New bacterial defense mechanism of the CRISPR-Cas system uncovered

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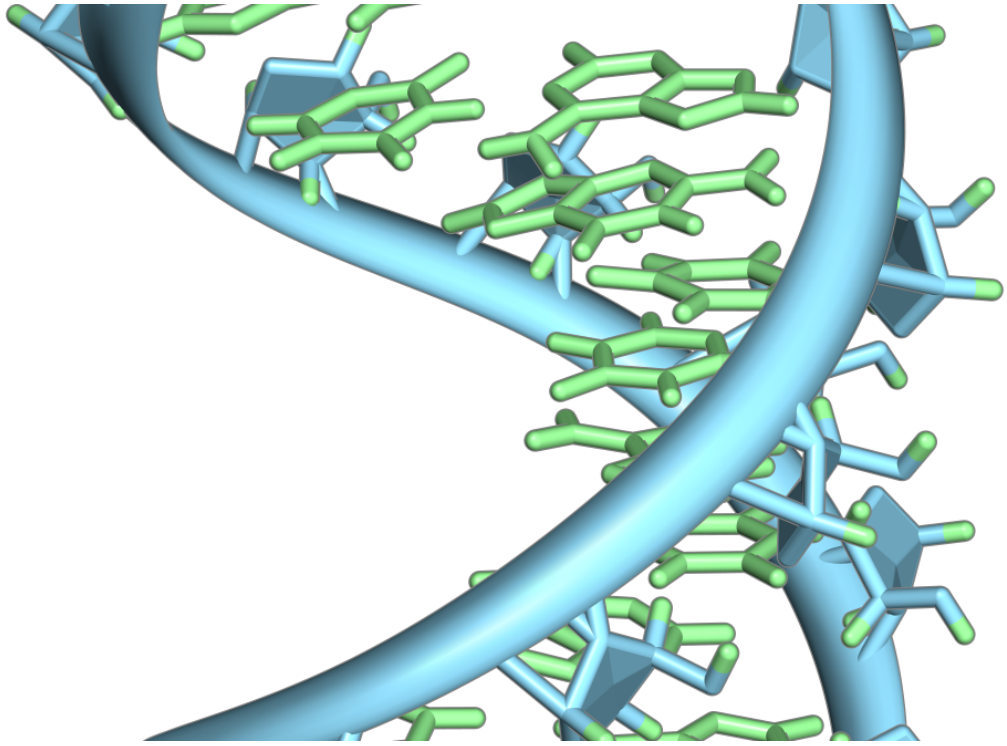

A hairpin loop from a pre-mRNA. Highlighted are the nucleobases (green) and the ribose-phosphate backbone (blue). Note that this is a single strand of RNA that folds back upon itself. Credit: Vossman/ Wikipedia

Researchers led by Martin Jinek of the University of Zurich have found an unprecedented mechanism by which bacteria defend themselves against invading viruses. When the bacterial immune system gets

overwhelmed, the CRISPR-Cas system produces a chemical signal that activates a second enzyme which helps in degrading the invaders' genetic material. This process is very similar to an antiviral mechanism of the human innate immune system.

The CRISPR-Cas system is an immune system that is found in many bacteria. It provides protection from viruses and other molecular parasites that can invade the bacterium and take over its genome. In these systems, the immunity is mediated by a complex multi-protein molecular machinery that uses RNA molecules as molecular guides to recognize the invader and target it for destruction. Until now, it has been known that the complex itself has nuclease activity – it can directly degrade the DNA and RNA of the invading viruses. Now, an international research team headed by Martin Jinek of the University of Zurich has found a new mechanism by which the invaders get destroyed.

Signaling molecule activates additional anti-viral enzyme

The targeting machinery of CRISPR-Cas systems is composed of RNA sequences derived from clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated proteins (Cas). While the CRISPR RNAs recognize the genetic material of the invader, the Cas proteins cleave it like a molecular scissors. In a subset of CRISPR-Cas systems (known as type III), the researchers made a surprising discovery. When the targeting machinery recognizes the invader, it synthesises a "second messenger": a small, circular RNA molecule. This signaling molecule can diffuse within the bacterial cell and activates another RNA-degrading enzyme called Csm6, which then helps to destroy the RNA of the virus.

Similar mechanism as in human innate immune

system

"In this way, when the CRISPR-Cas system in the infected bacterial cell becomes overwhelmed," Martin Jinek explains, "it signals an alarm by means of the second messenger to get help from another defense mechanism to eliminate the virus." In their study, the researchers were able to identify a unprecedented defense mechanism in bacteria. Moreover, second messenger molecules produced by the CRISPR-Cas system have never been observed in nature before. Furthermore, the newly found bacterial defense mechanism has some unexpected similarities to a well-known antiviral mechanism that operates in the human innate immune system. "So bacteria, in their own way, fight viral infections in a way that is surprisingly similar to what human cells do," Jinek adds.

More information: Ole Niewoehner et al. Type III CRISPR–Cas systems produce cyclic oligoadenylate second messengers, *Nature* (2017). DOI: 10.1038/nature23467

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