For microbes fighting viruses, a fast response means a better defense

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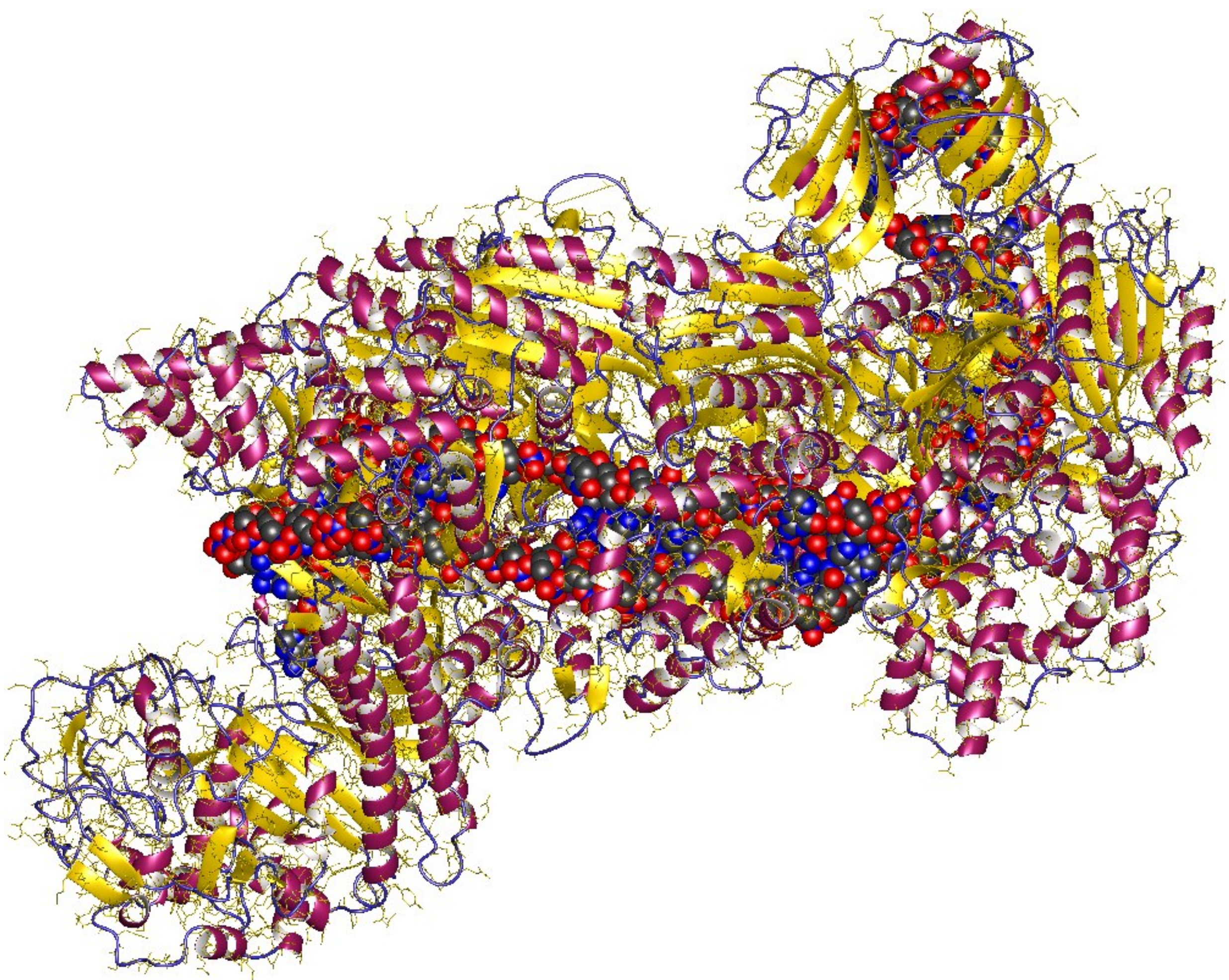

CRISPR (= Clustered Regularly Interspaced Short Palindromic Repeats) + DNA fragment, E.Coli. Credit: Mulepati, S., Bailey, S.; Astrojan/Wikipedia/ CC BY 3.0

In battles between germs, the opening shot is often an injection. A virus, intent on infecting a microbe, punctures the cell's protective wall and inserts its own genetic code. New research from The Rockefeller University reveals how microbes act quickly to fend off the incoming threat using CRISPR, a bacterial immune system that also serves as a powerful tool for editing genomes.

The discovery, described in *Nature* on March 29, answers a long-standing question as to how CRISPR works.

Scientists already knew the basics: When a bacterial cell is invaded by viral DNA, its CRISPR system captures snippets of it and catalogs those DNA pieces. Should the same virus show up again, the system will quickly recognize it.

"For about a decade, we've known that CRISPR works by acquiring pieces of viral DNA, but it's been a mystery exactly when this key step in CRISPR immunity occurs during an infection," says Luciano A. Marraffini, head of the Laboratory of Bacteriology, who studies CRISPR systems in their native bacteria.

Experiments in his lab revealed that CRISPR springs into action early on, when the virus is injecting itself into the cell.

Choosy CRISPR

To pinpoint the timing, the research team designed an experiment to stop the viral life cycle at different points. Joshua W. Modell, a postdoc, and Wenyan Jiang, a graduate student, then examined the CRISPR systems to see when and how they acquired spacers from the virus.

Just any DNA won't do for CRISPR; previous research has shown it favors spacers from the loose ends of DNA. This preference narrows the options, since viral DNA takes linear form only during certain points in the infection; the rest of the time its two ends stick together, creating a circle.

The team halted the infection at three points. But regardless of when they stopped it, CRISPR continued to acquire spacers, indicating it picks them up at the beginning, around when the virus injects its genome—as a strand—into the cell.

An early defense

This timing matters. By taking spacers from the first part of the virus to enter the cell, CRISPR ensures it will attack the virus as soon as it shows up next time. When the researchers altered CRISPR systems to contain spacers that matched sequences at the end of the viral genome, the last part to be injected, the microbes struggled to proliferate.

"It turns out that the CRISPR system is very clever," says Modell. "It takes advantage of a nuance of the viral infection cycle to halt an infection as early as possible."

More information: Joshua W. Modell et al, CRISPR–Cas systems exploit viral DNA injection to establish and maintain adaptive immunity, *Nature* (2017). DOI: 10.1038/nature21719

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