

## Research Article

# The Controversy on the Role of ACE2 Receptor in COVID-19 Infection: The Protective Shift toward the ACE2 Axis

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### Abstract

**Background:** Angiotensin-converting enzyme 2 (ACE2) is recognized as the main cellular receptor for the new coronavirus, SARS-CoV-2, that facilitates its entry into the host target cell, leading to the fatal viral infection, coronavirus disease 2019 (COVID-19). Thus, it is considered as a main therapeutic target in the SARS-CoV-2 infection. The dual role of ACE2 as a gate for SARS-CoV-2 virus and as a part of lung and multi-organ protection has built a scientific debate that affects the choice of treatments used against COVID-19 patient. ACE2 inhibitors like anti-ACE2 antibodies were first introduced as therapeutic solutions that, theoretically, would decrease the availability of target molecules for SARS-CoV-2 by downregulating ACE2 expression. However, animal studies showed that ACE2 upregulation acts as a counterbalance to the hypertensive pro-inflammatory angiotensin I-converting enzyme (ACE) in the renin–angiotensin system (RAS) and results in a protective role against acute lung injury – a fatal consequence of the disease. The current study tests the effect of ACE2-activating treatments against the outcome of genetic variations in the population that have ACE2-upregulatory effects.

**Conclusion** Despite its role as a receptor for the SARS-CoV-2 virus, experimental studies and the genetic polymorphisms in populations that have ACE2 upregulation revealed a protective role against COVID-19 infection.

**Keywords:** ACE2 ACE COVID-19 treatments genetic variations

## 1. Introduction

The mechanism for SARS-CoV-2 infection necessitates the binding of the virus to the membrane-bound form of angiotensin-converting enzyme 2 (ACE2) receptor, followed by the internalization of the complex by the infected host cell [1]. The main function of ACE2 is to regulate the blood pressure by opposing the action of angiotensin II (Ang II), the active peptide of the classical renin–angiotensin system (RAS). The RAS can be classified into two main axes that counteract each other to maintain vascular homeostasis: the classical vasoconstrictive axis including angiotensinogen, renin, angiotensin-converting enzyme, Ang I, Ang II, angiotensin II receptor type 1 (AT1R), and the vasorelaxant axis including ACE2, angiotensin-(1-7), and Mas receptor

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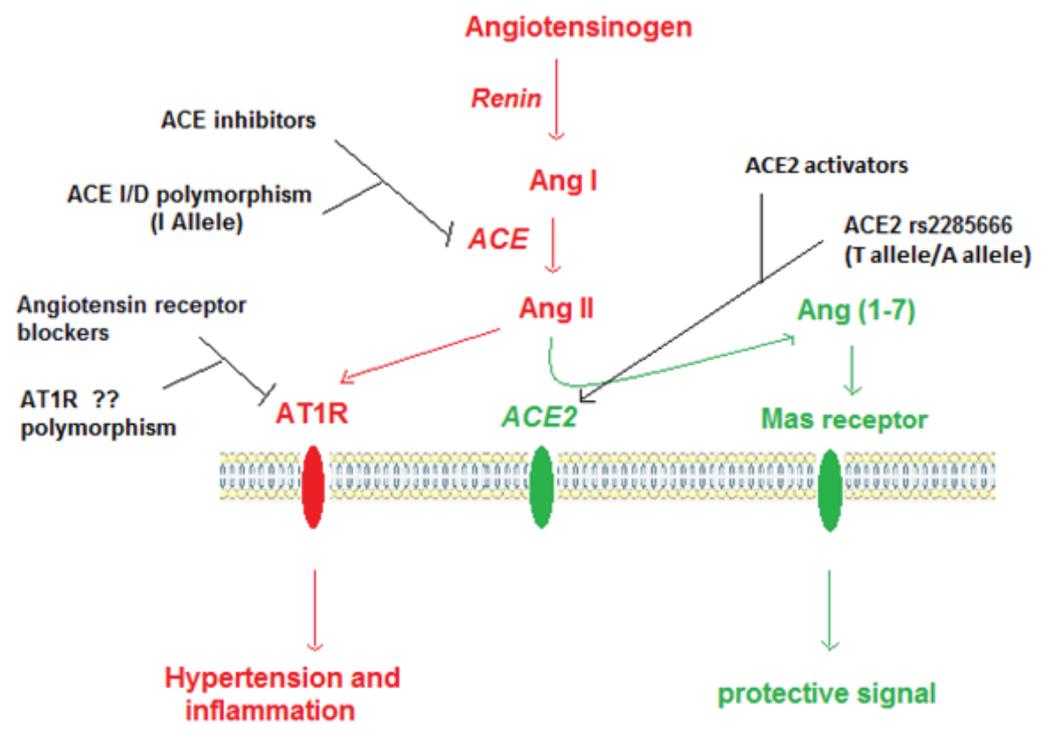
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(MasR) [2]. ACE2 acts primarily to counterbalance the effect of ACE. As ACE generates Ang II from angiotensin I, which has hypertensive pro-inflammatory effects, ACE2 generates angiotensin (1-7) from Ang II, which has potentially beneficial vasodilatory and anti-inflammatory properties [3- 5], see Figure 1. Some researchers believed that the increased expression of the ACE2 receptor may elevate the rate of SARS-CoV-2 infection via increasing viral load, morbidity, and mortality. Accordingly, they assumed that ACE2 inhibitors like anti-ACE-2 antibodies could be used to block SARS-CoV-2 binding to the receptor [6, 7]. However, preclinical studies showed that the combination of the coronavirus spike protein and ACE2 reduces ACE2 expression, leading to acute lung injury and pulmonary edema symptoms, which are the main symptoms of the disease [8]. Recently, recombinant soluble ACE2 has been introduced to neutralize SARS-CoV-2 by binding to the viral spike protein, and at the same time minimizing injury to multiple organs, including lungs, kidneys, and heart [9, 10]. The current study believes that the shift from ACE to the ACE2 axis has a beneficial effect against COVID-19. In this study, the effect of ACE2-activating treatment is discussed and compared to the protective effect of ACE2 upregulating genetic polymorphisms in populations.



**Figure 1:** The possible therapeutic targets in the renin–angiotensin system (RAS) and protective genetic polymorphisms. The red lines represent the ACE axis and the green lines represent the ACE2 axis that counteracts the ACE action. AT1R, ACE2, and Mas receptor represent the membrane-bound receptors. The possible therapeutics in ACE and ACE2 axes are coupled with genetic polymorphisms that have comparable upregulatory or downregulatory actions.

## 1.1. COVID-19 treatment and ACE2

The use of medications that have ACE2-activating effects as a treatment for COVID-19 was questioned. Theoretically, it was assumed that increasing the levels of ACE2 would increase the availability of target molecules for SARS-CoV-2 [11]. An example of ACE2-activating treatments is anti-hypertensive treatments – angiotensin-converting enzyme inhibitor (ACEI) and angiotensin-receptor blocker (ARB) that elevate the expression of ACE2. Despite the argument, a retrospective study by Zhang *et al.* found that COVID-19 patients, who were taking ACEIs and ARBs as a hypertension treatment, have a low mortality rate. This is in line with the animal studies that showed a potential protective effect with high ACE2 levels as a result of the increasing production of the vasodilator angiotensin 1–7, which ameliorates the severity of acute lung injury in SARS-CoV-infected mice [12]. On the other hand, the deficiency *ACE2* gene in animal studies showed comparable pathological changes found in human lung failure, including SARS and avian influenza A [12, 13]. The drop in the levels of ACE2 in infective cells due to the interaction of the spike protein of the coronavirus with ACE2 is also found to be responsible for the lung damage in COVID-19. This led to the idea of introducing soluble ACE2 that can neutralize SARS-CoV-2 by binding the viral spike protein, and at the same time minimizing injury to lungs and other organs [10].

## 1.2. Genetic variations and COVID-19 infection

The genetic polymorphisms of the ACE axis that decrease the activity of the RAS system along with the polymorphisms that upregulate the ACE2 axis are hypothesized to be protective by shifting the balance toward the ACE2 axis, see Figure 1. The I allele of ACE I/D polymorphism has lower tissue and plasma activity than the D allele. Individuals with the I allele are prone to be at lower risk of having hypertension than those with the D allele. It was found that the occurrence of acute respiratory distress syndrome (ARDS) and the mortality rate are higher in patients with DD genotype compared with the I allele, and the ACE I/D polymorphism was an independent prognostic factor for ARDS for 30-day survival [14, 15]. A recent study that investigated the geographic distribution of I and D alleles and the prevalence of COVID-19 infection found that with an increase in the I/D allele ratio (I allele increases or D allele decreases), the recovery rate also increases. This explains the higher recovery rate observed among the populations with a high I/D allele ratio such as the East Asian countries of China, Japan, and South Korea, while European countries like Spain, Italy, and the UK with a low I/D allele ratio took the worst-hit of the disease [16]. This is in agreement with another ecological study on high-income countries that found an association between the high frequency of the D-allele and the increased COVID-19 incidence and mortality rate [17]. The point is that genetic polymorphism of the *ACE* gene that has ACE-downregulating effect increases ACE2 and are found to have low infection and mortality rates in different populations, thus it is comparable to ACE inhibitors. On the other hand, ACE2 genetic polymorphisms that directly increase its expression level are also found to be associated with the course of infection. A wide genetic association study in India revealed that the alternate allele

(TT-plus strand or AA-minus strand) of *ACE2 rs2285666* elevate the expression level by up to 50%, and are found to have a strong correlation with low infection rate and low mortality rate among Indian populations [18].

Other witnesses are the vulnerable conditions like aging, COPD, smoking, hypertension, diabetes, and other cardiovascular disorders that have low ACE2 levels and are known to be at high risk of infection, while healthy individuals like healthy athletes and children have high levels of expression that render them to be more protected [19–22].

## 2. Conclusion

Genetic association studies revealed that genetic polymorphisms that result in high ACE2 levels are associated with low infection and low rates [16-18]. This can be taken as evidence for the protective shift toward the ACE2 axis. Thus, the use of “shift toward ACE2 axis” treatments, including both ACE2-activating and ACE downregulatory drugs, can be applied to COVID-19 and comorbidities like the safe use of metformin, the antidiabetic drug that has ACE2-activating effect, for COVID-19 patients with diabetes. Of note, the relative risk of a particular genetic polymorphism or a combination of genetic polymorphisms in populations with a low rate of infection can reflect the better choice for therapeutic targets. For example, the high relative risk of ACEI/D reflects the importance of ACE inhibitors. The same for other genetic variations like the relative risk of ACE2 rs2285666 and the effect of ACE2 activators, AT1R A1166C and AT1R blockers.

## Conflicts of Interest

The author has no conflicts of interest to disclose.

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