



ACE2 in SARS-CoV-2-Mediated COVID-19: A Brief Review

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Received 2022 August 17; Revised 2022 September 03; Accepted 2022 September 05.

Abstract

Angiotensin-converting enzyme 2 (ACE2) is widely known as the essential receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is the cause of the globally known coronavirus disease 2019 (COVID-19) pandemic, which has been the leading cause of virus-related mortality since early 2020. A wide range of human cells in different human organs express ACE2. The importance of ACE2 in the involvement of human organs during COVID-19 and its critical role in the process of target cell infection have rendered it an interesting therapeutic target. In this review, we briefly focus on ACE2 and its general roles in the human body and highlight the roles of ACE2 in the emergence of COVID19. Ultimately, we discuss the strategies for preventing virus entry using ACE2 blocking.

Keywords: ACE2, SARS-CoV-2, COVID-19

1. Context

Coronavirus disease 2019 (COVID-19) is an infectious disease initiated when an individual is infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a recently emerged coronavirus. This infectious disease was documented in late 2019 in Wuhan, China (1). Alike previous coronaviruses such as SARS-CoV-1 and Middle East respiratory syndrome-related coronavirus (MERS-CoV), SARS-CoV-2 is simply transferred through human-to-human contact (1). Risk factors for a poor prognosis in COVID-19 patients include older age, high body mass index (BMI), and numerous clinical conditions such as overweight, heart-related conditions, diabetes, or respiratory system disorders (1).

Angiotensin-converting enzyme 2 (ACE2) acts as an essential enzyme in the renin-angiotensin system (RAS) (2, 3). ACE2 is also engaged in systemic vascular resistance (2, 3). Additionally, ACE2 also acts as the entry mediator for SARS-CoV-2, with important roles in the emergence and progression of COVID-19 (2). In detail, ACE2 provides viral entry into human cells via binding of the viral spike (S) pro-

tein of SARS-CoV-2 (2). This mechanism leads to virus internalization and cell infection by SARS-CoV-2 (2). It is worth mentioning that SARS-CoV-1 also uses this action mechanism for target cell entry and infection (2, 3). However, various studies have demonstrated that SARS-CoV-2 is more pathogenic than its predecessor due to its 10- to 20-fold increased binding affinity (2). According to recent studies, SARS-CoV-2 cell entry and its pathologic activity and reactions majorly take place in cells of the (upper) respiratory tract (2). In addition, local expression of ACE2 by other organs in the body (e.g., the kidneys or the gastrointestinal tract) renders these parts of the body also susceptible to virus infection (2).

Identifying the precise function of ACE2 in the successful entry of SARS-CoV-2 and the emergence of COVID-19 is important. Hence, to better understand the action mechanisms of the disease, in this review, we focus on the critical role of ACE2 in SARS-CoV-2 successful internalization, replication, and the onset of the COVID-19 disease. We also briefly review strategies using ACE2 as a therapeutic target for targeting SARS-CoV-2 entry, infection, and replication.

2. Structure of ACE2, Location in the Body, and Its Function as the Coronavirus Entry Point

ACE2 is a homologue of ACE. This enzyme can be found in two forms: Integrated in the cell membrane (namely mACE2) or in a soluble condition (sACE2) (3, 4).

Lung alveolar epithelial cells as well as small intestinal epithelial cells exhibit high-level expression of ACE2 on their surface. This finding justifies why both respiratory and gastrointestinal systems are highly affected by SARS-CoV-2 (2, 3). ACE2 is also expressed by particular cells, skin, and the nasal epithelia (2-4). Some coronaviruses, including SARS-CoV-2, use mACE2 as an entry point for entering human cells (1-4). In fact, mACE2 serves as the principal entry point into human cells for SARS-CoV-2. In detail, the spike protein of SARS-CoV-2 binds mACE2 (at the enzymatic domain site) on the surface of human cells. This reaction leads to endocytosis of the enzyme-virus complex followed by their translocation into intracellular endosomes (4). The host serine protease TMPRSS2 is responsible for priming of the S protein required for the entry process of the virus (5, 6). In this regard, researchers are currently investigating the inhibition of TMPRSS2 as a therapeutic strategy for blocking virus entry into human cells (5-7). Additionally, other researchers demonstrated that disruption of S-protein glycosylation remarkably interferes with the proper virus entry (8, 9).

3. ACE2 in SARS-CoV-2-Mediated COVID-19 and Using It as a Therapeutic Target

Ever since the precise action mechanisms of SARS-CoV-2 entry and the receptors involved in this process were discovered, researchers have assessed various strategies for blocking the virus from infecting human cells. Majorly, there are two key strategies for blocking the capability of the virus for cell infection. One strategy entails the direct targeting of the viral glycoproteins, while the other one includes targeting the receptors of the virus of the surface of target cells.

The first strategy is believed to be more efficient because genome sequence of SARS-CoV-2 is publicly accessible in genome databases making it easy to use various virus glycoproteins, including the S protein, for immunizing mice or rabbits for the generation of neutralizing antibodies (10, 11). The screened neutralizing antibodies are required to be tested *in vitro* and in preclinical assessments using animal models to be able to conclude that they are capable of SARS-CoV-2 neutralization and prevent infection (10, 11). In this case, a set of different antibodies might be required to fully neutralize SARS-CoV-2 and prevent it from infecting body cells.

The second strategy is believed to be superior to the first one in terms of effectiveness since, unlike the glycoproteins on the surface of viruses, the receptors of the virus of the surface of human target cells do not change. This mechanism prevents the occurrence of virus escape from binding to therapeutic agents. Both SARS-CoV and SARSCoV-2 use ACE2 as the receptor. In this case, strategies using targeting agents to block ACE2 can be used both for the prevention of SARS-CoV and SARSCoV-2 infection. In this strategy, soluble small or large inhibitor molecules are used that prevent the binding of virus to human ACE2 (12). Such molecules also can be monoclonal antibodies that bind to ACE2.

There are also more novel approaches that benefit from both the mentioned strategies. For instance, some researchers used sACE2, that binds to the SARS-CoV-2 S protein, nullifies infecting capability of the virus, and prevents its entry and target cell infection. One study demonstrated that recombinant human sACE2 suppresses the entry capability of SARS-CoV-2 to target cells *in vitro* (12). The affinity of sACE2 for the SARS-CoV-2 S protein is around 1.70 nM, which is very similar to the affinity of monoclonal antibodies. Therefore, this strategy can be considered a suitable and effective approach for the prevention of SARS-CoV-2 infection (13, 14).

Sheikhi and Hojjat-Farsangi proposed the generation of a chimeric sACE2 protein made of sACE2 fused to anti-CD16 VHH (15). In detail, there are three classes for human receptors for IgG (Fc γ R): CD64 (Fc γ RI), CD32 (Fc γ RII), and CD16 (Fc γ RIII). CD16 is a membrane-spanning activating receptor expressed on natural killer (NK) cells, a fraction of T cells, monocytes, and macrophages. This molecule is engaged in immune system-related cellular pathways, such as antibody-dependent cell-mediated cytotoxicity (ADCC) and phagocytosis. The Fc portion of antibodies is capable of binding to both activating and inhibitory Fc receptors (16, 17). However, these researchers proposed that chimeric ACE2-Fc molecule might not be effective therapeutics against SARS-CoV-2 based on the size of the Fc domain, as well as its low affinity for CD16 (15). Therefore, the researchers proposed using nanobodies based on their various advantages over conventional antibodies, including similar affinities with smaller size (15). Moreover, scFvs do not have an artificial linker peptide, which can lead to *in vivo* immunogenicity (15). In general, Sheikhi and Hojjat-Farsangi focused on various advantages of the sACE2-anti-CD16 VHH bi-specific molecule in comparison with ACE2-Fc, which included binding to CD16 and activating receptors, rapid permeation into different tissues due to the small size of the molecule, and the ability for the production of the molecule in large quantities in both prokaryotic and eukaryotic cell lines (18-20). The sACE2-anti-CD16

VHH bi-specific molecule has the capability to be applied for blocking the S protein (15). Moreover, the high affinity of this molecule for FcγRIII (CD16) can result in initiation of ADCC, leading to the elimination of cells infected by the virus (15).

4. Conclusions

It has been more than two years since the first cases of COVID-19 were identified. Today, vaccines are known as the most effective, efficient, and affordable approach for the prevention of the disease. However, treatment strategies should be applied before irreversible organ damages take place in patients. As briefly discussed in this article, targeting viral surface glycoproteins or their receptors on the surface of target cells can prevent virus-target cell binding and target cell infection. There are numerous strategies for this aim, which are different in terms of action mechanism and effectiveness. Overall, ACE2-based targeting strategies are believed to be more reliable and effective for the prevention of viral entry since viral glycoproteins are subjected to structural changes following which new variant of viruses emerge.

Footnotes

Authors' Contribution: SDS, NB, SS, FKS, FC, MS, MRV, and SMJM contributed to writing. PSK, PSK, and AS contributed to writing and revising the manuscript.

Conflict of Interests: The authors declare no conflict of interest.

Funding/Support: This article was financially supported by a grant from Dezful University of Medical Sciences, Dezful, Iran (number 1399.174).

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