

Review Article



Aging may alter immune responses to COVID-19 vaccination

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Summary

The immune system weakens with age through immunosenescence, making older adults more vulnerable to infections and cancers. Viral pandemics like COVID-19 hit this group hardest, with the elderly facing the highest infection and death rates, especially those with underlying conditions. With the global older population expected to double by 2050, future outbreaks will continue to target this age group. Recent vaccine research shows that aging alters immune responses in complex ways. While older individuals may produce similar levels of neutralizing antibodies after repeated vaccination, other protective functions, like antibody-dependent cellular cytotoxicity, decline significantly. The broad immunity that defends against multiple virus strains also appears impaired in the elderly. Given these findings and the limitations of herd immunity strategies, strengthening elderly immune systems through proper nutrition, healthy lifestyles, and tailored vaccination approaches is critical. Standard vaccines may not be enough. Designing vaccines and schedules specifically to overcome aging-related immune weaknesses should be a priority for protecting this growing population against future pandemics.

Keywords: COVID-19, Vaccination, Aging, Immunosenescence, Immune response

Received: December 28, 2025, **Revised:** February 14, 2026, **Accepted:** March 9, 2026, **ePublished:** April 27, 2026

Introduction

The immune system undergoes dramatic changes and declines during aging, termed immunosenescence.¹ These alterations of immune responses can exacerbate inflammation and possibly play an important role in the consequences of old age, including cancer, autoimmune disorders, cardiovascular diseases, Alzheimer's disease, and dementia.² Immunosenescence, by affecting immune response, makes humans susceptible to pathogen-related infections and provides a poor response following vaccination against a new antigen.³ Therefore, one of the main reasons for the higher severity and mortality of aged people during infectious epidemics such as SARS, MERS, and H1N1 epidemics is the age-related weakening of the immune system.

The coronavirus disease (COVID-19) is a highly transmissible and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in China and rapidly spread to other countries across the world.⁴ Coronavirus is a member of the coronaviridae family, which generally causes fever, acute lung injury

(ALI), and acute respiratory distress syndrome (ARDS), thereby leading to pulmonary failure and even fatality.^{5,6} Recent studies indicated that the elderly, especially men, are mostly infected by COVID-19, showing more severe symptoms and are more likely to die from COVID-19 than youngsters.⁷ This review aims to narrate the changes in the immune system with age and why COVID-19 is lethal in the elderly.

Evolution of the Immune System

The mammalian immune system is composed of adaptive and innate arms that cooperate for an effective immune response. The innate immune system provides the first line of defense against foreign pathogens with a contribution of toll-like receptors (TLR), humoral factors such as complement, and circulating cells of the innate immune system, including neutrophils, natural killer (NK) cells, monocytes, macrophages, and dendritic cells.⁸ Innate immune system components are present in early life. However, the function of all components of innate immunity is rather weak in neonatal compared with later life because of developmental changes and functional



maturation, which occur in various periods of fetal life.⁹

Like innate immunity, the neonate's adaptive immune responses are seemingly immature. So newborns are at higher risk of infectious diseases.¹⁰ In this period of immune immaturity, maternal IgG antibodies are transplacentally transferred from the mother to the newborn via a neonatal Fc receptor (FcRn) and secretory immunoglobulin A in the breast milk, protecting against many infectious diseases that the mother previously experienced.¹¹ When maternal antibody protection fades by about six months of age, antibody and T cell responses gradually mature in newborns and partial protection is provided. The development of T cells occurs in the thymus.¹² Most T cells, which have never encountered foreign antigens, are naïve and express the CD45RA marker at birth. These neonatal T cells proliferate poorly when activated through their T cell receptor (TCR) and skew toward the Treg cell lineage. As the child grows, Treg cell numbers decrease remarkably, and the percentage of memory Th1, Th2, and Th17 cells is gradually elevated proportionally to the number of naïve T cells.¹³

Neonatal circulating B cells, which develop in the bone marrow (BM), are naïve, lack antigenic exposure, and express only partially developed antibody receptors

specific for an immunogen. Naïve B cell is activated by binding the B cell receptor (BCR) to its specific (cognate) antigen. Activated B cells internalize and digest antigen to peptides for presenting to T follicular helper cells (TFH) in lymph nodes' germinal centers (GCs). The interaction of TFH with B cells promotes the maturation of B cells to memory B cells or long-lived plasma cells and leads to class (isotype) switching and somatic hypermutation of antibodies.¹⁴ In addition, neonate exposure to dietary antigens (formula milk or breast milk) and neonate-mother communication result in neonate gut colonization of commensal bacteria, which profoundly affects the maturation of the adaptive immune system. Also, cross-reactivity of carbohydrate antigens of ABO blood groups with gut bacteria primes B cells and induces IgM antibody responses. So as children grow older, the highly diverse immune repertoire is also formed by numerous infections and vaccinations.¹⁵

Effects of Aging on Innate Immunity

The innate immune system consists of the physical barrier and various cells specified for rapid response against invading pathogens. Innate immunity responses in the aged people are compromised, resulting from the alteration

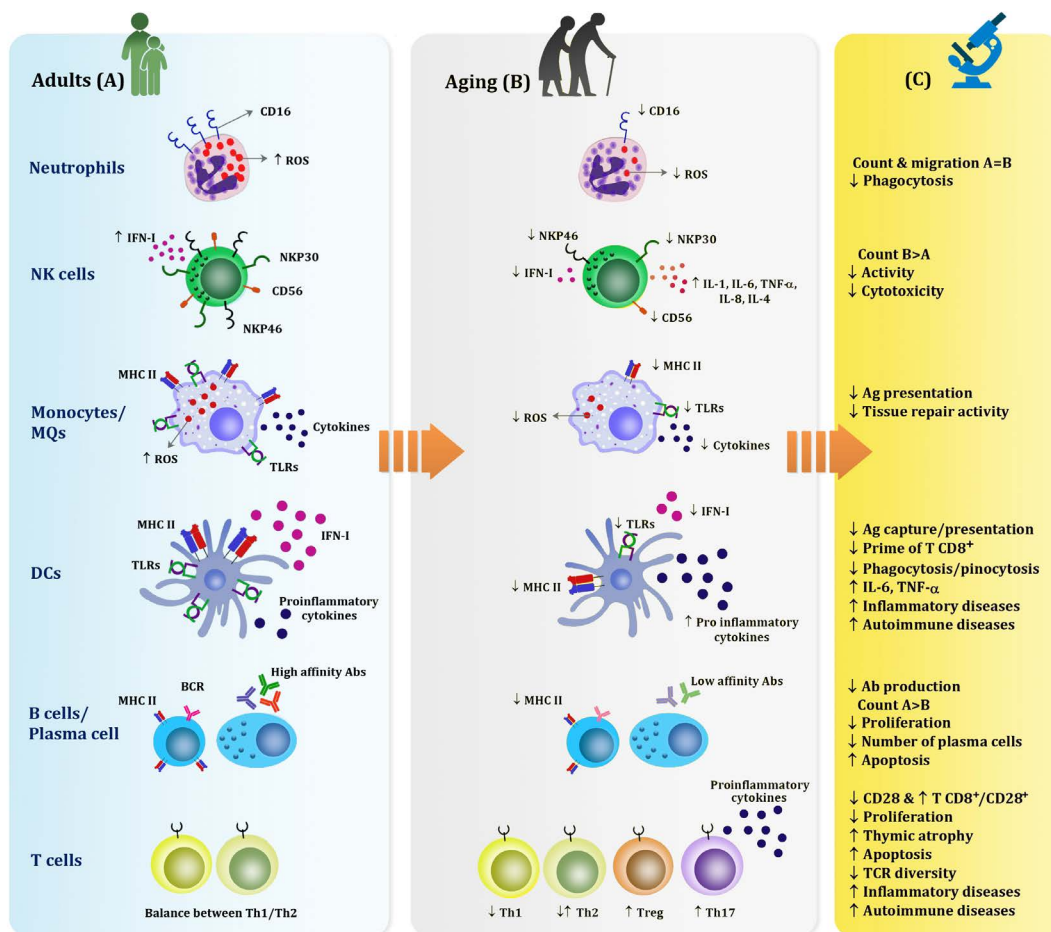


Figure 1. Different changes in immune system components in aging. A: Immune cells characteristics in adults B: Immune cell changes in aging C: The effect of immune cell changes

in the population and function of its elements (Figure 1).¹⁶ Here we will describe the details of these changes.

Physical Barriers

Skin and mucus act as the first line of defense against pathogens that show significant changes in structure and cellular composition with age.¹⁷ Age-associated changes in the skin consist of decreased replacement of keratinocytes and production of sweat, depletion of Langerhans and melanocyte cells, and a thinner epidermal layer due to keratinocyte atrophy.¹⁸ Moreover, higher levels of pro-inflammatory cytokines in the skin of aged people inhibit collagen synthesis.¹⁹ Furthermore, aging impairs the immunological defense of the skin, resulting in an increased incidence of cancer and skin infections in the elderly. Concerning the mucus layer, the firm protective mucus layer is thinner, and its ability to trap pathogens decreases in the elderly. Additionally, IgA concentration is significantly reduced in these people.²⁰

The respiratory epithelium is the first line of defense against inhaled antigens and irritants. It consists of columnar ciliated and goblet cells that provide physical clearance in the respiratory system.²¹ Goblet cells synthesize mucus, and ciliated cells are responsible for propelling mucus with its trapped foreign particles toward the pharynx. After exposure to an antigen, the airway epithelial cells release a broad range of cytokines and chemokines that activate (growth, proliferation, differentiation, apoptosis, etc.) and recruit inflammatory cells into the lung.²² Interestingly, the ability of cilia to clear mucus from the lungs in the nasal epithelium decreased significantly with age. Studies revealed an increased mucus production in aged humans and old BALB/c mice sensitized and challenged intratracheally to ovalbumen.²³

Age-related impairment in the lung epithelial barrier function may contribute to the susceptibility of the elderly to lower respiratory tract infection and pathogenesis of late-onset asthma.²⁴ Airway epithelium in asthma patients displays morphological changes, including disruptions of the epithelial cell tight junctions and increased susceptibility to apoptotic effects of oxidants. Moreover, the production of interferon- α (IFN- α) and IFN- β in response to rhinovirus, a major cause of lower airway problems in the elderly, is defective. Respiratory viral infections may promote epithelial damage and serve as an initiating event in the pathogenesis of late-onset asthma.²⁵

Dendritic Cells

Dendritic cells (DC) are responsible for antigen processing and presentation, which play a pivotal role in linking the innate and adaptive immune systems.²⁶ Aging influences the DC capacity to capture antigens and migrate to lymphoid organs. These changes are responsible for impaired T cell response in the elderly. Phagocytosis of apoptotic cells by DCs is severely affected with age, associated with autoimmunity and inflammation in the elderly.²⁷ Reduced

antigen presentation and phagocytosis in aged DC are associated with mitochondrial dysfunction. Decreased ATP levels and baseline oxidative phosphorylation, on the other hand, increased Reactive Oxygen Species (ROS) production are some of these dysfunctions.²⁸ Other age-related significant alterations are observed in signaling pathways, as well as the expression and function of DCs' TLRs. The impaired AKT signaling pathway, which has an important role in regulating TLR expression in DCs, leads to increased secretion of pro-inflammatory cytokines by aged DCs.^{29,30} Plasmacytoid dendritic DCs from aged subjects cannot secrete protective cytokines such as IFN- α and IFN- λ and prime the specific CD8⁺T cell in response to the influenza virus, which results in a decreased ability of the elderly to combat infections.³¹

Natural Killers

The natural killer (NK) cells are an important component of innate immunity against virus-infected and tumor cells.³² These cells can be divided into two populations based on differential surface expression of CD56, including CD56^{bright} and CD56^{dim}, which represent different cytokine patterns and cytotoxic activities.³³ During aging, the circulating NK pool's function, frequency, and composition may alter, which affects the immune system. Age-associated NK cell alteration contributes to increased reactivation rates of latent Mycobacterium tuberculosis, poor resolution of inflammation, and a higher incidence of viral infection.³⁴ The absolute number of NK cells increases in the elderly with a decrease in CD56^{bright} population and an increase in CD56^{dim} mature cells; however, *their* functional activity is decreased and displays a significant decrease in the expression of activating receptors (e.g., NKp30 and NKp46).³⁵ In addition, NK cell proliferation rate and cytokine production in response to interleukin-2 (IL-2) are reduced during aging. The concentration of IFN- γ and IFN- α secreted from NK cells is decreased, whereas IL-1, IL-4, IL-6, IL-8, IL-10, and TNF- α levels increase.³⁶ On the other hand, NKT cell (CD3⁺CD16⁺CD56⁺ cells) numbers decrease in elderly subjects and, similar to NK cells, indicate reduced proliferation following the activation by IL-2 and α -GalCer, a specific ligand for CD1d on iNKT cells.^{37,38} Given their role in pathogen clearance, especially viruses, virus-induced infections may be more severe in the elderly.

Neutrophils

Neutrophils, also known as polymorph nuclear (PMN) leukocytes, are the first cells recruited to the infection site by cytokines and chemokines, mainly IL-1 and IL-8, respectively.³⁹ They detect microbial pathogens and eliminate them via phagocytosis and the degranulation process of neutrophil extracellular traps (NETs) when a microorganism is too large to be ingested. The age-related changes in neutrophils lead to higher susceptibility to infectious diseases.⁴⁰ Although neutrophil levels and the

chemotactic responses of neutrophils remain unchanged in the healthy elderly, decreased generation of superoxide and phagocytic capacity with a reduced CD16 expression are necessary for FcR-mediated phagocytosis, which is observed in elderly neutrophils.⁴¹

Essential factors for migration are regulated by PI3K activity. Reduced neutrophil migration due to constitutive PI3K activity has been described in aged neutrophils.⁴² When inflammation occurs, inflammatory cytokines trigger the delay of apoptosis in neutrophils; then, neutrophils can be fully activated at the inflammation site. Increased apoptosis of neutrophils in the elderly may lessen an effective anti-pathogen activity, causing more frequent and more severe respiratory infections in these subjects.⁴³ The effect of aging on the airway's neutrophils differs from peripheral blood changes. In elderly patients with asthma, neutrophils increase in the airspace and display increased MMP-9, neutrophil elastase, IL-8 secretion, and sputum levels that possibly contribute to greater severity of asthma in the elderly.⁴⁴

Monocytes and Macrophages

Macrophages' main function is the phagocytosis of pathogens and the production of reactive oxygen/nitrogen (ROS/NOS) species. Macrophages express TLRs, which recognize pathogen-associated molecular patterns (PAMPs) and release various cytokines, chemokines, growth factors, and enzymes in response to pathogens. In addition, these cells also express class II major histocompatibility complex (MHC-II) molecules on their membranes and present antigens to lymphocytes.⁴⁵ Aging impacts multiple aspects of macrophage functions, including reduced generation of nitrous oxide and superoxide, reduced phagocytosis capability, and diminished wound repair and tissue regeneration processes. The surface expression of some key molecules also changes. Macrophage ability to present antigens is reduced with age, resulting from a reduction in the expression of the MHC-II gene. Age-related decreased surface expression and altered downstream TLR-mediated signaling decrease the secretion of cytokines and chemokines upon TLR activation.⁴⁶ Activated macrophages are classified into two subpopulations: pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes. Herein, M1 macrophages are activated by IFN- γ or LPS and secrete pro-inflammatory cytokines, mediating pathogen phagocytosis. Alternatively, activated macrophages, called M2 macrophages, are induced by IL-4 and IL-13 and produce anti-inflammatory cytokines.⁴⁷ Aging does not affect macrophage polarization, but old mice exhibit decreased M1 and M2 markers expression in adherent splenocytes.⁴⁸

Effects of Aging on Adaptive Immunity

In addition to innate immunity, aging also affects adaptive immunity. Both cell-mediated and humoral immunity

are important for pathogen clearance and protective immunity against reinfection. A diverse repertoire of antigen receptors on T and B lymphocytes mediates the specific recognition of antigens. Consequently, activation and clonal expansion of lymphocytes mediate adaptive immune response against antigens.⁴⁹ Aging negatively affects de novo development and function of T and B cells and is responsible for the increased prevalence and severity of infectious diseases in the elderly.⁵⁰ In the following, we will describe the effect of aging on the prevalence and function of B and T lymphocytes. Hematopoietic stem cells (HSCs) include lymphoid (Ly-HSCs) and myeloid (My-HSCs) lineages. These first-line cells continuously produce all peripheral blood cells, especially immune system cells⁵¹. The behavior of HSCs changes with age, possibly resulting from DNA damage and shortening of telomeres. Human HSCs' regenerative capacity diminishes with age and shows a phenotypic shift from lymphoid lineage to the myeloid lineage. Therefore, differentiation into lymphoid cells (both T and B cells) decreases, resulting in a reduced number of naïve cells that migrate to secondary lymphoid tissues such as the spleen.⁵² The expression of Ink4a and Arf in pro-B cells and Ink4a in pro-T cells was dramatically upregulated with age. These factors suppress the proliferation of B cell progenitors in the BM and T cell progenitors in the thymus. Moreover, Ink4a and Arf induce apoptosis in these lymphocytes.⁵³

In addition, defects in cell-intrinsic transcriptional programs, such as epigenetic deregulation, replication stress, and deficient DNA repair, which induce aging in HSC, extrinsic conditions, and changes in the local microenvironment, can affect stem cell aging.⁵⁴ Another age-associated change in the HSC microenvironment includes an increase in adipocytes of the BM and a decline in the BM niche that supports HSC survival.⁵⁵ These changes, possibly due to decreased IL-7 secretion by aged stromal cells, have been implicated in B cell lineage aging and decreased local production of transforming growth factor-1 (TGF- β 1) in the BM microenvironment.⁵⁶ Aging affects lymphoid progenitors and the lymphocytic pool. The composition and quality of the mature lymphocyte pool are profoundly altered by aging, which is discussed in the following. T cell progenitors in the BM lack CD4⁺ and CD8⁺ coreceptors that undergo T cell receptor (TCR) rearrangement in the thymus to generate CD4⁺CD8⁺ double-positive (DP).⁵⁷ After approximately one year of life in humans, thymus involution begins, and by the 7th decade of life, 90% of the thymopoietic space is replaced with adipose tissue.⁵⁸ In parallel with thymus involution, TCR diversity within the repertoire of naïve T cells and the thymic output of naïve cells significantly decreases.⁵⁹ Although a decrease in naïve T cells occurs with aging, the absolute number of T cells remains relatively constant or with a little change due to an increase in the number of CD4⁺ and CD8⁺ memory T cells. However, despite prolonged survival, these memory

cells may have poor antigen responses.⁶⁰

Moreover, T cells display defective function with aging, contributing to increased susceptibility to infection, autoimmune disease, and cancer. The hallmark of the age-associated defect in T cell function is a decline in the immunological synapse formation and loss of CD28 expression.⁶¹ Loss of this molecule occurs during the lifetime of antigen or pathogen exposure. Loss of CD28 expression is responsible for decreased interleukin IL-2 production, while increased susceptibility to apoptosis and impaired differentiation into Th subsets (both Th1 and Th2) cells upon activation.⁶² Although aged naïve T cells do not differentiate into Th1 and Th2 cells, they easily differentiate into the Th17 phenotype. So older people have an increased Th17 frequency. Th17-related cytokines play an important role in autoimmune diseases and human inflammatory conditions.⁶³

The proportion of T regulatory (Treg) cells increases with age, but there are inconsistent results regarding the function of Treg cells in aged people. Previous studies suggested a decline in the suppressive activity of Treg cells, but evidence from more recent studies shows that it is preserved or even enhanced. Thus, an age-related reduced response to tumors and viruses is possibly due to the age-related increase in Treg cells and poor memory response to new antigens.⁶⁴ Additionally, downstream signaling of TCR activation is also significantly altered in people aged.⁶⁵ Age-related decline in Mitogen-activated protein kinase (MAPK) plays a key role in impaired T cell activation, differentiation, and cytokine production. Reduced signaling pathways lead to Ca²⁺ influx, resulting in decreased intracellular calcium levels and alterations in the signal transduction pathways of NF-κB and MAPK.⁶⁶

B cells are continuously generated in the BM and then migrate to the periphery. Aging is associated with declines in the BM microenvironment, possibly resulting from reduced stromal cell-derived IL-7.⁶⁷ Age-related changes in the BM lead to a decline in the number of human B cell precursors and new naïve B-cell generation rates.⁶⁸ The most important function of B lymphocytes is antibody production. The decline in antibody production diversity and quality occurs in B lymphocytes with age. Cell intrinsic defects contribute to lower antibody affinity in the elderly. E47, which regulates immunoglobulin class switching, is downregulated in aged humans' B cells, resulting in decreased activation-induced cytidine deaminase (AID) enzyme induction. AID causes mutations by converting cytosine to uracil in the immunoglobulin to produce antibody diversity.⁶⁹ The number of plasma cells in the BM is significantly reduced with age, leading to a low affinity of antibodies to antigens.^{70,71}

Sex-Related Changes in the Immune System

Aging affects innate and adaptive immunity in both sexes, but this age-related alteration is different between males and females. Aged males indicate a higher innate immune

response and increased pro-inflammatory cytokines (IL6 and IL18), making them more susceptible to infections and reducing their responsiveness to vaccination.⁷² Despite males, females display stronger adaptive immune responses, contributing to faster pathogen clearance and greater vaccine efficiency. On the other hand, robust immune responses are associated with increased susceptibility to inflammatory and autoimmune diseases in females.⁷³ Sex differences in Age-related changes arise from differences in the distribution of immune cells and chromatin accessibility between the genders. Studies revealed a male-specific decrease in chromatin accessibility for adaptive immunity genes and increased accessibility for innate immunity and pro-inflammatory processes. Comparing sexes in the adaptive immune cells, females have higher CD4⁺ and CD8⁺T cells and more circulating B cells, whereas males have a higher level of central memory CD4⁺T cells. Regarding *sex-specific differences in the innate immune cell*, more active NK cells and macrophages and a higher proportion of intermediate (CD14^{hi}CD16^{low}) monocytes have been reported in older females. So sex significantly influences the cellular and molecular basis of aging and should be considered in interventions/therapies for immune-related conditions common in aged people.^{74,75}

Aging and Viral Infections

Viral infections trigger an innate immune response, which plays a critical role in eradicating viral infection and inducing an effective adaptive immune response. Anti-viral innate immune responses are initiated by recognizing viral components by host pattern-recognition receptors (PRRs). Following virus entry, innate receptors expressed at the host cell surface, such as TLRs, detect extracellular viruses, either dead or alive, and receptors within cells, such as NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs), and AIM-2-like receptors (ALRs), recognize cytosolic viral infections. Receptor engagement causes the rapid production of pro-inflammatory cytokines and IFNs. Pro-inflammatory cytokine secretion is associated with the recruitment of cells involved in inflammation. In addition to helping to clear the virus, this process contributes to tissue damage.⁷⁶ Moreover, type-I IFNs (IFN-α/β) secreted from infected cells interact with their receptors, which results in upregulating genes that inhibit virus spread. Additionally, type-II INF (INF-γ) stimulates NK cells, which recognize infected cells and induce apoptosis in these cells. Deficiency in IFN response or the lack of functional type-I IFN receptors leads to viral persistence and frequent infection.⁷⁷

Adaptive immune response against viruses begins with viral protein uptake by antigen-presenting cells (APCs), which degrade viral protein to peptides and present viral antigens to naïve T lymphocytes via HLA-I or HLA-II in local draining lymph nodes. Furthermore, CD8⁺T cells, which recognize peptides bound to HLA-I, migrate

to the site of infection and can directly destroy virus-infected cells, thereby contributing to tissue damage. On the other hand, CD4⁺T cells are other important immune cells that recognize the peptide through HLA-II, helping B cells secrete antibodies. Secreted antibodies bind to infected cells, activate complement, and cause inflammatory reactions. Collectively effective innate and adaptive immune responses are essential for controlling viral infections.⁷⁸ Adaptive and innate antiviral immune responses are reduced in the elderly, increasing susceptibility to viral infections. Age-related change in innate immune cells leads to a reduced secretion of IFNs, which is necessary for virus elimination. Also, despite the increase in the number of NK cells, the cytotoxicity of these cells decreases with aging and affects the control of viruses. Antiviral cellular immunity displays alteration in aged people. CD8-specific responses against virus-infected cells are delayed, and the number of naïve T cells and their ability to proliferate and differentiate into effector cells are reduced in older people, resulting in virus replication and spread.⁷⁹

Specific Examples of Viral Infection With Aging

Influenza is the most common viral pneumonia, responsible for repeated hospitalization and deaths among the elderly. The annual flu vaccine effectively prevents it, but older people do not respond effectively to the vaccine.⁸⁰ Detection of living influenza virus by PRRs stimulates pro-inflammatory cytokine secretion. Age-related decrease in the function and expression of TLR1, TLR3, TLR8, and TLR7 in DCs reduces cytokine production after TLR activation. Plasmacytoid DCs also secrete lower IFN-I and IFN-II in aged humans, so these cells cannot prime CD4/CD8⁺T cells effectively. These alterations are associated with poor cellular and humoral immunity to influenza.⁸¹

The humoral immune system produces antibodies against different influenza antigens and is important for virus neutralization. Impaired antibody response to influenza vaccination in the elderly is related to a decline in helper functions of CD4⁺T cells, reduced expression of co-stimulatory receptors such as CD28 and CD40L, and reduced GC-related responses. Consequently, antibodies are produced at a lower level with low-affinity post-vaccination in the elderly.⁸² Influenza-specific CD4⁺ and CD8⁺ memory T cells are responsible for influenza virus clearance. Also, these memory cells boost the following vaccination in older people, but IFN- γ secretion and influenza-specific cytolytic activity decrease with aging.^{83,84} Varicella-zoster (VZV) affects a significant portion of the elderly and causes a highly contagious infectious disease known as Shingles in adults. After primary infection during childhood, VZV causes chickenpox. VZV-specific activated T cells that produce IFN- γ play an important role in protecting against infections. Nevertheless, specific memory response to the VZV is undetectable and leads

to the reactivation of the virus during aging. Additionally, a higher percentage of Treg cells and reduced absolute numbers of CD3⁺, CD4⁺, and CD8⁺T cells in aged people are associated with decreased VZV-specific immune response and less effective vaccines.^{85,86}

Following cytomegalovirus infection, innate and acquired immune responses are induced, but cytomegalovirus (CMV) has different mechanisms for escaping from the immune system and may remain hidden in cells, and is reactivated if the immune system is weakened.⁸⁷ Latent CMV infection affects T cell distribution in older people and leads to a reduction in naïve T cell levels but increases CMV-specific memory CD8⁺T cell number and much less CMV-specific memory CD4⁺T cell number. As a result, immunological response to a new antigen or vaccination is impaired in aged people. Humoral immunity is also compromised in CMV infection due to low B cell numbers.⁸⁸ Moreover, CMV infection induces chronic stimulation of immune cells and the secretion of inflammatory mediators such as TNF- α and IL-8.⁸⁹

Human immunodeficiency virus (HIV) infection may increase among the elderly population. In addition to reducing the acquired and innate immune response during aging, antiviral drugs have more side effects and less efficacy in the elderly.^{90,91} Elderly HIV-infected patients present depletion and dysfunction of CD4⁺T cell counts, decreased number of naïve T cells, telomere shortening in CD4⁺ and CD8⁺T cells, lower T cell proliferation, and altered cytokine profiles (e.g., lower IL-2 production while higher IFN- γ production). Moreover, naïve T cell recovery following CD4 depletion would not happen in elderly HIV-infected patients because of thymic involution in aged people.^{92,93}

West Nile virus (WNV) is the cause of viral encephalitis, which has a high prevalence and the risk of disease increases with age. Altered innate immune response in the elderly may increase susceptibility to WNV. Resting macrophages in older people express a reduced level of endosomal TLR3 and present an elevated level of several cytokines, including TNF- α , IL-6, and IFN- β , during *in vitro* infection with WNV. Increased levels of cytokines may facilitate the entry of WNV into the brain of the elderly. Moreover, impaired activation of WNV-specific T cell response in aged mice, including defects in cytokine (such as IFN- γ and TNF- α) and lytic granule production, contributes to age-related WNV susceptibility.⁹⁴

Immune Response to SARS-CoV-2

Coronaviruses are spherical, containing a 29-kbp positive-sense single-stranded RNA genome, which encodes structural proteins.⁹⁵ SARS-CoV-2 attaches to angiotensin-converting enzyme 2 (ACE2)-expressing target cells such as alveolar type II cells or other cells, including the lungs, heart, renal system, and gastrointestinal tract S-protein.⁹⁶ Following the attachment, SARS-CoV-2 fuses its membrane with the host cell membrane and releases

the viral genome into the host cells' nucleus.⁹⁷ Endosomal RNA receptors, including TLR3 and TLR7, and cytosolic RNA sensors, such as RIG-I/MDA5, recognize dsRNA and induce type-I IFNs and other pro-inflammatory cytokines in the host cells. Accessory proteins of SARS-CoV-2 can interfere with TLR3 signaling and inhibit antiviral IFN-mediated responses, resulting in uncontrolled viral replication.⁹⁸ When the virus enters the cells, APCs present SARS-CoV-2 antigens to T cells and induce an adaptive immune response. Viral antigen presentation mainly depends on class I MHC molecules (MHC-I), but MHC-II molecules also contribute to the presentation. Both CD8⁺T and CD4⁺T cells are critical to viral clearance. CD8⁺T cells recognize peptides bound to MHC-I, while CD4⁺T cells recognize peptides bound to MHC-II.^{99,100} Moreover, SARS-CoV-2 infection makes plasma cells produce antibodies. Plasma cells produce specific neutralizing antibodies, including IgA, IgM, and IgG responses, which target the receptor-binding domain of the S-protein, thereby possibly blocking viral entry to the host cells.¹⁰¹

COVID-19 and Aging

Patients with COVID-19 show many clinical features. Dominant symptoms are fever, cough, fatigue, and sore throat. Also, the patients develop pneumonia with abnormal findings on chest CT.¹⁰² The mechanisms underlying the pathogenicity of SARS-CoV-2 are not fully understood, but it has been revealed that cytokine storm and lymphocytopenia play major roles in the immunopathogenesis of COVID-19.¹⁰³ Cytokine storm is an aggressive inflammatory response initiated by virus replication in the airways, resulting in increased concentrations of pro-inflammatory cytokines.^{104,105} Delayed or suppressed type-I IFN response causes a release of large amounts of pro-inflammatory cytokines (IFN- α , IFN- γ , IL-1 β , IL-6, IL-12, IL-18, IL-33, TNF- α , and TGF β) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10). This phenomenon correlates with the development and progression of ARDS and multiple organ failure.^{106,107} SARS-CoV-2 triggers IL-6 secretion that promotes Th17 responses. Th17 cytokines, including IL-17, reduce the number of Treg cells. On the other hand, Th17 cytokines promote neutrophil recruitment to the airway, leading to ALI.¹⁰⁸ Cell-mediated immunity, which consists of T cells (T helper and T cytotoxic) and NK cells, is essential for controlling viral infection. SARS-CoV-2 can also infect T cells, impair the function of CD4⁺T cells, and promote excessive activation and possibly subsequent exhaustion of CD8⁺T cells. Moreover, it augments the apoptosis of T cells, leading to lymphocytopenia and eventually diminishing host anti-viral immunity.¹⁰⁹

Based on hospitalized patients' data, a high proportion of severe groups are older men and display a significant age-dependent difference in immune status compared to non-severe ones.¹¹⁰ In COVID-19-confirmed older cases,

neutrophil counts are remarkably higher and tend to develop a higher expression of pro-inflammatory cytokines and chemokines. The higher inflammatory response in aged people is related to an increased mortality rate due to ARDS.¹¹¹ Age impacts COVID-19-specific lymphocyte responses and NK cells. The counts of NK cells, T cells, and B cells were significantly lower in severe disease patients. It should be noted that all lymphocyte subsets, including CD4⁺T and CD8⁺T cells, are significantly decreased in this group of patients.^{112,113} The frequency of functional CD4⁺and non-exhausted (PD-1⁻CTLA-4⁻TIGIT⁻) CD8⁺T cells in patients with severe COVID-19 is significantly lower and may reduce their cellular immune response to SARS-CoV-2.¹⁰⁹ Patients with COVID-19 also have higher naïve CD4⁺T cell subpopulations and smaller percentages of memory cells. The severe group presents a lower level of Treg cells, which is closely related to inflammatory responses, increased cytokine production, and exacerbated tissue damage. It can be concluded that age has an impact on the severity and pathogenesis of SARS-CoV-2 infection.¹⁰⁴

Conclusion

After age 60, the body's natural decline seriously weakens the immune system, making older people much more vulnerable to severe infections and cancers. This is a growing global issue as the population ages. The COVID-19 pandemic clearly showed this, with the elderly suffering the highest rates of severe illness and death. Since relying on herd immunity is not safe for this group, it is crucial to focus on strengthening their immune systems directly. Key ways to do this include ensuring good nutrition with nutrients like zinc and vitamin D, along with a healthy lifestyle featuring regular exercise and avoiding smoking and alcohol. Recent research into COVID-19 vaccines has given us a clearer picture of how aging alters immune responses, revealing that the effects are complex. Furthermore, the type of vaccine and the schedule may influence outcomes, with some research suggesting that starting with certain vaccine types might better preserve long-term immune memory. A critical concern is that the broadly protective, pan-coronavirus immunity that helps defend against various strains appears to be particularly impaired in older individuals, leaving them more exposed to new variants. Given these findings, simply providing a standard vaccine may not be enough. The goal of strengthening immunity in the elderly now includes the need for tailored vaccination strategies, such as designing new formulas or schedules specifically intended to overcome the identified weak spots in the aging immune system.

Acknowledgments

We would like to express our very great appreciation to Reza Falak, Chairman of the Department of Immunology, Iran University of Medical Sciences, Tehran, Iran, for his valuable and constructive

suggestions during the writing of this review article.

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Competing Interests

The authors declare no conflict of interest.

Ethical Approval

Not applicable.

Funding

None.

Intelligence Use Disclosure

This article has not utilized artificial intelligence (AI) tools for research and manuscript development, as per the GAMER reporting guideline.

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