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COMMENTARY

The role of SARS-CoV-2 antibodies in COVID-19: Healing in most, harm at times

Key words: antibodies, COVID-19, immunopathology.

Understanding the immunopathology of severe pulmonary disease and critical illness in patients with coronavirus disease 2019 (COVID-19) is essential to the development of immunotherapies for this condition. Immunological abnormalities associated with a poor outcome in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection include lymphopaenia (affecting $CD4^+$ T cells, $CD8^+$ T cells, natural killer (NK) cells and B cells), neutrophilia and increased serum levels of markers of inflammation, including multiple pro-inflammatory chemokines and cytokines.[1] Evidence is also emerging that monocyte/macrophage dysfunction may be central to the immunopathology[1] and that the functional characteristics of antibodies to SARS-CoV-2 spike protein (SP) might be a determinant of disease outcome.

Antibody responses against enveloped viruses, such as SARS-CoV-2, are usually comprised of immunoglobulin (Ig) M, IgG3, IgG1 and IgA antibodies to glycoproteins of the virus envelope and to nucleoproteins (NP, internal to the envelope). IgG (IgG3 and IgG1) antibodies against virus envelope glycoproteins possess various functional characteristics that confer the most efficacious systemic antibody response against viruses, as exemplified by human immunodeficiency virus (HIV)-1 infection.[2] These functional characteristics result in virus neutralization, by binding of antibody Fab regions to viral antigens and impairment of virus binding to cell receptors, and activation of antiviral effector cells, by binding of antibody Fc regions to Fcγ receptors on NK cells, to induce antibody-dependent cellular cytotoxicity of virus-infected cells, or on plasmacytoid dendritic cells and conventional dendritic cells, to induce opsonophagocytosis of virus particles by those cells and activation of their antiviral responses directly and/or via NK cells and T cells. While antibodies to the nucleoproteins of enveloped viruses, such as SARS-CoV-2, are a valuable serological marker of infection,[3] their role in the control of virus replication has not been clearly established.

By day 14 after symptom onset, the serum of 95–100% of patients with COVID-19 contains IgM and/or IgG antibodies to the SP of the SARS-CoV-2 envelope, including antibodies to the receptor-binding domain (RBD) of the SP, which strongly correlate with antibodies that neutralize viral replication in cell cultures (i.e. neutralizing antibodies).[4–6] From the limited amount of data available,[6] SARS-CoV-2-neutralizing antibodies correlate poorly with the clinical course of COVID-19. In contrast, Zhao *et al.*[4] reported that high serum levels of 'total' (IgM, IgG and IgA) antibodies to SARS-CoV-2 SP at an average time of day 14 or later after symptom onset were independently associated with a worse clinical classification. This association was not observed for either IgM antibodies to the SARS-CoV-2 SP or IgG antibodies to SARS-CoV-2 NP. Similarly, Qu *et al.*[7] reported that IgG antibodies to SARS-CoV-2 were higher in patients with critical disease, although the assay used detected antibodies to both SARS-CoV-2 SP and NP. One interpretation of these findings is that higher IgG antibodies to SARS-CoV-2 SP at about 2 weeks after symptom onset are associated with greater disease severity. While more data are needed to confirm these findings, they do suggest that a greater understanding of the role that IgG antibodies to SARS-CoV-2 SP play in controlling infection and in disease pathogenesis is needed.

As well as exerting virus neutralization and other protective antibody functions, IgG antibodies to SARS-CoV-2 SP might enhance the infection of immune cells and/or the immunopathogenesis of COVID-19. Antibody-dependent enhancement (ADE) of virus uptake by macrophages is an undesirable action of IgG antibodies (i.e. enhancing antibodies) that has been most comprehensively described in dengue virus infection but has also been demonstrated for SARS-CoV-1.[8] ADE of SARS-CoV-1 infection of immune cells does not result in productive infection of those cells[8] but might

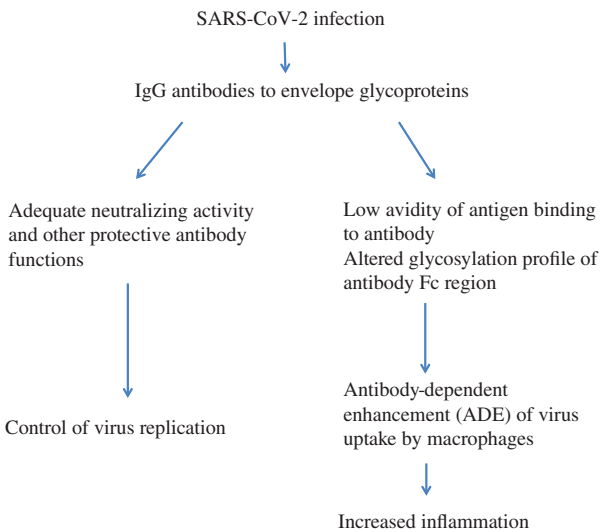

Figure 1 The antibody responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are generally neutralizing and the virus is eliminated. However, the antibody response can enhance the inflammatory response through antibody-dependent enhancement (ADE).

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Table 1 Summary of data on antibodies to SARS-CoV-2

SARS-CoV-2 protein (antigen)	Ig isotypes	Serological test for SARS-CoV-2 infection	Protective functions	Disease-enhancing activity
Spike protein (RBD)	IgM, IgG3, IgG1, IgA	Yes	Neutralization of viral binding to ACE2 (IgG3, IgG1 and probably IgA at mucosal surfaces)[†]	Possible[‡]
Nucleoprotein	IgM, IgG[§]	Yes	Unknown	Unlikely

[†]Other protective antibody functions, such as enhancement of NK cell-mediated cytotoxicity (antibody-dependent cellular cytotoxicity) or opsonophagocytosis of viral particles, might also contribute (data not available).

[‡]On the basis of reports that SARS-CoV-1 non-productively infects immune cells ex vivo and activates monocytes/macrophages in vivo.

[§]Data on other isotypes not reported.

ACE2, angiotensin converting enzyme 2; Ig, immunoglobulin; NK, natural killer; RBD, receptor-binding domain; SARS-CoV, severe acute respiratory syndrome coronavirus.

affect macrophage function. For example, in a macaque model of SARS-CoV-1 infection, the presence of serum IgG antibodies to SARS-CoV-1 SP was associated with acute lung injury characterized by macrophage activation and skewing of macrophages towards a pro-inflammatory M1 phenotype.[9] This may contribute to the pulmonary immunopathology demonstrated in macaque models of SARS, which is characterized by tissue infiltration by macrophages and neutrophils and increased production of pro-inflammatory cytokines and chemokines.[10] Similar mechanisms may also underlie the monocyte/macrophage dysfunction reported in severe COVID-19.[1] Additional evidence that SARS-CoV-1 SP antibodies might drive pulmonary immunopathology in SARS came from studies of mice immunized with SARS-CoV-1 vaccines, where production of SARS-CoV-1 SP antibodies was associated with the occurrence of pulmonary immunopathology, characterized by a Th2 response, following virus challenge.[11]

If the amount of SARS-CoV-2 SP IgG antibody-enhancing activity, relative to neutralizing and other protective antibody functions, is a determinant of COVID-19 occurrence and severity, it will be important to determine the underlying mechanisms as this might influence the development of not only human monoclonal antibodies and convalescent plasma as therapies for COVID-19, but also the selection of antigens for preventative vaccines. In a study of SARS-CoV-1 infection in non-human primates, antibodies to different peptides of the SP exerted either neutralizing or enhancing activity,[12] suggesting that antigen characteristics are important. Antibody characteristics may also be important because SARS-CoV-1 infection of a promonocyte cell line was enhanced by low concentrations of SARS-CoV-1 SP antibodies, whereas high antibody concentrations resulted in virus neutralization.[13] However, as higher serum SARS-CoV-2 SP antibody levels have been associated with worse clinical outcomes in COVID-19 patients,[4] other antibody characteristics may be more important. Clues to the nature of such antibody characteristics might be provided by studies of dengue virus infection, where low antibody neutralization activity correlated with low avidity of antigen binding to antibody Fab regions[14] while ADE correlated with an altered glycosylation profile of the Fc region of IgG antibodies, which enhanced binding of antibodies to FcγRs on immune cells and the uptake of virus complexed with antibodies into those cells.[15] As both production of high avidity antibodies, which is dependent on germinal centre function, and antibody glycosylation are adversely affected by older age,[16,17] these characteristics of IgG antibody function might be age-related risk factors for COVID-19 (Fig. 1) and require investigation.

In conclusion, assessment of antibodies to SARS-CoV-2 should take into consideration potential differences in functional effects and diagnostic utility (Table 1). For example, considerations of whether people who have recovered from COVID-19 have immunity to SARS-CoV-2 and should be issued with an 'immunity passport' (https://www.who.int/news-room/commentaries/detail/immunity-passports-in-the-context-of-covid-19) should not only consider evidence that serum SARS-CoV-2 antibodies have variable neutralization activity,[18] but also the possibility that some individuals might have antibodies that could enhance disease pathogenesis.

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