Study identifies shared molecular mechanisms across SARS-CoV-2 variants that allow virus to thrive despite vaccination

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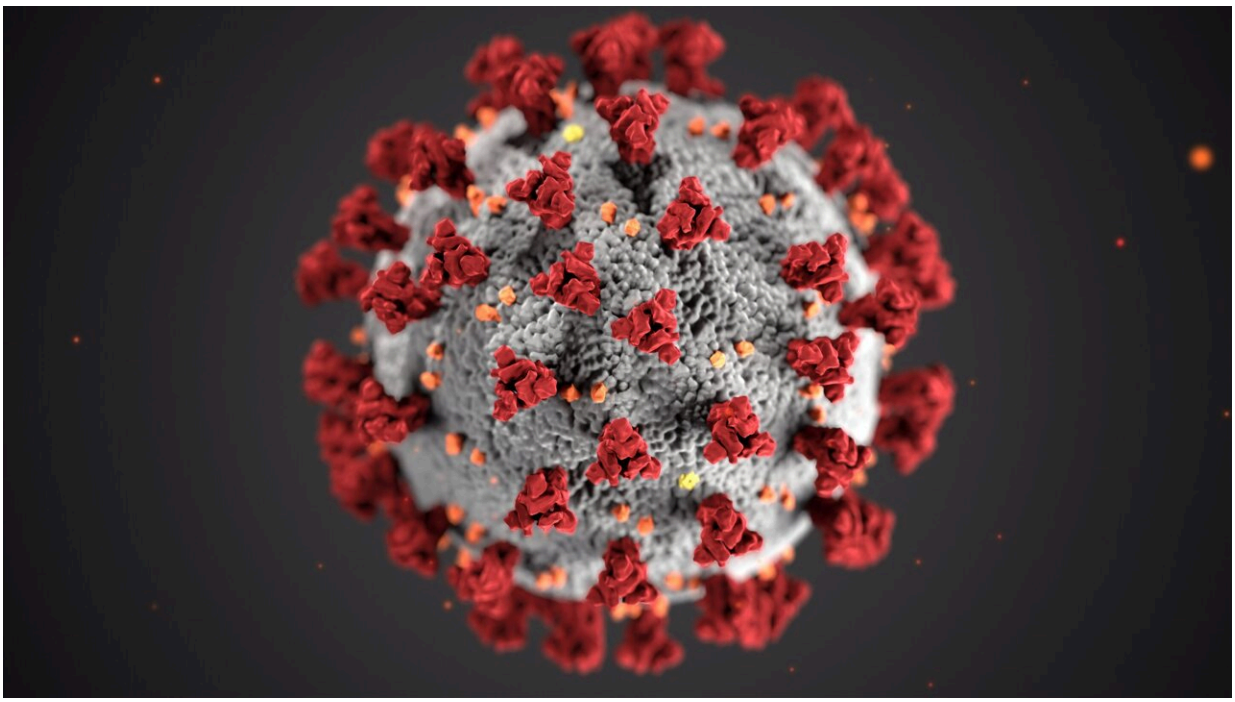

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In a study published online in *Cell* , scientists at UCSF QBI, University College London and the Icahn School of Medicine at Mount Sinai reported breakthrough findings on convergent evolutionary mechanisms shared by COVID-19 variants, allowing them to overcome both adaptive

and innate immune system barriers.

In the paper titled, SARS-CoV-2 Variants Evolve Convergent Strategies to Remodel the Host Response, published in *Cell*, scientists carried out an unprecedented, systematic comparative study using the most infectious COVID-19 variants, namely alpha, beta, gamma, delta and omicron to identify specific viral mutations responsible for hijacking a common host pathway, thereby leading to increased transmissibility, infectivity and survival.

Specifically, they discovered a convergence in potent suppression of interferon-stimulated genes through several viral proteins, including Orf6 and Orf9b, which serve as innate immune antagonist proteins capable of blocking innate host immune response.

The study, led by the laboratories of Nevan Krogan, Ph.D., Director of the Quantitative Biosciences Institute (QBI) at the School of Pharmacy at UC San Francisco, Senior Investigator at Gladstone Institutes, was a collaborative effort that involved 16 institutions in six countries, including University College London (UCL) in London, England (Greg Towers and Clare Jolly) and Icahn Mount Sinai (Adolfo Garcia-Sastre and Lisa Miorin) among others.

"Unfortunately, we continue to see new mutations and strains of SARS-CoV-2 despite innovations in new vaccines," said Dr. Krogan, who founded the QBI Coronavirus Research Group (QCRG).

"We evaluated each of the viral variants in isolation and discovered that there was a common mechanism involving several viral proteins, including Orf6 and Orf9b, that potently suppresses innate immunity. This finding is consistent with our investigation of early SARS-CoV-2 variants where certain viral proteins were highly expressed in infected cells which helped the virus infect our cells."

"With our additional research across SARS-CoV-2 variants, we now see this as a crucial finding that, if targeted effectively, could be turned into a significant vulnerability for this virus, which also has important implications for management of future pandemics."

In a second paper, titled "Impact of SARS-CoV-2 Orf6 and its variant polymorphisms on host responses and viral pathogenesis," also published in *Cell Host & Microbe*, the researchers further detailed the role of Orf6 in subverting important pathways involved in the host antiviral response.

"In this study we found that Orf6 is a major SARS-CoV-2 innate immune antagonist by selectively interfering with nucleocytoplasmic trafficking through direct interactions with the nuclear pore complex," said Lisa Miorin, Ph.D., Assistant Professor Department of Microbiology at Mount Sinai.

"We show that the absence of ORF6, or the introduction of ORF6 loss-of-function mutations, significantly influences the host antiviral responses resulting in SARS-CoV-2 attenuation in animal models."

Adolfo García-Sastre, Ph.D., Professor of Medicine (Infectious Diseases), Microbiology and Pathology, Molecular and Cell Based Medicine and Director of the Global Health and Emerging Pathogens Institute at Mount Sinai added, "These observations provide a potential new way to address viral pandemics by targeting a common pathway that the virus uses for infectivity, a different approach from vaccines that are created to target mutated Spike proteins within individual variants."

"By investigating the variant's ability to suppress the host immune response we have uncovered what appears to be a mechanism that viruses use that can be exploited."

Mehdi Bouhaddou, Ph.D., Assistant Professor Department of

Microbiology, Immunology, and Molecular Genetics at the University of California, Los Angeles (UCLA) who contributed to the research during his prior post-doctoral fellowship at UCSF commented, "Similar to treatment regimens for HIV, we believe the future approach to managing pandemics will require a drug combination cocktail."

"Here, this could include a combination of vaccines and antiviral innovations to target the virus. Specifically, combination therapy approaches to target the adaptive immune response (e.g., vaccines, antibody treatments) and another inhibiting viral innate immune antagonist proteins (e.g., Orf6 and Orf9b) or activating the innate immune response, could be the most effective. Perhaps with this approach, we may be able to get ahead of viruses before they reach pandemic levels."

To understand the effect of viral mutations on viral replication and cellular responses, the researchers systematically studied the five SARS-CoV-2 variants of concern during infection in human airway epithelial cells. Their analysis pinpointed cellular pathways that are similarly modulated across variants during infection and represent putative targets for pan-coronavirus antivirals.

They observed most of the variants improve their ability to inhibit the host innate immune response, which likely contributed to variant dominance by improving transmission. They reason this reflects a strong selection imposed by the human innate immune system on the virus, whose ancestor likely adapted to evade innate immunity in a non-human species.

The researchers concluded that a major force in shaping SARS-CoV-2 virus-host adaptations is related to evasion of innate and adaptive responses, a finding that has also been shown in research evasion of innate immune responses in HIV.

More information: Nevan J. Krogan, SARS-CoV-2 variants evolve convergent strategies to remodel the host response, *Cell* (2023). DOI: 10.1016/j.cell.2023.08.026. www.cell.com/cell/fulltext/S0092-8674(23)00915-7

Lisa Miorin, Impact of SARS-CoV-2 ORF6 and its variant polymorphisms on host responses and viral pathogenesis, *Cell Host & Microbe* (2023). DOI: 10.1016/j.chom.2023.08.003. www.cell.com/cell-host-microbe … 1931-3128(23)00328-1

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