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Commentary

Human antibody responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) hold intense interest, with research efforts directed at optimizing antibody-based interventions and monitoring immune status. By relating individual variations in antibody response to coronavirus disease 2019 (COVID-19) severity, beneficial antiviral immune responses may be identified in detail. In this issue of the *JCI,* Secchi and collaborators describe antibody response profiles in 509 patients with COVID-19 from Italy during the 2020 pandemic. The research team found that multiple antibody types to multiple SARS-CoV-2 antigens developed over four weeks. Notably, IgG against the spike receptor binding domain (RBD) was predictive of survival and IgA against the viral spike protein (S protein) associated with rapid virologic clearance. These results may help guide selection of convalescent plasma, hyperimmune products, monoclonal antibodies, and vaccine strategies for COVID-19.

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Protective antibody responses to SARS-CoV-2

Since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, therapeutic antibodies have rapidly advanced as a promising approach to coronavirus disease (COVID-19) (1). The oldest antibody therapeutic approach, convalescent plasma (CP) infusion, is widely regarded to work by transferring antibodies from a recovered donor to a patient who has not yet developed an efficacious antibody response. CP was mobilized early in the COVID-19 epidemic and has been delivered to well over 70,000 patients in the United States at the time of this writing (2). From patients treated in the first half of 2020, signals of reduced mortality have emerged, particularly in those treated in the canonical, historical context of early disease (3–5). While important randomized control trials examining CP for COVID-19 continue, the emerging evidence for efficacy is encouraging.

The salutary effects of CP in an enveloped respiratory virus infection like COVID-19 may occur through multiple immune mechanisms dependent on antigen recognition by antibody Fab regions and, to varying degrees, isotype and class features of the Fc region (6, 7). Candidate mechanisms include antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and direct inhibition of receptor-mediated host cell interactions. Beyond these direct antiviral mechanisms, antibodies may exert beneficial antiinflammatory effects by clearing of proinflammatory products (8). In SARS-CoV-2–infected individuals, distinctive combinations of antibody abundance, isotype, subclass, antigen specificity, and epitope specificity may facilitate or suppress these antiviral and antiinflammatory effects. Given the protean manifestations of SARS-CoV-2 infections, it is plausible that individual differences in antibody-mediated immune responses are clinically meaningful.

▶ **Related Article: p. 6366**

Individual variations in antibody responses

Physicians have perceived and acted upon individual differences in humoral immune responses well before the modern understanding of viruses and antibody structure. In 1918, two physicians at the US Naval Hospital on the banks of the Mystic River in Chelsea, Massachusetts, USA, were faced with more than 400 patients who had fallen ill with 1918 influenza (9). Inspired by reports of convalescent serum therapy for poliomyelitis, they adapted this approach for patients who developed influenza pneumonia. Soldiers on base who had recovered from this illness volunteered to give convalescent serum (CS, used before plasma became the preferred preparation) for this approach. By carefully monitoring patient responses to treatment for over 24 hours, the physicians perceived differences in therapeutic efficacy between different serum donors. In a rapid optimization cycle, donors whose sera resulted in a rapid clinical response were called back to donate more, which they were eager to do. Laboratory characterization was used to avoid serum-associated hemolysis but no correlates of efficacy were identified. The physicians concluded that efficacy was greatest when serum was given within 48 hours of pneumonia diagnosis. In a patient population where the influenza pneumonia diagnosis was associated with 30%–60% mortality, treating patients with CS showed substantial impact, with mortality in the serum-treated patients at under 5%. These results are consistent with the benefit observed in a 2006 meta-analysis of CS for 1918 influenza (10).

During the present COVID-19 pandemic, the century-old experimental approach of donation, infusion, and eval-

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uation has been effectively replaced by a larger scale approach in which clinical outcomes are retrospectively related to laboratory characterization of the infused CP. Early in the pandemic, the unavailability of sophisticated laboratory characterization could be regarded as de facto blinded and randomized administration of CP with varying serologic characteristics. As improved serologic assays became available, patients could become effectively unblinded with regard to characteristics of the CP they received. This approach was applied to patients from a large emergency access program, through which over 70,000 US patients with COVID-19 were treated by more than 10,000 physicians. Many patients were treated before widespread serologic testing of CP donors was available (3). When anti–SARS-CoV-2 spike antibody titers (determined retrospectively) in CP were related to outcomes in more than 1000 recently admitted (within 72 hours) CP recipients, a mortality benefit was evident in patients who received high titer CP. In Israel, a similar, significant dose-dependence was observed in a smaller retrospective analysis of 49 patients receiving CP for COVID-19 (11). These results suggest that individual differences in SARS-CoV-2 spike antibody responses affect COVID-19 severity when transferred to acutely ill patients.

Serologic responses to SARS-CoV-2

The above studies evaluate CP through quantitative analysis of IgG responses to the SARS-CoV-2 S1 spike protein. A comprehensive accounting of human antibody responses to SARS-CoV-2 would include all potential virally encoded proteins. SARS-CoV-2 encodes numerous proteins capable of stimulating antibody responses (12). The best known of these SARS-CoV-2 proteins is the trimeric spike (S) glycoprotein that adorns the extracellular surface of the virion, which has two subunits (S1+S2) and a receptor binding domain (RBD). The RBD interacts with the human ACE2 receptor to effect viral entry into host cells (13). SARS-CoV-2 also encodes a number of other proteins, including ORF6 to ORF10, with unclear functions. Some of these ORFs may facilitate host immune evasion. The multidomain structure of larger proteins, such as the spike protein, presents numerous epitopes to which antibody responses may develop. The accessibility of these different antigens to antibodies varies substantially in intact, enveloped SARS-CoV-2 viral particles during COVID-19.

To date, current FDA-approved SARS-CoV-2 serologic assays detect antibodies that bind spike or nucleocapsid proteins (NPs). Both proteins represent relatively well-characterized coronavirus protein families and perform well at distinguishing SARS-CoV-2–specific antibodies from antibodies recognizing other coronaviruses. These assays are positively associated with viral neutralization to varying degrees (14–15). Assays that measure S1 spike-specific antibodies reveal higher titers in patients who have recovered from severe disease. Although seemingly paradoxical, it is important to note that these results are from survivors likely to have experienced more profound immune stimulation with high viral loads — and thus more antibody.

In this issue of the *JCI*, Secchi et al. extensively investigated antibody responses to SARS-CoV-2 in more than 500 patients in a Milan, Italy, hospital cohort during the peak of the pandemic in early 2020 (16). Among patients with COVID-19, the investigators detected widespread IgG reactivity to trimeric spike S1+S2 and NPs. Reactivity to a protein representing the RBD of the S1 spike protein was similarly robust in the study population. Antibodies to viral ORF proteins were detected less frequently, with potential reactivity to ORF6 and ORF9b proteins detected in a patient subgroup and no detected reactivity to ORF7a, ORF8, or ORF10. Among an array of antigen-isotype combinations, Secchi et al. found that the development of IgG to the RBD was associated with improved survival in patients with COVID-19, while IgA to trimeric spike (S1+S2) was associated with a faster time to viral clearance. The correlation between anti–RBD antibodies and favorable clinical outcomes was also seen in two smaller (n = 22 and n = 40) cohorts in which deceased patients exhibited a lower RBD/NP IgG ratio than survivors. Secchi et al. observe longitudinal anti–RBD antibody profiles consistent with the canonical progression from an early IgM response to an IgG predominant response over several weeks. These results point to an important role for antibody binding to spike protein and particularly the spike RBD in COVID-19 (16).

Implications and prospects

These results suggest an influential role for antibodies that recognize the SARS-CoV-2 RBD in patients with COVID-19. Whether this antibody binding to this antigen is of singular importance or is simply the most readily discerned de facto antibody immune strategy among many is unclear. Any given individual is likely to mount a complex antibody response with multiple beneficial epitope-specific or combinatorial antibody interactions. Although it is tempting to ascribe a direct functional role to anti–RBD IgG, it is possible that elevated circulating anti–RBD IgG is an indirect marker of other beneficial immune responses, including high tissue IgM or associated T cell responses related to affinity maturation (17).

Within our current understanding of the SARS-CoV-2 interactions with human cells, the association between anti–RBD IgG and favorable clinical outcomes invites speculation on direct antiviral mechanisms. Certainly, widespread IgG binding to the RBD may interfere with ACE2 receptor-mediated viral entry. Indeed, antibodies that bind spike and RBD are associated with in vitro viral neutralization (15, 18), and monoclonal antibodies with this neutralizing property are presently in clinical trials. It is also plausible that, in the context of the SARS-CoV-2 viral structure, the RBD domain is especially accessible to antibody binding and provides a highly available anchor point for Fc-mediated interactions with the immune system. Recent analyses of a SARS-CoV-2 primate infection model identified multiple, overlapping mechanisms of protective immunity driven by spike and RBD-based vaccines, including complement deposition by spike-specific antibodies (19). Fc-dependent immune responses may facilitate a physiologic antiviral effect when only a small fraction of each virion's RBD domains are bound.

While further investigation may better support the mechanistic origins of these correlative findings, these results serve as a plausible guide for COVID-19 medical interventions in the near term. Specifically, anti–RBD IgG assays are worth considering when characterizing and qualifying

CP and hyperimmune globulin for clinical use. Similar assays, perhaps with greater emphasis on IgA, may show similar value for evaluating immune status and vaccine responses.

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