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Commentary

An intrinsic connection between COVID-19 and aging

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a rapidly spreading outbreak of coronavirus disease 2019 (the COVID-19 pandemic). COVID-19 has severely affected healthcare systems worldwide, as well as the global economy, and has significantly increased morbidity and mortality rates. The majority of COVID-19-related deaths occurred in older individuals, primarily among those with concomitant diseases, including metabolic, respiratory, and cardiovascular diseases. Aging hallmarks, such as cellular senescence, chronic inflammation, and genomic instability, partially explain the increased disease severity at the molecular level with advancing age. Other multifactorial considerations, including healthcare facilities, socioeconomic status, and dissemination of epidemic information, may help control morbidity in the elderly population. While the World Health Organization declared an end to the emergency status of COVID-19 in May 2023, physical and emotional impairments may persist after recovery from the virus. Precautions should therefore be taken to prevent future pandemics, and suitable emphasis should be placed on addressing persistent COVID-19 and preventing future pandemics.

Keywords: COVID-19, SARS-CoV-2, aging, senescence

1. INTRODUCTION

Over the last 3 years severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an ongoing global pandemic of coronavirus disease 2019 (COVID-19) [1]. Following the initial identification of SARS-CoV-2 in November 2019, the virus rapidly spread worldwide. The World Health Organization (WHO) declared COVID-19 a severe pandemic on 11 March 2020 [1]. COVID-19 has persisted in most countries for > 3 years and is among the most widespread and long-lasting pandemic to threaten human lives in human history. In May 2023, the WHO declared an end to the COVID-19 global emergency phase, and the US government lifted the federal COVID-19 public health emergency declaration [2]. However, the economic and social impact of COVID-19 are long-lasting, and more in-depth studies are warranted to ensure rapid responses and effective eradication of future outbreaks with pandemic potential.

The characteristics of COVID-19, such as the high virulence and primary spread through aerosol droplets, accelerated the global spread [3]. Individuals infected with this virus can be minimally symptomatic initially with or without high fever, cough, fatigue, vomiting, or shortness of breath [4]. Owing to the abrupt outbreak, no specific and effective treatment strategies existed, resulting in a high early-stage mortality rate. With the rapid and comprehensive dissemination worldwide, the pandemic exerted a profound global effect, including an economic and social impact, and international collaboration and research efforts, particularly in the public health field. By July 2023, shortly after the global public health emergency had ended in May 2023, nearly 767 million cases of COVID-19 had been recorded, and 6.9 million confirmed deaths had occurred, the highest rates in recorded human history. Recent reports indicate that older individuals generally have a higher risk of SARS-CoV-2 infection. Notably, > 80% of COVID-19-related deaths occurred among people ≥ 60 years of age [5, 6]. Furthermore, the Centers for Disease Control and Prevention (CDC) website reported that the COVID-19 fatality rate is 27.4% in the > 85 year age group, which accounts for 2% of the US population (https://www.cdc.gov/coronavirus, accessed in August 2023). Similarly, COVID-19 statistics published in 2023 suggest that the risk of severe disease and death is much higher among older adults worldwide [7].

Commentary

1.1 Aging hallmarks and COVID-19 vulnerability

Mechanical relationships between COVID-19 and aging merit particular attention. Aging is a natural biological process characterized by progressive deterioration of bodily functions. In-depth research at the molecular and cellular levels has revealed various characteristic features or hallmarks of aging in humans, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, disabled macroautophagy, chronic inflammation, and dysbiosis [8]. Some hallmarks of aging, including impaired immune responses, increased complications of disease and injury, and increased susceptibility to infection, may have critical roles in severe illness caused by COVID-19 [9, 10]. Consequently, COVID-19 affects older individuals more easily, induces more severe symptoms, accelerates aging, and disrupts the internal aging clock (**Figure 1a,b**). Given the close correlation between chronologic age and DNA methylation status, aging can be tracked by the DNA methylation profile of an individual, which is termed an epigenetic clock [11]. Epigenetic clock measurement in blood samples collected from patients with COVID-19 using a methylation array indicated that SARS-CoV-2

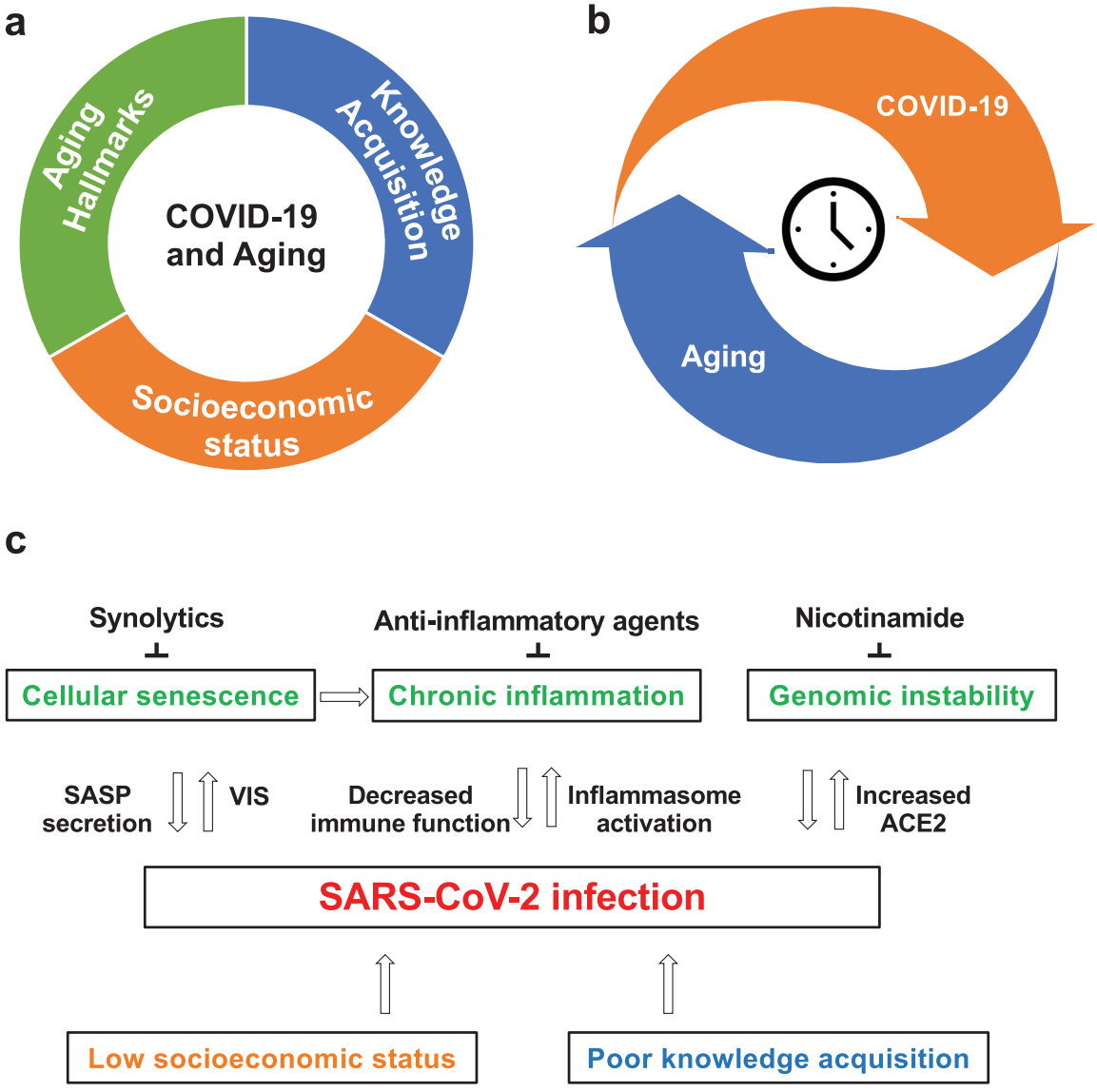

Figure 1 | Crosstalk between COVID-19 and aging.
(a) Multiple layers of factors influencing the responses of aging individuals to COVID-19. (b) Intrinsic interplays between COVID-19 and aging regulate the "aging clock." (c) Factors affecting the risk of COVID-19 infection and disease severity of aging individuals, and potential therapeutic interventions.

infection accelerates epigenetic aging, and the degree of methylation clock acceleration correlates with COVID-19 severity [12].

Multifactorial considerations contribute to the elevated risk of severe illness and complications among older adults during the pandemic and provide insight into why aging hallmarks are among the major underlying mechanisms of vulnerability. Increased susceptibility to infection is partly due to declining cellular function attributed to several aging hallmarks, including cellular senescence, chronic inflammation, and genomic instability (**Figure 1c**). Senescent cells gradually accumulate in aging individuals and induce a senescence-associated secretory phenotype (SASP), a fundamental senescence feature in which distinct pro-inflammatory and tissue-remodeling factors, including inflammatory cytokines, extracellular matrix activators, and coagulation-promoting factors, are secreted. The SASP elicits secondary cellular senescence in adjacent cells, inducing a pro-inflammatory state that disrupts appropriate immune responses. Immunosenescence, an age-dependent decline in immune function, is thought to be the primary cause of vulnerability to infection in aging individuals [13]. Immunosenescence occurs mainly through thymus degeneration, which impairs T cell output, facilitates T cell senescence, and results in chronic inflammation that might be induced by SASP. These factors facilitate progressive immune dysfunction with age, leading to increased susceptibility to viral infections. Moreover, SARS-CoV-2 infection has been reported to induce inflammasome activation, leading to an acute inflammatory response and tissue damage [14]. A recent study also demonstrated a mechanism by which genomic instability enhances susceptibility to viral infections. SARS-CoV-2 exploits angiotensin-converting enzyme 2 (ACE2) expressed on the host cell surface as a docking receptor to penetrate the cell membrane through an interaction between the viral surface spike protein and ACE2 [15]. Age-dependent accumulation of DNA damage through genotoxic stress increases the level of ACE2 protein on host cell surfaces, enhancing susceptibility to SARS-CoV-2 infection [15]. Patients $\geq$ 60 years of age exhibit increased ACE2 levels compared to patients $\leq$ 50 years of age. These findings suggest that SARS-CoV-2 infection likely accelerates the aging clock in infected tissues that are prone to various stresses owing to chronic diseases and lifestyle over time. The findings may also partly explain the tissue and age selectivity of vulnerability to this disease. This study proposed that DNA damage is a potential therapeutic target for COVID-19. Nicotinamide, a compound that facilitates DNA damage repair, inhibits SARS-CoV-2 infection in cell cultures and animal models [15]. Additionally, age-related physiologic changes in tissues, such as reduced lung capacity, decreased respiratory ability, and attenuated ability to clear mucus from the body, make older adults more vulnerable to respiratory infections [16]. Furthermore, older adults, particularly those > 65 years of age, are more likely to have age-related chronic and general health conditions, including diabetes, respiratory disorders, heart diseases, and chronic respiratory and vascular conditions, which increase the risk of severe symptoms and mortality due to COVID-19 [17]. It is therefore necessary to pay more attention to and take measures to provide appropriate care to older adults while taking individual circumstances into consideration.

1.2 COVID-19-induced senescence and aging

Susceptibility to infection is enhanced by multiple risk factors, including cellular senescence. Accumulating evidence indicates that viral infections accelerate the induction of cellular senescence (virus-induced senescence [VIS]) [10]. Mechanistically, SARS-CoV-2 infection causes viral replication stress and mitochondrial dysfunction, leading to elevated reactive oxygen species (ROS) production and resulting in subsequent activation of the downstream NF-κB signaling pathway. SARS-CoV-2 infection also stimulates the viral RNA-sensing pathway, in part through Toll-like receptor 3, leading to activation of the cGAS/STING/IRF3 signaling axis to activate the innate immunity pathway. Infection-elicited activation of NF-κB and IRF3 transcription factors induces the expression of downstream target genes encoding senescence phenotype-causing proteins, including SASP factors, cell cycle negative regulators (e.g., $p16^{INK4A}$ and $p21^{CIP1}$) and pro-survival anti-apoptotic proteins and kinases (e.g., BCL2 and SRC family proteins) [10]. Consequently, virus-induced senescent cells secrete SASP factors that propagate a pro-inflammatory status to surrounding non-senescent cells. Moreover, VIS-mediated SASP induces NPRL3 inflammasome activation and NF-κB-mediated gene expression, further promoting autocrine and paracrine senescence. In a positive feedback loop, pro-inflammatory stimulation induces expression of the SARS-CoV-2 receptor ACE2, enhancing susceptibility to viral infection. Consequently, accumulation of virus-induced senescent cells impairs tissue repair and regeneration capacity, leading to accumulation of tissue damage and acceleration of the aging process (**Figure 2**).

SARS-CoV-2 infection increases levels of aging markers in the airway mucosa and serum SASP factors through VIS [18]. Therefore, SARS-CoV-2-mediated VIS may be a primary driver of disease severity factors, such as cytokine storm, endothelial inflammation, aberrant macrophage activation, and pulmonary thrombosis, in older patients. This study also showed that targeting the VIS is a potential therapeutic intervention strategy. In this regard, the administration of senolytic reagents, which selectively target senescent cells, effectively eliminate SARS-CoV-2-induced senescent cells and alleviate symptoms in patients with COVID-19 [18]. An independent study also demonstrated the efficacy of senolytics against COVID-19 by showing that senolytics significantly reduced coronavirus-mediated mortality in aged mice [19]. Furthermore, resveratrol, a natural anti-aging compound, has shown potential anti-SARS-CoV-2

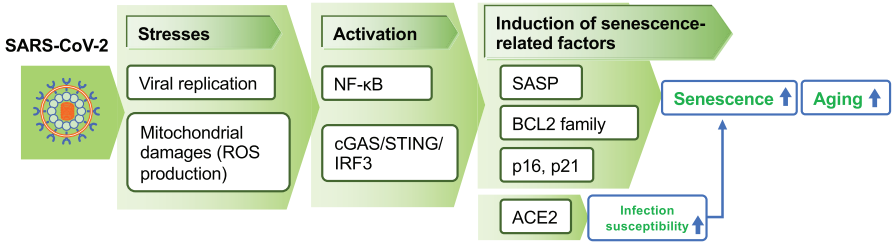

Figure 2 | Signaling pathways through which SARS-CoV-2 induces cellular senescence.
SARS-CoV-2 infection activates the NF-κB and cGAS/STING/IRF3 signaling pathways, inducing senescence-related gene expression and virus-induced senescence (VIS). Secretion of pro-inflammatory cytokines by senescent cells causes paracrine senescence, leading to tissue damage and accelerated aging.

efficacy through pleiotropic effects, including suppression of the NF-κB signaling, enhancement of cellular antioxidative activity, and blocking of the interaction between the SARS-CoV-2 spike protein and the ACE2 receptor protein [20]. Therefore, progress in anti-aging research has provided important avenues for alleviating post-infection severity and preventing COVID-19-associated complications.

1.3 Socioeconomic and knowledge gaps as COVID-19 risk factors among the elderly

The elderly mainly reside in healthcare facilities, including nursing homes and assisted living centers, with communal living spaces and close interactions, which increase the probability of infection. Approximately 50% of COVID-19 deaths in the US occurred in nursing homes [21]. Nursing facilities with trained staff provide comprehensive medical care and assistance in daily activities that benefit older adults. Nevertheless, due to the unique characteristics and rapid transmissibility of COVID-19, communal living spaces, close interactions, and shared dining areas facilitate spread of the virus and increase the vulnerability of older adults to severe illness. As another topic, a study conducted in Hong Kong reported a close correlation between the domiciliary environment and the SARS-CoV-2 infection rate in the elderly population [22]. Housing environments likely reflect social and economic status, with populations having higher socioeconomic status trending toward better health status, specifically in terms of reserve capacity and resilience. Consistent with this idea, the study showed that in a comparison between public and private housing, the infection rate disparity was three-fold higher among the elderly (21.2% vs. 6%) than among young adults (16.9% vs. 11%). These data suggest that lower socioeconomic status may be a risk factor for the elderly, which may be common worldwide, particularly in developing countries with relatively wider socioeconomic gaps. A recent commentary in *Nature Medicine* entitled "The poorest and most vulnerable communities should be the first to be vaccinated" called for prioritizing care for children in vaccine-zero areas, where the highest vulnerability exists [23]. The same precautions may also need to be considered for the elderly. Additional measures are required to protect older adults from severe illness, including appropriate policies, ongoing monitoring of infection practices, sufficient resources, close mental and emotional health attention, and priority access to vaccination.

The degree to which older adults are informed should also be considered. Accurate and reliable dissemination of information about COVID-19, including transmission and preventive measures, is necessary for older individuals to make appropriate decisions, such as wearing masks, maintaining a physical distance, and following proper hygiene to significantly reduce the risks of infection and severe illness [24, 25]. Additionally, accurate knowledge of COVID-19, including the symptoms, can help older adults alleviate anxiety and fear. Furthermore, available healthcare guidelines and telemedicine can efficiently provide a means for older individuals to obtain proper consultations, suitable medical advice, and ongoing treatments without exposing themselves to a high-density hospital environment that may lead to unwanted exposure to the virus and subsequent infection [26]. Older adults experienced increased feelings of isolation and loneliness during the pandemic, resulting from limited interactions with their family and friends due to the necessary visitation restrictions [27]. Accurate, timely, age-appropriate, and understandable information about the pandemic, mainly provided by government public health authorities and community organizations, is crucial for the elderly to make informed decisions and be better equipped with prevention and therapeutic options in future pandemics.

2. SUMMARY AND PERSPECTIVES

The COVID-19 pandemic is a global, high-impact public health problem, with health consequences likely to persist for many years. Although this pandemic outbreak is generally over, COVID-19 has caused millions of deaths worldwide and disrupted routine healthcare services. Older individuals, particularly those with age-related chronic and general health conditions, faced increased vulnerability mainly due to weakened immune systems.

Some aging hallmarks, including cellular senescence, chronic inflammation, and genomic instability explain the molecular mechanisms rendering older adults more susceptible to COVID-19. Consideration of the socio-economic gap and dissemination of proper epidemic information also helps to protect older adults from pandemics. It is thus crucial to note that, while older people face a higher risk of contracting disease in future pandemics, individuals and hospitals should take effective preventive measures to mitigate the spread of the virus and reduce severe illness based on the invaluable knowledge obtained from this pandemic. A deeper understanding of the molecular mechanisms of aging and development of agents that can effectively retard or even reverse the aging process [18, 28] may also aid prevention efforts in future pandemics and their effects on elderly populations.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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