Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letters to the Editor

Angiotensin-Converting Enzyme 2 as the Molecular Bridge Between Epidemiologic and Clinical Features of COVID-19

To the Editor:

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 ACEi at the cellular level. The renin-angiotensin system has 2 arms (Figure 1, upper panel): the pressor (conventional) arm, composed of angiotensin II, ACE, angiotensin II-type 1 receptor (AT1R), and the depressor (nonconventional) 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. Whereas 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

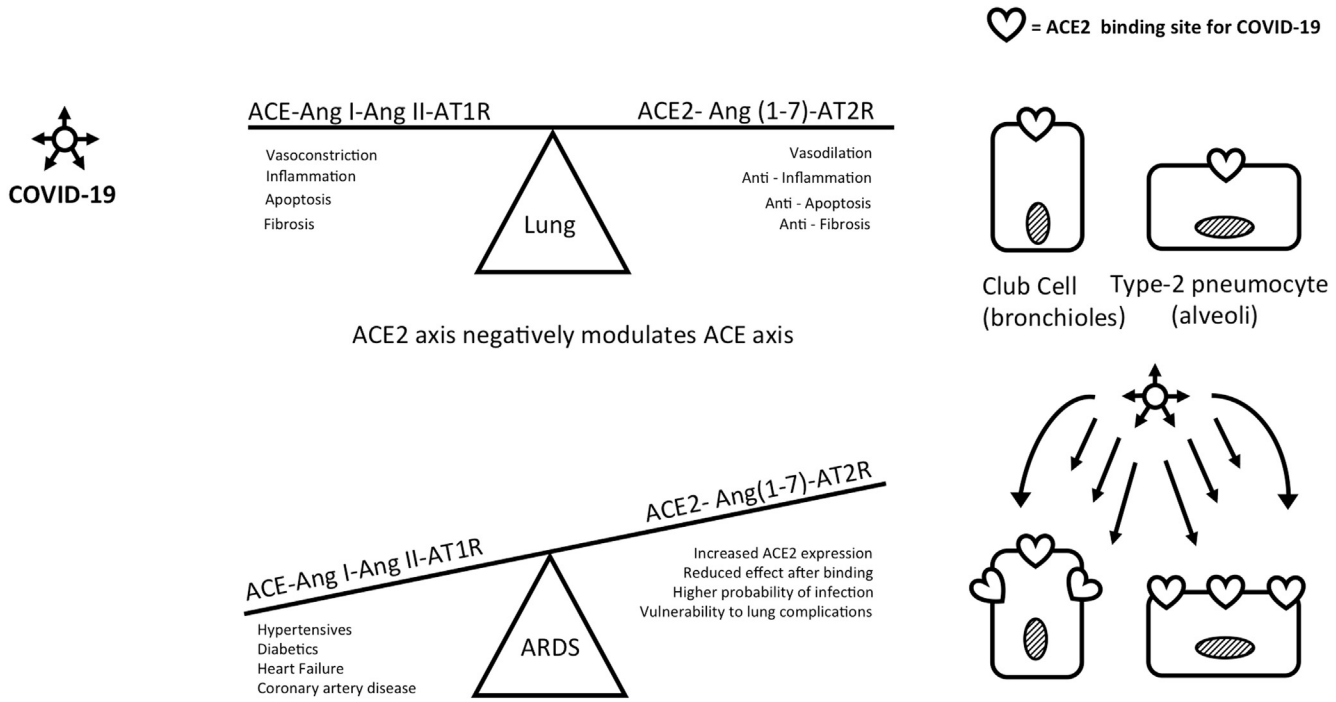

Figure 1. (**Upper panel**) The normal physiology of ACE (the worst of all enzymes) and ACE2 (the best of all enzymes). COVID-19 uses ACE2 (in club cells in distal bronchioli and pneumocytes type 2 cells in alveoli) as a binding site. (**Lower panel**) The expression of ACE2 is increased in highly prevalent cardiovascular diseases, theoretically augmenting the possibility of infection. After binding with spike receptors of COVID-19, ACE2 loses efficacy, and ACE2 counter-effect against ACE is attenuated or lost despite greater expression of ACE2.

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COVID-19 spike protein to ACE2 downregulates 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 1, 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 because a 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.

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