Immune system culprit in severe COVID cases found

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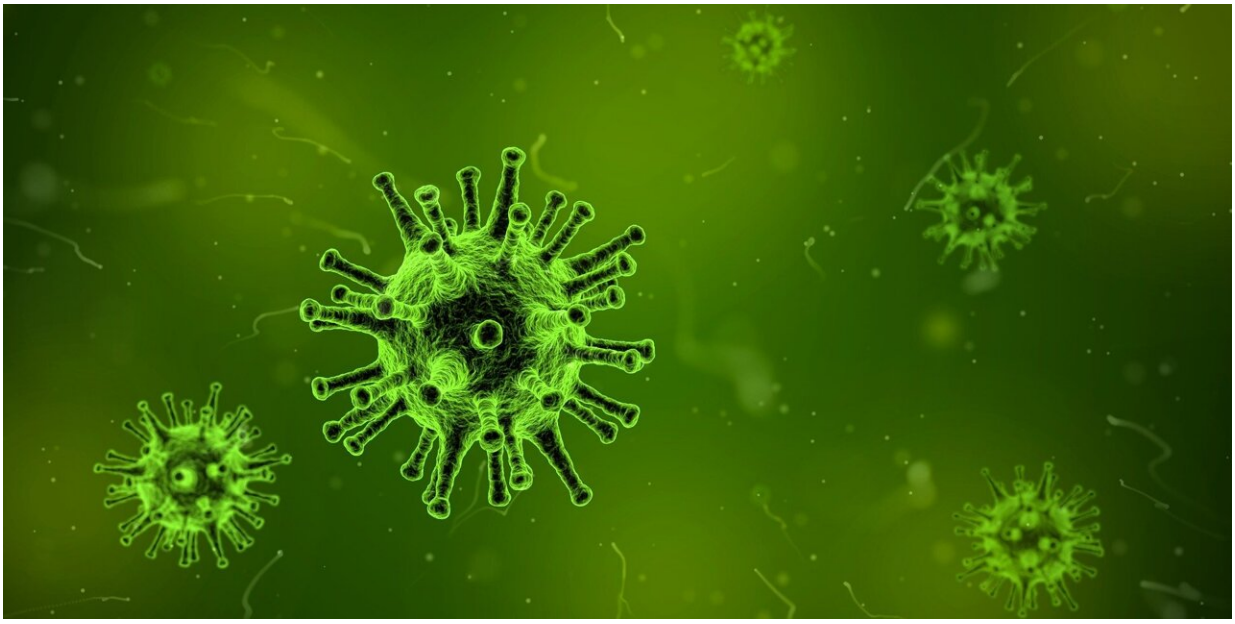

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Yale researchers have identified a particular immune response pathway that leads to severe illness and death in people infected by the SARS-CoV-2 virus.

The study was published April 28 in the journal *Nature*.

Researchers have known that once the COVID-19 virus infects the lungs

it can trigger what has been called a "cytokine storm," or an overactive immune response that leads to deadly inflammation in the lungs. For the new study, a Yale team led by postdoctoral fellow Esen Sefik, who is part of the lab of senior author Richard Flavell, studied the effects of SARS-CoV-2 infection in mice engineered to have a human immune system.

To their surprise, they found that immune cells themselves, not just epithelial cells lining the lung, can harbor the virus. When the body detects the virus in these cells, inflammasomes, part of the immune system's early warning system, produce and release cytokines which prompt these immune cells to commit suicide in an attempt to abort infection. However, the cytokines also recruit even more inflammatory cells to the lungs from the blood, which drives a vicious cycle that leads to pneumonia.

"It's like a broadcast system, but in this case the message is lethal," said Flavell, Sterling Professor of Immunobiology and investigator for the Howard Hughes Medical Institute.

In the mouse model of COVID-19, researchers were able to rescue infected mice from pneumonia by blocking the NLPR3 inflammasome pathway. With the inflammasome pathway blocked, immune system cells were still infected. But they were no longer inflammatory and therefore could not contribute to damaging levels of inflammation, researchers found.

One byproduct of this rescue, however, is that the cells no longer die and as a consequence release more virus. Nonetheless, blockade of the inflammasome pathway along with antiviral treatment could provide a way to treat COVID-19 pneumonia and prevent severe cases of COVID -19, researchers say.

Although there are no approved drugs that block the NLPR3 pathway, several pharmaceutical and biotech companies are developing them, Flavell said.

More information: Esen Sefik et al, Inflammasome activation in infected macrophages drives COVID-19 pathology, *Nature* (2022). DOI: 10.1038/s41586-022-04802-1

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