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Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy?

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A new coronavirus, referred to as SARS-CoV-2, is responsible for the recent outbreak of severe respiratory disease. This outbreak first detected in Wuhan, China in December 2019, has spread to other regions of China and to 25 other countries as of January, 2020. It has been known since the 2003 SARS epidemic that the receptor critical for SARS-CoV entry into host cells is the angiotensin-converting enzyme 2 (ACE2). The S1 domain of the spike protein of SARS-CoV attaches the virus to its cellular receptor ACE2 on the host cells. We thought that it is timely to explain the connection between the SARS-CoV, SARS-CoV-2, ACE2 and the rationale for soluble ACE2 as a potential therapy.

The angiotensin-converting enzyme 2 (ACE2) is a monocarboxypeptidase best known for cleaving several peptides within the renin–angiotensin system and other substrates, such as apelin. This enzyme is barely present in the circulation, but widely expressed in organs, such as the kidneys and the gastrointestinal tract, with relatively low level of expression in lungs [1]. Expression of ACE2 has been reported in type 2 pneumocytes [2]. Of potential interest, RNA expression of ACE2 in lung AT2 cells was higher in one Asian donor as compared with white and African American donors [3].

Functionally, there are two forms of ACE2. The full-length ACE2 contains a structural transmembrane domain, which anchors its extracellular domain to the plasma membrane. The extracellular domain has been demonstrated as a receptor for the spike (S) protein of SARS-CoV [4], and recently, for the SARS-CoV-2 [5]. The novel coronavirus is evolutionary related to Bat-SARS, which likewise uses membrane-bound ACE2 as the receptor [6]. The soluble form of ACE2 lacks the membrane anchor and circulates in small amounts in the blood [7]. We propose that this soluble form may act as a competitive interceptor of SARS-CoV and other coronaviruses by preventing binding of the viral particle to the surface-bound, full-length ACE2. Indeed, *in vitro* studies showed that SARS-CoV replication was blocked by a soluble form of ACE2 in the monkey kidney cell line, Vero-E6 [8,9]. Moreover, ACE2 fused to the Fc portion of immunoglobulin has just been reported to neutralize SARS-CoV-2 *in vitro* [10] and the SARS-CoV-2 binds ACE2 with higher affinity than SARS-CoV [11]. In this context, provision of soluble recombinant human ACE2 protein could actually be beneficial as a novel biologic therapeutic to combat or limit infection progression caused by coronaviruses that utilize ACE2 as a receptor (Figure 1).

Soluble recombinant ACE2 protein has therapeutic potential for a vast array of therapeutic indications [12] and novel shorter ACE2 variants are being tested in mouse studies for treatment of kidney diseases [13]. If given in its soluble form as an appropriate recombinant ACE2 protein, a new tool may be at hand to combat the spread of coronavirus in susceptible individuals by limiting coronavirus attachment to the cell membranes, cell entry, and replication. To our knowledge, studies in animals or humans testing the therapeutic potential of soluble recombinant ACE2 proteins are not yet available. The potentially beneficial effect (or not) of soluble recombinant ACE2 proteins to attenuate coronavirus infection should be urgently tested. Mouse models that carry the human version of ACE2 with the mouse version deleted should greatly facilitate research in this rapidly emerging field.

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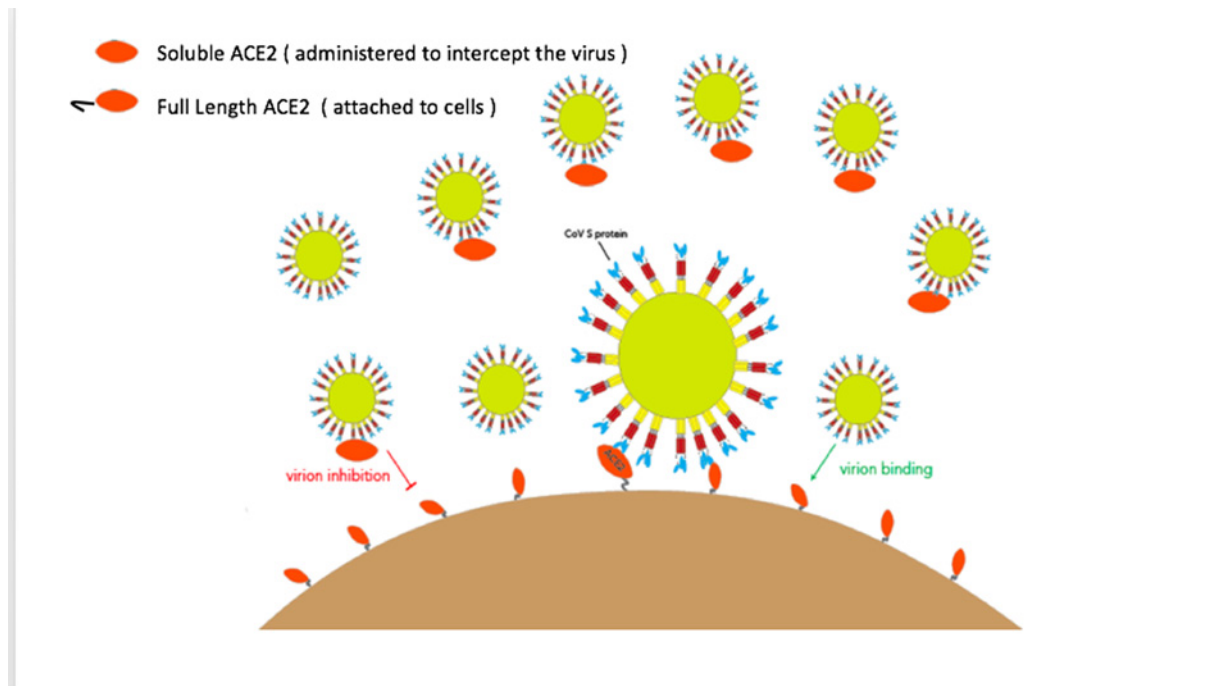


Figure 1. Schematic of coronavirus (CoV) spike protein (S) binding to the surface receptor which is the full-length ACE2 Soluble ACE2 administration may intercept the coronavirus. (Drawn by Nicole Inniss, Ph.D).

Competing Interests

D. Batlle and J. Wysocki: co-inventors Patent: ‘Active Low Molecular Weight Variants of Angiotensin Converting Enzyme 2’; and have also submitted a patent on the potential use of novel ace2 proteins for coronavirus infection D. Batlle: Founder of ‘Angiotensin Therapeutics’.

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Abbreviation

ACE2, angiotensin-converting enzyme 2.

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