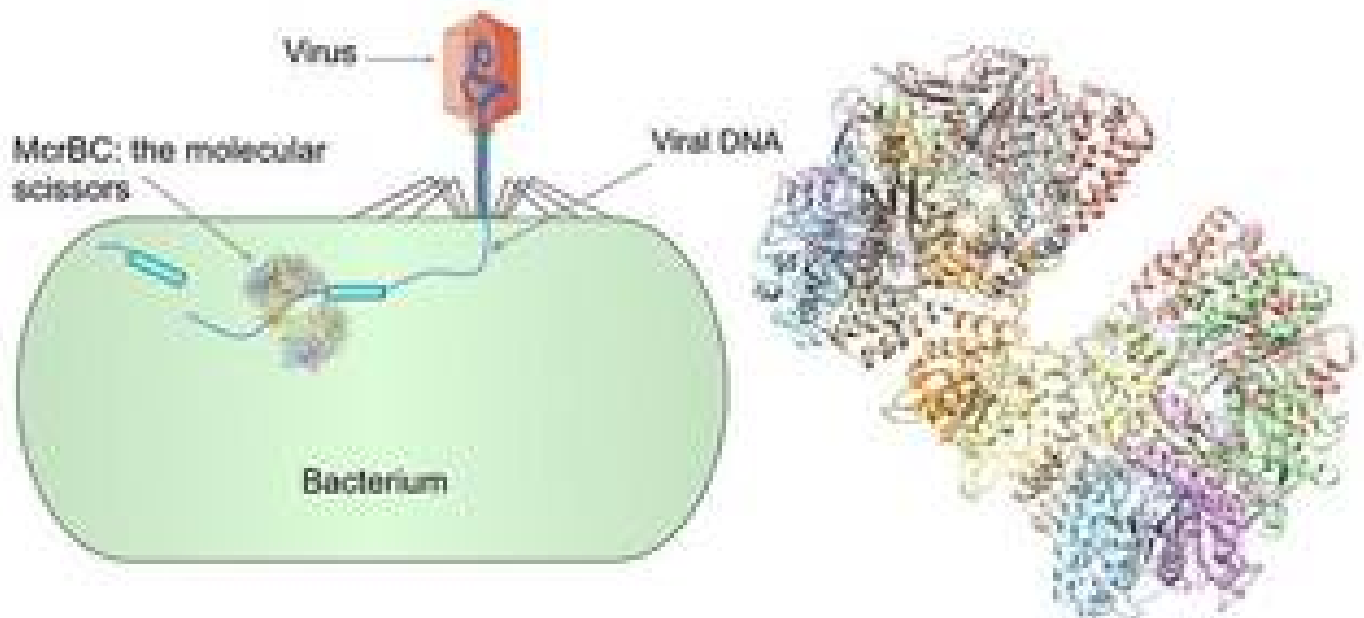


HEALTH

IISER team's find may help fight drug-resistant infections

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Researchers determine structure of McrBC, which prevents viral infections in bacteria

A team of scientists at the Indian Institute of Science Education and **Research** (IISER) in Pune claims to have determined the atomic structure of McrBC — a complex bacterial protein which helps prevent viral infections in a bacterial cell and functions as a molecular scissor.

The pathbreaking structure of the McrBC as determined by Dr. Kayarat Saikrishnan, an associate professor of biology and his team at the IISER, was published last month in two prestigious, peer-reviewed scientific journals — *Nature Communications* and *Nucleic Acids Research* (which is published by the Oxford university Press) — and is said to be a major step towards understanding the working of the molecular scissors.

This is the first report of the high-resolution structure from India determined using electron cryomicroscopy, commonly known as cryo-EM.

The determination of the McrBC's structure has long-term implications in 'phage therapy' and could help combat drug-resistant infections in the future, says Dr. Saikrishnan. Phages are groups of viruses that infect and kill bacterial cells and phage therapy is the therapeutic use of bacteriophages to treat bacterial infections.

How the 'scissors' work

"Like the human immune system, which fights viruses, bacteria too have an elaborate defence system to combat phages (the viruses which infect bacterial cells). These phages inject their DNA into the bacterial cell, wherein they multiply and duplicate the virus that eventually bursts out of that cell to infect many more. To prevent infection, bacteria have specialised 'molecular scissors' which specifically cut the foreign DNA, thus preventing their multiplication in bacterial cells," he explains, adding that the molecular scissors not only cut the viral DNA, but also regulate the entry of other foreign DNA that might host an antibiotic resistance gene.

Speaking to *The Hindu* about the importance of the McrBC's structure, Dr. Saikrishnan said the understanding of the molecular scissors would aid in combating multidrug resistant microbes. "As McrBC-like molecular scissors prevent viral infections of the bacterial cell, the design of such 'inhibitors' will be facilitated by their 3D structures," he said.

Thus far, despite contributions by research groups, relatively little has been known about how these enzymes (protein molecules in cells) work and the structure of the McrBC has remained elusive, Dr. Saikrishnan said.

'Like a blueprint'

"[The McrBC's] unique feature is that it requires to be powered by an inbuilt motor that uses GTP (guanosine triphosphate) — an energy currency of the bacterial cell — as 'fuel' to cut the foreign DNA. It is important to know how the machinery works in order to be able to regulate it. If you have a drug-resistant strain in bacteria, it is often seen that this machinery is absent and they become resistant to antibiotics," he said, remarking that the technological revolution in the field of cryo-EM had allowed the determination of the three-dimensional position of every atom in biomolecules such as the McrBC.

“Just like the blueprint of a machine which illustrates its working, the atomic structure of McrBC reveals the details of its working parts and is a snapshot of the molecular machine designed by nature in action. Information derived from the 3D structure of proteins is integral to designing their activators and inhibitors,” said Dr. Saikrishnan.

Trailblazing work in the field of bacterial immunity against viruses was first undertaken by in the early 1950s renowned Italian microbiologist Salvador Luria, who discovered the phenomenon of host-controlled restriction and modification of a bacterial virus.

“The phenomenon that the Nobel Prize-winning Luria discovered was later found to be a result of the action of McrBC, which only cuts DNA that is labelled by a specific chemical mark. Interestingly, this chemical mark is also seen in human DNA that regulates the reading of the encoded genetic information. Consequently, McrBC is used as a laboratory tool to study the readability of human and other genomes,” Dr. Saikrishnan explained.

Studying phage therapy

Commenting on the potential importance of the McrBC's structure in 'phage therapy' and the renaissance in the latter phenomenon to treat bacterial infections, he said research into phage therapy in western countries declined in the 1940s after Alexander Fleming's discovery of antibiotics.

However, it continued in the erstwhile Soviet Union, particularly in Georgia, mainly owing to the presence of Felix d'Herelle, the pioneering French-Canadian microbiologist who was one of the co-discoverers of bacteriophages. D'Herelle had travelled to Georgia in the 1930s at the invitation of Soviet dictator Joseph Stalin.

“While research [into phage therapy] was virtually abandoned in the West, it went on in Georgia. However, much of it was obscured owing to the Cold War and the Iron Curtain. Meanwhile, by the 1960s, the number of new antibiotics that were discovered the world over had started to decrease in a dramatic manner. What was also observed was that the bacteria had started acquiring resistance to these antibiotics. The main reason for the renaissance in phage therapy in the West and elsewhere is that antibiotics are losing ground,” Dr. Saikrishnan said.

He said the University of Pennsylvania had first started the project of actively collecting bacteriophages as recently as 2015.