HOST-PARASITE INTERACTION

CRISPR-Cas systems on the offensive

CRISPR-Cas systems are known as bacterial immune systems for protection against phage infections and plasmids. However, many of these mobile genetic elements have obtained partial or complete CRISPR-Cas systems from their hosts and use them for their own purposes e. g. to eliminate competitors. These observations provide impressive insights into the evolution of host-parasite interaction and the subtle border between parasites and symbionts.

CRISPR-Cas systems are generally perceived as microbial immune systems that protect bacteria and archaea against viruses (called bacteriophages if they infect bacteria) [1]. These systems take pieces of viral DNA and store them as immune memory encoded as DNA spacers in one or more specific places in the microbial genome termed CRISPR arrays. Each of these arrays is continuously transcribed to make a long RNA molecule in the microbial cell. This long RNA molecule is then processed to mature CRISPR-RNAs (crRNAs). Together with proteins that bind, it "scans" all DNA in the cell. If any of these crRNAs matches a foreign DNA, the crRNA-bound protein will digest and destroy it, thus generally stopping viral infection in its early stages. Another variety of these systems does not cut the DNA, but rather binds to it and prevents its transcription into messenger RNA thereby silencing the gene that their spacers match [2].

However, it is not only viruses that threaten a cell. There are other mobile genetic elements like plasmids (selfish DNA elements that behave like independent minichromosomes). They are often in-between parasites and symbionts: They exploit their bacterial host for their reproduction, but often also encode genes that are beneficial for the host. In addition, different plasmids compete with each other. If more than one type of plasmid occupies a cell, they have to share the resources of the host which is disadvantageous for them. Therefore, they may try to eliminate incoming competitors.

However, paradoxically, many CRISPR-Cas systems, in both bacteria and archaea, are themselves encoded on mobile genetic elements, such as viruses or plasmids. Since premature host death will prevent the plasmid from spreading further (both to daughter cells when cells divide and horizontally to sister cells), it is in a plasmid's "best interest" to protect its host from viruses. Consequently, plasmids often encode multiple anti-phage defence systems, and some of them – like CRISPR-Cas – also protect against competing plasmids.

Some bacteriophages also encode CRISPR-Cas systems. This can be attributed to the fact that in dense microbial communities quite often more than a single phage tries to infect a bacterial cell at the same time, leading to competition. The vast majority of bacteriophages that encode CRISPR only encode the CRISPR arrays (the immune memory without any associated proteins) [3]. These CRISPR arrays generally have spacers matching the genomes of competing bacteriophages that can also infect the same host. These arrays are DNA that the bacteriophage somehow "picked up along the way", presumably when it infected a previous host that had CRISPR-Cas. Once a phage that has such a CRISPR array enters a host with a CRISPR-Cas system this will result in continuous protection against those phage competitors whose DNA matches those spacers.

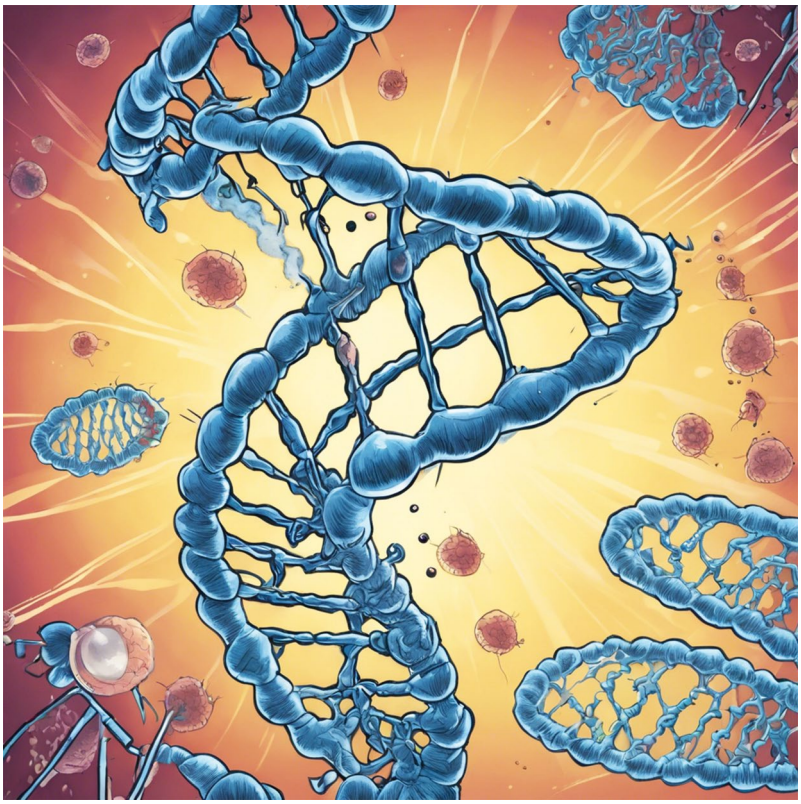

FIGURE 1 DNA conflicts between selfish elements can be mediated by CRISPR-Cas systems. Figure generated with Artificial Intelligence.

These stand-alone CRISPR arrays are therefore a way to direct the bacterial CRISPR-Cas-based immune response away from the phage and against potential competitor bacteriophages.

CRISPR-Cas systems used to eliminate competitors

Less than ten percent of bacteriophages [3] actually have the additional genetic capacity to produce CRISPR-associated proteins. Thus, these viruses can either acquire new immune memory from other viruses, digest the DNA of competitors in the cell using their own CRISPR-Cas machines, or, rarely, even perform both of these functions. These systems are encoded by gene clusters that were "stolen" from the host and have later evolved for a bacteriophage lifestyle. An example for such an evolutionary process was observed in a class of CRISPR-Cas systems that when expressed by a bacterium not only digest RNA and DNA of the invading phage but also degrade the RNA of the bacterium. These systems, when activated by infection, eventually make the cells enter a dormant lifeless state that does not support bacteriophage replication. Such a "suicidal" activity would not benefit a bacteriophage and consequently phage-encoded systems of that type have accumulated mutations so that the dormancy-inducing part of the system has become totally inactive.

Bacteriophages also tend to generally have shorter proteins than their hosts and they are encoded by short genes. Presumably, having shorter genes is beneficial for bacteriophages since the DNA that can be packaged into a capsid is limited in size, and possessing shorter genes means that the phage can encode more of them. Additionally, replicating shorter DNA genomes may allow faster replication of the bacteriophage. In line with such genome size minimization benefits, some bacteriophages have unusually compact CRISPR-Cas systems based on a single protein that is very small and yet capable of both processing the crRNA and digesting the DNA of competitors [3].

Some bacteriophages with full CRISPR-Cas systems can use their systems to attack the host bacterium rather than just their competitors. These phages have CRISPR spacers that match the DNA of key host genes, indicating that they either silence host genes [4] or simply cut the DNA of the host as part of the infection process in which they rapidly overwhelm and kill the bacterium. This has been shown for a bacteriophage that infects the known pathogen *Vibrio cholerae* [5]. In this fascinating example, the phage system attacks and neutralizes a host region of the genome that defends against bacteriophages by cutting its DNA. This is a striking case of a defence system used by a bacteriophage to attack the host and eventually destroy not only its defensive capability but also its entire DNA.

In summary, CRISPR-Cas systems can be considered as "guns for hire" [6], DNA-digesting and DNA-silencing weapons that can be used by and against diverse genetic elements. They are thus an important part of an ongoing molecular arms race that continuously occurs in microbial life.

Literatur

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