Letter to the Editor

DOI: 10.5582/bst.2022.01524

Is targeting angiotensin-converting enzyme 2 (ACE2) a prophylactic strategy against COVID-19?

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SUMMARY Prophylaxis against COVID-19 is greatly needed for vulnerable populations who have a higher risk of developing severe disease. Vaccines and neutralizing antibodies against SARS-CoV-2 are currently the main approaches to preventing the virus infection. However, the constant mutation of SARS-CoV-2 poses a huge challenge to the effectiveness of these prophylactic strategies. A recent study suggested that downregulation of angiotensin-converting enzyme 2 (ACE2), the receptor of SARS-CoV-2 entry into human cells, can decrease susceptibility to viral infection *in vitro*, *in vivo*, and in human lungs and livers perfused *ex situ*. These findings indicate the potential to use agents to reduce ACE2 expression to prevent COVID-19, but the efficacy and safety should be verified in clinical trials. Considering ACE2 performs physiological functions, risks due to its downregulation and benefits from prophylaxis against SARS-CoV-2 infection should be carefully weighed. In the future, updating vaccines against variants of SARS-CoV-2 might still be an important strategy for prophylaxis against COVID-19. Soluble recombinant human ACE2 that acts as a decoy receptor might be an option to overcome the mutation of SARS-CoV-2.

Keywords ACE2, COVID-19, SARS-CoV-2, neutralizing antibodies, prophylaxis

To the Editor,

The rapid global spread of SARS-CoV-2 highlights the requirement for prophylaxis, and especially for vulnerable populations who have a higher risk of developing severe disease, such as older adults (over the age of 65) and patients with comorbidities including cardiovascular disease, chronic respiratory disease, and diabetes (*1,2*). A number of vaccines and neutralizing antibodies against SARS-CoV-2 have been developed thus far and they have played important roles in preventing or decreasing the rate of severe COVID-19 (*3,4*). However, the constantly emerging variants of the virus pose a huge challenge to the effectiveness of these prophylactic strategies (*5*).

Angiotensin-converting enzyme 2 (ACE2) is central to SARS-CoV-2 infection since it facilitates viral entry into human cells (*6*). ACE2 is ubiquitously expressed in the human body in respiratory epithelial cells, type II alveolar cells, small intestinal epithelial cells, vascular endothelial and artery smooth muscle cells, and the brush border of proximal tubular cells in the kidney (*7-9*). Increased ACE2 expression may confer increased susceptibility to host cell entry by SARS-CoV-2 (*7*), which suggests a possible strategy of preventing SARS-CoV-2 infection through modulation of ACE2 expression. A recent study elucidated a novel mechanism controlling ACE2 expression: farnesoid X receptor (FXR) was identified as a direct regulator of ACE2 transcription (*10*). A point worth noting is that ursodeoxycholic acid (UDCA), a drug widely prescribed for cholestatic disorders, was found to downregulate ACE2 expression by suppressing FXR signaling in gallbladder cholangiocytes, airway and intestinal organoids *in vitro*, in the respiratory, biliary, and intestinal epithelium in mice and hamsters, and in human lungs and livers perfused *ex situ*, leading to reduced susceptibility to SARS-CoV-2 infection (*10*). Moreover, treatment with UDCA reduces ACE2 expression in nasal epithelial cells of humans and correlates with lower serum ACE2 levels in patients with cholestatic liver disorders. This study indicated the potential to use FXR antagonists, such as UCDA, to prevent COVID-19, but the efficacy and safety should be verified in clinical trials.

ACE2 is a pivotal counter-regulatory enzyme to angiotensin-converting enzyme (ACE), a central enzyme of the renin-angiotensin system (RAS) (*11*). ACE catalyzes the conversion of angiotensin I (Ang I) to angiotensin II (Ang II), which activates AT_1R and induces vasoconstriction, renal sodium reabsorption and

potassium excretion, aldosterone synthesis, elevation of blood pressure, and activation of inflammatory and pro-fibrotic pathways (*12-14*). ACE2 cleaves Ang I and Ang II and ultimately yields angiotensin (1-7), which activates its receptor MasR and exerts vasodilatory, anti-inflammatory, anti-oxidative, and anti-fibrotic actions (*12,15*). Thus, the balance of ACE/ACE2 determines the availability of different angiotensin peptides, and ACE skewing may result in elevated concentrations of Ang II and contribute to increased oxidative stress, inflammation, and development of hypertension, metabolic syndrome, and diabetes (*14,16*). Knocking out ACE2 was found to lead to increased Angio II and a severe cardiac contractility defect in mice, suggesting that ACE2 is an essential regulator of cardiac function (*17*). ACE2 has also been found to be protective in severe acute lung injury and cardiovascular and metabolic diseases, including diabetes and its complications (*11,18,19*). In addition to its catalytic activity, ACE2 is required for the expression of B^0AT1, a neutral amino acid transporter on the luminal surface of intestinal epithelial cells (*20*). This RAS-independent function of ACE2 is associated with regulating intestinal amino acid homeostasis, expression of antimicrobial peptides, and the ecology of the gut microbiome (*20*). When challenged with factors inducing epithelial damage, mice deficient in ACE2 displayed increased susceptibility to intestinal inflammation (*20*). Given the physiological function of ACE2, risks due to its downregulation and benefits from prophylaxis against SARS-CoV-2 infection should be carefully weighed.

Updating vaccines against the variants of SARS-CoV-2 remains an important approach for prophylaxis against COVID-19. Considering SARS-CoV-2's affinity for binding to ACE2, recombinant human ACE2 (rhACE2) may act as a decoy receptor that blocks the virus to bind ACE2 located on the cell membrane. Alteration of enzyme activity but preservation of SARS-CoV-2 binding activity may be necessary for rhACE2 to avoid systemic cardiovascular reactions during systemic administration. Theoretically, this might be an alternative prophylactic or therapeutic strategy to overcome the mutation of SARS-CoV-2 to some extent.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received December 11, 2022; Revised December 20, 2022; Accepted December 23, 2022.

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