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New findings on SARS-CoV-2 protein shed light on virus's ability to infect cells

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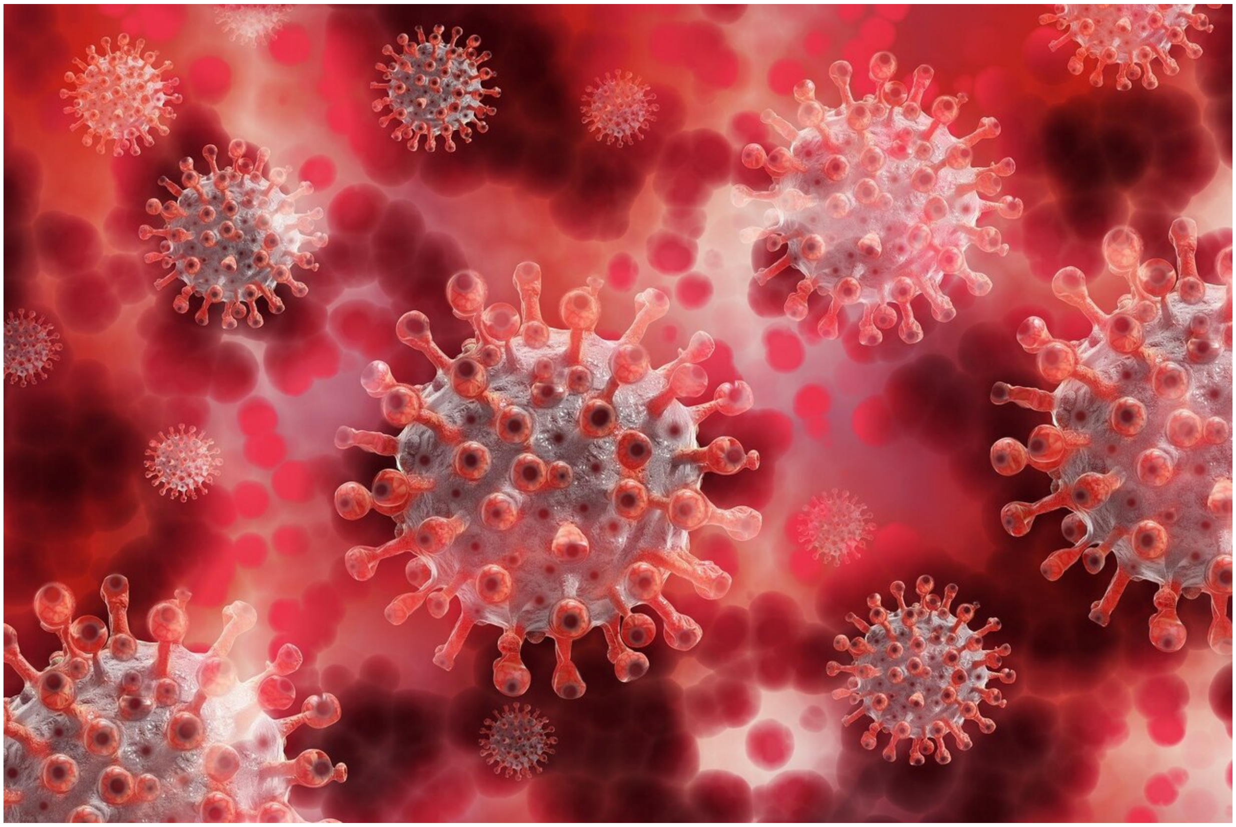

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At the start of a COVID-19 infection, the coronavirus SARS-CoV-2 docks onto human cells using the spike-like proteins on its surface. The spike protein is at the centre of vaccine development because it triggers an immune response in humans. A group of German scientists, including members of the European Molecular Biology Laboratory (EMBL) in Heidelberg, the Max Planck Institute of Biophysics, the Paul-Ehrlich-Institut, and Goethe University Frankfurt have focused on the surface structure of the virus to gain insights they can use for the development of vaccines and of effective therapeutics to treat infected patients.

The team combined cryo-electron tomography, subtomogram averaging, and molecular dynamics simulations to analyze the molecular structure of the spike protein in its natural environment, on intact virions, and with near-atomic resolution. Using EMBL's state-of-the-art cryo-electron microscopy imaging facility, 266 cryotomograms of about 1000 different viruses were generated, each carrying an average of 40 spikes on its surface. Subtomogram averaging and image processing, combined with molecular dynamics simulations, finally provided the important and novel structural information on these spikes.

The results were surprising: the data showed that the globular portion of the spike protein, which contains the receptor-binding region and the machinery required for fusion with the target cell, is connected to a flexible stalk. "The upper spherical part of the spike has a structure that is well reproduced by recombinant proteins used for vaccine development," explains Martin Beck, EMBL group leader and a director of the Max Planck Institute (MPI) of Biophysics. "However, our findings about the stalk, which fixes the globular part of the spike protein to the virus surface, were new."

"The stalk was expected to be quite rigid," adds Gerhard Hummer, from the MPI of Biophysics and the Institute of Biophysics at Goethe University Frankfurt. "But in our computer models and in the actual images, we discovered that the stalks are extremely flexible." By combining molecular dynamics simulations and cryo-electron tomography, the team identified the three joints—hip, knee and ankle—that give the stalk its flexibility.

"Like a balloon on a string, the spikes appear to move on the surface of the virus and thus are able to search for the receptor for docking to the target cell," explains Jacomine Krijnse Locker, group leader at the Paul-Ehrlich-Institut. To prevent infection, these spikes are targeted by antibodies. However, the images and models also showed that the entire spike protein, including the stalk, is covered with chains of glycans—sugar-like molecules. These chains provide a kind of protective coat that hides the spikes from neutralizing antibodies: another important finding on the way to effective vaccines and medicines.

More information: Beata Turoňová et al. In situ structural analysis of SARS-CoV-2 spike reveals flexibility mediated by three hinges. *Science* 18 Aug 2020: DOI: 10.1126/science.abd5223, science.sciencemag.org/content … 8/17/science.abd5223

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