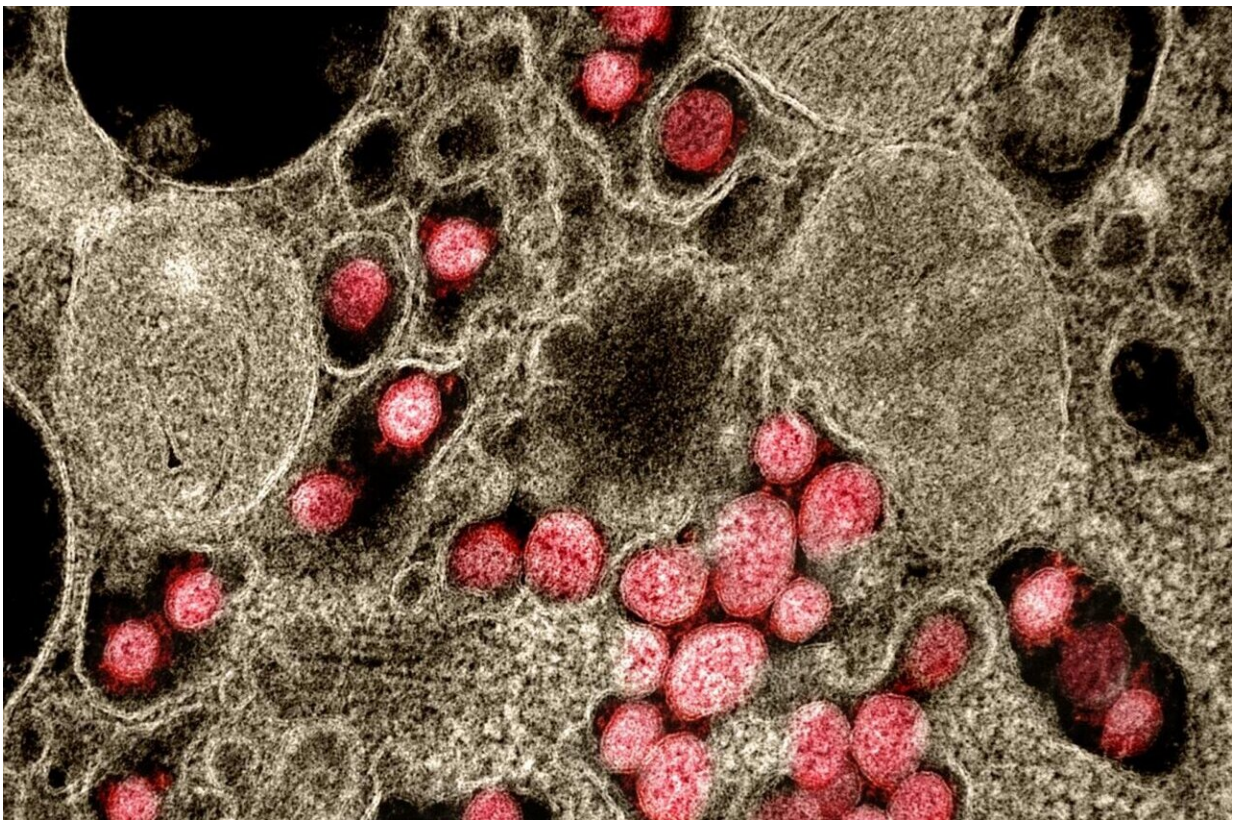


T cell response not critical for immune memory to SARS-CoV-2 or recovery from COVID-19

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Transmission electron micrograph of SARS-CoV-2 virus particles isolated from a patient. Credit: NIAID

New research conducted in monkeys reveals that T cells are not critical

for the recovery of primates from acute COVID-19 infections. T cell depletion does not induce severe disease, and T cells do not account for the natural resistance of rhesus macaques to severe COVID-19. Furthermore, strongly T cell-depleted macaques still develop potent memory responses to a second infection.

The findings, published in the *mBio*, an open-access journal of the American Society for Microbiology, have implications for the development of second-generation vaccines and therapeutics.

"We started this study early in the pandemic, trying to figure out how to make a good model to study the disease in humans using animals. The monkeys turned out to be more resistant to the disease than we expected, so we wanted to try to figure out why that was and try to gain some insights into the disease in humans as well," said lead study author Kim Hasenkrug, Ph.D., senior investigator in the Laboratory of Persistent Viral Diseases, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases, National Institutes of Health, in Hamilton, Montana. "We now know that the antibody response is the most critical response for protection by vaccination, not the T cell response."

In the new study, the researchers used classic reagents known to deplete CD4+ and CD8+ T [cells](#) in rhesus macaques. While CD8+ T cells directly attack infected cells and kill them, CD4+ T cells are helper T cells that trigger the immune response by recognizing pathogens and secreting cytokines, small proteins, that signal other [immune cells](#) to act, including CD8+ T cells and antibody-producing B cells.

One week after depleting the macaques of CD4+ T cells, CD8+ T cells, or both at the same time, the researchers infected the animals with SARS-CoV-2. "We depleted, we infected them and then we continued the depletions during the first week of infection to make sure the animals

were well depleted. Then we studied their blood to see how they were responding in terms of their T cells and B cells," said Hasenkrug. For six weeks, the researchers studied nasal swabs and bronchoalveolar lavages to measure virus in the nose, mouth and lungs, and rectal swabs to see if the gut was shedding virus. After six weeks, the researchers re-challenged the monkeys with SARS-CoV-2 and they repeated their collection of virus and blood samples, which allowed the researchers to evaluate immune memory responses. "If there is a memory response, you get a much quicker immune response and control of the virus. That is how vaccinations work. Once your body has seen a viral pathogen, the next time it sees it, you can get a much faster and stronger immune response," said Dr. Hasenkrug.

The researchers found that the monkeys were able to mount a good memory response against the virus regardless of T cell depletion. "We found we got really good memory responses regardless of whether we depleted T cells or not. Basically, we found very strong virus neutralizing antibodies, and they are the most important antibodies in controlling the infection. That was unexpected by most immunologists, virologists and vaccinologists," said Hasenkrug.

"The other thing that happens during a memory response is that antibodies mature, becoming, stronger and more potent at binding the viral pathogen. We saw indications of this through what's called "class switching," said Hasenkrug.

"Class switching" was also unexpected in these monkeys with depleted T cells. "We don't have a firm explanation as to why that happened, but we think it involves some sort of compensatory response, which you can see in our study. For example, when we depleted CD8+ T cells, we saw stronger CD4+ T cell or B cells responses in some animals. When the animals are missing something, they will try to make up for it by making more of something else."

Hasenkrug doesn't know why the T cells didn't turn out to be more important, but it is probably a good thing that they are not required, because then, people who fail to mount sufficient T cell responses still have opportunities to recover.

"This implies that the innate [immune response](#) is critical for initial control of the virus, rather than the adaptive immune responses we studied," said Hasenkrug.

Provided by American Society for Microbiology

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