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Options for COVID-19 Entry into Pulmonary Cells

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ABSTRACT

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Seven billion people all over the world are currently threatened by the Coronavirus Disease 2019 (COVID-19) virus, and the scientific community has been mobilized to the best of its ability to counteract this threat. Here we consider it to be essential to highlight certain contradictions in COVID-19-related studies on the Angiotensin Converting Enzyme 2 (ACE2) that have been performed so far. Although ACE2 has been reported as the main mechanism of COVID-19 for entry into pulmonary cells, a careful review of the literature and publicly available data sets suggest this may not be the only or even the main mechanism for entry of COVID-19 into pulmonary cells.

As scientists around the world are trying to counteract the spread of COVID-19, the mechanism underlying the entry of the virus into pulmonary cells has become a critical and hot topic [1,2]. The ACE2 protein was previously identified as a receptor for the virus [3]. However, when we examined the levels of the ACE2 transcript and the corresponding protein using the Human Protein Atlas search engine [4], we found extremely low levels of both transcript and protein in the lung tissues. The results were confirmed by data extracted from four different publicly available expression data sets, including those from Consensus, HPA, GTEx and FANTOM5. We also examined the ACE2 expression at the single-cell resolution by searching two data sets of single-cell RNA-sequencing (scRNA-seq) of the entire lung cell population in mouse and human [5,6]. The results showed that the expression of ACE2 was undetectable in the various subtypes of pulmonary cells. This makes it difficult to understand how such a low level of ACE2 allows COVID-19 to enter the pulmonary cells and cause enormous injury to most of the cellular subtypes [7].

During the search process, as would be expected, we found that ACE2 was highly expressed in kidney tissues and kidney epithelial cells. This finding directed us to review how the interaction between COVID-19 and ACE2 was identified. ACE2 was first reported as the receptor for SARS-CoV by the research groups of Drs. Hyeryun Choe and Michael Farzan [3], who used 293T and Vero E6 as cell models [3]. Subsequently, the hypothesis that cell entry of SARS-CoV was mediated by ACE2 was extensively tested in these two cell types [8,9]. Since 293T and Vero E6 are kidney-derived cell lines, it is not surprising to find high expression of ACE2 to interact with SARS-CoV [3]. However, in the pulmonary cells, it might be a different story because of the almost undetectable ACE2 expression.

Recently, more detailed examinations of ACE2 expression in lung tissue and pulmonary epithelial cells was reported in two excellent studies [10,11]. In these reports, ACE2 was expressed in less than 1% of the pulmonary cells [10,11]. Specifically, ACE2 was expressed in bronchiolar club cells, but not at all or at an extremely low level in ciliated cells [10,11]. In contrast, a high density of COVID-19 virus particles was found in the ciliated cells, where the COVID-19 virus also replicated [7]. The results suggest that the cells without ACE2 also can be infected by COVID-19.

Thus, the interaction between ACE2 and COVID-19 is well supported to be a potential mechanism for virus entry into ACE2-enriched cells such as kidney cells. However, it is still questionable if the same mechanism is used by the virus in pulmonary cells. The PubMed search engine identified only 57 published articles when searching for "ACE2 pulmonary epithelial cells", as compared to 2006 articles when the search term "ACE" was used. Unfortunately,

none of the 57 studies used pulmonary cells as models for their investigations of SARS-CoV or COVID-19.

The strongest evidence of ACE2-mediated entry of SARS-CoV into pulmonary cells was obtained from ACE2 knockout mice [12]. Based on the infection and replication of SARS-CoV in the respiratory tracts of mice [13], the study showed lower collective titers of SARS-CoV in ACE2 knockout mice than in wild type mice after infection [12]. However, wild type mice exhibited mild lung injuries after infection with extremely high titers of SARS-CoV collected from lungs [12]. The studies brought into question the specificity of viral infection across different species and suggested that mouse ACE2 mediated the entry of SARS-CoV into the pulmonary cells, even though its expression was extremely low. This study contradicted a very recent study, which showed that mouse recombinant soluble ACE2 had no effect on SARS-CoV-2 infection in Vero E6 cells, whereas human recombinant soluble ACE2 prevented infection [14]. The results indicated that mouse ACE2 could not even bind to SARS-CoV-2 [14].

Thus, there is evidence of an interaction between ACE2 and SARS-CoV or COVID-19, and human soluble ACE2 might be a useful treatment to neutralize the virus binding. However, it is still questionable if ACE2 is the receptor for COVID-19 that mediates the entry into the lung cells. Indeed, a study that took advantage of a pulmonary cell cDNA library identified CD209L as another SARS-CoV binding protein, but detailed experiments supporting this as a viral entry point were not performed [15]. In all, we expect that additional studies on alternative entry points of COVID-19 will be available in the near future and able to sort out these important discrepancies in the search for viable treatment strategies.

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Competing Financial Interests

The authors have declared that no conflict of interest exists.

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