Researchers discover hidden SARS-CoV-2 'gate' that opens to allow COVID infection

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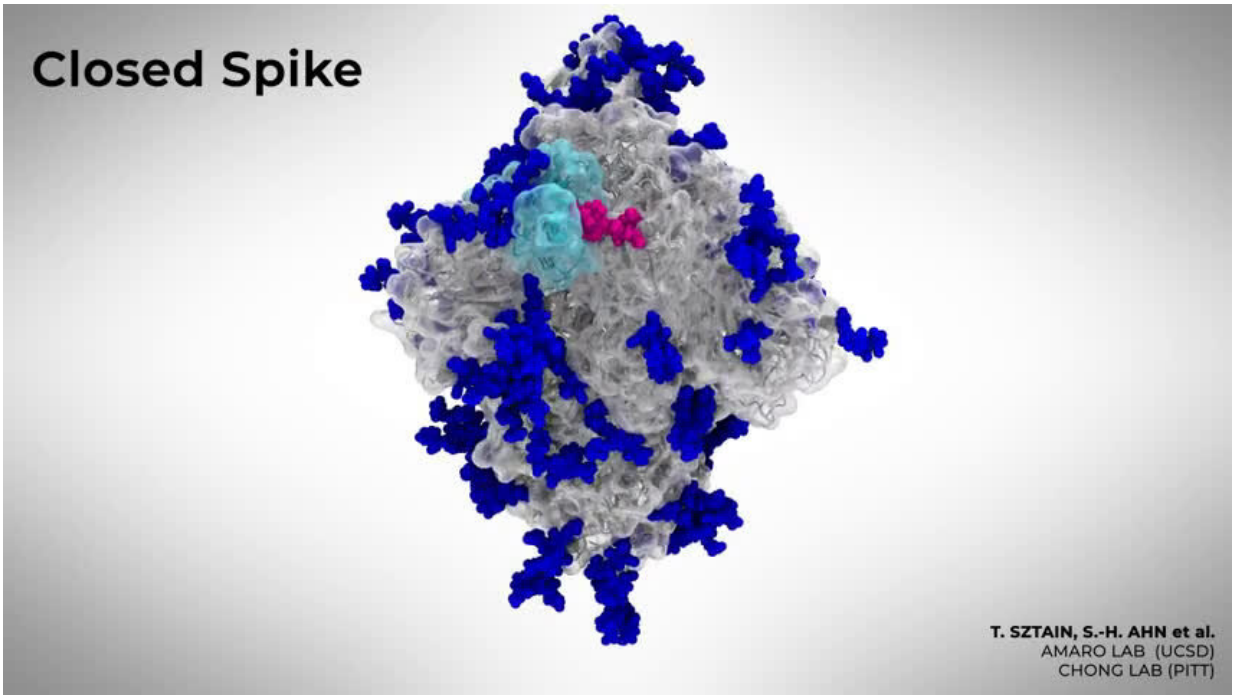

Since the early days of the COVID pandemic, scientists have aggressively pursued the secrets of the mechanisms that allow severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to enter and infect healthy human cells.

Early in the pandemic, University of California San Diego's Rommie

Amaro, a computational biophysical chemist, helped develop a detailed visualization of the SARS-CoV-2 spike protein that efficiently latches onto our cell receptors.

Now, Amaro and her research colleagues from UC San Diego, University of Pittsburgh, University of Texas at Austin, Columbia University and University of Wisconsin-Milwaukee have discovered how glycans—molecules that make up a sugary residue around the edges of the spike protein—act as infection gateways.

Published August 19 in the journal *Nature Chemistry*, a research study led by Amaro, co-senior author Lillian Chong at the University of Pittsburgh, first author and UC San Diego graduate student Terra Sztain and co-first author and UC San Diego postdoctoral scholar Surl-Hee Ahn, describes the discovery of glycan "gates" that open to allow SARS-CoV-2 entry.

"We essentially figured out how the spike actually opens and infects," said Amaro, a professor of chemistry and biochemistry and a senior author of the new study. "We've unlocked an important secret of the spike in how it infects cells. Without this gate the virus basically is rendered incapable of infection."

Amaro believes the research team's gate discovery opens potential avenues for new therapeutics to counter SARS-CoV-2 infection. If glycan gates could be pharmacologically locked in the closed position, then the virus is effectively prevented from opening to entry and infection.

The spike's coating of glycans helps deceive the human immune system since it comes across as nothing more than a sugary residue. Previous technologies that imaged these structures depicted glycans in static open or closed positions, which initially didn't draw much interest from

scientists. Supercomputing simulations then allowed the researchers to develop dynamic movies that revealed glycan gates activating from one position to another, offering an unprecedented piece of the infection story.

"We were actually able to watch the opening and closing," said Amaro. "That's one of the really cool things these simulations give you—the ability to see really detailed movies. When you watch them you realize you're seeing something that we otherwise would have ignored. You look at just the closed structure, and then you look at the open structure, and it doesn't look like anything special. It's only because we captured the movie of the whole process that you actually see it doing its thing."

"Standard techniques would have required years to simulate this opening process, but with my lab's 'weighted ensemble' advanced simulation tools, we were able to capture the process in only 45 days," said Chong.

The computationally intensive simulations were first run on Comet at the San Diego Supercomputer Center at UC San Diego and later on Longhorn at the Texas Advanced Computing Center at UT Austin. Such computing power provided the researchers with atomic-level views of the spike protein receptor binding domain, or RBD, from more than 300 perspectives. The investigations revealed glycan "N343" as the linchpin that pries the RBD from the "down" to "up" position to allow access to the host cell's ACE2 receptor. The researchers describe N343 glycan activation as similar to a "molecular crowbar" mechanism.

Jason McLellan, an associate professor of molecular biosciences at UT Austin and his team created variants of the spike protein and tested to see how a lack of the glycan gate affected the RBD's ability to open.

"We showed that without this gate, the RBD of the spike protein can't take the conformation it needs to infect cells," McLellan said.

More information: A glycan gate controls opening of the SARS-CoV-2 spike protein, *Nature Chemistry* (2021). DOI: 10.1038/s41557-021-00758-3 , www.nature.com/articles/s41557-021-00758-3

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