Rockefeller scientists resolve debate over how many bacteria fight off invaders

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Every inch of our body, inside and out, is oozing with bacteria. In fact, the human body carries 10 times the number of bacterial cells as human cells. Many are our friends, helping us digest food and fight off infections, for instance. But much about these abundant organisms, upon which our life depends, remains mysterious. In research reported May 7 in *Cell*, scientists at Rockefeller finally crack the code of a fundamental process bacteria use to defend themselves against invaders.

For years, researchers have puzzled over conflicting results about the workings of a type of immune system found in many species of bacteria. Some data showed that, when a virus invaded a bacterial cell, this mechanism—known as type III CRISPR-Cas—would target the virus's DNA, preventing it from adopting the bacteria's machinery in order to copy itself and infect more bacteria. But other experiments suggested type III CRISPR-Cas could only disable a virus by cleaving the viral RNA.

Luciano Marraffini and Poulami Samai, both at Rockefeller, wanted to get to the bottom of this puzzle. In their experiments, Samai, a postdoctoral fellow, tested the cleavage of DNA and RNA by the type III CRISPR-Cas system. But she added a key ingredient no one else had before, a protein known as RNA polymerase, which the cell uses to transcribe DNA to RNA. She and Marraffini, head of the Laboratory of Bacteriology, saw that CRISPR-Cas did, indeed, cleave the RNA produced from a virus's DNA—but it would also cleave the virus's DNA.

There are advantages to such a two-pronged system, says Marraffini. Many viruses integrate into the genomes of the cells they infect and remain dormant, he says, causing no harm. In fact, these viruses can be beneficial to bacteria, by carrying toxins that help bacteria promote their own survival, for instance. The diphtheria toxin, for instance, is secreted by a species of bacteria, but the gene encoding the toxin comes from a virus. "By requiring viruses to begin transcribing their DNA into RNA before disabling them, the type III CRISPR-Cas system leaves dormant viruses intact, allowing them to continue benefiting the bacteria that host them," he notes.

Learning the details of how microbes carry out their functions can have important implications for health and science, Marraffini says. Besides being an incredibly abundant form of life on the planet, fueling the health and disease of every species and ecosystem, microbes have been the source of a number of technological tools that have revolutionized science and medicine.

"More than forty years ago, scientists discovered enzymes that cut DNA from studying the viruses that infect bacteria, inspiring a new class of tools that created a revolution in biomedicine," says Marraffini. Now, new technology based on another type of CRISPR-Cas is leading another wave in that revolution, allowing scientists to quickly and easily manipulate genomes in ways they never could before. "This is a testament to how the basic biology of microbes can be very useful. Microbes are a crucial part of biology on the planet, and it's important to understand how they work."

More information: Co-transcriptional DNA and RNA Cleavage during Type III CRISPR-Cas Immunity, www.cell.com/cell/abstract/S0092-8674(15)00444-4

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