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Commentary

Differential expression of ACE2 in the respiratory tracts and its relationship to COVID-19 pathogenesis

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Since its initial outbreak in December 2019 in Wuhan, China [1], COVID-19 has quickly and firmly established itself as one of the most devastating global pandemics in history. Not only has it resulted in hundreds of thousands of lives lost worldwide, but it has also led to unprecedented damage to national economies and ways of life, which will take years to recover from. Medical and scientific communities have been racing to study the disease and find efficient strategies for cure and prevention. Enormous efforts and resources have been invested in the study of the disease, including the biology of the virus, as well as potential treatment options and vaccine development. Significant progress has been made with new findings contributing to the scientific literature on a daily basis.

But much is still unknown about the pathogenesis of the virus. Lung biopsy and autopsy studies have revealed that in many early-phase and non-fatal cases of COVID-19, pulmonary pathology is characterized mainly by alveolar proteinaceous fluid exudation and the accumulation of macrophages [2]. In severe or fatal cases, however, the core pathological change seems to be diffuse alveolar damage (DAD) with the formation of hyalinized membranes [3]. In addition, endothelial cell damage, thrombosis of small blood vessels [4], and superimposed bronchopneumonia [3] can be seen in a significant subset of these patients. From a demographic perspective, fatal SARS-CoV-2 infection has been seen in all groups of patients, but risks for increased disease severity and fatal outcome have been strongly correlated with advanced age, male gender, and underlying comorbidities [5, 6]. Elucidating the underlying mechanisms for this risk association may shed light on how to better treat patients to prevent death.

One promising research pathway has been the transmembrane angiotensin-converting enzyme 2 (ACE2), which has been identified as the receptor for SARS-CoV-2 attachment and entry. ACE2 could thus determine the outcome of infection, and accordingly, many investigators have been examining its role in the pathogenesis of COVID-19.

Previously, higher levels of ACE2 and transmembrane serine protease 2 (TMPRSS2) expression have been identified in the upper airways and the lung parenchyma [7, 8], corresponding to initial viral transmission and severe lung disease, respectively. These previous studies, however, do not demonstrate the exact cellular locations of these proteins. But in this issue of *EBioMedicine*, Ortiz Bezara et al. [9] took these findings further. In addition to single cell RNA-sequencing data analysis [Gene Expression Omnibus (GEO)], Bezera et al. conducted elegant immunohistochemical studies to examine the expression of ACE2 and TMPRSS2 in a series of archival upper and lower respiratory tract tissue sections. They confirmed that ACE2 expression tends to be highest in regions of the sinonasal cavity and pulmonary alveoli. And in the lungs, ACE2 protein was found on the apical surface of a small subset of alveolar type II cells and colocalized with TMPRSS2, a cofactor for SARS-CoV2 entry.

Their study, however, found no correlation between the distribution of these receptor proteins and disease severity. In other words, age, sex, and comorbidities—all factors associated with more severe outcomes - do not appear to be associated with an increase in ACE2 protein expression [9]. This finding differs from a recent study [10], and it is significant in several respects. For one, it reflects the complexity of COVID-19 pathology and pathogenesis. With the knowledge that ACE2 serves as the entry point for SARS-CoV-2 infection, it would be convenient to attribute more severe disease to higher viral load in affected cells due to easier viral entry (and thus, higher density of receptor). And this in turn may be associated with other known risk factors of disease severity such as advanced age, male gender, and existence of comorbidities. More importantly, if this were true, a drug that inhibits or blocks ACE2 would prove effective in treating patients. But so far, such a “targeted” therapy has not appeared.

To be clear, efforts to find a single molecular mechanism for disease progression *have* led to the development of successful targeted treatments for some cancers. But the progression and outcome of infectious diseases can be much more complex and depend on

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complicated host-pathogen interactions. On the pathogen (SARS-CoV-2 here) side, for instance, virulence, replicability and pathogenicity are determined by the nucleic acid sequence of the virus and dosage of the initial infection. On the host side, the issues are even more complex. For instance, the density of receptors can affect how efficiently a virus establishes initial infection and replication. Receptor density may also determine the severity of virus-induced direct cellular injury.

In COVID-19 in particular, this initial direct viral attack may play a significant role in damaging type II pneumocytes and vascular endothelial cells, as well as the degree of DAD at the tissue level. Past this point, however, we've learned that other host factors, like innate and acquired host immunity, take on greater importance. For example, both the activation of pulmonary macrophages and hyper-reactivity of a cytokine cascade have been observed in many severely ill COVID-19 patients, which suggests that COVID-19 pathogenesis may be linked to innate immunity, viral-specific antibodies, and T cell responses. Those factors may in turn be affected by features like the age and gender of a patient, as well as a patient's other underlying disorders.

This notion is supported by the findings of Bezara et al., though we acknowledge that the study was not conducted in COVID-19 patients. So, we still cannot exclude the possibility that SARS-CoV-2 infection modifies ACE2 expression in the respiratory tract of certain patients. Going forward, we must keep an open mind and hope that further host-level studies will yield more definitive answers to this complicated problem in COVID-19 pathogenesis.

Author disclosure

The authors have no conflicts of interest to declare.

Author contribution

Chunxiu Yang and Yueying Li: literature search and writing (These authors contributed equally). Shu-Yuan Xiao: design, writing, editing, and final proof.

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