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Prophages domesticated by bacteria promote the adaptability of bacterial cells

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Abstract: Prophages are temperate phages integrated into the host bacterial genome. They play an important role in the adaptation and the pathogenicity of bacteria, especially pathogenic bacteria. In this review, we described the distribution of prophages in different hosts and different environments, and focused on the significance of prophages. At the single-cell level, prophages can help the host adapt to harsh external environments by directly carrying virulence genes, encoding regulatory factors and activating lysogeny. At the population level, prophages can influence the overall evolutionary direction and ecological function of the host bacterial community. This review will help us understand the important role of prophages as unique organisms in individual bacteria and microbial populations.

Introduction

In 1915 and 1917, Fredrick Twort and Felix D'Herelle (Alisky *et al*., 1998; Twort, 1915) discovered bacteriophage for the first time in two separate studies. As a virus of bacteria, bacteriophage can parasitize bacteria and use the energy and large-molecule synthesis systems of bacteria for reproduction. Although bacteriophages have been widely studied, they are still considered as dark matters in the biosphere. Bacteriophages and bacteria are both highly abundant and genetically diverse organisms in nature, and the number of phages far exceeds that of the bacteria, reaching to 10^{31} (Argov *et al*., 2017). Bacteriophage can be found in many different ecological environments including water, soil and gastrointestinal ecosystems and is a key factor affecting the construction of bacterial populations because of its ubiquitous presence and richness in the environment. The parasitic relationship between bacteria and phages also determines their complex co-evolutionary processes.

As an abundant species in nature, bacteriophage genomes differ in size ranging from 2,3 kp to 316 kp (Hatfull, 2008). According to their life history, phages can be divided into two categories: the lytic phages and the temperate phages, the former of which display only lytic cycles and can enter their hosts, and then use the system of hosts to carry on the genetic replication and the synthesis of their own structure proteins as well as some auxiliary proteins such as transcriptional repressors, endolysins and holins. The lytic phages are usually used for phage treatment because they can lyse cells in a short time. Some phage-encoded proteins (lysins and holins) are also used for phage therapy because of their good tissue penetration, low immunogenicity and low probability of bacterial resistance (Drulis-Kawa *et al*., 2012). Unlike the lytic phages, the temperate phages can undergo either lytic cycles or lysogenic cycles. The temperate phages in lysogenic cycles are integrated into the host's genomes and replicate with the host genomes. These temperate phages, which have been inserted into the bacterial genomes, are called prophages. Some phage genes are also expressed in lysogenic cycles. We summarized some prophage-encoded proteins and their effects (Tab. 1). They are mostly related to the maintenance of lysogeny and have regulatory functions such as preventing the transcription of genes, morphogenesis and some lytic components related to the lytic life-cycle of phages. Some proteins are specific virulence factors and have specific functions, which may be beneficial to their hosts (Duerkop *et al*., 2014). Some prophage-encoded proteins (integrase and excisionase) are used for constructing some plasmids. Based on the genomic integrity, prophages can be divided into two categories: the full-length prophages and the defective prophages. Among them, the full-length prophage is a kind of prophage whose genome is complete. It has perfected integration and lysis cassette. The full-length prophage maintains the lysogenic state in host through transcriptional repressors (Dodd *et al*., 2001), which is a switch that determines when the phage undergoes lytic cycles or lysogenic cycles. And it can be excised from the bacterial genome depending on the integrase gene under appropriate conditions to enter the lytic phage life history

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TABLE 1

Proteins encoded by prophages

Prophage-encoded protein	Effect	Example	References
Exotoxin	The main pathogenic factors, increase the pathogenicity of bacteria	Diphtheria toxin, botulinum toxin	(Feiner *et al.*, 2015)
Virulence protein	Enhance adhesion, invasion, the tolerance of host bacteria	Effector protein SopE in the *S. typhimurium*	(Twort, 1915)
Immune evasion protein	Help bacteria resist and immune evasion	Wall teichoic acid (WTA) glycosyltransferase in *Staphylococcus aureus*	(Gerlach *et al.*, 2018)
Resistance-gene-encoded protein	Confer bacterial resistance	The resistance to β-lactam antibiotics of *S. aureus*	(Davies *et al.*, 2016)
Regulatory protein	Regulate the transcription and expression of genes and morphogenesis on the bacterial genome	Regulatory sRNAs in *E. coli (EHEC) O157*	(Duerkop *et al.*, 2014; Tree *et al.*, 2014)
Integrase protein	Excision and integration of prophage genomes and maintenance of lysogeny	Prophages in *E. faecalis*	(Duerkop *et al.*, 2014; Fu *et al.*, 2017)
Functional protein	For the lytic pathway, replication, packaging, head/tail morphogenesis, and lysis functions	Prophages in *E. faecalis*	(Duerkop *et al.*, 2014)

(Duerkop *et al.*, 2014; Fu *et al.*, 2017). On the contrary, the defective prophage loses the ability to excise from the host genome or apparently lacks the necessary gene. It is considered as an ancient phage fossil kept on the host genome during evolution. Some studies have confirmed that the defective prophages and the full-length prophages belong to two different types of prophages (Rezaei Javan *et al.*, 2019). The former is not a simple lysogenic residue of the latter. Carrying the full-length prophages, the bacteria are at risk of being lysed and killed by phages. Carrying the defective prophages, the bacteria increase the energy load. From this perspective, it is extremely risky and unreasonable for bacteria to carry prophages; however, the prophages were widespread present in many bacterial genomes in nature, indicating that these prophages must be beneficial to the survival of the host bacteria.

Bobay *et al.* (2014) studied the evolution of prophages in bacterial genomes. They found that there were more than 300 vertically inherited prophages in the enterobacterial genomes, some of which are very old and may predate the time of evolutionary isolation between *Escherichia coli* and *Salmonella enterica*. An isolate of *Vibrio diazotrophicus*, widely distributed in the ocean, carries a prophage encoding the zonula occludens toxin (Zot) gene. Scientists have found that the bacteria originated from sediments 79.5 meters below the ocean floor, and the corresponding sedimentary age is estimated between 16,000 and 80,000 years old (Daniel *et al.*, 2018). These studies all indicate that prophages have undergone a long-term interaction or co-evolution with their host bacteria, also indicating that the prophages or their genes are beneficial to the host bacteria.

Prophages Are Widely Distributed in Different Bacterial Genomes

Prophages are available in almost all bacterial populations. Some studies predicted that prophages and prophage-like elements account for 20% of the entire bacterial genomes (Pfeifer *et al.*, 2019). As of December 2019, the prophage information for bacteria of at least 27 genera has been collected (Tab. 2). There are multiple phage lineages associated with the plant pathogens. Analysis revealed that there are more than 5000 prophage-related genes in 37 bacterial genomes and some phage genes are in active transcription state under certain plant infection conditions (Varani *et al.*, 2013). The distribution of those prophages may be related to the pathogenicity of the hosts. Rezaei Javan *et al.* (2019) analyzed 70 different *Streptococcus* including more than 1,300 genomes. Nearly 800 prophages were identified. The highly recombined *S. pneumoniae* genome contained a highly conserved defective prophage. The study confirmed its existence for decades, suggesting that the prophage may provide important biological functions for bacteria. Two prophages phiRv1 and phiRv2 exist in the genome of the pathogenic bacterium *Mycobacterium tuberculosis* H37Rv (Bibb and Hatfull, 2002; Cole *et al.*, 1998). And some genes of the prophages phiRv1 and phiRv2 were expressed under certain stress (Fan *et al.*, 2015). The *Vibrio* genus is ubiquitously distributed in the ocean, accounting for 0.5–5% of the total bacterial community. Some studies found that the prophage-like elements encoding certain properties (such as virulence and antibiotic resistance, etc.,) are widely distributed in environmental *Vibrio*, including non-pathogenic strains (Daniel *et al.*, 2018). Paul (2008) screened the genomes of 113 marine bacteria and found 64 types of prophage-like elements. In addition, the comparative genomic analysis of *Shewanella* strains isolated from periodically or permanently cold geographic environments and *S. oneidensis* isolated from sediments also revealed the presence of prophage. Further research found that the excision of the prophage CP4So in *S. oneidensis* was related to genetic changes when

TABLE 2

Prophages in sequenced bacterial genomes

Genera/Species	Prophage and prophage-like elements	Classification	Environment	References
Mycobacterium	33	11 (full-length prophages)	In the human body	(Fan *et al.*, 2015; Fan *et al.*, 2014)
Marine bacteria (113)	64	21 (GTA-like elements)	In oceans	(Paul, 2008)
Streptococcus (1306 genomes)	800	415 (full-length prophages) 348 (satellite prophages)	In the human body and some animals	(Rezaei Javan *et al.*, 2019)
Soft Rot Pectobacteriaceae	85	37 (full-length prophages) 48 (defective prophages)	In plants	(Czajkowski, 2019)
Streptococcus mutans	35	Cluster A Cluster B Cluster C	In the human body	(Fu *et al.*, 2017)
Streptococcus suis	12	5groups (Group1-5)	In pigs	(Tang *et al.*, 2013)
Wolbachia	15	serine recombinase group 1 WO (sr1WO) serine recombinase group 2 WO (sr2TWO) serine recombinase group 3WO (sr2WO)	In diverse insects (including filarial nematode species and arthropod species)	(Crainey *et al.*, 2017; Kent and Bordenstein, 2010; Kent *et al.*, 2011)
Candidatus Liberibacter asiaticus	33	Type 1~Type 4	In citrus plants	(Dominguez-Mirazo *et al.*, 2019)
Helicobacter sp	16	Helicobacter phage Cluster A (9 (full-length prophages)) Helicobacter phage Cluster B Helicobacter phage Cluster C Helicobacter phage Cluster D	In the upper gastrointestinal tract of mammals and some animals	(Fan *et al.*, 2016)
Moraxella catarrhalis	163	4 clades (32 full-length prophages)	In the upper respiratory tracts of human	(Ariff *et al.*, 2015)
Lactococcus spp	14	three main groups (the936, c2, and P335 groups)	In the dairy environment	(Deveau *et al.*, 2006; Ventura *et al.*, 2007)
Lawsonia intracellularis	1	–	In some mammalians and ratite birds	(Vannucci *et al.*, 2013)
Bifidobacterium spp	71	5 groups (Group1-5)	In the mammalian gut and the digestive tract of birds and social insects	(Lugli *et al.*, 2016; Mavrich *et al.*, 2018)
E. coli K-12	11	–	In the human body and some animals	(Mehta *et al.*, 2004)
E.coli O104:H4	15	–	In the human body and some animals	(Ahmed *et al.*, 2012)
E.coli O157:H7 EDL933	18-20	–	In the human body and some animals	(Casjens, 2003)
E.coli O157 VT-2 Sakai	18	–	In the human body and some animals	(Casjens, 2003)
E.coli CFT073	8	–	In the human body and some animals	(Casjens, 2003)
Agrobacterium tumefaciens C58	2	–	In soil	(Casjens, 2003)
Bacillus	9	–	In soil, water, air and animal intestines	(Casjens, 2003)

(Continued)

Table 2 (continued).

Genera/Species	Prophage and prophage-like elements	Classification	Environment	References
Brucella melitensis	2	–	In many kinds of livestock	(Casjens, 2003)
Clostridium	4	–	In soil and intestines of human and animals	(Casjens, 2003)
Listeria monocytogenes	8	–	In nature	(Casjens, 2003)
Neisseria meningitidis	5	–	In the human body	(Casjens, 2003)
Pseudomonas	6	–	In nature	(Casjens, 2003)
Ralstonia solanacearum GMI1000	8	–	In plants	(Casjens, 2003)
Salmonella enterica	19	–	In the human body and some animals	(Casjens, 2003)
Shewanella oneidensis MR –1	3	–	In oceans	(Casjens, 2003)
Shigella flexneri 2a 301	11	–	In the intestines of humans and primates	(Casjens, 2003)
Staphylococcus aureus	6	–	In nature	(Casjens, 2003)
Yersinia pestis	12	–	In human body	(Casjens, 2003)
Lactobacillus reuteri (28 L. reuteri strains)	17	–	In the intestinal tract of vertebrates	(Oh *et al.*, 2019)
Enterococcus	7	–	In mammals and insects	(Duerkop *et al.*, 2014)
Vibrios (1874 genome sequences)	5674	–	In oceans and marine animals	(Daniel *et al.*, 2018)
Plant-Pathogenic (37 genomes)	308 (5,169 potential genes of phage origin)	essential phage genes (structural genes, nonstructural genes) nonessential phage genes (IS transposases, TA systems, RM systems, nonphage genes)	In plants	(Varani *et al.*, 2013)

Abbreviation: GTA, gene transfer agent; IS, insertion sequence; TA, toxin-antitoxin; RM, restriction-modification

the temperature of host bacteria dropped (Zeng *et al.*, 2016). Prophages were also found in other bacterial genomes (Tab. 1). The above studies showed that prophages were widely distributed in different environmental genomes and active in the bacteria. It is speculated that the prophages may encode some proteins with important functions, which is responsible for the evolution and pathogenicity of the host bacteria.

It should be pointed out that many bacteria carried more than one type of prophages and almost all pathogenic bacteria contained at least one prophage (Paul, 2008). Touchon *et al.* (2016) analyzed more than 2,000 bacterial genomes and revealed that about half of these genomes were lysogenic (carrying prophages), and each lysogenic bacterium carried three types of prophages on average. Carrying a variety of prophages is commonly seen in bacterial pathogens and their expression can be enhanced when key proteins were encoded by multiple prophages. The genome of *E. coli O157: H7* RIMD0509952 has identified 18 co-existing prophages and 6 prophage-like elements. It can enhance the expression of prophage-encoding genes in this way. Carrying multiple prophages has a competitive advantage over a single lysogenic bacterium. The stx prophage in *E. coli* has shown a cumulative effect on the expression of Shiga toxin during infection (Feiner *et al.*, 2015). In addition, *S. enterica* contained two functional prophages, Gifsy-1 and Gifsy-2. These two prophages involved in defensing against macrophages killing by working together (Wang and Wood, 2016).

At the Single-Cell Level, Prophages Help Host Bacteria Adapt to Harsh External Environments

What effect or influence does the prophage have for bacteria? In fact, many research groups have found that prophages, as mobile and integrated genetic elements on the bacterial genome, are closely related to the evolution and adaptation

to harsh environments of host bacteria. Bacterial genome sequencing results showed that the pathogenic strains carried more prophage-related genes than the non-pathogenic strains. As genetic elements on the bacterial genome, the effect of prophages is prominent on pathogens to help bacteria adapt to the hostile environment in the host cell and improve the intracellular survival (Argov *et al.*, 2017; Feiner *et al.*, 2015; Obeng *et al.*, 2016; Salmond and Fineran, 2015). There are three ways that prophages may help their hosts adapt to harsh external environments (Fig. 1).

Prophages can directly carry virulence genes (Fig. 1A)
These genes were classic virulence factors that help pathogens infect host cells and escape from the host's immune system. They can help bacteria in different ways. Some prophages can encode Exotoxin. As classic virulence factors, they are the main pathogenic factors of some bacteria, for example, diphtheria toxin of *Corynebacterium diphtheria*, botulinum toxin of *Clostridium botulinum*, shiga toxins of *E. coli O157: H7* and cholera toxin of *V. cholera* (Feiner *et al.*, 2015; Wang *et al.*, 2010). Some prophage-encoded virulence proteins can enhance the adhesion and invasion of bacteria and increase the pathogenicity of bacteria such as *S. mitis strain SF100* and *Enterococcus faecalis* (Bensing *et al.*, 2001; Matos *et al.*, 2013), which harbor two proteins PblA and PblB encoded by prophages. These proteins are believed to promote the binding of bacteria to host cells and be related to bacterial adhesion. In the *S. typhimurium*, the prophage-encoded effector protein SopE can promote bacterial invasion (Twort, 1915). The virulence genes carried by some prophages can help pathogenic bacteria adapt to hostile environments and increase the survival rate of pathogenic bacteria in the host cells. Wang *et al.* (2010) found that some prophages and their encoded proteins can increase the tolerance of bacteria to oxidative and acid stresses in *E. coli K-12 BW25113*. In serotype *S. typhimurium*, the prophage SopEφ can increase the production of inducible nitric oxide synthase (iNOS), thereby increasing the survival rate in cells under hypoxic conditions (Obeng *et al.*, 2016). Some prophage virulence proteins can confer the ability to resist and evade the host's immune system on pathogenic bacteria. Shiga toxin (Stx) encoded by prophages in *enterohemorrhagic E. coli* (EHEC) can inhibit the PI3K/Akt/NF-κB signaling pathway in host cells and further reduce the expression of chemokines CCL20 and IL-8, thus inhibiting the human intestine natural immune response to help bacteria escape from the immune system killing (Gobert *et al.*, 2007). Methicillin-resistant *Staphylococcus aureus* (MRSA) contains some prophages that encode an alternative wall teichoic acid (WTA) glycosyltransferase. This enzyme modifies WTA and changes its immunogenicity to help MRSA immune evasion (Gerlach *et al.*, 2018). The biofilm formed by bacteria show increased resistance to antibiotics and host immune. Prophages also play a key role in the development and maturation of biofilms of several pathogens such as *Pseudomonas aeruginosa*, *S. pneumoniae*, *Bacillus anthracis* and *E. coli* (Secor *et al.*, 2015, 2016; Wang *et al.*, 2010). In addition, some prophages also encode the antimicrobial resistance (AMR) genes to confer bacterial resistance, helping increase the bacterial survival in harsh environments (Wang and Wood, 2016). The prophage TEM123 encodes a metal-β-lactamase gene that conferred resistance to β-lactam antibiotics on *S. aureus* (Davies *et al.*, 2016). Surveillant data from British

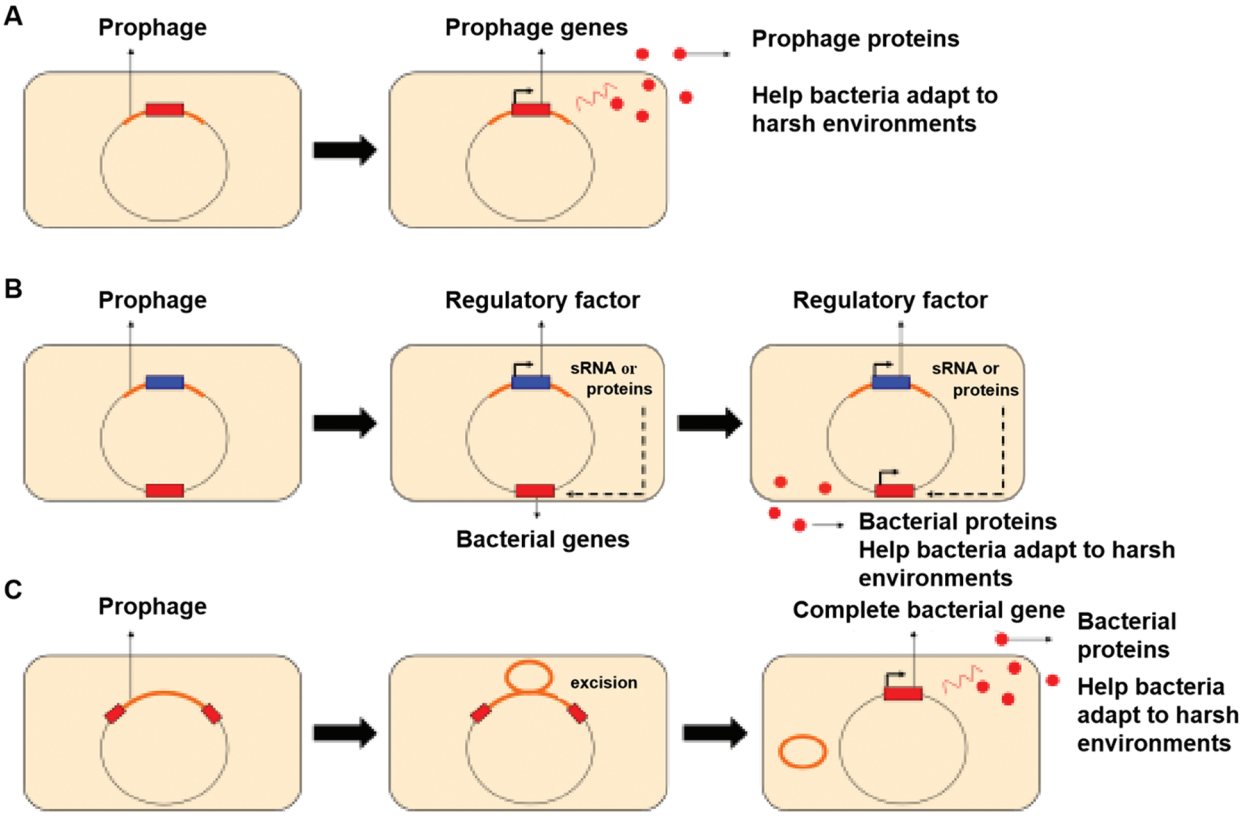

FIGURE 1. At the single-cell level, prophages help host bacteria adapt to harsh environments.

public health authority in 2017 showed that invasive *S. typhimurium* in Africa carried specific prophages and antibiotic resistance genes (Wahl *et al*., 2019). Recent studies also found P1-like plasmid prophage pSJ46 carried β-lactamase (bla) CTX-M-27 resistance gene in *S. isolate SJ46* (Gilcrease and Casjens, 2018; Yang *et al*., 2017).

Prophages can also encode some regulatory factors (protein or sRNA, etc.) (Fig. 1B)

They can regulate the expression of key genes on the bacterial genome to improve the adaptability of bacteria to the external environment, especially the pathogenicity of pathogenic bacteria. For example, the prophage P22 of *S. typhimurium* can encode a pid protein in a pseudolysogenic state, which can regulate the expression of dgoR-KAT operon. The dgoR-KAT operon of *S. typhimurium* is mainly responsible for the uptake and metabolism of the carbon source D-galactonic required for intracellular growth. In this way, the prophage P22 increased the intracellular survival rate of *S. typhimurium* by expressing the regulatory factor pid (Cenens *et al*., 2013). 55 phage-encoded regulatory sRNAs were identified in *E. coli (EHEC) O157*. Among them, AsxR-anti-sRNA and AgvB-anti-sRNA were interacted with bacterial sRNA-FnrS and GcvB respectively, and then further regulated the expression of target mRNA in bacteria to increase the competitiveness of *E. coli (EHEC) O157* in the gastrointestinal tract (Tree *et al*., 2014). The prophages in *B. anthracis* can encode a replacement σ factor, which can induce to produce extracellular polysaccharides and biofilms, thereby improving the survival rate of bacteria in harsh environments (Tree *et al*., 2014). In *C. difficile*, the prophage phiCDHM1 encoded AgrB, Agrc and AgrD, which are involved in the quorum sensing of bacteria and thus affect the expression of bacterial genes (Sekulovic and Fortier, 2015). Prophages carried by some marine bacteria contained cI repressor, which can interact with the operon of *pckA*, a gene encoding phosphoenolpyruvate carboxykinas. The prophage gene can shut down *pckA*, which make the bacteria to grow slowly in a glucose-free environment and improve the survival of bacteria in adverse environments (Paul, 2008).

Active lysogeny (Fig. 1C)

The prophage can be used as a phage regulatory switch (Phage-RS) to control the expression of key genes to help bacteria adapt to harsh external environments. Prophages inserting into the virulence gene of bacteria can destroy the integrity of this gene. The excision and integration of prophages can be used as a regulatory switch for the expression of the key gene (Ofir and Sorek, 2018). When the prophage is inserted into the genome, the key gene cannot be expressed normally. When the prophage is accurately excised from the genome, the key gene is restored and encoded. The expression and secretion of key proteins can help host bacteria resist the harsh environments. Prophage ϕ10403S in *Listeria monocytogenes* genomes acts as a Phage-RS to control the expression of the gene *comK*. When *L. monocytogenes* infected the mammalian cells, the prophage ϕ10403S was excised from the genome and *comK* was expressed to help *L. monocytogenes* survive in phagosomes (Feiner *et al*., 2015; Rabinovich *et al*., 2012). Prophage SpyCIM1 was found as a Phage-RS in the human pathogen *S. pyogenes* to control the expression of MutSL, a bacterial DNA mismatch repair system (MMR). SpyCIM1 is excised from the host genome and replicated as an episome during the exponential growth of bacteria, leaving a fully functional MMR system and resulting in a low mutation rate. Under certain stress such as nutritional deficiencies or environmental stress, SpyCIM1 was integrated into the *mutSL* operon, increasing the mutation rate by 160 times, thereby increasing the possibility of bacterial survival (Feiner *et al*., 2015). In *B. subtilis*, a prophage called skin as Phage-RS controls the expression of the *sigK* gene. The *sigK* gene expresses the σ^K transcription factor which can regulate certain genes required in the final stage of mother cell differentiation like spore polysaccharide biosynthesis, mother cell metabolism, germination and mother cell lysis. During the formation of spores in a harsh environment, the prophage skin was excised and caused the expression of *sigK* (Feiner *et al*., 2015).

At the Population Level, the Prophages Affect the Evolution and the Ecological Function of Host Bacteria

Prophages influence the evolutionary direction of the host population

The relationship between prophage and bacterium is multifaceted. Although the bacteria bear the risk of being lysed and a certain energy load, they also acquire ecological and evolutionary advantages from prophages (Fig. 2). The induction and integration of prophages promote the gene transmission and contribute to the genetic diversity and functional adaptation of host bacteria. From the perspective of the population, high abundance, diversity and turnover rate of prophages led to the continuous input of new genes in bacterial genomes. Prophages serve as transfer vectors for bacteria, mediate horizontal gene transfer and provide bacteria new functional genes to promote bacterial evolution (Canchaya *et al*., 2003; Tang *et al*., 2019; Varani *et al*., 2013). In *E. coli*, prophage genes account for more than 35% of the species' genetic diversity (Bobay *et al*., 2014). The representative strains of *S. typhimurium* LT2, ATCC14028 and SL1344 all contain two types of prophages: Gifty-1 and Gifty-2, which carry virulence genes. Most prophage-related genes can be efficiently transferred between *Salmonella* strains of the same or different serotypes to drive the evolution of *Salmonella* (Figueroa-Bossi *et al*., 2001). Tang *et al*. (2019) found that prophages can change the arsenic speciation and increase the soil ecotoxicity by transducing arsenic resistance genes of bacteria in soil (Tang *et al*., 2019). In addition, the integration and random insertion into the host genomes of prophages may cause gene mutations, which may be beneficial to adapt the host to the new environment because it can accelerate the evolution process of bacterial population (Argov *et al*., 2017). A recent study found that the *P. aeruginosa* population which was co-cultured with the temperate phage ϕ4 adapted faster to simulate lung environment than the bacterial population not co-cultured, suggesting that the presence of prophage drove

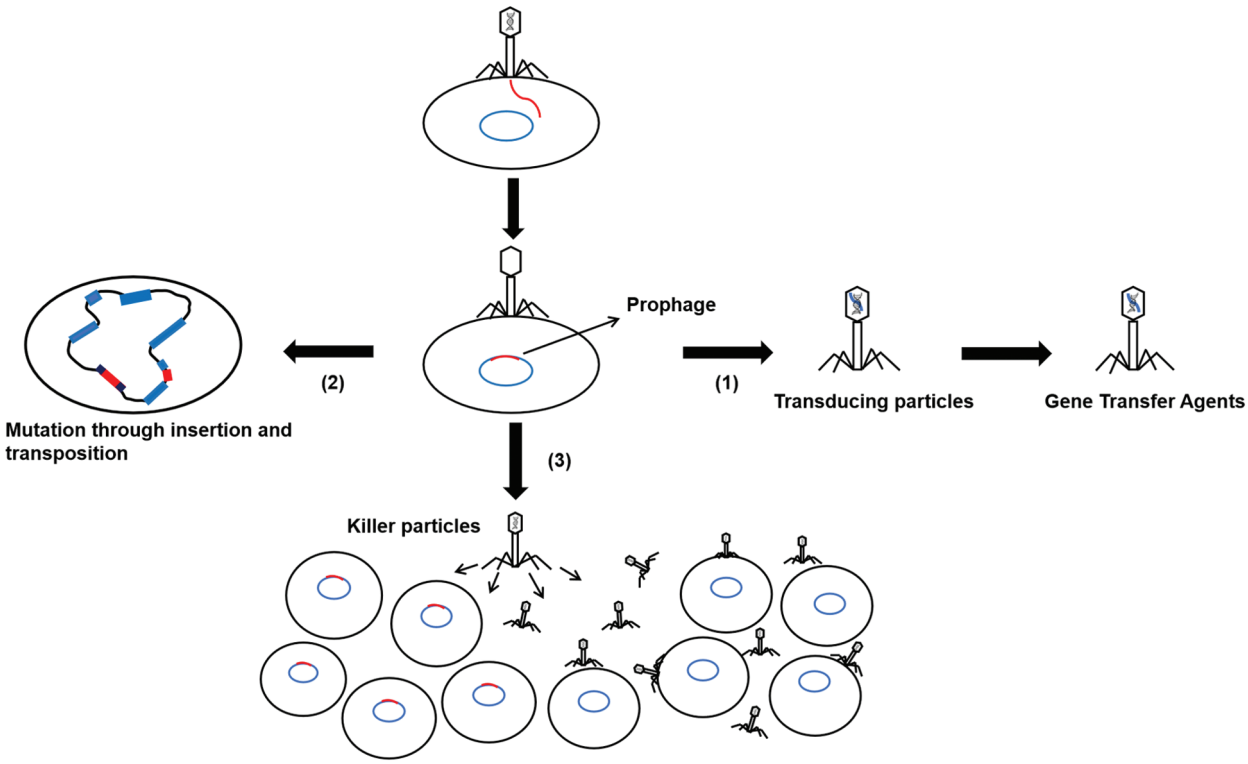

FIGURE 2. At the population level, prophages influence the evolutionary direction of the host populations.
(1) Temperate phages can mediate horizontal gene transfer of bacteria through transduction. (2) Prophages can accelerate host evolution through insertion and transposition which generate novel mutations and rearrangements. (3) Temperate phages can create infectious phage particles under stress which go on to kill susceptible competitors in the process of self-sustaining infection while these lysogens are immune.

rapid evolution process (Obeng *et al.*, 2016). In Xylella and Xanthomonas, prophage is related to genome rearrangements and bacterial differentiation (Varani *et al.*, 2013). It is worth noting that some prophages can still maintain the ability to lyse bacteria (Argov *et al.*, 2017). Under stress conditions, prophages are transformed into lytic phages such as antibiotics, ultraviolet (UV) light or reactive oxygen species (Duerkop *et al.*, 2014). Although a single bacterium bears the risk of being lysed, the released progeny phages can infect and kill susceptible bacteria, thereby increasing the survival capability of bacterial population (Wang *et al.*, 2010).

Prophages affect ecological function of host population

The complex interaction between bacteria and prophages is critical to the ecological function of the microbial community and global biogeochemical cycles (Howard-Varona *et al.*, 2017). For example, in the marine environment, the phage is the most numerous and diverse organism, and the transformation of lysogenic and nonlysogenic strains exerts important effects on the structure of marine microbial communities. In addition, prophages harbor a class of genes which are auxiliary metabolic genes (AMGs). After integration into the host bacterial genome through prophages, they can affect the biogeochemical cycle such as carbon, nitrogen and sulfur cycling at the level of bacterial population (Argov *et al.*, 2017). The prophage in marine bacteria SUP05 encodes sulfur reduction-related DsrC, which may regulate important electron transfer reactions and play a role in the sulfur cycling (Warwick-Dugdale *et al.*, 2019). In other marine bacteria *Anabena spp.* and *Nostoc spp* genomes, prophages can interrupt nitrogen-fixing genes (nifD, fdxN and hupL) during N-limitation, thereby affecting the nitrogen cycling (Warwick-Dugdale *et al.*, 2019).

Concluding Remarks

In general, phages, as natural enemies of bacteria, have been widely domesticated by their host bacteria with obvious benefits to bacteria. Prophages are integrated into bacterial genomes and used by bacteria in various ways to resist harsh environments and help bacteria survive. In this review, we outlined prophages widely distributed in different bacterial genomes, and highlighted the role of prophages in the adaptation of host to the environment. At the single-cell level, prophages can help host bacteria adapt to harsh external environments in a number of ways. At the population level, prophages can influence the overall evolutionary direction and ecological function of bacterial communities. At present, people's attention and research on prophages are continuing. The role of prophages and their genes in the physiological growth of bacteria, especially in the pathogenicity of pathogenic bacteria, is still worthy of further study. In short, the arms race between bacteria and phages or prophages will continue. The dynamic changes between them will promote biological evolution and increase species diversity in nature, and the complex interaction between bacteria and phages or prophages allows them to co-exist stably.

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