

Brief Insight into the Physiological Perspective of Renin-Angiotensin-Aldosterone-System as a Gateway in Pathogenesis of COVID-19

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ABSTRACT

The world is facing an unprecedented crisis due to “COVID-19” pandemic and the numbers of cases are constantly soaring. ACE2 is ubiquitously present in different organs including nasal epithelium, conducting airways and alveolar epithelium. It is found that S-protein of SARS-CoV-2 activated by TMPRSS2 targets ACE2 for gaining entry into host cells. Eventually the downregulation of ACE-2 occurs, either directly because of viral binding and endocytosis or indirectly because of cell lysis or ADAM17 activity. This results in homeostatic disruption of ACE/ACE2 system balance and the activity of activator pathways of Renin-Angiotensin-Aldosterone-System (ACE/angiotensin II/AT₁R pathway) remains uninhibited by inhibitor pathways (angiotensin-(1-7)/ACE-2/MasR pathway). This will flare up immune response, destroy the alveolar type II pneumocyte and release pro inflammatory cytokines such as IL-6, TNF, etc. As a result “COVID-19” manifests as different symptoms of ranging from mild flu like to severe ARDS. This review highlights further prospect of studies on ACE2 or S-protein as a therapeutic agent or target.

Keywords: COVID-19, SARS-CoV-2, ACE2, Renin-Angiotensin-Aldosterone-System, TMPRSS2, ADAM17.

INTRODUCTION

“COVID-19” has wreaked havoc on humans in multiple spheres of our lives ranging from health to economy. It has brought unimaginable change in contour of

our daily lives. On 12th March 2020, WHO declared “COVID-19” as a global pandemic. [1] Striking irrespective of race, religion, colour, caste, creed, and language the virus has pushed the mankind to an existential crisis. Till July 6, 2020 (time when article is prepared) there has been 1,13,27,790 confirmed “COVID-19” cases (including 5,32,340 deaths) around the world and 6,97,413 total cases (19,693 death) in India [1,2] and the numbers are constantly soaring.

“COVID-19” is the new coronavirus disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) that began in Wuhan, China in December 2019. [2] It is now well recognized that SARS-CoV-2 virus has major effects on the respiratory system and these symptoms of COVID-19 are extremely heterogeneous, ranging from minimal symptoms (fever, dry cough and dyspnea) to significant hypoxia with ARDS. [3] Features of this pandemic have close resemblance with another coronavirus (SARS-CoV) epidemic named as Severe Acute Respiratory Syndrome (SARS) epidemic which occurred in the year 2002-2004. The main targets of SARS were the lungs, immune organs, and systemic small vessels, resulting in systemic vasculitis, decreased immune function, and respiratory distress. [4] A metalloproteinase named angiotensin-converting enzyme-2 (ACE-2) was identified as a functional receptor for SARS-CoV in 2003. [5] There is

a convincing evidence regarding surface expression of ACE-2 protein on nasal and oral mucosa, nasopharynx and lung alveolar epithelial cells along with other organs. [6] Recently, Zhou P et al confirmed that SARS-CoV-2 also uses the angiotensin converting enzyme II (ACE-2)-as same cell entry receptor like previous SARS-CoV. [7]

Renin-angiotensin-aldosterone-system (RAAS) and Angiotensin converting enzyme (ACE):

The renin-angiotensin-aldosterone system (RAAS) is an elegant cascade of vasoactive peptides that orchestrate key processes in human physiology. One of the RAAS components, renin, in the circulation cleaves Angiotensinogen to generate Angiotensin I (AT-I). AT-I is again cleaved to yield Angiotensin II (AT-II) by an enzyme known as Angiotensin Converting Enzyme (ACE). Angiotensin II exerts its main actions by binding to the receptor, AT₁R. [8] Angiotensin II, in addition to its pro-vasoconstrictive and hypertensive features, is able to activate various cells of the immune system, causing thrombosis, fibrosis and release pro-inflammatory cytokines such as IL-6, TNF, etc. This could therefore be a potential element in the development of inflammatory lung injury. [8,9]

ACE-2 has 42% sequence identity and 61% sequence similarity with the two active sites of ACE. [10] It acts in a counter-regulatory fashion to angiotensin II. [8] ACE-2 cleaves Angiotensin I to yield Angiotensin (1-9). Further, Ang-(1-9) is then cleaved to Ang-(1-7) in a minor pathway. Angiotensin II can also be cleaved by ACE-2 into Ang-(1-7), which through its receptor (Mas) exerts actions like anti-thrombosis, anti-fibrosis, vasodilation etc. which are physiologically antagonistic to the classical effects described above. [11,12]

So, RAAS can thus be divided into an “activator” system comprising the classical and historical ACE/angiotensin II/AT₁R pathway and an “inhibitor” system comprising the angiotensin-(1-7)/ACE-

2/MasR pathway. The latter is able to both deactivate angiotensin II and counter its effects. [11] Under normal circumstances; a homeostatic balance of ACE/ACE2 system is maintained in our body. [12]

Binding of SARS-CoV-2 with ACE-2:

SARS-CoV-2 consists of four structural proteins; Spike (S), membrane (M), envelop (E) and nucleocapsid (N) proteins. [13] The virus binds to the Angiotensin Converting Enzyme 2 (ACE-2) via its spike protein. [14] This spike protein is activated by TMPRSS2 (transmembrane proteases type 2) proteases following which SARS-COV2 binds to the extracellular domain of membrane ACE-2. [15] Moreover, the affinity of SARS-COV-2 for ACE-2 is greater than that of SARS-COV, the virus responsible for SARS epidemic in 2002-2004. [14] Binding to ACE-2 stimulates clathrin-dependent endocytosis of both ACE-2 and the SARS-CoV-2. [8,16] This is a critical step in the pathogenesis of any viral infection as viruses generally are obligate intracellular organisms. Viral RNA enters the nucleus for replication. Viral mRNA is used to make new viral proteins and released to attach nearby ACE-2 positive cells. [13,14] Binding of the spike protein to ACE-2 also induces ADAM-17 (ACE2 disintegrin and metallopeptidase domain 17) mediated shedding of ACE-2, which also reduces the amount of ACE-2 expressed on the cell surface. [8]

Once, the virus has entered the body there can be dual modes of its effects concerning ACE-2 as described below.

Viral-ACE-2 interaction on the classical pathway:

When the virus interacts with ACE-2 to gain entry into the cells, the downregulation of ACE-2, either directly because of viral binding and endocytosis or indirectly because of cell lysis or ADAM17 activity alters the delicate ACE/ACE2 system balance. [8,12] Without the inhibitory influence of the angiotensin-(1-7)/ACE2/MasR pathway, the unopposed activity of the classical “activator” RAAS

can cause local activation of immune cells and flare up an immune response aggravating the already existing COVID-19-induced inflammation in organs such as, notably, the lung and other systemic signs of inflammation.^[12]

Effects of viral-ACE-2 interaction on the alveolar type II pneumocytes:

The initial days after acquiring the infection are asymptomatic. The inhaled virus (SARS-CoV-2) most likely binds to the epithelial cells in the nasal cavity and starts replicating.^[17] There is local propagation of the virus triggering a limited and localized innate immune response.^[18] Few days later, about 80% of the infected patients, develop mild symptoms which are mostly restricted to the upper and conducting airways.^[19] The virus propagates and migrates down the respiratory tract along the conducting airways, and a more robust innate immune response is triggered.^[18] For most patients, the activated immune response contains the disease. But unfortunately, about 20% of the infected patients progress to the next stage of the disease which is severe. And among them, some can develop even a very severe disease with clinically worsening respiratory signs and pathologically characterized by increasing amount of pulmonary infiltrates.^[19] In the lungs, ACE-2 is expressed by alveolar type II pneumocytes which comprise only 5% of the alveolar cells but produce the pulmonary surfactants, which are chemicals critical for maintaining normal ventilation and preventing collapse of alveoli. These cells also act as progenitors for alveolar type I pneumocytes which are responsible for the exchange of gases in the lung. As discussed previously because of the high affinity of this virus for ACE-2, SARS-CoV-2 thus targets and kills the cells which are not only important for normal ventilatory dynamics but also serve as the regenerative pool for the Type I pneumocytes which are concerned with gaseous exchange.^[20] Therefore, destruction of alveolar cells, deficiency of surfactant associated with activation of secondary

pathways of aberrant wound healing heralds a process of severe injury and scarring followed by fibrosis of injured alveolar epithelium. This probably explains in part, the development of severe lung injury with pulmonary infiltrates and ARDS in COVID-19.^[21,22]

CONCLUSION

There seems to be a growing corpus of evidence in medical literature as far as the role of ACE-2 is concerned. It could function as the functional receptor for S-protein of SARS-CoV-2 and lead to a downstream series of events contributing to the pathophysiology of lung injury. The world is still trying to decipher the full plethora of effects of this new virus. In such a scenario, it needs to be seen whether this particular facet of host and virus interaction can be explored to obtain therapeutic benefits. And in this regard, endogenous regulation ACE-2 gene expression, antibodies or compounds with higher affinity for ACE-2 than the virus can serve as avenues for future scientific research.

REFERENCES

1. WHO announces COVID-19 outbreak a pandemic [homepage on internet]. World Health Organization: Coronavirus disease (COVID-19) outbreak. c2020 [Accessed 6 July 2020]. Available from: <http://www.euro.who.int/>.
2. COVID-19 INDIA [homepage on internet]. Ministry of Health and Family Welfare, Government of India as, c2020 [Accessed 6 July 2020]. Available from: <https://www.mohfw.gov.in/>.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395 (10223): 497–506.
4. Ding Y, Wang H, Shen H, Li Z, Geng J, Han J et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. *J Pathol*. 2003; 200(3): 282–9.
5. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA et al. Angiotensin-converting enzyme 2 is a functional receptor

- for the SARS coronavirus. *Nature*. 2003 Nov 27; 426(6965): 450–4.
6. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, Goor HV. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004; 203(2):631–7.
 7. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020; 579(7798):270-3.
 8. Clarke NE, Turner AJ. Angiotensin-Converting Enzyme 2: The First Decade. *International Journal of Hypertension* 2012; Available from: <https://doi.org/10.1155/2012/307315>
 9. Marshall RP, Gohlke P, Chambers RC, Howell DC, Bottoms SE, Unger T et al. Angiotensin II and the fibroproliferative response to acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2004, 286(1):156-64.
 10. Zhao Y, Xu C. Structure and Function of Angiotensin Converting Enzyme and Its Inhibitors. *Chin J Biotech*, 2008, 24(2), 171-76.
 11. Alexandria J, Cracowskib JL, Richardc V, Bouhanick B. Renin-angiotensin-aldosterone system and COVID-19 infection. *Annales d'Endocrinologie* 2020; 81(2): 63–7.
 12. Santos RAS, Ferreira A J, Silva ACS. Recent advances in the angiotensin-converting enzyme2–angiotensin(1–7)–Mas axis. *Exp Physiol* 2008 ;93(5): 519–27.
 13. Bosch BJ, Zee RVD, Haan CA, Rottier PJ. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. *J Virol*. 2003; 77(16):8801-11.
 14. Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV. *Biochem Biophys Res Commun*. 2020; 525(1):135-40.
 15. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; 181(2):271-280.
 16. Inoue Y, Tanaka N, Tanaka Y, Inoue S, Morita K, Zhuang M et al. “Clathrin-dependent entry of severe acute respiratory syndrome coronavirus into target cells expressing ACE2 with the cytoplasmic tail deleted,” *J Virol*. 2007;81(16): 8722–9.
 17. Wan Y, Shang J, Graham R, et al. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. *J Virol* 2020 Mar 17; 94(7):e00127-20.
 18. Mason R J. Pathogenesis of COVID19 from a cell biology perspective. *Eur Respir J* 2020; 55: 2000607. Available from: <https://dx.doi.org/10.1183/13993003.00607-2020>
 19. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and prevention. *JAMA* 2020 Feb 24. doi: 0.1001/jama.2020.2648.
 20. Barkauskas CE, Crouse MJ, Rackley CR, Bowie EJ, Keene DR, Stripp BR, et al. Type 2 alveolar cells are stem cells in adult lung. *J Clin Invest* 2013;123(7):3025–36.
 21. Rivellese F, Prediletto E. ACE2 at the centre of COVID-19 from paucisymptomatic infections to severe pneumonia. *Autoimmun Rev*. 2020. Jun; 19(6): 102536.
 22. Li Y, Wu Q, Sun X, Shen J, Chen H. Organoids as a powerful model for respiratory diseases. *Stem Cells Int*. 2020 Mar 11; 2020:5847876.

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