoring and protecting the borders of the body from microbial invasion and maintaining peaceful interactions between cells through tolerance and suppression of inflammation and excessive responses [9,10].

Ultimately, the goal for the immune system is to develop a balance between the effector functions and the maintenance and regulatory functions without compromise to the protections from microbial attack or tumor surveillance. With aging, the system accumulates weapons and components dedicated to previously encountered enemies (antibodies and T cells), but is less capable of developing weapons against newer ones and to controlling responses to life's challenges (inflammaging) making it more difficult to maintain the balance between effector/inflammatory and regulatory/suppressive functions. This can compromise the system and increase susceptibility to diseases, including inflammatory diseases, and cancers. This review will discuss the development, actions, and consequences of the changes in the immune system as we age and distinctions due to sex and gender (Table 1).

Table 1. Milestones of immune development**.**

	Fetus	Neonate	Childhood	Older adults
Innate immunity	-Yolk sac source of tissue resident and other macrophages and granulocytes. -Fetal liver source of soluble factors, e.g. complement, and hematopoietic stem cells for myeloid and lymphoid cells followed by bone marrow as source.	-Granulocyte, macrophage and complement provide protections. -Establishment of microbiome promotes expansion of protections.	-Granulocyte and macrophage functions optimized and controlled by T helper cells. -Innate immune memory activated by strong stimuli (LPS, viral infections, BCG, etc.) extends and broadens protections. -More active NK cell response limits need for more inflammatory antiviral immunity (e.g. EBV infection).	-Reduced chemotaxis, phagocytosis, and production of reactive oxygen species limits function of neutrophils and macrophages. -Decreased sensitivity of Toll like receptors on dendritic cells and decreased efficiency of antigen presentation to T cells. -Increased systemic inflammation contribute to autoimmune and chronic diseases. -Compromised type 1 interferon response due to deficient sensors and autoantibodies reduces their antiviral response.

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	Fetus	Neonate	Childhood	Older adults
Adaptive immunity	-Development of lymphocytes occur in parallel with fetal liver and then bone marrow, thymus, and secondary lymphoid organs. -Primarily B1 cells producing IgM throughout most of gestation with B2 cells later capable of broader response. -Tregs dominate to limit responses to maternal antigens and to developing and apoptotic fetal cells.	-Microbiota from maternal and fetal stool and skin educate immune response and facilitate development of MALT. -Maternal IgG provides protection for ~3 mo. -Milk provides IgA, IgG for protection and TGFβ for modulation of response. -T cell response at birth switches from Treg, Th2 dominant to better balance with Th1 and Th17 (facilitated by exposure to microbiota).	-New antigenic challenges and vaccines build antigenic response repertoire. -Mucosal exposures to food, inhaled antigens, etc. expands IgA, MALT, and regulatory responses. -Presence of IFNγ producing CD8 T cell enhancing antiviral response which dissipates in adolescence.	-Decreased response to new antigens due to less naïve B and T cells with atrophy of bone marrow, lymph nodes, and thymus gland. -Treg numbers decrease blunting control of autoimmunity and inflammation. -Accumulation of memory CD4 and CD8 T cells to CMV, EBV, etc. blunt response to future infections. -Decreased function of germinal centers attenuates B cell differentiation into plasma and memory cells. -Increase in antigenic mimics and chemically modified proteins and reduced tolerance promote autoantibodies and exacerbate infectious disease. -Impaired response to vaccines.

Abbreviations: LPS: lipopolysaccharide; BCG: Bacillus Calmette Guerin; NK: natural killer cell; EBV: Epstein Barr virus; CMV: cytomegalovirus; IFN: interferon; MALT: mucosal associated lymphoid tissue.

2. Fetus to neonate and childhood: Learning, forming and protecting

While in the womb, the fetus is protected from infection by isolation and by mother's immune system. As described later, she shares her IgG protections with the fetus but her cell mediated immunity is blunted to prevent rejection of "the most common tissue graft".

Development of the fetal immune system starts in the yolk sac with the development of tissue resident macrophages and granulocytes [7]. Although functional, their responses are weak. Hematopoietic stem cells for dendritic cells (DC), other myeloid cells and for lymphocytes develop in parallel with the development of the fetal liver and then in the bone marrow, thymus and secondary lymphoid organs [11]. Yolk sac and fetal liver generate tissue resident macrophages and DCs, such as Kupffer cells, alveolar macrophages, microglia and Langerhans cells. T cells, B cells and immunoglobulin can be detected prior to 20 weeks post gestation. Lymphocyte precursors mature into B cells in the bone marrow or move to the thymus to become T cells. The T cells are primarily regulatory to ensure tolerance towards wayward maternal cells and molecules and to limit the detrimental responses that may occur to the extensive growth, death and remodeling that accompanies fetal development. B cells are primarily B1 natural B cells producing immunoglobulin M (IgM) to facilitate opsonization and future recognition of microbial polysaccharides, including ABO blood antigens. Classical B2 cells, with the potential for a broader antibody repertoire, arrive

much later, near birth, with the development of functional bone marrow, lymph nodes and T cells [12]. Antibody production continues with a slow increase in IgA levels over the course of the first year [13].

Many changes occur upon birth as the system suddenly gets exposed to the microbial world. Protection of the mucoepithelial borders of the body is one of the earliest priorities for the neonatal immune system as the borders get populated with normal and other flora. Prior to the development of mature helper T cell responses (Th17 responses, to enhance neutrophil function: and Th1 responses, to enhance macrophage functions) the phagocytic and killing ability of these cells and the protections they provide are not optimal [12]. Alternative T cells, including invariant natural killer (iNKT) cells, mucosal-associated invariant T (MAIT) cells, interleukin-8-secreting naïve T cells and γδT cells help to bridge this gap with production of cytokines and chemokines [14–19].

While the neonatal immune system develops, the neonate is protected by maternal IgG that crossed the placenta, facilitated by the neonatal Fc receptor [20]. The acquired protection lasts for up to 3 months before dissipating due to the normal turnover of IgG. [21–23]. After birth, mother's milk supplies IgA and IgG to protect the GI tract and help to select the colonizing microbiota. The IgG is absorbed by the neonatal Fc receptor in the intestines [23]. Maternal vaccination and boosting (e.g. Tdap) immunizations can enhance these protections [23]. Mother's milk also provides TGFβ and other stimuli of tolerance to promote a regulated, immunotolerant gut immune response [24].

Birth and exposure to microbial challenges promote transition from the tolerogenic regulatory (Treg) and humoral (Th2) responses of the womb to a more complete antimicrobial response. There is a critical window of opportunity of approximately 100 days for development of a healthy, balanced and responsive immune system facilitated by exposure to maternal flora acquired while traversing the birth canal and from skin upon cuddling [25,26]. The transfer of healthy microbiota educates the immune system and provides the trigger that allows development of proinflammatory antimicrobial proinflammatory Th17 and Th1 responses [27]. Th17 cytokine conversations (IL17, IL22, TNFα) enhance epithelial functions, including antimicrobial peptide production, and neutrophil recruitment and activation. The Th1 cytokine conversations (interferon (IFN)-γ, IL2, TNFβ) include activation of macrophages and other lymphocytes and promotion of immunoglobulin class switching to IgG. Specific microbes play a significant role in this process. For example, the polysaccharide A from the capsule of *Bacteroides fragilis* is sufficient to induce CD4 T cell expansion [27] and *Bifidobacteriumlongum* subspecies *infantis* (*B. infantis*) can promote Th1 responses with IFN-γ that can dampen excessive Th17 induced inflammation [25,28]. As a corollary to the hygiene hypothesis [29,30], lack of exposure or removal of a neonate's microbiota with antimicrobial treatment during this critical period can compromise the development of a healthy personal microbiome, its education of the immune response, and put the individual at risk to development of atopy, allergies, asthma, type 1 diabetes, obesity and other problems [31]. Compromise of the skin barrier early in life can also allow entry to *Staphylococcus aureus* to reinforce the early predilection towards Th2 responses and cause eczema and initiate the atopic march towards allergies and asthma [29].

Prior to maturation of cell mediated responses and the protections that they elicit, the fetus and neonate remain susceptible to potentially life-threatening intracellular infections, including the TORCH (toxoplasma, other, rubella and rubeola (measles), cytomegalovirus, herpes simplex virus, hepatitis and HIV) infections as well as other herpesviruses, paramyxoviruses, influenza, malaria, tuberculosis and listeria [32]. The immaturity of these responses and potential presence of maternal

IgG can also compromise the efficacy of certain vaccines, including the measles, mumps, rubella, varicella vaccines (MMRV). Although the Bacillus Calmette–Guérin (BCG) vaccine is a strong immunogen, its administration soon after birth may limit the longevity and efficacy of the response in some individuals for these reasons [33].

Immunity continues to develop through childhood with constant exposure to new antigenic challenges through infections and vaccines. Immunizations that elicit antibody (e.g. TdaP, HIB) can be initiated in the first 6 months but those that require replication of live attenuated viruses and induction of cell mediated protective responses (MMRV) are deferred until after 12 months of age.

Innate immune memory is induced by exposure to strong activators, such as LPS, viral infections, or BCG, which encourage opening of chromosomal sequences to promote effector gene expression and innate stem cell differentiation to increase protections against a broad range of pathogens for extended periods [34]. Innate immune memory provides children with a more generic protection system as the antigen specific immunity develops its repertoire. In a study to determine why SARS-CoV-2 infection is more mild in children than adults [35], children were shown to be more prepared for a viral attack with higher basal levels of receptors for viral RNA (RIG-1, MDA5 and LGP2) and other microbial associated molecular patterns ((MAMPs), also known as pathogen associated molecular patterns (PAMPs)) to promote more IFN production, more activated neutrophils and innate cells in the upper airways, and the presence of a subpopulation of cytotoxic CD8 T cells which are highly active and excellent producers of IFN-γ. In addition to these protections, the blood levels of an antiviral natural killer cell decrease with age below a threshold of protection in most individuals by teenage years correlating with increased symptomatology of Epstein Barr virus (EBV) mononucleosis in adolescents and adults [36]. These responses may also explain the more mild course of varicella zoster virus (VZV) disease in children. Similar “on-call” innate protections may also limit the severity of other mucoepithelial oral and respiratory acquired virus infections prior to teen years.

3. Sex and gender: Overprotective but somewhat less discriminating in women

Overall, girls and women have a more potent immune response than boys and men. Upon attaining puberty and even after menopause, immune responses in women favor CD4 helper T cell function, increased B and T lymphocyte proliferation upon challenge and increased antibody production, while CD8 T cell function, including killer T cells, is a more favored response in men. This can be attributed to both sex (genetics) and gender (hormonal) differences [8,37–40]. In addition to enhanced protections, females respond stronger to vaccines but account for 70–80% of autoimmune diseases (Table 2).

Table 2. Discerning immune function between male and female.

	Male	Female
Overall	-Stronger proinflammatory cytokine but weaker humoral and T cell response increases susceptibility to viruses and cancer but lowers potential for autoimmunity.	-Stronger humoral response and T cell response, response to infections and vaccines but more autoimmunity.
Chromosomal	-Response to yellow fever vaccine upregulates only 67 genes. -Increased risk for X-linked immunodeficiency. -Y chromosome contains regulatory response genes that can affect immune response. -CD8 T cell function more active.	-Response to yellow fever vaccine upregulates 660 genes. -Less potential for X-linked immunodeficiency due to potential expression from either X chromosome. -Expression of TLR 7 and 8 from both X chromosomes in pDCs induce strong antiviral response but increase risk for SLE. -More potent cytokine response due to upregulation of IL2R gene. -Increased mucus production through upregulation of IL13RA2 gene. -Increased proliferation of B and T cells upon challenge and increased antibody production. -Increased FOXP3 transcription enhances regulatory T cell development. -X chromosome enriched in immune modulating microRNAs.
Hormonal Influences	-Lower concentrations of estradiol: • Allow more robust proinflammatory response. -Increased response to LPS by neutrophils and monocytes results in higher expression of TNFα and inflammation. -Androgens • Suppress development of the thymus and result in decreased T cell response in men compared to women • Enhance negative selection through increased expression of AIRE protein • Promote expression of regulatory cytokines (IL10 and TGFβ) • Decrease humoral Th2 responses • Reduce macrophage response which can dampen severity of septic shock.	-Higher concentrations of estradiol: • Promote anti-inflammatory effects by modulating interferon γ action • Enhances humoral Th2 response • GPER1 activation via estrogen converts proinflammatory Th17 cells into regulatory T cells. -Reduced response to LPS by neutrophils and monocytes results in less TNFα and inflammation during infection. -Pregnancy: Initial pro-inflammatory response occurs during implantation and placentation and turns into an anti-inflammatory response upon fetal growth • Expression of HLA-E, F, G, and C by trophoblasts limits cell mediated immunity but allows some antiviral responsivity • Decidual NK cells limit fetal rejection • Increased production of IL-10 and TGFβ inhibits T cell and inflammatory responses • Regulatory responses during pregnancy increase risk of TORCH infections and other viral infections but also decreases symptomatology of autoimmune diseases.

Abbreviations: pDC: plasmacytoid dendritic cells; SLE: systemic lupus erythematosus; GPER1: G protein-coupled estrogen receptor-1.

Even before menarche, the immune response of girls is different from boys due to genetic differences. Several important immune functions are encoded on the X chromosome [37–40]. In addition, the X chromosome encodes several immunomodulating microRNAs [40]. Among the genes expressed on the X chromosome are those for Toll like receptors (TLR) 7 and 8 proteins (important for responses to microbial DNA and RNA), cytokine receptors that promote cell growth (IL2RG) or mucus production (IL13RA2); and the FOXP3 transcription factor that promotes the development of regulatory T cells. The importance of these genes is evidenced by the numerous X-linked immunodeficiencies, much more likely in males with only one X chromosome, than females including X-linked chronic granulomatous disease (NADPH-oxidase complex (the catalytic subunit; gp91-phox protein), X-linked lymphoproliferative disease (SLAP), Wiskott–Aldrich syndrome (WASp), hyper IgM syndrome (CD40 ligand), immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX), and X-severe combined immunodeficiency (common γ chain IL-2 receptor γ).

In the plasmacytoid dendritic cell (pDC), the principal cell that promotes the systemic type 1 IFN and cytokine response during viremia, TLR7 is expressed from both X chromosomes [41]. TLR7 is the pathogen associated molecular pattern receptor (PAMPR) that recognizes single stranded RNA generated during RNA viral infections and by other conditions. For this and other reasons, women are less likely to have serious outcomes from COVID-19 disease [42]. An X-linked deficiency in the TLR7 gene, more common in males, compromises the type 1 IFN response to RNA viruses which increases the risk for life-threatening COVID-19 disease [43]. Unfortunately, since Type 1 interferon is a key driver of systemic lupus erythematosus (SLE), the increased sensitivity to RNA and DNA increases the risk of women for induction and exacerbation of this disease.

With sexual maturation, the differences in immunity expand due to the influences of estrogen, progesterone and prolactin in women and androgens in men. Estradiol, the active form of estrogen, binds to protein receptors (ERα or ERβ), promoting their movement from the cytoplasm to the nucleus to control many of the genes that promote and regulate inflammation and T and B cell function. Small concentrations of estrogen enhance immunity while large concentrations act more like corticosteroids and are immunosuppressive. Overall, estradiol provides an anti-inflammatory effect which modulates the proinflammatory responses mediated by IFN-γ (Th1 proinflammatory T cell responses) and promotes the humoral (Th2) responses. This modulates anti-viral, anti-tissue graft (including responses to a fetus, which is a tissue graft) and anti-tumor cell-mediated-responses. Estradiol increases neutrophil and NK cell numbers. Seemingly paradoxical, estradiol reduces the response to lipopolysaccharide (LPS) by neutrophils and monocytes such that women will express less TNFα and inflammation in response to lipopolysaccharide (LPS) than men [44]. Activation of the cell surface GPER1 receptor by estrogen can convert proinflammatory IL17 producing T (Th17) cells into induced regulatory T cells, cells which produce cytokines to inhibit proinflammatory responses and promote humoral responses [45]. Estrogen also has other effects that modulate the immune response [46]. In addition, progesterone, produced during estrous cycle and pregnancy, is also anti-inflammatory.

The levels of estradiol vary over a woman's life span, before, during and after menarche, and during pregnancy, and its influence on immunity varies accordingly [47]. During menstruation, regulatory responses and Treg cells are at the highest levels when estradiol concentrations are high before ovulation [47]. Post menarche, the endocrine influence dissipates but women still have a more

potent immune response than men. After menopause, some of the immune benefits of estradiol can be recovered by hormone replacement therapy.

The immune system undergoes a major change during pregnancy to protect and not reject the fetus [48]. There is an initial pro-inflammatory phase during implantation and placentation, an anti-inflammatory phase during fetal growth and another pro-inflammatory phase during parturition to facilitate birth. During the fetal growth phase, the presence of the fetus, which is essentially a tissue graft, is tolerated by isolating and altering its immunological appearance and suppressing T cell rejection responses. Trophoblasts surrounding the fetus express HLA-E, F and G and small amounts of HLA-C rather than the classical cytotoxic T cell targets of HLA-A and HLA-B. HLA-C maintains some amount of antiviral responsivity while HLA-E and HLA-G can induce regulatory responses. HLA-G can also be cleaved, solubilized and antagonize T cell responses. Different types of Tregs increase in number during pregnancy and produce regulatory cytokines IL10 and TGFβ [49]. The numbers of uterine/decidual NK cells (dNK) increase and play a large role in preventing rejection of the fetus [50–53]. Derived initially from uterine NK (uNK) cells and later recruited from the blood, they dominate the number of resident lymphocytes and modulate immune responses. Similarly, decidual macrophages secrete anti-inflammatory cytokines and indoleamine 2,3-dioxygenase (IDO) to inhibit T cell responses. Pregnant women and their fetus remain susceptible to viral and other intracellular infections but the more potent interferon and humoral responses of women may partially compensate for the reduced CD8 T cell responses to extend antiviral protections during this time. The suppression of T cell responses during pregnancy also reduces the symptomatology of some autoimmune diseases, including rheumatoid arthritis [54].

Aging of boys to men with increased androgen production has less of an effect on the immune response than estrogen has for girls and women. Male androgens generate different outcomes than estrogen by binding to a different cytoplasmic receptor (androgen receptor (AR)) which binds to different DNA sequences [55]. On a global scale, androgens have a suppressive effect on the development of the thymus, which can reduce the T cell response in men compared to women, and yet, androgens increase the ability of the thymus to cull autoimmune T cells from newly generated T cell precursors by increasing expression of the autoimmune regulator (AIRE) protein. These effects are lessened upon castration. Androgens also promote the expression of the regulatory cytokines, IL10 and TGFβ. TGFβ at high concentrations suppresses inflammation but at normal low concentrations combined with the acute phase cytokine, IL-6, it promotes the proinflammatory Th17 response. The Th17 response is more active in males than females. Androgens also decrease humoral Th2 responses [55,56]. With the same stimulus, IL-17 (Th17 responses) is more likely to be produced than IFNγ (Th1) in males and Th1 responses more than Th2 [57–61]. The dominating presence of testosterone over estradiol in men seems to protect them from autoimmune diseases including MS, RA and SLE but increases their susceptibility to cancer, viral infections and lessen their response to vaccines [56]. In addition, testosterone's action on macrophages may also reduce the severity of septic shock [57]. Testosterone is also attributed with increasing susceptibility of men to HIV disease [58] due to less antiviral activity by plasmacytoid dendritic cells. In addition, numerous regulatory response genes that can affect the immune response are encoded on the Y chromosome [59].

The difference in response to vaccines provides one of the best indications of the difference in immune response between men and women. Women develop a much stronger innate immune response to equivalent vaccine doses and are at greater risk for adverse effects [38,39]. The response

to the live 17D yellow fever vaccine illustrates this for both the response to the vaccine and to flavivirus infections. Whereas men upregulate 67 genes in response to 17D, women upregulate 660 genes. In addition to type 1 IFN, these genes encode many of the proinflammatory cytokines, chemokines and activities that elicit the classical "flu-like" symptoms of a virus infection. For most influenza vaccines, which are inactivated subunit vaccines, women elicit much higher antibody titers than men and are more likely to exhibit local and systemic events, including pain at the injection site, headache and fatigue [63]. Antibody responses to the hepatitis A and B virus vaccines were similarly higher in women than in men [40]. Women are also 3–5 times more likely to have adverse events than men from the new mRNA based COVID-19 vaccines [42,63].

In summary, except during pregnancy, women have a more potent Type 1 IFN, T cell and humoral immune response, whereas males have a more potent proinflammatory response [38]. These differences translate to increased risk to serious COVID-19 disease for men [42] and a more potent response to vaccines for women. The more potent immune response also puts women at higher risk for autoimmune responses than men.

4. Older adults: decreased responsivity but more reactivity

Aging takes its toll on all cells of the body including immune cells due to oxidative stress, reduced telomerase activity and the limited life span of even hematopoietic stem cells leading to immunosenescence [64,65]. With aging, there is also decreased ability to initiate new immune responses or regulate others which increases susceptibility to new microbial and tumor challenges and the potential for inflammatory and autoimmune responses [2–7]. Genetic deficiencies, normally compensated by stronger immune responses, may become more evident upon disease challenge. The reduction in immune responsiveness can be seen in reduced responsiveness to vaccines [66,67] and increased sensitivity to certain infections. This reduction also extends towards reduced immunosurveillance of tumors and decreased immune regulation which increases risk for diseases such as rheumatoid arthritis.

Neutrophils and macrophages are less competent in the older adult [68,69]. Although the numbers of these cells are not necessarily reduced, these cells have more difficulty getting to (reductions in chemotaxis), phagocytizing, and killing microbes (reduced production of reactive oxygen species) [70]. As a result, classic symptoms to infections may be atypical as with less cough, fever and sputum for pneumonia [71]. Dendritic cells (DC) are also less functional due to reduced ability to sense and respond to microbes through Toll like receptors (TLR) and then process and present antigen on MHC molecules to initiate T cell and subsequent immune responses [3]. The numbers of Langerhans cells, the skin resident DC, decreases with age, especially with excess sun exposure, compromising skin health and immune responses [72,73].

The ability to mount a response to a new antigenic challenge (like SARS-CoV-2 [74]), regulate that response, and then promote healing responses also decreases with age [2–7]. The constant production of naïve lymphocytes decreases due to changes in the bone marrow, lymph nodes and shrinkage of the thymus as well as a reduction in the number of hematopoietic stem cells. Changes to the fibroblastic reticular cells alter the architecture of the bone marrow, thymus, lymph nodes and spleen affecting their interactions and the stimuli for lymphocyte development and activation [2,75,76]. The remaining stem cells within the bone marrow are more likely to generate myeloid rather than lymphoid cells, further reducing the ability to generate new naïve lymphocytes.

Decreased generation of naïve T cells is indicated by decreased production of the DNA excision circles in T cells (TRECs) that accompany genetic recombination of the T cell receptor genes [77]. In the older-old population, CD8 T cells undergo a more rapid decline than CD4 T cells [78]. With less naïve lymphocytes being produced, the chance of producing a functional recombination of antigen receptor genes (TCR, BCR, or antibody molecules) decreases and this compromises the ability to generate a new immune response.

The generation of new immune responses is further compromised by competition with established memory cells. Going back to the computer analogy, as we age, the memory capacity fills up and this compromises other functions. We accumulate memory CD4 and CD8 T cells to chronic infections and to autoantigens and these can compete for the development of new immune responses. This is especially true for chronic-latent infections of cytomegalovirus (CMV) and Epstein Barr virus (EBV). These herpesviruses remain latent in macrophages and B cells, respectively, cells that are potent antigen presenting activators of T cells. For example, healthy middle-aged people may have 10% or more of their CD4 and CD8 T cells dedicated to CMV and older individuals will have higher percentages [79–81]. Chronic stimulation of immune responses to these or other viruses can also cause the T cells to become senescent, which can blunt the potential for future responses.

Antibody responses can also diminish in the older adult due to a decrease in the number and function of germinal centers in lymph nodes, which is the site of B cell differentiation into plasma cells and memory cells. This specifically compromises the response to *C. difficile*, which is a problem for older adults [82]. Senescence of responses may also occur due to a reduction in specific memory lymphocyte cells due to shortening of the telomere, changes in expression of intracellular activation molecules, changes in metabolism or lack of antigenic stimulation to renew the clone [82–84].

Treg control may also decrease. Although the numbers of Tregs may not decrease extensively due to clonal expansion of existing memory cells, there will be less diversity in the response due to the involution of the thymus and reduction in generation of new Tregs [85]. These cells are important for limiting inflammation, promoting tissue repair, as well as development of immune memory in response to infection.

The generation of autoantibodies increases in healthy older individuals [86] due to decreases in regulation but also due to the increased presence and exposure to antigenic mimics and chemically modified proteins. Inflammation, diabetes, alcoholism, smoking, certain drugs and other challenges increase citrullination, glycation, aldehyde modification and haptenization of proteins to allow generation of autoantibodies and T cell responses [87]. This increases risk for rheumatoid arthritis and other autoimmune diseases. Autoantibodies to cytokines [88,89], hormones and other induced proteins may also develop due to a lack of tolerance mechanisms to these proteins which increases risk to infectious disease. For example, autoantibodies capable of neutralizing type I IFNs, such as IFN-α, are present in ~4% of individuals over 70 years old and can exacerbate the presentation of viral infections, including COVID-19 [90].

Susceptibility to inflammatory, autoimmune and even chronic diseases increases due to the accumulation of biological and inflammatory insults, termed immunobiography [91,92], which can increase systemic inflammation, termed inflammaging [91–94]. In addition to environmental challenges, stress also takes its toll on the immune system. Known for a long time to affect the immune system [95], life stress also exacerbates the changes in T cells that occur with aging [95,96]. Inflammaging results in part from enhanced and accumulated responses to normal flora, especially

GI flora, in part due to a lessening of regulation of the immune response [93,94]. Inflammaging increases systemic levels of the acute phase and proinflammatory cytokines (IL1, TNFα, IL6; IL12, IL23, IL17, IFNγ) [93,97]. Chronic exposure to TNFα, IL1 and IL6 have global effects on the body which include changes and increased permeability of the blood brain barrier which increases susceptibility to Alzheimers and Parkinsons diseases. In addition, systemic inflammation is likely to alter the outcome to apoptotic cells (efferocytosis) to favor activation of autoreactive T and B cells instead of tolerance [98]. Systemic inflammation can also compromise healing after trauma or infection.

The immune system of men and women age differently [2–7,99]. Decreases in growth hormone and sex hormone production in the older adult affects both genders, but differently. Compared to younger adults, men over 65 years-of-age had more immunosenescence and a greater decrease in naïve T cells, other T cells, and B cells, but greater inflammatory cell activity, including monocytes, than women, whose B cell and antibody activity did not diminish.

Immunosenescence combined with limited exposure to childhood or other infections may increase susceptibility to recurrence of latent infections, including herpes and other latent viral, mycobacterial or fungal infections [100,101]. For pediatric infections such as varicella, *Hemophilus influenzae B*, and other microbes, the lack of antigenic rechallenge of an older person may cause a dissipation of memory B cells, plasma cells, memory T cells and antibody dropping them below a threshold of protection.

The increased risk of older adults for serious COVID-19 disease is due to a combination of the immune and other deficits that accompany aging [74,102]. Reductions in type 1 IFN production due to decreased sensing and ability to respond to the viral RNA combined with the presence of auto-antibody to IFN [90] in many older adults severely compromises the critical initial protections against SARS-CoV-2. Reduced innate and antigen responsivity of the immune system (immunosenescence) and inflammaging also limit protective responses to this new challenge.

The changes in the immune system with aging also affects the efficacy of vaccines and vaccination [66,67,103]. For example, the efficacy of the influenza vaccine drops from 70–90% in children and adults to 30–50% in individuals over 65 years, and similar reductions are true for pneumococcal polysaccharide and hepatitis B virus (HBV) vaccines [67]. In addition, there is a more rapid decline in antibody protections suggesting the need for more frequent boosting. The response to the annual influenza vaccine is further compromised by the immunological derivation of 'original sin'. Essentially, there is a preferential expansion of memory cells directed against the dominant antigens that the new vaccine strain shares with an earlier vaccine strain which then prevents the expansion of those naïve B cells that only recognize the antigenic nuances of the current strain of virus. This can limit the specificity and potency of the antibody response towards a newer strain [104]. The Advisory Committee on Immunization Practices (ACIP) recommends the high dose quadrivalent or the MF59 adjuvanted influenza vaccines for adults over 65 years of age to improve immunization efficacy.

The inflammaging and immunosenescence of the immune system also contributes to the aging of the rest of the body [1]. The aged system is less capable of performing its basic functions, including surveillance for tumors and other aberrant cells, clearance of these and apoptotic cells, production of cytokines to support epithelial maintenance (e.g. IL22) and repair, protection of the mucoepithelial borders and protection from infection and self-regulation against autoimmunity. The

deficits are less likely in centenarians who have maintained their immune functions with the means to counteract the effects of inflammaging as part of their longevity [105].

5. Summary

The immune system does an amazing job fulfilling its duties, except when it doesn't. The importance of the different components and their actions is demonstrated by the consequences of genetic errors and the subsequent loss or disruption of their normal function. Over a lifetime the system provides maintenance of body processes and systems, self-regulation, surveillance, protection of the mucoepithelial borders and protection from microbial invasion. Although we are born with some of these abilities, much of the system must be learned, honed and then regulated. Building a system, whether a military, municipal or immune, requires many components which have to learn their roles and work together. Humans have the advantage that many of these responsibilities are provided to the fetus within the womb while the system develops and then defenses of the neonate are assisted by the antibody protections provided by the mother while the system learns and matures after birth. Throughout childhood and the procreative years, the immune system fulfils its responsibilities competently to ensure survival in the microbial world and maintain the human species. Aging of the immune system brings immunosenescence, inflammaging, increased errors and decreased surveillance which increases risk for new infections (e.g. COVID-19, influenza), recurrence of latent infections, cancer and autoimmune and inflammatory diseases. As the immune system progressively fails with old age, there is a return to the need for external care and protections, not from the mother, but from the medical community. With greater understanding of the surveillance, effector or regulatory deficits upon aging, better therapies can be developed.

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