Letter regarding: Another strategy for off-target ACE2

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Abstract

The angiotensin-converting enzyme 2 (ACE2) is a type I integral membrane protein (amino acids 805) that contains a transmembrane domain (amino acids 740-763) and extracellular region (ectodomain). The extracellular region is composed of a metalloprotease zinc-binding site (amino acids 374-378, HEMGH) that is the single catalytic domain of the ACE2. The ACE2 ectodomain undergoes shedding by a disintegrin and metalloproteinase domain-containing protein 17 a protease up-regulated in heart failure (HF) consequently releases a soluble form of ACE2. Increasing soluble ACE2 levels are associated with HF, adverse cardiac remodelling and correlated with B-type natriuretic peptide levels. The spike protein (S) of severe acute respiratory syndrome coronavirus 1 (SARS-CoV) attaches the virus to its cellular receptor ACE2. The structural analysis demonstrated that S subunit 1 (S1) and the C-terminal domain of the SARS-CoV-2, otherwise known as the receptor-binding domain, bound to soluble ectodomain protein of human ACE2. The construction of a fusion protein consisting of the extracellular domain of human ACE2 linked to the fragment crystallisable region (Fc) domain of human IgG1 (ACE2-Ig), the ACE2 variant in which two active-site histidines have been altered to asparagines (mACE2-Ig), and the inhibition of metalloproteinase with chelator agents that removes zinc that leads disrupting the catalytic site of the ACE2 ectodomain which is indispensable for the Covid-19 attachment could be another promising potential therapeutic approach.

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Congratulations to Calderone and Brogi for their letter regarding the off-target ACE2 ligands and approved drugs with possible off-target ACE2-modulatory effects.[1]

The angiotensin-converting enzyme 2 (ACE2) is a type I integral membrane protein (amino acids 805) that contains a transmembrane domain (amino acids 740-763) and extracellular region (ectodomain). The extracellular region is composed of a metalloprotease zinc-binding site (amino acids 374-378, HEMGH) that is the single catalytic domain of the ACE2, which is 42% identical to each of the two catalytic domains in angiotensin-converting enzyme (ACE), ACE functions as a dipeptidase whereas ACE2 as a carboxypeptidase.[2,3] The ACE2 ectodomain undergoes shedding by a disintegrin and metalloproteinase domain-containing protein 17 (ADAM17) also known as tumour necrosis factor alpha-converting enzyme, a protease up-regulated in heart failure (HF) consequently releases a soluble form of ACE2.[4]

Some studies have demonstrated that increasing soluble ACE2 levels are associated with HF, adverse cardiac remodelling and correlated with B-type natriuretic peptide levels.[5,6,7] Hence, increasing soluble ACE2 activity indicates either an adaptive or maladaptive physiologic process operative in HF. [7]

The spike protein (S) of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) attaches the virus to its cellular receptor ACE2.[8] Zhou P et al. demonstrated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) share 79.6% sequence identity to SARS-CoV-1 and uses the same cell entry receptor ACE2 and does not use other coronavirus receptors as aminopeptidase N or dipeptidyl peptidase.[9] Similarly, Jia HP et al. showed the membrane-associated form of ACE2 serves as a SARS-CoV-1 receptor in vitro, and soluble ACE2 retains it is coronavirus receptor properties, furthermore identified a single mutation (ACE2-L584A) that prevented ACE2 shedding process.[10] Structural analysis of ACE2 has revealed the presence of a single catalytic domain that is located in the ectodomain was identified as a functional receptor for SARS-CoV and the ectodomain is indispensable to viral attachment through a defined receptor-binding domain (RBD) on S mediates this interaction.[11] Wang Q et al. demonstrated that S subunit 1 (S1) and the C-terminal domain of the SARS-CoV-2, otherwise known as the RBD, bound to soluble ectodomain protein of human ACE2 with 4-fold higher binding affinity compared with the SARS-CoV-1 receptor binding domain.[12]

Here are some strategies for targeting the ACE2 not mention before. Lei C, et al. constructed a fusion protein consisting of the extracellular domain of human ACE2 linked to the fragment crystallisable region (Fc) domain of human IgG1 (ACE2-Ig) and an ACE2 variant in which two active-site histidines have been altered to asparagines (mACE2-Ig), SARS-CoV and SARS-CoV-2 were neutralised in vitro with both recombinant ACE2.[13] On the other hand, ACE2 activity is unaffected by 10 μM lisinopril, enalaprilat, or captopril, but activity was completely inhibited by 10 μM of calcium ethylenediaminetetraacetic acid (EDTA).[14] This reinforces the proposition that ACE2 is a metalloprotease, but with a distinct substrate and inhibitor specificity from ACE. Therefore, chelating agents such as EDTA removes zinc, which is essential for activity and leads to complete inactivation. 3 g of EDTA IV weekly have shown a safety profile in patients with cardiovascular disease.[15] It is know so far that the ACE2 ectodomain contains the a single catalytic domain composed of the metalloprotease zinc binding site (amino acids 374-378, HEMGH) and structural anaylisis have demonstrated that SARS-CoV-2 uses thise ectodomain for viral attachment, another potential therapeutic could be the disruption of the metalloprotease zinc binding site by the uses of chelator agent as EDTA with a low cost compared with many other treatments. Therefore this should be test in laboratory, in caso to prove the SARS-CoV-2 is neutralized in vitro, then a clinical trial should perform.

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