Acta Pharmacologica Sinica

www.nature.com/aps

CORRESPONDENCE

Recombinant human ACE2: potential therapeutics of SARS-CoV-2 infection and its complication

Acta Pharmacologica Sinica (2020) 41:1255–1257; https://doi.org/10.1038/s41401-020-0430-6

Dear Editor,

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pneumonia outbreak in Wuhan city, China, followed by global spread [1, 2]. As of 9 April, 2020, millions of confirmed cases of SARS-CoV-2 infection have been reported, and the global death toll of SARS-CoV-2 infection has surged to tens of thousands of victims, making it a public health emergency of international concern (PHEIC). However, no specific antiviral drug or vaccine for SARS-CoV-2 treatment exists. The high infectivity and the increasing fatality of SARS-CoV-2 highlight the demand for drug discovery. SARS-CoV-2 is closely related to severe acute respiratory syndrome coronavirus (SARS-CoV) [2]. Full-genome sequencing analysis indicated that SARS-CoV-2 shares a high-sequence identity with SARS-CoV [3]. The spike protein (S-protein) of coronaviruses interacts with cell receptors to mediate viral entry into target cells [4]. Additional evidence suggests that both SARS-CoV and SARS-CoV-2 employ angiotensin-converting enzyme 2 (ACE2) as the entry receptor and that the receptor-binding domain (RBD) of the S-protein directly binds to ACE2, triggering endocytosis of virus particles [5–7]. A recent study suggested that the binding affinity between ACE2 and the RBD of SARS-CoV-2 is 10–20 times stronger than that with the RBD of SARS-CoV [5], which likely explains the increased infectivity of SARS-CoV-2.

ACE2 is not only a functional receptor of coronaviruses, but also acts as an important negative regulator of the renin–angiotensin system (RAS) through conversion of the vasoconstrictor angiotensin II (Ang II) to its metabolite angiotensin-(1–7) (Ang 1–7) and angiotensin I(Ang I) to angiotensin-(1–9) (Ang 1–9) [7–9]. The ACE2/Ang 1–7 axis plays a series of roles in the improvement of endothelial dysfunction, anti-inflammation, anti-hypertension, anti-thrombus, and anti-fibrosis activity, and cardiovascular protection [10–14]. The protective effect of ACE2 is associated with attenuating Ang II levels and increasing Ang 1–7 levels in lung pathophysiology [10]. Emerging evidence has shown that RAS signaling and ACE2 play crucial roles in SARS-CoV-induced acute respiratory distress syndrome (ARDS) and lethal avian influenza A(H5N1, H7N9)-induced acute lung injury (ALI) [14, 15]. According to pathological findings, SARS-CoV-2 is also associated with lung failure and ARDS [16], and the majority of severely ill patients with SARS-CoV-2 infection have underlying comorbidities, such as cardiovascular disease, diabetes, and cerebrovascular disease [1]. The anti-trypanosomal agent diminazene aceturate (DIZE) was reported to be an ACE2 activator, which has a structure similar to that of the established ACE2 activator xanthenone [17, 18]. DIZE was suggested to exert protective effects in cardiovascular disease through modulating ACE2 activation and expression to increase Ang 1–7 production and improve vascular function [17]. Owing to the role of ACE2 in the entry of SARS-CoV-2, the upregulated expression of ACE2 had an unwanted effect. Therefore, DIZE is not suggested to be applied in the treatment of SARS-CoV-2 infection. However, the addition of exogenous ACE2 could be a potential treatment for SARS-CoV-2 infection, which might not only restrain the spread of SARS-CoV-2 by blocking its interaction with ACE2 on the host cell, but also modulate RAS to treat SARS-CoV-2-related underlying comorbidities and protect the lung from developing ARDS.

Given that ACE2 is generated mainly in Clara cells and type II alveolar epithelial cells, the production of ACE2 is severely impaired after epithelial injury in the development of ARDS [19]. In addition, the expression of ACE2 is also severely decreased in patients with pulmonary fibrosis [20]. Therefore, injection of recombinant human ACE2 (rhACE2) is currently considered for treating ARDS and pulmonary arterial hypertension [21]. Circulatory levels of ACE2 activity were markedly increased by rhACE2, which further effectively lowered Ang II levels and generated Ang 1–7 from Ang II (Fig. 1). Although Ang II receptor and ACE blockage were also effective in lung failure in animal models, this treatment could cause potential adverse effects, causing systemic hypotension in humans [22]. As shown in Fig. 1, rhACE2 also acts as a potential therapy for hypertension, heart failure, kidney injury, and liver fibrosis [22–24].

Currently, phase I (NCT00886353) and phase II (NCT01597635) clinical studies with a recombinant version of the catalytic ectodomain of human ACE2 (GSK2586881) have been successfully completed, providing safety and efficacy for ARDS treatment [25, 26]. The administration of rhACE2 was well tolerated without clinically significant hemodynamic changes in healthy subjects and patients with ARDS [26]. During the administration period, no antibodies to rhACE2 were detected, and no serious adverse events were reported [25]. The twice-daily doses of GSK2586881 treatment-regulated angiotensin system peptide, leading to a significant reduction in the concentration of Ang II, accompanied by a rapid rise in Ang 1–7 and Ang 1–5 concentrations, and caused a reduction in IL-6 concentration [26]. However, given the small cohort of critically ill patients, infusion of GSK2586881 did not contribute to ameliorated ARDS through physiological or clinical measures, and a clear role of GSK2586881 in the increased reports of adverse events referring to hypernatremia, pneumonia, dysphagia, and rash was difficult to establish. Therefore, to assess clinical outcomes powerfully, further clinical trials need a larger sample size. Recently, Monteil et al. [27] reported that hrACE2 could significantly inhibit SARS-CoV-2 infection of Vero-E6 cells, and of human capillary and kidney organoids, providing an evidence that rhACE2 might not only reduce lung injury but also block early entry of SARS-CoV-2 infections in target cells. Further studies are needed to illuminate the effect of hrACE2 in SARS-CoV-

Received: 5 March 2020 Accepted: 22 April 2020
Published online: 24 June 2020

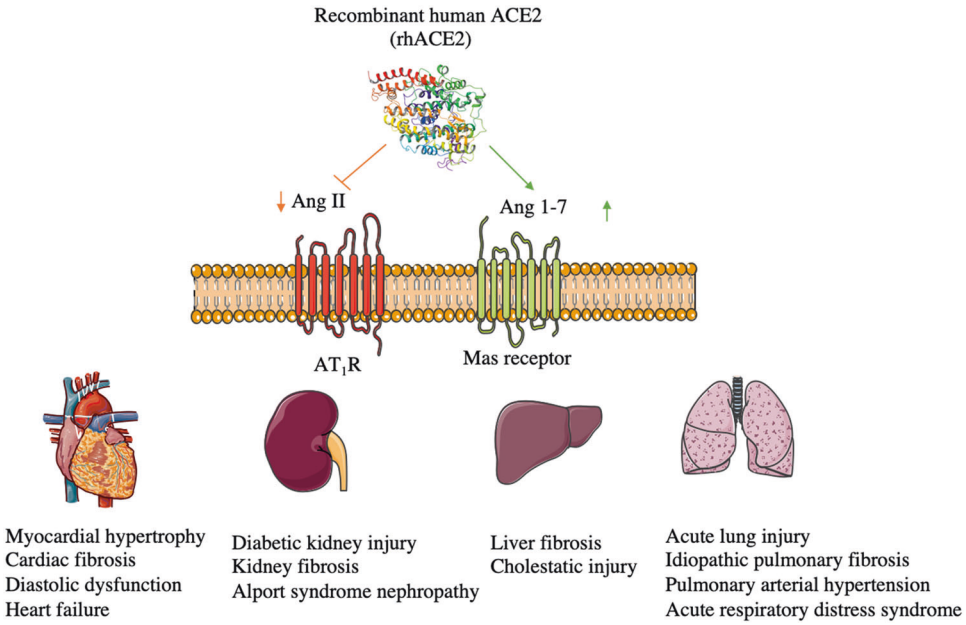

Fig. 1 The mechanism and functions of rhACE2. rhACE2 is able to lower Ang II levels and increase Ang 1–7 levels effectively and exert protective effects in the heart, lung, liver, and kidney.

2 infections from bench to clinic. To ensure the quality of the data and clinical success of rhACE2, the trials for using rhACE2 in patients with SARS-CoV-2 infection or ARDS should consider the patient's stratification and continuous infusion dose. First, various plasma Ang II levels may pose some difficulties in identifying responders. Hence, before GSK2586881 infusion, the Ang II concentrations and the ratio of ACE2/ACE activity of enrolled patients were evaluated for improved risk stratification. ACE gene insertion/deletion (I/D) polymorphisms play an important role in the development of hypertension, nephritis, and cardiovascular diseases in different ethnic populations by influencing ACE and Ang II activities [28, 29]. Identifying the specific population that is most likely to benefit from rhACE2 represents a bright prospect. Second, due to the short half-life of soluble ACE2 in vivo, a continuous infusion of rhACE2 may enhance efficacy. In addition, an excess of rhACE2 is likely to influence the balance of the RAS; therefore, it is important to identify the effective infusion dose to prevent underlying RAS-related adverse events. Recently, it was reported that a chimeric fusion of rhACE2 and IgG2 Fc fragments could improve rhACE2 plasma stability [22]. This rhACE2-Fc fusion protein retained full peptidase activity and had extended plasma half-life in mice [24]. The strategy for rhACE2-Fc will be expected to provide patients with added convenience, largely reducing administration frequency and greatly improving treatment effectiveness [30]. Taken together, these findings indicate that rhACE2 would represent a potential therapeutic strategy for SARS-CoV-2 infection and its complications.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation (No. 81973320, No.81673509, and No. 81903714) of China and the Macau Science and Technology Development Fund (FDCT) (No.0002/2019/APD, 067/2018/A2, 033/2017/AMJ, and 0007/2019/AKP).

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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