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Commentary

The Novel Coronavirus and Cellular Entry: A Therapeutic Conundrum?

John R Zysk*

Adjunct Professor, Piedmont Virginia Community College, Charlottesville, Virginia, United States

***Corresponding Author:** John R Zysk, Adjunct Professor, Piedmont Virginia Community College, Charlottesville, Virginia, United States.

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"*Disease is the retribution of outraged Nature".*

Hosea Ballou

Early this year, the novel coronavirus (SARS-CoV-2) pandemic sprang with incredible swiftness and caught the world unawares. As of this writing (little more than six months), at least 13 million people have been infected and over 570,000 have died [1] of the disease (COVID-19). The pathogenesis of the virus includes acute lung injury (ALI), heart failure and kidney disease [2]. While governments, pharmaceutical and biotech companies, research institutes, universities and hospitals pursue the urgent task of developing a vaccine, hopes of a positive outcome before the end of the year are being met with several challenges. Even with newer and more rapid approaches (e.g., nucleic acid vaccines), the development and clinical testing of a vaccine for safety and efficacy will take time. If initial clinical trials are successful, the manufacture, scaleup, storage/stability testing and distribution of the product must also be considered in the timeline. Meanwhile, effective therapies that could aid during this period are severely wanting. A dire need for effective therapy will be especially important if, barring ethical concerns, human challenge trials are expedited. Since my own previous experience has been in the area of drug discovery and not vaccine development, I would like to provide a perspective regarding a proposed therapy that could involve re-purposed drugs and therefore, might be introduced in a timely manner. But first, a brief look at the therapeutic landscape for COVID-19 at present. Please note that due to the urgency of the pandemic, many of the recent references are publications that have not been peer reviewed.

Early on, the antimalarial drug hydroxychloroquine was touted as a possible treatment for SARS-CoV-2 but has since been discounted by the World Health Organization [3]. The results were presented by the Solidarity Trial (established by WHO) which showed little or no reduction in the mortality of hospitalized COVID-19 patients when compared with standard care. The same assessment was also presented for the HIV Type 1 aspartate protease inhibitor lopinavir [4]. That study involved a randomized, controlled, open-label trial of 199 patients with severe COVID-19. Although the authors of the study conclude that lopinavir-ritonavir (a cytochrome p450 inhibitor that extends the half life of Lopinavir) did not significantly improve the clinical outcome of the patients, they did not discount the possibility of combining these drugs with other antiviral agents, an approach that was taken with SARS [5,6] and a trial that is currently underway with MERS-CoV [7]. More encouraging are recent results from the RECOVERY trial demonstrating that the synthetic glucocorticoid dexamethasone reduces mortality by one third in patients receiving invasive, mechanical ventilation and by one fifth in patients receiving oxygen through noninvasive treatment [8]. However, for patients not receiving respiratory aid, mortality was not reduced. The takeaway from this preliminary study is the recommendation that dexamethasone be used only in patients with COVID-19 who are on mechanical ventilation [9]. Perhaps the most promising news regarding COVID-19 therapy is the preliminary report on the effects of remdesivir (GS-5734) in adults hospitalized with lower respiratory tract involvement [10]. Remdesivir, an RNA-dependent RNA polymerase inhibitor developed by Gilead Sciences, Inc. was found to reduce risk of mortality by 62% compared with standard care in a double-blind, randomized study initially involving 1063 patients: 541 assigned to remdesivir treatment and 522 to the placebo group. While further studies are recommended, these encouraging results have prompted the FDA to grant Emergency Use Authorization (EUA) of remdesivir for the treatment of COVID-19 [11]. Although the RECOVERY and remdesivir trials offer some hope for patients with COVID-19, there is still no effective treatment for the disease.

Another important therapeutic route being pursued involves the mechanism by which SARS-CoV-2 gains entry to cells. Like the SARS virus (SARS-CoV), the spike protein on SARS-CoV-2 contains a specific domain that binds to angiotensin converting enzyme 2 (ACE2) [12], a homologue of angiotensin converting enzyme (ACE) [13]. Essentially, the spike protein acts as a ligand for ACE2, which becomes a receptor for the SARS-CoV-2. Following binding, the virus is internalized by the cell through an endocytosis mediated mechanism [14]. ACE2 is expressed in several tissues, including lung epithelium, kidney and intestine [15]. Comorbidity for many patients with SARS-CoV-2 includes hypertension and ALI. Both ACE and ACE2 are part of the renin-angiotensin system (RAS) that controls blood pressure and fluid/electrolyte balance [16]. ACE converts the peptide hormone angiotensin I (Ang I) to angiotensin II (Ang II), a powerful driver of hypertension. Ang II also promotes inflammation which mediates ALI and fibrosis [2,16]. ACE2 converts Ang II to the hypotensive peptide Ang 1-9. A delicate balance exists between ACE/Ang II and ACE2/Ang 1-9 whereby normal blood pressure is maintained. SARS-CoV-2 is hypothesized to upset this balance by blocking and downregulating ACE2 (ACE2 is a Type I membrane-bound receptor [17]). Hence, a logical target for COVID-19 is the RAS system, since ACE inhibitors and Ang II receptor blockers commonly used to regulate hypertension may also upregulate ACE2 [18,19]. Herein lies a conundrum: upregulation of ACE2, while lowering blood pressure, could also provide more binding sites for the virus. It has, in fact, been suggested that the use of ACE inhibitors as well as Ang II receptor blockers (ARBs, the Ang II receptor is part of the ACE/Ang II pathway) may increase the risk of infection by SARS-CoV-2 and COVID-19 [12,18]. It must be emphasized however, that this is speculation since increased expression of ACE2 has been demonstrated in heart and kidney in animal models but has not been tested in lung tissue nor in humans since this would be technologically challenging [20]. Moreover, there are recommendations not to abandon RAS blockers because of their potential protective pulmonary and cardiovascular benefits [20]. Another recent clinical study associates the use of ACE inhibitors and statins with better survival among patients with COVID-19 although the authors caution that this was not a controlled, randomized trial [21].

There is still uncertainty as to the effects of ACE2 on infectivity by SARS-CoV-2. Much of this concerns the abundance of ACE2 at the cell surface, particularly in epithelial lung cells. Besides control of cell surface receptors by transcription, translation and internalization, the phenomenon of ectodomain shedding must be considered. Structurally, ACE2 is comprised of an extracellular component (the ectodomain) that is attached to the transmembrane domain. The extracellular component of ACE2 can be release from the cell surface through a mechanism involving a disintegrin and metalloproteinase domain (ADAM 17) that has been found to release the ectodomains of various membrane-anchored cytokines and receptors [22]. Although the ectodomain of ACE2 retains its enzymatic function, there is uncertainty regarding its effect on the RAS system. It has been suggested that ACE2 must be associated with the cell surface to serve as a receptor for SARS-CoV-2 and that soluble ACE2 (the ectodomain) may play a role in modifying the inflammatory processes in the airway mucosal surface [23]. The bottom line regarding the uncertainty that ACE2 may play in COVID-19 is that more studies are needed regarding the role of ADAM 17 and other proteases on shedding of ACE2 and its relation to infection by SARS-CoV-2 [24]. Despite the therapeutic conundrum regarding ACE2, a better understanding of its role in SARS-CoV-2 infection or prevention is providing researchers and clinicians with novel potential therapies. New approaches such as the use of small compounds as viral entry inhibitors [25] and neutralizing antibodies [26] are being considered based on earlier work with SARS-CoV. Limited tests have even been performed with soluble recombinant human ACE2 in healthy human volunteers with no known ill effects [27]! These studies and other trials with repurposed drugs are encouraging and may provide effective therapies in a timely manner while vaccine development is progressing.

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