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THE COVID-19 VIRUS AND ITS POLYPROTEINS

Relevant for: Developmental Issues | Topic: Health & Sanitation and related issues

Electron microscope image of the coronavirus that causes COVID-19. The sample was isolated from a patient in the U.S. Excitement about treating the new coronavirus with malaria drugs is raising hopes, but the evidence that they may help is thin. Photo: U.S. National Institutes of Health/AP

Everyday, we hear about the novel coronavirus (COVID-19), how it is easily infecting and transmitting itself from people to people, and how scientists and medical experts are waging a war against its spread. We also hear how different this is from bacteria, and why treating people with antibacterial drugs may not help wipe this out. What then is the difference between a virus and a bacterium? Well, bacteria are alive. Each bacterial cell has its own machinery to reproduce itself. Take a bacterial cell, and put it in a solution containing nutrients, it grows itself and multiplies in millions. The genes in the cells (genome, made up of DNA molecules, the information contained in which is transcribed as a message to the messenger molecules called RNA), and the message therein is translated into action molecules called proteins, which are the foot-soldiers that help the growth and multiplication of the bacterium. Coronaviruses do not have DNA as their genome, but RNA; in other words, they can only translate and not transcribe. Thus, they are ‘dead’, unable to renew and grow themselves; they need help. This they achieve by infecting ‘host cells’ which they bind to, and multiply by the millions. With no host cell to help, a virus is simply a dead storage box.

COVID-19 | The SARS-CoV-2 is mutating, say scientists

Upon infection, the entire RNA with its 33,000 bases is translated in one shot as a long tape of amino acid sequences. Since this long chain contains several proteins within it, it is called a “polyprotein” sequence. One needs to analyse this long chain, find the relevant proteins, isolate and study what each of them does in helping infection. (Scientists call the polyprotein a ‘single reading frame’, containing several ‘open reading frames’, namely those that contain a start code and end with a stop code, each containing the relevant protein to be expressed by the host cell). This strategy allows the viral genome to be compact, and express the protein when the need arises. This is somewhat like a thrifty individual who keeps his money in a fixed deposit in a bank, and withdraws chosen amounts as the demand arises. For the virus, the demand is to multiply upon infecting the host. No demand, no withdrawal, no infection, no multiplication!

Finally, India shares two SARS-CoV-2 genome sequences

As the recent review by Yu Chen and colleagues from China in the Journal of Medical Virology points out (https://doi.org/10.1002/jmv.25681), COVID19 has RNA-based genomes and subgenomes in its polyprotein sequence, that code for the spike protein (S), the membrane protein (M), the envelope protein (E), and the nucleocapsidprotein (N, which covers the viral cell nuclear material) - all of which are needed for the architecture of the virus. In addition to these, there are special structural and accessory proteins, called non-structural proteins (NSP), indeed 16 of them, which serve specific purposes for infection and viral multiplication.

We thus have a large set of proteins in the virus, against which a number of potential molecules and drugs can be tried to interfere and stop the production of these viral proteins. Indeed, this has been tried to advantage by several recent publications during the last month alone. One of them has attempted to target the translation of the key enzyme RDRp in the virus, whose production was stopped by the drug Remdesavir. Three studies from the US, Germany and

China have come up with methods to stop the production of the enzyme (called CL3pro, also called as Mpro) which is needed to make the spike (S protein). And the paper by Yu Chen et al, quoted above lists as many as 16 NSPs in the viral polyprotein, which can be targeted by potential drug molecules. (And Dr PandurangaRao from Boston is quoted as stating that the enzyme nsp12 to be a high-value target).

It is important in this context to cite the longstanding excellent work being done by an Indian researcher, Thanigaimalai Pillaiyar (what an auspicious name- in homage to the street he was born in the village, he was born in Thiruvannamalai district in Tamilnadu!), who is settled as a medicinal chemist working at the University of Bonn, Germany since 2013. In a paper full of insight, which he published in 2015-16, titled: 'An overview of SARS-CoV 3CL protease inhibitors: peptidometrics and small molecule chemotherapy', that appeared in *Journal of Medicinal Chemistry,* 2016, 59 (6595-6628)(10.1021/acs.jmedchem.5b01461). In this paper, he used the X-ray crystal structure of a related virus TGEV (Transmissible Gastroenteritis Virus), found by 3D modelling a key enzyme of the SARS-CoV, called Chymotrypsin-like Cysteine Protease (3CLpro) also called the main protease (Mpro), and found that this enzyme fits into the virus structure in a lock and key manner. The next step after this molecular modelling was to find drugs that can deactivate this binding and thus inhibit the SARS-CoV from infecting. A total of about 160 known drugs were predicted to be of value with varying efficiency. Recall that this prediction and the drug list was suggested by him before the crystal structure (or the cryo-electron microscopy of COVID-19 was known) 3-4 years later! Pillaiyar and coworkers have updated their findings in their recent paper in January 2020, in the journal *Drug Discovery Today* (https://doi.org.10.1016/j.drudis.2020.01.015).

India is well versed with expertise in the area of organic and medicinal chemistry since the last 90 years and in manufacturing quality drug molecules, and exporting them for use at home and across the world since the 1970 patents act of India. Our expertise today, in both the public and private sector, includes not just synthesizing made-to-order molecules, but has added new methods involving computer modeling of target proteins from bacteria and viruses, homology modelling, drug design, repurposing of drugs, and other methods. (It is worth noting that Dr. Pillaiyar has active collaboration for quite some time with Sangeetha Meenakshisundaram at the Srikrishna College of Engineering and Technology, Coimbatore, and Manoj Manickam at the PSG Institute of Technology and Applied Research, also at Coimbatore). The CSIR has taken upon itself the express task of coming out with molecules and methods to counter the dreaded virus, and we have every hope that they will succeed in the nearest future!

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