Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial overview: Viral pathogenesis

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Antonio Bertoletti has always been interested in studying HBV immunopathogenesis with a particular focus on immunologically based therapies for the treatment of chronic HBV infection and hepatocellular carcinoma. He was trained as an infectious-disease specialist at University of Parma, Italy, and he then worked at The Scripps Research Institute, University College of London and now at Duke-NUS Medical School, Singapore. After the start of the COVID-19 pandemic, his laboratory has been actively involved in the characterization of SARS-CoV-2-specific T-cell immune response in infected and vaccinated individuals.

Two years after the start of the COVID-19 pandemic, epidemiological, virological, and immunological situations worldwide have considerably changed. Most of world population is no longer immunologically naive (either because of infection or vaccination), the SARS-CoV-2 lineage that caused the initial pandemic wave is no longer circulating in humans, while a number of variants of concern have over time become dominant (at the time of writing the most prevalent being the Omicron BA.2 variant). The scientific community has responded to this pandemic by generating an unprecedented wealth of data that have clarified many aspects of the interaction of SARS-CoV-2 with the human host; however, some of the research questions that emerged at the beginning of the pandemic are still relevant today.

The impact of innate and adaptive immune responses on viral control and disease pathogenesis, the quality and specificity of antibodies and T cells and their relative importance in protection from infection and disease, and the mutational landscape underlying changes in transmissibility and pathogenicity remain key aspects that need to be further investigated for our society to adapt to this rapidly changing pathogen. Human studies cannot be uncoupled from the generation or refinement of animal models faithfully recapitulating the human disease.

This issue of *Current Opinion of Virology* is meant to shed some light on some of these important questions.

In two articles dedicated to the role of innate immunity in the control of SARS-CoV-2 infection and in the pathogenesis of COVID-19, Niklas Björkström et al. [1] and Ivan Zanoni [2] elucidate the role of natural killer (NK) and unconventional T cells, and of type-I and type-III interferons, respectively.

Björkström and Ponzetta cover not only the antiviral activity of NK and unconventional T cells (i.e. mucosal-associated invariant T cells [MAIT cells], γδ T cells, invariant Natural Killer T cells (NKT), and double-negative αβ T cells) — likely enhanced by their propensity to localize at sites of SARS-CoV-2 infection (upper and lower respiratory tract) — but also nicely summarize the different experimental evidences showing an association between prolonged dysfunctional NK-cell activation in the lungs

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Matteo Iannacone was trained at The Scripps Research Institute and at Harvard Medical School before establishing his laboratory at San Raffaele Scientific Institute & University. He uses hepatitis B, SARS-CoV-2, and other viruses as a convenient excuse to study basic elements of immunology, cell biology, and pathology.

and severe COVID-19 [1]. In particular, an increased MAIT cell activation has been suggested to contribute to severe COVID-19 [1]. The challenge ahead is to understand and possibly fine-tune the balance between protective and pathologic involvement of these innate immune cells. Interestingly, MAIT cells were found to be a critical determinant of adenoviral-based vaccine efficacy [3].

A similar dichotomy between protection and damage is also evident in "*Interfering with SARS-CoV-2: are interferons friends or foes in COVID-19?*" [2]. Here, Ivan Zanoni elucidates how SARS-CoV-2 triggers type-I and type-III interferon responses and how it can partially suppress this early innate immune-defense mechanism. The authors also discuss how the prolonged activation of such pathways might actually be detrimental in patients with COVID-19. The development of novel therapeutic interventions based on type-I and/or type-III interferons requires a better understanding of the complexity and specificity of the different members of the interferon family, including timing [4], dosing, location, and cellular targets.

In the review entitled "*Know your enemy and know yourself — the case of SARS-CoV-2 host factors*" [5], Yaw Shin Ooi and coworkers present a detailed overview of the major stages of the SARS-CoV-2 infection cycle. The steps necessary for attachment and entry into host cells, the mechanisms of translation and RNA replication, followed by virus assembly and virion secretion, are described in detail. This molecular information has been and is being used for the rational design of host-directed antiviral drugs. The authors also highlight how the practical difficulties of studying SARS-CoV-2 in a Biosafety Level-3 (BSL-3) containment set off the rapid implementation of surrogate infection systems, while the latter have the advantage of being handled in a Biosafety Level-2 (BSL-2) environment accessible to most laboratories, they might not recapitulate the entire natural SARS-CoV-2 replication cycle and thus should be interpreted with caution.

The issue of using appropriate systems to study SARS-CoV-2 infection is not only associated with *in vitro* studies. In a paper entitled "Immune response to human respiratory coronaviruses infection in mouse models", Jincun Zhao and coworkers discuss how mouse models can be the ideal tool for studying the immunobiology and the pathogenesis of different human respiratory coronaviruses [6]. They highlight the pros and cons of studying coronavirus pathogenesis in mouse model and how the selection of the appropriate mouse model should be based on the study objectives, since differences in tropism and disease progression are observed in different mouse models [6,7].

This Viral Immunology issue of Current Opinion of Virology could not be complete without discussing some specific aspects of humoral and cellular immunity to SARS-CoV-2. We invited Sophie A Valkenburg and coworkers to discuss the role of antibodies that target nonstructural proteins [8]. Not surprisingly, most studies on antibodies focused on characterizing the neutralizing ability of antispike antibodies. However, antibodies can have functions that go beyond virus neutralization, such as blocking interaction of viral structures with host proteins, directing NK cells or macrophages toward infected cells, or even promoting infection [9]. In the paper entitled "*Antibody landscapes of SARS-CoV-2 can reveal novel vaccine and diagnostic target*s", the authors describe all these possibilities, focusing in particular on

the role of antibodies against nonstructural accessory proteins of SARS-CoV-2 in diagnosis and pathogenesis.

The large quantity of proteins produced by SARS-CoV-2 during its replication within hosts can elicit not only antibodies but also broad T-cell immunity. Indeed, the multispecificity of T cells toward distinct structural and nonstructural proteins is a hallmark of the immune response to SARS-CoV-2 [10]. Whether T cells recognizing different epitopes have, however, similar antiviral potential, is still a matter of discussion. Here, Tao Dong and colleagues discuss exactly the issue of T-cell immunodominance in SARS-CoV-2 infection [11]. They review the mechanisms that regulate the processing and presentation of different viral epitopes within infected cells and how immunodominance is established in infected individuals. We are still quite a long way from understanding such rules in SARS-CoV-2 infection, but emerging data are starting to shed light on immunodominant T-cell epitopes and their relation to mutations occurring in the circulating variants of concern.

Indeed, in the last paper of this collection, Lucy Van Dorp et al. describe the unprecedented scale of the international efforts to trace the sequence of SARS-CoV-2 genomes to define such variants [12]. Their article entitled "*COVID-19, the first pandemic in the post genomic era*" recapitulating the effort to trace the virus, provides the evidence demonstrating the ability of SARS-CoV-2 to accumulate mutations that lead to more transmissible lineages and hypothesizes that immune-escaping mutations will eventually emerge and that SARS-CoV-2 will become an endemic circulating pathogen. We need to congratulate the authors for their perfect predictions, and for hypothesizing that changes in virulence and the progress of vaccination could reduce morbidity and mortality to a fraction of that experienced during the initial phase of the pandemic. The wish is also that their comment about the gradual, not sudden, loss of vaccine-induced immunity against emerging SARS-CoV-2 variants, will be correct.

References

1. Björkström NK, Ponzetta A: **Natural killer cells and unconventional T cells in COVID-19**. *Curr Opin Virol* 2021, **49**:176-182.
2. Zanoni I: **Interfering with SARS-CoV-2: are interferons friends or foes in COVID-19?** *Curr Opin Virol* 2021, **50**:119-127.
3. Provine NM, Amini A, Garner LC, Spencer AJ, Dold C, Hutchings C, Reyes LS, FitzPatrick MEB, Chinnakannan S, Oguti B, *et al.*: **MAIT cell activation augments adenovirus vector vaccine immunogenicity**. *Science* 2021, **371**:521-526.
4. De Giovanni M, Cutillo V, Giladi A, Sala E, Maganuco CG, Medaglia C, Lucia PD, Bono E, Cristofani C, Consolo E, *et al.*: **Spatiotemporal regulation of type I interferon expression determines the antiviral polarization of CD4+ T cells**. *Nat Immunol* 2020, **21**:321-330.
5. Lee WS, Yousefi M, Yan B, Yong CL, Ooi YS: **Know your enemy and know yourself – the case of SARS-CoV-2 host factors**. *Curr Opin Virol* 2021, **50**:159-170.
6. Zhuang Z, Liu D, Sun J, Li F, Zhao J: **Immune responses to human respiratory coronaviruses infection in mouse models**. *Curr Opin Virol* 2022, **52**:102-111.
7. Fumagalli V, Ravà M, Marotta D, Lucia PD, Laura C, Sala E, Grillo M, Bono E, Giustini L, Perucchini C, *et al.*: **Administration of aerosolized SARS-CoV-2 to K18-hACE2 mice uncouples respiratory infection from fatal neuroinvasion**. *Sci Immunol* 2022, **7**:eabl9929.
8. Hachim A, Kavian N, Valkenburg SA: **Antibody landscapes of SARS-CoV-2 can reveal novel vaccine and diagnostic targets**. *Curr Opin Virol* 2021, **50**:139-146.
9. Junqueira C, Crespo Â, Ranjbar S, Lacerda LB, de, Lewandrowski M, Ingber J, Parry B, Ravid S, Clark S, Schrimpf MR, *et al.*: **FcγR-mediated SARS-CoV-2 infection of monocytes activates inflammation**. *Nature* 2022, **606**:576-584, https://doi.org/10.1038/s41586-022-04702-4
10. Bertoletti A, Le Bert, Qui M, Tan AT: **SARS-CoV-2-specific T cells in infection and vaccination**. *Cell Mol Immunol* 2021, **18**:2307-2312, https://doi.org/10.1038/s41423-021-00743-3
11. Wellington D, Yin Z, Kessler BM, Dong T: **Immunodominance complexity: lessons yet to be learned from dominant T cell responses to SARS-COV-2**. *Curr Opin Virol* 2021, **50**:183-191.
12. Dorp L van, Houldcroft CJ, Richard D, Balloux F: **COVID-19, the first pandemic in the post-genomic era**. *Curr Opin Virol* 2021, **50**:40-48.