How B cells recognize new variants of SARS-CoV-2

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The first author of the study, Dr Matthias Bruhn, in the lab Credit: TWINCORE/Grabowski

B cells are part of the immune system's memory. Their memories of previous infections or vaccinations provide the template for antibodies

that have a protective effect the next time they come into contact with a pathogen.

Researchers at TWINCORE, Center for Clinical and Experimental Infection Research, have now been able to show that the combination of infection and subsequent vaccination in the case of the SARS-CoV-2 coronavirus even protects against future variants of the virus by the memory cells virtually predicting the future. The team describes how this works in the *European Journal of Immunology*.

During the corona pandemic, the vaccination against SARS-CoV-2 did not offer optimal protection. However, a booster vaccination against the same variant or after another infection creates what is known as "hybrid immunity," which generates a much broader protective effect.

The TWINCORE team, in cooperation with scientists from the Hannover Medical School and the German Primate Center Göttingen, has now been able to show why this even protects against new virus variants with which the immune system had no previous contact, using samples from a patient.

The patient was additionally vaccinated against SARS-CoV-2 months after recovering from COVID-19, and his antibodies were also able to inactivate new variants of the virus in the laboratory.

"This effect is based on a step in antibody maturation called somatic hypermutation," says Dr. Matthias Bruhn, first author of the study and postdoctoral researcher at the Institute for Experimental Infection Research at TWINCORE. The B cell receptors change slightly due to individual somatic mutations that occur during the maturation of the antibodies. This diversification results in a mixture of different B cells.

"According to previous doctrine, we would have expected somatic

hypermutation to increase the affinity of the antibodies, in other words, their binding strength to the antigen increases," adds Bruhn.

The fact that mutated antibodies can now also recognize new, previously unknown virus variants that the body has not yet come into contact with, surprised the researchers.

"You might think that the memory cells could predict a future infection with a mutated virus," says Bruhn. But the B cells probably don't have any supernatural abilities. "We assume that this is a stochastic phenomenon," says Bruhn. A probability calculation, so to speak.

"The mutations do not occur in a targeted manner. Many variations do not bring any advantage, and cells that express such antibodies are sorted out during maturation." However, when many different B cells develop, there are always some that have a higher binding affinity for the antigen or, as observed here, can even bind completely new antigens. "In evolution, diversity is always a good thing," says Bruhn.

The findings are also consistent with experience from clinical practice. Monoclonal antibodies, some of which have been used to treat or prevent SARS-CoV-2 infections, lose their effectiveness even with the smallest changes in the virus, as they lack diversity. The WHO therefore no longer recommends usage of such products.

However, Matthias Bruhn originally wanted to research precisely the usability of monoclonal antibodies for the treatment and prevention of corona infections and had even received initial funding from the Federal Ministry of Education and Research (BMBF) as part of the GO-Bio initial program. Although this did not result in commercial utilization, it laid the foundation for the research work described here.

The researchers were able to gain important insights and now want to

investigate in more detail whether and how somatic hypermutation can be exploited. To do this, they want to select individual antibodies and determine their diversity. By making targeted changes, they could then achieve optimal adaptation to virus variants.

"The result would be a future-proof antibody product that is suitable for use in the clinic," says Bruhn. "But we are still at the very beginning."

More information: Matthias Bruhn et al, Diversification of the VH3-53 immunoglobulin gene segment by somatic hypermutation results in neutralization of SARS-CoV-2 virus variants, *European Journal of Immunology* (2024). DOI: 10.1002/eji.202451056

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