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Letter

Antibodies and infected monocytes and macrophages in COVID-19 patients

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Abstract: The SARS-CoV-2 virus causes the COVID-19 disease associated with over 6.2 million deaths globally. Multiple early indicators raised the potential risk of the SARS-CoV-2 virus infecting monocytes and macrophages via Fc-receptor antibody binding based on closely related beta coronaviruses. Antibody Fc-receptor infection of phagocytic monocytes and macrophages is one type of antibody dependent enhancement of disease. Increased COVID-19 severity correlated with early high antibody responses on initial infection for unvaccinated adults. Clinical evidence suggests that for moderate antibody titer levels, antibodies binding to SARS-CoV-2 may contribute to viral spread, cytokine dysregulation, and enhanced COVID-19 disease severity. Primary immune responses appear to have too low of antibody titer to significantly contribute to Fc-receptor uptake by monocytes and macrophages for COVID-19 patients. Very high antibody titers created by SARS-CoV-2 vaccines also appear to inhibit Fc-receptor uptake and infection of monocytes and macrophages; this inhibition appears to decrease as antibody titer levels decrease. Cross reactive antibodies to other coronaviruses or moderate levels of SARS-CoV-2 antibodies may be contributing to antibody dependent enhancement of disease in critical COVID-19 patients.

Keywords: antibodies; antibody dependent enhancement; ADE; COVID-19; monocytes; macrophages; vaccines

1. Introduction

The main receptor for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the angiotensin converting enzyme 2 (ACE2) protein. Coronavirus disease 2019 (COVID-19) starts with viral infection of ACE2 expressing respiratory cells. The major difference between

SARS-CoV-1 and SARS-CoV-2 are exposed surface residues of the spike protein [1]. Infection of human immune cells by the SARS-CoV-1 virus was demonstrated to be dependent upon the Fc receptor [2]. By inference, SARS-CoV-2 expanded cellular tropism by infection of phagocytic immune cells was proposed to be a risk for antibody dependent enhancement of disease for COVID-19 patients [1]. Assuming that the antibody dependent enhancement (ADE) risk was negligible, multiple vaccines have been developed and widely disseminated targeting the SARS-CoV-2 spike protein. While antibody titer levels are high within vaccinees, this approach has demonstrated positive vaccine effectiveness. As antibody titer levels have decreased, vaccinated individuals have been provided the option for one or more vaccine boosters that currently use the original vaccine strain spike protein. COVID-19 infection of vaccinated individuals are referred to as "breakthrough" cases. Along with unvaccinated individuals, both vaccinated and vaccine boosted individuals are susceptible to one or more SARS-CoV-2 infections. Individuals with multiple reinfections or ongoing SARS-CoV-2 infections are referred to as having "chronic COVID".

2. Model

The SARS-CoV-2 can leverage Fc-receptor update to infect monocyte and macrophage phagocytic innate immune cells for expanded cellular tropism to innate immune cells [3]. Low SARS-CoV-2 antibody titers (i.e., primary immune response level) is too low for significant contributions to compromising innate immune cells [4]. Very high SARS-CoV-2 antibody titers (i.e., following second vaccination or boosting) may interfere with expanded cellular tropism to innate immune cells (perhaps multiple antibodies bound to virons could potentially the block viral membrane fusion mechanism). Hence, moderate SARS-CoV-2 antibody titers pose the greatest potential risk for Fc-receptor expanded tropism to innate immune cells (monocytes and macrophages); when this occurs, it is referred to as antibody dependent enhancement of disease. Infected monocytes and macrophages can disseminate the SARS-CoV-2 virus to additional organs and contribute to viral dysregulation of cytokines and immune response.

3. Discussion

3.1. SARS and COVID-19 antibody clinical observations

Patient antibody serology levels provide indirect evidence for antibodies correlating with disease severity. For SARS patients, high IgG antibody titer levels correlate with increased disease severity [5–8]. Likewise, in COVID-19, high antibody responses are correlated with disease progression and severity [9–16]. Nucleocapsid antibody responses were found to be elevated in deceased individuals (N = 22) [17].

3.2. Antibody titer level impact

Wan et al. [4] describe that expanded host cell tropism of some phagocytic cells is dependent upon antibody dose. Expanded host cell tropism increases with antibody level and then decreases for high antibody levels [4]. This antibody titer model is consistent with patient antibody serology levels correlating with disease severity. In addition, high antibody titer levels from the second vaccine dose

or boosting doses appear to interfere in some manner with expanded host cell tropism to phagocytic cells.

3.3. Cross-reactive antibodies

Cross-reactive antibodies from previous betacoronavirus infections have been reported for 93% (N = 44) adults and 55% (N = 86) children [18] and 40% (N = 50) children [19]. COVID-19 patients with early anti-SARS-CoV-2 IgG recall-type responses had increased disease severity [20]. Poorly neutralizing "original antigenic sin" antibodies were found in severe COVID-19 patients with preexisting seasonal common cold coronaviruses antibodies [21]. Memory B cell responses with cross-reactive antibodies is consistent with the model of expanded viral tropism to monocytes and macrophages.

3.4. Convalescent plasma treatment

SARS patients treated with convalescent plasma had a mortality rate of 6.3% if treated before 14 days and 21.9% if treated after 14 days [22]. Early treatment of COVID-19 patients with convalescent plasma in the NCT04355767 trial resulted in five deaths in the treated group of 257 patients compared to one death in the 254 placebo group [23]. The large RECOVERY trial of 16287 patients found no benefits of convalescent plasma treatment of COVID-19 patients [24]. A small trial of high-dose convalescent plasma treatment of severe COVID-19 patients also found no benefits [25]. Meta-analysis of 33 convalescent plasma trials (20 unpublished) confirmed lack of benefits for treating COVID-19 patients [26]. On July 21, 2021, the World Health Organization recommended against the use of convalescent plasma to treat COVID-19 patients. The lack of efficacy of convalescent plasma treatment of COVID-19 patients is consistent with the model of expanded viral tropism to monocytes and macrophages facilitated by Fc receptor update of virons bound by antibodies.

3.5. SARS-CoV-2 Infected Macrophages in COVID-19 patients

Some studies cannot detect evidence for SARS-CoV-2 infection of monocytes and macrophages [27]. While others find that SARS-CoV-2 efficiently infects monocytes and macrophages from COVID-19 patients [28]; infected monocytes and macrophages were associated with secretion of interleukin 6 (IL-6), IL-10, and transforming growth factor beta (TGF-β) [28]. SARS-CoV-2 infection of macrophages were observed in hilar lymph nodes in autopsy examination of three COVID-19 patients [29]. Single-cell RNA sequencing on 10 bronchoalveolar lavage fluid samples with severe COVID-19 were enriched in T cells and likely infected alveolar macrophages [30]; these infected alveolar macrophages and T cells form a positive feedback loop that drives persistent alveolar inflammation [30]. Postmortem examinations of six cases observed SARS-CoV-2 infection of $CD169^{+}$ macrophages with ACE2 receptors in spleens and lymph nodes resulting in tissue decimation [31]. After examinations of autopsies of two COVID-19 patients, Wang et al. [32] proposed that infected macrophages might be drivers of the "cytokine storm" that occurs in some severe COVID-19 patients. Infected macrophages and mature adipocytes were detected in adipose tissue of COVID-19 patients [33]; these infected macrophage cells were associated with increased

inflammatory profile [33]. Results further suggest that SARS-CoV-2 was infecting macrophages through a non-canonical entry receptor (i.e., not ACE2) [33]. An endomyocardial biopsy detected infected macrophages but not myocytes in a COVID-19 patient with acute cardiac injury [34]. A high content screen identified compounds ranolazine and tofacitinib as candidates to protect cardiomyocytes from macrophage-induced cardiotoxicity [35]. A recent study found about 6% of all blood monocytes were infected with SARS-CoV-2 in COVID-19 patients [3]; infection of monocytes depended upon uptake of antibody-opsonized viruses by Fcγ receptors [3].

It has been proposed that SARS-CoV-2 infection of monocytes and macrophages is abortive and does not contribute to viral replication [3]. An *in vitro* study demonstrated that SARS-CoV-2 virus can infect monocytes and monocyte-derived macrophages from infected cells [36]. While the SARS-CoV-2 could persist in these infected monocytes and macrophages, the virus did not replicate but was able to infect other cells [36]. SARS-CoV-2 is able to form syncytia of infected cells with neighboring cells leading to the formation of multi-nucleate enlarged cells; syncytia formation may be a possible mechanism for SARS-CoV-2 to spread to new tissues. This ability to infected other cells demonstrates a pathway by which the virus can infect monocytes and macrophages, migrate into new tissues, and enable the virus to infect susceptible cells [36].

4. Conclusions

Clinical evidence clearly establishes that a subset of monocytes and macrophages are being infected by SARS-CoV-2 in some COVID-19 patients. Infection of monocytes and macrophages is mediated by Fc receptor uptake. Scientific and clinical studies support the conclusion that Fc receptor mediated infection of monocytes and macrophages in some COVID-19 patients is one type of antibody dependent enhancement of disease; this expanded cellular tropism to innate immune cells may have pathogenesis implications in COVID-19 patients with multiple reinfections and chronic COVID-19. SARS-CoV-2 infected monocytes and macrophages in COVID-19 patients remains an important and neglected area of medical research in this ongoing COVID-19 pandemic.

Conflict of interest

The author declare no conflict of interest.

References

1. Ricke DO (2021) Two different antibody-dependent enhancement (ADE) risks for SARS-CoV-2 antibodies. *Front Immunol* 12: 443. https://doi.org/10.3389/fimmu.2021.640093
2. Jaume M, Yip MS, Cheung CY, et al. (2011) 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* 85: 10582–10597. https://doi.org/10.1128/JVI.00671-11
3. Junqueira C, Crespo Â, Ranjbar S, et al. (2022) FcγR-mediated SARS-CoV-2 infection of monocytes activates inflammation. *Nature* In press. https://doi.org/10.1038/s41586-022-04702-4

4. Wan Y, Shang J, Sun S, et al. (2020) Molecular mechanism for antibody-dependent enhancement of coronavirus entry. *J Virol* 94: e02015-19. https://doi.org/10.1128/JVI.02015-19
5. Lee N, Chan PKS, Ip M, et al. (2006) Anti-SARS-CoV IgG response in relation to disease severity of severe acute respiratory syndrome. *J Clin Virol* 35: 179–184. https://doi.org/10.1016/j.jcv.2005.07.005
6. Peiris J, Lai S, Poon L, et al. (2003) Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 361: 1319–1325. https://doi.org/10.1016/S0140-6736(03)13077-2
7. Hsueh PR, Hsiao CH, Yeh SH, et al. (2003) Microbiologic characteristics, serologic responses, and clinical manifestations in severe acute respiratory syndrome, Taiwan. *Emerg Infect Dis* 9: 1163–1167. https://doi.org/10.3201/eid0909.030367
8. Wang H, Rao S, Jiang C (2007) Molecular pathogenesis of severe acute respiratory syndrome. *Microbes Infect* 9: 119–126. https://doi.org/10.1016/j.micinf.2006.06.012
9. Pujadas E, Chaudhry F, McBride R, et al. (2020) SARS-CoV-2 viral load predicts COVID-19 mortality. *Lancet Respir Med* 8: e70. https://doi.org/10.1016/S2213-2600(20)30354-4
10. Yan X, Chen G, Jin Z, et al. (2022) Anti-SARS-CoV-2 IgG levels in relation to disease severity of COVID-19. *J Med Virol* 94: 380–383. https://doi.org/10.1002/jmv.27274
11. Luo YR, Chakraborty I, Yun C, et al. (2021) Kinetics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody avidity maturation and association with disease severity. *Clin Infect Dis* 73: e3095–e3097. https://doi.org/10.1093/cid/ciaa1389
12. Fajnzylber J, Regan J, Coxen K, et al. (2020) SARS-CoV-2 viral load is associated with increased disease severity and mortality. *Nat Commun* 11: 5493. https://doi.org/10.1038/s41467-020-19057-5
13. Chen W, Zhang J, Qin X, et al. (2020) SARS-CoV-2 neutralizing antibody levels are correlated with severity of COVID-19 pneumonia. *Biomed Pharmacother* 130: 110629. https://doi.org/10.1016/j.biopha.2020.110629
14. Chen H, Qin R, Huang Z, et al. (2021) Characteristics of COVID-19 patients based on the results of nucleic acid and specific antibodies and the clinical relevance of antibody levels. *Front Mol Biosci* 7: 605862. https://doi.org/10.3389/fmolb.2020.605862
15. Young BE, Ong SWX, Ng LFP, et al. (2021) Viral dynamics and immune correlates of coronavirus disease 2019 (COVID-19) severity. *Clin Infect Dis* 73: e2932–e2942. https://doi.org/10.1093/cid/ciaa1280
16. Liu X, Wang J, Xu X, et al. (2020) Patterns of IgG and IgM antibody response in COVID-19 patients. *Emerg Microbes Infect* 9: 1269–1274. https://doi.org/10.1080/22221751.2020.1773324
17. Atyeo C, Fischinger S, Zohar T, et al. (2020) Distinct early serological signatures track with SARS-CoV-2 survival. *Immunity* 53: 524–532. https://doi.org/10.1016/j.immuni.2020.07.020
18. Fraley E, LeMaster C, Banerjee D, et al. (2021) Cross-reactive antibody immunity against SARS-CoV-2 in children and adults. *Cell Mol Immunol* 18: 1826–1828. https://doi.org/10.1038/s41423-021-00700-0
19. Shrwani K, Sharma R, Krishnan M, et al. (2021) Detection of serum cross-reactive antibodies and memory response to SARS-CoV-2 in prepandemic and post-COVID-19 convalescent samples. *J Infect Dis* 224: 1305–1315. https://doi.org/10.1093/infdis/jiab333
20. Miyara M, Saichi M, Sterlin D, et al. (2022) Pre-COVID-19 immunity to common cold human coronaviruses induces a recall-type IgG response to SARS-CoV-2 antigens without cross-neutralisation. *Front Immunol* 13: 790334. https://doi.org/10.3389/fimmu.2022.790334

21. Aguilar-Bretones M, Westerhuis BM, Raadsen MP, et al. (2021) Seasonal coronavirus-specific B cells with limited SARS-CoV-2 cross-reactivity dominate the IgG response in severe COVID-19. *J Clin Invest* 131: e150613. https://doi.org/10.1172/JCI150613
22. Cheng Y, Wong R, Soo YOY, et al. (2005) Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol* 24: 44–46. https://doi.org/10.1007/s10096-004-1271-9
23. Korley FK, Durkalski-Mauldin V, Yeatts SD, et al. (2021) Early convalescent plasma for high-risk outpatients with Covid-19. *N Engl J Med* 385: 1951–1960. https://doi.org/10.1056/NEJMoa2103784
24. Horby PW, Landray MJ, Grp RC (2021) Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet* 397: 2049–2059. https://doi.org/10.1016/S0140-6736(21)00897-7
25. De Santis GC, Oliveira LC, Garibaldi PMM, et al. (2022) High-dose convalescent plasma for treatment of severe COVID-19. *Emerg Infect Dis* 28: 548–555. https://doi.org/10.3201/eid2803.212299
26. Axfors C, Janiaud P, Schmitt AM, et al. (2021) Association between convalescent plasma treatment and mortality in COVID-19: a collaborative systematic review and meta-analysis of randomized clinical trials. *BMC Infect Dis* 21: 1170. https://doi.org/10.1186/s12879-021-06829-7
27. García-Nicolás O, V'kovski P, Zettl F, et al. (2021) No evidence for human monocyte-derived macrophage infection and antibody-mediated enhancement of SARS-CoV-2 infection. *Front Cell Infect Microbiol* 11: 644574. https://doi.org/10.3389/fcimb.2021.644574
28. Boumaza A, Gay L, Mezouar S, et al. (2021) Monocytes and macrophages, targets of severe acute respiratory syndrome coronavirus 2: the clue for coronavirus disease 2019 immunoparalysis. *J Infect Dis* 224: 395–406. https://doi.org/10.1093/infdis/jiab044
29. Martines RB, Ritter JM, Matkovic E, et al. (2020) Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States. *Emerg Infect Dis* 26: 2005–2015. https://doi.org/10.3201/eid2609.202095
30. Grant RA, Morales-Nebreda L, Markov NS, et al. (2021) Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. *Nature* 590: 635–641. https://doi.org/10.1038/s41586-020-03148-w
31. Feng Z, Diao B, Wang R, et al. (2020) The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly decimates human spleens and lymph nodes. *medRxiv Preprint*. https://doi.org/10.1101/2020.03.27.20045427
32. Wang C, Xie J, Zhao L, et al. (2020) Alveolar macrophage dysfunction and cytokine storm in the pathogenesis of two severe COVID-19 patients. *eBioMedicine* 57: 102833. https://doi.org/10.1016/j.ebiom.2020.102833
33. Martínez-Colón GJ, Ratnasiri K, Chen H, et al. (2021) SARS-CoV-2 infects human adipose tissue and elicits an inflammatory response consistent with severe COVID-19. *bioRxiv Preprint*. https://doi.org/10.1101/2021.10.24.465626
34. Tavazzi G, Pellegrini C, Maurelli M, et al. (2020) Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail* 22: 911–915. https://doi.org/10.1002/ejhf.1828

35. Yang L, Han Y, Jaffré F, et al. (2021) An immuno-cardiac model for macrophage-mediated inflammation in COVID-19 hearts. *Circ Res* 129: 33–46. https://doi.org/10.1161/CIRCRESAHA.121.319060
36. Percivalle E, Sammartino JC, Cassaniti I, et al. (2021) Macrophages and monocytes: "Trojan horses" in COVID-19. *Viruses* 13: 2178. https://doi.org/10.3390/v13112178