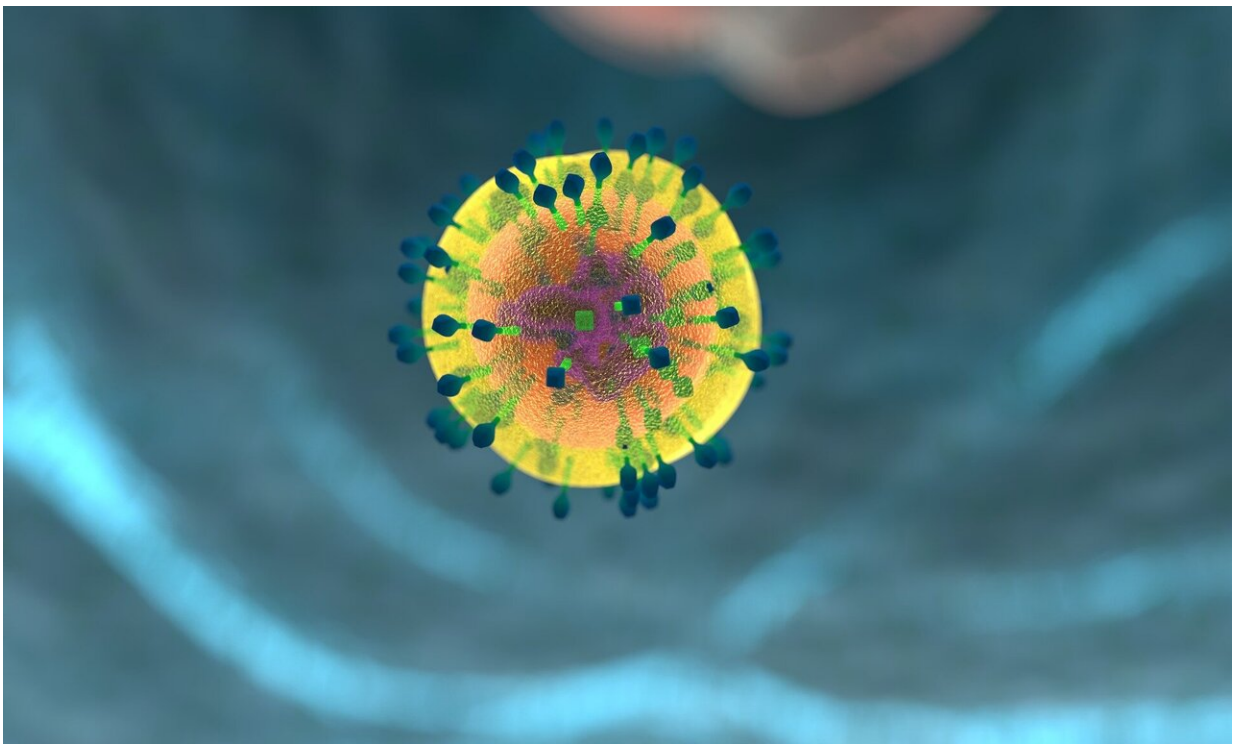
T-cell responses may help predict protection against SARS-CoV-2 infection in individuals with and without cancer

February 18 2022



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T-cell responses directed against the receptor-binding domain of the SARS-CoV-2 spike protein were associated with protection from SARS-CoV-2 infection in vaccinated individuals with or without cancer, with

lower T-cell responses observed in patients with blood cancers, according to results from a study published in *Cancer Discovery*.

The efficacy of COVID-19 vaccines has been typically measured by antibody levels, but this may not be a reliable metric, explained Laurence Zitvogel, MD, Ph.D., a professor at the Gustave Roussy Institute in Villejuif, France. "Humoral immune responses monitored by antibody titers are only transiently helpful and not well correlated with protection," she said. "Antibodies do not last more than a couple of weeks in a given individual post-infection or post-vaccination. Data show that antibodies against the SARS-CoV-2 spike protein have failed to predict actual protection against reinfection or breakthrough infection."

Measuring antibody levels is a way to monitor the presence and the activity of memory B cells, which are immune cells that produce antibodies and represent the first arm of adaptive immunity. T cells, another type of immune cell, represent the second arm of long-term immunity and can be amplified during infection to kill infected cells directly.

In this study, Zitvogel and colleagues examined whether T-cell responses could be a reliable indicator of protection against SARS-CoV-2 infection in healthy individuals and in patients with cancer who had not been exposed to the virus during the first wave of the pandemic. Using blood samples collected prior to infection with SARS-CoV-2, they performed various in vitro experiments to assess how the polarity and repertoire of T-cell responses correlated with susceptibility to infection with SARS-CoV-2 during subsequent waves of the pandemic.

T-cell polarity was assessed by identifying the types of cytokines—which are immune-stimulating proteins—released by the T cells of each individual when exposed to a viral antigen. The release of

the IL-2 cytokine was indicative of Th1 T cells, whereas the release of the IL-5 cytokine indicated Th2 T cells. Zitvogel and colleagues examined the makeup of each individual's T-cell pool to determine the proportion of Th1 and Th2 T cells.

They found pre-existing SARS-CoV-2-specific T cell responses in about 20-25 percent of the population, both in healthy individuals and in cancer patients. In addition, they observed that the types of cytokines released by memory T cells were associated with protection against SARS-CoV-2 infection. An imbalance between the IL-2 and IL-5 cytokines was associated with a higher susceptibility to SARS-CoV-2 infection, with an IL-2/IL-5 ratio less than 1 predicting infection, regardless of cancer status. This suggests that the relative levels of cytokines released by T cells may provide insight into susceptibility to SARS-CoV-2 infection, explained Zitvogel.

Further analysis revealed that T cells from individuals who had developed a primary infection, breakthrough infection post-vaccination, or reinfection with SARS-CoV-2 did not react to the receptor-binding domain of the spike protein, despite having immune responses against other regions of the viral genome. Zitvogel and colleagues proposed that the lack of reactivity to the spike receptor-binding domain may have made these individuals more susceptible to infection. Additionally, Zitvogel proposed that T-cell reactivity to the receptor-binding domain could even drive evolution of the spike protein, potentially contributing to the emergence of new viral variants.

Zitvogel and colleagues also examined post-vaccination T-cell responses in healthy individuals and in patients with solid or blood cancers. They found that post-vaccination T-cell responses varied among these populations, with patients with blood cancers having significantly lower responses than patients with solid tumors and cancer-free individuals. Ten percent of patients with blood cancers had T cells that were reactive

to the receptor-binding domain of the spike protein, compared with 49 percent of cancer-free individuals and 34 percent of patients with solid tumors.

The researchers observed that vaccine-induced T-cell responses against the original, wild-type sequence of the spike receptor-binding domain were poorly cross-reactive against the receptor-binding domain of the alpha, beta, and delta viral variants. "This may explain why the omicron variant of SARS-CoV-2 is currently spreading among the vaccinees," said Zitvogel. "The available vaccines were developed against the original sequence of the receptor-binding domain and not against the mutated sequences found in the variants."

Together, the results of this study indicate that both the polarity and the specificity of T-cell immune responses may be involved in protection against SARS-CoV-2 infection, concluded Zitvogel. "Our data suggest that there should be a greater focus on monitoring long-term T-cell responses rather than antibody titers, which are only reliable for a short time after vaccination."

Furthermore, Zitvogel noted that antibody titers and T-cell responses against the spike receptor-binding domain from current and emerging variants of concern should be monitored, rather than those against the original strain of the virus. Given the low T-cell responses after vaccination in patients with blood cancers, Zitvogel added that booster vaccinations should be strongly encouraged for these patients.

In addition, she noted that the results of this study could inform vaccine development against emerging variants of SARS-CoV-2. "For the greatest efficacy, the next generation of vaccines should elicit T-cell responses against the receptor-binding domain of the spike protein of emerging viral variants," Zitvogel said.

A limitation of the study is that it only examined immune responses from blood and may have missed potential impacts of mucosal immunity. An additional limitation is that researchers did not measure T-cell responses against non-structural viral proteins. Third, researchers employed cross-sectional comparisons among various patient categories instead of conducting a longitudinal paired follow-up after vaccination.

More information: The polarity and specificity of antiviral T lymphocyte responses determine susceptibility to SARS-CoV-2 infection in cancer patients and healthy individuals, *Cancer Discovery* (2022).

Provided by American Association for Cancer Research