

VIROLOGY

Phages make a group decision

It emerges that phage viruses, which infect bacteria, use small peptides to communicate with each other. This observation of intercellular communication also reveals how viruses make a key developmental decision. [SEE ARTICLE P.488](#)

ALAN R. DAVIDSON

When a major decision looms, people often seek advice from friends or relatives. Erez *et al.*¹ reveal on page 488 that bacterium-targeting viruses known as phages also show a collaborative aspect to a developmental decision-making process. In this case, intercellular communication occurs through the use of a viral peptide. Intercellular molecular communication between viruses hadn't been observed before, and this study illuminates a previously unknown mechanism of viral action.

After injecting the phage genome into a bacterial host cell, most phages have two life-cycle options. The phage can enter the lytic developmental pathway and eventually destroy its bacterial host in a process that will release dozens of new phage particles into the environment. Alternatively, it can follow the pathway of lysogeny, sparing the host cell, protecting it from subsequent phage infection, and integrating the phage genome into the host genome². Depending on the prevailing conditions, either lytic or lysogenic phage development might be

more advantageous for the survival of a phage population.

The importance of the decision between lytic and lysogenic development for the evolutionary success of phages is emphasized by the complexity of the regulatory mechanisms involved. Hundreds of research papers have been generated from studies of the decision between lysis or lysogeny for the phage lambda, which infects the bacterium *Escherichia coli*, and this model system has been described in Mark Ptashne's widely read book *A Genetic Switch*³. However, even this highly studied system is not fully understood⁴. These previous studies focused on the many intracellular signalling pathways and genetic circuits that contribute to the process of deciding between lysis and lysogeny. The remarkable finding by Erez *et al.* is that the choice in some phages is also profoundly influenced by communication, by means of small molecules, between phages infecting other cells in a culture.

The initial goal of Erez and colleagues' study was to test whether bacteria that have been infected by a phage might produce and secrete molecules to alert other bacterial cells

to phage infection. To test this hypothesis, the authors infected *Bacillus subtilis* bacteria with four different phages and screened the culture medium three hours later for the presence of molecules that could inhibit phage infection. Surprisingly, rather than identifying a bacterially produced molecule, the authors found a molecule that was synthesized by one of the phages, phi3T. This viral molecule protected *B. subtilis* cells from infection by phi3T, but not from infection by the other phages tested. Additional experiments showed that this molecule was a small peptide that protected bacterial cells from phage-induced lysis by promoting phage lysogeny.

An idea for how this viral communication system might work came from a comparison with bacterial communication systems. Quorum sensing is a mechanism used by some bacteria to sense the population level of their nearby close relatives⁵. In the Gram-positive group of bacteria, this process often involves the secretion of a small peptide (frequently less than 10 amino-acid residues in length) from one bacterium that is then taken up by another bacterium, stimulating changes in

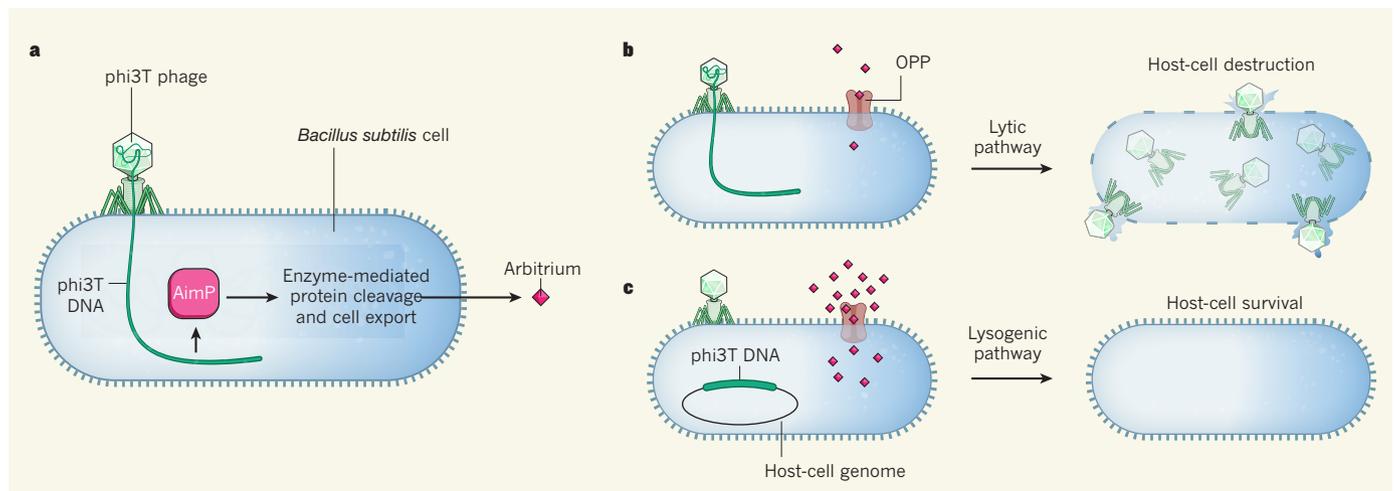


Figure 1 | Phages use a small peptide to communicate with each other. a, Erez *et al.*¹ investigated *Bacillus subtilis* bacterial cells infected by a phage virus called phi3T. They identified a phage protein, AimP, that undergoes enzyme-mediated cleavage to form a peptide fragment that is exported from the bacterial cell. This fragment, termed arbitrium, enables intercellular viral communication, a phenomenon that had not been observed previously. b, Arbitrium is taken up by neighbouring bacterial cells through the

bacterial OPP transporter protein. If low levels of arbitrium are present in a bacterial cell, phage infection has a higher probability of following the lytic developmental pathway that eventually destroys the host cell and releases further virus particles into the environment. c, High levels of arbitrium in a bacterial cell increase the probability that phage infection will result in the lysogenic developmental pathway, which results in the phage genome being integrated into the host-cell genome and in host-cell survival.

gene expression⁶. Erez *et al.* sequenced the phi3T genome and identified a gene encoding a protein 43 amino-acid residues long that they named AimP. This protein shows strikingly similar features to those of proteins involved in quorum sensing and other peptide-mediated signalling pathways in *B. subtilis*.

Erez *et al.* found that, during bacterial infection by phage phi3T, enzyme-mediated cleavage of AimP produced a six-residue peptide, called arbitrium by the authors, which was secreted from the bacteria. Uptake of arbitrium by other bacterial cells through the bacterial oligopeptide permease (OPP) transporter protein increased the probability that phi3T infection of the bacteria would result in lysogeny. At the high concentrations of arbitrium reached during the late stages of a phage-infection process, bacterial-cell lysis was strongly suppressed because of the high frequency of phage lysogeny (Fig. 1).

The authors found that arbitrium acts by binding to an intracellular phage protein, AimR, and inhibiting its activity. AimR can bind to a specific site on the phage genome and activate transcription of the *aimX* gene, which promotes the lytic pathway through an unknown mechanism. Erez and colleagues observed that arbitrium in bacterial cells reduces the expression of *aimX*, and thus increases the probability of lysogeny.

Notwithstanding the complexity of the arbitrium system, the logic is simple. During

the initial period of phage infection, when the concentration of phage particles is low and that of bacteria high, the production of phage particles through the lytic pathway could provide a successful bacterial-infection strategy. However, as the number of phage particles increases, the concentration of host cells might decrease to a level at which phage particles could no longer find a host cell to infect. In this context, an approach to preserve host cells and phage genomes by promoting the phage's lysogenic life cycle would be preferable. Interestingly, the probability of phage lambda lysogeny increases when multiple phages simultaneously infect the same cell⁷. However, the phi3T system provides the first example that I know of in which phages infecting different cells have been shown to communicate with one another through a small molecule, and this communication aspect is what makes the work by Erez and colleagues so exciting.

The authors found that communication systems similar to that involving arbitrium exist in more than 100 phages, indicating their general utility for phage survival. Furthermore, Erez *et al.* demonstrated that the arbitrium system of another phage operates in a similar manner, although it uses a different peptide sequence. These arbitrium peptides affect only the phage that produces them. The authors observed a wide diversity of peptide sequences among phages that had arbitrium-like systems, implying an evolutionary

drive for phage specificity. These phages are 'speaking' different molecular languages and so convey messages only to their own kind.

Small-molecule communication between phages enables the viruses to strongly influence the decisions of their descendants. Such communication provides a stunning example of the complexity and nuance of function that can be achieved by 'simple' entities. Despite extensive investigation of phage genomes, most have many genes of as yet unknown function. Erez and colleagues' discoveries provide a hint that some uncharacterized phage genes might be involved in mechanisms that increase the viruses' evolutionary fitness. Perhaps we will find that phages can communicate with each other on many other topics, too. ■

Alan R. Davidson is in the Departments of Molecular Genetics and Biochemistry, University of Toronto, Toronto M5S 1A8, Canada.

e-mail: alan.davidson@utoronto.ca

1. Erez, Z. *et al.* *Nature* **541**, 488–493 (2017).
2. Oppenheim, A. B., Kobilier, O., Stavans, J., Court, D. L. & Adhya, S. *Annu. Rev. Genet.* **39**, 409–429 (2005).
3. Ptashne, M. *A Genetic Switch* (Blackwell, 1992).
4. Golding, I. *Annu. Rev. Virol.* **3**, 453–472 (2016).
5. Waters, C. M. & Bassler, B. L. *Annu. Rev. Cell Dev. Biol.* **21**, 319–346 (2005).
6. Monnet, V., Juillard, V. & Gardan, R. *Crit. Rev. Microbiol.* **42**, 339–351 (2016).
7. Kourilsky, P. *Mol. Gen. Genet.* **122**, 183–195 (1973).

This article was published online on 18 January 2017.

PHYSICS

Optical transition seen in antihydrogen

Precise measurements of antimatter systems might cast light on why the Universe is dominated by matter. The observation of a transition in an antihydrogen atom heralds the next wave of high-precision antimatter studies. [SEE LETTER P.506](#)

STEFAN ULMER

On page 506, Ahmadi *et al.*¹ report a milestone in antimatter research — the first measurement of a light-induced transition in a pure antimatter atom, antihydrogen. This experimental masterpiece paves the way for investigations of unexplored regions of the antimatter world with unprecedented sensitivity.

In the standard model of particle physics, every particle has its own antimatter counterpart — particles of quasi-identical fundamental properties, the most well-known of which have opposite magnetic moments and electric charge from the matter particle. However, these anti-particles are not just 'model'

particles. They can be observed in radioactive decay processes, cosmic rays and high-energy reactions such as particle collisions.

Anti-particles can even be produced using a process called pair production, an application of Einstein's famous equation of mass–energy equivalence, $E = mc^2$. When the kinetic energy (E) of a collision reaction exceeds a certain threshold, collisions naturally produce particles of mass m . The particles are produced in matter–antimatter pairs as a consequence of several conservation laws. Electrons and positrons are examples of matter–antimatter counterparts from the lepton family of particles, whereas protons and antiprotons are from the baryon family.

These reactions can be reversed in processes

called annihilations. Some annihilations produce tiny excesses of matter², but these are almost ten orders of magnitude too small to explain why, on cosmological scales, the Universe is composed almost entirely of matter. This imbalance is one of the most intriguing puzzles and hottest topics in modern physics.

Experimentalists compare the fundamental properties of matter particles with those of their antimatter counterparts with high precision, hoping to find tiny dissimilarities that might contribute to a consistent explanation for the Universal imbalance. In the 1980s, the fundamental properties of charged leptons were compared³ with some precision, down to parts per billion. Then, in the 1990s, techniques were developed to catch and cool antiprotons in electromagnetic containers known as Penning traps. This led to a comparison⁴ of the charge-to-mass ratio of protons with that of antiprotons with a precision of 90 parts per trillion (p.p.t.). A later study improved the precision to 69 p.p.t. (ref. 5).

Electrically neutral matter–antimatter counterparts have also been investigated. For example, neutral K-meson masses were compared⁶ with fractional precisions of the order of parts per quintillion (1 quintillion is 10^{18}). The study of another neutral system, antiprotonic helium (which consists of an antiproton and an electron orbiting a helium nucleus), has also