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Review

Aging and Infection: Impact of Immunosenescence and Inflammaging in Respiratory Viral Infections

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Immunosenescence • Aging • Inflammaging • Immunity • Respiratory viral infection

Abstract
A strong yet appropriate immune response is essential for the timely control and clearing of respiratory viral infections. However, as physical condition declines with age, so does our immune function. Immunosenescence is an age-related immune dysfunction marked by dysregulation of innate immune pathways, thymic involution, decreased T and B cell numbers and function, altered metabolism, and epigenetic changes. Additionally, older individuals often develop inflammaging, a condition characterized by elevated levels of proinflammatory markers. This deterioration of immune function in older adults significantly impairs viral control and increases disease severity. Studies unanimously show a progressive rise in hospitalization and mortality rates with age. In this review, we aim to discuss the complex relationship between aging, immunosenescence, and inflammaging during respiratory viral infections. Furthermore, this review discusses the underlying mechanisms that increase susceptibility, disease severity, and higher hospitalization rates among older adults.

Introduction

Aging in humans is accompanied by a gradual, irreversible process and a complex phenomenon from psychological, physiological, cellular, molecular, physicochemical, and metabolic perspectives [1-3]. Aging affects multiple organs and systems, significantly influencing the development and advancement of cancer and infectious diseases [4]. There is a global consensus that infections in elderly individuals are more frequent and more severe [5-8]. Immunosenescence refers to the decline in immune system function with age, characterized by a decrease in the numbers and impaired activity of innate immune cells, as well as T and B cells [9]. Immunosenescence often accompanies decreased lung elasticity, reduced alveolar surface area, chest wall stiffening, and increased infiltration of

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proinflammatory neutrophils and macrophages into the lungs. These changes contribute to elevated chronic inflammation, or inflammaging, marked by higher levels of proinflammatory markers such as interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor alpha (TNF-alpha), IP-10, Ferritin, and others [10-12].. Immunosenescence and inflammaging have recently gained increasing attention for their role in cancer development and severity during respiratory tract infections [12, 13]. During respiratory tract infection, aged alveolar macrophages and neutrophils in the lung secrete elevated levels of inflammatory factors such as IL-1β, IL-6, and TNF-α, thereby accelerating lung inflammation, dysfunction, vascular permeability, fluid accumulation, and lung damage. These age-related lung pathologies delay time to infection control, increase hospitalization, and mortality among elderly patients. These studies have reported immunosenescence and inflammaging as key factors in the increased susceptibility, hospitalization, and mortality among elderly individuals [14-16]. Given the multidimensional complexity of ageing, immunosenescence, and inflammaging, this review will summarize the impact of aged immunity on the outcome and severity of respiratory tract viral infections in elderly individuals. This will help us understand and potentially suggest intervention strategies to create personalized treatments that improve outcomes for respiratory tract viral infections among elderly individuals.

Age-Related Changes in Innate Immune Response

The human innate immunity consists of a network of cells, including neutrophils, natural killer (NK) cells, monocytes, macrophages, and dendritic cells, that are essential in initiating and orchestrating the host's immune response to an antigen [17]. The impact of aging on the innate immune system is highly complex. Reports using old mice have clearly demonstrated that innate immunity deteriorates severely with age, likely due to a combination of intrinsic and extrinsic factors [18, 19]. For instance, age-related effects are observed in the activation and functions of all innate immune cell types, linked to defective toll-like receptors (TLR). Aging results in significant dysregulation of TLRs, leading to impaired and delayed innate immune activation and decreased cytokine production [20-22]. Furthermore, age-related innate immunosenescence is accompanied by an inappropriate and elevated secretion of proinflammatory cytokines and chemokines [10-12]. In addition to such intrinsic effects, aging also leads to a decrease in the number of circulating innate immune cells [23]. In short, innate immunosenescence and inflammaging are two paradoxes that make older adults susceptible to infections and chronic inflammation.

Monocyte-derived macrophage

The first effect of aging in monocytes or monocyte-derived macrophages is a reduction in their numbers [24]. Moreover, age-related decreases in macrophage function to various infections and cancers have been reported [25, 26]. A defective TLR4 and age-associated decreases in LPS-induced responses were observed in aged mice. This results in decreased levels of IL-1β, IL-6, and TNF-α and reduced cellular activation [27, 28]. Further studies have shown decreased TLR gene expression and reduced cytokine production in response to activation of TLR2, TLR6, TLR3, TLR4, TLR5, and TLR9 in splenic and peritoneal macrophages [29, 30]. Reports have shown age-related decreases in TLR signal transduction through MAP and JNK kinase pathways in macrophages of aged mice [22, 31]. Similarly, in humans, TLR function in monocytes has been shown to decline with age, leading to age-related declines in cytokine production. Monocytes from humans aged≥65 years exhibit an impaired TLR1/2 function and a reduced TLR1/2-induced IL-6 and TNF-α production [31]. Given that ligation of TLRs on macrophages triggers phagocytosis and antigen presentation [32], elderly individuals exhibit reduced phagocytic capacity [16]. Several other studies have found that antigen presentation by macrophages declines with age, possibly due to decreased expression of MHC class II molecules in both humans and mice [33, 34]. An age-related defect in the upregulation of the co-stimulatory protein CD80 on these monocytes was also observed [35]. Although neutrophils do not play a role comparable to that of macrophages during viral

infection, a similar age-related effect is observed in neutrophils. Aged neutrophils exhibit a decreased phagocytic ability with reduced production of neutrophil-derived cytokines. Moreover, aging also negatively affects the production of superoxide anion and nitric oxide in neutrophils [35-37]. Such an age-related reduction in macrophage numbers and function impairs timely respiratory viral control and results in severe clinical consequences.

Myeloid and plasmacytoid dendritic cells

As with monocytes, macrophages, and neutrophils, aging reduces the number and function of dendritic cells (mDC and pDC) [38]. These age-related dysfunctions of DCs are characterized by defective DC trafficking and impaired CCR7 signal transduction [39]. In mouse model experiments, an age-associated reduction in DC-SIGN expression was observed on immature bone marrow-derived DCs. Furthermore, these aged DCs exhibit defective TLR function and reduced T-cell priming [40, 41]. Given the crucial role of pDCs in coordinating the host immune response to viral infections [42], a deficiency in pDCs will clearly result in poor viral clearance. The function of pDCs declines with age [38]. A recent report showed that older individuals showed an age-related decline in IFN-α production induced by TLR-7 and TLR-9 in pDCs [43]. Furthermore, pDCs from older adults exhibited a general age-related defect in intracellular production of TNF-α, IL-6, and p40 across TLR1, TLR2, TLR3, TLR4, TLR5, and TLR8 [39, 44]. Considering the effects of aging on pDCs, it is tempting to suggest that the observed TLR functional defects indicate a elevated level of cytokine production that could contribute to an age-related pro-inflammatory environment. Another study using a mouse model reported that pDCs from older mice produced less IFN-α during herpes simplex virus-2 (HSV-2) infection [44]. These lower levels of IFN-α were associated with impaired induction of IRF-7 expression upon TLR9 stimulation [39, 44]. Activation of mDCs through TLRs triggers their maturation and migration to secondary lymphoid organs, where they present antigens to T cells. DCs from older adults gradually lose their ability to effectively present antigens to T cells [45]. These DCs show reduced expression of costimulatory molecules and lower IL-12 production [38, 45]. Considering how aging impairs macrophages' and DCs' ability to present antigens, the age-related decrease in T cell proliferation and function might worsen due to impaired antigen presentation. Overall, the precise understanding of DC dysfunction with aging is still evolving. However, these findings may provide additional reasons for the reduced control of respiratory viral infections observed in older individuals.

Natural Killer (NK) cells

Unlike myeloid innate immune cells, the total number of NK cells increases with age [46]. This is primarily due to an increase in $CD56^{dim}$ NK cells. However, aging reduces NK cell-mediated cytotoxicity against virus-infected cells [47, 48]. In humans, aging leads to increased surface expression of inhibitory receptor KLRG1 on NK cells, resulting in impaired NK cell cytotoxicity [49]. In addition, these aged-NK cells exhibit lower expression of the NK cell activating receptors NKp30 and NKp46 [50]. Decreased NK effector functions, including reduced IFN-γ secretion, and lower expression of perforin and granzyme, typically characterize dysfunctional NK cells. The release of IFN-γ and TNF-α by activated NK cells helps coordinate the recruitment and activation of macrophages and neutrophils [50, 51]. This could be the reason why a reduction in NK cell cytotoxic subtypes and their functions is associated with an increased risk of viral infections. Moreover, aged NK cells are reported to produce lower levels of cytokines and chemokines such as RANTES, MIP1α, IL-8, and IL-2 [52]. Some studies on aging in NK cells suggest that age-associated alterations in NK function may, in part, result from changes in zinc homeostasis in older individuals, and there is evidence that NK cell function can be improved with zinc supplementation [53]. Another possible cause of NK cell dysfunction with age is the age-related decline in IL-2 levels. Given that IL-2 is crucial for NK cell proliferation, differentiation, activation, and function [54], a report has shown that IL-2 treatment of NK cells from older adults increases production of IFN-γ and TNF-α. IL-12 stimulates STAT4 signaling, leading to NK cell survival, promotes IFN-γ and

TNF-α secretion, and enhances NK cell-mediated cytotoxicity. However, stimulation of aged NK cells with IL-12 reduces cytokine production. [48]. These findings suggest a potential use of IL-2 to enhance the NK cell response in the elderly population.

Effects of Aging on T and B Cell Function

The B and T cells are integral components of the adaptive immune response. Their timely and effective activation and function determine the outcome of viral infections, cancer, and vaccine efficacy [55]. This highlights the importance of T and B cells' functions in human health. Unfortunately, as we age, our T and B cells lose their functions.

CD4 and CD8 T cell

The impact of aging on T cell responses is primarily attributed to declines in naïve T cell production in the bone marrow and thymus [56]. As we age, ROS-induced DNA damage accumulates, along with decreased expression of DNA repair genes, leading to reduced HSC activity [57, 58]. This leads to a reduction in the number of naïve T cells, resulting from both reduced lymphoid progenitors and thymic involution. The thymus is the primary site for T cell differentiation and maturation and plays a crucial role in adaptive immunity. Age-related thymic involution is primarily characterized by the deterioration of tissue structure, a decrease in thymocytes, and a decline in thymus mass. This leads to reduced T cell production, loss of T cell receptor diversity, and reduced T cell clonal expansion capacity. Additionally, aging reduces the capacity of naïve T cells to differentiate into memory T cells [59-61]. For instance, a study has shown that aged naïve $CD4^+$ T cells exhibit decreased responsiveness to T cell receptor stimulation and reduced cytokine secretion compared to naïve $CD4^+$ T cells from young adults. Moreover, the cytokine-mediated function of CD4 T cells to activate B cell differentiation and function is significantly reduced with age [62-64]. These age-related defects in naïve CD4+ T cells are due to the chronological age of naïve CD4+ T cells rather than the individual's chronological age [64, 65]. Moreover, CD4 T cells from aged mice showed decreased CD4 expression and increased expression of inhibitory molecules such as CD5 and PD-1 compared with CD4 T cells from young mice [64, 66, 67]. IL-2 secretion is one of the most significant outcomes of TCR stimulation of naïve CD4 T cells, and the secreted IL-2 helps in T cell survival and proliferation [68]. However, aged naïve CD4 T cells show reduced IL-2 production and proliferation when stimulated by an antigen-presenting cell [69, 70]. The age-related decline in CD4 T cells' ability to produce IL-2 could explain the reduced generation of Th1 or Th2 responses in elderly individuals. Unlike in NK cells, age-associated impairment of CD4 T cell memory function, characterized by reduced proliferation and cytokine secretion, could not be overcome even by exogenous IL-2 [69, 70]. Furthermore, effector CD4 T cells from older individuals show reduced expression of differentiation and activation markers such as CD25 and CD62L [71].

The outcome of most viral infections depends on an effective CD8 T cell response; any factor that affects the activation and function of CD8 T cells will impact the outcome of a viral infection [72]. Similar to CD4 T cells, aging leads to a decrease in the number of naïve and memory CD8+ T cells and effector function [73-75]. Specifically, age-related alterations in CD8 T cells include reduced CD28 expression [76, 77] and elevated expression of exhaustion and inhibitory receptors such as PD-1, TIM-3, LAG-3 [78]. These findings suggested that aging causes multifactorial dysfunction of CD4 and CD8 T cells, leading to increased susceptibility to infection and delayed, poorer virus clearance.

B Cell and Humoral Immunity

B lymphocytes are equally affected by aging. As we age, there is a significant reduction in the production of B-cell precursors in the bone marrow [79]. Reports have suggested that HSCs' bias toward producing myeloid cells rather than lymphocytes is another reason for the reduced number of B cells [80, 81]. Studies using aged mice showed that aging negatively affects B cell production in the bone marrow, resulting in decreased numbers of B-1 and B-2 cells [82-84]. The age-related decline in B cell numbers is accompanied by dysfunction in B

cell antibody production. Both human and mouse studies showed that aging downregulates class-switch recombination in peripheral B cells [84, 85]. This might explain why aged plasma cells primarily secrete IgM, whereas young plasma cells secrete IgG. Viral infections and vaccination in elderly individuals resulted in significantly lower levels of IgM and IgG antibodies than in younger adults. Moreover, antibodies secreted by aged B cells also showed decreased affinity [86]. Therefore, aging affects not only the quantity of antibodies but also their quality. Furthermore, studies have revealed that age-related adipose-resident B cells contribute to inflammaging by activating pro-inflammatory T cells to produce inflammatory cytokines [87, 88]. These effects of aging on humoral immunity explain why elderly individuals are less protected against reinfection after a primary exposure or vaccination. Therefore, advanced research to investigate the mechanisms underlying age-related declines in B cell number, reduced antibody levels, and low affinity, as well as the development of innovative B cell-specific therapies, will have a global impact.

Inflammaging

Monocytes, macrophages, dendritic cells, NK cells, and T and B cells from elderly individuals are shown to produce elevated levels of IL-1β, IL-6, IP-10, TNF-α, and other pro-inflammatory cytokines and chemokines [89]. The underlying mechanism of how aged immune cells with immune dysfunction produce these inflammatory markers is poorly understood. However, age-related immunopathology has been primarily associated with inflammaging and not immunosenescence. Elevated serum TNFα and IL-6 levels among older adults have been used as critical predictors of age-related morbidity and mortality [89]. For instance, high serum levels of IL-1β, TNFα, and IL-6 are considered risk factors and accelerators of cardiovascular diseases, neurodegenerative diseases, cognitive defects, and impaired memory among elderly individuals [89-91]. A classic example of the impact of aging on inflammation and clinical outcomes was observed during the COVID-19 pandemic [5]. SARS-CoV-2 infection in the elderly triggers an overwhelming inflammatory response (IL-1β, TNFα, CRP, and IL-6), leading to severe pneumonia and organ damage [5, 92, 93]. Age-induced immunological imbalance and age-related priming for inflammation led to increased vulnerability to severe disease, prolonged post-viral persistence, and death among the elderly population [61, 94, 95].

Impact of Immunosenescence and Inflammaging on Respiratory Tract Viral Infections

By the end of 2024, more than 1 billion people, or 12% of the world's population, were aged 60 and above [96]. Given the global prevalence of respiratory tract viral infections and their severe clinical outcomes among elderly individuals, understanding the complexities of immunosenescence and inflammaging associated with these infections is a global health priority. This section explores how immunosenescence and inflammaging are associated with delayed and impaired respiratory virus clearance, immunopathological effects, clinical symptoms, and increased mortality among elderly individuals.

Aging and RSV infection

Respiratory syncytial virus (RSV) is an RNA virus in the family Pneumoviridae and is one of the most common causes of acute lower respiratory infections in children worldwide. For the past decade, RSV infection has been one of the leading global health concerns, causing a significant burden among infants and the elderly [97]. Recent epidemiological studies have reported an estimate of over 33 million cases of acute RSV-associated lower respiratory tract infections, 3.6 million hospital admissions, and over 100, 000 deaths worldwide [98, 99]. Depending on the age of the RSV-infected individuals, symptoms are nonspecific and vary greatly. Infants frequently develop the characteristic bronchiolitis syndrome, while younger adults are usually asymptomatic or experience only mild flu-like symptoms. In contrast, elderly individuals can range from mild cold-like illness to severe respiratory problems such as acute pneumonia and respiratory failure [100].

Upon infection, RSV quickly activates the host's innate immune response. Detection via TLR2, TLR3, and TLR7 triggers the activation of NF-κB and IRF signaling pathways. This leads to the secretion of antiviral IFNs and pro-inflammatory cytokines or chemokines. Subsequently, dendritic cells, macrophages, NK cells, and neutrophils are recruited and infiltrate the lungs [101, 102]. However, these innate immune signalling and timely RSV control are significantly affected by age. Innate immune cells in infants are immature and have impaired functions, slower response times, and a tendency towards an anti-inflammatory T-helper-2 (Th2) response, which may result in delayed viral control [103]. For instance, RSV infection in infants often causes pathological effects due to delayed and dysregulated IFN-I signalling, which leads to a skewed Th2 response. This results in increased secretion of IL-6, IL-1β, and TNF-α into the mucus and airways, leading to bronchiolitis [102, 104, 105]. The persistent challenge faced by innate immune cells in clearing RSV also leads to the release of additional inflammatory cytokines and chemokines, resulting in lung damage rather than effective clearance. RSV-associated bronchiolitis in infants, caused by ongoing airway inflammation, can also increase the risk of developing long-term asthma [106, 107]. Therefore, the outcome of RSV infection in an infant depends on a balance between efficient antiviral function and avoidance of lung immunopathology.

RSV infection in younger adults elicits a strong cellular immune response, leading to rapid viral clearance and often resulting in asymptomatic infection. In an immunocompetent adult, these cellular-mediated processes initiate inflammation, antiviral defence, and viral control [108, 109]. However, adults older than 65 years can develop severe disease, such as pneumonia or bronchitis. This age-related worsening of RSV infection in the elderly is attributed to paradoxical changes in the host immune response [110]. Monocytes, macrophages, and dendritic cells from older adults show defective TLR function. These age-related defects in TLR signaling lead to impaired cellular activation and function, reduced phagocytic capacity, ineffective signaling, and poor antigen presentation. Although one immune evasion mechanism of RSV is to reduce IFN-I secretion and numerous downstream ISGs that limit viral replication, it is unclear whether aging affects RSV's evasion potential [20, 111]. Furthermore, in older individuals, plasmacytoid dendritic cells (pDCs) exhibit decreased IFN-α production after stimulation [44]. Impaired migration of myeloid dendritic cells (mDCs) and a reduced capacity of mDCs to promote T cell proliferation and priming were observed in older adults, resulting in a lower IFN-γ response. An additional layer of complexity in innate immunosenescence involves increased production of proinflammatory cytokines, such as IL-6, IL-1β, and TNF-α, and CRP, by innate immune cells from older adults. This proinflammatory cytokine surge has been identified as a primary cause of the observed lung immunopathology and the leading cause of severe RSV-associated complications [105, 112, 113]. Innate immunosenescence in older adults leads to persistent RSV spread in the lungs. Persistent and prolonged RSV replication and spread in the lungs lead to increased neutrophil recruitment to the airways, resulting in increased secretion of proinflammatory cytokines and chemokines, which cause airway damage [113, 114]. Neutrophil-mediated inflammation during RSV in elderly patients is reported to be the leading cause of lung immunopathology and symptoms associated with severe pneumonia in older adults [115]. Given that aging is associated with decreased expression of T cell homing markers and increased expression of T cell exhaustion markers, one could speculate that the T cell response is abrogated during RSV infection. Aged T cells have been reported to respond poorly to RSV infection. This is characterized by a decline in T cell proliferation, a decrease in the number of RSV-specific CD4+ and CD8+ T cells, and reduced effector function measured by IFN-γ production [116-118]. In addition, aging exacerbates B cells' capacity to produce RSV-specific IgG. RSV infection in the elderly leads to decreased class-switched B cells and impaired antibody production [119, 120]. Moreover, aging is associated with a decrease in the number of memory T and B cells, suggesting increased susceptibility to RSV reinfection [100].

Aging and Influenza virus infection

Influenza virus infection is a highly contagious airborne disease that leads to acute febrile respiratory illness. The virus is part of the Orthomyxoviridae family and includes three types: A, B, and C. Among these, influenza A is the most common and severe, primarily affecting humans. [121]. Recent outbreaks of H1N1 (swine flu), H5N1 (bird flu), and H7N9 have underscored that influenza viruses pose a significant threat to human health [122]. Most individuals infected with influenza experience no or only mild flu-like symptoms. However, aging is the primary factor behind influenza-related complications, including pneumonia, acute cardiovascular and renal comorbidities, and even death. Epidemiological reports have shown a significant rise in hospitalizations and deaths from influenza-associated illness among older adults [121, 123, 124].

Monocytes, alveolar macrophages, neutrophils, and DCs are the initial cells to respond to influenza infection in the respiratory tract. These innate immune responses provide protection by activating antiviral defenses and secreting cytokines and chemokines that attract other immune cells [125, 126]. However, macrophages can also contribute to pathological immunity after influenza virus infection and produce cytokines to regulate excessive inflammation [126]. In elderly individuals, influenza infection is linked to reduced macrophage numbers and impaired TLR stimulation [27]. Additionally, these aged macrophages exhibit reduced cytokine responses while displaying elevated levels of proinflammatory markers. Influenza infection has been shown to induce inflammation, causing lung injury and life-threatening pneumonia. Lung monocytes, neutrophils, and DC can also drive this acute inflammation caused by influenza infection [127, 128]. As age increases, this inflammation tends to worsen, as it has been associated with higher baseline levels of IL-6, IL-1β, and TNF-α [89, 129, 130]. Comparisons of young and old mice studies have shown that peritoneal phagocytic function is impaired with age. Similarly, many studies have revealed age-associated differences in macrophage functionality in humans [127]. Experimental studies have shown that dendritic cells from aged individuals have reduced ability to capture antigens, impaired migration, and diminished capacity to activate T cells [40]. Additional studies in mice show that NK cells in the lungs of older mice produce less IFN-γ during influenza infection. Aged mice exhibit a reduction in both the number and functionality of NK cells, which are characterized by a higher presence of immature and less fully matured NK cells [131, 132]. These age-related changes could weaken NK cells' capacity to support a robust early antiviral response during influenza infection. These observations can be linked to humans, where low NK cell counts in the lungs, diminished cytolytic activity, and decreased secretion of cytokines and chemokines are associated with fatal influenza cases and aging [131, 133, 134].

Natural influenza infection triggers a significant increase in CD4 and CD8 T cell response, however, CD8 T cells are the primary determinant of viral clearance during influenza infection [135]. However, aging is associated with a decline in the TCR repertoire, reduced expression of T cell homing markers, lower expression of co-stimulatory receptors, increased expression of inhibitory markers, and increased expression of T cell exhaustion markers [59-61]. Influenza virus-specific $CD8^+$ T cells are generally essential in the clearance of virus-infected cells and production of IFN-γ [135]. Stronger CD4 T cells are associated with better protection against reinfection [136]. On the other hand, B cells mount a multifaceted response that involves rapid IgM secretion and lung infiltration to control initial viral spread [137]. Subsequently, the activation and differentiation of antibody-secreting plasma cells lead to the production of influenza-specific IgG, which is essential for controlling acute influenza infection. However, influenza infection in older adults can lead to decreased IgM levels, reduced IAV-specific IgG, and shortened B cell activation periods. Moreover, aging is associated with decreased antibody levels, reduced affinity maturation, and overall lower antibody quality, thereby increasing the risk of influenza reinfection [138-140].

Aging and COVID-19

The SARS-CoV-2 virus is the causative agent of coronavirus disease 2019 (COVID-19), which manifests as an acute respiratory illness that can range from asymptomatic infection to severe pneumonia and respiratory failure. During the SARS-CoV-2 pandemic, we have unanimously witnessed an increase in hospitalization and death among the older population [141]. Aging significantly influences the interaction between cellular and inflammatory responses, SARS-CoV-2 replication, COVID-19 progression, hospitalization, and recovery time [142, 143]. Studies indicate that aging disrupts the balance between the cellular innate immune response and proinflammatory response during SARS-CoV-2 infection [144, 145]. Unbalanced cellular and inflammatory immune responses may cause immunopathology and hyperinflammation. However, an impaired immune response can lead to poor viral control and persistent viral infection. Aging is linked to diminished innate and adaptive immune responses in COVID-19 [146]. For instance, monocyte analysis revealed decreased activation, diminished antigen-presenting ability, and higher IP-10 levels in older adults with COVID-19. Similarly, aging results in reduced DC activation and decreased capacity for antigen cross-presentation during the initial phase of COVID-19 [5, 147, 148]. In contrast, older adults show increased NK cell activation, cytokine production, and IL-2 secretion [149]. Furthermore, older age was associated with reduced CD8 T cell activation and premature exhaustion. Older COVID-19 patients have a higher proportion of exhausted PD-1-positive effector memory and central memory CD8 T cells compared to younger patients [150, 151].

It is well understood that hyperinflammation plays a central role in the development of severe and fatal COVID-19, and age is also recognized as a significant risk factor for disease progression. Consistent with this evidence, reports indicate that COVID-19 patients over 65 have elevated levels of several soluble proinflammatory markers, including CRP, ferritin, IP-10, and IL-6. Such a chronic inflammation among older individuals (inflammaging) had more coexisting conditions, such as COPD, coronary heart disease, hypertension, malignancy, and type 2 diabetes [152, 153]. These factors have resulted in delayed clinical recovery, disease progression to intensive care unit admission, or death in older COVID-19 patients.

Aging and other respiratory viral infections

Other respiratory viral infections include rhinoviruses, adenoviruses, and parainfluenza viruses. Although these viral infections typically cause mild flu-like symptoms, reports indicate that aging is linked to more severe respiratory complications.

The rhinovirus is a single-stranded RNA virus, a member of the enterovirus genus in the Picornaviridae family. It is the most common respiratory viral infection and is mainly responsible for the common cold, accounting for at least half of all cold cases. In immunocompetent young adults, rhinovirus infections cause a mild common cold, including a runny nose, congestion, sneezing, and a sore throat [154]. Aging significantly amplifies the severity of rhinovirus infections, leading to severe respiratory complications, hospitalizations, and even death [155, 156]. Compared with younger adults, elderly individuals exhibit slower rhinovirus clearance due to reduced IFN-α secretion by host immune cells [157]. Rhinovirus infection in older individuals with asthma can lead to severe asthmatic attacks. Rhinovirus infection in the elderly leads to eosinophilia and impaired interferon antiviral responses. An increased level of proinflammatory markers such as IP-10 and RANTES was reported among older individuals with rhinovirus infections. This may explain the age-dependent severity of rhinovirus infections and the association of rhinovirus-induced respiratory complications and asthma development [154, 158, 159].

Adenovirus infection can cause mild flu-like symptoms. However, due to immunosenescence and inflammaging, adenovirus infection in older adults can progress to bronchitis and pneumonia. These complications are often accompanied by pink eye, diarrhea, or vomiting, leading to hospitalization [160-162]. Similarly, the human parainfluenza viruses (HPIV) are RNA viruses belonging to the Paramyxoviridae family; they are common respiratory virus that typically causes mild, cold-like symptoms [163].. Children, immunocompromised individuals, and elderly individuals are at a high risk of HPIV

infections and complications. Aging significantly aggravates HPIV, leading to more severe illness, complications like pneumonia, longer recovery time, and increased hospitalization rates [164]. In older adults, innate immune cells exhibit impaired TLR7/9 and RIG-1 signaling, leading to reduced phosphorylation of IRF7 and TBK-1. This leads to lower IFN-1 secretion by aged monocytes and dendritic cells. Delayed IFN-I signaling weakens NK cell and macrophage responses, diminishing the effectiveness of subsequent T-cell and B-cell responses. During HPIV infection, delayed or reduced IFN-1 is associated with disease progression and severity in older adults. Age-related decline in innate immune cells, along with increased IP-10 and IL-6, reduced T-cell function, indicated by lower IFN-γ levels, and dysregulated B-cell antibody production, results in poorer HPIV control. Therefore, leading to HPIV-associated hospitalization among elderly patients [120, 165, 166].

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Conceptualization, L.B.C.; writing—original draft preparation, J.A., A.A., L.B.C.; writing—review and editing, J.A., A.A., L.B.C.; supervision, L.B.C.; funding acquisition, L.B.C. All authors have read and agreed to the published version of the manuscript.

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