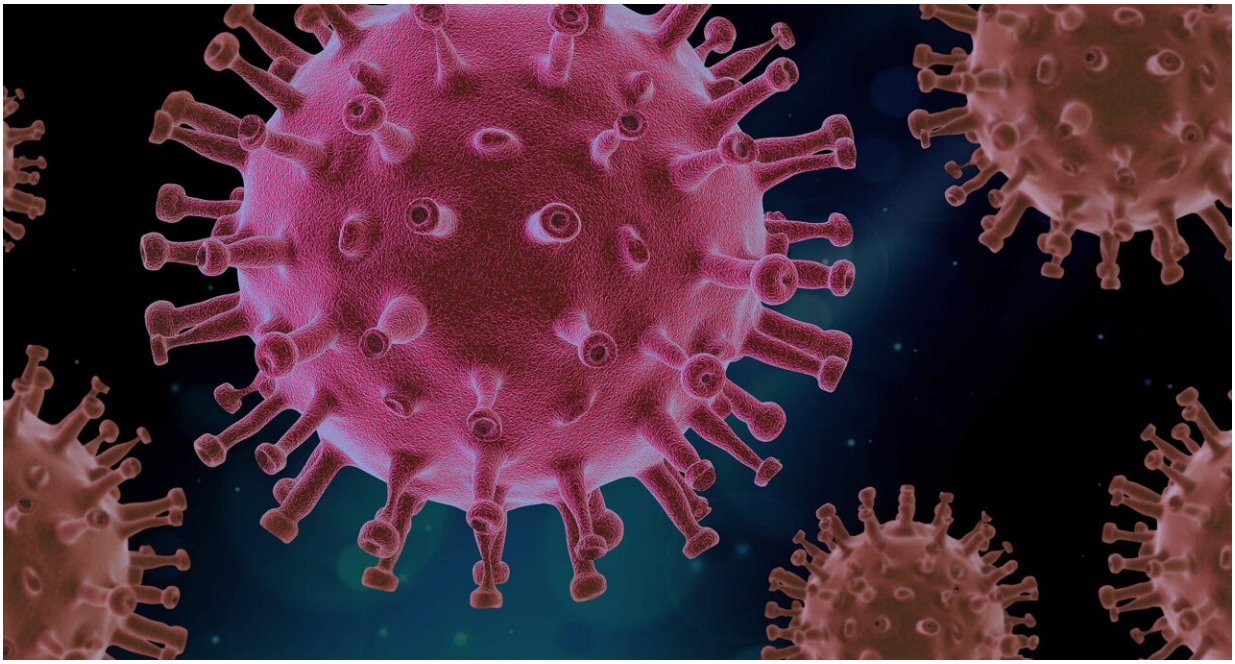
Can COVID-causing coronavirus outwit human innate immune response?

March 28 2022, by Debra Melani



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As Americans cross their fingers, hoping the pandemic stays behind them, scientists across the country remain focused on the novel coronavirus, intent on combating its next move.

For many researchers, that means examining mutations in the infamous spike protein and studying ways the virus outsmarts vaccines and their

triggered antibody response. Discovery in the area remains critical in understanding the pandemic's course.

But experts at the University of Colorado Anschutz Medical Campus say their research underscores the need to investigate the still mysterious SARS-CoV-2 further, a virus that boasts the largest genome known among any RNA viruses so far.

Their findings show the virus has evolved in ways that could outwit the body's own innate immune response, presenting both a worrisome move and a potential pathway to better therapies against COVID-19.

Innate immunity evasion: 'A driving force'?

Since the virus was first identified in Wuhan, China, in December 2019, the labs of Mario Santiago, Ph.D., and Eric Poeschla, MD, both faculty at the University of Colorado School of Medicine Division of Infectious Diseases, have been tracking the sensitivity of its variants to interferons. Named for their interference in viral replication, interferons are a major component of the innate arm of the immune response and serve as a first line of defense against infection.

In the study reported last month at the Conference on Retroviruses and Opportunistic Infections, the researchers compared how 17 different human interferons inhibit the "ancestral" virus versus the five subsequent variants of concern: alpha, beta, delta, gamma and omicron. Their data revealed that all five variants were more resistant to antiviral interferons than were the ancestral isolates.

"That suggests that evasion of innate immunity might be a driving force for SARS-CoV-2 evolution," Santiago said. The chief concern is that a more lethal variant could emerge as the virus learns new ways to battle human immunity.

A research focus 'underappreciated'

"It's really important to understand how this virus is adapting to the human innate immune system, because the key thing to keep in mind is that it's newly emerged," said Poeschla, an expert on cross-species virus transmission. "It's still adapting to us."

The strongest evidence suggests the virus jumped from bats to humans, possibly through an intermediate mammal (such as a racoon, dog or civet cat), first sickening people in China in late 2019.

"It's evolving unpredictably as it adapts to Homo sapiens," Poeschla said. "And this work identifies an underappreciated thing—that it's adapting to get resistant to interferons—especially when you compare it to the first known viruses from southern China that spread to the rest of the world."

To begin to understand if the virus has adapted to human interferons, the team obtained ancestral SARS-CoV-2 isolates from January 2020 and representatives of the five variants of concern isolated during the consecutive waves of infection from November 2020 to November 2021.

The researchers found that it required more interferons to inhibit the variants of concern than the ancestral isolates. For example, interferons were 100-fold less protective against the alpha strain—the first variant of concern out of the gate, detected in Great Britain in November 2020.

Bats to humans: 'A big genetic distance'

The virus's origin—probably in bats somewhere in Southeast Asia—creates more mysteries, said James Morrison, Ph.D., a researcher

in Poeschla's lab.

"That's a big genetic distance, to switch hosts from another non-primate mammal and be able to spread person to person in humans," Morrison said. "When viruses do that, they usually have to make significant changes," he said, noting, for example, that fewer adaptations generally have to be made when a virus jumps to humans from the more genetically similar chimpanzee.

"After that switch, it's still exploring a large potential 'mutational space.' And so far, this virus has been surprising in what a 'generalist' it is. It can infect large numbers of diverse mammals—such as ferrets, deer, and rodents—which is unusual for viruses. So it's really hard to predict how much this virus will still change and whether it will become either more or less virulent or more transmissible. It's still unclear what's going to happen in terms of new variants that may arise."

A critical role in halting severe disease?

The implications of SARS-CoV-2 resisting human's first line of defense could be great. "Innate immunity has to act within literally minutes to hours," Poeschla said. "That's mediated to a large extent by interferons and the antiviral genes that interferons turn on."

When scientists knock the interferon signaling system out in mice or monkey models, or when people have defects on this innate immune pathway, they tend to be more susceptible to disease and also to having higher viral loads, Santiago said.

"What this suggests is that if you have variants that can escape this interferon pathway better, they may have a propensity to have a higher level of initial replication, which could impact transmission and pathogenesis (disease progression)," Santiago said.

"It's possible that what happens in the earliest hours in terms of the virus replicating and where it replicates is very important until the antibodies can kick in," Poeschla said. "So that if you limit early replication through the interferon system you may—and this is speculation—produce effects that are milder: less disease, less inflammation of the lung," he said.

"A main reason people die from SARS-CoV-2 is they get an initial burst of viral replication, and then they get this subsequent massive inflammatory overreaction that leads to, most prominently, a severe pneumonia where the air spaces fill with fluid and cells. So understanding how the variants evade that initial front-line defense system is really important," Poeschla said.

Finding the mechanisms behind the inhibition is next on the scientists' checklist, Santiago said. "If we figure out the mechanism for how these interferons inhibit the virus, could those be potential new drug targets that we can exploit for better therapies? That's the most exciting part and what we intend to find out."

More information: Kejun Guo et al, Interferon Resistance of Emerging SARS-CoV-2 Variants, (2021). DOI: 10.1101/2021.03.20.436257 pubmed.ncbi.nlm.nih.gov/33758840/

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