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Editorial

ACE2 and RAAS: Therapeutic intervention point for COVID-19

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ABSTRACT

COVID-19 has caused widespread mortality and morbidity and significant economic disruption. Several potential therapeutic and/ or preventive approaches to address the pandemic are being worked out, a few effective vaccines are under clinical trials and few vaccines has been approved but still the expected result has not been achieved. Some Spiritual Leader claims it to be natural process and can be protected by chant of Mantra 'Pujya Anakarananta Nirakar niranjan shivajyoti mahamanav pita'.

Renin-Angiotensin-Aldosterone System (RAAS) is no more a mere research area in cardio-pulmonary and renal physiology alone but has gained focus as an infection and therapeutic point for COVID-19. This article discusses about ACE2 receptor as a centre point of infection of SARS-CoV-2 and also suggests it as the therapeutic intervention point for COVID-19.

Keywords: *ACE2, COVID-19, Namoshivayay, RAAS, SARS-CoV-2,*

The novel corona virus (2019-nCoV) officially known as SARS-CoV-2(severe acute respiratory syndrome coronavirus-2) is the virus responsible for the ongoing COVID-19 outbreak [1]. It was first seen as a cluster of acute respiratory illness in Wuhan, Hubei Province, China [2]. Since then, it has been spreading rapidly to almost all countries of the world and has been declared a pandemic by the World Health Organization (WHO) on 12th March 2020 [2].On May 19, 2021, over 164,626,458 coronavirus cases, including 3,413,801 deaths, have already been confirmed around the world [3].It has caused widespread morbidity and mortality and significant economic disruption around the world [4].Several anti-viral drugs like Remdesivir [5], Hydroxychloroquine and chloroquine [6]have been used but with little effect. Dexamethasone also has shown to reduce mortality in severely ill patients with Covid-19 [7].

Many spiritual leaders describe it as a natural phenomenon and medical science can only treat the symptoms like pneumonia and difficulties in breathing and their consequences. Mahamanav Pita- popular as spiritual divine guru claims that his body embodied the 'Ansa' (nearest meaning in English is component) of 'Shristikarta' and other forms of 'Shiva' guaranteed that his mantra can save anyone and chanting of it every day will not allow the virus to enter one's body. One of the mantra he gave was: 'Pujyapita Anankarananta Nirakarniranjan Shiva Jyoti mahamanav Pita'. It has to be chanted 7 times in one sitting. It has to be

done in three siting in the morning, midday and in the evening [8]. This is not the scope of this paper, so will be discussed elsewhere.

Several potential therapeutic and/or preventive approaches to address the pandemic are being worked out, a few effective vaccines are under clinical trials and a few vaccines has been approved but still the expected result has not been achieved [4, 7-12]. However very recently different vaccine platforms are currently available which include live attenuated vaccines, inactivated vaccines, recombinant protein vaccines, vector vaccines, DNA vaccines and RNA vaccines [11]. Vaccines increase the endogenous synthesis of SARS-CoV-2 Spike proteins from a variety of cells [11]. Here I would like to suggest that viral entry is the first step in the SARS-CoV-2 lifecycle and is mediated by the trimeric spike protein [9-11]. Being the first stage in infection, entry of SARS-CoV-2 into host cells is an extremely attractive therapeutic intervention point [10]. SARS-CoV-2 enters the host cell by binding to surface domain of membrane-bound angiotensin-converting enzyme 2 (mACE2). So, we can say that Covid-19 is an ACE2 centric infective disease [12] and all the clinical manifestations of the disease are related to the organs with abundant amount of ACE2 receptors [9, 12]. The pattern of multiorgan dysfunction seen in COVID-19 patients is likely related to this pattern of ACE2 expression and resultant widespread infection [10, 12].

The research works on pathogenesis of SARS-CoV confirms that the ACE2 is the main receptor for binding and uptake of SARS-CoV-2 [11, 13] with receptor CD147 as an exception [14]. So, all the research for therapeutic solution to COVID-19 should focus on ACE2 and important physiological mechanisms involving ACE2. ACE2 is primarily expressed at higher levels in type II alveolar cells in the lungs, proximal tubule cells in nephron, myocardial cells, epithelial cells of ileum and esophagus of human [15-16]. ACE2 is also expressed to a lesser extent at different levels of the respiratory apparatus including olfactory epithelium, nasopharynx, trachea and bronchi [17-18] ACE2 circulates in very small amounts and is generally undetectable but it can be substantially increased in heart-failure, hypertension, obesity, and diabetes mellitus [19].

ACE2 and RAAS (Renin-Angiotensin-Aldoesterone System): COVID-19 and research on its pathogenesis remind us of the significance of the renin-angiotensin-aldosterone system (RAAS) in cardiovascular, pulmonary, and kidney physiology [13]. In short, the RAAS comprises of two major pathways; the first one ACE converts angiotensin I (Ang I) into Ang II, which acts on the Ang II type 1 receptor (AT_1R) to increase blood pressure via increased renal water and sodium re-absorption and vasoconstriction. It also stimulates pro-inflammatory chemokines to promote inflammation [20-22]. The second is the counter-regulatory mechanism which consist of ACE2 (the composition of which is 60% like ACE) that generate Ang_{1-7} that then acts at G-protein coupled MAS [Mitochondrial assembly] receptor to reduce blood pressure and inflammation [13, 15, 20]. ACE2 first metabolizes Ang II into Ang_{1-7} and can convert Ang I to Ang_{1-9}, which is further metabolized by ACE into Ang_{1-7} The balance between these two pathways is a key determinant of both acute and chronic cardio-pulmonary and renal diseases [13, 15] and so

is important in the clinical picture and outcomes of Covid 19. The beneficial effects of RAAS inhibitors such as AT_1R blockers (ARBs) and ACE inhibitors is mainly due to shifting this balance away from ACE—Ang II and toward ACE2—Ang_{1-7} [9-10, 20-22].

SARS-CoV-2 binds to ACE2 receptors and enters the cell through the fusion of its membrane leading to down-regulation of these receptors. The loss of ACE2 receptor activity will lead to less angiotensin II inactivation and less generation of $antiotensin_{1-7}$ [20-22]. In various experimental models of lung injury, the imbalance between angiotensin II overactivity and of $antiotensin_{1-7}$ deficiency triggered inflammation, thrombosis, and other adverse reactions [21-23]. In COVID-19, such imbalance could play an important role in influencing the clinical picture and outcome of the disease. According to this line of thinking, ACE2 is at the core of COVID-19 research and drug development; recombinant ACE2, exogenous $angiotensin_{1-7}$, and angiotensin receptor blockers seem particularly promising [10, 24-26]. Preclinical data also suggest ACE2 might be down-regulated after SARS-CoV-2 binding, and treatments that increase ACE2 may prevent cardiopulmonary injury [27].

Human ACE2 (hACE2) inhibits SARS-CoV-2 viral infection in human organoids in vitro [24]. Zoufaly et al probably for the first time showed that the virus decreased rapidly from the serum and slightly later from the nasal cavity and lungs after hrsACE2 (human recombinant soluble ACE2) (APN01) therapy. His findings that hrs ACE2 treatment did not interfere with generation of neutralizing antibodies is an important aspect of this treatment favoring further research on this line [26]. Similarly, Monteil *et al*. showed that

in vitro, hrsACE2 drastically reduced viral recovery from host cell cultures, indicating prevention of host cell binding. He also showed that infection was not completely halted by hrsACE2 in vitro, treatment slowed viral replication in both organoid models, indicating the soluble enzyme may inhibit the spread of infection and lower viral loads which may correlate with disease [24]. Christopher BR declares hrsACE2 has already passed through phase I and II clinical trials (NCT00886353, NCT01597635) for acute respiratory distress syndrome and has received regulatory approval (NCT04335136) for continued study in the fight against COVID-19 [10].

Development, testing of efficacy and mass production of recombinant ACE2 therapies is a further workout needed in therapy of Covid -19.

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