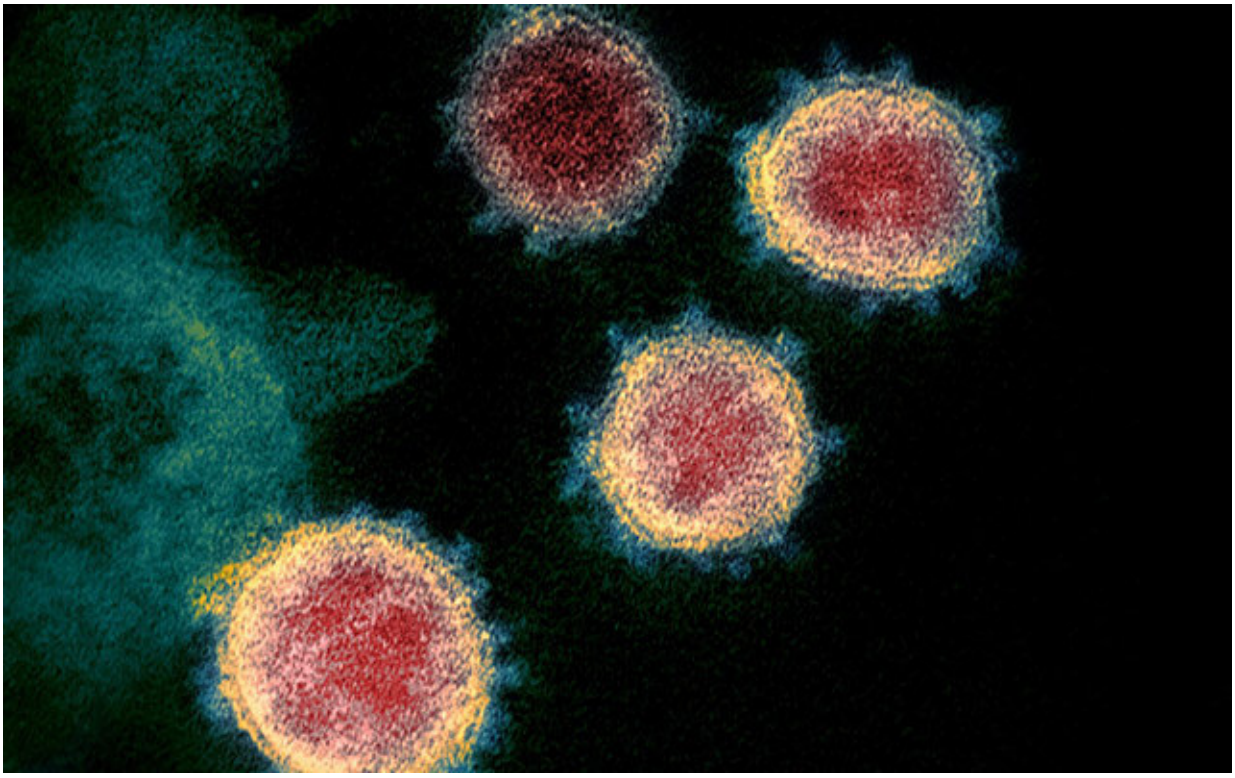
MedicalXpress

Studies reveal potential weaknesses in SARS-CoV-2 infection

December 10 2020



A colorized scanning electron micrograph of the SARS-CoV-2 virus. Credit: NIAID

A single protein that appears necessary for the COVID-19 virus to reproduce and spread to other cells is a potential weakness that could be targeted by future therapies.

The molecule, known as transmembrane protein 41 B (TMEM41B), is believed to help shape the fatty outer membrane that protects the virus' genetic material while it replicates inside an infected cell and before it infects another.

The latest finding comes from a pair of studies led by researchers at NYU Grossman School of Medicine and NYU Langone Health's Perlmutter Cancer Center, and colleagues at Rockefeller University and elsewhere.

Published in the journal *Cell* online Dec. 8, the studies revealed that TMEM41B was essential for SARS-CoV-2 to replicate. In a series of experiments, researchers compared how the COVID-19 virus reproduces in infected cells to the same processes in two dozen deadly flaviviruses, including those responsible for yellow fever, West Nile, and Zika disease. They also compared how it reproduces in infected cells to three other seasonal coronaviruses known to cause the common cold.

"Together, our studies represent the first evidence of transmembrane protein 41 B as a critical factor for infection by flaviviruses and, remarkably, for coronaviruses, such as SARS-CoV-2, as well," says the studies' co-senior investigator John T. Poirier, Ph.D.

"An important first step in confronting a new contagion like COVID-19 is to map the molecular landscape to see what possible targets you have to fight it," says Poirier, an assistant professor of medicine at NYU Langone Health. "Comparing a newly discovered virus to other known viruses can reveal shared liabilities, which we hope serve as a catalogue of potential vulnerabilities for future outbreaks."

"While inhibiting transmembrane protein 41 B is currently a top contender for future therapies to stop coronavirus infection, our results identified over a hundred other proteins that could also be investigated as

potential drug targets," says Poirier, who also serves as director of the Preclinical Therapeutics Program at NYU Langone and Perlmutter Cancer Center.

For the studies, researchers used the gene-editing tool CRISPR to inactivate each of more than 19,000 genes in human cells infected with each virus, including SARS-CoV-2. They then compared the molecular effects of each shutdown on the virus' ability to replicate.

In addition to TMEM41B, some 127 other molecular features were found to be shared among SARS-CoV-2 and other coronaviruses. These included common biological reactions, or pathways, involved in cell growth, cell-to-cell communication, and means by which cells bind to other cells. However, researchers say, TMEM41B was the only molecular feature that stood out among both families of viruses studied.

Interestingly, Poirier notes, mutations, or alterations, in TMEM41B are known to be common in one in five East Asians, but not in Europeans or Africans. He cautions, however, that it is too early to tell if this explains the relatively disproportionate severity of COVID-19 illness among some populations in the United States and elsewhere. Another study finding was that cells with these mutations were more than 50 percent less susceptible to flavivirus infection than those with no gene mutation.

Poirier says more research is needed to determine if TMEM41B mutations directly confer protection against COVID-19 and if East Asians with the mutation are less vulnerable to the disease.

The research team next plans to map out TMEM41B's precise role in SARS-CoV-2 replication so they can start testing treatment candidates that may block it. The team also has plans to study the other common pathways for similar potential drug targets.

Poirier adds that the research team's success in using CRISPR to map the molecular weaknesses in SARS-CoV-2 serves as a model for scientists worldwide for confronting future viral outbreaks.

More information: William M. Schneider et al. Genome-scale identification of SARS-CoV-2 and pan-coronavirus host factor networks, *Cell* (2020). DOI: 10.1016/j.cell.2020.12.006

H.-Heinrich Hoffmann et al. TMEM41B IS A PAN-FLAVIVIRUS HOST FACTOR, *Cell* (2020). DOI: 10.1016/j.cell.2020.12.005

Provided by NYU Langone Health