Study reveals immune-system paralysis in severe COVID-19 cases

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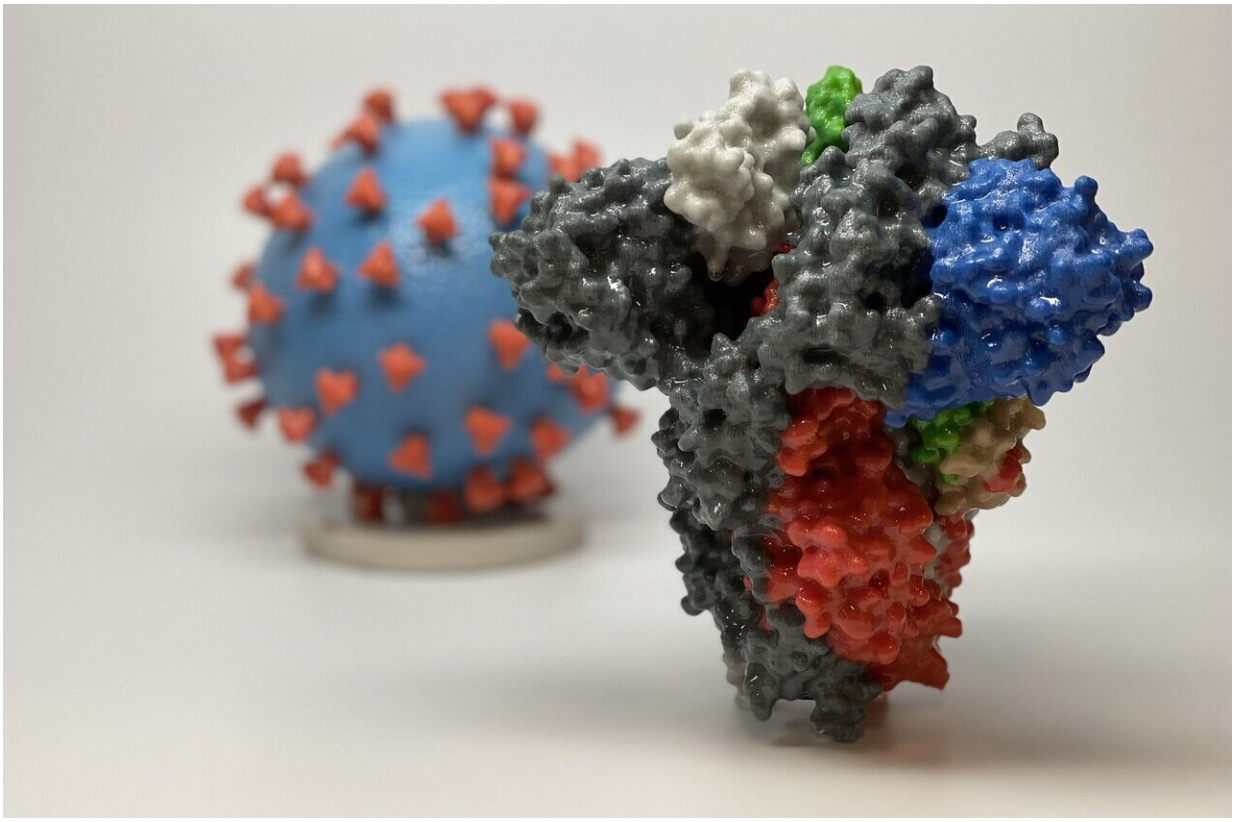

3D print of a spike protein of SARS-CoV-2, the virus that causes COVID-19—in front of a 3D print of a SARS-CoV-2 virus particle. The spike protein (foreground) enables the virus to enter and infect human cells. On the virus model, the virus surface (blue) is covered with spike proteins (red) that enable the virus to enter and infect human cells. Credit: NIH

A Stanford study shows that in severely ill COVID-19 patients, "first-responder" immune cells, which should react immediately to signs of viruses or bacteria in the body, instead respond sluggishly.

Some people get really sick from COVID-19, and others don't. Nobody knows why.

Now, a study by investigators at the Stanford University of Medicine and other institutions has turned up immunological deviations and lapses that appear to spell the difference between severe and mild cases of COVID-19.

That difference may stem from how our evolutionarily ancient innate immune system responds to SARS-CoV-2, the virus that causes the disease. Found in all creatures from fruit flies to humans, the innate immune system rapidly senses viruses and other pathogens. As soon as it does, it launches an immediate though somewhat indiscriminate attack on them and mobilizes more precisely targeted, but slower-to-get-moving, "sharpshooter" cells belonging to a different branch of the body's pathogen-defense forces, the adaptive immune system.

"These findings reveal how the immune system goes awry during coronavirus infections, leading to severe disease, and point to potential therapeutic targets," said Bali Pulendran, Ph.D., professor of pathology and of microbiology and immunology and the senior author of the study, which will be published Aug. 11 in *Science*. Lead authorship is shared by Stanford postdoctoral scholars Prabhu Arnunachalam, Ph.D., and Florian Wimmers, Ph.D.; and Chris Ka Pun Mok, Ph.D., and Mahen Perera, Ph.D., both assistant professors of public health laboratory sciences at the University of Hong Kong.

Three molecular suspects

The researchers analyzed the immune response in 76 people with COVID-19 and in 69 healthy people. They found enhanced levels of molecules that promote inflammation in the blood of severely ill COVID-19 patients. Three of the molecules they identified have been shown to be associated with lung inflammation in other diseases but had not been shown previously in COVID-19 infections.

"These three molecules and their receptors could represent attractive therapeutic targets in combating COVID-19," said Pulendran, who is the Violetta L. Horton Professor. His lab is now testing the therapeutic potential of blocking these molecules in animal models of COVID-19.

Bacterial debris and immune paralysis

The scientists also found elevated levels of bacterial debris, such as bacterial DNA and cell-wall materials, in the blood of those COVID-19 patients with severe cases. The more debris, the sicker the patient—and the more pro-inflammatory substances circulating in his or her blood.

The findings suggest that in cases of severe COVID-19, bacterial products ordinarily present only in places such as the gut, lungs and throat may make their way into the bloodstream, kick-starting enhanced inflammation that is conveyed to all points via the circulatory system.

But the study also revealed that, paradoxically, key cells of the innate immune system in the blood of COVID-19 patients became increasingly paralyzed as the disease got worse. Instead of being aroused by the presence of viruses or bacteria, these normally vigilant cells remained functionally sluggish.

If high blood levels of inflammation-promoting molecules set COVID-19 patients apart from those with milder cases, but blood cells are not producing these molecules, where do they come from? Pulendran

believes they originate in tissues somewhere in the body—most likely patients' lungs, the site of infection.

"One of the great mysteries of COVID-19 infections has been that some people develop severe disease, while others seem to recover quickly," Pulendran said. "Now we have some insights into why that happens."

Pulendran is a member of Stanford Bio-X and a faculty fellow of Stanford ChEM-H.

More information: Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans, *Science* 11 Aug 2020: eabc6261, DOI: 10.1126/science.abc6261 , science.sciencemag.org/content … 8/10/science.abc6261

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