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SARS-CoV-2, COVID-19 and the aging immune system

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The coronavirus disease 2019 (COVID-19) pandemic is a global health threat with particular risk for severe disease and death in older adults and in adults with age-related metabolic and cardiovascular disease. Recent advances in the science of aging have highlighted how aging pathways control not only lifespan but also healthspan - the healthy years of life. Here, we discuss the aging immune system and its ability to respond to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We specifically focus on the intersect of severe COVID-19 and immunosenescence to highlight pathways that may be determinant for the risk of complications and death following infection with SARS-CoV-2. New or adapted therapeutics that target aging-associated pathways may be important tools to reduce the burden of death and long-term disability caused by this pandemic. Proposed interventions aimed at immunosenescence could enhance immune function not only in older adults but in susceptible younger individuals as well, ultimately improving complications of severe COVID-19 for all ages.

The immune system changes with age in nearly every aspect, generally resulting in a decline in pathogen immunity with increased age. This diminished capacity of the aged immune system is clinically evident, as aging is associated with high morbidity and mortality rates for various infections and significant reductions in vaccine efficacy[1–6]. Thus, as the emergent SARS-CoV-2 coronavirus began to circulate the globe early in 2020, it was reasonable to expect that the older population might be especially susceptible to poorer outcomes of COVID-19, the disease caused by SARS-CoV-2. Indeed, data from Wuhan, China showed that age was the primary risk factor associated with COVID-19 progression to acute respiratory distress syndrome (ARDS) and end-organ failure[7], which has since been corroborated by many others[8–10].

COVID-19 has taken a devastating toll on the entire population, but particularly older adults. As of 24 May 2021, the Centers for Disease Control and Prevention reported nearly 590,000 total deaths from COVID-19 in the United States alone, with an estimated 80% of those deaths occurring in individuals aged 65 years or older[11,12]. Compared to a 5–17-year-old reference group, the rate of hospitalization and death due to COVID-19 is approximately 1,300 times higher in individuals between the age of 65 and 74 years and 8,700 times higher in individuals 85 years and older in the United States[11]. While aged individuals have a higher prevalence of comorbidities that are also independently associated with increased risk of severe COVID-19, including cardiovascular disease, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, cancer and others[10], chronological age is still the single greatest risk factor for COVID-19 mortality[13].

Thus, this review will focus on the intersect between aging and detrimental SARS-CoV-2 host–pathogen interactions during severe COVID-19 and detail physiological and immunological mechanisms underpinning both circumstances. We will also highlight targets for new or adapted therapeutics that may improve aspects of immunosenescence implicated in these shared pathways. Directed enhancement of the aging immune system may subsequently reduce the burden of death and long-term disability caused by COVID-19.

Aging, inflammaging and immunosenescence: an overview

As humans age, the presence of systemic basal inflammatory mediators increases independently of acute immune challenges in a phenomenon known as inflammaging. This persistent, low-grade, chronic inflammation has been speculated to drive many chronic diseases associated with aging and is also a main contributor to immunosenescence, a term defined as overall changes to the immune system as we age, including a reduced ability to fight new infections[14]. It is generally accepted that inflammaging occurs in response to an accumulation of exogenous and endogenous physiological stresses over time and is primarily mediated by immune cells and senescent cells (Fig. 1)[14,15]. The relative variability in these many stressors from person to person is likely to explain why humans have wide variances in their biological inflammatory age across set chronological age time points[15,16]. This is important to consider when studying older adults, as those aged ≥65 years old are not a monolithic group.

Immune cells produce many of the inflammatory mediators found in aging tissues, which can also impact their own function. The increased presence of pro-inflammatory cytokines or danger signals leads to constitutive low-level engagement of immune cell signaling events such as those from Janus kinase (JAK)–signal transducer and activator of transcription (STAT), MyD88, nuclear factor (NF)-κB and inflammasomes, resulting in high basal activation but impaired immune cell responses to further cytokine and pattern-recognition receptor (PRR) stimulation[17,18]. Thus, many immune cell subsets become hyporesponsive to acute challenges as we age[17,19–25]. This may help to explain why mediators of systemic chronic inflammation have been linked to suboptimal vaccine responses not only in older adults[26,27] but in younger individuals as well[28]. Immunosenescence is further characterized by

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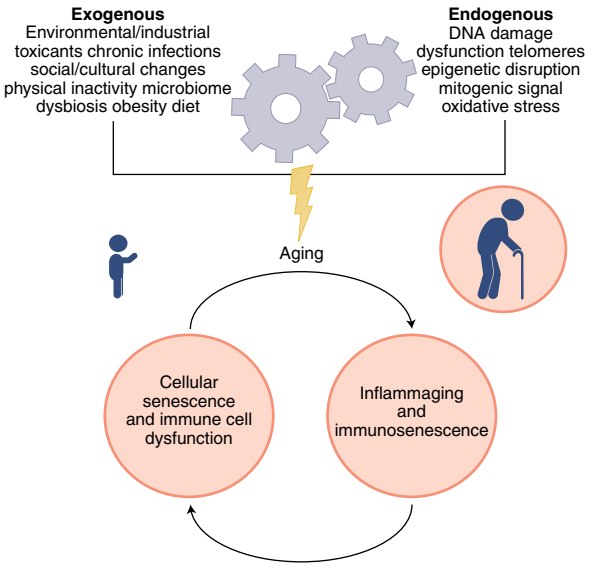


Fig. 1 | Factors that contribute to inflammaging and immunosenescence. Both exogenous and cell-endogenous factors contribute to chronic inflammation with age, which is primarily mediated by immune cells and senescent cells. Senescent cells persist and accumulate during aging, and they display an abnormal secretory phenotype, characterized by the production of inflammatory mediators, matrix metalloproteinases, fibronectin and ROS. These inflammatory mediators contribute to inflammaging, which, over time, affects immune cell function, promoting immunosenescence. The endogenous and exogenous factors listed here can also directly affect the inflammatory potential of the immune system, which further promotes a feed-forward loop of inflammaging and immunosenescence.

an impairment in antigen presentation and naive T cell priming, a propensity for myeloid lineage differentiation in the bone marrow, altered type I interferon (IFN) responses, diminished $CD8^+$ T cell cytotoxic function, decreased phagocytic function for many innate immune cell types, a restricted naive T cell and B cell repertoire and impaired production of high-avidity antibodies[29,30]. These immunological changes weaken immune responses to most viruses, leaving older individuals particularly vulnerable to influenza, SARS-CoV-2 and other lethal coronaviruses, such as SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoV[31]. The effects of aging on the human immune system have been extensively reviewed elsewhere[30,32–34]; thus, we will focus on aspects of the aging immune system that specifically overlap with characteristics of the immune response during severe COVID-19 outcomes.

COVID-19: an overview in pathogenesis

SARS-CoV-2 is the causative agent of COVID-19, declared a global pandemic by the World Health Organization on March 11, 2020 (ref. [35]). SARS-CoV-2 has a single-stranded, positive-sense RNA genome[36]. Attachment and entry of SARS-CoV-2 to target cells is initiated when the virus engages its cognate receptor, angiotensin-converting enzyme 2 (ACE2), via the receptor-binding domain (RBD) of the viral spike protein, also called the S protein[37]. Host transmembrane protease serine 2 (TMPRSS2) promotes S protein priming and facilitates viral entry[38]. Primary cell types for SARS-CoV-2 entry into the body include nasal epithelium, alveolar type II pneumocytes, superficial conjunctival cells and many types of enterocytes in the gut[39]. Virus entry into such cells leads to viral replication, destruction of infected cells and triggering of an innate immune response. These processes occur early during the SARS-CoV-2 incubation period of approximately 5 d. SARS-CoV-2 is likely to be initially detected by host cells via Toll-like receptor (TLR)7 and TLR8, which sense single-stranded RNA, and potentially TLR3, which senses double-stranded RNA intermediates[40]. TLR signaling engages IFN-regulatory factors (IRFs) and MyD88–NF-κB signaling pathways, leading to the production of type I IFNs and pro-inflammatory cytokines (interleukin (IL)-6, tumor necrosis factor (TNF)-α and IL-1β)[40]. Host cell damage resulting from SARS-CoV-2 infection can also lead to release of endogenous damage-associated molecular patterns (DAMPs), such as ATP, DNA and oxidized phospholipids[41]. DAMPs serve as danger signals for inflammasomes, multiprotein immune complexes that cleave and activate IL-1β and IL-18, and are also directly sensed by PRRs including TLRs to further propagate inflammation[40,42]. Pro-inflammatory cytokine and chemokine production recruits and activates innate immune cells, including neutrophils, natural killer cells, dendritic cells (DCs) and monocytes. Activated DCs and viral antigens eventually migrate to the draining lymph nodes, where they engage the adaptive immune system, T cells and B cells, with potential to clear the virus.

After the viral incubation period, in most cases, a young healthy individual will clear the virus with this coordinated immune response. However, patient symptoms can vary greatly, from asymptomatic to severe, with the latter being more common in older adults[43,44]. Patients with severe COVID-19 have higher levels of circulating cytokines and chemokines, contributing to enhanced risk for critical outcomes of COVID-19: pneumonia, cytokine storm, ARDS[45], sepsis and coagulopathy[46,47]. ARDS is a severe and often fatal complication of COVID-19. It is clinically defined by the acute onset of respiratory failure, hypoxemia, bilateral lung infiltrates on chest imaging not fully explained by effusions, collapse and/or nodules and lack of cardiogenic-related edema[48]. During COVID-19, ARDS manifests as a diffuse alveolar damage pattern seen in autopsies of patients with COVID-19 and is linked to a combination of lung immune cell infiltration, cytokine storm and tissue damage from secreted proteases, reactive oxygen species (ROS) and viral killing[49,50]. Cytokines that mediate manifestations of ARDS, such as IL-6 and TNF-α, can also facilitate vascular permeability, systemic shock and multi-organ failure[41,51]. Many patients with severe COVID-19 also develop bacterial pneumonia, a secondary bacterial infection of the lungs[52]. These bacterial infections bolster pro-inflammatory responses that perpetuate cytokine storm, systemic inflammation and ARDS phenotypes[53].

Mouse studies of SARS-CoV-2 show a higher viral burden in older mice in the first few days after infection, suggesting that aging may also lead to a delay or dysfunction in the initial triggering and priming stages of the immune response[54,55] that is propagated in part by suboptimal antigen-specific adaptive immunity[56]. The onset of ARDS in severe cases typically occurs around day 12 after symptom onset[44,57], when viral shedding appears to be mostly resolved[58], followed by death or recovery around 7–12 d later[44,57]. Therefore, severe cases of COVID-19 are not simply due to an inability to clear the viral infection but rather due to a sustained, dysregulated and highly destructive inflammatory response. A basic summary of clinical progression and associated immune responses during mild and severe COVID-19 is depicted in Fig. 2.

Immune system dysregulation associated with aging and severe COVID-19: innate immunity

Primary goals of the innate immune system in response to a viral infection are (1) to initiate a local inflammatory response to activate and recruit immune cells, (2) to directly eliminate virally infected cells and (3) to prime the adaptive immune response. As we age, the ability to achieve these three goals is either diminished or dysregulated. Here, we discuss components of the innate immune system, describe inflammatory processes implicated in both inflammaging and severe COVID-19 and provide a summary in Fig. 3.

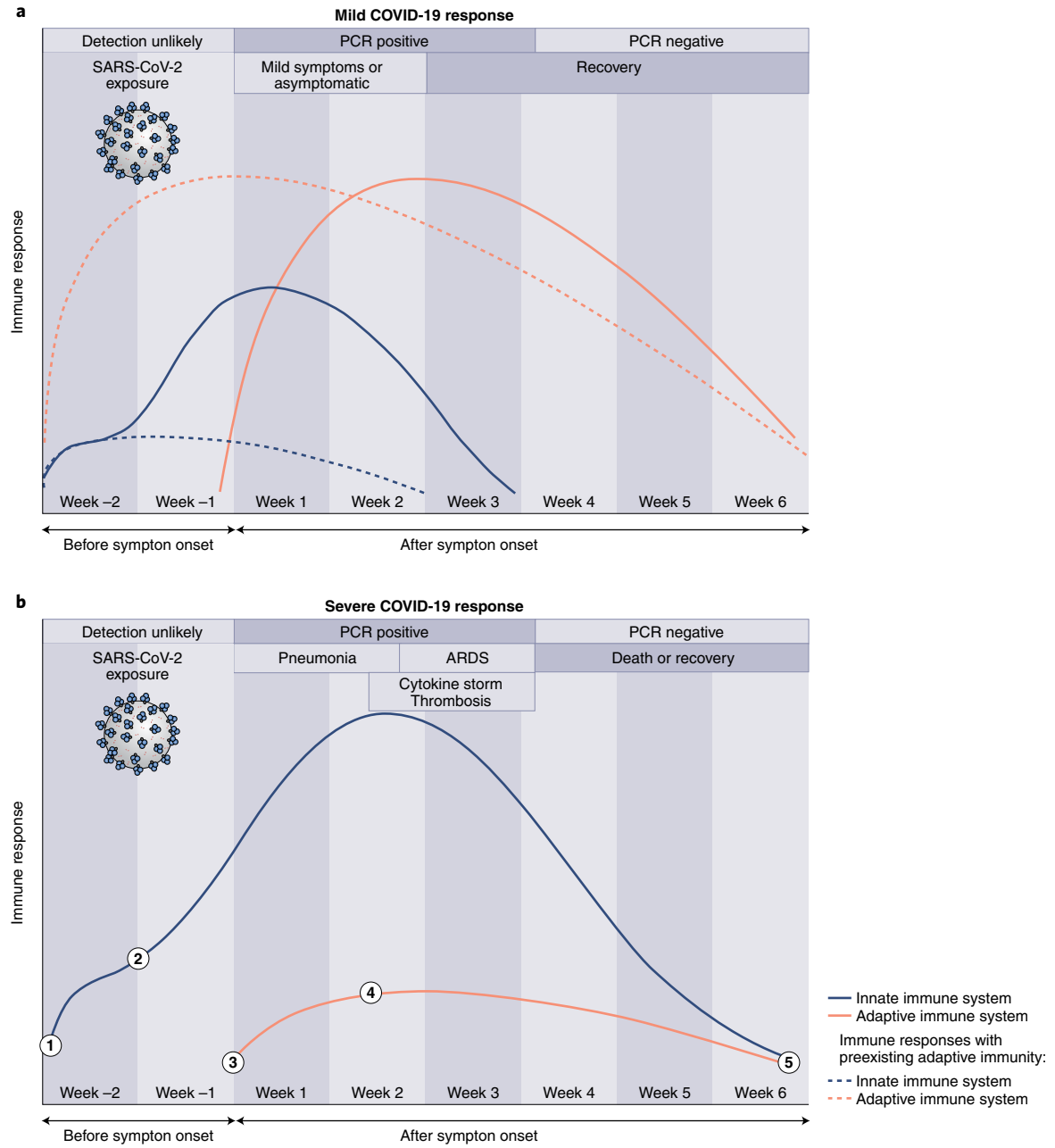


Fig. 2 | Immune response patterns and clinical disease courses for mild and severe COVID-19. For mild COVID-19 (**a**) and severe COVID-19 (**b**), graphs show the general disease course timeline and the magnitude of innate (blue) and adaptive (orange) immune responses over time. Dashed lines represent the time course for response in patients with pre-existing adaptive immunity. For severe COVID-19 (**b**), there are five main points of interest in the immune response that could be influenced by an aging immune system: (1) heightened basal inflammation (inflammaging) at the point of SARS-CoV-2 inoculation may predispose older adults to an already pro-inflammatory local environment; (2) innate immune cell dysfunction associated with aging may alter early immune responses; (3) delayed and/or diminished adaptive responses due to poor naive clonal diversity, weak or ineffective pre-existing immunity and poor T cell priming; (4) altered T cell effector function and antibody responses due to immunosenescence; and (5) the possibility of a reduced memory response and potential long-lasting effects on the immune system that may further promote immunosenescent phenotypes.

Anti-inflammatory effects of ACE2. The primary SARS-CoV-2 cellular receptor ACE2 can play a direct role in early inflammatory processes through the renin–angiotensin–aldosterone system signaling pathway, thereby aiding in one of the primary goals of the innate immune system: initiating a local inflammatory response to activate and recruit immune cells. ACE2 converts angiotensin II (an inflammatory mediator) to angiotensin 1–7 (an anti-inflammatory mediator). Angiotensin II signaling generates a pro-inflammatory state in vascular cells, leading to enhanced vascular permeability and local inflammation[59]. In mouse models of ARDS, the anti-inflammatory effect of ACE2 was shown to be protective against severe acute lung injury[60]. Angiotensin 1–7 was also shown to decrease the production of pro-inflammatory cytokines, specifically IL-6, TNF-α and IL-8, through inhibition of the p38–mitogen-activated protein kinase (MAPK)–NF-κB signaling pathway while also upregulating expression of the anti-inflammatory cytokine IL-10 (ref. [61]). An increased presence of angiotensin II during the early response to SARS-CoV-2 has been postulated to play a role in

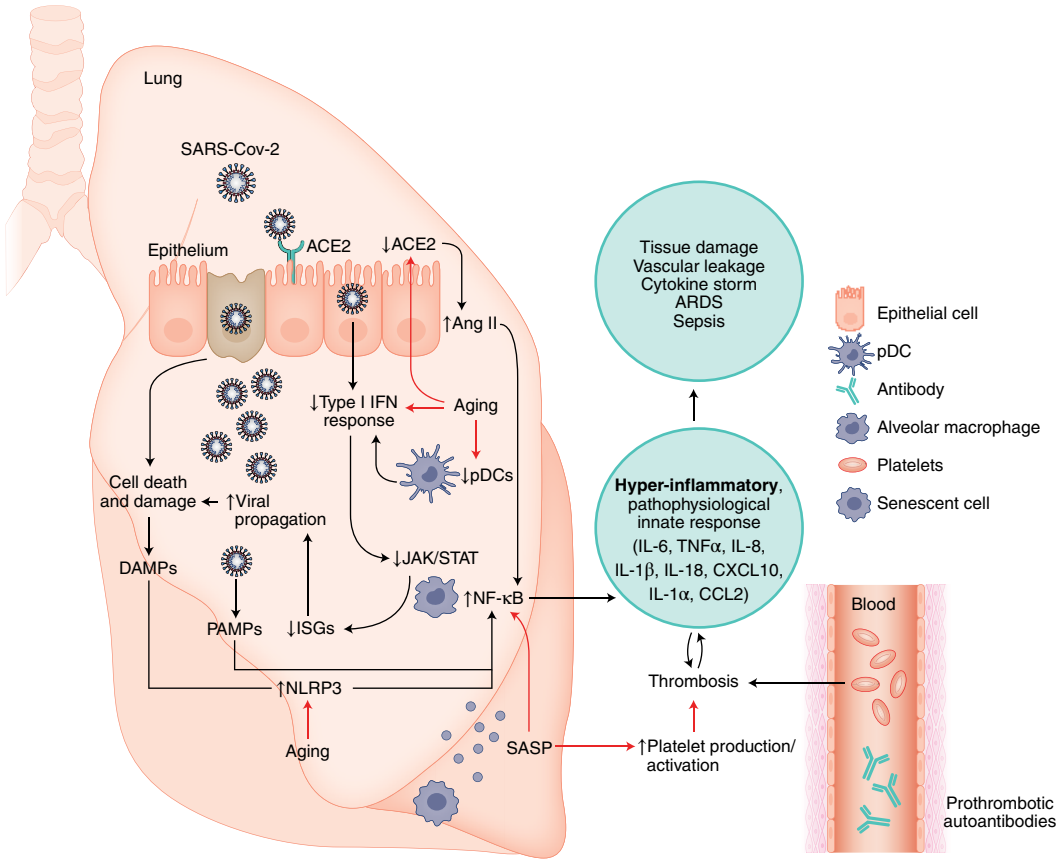


Fig. 3 | An aging innate immune system may predispose a patient to severe COVID-19. Consequences of the virus are indicated by black arrows, while consequences of aging are indicated by red arrows. SARS-CoV-2 first enters cells by binding to ACE2, and viral entry then leads to the shedding of ACE2. Aging may also be associated with reduced expression of ACE2, and low expression of ACE2 after infection potentially mediates a pro-inflammatory state through the production of angiotensin (Ang) II. Severe COVID-19 has also been correlated with reduced type I IFN responses, a defect that may be compounded by aberrant type I IFN signaling with age. This could be made worse by the notable reduction in the total number of pDCs found in patients with severe COVID-19. Aged pDCs also have a reduced ability to produce type I IFNs, and the pro-inflammatory nature of the SASP in older individuals desensitizes JAK–STAT signaling in innate immune cells. All of this would compound the loss of type I IFN signaling during severe COVID-19, ultimately leading to reduced expression of antiviral IFN-stimulated genes (ISGs) and permitting enhanced viral propagation. This viral replication leads to cell death and damage, causing the production of immunostimulatory DAMPs and PAMPs. Signaling in response to these signals generally activates the NF-κB transcription factor, which is also the main immune signaling pathway engaged by SASP mediators and the persistent basal stimulation of PRRs in older adults. NF-κB signaling promotes production of pro-inflammatory cytokines. DAMPs linked to both aging and viral infection can also trigger activation of inflammasomes such as NLRP3, potentiating cytokines such as IL-1β and IL-18, as well as triggering further cell death through pyroptosis. SASP mediators and the autoimmune-prone environment associated with aging may also predispose aged individuals to a pro-thrombotic environment, and thrombosis and inflammation continue to promote one another in a feed-forward loop, which further contributes to the hyperinflammatory, pathophysiological innate response that causes the devastating outcomes observed in severe COVID-19.

promoting cytokine storm phenotypes associated with severe COVID-19, probably because of excessive production of TNF-α and local macrophage activation[62]. Interestingly, there is a reduction in ACE2 expression in lungs of old rats when compared to those of their younger counterparts[63], and one study showed a decrease in *ACE2* mRNA in multiple tissues in older humans when compared to that in their younger counterparts[64]. ACE2 is also downregulated in humans with cardiovascular disease and diabetes, which also correlate with severe COVID-19 (ref. [65]). Decreased expression of ACE2 could mean less potential for SARS-CoV-2 invasion of host cells, but further reduction of ACE2 levels caused by viral entry may exacerbate a heightened pro-inflammatory response that helps to mediate cytokine storm, acute lung injury and ARDS. This hypothesis is supported by research showing elevated levels of angiotensin II in the plasma of patients with severe COVID-19 (ref. [66]). Moreover, a study of SARS-CoV-2 infection in old and juvenile rhesus macaques showed lower levels of ACE2 in old macaques than in young macaques after SARS-CoV-2 infection, supporting the hypothesis that ACE2 is dysregulated in older individuals, even across species[67].

A propensity for pro-inflammatory cytokine production. An uncontrolled inflammatory response to SARS-CoV-2 can lead to harmful and even irreversible tissue damage, both locally and systemically. The majority of patients with severe COVID-19 demonstrate substantially elevated serum levels of pro-inflammatory cytokines and chemokines, including IL-6, IL-1β, IL-2, IL-8, IL-17, granulocyte (G)-colony-stimulating factor (CSF), granulocyte–macrophage (GM)-CSF, C–X–C motif chemokine ligand (CXCL)10, C–C motif chemokine ligand (CCL)2, CCL3 and TNF[49,54,68]. In mouse studies of SARS-CoV-2 in which aging mice were directly investigated, similar cytokines, including IL-6, IL-1α, IL-1β, TNF-α and the chemokine CCL2 were also linked to the aged host response to SARS-CoV-2 (refs. [54,55]). Many of these cytokines are also elevated basally in older individuals owing to inflammaging. For instance, elevated IL-6 levels have been an especially stable

indicator of poor outcomes in patients with COVID-19, and studies have demonstrated that IL-6 is also among the most reliable aging parameters[69]. The presence of IL-6 is a clinical hallmark of vascular activation of NF-κB[70], a major transcription factor that regulates many pro-inflammatory genes of innate immune cells. There is a close link between aging, NF-κB signaling and inflammation[71]. Moreover, an anti-IL-6 receptor antibody could attenuate COVID-19 severity in a cohort of predominantly older patients (median age, 67 years), pointing to some cytokines as important drivers of exaggerated disease[72]. IL-1β and IL-18 are also critical in inflammaging; these cytokines are products of the NLR-family pyrin domain-containing (NLRP)3 inflammasome and contribute to the pathology of aging-related diseases[73]. In aging patients, SARS-CoV-2 can potentiate NLRP3 inflammasome activation and IL-1β and IL-18 levels, pyroptosis and the release of DAMPs (including ATP), further heightening inflammation and COVID-19 pathogenesis[74,75]. ROS levels increase with age owing to mitochondrial dysfunction and inflammation and can also drive NLRP3 inflammasome activation, which is likely to further contribute to COVID-19 pathophysiology in older patients[58,76,77]. Interestingly, metformin may lower risk of severe COVID-19, as it reduces ATP and mitochondrial ROS levels, which can fuel NLRP3-mediated IL-1β production[78]. Additionally, treatment with an IL-1 receptor antagonist has led to improvements in mortality in severe COVID-19 (ref. [79]), and the NLRP3 inflammasome is considered an emerging target for COVID-19 (ref. [80]).

Despite elevated NF-κB signaling observed at baseline during aging, many immune cells (including B cells, T cells and DCs) isolated from an inflammaging environment were shown to be hyporesponsive to acute ex vivo stimuli, although monocytes appear to stand out as being hyper-responsive[81]. Consistent with these observations, mass cytometry and single-cell RNA-seq analysis of monocytes from older patients with COVID-19 showed that they were enriched for the IFN-γ response and the expression of TNF-α, IL-1β and CXCL8 (ref. [76]). Aged monocytes were also enriched for broad pathways linked to TLR signaling, oxidative stress, MAPK and NF-κB, as well as the senescent cell marker p21, leading the authors to speculate that the presence of inflammatory aged or senescent cells with a senescence-associated secretory phenotype (SASP) was one mechanism for exuberant inflammatory tone in these cells during COVID-19 (ref. [76]). Indeed, senescent cells persist and accumulate during aging[82], and they display an abnormal secretory phenotype characterized by the presence of inflammatory cytokines that contributes to inflammaging. This SASP is characterized by the production of cytokines, chemokines, growth factors, matrix metalloproteinases, fibronectin and ROS[83]. In support of a role of cellular senescence in COVID-19 pathology, a recent study showed that in vitro exposure of senescent mouse and human cells to pathogen-associated molecular patterns (PAMPs) and the viral S protein leads to significantly increased SASP production and expression of the viral entry genes *ACE2* and *TMPRSS2,* compared to non-senescent cells. Using a β-coronavirus mouse hepatitis virus that has some relation to SARS-CoV-2, the study demonstrated that targeting senescent cells in genetically modified mice and with senolytics (fisetin and dasatinib with quercetin) could reduce inflammation and improve survival[84].

Neutrophils from older individuals exhibit some hyporesponsive attributes including: decreased bactericidal activity, decreased respiratory burst and decreased neutrophil extracellular trap formation[85]. However, neutrophils from older adults also display aberrant migration and enhanced degranulation, suggesting that neutrophils of aged individuals are not able to fight off pathogens efficiently but still produce highly inflammatory and damaging molecules in a potentially non-localized fashion[86]. Moreover, elevated levels of IL-6, either as part of the host pathogen response or due to inflammaging, engender prolonged neutrophil survival by reducing apoptosis[87], and neutrophilia is in fact an indicator of poor clinical outcomes for COVID-19 (ref. [88]).

Thus, aged individuals may have dysregulated innate immune cell function and inflammatory responses to SARS-CoV-2. Consistently, studies have shown that the sustained presence of increased neutrophils and monocytes in the blood is associated with severe COVID-19 disease[89,90]. As mentioned, these changes occur in part due to age-related high basal TLR activation, changes in oxidative stress pathways, inflammasome activation, increased senescent cell burden and the SASP, as well as other pathways such as reduced autophagy and DNA damage with age[91]. Thus, SARS-CoV-2 infection combined with inflammaging leads to an exaggerated innate immune response and worsened outcomes of COVID-19. However, more studies are needed to tease apart the complex interconnections between inflammaging and susceptibility to severe COVID-19.

The pro-thrombotic nature of senescent cells and severe COVID-19. While the connection between the pro-inflammatory profile of senescent cells and the exuberant pro-inflammatory environment of severe COVID-19 is important to note, there is another intriguing connection between the two: thrombosis. Senescent cells have a paracrine pro-coagulation effect[92]. Induction of cellular senescence via doxorubicin treatment in a senescence reporter mouse, p16-3MR, was associated with significantly shorter tail bleed times, greater platelet count, more highly activated platelets and higher levels of thrombopoietin in the serum[92]. Elimination of senescent cells in vivo reversed these pro-thrombotic phenotypes. Stable isotope labeling by amino acids in cell culture analysis of human senescent cells and ex vivo experiments also showed that human platelets sensitized by senescent cell supernatants were more highly activated[92].

Pro-thrombotic coagulopathy, high levels of D-dimer, venous thromboembolism, arterial thromboses and fibrin-based occlusion of small blood vessels have all been associated with cases of severe COVID-19 (refs. [7,44,49,93–99]). Mechanistically, pro-inflammatory cytokines lead to the expression of tissue factor (CD142), the initiator of blood coagulation, on platelets, monocytes, macrophages and endothelial cells. Complement activation, neutrophil extracellular traps and lung hypoxia further propagate pro-thrombotic conditions, which work in a feed-forward loop with ongoing inflammation, connecting thrombosis and the innate immune system[100]. A study also described the production of viral-induced pro-thrombotic autoantibodies against phospholipids and phospholipid-binding proteins during cases of severe SARS-CoV-2 infection[101]. Thus, the combination of a heightened inflammatory response to SARS-CoV-2 with the already thrombotic-prone microenvironment associated with aging may further potentiate the coagulopathy associated with worsened outcomes of COVID-19.

Loss of type I IFN responses. Reduced type I IFN levels have been observed in the serum of patients with life-threatening COVID-19 (ref. [102]). In a rhesus macaque model of SARS-CoV-2 infection, old macaques also had reduced type I IFN and Notch signaling pathways in their lungs when compared to their juvenile counterparts[67]. Reduced type I IFN responses in humans are in part linked to a reduction in numbers of plasmacytoid DCs (pDCs), strong producers of IFN-α, which has also been reported in cases of severe COVID-19 (ref. [103]). Ten per cent of all patients with life-threatening COVID-19, however, also harbor autoantibodies against type I IFNs[104]. Moreover, patients with severe symptoms can also carry loss-of-function variants in multiple genes linked to TLR3 and IRF7 pathways, involved in both the induction and amplification of type I IFNs[105]. If type I IFNs are present early and properly localized to sites of infection, they can effectively limit viral propagation, as type I IFNs are responsible for optimal activation of macrophages, antigen presentation by DCs and enhanced antiviral effector T cell responses[106]. Likewise, IFN-induced transmembrane family

(IFITM) proteins may inhibit SARS-CoV-2 entry, as demonstrated for previous coronaviruses[107,108].

Studies have revealed the importance of type I IFN responses in regulating monocytes and neutrophils early after SARS-CoV-2 infection. Peripheral blood from patients with mild COVID-19 contained more classical monocytes ($CD14^+CD16^-$) exhibiting an early and transient type I IFN signature[109,110]. Conversely, monocytes and neutrophils from patients with severe COVID-19 expressed more genes involved with NF-κB signaling and ROS or nitric oxide synthase production throughout the course of the disease[109]. Non-classical ($CD14^+CD16^{++}$) and intermediate ($CD14^{++}CD16^+$) subsets of monocytes are pro-inflammatory and known to expand during viral infections[111]. Thus, their expansion in response to SARS-CoV-2 infection is expected[112,113]; however, a dysregulated exuberant response from these cells would also contribute to the highly inflammatory environment observed in severe COVID-19 pathophysiology. Intriguingly, non-classical monocytes were also shown to produce the type I IFN IFN-α in response to TLR3 (ref. [114]). Thus, it is important to consider the kinetics of the dysregulation of non-classical monocytes in severe outcomes, as an early loss of this subset of monocytes has been described by some[109,110] and may further contribute to the reduced type I IFN response observed in patients with severe COVID-19.

Aging leads to a delay in type I IFN responses, linked to changes in viral sensing, which was also observed for SARS-CoV-1 (ref. [31]). While the mechanisms of this are not entirely known, aging compromises both primary and secondary retinoic acid-inducible gene (RIG)-I signaling pathways that control expression of many type I IFN genes[115]. This is associated with reduced production of type I IFNs in those >65 years of age, impairing their antiviral responses, similar to that observed with respiratory influenza A virus[115]. During SARS-CoV-1 infection, levels of type I IFN signaling proteins downstream of RIG-I are further reduced due to infection-induced mitochondrial dysfunction linking to the viral sensor MAVS[116]. Given basal mitochondrial dysfunction, as well as a reduction in TNF receptor-associated factor (TRAF) adaptor protein and phosphorylated IRF3 levels linked to RIG-I signaling in older adults[115,117], they are particularly vulnerable to such RIG-I insufficiency. Interestingly, RIG-I can restrain SARS-CoV-2 replication in human lung cells, although the mechanism does not require its type I IFN signaling ability[118]. Older individuals also display reduced total numbers of pDCs at baseline, and their pDCs often show reduced TLR7 expression[117] and have diminished capacity to produce type I IFNs[119–121]. While there is a strong overlap of reduced type I IFN responses between older adults and patients with severe COVID-19, additional mechanistic connections between the two require further investigation.

Decline in antigen presentation and T cell priming. Innate immunity plays a critical role in the initiation of adaptive immune responses by ensuring proper activation of T lymphocytes. To achieve effective T cell priming, innate immune cells must accomplish two tasks: (1) present antigen via major histocompatibility complex (MHC) molecules alongside co-stimulatory receptors via cell–cell interactions between the T cell and the antigen-presenting cell (APC) and (2) produce the proper cytokines to skew $CD4^+$ T cell differentiation toward the appropriate effector response specific to the invading pathogen. Defects in the ability of APCs to accomplish either of these tasks can have detrimental effects on the adaptive immune response and alter disease outcome.

APCs, such as DCs and monocytes, taken from the blood of patients with acute COVID-19 display impaired antigen-presenting abilities. When stimulated ex vivo, DCs taken from the blood of patients with COVID-19 had minimal expression of CD80, CD86, C–C motif chemokine receptor (CCR)7 and human leukocyte antigen (HLA)-DR[103]. HLA-DR expression on monocytes from patients with severe COVID-19 is also reduced relative to that from patients with mild symptoms[109,110,112,122]. Aging negatively affects antigen presentation as well. Monocyte populations shift with aging, and there is an accumulation of non-classical monocytes that significantly downregulate HLA-DR[123]. Other work suggests reduced levels of MHC class II, CD40 and CD86 on aged DC subsets after activation with TLR agonists; although there are conflicting reports, as previously reviewed[124]. During SARS-CoV-1 infection, lung DCs from older mice displayed an impaired ability to migrate to the draining lymph node, which negatively affected subsequent T cell priming[125]. This migration defect was caused by increased levels of prostaglandin D2 in elderly mouse lungs, which directly reduced the surface expression of CCR7 on DCs[125].

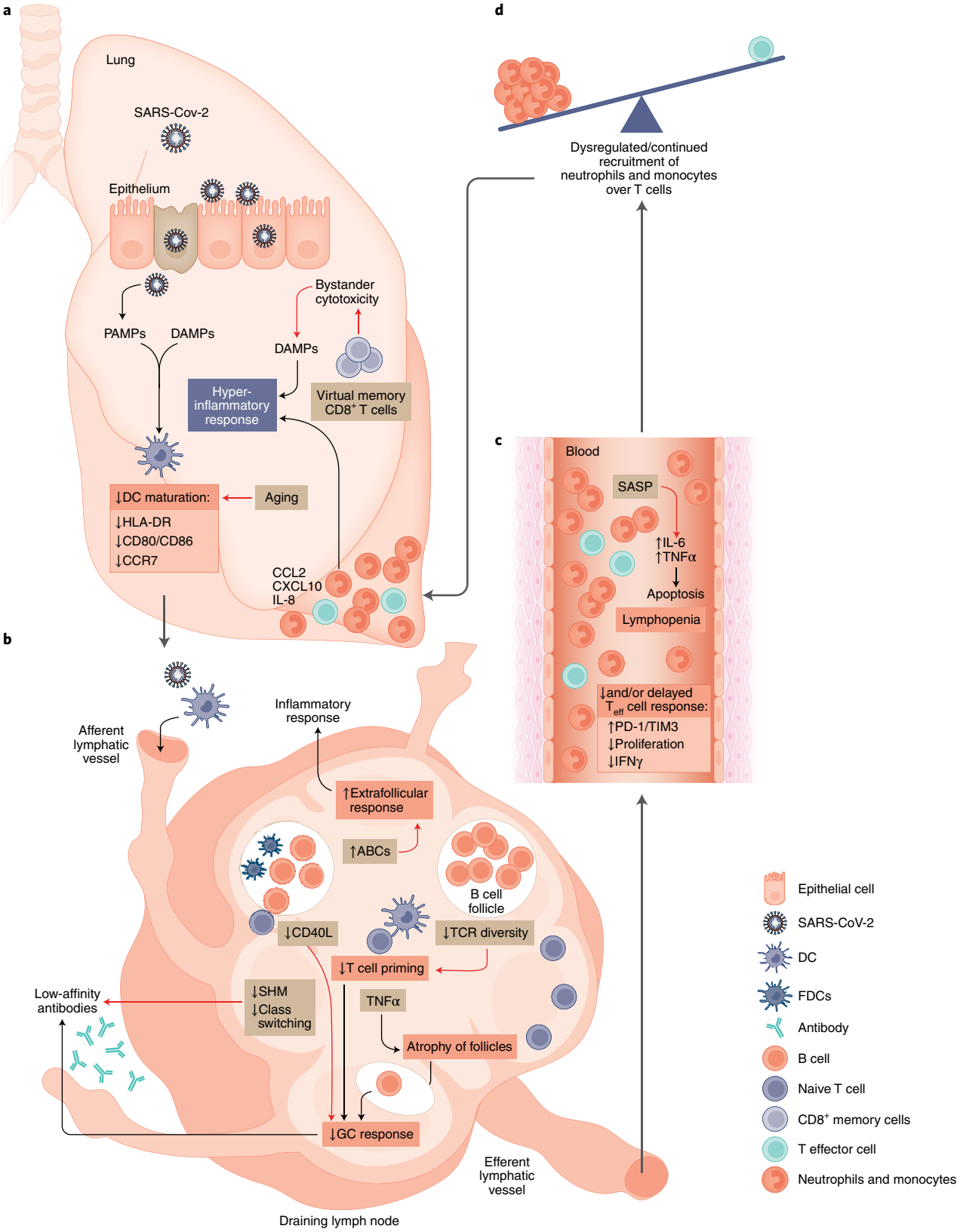
Aging predisposes an individual to impaired antigen presentation and T cell priming. Thus, a virus that further reduces the immune system's capacity for these essential tasks could render older adults especially susceptible to worse disease outcomes due to improper adaptive immune responses.

Immune system dysregulation associated with aging and severe COVID-19: adaptive immunity

The role of adaptive immunity in controlling SARS-CoV-2 infection has been a major scientific focus, as generating robust immunological memory is the primary goal of current vaccines. Adaptive immunity is carried out by three broad populations of lymphocytes: B cells, $CD4^+$ T cells and $CD8^+$ T cells. B cells are responsible for producing antiviral antibodies. $CD4^+$ T cells act as 'helper' cells, producing cytokines to bolster the antiviral immune response and aid B cells in the production of long-lasting, neutralizing

Fig. 4 | Aging adaptive immune system responses during severe COVID-19. a–d, It has been hypothesized that a delayed and/or weak adaptive immune response helps to drive the dysregulated and continued recruitment of neutrophils and monocytes. These cells facilitate a nonspecific and highly destructive hyperinflammatory response that contributes to the outcomes observed in patients with severe COVID-19. Failures of the adaptive system would begin at sites of infection (**a**), where DCs are initially activated by PAMPs and DAMPs in response to SARS-CoV-2. Patients with severe COVID-19 have DCs with a reduced maturation profile. **b**, Aging also negatively affects DC maturation, furthering the potential for improper priming of naive T cells in lymph nodes in older adults. There appears to be a loss of GC reactions with atrophy of lymphoid follicles, associated with atrophy of secondary lymphoid organs (SLOs) in fatal cases of COVID-19. These factors, combined with decreased CD40L expression on aged $CD4^+$ T cells and reduced AID expression in aged B cells, could culminate in greatly impaired high-avidity, long-lasting antibody production that is dependent upon the success of GC reactions. Reductions in levels of GC reactions are also linked to extrafollicular and age-associated B cell (ABC) responses, which may potentiate 'lupus-like autoimmune inflammation'. As we age, the naive TCR repertoire also decreases, making DC accessibility to SARS-CoV-2-specific naive T cells potentially even more challenging and delaying priming responses. **c**,**d**, Lymphopenia is also strongly associated with severe COVID-19 outcomes. The aged microenvironment may contribute to this phenotype, as the SASP mediators IL-6 and TNF-α can cause enhanced T cell apoptosis. Furthermore, the presence of virtual memory $CD8^+$ T cells at sites of SARS-CoV-2 infection may contribute to a hyperinflammatory response through the action of bystander cytotoxicity, which occurs in a non-antigen-specific manner and can be highly destructive if left unregulated. AID, activation-induced cytidine deaminase; FDC, follicular dendritic cells; SHM, somatic hypermutation; T_{eff} cell, effector T cell. Immune responses to the virus are indicated by black arrows, and consequences of aging are shown by red arrows.

antibodies. CD8⁺ T cells directly kill virally infected cells while also producing antiviral cytokines. Collectively, these three arms of the adaptive immune response have proven critical in controlling viral infections, including that with SARS-CoV-2. With age, adaptive immunity wanes, potentially allowing SARS-CoV-2 to evade or subvert this arm of the immune system. Here, we review adaptive immunological responses to SARS-CoV-2 and comment on how features of the aging immune system may contribute to a defective adaptive response during severe COVID-19. A summary is depicted in Fig. 4.



T lymphocytes. Adaptive responses to SARS-CoV-2 begin around 1 week after symptoms (Fig. 2), with SARS-CoV-2-specific CD4+ and CD8+ T cells being observed as early as 4 d after symptom onset[126]. SARS-CoV-2 infection elicits a CD4+ type 1 helper T (T_H1) cell response, with IFN-γ and IL-2 being the primary cytokines produced by these cells, as well as some TNF-α[112,126–129]. Indeed, many chemokines that are elevated in the blood of patients with COVID-19, such as CXCL9 and CXCL10, are involved in recruiting and/or differentiating naive T cells into T_H1 cells. Both CD4+ and CD8+ T cells confer protection against previous coronaviruses[130]. Current evidence suggests that an early, robust and diverse T cell response directed against SARS-CoV-2 correlates with milder COVID-19 outcomes[126,131,132]; however, excessive cytokine release from T cells could also contribute to aberrant activation of monocytes during cytokine storm. As aging impacts many aspects of T cell biology, it is important to understand how these changes may influence worsening outcomes of SARS-CoV-2 infection in the older population.

Reduced naive lymphocyte clonal diversity. Maintaining a diverse TCR repertoire is critical for optimal functioning of the immune system, but naive CD4+ and CD8+ TCR diversity diminishes as we age[133]. There are many factors that may contribute to the restricted TCR repertoire in older adults, but the exact mechanisms underpinning this phenomenon are still debated. Thymic involution, a process by which the thymus gradually atrophies as we age, prevents development of new T cells in older individuals, thus restricting the TCR repertoire. Evidence suggests that newly generated naive T cells that do manage to enter the aged T cell repertoire display reduced T effector cell qualities upon activation and generate less effective memory cells[134]. Nascent T cell generation, however, may only be a part of the story, especially with regard to CD8+ T cells. In humans, tightly regulated homeostatic proliferation and active maintenance of T cell quiescence are imperative for a stable peripheral naive T cell compartment, and these two factors may play a prominent role in sustaining naive T cell diversity as we age[135]. Additionally, chronic antigen stimulation can lead to an expanded, oligoclonal T cell memory pool that further exacerbates the diminished presence of polyclonal naive T cells.

Severe COVID-19 has been associated with lower TCR diversity against SARS-CoV-2 epitopes[131,132]. Specifically, when compared to those with mild COVID-19, patients with severe disease generated a weaker T cell response to the N-terminal portion of the SARS-CoV-2 S protein, a region that includes the critical RBD[128]. Low frequencies of naive T cells have also been correlated with severe COVID-19 outcomes[126]. These findings could suggest a connection between the diminished naive TCR repertoire of older individuals before SARS-CoV-2 infection and worsened disease outcome.

Lymphopenia. COVID-19 severity is associated with lymphopenia, and many studies have shown a correlation between poor disease outcome and reduced total numbers of peripheral T cells in the blood[136]. It was even suggested that a patient's blood lymphocyte percentage can be used clinically as an independent prognostic measure to identify moderate, severe and critically ill disease trajectories to inform early therapeutic decisions[137]. Lymphopenia observed in severe COVID-19 may prove even more detrimental for aged individuals, as immunosenescence leads to poorer T cell responses that could be further exacerbated by a decline in T cell numbers.

Initially, it was speculated that COVID-19-associated lymphopenia may be a direct result of increased T cell migration to sites of infection. However, while lymphocytes do accumulate in the lungs of deceased patients with COVID-19, this migration probably does not completely account for the magnitude of observed lymphopenia. One group analyzing bronchoalveolar lavage fluid by single-cell RNA-seq found that the total number of CD8+ T cells with a tissue-resident phenotype was actually greater in patients with moderate disease than that in those with severe disease[138]. The same study also concluded that lung macrophages present in bronchoalveolar lavage fluid of patients with severe COVID-19 expressed chemokines more likely to recruit inflammatory monocytes and neutrophils, while lung macrophages from patients with moderate COVID-19 expressed higher levels of T cell-recruiting chemokines, supporting the hypothesis that T cell migration to the lungs does not account for lymphopenia observed in the blood in severe disease[138]. Other hypotheses to explain the depletion of T cells during SARS-CoV-2 infection include direct infection of T cells with the virus and/or increased prevalence of activation-induced cell death in response to either cognate antigen stimulation or as an effect of the cytokine milieu[41]. Lymphopenia does correlate with serum levels of IL-6, IL-10 or TNF-α[139,140], and the IL-6 receptor antagonist tocilizumab increased the number of circulating lymphocytes in patients with COVID-19 (ref. [122]).

One cohort of 522 patients with COVID-19 revealed a strong association between lymphopenia and age in addition to the association between lymphopenia and disease severity, such that patients older than 60 years had the lowest total number of T cells in their blood[139]. In the case of influenza virus, aged CD8+ T cells showed reduced expansion or proliferative capacity, and this decrease in virus-specific CD8+ T cells negatively affected viral clearance in older patients[134]. Studies aimed at further delineating a similar association between lymphopenia, aging, T cell expansive capacity and SARS-CoV-2 infection may be of great interest for future investigation.

Decline in effector T cell function and enhanced cellular exhaustion. T cell effector functions tend to decrease with age, while T cell exhaustion increases. Analysis of blood from patients with severe versus mild COVID-19 during the acute phase of illness has revealed contradictory reports about whether T cells are functioning properly following SARS-CoV-2 infection. Some studies have found reduced effector functions for CD4+ T cells, that is, IFN-γ, IL-2 and/or TNF-α production, in patients with severe disease[141], while others have shown no differences[142]. For CD8+ T cells, there are reports of diminished CD8+ cytotoxicity and cytokine production in severe cases[126,132], while others report the opposite[141], and still others find no differences[142]. The differences across many studies may be due in part to the timing of cytokine sampling. Given that aging reflects a state of impaired adaptive immunological function, we favor a model in which aging predisposes an individual to exhausted or compromised effector T cells with reduced cytokine production and/or cytotoxicity, compromising viral clearance during acute stages of the disease. Consistent with this hypothesis, one study identified the presence of IFN-γ-producing CD8+ T cells during acute stages of disease as the strongest predictor of mild COVID-19 outcomes[126]. Moreover, CD4+ and CD8+ T cells also display greater expression of exhaustion markers (programmed cell death protein (PD)-1, T cell immunoglobulin- and mucin domain-containing protein (TIM)3, etc.) in severe COVID-19 cases than those in mild ones[139]; however, these markers may simply represent activation rather than functional exhaustion, as one paper recently suggested[143].

Pre-existing immunity to SARS-CoV-2. SARS-CoV-2-reactive CD4+ T cells are observed in up to 40–60% of unexposed individuals[127]. One study used cell-sorting experiments to show that SARS-CoV-2-reactive T cells identified from SARS-CoV-2-unexposed individuals were primarily from the memory T cell compartment and they were also reactive to other human coronaviruses[144]. Therefore, many individuals have existing memory T cells that were generated from endemic human coronavirus infections and can cross-react with SARS-CoV-2 epitopes, known as SARS-CoV-2-cross-reactive memory T cells[128]. Another study concluded that severe COVID-19

may even be associated with a lack of these pre-existing SARS-CoV-2-cross-reactive memory T cells in the TCR repertoire[131].

Given the relationship between COVID-19 severity and age, these findings require further investigation. For instance, it will be important to know whether older individuals have been exposed to more human coronavirus infections and whether this exposure translates into robust memory T cell responses. Indeed, the lack of TCR diversity with age may prevent broad memory T cell development from prior exposures to 'common cold' endemic human coronaviruses. Memory T cells generated by the elderly may also not be maintained as well in the peripheral repertoire, perhaps due to niche competition from the effects of memory inflation[145]. COVID-19 severity has been linked to the incidence of cytomegalovirus (CMV), a primary pathogen associated with memory inflation, but more work is needed to establish how CMV and other latent viruses in older adults affect new memory T cell formation, function and longevity[146].

As we age, $CD8^+$ T cells can also lose their naive quiescent state and differentiate in response to IL-15 signaling without the presence of their cognate antigen. These 'virtual memory' $CD8^+$ T cells have been most widely studied in mice[147], but a human equivalent population has been identified ($CD45RA^+KIR^+NKG2A^+Eomes^+$) and similarly positively correlates with age[147]. Virtual memory $CD8^+$ T cells are innate-like in that they can become activated by cytokines (IL-15, IL-18 and type I IFNs) and mediate cytotoxic effects without the need for their cognate antigen during viral infections. While this could provide a benefit in clearance of the virus, it could also prove highly damaging to the host if left unregulated[148]. Whether or not these cells play a role in COVID-19 outcomes has yet to be studied.

B lymphocytes. In response to SARS-CoV-2 infection, B cells produce detectable levels of immunoglobulin (Ig)M, IgG and IgA antibodies specific to SARS-CoV-2 at around 1 week after symptom onset, and, by 2 weeks, the majority of patients seroconvert for IgG and IgM. This response occurs concurrently with the detection of circulating SARS-CoV-2-specific T follicular helper cells, suggesting a role for T cell-dependent antibody production[126]. Neutralizing antibodies specific to the RBD of SARS-CoV-2 have been discovered in both mice and humans[149,150], and passive transfer of these antibodies reduces disease severity and offers protection in mouse models of SARS-CoV-2. Convalescent patient serum samples have also yielded promising results in the clinic[151]. However, the natural role that antibodies play during the course of COVID-19 progression remains contested.

Many studies have reported a correlation between higher IgG antibody titers and severe disease, but others have found either the opposite or no correlation between antibody production and disease severity[126]. These seemingly contradictory results might possibly be explained by the dual role played by antibodies during viral infections: although neutralizing antibodies are generally beneficial to viral clearance, the early production or prior existence of already circulating, non-neutralizing antibodies can lead to antibody-mediated enhancement of viral entry and induce a severe inflammatory response. This is called antibody-dependent enhancement of disease; however, there is currently no evidence supporting a role for antibody-dependent enhancement during SARS-CoV-2 infection[152]. Interestingly, the presence of IgG antibodies with an afucosylated IgG Fc tail during acute SARS-CoV-2 infection have also been associated with severe COVID-19 outcomes, perhaps owing to their stronger pro-inflammatory activity via FcγRIIIa[153].

The quality of the humoral immune response declines with age, as aged B cells display a diminished potential to undergo somatic hypermutation[154], which could prevent aged individuals from generating robust neutralizing antibody titers to aid the clearance of natural infection and generate effective immunity against reinfections. Consistently, levels of viral S protein-specific IgG during early time points of acute SARS-CoV-2 infection in rhesus macaques are reduced in older macaques compared to those in young ones, consistent with age crippling the formation of class-switched antibody titers needed to clear the viral infection[155].

Another change in B cells that occurs in animal models and in humans with aging is the accumulation of age-associated B cells with unique properties[156]. In mice, these cells are promoted by TLR7 responses[156], which are relevant, being a major PRR for SARS-CoV-2. In humans, these cells are found in the late memory fraction (IgD^-CD27^-, also called double-negative B cells), secrete inflammatory mediators such as TNF-α, IL-6 and IL-8 and have been implicated in autoimmune disease, chronic viral infections and, more recently, in COVID-19 (refs. [156–158]). During COVID-19, critically ill patients show expansion of such cells, which also express CD11c and T-bet in a skewed extrafollicular B cell response, with signatures of lupus-like autoimmune disease[158].

Consistent with a dominant extrafollicular B cell response, studies have consistently reported defective germinal center (GC) responses in secondary lymphoid organs of patients who have succumbed to SARS-CoV-2 infection[129,159]. One of these studies also noted diminished GC formation that occurred concurrently with high levels of TNF-α in lymph node follicles, and TNF-α was previously demonstrated to inhibit follicular helper T cell differentiation and subsequent GC formation[160]. TNF-α production also increases as we age and could contribute to this observed phenotype[161–163]. Other hallmarks of aging also affect GC formation. Expression of CD40 ligand (CD40L), a co-stimulatory molecule critical for successful T cell and B cell interactions, decreases on aged $CD4^+$ T cells[134]. Additionally, lymphopenia observed in older adults as well as in patients with severe COVID-19 could imply a reduction in the availability of $CD4^+$ T cells to engage with B cells. This dilemma would be heightened by the lack of TCR and BCR clonal diversity in aged individuals, as the probability of cognate T cell–B cell interactions would be greatly reduced.

Another consequence of aging is the loss of tolerance and the emergence of autoantibodies. Recent work on SARS-CoV-2 has linked life-threatening COVID-19 to the presence of autoantibodies specific to type I IFNs, especially in men[104]. These autoantibodies were found across multiple ages, although there was a higher prevalence in patients over 65 years of age. Thus, it remains to be determined whether the loss of tolerance with aging facilitates production of these and other autoantibodies that might worsen clinical outcome in COVID-19. Moreover, the mechanistic basis of the sex bias to produce such autoantibodies specifically in males also warrants further investigation.

Bolstering immunity in older adults to combat COVID-19

Biomarkers of aging. While we associate immunosenescence with the chronological process of aging, this paradigm can be misleading. People of the same chronological age can have a widely variable 'immunological age'. Important work is being carried out to identify biomarkers associated with immunological aging, in the hope of developing prognostic tools for assessing an individual's risk of developing specific age-related diseases[16]. Identifying biomarkers indicative of immunosenescent phenotypes would also be of great interest for the development of therapeutics that could pre-emptively bolster viral immunity not only in older individuals but also in susceptible younger individuals.

Identifying biomarkers of immunosenescence represents an especially exciting area of research, as the effects of aging have been shown to be amenable to interventions. For example, epigenetic changes associated with aging, including Horvath's methylation clock[164], appear to be responsive to unique pharmacological interventions. One year of treatment with dehydroepiandrosterone, metformin and recombinant human growth hormone therapy in elderly men resulted in a 1.5-year reduction in 'epigenetic age'

and significantly regenerated the thymus[165]. Many strategies have already been proposed to ameliorate the declining immune system in older adults[166]. Below, we will highlight how current strategies to combat aging could be linked to improve immune function in the face of SARS-CoV-2.

Interventions for immunosenescence and COVID-19. *Rapamycin and rapalogs.* Sirolimus (rapamycin) and rapalogs, derivatives and mimetics of rapamycin, have often been studied in the field of aging. These drugs target critical factors in the rapamycin (TOR) pathway and are commonly used clinically as immunosuppressants. Animal models exploring the effect of rapamycin and rapalogs on longevity have determined their ability to extend lifespan[167–169]. While they are immunosuppressive at high doses, these compounds exert immunostimulatory effects at lower doses[170]. Administration of a rapalog, mTOR inhibitor RAD001, improved response to the influenza vaccine in older individuals by around 20%[171].

The mechanism of immunostimulatory action by rapamycin and rapalogs is not quite clear. One possibility is that inhibition of mTORC1 could be relieving feedback inhibition on other inflammatory and metabolic pathways, thus boosting immunity. One such pathway could be insulin signaling. Insulin is a critical mediator of adaptive immune effector function against respiratory infections[172], and mTORC1 activation of S6 kinase blocks insulin signaling[173,174]. mTOR was also shown to regulate STAT signaling[175], and studies in older humans show that elevation in baseline phosphorylation of STAT proteins in T cells distinguishes healthy aging individuals from unhealthy aging individuals based on cardiovascular aging phenotypes[17]. However, rapamycin was also observed to enhance the expression of IL-6 (refs. [176–178]), which is associated with poor COVID-19 outcomes, and patients with type 2 diabetes and COVID-19 had significantly increased mortality rates when receiving insulin treatment during the course of their hospitalization[179]. Thus, before any treatment or adjuvant uses for rapamycin and rapalogs are considered, further investigation into how mTOR and other nutrient-sensing pathways alter immunosenescence and COVID-19 outcomes are necessary.

Senolytics. Numerous clinical trials are also underway to test the role of senolytic compounds on aging. Senolytics, such as fisetin and quercetin and dasatinib (D + Q), clear senescent cells and reduce the pro-inflammatory and pro-thrombotic effects of the SASP. Several small studies have found an improvement in symptoms of inflammation with the administration of senolytics. For example, D + Q resulted in a reduction in SASP-associated pro-inflammatory cytokines during idiopathic pulmonary fibrosis, an age-related lung disease[180], and a recent study showed that fisetin and D + Q reduced SASP and improved survival in a mouse model of β-coronavirus[84]. Quercetin may also have beneficial renal-protective and senolytic-independent effects during SARS-CoV-2 infection[181]. However, more work is needed to determine whether senolytics could be a viable option in humans to rejuvenate an aged immune system as either a preventative measure before SARS-CoV-2 infection or as a treatment option during acute infection.

NAD^+ precursors. Therapeutics targeting NAD^+ metabolism have also been proposed as potential treatments for age-related immune decline, as reduced NAD^+ levels are associated with impaired mitochondrial function, immune cell metabolic reprogramming and cell function[182]. A recent paper described the downregulation of nuclear-encoded mitochondrial genes related to cellular respiration and complex I during infection with SARS-CoV-2, suggesting that proper mitochondrial function of immune cells is essential for containing viral propagation[183]. Immune system activation can further reduce NAD^+ levels, as was recently shown in macrophages treated with PAMPs, including viral TLR ligands, and in aging mouse tissues that contain CD38-dependent NADase activity[184]. Administration of the NAD^+ precursor nicotinamide mononucleotide in mice has been somewhat promising at restoring NAD^+ levels and improving mitochondrial function[185]. A similar NAD^+ precursor, nicotinamide riboside, was also able to restore NAD^+ levels in mice and humans[186].

Diet modulation. There is a mutual interaction between nutrition, immune function and inflammatory state, as detailed among the hallmarks of immunosenescence[187]. Notably, a high rate of long-living people and the low incidence of cardiovascular disease in many Mediterranean countries suggests the importance of a diet rich in fruits, vegetables, whole grains, legumes, fish high in omega-3 fatty acids and extra virgin olive oil[188]. This particular diet results in a reduction in both oxidative stress and inflammation and regulation of eubiosis of the gut microbiota, which, in turn, all contribute to an improvement in immune responses[189]. The use of probiotics in older adults was also shown to regulate inflammatory conditions: specifically, probiotics can attenuate the production of both IL-1β and IL-6 (ref. [190]), which are associated with severe COVID-19. The Mediterranean diet also modulates the level of many biomarkers of inflammation, including IL-6 (ref. [187]).

Another possible dietary approach to the reversion of immunosenescence is caloric restriction. NF-κB, mTOR, AMP-activated protein kinase (AMPK) and MAPK are pathways that are involved in both aging and inflammation and have been shown to be affected by caloric restriction, resulting in downregulation of inflammatory markers, such as IL-6 and IL-1β[191,192]. Clinical trials using metformin, which activates AMPK, to target aging have already begun[193]. Additionally, ketones, which are largely produced during either ketogenic diets or fasting periods, can impact immune function and may have possible therapeutic effects for COVID-19 (ref. [194]). If caloric restriction can reverse the age-related upregulation of inflammatory genes, future studies should compare COVID-19 responses in elderly patients segmented by caloric intake and fasting regimes. Undernutrition, however, is common in older people and is also linked to impaired immune responses[187]. Restricting glucose use can also be fatal in mice during viral infection, even though it proves beneficial for fighting bacterial infections[195]. Therefore, more work is needed to determine whether reduced caloric intake or specific types of nutritional supplementation may boost or hinder immune responses with age in the specific context of SARS-CoV-2 infection.

Conclusions and perspectives

The serious effects of SARS-CoV-2 infection are likely to be caused by a pathological hyperinflammatory response initiating uncontrolled local tissue damage, vascular leakage, systemic cytokine storm and thrombosis. Research has begun to identify pathophysiological mechanisms underlying these events in response to SARS-CoV-2, and some recurring observations in cases of severe disease have emerged: (1) early defects in type I IFN production and signaling, (2) suboptimal T cell responses and (3) dysregulated monocyte and neutrophil inflammation. While there is much work left to elucidate why some develop severe disease while others are asymptomatic, we can begin to propose why an aged immune system may be especially vulnerable to these severe outcomes.

Basal inflammaging is driven by NF-κB signaling and generally renders immune cells initially hyporesponsive to acute activation, with the possible exception of monocyte subsets[71,81]. A lack of early type I IFN responses during severe COVID-19, compounded with the JAK–STAT hyporesponsiveness of aged immune cells[17], could facilitate early viral replication and overburden the immune system during early responses to SARS-CoV-2 invasion in older individuals. Once the aged immune system overcomes initial signaling thresholds and local viral load peaks, massive amounts of

pro-inflammatory cytokines would be released, and tissue destruction and vascular permeability may become tipped too far in favor of propagating continued, hyperinflammatory, pathological innate responses. This 'tipping point' may also be reached through further TLR4 priming due to secondary bacterial superinfections resulting from the initial viral invasion[53]. Meanwhile, poor adaptive responses to SARS-CoV-2 in older individuals could be partly driven by ineffective T cell priming, a lack of naive T cell diversity, diminished antibody maturation and/or inefficient pre-existing memory; these characteristics of immunosenescence are likely to be compounded by viral evasion tactics and improper early innate responses. Without the help of a fully functional antigen-specific immune response, the broadly acting innate immune system will continue to drive highly destructive effects of inflammation in an unregulated manner, leading to the enhanced morbidity of severe COVID-19.

SARS-CoV-2 has highlighted gaps in our knowledge of the aged immune system. Even a basic understanding of how specific immune cell subsets react to insults as we age remains a major topic of research. Most studies involve the interrogation of human immune cells taken from the blood, but analysis of human cells from specific tissues is lacking. While mouse studies allow us to glean information on immunosenescence, differences between mouse and human immune aging have already been discovered, such as in mechanisms controlling naive T cell repertoire diversity[135]. Furthermore, immune cell subsets are not always perfectly conserved across the two species, such as in the case of monocyte subsets[196]. These examples emphasize the need for caution when extrapolating data from one model to the next. Aging immunology studies should also better integrate emerging insights from geroscience, especially from inflammaging research, which has recently described pivotal roles for mitochondrial dysfunction, proteostasis, nutrient sensing and physical changes in the tissue microenvironment in modulating immune pathways[197–200].

Recent early successes of the Pfizer and Moderna mRNA COVID-19 vaccines appear promising for the elderly population. In stage III clinical trials, the Pfizer vaccine (BNT162b2) had a 94.7% success rate for those aged 65 years or older (with a 95% confidence interval of 66.7–99.9%)[201], and the Moderna vaccine (mRNA-1273) was 86.4% efficient in the same age group (with a 95% confidence interval of 61.4–95.2%)[202]. While these preliminary results are exciting, both studies assessed vaccine efficiency for only about 90 d after complete dosing. A more recent study with BNT162b2 showed that people over the age of 80 had lower anti-SARS-CoV-2 antibody titers 17 d after the second dose when compared to those under 60 years of age, including 31% with no detectable neutralizing antibodies[203]. Thus, long-term follow-up studies are needed to determine whether there is sustained efficacy in older individuals. Still, many people have already been infected with SARS-CoV-2, and the long-term effects of this infection have yet to be extensively detailed. Chronic infections, such as with CMV, greatly affect aging phenotypes, and it is possible that COVID-19 may leave a lasting imprint on human physiology as well.

The field of geroscience has been given a boost of attention from the COVID-19 pandemic, which will hopefully lead to even more advances and breakthroughs in the near future. Indeed, our first defense against any virus is a properly functioning immune system; thus, we need to further elucidate mechanisms of immunosenescence and pursue the development of therapeutics that will enhance 'healthspan' in a pre-emptive way.

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Competing interests

J.M.B., D.F., A.J.C., E.V. and D.A.W. declare no competing interests related to this study. D.R. is a chief science officer at Hooke by Healthy, Longevity Optimisation, a longevity clinic and research center.

Additional information

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