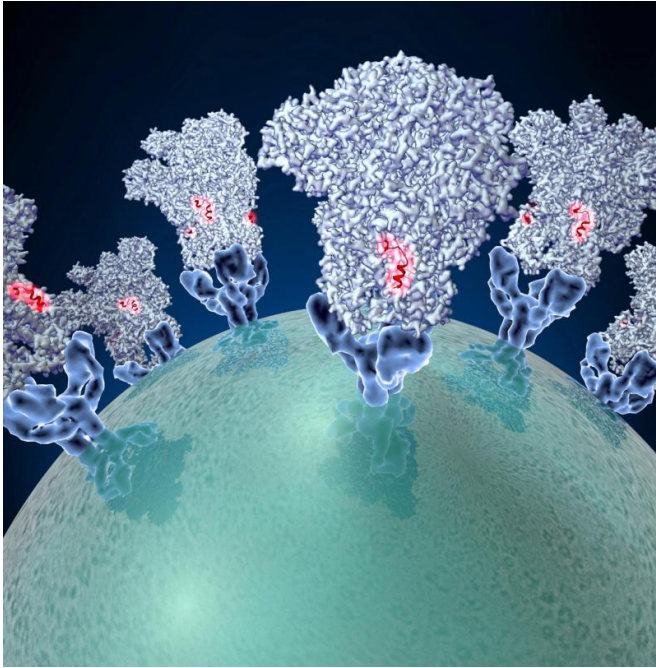


Electron microscopy captures snapshot of structure coronaviruses use to enter cells

27 February 2016



Coronaviruses -- the agents behind outbreaks of new kinds of pneumonia -- employ molecular tactics to infect cells. Credit: Veessler Lab/University of Washington

High-resolution cryo-electron microscopy and supercomputing have now made it possible to analyze in detail the infection mechanisms of coronaviruses. These viruses are notorious for attacking the respiratory tract of humans and animals.

A research team that included scientists from the University of Washington (UW), the Pasteur Institute and the University of Utrecht has obtained an atomic model of a coronavirus spike protein that promotes entry into cells. Analysis of the model is providing ideas for specific vaccine strategies. The study results are outlined in a recent UW Medicine-led study published in *Nature*. David Veessler, UW assistant professor of biochemistry, headed the project.

These viruses, with their crowns of spikes, are responsible for almost a third of mild, cold-like symptoms and atypical pneumonia worldwide, Veessler explained. But deadly forms of coronaviruses emerged in the form of SARS-CoV (severe acute respiratory syndrome coronavirus) in 2002 and of MERS-CoV (Middle East respiratory syndrome coronavirus) in 2012 with fatality rates between 10 percent to 37 percent.

These outbreaks of deadly pneumonia showed that coronaviruses can transmit from various animals to people. Currently, only six coronaviruses are known to infect people, but many coronaviruses naturally infect animals. The recent deadly outbreaks resulted from coronaviruses overcoming the species barrier. This suggests that other new, emerging coronavirus with pandemic potential are likely to emerge. There are no approved vaccines or antiviral treatments against SARS-CoV or MERS-CoV.

The ability of coronaviruses to attach to and enter specific cells is mediated by a transmembrane spike glycoprotein. It forms trimers decorating the virus surface. Trimers are structures assembled from three identical protein units. The structure the researchers studied is in charge of binding to and fusing with the membrane of a living cell. The spike determines what kinds of animals and what types of cells in their bodies each coronavirus can infect.

Using state of the art, single particle [cryo-electron microscopy](#) and supercomputing analysis, Veessler and his colleagues revealed the architecture of a mouse coronavirus spike glycoprotein trimer. They uncovered an unprecedented level of detail. The resolution is 4 angstroms, a unit of measurement that expresses the size of atoms and the distances between them and that is equivalent to one-tenth of a nanometer.

"The structure is maintained in its pre-fusion state, and then undergoes major rearrangements to

trigger fusion of the viral and host membranes and initiate infection," Veesler explained.

The coronavirus fusion machinery is reminiscent of the fusion proteins found in another family of viruses, the paramyxoviruses, which include respiratory syncytial virus (the leading cause of infant hospitalizations and wheezing in children) as well as the viruses that cause measles and mumps. This resemblance implies that the coronavirus and paramyxovirus fusion proteins could employ similar mechanisms to promote viral entry and share a common evolutionary origin.

The researchers also compared crystal structures of parts of the spike protein in mouse and human coronaviruses. Their findings provide clues as to how the molecular structure of these protein domains might influence which specific animal species the virus is able to infect.

The researchers also analyzed the structure for possible targets for vaccine design and anti-viral therapies. They observed that the outer edge of the coronavirus spike trimer has a fusion peptide - a chain of amino acids - that is involved in viral entry into host cells. The easy accessibility of this peptide, and its expected similarity among a number of coronaviruses, suggests possible vaccine strategies to neutralize a variety of these viruses.

"Our studies revealed a weakness in this family of viruses that may be an ideal target for neutralizing coronaviruses," Veesler said.

There may be a way, the researchers noted, to elicit broadly neutralizing antibodies recognizing this peripheral peptide. Neutralizing antibodies protect against infections by stopping a mechanism in a pathogen. Broadly neutralizing antibodies would be effective against several strains of pathogen, in this case coronaviruses. The physical structure of the fusion peptide inspires ideas for the design of proteins that would disable it.

"Small molecules or protein scaffolds might eventually be designed to bind to this site," Veesler said, "to hinder insertion of the fusion peptide into the host cell membrane and to prevent it from

undergoing changes conducive to fusion with the host cell. We hope that this might be the case, but much more work needs to be done to see if it is possible."

The coronavirus spike protein structure described in this Letter to *Nature* is expected to resemble other coronavirus spike proteins.

"Therefore, the structure we analyzed in the mouse coronavirus is likely to be representative of the architecture of other coronavirus spike proteins such as those of MERS-CoV and SARS-CoV," the researchers observed.

The researchers summed up their paper, "Our results now provide a framework to understand coronavirus entry and suggest ways for preventing or treating future coronavirus outbreaks."

"Such strategies," Veesler said, "would be applicable to several existing coronaviruses and to emerging future strains of coronavirus that conserve this same structure for entering cells."

More information: Alexandra C. Walls et al. Cryo-electron microscopy structure of a coronavirus spike glycoprotein trimer, *Nature* (2016). [DOI: 10.1038/nature16988](https://doi.org/10.1038/nature16988)

Provided by University of Washington

APA citation: Electron microscopy captures snapshot of structure coronaviruses use to enter cells (2016, February 27) retrieved 16 November 2019 from <https://medicalxpress.com/news/2016-02-electron-microscopy-captures-snapshot-coronaviruses.html>

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