CRISPR-Cas9 may be a double-edged sword for bacteria

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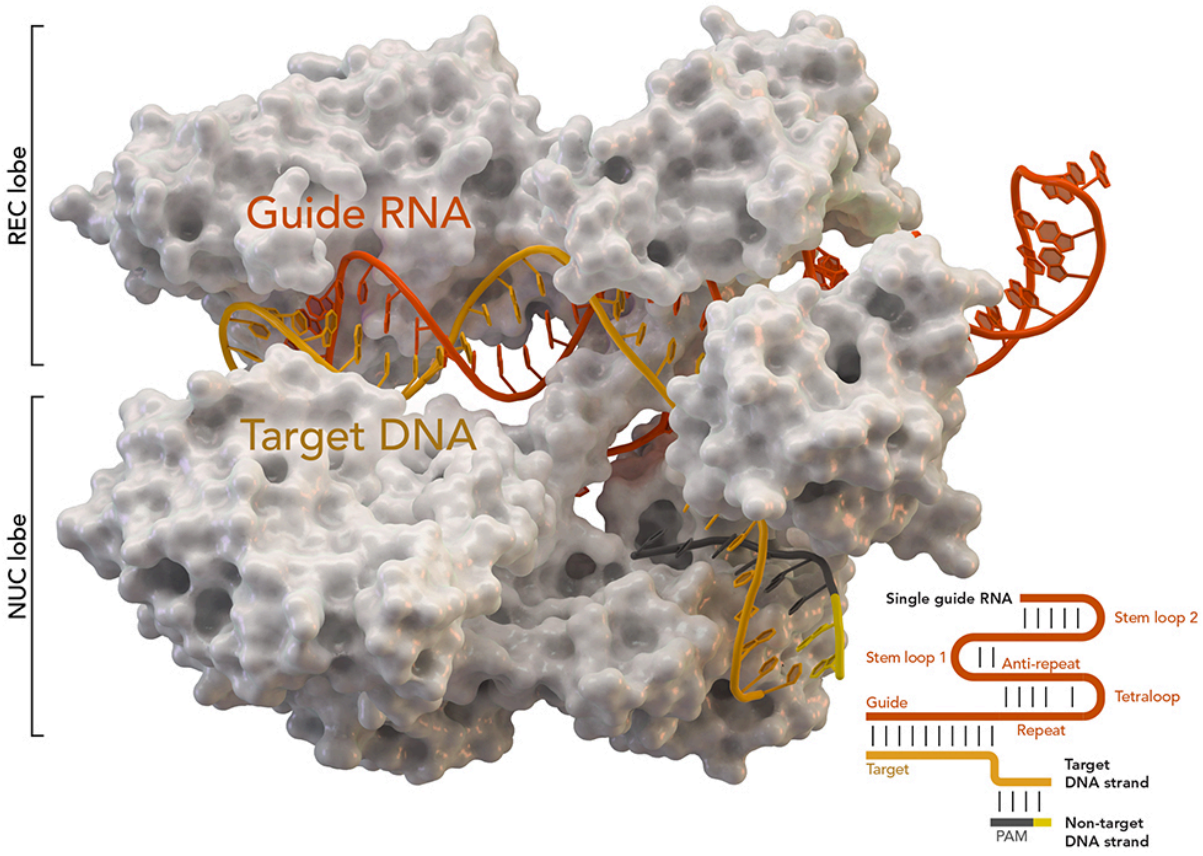

CRISPR-associated protein Cas9 (white) from Staphylococcus aureus based on Protein Database ID 5AXW. Credit: Thomas Splettstoesser (Wikipedia, CC BY-SA 4.0)

A team of researchers with the Catholic University of America has found evidence that suggests a defense mechanism used by bacteria to ward off phage attacks might also be benefiting the phages. In their paper published on the open access site *Science Advances*, the group describes testing the impact of CRISPR-Cas9 on phages that infect Escherichia coli and what they found.

In nature, CRISPR-Cas9 is a defense mechanism used by bacteria to ward of phage viral attacks—bacteria such as E. coli fight off phages by cutting their genomes and inserting sequences of it into their own genome, which they use to detect and destroy phages in the future. Phages, on the other hand, attack by hijacking the ability of bacterial cells to replicate and creating an environment in which they can make new viruses. Because of their ability to snip, edit, insert and close a genome, scientists have been manipulating bacteria and their editing skills to edit genes of other species such as humans. In this new effort, the researchers have found that the defense mechanism used by bacteria might also be helping the phages, by causing them to mutate in beneficial ways faster than they would have otherwise. Because of this, the researchers suggest the technique used by the bacteria might be a double-edged sword.

The researchers noted that due to the excitement of the discovery of the usefulness of CRISPR-Cas9 in gene editing, study of the natural process has taken a back seat. To learn more, they chose to focus on the impact of the process on the phages rather than the bacteria. To that end, they studied the genetic makeup of plaques in E. coli cultures with phage infections. They found that the phage genomes tended to evolve six times more rapidly than did those not attacked by the bacterial defense mechanism, making them more resistant to future CRISPR attacks.

The researchers suggest the ongoing war between bacteria and phages has been successful on both sides, as they are today two of the most

abundant species on Earth.

More information: Pan Tao et al. Unexpected evolutionary benefit to phages imparted by bacterial CRISPR-Cas9, *Science Advances* (2018). DOI: 10.1126/sciadv.aar4134

Abstract

Bacteria and bacteriophages arm themselves with various defensive and counterdefensive mechanisms to protect their own genome and degrade the other's. CRISPR (clustered regularly interspaced short palindromic repeat)–Cas (CRISPR-associated) is an adaptive bacterial defense mechanism that recognizes short stretches of invading phage genome and destroys it by nuclease attack. Unexpectedly, we discovered that the CRISPR-Cas system might also accelerate phage evolution. When Escherichia coli bacteria containing CRISPR-Cas9 were infected with phage T4, its cytosine hydroxymethylated and glucosylated genome was cleaved poorly by Cas9 nuclease, but the continuing CRISPR-Cas9 pressure led to rapid evolution of mutants that accumulated even by the time a single plaque was formed. The mutation frequencies are, remarkably, approximately six orders of magnitude higher than the spontaneous mutation frequency in the absence of CRISPR pressure. Our findings lead to the hypothesis that the CRISPR-Cas might be a double-edged sword, providing survival advantages to both bacteria and phages, leading to their coevolution and abundance on Earth.