Soluble ACE2 as a potential therapy for COVID-19

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Abstract

Soluble angiotensin-converting enzyme 2 (sACE2) could be a therapeutic option to treat coronavirus disease 2019 (COVID-19) infection. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) utilizes ACE2 receptors on cell surfaces to gain intracellular entry, making them an ideal target for therapy. High-affinity variants of sACE2, engineered using high-throughput mutagenesis, are capable of neutralizing COVID-19 infection as decoy receptors. These variants compete with native ACE2 present on cells by binding with spike (S) protein of SARS-CoV-2, making native ACE2 on cell surfaces available to convert angiotensin II to angiotensin-1,7, thus alleviating the exaggerated inflammatory response associated with COVID-19 infection. This article explores the use of sACE2 as potential therapy for COVID-19 infection.

ARDS; COVID-19; lung injury; SARS-CoV-2; soluble ACE2

Angiotensin-converting enzyme 2 (ACE2) is a membrane-bound peptidase present in most tissues (1). The spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to the ACE2 protein to gain intracellular entry. COVID-19 infection can lead to severe pulmonary tissue damage and acute respiratory distress syndrome (ARDS) (1). ACE2 blockade, to prevent virus entry, is being studied as a therapeutic approach for this disease. In addition to ACE2 blockade, repurposing existing therapeutics such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor 1 blockers (ARBs) is also a potential method to prevent or treat COVID-19 (2–4). This article discusses the possible use of soluble forms of the ACE2 protein as a decoy receptor to neutralize COVID-19 infection.

Soluble ACE2 (sACE2) is an engineered variant of ACE2 with its transmembrane domain removed, such that it binds to the S protein of SARS-CoV-2 and thus neutralizes it (5, 6). Therefore, sACE2 is a potential therapeutic agent to treat COVID-19 (7–9). It could act as a decoy receptor and inhibit binding of SARS-CoV-2 to membrane-bound receptors, thereby decreasing entry of the virus into tissue (7). The pharmacodynamics and pharmacokinetics of sACE2, also referred to as recombinant human ACE2, have been previously studied in healthy individuals in pilot clinical trials and are safe to use in subjects (10). In a pilot clinical trial in subjects with acute respiratory distress syndrome, sACE2 was shown to be well tolerated, paving the way for future use in other conditions (11).

It is hypothesized that the number of ACE2 receptors present on cell surfaces is significantly downregulated with exposure to SARS-CoV-2; this decrease leads to a subsequent increase in angiotensin II (Ang II), resulting in inflammation, vasoconstriction, pulmonary edema, and impaired lung function (2, 3, 9, 12). Because increased levels of Ang II may be closely associated with the exaggerated inflammatory response in severe cases of COVID-19, therapeutics to block the inflammatory properties of Ang II have been proposed to combat COVID-19 infection (13). Renin inhibitors, ACE inhibitors, and ARBs reduce the amount of Ang II and increase the availability of ACE2 on cell surfaces in lungs (2–4). This could increase conversion of Ang II to angiotensin 1–7 (Ang 1,7), reverse the deleterious effects of Ang II, and thus promote anti-inflammatory and vasodilatory properties to prevent and treat from acute lung injury in COVID-19 (3).

S protein of SARS-CoV-2 has two subunits, S1 and S2. The S1 subunit contains the ACE2 receptor binding domain (RBD). Studies have examined the interaction between RBD of S protein and ACE2 and indicate that mutations in the sACE2 structure could result in increased affinity of the S protein for RBD (5). Engineered sACE2 variants could outcompete S protein of native ACE2 binding to RBD on SARS-CoV-2 (Fig. 1). Through mutagenesis studies, favorable mutations with enhanced RBD-sACE2 binding in variants have been observed and may have potential therapeutic implications (5). One such engineered variant of sACE2 neutralizes SARS-CoV-1 as well (5). This suggests that this decoy receptor utilizes similar intracellular entry mechanisms for other coronaviruses.

ACE2 deficiency can lead to severe pulmonary damage and ARDS in animal models, suggesting that ACE2 plays a critical role to protect against severe lung injury (12). Exogenous administration of soluble recombinant ACE2 protects ACE2-deficient animal models from lung failure (12).
ACE2 converts Ang II to Ang 1,7, an antagonist of Ang II, with vasodilatory, antiangiogenic, antifibrotic, and anti-inflammatory properties and also protects against cardiovascular disease (10). Binding of S protein of SARS-CoV-2 to sACE2 would theoretically make native ACE2 on cell surfaces more readily available for conversion of Ang II to Ang 1,7 and reduce inflammation associated with increased Ang II levels in COVID-19 infection (5). Not only does the sACE2 function as a decoy receptor, its catalytic activity as an enzyme in the renin-angiotensin-aldosterone (RAS) system could be highly beneficial to decrease levels of Ang II. Engineered variants of sACE2 may possess catalytic activity and contribute to the conversion of Ang II to Ang 1,7 to treat respiratory distress as well (5).

In summary, sACE2 may be useful to treat COVID-19 infection. SARS-CoV-2 requires ACE2 to gain intracellular entry, making ACE2 an ideal target for pharmacological therapy. High-affinity variants of sACE2 bind to spike (S) protein of SARS-CoV-2 and thereby neutralize infection as decoy receptors. These high-affinity variants outcompete native ACE2 present on cells by binding with the S protein of SARS-CoV-2, making native ACE2 on cell surfaces readily available for conversion of Ang II to Ang 1,7 (Fig. 1). Numerous methods to increase ACE2 levels are being explored to 1) decrease levels of Ang II to prevent the inflammatory effects of COVID-19 infection and 2) increase the levels of Ang-1,7 and enhance the protective effects of this molecule. Clinical trials are necessary to demonstrate the efficacy of sACE2 in COVID-19 infection.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

S.K. drafted manuscript; S.K., R.F.L. and N.K. edited and revised the final version of manuscript.

**REFERENCES**

1. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. Am J Physiol Heart Circ Physiol 318: H1084–H1090, 2020. doi:10.1152/ajpheart.00217.2020.
2. Bloch MJ. Renin-angiotensin system blockade in COVID-19: good, bad, or indifferent? J Am Coll Cardiol 76: 277–279, 2020. doi:10.1016/j.jacc.2020.06.003.
3. Gwurtz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res 81: 537–540, 2020. doi:10.1002/ddr.21656.
4. Khera R, Clark C, Lu Y, Guo Y, Ren S, Truax B, Spatz ES, Murugiah K, Lin Z, Omer SB, Vojta D, Krumholz HM. Association of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with the risk of hospitalization and death in hypertensive patients with coronavirus disease-19 (Preprint). medRxiv, 2020. doi:10.1101/2020.05.17.20104943.
5. Chan KK, Dorosky D, Sharma P, Abbasi SA, Dye JM, Kranz DM, Herbert AS, Procko E. Engineering human ACE2 to optimize binding to the spike protein of SARS coronavirus 2. Science 369: 1261–1265, 2020. doi:10.1126/science.abc0870.
6. Monteil V, Kwon H, Prado P, Hagelkruys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E, Hurtado Del Pozo C, Prosper F, Romero JP, Wünsberger G, Zhang H, Slutsky AS, Conder R, Montserrat N, Mirazimi A, Penninger JM. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell 181: 905–913, 2020. e907 doi:10.1016/j.cell.2020.04.004.
7. Batlle D, Wysocki J, Satchell K. Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? Clin Sci (Lond) 134: 543–545, 2020. doi:10.1042/CS20200163.

8. Davidson AM, Wysocki J, Batlle D. The interaction of SARS-CoV-2 and other coronavirus with Angiotensin Converting Enzyme 2 (ACE2) as their main receptor: therapeutic implications. Hypertension 76: 1339–1349, 2020. doi:10.1161/HYPERTENSIONAHA.120.15256.

9. Roshanravan N, Ghaffari S, Hedayati M. Angiotensin converting enzyme-2 as therapeutic target in COVID-19. Diabetes Metab Syndr 14: 637–639, 2020. doi:10.1016/j.dsx.2020.05.022.

10. Haschke M, Schuster M, Poglitsch M, Loibner H, Salzberg M, Bruggisser M, Penninger J, Krähenbühl S. Pharmacokinetics and pharmacodynamics of recombinant human angiotensin-converting enzyme 2 in healthy human subjects. Clin Pharmacokinet 52: 783–792, 2013. doi:10.1007/s40262-013-0072-7.

11. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, Hall R, Poirier G, Ronco JJ, Tidswell M, Hardes K, Powley WM, Wright TJ, Siederer SK, Fairman DA, Lipson DA, Bayliffe AI, Lazaar AL. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care 21: 234, 2017. doi:10.1186/s13054-017-1823-x.

12. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui CC, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 436: 112–116, 2005. doi:10.1038/nature03712.

13. Miesbach W. Pathological role of angiotensin II in severe COVID-19. TH Open 4: e138–e144, 2020. doi:10.1055/s-0040-1713678.