

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

Perspective

The COVID-19 (SARS-COV2) pandemic¹ 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 the disparity of symptoms from extremely mild in children² and young adults³ 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 spreaders⁴ to the general population.

The primary cause of mortality in COVID-19 is respiratory failure secondary to severe pneumonia⁵ 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 bronchioles⁸ and alveoli⁹ 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 receptors¹⁴ 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 the probability of viral integration. This could partially account for the asymptomatic nature of the disease in younger persons, but would not fully explain it.

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

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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 oedema²⁴ with ARDS as seen in COVID-19. The lung would remain the most severely affected region in the body²⁵ 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 ACE²⁶ 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 occurred 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.

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.

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Conflicts of interest

None.

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