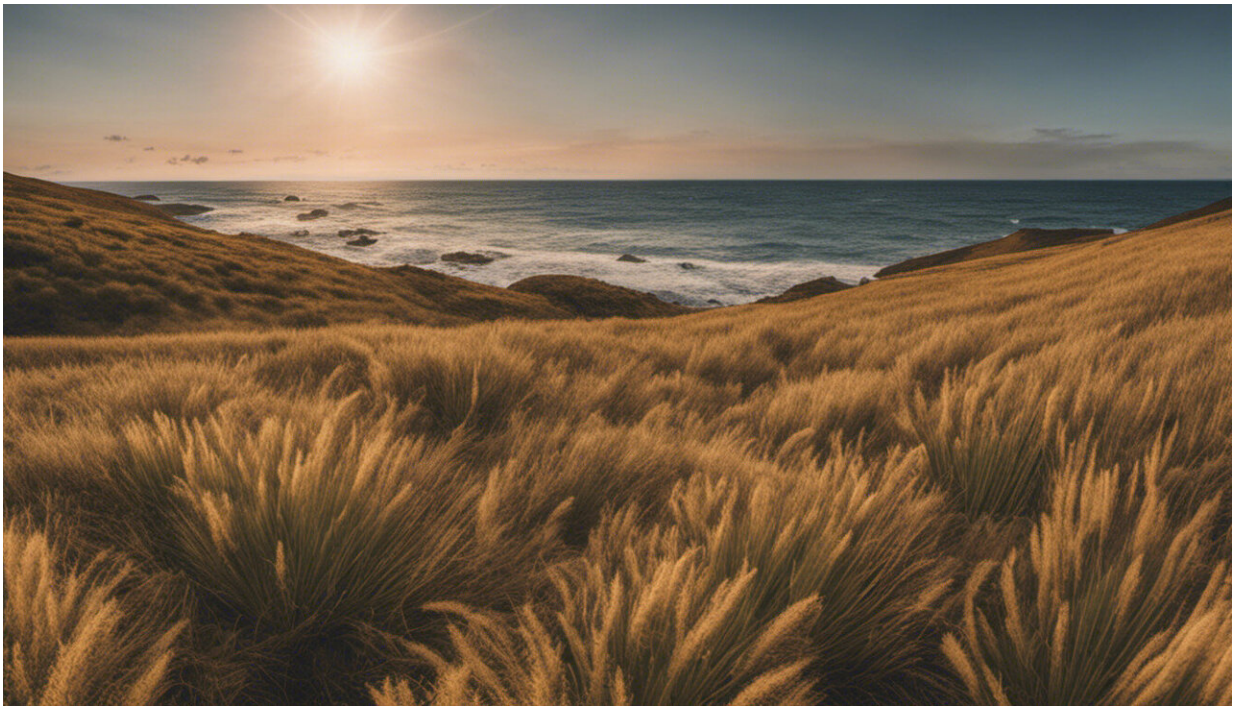
What causes severe COVID symptoms? Research examines role of immune systems

October 21 2022, by Andrew Nellis



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Since the earliest months of the COVID-19 pandemic, physicians and scientists worldwide have been working to understand how exactly the virus makes us sick. That task, already complicated by COVID's rapid spread, is made more challenging by some of its unusual, seemingly inexplicable symptoms, such as blood pressure dysregulation and blood

clots.

Now, research from the University of Chicago's Pritzker School of Molecular Engineering (PME) shows that the immune system may unintentionally contribute to the disease's strangest symptoms.

The findings, published in *Science Advances*, show that some people with severe COVID-19 can develop autoantibodies—antibodies directed against a person's own proteins—that disturb a critical component involved in blood pressure regulation.

"Our research shows that these autoantibodies may play a larger role in secondary complications of COVID-19 than people realize, and by monitoring for these responses, we may be better able to treat the disease," said Melody Swartz, William B. Ogden Professor of Molecular Engineering.

Following the trail

SARS-CoV-2, the virus that causes COVID-19, infects the body by way of biomolecular hijacking. The virus is covered with spike-shaped proteins that enter cells by attaching to the receptor ACE2, found on cells lining the mouth, nose, and lungs. ACE2 normally functions as a critical regulator of blood pressure by interacting with the peptide angiotensin II (AngII).

Researchers discovered the virus's entry mechanism early in the pandemic, but that discovery gave rise to another question that puzzled Prof. Swartz. If the body was generating antibodies against the virus's spike protein, could some of these antibodies also erroneously bind to AngII and thus disturb this key blood pressure regulation system?

If Swartz's hypothesis proved correct and autoantibodies that could

thwart the important functions of AngII were being generated, it might explain the growing reports of COVID-19 patients experiencing wild fluctuations in blood pressure. Since AngII and the ACE2 receptor together play significant roles in regulating blood pressure, interfering with either could trigger any number of problems.

"We've known that COVID-19 enters cells via the ACE2 receptor," said Priscilla Briquez, first author of the paper and PME postdoctoral researcher during the study, now an assistant professor at the University of Freiburg. "But the question became how the entry of the virus would impair blood pressure regulation. Most people focused on the receptor alone, but we suspected an autoimmune response would be equally likely."

Gathering evidence

Using samples and clinical data collected by the lab of Thomas Gajewski, professor of medicine at the University of Chicago, Swartz analyzed plasma samples from 115 patients hospitalized for severe COVID-19. Of these, they found that 63% had autoantibodies targeting AngII—exactly what Swartz had predicted.

Moreover, the antibody's presence coincided with lower blood oxygenation, increased blood pressure dysregulation, and higher overall disease severity. While not everyone with the autoantibodies experienced severe symptoms, and not everyone with severe symptoms had autoantibodies, the correlation with illness severity—particularly that related to blood pressure regulation—was significant.

Briquez points out that antibodies against AngII are transient, but their existence shows that the body can produce autoimmune responses to COVID-19. Understanding the full breadth of that response may offer new clues to fighting the disease. Further study may examine whether

antibodies against AngII emerge after most COVID symptoms subside and whether any recurrence coincides with symptoms of long COVID-19.

"Others have found that COVID-19 can cause a person to develop a wide range of autoantibodies," said Swartz. "Now we know that this can happen to a critical blood pressure regulator like angiotensin II, which may give a clearer picture of the underlying pathology causing severe cases."

More information: Priscilla S. Briquez et al, Severe COVID-19 induces autoantibodies against angiotensin II that correlate with blood pressure dysregulation and disease severity, *Science Advances* (2022). DOI: 10.1126/sciadv.abn3777

Provided by University of Chicago