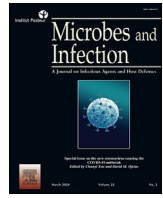




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## Is COVID-19 receiving ADE from other coronaviruses?

Jason A. Tetro

College of Biological Sciences, University of Guelph, Guelph, Ontario, N1G 2W1, Canada



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## ABSTRACT

One of the most perplexing questions regarding the current COVID-19 coronavirus epidemic is the discrepancy between the severity of cases observed in the Hubei province of China and those occurring elsewhere in the world. One possible answer is antibody dependent enhancement (ADE) of SARS-CoV-2 due to prior exposure to other coronaviruses. ADE modulates the immune response and can elicit sustained inflammation, lymphopenia, and/or cytokine storm, one or all of which have been documented in severe cases and deaths. ADE also requires prior exposure to similar antigenic epitopes, presumably circulating in local viruses, making it a possible explanation for the observed geographic limitation of severe cases and deaths.

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There are numerous questions regarding the nature of the current COVID-19 epidemic. One of the most perplexing happens to be the significant discrepancy of serious cases and deaths between areas within the Hubei Province, where the outbreak initiated, and the rest of the world.

An examination of patient cases within the Hubei region reveals some useful data regarding the pathogenesis of this virus [1–3]. Severe cases tend to occur in men and many suffer from one or more co-morbidities such as cardiovascular and cerebrovascular disease as well as diabetes. Several sequelae also have been observed including cellular immune deficiency, coagulation activation, myocardia injury, hepatic and kidney injury, and secondary bacterial infection. In the majority of cases of severe disease and death, lymphopenia and sustained inflammation has been recorded. Notably, these observations in COVID-19 patients are similar to those who suffered from severe acute respiratory syndrome (SARS) during the 2003 epidemic [4].

Based on this information and the similarity of symptoms to SARS, COVID-19 appears to constitute a major threat to human health justifying the World Health Organization's declaration of a Public Health Emergency of International Concern. Yet, examining the situation outside of Hubei Province provides a very different perspective. Most infected individuals have a mild disease and do not progress into severe stages of infection. Moreover, patients appear to be able to recover with little to no medical intervention. Based on this evidence, the virus would not be considered a major

threat to public health. Instead, it appears to be no more concerning than the influenza virus [5].

This geographic discrepancy in pathogenesis may appear to defy explanation. Yet there may be a biological mechanism behind this epidemiological anomaly. Individuals suffering the most may have been primed by one or more prior coronavirus exposures, and due to antigenic epitope heterogeneity, are experiencing the effects of antibody dependent enhancement (ADE).

This postulate isn't novel as it has been found and characterized in the SARS coronavirus, SARS-CoV. Enhancement was identified by Yang et al. [6] in 2005 and was hypothesized as being the reason for such a high mortality rate in China [7]. At the time, the priming strains were thought to be human coronaviruses known to cause mild infection such as 229E [7]. The mechanism was characterized by Yip et al. [8,9] and revealed that anti-Spike protein antibodies were indeed responsible for the infection of immune cells. Wang et al. [10] revealed that enhancement may be improved by increasing dilutions of antibodies, suggesting a temporal relationship between priming and enhancement.

While the molecular and immunological host response to SARS-CoV-2 infection has not yet been fully elucidated to confirm ADE is occurring, the current clinical evidence suggests this is a possibility. Based on previous studies using SARS-CoV using *in vitro* studies [11] and mouse models [12], ADE hinders the ability to manage inflammation in the lung and elsewhere. This may lead to acute respiratory injury, acute respiratory distress syndrome, and other observed inflammation-based sequelae as seen in many of the documented cases of severe COVID-19 disease. In addition, ADE

E-mail address: [jason@jasontetro.com](mailto:jason@jasontetro.com).

offers a viable explanation for the geographic discrepancy in severity of cases.

In the context of identifying the priming coronavirus, it is worthwhile looking at SARS-CoV as its introduction to humans has been suggested to have occurred in the Hubei Province [13]. The genetic sequence possesses numerous dissimilarities to the virus responsible for COVID-19, tentatively named SARS-CoV-2 [14], with approximately 79% homology [15]. For example, Hua et al. [16] identified two specific epitopes on the SARS-CoV spike protein, 447–458 and 789–799. A BLAST comparison with the spike protein of SARS-CoV-2 reveals 72.7% and 100% similarity respectively. Several other identified epitopes on the SARS-CoV spike protein [13] do not share perfect alignment with SARS-CoV-2 and may also be involved in ADE.

Although prior SARS-CoV exposure or infection may play a role in ADE, it likely is not the predominant priming virus. Seroprevalence studies have shown a very low level of SARS-CoV seroconversion in the population apart from workers with direct contact with animals such as traders [17]. Moreover, several bat coronavirus strains [6] have been identified as being closely related to SARS-CoV-2 with higher homology than SARS-CoV. There may have been past introductions and circulations of mild strains of similar coronaviruses that were asymptomatic or mistaken for a regular common cold virus. A few potential candidates have been isolated in Hubei province [18] and may serve as the basis for retrospective serological testing to confirm prior infection and resultant risk for ADE has occurred.

We are just beginning to understand the dynamics of COVID-19 in humans and the impact of the virus on the individual. Further studies need to focus on how the virus interacts with the host leading to the wide variance in observed symptoms and the apparent geographically based discrepancy of severity between Hubei Province and the rest of the world. Should ADE be proven to be a mechanism of pathogenesis, both treatment regimens and vaccine development will need to take this phenomenon into consideration to ensure it is mitigated and in the case of a vaccine, avoided altogether.

#### Declaration of Competing Interest

None declared.

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