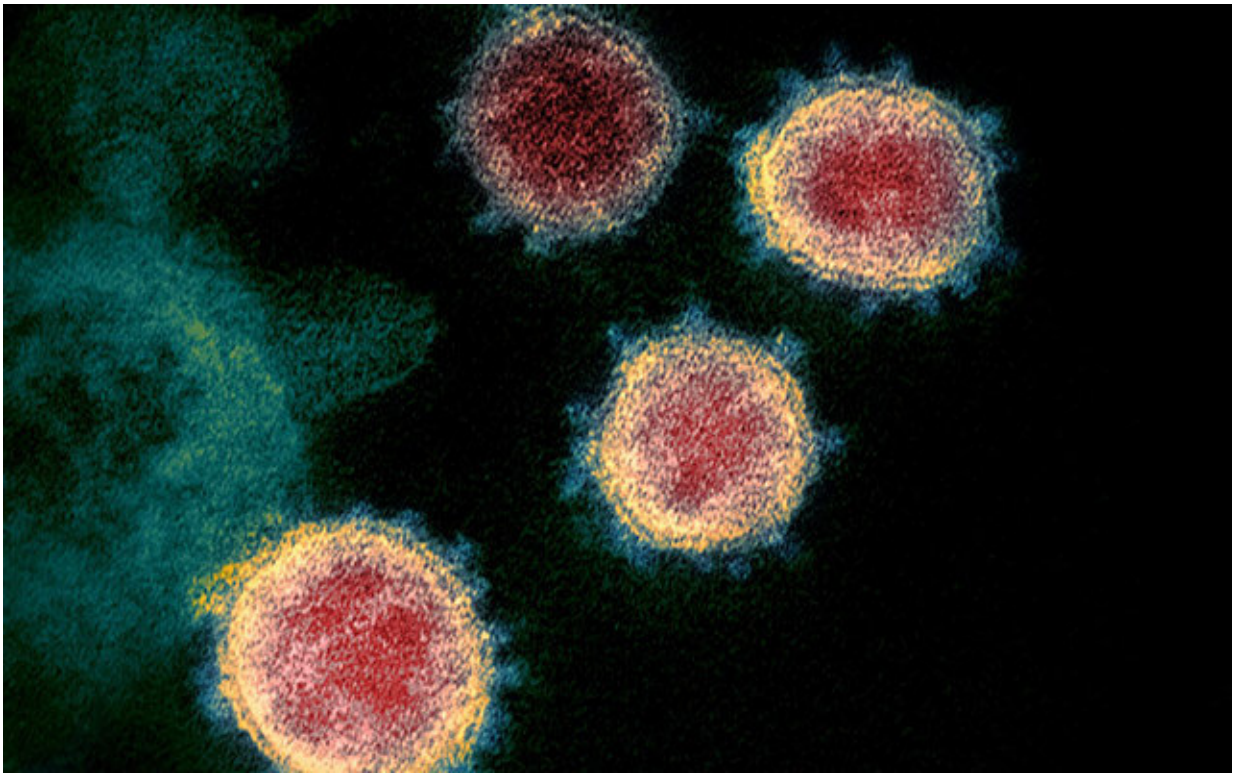
Coronaviruses do not readily induce cross-protective antibody responses

May 18 2020



A colorized scanning electron micrograph of the SARS-CoV-2 virus. Credit: NIAID

Patients infected with either severe acute respiratory syndrome coronavirus (SARS-CoV) or SARS-CoV-2 produce antibodies that bind to the other coronavirus, but the cross-reactive antibodies are not cross

protective, at least in cell-culture experiments, researchers report May 17 in the journal *Cell Reports*. It remains unclear whether such antibodies offer cross protection in the human body or potentiate disease. The findings suggest that more research is needed to identify parts of the virus that are critical for inducing a cross-protective immune response.

"Since coronavirus outbreaks are likely to continue to pose global health risks in the future, the possibility of developing a cross-protective vaccine against multiple coronaviruses has been considered," says co-senior study author Chris Mok of the University of Hong Kong. "Our findings, albeit limited at present, would suggest that broadly cross-neutralizing antibodies to coronaviruses might not be commonly produced by the human immune repertoire. Moving forward, monoclonal antibody discovery and characterization will be crucial to the development of a SARS-CoV-2 vaccine in the short-term, as well as a cross-protective coronavirus vaccine in the long term."

From late 2002 to 2003, more than 8,000 people worldwide became sick with severe acute respiratory syndrome (SARS), resulting in more than 700 deaths. The virus responsible for this outbreak, known as SARS-CoV, shares approximately 80% of its genomic nucleotide sequence identity with that of SARS-CoV-2, which causes coronavirus disease 2019 (COVID-19). The two coronaviruses also enter and infect cells the same way. During this process, the receptor-binding domain (RBD) of the spike (S) protein, which is located on the surface of the coronavirus, binds to a human cell receptor called angiotensin-converting enzyme 2, triggering viral fusion with the host cell.

Past studies have shown that protective antibodies against SARS-CoV bind to the RBD. But relatively little is known about the antibody response induced by SARS-CoV-2 infection. It is also unclear how infection with SARS-CoV influences the antibody response against SARS-CoV-2, and vice versa. Gaining insight into these questions could

guide the development of an effective vaccine for SARS-CoV-2 and shed light on whether such a vaccine would also cross-protect against similar viruses.

"There are related viruses still circulating in bats, and it is unclear whether any of these may also threaten human health in future," says co-senior study author Malik Peiris of the University of Hong Kong. "As such, whether infection by one of these viruses cross-protects against another is an important question."

To address this gap in knowledge, the researchers analyzed blood samples collected from 15 SARS-CoV-2-infected patients in Hong Kong between 2 and 22 days after the onset of symptoms. Compared to blood samples from healthy controls, the five samples collected from patients 11 days after symptom onset or later had antibodies capable of binding to the RBD and other parts of the S protein on both SARS-CoV-2 and SARS-CoV.

The researchers also analyzed blood samples collected from seven patients 3 to 6 months after infection with SARS-CoV. Compared to blood samples from healthy controls, those collected from patients had antibodies capable of binding to the RBD and other parts of the S protein on SARS-CoV-2. Taken together, these findings show that infection with one coronavirus induces the production of antibodies that can bind to both RBD and non-RBD regions of the S protein on the other coronavirus.

Using cell-culture experiments, the researchers next tested whether infection with SARS-CoV-2 induces SARS-CoV-2-specific neutralizing antibodies, which protect host cells by preventing the virus from interacting with them. All 11 blood samples collected 12 days or later after the onset of symptoms had neutralizing antibodies against SARS-CoV-2. But only one blood sample had cross-neutralizing antibodies

against SARS-CoV, and this response was very weak. Similarly, five blood samples from patients infected with SARS-CoV had neutralizing antibodies against this virus, but none could cross-neutralize SARS-CoV-2. Additional experiments in mice supported the findings from patients.

For now, the clinical implications remain unclear. One possibility is that cross-reactive, non-neutralizing antibodies offer cross protection against viruses in the body, even though they don't protect cultured cells. This phenomenon has been observed for other types of viruses. On the other hand, non-neutralizing antibodies against SARS-CoV-2 could enhance viral entry into cells and viral replication through a process called antibody-dependent enhancement of infection, which has been previously reported for SARS-CoV.

"Whether antibody-dependent enhancement plays a role in SARS-CoV-2 infection needs to be carefully examined in the future," says co-senior study author Ian Wilson of the Scripps Research Institute. "Addressing this question will be critical for developing a safe and effective universal coronavirus vaccine."

More information: Huibin Lv et al, Cross-reactive antibody response between SARS-CoV-2 and SARS-CoV infections, *Cell Reports* (2020). DOI: 10.1016/j.celrep.2020.107725

Provided by Cell Press