MICROBIOLOGY

Microbial warfare against viruses

Many new antiviral defense systems are found in bacteria and archaea

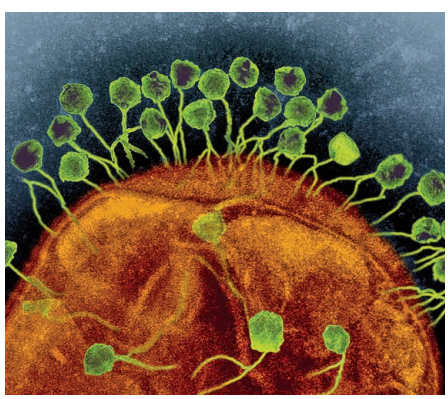
By **Jin-Soo Kim**[1,2]

Immune systems are divided into two types: innate and adaptive immunity. The innate immune system consists of components that are present in host organisms before infection by a pathogen and provides the first line of defense. For example, the restriction endonuclease system in prokaryotes degrades invader DNA (*1*). The adaptive immune system is activated after infection and provides immunological memory and long-lasting protection against the same pathogen. The CRISPR system captures a small piece of foreign DNA as a memory and recognizes and cleaves the same foreign DNA on reexposure (*2*), serving as adaptive immunity in prokaryotes. On page 1008 of this issue, Doron *et al.* (*3*) unveil previously unknown immune systems in bacteria and archaea against invading genetic elements, including plasmid DNA and bacteriophages (viruses that infect bacteria). Some of these systems may provide powerful tools for biomedical research and biotechnology, like restriction endonucleases and CRISPR.

Because genes in one immune defense system are often found next to genes in another defense system, forming "defense islands" in microbial genomes, Doron *et al.* hypothesized that unknown defense systems could be found near already-known antiviral systems. They computationally analyzed tens of thousands of genes in >45,000 bacterial and archaeal genomes and found dozens of candidate defense gene families with unknown functions in the vicinity of known defense systems. To characterize these gene families, they expressed candidate genes in two heterologous model bacteria, *Escherichia coli* and *Bacillus subtilis*. These recombinant bacteria were then challenged with a diverse set of bacteriophages. Remarkably, 9 of the 26 candidate systems conferred protection against at least one bacteriophage. Doron *et al.* named the nine gene families after legendary guardians such as Zorya and Thoeris, protective deities from Slavic and Egyptian mythologies, respectively.

These defense systems consist of either a single gene or multiple (up to 14) genes. Many of these encode proteins that recognize nucleic acids, such as helicases and nucleases, suggesting they have roles in recognition and destruction of foreign genetic elements. Interestingly, the Zorya system contains two genes encoding inner membrane proteins with flagellar motorlike domains. Doron *et al.* speculate that these two membrane proteins may form a proton (H^+) channel to depolarize membrane potential upon bacteriophage infection, leading to cell death—a previously unknown mechanism of antiviral defense in prokaryotes.

Thoeris is another interesting system that was identified by the enrichment of a gene family encoding the Toll-interleukin receptor (TIR) domain. The TIR domain is ubiquitously found in innate immune systems such as the Toll-like receptor and interleukin-1 receptor of invertebrates and mammals and many pathogen-resistance proteins in plants (*4*). These TIR proteins recognize diverse pathogen-associated molecular patterns (PAMPs) to trigger host immune responses. Doron *et al.* suggest that the Thoeris TIR protein is an evolutionary ancestor of these eukaryotic PAMP receptors. Unlike adaptive immune systems that are highly diverse, innate immune systems are conserved across the three kingdoms of life.



An electron microscopy image shows viruses (bacteriophage) surrounding a microbial cell.

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Different from the other nine antiviral systems, the Wadjet system, named after an Egyptian goddess, failed to provide *B. subtilis* protection against 10 bacteriophages tested by Doron *et al.*, but significantly reduced transformation efficiency of plasmid DNA, suggesting that it may target foreign plasmid DNA, a molecular parasite.

It is of particular interest to find out how these systems recognize foreign components, whatever they are, in a targeted manner. Some of these systems may find use as molecular tools, like the well-known members of the bacterial and archaeal immune systems. Historically, microbial defense systems have been successfully repurposed for broad applications in research, medicine, and biotechnology. For example, restriction endonucleases cut DNA precisely in vitro, enabling recombinant DNA technology (*5*). More recently, genome editing has been revolutionized by CRISPR–CRISPR-associated (Cas) systems (*6*–*9*). Perhaps the microbial defense genes found by Doron *et al.* will lead to innovations and applications in biotechnology and medicine.

There are likely to be other unknown defense genes hiding in microbial genomes. Doron *et al.* might have missed bona fide antiviral genes that are poorly expressed in the two model bacteria or that can protect other host bacteria against bacteriophages not tested in this study. The 10 validated defense systems are likely to be innate rather than adaptive immune systems, because adaptive immune systems like CRISPR cannot be identified by a single round of phage infection or plasmid transformation. The study of Doron *et al.* will encourage researchers to search for microbial defense genes and to investigate the molecular mechanisms of these defense systems. To do so, researchers will rely on molecular tools like CRISPR and on current and improved methods of reading, writing, and editing genes and genomes. To rephrase Sydney Brenner's remarks, with respect, progress in science is cyclic: new techniques leading to new discoveries, to new ideas, and then to new techniques again. ■

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