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INTRODUCTION

Immunity to SARS-CoV-2 infection*

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Over the past two and a half years, the SARS-CoV-2 pandemic has taken a heavy toll on human health worldwide. As of summer 2022, it is estimated that over 500 million people have been infected with SARS-CoV-2, and over 6 million people have died of COVID-19.[1] Yet in the midst of this overwhelming human tragedy, the SARS-CoV-2 pandemic has provided an unprecedented opportunity to study immune responses to a novel pathogen, its variants, and vaccines. These studies guided life-saving COVID-19 public health strategies, allowed for the real-time identification of immune-evasive variants, and revealed correlates of immune protection. Decades of prior research in virology, vaccinology, epidemiology, and immunology provided the foundation for these advances and for the rapid generation of SARS-Cov-2 vaccines, over 11 billion doses of which have been administered. These vaccines, along with newly developed therapeutics, have saved millions of lives.

During the time that these foundational scientific concepts were being built, not only were there very few women scientists, but those who contributed scientific findings were often not given due credit. During the SARS-CoV-2 pandemic, however, although still proportionately unjust,[2,3] the contributions and impact of women's voices were immense. Women scientists, journalists, clinicians, and public health officials contributed to our daily understanding of this pandemic in previously unprecedented ways. In this issue, we celebrate the efforts and contributions of just a few of the outstanding scientists who also happen to be women, who have contributed to our understanding of the biology of SARS-CoV-2 infection, immunity to this pathogen, and production of life-saving vaccines. Woven throughout these reviews one can also recognize the ongoing struggle for funding, recognition, collaborators, and even acceptance of the significance of specific lines of investigation.

While my group did not contribute a review to this edition, we have contributed a cover image generated by Anna Hooser from the Benaroya Research Institute that was initially developed to represent our work exploring immunological mechanisms of "hybrid immunity".[4] Hybrid immunity is the synergism between the responses to infection and subsequent vaccination that together promote the most robust and durable immunity against disease.[5] Our team of extraordinary, collegial scientists, clinicians, research coordinators, and volunteers in Seattle first published evidence for lasting, functional immunological memory in response to SARS-CoV-2 infection within months of the beginning of the pandemic.[6] We next embarked on understanding why individuals who were either previously infected or vaccinated were less protected than those who were infected first and then vaccinated thereafter. We found that the protective advantage of hybrid immunity likely stems from a combination of higher numbers of SARS-CoV-2-specific memory B cells, higher neutralizing antibody titers, and infection-imprinted IFN-gamma and IL-10 cytokine production from CD4+ T cells. And while some of these different qualities could be normalized by additional antigen exposure via vaccination, others were not. The cover image is associated with this work, representing the immune response to SARS-COV-2 infection (red) then to COVID vaccination (blue) and most recently to hybrid immunity (purple). The "sculpture" of the human immune response to SARS-CoV-2 became more complete as the pandemic and our immunological investigations continued. As stated by co-first author Dr. Peter Morawski, who conceptualized the image, "Ivy is seen as a vigorous and aggressive plant, invasive and destructive, as was COVID-19 on the world. The tallest pillar, hybrid immunity, rises the furthest above the ivy." After reading the reviews in this edition, I realized that this image, albeit originally for a different purpose, was also an appropriate analogy to highlight the importance of diverse responses as opposed to the homogeneous. Each investigator focuses on revealing a different part of the whole, and when their contributions are combined, a more complete picture emerges. Diverse responses are not only important in immunity but also in our research communities and study focus. Ensuring that we include diverse voices in science allows us to see the complete picture more efficiently.

*This article introduces a series of reviews covering SARS-CoV-2 Immunity appearing in Volume 309 of *Immunological Reviews*.

We begin with Dr. Helen Chu, an Associate Professor at the University of Washington School of Medicine and a Principal Investigator in the Seattle Flu Study. Dr. Chu's foresight and research team not only identified the first known locally transmitted case of the novel coronavirus in the United States[7] but also led the way for creating a system of biospecimen sample collection and distribution that created the framework for SARS-CoV-2 pandemic research. In this review, she describes "mobilizing and coordinating regulatory, clinical and laboratory teams" to ensure that other researchers had the appropriate samples to understand many aspects of the virus and the immune response to it.[8] Her success is evidenced by the multitude of studies enabled by the care by her team to curate their sample repository. Herein, she describes how her group established their cohort and undertook observational studies, and provides lessons learned to prevent delays and mistakes that are now avoidable in the next pandemic.

Next, Dr. Elina Zuniga, Professor at the University of California San Diego, and her team describe the essential functions of cytokines of the Interferon family in protection against SARS-CoV-2.[9] They provide a comprehensive review of the antiviral functions of Interferon family members, specifically Type I and III, but importantly highlight the nuances of the timing and localization of Interferon production in determining disease outcome. Key viral Interferon evasion mechanisms, as well as interferon therapeutic potential, are discussed as important reminders of how to mitigate the next viral pandemic.

Dr. Donna Farber focuses on key characteristics of tissue immunity to SARS-CoV-2 infection, again reminding us of the need for a balanced immune response to ensure protection, but not at the expense of inducing pathology.[10] Dr. Farber and her team focus on the immune response to SARS-COV-2 at the site of infection using airway washes, lymph node aspirates, and post-mortem tissue analyses to visualize the formation of tissue-resident memory cells. Future vaccines may be able to induce these cells to better prevent infection.

Dr. Frances Lee examines the diversity of SARS-COV-2-specific B cells, specifically the antibody-secreting cells (ASCs), and their antibodies that can be found in the circulation or bone marrow after SARS-CoV-2 infection or immunization[11] Although we have learned a significant amount about the different types of B cells that can be formed in response to infection or vaccination, we still do not understand what regulates the durability of these responses or how best to generate the cells that produce this protection. Dr. Lee and others' studies have positioned us to better understand immunity evoked during the next viral pandemic.

Although antibody-mediated virus neutralization occupies so much of the focus on SARS-CoV-2-specific antibodies, Dr. Taia Wang and colleagues remind us that the structural heterogeneity of IgG antibody ligands impacts downstream binding to CD16a (FcGRIIIa) and CD16a-mediated functions during viral infection.[12] Specifically, they review the literature describing how afucosylated IgG immune complex signaling through CD16a can contribute to the overwhelming inflammatory response central to the pathogenesis of both severe COVID-19 and Dengue virus.

Drs. Michal Tal and Jennifer Gomerman are part of a team of international SARS-CoV-2 researchers that quickly realized that the classical model of "publish first at all costs" was maladaptive for the circumstances and needed to be supplanted by a more collaborative solution-focused and careful approach.[13] Through this woman-lead collaboration, they have developed a new understanding of how mucosal immunity to infection or vaccination can be measured, the types of vaccines best able to induce mucosal immunity, and potential correlates of protection against breakthrough infection. Helpfully, they also provide a perspective on what may be required for next-generation pan-sarbecovirus vaccine approaches.

The review by Dr. Sabra Klein highlights the importance of taking sex into account as a biological variable in susceptibility to infectious disease.[14] Early data from the pandemic revealed that men were more likely to be hospitalized and die from COVID-19 than women. Although Dr. Klein had spent years describing how sex differences could emerge within different immunological contexts, she found herself having to re-educate both scientists and the public alike about significant differences in viral-specific responses in men and women. Like many other authors in this issue, after years of planning and fighting to generate the funding and recognition of the importance of her work, Dr. Klein's studies proved to be essential.

Drs. Kristina De Paris and Sallie Permar of the UNC School of Medicine and Weill Cornell Medicine, respectively, share their knowledge regarding pediatric SARS-CoV-2 infection and the importance of early life SARS-CoV-2 vaccination.[15] It is a timely review of the risks and benefits of SARS-CoV-2 vaccination in early life which in the end advocates for the SARS-CoV-2 vaccine to "become a routine pediatric vaccine recommended and available worldwide."

Lastly, we include a review from Dr. Myrsini Kaforou and colleagues who focus on the immune response to tuberculosis both before and during the pandemic.[16] For the first time in a decade, due to the pandemic, tuberculosis mortality has increased.[17] Better understanding of how transcriptomics can reveal immune responses in the 1.2 million children that develop TB disease annually will help to develop better vaccines. It is important to remember that even when we move past the critical phase of the SARS-CoV-2 pandemic, infectious disease research funding, not only to prepare for future pandemics but also for the many other pathogen-mediated diseases that ravage our world, is imperative.

We hope that you too enjoy the reflections and contributions of these scientists.

CONFLICT OF INTEREST

The author is a member of the Neoleukin and Vaxart Scientific Advisory Boards.

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