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Spotlight

SARS-CoV-2 vaccination washes away original antigenic sin

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According to Röltgen and colleagues vaccination generates antibody breadth, whereas SARS-CoV-2 infection does not. Vaccination results in germinal center B cell responses and generates immunological breadth, with antibodies that bind viral variants. COVID-19 from SARS-CoV-2 infection does not induce germinal centers; it sustains immune imprinting, also known as ‘original antigenic sin’, and this results in limited immunological breadth.

A recent study from Röltgen and colleagues in *Cell* [1] examined antibody responses induced by a range of vaccines for coronavirus disease 2019 (COVID-19) and compared them with responses induced by prior infection. The main focus was to see whether antibodies generated in these different contexts differed in their ability to recognize severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike proteins from variant viral strains.

Most currently used vaccines for COVID-19 express, or induce the expression of, the Spike protein of the Wuhan-Hu-1 strain of SARS-CoV-2. Chemically inactivated viral vaccines in use are also based on the Wuhan-Hu-1 strain of SARS-CoV-2 but include all the proteins of the virus, not just the Spike protein, albeit in a partially denatured form.

The authors examined vaccinated subjects from cohorts in Northern California

as well as from Mongolia and thus accessed information about antibodies made in response to an mRNA vaccine, two adenoviral vaccines, and one chemically inactivated vaccine. These were compared with antibody responses in COVID-19 patients. While it was already known that mRNA vaccination provides higher titers of antibodies than other vaccine categories, these studies revealed that vaccination in general generates greater antibody breadth than natural infection [1].

Natural infection with SARS-CoV-2 results in a relatively large proportion of short-lived IgM and IgA antibodies but also generates some IgG responses. Overall, the titers of antibodies generated during acute COVID-19 can be comparable with those seen with many vaccines. While different vaccines produce different magnitudes of antibody responses, there is one significant feature that distinguishes the antibodies generated by all vaccines from those generated after natural SARS-CoV-2 infection: vaccine-induced antibodies have ‘breadth’ and these antibodies acquire the ability to bind different viral variant Spike proteins, such as those from the beta, gamma, and delta SARS-CoV-2 variants. Natural infection with SARS-CoV-2 does not generate comparable breadth.

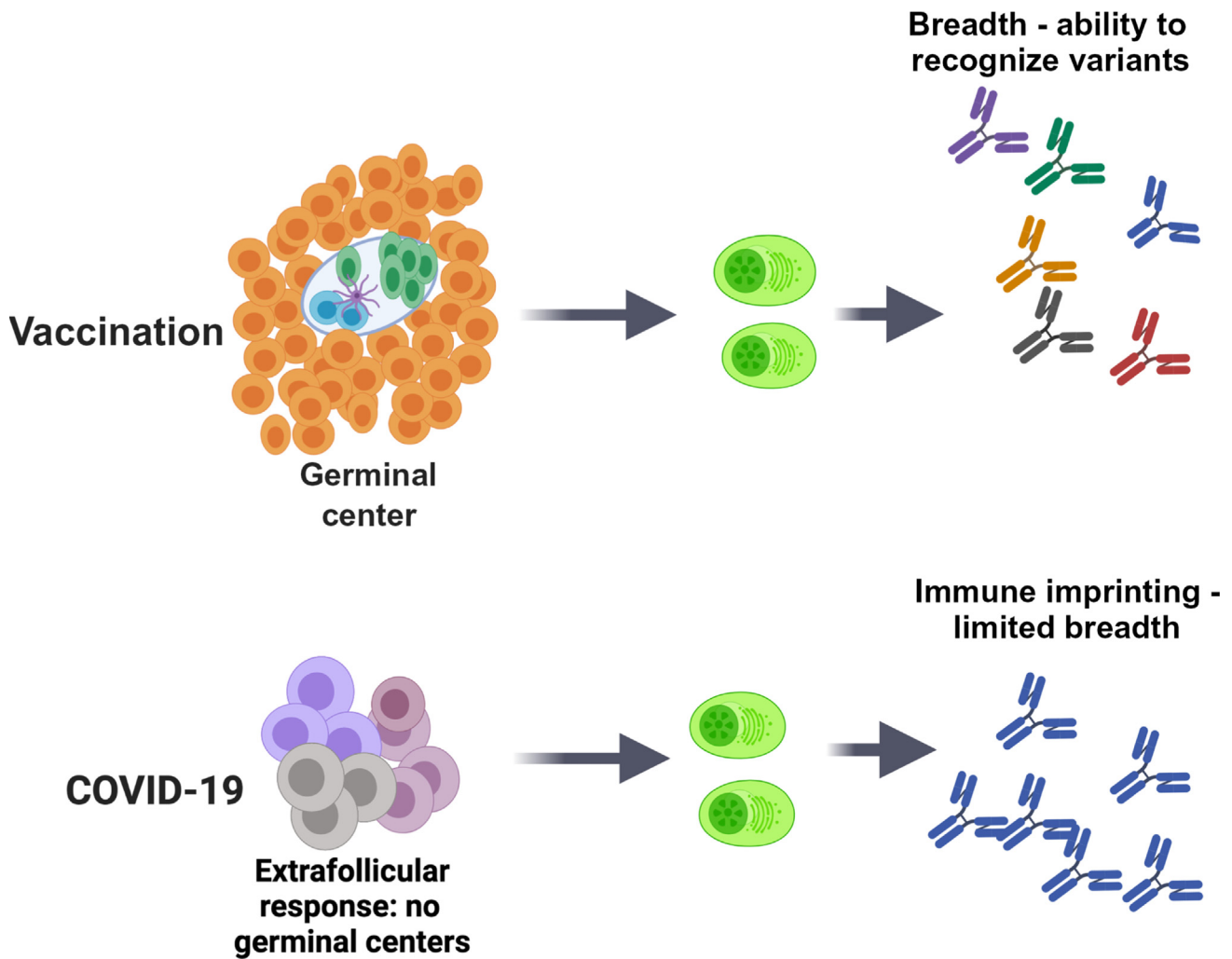
One of the major changes that was seen in severe COVID-19, and described in the early months of the pandemic, was the failure to form germinal centers, linked specifically to the absence of Bcl-6 expressing CD4⁺ T follicular helper cells [2]. In contrast, subsequent studies that sampled lymph nodes after mRNA vaccination had, not surprisingly, revealed the presence of robust germinal centers (Figure 1) for at least 2 months after vaccination [3].

In their studies [1], Röltgen and colleagues confirmed previous findings [2,3] showing

the absence of germinal centers in COVID-19 and the robust formation of germinal centers after vaccination (Figure 1). They extended these studies by examining the fate of both the vaccine Spike mRNA and the Spike protein in the lymph nodes of vaccinated individuals over a 2-month period [1]. They showed the presence of Spike protein in the germinal centers of lymph nodes for almost 2 months after immunization. Perhaps that was not surprising, given the ability of follicular dendritic cells in germinal centers to hold on to antigen–antibody complexes for extended periods of time. That might have been the presumptive inference made to explain the persistence of the Spike antigen, but for an even more remarkable finding. What was particularly surprising was the specific expression of Spike mRNA for extended periods of time in the germinal center regions of lymph nodes of vaccinated individuals. Could continuing persistence and translation of the mRNA in lymph nodes be the underlying cause of the persistence of antigen in germinal centers and indeed the prolonged life of germinal centers after vaccination?

This final intriguing finding is quite remarkable and needs to be validated by others. A study performed prior to the pandemic on mRNA vaccination in rhesus macaques utilized novel tools to follow the fate of both mRNA and protein but was performed over a relatively short duration [4]. It would be important for studies on non-human primates to be performed over extended time periods with similar tools. mRNA modifications reduce immunogenicity but also enhance translatability as well as mRNA stability. So, while survival of the mRNA *in vivo* for a few more days may have been predicted in the Röltgen *et al.* study [1], the importance of discovering whether mRNA actually persists for weeks and months and is translated for an extended period of time cannot be overstated.

The concept of ‘original antigenic sin’ posits that antibodies induced upon the



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Figure 1. Spike vaccination generates greater antibody breadth than natural severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19). Vaccination leads to germinal center formation and greater antibody breadth while natural SARS-CoV-2 infection and COVID-19 itself results in germinal center disruption and the production of antibodies with diminished breadth, as assessed by their relative inability to bind viral variants [1]. Figure created with Biorender.com

first exposure to an antigen dominate even after subsequent challenges with antigens that vary slightly from the original. This process has sometimes also been called immune imprinting or antigen imprinting [5,6]. It may well be that ‘original antigenic sin’ only applies to certain infections and not to all vaccinations. It is likely that ‘optimal’ immune responses with proper germinal center formation facilitate the ability for antibodies to gain breadth and discern

variant antigens, while suboptimal immune responses do not. This study by Scott Boyd’s laboratory [1] provides some interesting insights, some of which fit previous evidence for a suboptimal immune response in acute COVID-19.

Declaration of interests

No interests are declared.

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References

- Röltgen, K. *et al.* (2022) Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination. *Cell* Published online January 25, 2022. <https://doi.org/10.1016/j.cell.2022.01.018>
- Kaneko, N. *et al.* (2020) Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19. *Cell* 183, 143–157

3. Turner, J.S. *et al.* (2021) SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses. *Nature* 596, 109–113
4. Lindsay, K.E. *et al.* (2019) Visualization of early events in mRNA vaccine delivery in non-human primates via PET-CT and near-infrared imaging. *Nat. Biomed. Eng.* 3, 371–380
5. Davenport, F.M. and Hennessy, A.V. (1957) Predetermination by infection and by vaccination of antibody response to influenza virus vaccines. *J. Exp. Med.* 106, 835–850
6. Francis, T., Jr., T., Jr., T., Jr (1960) On the doctrine of original antigenic sin. *Proc. Am. Philo. Soc.* 104, 572–578