Studies reveal key clues about COVID-19 immunity, immune recall

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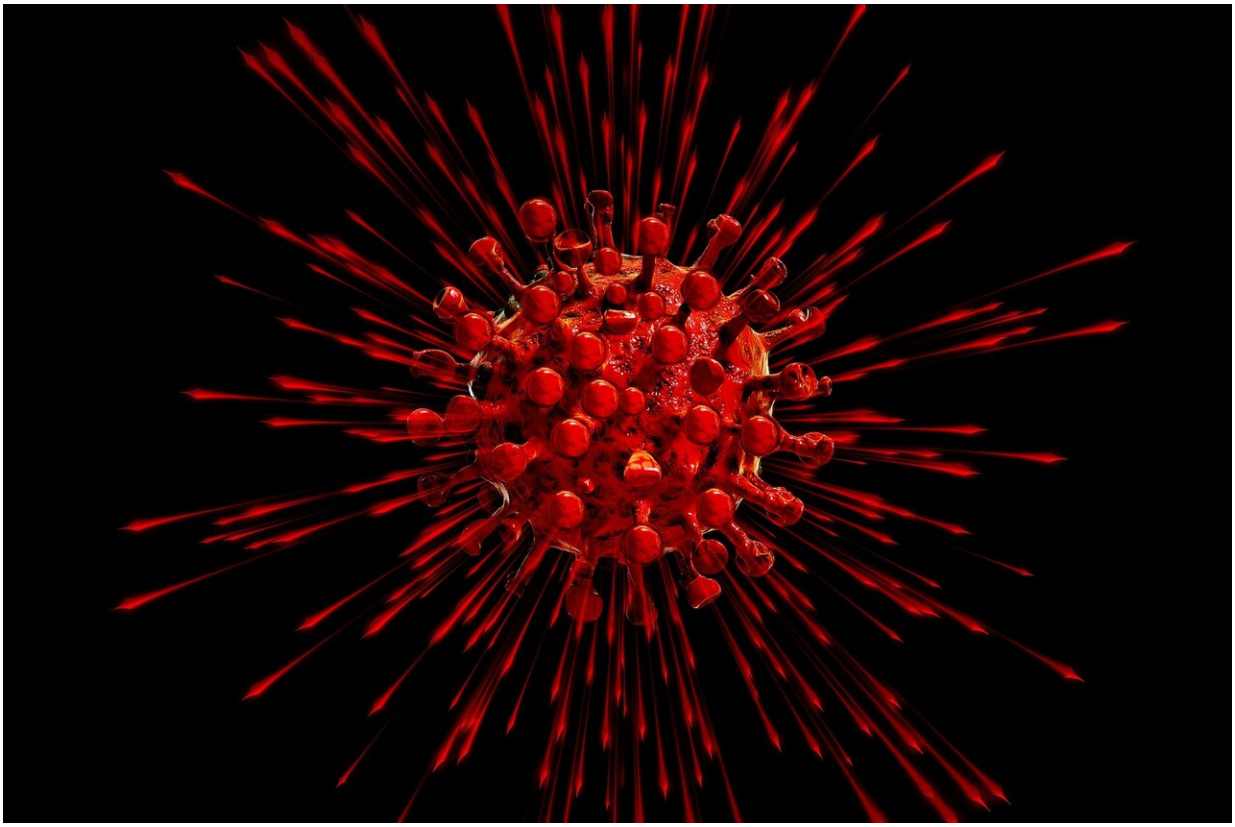

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How does the immune system remember and recognize viral invaders it has encountered in the past? A trio of newly published studies of people infected with SARS-CoV-2, vaccinated against the virus, or both are

providing tantalizing new clues about the factors that influence the speed and magnitude of the immune system's response to subsequent infection with variants of SARS-CoV-2.

These insights could help researchers work backward to further improve vaccines, with the ultimate goal of creating either a multi-variant vaccine that could shield people from multiple strains or even a pan-coronavirus vaccine that could provide protection against variants that have yet to emerge.

The three studies, published in *Science Immunology* and led by investigators at Brigham and Women's Hospital, Harvard Medical School, Massachusetts General Hospital, and the Ragon Institute of MGH, MIT and Harvard, provide intriguing answers about how long COVID-19 immunity lasts and the nature of immune recall after infection, vaccination or both.

"If we want to ask more of our immune system, we need to know what it is capable of," said Duane Wesemann, associate professor of immunology HMS and a researcher at the Brigham's Division of Allergy and Clinical Immunology. Wesemann is one of the senior authors on two of the papers and a co-author on the third.

"Our findings suggest that there are differences between people—some people have antibody responses that are relatively more sustained with greater breadth than others, and that may contribute to greater protection against future infection," he added. "If we can understand and tap into what gives some people an immunological edge, we may be able to coax the immune system through improved vaccine strategies to give a little more."

In one study, Wesemann and colleagues looked at immunity after infection with the original strain of the SARS-CoV-2, first identified in

Wuhan, China. The team assessed 73 antibodies made in response to infection with the ancestral strain to determine which, if any, were effective against five variants—Alpha, Beta, Gamma, Delta and Omicron. They found that certain antibodies generated from infection with the original strain could neutralize variants of concern—results that confirm why vaccines formulated against the original strain can still provide protection against variants.

Using sophisticated imaging techniques, the researchers were able to track how the shapeshifting structure of the mutating virus engages with the immune system. They pinpointed mutation-prone sites of the viral spike protein that the pathogen uses to invade human cells, and to visualize how these sites interact with sites on antibodies that neutralize the virus and prevent it from entering cells.

In a second paper, investigators looked at immune recall—the process of summoning up memory cells into action to fight repeat invasions with the same pathogen. The team analyzed the immune system's response after infection, vaccination and boosting by studying blood samples from individuals with different medical trajectories—those who had recovered from SARS-CoV-2 infection but were not vaccinated, those who recovered from infection and were then vaccinated against COVID-19, or those who were never infected but had been vaccinated and boosted. The team found evidence that people who had been infected and vaccinated as well as people who had been vaccinated and boosted could mount a strong and broad response across variants, including Omicron. In addition, the researchers found evidence suggesting that memory of prior infection with common cold coronaviruses—mild viruses that circulated before SARS-CoV-2—might be responsible for the robust, sustained immune response in a small subset of unvaccinated individuals who recover from COVID-19. These individuals, known as "sustainers," experience swift resolution of COVID-19 symptoms and have a prolonged, sustained

antibody response.

"We're very excited about this idea that some people sustain their antibodies and have memory B cells that can react across variants—it raises some interesting possibilities as we think about a pan-coronavirus vaccine," said Wesemann.

In a third study led by Andrew Luster, MD, Ph.D., and James Moon, Ph.D., both of the Center for Immunology and Inflammatory Diseases and Division of Rheumatology, Allergy and Immunology at MGH, investigators sought to better understand the role of $CD4^+$ T cells in COVID-19 immunity by directly identifying those that recognize SARS-CoV-2. Analyzing blood samples from patients who had recovered from infection during the first wave of the pandemic in Boston, they found that certain $CD4^+$ T cell subsets—circulating T follicular helper (Tfh) cells and T helper-1 (Th1) cells—were more common in individuals who had milder disease and did not require hospitalization. This cellular response appeared to persist for several months, potentially giving the immune system an advantage for subsequent exposure to SARS-CoV-2, including variants. In addition, T follicular helper cells specific for SARS-CoV-2 were found to be more common in the same group of antibody "sustainers" observed in the Wesemann study, suggesting a link between these T cells and more prolonged antibody responses.

"Our study demonstrates that the quality of the $CD4^+$ T cell response to SARS-CoV-2 was better in patients with less severe infections, and that this was reflected by the presence of sustained antibodies. This supports the general immunological theory that optimal antibody responses require robust $CD4^+$ T cell help and that vaccines should be designed to also maximize responses by this component of the adaptive immune system," said Luster.

Wesemann, Luster, Moon and their collaborators are continuing to

analyze samples from people who have been infected with or vaccinated against COVID-19 to identify immunological features that may confer the broadest possible immunity against coronaviruses and variants.

More information: Ian W. Windsor et al, Antibodies induced by ancestral SARS-CoV-2 strain that cross-neutralize variants from Alpha to Omicron BA.1, *Science Immunology* (2022). DOI: 10.1126/sciimmunol.abo3425

Yuezhou Chen et al, Immune recall improves antibody durability and breadth to SARS-CoV-2 variants, *Science Immunology* (2022). DOI: 10.1126/sciimmunol.abp8328

Ryan W. Nelson et al, SARS-CoV-2 epitope-specific CD4 + memory T cell responses across COVID-19 disease severity and antibody durability, *Science Immunology* (2022). DOI: 10.1126/sciimmunol.abl9464

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