EMBnet.journal
Bioinformatics in Action

a way in

Vivienne Baillie Gerritsen

As children in Scotland, back home from school and when the weather was dry, we would fling our schoolbags into the hall and grab a few golf clubs, a ball and a tee. There was no need for a change of clothes or shoes, whatever we were wearing was good enough. The course was along the coast on the edge of the North Sea, and the balls we used were found in the dunes where they had been lost by more experienced players. We had four clubs – a driver, two irons and a putter. Putting was the best part of the game. You would aim carefully for the long slim rod with the little red flag, taking into account the odd clump of grass or small mounds on the green and then, holding your breath, watch the little white ball as it made its meandering way to the base of the rod to drop, almost as an afterthought, into the hole. Well… it so happens that viruses infect cells in a similar manner… Viruses need to get inside cells in order to multiply, and this is what brings on infection. Like the flagged pole that marked the way in for our golf ball, viruses recognise molecules on the surface of cells to which they bind, thus enabling them – or parts of them – to enter the host cells where they rapidly spread. The coronavirus which is wreaking havoc across the planet as I write these words, is able to recognise a protein on the surface of a variety of human cells known as angiotensin-converting enzyme 2, or ACE2.

Coronavirus, illustration by David Goodsell

Courtesy of the artist

Viruses are unable to multiply on their own, so they seek help. Cells are their only bet: plant cells, animal cells or even bacteria – every virus has its specificity. Why? Because cells have all the machinery viruses need to produce their little ones: virions. There are many different kinds of viruses and many ingenious ways of infecting cells but, to cut a long story short, the sole aim of a virus is to have its genome read and translated, so that the host cell produces everything the virus needs to make its progeny – by the thousands. Once the cell cannot contain them anymore, it literally bursts and the virions are released into the environment to repeat what their parents have just done. Infection spreads rapidly.

What is more, spontaneous mutations are bound to occur and progeny – thanks to the brief time-lapse between generations and the laws of natural selection – are not only a little different from their parents but also frequently better at reproducing themselves. This is one of the reasons it can be so difficult to develop vaccines.

Why do viruses exist, you may wonder. It is a question no one can answer. Viruses may seem to cause more harm to Nature than they do good. However, this is not quite true. Their aim is not to cause disease but to replicate - and in so doing, they unfortunately also frequently cause damage, sometimes leading to death. It so happens, too, that our genomes - like those of plants and other animals - carry myriads of small stretches of genetic material which have been acquired over time through bouts of viral infection, and passed down to future generations. Some of this material turns out to be genetically beneficial. For instance, in mammals, the foetal placenta is separated from the mother's tissues thanks to a gene of viral origin. Some organisms also live in symbiosis with viruses - in this way, greenfly carry with them plant viruses that muffle the reactivity of plants they attack. What we know for sure is that viruses have been around for a very long time. In fact, they were probably part of the primordial genetic pool, and perhaps on the earth's surface before even cells appeared. But that is open to debate.

So, although viruses seem to be as old as life itself, no one knew what a virus looked like until the advent of electronic microscopy in the 1930s. Towards the close of the 19th century, scientists had begun to suspect that fluids like sap and pus held infectious substances that

the Dutch microbiologist Martinus Beijerinck (1851-1931) named "virus" from the Latin meaning slime, or poison. The first actual virus to be observed under the electron microscope was the plant tobacco mosaic virus, which looks like a small space shuttle. Its full structure was elucidated in 1955 on the basis of information gathered by the English chemist Rosalind Franklin (1920-1958). Following this, the architecture of many other viruses was elucidated as well as the vectors they use to reach their host cells – such as insects, body fluids, water or air. Today, over 5,500 viruses have been identified while new viruses and strains continue to be unveiled.

Coronavirus is spherical in shape. Its outside envelope protects the virus's genome, which the host cell will dutifully read and translate to produce hordes of coronavirions. The coronavirus which is creating global chaos at this very moment has been baptized SARS-CoV-2, for Severe Acute Respiratory Syndrome coronavirus "number 2", a cousin of SARS-CoV that spread across 26 countries in 2003 but was far less severe than SARS-CoV-2. Like all coronaviruses, SARS-CoV-2's surface is riddled with a protein known as the spike (S) protein that assembles as a crown around the virion, hence "corona". S proteins recognise angiotensin-converting enzyme 2, ACE2, on the surface of human cells that are abundant in our lungs and our cardiovascular and renal systems. Upon recognition, SARS-CoV-2 binds to the cell via ACE2. This may well initiate a structural change in both proteins finally resulting in the entry of ACE2 and the virus into the cell by way of a small intracellular bubble-like compartment known as an endosome. It is not hard to understand, then, why this particular coronavirus is able to cause respiratory distress, and is dangerous for those already suffering from a cardiovascular disease.

Like all viruses, SARS-CoV-2 is simply twisting a protein's fate – and a cell's – for its own benefit; ACE2 did not evolve for the sake of a virus. What does it do? ACE2 is a metallopeptidase that modifies angiotensin – a peptide hormone that causes vasoconstriction and an increase in blood pressure. ACE2 is claw-like in appearance; the "claw" protrudes from the cell membrane while a short tail-end anchors it in the cell's membrane. Two ACE2 monomers join to form an active dimer. ACE2 is an integral component of what is known as the renin-angiotensin system that controls blood pressure, as well as fluid and salt balance. In particular, ACE2 converts angiotensin into three smaller hormones Ang (1-7), Ang (1-9) and alamandine – all of which are involved in increasing vasodilation and reducing fibrosis, the exact opposite of what occurs with angiotensin. During viral infection by SARS-CoV-2, the S protein is thought to bind to ACE2 on the very tip of the claw, from where the virus will find its way in.

One of ACE2's original roles is to produce hormones that have positive cardiovascular effects – which makes it an ideal candidate for developing therapies against high blood pressure for instance. ACE2 is also an open door, though, for SARS-CoV-2. Understanding how exactly the S protein binds to ACE2 could provide a means to develop ligands or antibodies that would help suppress viral infection – without neutralizing ACE2 function. It is a complicated matter, given that ACE2 is probably not the only path SARS-CoV-2 uses to enter cells and that, like all viruses, the virus has this debilitating habit of mutating at a swift rate. Much has been understood over the past years and yet, as always, so little too. Research is moving fast these days to find something that will help to fight off SARS-CoV-2 infection and its disease, COVID-19. It is mind-boggling how a such a tiny parcel of chemistry – and not of our making – has managed to bring human society to near asphyxiation. The rest of nature, however, seems to be getting a well-deserved breath of fresh air.

Cross-references to UniProt

Angiotensin-converting enzyme 2, *Homo sapiens* (Human): Q9BYF1

References

1. Mendoza-Torres E., Oyarzún A., Mondaca-Ruff D., et al.
ACE2 and vasoactive peptides: novel players in cardiovascular/renal remodeling and hypertension
Therapeutic Advances in Cardiovascular Disease 9:217-237(2015)
PMID: 26275770

2. Yan R., Zhang Y., Li Y., Xia L., Guo Y., Zhou Q.
Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2
Science 10.1126/science.abb2762 (2020)
PMID: 32132184

3. Guo Y.-R., Cao Q.-D., Zhong-Si H., et al.
The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status
Military Medical Research https://doi.org/10.1186/s40779-020-00240-0 (2020)
PMID: 32169119

proteinspotlight

SIB Swiss Institute of Bioinformatics

Protein Spotlight (ISSN 1424-4721) is a montly review written by the **Swiss-Prot** team of the **SIB Swiss Institute of Bioinformatics**. Spotlight articles describe a specific protein or family of proteins on an informal tone. http://web.expasy.org/spotlight/