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Commentary

Narrating the natural history of live infection by SARS CoV-2 VOC in animal models

Daniel M Altmann

Department of Immunology and Inflammation, Imperial College London, Northern Ireland W12 0NN United Kingdom

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The requirement for rapid answers during the COVID-19 pandemic has stress-tested the resources of 21st century immunology, virology and vaccinology research, with life-and-death need for meaningful answers. Unsurprisingly, given the scale and features of the disease, many of the answers have come out of analysing the sadly abundant supply of infected people at different stages of disease severity. Such studies, from vaccine trials to characterisation of neutralising antibody epitopes, have yielded a huge body of knowledge that within less than 2-years has eclipsed the datasets for many or most other infectious diseases. However, such is the arms race against SARS-CoV-2 and its emerging variants of concern (VOC) that the questions keep coming and keep changing. Some are not of the type easily answered by sampling human cells or sera following real-life, natural exposure. For example, because a study of the earliest events following acute infection requires knowledge of viral isolate sequence, challenge dose and timing, or because of the need to understand the details of viral infection, inflammation and pathogenesis in the lungs or other target organs. For many of these research questions, the answers need to come either from human challenge studies or from animal infection models. Human challenge studies are now well underway but have to encompass several safety and ethical constraints, including virus isolates and dose and invasiveness of tissue sampling [1]. That leaves a gap to be filled by animal studies [2]. However, delivering pathologically and immunologically pertinent and illuminating animal models of human infectious diseases has been notoriously difficult. Even if the hurdle of species-specific receptors is overcome by sequence conservation or transgenesis, there is the common problem that specific patterns of multi-system pathology may be poorly reiterated. In the case of COVID-19, animal model studies have encompassed K18-ACE2 transgenic mice, Syrian hamsters, ferrets and non-human primate (especially macaque) studies [2]. As in all animal models of human disease pathology, there are trade-offs between maintenance costs and therefore group sizes, the pertinence of pathology and disease course and, importantly, availability of appropriate reagent sets and cellular markers such as required for flow cytometry, tissue staining or cell separation. Macaque infection has been the gold standard, illuminating key questions such as the elucidation of vaccine efficacy, correlates of protection and immune response patterns after infection by VOC [3–5]. However, studies are limited by constraints with respect to high cost, small group sizes, the small number of appropriately equipped research facilities and, in many countries, ethical hurdles. Work in the ferret model offers upper respiratory tract viral RNA replication and relatively pertinent lung pathology [6]. ACE2 transgenic mice have been invaluable, especially for mechanistic questions of protective immunity, though the requirement to express ACE2 using a tissue-specific promoter such as K18 imposes a filter on cell-types susceptible to viral entry which is unlike the human pattern of infection and therefore, of multi-organ disease [7].

O'Donnell and colleagues have now reported detailed comparative analysis of infection in Syrian golden hamsters, looking at differences between the early stages of infection using the ancestral Wuhan Hu-1 isolate, alpha or beta VOC – precisely the type of questions that are so hard to address in other settings [8]. They find for example that after infection with alpha VOC there is a significantly higher peak of viral RNA in the lungs than with the other strains. Importantly, it is shown that the repertoire of neutralizing antibodies elicited by infection with each of the VOC is rather poorly cross-neutralizing against other strains. These findings have important ramifications on a planet where we aim for protective immunity, often through prior infection with diverse VOC, overlaid with vaccines carrying Wuhan Hu-1 spike sequence. Furthermore, alpha VOC infection is distinctive in terms of its induction of novel lung transcripts implicated in tissue remodelling and Th2 activation.

Decoding the differential pathology, immunology and virology of VOC alpha to delta infections, as well as any others that may emerge, will continue to be challenging. The fast-track, minimal standard that has emerged has been to determine any loss of neutralisation of vaccine-induced antisera, along with any effects on vaccine efficacy and transmission. Relevant, accessible animal infection models offer the chance to supplement these data with additional mechanistic insights.

Contributors

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E-mail address: d.altmann@ic.ac.uk

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Declaration of Competing Interest

The author declares no conflicts of interest.

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