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Immunity to the coronavirus remains a mystery. Scientists are trying to crack the case

Partially Politics (https://partiallypolitics.com/author/timkaelin/)

6 July 2020, 2:28 PM 1

Scientists stress that just because someone has recovered from Covid-19 and produced antibodies to the coronavirus does not mean they are protected from contracting it a second time. No one's yet proven that.

That, then, leaves open the question: What does immunity look like?

(https://pro.manwardpress.com/m/1561037)

Experts anticipate an initial coronavirus infection will lend people some level of immunity for some amount of time. But they still don't know what potpourri of antibodies, cells, and other markers in a person's blood will signify that protection. And determining those "correlates of protection" is crucial both so individuals can know if they are again at risk, and so researchers can understand how well potential vaccines work, how long they last, and how to accelerate their development.

"What you would like is to have some blood measure that serves as a correlate of that protective efficacy or immunity," said Sarah Fortune, the chair of immunology and infectious diseases at Harvard's T.H. Chan School of Public Health. "Which sounds like it's simple, but it's much more complicated than you'd think."

Knowing the correlates of protection is different from knowing the mechanism of protection. Immunity is a Rube Goldberg machine, a choreography of different proteins and cells that results in the body fending off a pathogen before it can gain a toehold. The scheme varies from pathogen to pathogen.

Correlates of protection, rather, are signals that someone is protected, the way glancing at a formidable offensive line makes clear that it can hold off the pass rush. They could include the presence of — as well as the levels of — certain types of antibodies, immune cells, or proteins that act like messengers in the immune system.

Scientists don't need to fully understand the correlates to make progress on vaccines. Already, researchers have launched a number of clinical trials for vaccine candidates to test whether they are safe and effective against Covid-19, the disease caused by the coronavirus. But scientists are relying on clues from how our bodies protect themselves from other viruses, including the other disease-causing coronaviruses, to guide what kind of immune response vaccines should aim to induce.

"We don't formally need to know" the correlates of protection, said John Mascola, the director of the National Institutes of Health's Vaccine Research Center. "One can make the vaccine somewhat empirically, which means make it and test it, and in the old days that's how all the vaccines were made."

Now, vaccine research and determining the correlates of protection often take place at the same time, Mascola said. And with the coronavirus, vaccine developers "are taking advantage of the fact that we think we know what kind of antibody response to generate, and that's what the designs are based on."

After clinical trials confirm one vaccine's effectiveness, other immunizations that produce the same immune responses could be accelerated into use, Anthony Fauci, the head of the National Institute of Allergy and Infectious Diseases, recently told STAT.

"If one vaccine proves efficacy in a clinical trial and another vaccine is behind it but it's getting the same correlate of immunity, you could bridge data and facilitate the approval of the second and the third one based on the efficacy of the first one," Fauci said.

Experts stress that it's still key to test vaccines in large-scale clinical trials, and not solely approve them based on correlates of protection. Only clinical trials demonstrate whether a vaccine lowers the risk of infection in people or makes them less likely to get severely ill.

To study the correlates of protection, scientists are now peering into the blood of people who have recovered from Covid-19 to map the defenses the immune system put up when the virus attacked. In recent weeks, they've described the type of antibodies produced, finding that

they can have powerful effects against one of the virus' key proteins, and that almost all patients who had the disease, even those who had mild infections, generated antibodies. Those are positive signs, given that a type of antibody, called a neutralizing antibody, is, in sufficient quantities, expected to offer some amount of protection for at least some amount of time. Scientists have also reported the rallying of immune cells, which can be involved in recognizing a virus and stopping it.

The thought is that the defenses the body mounted to vanquish the virus the first time provide clues to what is required to fend off a second attack.

To confirm that people who recover from Covid-19 are protected and to determine how long that lasts, scientists have to track people and see what happens to them if they encounter the virus again. That research often focuses on health care workers who are more likely to be exposed repeatedly. (Scientists can't ethically expose people to the virus again intentionally.)

But with animals, researchers can "challenge" those that are vaccinated or have had an initial infection to see if they can ward the virus off — which is what recent studies in monkeys demonstrated. Scientists found that the animals generated neutralizing antibodies after they first contracted the virus or when they were given experimental vaccines, and that the higher the level of the antibodies the monkeys had (the higher the "titer," in scientific parlance), the more protected they were against the pathogen when scientists sprayed a second dose into their noses.

"That is a suggestion that neutralizing antibodies to the virus can protect" against reinfection, said Dan Barouch, the director of Beth Israel Deaconess Medical Center's Center for Virology and Vaccine Research, who steered that research.

If that finding extends to people, "we will start to be able to use that as a predictor of success," Barouch said. That is, in experiments with vaccine candidates, researchers can start to see what levels of neutralizing antibodies they are producing, and prioritize those that seem to generate more promising responses.

Everything we know about coronavirus immunity and antibodies — and plenty we still don't

With some diseases, researchers also run "human challenge trials" of vaccines — in which volunteers are given an experimental vaccine and then exposed to the virus — in an attempt to speed up the process of testing them. Scientists are divided over the ethics of such trials for the coronavirus, but those who are supportive say one benefit could be establishing the correlates of protection, indicating which parts of the immune system need to be active to insulate someone from the virus.

Scientists often home in on neutralizing antibodies as correlates, but there can be other markers as well. They include other types of antibodies, like binding antibodies; immune cells like T cells and B cells; and cytokines — small proteins released by immune cells that serve as messengers. In the monkey study, for example, Barouch and colleagues also found an association between protection and the level of another type of antibody, though it wasn't as strong as the correlation between protection and neutralizing antibodies.

"There are a whole bunch of other things that people look at for correlates of protection," said virologist Angela Rasmussen of Columbia University.

One challenge is that people respond differently to infections; some studies, for example, have found people who recovered from Covid-19 actually generated low levels of antibodies. But because the immune system is so complex, having low levels of antibodies does not necessarily mean that a person won't be safeguarded. All that can make it harder to define exactly what immunity looks like.

"Some people who've had this have not had high antibody titers or have had low antibody titers," said Anna Durbin, a vaccine researcher at Johns Hopkins University. "We still don't know what's going to happen to them if they're re-exposed."

Covid-19 'immunity certificates': practical and ethical conundrums

Durbin also noted that what's happening with immune cells and antibodies in someone's blood may not mean the cells in the upper airway — which the coronavirus targets — are similarly defended.

Certain antibodies in the blood might stave off severe illness, but they won't necessarily be able to fully prevent the virus from reinfecting cells in the nose and throat.

Because of the difficulties of stopping upper respiratory infections, scientists are already anticipating that Covid-19 vaccines may not provide complete protection — called sterilizing immunity — but will rather reduce the risk of contracting the virus and of getting critically sick.

"I am not convinced we're going to have a singular, absolute correlate of protection," Durbin said.

'We don't actually have that answer yet': WHO clarifies comments on asymptomatic spread of Covid-19

With Covid-19, immunity — whether from an infection or a vaccine — is expected to wane over perhaps a few years; that is what happens with the four human coronaviruses that cause colds. If that pattern extends to this virus, people will gradually become more susceptible to the virus after some amount of time (though they may be less likely to get a severe case). Tracking the levels of the different correlates could provide clues to how long immunity lasts, and when a person becomes vulnerable again. It could also indicate when people might need another dose of the vaccine.

"When we're trying to evaluate an immune response, we don't only want to see we engage the proper immune responses for protection," said Scott Hale, a University of Utah immunologist. "We also want to make sure there's some form of long-lasting immunity in case you're exposed to the pathogen in a year or five years or 10 years."

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