The role of angiotensin-converting enzyme 2 as a critical structure to COVID-19 infection
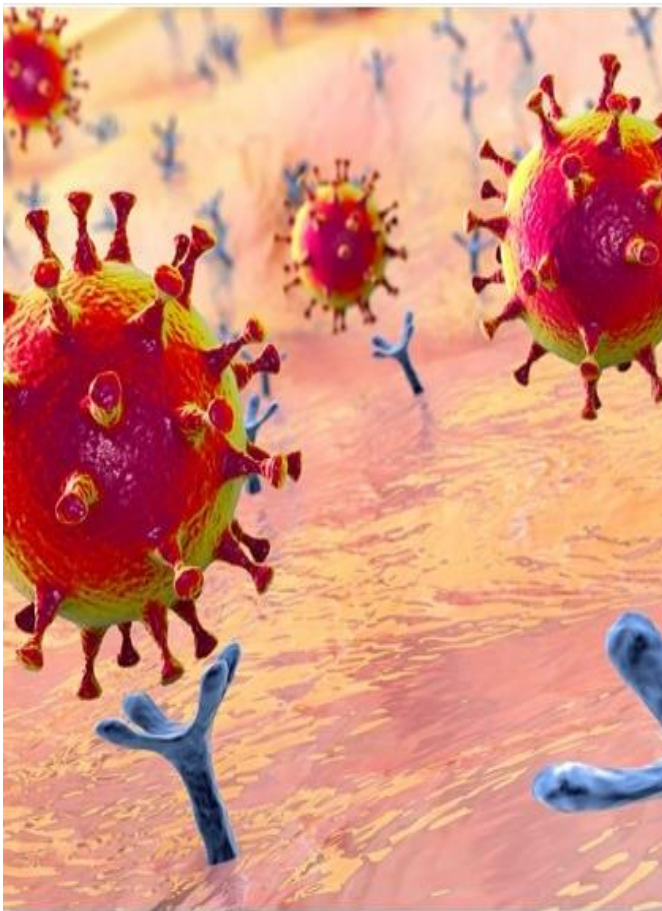
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Graphical Abstract	Abstract
	COVID-19 (Coronavirus Disease 2019) is a pandemic infection caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Once in the body, COVID-19 can cause acute respiratory distress syndrome (ARDS) and multiorgan failure. The mandatory cellular structure for virus invasion is the membrane-bound form of angiotensin-converting enzyme 2 (ACE2). After SARS-CoV-2/ACE2 binding, this complex is internalized by the host cell, RNA is released and viral replication starts. ACE2 is part of the renin-angiotensin-system (RAS), that is critical in the physiological regulation of several body systems and specially in cardiovascular and blood pressure maintenance. The primary role of the positive RAS axis, by the ACE1 isoform, is to increase sympathetic nervous system tension, cause vasoconstriction, increase blood pressure, and promote inflammation, fibrosis, and myocardial hypertrophy. On the other hand, ACE2 acts in an opposite way to counteract these actions and maintain homeostasis. It is well established that RAS axis is directly related to the changes observed in hypertension pathophysiology. Thus, this work proposes to analyze the role of ACE2 in hypertension as a risk factor for COVID-19 and to evaluate the related emerging therapeutic strategies. *Keywords: COVID-19; ECA2; hypertension.*

Introduction

A novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was discovered in December 2019 in Wuhan, China, and an ongoing pandemic of coronavirus disease 2019 (COVID-19). Similar to other coronaviruses (SARS-CoV-1 and MERS-CoV), human-to-human transmission is well established for this virus, which has now spread globally.

Identically to SARS-CoV-1, which was responsible for the SARS outbreak in 2002-2004, the main target of SARS-CoV-2 is the respiratory tract, leading to typical clinical signs including fever, dry cough, fatigue and dyspnoea [1]. Typically, the disease progresses to a severe form in 10-20% of patients, requiring hospital admission or even intensive care unit (ICU) treatment [2]. Therefore, the clinical spectrum of COVID-19 ranges from asymptomatic upper respiratory infection to critically ill pneumonia associated with acute respiratory distress syndrome (ARDS).

The SARS-CoV-2 virus infects human cells by first binding via its S protein to its target angiotensin-converting enzyme 2 (ACE2), a 120 kDa integral membrane glycoprotein on the surface of cells in the lungs, heart, kidneys and intestine [3]. The ACE1-Ang II-AT1R pathway is called the classical renin-angiotensin system (RAS) axis, which plays a decisive role in regulation, while the ACE2-Ang 1-7-MasR-based pathway is called the counter-regulatory RAS axis, which plays a negative role in regulation [4]. After the moment of SARS-CoV-2 infection on the cell, ACE2 has its expression stopped and this compromises several physiological mechanisms, in special the blood pressure regulation. Thus, this work proposes to analyze the role of ACE2 in hypertension as a risk factor for COVID-19 and to evaluate the related emerging therapeutic strategies.

Results and Discussion

In the classical endocrine model of the RAS, renin cleaves its substrate, angiotensinogen (AGT), to produce the inactive peptide, angiotensin I (Ang I), which is then converted to angiotensin II (Ang II) by endothelial angiotensin-converting enzyme (ACE1). The catalytic activity of ACE1 to activate Ang II occurs most extensively in the lung. Ang II mediates vasoconstriction as well as aldosterone release from the adrenal gland, resulting in sodium retention and an increase in blood pressure through the angiotensin 1 receptor (AT1R).

Nevertheless, it is also known that RAS also includes counter-regulatory systems to balance the hypertensive actions of ACE1. In particular, Ang II generation at the tissue level by the tissue specific RAS appears to have physiologic effects that are as important as circulating/systemic Ang II and, under some circumstances, more important than circulating Ang II. Therefore, the RAS system is not only involved in controlling blood volume and blood pressure but with the tissue specific local systems, it directs tissue remodeling, endothelial dysfunction, and fibrosis [5].

ACE2 was established as the functional host receptor for SARS-CoV-2 (Figure 1). Binding kinetics revealed a 10-20-fold higher binding affinity as compared to the SARS-CoV-1 virus. These findings may partially explain the apparently easier transmissibility of SARS-CoV-2 and that increased ACE2 expression may confer increased susceptibility to host cell entry of SARS-CoV-2 [6]. However, cell infection by SARS-CoV-2 induces ACE2 downregulation through its internalization as a mechanism contributing to the severity of lung pathologies, since the protective role of ECA2 is prevented by the virus.

Figure 1. Representative of SARS-CoV-2 infection by ACE2 and possible treatment strategies.
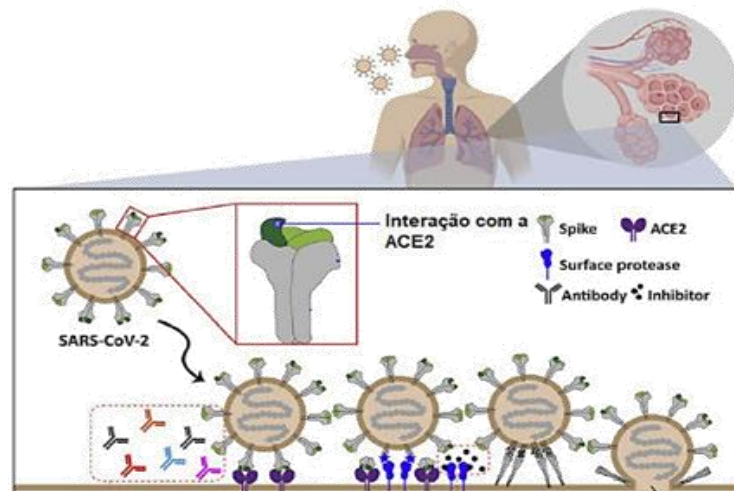
Adapted from www.diagno.ind.br/covid-19-consideracoes-e-principais-alteracoes-no-hemograma

Therefore, SARS viruses decrease ACE2 activity and expression, which creates an imbalance in signaling by ACE1 and ACE2 products. This imbalance increases Ang II/AT1 signaling and is superimposed on concurrent pathology (e.g. chronic lung disease and cardiac remodeling in the lung and heart, respectively). Ang II is a pivotal mediator of injury in both tissues; enhancement of its effects together with signaling from co-morbidities can increase severity of COVID-19. In patients more susceptible to the damaging effects of Ang II, e.g. elderly, diabetic or hypertension, the decrease in ACE2 activity by SARS viruses can unleash a cascade of injurious effects through a heightened imbalance in the actions of the products of ACE1 versus ACE2. These imbalance implies the potential of pharmacological approaches that redress this imbalance via (a) decrease in ACE1 activity, (b) blockade of AT1 and/or (c) increase in ACE2-mediated signaling by affinity-trapping the SARs virus, enhancement of ACE2 activity, or agonists for receptors of ACE2-derived peptides [3] (Figure 2).

Figure 2. Repercussions of SARS-CoV-2 interaction with ECA-2 and RAS axis.
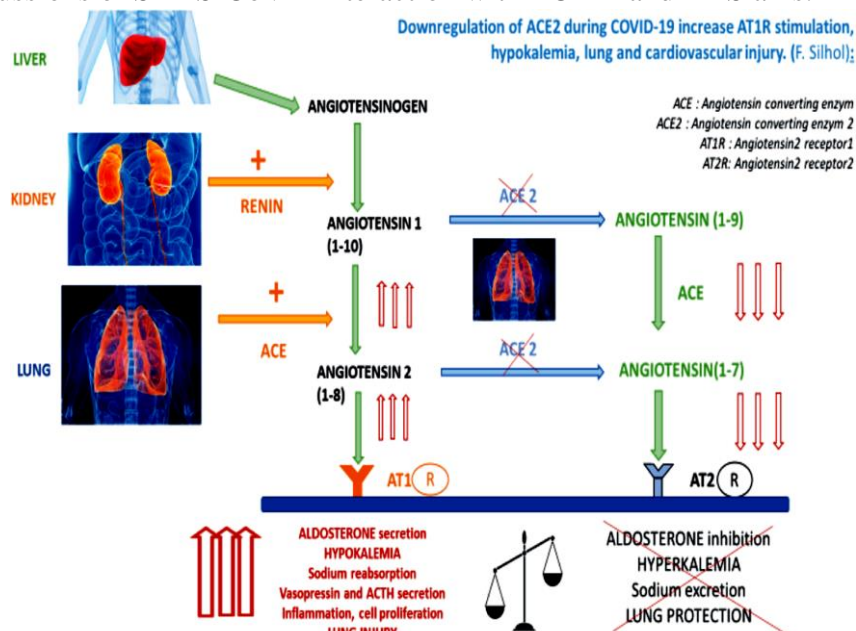
Adapted from Silhol et al. 2020 [7].

Conclusions

Thus, ECA2 showed to be the key to SARS-CoV-2 accessing the human cells and initiate all COVID-19-related pathophysiological processes. In this process, the virus brake the balance in RAS axis that may be one of the ways involved in severe cases of COVID-19. Finally, more researches are welcome to better understand the action of drugs in RAS axis during the active phase of infection and to reduce infection symptoms and give a better prognosis to COVID-19-pacients.

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