STATE OF THE ART REVIEW

ACE2: The Major Cell Entry Receptor for SARS-CoV-2

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Abstract

Despite the unprecedented effort of the scientific community, the novel SARS-CoV-2 virus has infected more than 46 million people worldwide, killing over one million two hundred thousand. Understanding the mechanisms by which some individuals are more susceptible to SARS-CoV-2 infection and why a subgroup of them are prone to experience severe pneumonia, and death should lead to a better approach and more effective treatments for COVID-19. Here, we focus our attention on ACE2, a primary receptor of SARS-CoV-2. We will discuss its biology, tissue expression, and post-translational regulation that determine its potential to be employed by SARS-CoV-2 for cell entry. Particular attention will be given to how the ACE2 soluble form can have a great impact on disease progression and thus be used in a potential therapeutic strategy. Furthermore, we will discuss repercussions that SARS-CoV-2/ACE2 binding has on the renin–angiotensin system and beyond. Indeed, although mostly neglected, ACE2 can also act on [des-Arg 937]-bradykinin of the kinin–kallikrein system regulating coagulation and inflammation. Thorough comprehension of the role that ACE2 plays in different pathways will be the key to assess the impact that SARS-CoV-2/ACE2 binding has on organismal physiology and will help us to find better therapies and diagnostic tools.

Keywords SARS-CoV-2 · ACE2 receptor · COVID-19

Introduction

In the last 20 years, humanity has witnessed an increasing number of pandemics that have hospitalized or killed hundreds of thousands of people, leaving our healthcare systems under unprecedented pressure. Severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome in 2012 (MERS) [1], and more recently the novel infection named COVID-19, detected in Wuhan China in 2019 are caused by closely related coronaviruses, SARS-CoV, MERS-CoV and SARS-CoV-2, respectively [2]. Their unexpected and periodic appearance combined with a high level of human-to-human transmission has made coronaviruses a threat to our societies and economies, forcing us to think not if but when another pandemic will arise. From this perspective, more needs to be done to better understand the mechanism of infection, if and how the hyperactivation of the immune reaction can be prevented, and which treatments can be provided, especially for people with comorbidities.

In this review, a focus will be given to the metallocarboxyl peptidase angiotensin receptor (ACE)2 that is used by SARS-CoV-2 to gain entry into human cells [3]. There are two forms of ACE2 [4]. The full-length mACE2 is located on cell membranes and consists of a transmembrane anchor and an extracellular domain. It is the receptor site for the spike (S) proteins of SARS-CoV-2. The S proteins on the envelope of SARS-CoV-2 are cleaved into S1 and S2 subunits, the S1 protein/receptor interaction being the pivotal determinant for SARS-CoV-2 to infect a host species [3]. The second form, sACE2, is a soluble form that is shed into the circulation [4]. This form of ACE lacks
membrane anchors and circulates in low concentrations. We will assess whether the level of expression of ACE2 and the ratio between mACE2 and sACE2 could explain why some people experience more severe symptoms than others. Furthermore, we will discuss the key role that ACE2 plays in regulating molecular pathways that go beyond the renin–angiotensin–aldosterone system (RAAS) and have been mostly ignored. We believe that efforts towards the full comprehension of the intricate roles that ACE2 plays in maintaining organismal physiology will be the key to better understand the multisystemic COVID-19 disease and help us to develop better therapies and diagnostic tools.

### Cell Entry Receptors: Lessons from Other Respiratory Viruses

Cell entry receptors are undoubtedly the key factors determining the tropism and influencing the severity of infection of a specific virus. Furthermore, the high rate of mutations to which these viruses are subject can allow them to change their specificity or binding affinity for a specific receptor. For instance, CoV-NL63, SARS-CoV, and SARS-CoV-2 use ACE2, but CoV-NL63 leads to mild respiratory tract illness, probably because of its low-affinity interaction with the receptor [5]. Although belonging to the same genus of its related SARS-CoV-2 (Table 1), MERS-CoV binds to dipeptidyl peptidase-4 (DPP4) [6] that plays an important role in glucose metabolism, apoptosis, and the immune system.

Coronaviruses are not the only family of viruses able to cause respiratory tract illness in humans. The A(H1N1) pdm09 influenza virus that caused the pandemic in 2009 shows a different tropism binding to α2-6- and α2-3-linked sialyl glycans [7] that are present on different cell types and play key roles in cellular communication and cell signaling among others. Finally, human rhinoviruses (HRV), which can cause severe illness if in combination with pre-existing conditions [8], use mainly the membrane form of the intercellular adhesion molecule-1 (ICAM-1) that is expressed in nasal and bronchial epithelial cells [9]. This interaction has been demonstrated to regulate differently the two soluble and membrane-bound forms, suggesting a different role during the infection [10].

#### Table 1 Human viruses strains

| Human viruses strains | Genus          | Major cell receptor | First report | Animal reservoir | Intermediate host | Pathology                     | Diagnostic test       |
|-----------------------|----------------|---------------------|--------------|------------------|--------------------|-------------------------------|-----------------------|
| HCoV-OC43             | Betacoronavirus| Sialic acid, HLA class I molecule | 1966         | Rodent           | Bovine             | Mild respiratory tract illness | RT-PCR, IF, ELISA, WB |
| HCoV-229E             | Alphacoronavirus| Human aminopeptidase N | 1967         | Bat              | Dromedary          | Mild respiratory tract illness | RT-PCR, IF, ELISA, WB |
| HCoV-NL63             | Alphacoronavirus| ACE2                | 2004         | Bat              | Unknown            | Mild respiratory tract illness | RT-PCR, IF, ELISA, WB |
| HCoV-HKU1             | Betacoronavirus| Sialic acid         | 2005         | Rodent           | Unknown            | Mild respiratory tract illness | RT-PCR, IF, ELISA, WB |
| SARS-CoV              | Betacoronavirus| ACE2                | 2003         | Bat              | Pangolin           | Severe acute respiratory syndrome | RT-PCR, IF, ELISA, WB |
| MERS-CoV              | Betacoronavirus| DPP4                | 2012         | Bat              | Dromedary          | Severe acute respiratory syndrome | RT-PCR, IF, ELISA, WB |
| SARS-CoV-2            | Betacoronavirus| ACE2                | 2020         | Bat              | Pangolin           | Severe acute respiratory syndrome | RT-PCR, IF, ELISA, WB |
| AH1N1                 | Orthomyxovirus | Sialic acid         | 2009         | None             | None               | Respiratory tract illness      | RT-PCR, IF, ELISA, WB |
| Rhinoviruses          | Picornaviridae | ICAM-1              | 1956         | None             | None               | Mild respiratory tract illness Asthma/COPD exacerbations | RT-PCR, IF, ELISA, WB |

List of human viruses strains. Human Coronavirus-OC43 (HCoV-OC43), Human Coronavirus-229E (HCoV-229E), Human Coronavirus-NL63 (HCoV-NL63), Human Coronavirus-HKU1 (HCoV-HKU1), Severe acute respiratory syndrome-Coronavirus (SARS-CoV), Severe acute respiratory syndrome-Coronavirus (SARS-CoV-2), Middle east respiratory syndrome-Coronavirus, Influenza A virus subtype H1N1 (A/H1N1), Angiotensin converting enzyme 2 (ACE2), Dipeptidyl peptidase-4 (DPP4), Intercellular adhesion molecule-1 (ICAM1), Reverse transcriptase-polymerase chain reaction (RT-PCR), Immuno-fluorescence (IF), Enzyme-linked immunosorbent assay (ELISA), Western Blot (WB)
Biology, Tissue Expression, and Post-translational Modifications of ACE2 Receptor

Biology

ACE2 was initially identified in 2000 as a homolog of the ACE receptor, sharing 40% identity and 60% similarity, respectively [11, 12]. Located on the X chromosome and precisely mapping on chromosomal location Xp22, it is formed by 18 exons and 20 introns generating 6 variants through alternative splicing [13]. ACE2, which consists of 805 amino acids, has only a single extracellular N-terminal domain containing the active catalytic site domain, a C-terminal membrane anchor, and a conserved HEXXH zinc-binding domain [11]. It acts as a carboxypeptidase removing single amino acids from the C-terminus of its substrates [14].

Experimental evidence has demonstrated that in the situation of cell energy stress, sirtuin 1 (SIRT1) can mediate ACE2 transcriptional activation [15]. Similarly, the reduced ACE2 level in apelin deficient mice was corrected by apelin treatment [16] suggesting that apelin acts as a positive regulator of ACE2 expression and might have a role in affecting other pathways regulated by ACE2. Apeilins are a family of peptides that activate the apelin receptor, which physically interacts with the angiotensin type I receptor (AT1R) [17], forcing it into a low-affinity state and reducing the binding and signaling of angiotensin II (AngII) [18]. Conversely, the microRNA 421 (miR421) has been shown to target a binding site in the 3'-UTR of ACE2 transcript, negatively regulating the receptor [19].

ACE2 Tissue Expression

Due to the wide spectrum of symptoms occurring in people affected by COVID-19, efforts have been made to study ACE2 tissue expression in both mRNA and protein levels, identifying the organs more susceptible to this infection. Surprisingly, the analysis of ACE2 expression in experimental models and in human transcriptome by using different databases revealed that it is very low in the lung, mainly limited to a small fraction of type II alveolar epithelial cells [20–22]. Since most people present respiratory difficulties in response to SARS-CoV-2 infection, these findings were explained by the fact that the release of inflammatory cytokines, such as interferons (IFNs) caused by SARS-CoV-2, can increase the expression ACE2 and potentiate the infection [23, 24]. However, Onabajo and colleagues recently showed that IFNs stimulation upon viral treatment induced the expression of a truncated ACE2 isoform designate as δACE2, which lacks 356 N-terminal amino acids, is not able to bind SARS-CoV-2 and, therefore, does not contribute to the potentiation of the infection [25].

Furthermore, the analysis of ACE2 mRNA and protein expression in experimental models, and evaluation of three different databases have demonstrated that small intestine, testis, kidney, heart muscle, colon, and thyroid gland are the overlapping tissues with the highest level of ACE2 expression, with no expression detected in blood cells [20, 26]. These data explain why people affected by COVID-19 experience gastrointestinal problems and kidney dysfunction [27, 28].

ACE2 Expression in Pathological Conditions

Several clinical reports have suggested that male sex combined with increasing age [29], smoking, and pre-existing comorbidities [30] represent risk factors for a poor outcome from the infection. Whether there is upregulation of ACE2 expression in smokers that could increase their sensitivity to infection is still a matter of debate. In the literature, there are reports supporting [31–33] and refuting [34–36] this hypothesis.

Since the beginning of the COVID-19 pandemic, hypertension and diabetes have been correlated with higher risk of mortality, and initial reports speculated that angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), which are commonly used therapeutic agents for these conditions, would up-regulate ACE2 expression, thus increasing the risk of severe illness [37]. Recent evidence has challenged this hypothesis, demonstrating both mechanistically and in large cohort studies that ACEi and ARBs do not up-regulate ACE2 and are not associated with an increased mortality [35, 36].

Interestingly, asthma has not been reported as a risk factor for COVID-19 illness and disease progression. Kimura and colleagues showed that interleukin (IL)-13, a cytokine up-regulated in type 2 asthma, down-regulates the level of ACE2 [38]. Furthermore, Jackson and colleagues demonstrated a negative correlation between ACE2 expression and allergen sensitization and asthma [39]. Intriguingly, Peters and colleagues found that asthmatic subjects treated with inhaled corticosteroids (ICS) had low ACE2 expression compared with untreated subjects, a finding suggesting that ICS treatment could be a predictor of decreased susceptibility to SARS-CoV-2 infection [40].

ACE2 Post-translational Modification

ACE2 is normally localized on the plasma membrane (mACE2) with the N-terminal containing the catalytic site protruding on the extracellular space using as substrate
different active peptides present in the interstitium. ACE2 can undergo proteolytic shedding by different proteases such as a disintegrin and metalloproteinase domain-containing protein (ADAM)10, ADAM17, and transmembrane protease, serine 2 (TMPRSS2). Binding of S1 subunit of the Spike protein of SARS-CoV-2 to the ACE2 receptor triggers the cleavage of ACE2 by ADAM17/tumor necrosis factor-converting enzyme (TACE) at the ectodomain sites [41] and a soluble form that retains its catalytic activity (sACE2) is produced [42]. Interestingly, TACE inhibitors can decrease viral entry in vitro and in vivo demonstrating their key role in determining SARS-CoV infectivity and their potential use as a target for antiviral therapies [43].

The significance of ACE2 shedding has not been fully elucidated, but in the context of the COVID-19 pandemic, the comprehension of the mechanism leading to ACE2 shedding, sACE2 function, and its plasma level can lead to the development of better therapies and diagnostic tools to follow disease progression and severity. For example, it has been shown that the binding of SARS-CoV with ACE2 induced ADAM17-dependent shedding, promoting SARS-CoV uptake into the cells [44].

TMPRSS2 is able to promote ACE2 proteolytic cleavage using different targets in the protein sequence. It cleaves ACE2 at the intracellular C-terminal domain and, differently from ADAM17 [45], does not produce a soluble form that retains the catalytic function [41]. However, like ADAM17, it is essential for SARS-CoV entry into the cell [45, 46].

ACE2 shedding can be stimulated by proinflammatory cytokines such as IL-1β and tumor necrosis factor (TNF)-α, and endotoxin [47] that could result in a positive effect reducing SARS-CoV-2 entry, but at the same time, may cause an increase in AngII and further activation of the AngII/AT1R axis worsening inflammation (discussed below) (Fig. 1). Different studies have demonstrated that an

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**Fig. 1** SARS-CoV-2 infection and dysregulation of the RAAS and KKS. Sars-CoV-2 binding to the ACE2 receptor can cause its internalization and possible dysregulation of both the RAAS and KKS. Indeed, without the counterbalance action of ACE2, AngII is not converted in Ang1–7 and able to overactivate its receptor AT1R promoting vasoconstriction, production of proinflammatory cytokines such as TNFα, IL6, IL1, and ROS generation through NADPH oxidase. ACE2 also plays a key role in the regulation of the KKS by inactivating LDEABK and DEABK making them incapable to bind the receptor BRB1. The overactivation of BRB1 receptor has been shown to promote inflammation and coagulation.
increased level of sACE2 correlates with disease severity [48, 49], possibly due to an increase in AngII.

Furthermore, an increase in Ca^{2+} caused by ionomycin treatment induces ADAM10-dependent ACE2 shedding [47], while calmodulin, a calcium modulated protein, by binding to ACE2, inhibits its shedding [50]. These findings highlight the interconnection between Ca^{2+} signal transduction pathways and ACE2 regulated pathways. The evidence that ACE2 can be cleaved from multiple proteases upon different stimuli indicates that the post-translational regulation of this ectoenzyme is of great importance in managing tissue homeostasis. This explains why its dysregulation caused by SARS-CoV-2 binding has such an intense effect on organismal physiology.

**ACE2 Polymorphisms and Susceptibility to SARS-CoV-2 Infection**

Due to the main role of ACE2 in mediating SARS-CoV-2 entry into cells, many studies have speculated whether ACE2 expression and polymorphism and serum sACE2 levels could explain why some people are more prone to experience a severe phenotype while others remain asymptomatic. Previous studies have demonstrated that specific residues in the ACE2 protein are essential for binding with SARS-CoV [51]. Therefore, genomic variability in those specific residues could modulate the binding between ACE2 and the SARS-CoV-2 Spike protein, accounting for a broad range of symptoms exhibited by people affected by COVID-19.

Studies that aimed to find mutations in the ACE2 sequences and allele frequency in different populations have demonstrated the existence of specific variance that could affect SARS-CoV-2 binding [52–54]. Furthermore, a bioinformatic approach has identified new ACE2 exons that could participate in alternative splicing by producing a truncated ACE2, lacking the N-terminus that could not bind the Spike protein, or the C-terminus generating a soluble ACE2 that would again reduce virus/cell binding and infectivity [55]. Identification of a genomic variability in TMPRSS2 that affects its expression is worthy of mention because it suggests that European and American populations could be more susceptible to SARS-CoV-2 infection [56].

We do not yet know whether a specific variability in the ADAM17 sequence is associated with a high level of sACE2 and whether there is a correlation with the SARS-CoV-2 infection. Indeed, since the beginning of this pandemic, opposite assumptions have been made. Some researchers think that elevated levels of sACE2 may be protective because they are capable of inhibiting the binding of SARS-CoV-2 to membrane-bound ACE2 [4] and would explain why women and children are less susceptible [57]. Conversely, recent studies have shown that high levels of sACE2 could be evidence of increased ACE2 expression, elevated ADAM17 activity or both and, therefore, greater susceptibility to SARS-CoV-2 infection [58, 59].

**Physiological Functions of ACE2**

Dissecting the roles that ACE2 has in maintaining organismal physiology will help us to better comprehend why its dysregulation caused by SARS-CoV-2 can have such a devastating effect, especially in the elderly with comorbidities. In the next sections, we will describe the molecular pathways in which ACE2 plays an important role. We will focus on the role that ACE2 plays in counterbalancing the RAAS but also on its important function in the kinin-kallikrein system (KKS) that has been mostly neglected although it plays an essential part in regulating the inflammatory process.

**ACE2 and the RAAS**

Despite having a high degree of homology with ACE, ACE2 shows a remarkable difference in substrate selection, catalyzing with high efficiency the conversion of the vasoconstrictor AngII in Ang1-7 that binds and activates its own seven-transmembrane G protein-coupled receptor (GPCR) called MAS to exert anti-inflammatory and anti-remodeling effects or, with less efficiency, the formation of Ang1-9 from AngI, which can be converted to Ang1-7 by ACE [60]. In doing so, ACE2 plays a counterbalance action in the RAAS, which is a critical regulator of blood volume and systemic vascular resistance and contributes to sodium reabsorption, inflammation, and fibrosis, preventing the possible adverse effect of AngII accumulation.

The interaction between SARS-CoV2 and ACE2 could negatively regulate the receptor [61] causing, in turn, an accumulation of AngII that through the unopposed RAAS activation via the AngII/AT1R can cause vasoconstriction, oxidative stress, inflammation, atrophy, and fibrosis [62]. There is evidence that AT1R can induce apoptosis in lung alveolar epithelial cells in response to AngII in rat and human alveolar epithelial cells [63]. Furthermore, AngII promotes endothelial dysfunction through cyclooxygenase-2 (COX-2) activation, which generates vasoactive prostaglandins and reactive oxygen species (ROS) [64]. Excessive production of ROS upon overactivation of the AngII/AT1R/ nicotinamide adenine dinucleotide phosphate (NADPH) oxidase axis has been correlated with hypertension [65], and atherosclerosis [66], and can induce apoptosis through the release of cytochrome C from damaged mitochondria, activation of caspase 3 or p38 mitogen-activated protein kinase (MAPK)/Jun N-terminal kinase (JNK) cascade. Other inflammatory mechanisms activated by an accumulation of
AngII can also involve the activation of nuclear factor (NF)-κB and transcription of the proinflammatory cytokines IL-6, IL-1β, and TNFα [67] (Fig. 1). Therefore, the activation of the immune response caused by the infection in combination with the high level of AngII could result in the hyperinflammatory state that is seen in the late phase of SARS-CoV-2-infected patients.

**Angiotensin A/ACE2/Alamandine/\nMAS-Related GPCR D (MrgD) Axis**

Ang A differs from AngII by a single amino acid (alanine) at the N-terminal. It shows affinity to AT1R and possibly activates all aforementioned pathways in the context of SARS-CoV-2 infection. As in the case of AngII, ACE2 is responsible for providing a further layer in RAAS regulation by catalyzing the conversion of AngA in alamandine. This conversion highlights again the key role of ACE2 in the regulation of RAAS. In fact, the produced peptide alamandine is able to bind to the MAS-related GPCR member D (MrgD) and exerts a protective action promoting vasorelaxation and an antiproliferative effect [68].

**ACE2 and the Kinin-Kallikrein System (KKS)**

The KKS plays a key role in the regulation of several physiological processes such as coagulation, inflammation, and pain [69]. It exerts its action through the production of active peptides such as bradykinin (BK), Lys-BK, [des-Arg9]-BK (DEABK), and Lys-[des-Arg9]-BK (LDEABK) [70]. By binding to bradykinin receptor-B2 (BRB2), BK and Lys-BK induce a local increase in nitric oxide production that has a potent vasodilator effect counterbalancing the vaso-constrictor effect of the RAAS [71]. Moreover, BK positively regulates tissue plasminogen secretion (tPA) and, therefore, plays an important role in thrombus formation [72]. DEABK and LDEABK act on bradykinin receptor-B1 (BRB1) and have important role in the inflammation process [73, 74]. In fact, differently from BRB2, BRB1 is expressed at very low level on endothelial cells but is induced upon tissue injury and is up-regulated by proinflammatory cytokine release such as IL-1β, TNFα, IL-2, and IFNγ [73]. Evidence has demonstrated that activation of BRB1 is able to aggravate the inflammation by causing the further release of proinflammatory cytokines and promoting neutrophil infiltration [75]. Therefore, DEABK and LDEABK can act as proinflammatory factors that exert their function through the BRB1 receptor.

It is interesting to note that ACE2, which does not inactivate BK, can cleave the terminal residue in DEABK and LDEABK, rendering them unable to interact with BRB1 [76, 77]. Therefore, ACE2 internalization due to SARS-CoV-2 infection will create an imbalance in the KKS system causing an overactivation of the DEABK/LDEABK/BRB1 axis, contributing to increased inflammation and rendering the lung environment more prone to local vascular leakage, leading to angioedema [76]. Consequently, approaches aimed at targeting the RAAS system, but not the KKS, will not be as effective in limiting the state of hyperinflammation typical of severe cases of SARS-CoV-2 infection (Fig. 1). The role of a dysregulated KKS remains theoretical in COVID-19 [78]. Nonetheless, an approach that could target both pathways to fight against COVID-19 has already been suggested [79].

**ACE2 as a Target for a SARS-CoV-2 Therapeutic Strategy**

ACE2 is attracting much interest as a therapeutic target in the fight against COVID-19 [4]. As described earlier, ACE2 can be shed from the cell and released into the circulation by ADAM17 while maintaining its catalytic activity and ability to bind SARS-CoV-2. It has been suggested to use human recombinant ACE2 (hrACE2) protein to saturate the viral S-protein and thus prevent cellular entry of SARS-CoV-2 [4]. Soluble hrACE2 (shrACE2) retains attractive physiological features due to its ability to inactivate SARS-CoV-2 present in the extracellular milieu. Differently from antiviral or anti-inflammatory therapies, shrACE2 can act upstream by decreasing the binding between SARS-CoV-2/mACE2, thus reducing infectivity [80]. Furthermore, it can also counteract the increase in AngII and DEABK/LDEABK preserving lung function. Administration of hrACE2 is well tolerated in healthy subjects [81], and it has been successfully used to treat patients with ARDS [82]. APN01 is a rhACE2 that is fully glycosylated (7 glycosylation sites) and occurs as a stable noncovalent homodimer. Its enzymatic activity relies on incorporated Zn²⁺. The use of twice-daily doses of APN01 infusion resulted in a rapid decrease in plasma AngII levels and an increase in Ang1-7 and Ang1-5 levels, as well as a trend to a decrease in plasma IL-6 concentrations [82]. Recently, Monteil and colleagues demonstrated that shrACE2 can decrease SARS-CoV-2 infection in vitro [83], and clinical trials are already underway (Clinicaltrials.gov #NCT04335136). Furthermore, a more effective way for the delivery of shrACE2 that would decrease protease degradation has already been suggested [84]. Although our knowledge of the role that endogenous sACE2 plays in human physiology is still limited, there is promising evidence that shrACE2 could be used as a valid therapy for SARS-CoV-2 infection.

Other potential therapeutic approaches include a SARS-CoV-2 spike protein-based vaccine, a TMPRSS inhibitor to block the priming of the spike protein, and blockage of
the surface ACE2 receptor by using anti-ACE2 antibody or peptides [81]. Camostat mesylate, approved in Japan to treat pancreatic inflammation, has been shown to block TMPRSS2 activity and prevent cellular infection by SARS-CoV-2 [45]. Another strategy that is being investigated in clinical trials is the administration of an antibody or a single-chain antibody fragment (scFv) that binds ACE2 and blocks the interaction of spike protein on the virion to ACE2 [85].

Furthermore, beyond the RAAS and KKS, ACE2 has been shown to act on other substrates such as apelin-13/17, neurotensin (1–11), β-casomorphin-(1–7), dynorphin A (1–13), and ghrelin among others [86]. These substrates are interesting potential therapeutic targets for COVID-19 [77], but we will not discuss them because their involvement in COVID-19 is still highly speculative.

**Conclusion**

Since the first outbreak in Wuhan, China, SARS-CoV-2 has spread worldwide, killing over one million two hundred thousand people. The rapid rate of adaptive mutations combined with high transmissibility renders coronaviruses an ongoing threat of causing future pandemics, with especially high risk for the elderly [87]. Although the scientific world is making an extraordinary effort, we are still far from fully understanding whether the overactivation of the immune system and the state of hyperinflammation due to SARS-CoV-2 infection can be controlled [88].

This would be particularly important in people with comorbidities such as diabetes and hypertension, which are conditions already associated with an inflammatory state. It is likely, even if not yet fully ascertained, that when these pathological states combine with the viral infection, the dysregulation of both the RAAS and the KKS due to ACE2 internalization mediated by SARS-CoV-2 could create the conditions for severe illness and a fatal outcome.

In conclusion, we believe that further efforts should be made to fully understand ACE2 transcriptional regulation and post-translational modification during the course of COVID-19 and in response to treatments. In fact, as already discussed, contrasting hypotheses have been formulated concerning the effect of therapies taken by millions of people that might increase ACE2 expression and susceptibility to SARS-CoV-2 infection. Furthermore, although COVID-19 is still primarily described as a respiratory viral illness, it is increasingly evident that it is a multisystemic disease. Therefore, it is essential to acquire a greater knowledge of the role that ACE2 plays in different organs and physiological pathways because of its widespread tissue expression. This may shed light on factors that modulate cell surface ACE2 receptor affecting viral cell entry and consequently susceptibility to SARS-CoV-2 infection. This, in turn, could have significant implications for identifying better therapies and screening tools to assess disease progression and severity.

**Compliance with Ethical Standards**

**Conflict of interest** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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