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The role of angiotensin-converting enzyme 2 in COVID-19 induced lung injury

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Summary. The novel coronavirus disease (COVID-19) has affected people around the world both physically and psychologically. As result, developing a coronavirus-specific vaccine and/or therapeutics is now a top priority for public health agencies. Since our findings of COVID-19 are relatively new, the current knowledge about the molecular mechanism involved in pathogenicity and virulence of the novel coronavirus is not advanced. Understanding angiotensin-converting enzyme 2 (ACE2), the receptor for the coronavirus, is significantly important. To better illustrate the role of ACE2 in the severity of COVID-19 and the impact of currently used drugs on this receptor, this paper briefly reviews newly published articles in this regard. (www.actabiomedica.it)

Keywords: Angiotensin-converting enzyme 2; COVID-19; Lung injury

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The novel pandemic of the 2019 coronavirus disease (COVID-19) has become a global concern worldwide [12]. The disease is caused by coronavirus 2 severe acute respiratory syndrome (SARS-CoV-2) [4]. Coronaviruses (CoVs) are positive-stranded RNA viruses with nucleocapsid envelopes and a crown-like appearance. One of the structural components of the CoVs is the spike glycoprotein, which consists of three S1-S2 heterodimers, which bind their receptor, angiotensin-converting enzyme 2 (ACE2) on the cellular membrane using the receptor-binding domain [11, 13]. This mediates the fusion of the viral and cellular membranes. Contact between these structural molecules stimulates the cleavage of spike protein through the enzyme transmembrane protease serine 2 (TMPRSS2). This subsequently triggers a molecular cascade that leads to the fusion of the host cell membrane and the viral membrane envelope, ensuring the entry of viral components into the cytoplasm [2, 10, 16].

ACE2 is a metalloproteinase, a crucial RAS regulator, which acts opposite to ACE, balancing vasoconstrictors and vasodilators by converting angiotensin I (Ang I) to Ang 1-9 and Ang II to Ang 1-7. In addition to the lungs, ACE2 is expressed in many organs, including the gastrointestinal tract, liver, gallbladder, heart, kidneys, and testicles, which can justify extrapulmonary manifestations in COVID-19 [5].

Different hypotheses have been formed about the possible role of ACE2 in the severity of the disease and death, and even the possibility of vaccine production by recruiting antibodies against SARS-CoV-2 spike protein [1, 14]. According to the first hypothesis, due to the role of ACE2 in the pathogenesis of COVID-19, theoretically, increased levels of ACE2 can play an important role in a higher load of the virus and in consequence may elevate the mortality rate

as well as the severity of complications. Therefore, any factor that increases the expression of ACE2 on the cellular membrane can be considered as a determining factor in the prognosis of the disease. Although Chloroquine (CQ) and hydroxychloroquine (HCQ) are not presently considered as possible therapies any more, a variety of potential mechanisms were discussed for CQ/HCQ against SARS-CoV-2. CQ can decrease glycosylation of ACE2 and thus prevents COVID-19 from its successful binding to the cell membranes [3]. Zinc is known to regulate the inflammatory response. Some studies suggested that zinc level modulation may be helpful in COVID-19 through various described mechanisms. A study has shown that Zn2+ may decrease the ACE2, thereby inhibiting the entrance of the virus [15]. A serine protease inhibitor, Camostat mesylate, has been recently approved for treatment in Japan, which is shown to block the TMPRSS2 function, essential to enter the cell through ACE2 [6].

Some underlying conditions are known to be risk factors for death. These factors include male gender, age over 65, smoking, high blood pressure, diabetes, cardiovascular disease, and respiratory diseases [17]. Studies have shown that one of the potential mechanisms of smoking is its impact on the gene expression of ACE2. In ever smokers, ACE2 gene expression is higher than that of never smokers in lung tissue, small and large airway epithelia, indicating that smoking leads to a higher number of viral receptors. In patients with chronic obstructive pulmonary disease, the expression of ACE2 increases in lower airways and can be the reason for the higher risk of severe COVID-19 in these patients [8]. Angiotensin receptor blockers (ARBs) and ACE inhibitors (ACEIs), which are both widely used by hypertensive or diabetic patients, can be associated with the increased mortality risk observed in these patients. Animal models and some human studies have mostly shown increased ACE2 expression upon the use of ACEI, ARB, Ibuprofen, and Thiazolidinediones [5]. Considering the above-mentioned points, it is recommended that drugs with this mechanism be replaced with alternative drugs until further clinical studies are performed.

Contrary to the mentioned hypothesis, there are shreds of evidence of potential protective effects of ACE2 on COVID-19. ACE2 is known to be probably protective in acute lung injury; this function is suggested to be related to the regulation of angiotensin response to the immune system and vascular cells in the pulmonary system [9]. Even recombinant ACE2 has been shown to be useful in animal models of acute respiratory distress syndrome/acute lung injury and could be considered as an option for COVID-19 therapy [7].

Because of the discrepancies in the studies, a unanimous consensus has not yet been reached on the actual role of ACE2 in patients with COVID-19. Due to the widespread use and essential role of some of the mentioned drugs, especially in high-risk patients, the need for further studies is agreed by all studies. ACEI and ARB have been repeatedly discussed in studies because of their life-saving functions in high-risk patients.

Studies that have taken a more cautious approach, have suggested replacing these drugs during the pandemic. For instance, calcium channel blockers can be considered as an alternative for ACEI and ARB. In contrast, professional associations, such as the European Society of Hypertension, American Heart Association, the European Society of Cardiology, Hypertension Canada, and the Renal Association and International Society of Hypertension still recommend the continued use of the mentioned drugs because of their life-saving effects on patients with diabetes and high blood pressure, which are at higher risk of mortality in COVID-19. As of the above-mentioned controversies, performing well-established researches as well as more clinical trials is recommended to determine the efficiency of these drugs in COVID-19 treatment.

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Conflict of interest

The authors declare no potential conflict of interest.

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