Surprise COVID discovery helps explain how coronaviruses jump species

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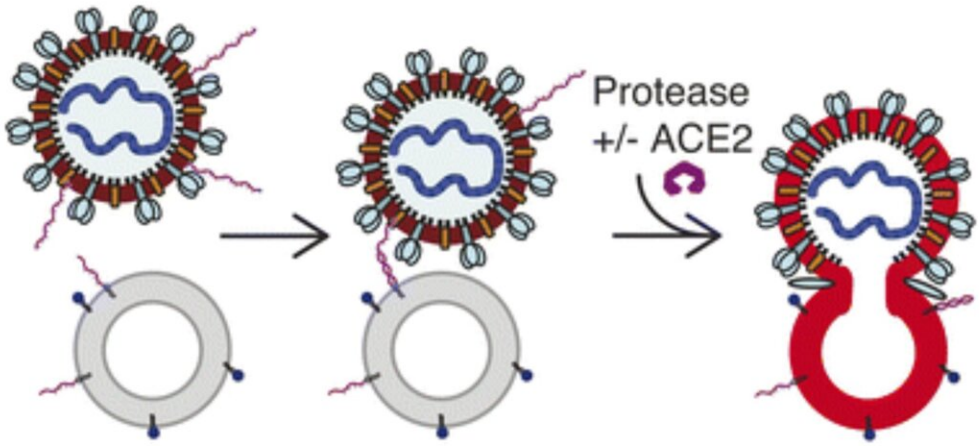

The SARS-CoV-2 coronavirus infects human cells via the ACE2 receptor. Structural evidence suggests that ACE2 may not just serve as an attachment factor but also conformationally activate the SARS-CoV-2 spike protein for membrane fusion. Here, we test that hypothesis directly, using DNA-lipid tethering as a synthetic attachment factor in place of ACE2. We find that SARS-CoV-2 pseudovirus and virus-like particles are capable of membrane fusion without ACE2 if activated with an appropriate protease. Thus, ACE2 is not biochemically required for SARS-CoV-2 membrane fusion. However, addition of soluble ACE2 speeds up the fusion reaction. On a per-spike level, ACE2 appears to promote activation for fusion and then subsequent inactivation if an appropriate protease is not present. Kinetic analysis suggests at least two rate-

limiting steps for SARS-CoV-2 membrane fusion, one of which is ACE2 dependent and one of which is not. Since ACE2 serves as a high-affinity attachment factor on human cells, the possibility to replace it with other factors implies a flatter fitness landscape for host adaptation by SARS-CoV-2 and future related coronaviruses. Credit: *Chemical Science* (2023). DOI: 10.1039/D2SC06967A

Unexpected new insights into how COVID-19 infects cells may help explain why coronaviruses are so good at jumping from species to species and will help scientists better predict how COVID-19 will evolve.

Throughout the pandemic, there has been much discussion of how COVID-19 infiltrates cells by hijacking a protein called ACE2 found on human cells. But the new research from the School of Medicine reveals that ACE2 isn't required for infection. Instead, the virus has other means it can use to infect cells.

That versatility suggests that coronaviruses can use multiple "doors" to enter cells, potentially explaining how they are so good at infecting different species.

"The virus that causes COVID-19 uses ACE2 as the front door to infect cells, but we've found that if the front door is blocked, it can also use the back door or the windows," said researcher Peter Kasson, MD, Ph.D., of UVA's Departments of Molecular Physiology and Biomedical Engineering. "This means the virus can keep spreading as it infects a new species until it adapts to use a particular species' front door. So we have to watch out for new viruses doing the same thing to infect us."

Understanding COVID-19

COVID-19 has killed almost 7 million people around the world. Thankfully, the availability of vaccines and the increase in population immunity means that the virus is no longer the threat it once was to most people (though it remains a concern for groups such as the immunocompromised and elderly).

With the expiration of the United States' official Public Health Emergency in May, most Americans have largely returned to lives similar to the ones they knew before the pandemic emerged in 2019. But COVID-19 continues to evolve and change, and scientists are keeping a close eye on it so that they can take quick action if a more dangerous variant emerges. They also continue to monitor other coronaviruses in case they jump to humans and become the next great public health threat.

As part of this effort, Kasson and his team wanted to better understand how the virus responsible for COVID-19, SARS-CoV-2, can enter human cells. Scientists have known that the virus essentially knocks on the cell's door by binding to ACE2 proteins. These proteins are bountiful on the surfaces of cells lining the nose and lungs.

SARS-CoV-2 can also bind with other proteins, however. Was it possible, the scientists wondered, that it could use those other proteins to infiltrate cells? The answer was yes. ACE-2 was the most efficient route, but it was not the only route. And that suggests that the virus can bind and infect even cells without any ACE-2 receptors at all.

That unexpected finding may help explain why coronaviruses are so adept at species-hopping, Kasson says. And that makes it even more important that scientists keep a close eye on them, he notes.

"Coronaviruses like SARS-CoV-2 have already caused one pandemic and several near misses that we know of," he said. "That suggests there

are more out there, and we need to learn how they spread and what to watch out for."

The findings are published in the journal *Chemical Science*.

More information: Marcos Cervantes et al, The ACE2 receptor accelerates but is not biochemically required for SARS-CoV-2 membrane fusion, *Chemical Science* (2023). DOI: 10.1039/D2SC06967A

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