



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Immune Deficiencies at the Extremes of Age

Jörg J. Goronzy, Claire E. Gustafson, Cornelia M. Weyand

Age is a major factor determining the quality and quantity of an immune response. This age dependency, apparent throughout life, is most obvious at the extremes of age. Both infants and older adults exhibit blunted immune responses to infections and vaccination. However, the underlying mechanisms for immune dysfunction are distinct. Infants are born with limited antigen exposure and an immature immune system, which, however, progressively develops throughout infancy and childhood. The mechanisms underlying the immune dysfunction in older adults are broadly termed *immunosenescence*. The term is reminiscent of *cellular senescence*, which is defined as the loss of the ability to proliferate as a result of an irreversible cell cycle block. However, it is misleading to interpret immune aging only as the accumulation of senescent cells, and similar to aging in general, numerous pathways are involved.¹ The decline in immune competence is not linear. As early as age 40 years, vaccine responses to selected vaccines (e.g., hepatitis B) start to decline. The incidence rate of herpes zoster, a reactivation of latent varicella-zoster virus (VZV), starts to increase at age 50 years, as does morbidity and mortality from influenza infection. A more abrupt transition appears to occur in the eighth decade of life.

In terms of public health, infections are major causes of morbidity in the very young and the very old. Although child mortality rates have dropped by almost 50% between 1990 and 2013, pathogenic infections are still one of the largest causes of infant mortality worldwide, accounting for more than 1.6 million deaths a year. Vaccinations have helped change the infectious landscape in children and young adults, but certain vaccines, such as those against *Streptococcus pneumoniae*, still have limited protective capacity at both extremes of age. Susceptibility to pathogenic infection and ineffectiveness of vaccination is even greater in older adults than in young infants. Moreover, during aging, a functional immune system is important for tissue repair and is of increasing importance in degenerative diseases, and it is vital for cancer surveillance. Immunosenescence is of increasing importance because of the changing population demographics, with increases in the number of individuals older than 65 years in both developed and developing countries.

INFANCY AND THE GENERATION OF AN IMMUNE SYSTEM

Infants first start to develop their immune system *in utero*, maintaining a fine balance between immunological tolerance that helps prevent proinflammatory responses *in utero* and the ability to respond to foreign antigen exposure upon birth. Immunosuppressive regulatory pathways utilized by the fetus

for protection against possible infections and maternal–fetal rejection *in utero* are still reflected in the newborn infant immune system, characterized by immune-suppressive, antiinflammatory, and immature cellular responses to foreign antigens. Although newborns and young infants lack the ability to mount effective immune responses against many pathogens, they acquire initial immune protection through the passive transfer of maternal immunoglobulin G (IgG) *in utero* via the placenta (termed “passive immunity”)² and from secretory IgA and antimicrobial factors present in maternal breast milk. Alternations in passive immunity (e.g., preterm birth) can lead to increased susceptibility to infections and breakdown of immune tolerance in the infant. Passive immunity can be enhanced by vaccination of pregnant mothers to promote the transfer of vaccine-specific IgG *in utero*. However, within the first months of life, as maternal IgG wanes and breastfeeding is discontinued, infants must actively develop their own innate and adaptive immune responses to initiate and maintain immune protection. An overview of the development of innate and adaptive cells, as well as the repertoire of diversity during aging, is outlined in Fig. 38.1.

INNATE IMMUNE DEVELOPMENT

The innate immune system is typically considered the first line of defense against infection. The development of the innate immune system begins *in utero*, with all the classic innate cells types present by the end of the first trimester; monocytes and dendritic cells (DCs) are the earliest cells observed at 4 weeks’ gestation (WG) followed by granulocytes and natural killer (NK) cells at 8 WG.³ These innate immune cells expand in number and mature during gestation; however, at birth the functionality of innate immune cells is still diminished significantly compared with later in life.

DYSFUNCTION OF INNATE IMMUNE CELLS

During early infancy, all cell types of the innate immune system demonstrate some impairment of function, ranging from reduced mobility to skewed cytokine production in response to innate immune stimulation. The most significant functional limitation of neonatal innate immune cells is their collective inability to kill pathogens. Limited chemotaxis in neutrophils is accompanied by a reduced ability to effectively kill pathogens as a result of poor phagocytosis and decreased secretion of neutrophil extracellular traps under inflammatory conditions, which in combination results in decreased killing of infectious pathogens. Moreover, NK cells and plasmacytoid DCs have reduced capacity to prevent

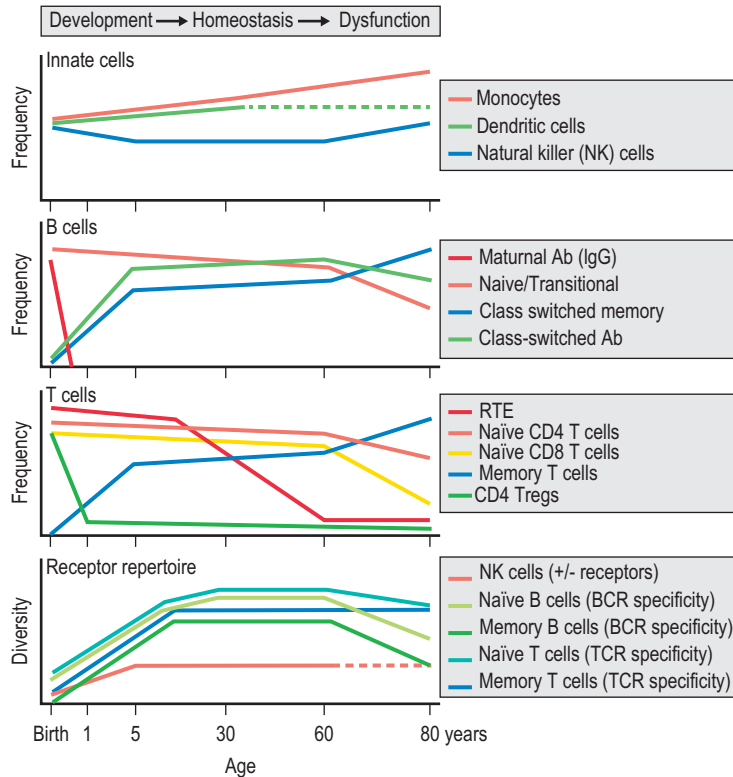


FIG 38.1 Innate and Adaptive Immune Cell Frequencies and Receptor Repertoire Diversity During Aging. The frequencies of different innate and adaptive B and T cells changes over the course of a lifetime (upper three panels). In addition to compartment size, diversity of antigen receptors is essential for immune function. During infancy, diversity of immune populations expands and is then maintained during adulthood (lower panel). Aging is characterized by the general decline in diversity within naïve B- and T-cell populations. Dotted lines indicate that the progression of these populations is either controversial or unknown.

infection through reduced cytotoxic function and lower secretion of interferon- ($\text{IFN-}\alpha$), respectively. In addition, antigen-presenting cells (APCs) are unable to provide effective help to T cells because of reduced expression of costimulatory molecules and skewed cytokine production toward more antiinflammatory, T-helper 2 (Th2)-inducing cytokines, such as interleukin-6 (IL-6). These combined limitations during early infancy lead to increased susceptibility to viral and bacterial infections and also contribute to the reduced functionality of adaptive immune cells.

KEY CONCEPTS

Characteristics of the Developing Innate Immune System

- Reduced antibacterial responses (*i.e.*, phagocytosis, secretion of neutrophil extracellular traps [NETs]) by neutrophils and monocytes
- Impaired neutrophil chemokinesis ("directed movement")
- Diminished capacity of antigen-presenting cells (APCs; *i.e.*, dendritic cells [DCs]) to provide proper costimulatory help to T cells
- Reduced antiviral responses (*i.e.*, interferon ($\text{IFN-}\alpha$) secretion) by plasmacytoid dendritic cells (pDCs)

ADAPTIVE IMMUNE DEVELOPMENT

Adaptive immune cells (T and B cells) begin to develop *in utero* around the start of the second trimester. It is important to note

that although lymphocytes initially develop within the fetal liver (≈ 7 WG) and then in bone marrow (≈ 12 WG), T-cell maturation occurs in the thymus, and B cells continue maturation in bone marrow *in utero* and after birth. Over the course of gestation, both naïve T-cell and B-cell compartments expand, reaching absolute cell concentrations greater than that of the adults by birth. Thus a defect in cellular generation cannot account for the immune limitations observed in infants. However, the composition of the each lymphocyte population within young infants is distinct from that of adults. At birth, both the newborn infant T- and B-cell compartments consist mainly of naïve and immature cells recently migrated out of the thymus or bone marrow (>90% of the population). Both infant T- and B-cell repertoires have less diversity within their receptors' antigen-binding regions compared with those of adults. T-cell receptors display reduced V-J complexity and fewer amino acid additions. In addition, B cells have decreased B-cell receptor diversity because of less affinity maturation (*i.e.*, somatic hypermutation; Chapter 7) compared with adult populations.

The increased levels of recent thymic emigrants and naïve T cells are maintained both in the periphery and in tissues during early infancy. Effector memory T cells can be found selectively in the lungs and gastrointestinal (GI) tract of young infants, likely because these mucosal tissues are the earliest sites of antigen exposure. Class-switch antibodies produced by B cells are required for mucosal protection (primarily IgA) and systemic protection

(primarily IgG) through opsonization, neutralization, or antibody-dependent cellular cytotoxicity (ADCC). However, infants demonstrate significantly lower levels of IgG and IgA compared with adults throughout the first year of life, in both the periphery and mucosae.

INFANCY AND FUNCTIONAL DIFFERENTIATION OF ADAPTIVE IMMUNE CELLS

The acquisition of a mature adaptive immune system requires exposure to antigens for cells to form immunological memory. Not only are infants born with limited antigen exposure and thus little memory, infant responses to antigenic stimulation in the T- and B-cell compartments display altered functions compared with that of adults. The most striking alterations are seen within the CD4 T-cell compartment, characterized by significantly increased frequency of immunosuppressive T regulatory cells (Tregs; 30–40% in infants vs 1–10% in adults).⁴ These changes accompany increased Th2 subsets and defective differentiation to effector Th1 and T-follicular helper (Tfh) cells during early infancy. Moreover, decreased expression of Lck in infant CD4 T cells leads to decreased T-cell activation upon antigen exposure.² Altered differentiation of CD4 Th subsets and blunted T-cell activation promotes a tolerance-inducing environment good for controlling unnecessary responses to foreign antigen exposure after birth. However, it also leads to inhibition of effective cytotoxic T cells and limits B-cell antibody responses against infectious pathogens and to vaccination (Fig. 38.2).

The reduced antibody titers observed during infancy can be accounted for by the functional inability of infant B cells to undergo class-switching from IgM to IgA or IgG upon antigen stimulation⁵ and the poor survival of antibody-secreting plasma cells within the infant bone marrow. Moreover, infant B cells have lower rates of somatic hypermutation compared with those of adults, which is important for affinity maturation and the generation of high-affinity antibodies. Although these defects can be partially attributed to extrinsic T-cell defects, such as poor Tfh generation, intrinsic defects in infant B cells (e.g., lack of costimulatory molecules and receptors to T cell-independent factors) also prevent effective antibody responses. Collectively, these neonatal B-cell defects lead to less effective and shorter-lived antibody responses against infectious pathogens and vaccines during early infancy.

KEY CONCEPTS

Characteristics of the Developing Adaptive Immune System

- High frequencies of naïve and immature T and B cells
- Skewing of CD4 T-cell population towards immunosuppressive regulatory T cells and T-helper 2 (Th2) cells
- Reduced functionality and memory responses of CD8 T cells to viral infections
- Limited ability of B cells to produce high-affinity, class-switched antibodies in response to both T cell-dependent and T cell-independent antigens

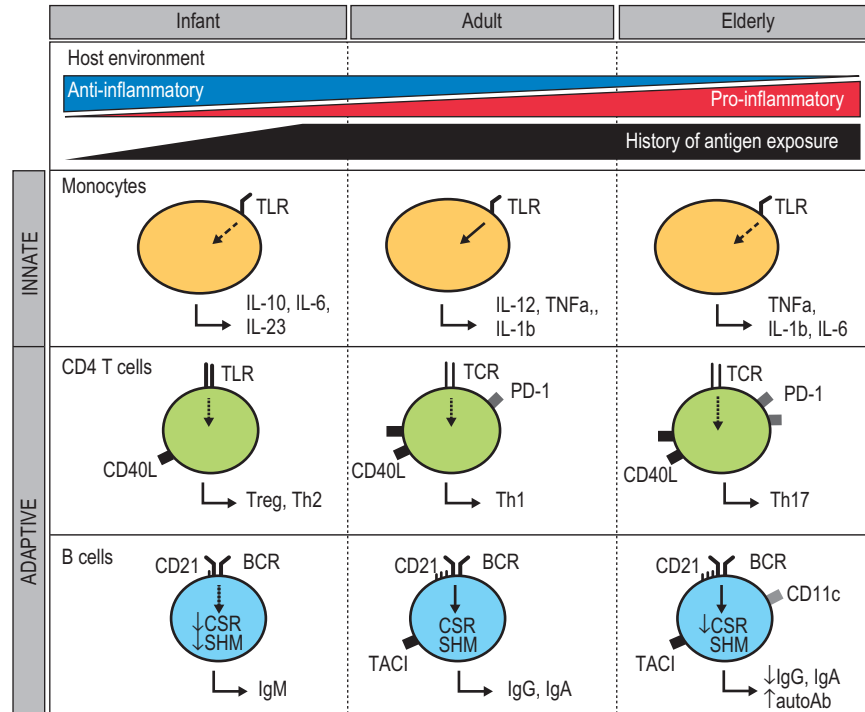


FIG 38.2 Innate and Adaptive Immune Cell Functionality During Aging. The infant immune environment is distinctly antiinflammatory characterized by altered Toll-like receptor (TLR) signaling from monocytes, blunted T-cell and B-cell receptor (TCR/BCR) signaling, and skewing toward T regulatory cells (Tregs). Infant B cells are incapable of class-switch recombination (CSR) or affinity maturation via somatic hypermutation (SHM) upon antigen exposure. Altered monocyte TLR signaling and altered function of adaptive immune cells is also observed in older adults, but with a distinct, more proinflammatory outcome.

INFANT IMMUNE DEVELOPMENT AND THE MICROBIOME

One of the first environmental exposures that infants experience is with colonizing bacteria. Within hours after birth, the infant intestinal tract is colonized with nonpathogenic bacteria (termed “microbiome”; Chapter 14). The microbiome can reach concentrations of 10^{10} bacteria per gram of stool by age 7 days, but only mirrors an adult-like composition after age 2 years. Early studies in animal models demonstrated that microbial colonization is essential for the normal development of the immune system during early infancy and throughout life.⁶ In particular, IgA, the most abundant antibody within the GI tract, requires the presence of colonizing bacterial for its development and long-term maintenance. Moreover, the specific composition of the microbiome influences the generation of innate lymphoid cells, CD4 T-cells subsets (e.g., Treg, Th17, Tfh), and antibody development. Perturbations in the infant microbiome, caused by such factors as mode of delivery, antibiotic treatment, and diet, may significantly alter developing immune responses.

It has been described that babies delivered via C-section have a microbiome composition distinct from vaginally delivered babies, the latter dominated by skin bacteria (e.g., *Staphylococcus*) instead of vaginal bacteria (e.g., *Lactobacillus*, *Prevotella*). These differences correlated with an increased incidence of allergy and asthma during childhood suggesting a causal link between microbiome and susceptibility to allergies. These findings are preliminary and more evidence is needed to support the notion that the microbiome influences the development of the infant immune system.

CLINICAL CONSEQUENCES FOR CHILDHOOD VACCINATION

Newborn and young infants are highly susceptible to pathogenic infection during the first months to year of life. Indeed, infections are one of the major causes mortality, accounting for more than 24% of global infant mortality. More than 1 million deaths per year are caused by respiratory tract infections (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, respiratory syncytial virus [RSV]) and almost the same amount by intestinal infections (e.g., rotavirus, *Escherichia coli*). The development and distribution of vaccines targeting these pathogens have significantly reduced infant infection rates and subsequent mortality; however, vaccine efficacy can vary, depending on the infant’s gestational age at birth, mode of vaccine delivery (oral vs intramuscular), interference by maternal antibodies acquired through passive immunity and via breast milk, and immaturity of infant immune responses, as described above. Additionally, infants require multiple vaccine boosters to elicit and maintain robust protective immunity against infectious pathogens (Chapter 90). Better understanding of the limitations of the human infant immune system that prevent effective immune responses, particularly at mucosal sites where these pathogens initially infect, would facilitate the generation of better vaccines designed to overcome these limitations and induce more rapid and robust immune protection during early infancy.

OLDER AGE AND IMMUNE CELL GENERATION

The immune system is in constant demand for cellular replenishment to compensate for peripheral losses and cell death. For

CLINICAL RELEVANCE

Consequences of Immaturity of the Developing Immune System

- Increased morbidity and mortality from bacterial infections (e.g., pneumococci)
- Increased morbidity and mortality from viral infection (e.g., influenza virus, respiratory syncytial virus [RSV])
- Ineffective primary vaccinations; multiple boosters required for most vaccines to elicit effective protection
- Susceptibility to allergy and asthma when microbiome colonization disrupted during early infancy

neutrophils, which have a short half-life, the body needs to produce $\approx 10^{10}$ cells/kg per day. Additionally, for lymphocytes, which are more long-lived but are also more numerous because of their wider tissue distribution, the daily need is in the order of several billion cells. Studies in the 1960s showed that the hematopoietic tissue in bone marrow decreases with age. A similar decline is seen for the frequencies of peripheral CD34⁺CD45⁺ hematopoietic stem cells (HSCs). In addition to these numerical differences, the functional potential of HSCs changes with age.⁷ Old HSCs exhibit a reduced capacity to regenerate the hematopoietic system. Telomerase expression in peripheral HSCs is not fully protective, and a shortening in telomeric length is seen with age, similar to differentiated mononuclear cells. Lymphoid differentiation potential diminishes with age in favor of myeloid differentiation as a result of altered lineage specification programs driven by DNA damage and epigenetic changes. This shift may contribute to the clinical observation that HSC-derived leukemia preferentially has a lymphoid phenotype in the young and a myeloid one in older adults.

KEY CONCEPTS

Aging Influences Immune Cell Generation and Population Homeostasis

- Aging influences immune cell generation and population homeostasis.
- Hematopoietic stem cells (HSCs) are reduced in frequency and biased toward myeloid lineages and against lymphoid lineages.
 - Myeloid cell generation is largely intact.
 - B-cell generation declines and B-cell repertoire selection is disturbed.
 - As a result of thymic involution, naïve T cells are generated from homeostatic proliferation of peripheral T cells.
 - Ability to rebuild a T-cell repertoire after lymphocyte-depleting interventions is severely compromised after mid-adulthood.
 - Virus-specific effector T-cell population accumulates.

As a consequence, lymphocyte replenishment is more affected by age than that of myeloid lineages. Peripheral neutrophil numbers do not decline and are able to recover after therapy-induced depletion (e.g., chemotherapy). Furthermore, there is no loss in the ability to generate robust neutrophilia in response to infection or other stressors.

In addition to HSC-intrinsic alterations in lineage commitments, defects in bloodborne factors and bone marrow niches contribute to a decline in B-cell generation.⁸ As a consequence, recovery after B-cell depletion (e.g., treatment with anti-CD20 antibodies to treat B-cell malignancies or autoimmune diseases) is

incomplete and delayed in older adults. Moreover, the frequency of typical memory B cells expressing CD27 declines, whereas other B-cell subpopulations increase. In particular, a functionally distinct B-cell population that responds to Toll-like receptor (TLR) stimulation has been described.⁹ These age-associated differences in B-cell selection and expansion may contribute to monoclonal gammopathies (in >5% of individuals older than 70 years; Chapter 80) or increased autoantibodies with increasing age. High-throughput sequencing of Ig genes has the promise to provide insights into the age-associated decline in B-cell responses at the single-cell level. Data so far have indicated that older individuals have prevaccination-expanded B-cell populations that have a high mutation load and are further expanded with vaccination, suggesting that the B-cell response in older individuals relies on the adaptation of a restricted repertoire of memory sequences.

T-cell generation is more affected by age than any other myeloid or lymphoid lineage because of the involution of the thymus. The thymus undergoes dramatic structural changes that begin during childhood and puberty.¹⁰ Thymopoietic niches disappear, and the numbers of thymic epithelial cells and thymocytes decline. In parallel, the thymic perivascular space increases. One major structural change that does not appear to be a compensatory response but, rather, is an active and regulated developmental step in thymic organ transformation is the accumulation and infiltration of adipocytes in the perivascular space. Thymic resection in children undergoing cardiac surgery reproduces many of the T-cell repertoire changes in 20-year-old individuals that are usually seen in 70- to 80-year-olds, confirming that thymic production during the growth period of childhood and adolescence is important. However, throughout adulthood, homeostatic proliferation of naïve T cells accounts for the bulk of T-cell generation.¹¹ For human CD4 T cells, this process is robust, and frequencies of naïve CD4 T cells only moderately decline with age. In contrast, the naïve CD8 T-cell compartment clearly shrinks. However, repertoire diversity (*i.e.*, the number of different T-cell receptors [TCRs]) remains very high for both naïve CD4 and CD8 T-cell subsets, suggesting that thymic activity is not necessary to prevent holes in the repertoire once a repertoire has formed. Strategies to reactivate thymic T-cell generation will be more important in older patients who cannot restore the naïve T-cell repertoire after a medical intervention, such as chemotherapy or bone marrow transplantation, compared with their healthy counterparts.

T-CELL POPULATION HOMEOSTASIS

The adaptive system responds to antigenic challenges with clonal expansion and differentiation into effector cells followed by clonal downsizing and persistence of long-lived memory T cells. Infections therefore leave a permanent imprint on the immune system, a mechanism on which vaccinations capitalize. However, the pathogen-induced clonal expansion also represents a challenge to homeostatic mechanisms that are supposed to maintain a balance among naïve, memory, and effector cells.¹² This is particularly evident in persisting infections where the offending pathogen cannot be cleared. Herpes virus infections are highly prevalent in an apparently healthy population without causing active disease, as they establish latency. Classic examples are varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). The effects of these herpes viruses with immune aging differ greatly; VZV tends to relapse with age, with reactivation presenting as shingles. A decrease in the frequency

of VZV-specific CD4 memory T cells has been postulated to explain this lack in viral control mechanisms. In contrast, EBV and CMV infections only relapse in severely immunocompromised individuals, but not during normal immune aging. The immune system commits extraordinary resources to controlling CMV, and CMV-specific CD8 T cells can make up a large fraction of the entire T-cell repertoire. Whether this memory inflation has broader implications for immune health remains a matter of controversy. Expansion of the CMV-specific T cells may compromise the size of naïve and central memory T cell repertoires; however, many of the CMV-specific CD8 T cells have the phenotype of end-differentiated effector T cells that lack the expression of CCR7, CD28, and CD27 and therefore do not compete for the same space as naïve cells.

CD45RA⁺CD28⁻ end-differentiated T cells express negative regulatory receptors of the killer lectin-like receptor (KLR), killer immunoglobulin-like receptor (KIR), and immunoglobulin-like transcript (ILT) families that appear to constrain their otherwise unopposed expansion. In spite of these inhibitory receptors, these cells are competent effector T cells capable of producing inflammatory cytokines and therefore possibly contributing to inflammation in older adults. End-differentiated CD45RA⁺ effector T cells should be distinguished from exhausted CD8 T cells.¹³ T-cell exhaustion is seen with chronic stimulation by highly replicating viruses or tumor cells and characterized by the expression of inhibitory receptors programmed death 1 (PD-1), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and lymphocyte activation gene 3 (LAG3).¹⁴ T-cell exhaustion is not a general feature *per se* of T-cell aging.

INFLAMMATION, AGING, AND THE AGING HOST ENVIRONMENT

The aging host environment is characterized by the continuous presence of inflammatory mediators independent of acute or chronic disease (Fig. 38.3).¹⁵ Even for the healthy older adult, IL-6 and tumor necrosis factor (TNF) serum levels are twofold to fourfold higher than in young adults. Low-level systemic inflammation plays an important role in the progression of several age-related diseases, including Alzheimer disease, atherosclerosis, and cancer. Moreover, inflammatory markers are associated with several conditions that are characteristic of older adults. IL-6 serum concentrations have been correlated with loss of mobility and advent of disability; increased mortality of older individuals has been shown among those who have higher levels of TNF- α . Increased IL-6 and cross-reactive protein (CRP) serum levels and increased white blood cell (WBC) counts, presumably resulting from increased production of neutrophils, predispose to, and are associated with, frailty. A causative relationship may also exist between the increased production of IL-6 or TNF- α and the age-associated loss in muscle mass, eventually presenting as sarcopenia. Long-lived individuals, such as centenarians, tend to have lower levels of proinflammatory cytokines and increased levels of antiinflammatory mediators, such as cortisone and IL-10, supporting the concept that low-level inflammation is detrimental to healthy aging.

Production of inflammatory cytokines is driven by several mechanisms. Failure of the adaptive immune system leads to a less effective control of chronic viral infections as well as incomplete response to exogenous challenges, resulting in increased and prolonged innate immune activation. Defective epithelial barrier function, as well as decline in the mucosa-associated

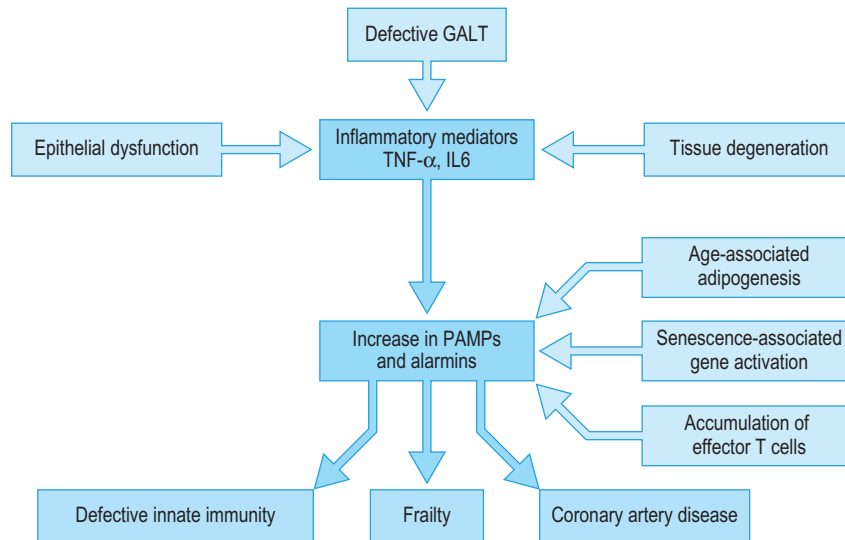


FIG 38.3 Inflammation in Older Adults. The schematic diagram depicts possible mechanisms that account for the increased production of inflammatory mediators with age. These mediators contribute to many of the age-associated diseases.

lymphoreticular tissue (MALT), results in increased leakage and increased systemic levels of lipopolysaccharide (LPS) and innate immune activation. Failure in maintaining T-cell population homeostasis and accumulation of effector T cells also favors an inflammatory response.

KEY CONCEPTS

Causes for Increased Constitutive Production of Inflammatory Mediators With Age (Inflammation in Older Adults)

- Activation of the innate immune system as a result of defective epithelial barrier function
- Activation of the innate immune system as a result of defective adaptive immunity
- Accumulation of adipocytes producing inflammatory mediators
- Accumulation and activation of T-effector cell populations
- DNA damage-induced transcription of inflammatory cytokine genes in senescent cells

The immune system, however, is not the only source of inflammatory cytokines. Adipocytes, in part replacing muscle cells in older adults, produce various inflammatory mediators. Cellular senescence has also been associated with the production of cytokines. Persistent DNA damage response signaling not only induces an irreversible cell cycle block that is characteristic of cellular senescence but also initiates a transcriptional program to secrete numerous growth factors, proteases, and inflammatory cytokines, termed the *senescence-associated secretory phenotype* (SASP).¹⁶

CELLULAR DEFECTS AND SENESCENCE

As described so far, immune aging occurs at the system level with organizational restructuring. Equally important are changes at the single-cell level, which are partly cell-intrinsic and partly caused by the host environment. The increased cytokine concentrations in older adults not only activate but also attenuate

signaling pathways. Low responsiveness to cytokine stimuli is frequently seen in those cells that have increased baseline activation of a signaling pathway (e.g., cells that constitutively have increased signal transducer and activator of transcription 3 (STAT3) or STAT1 phosphorylation respond less to IL-6/granulocyte macrophage–colony-stimulating factor (GM-CSF) or type I/II IFNs, cytokines that activate these STATs). Attenuation of signaling pathways by induction of negative feedback loops explains, in part, the reduced responsiveness and functionality of cells of the innate immune system.

Although neutrophil and monocyte/macrophage numbers remain normal, many of their functions decline with age.¹⁷ Decreased chemotaxis in neutrophils delays tissue infiltration; reduced phagocytosis and respiratory burst compromise the ability to control bacterial infections; and TLR-induced monocyte/macrophage activation is dampened in older adults. Declines in responsiveness, for example, to TLR stimulation, are partly reversible *in vitro*, suggesting that they are not intrinsic. Adaptive immune cells are also directly affected by the proinflammatory environment in the aging host.

Equally important are cell-intrinsic changes that appear to be a consequence of the replicative history and failures in cellular processes, such as DNA repair and autophagy. The program most obviously influenced by age is cellular senescence. In all hematopoietic cell lineages, including stem cells, telomeric lengths decline with age. This is of particular importance for T cells because much of their response depends on their ability to proliferate and clonally expand.¹⁸ Telomeric erosion results not only from cumulative replicative history and DNA damage but also from decline in the ability to express telomerase and repair telomeric ends.

Lymphocytes in older adults are more differentiated than those in the young. Although most obvious for CD8 T cells, increasing differentiation can also be noted for B cells and CD4 T cells (Fig. 38.4). Differentiation is generally driven by antigen recognition but could also occur in the absence of exogenous antigen under the influence of cytokines. Proliferation alone may be sufficient to drive initial steps of differentiation. A classic

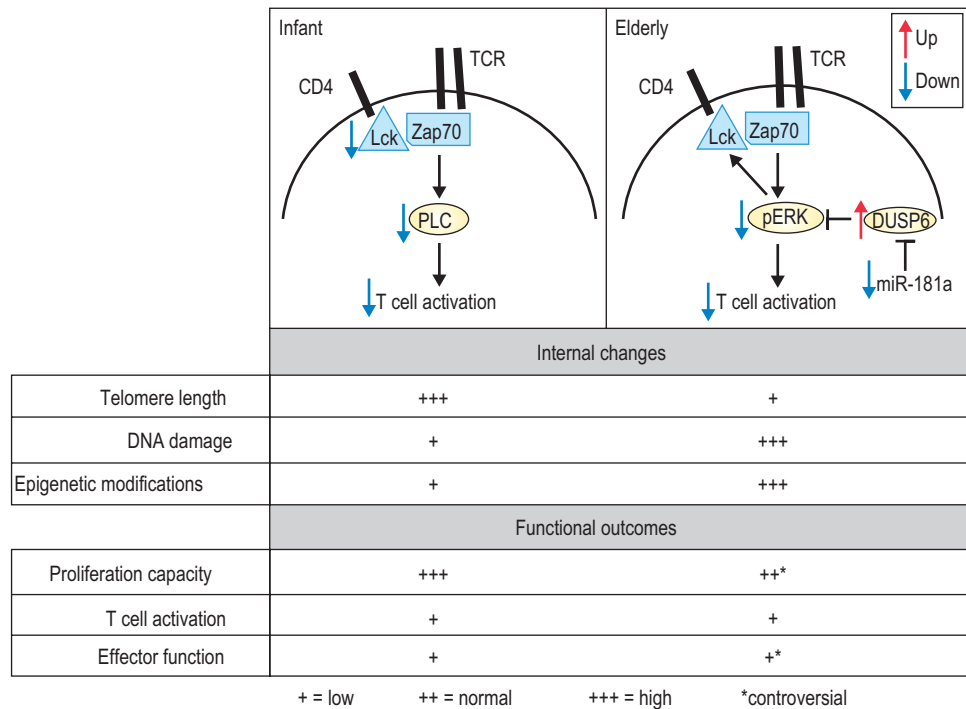


FIG 38.4 Intrinsic Differences in CD4 T Cells at the Extremes of Age. CD4 T cells from infants and older individuals demonstrate similar dysfunctions, including poor activation and reduced effector functions, although as a result of distinct mechanisms. Signaling cartoons illustrate the best documented defects. Moreover, infant and older adult T cells have very different internal changes to their DNA, including telomere length, the amount of DNA damage, and epigenetic modifications.

KEY CONCEPTS

Cellular Dysfunction With Age

- Exposure to aging host environment (e.g., inflammatory cytokines) activates negative regulatory signaling loops.
- Telomeric erosion impairs proliferative competence and restrains clonal expansion.
- End-differentiation reduces functional plasticity.
- Activation of specific gene programs modifies cell function:
 - Gene programs associated with differentiation (e.g., microRNA [miRNA])
 - Gene programs associated with T-cell exhaustion (e.g., expression of programmed death-1 [PD-1])
 - Loss of CD28 on T cells
 - Gain in natural killer (NK) cell-associated regulatory receptors on T cells (e.g., killer immunoglobulin-like receptor [(KIR), killer lectin-like receptor [KLR], immunoglobulin-like transcript [ILT])
 - Senescence-associated gene activation (e.g., inflammatory mediators)

example is the acquisition of memory-like and effector phenotypes with lymphopenia-induced homeostatic proliferation. So-called virtual memory cells, which presumably have never seen an exogenous antigen, have been identified in mouse models; clonal expansions are also seen within the human naïve T-cell compartment. Some of the changes in gene expression that are seen in naïve T cells with age may represent partial differentiation, such as declines in the microRNA miR181a and changes in the expression of phosphatases and other signaling molecules.¹⁸ Increased expression of cytoplasmic phosphatases impairs the TCR-induced

activation of naïve T cells. Changes in cell surface molecules that are seen with terminal differentiation, such as the gain in CD57 and the loss of CD27 and CD28 expression, are the most striking. Of functional importance, predominantly for CD8 T cells, is the gain in expression of cell surface receptors that are usually only found in NK cells. Most of these receptors have inhibitory function, but some of them also stimulate. Since expression of these receptors on individual cells is stochastic, the consequences can range from immunosuppression to autoreactivity.

CLINICAL CONSEQUENCES OF IMMUNE AGING— IMMUNODEFICIENCY, AUTOIMMUNITY, AND ACCELERATED DEGENERATIVE DISEASES

The most profound and most noted consequence of human senescence is the increased susceptibility to infections. Upper respiratory bacterial and urinary tract infections are frequent in the older population and less contained by the innate immune system and preexisting adaptive immunity. Not surprisingly, the immune system of an older adult is not able to induce a protective response to new antigens to which the individual has not been exposed to in the past. Clinically important examples are the severe acute respiratory syndrome (SARS) epidemic and West Nile fever virus infection. First-time vaccinations with live viruses, for example, yellow fever virus, are associated with increased morbidity and even mortality in older adults. Despite annual vaccination, influenza infections continue to be associated with high morbidity and mortality. Pneumonia caused by RSV, usually

infecting young children, is not uncommon. Immune competence to chronic infections is also compromised with age. The best example here is the reactivation of VZV manifesting as shingles.

CLINICAL RELEVANCE

Consequences of Immune Aging

- Increased morbidity and mortality from bacterial infections (e.g., pneumococci)
- Increased morbidity and mortality from viral infections (e.g., influenza, West Nile fever)
- Reactivation of latent virus (e.g., varicella zoster virus)
- Ineffective primary and booster vaccinations
- Acceleration of degenerative diseases as a result of the production of inflammatory mediators (e.g., atherosclerotic disease, Alzheimer disease, osteoarthritis)
- Increased incidence of autoimmune disease (e.g., polymyalgia rheumatica, giant cell arteritis, rheumatoid arthritis)

Vaccinations against pneumococcal antigens, influenza strains, and VZV are recommended in older adults; however, the efficacy of vaccination is reduced.

Immune aging also predisposes for autoimmune manifestations and a breakdown in self-tolerance.¹⁹ Autoantibodies are a common finding in healthy older adults; many of these autoantibodies are specific for common autoantigens, such as IgG Fc or nuclear components. The risk for several autoimmune diseases, most notably polymyalgia rheumatica and giant cell arteritis, increases with age. Although polymyalgia rheumatica predominantly presents as an activation of innate immunity, giant cell arteritis is clearly a disease of the adaptive immune system with T cell–dependent granulomatous inflammation in the vascular wall of mid-sized and large arteries.

The low-grade inflammation in the aging host has direct clinical consequences in promoting frailty and sarcopenia and accelerating degenerative diseases, including coronary artery disease, osteopenia, and Alzheimer disease. Accelerated immune aging may be one of the reasons that autoimmune diseases, such as rheumatoid arthritis (RA), are associated with a shorter life span and increased risk for cardiovascular morbidity. Inflammation as a manifestation of accelerated aging has been also implicated in the increased morbidity and mortality of patients with HIV infection in spite of highly active antiretroviral therapy (HAART).²⁰

STRATEGIES AND INTERVENTIONS ON THE HORIZON

Vaccinations hold the promise for reducing increased susceptibility to infections in young children and older adults, but improving vaccine responses has proven to be a challenge. Current strategies for targeting more elusive pediatric pathogens (e.g., RSV) included maternal vaccination (*i.e.*, the mother is vaccinated during pregnancy and vaccine-specific IgG is transferred *in utero* to the infant) and the development of infant-specific vaccine adjuvants utilizing newer understanding of the developing infant immune system. Also, further investigations into the role of microbiome and immune development (or dysfunction) may open new strategies to influence immune system development to reduce immune deficiencies and prevent inappropriate hyperactivity.


In older adults, a proper T-cell response to infectious organisms or to vaccines depends on the availability of a T-cell repertoire

that includes antigen-receptor specificities to respond to vaccination. Repertoire contraction resulting from thymic involution or memory inflation appears to be less severe than originally thought, and currently explored interventions to restore thymic activity may only be meaningful for selected populations, such as bone marrow recipients. Deficiency in the antigen-presenting system and in costimulatory signals may be overcome by identifying new adjuvants. Increasing the vaccine dose is another promising approach. Live vaccines or self-replicating constructs that also accomplish higher antigen loads may not have a sufficient safety profile in older adults. Direct targeting of signaling defects in older T cells resulting from increased expression of cytoplasmic phosphatases or inhibitory cell surface receptors will be feasible, as shown for checkpoint inhibitors in oncology; however, such approaches need to demonstrate a much better safety profile.

Interventions to influence inflammation in older adults at present needs to be nonspecific, given the multitude of underlying mechanisms. Immunomodulatory therapy is obviously standard practice in patients with autoimmune disease who exhibit accelerated aging and increased all-cause mortality. Calorie restriction to slow immune aging to an extent that it is effective is generally not well accepted. Statins and aspirin are being routinely used to prevent cardiovascular disease; their effect may be mostly antiinflammatory. Future interventions will require the development of mild and low-toxicity medications to reduce low-grade inflammation while not impairing the ability to prevent innate immune activation in response to harmful antigens.

ON THE HORIZON

- Improved vaccination strategies tailored to the infant or aged immune system (novel adjuvants, novel vaccine delivery systems)
- New vaccines for pregnant females to confer passive immunity
- Manipulation of the microbiome composition to influence immune system development
- Thymic rejuvenation (e.g. with KGF, IL-7 and other mediators)
- Prevention of chronic infection that accelerate immune aging (e.g. immunization for CMV)
- Pharmacological approaches to improve T and B cell activation, clonal expansion and differentiation
- Treatment of inflamm-aging

Please check your eBook at <https://expertconsult.inkling.com/>  for self-assessment questions. See inside cover for registration details.

REFERENCES

1. Lopez-Otin C, Blasco MA, Partridge L, et al. The hallmarks of aging. *Cell* 2013;153(6):1194–217.
2. Basha S, Surendran N, Pichichero M. Immune responses in neonates. *Expert Rev Clin Immunol* 2014;10(9):1171–84.
3. Gollwitzer ES, Marsland BJ. Impact of Early-Life Exposures on Immune Maturation and Susceptibility to Disease. *Trends Immunol* 2015;36(11):684–96.
4. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. *Proc Biol Sci* 2015;282(1821):20143085.
5. Siegrist CA, Aspinall R. B-cell responses to vaccination at the extremes of age. *Nat Rev Immunol* 2009;9(3):185–94.
6. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol* 2009;9(5):313–23.
7. Geiger H, de Haan G, Florian MC. The ageing haematopoietic stem cell compartment. *Nat Rev Immunol* 2013;13(5):376–89.

8. Kogut I, Scholz JL, Cancro MP, et al. B cell maintenance and function in aging. *Semin Immunol* 2012;24(5):342–9.
9. Naradikian MS, Hao Y, Cancro MP. Age-associated B cells: key mediators of both protective and autoreactive humoral responses. *Immunol Rev* 2016;269(1):118–29.
10. Palmer DB. The effect of age on thymic function. *Front Immunol* 2013;4:316.
11. Goronzy JJ, Fang F, Cavanagh MM, et al. Naive T cell maintenance and function in human aging. *J Immunol* 2015;194(9):4073–80.
12. Nikolich-Zugich J, Li G, Uhrlaub JL, et al. Age-related changes in CD8 T cell homeostasis and immunity to infection. *Semin Immunol* 2012;24(5):356–64.
13. Akbar AN, Henson SM. Are senescence and exhaustion intertwined or unrelated processes that compromise immunity? *Nat Rev Immunol* 2011;11(4):289–95.
14. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. *Nat Rev Immunol* 2015;15(8):486–99.
15. Kanapuru B, Ershler WB. Inflammation, coagulation, and the pathway to frailty. *Am J Med* 2009;122(7):605–13.
16. Tchkonina T, Zhu Y, van Deursen J, et al. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *J Clin Invest* 2013;123(3):966–72.
17. Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. *Nat Rev Immunol* 2013;13(12):875–87.
18. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. *Nat Immunol* 2013;14(5):428–36.
19. Goronzy JJ, Weyand CM. Immune aging and autoimmunity. *Cell Mol Life Sci* 2012;69(10):1615–23.
20. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med* 2011;62:141–55.

MULTIPLE-CHOICE QUESTIONS

1. The developing immune system is characterized by:
 - A. Increased frequencies of regulatory T cells.
 - B. Innate immune system activation.
 - C. Frequent presence of autoantibodies caused by tolerance defects.
 - D. Hematopoietic stem cells preferentially differentiating into myeloid and not lymphoid lineages.
2. An inflammatory environment in older adults is:
 - A. Less pronounced in frail older adults.
 - B. Caused by thymic involution.
 - C. Characterized by the production of cytokines from various cell types.
 - D. Results from failure of naïve T cells to differentiate.
3. The following consideration to vaccinations in older individuals is correct:
 - A. Annual influenza vaccinations are not always protective and are therefore not recommended in older individuals.
 - B. Vaccinations with live viruses (*e.g.*, yellow fever vaccine) are potentially harmful.
 - C. Only booster, but not primary, vaccine responses are impaired in older individuals.
 - D. Vaccinations even with inactivated or component vaccine carry a higher risk in older adults.
4. T cells are derived from hematopoietic stem cells that differentiate in the thymus. Which of the following statements is correct?
 - A. Thymic involution leads to a rapid loss of naïve T cells.
 - B. Upon thymic involution, peripheral homeostatic proliferation of existing T cells to is effective to at least partially compensate for T cell loss.
 - C. The thymus starts to involute after the age of 50 years.
 - D. Generation of T cells by homeostatic proliferation can increase the T-cell receptor repertoire.