Dysregulation of ion transport in the lung epithelium infected with SARS-CoV-2

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As of April 14, 2021, ~138 million people worldwide and ~31 million in the United States have been diagnosed with COVID-19 disease, and ~3 million people worldwide and ~565,000 people in the United States have died (https://coronavirus.jhu.edu). Most patients with SARS-CoV-2 infection are asymptomatic or have mild disease; however, some patients develop severe pneumonia and acute respiratory distress syndrome (ARDS) requiring mechanical ventilation and even lung transplant (1–5). In some of these patients, the disease triggers an exuberant inflammatory condition, termed “cytokine storm” due to dysregulated immune response, which can lead to multi-organ failure and increased fatality rates (6, 7).

Pulmonary edema is a hallmark of ARDS, characterized by disruption of the alveo-capillary barrier and flooding of the airspaces with proteinaceous fluid and inflammatory cells (8–10). The upper and lower respiratory epithelium are lined by a thin fluid layer, referred to as airway surface liquid and alveolar lining fluid, respectively (11). Their composition is maintained by tightly regulated processes of secretion and absorption mediated by ion channels and pumps of the respiratory epithelial cells. Lung injury induces changes in the alveolar-capillary barrier, dysregulation of epithelial Na,K-ATPase, epithelial sodium channel (ENaC), and cystic fibrosis membrane conductance regulator (CFTR), leading to the accumulation of edema and impaired alveolar fluid clearance (11–16). Two recent articles have discussed the role of transepithelial ion transport during SARS-CoV-2 infection of the respiratory tract.

The first article by Abdel Hameid et al. (17) proposes that SARS-CoV-2 may alter evolutionary conserved second messenger signaling cascades via activation of G protein-coupled receptors (GPCRs) or by directly modulating G protein signaling. Based on the well-known reciprocal relationship between ENaC and CFTR (18, 19), the authors speculate that stimulation of GPCR signaling leads to activation of CFTR-mediated Cl⁻ transport, which may overwhelm absorptive pathways such as ENaC-dependent Na⁺ uptake. This process would trigger a pathophysiological cascade, leading to accumulation of lung edema, which is observed in the more severe cases of patients with COVID-19 and ARDS. CFTR is regulated via the cAMP/PKA pathway (20), a pathway known to be hijacked by microorganisms, such as cholera toxin, which by activating the adenylate cyclase triggers chloride secretion through CFTR (21). The authors also propose a role for exchange protein directly activated by cAMP (EPAC1) pathway, which is an alternative cAMP effector that interacts with CFTR through the Na⁺/H⁺ exchanger regulatory factor 1 (NHERF1) (22). The EPAC1 pathway has been reported to play a role in MERS-CoV and SARS-CoV infections (23). However, it is well known that viral infections cause ENaC inhibition by mechanisms not involving GPCR activation. For example, the influenza M2 protein, which functions as a proton-conducting channel, decreases ENaC and CFTR activity by causing the degradation of these transport proteins (24). In this case, only the ENaC would contribute to the dysregulation of fluid homeostasis. The authors acknowledge the speculative nature of their reasoning as they do not show any relation between SARS-CoV-2 infection and the function and/or expression levels of CFTR.

The study by Kryvenko and Vadász (25) focuses on the effects of lung injury, including SARS-CoV-2 infection, on Na,K-ATPase downregulation. There is significant evidence that links the downregulation of the Na,K-ATPase to the disruption of the alveolar barrier in models of lung injury since this ion transporter and adhesion molecule is required for normal alveolar epithelial function (12, 15, 16, 26–28). Therefore, the authors propose that the decrease of Na,K-ATPase abundance at the plasma membrane of alveolar epithelial cells contributes to the impairment of alveolar epithelial function due to SARS-CoV-2 infection. Furthermore, the authors propose that the disruption of the alveo-capillary barrier leads to persistence of lung injury, which contributes to the extrapulmonary manifestations of COVID-19. Several publications report decreases in mRNA and total protein level of Na,K-ATPase subunits in SARS-CoV-2-infected cells and in postmortem lung tissue samples from patients with COVID-19 (29–32). These data suggest decreased transcription and translation of the Na,K-ATPase. Moreover, the authors present a convincing analysis of the cellular processes affected by SARS-CoV-2 infection, which impair the maturation of Na,K-ATPase molecules and their delivery to the cell plasma membrane. Particularly, data reporting that SARS-CoV-2 infection causes ER stress (32–35) suggest impairment of chaperone-assisted folding of transmembrane proteins, including the Na,K-ATPase, in the ER lumen. In addition, the SARS-CoV-2 spike protein is extensively glycosylated and highjacks the host glycosylation and glycan-
dependent protein folding machinery, which could disrupt the Na,K-ATPase maturation that critically depends on the glycosylation of one of its subunits (36). Also, SARS-CoV-2 infection interferes with signaling cascades that normally regulate the plasma membrane Na,K-ATPase abundance by promoting its endocytosis.

Both articles discuss potential contributions of the ion transport proteins to the pathophysiology of acute lung injury and respiratory distress in patients with severe COVID-19 disease. However, they fail to discuss that in severe cases of SARS-CoV-2, the cytokine storm may lead to increased cell death causing a “leaky” epithelium (37, 38). It has been described that cytokines such as IL-1β, IL-6, and TNFα, are increased in the lungs of patients with SARS-CoV-2 and may lead to destabilization of CFTR, ENaC, and Na,K-ATPase (37). Along with these data, it has been reported that dexamethasone is associated with improved outcomes in patients with COVID-19 disease (39). Dexamethasone is known to upregulate ion transport proteins, including ENaC, CFTR, and the Na,K-ATPase (40–42), suggesting a role for ion-transport mechanisms in the pathophysiology and outcome of patients with ARDS due to SARS-CoV-2 infection. As mentioned above, during viral pneumonitis and ARDS, the alveolar epithelial barrier is disrupted by overwhelming epithelial cell death and also by dysregulation of the epithelial ion transport (43). We reason that SARS-CoV-2 infection alters the cellular processes that impair the function of ion transport proteins, such as CFTR, ENaC, and the Na,K-ATPase, which results in hypoxia and hypercapnia, further impairing ion-transport mechanisms (37, 38).

Although not much data are available on the mechanisms regulating the repair of the lungs after the acute phase of COVID-19, they are probably similar to lung repair after influenza pneumonitis or other severe causes of lung injury where ion-transport mechanisms are paramount. If the lung is not overwhelmingly injured, necessitating lung transplant, the alveolar epithelium must regain normal function after SARS-CoV-2-induced injury for the patients to survive.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

L.A.D., O.V., and J.I.S. drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

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