



# Remodeling of the Immune Response With Aging: Immunosenescence and Its Potential Impact on COVID-19 Immune Response

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### Specialty section:

This article was submitted to  
*Cytokines and Soluble Mediators in  
Immunity*,  
a section of the journal  
*Frontiers in Immunology*

**Received:** 20 April 2020

**Accepted:** 30 June 2020

**Published:** 07 August 2020

### Citation:

Cunha LL, Perazzio SF, Azzi J,  
Cravedi P and Riella LV (2020)  
*Remodeling of the Immune Response  
With Aging: Immunosenescence and  
Its Potential Impact on COVID-19  
Immune Response.*  
*Front. Immunol.* 11:1748.  
doi: 10.3389/fimmu.2020.01748

Elderly individuals are the most susceptible to an aggressive form of coronavirus disease (COVID-19), caused by SARS-CoV-2. The remodeling of immune response that is observed among the elderly could explain, at least in part, the age gradient in lethality of COVID-19. In this review, we will discuss the phenomenon of immunosenescence, which entails changes that occur in both innate and adaptive immunity with aging. Furthermore, we will discuss inflamm-aging, a low-grade inflammatory state triggered by continuous antigenic stimulation, which may ultimately increase all-cause mortality. In general, the elderly are less capable of responding to neo-antigens, because of lower naïve T cell frequency. Furthermore, they have an expansion of memory T cells with a shrinkage of the T cell diversity repertoire. When infected by SARS-CoV-2, young people present with a milder disease as they frequently clear the virus through an efficient adaptive immune response. Indeed, antibody-secreting cells and follicular helper T cells are thought to be effectively activated in young patients that present a favorable prognosis. In contrast, the elderly are more prone to an uncontrolled activation of innate immune response that leads to cytokine release syndrome and tissue damage. The failure to trigger an effective adaptive immune response in combination with a higher pro-inflammatory tonus may explain why the elderly do not appropriately control viral replication and the potential clinical consequences triggered by a cytokine storm, endothelial injury, and disseminated organ injury. Enhancing the efficacy of the adaptive immune response may be an important issue both for infection resolution as well as for the appropriate generation of immunity upon vaccination, while inhibiting inflamm-aging will likely emerge as a potential complementary therapeutic approach in the management of patients with severe COVID-19.

**Keywords:** immunosenescence, inflammaging, SARS-CoV-2, COVID-19, immunopathogenesis

## INTRODUCTION

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was discovered as the causative agent of an outbreak of viral lower-respiratory tract infections centered in Wuhan (China) (1). Since then, SARS-CoV-2 has caused a widespread outbreak of severe acute respiratory syndrome throughout China, with exported cases occurring in other continents, including the United States, in a worldwide pandemic (1). Interestingly, a strong age gradient in the risk of death was observed among patients with coronavirus disease (COVID-19) (2). In this scenario, the remodeling of immune response that is observed among the elderly could be a possible explanation for the higher lethality of COVID-19 noted on this population.

The immune response is dynamically remodeled with aging, a phenomenon denominated as immunosenescence. This phenomenon increases susceptibility to a myriad of clinical conditions such as infections, autoimmune disorders, and malignancies. Recent data had shed light on the physiological aspects of immunosenescence, which is now considered an immune adaptation to the aged microenvironment rather than merely a collapse of the system (3).

Both the innate and adaptive immunity is affected by aging. Some individuals experience a sustained innate immune system activation, inducing proinflammatory cytokines secretion and innate immune cells' recruitment (4). Innate immunity hyperactivation may be detrimental and impair global functionality, causing a clinical phenotype known as frailty syndrome. Frailty syndrome is defined as a state of cumulative decline in several physiological systems with a disproportionate vulnerability to stressor events (5). Frailty syndrome prevalence increases with age, it is multifactorial in etiology, and the physical component of frailty can be objectively assessed by the Fried Frailty Score (Phenotype Score) and the Frailty Index (Deficit Accumulation Index) (6).

Likewise, adaptive immunity remarkably changes as age increases, which can be summarized into two main topics: (1) bone marrow reorganization and hematopoietic stem cell pool differentiation into myeloid lineage, outnumbering lymphoid compartment; and (2) physiological thymic involution, compromising naïve T cells generation. The sum of these two factors can help explain the prior known impairment of the regenerative capacity of lymphocytes compared to myeloid-derived cells in the elderly (7).

Infectious diseases are more prevalent among the elderly. When compared to younger counterparts, the elderly more frequently present with respiratory and urinary tract infections, and those patients usually have a worse prognosis (8, 9). It is possible that the impaired barrier function of mucosae and diminished adaptive immune response (both cellular and humoral) are the reasons for the increased susceptibility to infectious microorganisms among the elderly (10). In addition, the natural killer (NK) cell senescence may affect the homeostasis of the immune system in the elderly, leading to an increased risk of cancer and additional risk of viral infections (11). Lastly, age-related cell dysfunctions leading to an exhausted phenotype

are also an important characteristic of the immune system remodeling with aging, which might accelerate tissue damage and disable modulatory mechanisms (12). Herein, we review the state of the art research on senescence-induced immune dysregulation, focusing on innate and adaptive cell functional analysis and its potential impact in viral immune responses, such as in COVID-19.

## PHYSIOLOGY OF IMMUNOSENESCENCE AND INFLAMM-AGING

Currently, the concept of immunosenescence refers to a comprehensive remodeling of the immune system and its microenvironment, involving both innate and adaptive compartments that occur with aging (13, 14). Many physiological phenomena have been proposed to explain the immune response remodeling over time, including chronic exposure to antigens, impaired telomerase activity, mitochondrial dysfunction, defective autophagy, endoplasmic reticulum stress, defective ubiquitin/proteasome system, and age-related changes in the composition of gut microbiota (15–18). Probably, a melting pot of diverse factors differently contributes to the final phenotype of the adapted and experienced immune system, named immunosenescence.

Aging of the immune system is characterized by an imbalance between stimulatory and regulatory mediators, such as cytokines and acute phase reactants, toward a sub-clinical chronic proinflammatory state called inflamm-aging. Inflamm-aging is thought to be caused by a low-grade inflammation secondary to continuous antigenic stimulation (19), whose source may be exogenous, like a pathogenic microorganism infection (20, 21), or endogenous (15–18), like post-translational-modified macromolecules (15). Population studies incorporate the notion that the immune response depends on environmental exposure and how it interacts with endogenous variables. In fact, diet, exercise, xenobiotic exposure, and other environmental factors may epigenetically affect the metabolic health of immune cells (22). Lifestyle factors, such as exercise and favorable dietary habits, positively affect the immune system (22), while poor nutrition and reduced muscle mass may predispose an individual to a proinflammatory condition (23).

### Innate Immune Response and Inflamm-Aging

Age-related remodeling of innate immunity modifies the homeostasis of NK cells, neutrophils, and monocytes/macrophages (24). NK cells from the elderly exhibit impaired perforin release upon stimulation and granule exocytosis (25, 26). It reduces the elimination of senescent cells, which, in turn, promotes senescent cell accumulation in aged tissue. Moreover, aging reduces the frequency of circulating NK p46<sup>+</sup> cells, a modulatory cell subset involved in the resolution of inflammation and elimination of effector cells (27, 28).

Neutrophils and macrophages are classically classified as part of innate immunity and possibly comprise the most important effector cells against bacterial infections. It is thought that age

is accompanied by a decline in production and secretion of most chemokines, including those responsible for neutrophil and monocyte chemoattraction (29). The absolute number of neutrophils seems to be maintained while the number of monocytes increase with age (30, 31). However, the function of these cells may be impaired among the elderly (32). The final consequence is that the delayed resolution of inflammation may be associated with age-related remodeling of neutrophils and macrophages (29).

In addition to their phagocytosis' capabilities, neutrophils are capable of releasing a mesh-like structure under specific circumstances, called neutrophil extracellular traps (NET), in an attempt to physically delimitate the pathogenic agent, mainly microorganisms, and facilitate its contact with microbicidal peptides and enzymes (33). NET is composed of a decondensed chromatin meshwork imbedded with granule proteins with antimicrobial properties. NET may also work as a physical path for immune cell migration to the inflammatory site (34). Neutrophil function is impaired in both animal models and humans with aging. Hazeldine et al. (35) observed that older adults have less IL-8 production, LPS-induced NET release, and cell migration compared to younger counterparts, probably secondary to an impaired signal transduction. Microbicidal killing, phagocytic activity (36), and degranulation capacity (37) of neutrophils are also reduced in the elderly. In addition, the same group investigated the migration pattern of neutrophils obtained from older compared to young adults. They observed that neutrophils from older subjects migrated with less accuracy than those from younger subjects. By inaccurately meandering among healthy tissues, neutrophils from the elderly inadvertently release more neutrophil proteinase that may contribute to tissue damage and systemic inflammation.

Reactive oxygen species (ROS) are free radicals produced after oxidative bursts in phagosomes, which are pivotal for the microbicidal function of phagocytes (38). In fact, ROS do not just directly contribute to the bacterial clearance, but additionally can trigger NET formation. The free radical ROS production by neutrophils in older adults is decreased (39, 40). Interestingly, polymorphonuclear leucocytes from the elderly are less capable of modulating the triggering receptor expressed on myeloid cell-1 (TREM-1)-induced oxidative bursts, suggesting that TREM-1 signal transduction altered with aging may be one of the mediators of the decrease in microbicidal potential of innate immune cells in older adults (41).

Animal models of premature immunosenescence have also shed some light into age-related remodeling of the immune system. Guayerbas et al. (42) described a mouse model of premature immunosenescence based on the demonstration of early decline of immune parameters and behavioral tests in Swiss outbred mice. Mouse model-derived peritoneal leukocytes exhibited reduced proliferative response, impaired NK activity, and increased *in vitro* TNF- $\alpha$  production compared to control mice (42). In addition, mouse model-derived macrophages of premature models were less functional with a striking loss of microbicidal activity (43).

The mice model of premature immunosenescence was refined and new models were developed as well (44, 45). Apparently,

the key phenomenon are the oxidative and inflammatory stresses, which, not without reason, are associated with several non-communicable chronic diseases prevalent among the elderly (44, 46). In fact, spleen and thymus cells from prematurely immunosenescent mice models have decreased antioxidant defenses and significantly increased oxidants and pro-inflammatory cytokines production (44–46). Interestingly, the antioxidant vs. oxidant imbalance observed in prematurely immunosenescent mice was similar to the one observed in old wild-type animals (44, 47). Hence, lab tests determining the oxidative burst profile of phagocytes (e.g., nitro blue tetrazolium test, dihydrorhodamine oxidation,  $O_2^-$  and  $H_2O_2^-$  production by chemoluminescence, etc.) may be useful for assessing inflamm-aging features (4).

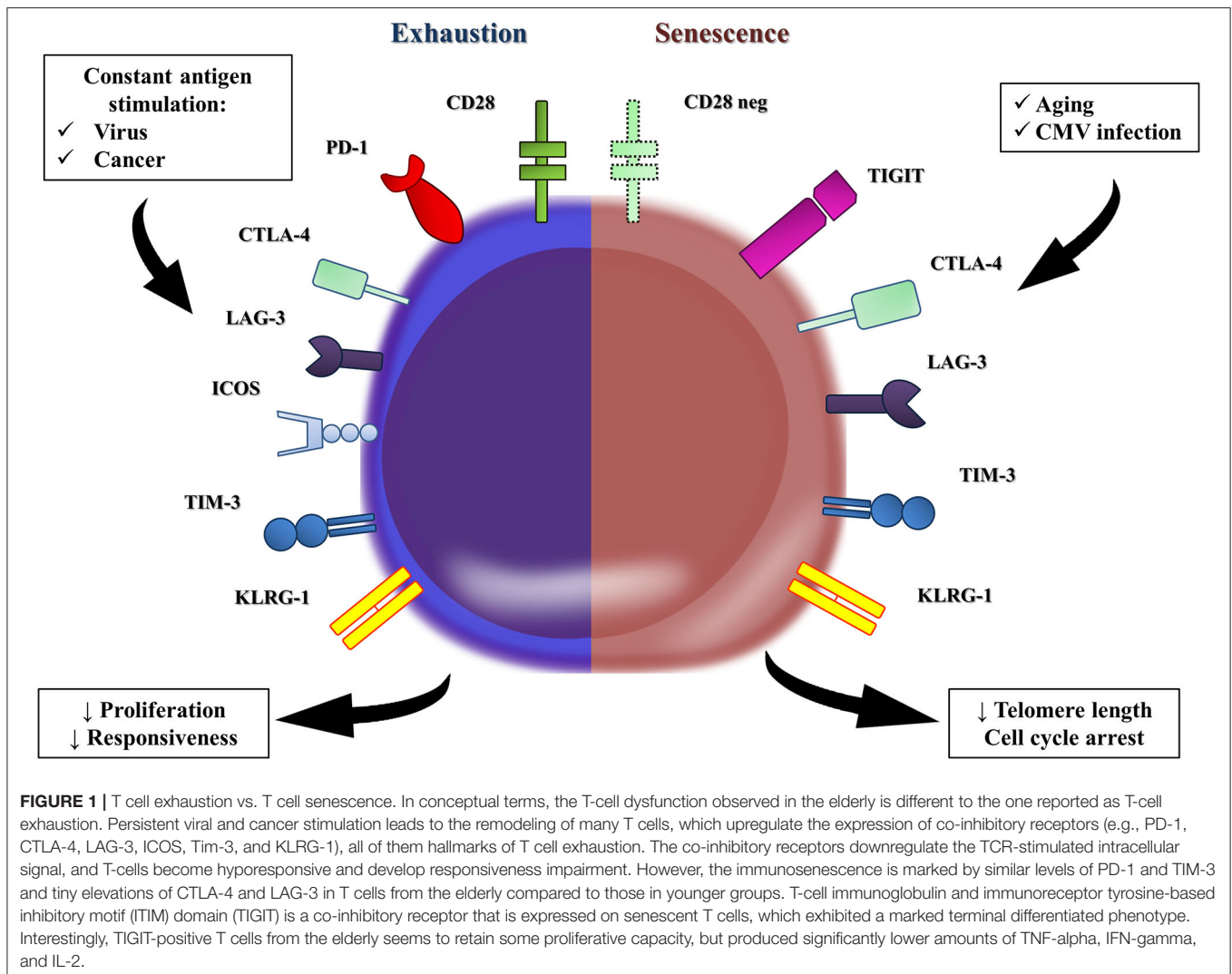
The state of chronic inflammation has to be counter-balanced by anti-inflammatory molecules (48). When not under control, the low-grade inflammation loses its defense role and turns into a damaging state to the whole organism (49). The practical consequence is that inflamm-aging is deleterious to human health, predicts frailty, and is associated with higher mortality rates (50–52).

## Remodeling of the Adaptive Immune System With Aging

Remodeling of the adaptive immune response also occurs with aging. Thymic involution and hematopoietic stem cell insufficiency play important roles in immunosenescence of adaptive immunity (53). In general, elderly individuals are less able to respond to neo-antigens, due to the reduction of new thymus-emergent T cells, though homeostatic proliferation can partially sustain the richness of the TCR repertoire (54, 55). Moreover, peripheral T cells usually present a reduced absolute number in aged individuals with an inverted CD4:CD8 ratio and expansion of terminally differentiated effector memory T cells (56, 57), associated with impaired proliferation ability, telomerase activity, and intracellular signaling (58, 59). Furthermore, most adult regulatory T lymphocytes are a terminally differentiated highly suppressive apoptosis-prone population with a limited capacity for self-renewal (60). This finding might explain, at least in part, the occurrence of age-related autoimmune conditions. In addition, the imbalance between innate and adaptive immunity may disturb the fine regulation of the effector immune response, leading to a severe acute pro-inflammatory state that may lead to organ rejection in transplanted patients (61, 62).

While naïve T and B cells become dysfunctional with aging, memory T and B cells' function is relatively maintained (63–65). In fact, naïve T lymphocytes obtained from the elderly present impaired cell binding of the immune synapse (66), reduced signal transduction (67), dysregulation of cytoskeletal function (68), defective protein glycosylation and activation (69), and insufficient IL-2 production (70).

Some authors advocate that age-related T-cell dysfunction is different from T cell exhaustion, a state of low cell responsiveness mediated by chronic conditions, such as viral infections and malignancies (**Figure 1**) (71). Constant antigen stimulation



progressively exhausts T cells by gradually upregulating the expression of inhibitory checkpoint receptors (e.g., PD-1, CTLA-4, LAG-3, ICOS, Tim-3, and KLRG-1) on CD4<sup>+</sup> T cells (72), which, in turn, downmodulate TCR-induced intracellular signaling (73). Interestingly, despite this conceptual difference between immunosenescence and T cell exhaustion, most of those cell exhaustion surface hallmarks are observed on dysfunctional immunosenescent cells, suggesting that these two phenomena share many mechanisms (54).

Exhausted T-cells accumulate over time (67, 74–77). Shimada et al. (74) demonstrated both gene and protein hyper expression of PD-1 and CTLA-4 in cells from old male C57BL/6 mice compared to young controls. Most PD-1<sup>+</sup> T cells were quiescent and presented an anergic effector memory phenotype with impaired proliferative response to mitogens (74). Similarly, Lee et al. (76) reported the accumulation of Tim-3<sup>+</sup> murine T cells with impaired proliferative capacity with aging.

Literature discussing T cell exhaustion and immunosenescence in humans is scarce, though. Song et al. (77)

described an elevated number of TIGIT<sup>+</sup> CD8<sup>+</sup> T cells from old adults, another hallmark of cell exhaustion apparently associated with immunosuppressant features in neoplasm or chronic infection mouse models (78, 79). TIGIT<sup>+</sup> CD8<sup>+</sup> T cells from old individuals seem to retain a proliferative capacity, although they impaired TNF-alpha, IFN-gamma, and IL-2 *in vitro* production and increased susceptibility to apoptosis (77). Therefore, we hypothesize that evaluation of the proliferative response to mitogens and *in vitro* cytokine production may be indirect ways to assess age-related remodeling of the immune system.

In regards to B cell compartment, vaccine trials suggest that B cell repertoire abridge over time, foremost observed in frail patients (80, 81). In addition, B cells from the elderly present both impaired antibody production and class switch recombination (82). Class switch recombination and immunoglobulin somatic hypermutation are crucial for humoral immune response and occur in mature B cells mediated by activation-induced cytidine deaminase, amongst other mediators (82, 83). Similarly, activated B cells from old mice have less activation-induced cytidine

deaminase expression and reduction of class switched antibodies (84, 85). Interestingly, *in vivo* activated CD4<sup>+</sup> T cells from old-aged individuals showed increased dual-specific phosphatase 4 (DUSP4) transcription, which, in turn, negatively correlated with antigen-specific B cells' expansion. Silencing of DUSP4 restored CD4<sup>+</sup> T cell-induced B-cell differentiation, suggesting that B cell dysfunction observed with aging is T cell-dependent. **Table 1** summarizes the main physiologic modifications of the immune system in the elderly.

## IMMUNE RESPONSE, IMMUNOSENESCENCE, AND COVID-19

Coronaviruses are a large family of viruses that cause upper and lower-respiratory tract illnesses in humans. SARS-CoV-2 is transmitted predominantly via respiratory droplets. Clinically, patients frequently present with fever, cough, myalgia, and fatigue (95). In a subset of patients, mainly elderly individuals, SARS-CoV-2 was shown to lead to bilateral pulmonary diffuse alveolar damage that may progress to acute respiratory distress syndrome (96, 97). Following the pulmonary phase, patients with poor outcome frequently evolve a life-threatening cytokine storm syndrome, characterized by bursts of pro-inflammatory cytokines and chemokines in the serum (96, 98). The uncontrolled systemic inflammation causes endothelial injury and activation of coagulation cascade. The consequence is an explosive process of disseminated intravascular coagulation and consumption of coagulation factors that leads to organ damage and death.

### Innate Immune Response and COVID-19

The innate immune response is the first level of response in the detection and clearance of a viral infection. In SARS-CoV-2, the spike protein (S) mediates the attachment, fusion, and entry of the virus in human cells (99). The protein S strongly binds to angiotensin-converting enzyme 2 receptor leading to the attachment of the virus to the host cell (99). The successful entry needs the priming of the S protein by TMPRSS2, a human cellular serine protease (100). Once in the host cell, SARS-CoV-2 can be detected by macrophages, which orchestrate the production of a pro-inflammatory microenvironment that inhibits viral replication, stimulates adaptive immunity, and recruits other immune cells to the site of infection.

Macrophages from elderly lungs may have a more pronounced production of IL-6 and other pro-inflammatory cytokines in response to stimuli (101). It is possible that IL-6 has a critical role in the immune response of the elderly that mounts against SARS-CoV-2 (102). IL-6 helps the differentiation of Th17 lymphocytes, but inhibits the production of Interferon- $\gamma$ , which is necessary for the activation of CD8<sup>+</sup> cells (102). In addition, IL-6 contributes to a pro-inflammatory microenvironment at the lung that impacts the integrity of the air-blood barrier (103). Patients with severe COVID-19 have a higher IL-6/Interferon- $\gamma$  ratio than those who present with a moderate disease, which could be related to the cytokine storm leading to lung injury (104–107). Indeed, patients with severe COVID-19 frequently have

lower absolute numbers of Interferon- $\gamma$  producing CD4<sup>+</sup> T cells compared to patients with moderate disease (108). Then, when patients with COVID-19 enter the immune dysregulation phase, the increase in IL-6 leads to a relative immunoparalysis that may impair the clearance of SARS-Cov-2 (98). Elderly patients with COVID-19 often present with a severe dysregulation of pro-inflammatory cytokines, such as IL-6 and IL-1  $\beta$ , which may result in worse outcome (105). Drugs that uncouple IL-1 $\beta$ /IL-1R signaling (anakinra) or IL-6/IL-6R signaling (tocilizumab) may have an immunomodulatory potential and are hypothesized to attenuate the dysfunctional immune response during the hyperinflammatory phase of COVID-19 (98, 109). In fact, some reports suggest that infusion of anakinra (109, 110) and tocilizumab (111) may improve the disease course in patients with severe COVID-19 presentation.

Neutrophils have traditionally been considered the primary immune cells active in the defense against bacterial infections. More recently, neutrophils' role in viral infection has emerged based on observations of its correlation with viral infection severity and neutrophils' biological ability to recognize viruses (via viral PAMPs) and respond to them with specific effector functions (112). Patients with severe COVID-19 more frequently present with a high neutrophil-to-lymphocyte ratio (113), in part driven by the relative lymphopenia or lymphocyte exhaustion. In addition, patients with severe COVID-19 are more susceptible to a greater burst of systemic inflammation and secondary bacterial infection that can lead to the increment of neutrophils. It is unclear if changes in neutrophils are only a reflection of the overall immune activation in COVID-19 or if they play a direct pathogenic role. Lastly, NK cells are less functional in the elderly, and studies have shown that severe COVID-19 patients have further depleted peripheral NK cell counts in comparison with mild cases and healthy controls (114–116). Generally, NK cells are capable of recognizing infected cells and of triggering direct cell toxicity. Further studies are needed to clarify how SARS-CoV2-infected cells interact with NK cells and if any apoptosis or downmodulation occurs and prevents the effective elimination of infected cells.

The airway epithelium is a physical barrier to pathogens (117). The integrity of the air-blood barrier is essential for the maintenance of lung homeostasis and represents an important branch of innate immunity (118). The invasion of the airway epithelial by SARS-CoV-2 may break the barrier integrity, triggering a vicious cycle of inflammation and tissue injury that is more pronounced among the elderly (119). Presumably, the same remodeling process that occurs in the immune system also happens at the lung microenvironment with aging (120). Data from animal models suggest that senescent lungs are more susceptible to settle a pro-inflammatory response when injured (121). In fact, bronchoalveolar lavage obtained from elderly patients with acute respiratory distress syndrome present with higher pro-inflammatory cytokine levels when compared to younger counterparts, suggesting that the lung may represent a small fraction of the inflamm-aging that occurs at the systemic level (122). This local phenomenon may help to explain why elderly patients with COVID-19 are more susceptible to a

**TABLE 1** | Summary of the age-related physiologic modifications of the immune system.

Cell	Immune response	Aging functional impairment	Clinical impact	References
NK	Innate	<ul style="list-style-type: none"> <li>• ↓ Perforin degranulation</li> </ul>	<ul style="list-style-type: none"> <li>• Wound healing</li> <li>• Susceptibility to infection</li> <li>• Susceptibility to cancer</li> </ul>	(26)
Neutrophil	Innate	<ul style="list-style-type: none"> <li>• ↓ Phagocytosis</li> <li>• ↓ ROS production</li> <li>• ↓ Intracellular killing</li> <li>• ↓ NET</li> <li>• ↓ Migration</li> </ul>	<ul style="list-style-type: none"> <li>• Wound healing</li> <li>• Susceptibility to infection</li> </ul>	(35, 86, 87)
Basophil	Innate	<ul style="list-style-type: none"> <li>• Delayed degranulation</li> </ul>	<ul style="list-style-type: none"> <li>• Susceptibility to helminth infection</li> <li>• Decrease in allergy parameters</li> </ul>	(88–90)
Eosinophil	Innate	<ul style="list-style-type: none"> <li>• Delayed degranulation</li> <li>• ↓ Superoxide production</li> </ul>	<ul style="list-style-type: none"> <li>• Susceptibility to helminth infection</li> <li>• Decrease in allergy parameters</li> </ul>	(88, 91)
T cell	Adaptive	<ul style="list-style-type: none"> <li>• ↓ Repertoire</li> <li>• Relative decrease of naïve T cells</li> <li>• Relative increase of memory T cells</li> </ul>	<ul style="list-style-type: none"> <li>• Impaired response to vaccination</li> <li>• Susceptibility to infection</li> </ul>	(54–60)
B cell	Adaptive	<ul style="list-style-type: none"> <li>• ↓ Repertoire of antibodies</li> </ul>	<ul style="list-style-type: none"> <li>• Impaired response to vaccination</li> <li>• Susceptibility to infection</li> </ul>	(80–82, 84, 85)
Dendritic cells	Adaptive	<ul style="list-style-type: none"> <li>• ↓ Antigen presentation</li> <li>• ↓ Tolerant response</li> </ul>	<ul style="list-style-type: none"> <li>• Susceptibility to skin and mucosal infection</li> <li>• Susceptibility to autoimmune disorder</li> <li>• Impaired response to vaccination</li> <li>• Transplant rejection</li> </ul>	(31, 92–94)

Arrow means diminished.

more severe lung injury that implies loss of lung function and respiratory failure (123).

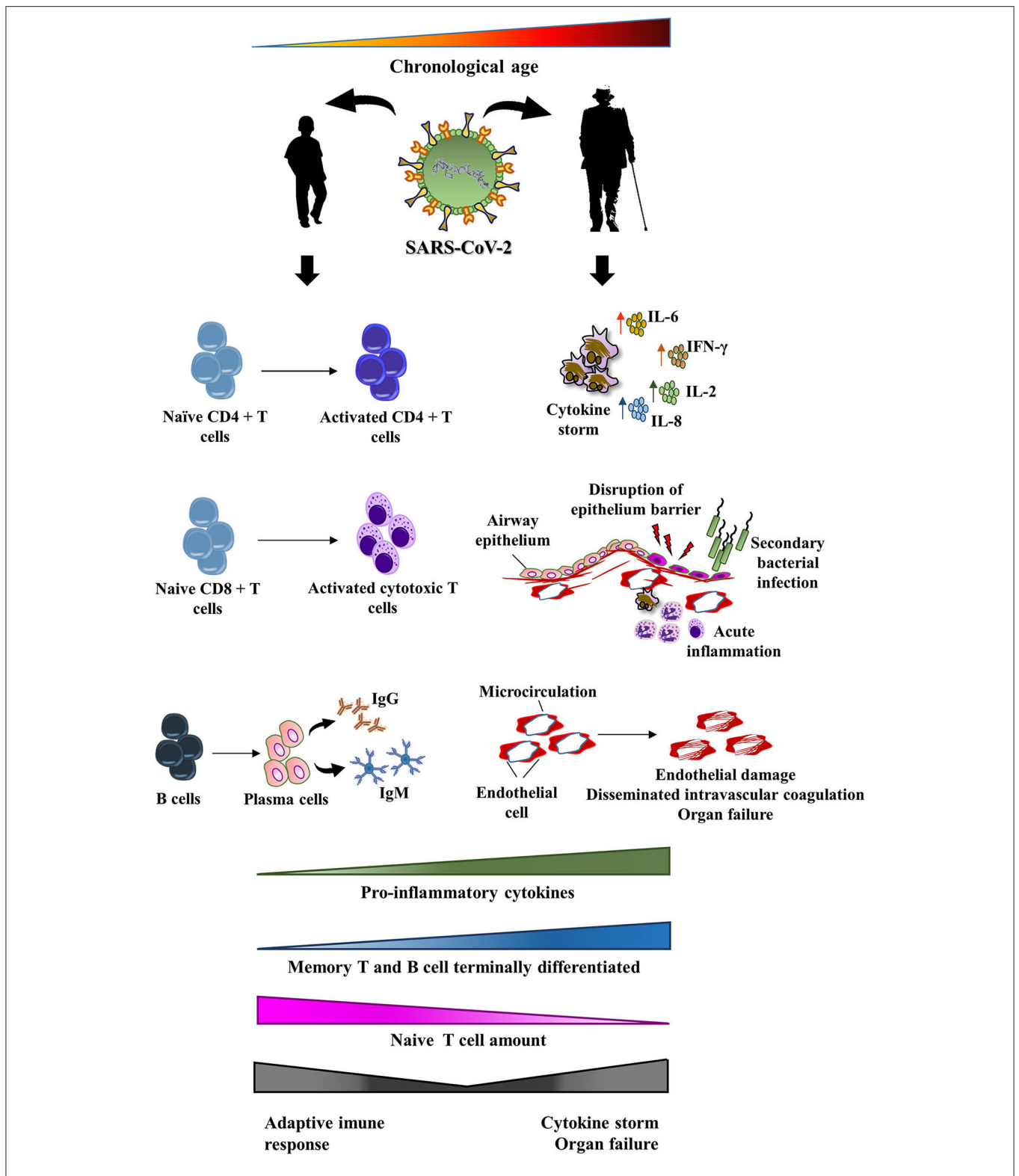
## Adaptive Immune Response and COVID-19

The initial inflammation in COVID-19 is propitious to the activation and differentiation of CD4+ and CD8+ T cells. The ideal final output is the development of an effective and specific immune response, involving both the production of anti-SARS-CoV-2 antibodies and the deployment of a large number of viral-specific cytotoxic lymphocytes that will ultimately eliminate the virus and achieve clinical recovery. In fact, when compared to severe H7N9 disease, reduced pro-inflammatory cytokines and chemokines were found in COVID-19 patients with good prognosis, reinforcing the idea that adaptive immunity is a key factor for a favorable outcome (124).

Thevarajan et al. (124) described a kinetic of the immune response in a 47-year-old woman with COVID-19 who presented a favorable outcome. They evidenced a persistent increase in antibody-secreting cells, follicular helper T cells, activated CD4+ and CD8+ T cells, and immunoglobulin M (IgM) and IgG antibodies that bound to SARS-CoV-2. The peak of both antibody-secreting cells and follicular helper T cells was markedly higher in the patient compared to healthy controls and both cell subsets were persistently increased during convalescence (day 20). The experience from the SARS epidemic of 2003 showed that convalescent SARS patients present with neutralizing antibodies against S protein (125). The sera stored from convalescent patients from the SARS epidemic of 2003 can cross-neutralize the S protein-mediated SARS-CoV-2 entry in patients with COVID-19 (100). This data raises the possibility that the S protein could be an important antigen to vaccine protocols. In fact, in analogy to the SARS epidemic of 2003, convalescent patients with SARS may present IgG and neutralizing antibodies peaking at 4

months after the disease and detectable up to 2 years afterwards, suggesting that memory B cells can be elicited during coronavirus infection (125).

Cellular immune response may play a critical role in the adaptive immune response in patients with COVID-19. Thevarajan et al. (124) observed the emergence and rapid increase in activated CD8+ T cells at days 7–9 after infection preceded the resolution of symptoms of one young patient with a good prognosis. Conversely, elderly patients and those requiring intensive care unit support presented a dramatically reduced number of CD4+ and CD8+ T cells (126). Lower total amounts of T cells, CD4+, and CD8+ T cells negatively correlated with patient survival (126). Diao et al. (126) noted that T cell absolute counting were negatively correlated to serum IL-6, IL-10, and TNF- $\alpha$  concentration in patients with COVID-19, suggesting that the failure of the adaptive immune response and the increase of pro-inflammatory cytokine may be associated with worse survival. It is also possible that increased IL-6 leads to a reduction in CD4+ T cells and NK cells in patients with COVID-19 and immune dysregulation (98). In fact, some pro-inflammatory cytokines, such as IL-6, may block the antiviral immune response by favoring T cells' exhaustion (102). Diao et al. further characterized the exhaustion status of 14 patients with COVID-19. They noted an increasing PD-1 and Tim-3 expression on T cells as patients progressed from prodromal to overtly symptomatic stages (126). Whether this reflects the emergence of exhaustive T cells with a defective capacity to eliminate the virus or a normal evolution of the immune response against the virus remains to be determined. If greater severity of disease is seen in patients with a higher frequency of exhausted T cells, a potential therapeutic approach could be attempted to block those inhibitory receptors, unleashing the T cell response against the virus.



**FIGURE 2 |** Potential impact of immunosenescence on the pathogenesis of COVID-19. SARS-CoV-2 infection may affect all age ranges, from children to the elderly. Among children, a mild-symptom disease usually occurs. They frequently crush the viral infection through an effective adaptive immune response. However, the remodeling of the immune system that happens with aging may lead to modifications in both adaptive and innate immunity. The final result of these changes may trigger a maladaptive immune response against SARS-CoV-2. In fact, the elderly are an at-risk group to a more aggressive disease that includes cytokine release syndrome, disruption of intrinsic lung defense, secondary bacterial pneumonia, endothelial injury, and end organ damage.

The diminished naïve T cell repository observed among the elderly may dramatically affect the adaptive immune response against SARS-CoV-2, since fewer naïve T cells will be capable of responding to new infections (127, 128). Furthermore, there is also a reduction in the number of regulatory T cells with aging, which help keep the immune system under tighter control (129). Since the elderly frequently present with a remodeled adaptive immune response, they may fail to enhance antibody production. Instead, a pro-inflammatory tone characteristic of inflamm-aging may convert the immune response of patients with COVID-19 in a life-threatening cytokine storm. On the contrary, young patients usually present with an enormous number of naïve T cells that had never encountered a virus. Then, naïve T lymphocytes are rapidly primed and innate immunity does not overwhelm the adaptive immune response. This may explain, at least in part, the favorable prognosis observed among young subjects. **Figure 2** shows the possible relationship between immune response in patients with COVID-19 and the remodeling process that takes place in the immune system with aging.

## CONCLUSION AND FUTURE PERSPECTIVES

The immune system faces a complex adaptation over time, culminating in functional and phenotyping alterations. The influence of age-related remodeling of the immune system is clinically observed within elderly features (e.g., frailty syndrome) that can be assessed by lab tests. Despite several promising

experimental methods, none are clinically validated so far, but certainly shed some light on the pathophysiology of immunosenescence. Novel mechanisms of inflamm-aging may rise in the near future, leading to new potential therapeutic targets for age-related disorders. Different from the chronological age, the “immune age” obtained by population studies may accurately reflect the molecular and cellular changes that occur over time (130). Immunosenescence may explain the lethality amongst the elderly with COVID-19 with a combination of ineffective T cell response, failed antibody production against SARS-CoV-2, and inflamm-aging that terribly collapses the homeostasis, leading to severe organ dysfunction. The biomarkers that are hallmarks of the remodeled immune response have been raised as new potential targets in patients with COVID-19. More studies are warranted to investigate how to help the elderly to elicit a functional adaptive immune response, as well as to diminish the harmful pro-inflammatory state of the disease.

## AUTHOR CONTRIBUTIONS

LC: conception and design, review of the literature, composition of the manuscript and final approval. SP, JA, and PC: design, critical review of the literature, composition of the manuscript, and final approval. LR: conception and design, selection of notable articles for review, critical review of the literature, composition of the manuscript, clinical, and translational orientation and final approval. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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