Discovery reveals how bacteria distinguish harmful versus helpful viruses

August 31 2014

Above, particles of the virus ΦNM1, applied at varying concentrations, killed cells in the *Staphylococcus aureus* "lawn," creating clear plaques. Researchers have shown Staph can detect whether a virus, such as ΦNM1, is destructive or potentially helpful. Credit: Zach Veilleux/Rockefeller University

When they are not busy attacking us, germs go after each other. But when viruses invade bacteria, it doesn't always spell disaster for the infected microbes: Sometimes viruses actually carry helpful genes that a bacterium can harness to, say, expand its diet or better attack its own

hosts.

Scientists have assumed the bacterial version of an immune system would robotically destroy anything it recognized as invading viral genes. However, new experiments at Rockefeller University have now revealed that one variety of the bacterial immune system known as the CRISPR-Cas system can distinguish viral foe from friend. And, the researchers report in a paper published August 31 in *Nature*, it does so by watching for one particular cue.

"Transcription—an initial step in the process that reads genes, including those of viruses—makes the difference," says researcher Luciano Marraffini, head of the Laboratory of Bacteriology. "The full genome of viruses in their lytic, or destructive phase, is transcribed. Meanwhile, a few of the genes from a virus are transcribed during its lysogenic, or dormant phase."

Viruses in their lytic phase make copies of themselves using a cell's machinery before destroying it to liberate these new viruses. Viruses in their lysogenic phase, meanwhile, quietly integrate into a host's genetic material. And this is where they offer their potential benefit to the bacteria, which co-opt viral genes for their own ends. In fact, some disease-causing microbes, such as the bacterium responsible for diphtheria, must pick up the right virus in order to attack humans.

Scientists have only discovered this adaptive bacterial immune system relatively recently. Its function relies on CRISPRs, sections of DNA that contain repeating sequences interspersed with unique sequences called spacers. (CRISPR stands for clustered regularly interspaced short palindromic repeats.) The spacer sequences match the sequences in the viral genetic code, making it possible for enzymes encoded by CRISPR-associated genes (Cas) to chop out single spacer sequences from the RNA transcribed from the CRISPR DNA. Other Cas enzymes then use

these spacer sequences as guides to target invaders for destruction.

The system can adapt to new invaders by acquiring new spacer sequences to target them. Recently, CRISPR-Cas systems have attracted significant scientific attention because their ability to make precisely targeted cuts in DNA can be put to use to genetically engineer all types of cells.

"Our understanding of CRISPR-Cas systems remains in the early stages, but, so far, it has generally been thought they lack a sophisticated way of discriminating their targets. In other words, once they target something, it will be chopped up," says the study's lead author, graduate student Gregory Goldberg. "For the first time, our work has shown that a CRISPR-Cas system, one found in *Staphylococcus* bacteria, can detect whether or not a virus is in its destructive phase and poses an immediate threat."

Most previous work has focused on lytic viruses. However, Staphylococci host many viruses capable of entering a lysogenic phase. The researchers also uncovered a telling asymmetry in the Staphylococcal CRISPR system's ability to effectively target a sequence and its counterpart on two strands of complimentary DNA. They suspected this discrepancy arose because transcription proceeds in a single direction for most viral genes, meaning one of the two target strands is not transcribed.

"The big clue showed up when we isolated a mutant virus that managed to evade destruction. Sometimes viruses can do this through a mutation in a target sequence that prevents the system from identifying them. But when we sequenced the genome of this phage, we found a mutation in a region that promotes transcription instead," Goldberg says.

In a series of experiments, he and colleagues tested their hypothesis that

the Staphylococcal CRISPR-Cas system, known as Type III-A, can tolerate an infection by a lysogenic virus, so long as the target sequences are not transcribed. They engineered a target sequence that would undergo transcription only in the presence of a specific chemical. As a result, the Type III-A CRISPR-Cas system only destroyed the target in the presence of this chemical.

"This discovery of a transcription requirement is likely to surprise many who work with these systems," Marraffini says. "Although we do not yet understand the mechanism behind it, we can say that the Type -III-A system is quite different from other CRISPR-Cas systems, of which there is a mysteriously large variety. Our discovery hints at the possibility that each CRISPR type and subtype recognizes and destroys its targets in different ways, each in tune with a particular bacterium's needs. If these different targeting mechanisms do exist, they could have important implications for biotechnology."

More information: Conditional tolerance of temperate phages via transcription-dependent CRISPR-Cas targeting, *Nature*, DOI: 10.1038/nature.13637

Provided by Rockefeller University

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