



SARS-CoV-2 Fragments May Cause Problems After Infection

Viral fragments left behind after the immune system fights off infection may help explain some unusual aspects of COVID-19.

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Most COVID-19 cases are mild, but many still lead to life-threatening complications. Severe cases feature an overactive immune response that causes dangerous inflammation. This inflammation affects many different tissues and cell types, including uninfected ones, and resembles that seen in some autoimmune diseases. It's not clear why SARS-CoV-2 can cause such inflammation while other coronaviruses responsible for common colds don't.

One way the immune system fights viruses is by breaking down the viral proteins into small fragments called peptides. An NIH-funded research team—led by Dr. Gerard Wong at the University of California, Los Angeles, in collaboration with Richard L. Gallo at the University of California, San Diego—investigated whether these peptides could continue to activate the immune system. Their results were published in [Proceedings of the National Academy of Sciences](#) on February 6, 2024.

The team used machine learning to search SARS-CoV-2 proteins for fragments that resemble molecules called antimicrobial peptides (AMPs). The body makes these molecules as part of its defense against infections. Certain AMPs can bind to double-stranded RNA (dsRNA), which is produced during some viral infections. The resulting AMP-dsRNA complexes have been shown to trigger inflammation and have been implicated in autoimmune conditions such as lupus, rheumatoid arthritis, and psoriasis. Among the SARS-CoV-2 AMP-like fragments, the team looked for those that carried a strong positive electric charge. This would allow them to bind dsRNA, which is negatively charged.

The researchers studied three SARS-CoV-2 fragments that both resembled AMPs and had a large positive charge. These fragments were also found in the airways of patients with severe COVID-19. The scientists dubbed these AMP-like peptides “xenoAMPs.” Notably, SARS-CoV-2 contained more potential xenoAMPs than common cold coronaviruses. SARS-CoV-2 xenoAMPs also mimicked real AMPs more closely than those from common cold coronaviruses.

XenoAMPs bound to dsRNA and caused it to form liquid crystalline structures like those formed when AMPs bind to dsRNA. These structures were the optimal size and shape for binding to certain

receptors that control the innate immune response. When tested in various types of human cells, the xenoAMP-dsRNA complexes enhanced inflammatory responses. They also triggered gene activity changes resembling those triggered by SARS-CoV-2 infection. Corresponding peptides from a common cold coronavirus did not bind and form such structures with dsRNA. They also did not enhance inflammation in the cells.

The researchers injected one of the xenoAMP-dsRNA complexes into the bloodstream of mice. After they did, the mice had higher levels of proinflammatory molecules in the blood, similar to those seen in people with COVID-19. They also had higher levels of various immune cells.

These findings could lead to new strategies for treating severe cases of COVID-19. They also suggest a way to determine whether future coronaviruses could cause similar inflammation. More generally, they show how viruses can continue to affect the host even after they're destroyed by the immune system.

"The textbooks tell us that after the virus is destroyed, the sick host 'wins,' and different pieces of virus can be used to train the immune system for future recognition. COVID-19 reminds us that it's not this simple," Wong explains. "For comparison, if one were to assume that after food gets digested into its molecular components, then its effects on the body are over, it would be very liberating. I wouldn't have to worry about the half-dozen jelly donuts I just ate. However, this simple picture is not correct."

This [research summary](#) was published by the National Institutes of Health on February 27, 2024.