Letter to the Editor

COVID-19: Critical Role of Angiotensin 1-7 in ACE2 Modulation

Dear Editor,

With the declaration of Novel Coronavirus Disease 2019 (COVID-19) as pandemic by World Health Organization (WHO), many countries have taken drastic measure to enforce movement control to curb COVID-19 outbreak. On 23 January 2020, it was reported that Malaysia had 4 patients suspected to have contracted the COVID-19. On the same day, Singapore confirmed its first case of COVID-19.[1] The first confirmed COVID-19 case reported in Malaysia was on 24 January 2020. To date, WHO has reported a total of 5.6 million confirmed cases, with 353,373 confirmed deaths among 216 countries around the world.[2] Current evidence suggests that COVID-19 patients could develop rapidly worsening respiratory failure and acute respiratory distress syndrome (ARDS).[3]

Similar to SAR-Cov (Severe Acute Respiratory Syndrome Coronavirus), COVID-19 is believed to be using the same entry point of Angiotensin Converting Enzyme 2 (ACE2) into the human host cells.[4,5] ACE2 is a carboxymonopeptidase that cleaves at the carboxy-terminal (C-terminal) end of a protein or peptide [6], and is expressed on respiratory and intestinal epithelial cells, endothelial cells, renal tubule cells and immune cells.[6–10] Tipnis et al (2000) also reported that the mammalian homologue of ACE has implications on cardiovascular and renal function.[11] Up to 96% of ACE2 is available as membrane-bound enzyme, and the minority of ACE2 (1–4%) presents as a soluble form in blood, urine, and other body fluids.[12,13] Additionally, the latest study by Wan et al (2020) reported that COVID-19 uses the same receptor-binding motif, as SAR-Cov that directly contacts with ACE2.[14]

There is an intrinsically high renin angiotensin system (RAS) activity in the lungs, creating a relatively higher concentration of ACE2 in the organ. Interestingly, Angiotensin Converting Enzyme (ACE) inhibitors, which are commonly prescribed for hypertension treatment, antagonise specifically the effect of ACE, but not ACE2. [15] ACE2 plays an important role in RAS, by converting Angiotensin II to Angiotensin 1-7 (Ang-(1-7)).[6,16] The formation of Ang-(1-7) is the requisite biologic effects of ACE2 to Angiotensin II.[17,18] Nonetheless, Angiotensin I is also converted to Ang-(1-7) via endopeptidases.[19] Ang-(1-7) provides vasoprotective effects by stimulating nitric oxide production and reduces reactive oxygen species' production.[20] The disequilibrium of RAS has a significant role in COVID-19 as it is involved in the modulation of the inflammatory response in the lungs. It may seem counter intuitive, but upregulation and higher levels of Ang-(1-7) as well as ACE2 were observed in patients receiving ACE inhibitors or even Angiotensin Receptor Blocker (ARB).[14,21] Of note is the fact that augmentation of ACE2 activity, as backed by animal in vivo study, could offer vasodilation, anti-oxidant, anti-inflammation and lung protective effect.[22]

Evidence has shown diabetic and hypertensive patients are susceptible to COVID-19 and face higher mortality rates.[23] The use of ACE inhibitors and ARB over the expression of ACE2 is debatable until the latest study indicated that these two antihypertensive drugs could increase the mortality rate of patients with COVID-19.[24] The arguable use of ACE inhibitors and ARB is further supported by Cure and Cumhur (2020), with the rising concern over cardiac arrhythmias and myocarditis events, provoked by increased cardiac ACE2 levels caused by both antihypertensive drugs and thus enhancing the penetration of SARS-CoV-2 into the heart tissue.[25]

However, evidence has shown that ACE2 is not inhibited by ACE inhibitor because ACE and ACE2 are different enzymes.[26] Literature has shown that ACE2 is consistently increased by ARB especially in cardiac tissue and renal vasculature, but at high doses.[26,27] Of note is a China study reported which lower mortality rate in COVID-19 hypertensive patients treated with ACE inhibitor/ ARB (adjusted HR, 0.30; 95%CI, 0.12-0.70; P = 0.01).[28] To date, there is no solid evidence to support discontinuation of the use of ACE inhibitor and ARB in COVID-19 patients.[29] With the lack of evidence to support the possible

protective effect of ACE2 augmentation rendered by ACE Inhibitor/ ARB, the downstream metabolite of ACE2, Ang-(1-7), provides the possible clue to this dynamic responsiveness.

Hypothetically, as a negative feedback effect, ACE2 level should decrease with elevation of Ang-(1-7) in RAS (Fig. 1). Compared to ACE2, Ang-(1-7) is the downstream metabolite that could exert vasodilation and anti-inflammation effect when it binds to Mas receptor.[30–32] Despite functioning as a receptor for Ang-(1-7), Mas has important physiological actions in biological active peptide by providing a clear molecular basis.[34] Treatment with Ang-(1-7) has significantly reduced levels of proinflammatory cytokines, oxidative stress and macrophage infiltration in the lungs.[32] If this hypothesis is proven, the anti-inflammation and lung protective effect could be warranted with the increase concentration of external Ang-(1-7) albeit with the reduced ACE2 as host cell for SARS-CoV-2. Therefore, the spread of COVID-19 could be diminished with the reduction in the amount of ACE2 which act as host cells. "Emerging and re-emerging infections" seems to be the current trend, and the threat of infections is unlikely to be eradicated abruptly.[35] Further inroads with broader approaches involving biological agents should be considered to mitigate COVID-19. A proof of concept study would provide the much-needed evidence to support this postulation.
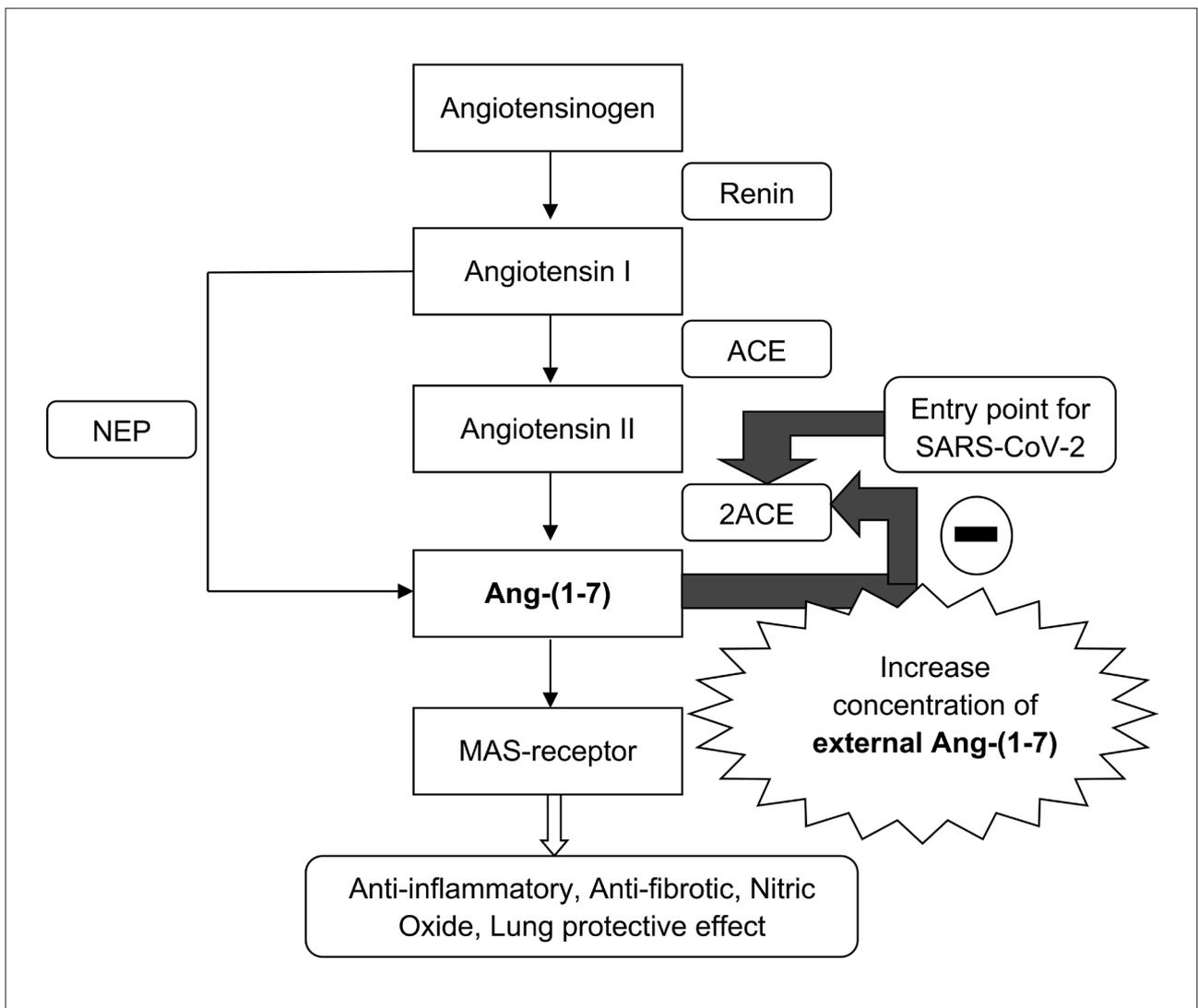

Figure 1. Negative feedback effect of Angiotensin 1-7 [Ang-(1-7)] in Renin Angiotensin System (RAS).

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