Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

EDITORIAL

Do We Really Understand the Relationship Between Expression of ACE2 and Coronavirus Disease 2019 Lung Pathophysiology?

Chunxiu Yang, MD,[a,b] Yueying Li, MD, PhD,[a,b] Shu-Yuan Xiao, MD[a,b,c,*]

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become the largest pandemic for more than a year, leading to more than 200 million infections and contributing to massive losses of human lives and economic productivities worldwide. Recent development with the delta variant further complicated the control of this pandemic. In addition to acute illness in severe cases, long-term sequelae caused by COVID-19 are emerging,[1] including pulmonary fibrosis and possibly persistent immune-related disorders.[2] From clinical and pathologic observations, it is evident that the virus can cause systematic infection and functional abnormalities in multiple systems to various degrees.[3,4] Nevertheless, the upper and lower respiratory tracts remain the main target of infection by SARS-CoV-2, and viral pneumonitis is the predominant manifestation and cause of mortality in most of the severely ill patients.[5,6]

Clinically, symptomatic COVID-19 may be roughly divided to three stages[4] based on the manifestations. The earliest stage is characterized by influenza-like symptoms. In the second stage, patients can develop viral pneumonia with pulmonary inflammation and coagulation dysfunctions, with elevated inflammatory biomarkers. The final stage of COVID-19 can be characterized by fibrosis.[4] These three stages can occur consecutively or simultaneously. Since our first descriptions of lung pathology in patients with early COVID-19 and fatal cases, there have been many autopsy-based studies,[4,7] yielding a spectrum or patterns of histopathology of the lungs. The acute changes range from epithelial injury and loss, diffuse alveolar damages (DADs), to subsequent infiltration by mixed inflammatory cellular infiltration, including activated macrophages[5,7] with associated inflammatory cytokine release. Some authors described these as the following patterns[4]: the epithelial pattern of lung injury is the most common change, characterized by DAD with hyaline membrane formation, whereas the vascular pattern of lung injury features microthrombi and proteinaceous and fibrinous exudates, and the fibrotic pattern is typified by interstitial fibrosis.

It is believed that all these were initiated by attachment of SARS-CoV-2 to host cells through the binding of its spike (S) glycoprotein and the ACE2, followed by the cleavage of ACE2 by the TMPRSS2, allowing for viral entry.[8] Despite its critical role in the initiation of viral infection, studies have revealed that ACE2 is expressed at very low levels in the lungs.[9] Evidently, there need to be other host receptors or mechanisms that promote the entry of SARS-CoV-2 into respiratory cells and tissue injury.

In this issue of the *Journal of Thoracic Oncology*, by performing bioinformatics analysis of several public domain data sets, Stewart et al.[10] evaluated the expression and regulation of ACE2 and TMPRSS2 in a variety of cell lines, tumor biopsy specimens, and data from cancer cell lines and bronchial organoids infected by SARS-CoV-2 and patient nasal epithelium. Single-cell transcriptional group level revealed that ACE2 is expressed in only a small number of cells in normal respiratory tract, and the expression of TMPRSS2 is more extensive than that of ACE2 in fibrotic lung tissue. In contrast, the authors found that ACE2 was highly expressed in NSCLC cell lines and The Cancer Genome Atlas tumors. Consistently, the data

*Corresponding author.

Drs. Yang and Li contributed equally to this work.

Disclosure: The authors declare no conflict of interest.

[a]Department of Pathology, Zhongnan Hospital of Wuhan University, Wuhan, People's Republic of China, [b]Wuhan University Center for Pathology and Molecular Diagnostics, Wuhan, People's Republic of China, and [c]Department of Pathology, University of Chicago Medicine, Chicago, Illinois

Address for correspondence: Shu-Yuan Xiao, MD, The University of Chicago Medicine, 5840 S Maryland Ave., Chicago, Illinois 60637. E-mail: syxiao@uchicago.edu or shu-yuan.xiao@uchospitals.edu

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2021.08.014

from 180 patients with lung cancer and COVID-19 from eight countries revealed that the mortality rate of patients with lung cancer infected with COVID-19 is higher than that of the general population.[11] Interestingly, our unpublished data revealed that ACE2 expression is extremely low in normal lung tissues adjacent to lung cancer, and in lung tissues of other diseases including hamartoma, alveolar cell tumor, and infectious diseases.

Previous studies had revealed that the expression of ACE2 can be down-regulated by SARS-CoV-1 infection, making the lung tissue more susceptible to acute injury, and less likely reinfection in the same tissue,[12] suggesting subsequent tissue injuries and lung diseases are secondary "downstream" events in the pathogenesis. These point to the possibility of another mechanism of COVID-19 pathology, which may involve epithelia-mesenchymal interactions or transformations (epithelial-to-mesenchymal transition [EMT]), facilitating the compromise of the epithelial barrier. As revealed in the study by Stewart et al.,[10] long-term exposure to SARS-CoV-2 up-regulated the expression of mesenchymal genes in human bronchial epithelial cells, including AXL, but down-regulated the expression of tight junction-related genes, suggesting cells infected with SARS-CoV-2 can undergo metabolic and transcriptional changes consistent with EMT. Destruction of tight junctions between cells can directly lead to damage of the alveolar epithelial barrier. The resultant pathologic changes of alveolar edema and proteinaceous exudation were consistent with the main pathologic changes of the lungs in patients with COVID-19,[3] which were DAD and interstitial dimension.[3] Considering the pathologic findings of pulmonary fibrosis observed in some patients with COVID-19, it may be reasonable to assume that EMT in COVID-19 could be consequential. Remarkably, AXL has been identified as a potential receptor for SARS-CoV-2 because AXL knockout can significantly reduce the infection of SARS-CoV-2 in human lung epithelial cells.[9] Notably, their study revealed that bemcentinib, an inhibitor of AXL, could down-regulate the expression of mesenchymal-related gene and up-regulate the expression of ACE2.[10] Postmortem biopsy results in patients with COVID-19 revealed that a subset of pneumocytes is double positive for epithelial and mesenchymal markers, CK7 and α-SMA, respectively, suggesting the establishment of pulmonary fibrosis through the EMT mechanism.[13] With these findings, it is suggested that EMT plays a vital role in the pathophysiology changes of COVID-19, including the SARS-CoV-2 infection and pulmonary fibrosis.

Although the findings in the study by Stewart et al.[10] are intriguing and promising, it is worthwhile to note that these analyses were heavily relied on data from various sources but not prospectively designed and well-controlled experiments. There might be variations owing to difference in data source, "signal" changes associated with passaging of cell lines, difference in types of malignancies, and age of cells. Cancer cell lines are susceptible to additional genetic and phenotypic changes, as compared with nontransformed cells in most patients with COVID-19. That being said, this study provided a valuable concept and basis for future studies focusing on cells with well-defined lineage history, well-defined cytologic phenotypes, and experiments with virus-infected cell cultures.

The new model proposed by Stewart et al.[10] seems to support the notion that although ACE2 is important in the initial infection of SARS-CoV-2, the progression and outcome of COVID-19 depend more on other complex host-pathogen interactions, including virulence, replication, and host immune response.[14] The observed EMT and reduction of ACE2 may be a previously unrecognized component in the pathophysiology of COVID-19 pneumonitis. Nevertheless, the findings of moderate expression of ACE2 in lungs with tumors, in contrast to healthy lung tissue which has only very low level of ACE2 expression, may be partially responsible for more severe diseases and worse prognosis in patients with lung cancer who suffer from COVID-19. Thus, patients with lung cancer need more effective preventive measures against SARS-CoV-2 infection during the pandemic. The spread of the delta variant of SARS-CoV-2 has made it more urgent to develop and test effective vaccines suitable for patients with lung cancer.

CRediT Authorship Contribution Statement

Shu-Yuan Xiao: Conceptualization, Original—draft preparation, Writing—review and editing.

Yueying Li, Chunxiu Yang: Original—draft preparation, Writing—review and editing.

References

1. Marshall M. The four most urgent questions about long COVID. *Nature*. 2021;594:168–170.
2. Wang EY, Mao T, Klein J, et al. Diverse functional autoantibodies in patients with COVID-19. *Nature*. 2021;595:283–288.
3. Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol*. 2020;33:1007–1014.
4. Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. *Mod Pathol*. 2020;33:2128–2138.
5. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol*. 2020;15:700–704.

6. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med*. 2020;383:120–128.
7. Caramaschi S, Kapp ME, Miller SE, et al. Histopathological findings and clinicopathologic correlation in COVID-19: a systematic review. *Mod Pathol*. 2021;34:1614–1633.
8. Lukassen S, Chua RL, Trefzer T, et al. SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. *EMBO J*. 2020;39:e105114.
9. Wang S, Qiu Z, Hou Y, et al. AXL is a candidate receptor for SARS-CoV-2 that promotes infection of pulmonary and bronchial epithelial cells. *Cell Res*. 2021;31:126–140.
10. Stewart CA, Gay CM, Ramkumar K, et al. Lung cancer models reveal SARS-CoV-2-induced EMT contributes to COVID-19 pathophysiology. *J Thorac Oncol*. 2021;16:1821–1839.
11. Garassino MC, Whisenant JG, Huang LC, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. *Lancet Oncol*. 2020;21:914–922.
12. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*. 2005;436:112–116.
13. Pandolfi L, Bozzini S, Frangipane V, et al. Neutrophil extracellular traps induce the epithelial-mesenchymal transition: implications in post-COVID-19 fibrosis. *Front Immunol*. 2021;12:663303.
14. Yang C, Li Y, Xiao SY. Differential expression of ACE2 in the respiratory tracts and its relationship to COVID-19 pathogenesis. *EBioMedicine*. 2020;60:103004.