Discovery of new COVID infection mechanism offers clue to SARS-CoV-2 leap to humans

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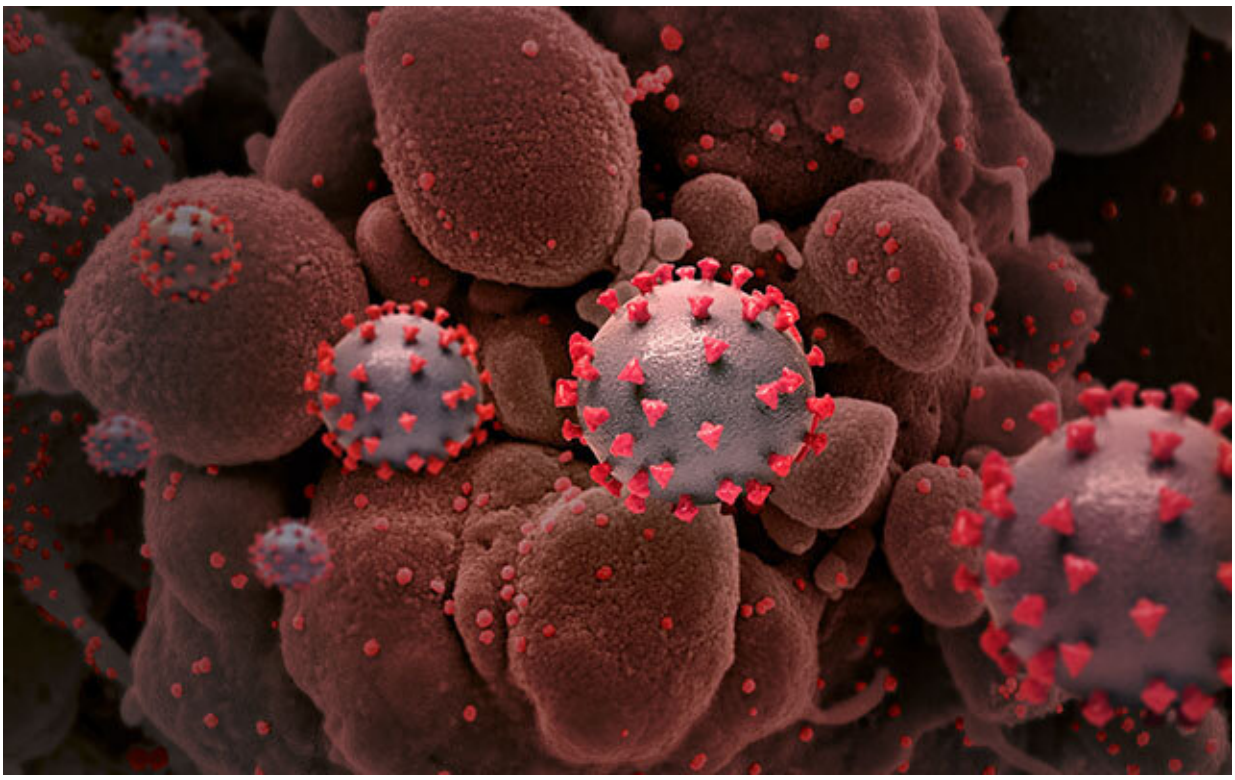

Creative rendition of SARS-CoV-2 particles (not to scale). Credit: National Institute of Allergy and Infectious Diseases, NIH

The original SARS-CoV-2 viral strain that emerged in early 2020 was able to latch on to sugars known as sialic acids, found on the surface of

human cells, an ability that later strains did not retain.

This binding was found using a combination of magnetic resonance and extremely precise high-resolution imaging, conducted at the Rosalind Franklin Institute and University of Oxford, and published in the journal *Science* this week.

This unique ability in the early strain also raises the possibility that this is how the virus first transferred from animals to humans.

Subsequent variants of concern, such as Delta and Omicron, do not have this ability to grab sialic acid and rely on receptors on their crown spikes to attach to proteins called ACE2 on human cells.

An international team led by scientists at the Rosalind Franklin Institute used magnetic resonance and complex imaging techniques to investigate further. Using a nuclear magnetic resonance (NMR) spectroscopy technique called saturation transfer difference, they developed a new, sophisticated analysis method to address the complex problem. They have called the technique universal saturation transfer analysis (uSTA).

Professor Ben Davis of the Rosalind Franklin Institute and University of Oxford, one of the paper's senior authors, said, "Two of the ongoing mysteries of the coronavirus pandemic are the mechanisms behind viral transmission and the origins of the zoonotic leap.

"There is evidence that some influenza viruses can grab sialic acid on the surface of human host cells, and this has been seen in Middle Eastern Respiratory Syndrome (MERS), which is a coronavirus. Although SARS-CoV-2 variants of concern had not shown this mechanism, our research finds that the viral strain that emerged in early 2020 could use this as a way of getting into human cells."

The binding mechanism is found on the end of the N-terminal domain, which is a part of the virus that evolves more rapidly. The domain has previously been implicated in sialic acid binding but until the Rosalind Franklin Institute team applied high-resolution precision imaging and analysis, this was unproven.

As to why the virus has discarded the sugar binding feature as it has evolved into new variants, Professor Davis hypothesizes that it may be necessary for the initial zoonotic leap into humans from animals but that it can then be hidden until it is required again—particularly if the feature is broadly detrimental to the virus's mission of replication and infection within humans.

The finding correlates with evidence from the first wave in Italy. The Italian Genomics Consortium saw a correlation between severity of COVID-19 illness and genetics, as patients with a particular gene mutation—one that affects the type of sialic acid on cells—were underrepresented in intensive care units. This suggested the virus was finding it easier to infect some genotypes compared to others.

Professor James Naismith, Director of the Rosalind Franklin Institute, says, "With our ultra-high precision imaging and new method of analysis we can see a previously unknown structure at the very end of the SARS-CoV-2 spike. The amazing thing is that our finding correlates with what the Italian researchers noted in the first wave, suggesting that this was a key role in early infection.

"The new technique can be used by others to shed light on other viral structures and answer extremely detailed questions. This work is an example of the unique technologies the Rosalind Franklin Institute was set up to develop."

More information: Charles J. Buchanan et al, Pathogen-sugar

interactions revealed by universal saturation transfer analysis, *Science* (2022). DOI: 10.1126/science.abm3125

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