Review

Angiotensin Converting Enzyme 2 (ACE2) and COVID-19: An overview of its structure, physiologic role and its involvement in SARS-COV2 infection and therapy

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SUMMARY

Coronavirus disease of 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is of a great global and national public health concern. Structural studies suggested that the SARS-CoV2 binds through its spike-protein to target cells by interacting with the angiotensin-converting enzyme 2 (ACE2) receptor which is widely expressed in the heart, kidneys, lungs, gut and testes cells. This article reviews the structural and physiologic roles of the human ACE2 and its correlation with the SARS-CoV2 infection and therapy. Evidence has been provided that the amino acids 318-510 of the viral spike protein represent the receptor-binding domain (RBD) which binds to ACE2, especially by means of the critical amino acids at positions 479 and 487, then allowing virus tropism and propagation. ACE2 play a crucial role in the down regulation of the renin-angiotensin-aldosterone system (RAAS). The RAAS ACE-Angiotensin II-AT1R regulatory axis promotes detrimental effects on the host, such as vasoconstriction, generation of reactive oxygen species, inflammation and matrix remodeling. However, the ACE2-Ang 1-7-MasR axis counterbalances the activation of the classical RAS system which inhibits cell growth, inflammation and fibrosis. The ACE2 has a protective effect against organ damage, lung injury and underlying chronic diseases such as hypertension, diabetes, and cardiovascular diseases wich are linked with poor prognosis of healing in patients with COVID-19. On account
of the protective effects of ACE2, the design and development of drugs enhancing its activity may become one of the most promising strategies for the therapy of COVID-19 in the future.

1. Introduction

The COVID-19 is a pandemic caused by a 2019 novel coronavirus, named Severe Acute Respiratory Syndrome-coronavirus 2 (SARS-CoV-2) which first appeared in the city of Wuhan in China. To the date of the writing of this manuscript, it caused over 9 473 214 confirmed cases and at least 484 249 deaths worldwide with 258 752 cases (5 564 deaths) in Africa, 4 709 927 cases (233 628 deaths) in Americas and 2 619 753 cases (195 535 deaths) in Europe, by June 26th 2020 (WHO/novel-coronavirus-2019/situation-reports). In Morocco, 11633 total confirmed cases and 218 total confirmed deaths were recorded by the same date (WHO, 2020).

The common symptoms of COVID-19 reported by the Centers for Disease Control and Prevention (CDC) are fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting and/or diarrhea (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html). In some patients, COVID-19 is associated with more severe symptoms that lead to multiple organ-dysfunction suggesting lung, myocardial, renal, enteric and/or liver damage, which may lead to death.

Different investigations revealed that the angiotensin-converting enzyme 2 (ACE2) is the host cell receptor used by the SARS-CoV-2 virus to bind to their target cells. The ACE2 plays a crucial role in the infectivity of the cells (Xu et al., 2020, Delanghe et al., 2020), but also in the activation of damaging effects of diverse tissues when it depleted from the cell membrane through the Angiotensin II/ADAM17 pathway (Gheblawi et al., 2020). Experimental models studies revealed a close relationship between ACE2 and heart failure, systemic and pulmonary hypertension, myocardial infarction, and diabetes cardiovascular complications. Additionally, there is a good correlation between damaged tissues in COVID-19 patients with the relatively high expression of ACE2 protein in the corresponding organs (Zou et al., 2020). Moreover, the high expression of ACE2 protein in some organs has an important role in the down-regulation of the rennin angiotensin system through the conversion of the angiotensin (Ang) I and Ang II peptides into Ang 1–9 and Ang 1–7, respectively (Gheblawi et al., 2020). Therefore, the ACE2/Ang 1–7 axis is now used as a potential target for therapeutic intervention to reduce the SARS-induced tissue damage. Indeed, it has been shown that the administration of ACE2 reduce systemic inflammation by shifting the RAAS peptide balance away from Ang II towards Ang 1–7, thereby improving the clinical symptoms (Gheblawi et al., 2020, Batlle et al., 2020, Sun et al., 2020).

A good knowledge of the structure, function, and tissue expression of ACE2 and the mechanism of its interaction with SARS-CoV2 is a prerequisite to elaborate efficient therapeutic strategies and for health professionals. Here, we reviewed the involvement of ACE2 in the physiopathology of COVID-19 and the possible therapeutic targeting of this enzyme to help fight this pandemic.

2. Structure of the ACE2 protein and corresponding gene

The ACE2 protein consists of an N-terminal peptidase domaine (PD) and a C-terminal Collectrin-like domain
(CLD) that ends with a single transmembrane helix and an intracellular segment (Yan et al., 2020, Gheblawi et al., 2020) (Figure 1: please use the following link: https://www.ahajournals.org/cms/asset/2d7a4b88-4bc8-4a08-9ebf-f219c16cb556/circresaha.120.317015.fig02.gif). The ACE2 gene is located on chromosome Xp22 and contains 18 exons (GenBank accession number for human ACE2 refseq gene: NG_012575).

3. Physiological Role of ACE2

The ACE2 plays multiple and distinctive physiological functions: as a down regulator of the renin-angiotensin system (RAS) and as a facilitator of amino acid transport. ACE2 is a zinc metallopeptidase (carboxypeptidase) that cleaves the Ang II into Ang-(1-7) and the Ang I into Ang-(1-9), which is then processed by additional peptidases to become Ang-(1-7) (Figure 1).

The ACE2 plays an important role in cellular entry, thus ACE2-expressing cells may act as target cells and are susceptible to 2019-nCoV infection (Zhou et al., 2020). AT1R/AT2R: Angiotensin Receptors 1/2; rhACE2: recombinant human ACE2.

It also functions, by its C-terminal domain, an homolog of collectrin (renal protein), as the chaperone for the membrane trafficking of the amino acid transporter B0AT1, also known as SLC6A19. This latter protein mediates the uptake of neutral amino acids inside the intestinal cells in a sodium dependent manner. It controls also the vasoconstriction and blood pressure (Yan et al., 2020, Gheblawi et al., 2020).

4. Tissue expression of ACE2 and its relationship to infection SARS-CoV2

ACE2 protein is expressed in lungs, heart, kidneys and intestine (Figure 2). Decreased expression of ACE2 is associated with cardiovascular diseases (Yan et al., 2020).

![Figure 1](https://www.ahajournals.org/cms/asset/2d7a4b88-4bc8-4a08-9ebf-f219c16cb556/circresaha.120.317015.fig02.gif)

**Figure 1** Schematic diagram of the renin-angiotensin system (RAS) showing the role of ACE2 as a negative regulator of RAS and its protective effect against organ injuries and treatment options aging on RAS (Zhang et al., 2020). ACE: Angiotensin Converting Enzyme; AT1R/AT2R: Angiotensin Receptors 1/2; rhACE2: recombinant human ACE2.

![Figure 2](https://www.ahajournals.org/cms/asset/2d7a4b88-4bc8-4a08-9ebf-f219c16cb556/circresaha.120.317015.fig02.gif)

**Figure 2** Bar plot of ACE2 expression in different normal tissues (FANTOM5 CAGE dataset).

The ACE2 plays an important role in cellular entry, thus ACE2-expressing cells may act as target cells and are susceptible to 2019-nCoV infection (Zhou et al., 2020).
post-mortem autopsy heart tissues from twenty patients who succumbed to SARS-CoV, seven heart samples had detectable viral SARS-CoV genome, which was characterized by increased myocardial fibrosis, inflammation, and reduced myocardial ACE2 expression (Gheblawi et al., 2020).

Exploration and validation the expression of ACE2 on the mucosa of oral cavity demonstrated that the ACE2 expressed on the mucosa of oral cavity. Interestingly, this receptor was highly enriched in epithelial cells of tongue. Those findings have explained the basic mechanism that the oral cavity is a potentially high risk for 2019-nCoV infectious susceptibility and provided a piece of evidence for the future prevention strategy in dental clinical practice as well as daily life. ACE2 expression was higher in tongue than buccal and gingival tissues suggesting that the mucosa of oral cavity may be a potentially high risk route of 2019-nCov infection (Xu et al., 2020).

It has been shown that a low expression of ACE2 is associated with cardiovascular diseases and an elevated level of circulating Ang II (Yan et al., 2020). A positive correlation was revealed between increased circulating Ang II level and viral load in COVID-19 patients compared to healthy controls suggesting a direct link between tissue ACE2 downregulation with systemic RAS imbalance, and facilitating the development of multi-organ damage from SARS-CoV-2 infections (Liu et al., 2020, Wang et al., 2020). Furthermore, accumulation of Ang II increases ACE2 proteolysis and ectodomain shedding by enhancing the catalytic activity of ADAM-17 (a disintegrin and metalloproteinase 17) through AT1R and /or directly, leading to RAS overactivation and inflammation. The injection of recombinant human ACE2 (rhACE2) showed attenuation of inflammation improving lung function and pathological injury caused by SARS-CoV (Gheblawi et al., 2020).

5. Interaction between SARS-CoV2 and ACE2 as the receptor

Like other human coronaviruses, SARS-CoV and HCoV-NL6, it has been shown that the SARS-CoV2 is able to use human ACE2 proteins as a receptor to enter solely ACE2-expressing cells through the specific interaction of the receptor-binding domain (RBD) of its spike protein with the extracellular peptidase domain (PD) of ACE2. Each PD accommodates one RBD through several critical residues namely, Lys417, Tyr453, Gln474, Phe486, Gln498, Thr500 and Asn501 which interact with Gln24, Asp30, His34, Tyr41, Gln42, Met82, Lys353, and Arg357 of ACE2-PD thus forming a network of hydrogen bonds (Van der Waals forces) (Figure 3). Similarities or variations in the keys residues (Table I) play critical roles for the cross-species transmission, host range, ACE2 recognition and cell entry of SARS-CoV. All the five residues in SARS-CoV and ACE2 are critical for recognition, cell entry, and host range of SARS-CoV (Yan et al., 2020, Zhou et al., 2020, Wan et al., 2020).

![Figure 3: Modeled structure of the interface between SARS-CoV2 RBD and human ACE2 (Wan et al., 2020).](image-url)
Although phylogenetic analysis points to a bat origin of SARS-CoV2, its binding to ACE2 of various animal species, suggests that these animals are candidate intermediate hosts (Wan et al., 2020).
Overall, there is a strong evidence that the high affinity binding of the RBD domain of SARS-CoV-2 to its human ACE2 receptor, may account for the greater pathogenicity of SARS-CoV-2 compared to SARS-CoV (Gheblawi et al., 2020).

Table I: Variations in critical residues involved in the interaction between the RBDs of SARS-CoV and 2019-nCoV coronaviruses and the PDs of ACE2 in different host species (Wan et al., 2020, Yan et al., 2020). PD: Peptidase Domain; RBD: Receptor Binding Domain; R: Arginine; N: Asparagine; D: Aspartic acid; E: Glutamic acid; G: Glycine; L: Leucine; K: Lysine; M: Methionine; F: Phenylalanine; P: Proline; S: Serine; T: Threonine; Y: Tyrosine; >: more adapted; >>>: much more adapted.

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<td>N=R</td>
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6. Correlation between ACE2 and symptoms/treatment options for COVID-19

It has been shown that the ACE2 system is a critical protective pathway against heart failure, lung disease and diabetes. This protective effect of ACE2 is mainly modeled by controlling gut dysbiosis and vascular permeability. In addition, the loss of ACE2 function, driven by endocytosis and activation of proteolytic cleavage following the infection by SARS-CoV-2, presented a critical link between immunity, inflammation and cardiovascular disease in COVID-19 patients (Gheblawi et al., 2020, Kuba et al., 2005, Cheng et al., 2020).
Potential therapeutic strategies may include the prevention of interaction between human ACE2 and SARS-CoV-2 by
blocking the receptor-binding domain (RBD) of the viral S-protein. In addition, to this RBD blocking strategy, other possible treatment options may include localized use of ACE2-derived peptides, small molecule inhibitors, ACE2 antibody or single chain antibody fragment against ACE2. As the ACE2/Ang 1-7/Mas receptor axis was crucial in COVID-19 development, it was intensively explored in therapeutic research. The results showed that the recombinant ACE2, Ang 1–7 analogs and Mas receptor agonists increase ACE2 effect and serve as potential therapies to mitigate clinical symptoms associated with RAS overactivation and inflammation. Indeed, clinical trials of recombinant human ACE2 have significantly lowered angiotensin II and increased angiotensin 1-7 in plasma (Gheblawi et al., 2020, Sun et al., 2020, Batlle et al., 2020, Kruse, 2020).

7. Conclusion

The ACE2 plays an important role in the infection with SARS-CoV2 by modeling the attachment and entry of the virus in target cells but also in the variation of clinical symptoms between patients with COVID-19 through the regulation of Renin-Angiotensin System. Moreover, the promising strategies for treatment of COVID-19 are based on the activation of the protective effect of ACE2 against inflammation, organ injuries, pulmonary and cardiovascular complications. To well understand the relationship between the ACE2 and COVID-19, especially in the Moroccan population, we will investigate in future studies the correlation between the genetic background, particularly the ACE2 gene variations, and variations of infectivity and clinical symptoms in patients with COVID-19. This research project is supported by the National Center for Scientific and Technical Research (CNRST) of Morocco.

Conflicts of Interest

The authors declare no conflict of interest, financial or otherwise.

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References


