ACE2 and SARS-CoV-2 – tissue or plasma, good or bad?

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Disclosure: no conflict of interest to declare.

The COVID-19 pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infecting millions and killing people worldwide, has fueled enormous interest in the mechanisms whereby this new coronavirus infects the lung and causes acute respiratory distress syndrome and multi organ failure [1].

The renin–angiotensin–aldosterone system (RAAS) is a cascade of vasoactive peptides that orchestrates key processes in human physiology. Pharmacological blockade of the RAAS with angiotensin converting enzyme (ACE)-inhibitors (ACEi), angiotensin-type-1-receptor blockers (ARB) or mineralocorticoid receptor antagonists reduces morbidity and mortality in various cardiovascular diseases. ACE2 was discovered 20 years ago and received its name because of its homology with ACE [2]. Membrane bound ACE2 enzyme functions to protect against organ injury by cleavage and disposal of angiotensin (Ang) II and formation of Ang 1–7 as shown in the upper panel of figure 1 [2]. Proteolytic shedding of membrane bound ACE2 by ADAM17, a disintegrin and metalloprotease, results in a soluble circulating form of ACE2 [2]. The circulating levels of ACE2 are usually low but can increase in several pathologies, including diabetes mellitus and cardiovascular disease [3,4]. Ang II up-regulates ADAM17, thus increasing soluble ACE2 levels [2]. The data on the regulation of ACE2 by pharmacological RAAS inhibition with ARBs or ACE inhibitors are controversial. Depending on whether the analysis of ACE was performed in tissue or plasma, and depending on patients risk profile, RAAS-inhibitors induced either an up-regulation or changes were absent [5].

Just two years after its identification as the new enzyme within the RAAS, ACE2 was reported to be the receptor for SARS-CoV in 2003 [6]. The resemblances of SARS-CoV and SARS-CoV-2 include a 76.5% homology in the amino acid sequence of the spike protein that both viruses use to infect mammalian cells [1]. As shown in the upper panel of figure 1 following ACE2 receptor binding, the host cell protease transmembrane protease serine subtype 2 (TMPRSS2) cleaves the SARS-CoV-2 spike protein for successful entry into the cell [7]. The cleavage of the spike protein may also be accomplished by cathepsin B and cathepsin L [3]. TMPRSS2 inhibitors like camostat block entry and might constitute a treatment option [7]. The binding affinity of SARS-CoV-2 and the host ACE2 receptor determines host susceptibility to the virus [3].

At the beginning of the SARS-CoV-2 pandemic, it was suggested that ACE inhibitors or ARBs may increase the risk of a SARS-CoV-2 infection or the severity of COVID-19 [8].This assumption was based on the aforementioned controversial data that RAAS inhibitors could lead to an up-regulation of

ACE2 [9]. Since worldwide many patients with cardiovascular disease are treated with ACE inhibitors or ARBs, these reports inevitably led to great uncertainty among patients and physicians. However, meanwhile multiple large, population-based studies from Europe, the U.S. and China clearly showed that there is no evidence that ACE inhibitors or ARBs affect the risk of COVID-19 or its severity [10-12]. Along this line, experts in the field of cardiovascular disease and pharmacology recommended that there is no need to discontinue life-saving RAAS-blockade [1,5,13,14].

In the context of the current discussion about the relevance of distinct ACE2 level and their regulation by the RAAS during COVID-19, it seems of enormous importance to make a clear distinction between tissue and plasma ACE2.

For instance, in the current issue of this journal, Rieder and colleagues investigated the activity level of the RAAS in 24 SARS-CoV-2 positive patients and 61 SARS-CoV-2 negative controls based on circulating RAAS components [15]. They found no differences between both groups in circulating ACE2 level, Ang II and aldosterone, and concluded that both groups have a comparable RAAS activity [15]. These data are in accordance with a previous study demonstrating no differences of plasma ACE2 and different circulating angiotensin peptides in SARS-CoV-2 negative vs. positive patients [16]. Despite the fact that these data need to be confirmed in larger cohorts including cases with more severe forms of COVID-19, they suggest that a SARS-CoV-2 infection per se does not instantly result in major changes of RAAS activity, and particularly not to alterations of soluble ACE2.

In contrast, this conclusion may not apply for changes of the tissue RAAS/ACE2. The characterization of the effects of SARS-CoV-2 in extra pulmonary organs is a matter of great interest. The kidney is a classical target organ of the RAAS. Acute kidney injury is a commonly described complication of COVID-19 that has been linked to increased morbidity and mortality. Single cell RNA sequencing data reveal that ACE2 and TMPRSS2 — genes that are considered to facilitate SARSCoV-2 infection— are enriched in multiple kidney-cell types [17]. This enrichment may facilitate SARS-CoV-2–associated kidney injury. Indeed viral load was detected in all kidney compartments with preferential targeting of glomerular cells [17]. Importantly, a recent report has documented replication-competent SARS-CoV-2 isolated from a post-mortem kidney, a finding that cannot be explained by passive renal uptake of viral remnants or inactive virus [18]. Moreover, SARS-CoV-2 renal tropism is associated with disease severity (i.e. premature death) and development of acute kidney injury [18]. Proximal tubular dysfunction is another feature of SARS-CoV-2 infection [19]. These data suggest that SARS-CoV-2 is able to target the kidney and results in a regulation of RAAS components such as tissue ACE2.

Soluble ACE2 as a therapeutic target

Although the circulating ACE2 levels in COVID-19 seem to be not substantially regulated (results in larger cohorts are still pending), there are promising approaches to develop soluble ACE2 as a therapeutic target. Since ACE2 is required for attachment of the virus to cells, a theoretical approach could be a decoy strategy as shown in the lower panel of figure 1. Increasing the amount of circulating ACE2 by increased shedding or administration of recombinant soluble ACE2 itself or fused to an immunoglobulin Fc domain to capture SARS-COV-2 in the bloodstream may prevent its binding to lung cells, as well as to other cell types [1]. Soluble ACE2 could be administered via intranasal spray, inhalation into the lung, or systemically to prevent or treat SARS-CoV-2 infection. The administered soluble ACE2 would bind to SARS-CoV-2 spike proteins, leaving the virus with less available spike protein to attach to the full-length ACE2 in the cell membrane. Moreover, a potential additional benefit of treatment with soluble ACE2 proteins may also lie in its applicability to future SARS-like coronavirus outbreaks [3]. Of great interest is a recent study showing that recombinant soluble hACE2protein resulted in a marked reduction of SARS-CoV-2 infectivity both in a cell line permissive for SARS-CoV-2 infection and in susceptible human vascular and kidney organoids [20,21]. An antibody or a nanobody made in cameloids directed against ACE2 would be another treatment option [20].

Conclusion

Davidson et al. stated recently that although the current SARS-CoV-2 pandemic is alarming and unprecedented in our lifetimes, it is not the first and will likely not be the last coronavirus outbreak [3]. Soluble ACE2 proteins that can bind SARS-CoV-2 and most likely also future coronaviruses are therefore a very interesting option for the prevention of viral particle binding to the surface-bound full-length ACE2, a process necessary for cell entry and infection. Hypertension researchers all over the globe accumulated an extensive expertise in studying the RAAS. Since ACE2, as a RAAS-component, represents a molecular intersection between hypertension and virology, the development of future therapeutic anti-SARS-CoV strategies will likely profit from the input of hypertension experts and close collaborations of hypertension scientists and virologists.

Figure legend

Figure 1

Membrane bound ACE2 converts Ang I and Ang II into Ang (1-9) and Ang (1-7). The protease ADAM17 sheds ACE2 into its soluble form. The spike protein of SARS-CoV-2 binds with its small receptor binding region to ACE2. This activates the TMPRSS2 and through fusion of its envelope with the cell membrane, the virus penetrates into the cells. Administration of recombinant ACE2 by itself or fused to an immunoglobulin Fc domain could be a decoy approach to avoid binding of the virus to membrane bound ACE2 i. e. in the lung. Another approach could be induction of increased shedding of membrane bound ACE2 or administration of antibodies against ACE2. Modified from [5,9].

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Figure 1