Deciphering how viruses choose to turn nasty or not to their bacterial host

March 13 2024

Researchers from the Shmunis School of Biomedicine and Cancer Research at Tel Aviv University have deciphered a novel complex decision-making process that helps viruses choose to turn nasty or stay friendly to their bacterial host. In a new paper, they describe how viruses co-opt a bacterial immune system, intended to combat viruses like themselves, in this decision-making process.

The study was led by Polina Guler, a Ph.D. student in Prof. Avigdor Eldar's lab, in addition to other lab members, at the Shmunis School of Biomedicine and Cancer Research, George S. Wise Faculty of Life Sciences. The paper was published in *Nature Microbiology*.

Bacteriophages, also known as phages, are types of viruses that infect bacteria and use the infected bacteria to replicate and spread. Even though the word 'bacteriophage,' meaning 'bacteria devouring' in ancient Greek, suggests destruction, many phages can adopt a "sleeping" mode, in which the virus incorporates itself into the bacterial genome. In fact, in this mode of action, the virus can even have a symbiotic relationship with the bacteria, and its genes can help its host prosper.

In general, Eldar explains that phages usually prefer to stay in the "sleeping", dormant mode, in which the bacteria "cares" for their needs and helps them safely replicate. Previous research published by the Eldar lab has shown that the phages' decision-making uses two kinds of information to decide whether to stay dormant or turn violent: the "health status" of their host and signals from outside indicating the

presence of other phages around.

"A phage can't infect a cell already occupied by another phage. If the phage identifies that its host is compromised but also receives signals indicating the presence of other phages in the area, it opts to remain with its current host, hoping for recovery. If there is no outside signal, the phage 'understands' that there might be room for it in another host nearby and it'll turn violent, replicate quickly, kill the host, and move on to the next target," Eldar explains.

The new study deciphers the mechanism that enables the virus to make these decisions. "We discovered that in this process the phage actually uses a system that the bacteria developed to kill phages," says Guler. If it does not sense a signal from other phages—indicating that it has a good chance of finding new hosts—the phage activates a mechanism that disables the defense system.

"The phage switches to its violent mode, and with the defense system neutralized, it is able to replicate and kill its host," describes Guler. "If the phage senses high concentrations of the signal, instead of disabling the defense system, it utilizes its defense activity in order to turn on its dormant mode."

"The research revealed a new level of sophistication in this arms race between bacteria and viruses," adds Eldar. Most bacterial defense systems against phages were studied in the context of viruses that are always violent. Far less is known about the mechanisms of attacks and interaction with viruses that have a dormant mode.

"The bacteria also have an interest in keeping the virus in the dormant mode, first and foremost to prevent their own death, and also because the genes of the dormant phage might even contribute to bacterial functions," says Eldar.

"This finding is important for several reasons. One reason is that some bacteria, such as those causing the cholera disease in humans, become more violent if they carry dormant phages inside them—the main toxins that harm us are actually encoded by the phage genome," explains Eldar.

"Another reason is that phages can potentially serve as replacements to antibiotics against pathogenic bacteria. Finally, phage research may lead to a better understanding of viruses in general, and many human-infecting viruses can also alternate between dormant and violent modes."

More information: Polina Guler et al, Arbitrium communication controls phage lysogeny through non-lethal modulation of a host toxin–antitoxin defence system, *Nature Microbiology* (2024). DOI: 10.1038/s41564-023-01551-3

Provided by Tel-Aviv University