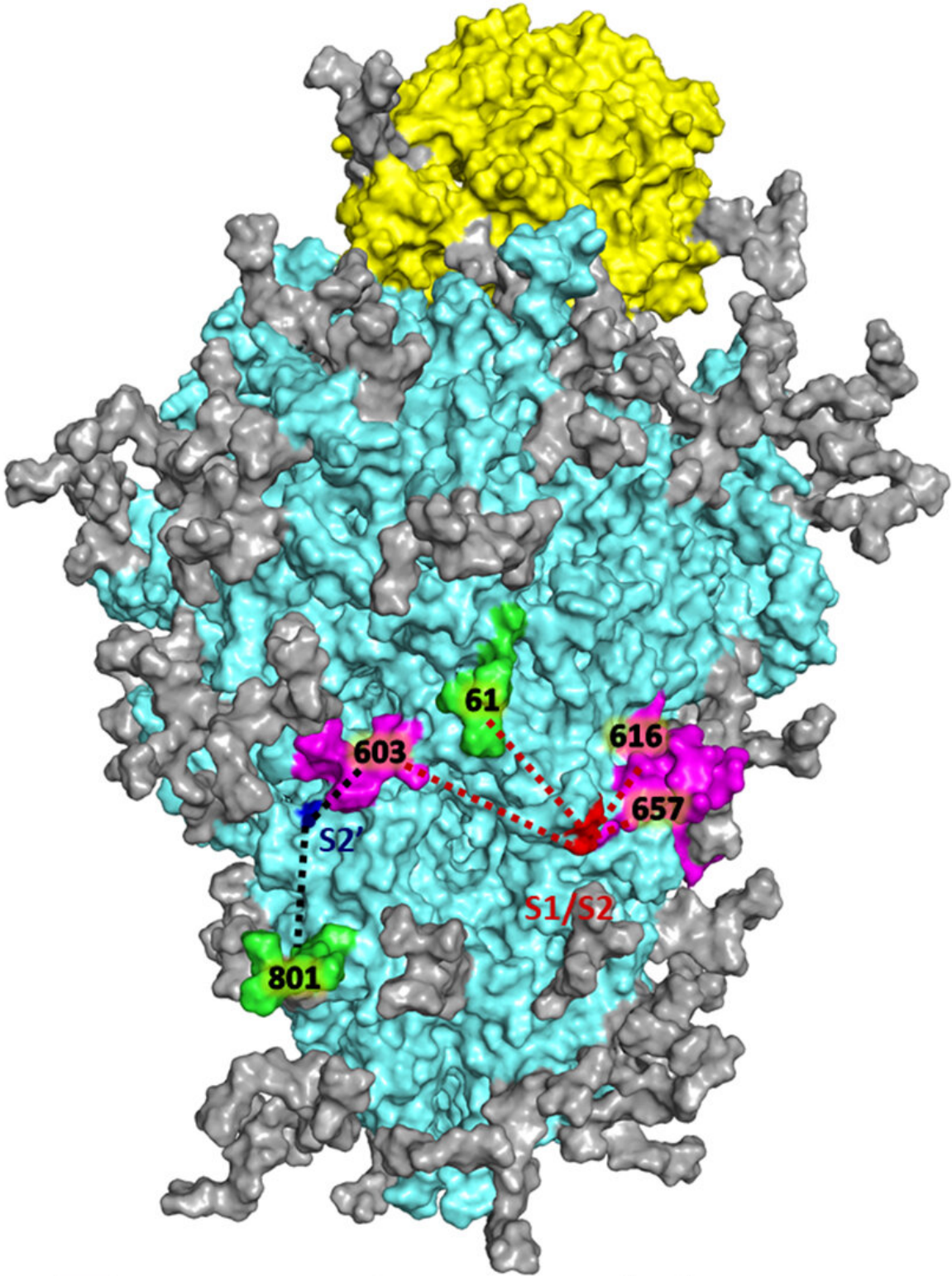


# Often overlooked, molecules called glycans regulate COVID-19 spike protein function

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 High-mannose     Complex     Other glycans

A molecular model shows the heavily glycosylated SARS-CoV-2 spike protein (cyan, with glycans in grey and other colors) bound to the cellular ACE2 receptor (yellow). A new study highlights the critical role of N-glycans, particularly those attached to the spike protein at sites known as N61 and N801, and N-glycan chaperone proteins in tuning SARS-CoV-2 infectivity. Credit: Credit: Qi Yang et al., *Science Advances* (2022). DOI: 10.1126/sciadv.abq8678

If you're an avid reader of science news, you've probably heard of viral proteins such as the COVID-19 spike protein.

Perhaps lesser known in the anatomy of viruses is a class of molecules called [glycans](#). But these are important, too.

Glycans are complex carbohydrates that decorate the surface of viruses, and "every virus has a different distribution of carbohydrates," says University at Buffalo engineering and medical researcher Sriram Neelamegham. As he explains, HIV uses glycans as a shield, employing these molecules to hide from virus-fighting antibodies. H1N1, a strain of the flu, leverages glycans to enter host cells, he adds.

And now, Neelamegham is among scientists illuminating the role that glycans may play in the function of SARS-CoV-2, the virus that causes COVID-19.

In a new study, his team analyzed a subset of glycans called N-glycans, with a focus on N-glycans that are attached to the SARS-CoV-2 spike protein. The researchers found that several of these N-glycans—in particular those attached to the spike protein at sites known as N61 and N801—are likely critical for SARS-CoV-2 function.

The research was published on Sept. 23 in *Science Advances*. Neelamegham, Ph.D., UB Distinguished Professor in chemical and biological engineering, biomedical engineering, and medicine, is senior author. Qi Yang, a UB Ph.D. student in chemical and biological engineering, is first author.

"We discovered that specific N-glycans seem to regulate the development and functional maturation of the SARS-CoV-2 spike protein," Neelamegham says. "This is important because the spike protein is very important for viral entry into host cells."

The study was conducted, in part, using artificially created replicas of the SARS-CoV-2 virus called virus-like particles (VLPs). The VLPs used in the research were designed to specifically prevent the formation of various N-glycans on the spike protein. During these investigations, modifications relating to N61 and N801 reduced the ability of VLPs to enter host cells by about 75-85%, suggesting that these glycans are critical vulnerabilities of the viruses, according to the research.

While more research is needed to determine the exact reason why this happens, it's possible that N61 and/or N801 may play a role in helping to fold the spike protein into the proper configuration, Neelamegham says.

In seeking to understand folding mechanics, his team investigated the roles of various intracellular carbohydrate-binding "chaperones" or "lectins" that assist with synthesis of the spike. These studies showed that a "chaperone" protein called calnexin, which facilitates this type of folding, regulates VLP entry into host cells. This is interesting, Neelamegham says, because calnexin is known to bind with N-glycans, though scientists aren't sure whether calnexin interacts specifically with glycans at N61 and N801 or not, among other glycans.

The findings highlight N-linked glycans on spike protein as potential

drug targets for COVID-19. One next step in the research would be to validate the findings using appropriate animal models, Neelamegham says. The research also underscores the importance of investigating the role of glycans in additional diseases caused by [viruses](#).

"Glycomics is a minor field compared to the study of proteins: More researchers are focused on proteins since the main targets of neutralizing antibodies are protein epitopes," Yang says. "But our results show that these glycans are indeed important in terms of viral function in SARS-CoV-2. That's why we choose to walk down this direction."

**More information:** Qi Yang et al, Role for N -glycans and calnexin-calreticulin chaperones in SARS-CoV-2 Spike maturation and viral infectivity, *Science Advances* (2022). [DOI: 10.1126/sciadv.abq8678](https://doi.org/10.1126/sciadv.abq8678)

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