

Misdirected Antibodies Linked to Severe COVID-19

Antibodies that mistakenly target the body's own immune-system proteins may account for about 20% of COVID-19 deaths.

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The severity of COVID-19 can differ drastically between individuals. Some people never know they've been infected, while others may end up needing intensive care or dying from the disease.

Several factors have been associated with severe COVID-19, including preexisting health conditions like obesity, diabetes, and high blood pressure. Men are more likely to die of the disease than women. And the risk of dying from COVID-19 increases with age.

Researchers around the world have been looking for other risk factors for severe or fatal infection with SARS-CoV-2, the virus that causes COVID-19. An international project called the COVID Human Genetic Effort has been searching for genetic and molecular differences that may increase the risk of severe COVID-19. The project is co-directed by Dr. Helen Su from NIH's National Institute of Allergy and Infectious Diseases (NIAID) and Dr. Jean-Laurent Casanova from Rockefeller University.

Two recent studies from the project, led by Casanova, found that some severe cases of COVID-19 could be linked to problems with immune-system proteins called type I interferons (IFNs). These IFNs are needed to fight off viral infections. In rare cases, genetic conditions blocked the production of these proteins. But more commonly, antibodies that mistakenly targeted the IFNs were found in the blood of people with severe or fatal COVID-19.

To better understand how common these autoantibodies are, Casanova and his colleagues screened for them in blood samples taken from more than 3,500 people with severe or fatal COVID-19 and more than 34,000 uninfected volunteers from 38 different countries. The new study was funded in part by several NIH components, primarily NIAID. Results were [published on August 19, 2021, in Science Immunology](#).

The team found that 20% of people hospitalized with severe COVID-19 had high or intermediate levels of autoantibodies to type I IFNs. Autoantibodies were also found in at least 18% of people who died from the disease. In contrast, people with no or mild symptoms had very low levels of these autoantibodies. The researchers estimate that the autoantibodies may account for about

20% of total fatal COVID-19 cases.

The risk of having such autoantibodies increased with age. For example, while fewer than 10% of people under the age of 40 with severe COVID-19 had active levels of these autoantibodies, more than 21% of those over the age of 80 had them.

The researchers also found evidence of autoantibody production in uninfected volunteers. They were found in less than 1% of people between 18 and 69 years; in 2.3% of those between 70 and 79 years; and in 6.3% of those 80 years and older. This suggests that type I IFN autoantibodies existed before infection and become more common past age 70.

In a related paper published in the same issue of *Science Immunology*, the researchers identified another rare genetic defect that occurs only in men and results in disruption of IFN production. They estimated that this genetic risk factor accounts for at least 1% of cases of life-threatening COVID-19 in men under the age of 60.

“We can neatly explain much of severe COVID-19 as a net defect in type I IFN,” Casanova says. “To an extent never seen for any other acute infectious disease, these... studies collectively provide a molecular and immunological explanation for about 20% of critical cases.”

Autoantibodies against IFNs—at even very low levels—can be screened for in the clinic. Testing for these autoantibodies could help identify uninfected people who need aggressive preventive measures or infected people who need early aggressive treatment.

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