overkill of effectors, which will be hard to come by. Moreover, the authors suggest to employ CRISPR-Cas technology to introduce mutations into RPN10 genes to generate SAP05-resistant alleles (Huang et al., 2021), but given the public resistance (pun intended) against transgenic crops, at least in Europe, one wonders whether such an approach would really be broadly applied in the field. Nevertheless, the more we learn about the mechanisms by which phytoplasmas do harm to their host plants, impressively exemplified by the exciting paper by Huang et al. (2021), the more likely it will be that one fine day we will have our own means to fight phytoplasma infections more efficiently than we manage today.

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Prophages self-destruct to eliminate competitors

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Bacteria have evolved many immune systems to combat their viral parasites (i.e., phages). In this issue of *Cell Host & Microbe*, Owen et al. discover a mechanism of anti-phage immunity that is mediated by a phage-encoded protein, and thus provide an example of how inter-phage conflict can promote survival of the bacterial population.

Bacterial viruses (known as phages) are considered to be the most numerous and genetically diverse biological entities on Earth (Dion, Oechslin, and Moineau, 2020). They reproduce by attaching to a specific host, injecting their genetic material, and exploiting the host's enzymes and energy stores to synthesize tens or hundreds of their progeny in a process that typically leads to bacterial lysis and death. Although strictly lytic phages replicate immediately after DNA injection, the temperate variety can choose to integrate into the host genome and persist as a prophage indefinitely before completing their replication cycle. Phages significantly outnumber their bacterial hosts in nearly every environment tested, and they threaten the survival of the host population (Parikka et al., 2017). In response, bacteria have evolved a diverse array of immune systems to defend against an inevitable attack. These systems target every step of the phage reproduction cycle, from blocking phage attachment, to chopping phage nucleic acids, to committing cell suicide before new phage particles can be constructed in a process known as abortive infection (Abi) (Hampton, Watson, and Fineran, 2020). Abi occurs through a variety of mechanisms and represents a last-resort strategy to prevent progeny phages from spreading to neighboring bacteria in the population (Lopatina, Tal, and Sorek, 2020).

Although Abi is typically regarded as an altruistic behavior that bacteria have evolved to promote the survival of their own population, Owen and colleagues recently discovered a unique

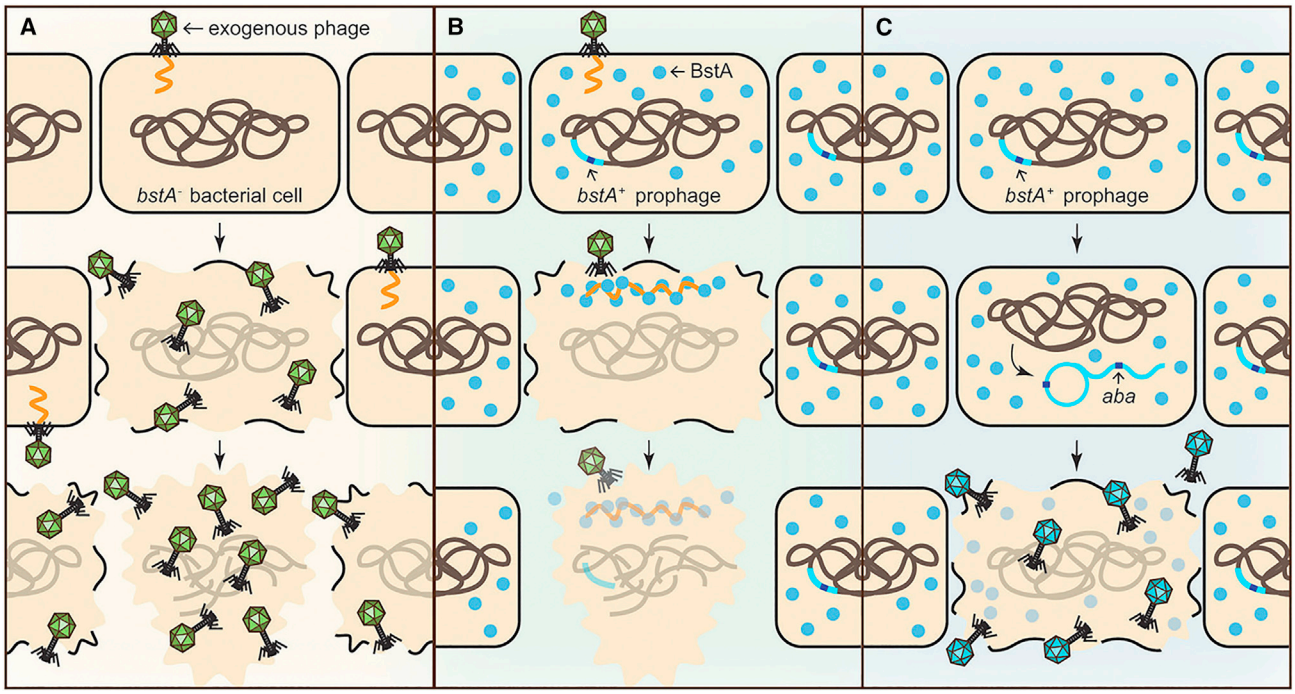

Figure 1. The BstA-*aba* immune system
(A) In the absence of BstA, a phage epidemic can spread unchecked and decimate the bacterial population.
(B) In the presence of a *bstA*-bearing prophage, BstA blocks exogenous phage replication and causes death of the infected cell while the remainder of the population survives.
(C) Due to the presence of the *aba* element encoded in the *bstA* locus, the *bstA*-bearing prophage can enter into its own lytic replication cycle without interference from BstA.

Abi mechanism that is triggered during phage-versus-phage conflict (Owen et al., 2021). This mechanism is mediated by a family of proteins called BstA which are found enriched in the genomes of prophages. Indeed, because prophage fitness is inexorably linked to the fitness of the host, prophages are known to carry a variety of factors that are intended to promote host fitness and survival (Taylor et al., 2019). Owen and colleagues used a series of elegant microscopy experiments to demonstrate that although BstA cannot rescue individual cells from being lysed when infected by an exogenous phage, it prevents these phages from overtaking the bacterial population (Figure 1). In the absence of invading phage, BstA remains diffusely localized in the cytoplasm, and cells continue to grow and divide normally. However, the instant a phage intruder injects its DNA, BstA forms discrete foci that co-localize with the foreign DNA, and this suggests a direct interaction. Follow-up experiments revealed that BstA suppress the replication of the invading phage DNA, potentially by occluding the replication origin. Although the precise sequence of events that follow remains unknown, the final outcome is clear—the host perishes along with the invading phage, while the remainder of the bacterial population (and the prophages within) are spared. This Abi system is encoded in prophages of diverse gram-negative bacteria, including *Salmonella*, *Klebsiella*, and *Escherichia* species.

Because BstA-carrying prophages can eventually complete their own lytic replication cycle in the absence of exogenous phage attack, one key question arises: How does BstA authorize the replication of the prophage that carries it? To answer this, the authors used a series of genetics experiments to identify an anti-BstA (*aba*) element encoded within the *bstA* locus and show that this DNA sequence is necessary and sufficient to defuse BstA's lethal downstream effects. Interestingly, each prophage carrying a *bstA* homolog requires a specific and compatible *aba* element—this ensures that incoming temperate phages harboring similar systems will still trigger the lethal effects of the BstA homolog deployed by the endogenous prophage. Precisely how the *aba* element neutralizes BstA's toxic effects is another area that requires further investigation.

BstA-*aba* systems are reminiscent of the prokaryotic toxin-antitoxin (TA) systems, however, they remain functionally distinct. TA systems are composed of a toxin (typically a protein) and an antitoxin (a protein or RNA) that are encoded adjacent to each other. While the toxin in the pair works to slow cell metabolism and growth, the anti-toxin counteracts these effects by sequestering, inactivating, or degrading the toxin. TA systems have well-established roles in stabilizing mobile genetic elements, and they are increasingly being recognized for their anti-phage effects (Song and Wood, 2020). However, at least two features of BstA-*aba* set these systems apart: their composition being of protein and DNA (as opposed to RNA) and their bactericidal (rather than bacteriostatic) effects. Further, it

is unclear whether BstA itself acts as a toxin to cause cell lysis and/or if other players are involved in perpetuating cell death.

This unique mechanism of Abi adds to the growing list of phage-encoded immune systems dedicated to deterring competing phages. For instance, prophages have long been known to employ mechanisms of superinfection exclusion (sie) which typically consist of membrane-associated proteins that block phage DNA injection; however, one study showed that sie systems in *Pseudomonas* prophages may also target downstream steps of the phage infection cycle (Bondy-Denomy et al., 2016). In addition, five distinct defenses were recently identified in a suite of *Mycobacteria* prophages—these systems work through a variety of mechanisms to block both temperate and lytic phage replication (Dedrick et al., 2017). It bears mentioning that the latter study also discovered corresponding countermeasures that competing phages have evolved to overcome the phage-encoded defenses, revealing a veritable phage-phage arms race. Finally, phages can also capture and repurpose immune systems that are more commonly employed by bacteria. In a notable example, a recent study discovered diverse phages with unusually large genomes that harbor a class of adaptive immune systems known as CRISPR-Cas, which use small RNAs in complex with CRISPR-associated (Cas) nucleases to identify and degrade phage-derived nucleic acids (Al-Shayeb et al., 2020). In addition to eliminating competing phages, these phage-encoded CRISPR-Cas systems are thought to play roles in regulating host gene expression. Given the preponderance of phages and scarcity of hosts in any given environment, combined with the sheer magnitude of time (i.e., billions of years) that they have had to interact with each other, it is reasonable to expect that many new mechanisms of phage-versus-phage combat are yet to be discovered.

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DECLARATION OF INTERESTS

The author declares no competing interests.

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