Immunology Lessons from the SARS-CoV-2 Pandemic

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We are one year into the pandemic with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19). Much has been written about the devastating effects the pandemic has had on nearly every aspect of human life. Indeed, the pandemic and society's responses dominate the daily news cycle. Rather than rehash the topics covered extensively by others, here we offer our view, as immunologists witnessing this unprecedented infectious disease outbreak, that the pandemic has provided significant opportunities for unique studies of human immune responses to SARS-CoV-2. Along with future investigations, these studies will yield lasting lessons that will enhance our overall understanding of the human immune system, not just responses to SARS-CoV-2.

A large amount of basic immunology understanding has come from studying animal models, particularly mice, but it is often challenging to translate basic principles learned with animals to how the human immune system works, and to the clinic. While study of viral infection in humans clearly cannot recapitulate the precision available in animal studies and ethical considerations generally preclude direct infection studies in humans, the pandemic has led to evaluations of the primary human immune response to a single infectious agent (albeit variants are emerging). The vast numbers of patients who can be studied within a short time frame help minimize the differences between individuals due to genetics, viral inoculation dose, timing, etc., as well as any technical challenges. Coupled with recent advances in single-cell analysis, such as single-cell RNA sequencing; mass cytometry; and genomic sequencing, these studies have already helped determine the parameters affecting COVID-19 outcomes and will provide foundational knowledge on which to interpret future studies of human immune responses to other pathogens, both common and rare.

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Studies of human responses to SARS-CoV-2 will also inform understanding of autoimmune and autoinflammatory diseases. Investigations of severe COVID-19 suggest a cytokine storm–like picture in some patients, with Janus kinase inhibitor therapies showing efficacy, suggesting specific cytokine inhibition may also be effective. Whether these interventions have general implications for treatment of severe infectious diseases will be of interest. The identification of patients with life-threatening COVID-19 who previously did not manifest unusually severe viral infections but had mutations in genes encoding factors involved in the antiviral response or autoantibodies against interferons was striking and unexpected. Several studies have now documented the presence of other autoantibodies in patients with severe COVID-19 and suggested such antibodies influence the outcome of the infection. The challenge of patients who have underlying autoimmunity or who are on immunomodulatory therapies and need to cope with SARS-CoV-2 infection and vaccination will likely be further elucidated, yielding information that may be useful when considering other infections and vaccinations in similar patients with altered immune systems.

Also relevant to autoimmunity are the long-haulers, i.e., those who have not fully recovered from acute COVID-19, as an altered immune system may be involved. Another syndrome following acute COVID-19 is the multisystem inflammatory syndrome in children (MIS-C), which resembles the autoimmune/autoinflammatory disorder Kawasaki disease. While there are clearly differences between some clinical manifestations of MIS-C and Kawasaki disease, they share a constellation of overlapping clinical findings that are relatively unique to these disorders. Moreover, therapies established for Kawasaki disease also appear to be beneficial for MIS-C, suggesting some commonalties between these disorders. A pathogen has been suspected for Kawasaki disease but never reliably identified. Interestingly, MIS-C often develops sometime after acute infection, when it is difficult to detect SARS-CoV-2 replication. Such findings suggest that the inflammation originally incited by a pathogen may continue or evolve in some patients, even after the infection has largely subsided. This scenario may underlie Kawasaki disease and other autoimmune conditions, leading to the prospect that these syndromes will one day be prevented by vaccination.

The rapid development of the first successful vaccines to SARS-CoV-2 by Pfizer with BioNTech SE and then by Moderna was based on a novel mRNA platform that had not been used previously for any US Food and Drug Administration (FDA)-approved vaccine. The relative ease with which vaccine mRNA sequences can be modified and then deployed promises to provide an encouraging strategy to keep up with SARS-CoV-2 variants that may escape immunity achieved with the first generation of vaccines, even for vaccines produced with other platforms. The resounding success in bringing these vaccines to initial FDA approval predicts the likelihood that the mRNA platform will be used for other infectious diseases, even to readily test antigens when little is known to guide selection of candidate targets. Another exciting opportunity with the now established mRNA vaccine strategy is its potential use for personalized immune responses to cancer. A large amount of non-COVID-19 work is underway to derive tumor-specific immune responses. Recurrent antigenic targets in certain types of cancer may ultimately guide development of specific cancer vaccines. While the vast array of patient HLA types suggests it will be a daunting task to derive such "off-the-shelf" vaccines that will be useful in all patients with a given cancer, the mRNA platform promises the possibility of quickly producing individualized cancer vaccines for each patient's tumor. Thus, the

development of vaccines to SARS-CoV-2 may lead to advances for both infectious and noninfectious diseases.

Therefore, while we are all witnessing a once-in-a-century pandemic, we are also facing an avalanche of immunological data as scientists mount an impressive effort to curb COVID-19. While the yearly publication schedule of the *Annual Review of Immunology* is not ideal for disseminating rapidly changing advances in how to treat COVID-19, it is well-suited for showcasing the lasting lessons learned from the pandemic that will impact human immunology for years to come. We look forward to covering these topics in future volumes of the *Annual Review of Immunology*.