Bacterial Viruses Thwart CRISPR-Cas9

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Decades of biomedical research have been focused on discovering and characterizing the genetic basis for countless human diseases, conditions, and traits. Unfortunately, we have been limited in our ability to provide genetic interventions to repair disease mutations. Moreover, many labs use 'cell lines' which represent a culture-based opportunity to study human cells in a dish, but we have not had the tools to reliably manipulate DNA sequences in this environment. Remarkably, the solutions to these problems came from an unexpected place, yogurt. When scientists at a dairy company were attempting to protect their bacterial starter cultures from bacterial viruses in order to convert milk into yogurt, they discovered that bacteria possess an adaptive immune system to protect them. This immune system is called CRISPR-Cas and we now appreciate that nearly half of all bacteria have some form of it. CRISPR-Cas protects bacteria from their viruses by storing a genetic record of past infections, like a vaccine punch card. If a given strain of bacteria "remembers" a previous viral encounter, CRISPR will be programmed to cut the DNA of that virus in the future. While this system has revolutionized our understanding of microbial evolution over the last ten years, in a shorter time (~5 years), this discovery has dramatically altered the trajectory for gene editing in higher organisms.

The CRISPR system is a programmable enzyme (a set of scissors) that cuts the DNA of a virus during infection. Researchers have co-opted this system from bacteria and transferred it into human cells and mice to use it to change the sequence of DNA in a way that was not possible before. This has revolutionized genetic research and has already materialized into many applications. In the Bondy-Denomy lab at UCSF, we study the natural functions that CRISPR performs in the bacterial world. We are very interested in the viruses that infect bacteria and how this immune system attacks the viral DNA. In an evolutionary tit-for-tat, viruses have developed the ability to encode proteins that interact directly with the CRISPR enzymes and stop them from working, to allow the virus to infect the bacterium. We have moved these "anti-CRISPR" proteins into human cells and shown that the proteins provide a robust "off-switch" for gene editing. This is a powerful tool that can be used to engineer circuits in the lab to enhance CRISPR-Cas technology, and may provide an essential safety measure as we move towards the therapeutic deployment of CRISPR-Cas gene editing.