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News & Research

Defective Evolution

Antibody development quality may predict COVID-19 outcomes

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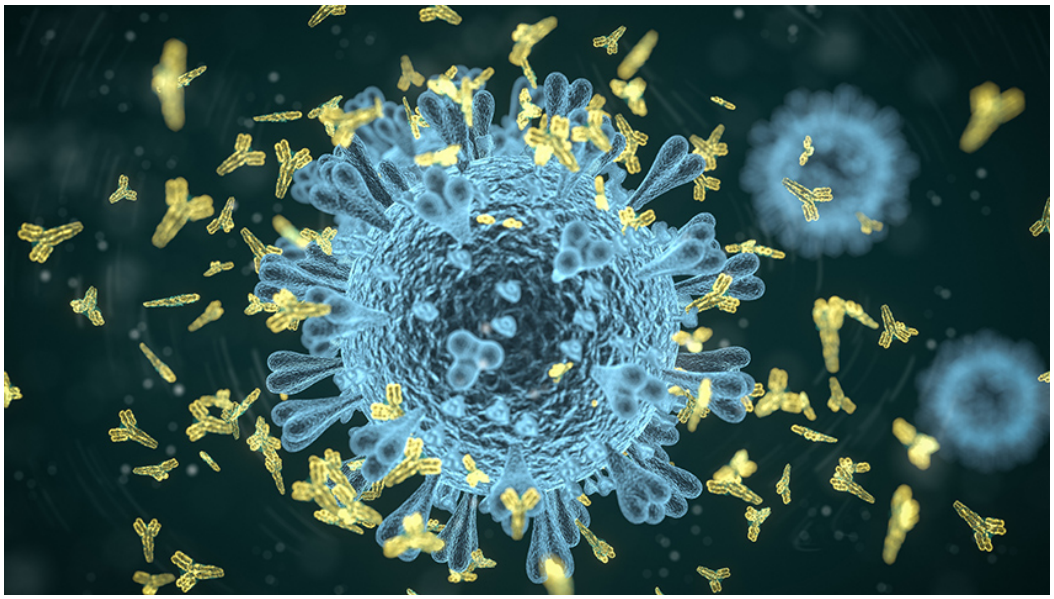

Illustration of antibodies binding to a coronavirus. Image: koto_feja/Getty Images.

This article is part of Harvard Medical School's continuing coverage of medicine, biomedical research, medical education and policy related to the SARS-CoV-2 pandemic and the disease COVID-19.

Surviving severe COVID-19 may depend on the quality of patients' antibody development and response to the SARS-CoV-2 virus that causes the disease, according to new research findings from **Galit Alter**, HMS professor of medicine at Massachusetts General Hospital, and colleagues.

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The study, published in the journal ***Cell***, profiled the antibody immune responses of 193 hospitalized patients with COVID-19. The research team compared responses from patients with moderate disease and severe disease, as well as patients who died from COVID-19.

While all patients developed antibodies against SARS-CoV-2, the way the antibodies developed, or evolved, differed between the three groups. For patients who didn't survive the disease, the antibody response never fully evolved.

"There was a significant defect in the development of IgG antibodies, which may be essential in the early control and elimination of the virus," said Alter, who is a core member of the Ragon Institute of MGH, MIT and Harvard and co-leads the **pathogenesis** working group of the Massachusetts Consortium on Pathogen Readiness.

"Here, we were able to see the global impact of this defective IgG evolution, resulting in a compromised ability to promote essential viral clearing immune functions," Alter said.

In a mature immune response, antibodies both block infection and direct the immune system to kill infected cells. To guide the killer immune response, antibodies attach to the Fc receptor, a docking site specific to antibodies that is found on all immune cells. Without strong Fc-receptor binding, antibodies may fail to grab and destroy the virus following infection.

Compared to survivors, patients who died from COVID-19 had antibodies that never fully developed the ability to strongly bind to Fc receptors and therefore may not have been able to fully trigger immune-killing activity.

Alter and colleagues also found that survivors' immune systems could recognize and target an area of the SARS-CoV-2 spike protein known as the S2 domain. The S2 domain is found in other coronaviruses that infect humans, so patients whose antibodies can target it may have preexisting immunity to the S2 domain of SARS-CoV-2 because of exposure to other, common coronaviruses.

Patients with antibodies that can recognize S2 domains on different coronaviruses may be able to use this preexisting immunity to generate killer antibodies faster and sooner following SARS-CoV-2 infection.

"If we can further understand the importance of cross-coronavirus immunity, researchers may be able to design vaccines able to counteract a much broader range of coronaviruses," said study co-first author Tomer Zohar, graduate student at MIT.

In further studies, Alter and colleagues are working to better understand the nature of protective immunity against SARS-CoV-2, including partnering with COVID-19 vaccine developers, with the aim of helping to bring an end to the pandemic.

Study co-first authors also include **Carolin Loos**, Stephanie Fischinger and Caroline Atyeo.

*Adapted from a Mass General **news** release.*

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