Structural analysis of COVID-19 spike protein provides insight into its evolution

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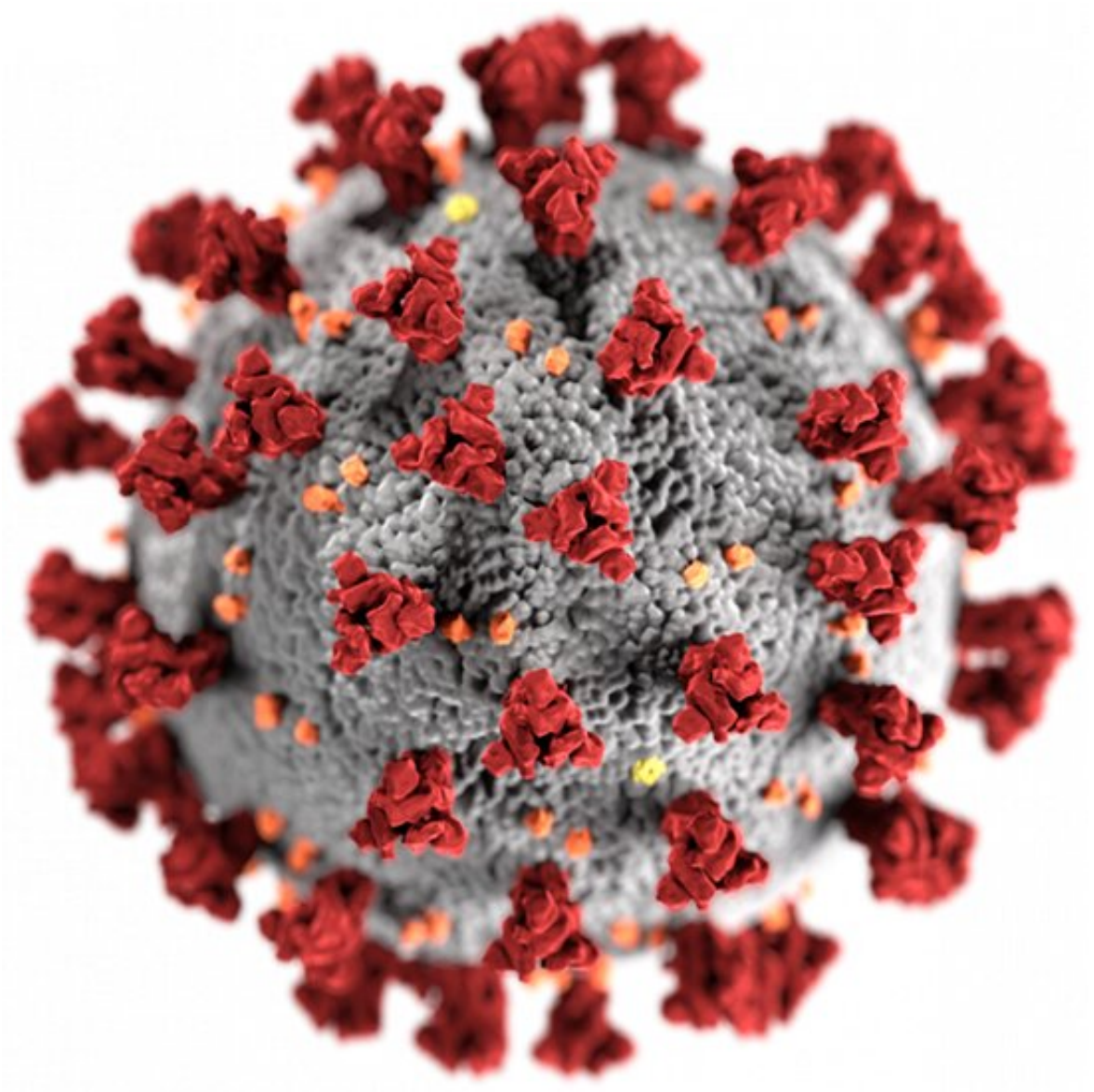

Image of the ultrastructural morphology exhibited by the 2019 Novel Coronavirus (2019-nCoV). Credit: CDC

Researchers at the Francis Crick Institute have characterised the structure of the SARS-CoV-2 spike protein as well as its most similar relative in a bat coronavirus. The structures provide clues about how the spike evolved and could help inform vaccine design.

A characterising feature of SARS-CoV-2, the virus that causes COVID-19, is the protein spikes which cover the surface, which the virus uses to bind with and enter human cells.

Analysing the structure of these spikes could provide clues about the virus' evolution. It is not yet known how SARS-CoV-2 evolved to infect humans and whether this happened directly from coronaviruses in bats or via an intermediary species.

In their study, published in *Nature Structural & Molecular Biology*, the researchers characterised the spike protein in high resolution using a technique called cryo-electron microscopy, which allowed them to achieve a greater level of detail than previously reported structures. They then compared this structure to the spike protein of a bat coronavirus, RaTG13, which has the most similar spike to that of SARS-CoV-2.

While the spikes as a whole were over 97% similar, the researchers found a number of significant differences at the location where SARS-CoV-2 binds with a receptor on human cells, called ACE2, and at the surfaces that keep the subunits of the spike together.

These differences mean the spike of SARS-CoV-2 is more stable and is able to bind around 1,000 times more tightly to a human cell than this bat virus.

Based on their findings, the researchers suggest it is unlikely that a bat

virus similar to RaTG13 could infect human cells. This supports the theory that SARS-CoV-2 is the result of different coronaviruses coming together and evolving over time, potentially also through several host species.

Antoni Wrobel, co-lead author and postdoctoral training fellow in the Structural Biology of Disease Processes Laboratory at the Crick, says: "The spike is the entry key that allows SARS-CoV-2 into human cells. Changes in the virus' genome, which affect the spike's structure, therefore have potential to make the virus either more or less able to enter the host's cell."

"At some point in the evolution of this virus, it seems to have picked up changes, like the differences we found, which made it able to infect humans."

Donald Benton, co-lead author and postdoctoral training fellow in the Structural Biology of Disease Processes Laboratory at the Crick, says: "The exact process of how SARS-CoV-2 evolved remains unclear and is something many researchers are trying to piece together. Our work provides a piece of this puzzle, as it suggests that the virus did not come straight from the bat coronaviruses currently known."

Steve Gamblin, group leader of the Structural Biology of Disease Processes Laboratory at the Crick says: "The world was caught off guard by SARS-CoV-2. Examining the structure of this virus, and its likely precursor, helps us understand where it came from, and how it interacts with human cells."

The Crick researchers will continue to study the structure of the virus, with a view to finding further clues as to its evolutionary path.

The spike protein structures are open-access, so other researchers can

use these in their work and to aid with drug discovery and vaccine design.

More information: Antoni G. Wrobel et al. SARS-CoV-2 and bat RaTG13 spike glycoprotein structures inform on virus evolution and furin-cleavage effects, *Nature Structural & Molecular Biology* (2020). DOI: 10.1038/s41594-020-0468-7

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