Angiotensin-converting enzyme 2 (ACE2) and COVID-19

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SARS-CoV-2 is the virus responsible for the COVID-19 pandemic which has resulted in over 609 million infections and 6.52 million deaths (Our World In Data, 2022). The angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV-1 and SARS-CoV-2, allowing their spike (S) glycoproteins to bind to the surface of human cells (Chen et al., 2021).

ACE2 is a type I transmembrane glycoprotein and zinc metallopeptidase containing 805 amino acids that can be found on the plasma membrane on many cell types within the body. The ACE2 protein is coded by the ACE2 gene which is located on chromosome Xp22 and is theorized to have evolved from ACE, due to their 42% shared sequence homology (Chen et al., 2021). Two functional forms of the ACE2 protein are expressed: the full length protein and its soluble counterpart (sACE2). Soluble ACE2 is formed by the shedding of the full-length ACE2 through metalloproteinase 17 (ADAM17). Unlike the soluble form, the full length ACE2 protein contains an extracellular transmembrane domain, connected to the plasma membrane (Chen et al., 2021).

The SARS-CoV-2 S protein is composed of a short intracellular tail, a transmembrane anchor, and a large ectodomain which has ‘S1’ and ‘S2’ functional units. The S1 subunit is responsible for binding by using its receptor binding domain to the extracellular peptidase domain of ACE2, exposing the S1/S2 interdomain protease site. At the S1/S2 site, the proprotein convertase furin cleaves the S protein while the transmembrane serine protease 2 or TMPRSS2 is cleaved at the S2 site to begin priming. These changes trigger the S2 subunit which inserts fusion peptides into the host membrane (Chen et al. 2021). As a result, the SARS-CoV-2 viral RNA is released and replicated and translated which prompts subsequent infection cycles (Lim et al., 2020).

ACE2 is responsible for regulating blood pressure, wound healing, and inflammation, in addition to the negative regulation of the renin-angiotensin-aldosterone system (RAAS) pathway, which furthermore regulates systemic arterial pressure. ACE2 modulates angiotensin II which increases blood pressure and inflammation and can cause damage to blood vessel linings, resulting in tissue injury breaking it down by converting it into other molecules (Bourgonje et al., 2020). Apart from the RAAS pathway, ACE2 is essential in conducting bradykinin metabolism in the lungs to prevent vasodilation and capillary leakage in the Kallikrein Kinin System (KKS) (Chung et al., 2020).

The role of ACE2 in SARS-CoV-2 pathogenesis provides opportunity for new therapies which are vital to reducing mortality throughout the COVID-19 pandemic, specifically in targeting the RAAS pathway to prevent disease progression, tissue injury, and multiple organ failure. Current therapeutic approaches involve the use of ACE inhibitors, angiotensin receptor blockers (ARBs), and AT receptor antagonists to reduce the production of angiotensin II in tissues and cell types associated with COVID-19 pathobiology. However, these therapies do not address ACE2 inhibition due to SARS-CoV-2 viral entry. The use of sACE2 as a recombinant to act as a decoy for the virus, increasing ACE2 availability for angiotensin II degradation, as well as the infusion of

angiotensin 1-7 to engage protective ACE2 effects are also possible alternatives for COVID-19 treatment; nevertheless, further preclinical data and human studies are required to assess the feasibility, dosing, cost, and long-term efficacy of these therapies (Sriram & Incel, 2020).