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Angiotensin converting enzyme 2 as the molecular bridge between epidemiologic and clinical features of COVID-19

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Running title: ACE2, ACE and COVID-19: the good, the bad and the ugly

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Pre-existent cardiovascular disease is a recognized risk factor for COVID-19 infection (1). COVID-19 spike protein uses the angiotensin-converting-enzyme 2 (ACE2) as the binding site to enter the host cell in tongue, bronchi and lungs. Any condition enhancing the expression of ACE2 would increase the vulnerability to infection. Heart failure, coronary artery disease, hypertension, diabetes, ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs) increase the expression of ACE2, which can be considered nature's endogenous ACE inhibitor at the cellular level. The renin-angiotensin system has 2 arms (Figure, upper panel): the pressor (conventional) arm, composed of Angiotensin II, angiotensin-converting-enzyme (ACE), Angiotensin II-type 1 receptor (AT1R), and the depressor (non conventional) arm consisting of Angiotensin 1-7, ACE2, MAS receptor (MAS R) and Angiotensin II, type 2 receptor (AT2R) (2). The ACE2 (the "good" guy, possibly "the best of enzymes") arm opposes the conventional arm and has beneficial effects in heart failure and acute respiratory distress syndrome (ARDS) (3). COVID-19 spike protein is the "ugly" character in the play. It uses the "good" ACE2 as the binding site. While ACE is detectable in the entire capillary network of the alveoli in the human lung, ACE2 is primarily produced in club cells of distal bronchioles and type 2 pneumocytes in alveolar epithelium. Both cell types are involved in preventing ARDS. Club cells secrete a solution similar to surfactant and proteins protective against airway inflammation and oxidative stress. Type-2 pneumocytes are "the defender of the alveolus" and synthesize, secrete and recycle all components of the surfactant that regulates alveolar surface tension in the lungs. The binding of COVID-19 spike protein to ACE2 down-regulates the enzyme, which in turn may contribute to ARDS for the unopposed, detrimental action of ACE (the "bad" guy or 'the worst of enzymes") on lung tissue, triggering vasoconstriction, inflammation, apoptosis and fibrosis. (Figure, lower panel). The Council on Hypertension of the European Society of Cardiology (4) highlighted the lack of any evidence supporting harmful effect of ACEi and ARBs in the context of the pandemic COVID-19 outbreak. This is important since an hypothesis suggests that ACEi might be helpful in treating COVID-19 ARDS. Chongqing Medical University is currently conducting a retrospective observational study that aims to evaluate the clinical differences between adult hypertensive patients with COVID-19 treated and those not treated with ACEi. This study will be completed by April 30, 2020.

References

Legend of figure

**Figure:** **Upper panel:** The normal physiology of ACE (the worst of all enzymes) and ACE2 (the best of all enzymes). COVID-19 uses ACE2 (in club cells in distal bronchioli and pneumocytes type 2 cells in alveoli) as a binding site. **Lower panel:** The expression of ACE2 is increased in highly prevalent cardiovascular diseases, theoretically augmenting the possibility of infection. After binding with spike receptors of COVID-19, ACE2 looses efficacy and ACE2 counter effect against ACE is attenuated or lost in spite of greater ACE2 expression.
ACE2 axis negatively modulates ACE axis

Increased ACE2 expression
Reduced effect after binding
Higher probability of infection
Vulnerability to lung complications

Vasoconstriction
Inflammation
Apoptosis
Fibrosis

Vasodilation
Anti-Inflammation
Anti-Apoptosis
Anti-Fibrosis

Lung

Club Cell (bronchioles)
Type-2 pneumocyte (alveoli)

ACE2 binding site for COVID-19

Hyptertensives
Diabetics
Heart Failure
Coronary artery disease

ARDS