Learning from our differences

Andrea J. Sant and Patrick C. Wilson

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Current SARS-CoV-2 vaccine recipients differ in infection history and the magnitude of their elicited antibody response. A large human cohort distinguished by these parameters are queried for effector T cell subsets, memory B cells and ability to recognize epitopes from SARS-CoV-2 variants of concern.

It is critical to understand the full complement of antigen-specific immunity induced by SARS-CoV-2 vaccination, and how previous infection and early vaccine responses predict ultimate protection from infection with SARS-CoV-2 variants of concern (VOCs). In this issue of *Nature Immunology*, Brasu et al.[1] assess the SARS-CoV-2-spike-specific antibodies and B cell and T cell responses to SARS-CoV-2 mRNA vaccination and boost protocols, as well as the outcome in terms of breakthrough infections, in a large human cohort longitudinally for up to 15 months after the first vaccination (Fig. 1). A notable feature of this study is that the members of the vaccine cohort were first distinguished on the basis of previous infection with SARS-CoV-2 as previously uninfected and vaccinated (V_N) or previously infected, recovered and vaccinated (V_R) individuals and were then segregated based on the bimodal distribution of their quantified serum spike-specific IgG antibodies at 3 months after vaccination. The high responders (V_NHR and V_RHR) were less likely to become infected with VOCs (Fig. 1). In essence, although the number of breakthrough infections were low, this study reports that only people who had the most robust antibody responses

to SARS-CoV-2 alongside abundant CD8+ T cell populations comprising both central and effector memory cells were protected from breakthrough infection with SARS-CoV-2 VOCs.

The analyses indicated that individuals with higher antibody titers and levels of spike-specific B cells and CD8+ T cells showed greater binding and neutralization against the Delta and Omicron VOCs. The improved antibody-mediated protection to the wild-type and VOC strains in the V_NHR and V_R groups may be explained by several contributing factors. Antibody titers result from a composite of the concentrations of antibody proteins in serum that are typically assumed to account for increased protection; the affinities of individual antibodies within the total polyclonal serum; and the binding to a greater number of individual epitopes simultaneously. Each of these factors likely contributes to improved antibody-mediated cross-protection against VOC strains. Although the VOC strains carry mutations of key neutralizing and protective spike-derived epitopes due to selective pressure, increased concentrations of antibodies – even those to non-neutralizing epitopes on the VOC strains – can still provide some degree of protection through Fc-mediated mechanisms[2,3]. These mechanisms can be direct, such as antibody-dependent cellular cytotoxicity (ADCC), which helps kill infected cells that actively bud virions or promote viral phagocytosis; or indirect, such as opsonization of viral antigens and promotion of improved innate responses alongside the CD4+ and CD8+ T cell responses. In addition, 'escape mutations' include both those resulting in loss of binding and those causing reduced binding affinity, depending on the antibody affected. Increased antibody titers could overcome loss of affinity in some cases, providing protection against VOC strains.

There are examples of continued affinity maturation of B cell receptors against the SARS-CoV-2 spike over time or with
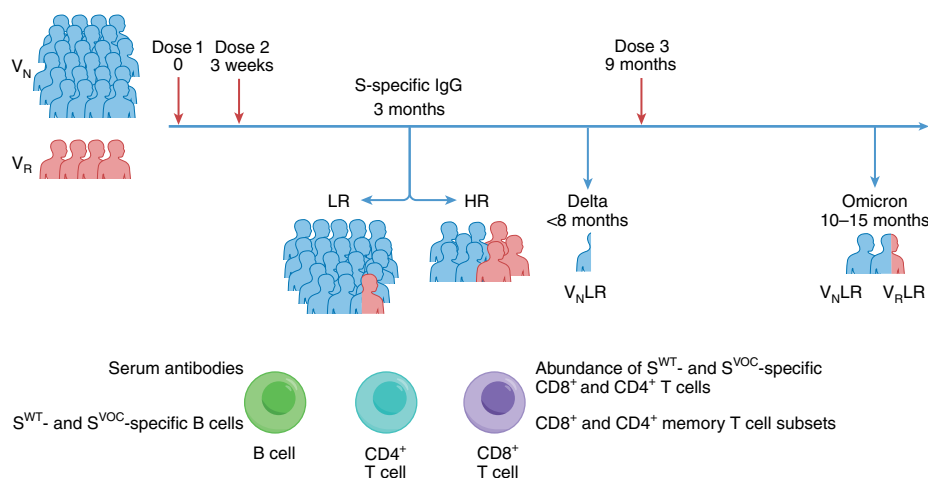
Fig. 1 | Assessing the effect of infection-elicited immune memory on responses to SARS-CoV-2 vaccination. Members of the cohorts studied by Brasu et al.[1] differed first in their infection history before vaccination (V_N, naive before vaccination; V_R, infection-recovered before vaccination) and later in the magnitude of their early antibody response to vaccination (LR, low responders;

HR, high responders). PBMC samples were obtained at the indicated sampling times and subjected to detailed analyses to follow SARS-CoV-2 specific CD4+ and CD8+ T cell subsets and effector function and spike-specific B cells over time. The members of the cohort were also tracked for more than a year for breakthrough infection.

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additional boosts[4,5]. This continued maturation allows B cell clones that are initially reactive only to the wild-type SARS-CoV-2 virus to become cross-reactive to VOC strains with further vaccine boosts[4]. It appears that the improved affinity conferred by extended affinity maturation can overcome the loss of affinity due to viral escape mutations. In regard to the increased numbers of epitopes that are bound simultaneously, there is now evidence that antibodies targeting additional epitopes accumulate over time after exposure[6]. Early responses, or those found in the V_N low responder (V_NLR) group, would predominantly bind the most superficial epitopes, which would also be the most susceptible to selective pressure and escape mutations. Conversely, more robust responses would provide a deeper dive and would be more likely to produce, by chance, antibodies to multiple epitopes shared by the wild-type and VOC virus strains.

The combination of waning of serum antibodies and emergence of drift variants less sensitive to protective antibodies induced by original strain of SARS-CoV-2[7] has led to a great deal of interest in evaluating the T cells elicited by infection and vaccination. It is important to know whether T cells persist in the vaccinated host with broad enough epitope specificity and effector function to respond to the altered peptide epitopes expressed by variant viruses. There are considerable, although in some cases conflicting, data on this issue, with most studies[8] that tested all VOC spike variants, including the current one, concluding that there are limited, if any, deficits in the ability of the T cells to maintain recognition of VOCs. This is likely due to the relatively broad epitope specificity of T cells and the diversity of MHC molecules available in a single human host. In addition to the specificity of the elicited T cells, the analysis of the cohort in the current study was enhanced by the diversity of T cell functions probed. Various surface markers can be used to identify distinct subsets of memory T cells, based on the expression of proteins associated with antigen experience, lymph node homing potential and predicted T cell effector ability to survey sites of infection and effector function[9]. Using these markers, Brasu et al.[1] examined the abundance, effector potential and surface phenotype of vaccine-elicited, persistent T cell populations.

Evidence for broad, functionally diverse T cell memory was found in both the CD8+ and CD4+ T cell compartments in the V_N and V_R groups. CD8+ T cells, thought to convey protection primarily through cytotoxic activity particularly at the site of infection, were robustly elicited by mRNA vaccines. In agreement with other reports[10], elicitation of CD8+ T cells and their maintenance in memory is thought to be a notable advantage of the mRNA vaccine platform, relative to the more common, protein-based vaccines. Diverse spike-specific memory CD4+ T cells induced by vaccination were also seen in each group and persisted in the hosts. Notably, the CD4+ T cells from the V_R individuals, unlike those from the V_N individuals, were selectively deficient in populating the host with effector memory 2 CD4+ T cells (T_{EM2} cells). The T_{EM2} cell phenotype is thought to identify memory T cells that convey highly differentiated effector functions, such as cytotoxicity. However, because of the ability of CD4+ T cells to potentiate protective, high-affinity antibody responses and the generation of these memory CD8+ T cells as well as their direct effector functions, such as cytokine production, the protection against breakthrough infection observed in all groups except the V_NLR group (who showed the weakest antibody response) was likely mediated, at least indirectly, by the vaccine-elicited CD4+ T cells.

Overall, this study provides an example of important findings, similarly reported in various other contexts, that link higher serum antibody titers to increased numbers of memory B cells and CD4+ and CD8+ T cells, and points to areas of importance for future studies. For example, it is likely that more detailed analyses of the fine specificity of the elicited antibodies targeting discrete sites associated with exclusive vaccine-induced immunity or infection-induced immunity, as well as those associated with hybrid immunity, will more firmly implicate these antibodies in resistance to subsequent infection. Also of interest are the potential links between antibody effector functions beyond neutralization that are induced by vaccines as compared to infection; and with the increase in VOC breakthrough infections that may go undetected—which may have occurred in some of the members of the cohort studied here—it will be important to evaluate the impact of 'hybrid immunity' on the B cell and T cell compartments. As the development and deployment of updated vaccines composed at least in part of spike proteins from VOCs[11] moves forward, it will be critical to explore the issues of competition among B cells and the possible complications of 'original antigenic sin' and the longevity of new specificities[11]. Finally, as has been noted in earlier studies of influenza vaccine responses[12], the genetic and cellular factors of the host that determine high versus low responder status will provide possible strategies to identify those who may benefit most from regular boosters and added adjuvants for protein-based SARS-CoV-2 vaccines or other vaccine strategies, in order to induce the most effective and persistent protective immunity.

Andrea J. Sant [1] ✉ and Patrick C. Wilson [2] ✉

[1]David H. Smith Center for Vaccine Biology and Immunology, Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, NY, USA. [2]Gale and Ira Drukier Institute for Children's Health, Department of Pediatrics, Weill Cornell Medicine, New York, NY, USA.
✉e-mail: andrea_sant@urmc.rochester.edu; pcw4001@med.cornell.edu

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Competing interests
The authors declare no competing interests.