Molecular Therapy
Editorial

The Road Less Traveled: SARS-CoV-2 and Cell-Mediated Immunity

When it comes to SARS-CoV-2 (severe acute respiratory syndrome-associated coronavirus 2), the dominant narrative seems to be all about antibodies to achieve sterile immunity. If it is not one of a myriad of vaccine candidates and their purported protective antibody titers, then it is convalescent antibodies or perhaps one of the several new broadly neutralizing antibody approaches to treat CoV-2 infection. It is impressive how much money and effort is ongoing in the development of antibodies to deal with CoV-2 despite studies from several decades ago indicating that, while protection from coronavirus infection is achievable with antibodies, these antibodies cannot eradicate ongoing infection and therefore most likely have little therapeutic impact.[1] Why then, would we spend so much effort on convalescent antibody approaches, for instance? It is not even clear that convalescent antibodies are effective and, even if a modest fraction of these antibodies were found to have some efficacy against the virus or coronavirus disease 2019 (COVID-19), how would such an approach be scaled up and distributed or even experimentally vetted without proper controlled studies and a standardized therapeutic?

What does appear important, based on previous coronavirus studies, is that antibody responses are only protective if they are expressed at the time of infection.[1] But is it even possible to achieve stable protective antibody concentrations at the time of infection in humans through vaccination? In ongoing studies, only ~4%–6% of Swedes sampled have antibodies to CoV-2. Surely more than 6% of the Swedish population must have been exposed to CoV-2 and may, in fact, have some level of immunity. More interesting are observations that antibodies to CoV-2 wane quickly in individuals who have recovered from COVID-19,[2] while, to date, only a few individuals have become re-infected with CoV-2.[3] So what drives immunity to CoV-2 if not antibodies and the humoral response? There seem to be signs in the literature that cell-mediated immunity may play a large and underappreciated role and that antibodies, and in general the T helper cell type 2 (Th2) humoral immune response, comprise only a small part of host responses to coronaviruses. Have we missed the forest for the trees?

Early studies noted distinct differences in the Th1 response to SARS-CoV-1 infection, which, similar to CoV-2, also results in acute respiratory distress syndromes (ARDSs). Most notable are the differences observed between young and old mice exposed to virus, with the older infected mice succumbing to ARDS within the first week following infection while younger mice remain largely resistant to the infection.[4] A fundamental observable difference between the two outcomes is that the young mice mounted a Th1 response, which included interferon gamma (IFN-γ) and interleukins IL-10 and IL-13.[4] These observations have been recapitulated in studies with strain-dependent variation in another coronavirus, murine hepatitis virus 3 (MHV3), which found that Th1 and macrophage responses were crucial in resistance of naive mice to virus challenge.[1] These collective observations suggest that INF-γ expression is a key correlate with regards to responding to and controlling coronavirus infections. Notably, INF-γ has been found to downregulate expression of ACE2 (the receptor for SARS-CoV-2),[5] and this downregulation in macrophages is correlated with the latter becoming refractory to infection with the closely related coronavirus MHV3.[6] Collectively, these noteworthy studies suggest that perhaps we may have largely focused on the wrong arm of the immune response. These insights bode well for those vaccines, such as mRNA or DNA vaccines, that express viral proteins from within the context of a cell to induce a cell-mediated response. Knowledge of Th1 responses, the role of INF-γ in ARDS, and to what extent macrophages may harbor CoV-2 infection and affect the local Th1 response should probably be paramount as we develop a vaccine. These aspects should be considered to eventually overcome many of the issues associated with SARS-CoV-2 infection and COVID-19 disease so as not to repeat the experiments of the past.

CONFLICTS OF INTEREST

The author declares no competing interests.

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