Your Immune System Evolves to Fight Coronavirus Variants

Antibodies can change to counter new forms of the shape-shifting virus, research hints

Monique Brouillette March 31, 2021

Credit: Jordan Siemens *Getty Images*

A lot of worry has been triggered by discoveries that variants of the pandemic-causing coronavirus can be more infectious than the original. But now scientists are starting to find some signs of hope on the human side of

this microbe-host interaction. By studying the blood of COVID survivors and people who have been vaccinated, immunologists are learning that some of our immune system cells—which remember past infections and react to them—might have their own abilities to change, countering mutations in the virus. What this means, scientists think, is that the immune system might have evolved its own way of dealing with variants.

"Essentially, the immune system is trying to get ahead of the virus," says Michel Nussenzweig, an immunologist at the Rockefeller University, who conducted some recent studies that tracked this phenomenon. The emerging idea is that the body maintains reserve armies of antibody-producing cells in addition to the original cells that responded to the initial invasion by SARS-CoV-2, the virus that causes COVID. Over time some reserve cells mutate and produce antibodies that are better able to recognize new viral versions. "It's really elegant mechanism that that we've evolved, basically, to be able to handle things like variants," says Marion Pepper, an immunologist at the University of Washington, who was not involved in Nussenzweig's research. Whether there are enough of these cells, and their antibodies, to confer protection against a shape-shifting SARS-CoV-2 is still being figured out.

Last April, when the pandemic was reaching its first peak in New York City, Nussenzweig and his colleagues sprang into action and began collecting the blood of COVID

survivors. There were disturbing early reports of reinfection and waning antibodies, and the scientists wanted to understand how long the immune system could sustain its ability to respond to the novel threat. They took blood samples from people who had been hit by SARS-CoV-2 one month after the infection and then again six months later. What the scientists found was somewhat encouraging. Blood collected at the later date did have lower levels of circulating antibodies, but that made sense because the infection had cleared. And levels of the cells that make antibodies, called memory B cells, remained constant or even increased in some people over time. After an infection, these cells hang around in the body's lymph nodes and maintain the ability to recognize the virus. If a person gets infected a second time, memory B cells activate, quickly produce antibodies and block the virus from creating a second serious infection.

In a follow-up test, the Rockefeller scientists cloned these reserve B cells and tested their antibodies against a version of SARS-CoV-2 designed to look like one of the new variants. (The experimental virus lacked the ability to replicate, which made it safer to use in the lab.) This virus had been genetically engineered to have specific mutations in its spike protein, the part of the coronavirus that attaches to human cells. The mutations mimicked a few of the ones currently found in the variants of concern. When researchers tested the reserve cells against this

mutated virus, they saw some cells produced antibodies that glommed on to the mutated spike proteins—even though these spikes were different than those on the original virus. What this means is that the antibodies had changed over time to recognize different viral features. The research was published in *Nature* in January. "What the paper shows us is that, in fact, the immune response is evolving—that there's some dynamic changes over this period of time," Nussenzweig says.

Recently he and his team tested the six-month-old B cell clones against other engineered viruses that more closely mimic variants of concern, such as B.1.351. This variant contains a set of mutations called K417N, E484K and N501Y. In a preliminary study that has not yet undergone peer review and was posted online on March 8, the researchers found a subset of antibodies produced by these cells showed increased abilities to recognize and block these highly mutated variants.

This phenomenon can be explained by a process called "somatic hypermutation." It is one of the reasons that your immune system can make up to one quintillion distinct antibodies despite the human genome only having 20,000 or so genes. For months and years after an infection, memory B cells hang out in the lymph nodes, and their genes that code for antibodies acquire mutations. The mutations result in a more diverse array of antibodies with slightly different configurations. Cells that make antibodies that are very good at neutralizing the original

virus become the immune system's main line of defense. But cells that make antibodies with slightly different shapes, ones that do not grip the invading pathogen so firmly, are kept around, too.

That kind of hoarding has long mystified immunologists. Why would your body hold on to second-rate B cells? Perhaps, Pepper says, it does so because the cells might be good at responding to closely related viral versions that could pop up. Viruses have been infecting hosts for millions of years, and variants are not a new phenomenon. To keep hosts alive, the immune system must have evolved a mechanism to keep up, and these corps of reserves—some producing antibodies that could be a better match for new viral versions—came in handy. Basically, in a struggle for life and death with a virus, it is good to have backups. Pepper has published results showing that people who recovered from COVID had evidence of increased mutation in their memory B cells after only three months.

Immunologist Shane Crotty of the La Jolla Institute for Immunology says the backup idea is a good one. "Memory B cells are your immune system's attempt to make variants of its own as a countermeasure for potential viral variants in the future," he says. In a study published in *Science* in February, Crotty and his colleagues showed that patients retained various degrees of immune reactions to the virus five to eight months after infection—and concluded that most people could have a durable

response. “Your immune system is creating a library of memory B cells that aren’t all the same so that they can potentially recognize things that aren’t identical,” Crotty says.

But are there enough of these reserve antibodies, and are they good enough at neutralizing new viral versions to protect us? The answer to this question is still unknown, but it may be a matter of timing. Laura Walker, an immunologist at Adagio Therapeutics in Waltham, Mass., recently published a study in *Science Immunology* showing about a 10-fold reduction in the neutralizing ability of circulating antibodies against the virus after five months. But like Nussenzweig’s team, she and her colleagues found there was a sustained memory B cell population. Walker’s group cloned a variety of memory B cells and tested their antibodies against the variants. She says the variants were able to evade many antibodies, but about 30 percent stuck to the new virus particles. This means that a new infection may still be able to get started before the B cell reserves ramp up their production of antibodies. But even though the virus will have a head start, and infection could occur, the B cell response could still limit it and provide protection against severe disease. “The question is whether there will be enough, and we don’t know that yet,” Walker says. But “I would expect that your antibody titers, even if low, should still prevent the worst of it, like hospitalization or death.”

Escape from serious COVID could also be aided by another line of immune system defenses: T cells. These cells do not go after pathogens directly, but a subclass of them seek out infected cells and destroy them. Immunologists say that T cells have a somewhat broad-brush approach to recognizing pathogens—they respond to fragments from various parts of the virus, unlike the highly spike-specific nature of B cells—and this makes them less likely to be fooled by variant shape-shifting. In a study released on March 1, which has not yet gone through peer review, Crotty and Alessandro Sette, also at the La Jolla Institute for Immunology, tested T cells from people who had been exposed to SARS-CoV-2, either naturally or through vaccination. Their T cell response was not dampened by the variants. Sette says that while a weakened B cell response could let the virus get a foothold, it is plausible that T cell activity will keep it from running rampant through the body. “In a scenario where infection is not prevented, you could have a T cell response that could modulate the severity of the infection,” he says.

In the coming months researchers will continue to track these cells, using newly developed gene sequencing tools and cloning techniques to follow our responses to variants and new vaccines. These methods are providing immunologists with new abilities to monitor the spectrum of a population’s reactions to a widespread infection in real time. “We have the ability to study and describe the

immune system in a way we have never been able to do before. It's an amazing window into the human immune response," Nussenzweig says.

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