The regulation of ACE-2 in the heart and lungs

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ABSTRACT

The pathogenesis of SARS-CoV-2 infection or COVID-19 disease remains an active and rapidly evolving area of investigation. Currently, the angiotensin-converting enzyme 2 protein (ACE-2) is the primary receptor implicated in the pathogenesis of SARS-CoV-2. In normal physiological responses, the ACE-2 has important roles in regulating the renin-angiotensin systems (RAS) in several organs, including the heart, kidney, and lungs. Dysregulation of ACE-2 has been linked to heart failure, pulmonary hypertension, and diabetic cardiovascular complications. Two main risk factors for COVID-19 include hypertension and cardiovascular disease. However, the precise mechanism causing these risk factors for COVID-19 infectivity remains unknown. In this paper, we provide possible molecular mechanisms that underlie the cardiovascular risk factors for COVID-19.

Keywords: SARS-CoV-2, COVID-19, angiotensin converting enzyme-2 (ACE-2), hormones, cardiovascular, hypoxia, metabolism, regulation, and pathophysiology

INTRODUCTION

First reported in Wuhan, China, the SARS-CoV-2 (COVID-19) virus has caused a worldwide pandemic leading to over one million deaths. The coronaviruses belong to a large family of single-stranded, positive-sense RNA viruses that infect both humans and animals. COVID-19 is the seventh human corona virus to be identified. Patients infected with SARS-CoV-2 present with fever, cough, and difficulty breathing. Advanced stages of COVID-19 can lead to pneumonia, acute respiratory distress syndrome (ARDS), and congestive heart failure.[1] Although a novel virus, the SARS-CoV-2 virus shares a high level of genome sequence homology (70–80%) with SARS-CoV-1.[1] This similarity extends to the receptor essential for the SARS-CoV-1 and -2 pathogenesis, namely the angiotensin-converting enzyme 2 receptor (ACE-2).[1]

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The ACE-2 receptor is a type-1 transmembrane metallocarboxypeptidase that regulates blood pressure with ACE through the renin-angiotensin systems (RAS).[2] It is located in the vascular endothelial cells, the renal tubular epithelium, lung, kidney, gastrointestinal tract, and Leydig cells of the testes.[3–5] This receptor degrades angiotensin II to generate angiotensin 1–7 and angiotensin 1–9, thereby negatively regulating RAS (Figure 1).[6,7] Specifically, angiotensin 1–7 and 1–9 are potent vasodilators in the heart, blood vessels, and kidneys.[8] Genetic mutations in the ACE-2 receptor have been linked to heart failure, systemic and pulmonary hypertension, myocardial infarction, and diabetic cardiovascular complications.[9] Clinical studies activating the ACE-2 receptor showed protective effects against hypertension and cardiovascular disease (Figure 1).[9–12] In particular, two phase II clinical trials demonstrated that the administration of recombinant human ACE-2 reduced systemic inflammation and shifted RAS peptides away from angiotensin II to angiotensin 1–7.[13,14] In preclinical studies, activated ACE-2 decreased pulmonary injury and vascular damage and prevented pulmonary hypertension, decreased lung fibrosis and arterial remodeling, and improved right ventricular function

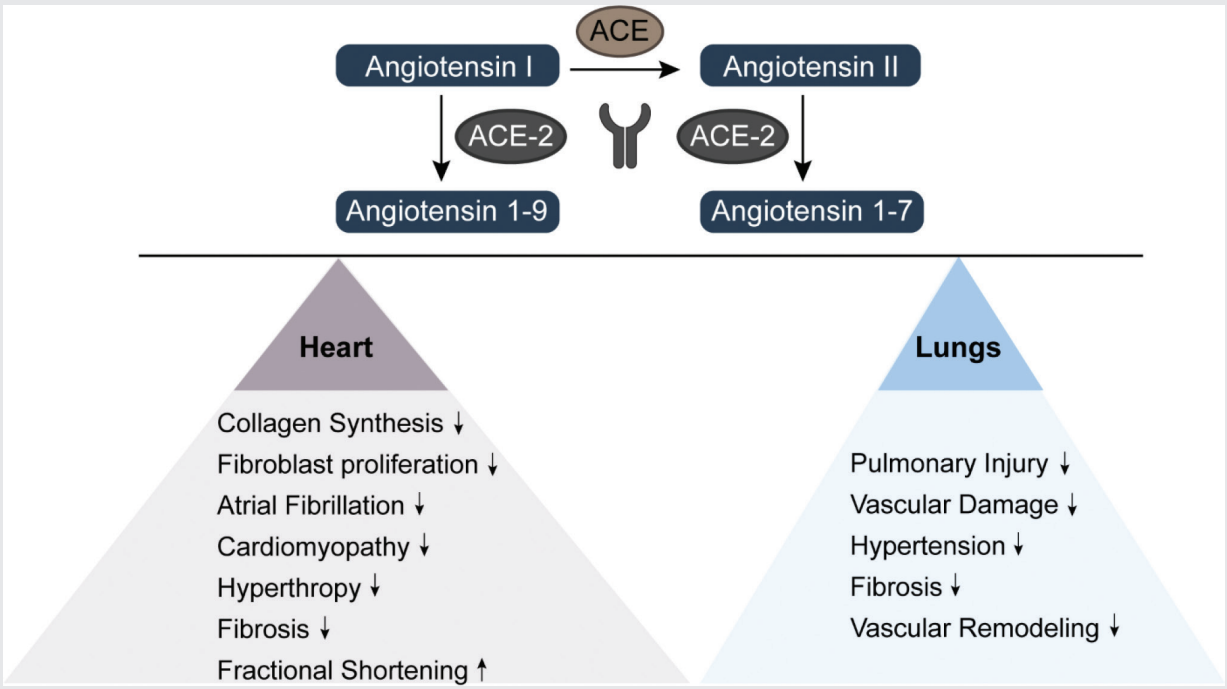

Figure 1. Role of ACE2 in the production of angiotensin 1–9 and 1–7 and their effect on the heart and lung health.

(Figure 1).[15–17] Given the COVID-19 pandemic, there is increased interest in understanding the ACE-2 receptor in the pathogenesis of SARS-CoV-2. In this paper, we summarize the normal physiological processes that regulate ACE-2 expression.

Cardiovascular regulation of ACE-2

Hypertension and cardiovascular disease are the major risk factors for COVID-19.[18–21] A study in Wuhan, China, showed that hypertension was associated with a hazard ratio of 1.70 and 1.82 for mortality and ARDS.[21] Subsequent studies found similar trends with increased hospital morbidity and mortality among COVID-19 patients with a history of hypertension.[18,20] It is hypothesized that older age and sex differences may account for increased mortality among COVID-19 patients with a history of hypertension.[18] Specifically, increases in ACE-2 expression may regulate the proliferation of smooth muscle cells and reduce the activity of angiotensin II with increased blood pressure.[22] In COVID-19 patients, the increase in ACE-2 expression may explain the increased susceptibility, morbidity, and mortality observed with hypertensive patients. However, this trend may exist in all organs. A murine study found that hypertension was caused by increased serum sodium levels and decreased ACE-2 expression in the kidneys.[23] Further study on hypertension and ACE-2 expression in different organs may provide more insight into the pathogenesis of SARS-CoV-2.

Several physiological processes regulate the expression on ACE-2 in the cardiovascular systems (Figure 2A). A pre-clinical study using human aortic smooth muscle cells found that in comparison to the static conditions, the repeated physiological stretching (10% elongation at 1 Hz) increased ACE-2 expression and activity.[22] A similar study examining stretched cardiac smooth muscle cells also found that transcription factors such as activator protein 1 and nuclear factor-κB amplified the ACE-2 expression.[22] Additional studies showed that angiotensin II and endothelin-1 reduced ACE-2 levels via activation of extracellular signal-regulated kinase (ERK) 1/2

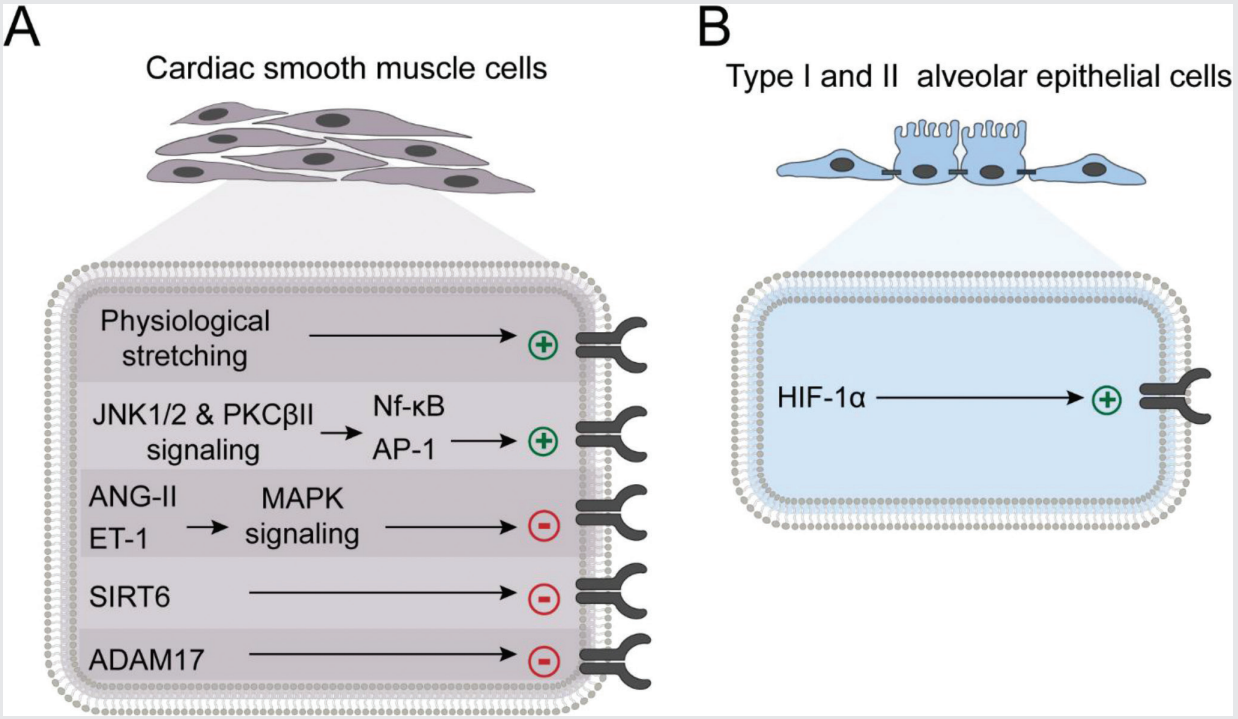

Figure 2. Regulation of ACE-2 in the heart (**A**) and in the lung (**B**). + indicates upregulation of receptor's expression and/or its activation. – indicates downregulation of receptor's expression and/or its inhibition.

and MAPK signaling pathways.[24,25] Therefore, it is believed that ACE-2 expression in the cardiovascular systems is regulated by several hypertrophic and anti-hypertrophic peptides.[24–26] A study examining the stress responsive protein deacetylase and mono-ADP ribosyltransferase enzyme, known as Sirtuin 6 (SIRT6), discovered that the enzyme reduced remodeling, fibrosis, and myocardial injury through activation of AMP-activated protein kinase (AMPK)-ACE2 signaling cascade.[27] Hypertensive mice treated with recombinant plasmids adeno-associated viral SIRT6-vector had a decrease in ACE-2 expression.[27] Other studies found that inhibition of the Wnt signaling pathway reduced cardiac fibrosis and hypertrophy by regulating the ADAM17/ACE-2 pathway through ectodomain shedding.[28,29] Therefore, it is possible that other physiological mechanisms regulating ADAM17 expression may directly contribute to the susceptibility of patients to COVID-19, attributable to the modified ACE-2 expression. More research is needed to determine which regulatory mechanisms in the cardiovascular system increase the risk of COVID-19 morbidity and mortality.

ACE-2 REGULATION IN THE LUNG

ACE-2 is highly expressed in the type I and type II alveolar epithelial cells of the lung.[30] The ACE-2 receptor protects the lung against injury through several mechanisms. The catalytic activity of ACE-2 degrades angiotensin II and prevents vasoconstriction, proapoptotic processes, and fibrotic processes in lung epithelial cells while simultaneously producing angiotensin 1–7.[31] Given the importance of ACE-2 in pulmonary physiology, the body actively regulates the expression of ACE-2 in alveolar cells (Figure 2). In particular, hypoxia stimulates the migration and proliferation of hematopoietic stem/progenitor cells through upregulation of the ACE-2 receptor.[32] It was later found that the hypoxia-inducible factor 1α (HIF-1α) was the key transcription factor that increased ACE-2 expression during hypoxia.[33] Therefore, it is possible

that patients with chronic lung disease may have an increased expression of ACE-2 that increases their risk for infections from COVID-19.

Future directions

Given the effects of SARS-CoV-2 on the heart and lungs, most studies have focused on the regulation of ACE-2 in these organ systems. However, there is an increasing evidence that metabolism may influence the expression of ACE-2 and the risk of infection. A recent meta-analysis of COVID-19 patients showed that obesity was a significant risk factor for mortality.[34] A similar finding of increased mortality among obese patients was observed in the H1N1 epidemic of 2009.[35] It is believed that obese individuals are at a higher risk for mortality from COVID-19 due to a combination of metabolic dysfunction, immune impairments, and adipose inflammation combined with physical and other medical comorbidities.[34] Several pre-clinical studies showed that other metabolic modulators, such as apelin, growth hormone, and SIRT1 (silent information regulator T1), increase ACE-2 expression.[36,37] It is possible that obesity may increase the risk of COVID-19 infection and mortality through an upregulation of ACE-2 receptors. For the foreseeable future, more investigation into the pathogenesis of COVID-19 will remain an integral component of identifying at risk patients and developing treatments.

Conclusion

The study of ACE-2 function in regular physiological responses provides possible mechanisms involved in SARS-CoV-2 infectivity and severity. In general, an increase in ACE-2 receptor would increase viral infection; specifically, a greater number of ACE-2 receptors increases the likelihood that SARS-CoV-2 will attach on epithelial surfaces and infect the host. In contrast, an increase in ACE-2 would reduce angiotensin II levels, which protects pulmonary epithelial cells. Given the importance of metabolic mediators in ACE-2 regulation, it is likely that multiple physiological functions influence the overall risk a given patient has for both contracting and developing severe COVID-19 disease. Furthermore, the time course of the SARS-CoV-2 virus may be another important factor for consideration. The COVID-19 disease occurs in two phases: the incubation and symptomatic phase.[38] The incubation phase lasts between 3–5 days during which the SARS-CoV-2 virus begins attaching to the pulmonary epithelial cells expressing ACE-2. A shorter or longer incubation period along with decreased or increased ACE-2 expression may both alter the overall risk of infectivity. During the symptomatic phase, it is unknown whether an increase in ACE-2 causes a corresponding increase in the infectivity of SARS-CoV-2. Further investigation on whether ACE-2 contributes to the pathogenesis after initial infection remains to be determined.

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