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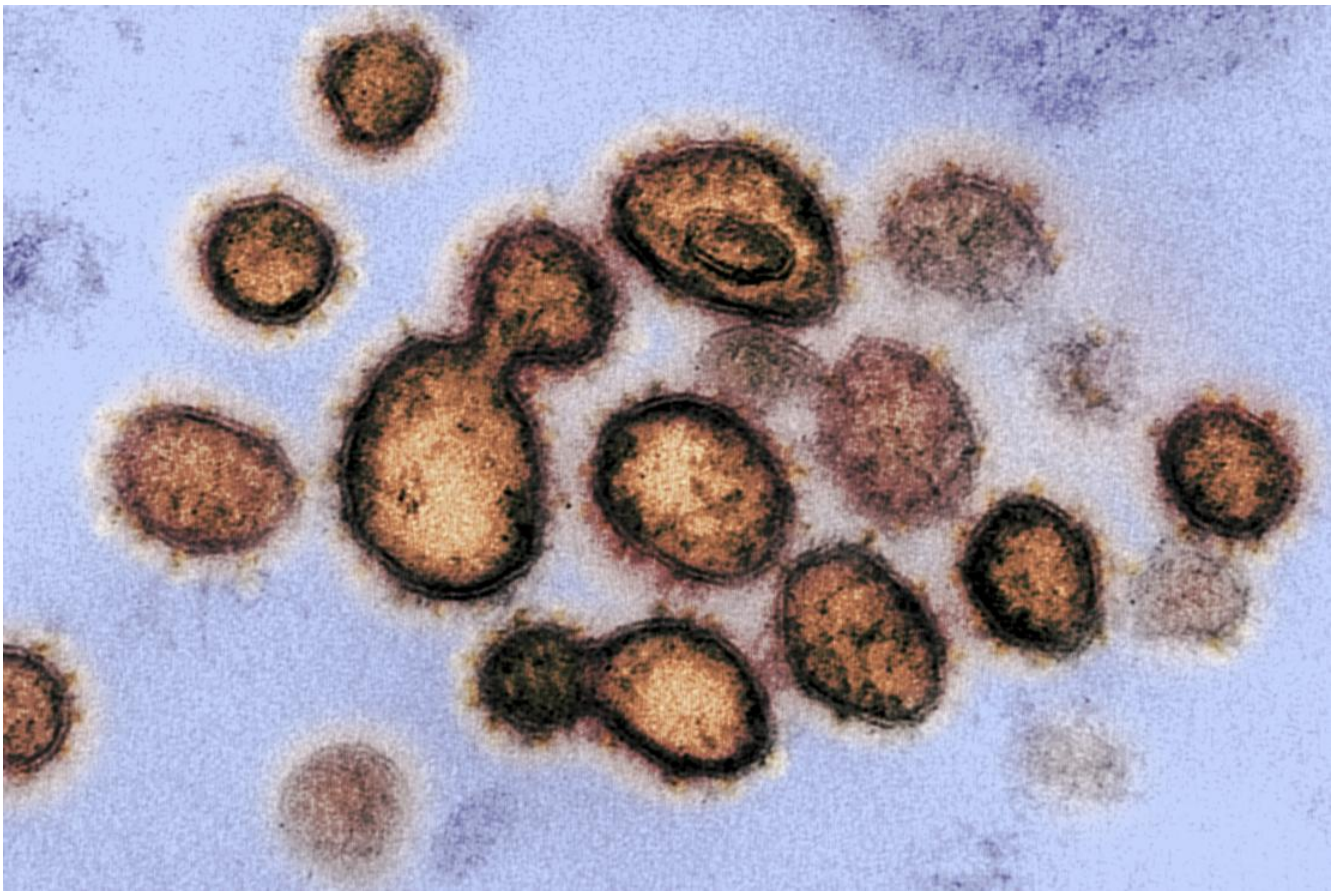

Q&A: How Covid-19 hijacks human cells

The virus that causes Covid-19 hijacks human cells by exploiting a 'doorway' that is potentially also used by other deadly viruses such as HIV, dengue and Ebola, according to recent research that may help to explain why the coronavirus is so highly infectious to a wide range of organs in the body.

Dr Yohei Yamauchi, a viral cell biologist at the University of Bristol, UK, who led the research, believes that the finding could not only lead to new drugs against Covid-19, but other anti-viral treatments that could be used to save patients' lives in future pandemics.

15 December 2020 - By RICHARD GRAY

Why is the molecular biology of viruses important?

I've always been interested in how cells are hijacked by viruses. When you look at a virus through a microscope, you can only see so much because they are really small compared to a cell. It is a bit like looking at a building from a satellite – you can't see the people inside or how they open the doors to get in. I'm trying to understand how a virus opens the door to get inside the cell and take it over at a molecular level – what cellular proteins and processes are involved.

How did you end up working on Covid-19?

For several years I have been studying flu and a few other viruses like Zika and HIV-1 (the most common HIV virus). We have been finding that many viruses use the same doors to get into a cell, but open them in their own individual ways. When the genetic sequence of Sars-CoV-2 (the virus that causes Covid-19) was published in February, we immediately recognised part of the sequence that codes for the spike protein.

What is the spike protein?

The Sars-CoV-2 virus has all these spikes sticking up from the virus particle that make it look like a crown – that is why it is called a coronavirus (corona is Latin for crown). These spikes are proteins that are like a hook on the outside of the virus particle, which allow it to recognise and bind to human proteins on the surface of cells. Without the spike protein, the virus would have no way of sticking to the surface of cells and infecting them.

The spike protein is also the ideal target for vaccines – both the Moderna and Pfizer/BioNTech vaccines target the spike protein – so understanding it helps to improve them.

Dr Yamauchi says that drugs that interrupt neuropilin 1 binding could be used against of a wide variety of viruses, in
Dr Yamauchi says that drugs that interrupt neuropilin 1 binding could be used against of a wide variety of viruses, including those that may emerge in future pandemics. Image credit - Yohei Yamauchi

What caught your eye about the Covid-19 spike protein?

The spike protein really differentiates this coronavirus from previous ones. We know about the ones that cause SARS or MERS. It's got these specific, unique sequences at the molecular level that allow it to bind to proteins on the cell surface. At some point this (novel) coronavirus obtained a sequence in its spike protein that allows it to be cleaved in two by an enzyme found in its host (humans) called furin. We had seen this furin cleavage in other viruses such as in the H5N1 highly pathogenic avian flu virus, where it appears in the flu equivalent of the spike protein. Other pathogenic viruses also have furin cleavage sites on the proteins that bind to cells – HIV, Ebola and Crimean-Congo haemorrhagic fever virus all have them.

Why is this important?

The scientific community already knew that Sars-CoV-2 had at some point obtained the ability to bind with a greater affinity to a receptor protein (a type of protein on the surface of a cell) called ACE2 compared to the S ARS coronavirus. But when the furin cleaves the spike protein, it exposes a new sequence which allows it to bind to another host cell protein and hijack its function. We identified that protein as neuropilin 1 and it could be this that makes Sars-CoV-2 so highly infectious in many organs.

What does neuropilin 1 normally do in the body?

Neuropilin 1 is a receptor protein found on the surface of many cells that triggers the transportation of the molecules that bind to it inside the cell. It also allows molecules to be passed from cell to cell. In 3D tissue, that means something binding to neuropilin 1 on the top layer of cells could easily reach the middle layers of cells.

Some people in cancer biology are very interested in it for this reason. If you can trigger neuropilin 1, you can increase the uptake of small drug molecules into otherwise solid tumours.

How does this help the virus?

This is still a hypothesis, but we think viruses able to trigger neuropilin 1 might be able to dig deeper into tissues without first having to replicate themselves in the upper layer of cells. That would be an amazing bypassing mechanism for a virus.

Would that make it harder for the immune system to spot them too?

Exactly. And it would eventually mean the virus spreads quicker. It would help to give it this broad tropism (ability to infect many different organs and tissues) we are seeing in Covid-19 compared to the coronavirus that caused SARS, which doesn't have that furin cleavage site. The current virus is able to cause neurological symptoms like loss of smell, and taste, it is causing myocarditis (inflammation of the heart) in some patients, as well as going to the lungs.

We think the CoV-2 virus might be using neuropilin 1 to facilitate trafficking into other types of cells by binding to cells on the surface of tissues that have neuropilin 1.

Can we use neuropilin 1 to find new treatments for Covid-19?

We are doing a follow up study on this, but we found that by interrupting the interaction between the viral spike protein and neuropilin 1 we can decrease infectivity in human cell cultures. Due to the intense study in cancer biology on neuropilin 1, there are already neuropilin 1-neutralising antibodies that have been in phase 2a clinical trials in the US against certain types of cancer. There is also a small molecule antagonist that competes with other molecules at the neuropilin 1 binding site. Those are already out there, so by fine tuning them and improving their affinity (ability to bind to neuropilin), we could produce some sort of drug that interrupts the interaction of the virus spike protein with neuropilin 1. It could be effective in reducing the severity of disease in patients.

> Researchers have discovered that the coronavirus spike protein can bind to a receptor called neuropilin 1, which give
> Researchers have discovered that the coronavirus spike protein can bind to a receptor called neuropilin 1, which gives it another way to enter human cells. Image credit - Ryan Allen

What are you doing next?

We have found that the spike protein can bind to neuropilin 1 in more than one place – it has at least two binding sites. The virus probably originated binding just at one place. Then it found by gaining this furin binding site, it either increased binding strength or triggered internalisation. We are now trying to understand its whole interaction. We have some preliminary data that if we can block the spike protein from binding to neuropilin 1 completely, it really impacts infectivity even more.

What might your research lead to longer term?

My theory is that neuropilin 1 has been and always will be a favoured receptor for a lot of viruses because of its multi-functionality in helping internalisation and spread through tissues. Each virus seems to have found a different way to bind to it.

It seems almost unavoidable that a future pandemic will also be caused by a virus that also binds to neuropilin 1. If we had a drug in advance that interrupts this interaction, we could use it at a very early stage of a pandemic and hopefully save patients' lives.

That is really the aim of the wider CHUbVi project that I am part of – we want to target the mechanisms viruses use to get into cells to make broad-spectrum antiviral drugs that can be used against a number of viruses.

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