Study details robust T-cell response to mRNA COVID-19 vaccines, a more durable source of protection

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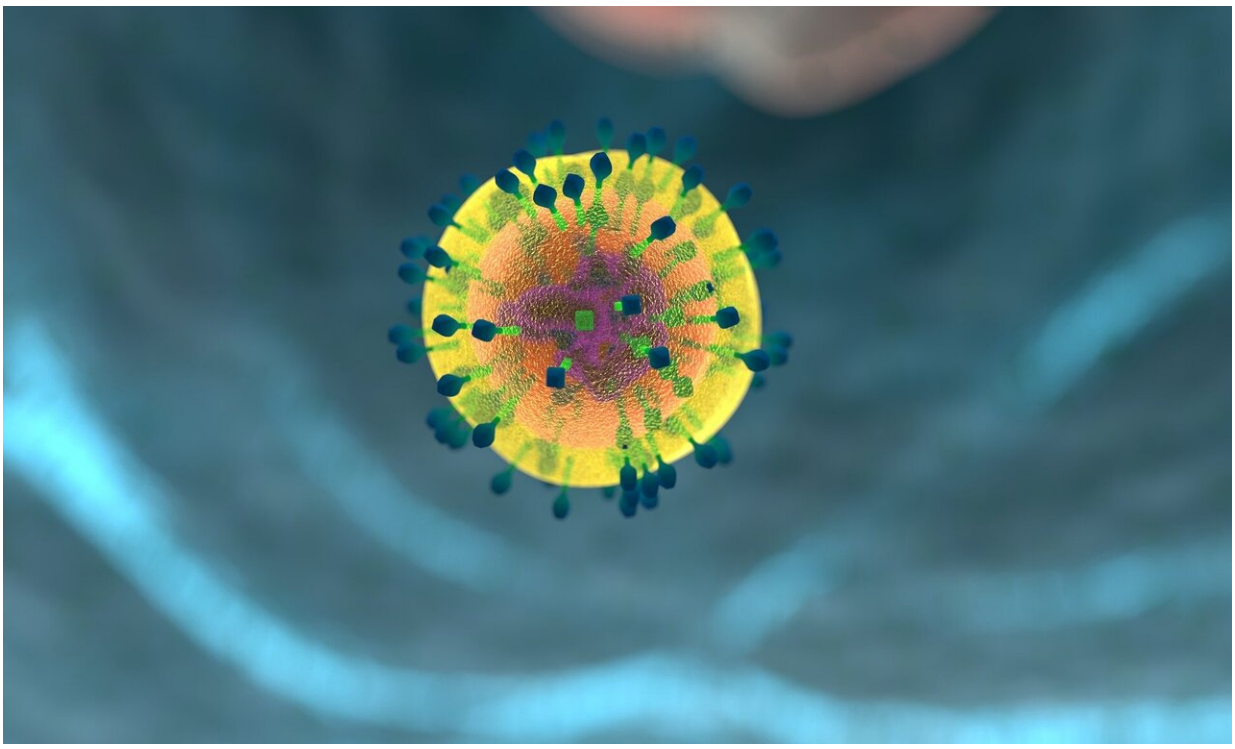

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Messenger-RNA (mRNA) vaccines against the coronavirus that causes COVID-19 provoke a swift and strong response by the immune system's T cells—the heavy armor of the immune system—according to a study

from researchers in the Perelman School of Medicine at the University of Pennsylvania. Although recent studies of vaccines tend to focus on the antibody response, the T-cell response is also an important and potentially more durable source of protection—yet little has been reported so far on the T-cell response to COVID-19 vaccines.

In the new study, which appears in the journal *Immunity*, the Penn Medicine researchers analyzed the T-cell responses in 47 healthy people who received two doses of the Moderna and Pfizer/BioNTech mRNA vaccines.

The results reveal the complex details of how the T-cell response to these vaccines unfolds, and underline the importance of a second dose for people with no history of COVID-19. The findings showed, however, that in people with a history of COVID-19, the T-cell response was already robust after the first vaccine dose, with no significant increase after the second dose, which may have implications for potential future booster shots.

"Our findings underscore the fact that we need to look at T cells, not just antibodies, if we want a complete picture of the vaccine response for those who have not had COIVD-19 and for those who have recovered from the disease," said senior author E. John Wherry, PhD, chair of the department of Systems Pharmacology and Translational Therapeutics and director of the Penn Institute of Immunology in the Perelman School of Medicine at the University of Pennsylvania.

Antibodies are forked proteins secreted by immune cells called B cells; they can bind tightly to specific viral structures on virus-infected cells. T cells also have antibody-like receptors that enable tight binding to specific viral structures, but they are whole cells, some of which—called "killer" T-cells—are capable of directly killing virus-infected cells they encounter. T cells therefore have long been regarded as the heavy armor

of the immune system. Their responses to vaccines are harder to study than antibody responses, though, so less is known about those responses, including in the case of COVID-19.

Researchers examined in detail the T-cell responses to mRNA vaccination in 36 healthy people who had no history of COVID-19, and 11 people who had previously recovered from COVID-19.

In the group of participants who did not previously have COVID-19, they found that the first vaccine dose elicited a rapid and strong response from helper T cells called CD4 T cells—some of which help marshal an antibody response, while others stimulate the proliferation of CD8 killer T cells. The strengths of those initial CD4 T cell responses generally predicted the later strengths of antibody and killer T-cell responses. However, the killer T cells tended not to appear in large numbers until after the second vaccine dose—confirming the importance of that second dose for people with no COVID-19 history.

By contrast, in the prior-COVID-19 group, helper and killer T cells specific for the COVID-19 coronavirus were already substantially present before the first dose. After that first dose, T cell numbers rose somewhat, but did not significantly increase after the second dose.

"For people who haven't had COVID-19, the first dose powerfully primes the pump, and the second dose turns on the whole engine—but having had COVID-19 is like having had that first vaccine dose already," Wherry said. "It is important to point out, however, that a complete understanding of the relative importance of these T cell responses, compared to antibody, in protection from future infections will require larger clinical studies."

The results also showed that the T-cell response in the weeks after mRNA vaccination includes T-cell types normally elicited by natural

infection—and in general, natural viral infection is known to be capable of inducing T-cell protection that lasts years and even decades.

"We need to do follow-up studies to confirm the longevity of the T-cell response to vaccination, but our results here support the idea that that response can be long-lasting," Wherry said.

More information: Mark M. Painter et al, Rapid induction of antigen-specific CD4+ T cells is associated with coordinated humoral and cellular immune responses to SARS-CoV-2 mRNA vaccination, *Immunity* (2021). DOI: 10.1016/j.immuni.2021.08.001

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