RESEARCH HIGHLIGHT

Four-wheel-drive immune protection

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In a recent study published in *Cell*, Zhang and colleagues provide the first longitudinal study comparing four different COVID-19 vaccines head-to-head for binding and neutralizing antibodies, spike-specific CD4+ or CD8+ T cells, and spike- and receptor-binding domain (RBD)-specific memory B cells (Fig. 1). Evaluating the impact of vaccination on the course of the COVID-19 pandemic is challenging. However, recent calculations estimate that COVID-19 vaccines have saved millions of lives by evoking adaptive immune protection. This has been mainly achieved by launching two novel vaccine platforms during the pandemic: mRNA- and vector-based vaccines. While high vaccine efficacy (VE) was shown for mRNA-based vaccines, immune correlates mediating protection against SARS-CoV-2 infection, and severe disease remains elusive.

Although serological studies were provided before, the new study stands out in several aspects: It is the first that used a side-by-side comparison of four different vaccines—among them vaccines from three different vaccine platforms: two mRNA-based vaccines (Moderna mRNA-1273 and Pfizer/BioNTech BNT162b2), a viral vector-based (Janssen/J&J Ad26.COV2.S), and a recombinant spike-protein-based vaccine (Novavax NVX-CoV2373). The authors used comparable workflow and assays for sample preparation and analysis, e.g., a batch preparation of spike-protein-derived peptides, thus, avoiding cross-laboratory differences. Moreover, the authors simultaneously assessed multiple parameters from the same study participants, including an in-depth cellular subset analysis. This is the first longitudinal study that determined the kinetics of vaccine-specific immune memory.

All four vaccine groups were similar in age, gender, and race/ethnicity distribution, with 30 participants each (12 for NVX-CoV2373). Five different time points were chosen for analyses: pre-vaccination, around days 15, 45, 105, and 185. For NVX-CoV2373, only two time points—days 120 and 185—were assessed. In addition, the immune memory elicited by the vaccines after six months was compared to those of natural infection. Of note, all four vaccines performed equal or superior to natural infection for all measured anti-spike humoral and cellular responses. In contrast, Ad26.COV2.S vaccinees showed lower numbers of responders, a significantly lower percentage of these subpopulations, and lower CD4+ cytotoxic lymphocyte percentages. In addition to differences in their mode of action, application characteristics can also be responsible for such variations, e.g., single dose application in Ad26.COV2.S. Heterologous booster application could be a potential strategy here since they have been shown to elicit immune responses that combine specific effects of various vaccines.

Zhang and colleagues also determined the kinetics of spike-specific CD8+ cells, again focusing on AIM and ICS profiles. In contrast to CD4+ cells, only a maximum number of 83% and 87% responders, respectively, could be detected for mRNA-1273 and an even lower rate for the other three vaccines (BNT162b2 > Ad26.COV2.S > NVX-CoV2373). Overall, memory CD8+ T cell frequencies and response rates were similar between mRNA-1273, BNT162b2, and Ad26.COV2.S immunizations. However, multifunctional spike-specific memory CD8+ cells were more common in mRNA-1273 recipients. There were only minimal multifunctional cells in NVX-CoV2373 vaccinees, which was expected for a protein-based vaccine. Of note, the study showed that individual T-cell kinetics fluctuate much more than antibody responses.

Finally, the authors characterized spike- and RBD-specific memory B cells, detected in 100% of vaccinees after 6 months. The relative amount of activated memory B cells was significantly higher for the two mRNA-based vaccines. Memory B cells did not show the same kinetics as antibody responses. Of note, while antibody titers waned over time, the frequency of spike-specific memory B cells increased and, comparable to T cell compartments, remained stable. Of note, spike-specific CXCR3+ memory B cells were significantly higher, specifically in Ad26.COV2.S vaccinees at day 105 and after 6 months, similar to infection. CXCR3+ memory B cells have been implicated as important

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modulators of mucosal immunity. However, their role in mucosal recruitment in the context of the current pandemic needs to be determined. Since ancient SARS-CoV-2 spike-derived peptides were used in this study, data might substantially differ for novel virus variants. It would be interesting to perform such a thorough longitudinal study in other cohorts, such as children or older people. Nevertheless, this study will stay unique since naive study participants might be impossible to recruit.

In conclusion, Zhang and colleagues underline the high immunogenicity of mRNA vaccines compared to other vaccine platforms by describing more reactive immune responses within the adaptive immune system. More importantly, the novel data will provide a basis to assess and guide future approaches to adapt and improve existing vaccine platforms.

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