



Review paper

Angiotensin-converting enzyme 2 as a potential therapeutic target for COVID-19: A review

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ABSTRACT

As of August 16, 2021, there have been 207,173,086 confirmed cases and 4,361,996 deaths due to the coronavirus disease (COVID-19), and the pandemic remains a global challenge. To date, no effective and approved drugs are available for the treatment of COVID-19. Angiotensin-converting enzyme 2 (ACE2) plays a crucial role in the invasion into host cells by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of COVID-19. Notably, ACE2 density is influenced by medical conditions, such as hypertension, or by drugs, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which can change the fate of SARS-CoV-2 infectivity. ACE2 is a target for these drugs and can be manipulated to limit the viral entry and replication within the cells. Different strategies aimed at blocking ACE2 with small molecules, peptides, and antibodies, or by neutralizing the virus through its competitive binding with human recombinant soluble ACE2 (hrsACE2) are currently under investigation. In this article, we review the current state of knowledge that emphasizes the need to find effective therapeutic agents against COVID-19 by exploiting ACE2 as a potential target. The increased soluble ACE2 levels and the application of hrsACE2 in patients with COVID-19 can be implemented to control the disease. It has not yet been established whether hypertension and other comorbidities, independent of age, have a direct role in COVID-19. Therefore, the use of renin-angiotensin system inhibitors, ACEIs and ARBs, should not be discontinued during COVID-19 treatment.

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1. Introduction

A series of coronavirus epidemics caused by severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), SARS-like virus, and the Middle East respiratory syndrome coronavirus occurred in 2002, 2004, and 2012, respectively. More recently, another virus which is similar to the coronaviruses and utilizes the same mode of entry (including the receptors) into the host cells caused the current coronavirus disease 2019 (COVID-19) pandemic; this virus was named SARS-CoV-2. Sequencing of the genomes for both SARS-CoV-1 and SARS-CoV-2 revealed that they share 79.5% sequence identity, and the comparison using pair-wise protein sequences also confirmed a high similarity between the two viruses,

indicating that both viruses belong to coronaviruses [1]. This review discusses angiotensin-converting enzyme 2 (ACE2), human recombinant soluble ACE2 (hrsACE2), ACE2 receptors, angiotensin (Ang) II, Ang (1–7), renin-angiotensin system (RAS) inhibitors, ACE inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). We have also focused on the impact of ACE2/hrsACE2 on disease prevention and their relationship with SARS-CoV-2 susceptibility. The highest prevalence of COVID-19 is in older patients, especially those with comorbidities, including diabetes mellitus, hypertension, obesity, and chronic kidney disease [2].

Li et al. [3] demonstrated that ACE2 is the receptor responsible for SARS-CoV-2 entry into host cells. In addition, ACE2, along with RAS activation, also functions as a receptor for SARS-CoV-1 [4]. Of note, the use of RAS inhibitors may influence ACE2 density [5–8]. It catalyzes the conversion of Ang-II (1–9) into Ang (1–7), which counteracts the adverse effects of RAS through the ACE2/Ang (1–7)/mitochondrial assembly (MAS) receptor axis. Several factors

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associated with COVID-19 pathogenesis, including ACE2 down-regulation, RAS activity, and the ACE2/Ang (1–7)/MAS axis, may result in multiple organ injury [9,10]. Strategies for blocking ACE2 using small molecules, such as antibodies and transmembrane protease serine 2 (TMPRSS2) inhibitors (camostat mesylate), are currently being implemented [4]. Generally, the expression of ACE2 in the lungs is reduced compared to that in other organs, including the heart and kidney [11]. ACEs do not have any impact on ACE2 expression as ACE and ACE2 are different enzymes [12].

2. RAS and ACE2

RAS is an important process in human physiology, which involves a cascade of vasoactive peptides [3]. It regulates several pathophysiological events, including blood pressure, inflammation, and coagulation [13]. ACE2 plays a significant role in RAS through Ang-I and Ang-II [14]. Angiotensinogen is produced by the liver and is cleaved into Ang-I through renin, and further conversion from Ang-I into the most important vasoconstrictor peptide, Ang-II, is mediated by ACE [15]. ACE and ACE2 display considerable homology (40% identity and 61% similarity) [16]. ACE2 is a mono-carboxypeptidase that can hydrolyze multiple peptides, including opioids, apelin, kinins, and angiotensin. It converts Ang-I into Ang (1–9) and Ang-II into Ang (1–7) in this metabolic pathway. Ang (1–7) counteracts the effects of Ang-II through the MAS receptor and thus, protects against organ injury. When it binds to MAS receptors, Ang (1–7) results in vasodilation, anti-inflammation, and anti-proliferation. Since this pathway has a favorable effect, it is known as the protective pathway of RAS [17], as shown in Fig. 1.

3. SARS-CoV-2 and ACE2 receptors

ACE2 works as a special receptor protein that helps with the interaction between the receptor-binding motif of SARS-CoV-2 and the host cell [18]. It is anchored, in full-length, to the apical plasma membrane in the polarized epithelia of the lungs, kidneys, and intestines [11,19]. In 2000, ACE2 was discovered as a homolog of ACE that can convert Ang-II into Ang (1–7) through the removal of carboxy-terminal phenylalanine [16]. To date, three receptors with similar affinity for Ang-II have been identified [1]. Of these three receptors, angiotensin type 1 receptor (AT₁R) binds to Ang-II, resulting in inflammation, vasoconstriction, cell proliferation, and blood coagulation, while angiotensin type 2 receptor helps reduce the effects mediated by AT₁R [20]. The ACE2/Ang (1–7)/MAS axis cause vasodilation, antioxidation, and anti-inflammation. The transmembrane domain of ACE2 anchors a cleavable domain, which is cleaved by the membrane-bound protease, a disintegrin and metallopeptidase domain 17 (ADAM17), and released into the blood [21,22]. Thus, ACE2 can attenuate vasoconstriction, sodium retention, pro-fibrotic effects, and pro-inflammatory effects of Ang II (1–9) by its degradation to Ang (1–7) [13]. The interaction between SARS-CoV-2 and ACE2 is the key feature for infectivity of COVID-19 [23]; hence, before discussing possible approaches to the prevention of SARS-CoV-2 and ACE2 complex formation, we must understand the infection process.

4. Role of ACE2 during SARS-CoV-2 infection

The degree of ACE2 expression differs between organs. ACE2 has a significantly greater affinity for respiratory epithelial cell surfaces than for other cell surfaces [24]. The first step of viral infection is entry into the host cells through the interaction of the viral envelope spike glycoprotein (S protein) with ACE2. In an animal model, the S protein of SARS-CoV-2 binds to ACE2, leading to its down-regulation, which results in lung damage [23]. Hoffmann et al. [4]

confirmed that ACE2 is a specific receptor for SARS-CoV-2 interaction. The SARS-CoV-2 S protein's affinity for ACE2 is higher (approximately 10- to 20-fold) than the affinity of the SARS-CoV-1 glycoprotein for ACE2 [25]. In another study by Zhou et al. [26], SARS-CoV-2 entered cells that express ACE2, but not cells expressing other receptors, such as aminopeptidase N and dipeptidyl peptidase 4, thus confirming SARS-CoV-2 entry through ACE2 [1]. After binding, the SARS-CoV-2-ACE2 complex enters the host cell through endocytosis, and a single-stranded viral genome is subsequently released into the cell cytoplasm and infection is established. As SARS-CoV-2 enters the host cell through ACE2, if the interaction or binding of SARS-CoV-2 with ACE2 is inhibited, the spread of infection may be mitigated [4,9]. There are a few approaches that can be adopted to inhibit this interaction. First, a competitive analog can be used to block the site where SARS-CoV-2 binds. Second, the upregulation of ACE2 leads to the release of increasingly soluble ACE2, thereby limiting its binding to SARS-CoV-2. Last, the use of hrsACE2 which has the ability to bind to the viral S protein reduces the interaction between SARS-CoV-2 and natural ACE2, resulting in the reduction of infection.

5. Potential therapeutic targets and ACE2

COVID-19 infection begins when the ACE2-SARS-CoV-2 complex is internalized [27]. The S protein does not occlude the catalytically active site of ACE2, and the process of SARS-CoV-2 binding is independent of the peptidase activity of ACE2 [28]. After binding to ACE2, the S protein of SARS-CoV-2 is cleaved by proteases that are readily expressed in the lungs, e.g., TMPRSS2, resulting in membrane fusion with the target cell [29–33]. During the process of binding, ACE2 is cleaved by ADAM17, causing ectodomain shedding, and TMPRSS2 also cleaves ACE2, resulting in virus uptake [29]. Soluble ACE2 levels are significantly high in urine, probably originating from the shedding of the proximal tubular membrane. ACE2 shedding also increases in a certain pathological state that increases soluble ACE2 levels and may be detected in blood, urine, and other body fluids [34,35].

ACE2 is the receptor responsible for coronavirus entry. Further entry depends on priming with TMPRSS2. This interaction can be blocked by TMPRSS2 inhibitors (camostat mesylate) and antibodies that can neutralize the S protein. Generally, ACE2 expression is observed in type-2 pneumocytes in the lungs. However, its expression is lower in the lungs than in other organs, such as the kidney and heart [11,36]. ACEs can increase Ang (1–7) levels, while ARBs increase both Ang II and Ang (1–7) levels, and thus, reduce organ injuries [37,38]. In a population-based study, it was proposed that the mortality rate in patients with pneumonia was significantly reduced using ACEs and ARBs [39]. ACE2 internalization is induced by Ang-II via AT₁R in ACE2-transfected neuroblastoma cells [40]; therefore, the potentially beneficial effect of ARBs should not be overlooked. During the severe acute lung injury induced by acid aspiration or sepsis in mice, alveolar ACE2 is downregulated [41], resulting in reduced Ang-II metabolism and an increased level of Ang-II. This increases alveolar permeability, resulting in lung injury. Therefore, maintaining high ACE2 expression using pre-existing ARBs may be protective. Moreover, SARS-CoV-2 and ACE2 interaction can be reduced using hrsACE2, which results in the reduction of virion entry into the target cells.

5.1. Interaction inhibition between SARS-CoV-2 and ACE2

Recently, researchers have focused on preventing SARS-CoV-2 cell entry by using inhibitors of the ACE2 receptor as a COVID-19 treatment option. Compounds that bind to ACE2 receptors with a high affinity, such as morphine and codeine, can compete with the

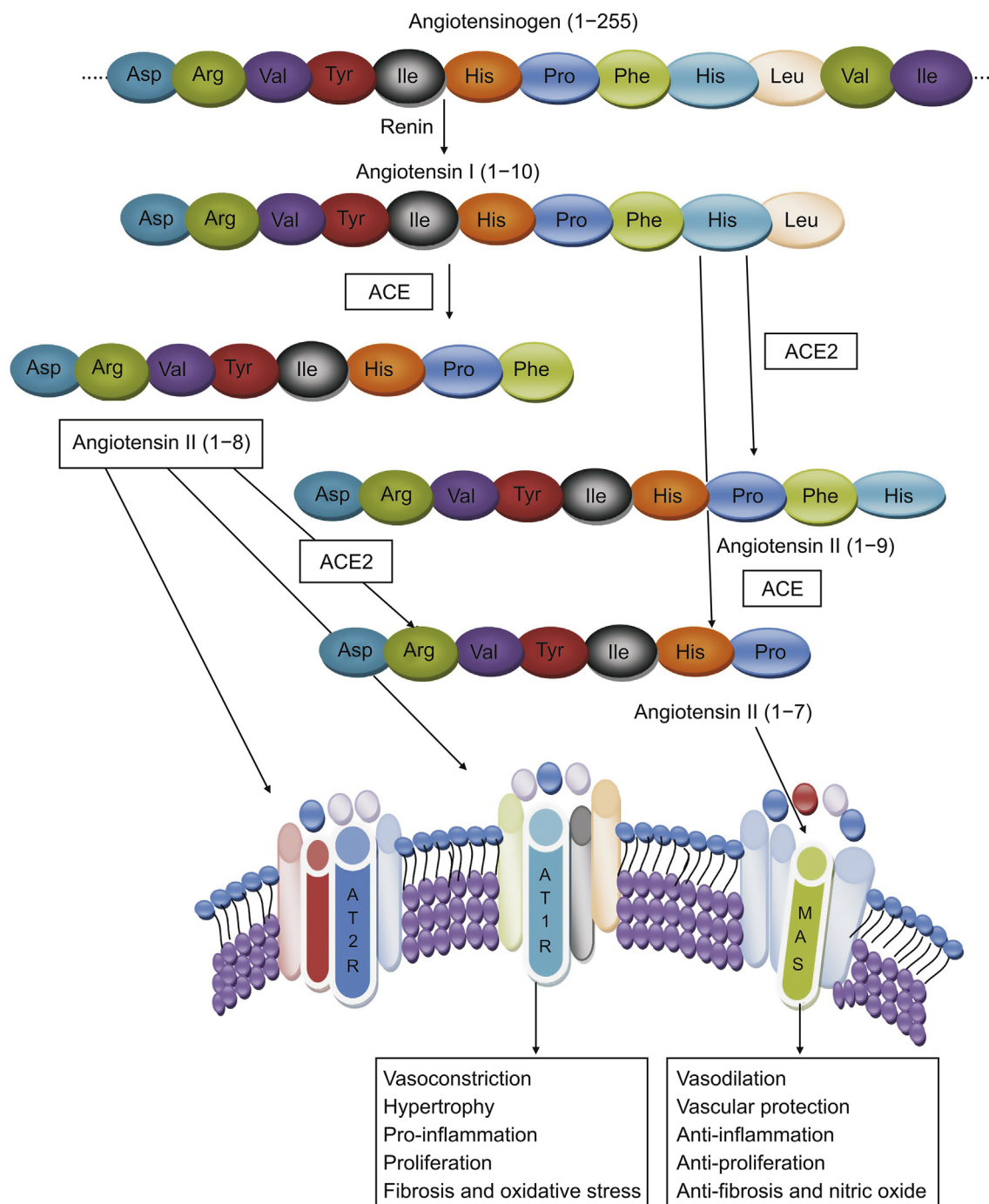


Fig. 1. Overview of the relation between renin-angiotensin system (RAS) and angiotensin-converting enzyme 2 (ACE2). ACE2 catalyzes the conversion of angiotensin (Ang) I into Ang (1–9) and Ang-II into Ang (1–7). Ang-II binds to angiotensin type 1 receptor (AT₁R), exerting harmful effects on the lungs through vasoconstriction, hypertrophy, proliferation, fibrosis, and oxidative stress. Ang (1–7) binds to the mitochondrial assembly (MAS) receptor axis, resulting in protective function through vasodilation, anti-fibrosis, vascular protection, anti-proliferation, and anti-inflammation effects.

virus [42]. Traditionally, morphine is used in anesthesia and for instant management of severe pain. Morphine being an analgesic drug and a natural opioid, its effect is mediated through the μ , δ , and κ opioid receptors. It has been observed that morphine (–6.6 kcal/mol) and codeine or methyl-morphine (C₁₈H₂₁NO₃; –7 kcal/mol) have high affinities for the ACE2 receptor (docking score < –10 kcal/mol) [43]. Thus, fewer receptors will be available for SARS-CoV-2 binding, thereby inhibiting viral entry into the host cell.

5.2. hrsACE2 and COVID-19

Studies on different human organ tissue samples have revealed that ACE2 expression occurs in the heart, kidneys, and in the principal target cells of SARS-CoV-2, the lung alveolar epithelial cells (site of dominant injury) [11]. Under normal conditions, the level of soluble ACE2 is extremely low, and its functional role in the lungs also seems relatively minimal [12], which can be enhanced

using hrsACE2. Recently, much attention has been paid to hrsACE2 (APN01, also known as GSK2586881) [44,45]. Previous studies also suggest that the use of hrsACE2, obtained from the supernatant of ACE2-transfected cells reduced plasma Ang-II and increased plasma Ang (1–7); as a result, it helps to prevent myocardial hypertrophy, fibrosis, and diastolic dysfunction [46]. In other studies, the use of hrsACE2 was safe in healthy human subjects and patients with acute respiratory distress syndrome [47,48]. Engineered, high-affinity variants of hrsACE2 function as decoy receptors and compete with native ACE2 present on cells, neutralizing SARS-CoV-2 [49]. Extensive experimental research on animals also demonstrates that hrsACE2 reduces acute lung injury in ACE2-deficient mice [50,51].

Myocardial injury markers are elevated during the course of COVID-19 [52] and continue to increase rapidly, leading to death [26]. Approximately 35% of the heart samples that were obtained during autopsies of patients who succumbed to the SARS crisis during Toronto SARS outbreak showed SARS-CoV-1 viral RNA, which was also linked with reduced ACE2 expression [53]. Administration of hrsACE2 in explanted human hearts with dilated cardiomyopathy resulted in normalized Ang-II levels [54]. Hypotheses are being tested to determine whether hrsACE2 can restore beneficial effects by balancing the RAS network and potentially preventing organ injury (trial registration number: NCT04287686) [55]. Such approaches support the hypothesis that ACE2 could be a potential target to limit SARS-CoV-2 entry and can be used for the treatment of patients with COVID-19, ultimately resulting in COVID-19 eradication.

6. COVID-19 and ARBs

There is a divided expert outlook on the subsequent impact of ACEI/ARBs and hrsACE2 therapies in treating COVID-19. The use of ACEIs/ARBs, renin inhibitors, and Ang (1–7) analogs can attenuate organ injury [37]. Several studies have shown that AT₁R blockers alter ACE2 expression more consistently at the mRNA and protein levels [38]. Patients with lung injury due to COVID-19 have elevated levels of Ang-II [56]. In a cohort study among hospitalized patients with COVID-19, ACEI and ARB exposure reduced ICU admission incidence rates [57]. Continued viral infection and replication in *in vitro* cultured cells contributed to reduced membrane ACE2 expression [58]. Research shows that ACE inhibitory peptides can stop the formation of Ang-II from Ang-I, thus resulting in the reduction of hypertension [59,60]. About 15% patients with SARS-CoV-2 had hypertension up to January 2, 2020 [61]. Angiotensin II type 1 receptor blockers was found to upregulate ACE2 in experimental animals [12]. In addition, ACEI and ARB can reduce the mortality rate in patients with pneumonia [39]. The disadvantages of indiscriminate withdrawal of these therapeutic molecules have been well documented [62]. Notably, increasing age is consistently associated with adverse outcomes of COVID-19 [63]. The severity risk of clinical manifestation of COVID-19 in males is higher than that in females, and it increases with age and chronic comorbidities. It has not yet been established whether hypertension and other comorbidities, independent of age, play a direct role in COVID-19 [64]. However, a meta-analysis demonstrated that the discontinuation of ARBs, ACEIs, and β -blockers resulted in a 2–4 times higher risk of death due to SARS-CoV-2, even when corrected for sex, age, and severity of symptoms during admission [65]. Therefore, it is recommended that patients with heart failure, high blood pressure, or other medical indications should not withdraw their treatment with ACEIs and ARBs unless a physician has advised doing so. The dangers of withdrawal from these medications would carry unacceptable risks of precipitating strokes and heart attacks. Discontinuing ACEI

and ARB is associated with an increased risk of death, even after adjusting for severe diseases.

7. Potential targets for vaccine development

Vaccines are used to prevent diseases and save millions of lives every year worldwide. They enhance the body's natural defense system and prepare it to fight against pathogenic organisms, including viruses and bacteria [66]. Different immunization vehicles for the prevention of COVID-19 with a few side effects have been developed by authorized bodies. Serum samples from convalescent patients with COVID-19 can neutralize SARS-CoV-2, suggesting that the viral S protein remains a promising target for vaccines [4]. By targeting the S protein on the virus's surface, researchers and vaccine experts have designed several vaccines. Studies have found that recombinant ACE2-Ig and SARS-CoV-2-specific monoclonal antibodies block SARS-CoV-2 entry [67–69]. Different companies and academic institutions, including Pfizer Inc., Moderna Inc., AstraZeneca Pharmaceuticals Ltd., Serum Institute of India, Indian Council of Medical Research, and Bharat Biotech, have developed COVID-19 vaccines using different technologies, including mRNA, vectors, and viral inactivation [70]. These vaccines provide assistance in the fight against COVID-19 and have reduced the number of cases worldwide.

8. Conclusions

Different research institutions, governments, and private sectors are working together to fight the impacts of the COVID-19 pandemic. The clinical databases and information currently available are insufficient. However, there are a few approaches based on blocking SARS-CoV-2/ACE2 interactions that may be potentially used to mitigate the impacts of COVID-19. Promising approaches to blocking the SARS-CoV-2 and ACE2 interaction include using a competitive analogue that can block or modify the SARS-CoV-2 binding site. Alternatively, ACE2 upregulation leads to the increased release of soluble ACE2 that can bind to SARS-CoV-2 and prevent its binding with ACE2. Additionally, the use of hrsACE2 may also be used to inhibit the interaction between SARS-CoV-2 and ACE2. As a biological drug, hrsACE2 is capable of competitively binding to SARS-CoV-2 and, thus, prevents the interaction between the virus and endogenous ACE2 to prevent entry into host cells, which confers protection against lung damage.

The abrupt withdrawal of RAS inhibitors results in clinical instability and adverse health outcomes. Currently, the available data are insufficient to support any adverse impact of RAS blockers in COVID-19. Since the information is lacking, there is no rationale to panic and to alter the prescription of a critically important class of antihypertensives. Major comorbidities include hypertension and diabetes, leading to a worse outcome of COVID-19. Moreover, increasing age is consistently associated with increasing COVID-19 severity.

Currently, no therapy has been established for patients with COVID-19. Effective drug development that can block viral entry into host cells is underway, and researchers working in this field are primarily targeting ACE2. The capability of hrsACE2 to act as a decoy receptor to bind with SARS-CoV-2 is a promising option and has been tested in humans and animal models. Blocking specific binding is a potentially promising target to mitigate the spread of SARS-CoV-2 infection. Therefore, soluble ACE2 is a better target for preventing viral interactions in the treatment of patients with COVID-19.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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