Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

MOJ Immunol. Author manuscript; available in PMC 2020 July 10.

Published in final edited form as:

MOJ Immunol. 2020 ; 7(1): 17–19.

COVID-19–A theory of autoimmunity to ACE-2

Philip McMillan, MB, BS, MRCP[1], **Bruce D. Uhal, PhD**[2]

[1]Doncaster & Bassetlaw NHSTrust, UK

[2]Department of Physiology, Michigan State University, USA

Perspective

The COVID-19 (SARS-COV2) pandemic[1] represents a significant challenge to the world from a health and financial perspective. The disease has a high mortality rate and is very contagious, making it difficult to manage. The complexity of COVID-19 is partly evidenced by file disparity of symptoms from extremely mild in children[2] and young adults[3] to much more severe in older age groups. Additionally, COVID-19 is asymptomatic in many younger people who have the potential to act as super spreaders[4] to the general population.

The primary cause of mortality in COVID-19 is respiratory failure secondary to severe pneumonia[5] and an atypical form of Adult Respiratory Distress Syndrome.[6] In certain individuals, the disease is characterised by a severe inflammatory response in the lungs with involvement of the liver and kidneys.[7] This has been presumed secondary to viral damage, but in reality the pattern of severe inflammation does not seem to follow that of any other similar viral infection.

COVID-19 binds to a specific ACE2 receptor that is located in the lungs within bronchioles[8] and alveoli[9] and other tissues in the body, including those of the kidney and small intestine.[10] The ACE2 enzyme is important in the regulation of angiotensin 2 levels related to control of blood pressure and inflammation.[11] The majority of these ACE2 enzymes are fixed to cell surfaces, mainly on the endothelium.[12] Whilst there can be viral replication in these cells and some inflammatory response, this does not explain the severity of inflammation in the lungs.

In addition to the cellular attached form, the ACE2 enzyme exists in the soluble form.[13] These soluble receptors act as dummy receptors[14] with only surface connections, yet maintain plasma activity on angiotensin II.[15] The purpose of these soluble receptors is not yet clear, but a large number on the surface of cells could lower file probability of viral integration. This could partially account for file asymptomatic nature of the disease in younger persons, but would not fully explain it.

Correspondence: Bruce D. Uhal, Ph.D. Department of Physiology, Michigan State University, East Lansing, MI 48824. bduhal@gmail.com.

Conflicts of interest

None.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

The soluble ACE2 receptors in people with hypertension and heart failure are oftentimes increased in the serum.[13,16] If the soluble receptor in serum combines with the SARS-COV2 virus, the whole particle could become an antigen. The COVID-19 virus has multiple spike proteins on the surface which would potentially bind to the elevated levels of soluble ACE2 enzyme in hypertension and heart disease and increase the risk of antigen formation. This complex of virus with multiple soluble ACE2 enzymes will be presented to macrophages to highlight antigens for antibody production. It is very possible that antibodies will be created that target the ACE2 cellular enzyme with increased angiotensin 2 levels.

The great danger in predisposed individuals is that the normally elevated levels of active serum ACE2 enzyme will be unable to reduce angiotensin 2 levels. This could contribute to pulmonary vasculature damage because of dysregulation of the renin-angiotensin axis.[17] Also, the production of anti ACE2 IgG antibodies (approximately day 10) will further target the ACE2 serum enzyme and form complexes to create vasculitic type symptoms.[18,19] It means that all organs that have ACE2 receptors would be targeted and cause a variety of symptoms, including the gastrointestinal tract.[20]

There is significant homology between ACE and ACE2 enzymes[21,22] which could indicate that if antibodies were produced against the ACE2 there could be cross reactivity with ACE.[23] In such a situation this could trigger severe pulmonary oedema[24] with ARDS as seen in COVID-19. The lung would remain the most severely affected region in the body[25] with potential vasculitic symptoms on other parts of the body. This difference in antibody linked epitopes could explain why some persons have mild versus severe disease. Shedding of the ACE[26] and ACE2 would increase the chance of immune complexes forming with end organ damage to liver and kidneys.

The overall autoimmune theory is that the combination of the virus and the soluble ACE2 receptor becomes antigenic, which may cause the formation of antibodies against not only the virus, but also parts of the ACE and ACE2 receptor. This pattern of lung injury also occurs in Pulmonary Hypertension secondary to Scleroderma with elevated levels of anti ACE2 antibodies.[27] The higher the levels of the soluble receptors in serum, the more likely it is that the body would respond in this way, that is, with an immune response. This could explain the severity of the inflammatory response in cardiac disease and hypertension causing high mortality globally.[28]

In the original SARS-COV1 viral epidemic in 2003, a similar degree of lung inflammation was observed, described as Hypersensitivity Pneumonitis.[29–36] This would fit with immune dysregulation as the cause of the lung damage that occured in these patients. If this is the case, then the solution for reducing mortality lies with identifying people who are at risk of having this kind of hyperimmune response. Measurement of serum ACE2 antibody titres would help to identify who is likely to progress into ARDS. Identification of the at-risk groups could be done with a blood test to measure the serum ACE2 levels, specifically targeting people with a history of cardiac disease and hypertension. Becoming more strategic in our thinking is essential to protecting the vulnerable whilst allowing life to continue as normal as possible for others.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

When mortality is reduced across the population there will be less concern for long term wellbeing. Without a system to reassure the public it is unlikely that we will achieve the benefit of getting persons back to work. Let us not forget that public fear is real and only reduced mortality will make a difference to people's concerns.

References

1. Na Zhu, Zhang Dingyu, Wenling Wanget al. A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine. 2020;382:727–733. [PubMed: 31978945]
2. Ping–Ing Lee, Ya–Li Hu, Chen Po–Yen, et al. Are children less susceptible to COVID-19?. Journal of Microbiology, Immunology, and Infection. 2020.
3. Graziano Onder, Rezza Giovanni, Brusaferro Silvio. Case–fatality rate and characteristics of patients dying in relation to COVID–19 in Italy. Jama. 2020.
4. Eunha Shim, Tariq Amna, Choi Wongyeong, et al. Transmission potential and severity of COVID–19 in South Korea. International Journal of Infectious Diseases. 2020;339–344. [PubMed: 32198088]
5. Yan-Chao Li, Bai Wan-Zhu, Hashikawa Tsutomu. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. Journal of medical virology. 2020;92(6):552–555. [PubMed: 32104915]
6. Luciano Gattinoni, Liu Xuesong, Xu Yonghao, et al. Covid–19 does not lead to a "typical" acute respiratory distress syndrome. American journal of respiratory and critical care medicine ja. 2020.
7. Yichun Cheng, Lao Ran, Wang Kyn, et al. Kidney disease is associated with in–hospital death of patients with COVID–19. Kidney International. 2020;97(5):829–838. [PubMed: 32247631]
8. Soeren Lukassen, Chua Robert Lorenz, Trefzer Timo, et al. SARS–CoV–2 receptor ACE2 and TMPRSS2 are predominantly expressed in a transient secretory cell type in subsegmental bronchial branches. Bio Rxiv. 2020.
9. Uhal Bruce D, Li Xiaopeng, Xue Anita, et al. Regulation of alveolar epithelial cell survival by the ACE–2/angiotensin 1–7/M as axis. American Journal of Physiology—Lung Cellular and Molecular Physiology. 2011;301(3):L269–L274. [PubMed: 21665960]
10. Inge Hamming, AT Lely MLC Bulthuis, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding ARS pathogenesis. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland. 2004;203(2):631–637.
11. Ravinder Reddy Gaddam, Chambers Stephen, Bhatia Madhav. ACE and ACE2 in inflammation: a tale of two enzymes. Inflammation & Allergy–Drug Targets (Formerly Current Drug Targets–Inflammation & Allergy). 2014; 13(4):224–234.
12. Oudit Gavin Y, Crackower Michael A, Back Peter H, et al. The role of ACE2 in cardiovascular physiology. Trends in cardiovascular medicine. 2003;13:(3):93–101. [PubMed: 12691672]
13. Katalin Uri, Fagyas Miklós, Siket Ivetta Mányiné, et al. New perspectives in the renin–angiotensin–aldosterone system (RAAS) IV: circulating ACE2 as a biomarker of systolic dysfunction in human hypertension and heart failure. PLoS One. 2014;9(4):e87845. [PubMed: 24691269]
14. Lambert Daniel W, Yarski Mike, Warner Fiona J, et al. Tumor necrosis factor–α convertase (ADAM17) mediates regulated ectodomain shedding of the severe–acute respiratory syndrome–coronavirus (SARS–CoV) receptor, angiotensin-converting enzyme–2 (ACE2). Journal of Biological Chemistry. 2005;280(34):30113–30119. [PubMed: 15983030]
15. Epelman Slava, Tang WH Wilson, Chen Stephen Y, et al. Detection of Soluble .Angiotensin–Converting Enzyme 2 in Heart Failure: Insights Into the Endogenous Counter–Regulatory Pathway of the Renin–Angiotensin–Aldosterone System. Journal of the American College of Cardiology. 2008;52(9):750. [PubMed: 18718423]
16. Zoltán Csanádi, Fagyas Miklós, Siket Ivetta Mányiné, et al. New perspectives in the renin–angiotensin–aldosterone system (RAAS) IV: Circulating ACE2 as a biomarker of systolic dysfunction in human hypertension and heart failure.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

17. Vinayak Shenoy, Qi Yanfei, Katovich Michael J, et al. ACE2, a promising therapeutic target for pulmonary hypertension. Current opinion in pharmacology. 2011; 11(2): 150–155. [PubMed: 21215698]
18. Julie Helms, Kremer Stéphane, Merdji Hamid, et al. Neurologic features in severe SARS–CoV–2 infection. New England Journal of Medicine. 2020.
19. Galván Casas C, Català A, Hernández G Carretero, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. British Journal of Dermatology. 2020.
20. Jinyang Gu, Han Bing, Wang Jian. COVID–19: gastrointestinal manifestations and potential fecal–oral transmission. Gastroenterology. 2020; 158(6):1518–1519. [PubMed: 32142785]
21. Yumiko Imai, Kuba Keiji, Penninger Josef M. The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. Experimental physiology. 2008;93(5):543–548. [PubMed: 18448662]
22. Turner Anthony J, Tipnis Sarah R, Guy Jodie L, et al. ACEH/ACE2 is a novel mammalian metallocarboxypeptidase and a homologue of angiotensin–converting enzyme insensitive to ACE inhibitors. Canadian journal of physiology and pharmacology. 2002;80(4):346–353. [PubMed: 12025971]
23. Kugaevskaya Elena V, Kolesanova Ekaterina F, Kozin Sergey A, et al. Epitope mapping of the domains of human angiotensin converting enzyme. Biochimica et Biophysica Acta (BBA)–General Subjects. 2006; 1760(6):959–965. [PubMed: 16580777]
24. Giovanni Camussi, Balyasnikova Irina V, Binevski Petr V, et al. Role of the membrane attack complex of complement in lung injury mediated by antibodies to endothelium. International archives of allergy and immunology. 1993; 102(3):216–223. [PubMed: 8219774]
25. Danilov SERGEIM. Lung is the target organ for a monoclonal antibody to angiotensin–converting enzyme. Lung. 1991;64(1):118.
26. Balyasnikova Irina V, Woodman Zenda L, Albrecht Ronald F, et al. Localization of an N–domain region of angiotensin–converting enzyme involved in the regulation of ectodomain shedding using monoclonal antibodies. Journal of proteome research. 2005;4(2):258–267. [PubMed: 15822901]
27. Yuko Takahashi, Haga Shiori, Ishizaka Yukihito, et al. Autoantibodies to angiotensin–converting enzyme 2 in patients with connective tissue diseases. Arthritis research & therapy. 2010;12(3):R85. [PubMed: 20470389]
28. Safiya Richardson, Hirsch Jamie S, Narasimhan Mangala, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID–19 in the New York City area. Jama. 2020;323(20):2052–2059. [PubMed: 32320003]
29. Tim Tsui Ping, et al. Severe acute respiratory syndrome: clinical outcome and prognostic correlates. Emerging infectious diseases 2003;9(9):1064–1069. [PubMed: 14519241]
30. Chappell Mark C. Angiotensin–converting enzyme 2 auto antibodies: further evidence for a role of the renin–angiotensin system in inflammation. 2010:128.
31. Danilov S, Martynov A, Muzykantov Faerman V, et al. Monoclonal antibodies to angiotensin–converting enzyme: a powerful tool for lung and vessel studies. Journal of molecular and cellular cardiology. 1989;21:165–170.
32. Picard C, Ronco, Moullier P, et al. Epitope diversity of angiotensin II analysed with monoclonal antibodies. Immunology. 1986;57(1): 19–24. [PubMed: 2417938]
33. Barba LILLY M, Caldwell PR, Downie GH, et al. Lung injury mediated by antibodies to endothelium. I. In the rabbit a repeated interaction of heterologous anti–angiotensin–converting enzyme antibodies with alveolar endothelium results in resistance to immune injury through antigenic modulation. The Journal of experimental medicine. 1983; 158(6):2141–2158. [PubMed: 6315852]
34. Caldwell PR. Lung injury induced by antibody fragments to angiotensin–converting enzyme. The American journal of pathology. 1981;105(1):54. [PubMed: 6271015]
35. Emanuele Cozzani, Rosa Gian Marco, Drosera Massimo, et al. ACE inhibitors can induce circulating antibodies directed to antigens of the superficial epidermal cells. Archives of dermatological research. 2011;303(5):327–332. [PubMed: 20563876]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

36. Skirgello Olga E, et al. Inhibitory antibodies to human angiotensinconverting enzyme: fine epitope mapping and mechanism of action. Biochemistry. 2006;45(15):4831–4847. [PubMed: 16605251]