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IISC SCIENTISTS DEVELOP MINIPROTEINS THAT MAY PREVENT COVID INFECTION

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Representational image of a 3D rendered microscopic view of a variant and strain of SARS-CoV-2. | Photo Credit: Getty Images

Researchers at the Indian Institute of Science (IISc) Bangalore have designed a new class of artificial peptides or miniproteins that they say can render viruses like SARS-CoV-2 inactive.

According to the study, published in the journal *Nature Chemical Biology*, the miniproteins can not only block virus entry into our cells but also clump virus particles together, reducing their ability to infect.

The researchers noted that a protein-protein interaction is often like that of a lock and a key.

This interaction can be hampered by a lab-made miniprotein that mimics, competes with, and prevents the 'key' from binding to the 'lock', or vice versa, they said.

The team used this approach to design miniproteins that can bind to, and block the spike protein on the surface of the SARS-CoV-2 virus, which helps it to enter and infect the human cells.

This binding was further characterised extensively by cryo-electron microscopy (cryo-EM) and other biophysical methods.

These miniproteins are helical, hairpin-shaped peptides, each capable of pairing up with another of its kind, forming what is known as a dimer. Each dimeric ‘bundle’ presents two ‘faces’ to interact with two target molecules.

The researchers hypothesised that the two faces would bind to two separate target proteins locking all four in a complex and blocking the targets’ action.

"But we needed proof of principle," said Jayanta Chatterjee, Associate Professor in the Molecular Biophysics Unit (MBU), IISc, and the lead author of the study.

The team decided to test their hypothesis by using one of the miniproteins called SIH-5 to target the interaction between the spike protein of SARS-CoV-2 and ACE2 protein in human cells.

The spike protein is a complex of three identical polypeptides, each of which contains a Receptor Binding Domain (RBD) that binds to the ACE2 receptor on the host cell surface, facilitating viral entry into the cell.

The SIH-5 miniprotein was designed to block the binding of the RBD to human ACE2.

When a SIH-5 dimer encountered an S protein, one of its faces bound tightly to one of the three RBDs on the S protein trimer, and the other face bound to an RBD from a different S protein.

This ‘cross-linking’ allowed the miniprotein to block both S proteins at the same time.

"Several monomers can block their targets. (But] cross-linking of S proteins blocks their action

many times more effectively," said Chatterjee.

Under cryo-EM, the S proteins targeted by SIH-5 appeared to be attached head-to-head, the researchers said.

“We expected to see a complex of one spike trimer with SIH-5 peptides. But I saw a structure that was much more elongated,” said Somnath Dutta, Assistant Professor at MBU and one of the corresponding authors of the study.

Dutta and others realised that the spike proteins were being forced to form dimers and clumped into complexes with the miniprotein.

This type of clumping can simultaneously inactivate multiple spike proteins of the same virus and even multiple virus particles.

The miniprotein was also found to be stable for months at room temperature without deteriorating.

To test if SIH-5 would be useful for preventing COVID-19 infection, the team first tested the miniprotein for toxicity in mammalian cells in the lab and found it to be safe.

Next, in experiments carried out in the lab of Raghavan Varadarajan, Professor at MBU, hamsters were dosed with the miniprotein, followed by exposure to SARS-CoV-2.

These animals showed no weight loss and had greatly decreased viral load as well as much less cell damage in the lungs, compared to hamsters exposed only to the virus.

The researchers noted that with minor modifications and peptide engineering, this lab-made miniprotein could inhibit other protein-protein interactions as well.

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