CMI

www.nature.com/cmi

EDITORIAL

SARS-CoV-2 immunity

Cellular & Molecular Immunology (2024) 21:101–102; https://doi.org/10.1038/s41423-024-01128-y

Dr. Antonio Bertoletti

Four years have swiftly passed since the identification of a novel coronavirus from patients with pneumonia that signs the start of the COVID-19 pandemic [1]. The world's social and economic landscape has largely reverted to its prepandemic state, and different issues unrelated to the pandemic are currently impacting various regions globally. The scientific community, which quickly modified its research focus during the initial years of the pandemic to generate a wealth of scientific data that helped in understanding and controlling SARS-CoV-2 infection, is also facing a new phase in the study of virus–host interactions.

The acute state of urgency has waned, yet SARS-CoV-2 infection persists. Novel variants derived from the initial lineage have evolved and endemically affect the human population [2]; however, through vaccination and natural infection, these viruses are no longer naïve and, thus, are better able, in the great majority of cases, to control the pathological consequences of SARS-CoV-2 infection.

This altered scenario has modified the research questions that the research community is now facing in the study of SARS-CoV-2 host interactions. In this special issue, we had tasked research groups that contributed significantly to elucidating various immunological aspects of SARS-CoV-2 infection to summarize the mechanisms of innate and adaptive immune responses against this disease. We also asked them to discuss how the legacy of these studies could be used to further reduce the impact of SARS-CoV-2 infection on human health and prevent future novel threats from novel viruses.

For instance, when developing new vaccines that could not only more efficiently curtail the spread of SARS-CoV-2 but also target other coronaviruses, we invited the Leo Swandling group [3] to explore the immunological aspects of existing "old" SARS-CoV-2 vaccines and methods to create new vaccines. One discussed strategy involved utilizing conserved regions of non-structural viral proteins, potentially resulting in a broadly protective vaccine against coronaviruses.

However, assessing the immunogenic and protective effects of such novel vaccine preparations has become progressively challenging. Finding a population of SARS-CoV-2-naïve individuals for testing is practically unfeasible. Hence, we invited Jing Sun's group to consolidate the merits and limitations of various animal models that had been developed to study SARS-CoV-2 pathogenesis and infection protection [4]. The generation or refinement of animal models that faithfully recapitulate human disease would be increasingly necessary to improve the strategies designed to achieve safer coexistence with SARS-CoV-2 and novel possible viral threads. Aligned with this argument, we included in this special issue a paper by the group of Alba Grifoni and Alex Sette that compared the immunodominance of SARS-CoV-2 spike- and nucleocapsid-specific CD4 and CD8 T-cell epitopes detected in mice or humans [5]. Since SARS-CoV-2-specific T cells play an important role in the containment of infection, the authors addressed the extent to which optimizing T-cell activity in animal models would reflect optimal T-cell immunogenicity in humans and, conversely, whether vaccine constructs with optimal T-cell activity in humans would be sufficiently immunogenic in animal models to allow meaningful preclinical testing.

Closely linked with general strategies for controlling SARS-CoV-2 infection, we included three reviews that summarized the present knowledge of immunity at the site of primary infection caused by respiratory viruses, the evolution of antibody responses occurring in infected and vaccinated individuals and the epidemiological and immunological features of asymptomatic coronavirus infections.

Briefly, in their review titled "Olfactory immune response to SARS-CoV-2", Sebastian Welford and Ashley Moseman explained the implications of SARS-CoV-2 infection of the olfactory mucosa and described the characteristics of this local immune response [6]. They also discussed the areas of future research on olfactory immunity that can facilitate the development of novel vaccines not only against SARS-CoV-2 but also against other respiratory pathogens.

Similarly, Lapuente, Winkler and Tenbusch, in their review argued that the pandemic provided a unique setting for studying de novo and memory B-cell and antibody responses in a novel and dynamic interplay between infection and distinct and novel (mRNA) vaccine-induced immunity [7]. This acquired knowledge will be of significant value for the development of novel vaccines not only in the context of SARS-CoV-2 but also in other endemic or new pandemic settings.

Furthermore, in the review "Silent battles: immune response in asymptomatic SARS-CoV-2 infection", Nina Le Bert and Taraz Samandari highlighted the wide spectrum of clinical presentations of SARS-CoV-2 infection [8]. They emphasized that even if

Received: 3 January 2024 Accepted: 3 January 2024
Published online: 18 January 2024

asymptomatic infection likely strongly contributes to the virus's rapid spread of the virus, it had also offered the blueprint of an extremely successful immune response where innate and T-cell immunity appeared to play a major role. Understanding this response has implications for health policy and strategies for viral control.

However, this special issue should not be complete without delving into specific aspects of innate immunity and acknowledging that SARS-CoV-2 infection can still yield severe consequences. Hence, the group of Ravindra Gupta provided a comprehensive review of the innate immune mechanisms active during SARS-CoV-2 infection [9] and how several viral proteins counteracted them. The authors also investigated the innate immune mechanisms activated by different vaccines and proposed that the etiology of long COVID-19 might be closely linked to a state of chronic innate immune activation.

In another review, Maxime Hoft, Wendy Burgers, and Catherine Riou summarized the features of the immune response against SARS-CoV-2 in individuals with HIV infection [10] and suggested that SARS-CoV-2 infection could still have severe consequences, particularly in individuals with immunological defects. Indeed, the suboptimal immune response present in individuals with advanced HIV disease clearly affected SARS-CoV-2 control and increased the risk of severe pathogenesis. It could also give rise to very prolonged infection that predisposes individuals to a selection of novel variants.

In conclusion, Valeria Fumagalli and Matteo Iannacone discussed the impact of different drug treatments on SARS-CoV-2 infection control [11]. The authors discussed the possible negative effects of direct antiviral treatment on the establishment of SARS-CoV-2-specific adaptive immune responses. On the other hand, they reported new findings related to the repurposing of drugs such as bisphosphonate that, through their immunomodulatory effects, appear to reduce the incidence of severe COVID-19 in the general population. They concluded their article by calling for the need for meticulous research investigations, a call that I feel should be extended to every single argument discussed within this special issue. Research in these different areas could not only achieve safer coexistence between humans and this novel coronavirus but also increase the understanding of virus–host interactions that the pandemic crisis has already promoted and could further increase and capitalize on the defense against novel infectious threats.

Antonio Bertoletti [1] ✉
[1] *Program in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore, Singapore.* ✉*email: antonio@duke-nus.edu.sg*

REFERENCES

1. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270–3.
2. van Dorp L, Houldcroft CJ, Richard D, Balloux F. COVID-19, the first pandemic in the postgenomic era. Curr Opin Virol. 2021;50:40–48.
3. Cankat S, Demael MU, Swadling L. In search of a pancoronavirus vaccine: next-generation vaccine design and immune mechanisms. Cell Mol Immunol. 2024;21:103–18.
4. Zhao C, Yuan Y, Hu Q, et al. SARS-CoV-2 infection in animal models. Cell Mol Immunol. 2024;21:119–33.
5. Neto TAP, Sidney J, Grifoni A, Sette A. Correlative CD4 and CD8 T-cell immunodominance in humans and mice: Implications for preclinical testing. Cell Mol Immunol. 2023;20:1328–38.
6. Wellford SA, Moseman EA. Olfactory immune response to SARS-CoV-2. Cell Mol Immunol. 2024;21:134–43.
7. Lapuente D, Winkler TH, Tenbusch M. B-cell and antibody responses to SARS-CoV-2: infection, vaccination, and hybrid immunity. Cell Mol Immunol. 2024;21:144–58.
8. Le Bert N, Samandari T. Silent battles: immune responses in asymptomatic SARS-CoV-2 infection. Cell Mol Immunol. 2024;21:159–70.
9. Sievers BL, Cheng MTK, Csiba K, Meng B, Gupta RK. SARS-CoV-2 and innate immunity: the good, the bad, and the "goldilocks". Cell Mol Immunol. 2024;21:171–83.
10. Höft MA, Burgers WA, Riou C. The immune response to SARS-CoV-2 in people with HIV. Cell Mol Immunol. 2024;21:184–96.
11. Fumagalli V, Iannacone M. The interplay of drug therapeutics and immune responses to SARS-CoV-2. Cell Mol Immunol. 2024;21:197–200.

COMPETING INTERESTS

The author has reported a patent for a method to monitor SARS-CoV-2-specific T cells in biological samples as pending and is the founder of TCD (T Cell Diagnostic) Ltd, a service company providing immunological analysis in human samples.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Antonio Bertoletti.