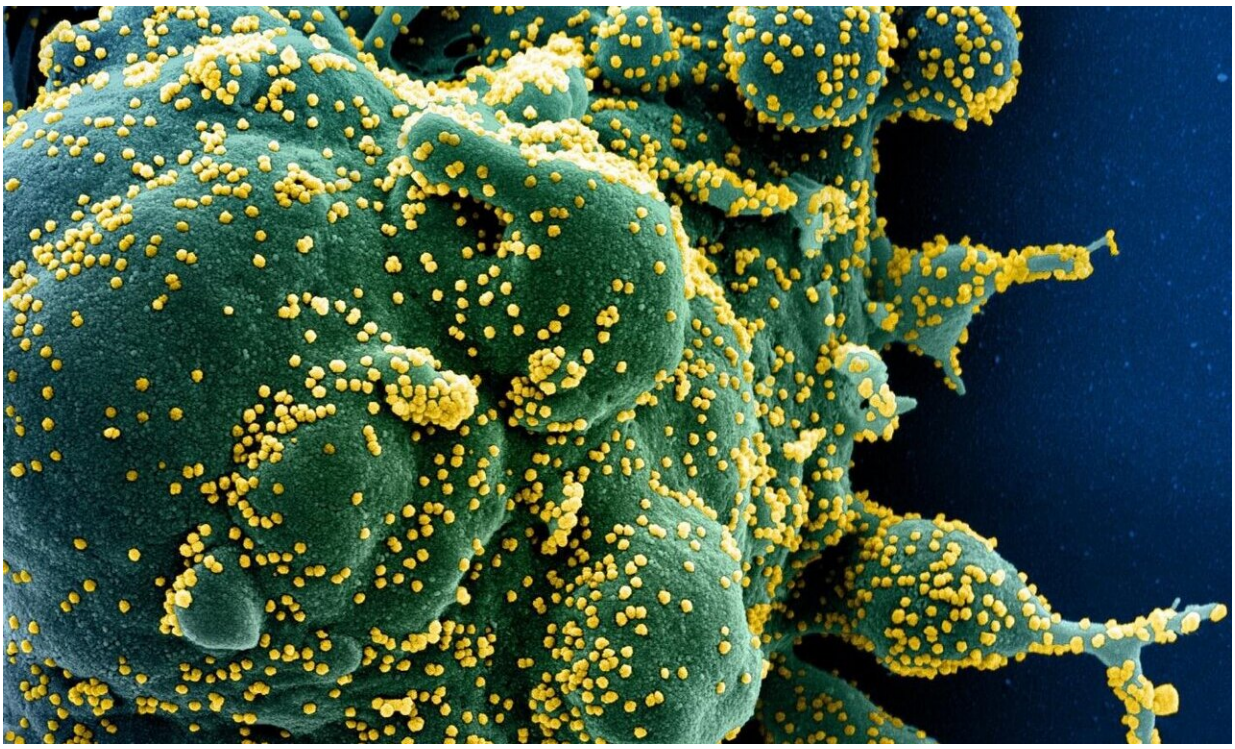
MedicalXpress

Researchers discover potential new therapeutic targets on SARS-CoV-2 Spike protein

February 22 2021



Colorized scanning electron micrograph of an apoptotic cell (green) heavily infected with SARS-COV-2 virus particles (yellow), isolated from a patient sample. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIH/NIAID

The COVID-19 pandemic has prompted considerable investigation into

how the SARS-CoV-2 Spike protein attaches to a human cell during the infection process, as this knowledge is useful in designing vaccines and therapeutics. Now, a team of scientists has discovered additional locations on the Spike protein that may not only help to explain how certain mutations make emerging variants more infectious but also could be used as additional targets for therapeutic intervention.

"Significant research is underway to examine how the receptor binding domain (RBD) at the tip of the club-shaped SARS-CoV-2 Spike protein attaches to an ACE2 receptor on a human cell, but little is known about the other changes that occur in the Spike protein as a result of this attachment," said Ganesh Anand, associate professor of chemistry, Penn State. "We have uncovered 'hotspots' further down on the Spike protein that are critical for SARS-CoV-2 infection and may be novel targets beyond the RBD for therapeutic intervention."

Anand and his colleagues used a process, called amide hydrogen-deuterium exchange mass spectrometry (HDXMS), to visualize what happens when the SARS-CoV-2 Spike protein binds to an ACE2 receptor. HDXMS uses heavy water or deuterium oxide (D2O), a naturally occurring, non-radioactive isotope of water formed from heavy hydrogen or deuterium, as a probe for mapping proteins. In this case, the team placed SARS-CoV-2 Spike protein and ACE2 receptors in heavy water and obtained footprints of ACE2 on the Spike protein.

"If you put the Spike protein and ACE2 receptor into a solution that's made with D2O, the surfaces and more floppy regions on both proteins will more readily exchange hydrogens for deuterium, compared to their interiors," said Anand. "And footprints of each protein on the binding partner can be readily identified from areas where you see little deuterium and only detect normal hydrogen."

Using this technique, the team determined that binding of the Spike

protein and ACE2 receptor is necessary for furin-like proteases—a family of human enzymes—that act to snip off the tip, called the S1 subunit, of the Spike protein, which is the next step in the virus's infection of the cell. The findings published on Feb. 8 in the journal *eLife*.

"The Spike proteins on the surface of the virus swivel to search and latch onto the ACE2 receptor," said Anand. "ACE2 can be likened to a hand holding strands of hair—the Spike protein clusters. Binding to Spike stabilizes it so it can be cut by furin protease scissors. After furin proteases clip the protein, the part that remains—the S2 subunit—is what fuses with the cell's membranes, allowing entry into the cell."

Anand noted that researchers have already learned much about how the Spike protein and ACE2 receptor bind together, but until now no one knew how this binding relayed the message to the furins to cut the protein. He explained that the phenomenon is called allostery, meaning "action at a distance."

"Our findings show ACE2 receptor binding to SARS-CoV-2 Spike protein causes long-range changes and allosterically enhances protease cutting at the distal S1/S2 cleavage site," he said.

Anand said that researchers are currently focusing only on therapeutics that block the Spike protein from binding to the ACE2 receptor.

"In this paper, we're suggesting that's not the only vulnerability that can be targeted," he said. "Maybe the S1/S2 cleavage that is necessary for furin cleavage can serve as a new target for inhibitory therapeutics against the virus. This study also may help in explaining how mutations in emerging variants might alter dynamics and allostery of ACE2 binding, potentially increasing infectiousness of the SARS-CoV-2 virus."

More information: Palur V Raghuvamsi et al, SARS-CoV-2 S protein:ACE2 interaction reveals novel allosteric targets, *eLife* (2021). DOI: 10.7554/eLife.63646