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Angiotensin-converting enzyme-2 (ACE2): New opportunity or red herring?

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Since early December 2019 when the first pneumonia cases of unknown origin were identified in Wuhan, the COVID-19 outbreak has been expanding from Wuhan throughout China, being exported to a growing number of countries Worldwide (1). In the absence of any specific therapeutic drug approach, one of the hypothesis catching the attention is the involvement of angiotensin-converting enzyme-2 (ACE2) cascade. ACE2 is a monocarboxypeptidase that cleaves away (**i**) phenylalanine from angiotensin (ANG) II, converting it to ANG-(1-7), and (**ii**) leucine from ANG I, converting it to ANG-(1-9) (**figure 1**). Altogether, ACE2, ANG-(1-9), and ANG-(1-7) negatively regulate the renin-angiotensin system (RAS), one of the most potent cardiovascular regulator and an important target for therapeutic drugs (2). Specifically, Ang 1-7 is a major component of the counter-regulatory axis of the RAS (3) and Ang 1-9 becomes relevant during ACE inhibition, since Ang I is abundantly present after treatment with RAS inhibitors and might determine an increase of Ang 1-9 (4). ACE2, which possesses also noncatalytic functions, has been described as the receptor for both two known coronavirus, i.e. the SARS-coronavirus (SARS-CoV) and the human respiratory coronavirus NL63 (5). ACE2 could be considered the host receptor for the novel coronavirus 2019-nCoV/SARS-CoV-2. Patients with diabetes mellitus and/or arterial hypertension under treatment with ACE-inhibitors (ACE-i) or angiotensin II type-I receptor blockers (ARBs) present with increased expression of ACE2 (6). Both of these diseases are strong risk factors for severe SARS-CoV-2 related disease. Thus, it should be prioritized investigations aimed at unraveling if morbidities SARS-CoV-2 related are influenced by current ACE-i/ARBs treatment. In this complex scenario and in the absence of effective therapies for COVID-19, public health relies on the identification of vulnerable (high-risk) populations based on clinical history or risk factors. In this view, smoke, a causative agent of pulmonary illnesses through its action on nicotinic receptors, is also significantly associated with high mortality rates in infections of various respiratory viruses including those that underlie annual (seasonal) influenza. Although smoking is associated to a rise in

ACE2 expression in the lung, active smoking does not seem significantly associated with a raised risk of progressing towards severe disease in COVID-19 (OR, 1.69; 95% CI, 0.41–6.92; p=0.254) (7). Conversely, it is worth mentioning that the activation of nicotinic receptors can directly impact the putative receptor for the virus (ACE2) leading to deleterious inflammatory signaling in lung epithelial cells, i.e. JAK/STAT pathway (8).The basal expression pattern of human ACE2 among ethnicities might be critical for the susceptibility, symptoms, and outcomes of 2019-nCoV/SARS-CoV-2 infection. In this perspective, East Asian populations have much higher ACE2 expression than white and African-American donors, although, in lung tissues from Asian and Caucasian populations, no significant differences were found (9). Considering that Black subjects show a high frequency of variants of candidate genes associated with low renin-resistant hypertension, it could be of interest to understand if hypertension in African-descent populations contributes to an imbalance in the activities of the ACE2/Ang-(1-7)/Mas and the ACE/Ang II/AT1 axes (10). In Africa, as of 31st March 2020, the WHO web site (11) reports a case fatality ratio of 2.4% among a cumulative total of 3671 confirmed cases across 41 countries in the region. Taking into account the different health system when compared to European region, mortality appears lower in the African one. Notably, despite distribution of ethnicity is not available, South Africa, the richest and the most developed country in the African region, shows the higher incidence of infection (1353 infected subjects) with only 5 deaths reported (rate 0.4%). Conversely, Algeria (Northern country) with 99% of population composed by Arabian or Berber ethnicities, has faced 584 infections with 35 recorded fatal events (rate 6%). Thus, this trend may be extremely interesting if confirmed. Finally, although COVID-19 cases were rare in infants and newborns, nine hospitalized infants diagnosed with COVID-19 in China from 8th December 2019 to 6th February 2020, were reported. Less than 1% of the cases were children younger than 10 years of age and most of them presented a milder clinical course. Interestingly, although epidemiology of acute respiratory distress syndrome showed no differences in activity of ACE and ACE2 between children and adults, markers involving the neutrophil response (MPO, IL-6, and IL-10) were significantly lower in neonates/children compared to adults/older adults (12).

Overall, as recently reported ACE2 could be a “double-edged sword” turning off the renin-angiotensin system and leading to beneficial effects but also mediates unique susceptibility to lung and cardiovascular disease in COVID-19 patients by acting as the SARS-CoV-2 receptor (13). An answer to this hypothesis, will probably come from an open label, randomized controlled trial evaluating the safety and efficacy of recombinant human ACE2 as a treatment for COVID-19 patients (NCT04287686) (14).

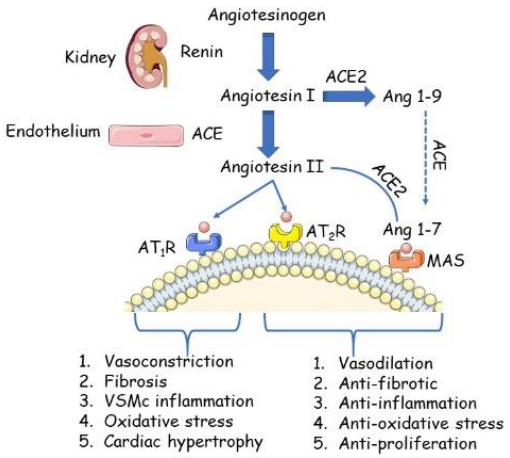

Figure 1. The enzymatic cascade that involves the renin-angiotensin system has been depicted along with key receptor systems and biological effects.
ACE,angiotensin-converting enzyme; Ang, angiotensin; ATR, Angiotensin receptor.

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