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LETTER TO THE EDITOR

Age-related decline of de novo T cell responsiveness as a cause of COVID-19 severity

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To the Editor,

So far, little attention has been paid to the link between immunosenescence and the dramatic mortality rate of coronavirus disease 2019 (COVID-19) in older age groups. Indeed, the number of cases of COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is very low among children and teenagers, in contrast to the increased frequency in adults and the elderly, who are also more at risk of developing very serious symptoms and death (Guan et al. 2020; Wu and McGoogan 2020). As shown in Fig. 1, a similar epidemiological profile was observed during previous coronavirus (severe acute respiratory syndrome coronavirus 1, SARS-CoV-1, and Middle east respiratory syndrome coronavirus, MERS-CoV) outbreaks (Jia et al. 2009; Salamatbakhsh et al. 2019). Notably, the same trend was also noted during West Nile virus and, with some exceptions in very young children, *Ebolavirus* outbreaks (Bower et al. 2016; Hayes et al. 2005). Likely this phenomenon is multifactorial. For instance, in elderly individuals with severe COVID-19, associated comorbidities are much more prevalent (Guan et al. 2020). In addition, the progressive accumulation of senescent cells during life may play a role in the vulnerability of old people to COVID-19, resulting in reduced functionality of the organs, such as the lungs, and facilitating conditions for the development of fibrosis. Moreover, senescent cells can generate a pro-inflammatory environment, referred to as SASP (for senescence-associated secretory phenotype), which includes many inflammatory cytokines (e.g., interleukin-6) and contributes to the basal hyperinflammatory status characteristic of the old person. This hyperinflammatory status might influence the expression of ACE2, CD147, cyclophilins, CD26, and other CoV-associated molecules in human tissues, thus favoring viral entry (Radzikowska et al. 2020). It likely also constitutes an already unbalanced pro-inflammatory background, on which the development of an exacerbated inflammatory response and acute respiratory distress syndrome may be facilitated upon SARS-CoV-2 infection.

An undoubtedly common important factor for the rapid spread of these viruses is that they are emerging pathogens introduced from scratch into the human population never previously exposed to them. The induction of de novo immune responses against such viruses relies on their recognition by naïve, and not memory, T cells. Since, the pool of naïve T cells decreases with age, reaching very low

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numbers in the elderly (Briceno et al. 2016), we believe that this may contribute to the age-dependent development of the disease and to the greater severity of symptoms and death in the elderly, characterizing these emerging infections.

Indeed, several pieces of evidence highlight the importance of T cell responses for CoV control. Results from murine models show that virus-specific $CD4^+$ and $CD8^+$ T cells are essential for CoV clearance (Chen et al. 2010; Zhao et al. 2010), which is, instead, delayed in mice lacking T cells or in old animals experiencing an age-dependent decrease of virus-specific $CD8^+$ T cells (Chen et al. 2010; Zhao et al. 2014; Zhao et al. 2011). The appearance of interferon (IFN)-γ secreting $CD4^+$ and $CD8^+$ T cells specific for the structural proteins of CoV has been observed in the lungs of infected mice and is associated with viral clearance (Chen et al. 2010; Zhao et al. 2009). Lung-infiltrating CoV-specific $CD8^+$ T cells display high cytotoxic potential (Zhao et al. 2010; Zhao et al. 2009), while depletion of $CD4^+$ T cells results in a diminished neutralizing antibody response along with higher viral titers in the lungs (Chen et al. 2010). Together, these data suggest that $CD8^+$ T cells are important for the killing of CoV-infected cells and $CD4^+$ T cells play a key role in the support of CoV-specific antibody responses and in the cell recruitment in the lung (Chen et al. 2010; Zhao et al. 2010; Zhao et al. 2009).

In humans, MERS-CoV, SARS-CoV-1, and SARS-CoV-2-infected patients with severe manifestations exhibit a pronounced T cell loss (Jiang et al. 2020; Li et al. 2004; Liu et al. 2020; Min et al. 2016; Qin et al. 2020; Wang et al. 2020; Wu et al. 2020) and $CD4^+$ and $CD8^+$ T cell numbers negatively correlate with the levels of pro-inflammatory cytokines associated with worst prognosis (Diao et al. 2020). Importantly, T cell count normalization coincides with the improvement of clinical conditions (Diao et al. 2020; Gu et al. 2005; Li et al. 2004). It has also recently been shown that activated effector $CD4^+$ and $CD8^+$ T cells appear in the blood of COVID-19 subjects a few days after the development of symptoms and precede their resolution, likely contributing to the infection clearance (Thevarajan et al. 2020). Moreover, the amount of virus-specific $CD4^+$ T cells directly correlates with humoral responses (Grifoni et al. 2020; Ni et al. 2020), and a larger proportion of tissue-resident $CD8^+$ T cells with effector potential has been reported in the bronchoalveolar lavage fluids of patients with moderate infection compared with severely ill subjects (Liao et al. 2020), whose circulating T cells are instead characterized by high expression of inhibitory checkpoints (Diao et al. 2020).

Naïve T cells represent the primary source to mount a necessary adaptive immune response against emerging viruses, such as CoV. However, the quantity of naïve T cells is progressively reduced and lymphopoiesis compromised with old age, due to thymic involution as well as defects of the lymphopoietic progenitors (Fali et al. 2018). The reduced naïve T cell pool may affect the global TCR repertoire and its diversity, and thus the capacity of an old immune system to detect neoantigens. Moreover, elderly people show a decreased number of naïve T cells, and the intrinsic properties and capacity of these cells to be activated and to differentiate are affected (Fali et al. 2019; Li et al. 2012). As a consequence, old individuals present with reduced priming capacity and impaired responses against neoantigens (Briceno et al. 2016; Nikolich-Zugich 2014). In addition, some of the comorbidities associated with aging are characterized by low naïve T cell frequencies (Rattik et al. 2019) and by metabolic alterations which may, in turn, negatively affect T cell metabolism and functionality (Nicoli et al. 2018). Overall, these observations indicate that successful generation of primary responses against novel viruses from the naïve T cell pool is compromised with aging and associated comorbidities, likely contributing to the age-related severity of emerging infections, such as that caused by SARS-CoV-2.

It is however important to highlight that the protection conferred by functional epitope-specific T cells should not be confused with the hyperactivation of the immune system that accounts for the severe tissue immune injury in COVID-19 patients with fatal prognosis. This detrimental inflammatory process, which is a further hallmark of aging, is the likely consequence of innate immune mechanisms. Although a high proportion of hyperactivated T cells have been found in COVID-19 subjects, the plasmatic cytokine profile, but not the T cell activation levels, distinguished between non-severe and severe SARS-CoV-2-infected subjects (Qin et al. 2020). Considering the relatively high median age of these patients, it is reasonable to speculate the presence of a low number of epitope-specific naïve T cells that could be primed. This suggests that most T lymphocytes infiltrating the lungs are not virus-specific but potentially harmful. If confirmed, this scenario would resemble that of other infections, such as HIV, where disease progression, although directly related with T cell hyperactivation, is inversely related with the number and functions of virus-specific T cells (Appay and Sauce 2008; Nicoli et al. 2016).

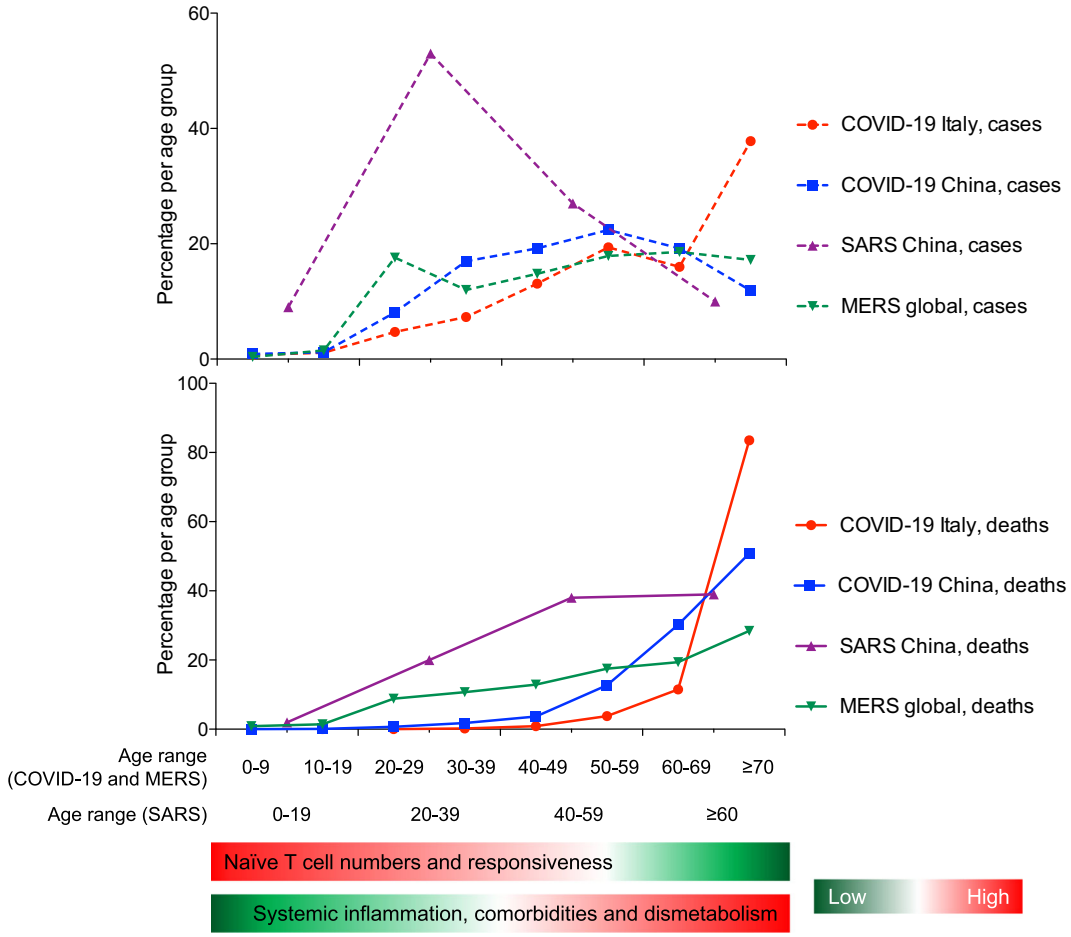

Fig. 1 Age-distribution of numbers of cases and deaths during coronavirus outbreaks and age-associated changes in immune profile. The age range for COVID-19 (Italy and China) and MERS is different from that of SARS due to a different aggregation in source datasets. Data for COVID Italy are from the COVID-19 Task Force of the Department of Infectious Diseases and the IT Service Istituto Superiore di Sanità, update of April 13, 2020; data for COVID China are from Wu et al. 2020; data for SARS China are from Jia et al. 2009; data for MERS global are from Salamatbakhsh et al. 2019

We think that the preservation of the naïve T cell pool and de novo T cell responsiveness may thus constitute a future priority to be addressed by researchers for the development of preventive strategies against emerging infections. Also, the enhancement of virus-specific T cell responses by immunotherapeutics avoiding unspecific activation and inflammation may be important in already infected patients before the onset of severe symptoms to prevent disease exacerbation and promote viral clearance. Finally, the activation of T cell responses, which have been shown to be long-lasting after SARS-CoV-1 and MERS-CoV infections, should also be considered in the development of vaccines against COVID-19. However, frail and elderly subjects have poor post-vaccination immune responses. For this reason, a great attention should be paid to mechanisms that impair SARS-CoV-2-specific immune responses, as the same mechanisms could negatively affect the effectiveness of future COVID-19 vaccines in these populations.

Code availability Not applicable

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Compliance with ethical standards

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