I.A. Sinyakin, T.A. Batalova

DISRUPTION OF TRANSPORT REGULATION OF IONS AND FLUID IN THE LUNGS WITH COVID-19

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The article discusses scientific data on impaired transport of ions and fluids in the lungs with COVID-19. The pathogenetic mechanism of impaired alveolar fluid clearance is indicated, which may represent one of the key factors in the pathophysiology of COVID-19-associated pneumonia and ARDS syndrome. Lung damage causes changes in the alveolar-capillary barrier, dysregulation of epithelial Na, K-ATPase, epithelial sodium channel (ENaC), and cystic fibrosis membrane conductance regulator (CFTR), which leads to the accumulation of alveolar fluid and impaired clearance. Thus, SARS-CoV-2 infection alters cellular processes that disrupt the function of ion transport proteins such as CFTR, ENaC, and Na+ / K+ -ATPase. This lesion further leads to hypoxia and hypercapnia, which further impairs the mechanisms of ion transport. Data on the involvement of TRPV4 (an osmotically activated channel associated with vanilloid receptor 4) in the pathogenesis of SARS-CoV-2 are presented. The study authors believe that inhibition of TRPV4 has important therapeutic benefits in COVID-19 patients. Inhibition of TRPV4 holds powerful promise for protecting the alveolar-capillary barrier in COVID-19 patients and even for regenerating the damaged barrier. A phase I of clinical trial using a selective TRPV4 inhibitor demonstrated a favorable safety profile in healthy control volunteers and in patients with cardiogenic pulmonary edema. The protection of the alveolar-capillary barrier with a selective TRPV4 inhibitor would also be useful in eliminating possible pulmonary fibrosis as a late consequence of COVID-19.

Keywords: COVID-19, ENaC, GPCR, SARS-CoV-2, TRPV4.

Introduction. The global COVID-19 pandemic continues to gain momentum and infect more and more of the world's population. The clinical picture of the new coronavirus infection is very diverse: from disorders of olfactory dysfunction (anosmia and hyposmia) [1] to severe acute respiratory distress syndrome (ARDS) requiring mechanical ventilation [4,16,26,35,46]. In some patients, the disease progresses in a very severe form associated with hyperactivation of proinflammatory cytokines, called "cytokine storm" due to dysregulation of the immune response, which can ultimately lead to multiple organ failure and death [27,36]. Speaking about the severity of the disease, it is necessary to remember about people at risk. The risk group for severe COVID-19 includes patients who have high expression of angiotensin-converting enzyme-2 in various tissues (diabetes mellitus (DM), cardiovascular diseases (CVD), chronic obstructive pulmonary disease (OPD) [2].

Pulmonary edema is the main clinical symptom of ARDS, characterized by impairment of the alveolar-capillary barrier, protein exudation, and migration of inflammatory cells to the focus [18]. The upper and lower respiratory epithelium are lined with a thin layer of fluid called airway surface fluid and alveolar lining fluid, respectively [32]. Their composition is supported by regulated processes of secretion and reabsorption mediated by ion channels and pumps of respiratory epithelial cells. Lung damage causes changes in the alveolar-capillary barrier, dysregulation of epithelial Na, K-ATPase, epithelial sodium channel (ENaC) and cystic fibrosis membrane conductance regulator (CFTR), which leads to the accumulation of alveolar fluid and impairment of its clearance [5, 6, 28, 32, 33, 43]. In this article, we critically discuss the available evidence on the role of transepithelial ion transport in SARS-CoV-2 respiratory tract infection.

The authors of the publication Abdel Hameid R. et al. [3] suggest that SARS-CoV-2 can change the evolutionary signaling cascades of the messenger by activating G-protein-coupled receptors (GPCR) or by direct modulation of G-protein signaling. Based on the well-known relationship between ENaC and CFTR [29, 37], scientists hypothesize that stimulation of GPCR signaling leads to activation of CFTR-mediated chlorine ion transport, which can suppress absorption pathways such as ENaC-dependent Na^+ uptake. This process could trigger a pathophysiological cascade of reactions leading to the development of pulmonary edema, which is observed in severe cases in patients with COVID-19 and ARDS. CFTR is regulated by the activation of cAMP / protein kinase A [30], which are known to be involved in the pathogenesis process during infection with Vibrio cholerae, activating adenylate cyclase and triggering the secretion of chlorine ions through CFTR [7]. The authors also propose the role of a candidate protein (exchange factor of directly activated cAMP 1) - EPAC1, which is an alternative effector of cAMP interacting with CFTR via Na^+ / H^+ antiporter 3-regulator-1 (NHERF1) [25]. Previously, it was reported that the EPAC1 pathway plays a role in infections with MERS-CoV (Middle East respiratory syndrome coronavirus) and SARS-CoV [41]. However, it is well known that viral infections cause inhibition of ENaC by mechanisms other than GPCR activation. For example, the influenza M 2 protein, which functions as a proton ion channel, reduces the activity of ENaC and CFTR, causing the degradation of these transport proteins [24]. In this case, only ENaC will contribute to the disruption of fluid homeostasis. The main significant drawback of this work is the lack of evidence by the authors of any association between SARS-CoV-2 infection and levels of function and / or expression of CFTR.

The study by Kryvenko V and Vadász [21] focuses on the effect of Na^+ / K^+ -ATPase on lung damage, including COVID-19 infection. There is significant evidence that downregulation of Na^+ / K^+ -ATPase is associated with alveolar barrier disruption in experimental models of lung injury, since this ion carrier is required for normal alveolar epithelium function [5, 13, 33, 42, 43, 44]. Therefore, the authors suggest that a decrease in the concentration of Na+ / K+ -ATPase on the plasma membrane of alveolar epithelium cells contributes to dysfunction of the alveolar epithelium due to infection with SARS-CoV-2. In addition, scientists suggest that disruption of the alveolar-capillary barrier leads to permanent damage to the lungs, which correlates with the extrapulmonary

SINYAKIN Ivan Alekseevich – student of the Amur State Medical Academy, 4th year, group 405, medical faculty, email: sinyakin.ivan2016@yandex.ru; **BATALOVA Tatyana Anatolyevna** – Associate Professor, Doctor of Biological Sciences, Head of the department of Physiology and Pathophysiology of the Amur State Medical Academy.

manifestations of COVID-19. Several foreign publications report a decrease in the level of mRNA and protein subunits of Na^+ / K^+ -ATPase in cells infected with SARS-CoV-2 and in postmortem autopsy samples of lung tissue from patients with COVID-19 [8, 9, 12, 19]. These data indicate a decrease in transcription and translation of Na^+ / K^+ -ATPase upon infection with SARS-CoV-2. In addition, a convincing analysis of cellular processes influenced by SARS-CoV-2 infection showed that maturation of Na^+ / K^+ -ATPase molecules and their delivery to the plasma membrane of the cell may be impaired. In particular, there is evidence that infection with SARS-CoV-2 causes stress to the endoplasmic reticulum (ER) [10, 19, 22, 38] and disrupts the folding of transmembrane proteins using a chaperone, including the key molecule Na^+ / K^+ -ATPase in lumen of the ER. In addition, molecular docking has shown that the SARS-CoV-2 spike protein is highly glycosylated and disrupts the mechanism of glycosylation and glycan-dependent folding of host proteins. This can disrupt the formation of Na, K-ATPase, which critically depends on the glycosylation of one of its subunits [45]. In addition, the pathogen SARS-CoV-2 disrupts the signaling cascades that usually regulate the content of Na^+ / K^+ -ATPase in the plasma membrane, promoting the penetration of the pathogen through clathrin-dependent endocytosis.

The Role of Cytokine Storm in Pulmonary Epithelial Damage. The authors of two articles discuss the potential contribution of ion transport proteins to the pathophysiology of acute lung injury and ARDS in patients with severe COVID-19. However, they did not indicate that in severe cases of COVID-19, a so-called cytokine storm develops, which can lead to increased cell death (apoptosis), causing a condition of the type of "leaky" epithelium [31,39]. In the literature, it has been described that the concentration of cytokines such as IL-1β, IL-6 and TNFa (tumor necrosis factor alpha) increases in the lungs of patients with COVID-19 and can lead to destabilization of CFTR, ENaC and Na^+ / K^+ -ATPase [37].

In medicine, the glucocorticosteroid dexamethasone has been used for decades, which has many pharmacological effects: anti-inflammatory, anti-allergic, immunosuppressive, anti-shock. Due to such a wide pharmacological spectrum, dexamethasone is still used in the treatment of COVID-19, since its use in multicenter studies has shown an improvement in patient outcome [20]. It is known that dexamethasone regulates ion transport proteins, including ENaC, CFTR and Na^+ / K^+ -ATPases [11,14,34], which indicates the role of ion transport mechanisms in the pathophysiology and outcome of patients with ARDS in the presence of SARS-CoV-2 infection.

As mentioned above, during viral pneumonitis and ARDS, damage to the alveolar epithelial barrier occurs, associated with generalized death of alveolocytes and epithelial cells, as well as dysregulation of ion transport in the lungs [40]. Thus, it can be concluded that SARS-CoV-2 infection alters cellular processes that disrupt the function of ion transport proteins such as CFTR, ENaC, and Na^+ / K^+ -ATPase. This violation further leads to hypoxia and hypercapnia, which further impairs the mechanisms of ion transport [31, 39]. A promising role for a TRPV4 inhibitor in the treatment of COVID-19.

In the original study, the authors investigated the role of TRPV4 (an osmotically activated channel associated with vanilloid receptor 4) in the pathogenesis of COVID-19. The researchers point out that inhibition of (TRPV4) permeable to Ca^{2+} ions as a strategy to address this problem, based on the fact that inhibition of TRPV4 was protective in various preclinical models of pulmonary edema, and that TRPV4 hyperactivation potentially damages the alveolar-capillary barrier with fatal outcome. TRPV4 are activated multimodal Ca^{2+} sensitive ion channels that have been identified as important regulators of the alveolar-capillary barrier. These channels are closely related to type I and II alvelocytes, as well as alveolar capillary endothelial cells [47]. In addition, TRPV4 are expressed and regulate the activation of innate immune cells, such as alveolar macrophages and neutrophilic granulocytes, which contribute to the destruction of the alveolar-capillary barrier through the release of proteases, cytokines and reactive oxygen species [15].

Thus, inhibition of TRPV4 holds powerful promise for protecting the alveolar-capillary barrier in COVID-19 patients and even for regenerating the damaged barrier. A phase I clinical trial using a selective TRPV4 inhibitor demonstrated a favorable safety profile in healthy control volunteers and in patients with cardiogenic pulmonary edema. Also in clinical practice, it is known about the late consequences of COVID-19 in the form of the development of pulmonary fibrosis, which is assumed to depend on the enhancement of TRPV4 function in pulmonary fibroblasts [17]. Thus, the protection of the alveolar-capillary barrier with a selective TRPV4 inhibitor would also be useful in eliminating possible pulmonary fibrosis as a late consequence of COVID-19.

Conclusions. With little data on the mechanisms regulating lung recovery after the acute phase of COVID-19, it can be assumed that these mechanisms will be similar to lung recovery after influenza pneumonitis or other serious causes of lung injury, where ion transport mechanisms are of paramount importance. If the lung is overwhelmingly intact, the alveolar epithelium should restore normal function after the alveolar-capillary barrier is disturbed by the pathogen SARS-CoV-2.

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