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MINI-REVIEW

Mechanisms of interactions between bacteria and bacteriophage mediate by quorum sensing systems

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Abstract

Bacteriophage (phage) and their host bacteria coevolve with each other over time. Quorum sensing (QS) systems play an important role in the interaction between bacteria and phage. In this review paper, we summarized the function of QS systems in bacterial biofilm formation, phage adsorption, lysis-lysogeny conversion of phage, coevolution of bacteria and phage, and information exchanges in phage, which may provide reference to future research on alternative control strategies for antibiotic-resistant and biofilm-forming pathogens by phage.

Key points

- *Quorum sensing (QS) systems influence bacteria-phage interaction.*
- *QS systems cause phage adsorption and evolution and lysis-lysogeny conversion.*
- *QS systems participate in biofilm formation and co-evolution with phage of bacteria.*

Keywords Quorum sensing systems · Bacteria-phage · Interactions · Mechanisms

Introduction

In nature, information exchange occurs within and between species of microorganisms to gain benefits or avoid harm for different microorganisms. The quorum sensing (QS) systems are widely present in microorganisms and play a key role in exchanging microbial information (Haque et al. 2019). As a communication mechanism between microorganisms, the QS system was first defined by Fuqua et al. in 1994 (Fuqua et al. 1994). QS can assess the number and density of individuals in a population, allowing specific gene expression to be induced only when a critical threshold concentration is reached, which initiates microbial-specific swarm behaviors and promotes mutual communication between microbial individuals to adapt to the environment (Abisado et al. 2018; Erez et al. 2017; Kü et al. 2000). QS systems regulate physiological processes, including biofilm formation, virulence factor expression, and metabolism, which are beneficial to bacterial survival and adaptation (Ha et al. 2018; Shepherd et al. 2019; Wang et al. 2019). Studies have observed that QS systems regulate the physiological processes of bacteria and play an important role in the interaction between bacteria and their predator (phage) (Justin et al. 2018; Rossmann et al. 2015).

Phage is a virus that can specifically infect bacteria. It attaches itself to a susceptible bacterium and injects its nucleic acid into the host cell. As a result, new phages assemble and burst out of the bacterium in the cell lysis process (Kutter and Sulakvelidze 2005). Due to the emergence of multidrug-resistant bacteria, phage has attracted increasing interest as an antibacterial agent. Phage coevolves with its host bacteria over time when it is applied for therapy. Thus, it is important to know the interaction mechanisms between phage and its host bacteria. As important systems for microorganisms, QS systems are involved in the

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interaction between phage and bacteria (Moreau et al. 2017; Qin et al. 2017; Saucedo-Mora et al. 2017). The extent of bacterial elimination by phage can be regulated by QS systems, a new antibacterial strategy (Broniewski et al. 2021; Laganenka et al. 2019; Qin et al. 2017; Silpe and Bassler 2019). There are many hypotheses about the mechanisms of bacterial QS systems involved in phage resistance, including complex signal transduction pathways, which need to be illustrated. It has been reported that *Escherichia coli* can resist phage infection through QS systems (Choi et al. 2012; Hoyland-Kroghsbo et al. 2013; Kobayashi 2007). Bacteria are likely to resist phage infection by QS systems (Hoyland-Kroghsbo et al. 2013). In QS systems, bacteria are dependent on signal molecules and receptor proteins (Even-Tov et al. 2016). In this review paper, we described the interaction between phage and bacteria in terms of biofilm, adsorption, fusion lysis switch, and eco-evolutionary mechanisms to provide a useful reference for readers.

Roles of biofilms in bacteria-phage interaction

Biofilm is a substance formed by bacteria on a solid surface under natural conditions, which is beneficial to the survival of bacteria (Llama Palacios et al. 2020; Sadiq et al. 2020). Bacterial biofilms can increase bacterial resistance to the external physical and chemical environments, making bacteria difficult to be killed by antibiotics or conventional disinfectants (Hall-Stoodley et al. 2004; Kaplan 2011; Saitou et al. 2009). QS system is one of the regulatory pathways of bacterial biofilm formation. It regulates the synthetic genes of flagella, exopolysaccharide, adhesin, and other substances through signal molecules, such as autoinducer-1 (AI-1), autoinducer-2 (AI-2), and N-acyl homoserine lactone (AHL), thereby affecting the formation of bacterial biofilms (Gu et al. 2020; Yang et al. 2013). When bacteria are subjected to external environmental pressures (e.g., phage), their QS systems promote the formation of biofilms to resist these pressures (Tufenkji et al. 2013).

The long-term bacteria-phage interaction has developed a variety of survival methods in the formation and lysis of biofilms (Oliveira et al. 2018; Sharma et al. 2018; Zhang et al. 2018). Phage can break down biofilms through depolymerases to achieve the purpose of sterilization of pathogenic bacteria (Knirel et al. 2020). The use of phages to destroy biofilms is one of the main directions for the study of killing bacteria. The mechanisms of bacteria-phage counterbalance mediated by QS in the state of biofilms are summarized in Fig. 1. After being infected by the phage, bacterial use the QS systems to enhance their ability and form biofilms (Molin et al. 2013), which constitute a physical barrier against the phage (Melo et al. 2020). However, phages use some strategies to act on biofilms to invade host bacteria (Ruoting et al. 2014; Silva et al. 2010).

Regulation of biofilm formation by bacteria through QS systems to resist phage

As phage attacks bacteria frequently, various strategies are developed by bacteria against phage infection, such as biofilm formation (Van Ooij 2009). Due to the tight binding between individual cells, some phage receptors are hidden, resulting in a decrease in phage adsorption rate (Rickard et al. 2003). The biofilm structure can prevent phages from entering the bacterial population (Jakob et al. 2019). This structure is composed of extracellular polymeric substances (EPS), which is also an important basis for maintaining the stability of the biofilm structure (Vermeulen et al. 2019). EPS is mainly composed of polysaccharides, proteins, nucleic acids, lipids, and environmental DNA (eDNA) (Federico et al. 2018). Proteins, such as Curli protein, can form

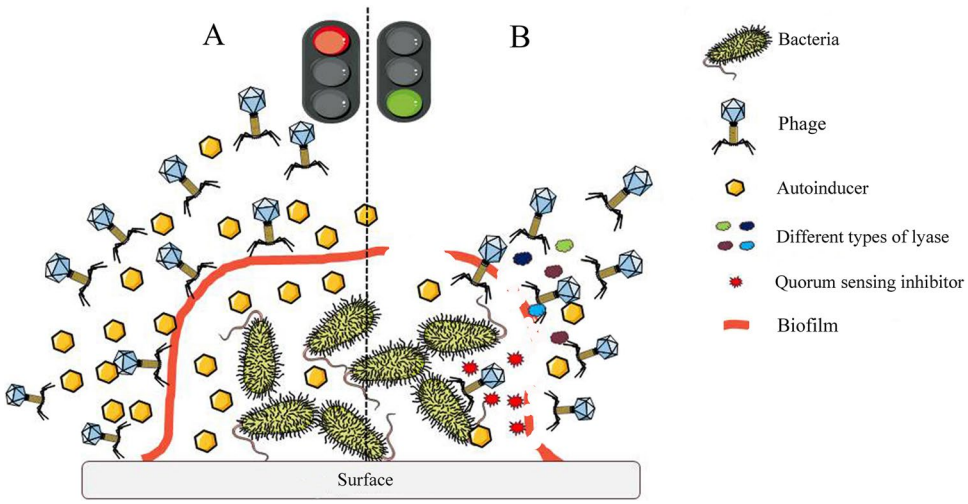

Fig. 1. Interactions between bacterial biofilm and phage. **A** Bacterial biofilm formation induced by signal molecules of QS systems lead to resistance to phage. **B** The phage or related substance produced by phage hinders the formation of bacterial biofilm

amyloid fibers to promote extracellular matrix formation and dense cell accumulation (Jakob et al. 2019). Proteolytic enzymes and endonucleases can lead to the inactivation of phages (Azeredo and Sutherland 2008). Phage infection causes a significant upregulation of expression levels of QS genes in *E. coli* and *Pseudomonas aeruginosa* (4.1–24.9-fold), resulting in enhanced biofilm formation (Zhang et al. 2020). When the *Vibrio anguillarum* PF430-3 is in a low cell density state (mutant Δ*vanT*), the phage receptor OmpK is highly expressed, making cells highly sensitive to phage KVP40, while mutant Δ*vanT* resists phage infection by enhancing biofilm formation (Demeng et al. 2015). When *V. anguillarum* 90-11-287 is in a low cell density state (mutant Δ*vanT*), the biofilm formation is increased, and H20-like phages can promote the biofilm formation of its host bacteria (Tan et al. 2020). When *V. anguillarum* is exposed to high cell density (mutant Δ*vanO*), it reduces the induction of prophages, leading to increased proteolytic activity and suppressed biofilm formation (Tan et al. 2020). These results suggest that the bacterial QS systems mediate the maturation of biofilms against phage infection.

Destruction of bacterial biofilms by phage

Phage is an important antibacterial agent related to clinical medicine, food safety, and environmental purification (Cristinaneguţ et al. 2016; Haddad et al. 2018; Harper 2018; Shlezinger et al. 2016). In some cases, phages can increase the biofilm formation of bacteria. Phages can also effectively destroy biofilms than antibiotics. The derivates of phage can hinder bacterial biofilm formation through various components, such as polysaccharide depolymerase enzymes (sialidase, acetylglycanase, xyloside, etc.) (Hughes et al. 1998; Pires et al. 2016; Solovieva et al. 2018).

The mechanisms of phage destroying the bacterial biofilms can be divided into five categories: (1) the lytic enzymes produced by the phage-associated genes can decompose the extracellular polysaccharide (e.g., peptidoglycan) of biofilms, and the deficiency of these components block the network connection of biofilms, resulting in the removal of biofilms (Chhibber et al. 2015; Gutiérrez et al. 2015; Kwiatek et al. 2016; Pires et al. 2016); (2) the lytic enzymes on the phage tail are usually hidden, and these enzymes are exposed when the tail comes into contact with bacteria. The enzymes on the tail of the phage can help the phage lyse the bacterial cell wall. Tail lyase enzymes can degrade the extracellular polymers of biofilms (Cornelissen et al. 2012; Hansen et al. 2019; Jianlong et al. 2013); (3) after entering the host, the phage trigger the host to express enzymes, which can degrade biofilms through the interaction mechanisms (Bartell and Orr 1969; Hanlon et al. 2001); (4) the phage can enter the biofilms through the hydrophobic channel of biofilms, thereby lysing the bacteria from the membrane (Briandet et al. 2008); (5) by releasing host QS inhibitors (e.g., lactonases), phage hampers the communication among bacteria individuals, facilitating the attacking ability of phage against bacteria (Kaistha and Umrao 2016; Lan et al. 2013; Pei and Lamas-Samanamud 2014). Studies of biofilm disruption by QS-related mechanisms by bacteriophage are listed in Table 1.

Exploration of enhanced ability of phage to destroy biofilms

Phage is a virus that can infect bacteria. They coevolve with each other over time and keep in dynamic balance (an arm race) (Sutton and Hill 2019). In many cases, phages do not eliminate host bacteria thoroughly. After treatment with phage P100 for 8 h, the biofilm is depolymerized. However, the planktonic

Table 1 Studies on the removal of bacterial biofilm by phage through quorum sensing systems

Name of bacteria(species)	Name of phage	Quorum sensing factors	References
ATCC 15692 (*P. aeruginosa*)	vB_Pae_QDWS	*las*	(Xuan et al. 2022)
ATCC 27853 (*P. aeruginosa*)	vB_PaeM_USP_1, vB_PaeM_USP_2, vB_PaeM_USP_3, vB_PaeM_USP_18 and vB_PaeM_USP_2	*lasI*、*pslA*、*lasB* and *phzH*	(Oliveira et al. 2021)
C6706 (*V. cholerae*)	VP882	*vqmR*	(Duddy et al. 2021)
ATCC 15692 (*E. coli*), ATCC 10798 (*P. aeruginosa*)	Phage PEB1 and PEB2	*sdiA*, *luxS*, *lasI* and *lasR*	(Zhang et al. 2020)
90-11-287 (*V. anguillarum*)	ϕH20-like phage	*vanT*	(Tan et al. 2020)
CC274 (*P. aeruginosa*)	PHAGE_ Pseudo_ phi297_ NC_ 016762-like phage	*bci*	(Ambroa et al. 2020)
BL21(*E. coli*) , TG1(*lacI*::*kan*) (*P. aeruginosa*)	Engineered T7 phage	AHL	(Pei and Lamas-Samanamud 2014)

Table 2 Studies on the removal of bacterial biofilm by phage combined with antibacterial agent

Phage	Antibacterial agents	Evaluation of effects	Source of references
T4	Cefotaxime	After adding phage titers of 10^4 PFU/mL and 10^7 PFU/mL, the minimum biofilm eradication concentration of cefotaxime to *E. coli* ATCC 11303 was reduced from 256 μg/mL to 128 μg/mL and 32 μg/mL	(Ryan et al. 2012)
Phage isolated from Alexandria University Hospital	Amikacin	Compared with phage or antibiotics, the amikacin-phage combination can significantly eradicate *P. aeruginosa* biofilm	(Nouraldin et al. 2016)
SAP-26	Rifampicin	When combined with rifampicin, it can eliminate 65% of the biofilm of *S. aureus*	(Rahman et al. 2011)
Sb-1	Daptomycin	The combined action of Sb-1 and antibiotics can eradicate the biofilm of rifampicin-resistant bacteria	(Wang et al. 2020b)
Phage (Xccφ1)-hydroxyapatite complex	Long Fatty Acids	The long-chain fatty acid combined with phage (Xccφ1)-hydroxyapatite complex has an effective ability to remove mature biofilms	(Papaianni et al. 2020)
vB_EcoM-WL-3 (ϕWL-3)	Ciprofloxacin, fosfomycin, gentamicin, meropenem or ceftriaxone	The co-administration of ϕWL-3 and antibiotics improves the antibiotic efficacy of *E. coli* strains against ciprofloxacin/ceftriaxone, especially after staggered contact, reducing the minimum biofilm bactericidal concentration (MBBC) values up to 512 times	(Wang et al. 2020a)
EC3a	Honey	The use of phage and honey is a better way to break through a single biofilm of *E. coli*. Honey can destroy the bacterial cell membrane and penetrate the biofilm matrix, promoting and enhancing phage infection	(Ana et al. 2018)
EFDG1	EFLK1	Cocktail #1 (1:1) kills *E. faecalis* V583 as efficiently as phage EFDG1. It is better than other cocktails in removing the *E. faecalis* V583 biofilm	(Leron et al. 2018)
38	39、41, CEV2, AR1, 42, ECA1 and ECB7	The number of bacteria has dropped dramatically and cannot be detected	(Viazis et al. 2011a; Viazis et al. 2011b)
LiMN4L	LiMN4p and LiMN17	After 75 min of mixing, the number of bacteria dropped dramatically and could not be detected	(Arachchi et al. 2013)
KPO1K2	Xylitol	Compared with phage or xylitol, the combination of bacteriophage KP01K2 and xylitol eliminated the *K. pneumoniae* biofilm and reduced the number of *P. aeruginosa* biofilms by 4 orders of magnitude. Also, the combined use of phage KP01K2, Pa29, and xylitol can reduce the underlying *P. aeruginosa* biofilm by 6 orders of magnitude	(Kaur et al. 2015)
Phage isolated from sewage samples from a sewage treatment plant in Colombia	Chlorine	The combination of phage and chlorine can control or destroy the bacterial biofilm on the surface of the object	(Yanyan et al. 2012)

Table 2 (continued)

Phage	Antibacterial agents	Evaluation of effects	Source of references
KP01K2	$CoSO_4$	Compared with the use of divalent cobalt ions or phage, the combination of divalent cobalt ions and *K. pneumoniae* phage KP01K2 can significantly reduce the *K. pneumoniae* B5055 biofilm	(Chhibber et al. 2013)

bacteria still exist after 48 h (Montaez-Izquierdo et al. 2012). Combined with an antibacterial agent, the phage can enhance the ability to inhibit or destroy bacterial biofilms (Table 2), suggesting that an appropriate antibacterial agent can be used as an adjuvant to maximize the bactericidal effect of phage.

Some gene products of phage and genetically engineered phage-related research have also entered the field of vision (Love et al. 2018; Shen et al. 2018). Compared with phage, the addition of phage-related gene products, for example, lysins, can improve the efficiency of sterilization while avoiding the spread of toxic genes and reducing the occurrence of bacterial resistance. Because of the presence of the bacterial biofilm decomposition genes in natural phage, the killing efficiency of phage against bacteria can be enhanced (Lu and Collins 2007; Pei and Lamas-Samanamud 2014). We summarized some related studies in this review paper. The expression of depolymerase can significantly increase phage activity (Pelkonen et al. 1992). Enzymatic phage can reduce the number of bacterial biofilm cells by about 4.5 orders of magnitude (removal rate = 99.997%) (Lu and Collins 2007). The extracellular polysaccharide depolymerase encoded by phage KP01K2 can hydrolyze the surface of *Klebsiella pneumoniae* biofilm, helping phage Pa29 to lyse the underlying *P. aeruginosa* biofilm (Chhibber et al. 2015). The biofilm count was significantly reduced when methicillin-resistant *Staphylococcus aureus* biofilm was treated with minocycline (4 μg / mL) for 3 h and subsequently with phage hemolysin MR-10 (Chopra et al. 2015). The Live/Dead Baclight^{TM} staining showed an increase in the number of dead cells after treatment with minocycline and hemolysin MR-10 (Chopra et al. 2015), which proved that the combination of minocycline and phage hemolysin MR-10 could effectively remove the biofilm formed by methicillin-resistant *S. aureus*. Phage LysGH15 (50 μg/mL) effectively prevented *S. aureus*, *S. epidermidis*, and *S. haemolyticus* from forming biofilms and destroyed biofilms formed at 24 h and 72 h (Zhang et al. 2018). These results suggest that the development of gene products can effectively improve or replace the ability of natural phages to kill bacteria in a biofilm state. Most studies are focused on the ability of phage and their derivative to remove biofilms, but there are a few studies on the interaction between bacteria-QS systems, which need to be further studied.

Bacterial QS systems participate in phage adsorption

Adsorption is the first step for phage to infect host bacteria. Various surface structures of bacteria are binding sites for phage adsorption, including flagella, pili, and other surface proteins. QS systems can block the adsorption of phage (Poisot et al. 2012). We have summarized the relevant research and presented associated mechanisms in Fig. 2.

QS systems regulate phage adsorption by flagella and fimbriae

Phage cannot complete the absorption process in the absence of bacterial appendages, such as flagella and fimbriae (Guerrero-Ferreira et al. 2011). Concealing the normal morphology of bacterial flagella or pili by QS systems can reduce the efficiency of phage adsorption (Hoyland-Kroghsbo et al. 2013; Kobayashi 2007). The QS system of Gram-negative bacteria is also known as the LuxI-LuxR type system, which mainly uses AHL as a signaling molecule (Sánchez-Sanz et al. 2018). *E. coli* cannot directly synthesize AHL signaling molecules. When exogenous AHL is added, the expression levels of flagellar-forming genes in *E. coli* can be inhibited, decreasing the adsorption rate of phage χ by about 3 times (Hoyland-Kroghsbo et al. 2013). Signaling molecules of the QS system in *Bacillus subtilis* can regulate the gene expression of flagellin (Kobayashi 2007), which is important for phage adsorption. Also, the regulation of the polar flagellum gene in *Burkholderia* spp. is mediated by QS systems and FlhDC (Kim et al. 2010). However, the removal of polar flagellum can promote the adsorption of bacteria by phage and enhance the infectivity of phage to *V. parahaemolyticus* (Zhang et al. 2016). These studies suggest that the QS systems can change the adsorption rate of phages by regulating the expression of the polar flagellum genes.

QS systems regulate phage adsorption by bacterial surface proteins

Besides flagella and fimbriae, various surface proteins of bacteria contribute to phage adsorption (Walderich and Höltje 1989). Some surface protein genes are downregulated

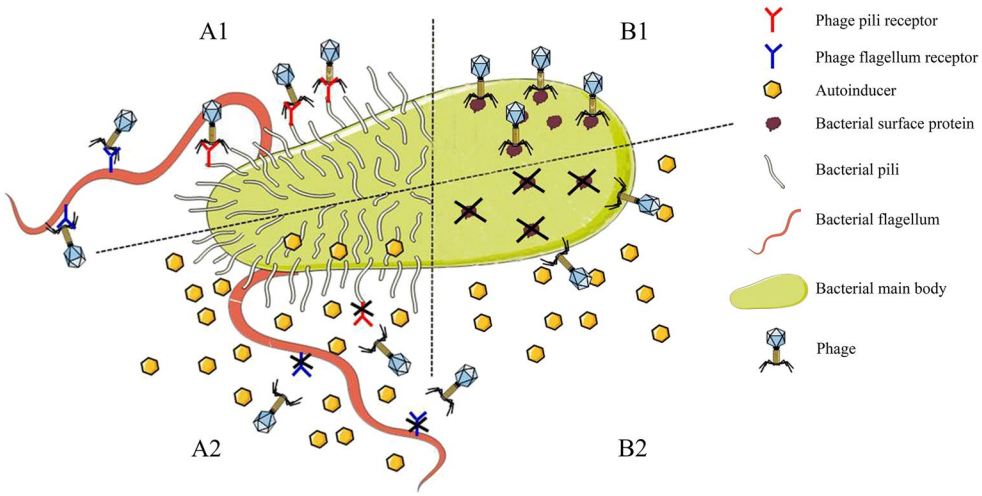

Fig. 2 QS systems block phage adsorption. A1: In the absence of signal molecules, phages bind to the bacterial flagella or fimbriae receptors to adsorb to bacteria. A2: The QS or exogenous signal molecules produced by bacteria can conceal the normal morphology of bacterial flagella or pili, resulting in reduced phage adsorption efficiency. B1: In the absence of signal molecules, phages adsorb to host bacteria by binding to their surface protein receptors. B2: The QS or exogenous signal molecules produced by bacteria can inhibit the expression of some bacterial surface protein to block phage adsorption

by QS systems, resulting in the inhibition of phage adsorption (López-Larrea 2012; Wang et al. 2014). The expression of surface protein LamB λ of *E. coli* can be inhibited with the participation of exogenous AHL signaling molecules and led to the blocking of phage adsorption (Wang et al. 2014). In addition, bacteria release a kind of membrane in their metabolic activities, called outer membrane vesicles (OMVs). Bacterial OMVs play an important role in host infection and antibiotic tolerance (Agarwal et al. 2018; Liu et al. 2017). The OMVs released by the bacteria can deceive the phage onto its surface, protecting the host bacteria and blocking the DNA replication of the phage (Manning and Kuehn 2011; Reyes-Robles et al. 2018). The formation of bacterial OMVs is regulated by QS system signaling molecules (Lauren et al. 2010). Phage adsorption may be prevented by forming OMVs mediated by the QS systems.

Bacterial QS systems regulate the lysis-lysogeny conversion of phage

Temperate phages are important components of the phage family, which can integrate their DNA into the chromosome of the host bacteria, and it is passed to the offspring genome that usually does not cause bacterial lysis (Laganenka et al. 2019; Silpe and Bassler 2019). This life cycle is called lysogeny. For the lambda-type phage, complex molecular mechanisms control the initial decision between lysis and lysogeny upon host infection (Oppenheim et al. 2005). The QS systems of *V. cholerae* are well studied (Kai and Bassler 2016). The relevant molecular mechanisms of lysis-lysogenic conversion of phage controlled by quorum sensing (QS) systems are shown in Fig. 3. Some researchers have discovered a QS system loop in *V. cholerae*, which is composed of the cytoplasmic receptor transcription factors (LuxR-solo and VQMA) and 3,5-dimethylpyrazin-2-ol (DPO) (Papenfort et al. 2017). The protein VQMA is simultaneously encoded by prophage VP882. The phage protein VQMA binds to the DPO produced by *V. cholerae* and leads the inactivation of proteins, such as phage vasopressin, resulting in lysis conversion of phage. It suggests that phage encode QS components, enabling them to integrate host cell density information into lysis-lysogen decisions. The activation of the QS pathway allows *Vibrio* phage (VP882) to produce an antidepressant called Qtip. Qtip promotes the lysis of host cells by interfering with the prophage inhibitory factor (cIVP882) (Duddy et al. 2021). A recent study showed that the QS system of *V. anguillarum* inhibited the induction of phage H20 at its high cell density and enhanced the ability of biofilm formation in *V. anguillarum*. The density of bacteria determined the phage transition from the lysogenic state to lytic state, and the self-inducing signal molecule (AI-2) played an important role in the process (Tan et al. 2020). In addition, the lysis of phage is controlled by cell metabolic state mediated by cyclic-3′,5′-AMP (cAMP) receptor protein (CRP) (Laganenka et al. 2019). Metabolism is an essential part of bacterial survival, and its utilization in the amplification of phage increases the viability of phage. Researchers have discovered that QS anti-activator protein, Aqs1, of *Pseudomonas* phage DMS3 can inhibit LasR, the main regulator of QS (Shah et al. 2021), which help phage fight against multiple bacterial defense systems.

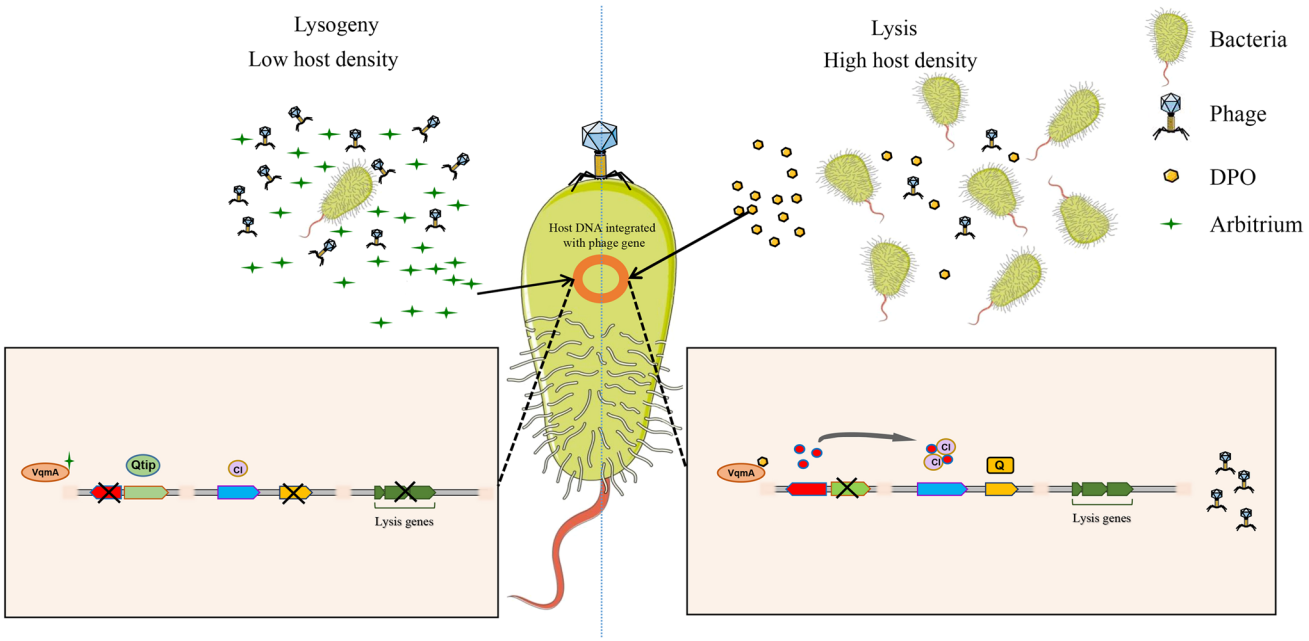

Fig. 3 Lysis-lysogenic conversion of phage controlled by QS systems. Cl repressor maintains lysogeny of the phage at low cell density. At high cell density, protein VqmA encoded by phage interacts with the host-produced QS autoinducer DPO, which activates the expression of anti-repressor protein Qtip, which binds to the Cl repressor, causing the activation of Q anti-terminator protein and resulting in the initiation of phage lysis pathway

Bacterial QS systems mediate bacteria-phage ecological evolution

Creatures constantly evolve in survival competition to maintain their relative adaptability to predators called the Red Queen hypothesis (Mclaughlin and Malik 2017). Although bacteria have multiple mechanisms to resist phage, the number of phages is 10 times over bacteria (Li et al. 2018; Paez-Espino et al. 2016). The phage-resistant strains can temporarily evasion of phage predation, but the subsequent emergence of the phage population, which can infect the phage-resistant bacteria, can threaten the life of bacteria (Shabbir et al. 2016). The rapid response ability of phage is mainly due to the rapid proliferation of phage and the high plasticity of phage genomes. In addition to binding to traditional bacterial receptors, phages can choose new receptors by modifying their receptor binding proteins (Samson et al. 2013). The clustered regularly interspaced short palindromic repeats gene (*Cas*) was discovered in 1987 and identified in 2005 as a strategy used by bacterium against the immune system of exogenous nucleic acids (Alexander et al. 2005; Ishino et al. 1987; Rodolphe et al. 2007). When infected by phage, the 5′ end of the clustered regularly interspaced short palindromic repeats (CRISPR) locus repeat adds a completely homologous sequence to the phage. When the phage infects the bacteria again, the bacteria become resistant to the phage. According to recent studies, population signaling molecules of bacteria can enhance phage resistance at high densities by modulating the activity of the CRISPR-Cas system (Høyland-Kroghsbo et al. 2016; Patterson et al. 2016). The coevolution mechanism between phage and bacteria can be studied by the use of competition experiments, experimental evolution, and mathematical modeling experiments, which can help design better plans during phage treatment (Cazares et al. 2020).

Bacteria can better adapt to the new environment by the acquisition of horizontal transfer genes mediate by phage (Canchaya et al. 2003; Takehiko et al. 2010). Under the pressure of antibiotics, the expression levels of virulence genes encoded by phage in bacteria were induced by the self-inducing signal molecule (AI-2) (Rossmann et al. 2015). The phage-containing supernatant released by *Enterococcus faecalis* V583ΔABC was used to infect probiotics (*E. faecalis*) by AI-2 stimulation, resulting in a significant increase in the pathogenicity of probiotics. It suggests that the application of phage in the intestine is not completely beneficial. Therefore, to use phage more safely, the mechanisms of the transfer of virulence and resistance genes need to be further studied.

QS systems mediate phage-phage information exchange

Previous studies have generally focused on the role of bacterial QS systems in bacteria-phage interactions. So, as a virus for phage, is there no mechanism for mutual communication? If so, do these inter-phage QS systems also play important roles in bacteria-phage interactions? We can confirm that there

is information exchange between viruses (including phage) (Díaz-Muñoz et al. 2017; Erez et al. 2017). Recent studies have shown that phage can encode a unique phage QS-like system to determine the timing of the lysis-lysogen switch (Doekes et al. 2021; Duddy and Bassler 2021). The proteolytic state of phage of the spBeta group can be determined by a small molecule communication system (Erez et al. 2017). When infects *Bacillus* spp., the phage produces a 6aa communication peptide released into the culture medium (Erez et al. 2017). The progeny phage determines whether it lyses the host based on the concentration of the 6aa communication peptide (Erez et al. 2017). This signal exchange between the two generations of phage prolongs the survival of phage. There are limited studies on the role of signal exchange between phages in bacteria-phage interaction.

Conclusions and future perspectives

Bacteria-phage interactions have been going on for billions of years, and many strategies have been developed (Peng and Chen 2020). Phage and bacteria jointly update their genetic information through horizontal gene transfer and gene mutation. QS systems are widely present in bacteria or phages and play a vital role in bacteria and phage interaction. Bacteria can inhibit the infection of phage through QS systems. On the contrary, phages can cross the defense line of their hosts by regulating the bacterial QS systems. Thus, the mechanisms of bacteria-bacteria, bacteria-phage, and phage-phage interactions mediated by QS systems need to be further elucidated, which is important for preventing diseases and pollution in the fermentation industry. In the laboratory, we generally study the interaction mechanisms of bacteria and phage. However, in the natural environment, bacteria-phage interactions are involved with complex intra- and inter-species information exchanges. However, further studies should be focused on this issue.

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Declarations

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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