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.

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Letter to the Editor

Plausibility of therapeutic effects of Rho kinase inhibitors against Severe Acute Respiratory Syndrome Coronavirus 2 (COVID-19)

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the cause of coronavirus disease-2019 (COVID-19) that was started from Wuhan, China, on 31 December 2019. The fast spread of the disease led to a pandemic with high morbidity and mortality rates [1].

SARS-CoV-2 is a member of a huge family of single-stranded enveloped RNA viruses which are able to produce a wide spectrum of complications from the common cold to serious conditions like severe acute respiratory syndrome (SARS-CoV) and middle east respiratory syndrome (MERS-CoV). SARS-CoV emergence in 2002-2003 resulted in over 8000 confirmed infected cases and approximately 800 deaths. Common symptoms of COVID-19 are very similar to those of SARS-CoV infection and include respiratory signs, cough, fever, dyspnea and breathing issues. In complicated cases, pneumonia, severe acute respiratory syndrome (SARS), renal failure and death are observed [1].

Molecular mechanisms involved in COVID-19 pathogenesis have not been stablished yet, but some studies investigated how other members of this family cause infection. SARS-CoV exert their effects by cytocidal and immune-mediated mechanisms. Cytocidal mechanisms encompass apoptosis, fibrosis and cellular fusion in lung tissues leading to the formation of syncytia. T cells, inflammatory cells cytokines and humoral antibodies against the spike protein are the core of immune-mediated mechanisms of SARS-CoV [2].

Recently, we reviewed how Rho/ROCK signaling pathway modulates acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), and indicated that by using specific Rho kinase inhibitors, we can prevent/treat such conditions. Activation of RhoA GTPase and its downstream effector, Rho kinase (ROCK), contributes to a burst in inflammatory features, immune cell migration, apoptosis, coagulation, contraction, and cell adhesion in pulmonary endothelial cells, leading to endothelium barrier dysfunction and edema as hallmarks of lung injury. Importantly, Rho kinase inhibitors such as fasudil, could significantly attenuate lung injury in different *in vivo* and *in vitro* models of ALI. Furthermore, excellent anti-fibrotic effects of Rho kinase inhibitors were shown in models of pulmonary fibrosis [3].

Moreover, recent reports revealed that angiotensin-converting enzyme 2 (ACE2) is the present receptor for SARS-CoV-2. ACE2 is widely expressed in alveolar epithelial cells and makes angiotensin II which is a negative regulator of the renin–angiotensin–aldosterone system, inactive. Since ACE2 opposes the actions of angiotensin II, it exerts beneficial effects against diseases such as lung injury, hypertension and cardiac remodeling. Envelope spike protein of SARS-CoV-2 mediates its attachment and fusion into the human cells through binding ACE2 with super-affinity and efficiency. In a mice model, it was documented that SARS-CoV suppresses ACE2 protein by binding via its spike protein, producing severe lung injury. Also, recombinant ACE2 protein protected mice in a model of acid aspiration or sepsis-induced ALI. Accordingly, considering ACE2 as a potential therapeutic target in severe acute respiratory syndrome of COVID-19 was strongly suggested [4,5,6].

Interestingly, Rho kinase inhibitors upregulate the axis of ACE2. Fasudil increased the activity and levels of ACE2 in an experimental model of hypertension. Also, Y-27632 and HA-1077 as Rho kinase inhibitors, significantly attenuated the downregulation of ACE2 in isolated rat pulmonary artery endothelial cells and restored decreased levels of ACE2 in an acute pulmonary embolism rat model [4,5,6]. Fig. 1 presents Rho kinase inhibitors effects that could be potentially beneficial in treatment of COVID-19.

Taken together, Rho kinase inhibitors seem to be potentially effective in prevention and treatment of the respiratory complications observed in deadly COVID-19. Possibly, their beneficial effects might be mediated via modulation of the immune system, protection of the respiratory tract cells, and especially, restoration of ACE2 levels. It should be noted that although several other agents are also able to inhibit virus cell entry, Rho kinase inhibitors can suppress pathways involved in lung tissue destruction. So, we assume that clinical trials on the effects of Rho kinase inhibitors against respiratory complications induced by SARS-CoV-2 infection, should be conducted.

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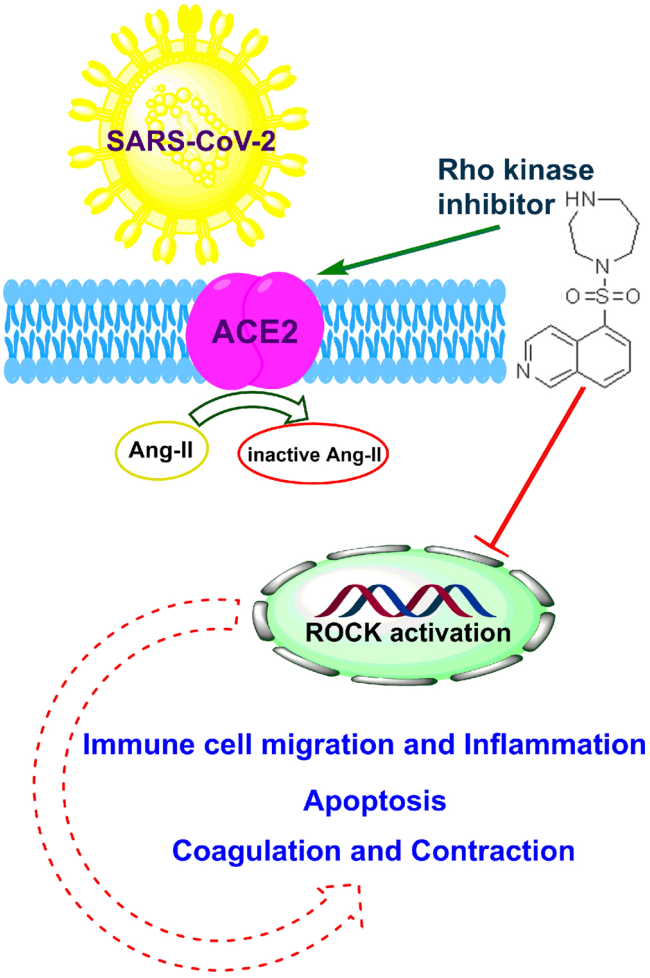

Fig. 1. Positive role of Rho kinase inhibitors in pulmonary endothelial cells infected with SARS-CoV-2.

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Farshad Abedi[a], Ramin Rezaee[b,c], Gholamreza Karimi[a,d,*]

[a] *Pharmaceutical Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran*

[b] *Clinical Research Unit, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*

[c] *Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

[d] *Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*

E-mail address: karimig@mums.ac.ir (G. Karimi).

* Corresponding author at: Pharmaceutical Research Center, Institute of Pharmaceutical Technology, Mashhad University of Medical Sciences, Mashhad, Iran.