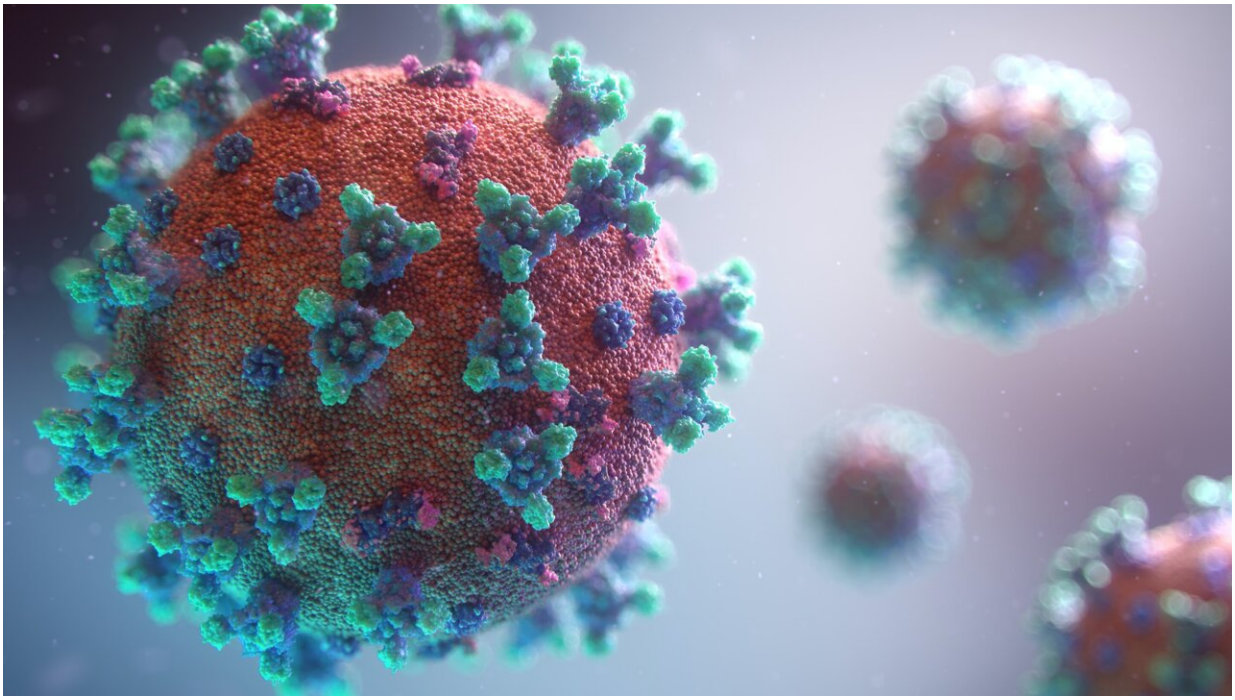
Blocking enzyme could hold the key to preventing, treating severe COVID-19

June 1 2022, by Emily Caldwell



Credit: Unsplash/CC0 Public Domain

Blocking an immune response-related enzyme holds promise in preventing or treating severe COVID-19 symptoms by reducing inflammation, tissue injury and blood clots in the lungs, new research in mice suggests.

Scientists who have long studied this molecule's functions in bacterial

infections traced development of extensive lung damage in infected mice to heightened levels of the enzyme triggered by the invading SARS-CoV-2 virus.

Versions of this enzyme exist and have similar functions in both mice and humans—they're called caspase 11 and caspase 4, respectively. After finding that the molecule is an attractive therapeutic target, researchers are exploring compounds that could safely and effectively block its activation.

"The whole idea is if this molecule is not there, the mouse will do better, which means if you target this molecule, then humans should do better," said co-senior study author Amal Amer, professor of microbial infection and immunity in The Ohio State University College of Medicine.

The research was published online recently in *Proceedings of the National Academy of Sciences.*

Amer teamed with Ohio State flu and COVID virologist Jacob Yount to look into caspase 11's role in coronavirus infection. Their labs ran a number of experiments comparing COVID infection outcomes in normal mice and mice genetically engineered so they don't produce the enzyme.

"From the first experiment, we saw caspase 11 knockout mice had less severe infections and started to recover after only a couple of days," said Yount, associate professor of microbial infection and immunity and co-senior author of the study.

Previous research has shown that caspase 11 in mice has many of the same immune-response functions as caspase 4 in humans. In both species, the enzyme is produced upon the onset of an infection.

This study supports the notion that what was seen in the mice has relevance to humans: The researchers analyzed nationally available COVID-19 patient data and found that caspase 4 was highly expressed in people hospitalized in the ICU—linking its presence to severe disease. Lung tissue samples from COVID patients also showed high activation of the molecule.

The sickest COVID-19 patients develop acute respiratory distress syndrome resulting from the combination of high levels of pro-inflammatory proteins called cytokines, fluid accumulation in air sacs that seeps into lung tissue and blood clots, or thrombosis, caused by damage to cells lining vessel walls.

In a series of experiments, the research team found that inhibiting caspase 11 reduced the intensity of multiple effects. They used a version of the SARS-CoV-2 virus that other scientists have engineered specifically to cause disease in mice. (The human coronavirus does not make mice sick.)

Among the most striking findings: lower recruitment and inflammatory priming of first-responder cells called neutrophils, white blood cells whose job is to heal wounds and clear away infection—they are important, but have a tendency to perpetuate inflammation that damages tissue and contributes to blood clot formation. A technique used to image the tiniest capillaries in mouse lungs also showed that while the blood vessels in the lungs of normal mice infected with the virus were spotted with clots, the capillaries of mice lacking caspase 11 remained free of thrombosis.

"What happens in the lung with COVID can be worse than with other infections. It's amazing that caspase 11 is controlling many of those unique aspects of COVID-19 pathology," Yount said.

Amer said this research has opened up new ways of thinking about the enzyme's possible role in a host of diseases. Its role in exacerbating lung damage in COVID-19 was an unexpected finding—the activation of caspase 11 and caspase 4 in bacterial infections has a protective function, setting up immune cells to kill bacterial pathogens.

Caspase 11 is known to need the help of a specific protein called gasdermin-D to ward off bacterial infections, but this work showed the enzyme intensified lung damage in COVID-19 infection without making use of gasdermin-D. The link to blood clotting also suggests caspase 11's effects in the presence of infection probably don't stop with the lungs, and may affect disease conditions in the heart, brain and elsewhere in the body.

"We discovered caspase 11 has other pathways, and we are looking at the function of caspase 11 in all of the types of cells that cause thrombosis," she said.

In the meantime, Amer's lab is already testing a caspase 11 blocker that she believes has potential to become a human drug candidate.

"This molecule has been found to inhibit thrombosis, inflammation and secretion of cytokines, and it also inhibits caspase 11," she said. "No one had put together that inhibition of caspase 11 has an effect on these downstream problems. This caspase inhibitor may save the day."

More information: Mostafa M. Eltobgy et al, Caspase-4/11 exacerbates disease severity in SARS–CoV-2 infection by promoting inflammation and immunothrombosis, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2202012119

Provided by The Ohio State University