Microbes and Infection 22 (2020) 72–73

Contents lists available at ScienceDirect

Microbes and Infection

journal homepage: www.elsevier.com/locate/micinf

Is COVID-19 receiving ADE from other coronaviruses?

Jason A. Tetro

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

ARTICLE INFO

Article history:
Received 12 February 2020
Accepted 13 February 2020
Available online 22 February 2020

Keywords:
COVID-19
Coronavirus
Antibody dependent enhancement

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.

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 occuring, 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.

https://doi.org/10.1016/j.micinf.2020.02.006
1286-4579/

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 be 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.

Acknowledgements

None.

References

[1] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13. pii: S0140-6736(20)30211-7.
[2] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506. pii: S0140-6736(20)30183-5.
[3] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. J Am Med Assoc 2020. https://doi.org/10.1001/jama.2020.1585.
[4] Cheung CY, Poon LLM, Ng IHY, Luk W, Sia S-F, Wu MHS, et al. Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis. J Virol 2005;79:7819–26.
[5] New coronavirus may be no more dangerous than the flu despite worldwide alarm: experts [Internet] Natl Post 2020 [cited 2020 Feb 9]. Available from: https://nationalpost.com/health/new-coronavirus-may-be-no-more-dangerous-than-the-flu-despite-worldwide-alarm-experts.
[6] Yang ZY, Werner HC, Kong WP, Leung K, Traggiai E, Lanzavecchia A, et al. Evasion of antibody neutralization in emerging severe acute respiratory syndrome coronaviruses. Proc Natl Acad Sci U S A 2005;102:797–801.
[7] Ho MS, Chen WJ, Chen HY, Lin SF, Wang WC, Di J, et al. Neutralizing antibody response and SARS severity. Emerg Infect Dis 2005;11:1730–7.
[8] Yip MS, Leung NH, Cheung CY, Li PH, Lee HHY, Daëron M, et al. Antibody-dependent infection of human macrophages by severe acute respiratory syndrome coronavirus. Virol J 2014;11:82.
[9] Jaume M, Yip MS, Cheung CY, Leung HL, Li PH, Kien F, et al. Anti-severe acute respiratory syndrome coronavirus spike antibodies trigger infection of human immune cells via a pH- and cysteine protease-independent FcγR pathway. J Virol 2011;85:10582–97.
[10] Wang SF, Tseng SP, Yen CH, Yang JY, Tsao CH, Shen CW, et al. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. Biochem Biophys Res Commun 2014;451:208–14.
[11] Yoshikawa T, Hill T, Li K, Peters CJ, Tseng C-TK. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. J Virol 2009;83:3039–48.
[12] Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe 2016;19:181–93.
[13] Donnelly CA, Fisher MC, Fraser C, Ghani AC, Riley S, Ferguson NM, et al. Epidemiological and genetic analysis of severe acute respiratory syndrome. Lancet Infect Dis 2004;4:672–83.
[14] Gorbalenya AE. Severe acute respiratory syndrome-related coronavirus – the species and its viruses, a statement of the Coronavirus Study Group. BioRxiv 2020. https://doi.org/10.1101/2020.02.07.937862.
[15] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;(20):30251–8. pii: S0140-6736.
[16] Hua R, Zhou Y, Wang Y, Hua Y, Tong G. Identification of two antigenic epitopes on SARS-CoV spike protein. Biochem Biophys Res Commun 2004;319:929–35.
[17] Leung GM, Lim WW, Ho LM, Lam TH, Ghani AC, Donnelly CA, et al. Seroprevalence of IgG antibodies to SARS-coronavirus in asymptomatic or subclinical population groups. Epidemiol Infect 2006;134:211–21.
[18] Wu Z, Yang L, Ren X, He G, Zhang J, Yang J, et al. Deciphering the bat virome catalog to better understand the ecological diversity of bat viruses and the bat origin of emerging infectious diseases. ISME J 2016;10:609–20.