

An Overview of the ACE2 Receptor as the Main Coronavirus Keyword

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Abstract

The epidemic caused by the spread of the infectious agent called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a huge challenge to various communities around the world. The high prevalence and widespread infectivity of this virus indicated that despite the relentless efforts of various biological scientists to provide appropriate treatment or control of the disease, no definitive treatment has been reported successfully. Since the source of infection of this virus is an entry into the host cell through the specific angiotensin-converting enzyme-2 (ACE2) receptor, in the present study, we reviewed the ACE2 receptor and its role in SARS-CoV-2 infection.

Keyword: SARS-COV-2, Angiotensin-converting enzyme 2, Spike protein

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Introduction

By the end of 2020, the world underwent dramatic changes resulting from the emergence of a new infection, the consequences of which changed the economic, political, social, and public health conditions of many countries. Following the widespread release of this infectious particle, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the World Health Organization (WHO) declared the infection as a pandemic on January 30, 2020.¹ According to a report released by the WHO, more than 64 million people worldwide were infected with the disease by December 2020, and according to official Statistics, the death rate was more than 1 500 000.²

Patients with SARS-CoV-2 often experience symptoms such as extreme tiredness, fever, cough, general weakness, and sputum production; however, the disease is not only limited to the symptoms associated with pneumonia but is also associated with gastrointestinal indications such as nausea, anorexia, vomiting, and diarrhea in some cases. There is also evidence of neurological disorders,

headaches, confusion, and cardiovascular symptoms such as chest distress and heart failure.^{3,4}

Although SARS-CoV-2 infection induces innate immune responses in the human body, this viral response system can induce subsequent immunopathological damages by inducing cytokine storms. Therefore, dealing with this virus requires careful evaluation of the type of infection process and recognition of its structural complexities.^{5,6} Despite this complexity, SARS-CoV-2 is not an unknown infection. Looking at the studies conducted on the last twenty years, 7 subfamilies of coronaviruses have caused mild or severe infections in humans, containing 229E,⁷ NL63,⁸ OC43,⁹ HKU1,¹⁰ Middle East respiratory syndrome beta coronavirus,¹¹ SARS-CoV (beta-coronavirus causing acute respiratory syndrome),¹² and more recently SARS-CoV-2, which causes the emerging disease the coronavirus disease 2019 (COVID-19).¹³ Many members of the coronavirus family can cause lung damage and, in some cases, multi-organ damage such as reverse myocardial changes, myocardial



stress, and cardiomyopathy.¹⁴⁻¹⁶

Coronaviruses contain structural proteins that play an important role in their life cycle.¹⁷ These proteins include the membrane, nucleocapsid, envelope, and glycoproteins spike, which is the main cause of entrance to host cells and can lead to a host immune response (Figure 1).^{18,19,20}

Spike glycoprotein homotrimer has two subunits named S1 and S2 units. Studies have shown that the S1 subunit has a domain that binds to the angiotensin-converting enzyme (ACE) receptor, and the S2 subunit binds directly to the receptor peptidase domain via a polar bond.²⁰ In addition to the S1 subunit, the coronavirus spike protein has other components such as the C-terminal that assists fusion membranes or virion attachment to cell membranes (subunit S2) and amphipathic heptad repeats involved in coiled-coil formation. Spike glycoprotein binding to the cell is facilitated by enzymes such as trypsin, furin, and cathepsin L.^{21,22}

The binding of SARS-CoV-2 to the ACE2 receptor present on the surface of alveolar pneumocytes is the starting point of the entry of this virus into the host's body.^{23,24} This receptor has the role of ACE for viral protein. Past studies have demonstrated that the highest level of ACE2 expression is in type 2 alveolar epithelial cells, and these cells can be considered the main host of SARS-CoV-2. However, since the mRNA expression of this receptor is carried out in almost all organs of the body, the infection can infect other organs as well.^{25,26}

Genetics and Polymorphism of Angiotensin-Converting Enzyme

The location of the ACE gene in humans is on the long arm of chromosome 17. This gene, which consists of 25 introns and 26 exons, is 21 kb in length.^{26,27} The main feature of the ACE enzyme is the catalysis of a dipeptide from the C-terminus of the oligopeptides that are the substrate of this enzyme.^{28,29} Bradykinin is a good substrate for ACE with a specificity constant (Kcat/Km) of 3900-5000 1-1s-mM, which is higher than the

specificity constant (147-189-mM-1s-1) for angiotensin I (Kcat/Km).³⁰ The polymorphism of this gene was first investigated by Rigat. Most of the polymorphisms discovered by Rigat are of the extrusion/deletion type. The size of D and I alleles in this gene is different due to the absence of the 287 bp sequence in intron 16; therefore, three types of genotypes including DD, DI, and II are formed.³¹ Moreover, D/I ACE polymorphism is strongly associated with the surface area of the ACE enzyme. The mean plasma ACE level in individuals with the D/D genotype is about twice as high as in individuals with the I / I genotype, while those with the D/I genotype exhibit an average level of an enzyme.³² Numerous studies on this gene indicate the possible association between this gene and human disorders such as Alzheimer's disease,³³ polycystic kidney disease,³⁴ diabetes and nephropathy,³⁵ coronary artery disease,³⁶ and complications during pregnancy such as recurrent miscarriage.³⁷ The ACE gene plays an important role in the renin-angiotensin system, and its D allele is also involved in the development of acute respiratory distress syndrome and is indicative of respiratory function in acute diseases.^{38,39} However, the reversal of the condition may also occur, and the D allele has been reported to maintain skeletal muscle stability in patients with chronic lung disease.³⁹

Researchers have previously found that angiotensin II is the result of ACE mitogen activity for lung fibroblasts. Moreover, both type 1 angiotensin receptor antagonists and ACE inhibitors have reduced interstitial fibrosis and collagen deposition in some experimental models. The inhibition of ACE activity by its inhibitor or antagonist reduces the severity of fibroblast degradation, collagen deposition, and interstitial fibrosis.⁴⁰ Additionally, considering that ACE is expressed in activated lymphocytes and alveolar macrophages, studies revealed that inactive pulmonary macrophages and inhibition of ACE reduce the expression of free radicals. However, its function in modulating inflammatory responses is not clearly defined.⁴¹ Furthermore, the free radicals produced by pulmonary macrophages, which cause respiratory disorders, increase with rising D-allele-related ACE activity. In addition, researchers believe that angiotensin II can cause tissue inflammation by inducing the migration of neutrophils,⁴² stimulating the activity of peripheral monocytes⁴³, and increasing the expression of molecules in endothelial cells.⁴⁴

Angiotensin-converting Enzyme 2 Function

ACE2 was first identified in 2000.⁴⁵ It can act as a catalyst in a variety of substrates and is a receptor for the coronavirus family or severe acute respiratory syndrome.⁴⁶ ACE2 is also a regulator of the renin-angiotensin-aldosterone system (RAAS) biochemical pathway.⁴⁷ In this system, the kidney Juxtaglomerular cells induce the activation of pro-renin by reducing the blood volume, and thus renin

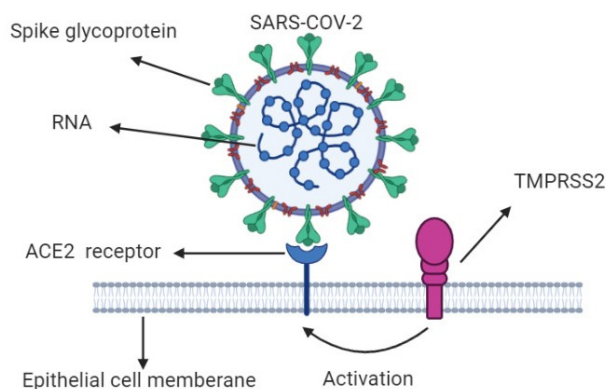


Figure 1. The Structure of the SARS-CoV-2 Virus and Its Location on the ACE2 Receptor. Note. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ACE2: Angiotensin-converting enzyme 2. Created with BioRender.com

is released into the blood. Renin can produce angiotensin 1 with the help of angiotensin, which is produced in the liver by the ACE. The lungs are responsible for producing this enzyme.⁴⁸ Angiotensin 1 produces ACE2, which is a peptide responsible for vasoconstriction and increases blood pressure by retaining water and sodium. Angiotensin 2 also stimulates the production of aldosterone from the adrenal cortex. As the absorption of water and sodium from the renal tubules under the influence of aldosterone increases, the volume of blood increases as well. The release of phenylalanine from angiotensin 2 via the ACE2 produces angiotensin 1-7, which dilates blood vessels and lowers blood pressure (Figure 2).⁴⁹

In addition to regulating the RAAS system, ACE2 can be effective in controlling pulmonary and vascular diseases as well as diabetes by regulating intestinal permeability and dysbiosis.⁵⁰ According to studies, an increase in ACE2 can be effective in controlling high blood pressure and cardiovascular disease; however, this has not yet been conclusively proven and needs further investigation.⁵¹ Similarly, some studies have shown that ACE2 can improve vascular and pulmonary damage by its catalytic activity, reduce pulmonary fibrosis and arterial regeneration, and improve right ventricular function.⁵²

Agents Affecting Angiotensin-converting Enzyme-2 Expression

ACE2 expression can be affected by smoking or diet. Studies have shown that smoking can alter the pathogenesis of SARS. ACE2 is significantly reduced in the blood of people who have smoked for a long time. Nicotine can inhibit the activity of the Mas receptor

at ACE2 / angiotensin (1-7),⁵³ thus affecting renin-angiotensin system homeostasis.⁵⁴ Additionally, the activity and expression of ACE2 can be altered by the intake of salt, glucose, and fat.^{55,56} The results of the study on the effect of diet on ACE2 activity indicated that high amounts of salt in the diet of these organisms increase the activity of this receptor. Too much salt in the diet can increase the ACE/ACE2 ratio in the glomerulus and thus impair kidney function by causing oxidative stress.⁵⁷

ACE-2 Receptor Expression and Its Role in the Severe Acute Respiratory Syndrome Coronavirus 2 Pathogenesis

According to some studies, human ACE2 is a specific receptor for SARS-CoV-2.⁵⁸ This receptor is expressed in various organs of the human body (Figure 3).⁵⁹ Therefore, these areas can potentially be exposed to the damage caused by SARS-CoV-2 infection and lead to various complications.

ACE2 plays an important role in the conversion of angiotensin 2 to angiotensin 7-1, which has an antagonistic effect on angiotensin 2.⁴⁹ Therefore, despite the role of ACE2 in pulmonary and cardiovascular injuries in patients with COVID-19, many efforts to treat this disease are based on the manipulation of the angiotensin-2-angiotensin-1-7 axis.⁶⁰ The RAAS system is blocked by ACE inhibitors, angiotensin 2 receptor antagonists, and mineralocorticoid antagonists such as statins, so patients with high blood pressure and cardiovascular failure who are routinely treated with these drugs are more likely to have more severe side effects when exposed to SARS-CoV-2.⁶¹ Therefore, the increased risk of this infection can

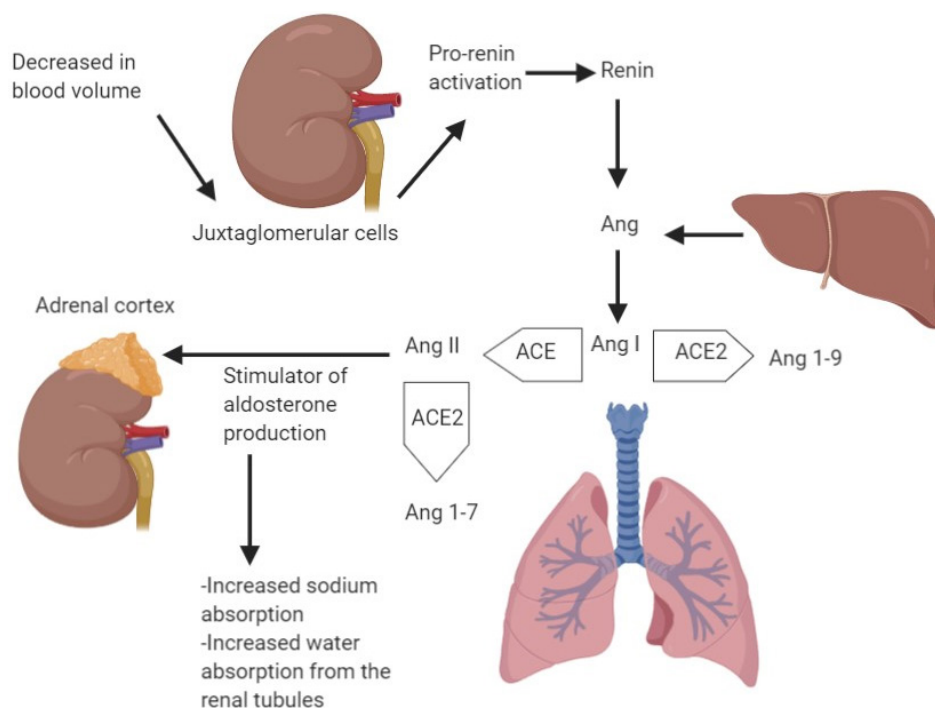


Figure 2. Renin-Angiotensin-Aldosterone System. Note. Renin-angiotensin-aldosterone system. Created with BioRender.com

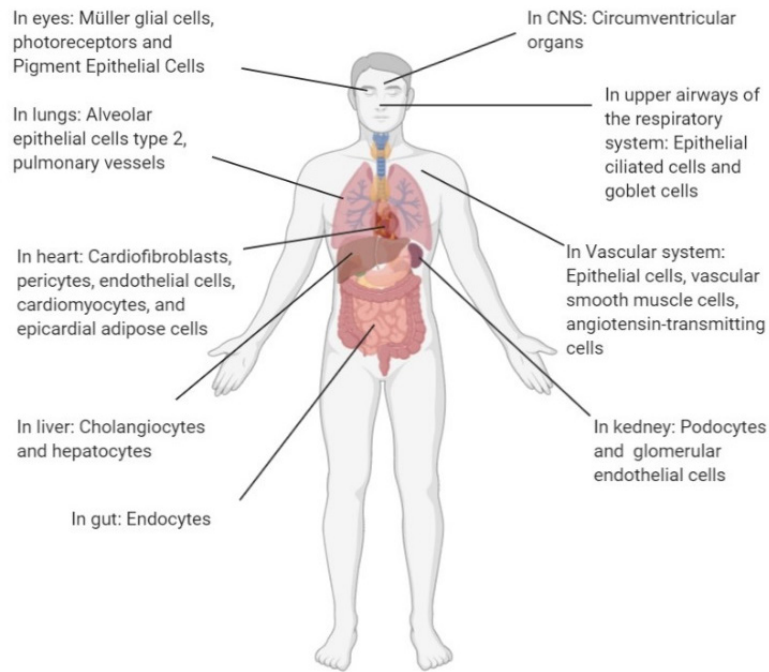


Figure 3. ACE2 Expression in Various Organs of the Human Body. *Note.* ACE2: Angiotensin-converting Enzyme 2. Created with BioRender.com

be justified in patients who previously had cardiovascular disease.

Unlike many organs in the body, recognizing and evaluating the distribution of ACE2 in the human heart are not easy. However, studies on pericytes have demonstrated that these cells can express high levels of ACE2 and therefore can be attacked as SARS-CoV-2 target cells.⁶² Damage to the pericytes following infection can cause capillary endothelial cell dysfunction and ultimately lead to microvascular insufficiency.⁶³ Research has shown that patients with underlying heart failure have higher expression of mRNA and viral proteins; therefore, it can be said that if patients with cardiovascular problems are infected with SARS-CoV-2, they will express more severe symptoms and will be more likely to have heart attacks compared to other people.⁶⁴

One of the tissues in which the ACE2 receptor is abundant is the brain. Thus, the infectious agent SARS-CoV-2 can alter the function of the central nervous system through these receptors and cause complications such as respiratory disorders (through the olfactory nerves and entering the brain), headache, nausea, and vomiting.⁶⁵ Evidence has shown that in addition to the infection of respiratory control neurons, which leads to respiratory disorders and death in patients, the entry of this infectious agent into brain tissue can induce a huge cytokine storm that causes widespread inflammation in these patients.⁶⁶

In addition to the brain, ACE2 is abundant in renal tissue. This receptor can play a role in the pathogenesis of kidney disease by regulating the metabolism of angiotensin peptide and therefore plays an important role in preventing possible tissue damage.⁶⁷ The examination

of the renal system of patients with SARS-CoV-2 has indicated the presence of nucleocapsid protein of this infectious agent in the renal tubules of infected patients.⁶⁸ However, due to the variety of clinical manifestations of the kidney in these patients, it is not possible to predict the occurrence of such consequences. Moreover, since a significant population of people around the world suffers from chronic renal failure, it is important to diagnose early manifestations, identify susceptible individuals, and control patients during SARS-CoV-2 infection.⁶⁹

Today, with the development of omics technology, valuable information such as the spatial structure of the proteome and transcriptome in various tissues of the body⁷⁰ and the expression quantitative trait loci in the kidneys have become available. ACE2 expression in kidney tissue can be genetically evaluated to analyze the effect of SARS-CoV-2 on the kidneys and predict events after infection of this organ. The results showed that significant expression quantitative trait loci were not obtained from the tubulointerstitial areas of all healthy individuals undergoing nephrectomy.⁷¹ Based on these findings, the expression of ACE2 in renal tubules is not significantly affected by genetic factors, and all individuals have an equal chance of developing renal infection due to SARS-CoV-2 infection.⁷²

The accurate diagnosis of SARS-CoV-2 kidney damage requires screening patients and routine renal tests such as serum creatinine measurement or Dipstick test for proteinuria and hematuria. Furthermore, due to the expression of ACE2 in renal tubules, the use of biomarkers of kidney damage such as neutrophil gelatinase-associated lipocalin and interleukin 8 is extremely important.^{73,74}

According to previous studies, the ACE2 receptor is more expressed in people who have greater visceral fat than other people, and due to the role of ACE2 in the RAAS system, the imbalance of this system in overweight people causes a risk factor SARS-CoV-2 for infection and progression level of this disease.⁷⁵ Although adipose tissue does not become specifically infected and does not cause direct clinical symptoms because this factor can significantly increase the mortality rate of patients, it should be prescribed by physicians, and the treatment team should be considered.⁷⁶ According to the studies conducted in this field, angiotensin II can be effective in causing insulin resistance and diabetes mellitus. Evaluations of animal models also indicated that ACE2 expression is higher in animals with diabetes.⁵⁹ Therefore, it can be concluded that high-risk groups at risk of COVID-19 are individuals with changes in the expression level of ACE2.

Studies have reported that ACE2 is more expressed in some areas of the body, including parts of the gastrointestinal tract such as the small intestine, testes, heart tissue, thyroid gland, and also in adipose tissue than in other tissues. In addition, this receptor has moderate expression in some areas (e.g., liver, colon, bladder, and adrenal gland), and it has low expression in areas such as blood vessels, bone marrow, and spleen.⁷⁷⁻⁷⁹ It should also be noted that the expression of this receptor is not related to gender and age.⁸⁰ However, in some tissues such as the skin, blood vessels, brain, and gastrointestinal tract, its expression in both genders is related to the level of the immune system.⁷⁹⁻⁸¹

Angiotensin-Converting Enzyme/Angiotensin-Converting Enzyme 2 Balance

Normally, angiotensin 1 is converted to angiotensin 2 by ACE. Angiotensin 2 causes vasoconstriction, increased oxidative stress, and high blood pressure.⁸² On the other hand, ACE2 causes the conversion of angiotensin 2 to angiotensin (1-7) and the dilation of blood vessels; therefore, the activity of ACE and ACE2 is in balance.⁸³ Some studies have displayed that ACE activity is higher than normal in patients with high blood pressure or diabetes. Therefore, angiotensin 2 is produced more than angiotensin (1-7) and the balance of ACE/ACE2 is disrupted. This imbalance can cause problems such as hypoxia, the inhibition of nitric oxide (NO), myocardial infarction, platelet accumulation, and kidney disorders.⁸⁴ In patients with COPD and ARDS, chronic hypoxia and a severe decrease in NO can result in severe lung damage.⁸⁵ In these patients, the high activity of ACE causes the increased production of angiotensin 2, and ACE2 cannot return this situation to the previous balanced state by producing sufficient amounts of angiotensin (1-7). As a result, a significant disorder occurs in the lung, heart, and kidney cells.⁸⁶

ACE 2 deficiency causes endothelial dysfunction and pro-inflammatory stimuli.⁸⁷ Accordingly, the increase in angiotensin 2 caused by ACE2 deficiency induces an increase in oxidative stress and a decrease in the synthesis of tetrahydrobiopterin, resulting in a sharp decrease in the level of endothelial NO.⁸⁸ ACE/ACE2 imbalance in diabetic patients due to the important role of ACE2 and angiotensin (1-7) in preventing the dysfunction of CAC cells and CD34 cells can cause cardiovascular dysfunction in patients with COVID-19. As a result, heart failure, cardiac arrest, and viral myocarditis are observed in these patients.⁸⁹ In addition, in diabetic patients, RAS dysfunction and the lack of ACE2 and angiotensin (1-7) can disturb the regulation of cardiac fibroblasts, cardiomyocytes, and endothelial cells and cause heart failure with ejection fraction and finally multi-organ failure and death of the patient.⁹⁰ Therefore, it can be inferred that trying to maintain the ACE/ACE2 balance can help prevent the progression of the disease.

Conclusion

The ACE2 receptor can be considered a key factor for infection caused by SARS-CoV-2. However, due to the nature of this receptor, an important step can be taken in treating or preventing the infection by adopting methods based on effective control (according to the management of possible complications) and disrupting the harmful function of the ACE2 receptor. However, the importance of the ACE receptor, specifically ACE2, should be noted in the normal functioning of many vital organs in the body.

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Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

Not applicable.

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