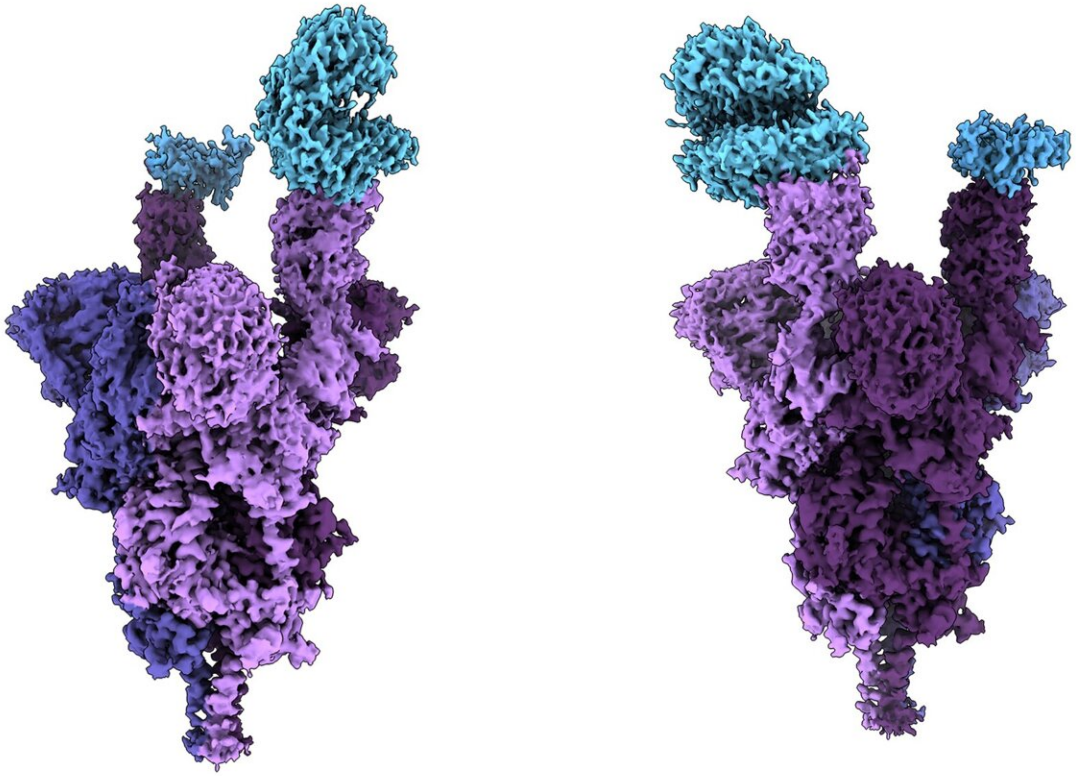
MedicalXpress

World's first molecular-level analysis of omicron variant spike protein

December 23 2021, by Brett Goldhawk



Atomic structure of the Omicron variant spike protein (purple) bound with the human ACE2 receptor (blue). Credit: Dr. Sriram Subramaniam

UBC researchers are the first in the world to conduct a molecular-level structural analysis of the omicron variant spike protein.

The analysis—done at near atomic resolution using a cryo-electron microscope—reveals how the heavily mutated variant infects human cells and is highly evasive of immunity. The findings shed new light on why omicron is highly transmissible and will help accelerate the development of more effective treatments.

Dr. Sriram Subramaniam (he/him), professor in UBC faculty of medicine's department of biochemistry and molecular biology, discusses the implications of his team's research, which is currently under peer review and available as a preprint at bioRxiv.

What did you examine with this study?

The omicron variant is unprecedented for having 37 spike protein mutations—that's three to five times more mutations than any other variant we've seen.

This is important for two reasons. Firstly, because the spike protein is how the virus attaches to and infects human cells. Secondly, because antibodies attach to the spike protein in order to neutralize the virus. Therefore, small mutations on the spike protein have potentially big implications for how the virus is transmitted, how our body fights it off, and the effectiveness of treatments.

Our study used cryo-electron microscopy and other tests to understand how mutations impact the behavior of the omicron variant at a molecular level.

What does your analysis reveal?

We see that several mutations (R493, S496 and R498) create new salt bridges and hydrogen bonds between the spike protein and the human

cell receptor known as ACE2. This appears to increase binding affinity—how strongly the virus attaches to human cells—while other mutations (K417N) decrease the strength of this bond.

Overall, the findings show that omicron has greater binding affinity than the original SARS-CoV-2 virus, with levels more comparable to what we see with the delta variant. It is remarkable that the omicron variant evolved to retain its ability to bind with human cells efficiently despite such extensive mutations.

What about the effectiveness of antibodies?

Our experiments confirm what we're seeing in the real world—that the omicron spike protein is far better than other variants at evading monoclonal antibodies that are commonly used as treatments, as well as at evading the immunity produced by both vaccines and natural infection.

Notably, omicron was less evasive of the immunity created by vaccines, compared to immunity stemming from natural infection in unvaccinated COVID-19 patients. This suggests that vaccination remains our best defense against the omicron variant.

What do these molecular-level changes tell us about the macro behavior of the omicron variant?

Both the characteristics we see as a result of spike protein mutations—strong binding with human cells and increased antibody evasion—are likely contributing factors to the increased transmissibility of the omicron variant. These are the underlying mechanisms fuelling the variant's rapid spread and why omicron could become the dominant variant of SARS-CoV-2 very quickly.

How do we treat a variant that is so effective at evading immunity?

The good news is that knowing the molecular structure of the spike protein will allow us to develop more effective treatments against omicron and related variants in the future. Understanding how the virus attaches to and infects human cells means we can develop treatments that disrupt that process and neutralize the virus.

An important focus for our team is to understand better the binding of neutralizing antibodies and treatments that will be effective across the entire range of variants, and how those can be used to develop variant-resistant treatments.

More information: Dhiraj Mannar et al, SARS-CoV-2 Omicron Variant: ACE2 Binding, Cryo-EM Structure of Spike Protein-ACE2 Complex and Antibody Evasion (2021). DOI: 10.1101/2021.12.19.473380

Provided by University of British Columbia