Beyond the spike: New antibody analysis predicts severe COVID-19 outcomes

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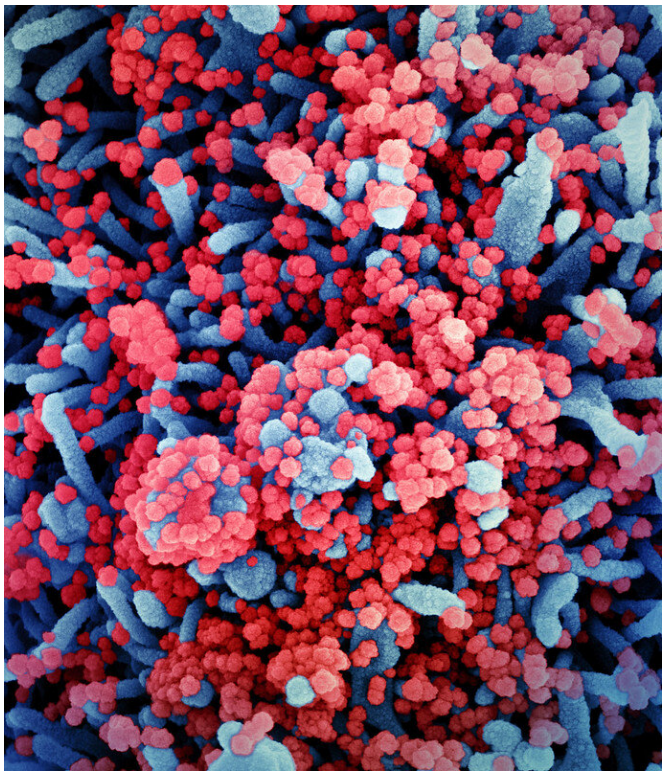

Colorized scanning electron micrograph of a cell (blue) heavily infected with SARS-CoV-2 virus particles (red), isolated from a patient sample. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID

Most research on immunity to the SARS-CoV-2 virus and COVID-19 vaccine development has focused on antibody responses to the spike protein and other viral surface proteins. But antibodies that recognize the virus's internal proteins could also be important for immunity and disease outcomes, according to a new study led by University of Pittsburgh, Georgia Institute of Technology and Emory University researchers.

In the study, online now in *Cell Reports*, the team performed the most comprehensive analysis to date of COVID-19 antibodies in a small set of patients with severe disease. They found that antibody profiles of internal viral proteins, including those conserved across coronaviruses, predicted which patients survived or died just as well as corresponding profiles for surface proteins, suggesting that targeting other parts of the virus beyond the spike protein could be important for enhancing COVID-19 vaccines and therapies.

"The novel aspect of this study is that we conducted very deep profiling of SARS-CoV-2 antibodies and looked at many different aspects of these antibodies," said co-senior author Jishnu Das, Ph.D., assistant professor of immunology and of computational and systems biology in Pitt's School of Medicine. "The whole world has been focused on the spike protein and the receptor binding domain, but this study is the first concrete evidence that specific antibodies against internal proteins are also positively associated with survival in severe COVID-19."

When the immune system encounters a virus, it produces antibodies that help neutralize and clear the infection. Each antibody specifically recognizes just one antigen, often a viral protein. Most COVID-19 immunity research has focused on the spike and other surface proteins, which form the virus's outer coat, but beyond these so-called "canonical antigens," SARS-CoV-2 has about 25 other internal proteins.

To see whether immune responses to these non-canonical antigens could predict survival outcomes in patients with severe COVID-19, Das teamed up with co-senior authors Aniruddh Sarkar, Ph.D., assistant professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University, and Harinder Singh, Ph.D., professor of immunology and the director of the Center for Systems Immunology at Pitt.

The researchers analyzed blood samples that had

been collected from 21 patients who were hospitalized with severe COVID-19 in 2020—prior to the approval of vaccines. Seven of these patients died from the disease, and the other 14 survived. Using a microscale antibody profiling platform developed by Sarkar, the team comprehensively analyzed antibodies to three canonical and four non-canonical antigens.

According to Sarkar, the platform analyzes three key features of antibodies. One is antigen specificity, or what the antibody is binding to. The second is effector function, which relates to the antibody's role in immune response. The third feature is glycosylation, or the addition of carbohydrate molecules to the antibody, which dramatically impacts antibody function.

"By simultaneously profiling these three features, we can get a far deeper understanding of a given antibody than just looking at antibody titers," explained Sarkar.

The researchers found that no single antibody feature could differentiate between patient survival outcomes. But when they analyzed overall antibody profiles—either canonical or non-canonical—they noticed clear differences between survivors and non-survivors.

"We were surprised to find such compelling evidence that antibodies directed at canonical and non-canonical antigens were equally predictive of survival outcomes," said Singh. "Our findings suggest that non-canonical antibodies may play a role in recovery from severe disease, although more research is needed to prove causation and pinpoint the mechanisms."

Most COVID-19 vaccines and monoclonal antibodies—artificial antibodies used to treat COVID-19 —have become less effective with the emergence of delta and omicron variants because mutations in the spike help the virus avoid detection. According to Singh, far fewer mutations have accumulated in the virus's internal proteins, suggesting that augmenting vaccines or therapies to target these non-canonical antigens could elicit more robust immunity against emerging variants of concern.

When the team restricted their analysis to antibodies against non-canonical antigens conserved across coronaviruses—including those that cause the common cold and other respiratory infections—in COVID-19 patients, they could still distinguish survivors and non-survivors. These antibodies were also found in nine pre-pandemic, healthy control subjects, suggesting that exposure to coronaviruses besides SARS-CoV-2 could induce antibody responses linked with favorable outcomes in severe COVID-19.

According to Das, these findings could inform development of pan-coronavirus vaccines.

In ongoing work, the team is using their platform to look at antibodies in vaccinated people with breakthrough infections compared with unvaccinated individuals. They're also interested in understanding whether different antibodies play different roles in protection against COVID-19 over time.

They also plan to extend the platform to understanding antibodies in other contexts, including rejection of organ transplants and other infectious diseases.

More information: Sai Preetham Peddireddy et al, Antibodies targeting conserved non-canonical antigens and endemic coronaviruses associate with favorable outcomes in severe COVID-19, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.111020

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