JIM Editorial

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Why does severe acute respiratory syndrome coronavirus 2 attack the aged more severely?

In the July 2020 issue of the *Journal of Internal Medicine*, Wu et al. conducted a retrospective study including 280 confirmed cases of COVID-19 at the early stage of the pandemic. They found that comorbidity, early antiviral treatment, and age were three major risk factors resulting in the poor prognosis of COVID-19 patients [1]. Although the benefits of addressing comorbidity and early antiviral treatment are clear, the impact of age is more complex. The clinical trial indicated that people older than 65 years have a higher risk of progressing to severe disease. However, there is a discrepancy in children's low mortality despite their immature immune systems being as weak as those of older adults [2].

Recently, Woodall et al. conducted an in vitro study using nasal epithelial cells (NECs)—the primary target of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—to study the age-related immune response to SARS-CoV-2 infections, ruling out the confounding factors in the immune system. They found age-specific nasal epithelial responses across different age groups [3]. The authors first identified characteristics of pediatric (<12 years), adult (30–50 years), and older adult (>70 years) cohorts. The adult cohort exhibited a higher abundance of basal/progenitor subtypes compared to pediatric cultures. Notably, NECs from pediatric subjects had the most goblet 2 cells, whereas basaloid-like cells were predominant in NECs from older adults, indicating a shift from goblet 2 cells to basaloid-like cells. Additionally, the receptors for SARS-CoV-2 entry into cells—transmembrane serine protease 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2) [4]—were differently expressed in pediatric (higher SARS-CoV-2 receptors expression in goblet 2 cells) and older adult cohorts (higher SARS-CoV-2 receptors expression in secretory and basal 2 cell types), suggesting that the virus targets are age-specific.

The authors then examined the speed of virus spread in varied age groups. Interestingly, they found a promotion of virus production in NECs from older adults compared to pediatric groups, including more virus-targeted cell types, more viral protein translation, and stronger total viral spread. As the cellular landscape of NECs is age-stratified, the authors reasoned that the pathological effect of SARS-CoV-2 infections is age-related and confirmed this hypothesis. They infected NECs from all three groups with SARS-CoV-2 and found negative effects on the morphology of NECs, including decreased culture thickness and epithelial integrity. Notably, damaged NECs in older adult cultures exhibited a compensatory effect, such as increased basal cell mobilization and epithelial escape. The escaped epithelial cells carried newly packaged viral particles, which may account for SARS-CoV-2 spread from the lung to other organs in older adults. Additionally, the results confirmed the upregulation of goblet 2 inflammatory cells, which are strongly associated with type I interferon (IFN) signaling, and downregulation of basal, secretory, and goblet cell populations in infected pediatric cultures. The IFN-activated state of pediatric airways was also observed in airway immune cells, exhibiting an overall anti-SARS-CoV-2 state [5]. In contrast, infected older adult cultures showed an increase in basal cell populations and an expansion of basaloid-like 2 cells, which are associated with tissue injury and fibrosis.

Next, to validate the in vitro NEC-based results with in vivo data, the authors analyzed eight scRNA-seq datasets obtained from the airways of COVID-19 patients across all age groups. The patient responses confirmed that goblet 2 inflammatory cells were induced and were the predominant type in the pediatric group after SARS-CoV-2 infection. An enrichment of the basaloid-like 2 cell cluster was identified in all age groups, with the most significant increase in the older adult group. Not surprisingly, with the integration analysis of existing in vivo COVID-19 datasets and the in vitro study, the authors confirmed an age-dependent action mode of both basaloid-like 2 and goblet 2 inflammatory cells in response to infection.

Lastly, the authors profiled the age-specific immune responses of NECs. Goblet 2 cells expressed high levels of entry receptors, especially the precursors of goblet inflammatory cells, named goblet 2 PLAU$^+$ cells. Once infected with SARS-CoV-2, goblet 2 PLAU$^+$ cells would shift to goblet 2 inflammatory cells, accompanied by upregulated expression of ACE2 and TMPRSS2. High viral reads and activated types I and II IFN signaling in goblet inflammatory cells confirmed this theory, making this cell type the central point of virus-induced immune cascade in COVID-19 patients. Surprisingly, the transmission ability of pediatric goblet inflammatory cells is relatively low, even though their original viral reads are high. This may be attributed to the anti-viral effect of goblet inflammatory cells. The authors further sequenced infected NECs and found that subgenomic SARS-CoV-2 RNAs of spike and ORF7a were more abundant in pediatric and adult samples than in older adult samples, both of which were representative of defective viral genomes and increased IFN production. Contrary to the pediatric cultures, SARS-CoV-2 infections in older adult NECs led to epithelial damage and activated the epithelial–mesenchymal transition repair pathway, and most importantly, the enriching basaloid-like 2 cells. The most severely infected and damaged basaloid-like 2 cells are probably fragmented and then release integrin beta 6 protein, which is associated with fibrotic lung disease and epithelial cancers. This is consistent with a single-cell transcriptomic research arguing that the entry of the virus into lung tissue can accelerate pulmonary fibrosis [6]. As the repair process is specific to older adults, the authors further applied a wound-healing assay to see whether this process would contribute to the stronger virus spread in older adult NECs. In this assay, SARS-CoV-2-infected older adult cultures exhibited a faster wound-healing rate than infected pediatric cultures. However, as a coin has two sides, the faster wound repair correlated with an increase in virus spread, as evidenced by more SARS-CoV-2-positive cells in wounded cultures.

All in all, the study published in *Nature Microbiology* concluded that the reason why pediatric patients show better resistance to SARS-CoV-2 infections than older adults is the higher abundance of goblet 2 inflammatory epithelial cells, which exert a strong IFN response and decrease with age [3]. This discrepancy in the landscape of NECs partially explains why children have a lower mortality rate, as the blunted IFN responses in the NECs have been reported to be associated with severe COVID-19 cases [7]. Of note, the authors solely discussed differences in NECs between children and the aged, but immunosenescence and chronic inflammation are inevitable as one ages and are critical in progression of SARS-CoV-2 infections [8]. Further studies should take these confounding factors into consideration and picture an overall immune landscape of SARS-CoV-2 infection.

Conflict of interest statement

The author declares no conflicts of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Yiwen Xie[1] & Hongcui Cao[1,2]

From the [1]State Key Laboratory for the Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, National Medical Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [2]Zhejiang Key Laboratory for Diagnosis and Treatment of Physic-Chemical and Aging-Related Injuries, Hangzhou, China

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Correspondence: Hongcui Cao, State Key Laboratory for the Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Rd., Hangzhou 310003, China.
Email: hccao@zju.edu.cn

