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Cyanophages: Billions of Years of Coevolution with Cyanobacteria

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Abstract

Prevalent in marine and freshwater ecosystems, cyanophages compose a class of double-stranded DNA viruses that specifically infect cyanobacteria. During billions of years of coevolution, cyanophages and cyanobacteria have significantly contributed to the biogeochemical cycling and genetic diversity of aquatic ecosystems. As natural predators of cyanobacteria, cyanophages hold promise as eco-friendly agents against harmful cyanobacterial blooms. Recent technical advances in omics and cryo-electron microscopy have revealed the remarkable diversity of cyanophages in genome sequence and tail morphology. In this review, we summarize the genomic and metagenomic data, phylogenetic analyses, and diverse three-dimensional structures of cyanophages, in addition to their interplays with hosts. We also discuss the in vivo assembly processes of cyanophages, the exploration of uncultured cyanophages and host pairing, and the synthetic engineering and potential applications of cyanophages.

Contents

1. INTRODUCTION

1.1. The Discovery of Cyanophages: A Brief History

Cyanophages are a class of viruses that specifically infect, and in some cases lyse, the ancient photosynthetic microorganisms known as cyanobacteria. These viruses are widespread in various aquatic ecosystems, including both marine and freshwater environments (59). In certain marine regions, cyanophages can account for up to 21% of double-stranded DNA (dsDNA) viruses (11). The first cyanophage, LPP-1, was reported in 1963, and it infects freshwater cyanobacteria of the genera *Lyngbya*, *Plectonema*, and *Phormidium* (89). LPP-1 was originally named algal virus (89) or phycovirus (92), as it infects the cyanobacteria that was then called blue-green algae. Because of the morphological similarity to bacteriophages and the adoption of "cyanobacteria" as a generally accepted term for their hosts, these viruses were formally designated cyanophages (67).

During the past 60 years, an increasing number of cyanophages have been isolated and identified from various aquatic environments; these cyanophages include A1 and A4, which infect the model cyanobacterium *Anabaena* sp. PCC 7120 (54). The host spectrum exhibited by these cyanophages varies from narrow, as in Ma-LMM01, which only infects a single strain of a species, *Microcystis aeruginosa* NIES-298 (123); to slightly broad, as in Mic1, which recognizes two different *M. aeruginosa* strains in the same species, FACHB-1339 and FACHB-1318 (49); to broad, as in Syn9, which lyses multiple genera of marine *Prochlorococcus* and *Synechococcus* (115). An exceptional case is YongM, which can infect and lyse 18 different cyanobacterial strains across 11 genera (131). Meanwhile, two or more distinct cyanophages can infect the same host cyanobacterial strain, as

exemplified by P-SSP7 and P-SCSP, both of which infect *Prochlorococcus* MED4 (8, 105), and by Pam1–Pam5, all of which infect *Pseudanabaena mucicola* Chao 1806 (26). While hundreds of marine cyanophages have been reported, only 47 of their freshwater counterparts have been isolated to date (**Table 1**). However, with the increasing attention on the environmental issues associated with heavily polluted urban water bodies in developing countries, a growing number of freshwater cyanophages have been isolated in recent years.

1.2. Contributions of Cyanophages to Aquatic Ecosystems

Cyanobacteria sequester CO_2 and generate O_2 via photosynthesis, and some cyanobacteria can also fix N_2 (**Figure 1**); these functions indicate that cyanobacteria play a pivotal role in primary production, the formation of the O_2-rich atmosphere, and the shaping of biogeochemical cycles on Earth (52, 91, 111). For example, the dominant cyanobacteria *Prochlorococcus* and *Synechococcus* contribute approximately 25% of total marine primary production (33). Coexisting cyanophages typically regulate the population dynamics and community structure of cyanobacteria. Indeed, cyanophage infection accounts for up to approximately 30% of daily cyanobacterial mortality (11). Following cyanophage infection, substantial amounts of dissolved and particulate organic matter are released from lysed cyanobacteria and then shunted to and reutilized by phytoplankton (including cyanobacteria) and heterotrophic bacteria within the microbial community (**Figure 1**). Ultimately, these organic fluxes are transferred to zooplankton and higher trophic levels in the food web via predation (**Figure 1**). Conversely, large aggregates and cell debris from lysate, along with refractory organic matter rejected by heterotrophic bacteria, contribute to sediment buried in deep bodies of water (**Figure 1**). Therefore, cyanophages may trigger a cascade that ecologically enhances primary production and biogeochemical cycling in aquatic ecosystems (97, 107). Moreover, via indirect cross talk with an array of bacteria, archaea, and viruses, cyanophages can also regulate the diversity of aquatic microbial communities (53, 135).

Beyond lysing cyanobacteria, cyanophages also express auxiliary metabolic genes (AMGs) that reprogram host cell metabolism and alter the associated biogeochemical cycling of elements, such as carbon, nitrogen, and phosphorus (9, 37, 135). For instance, during cyanophage infection and subsequent amplification, AMG-induced alterations in cyanobacterial photosynthesis and central carbon metabolism severely inhibit cyanobacterial CO_2 fixation, potentially resulting in a loss of 0.02–5.39 Pg of carbon per year in the marine ecosystem (83).

Along with the elevation of CO_2 levels and global warming, eutrophication in water bodies may cause fast and excessive growth of cyanobacteria and the formation of dense and harmful blooms. Cyanobacterial blooms pose serious threats to human and animal activities because they exert light-shading effects, deplete oxygen and nutrients in water bodies, and produce cyanotoxins (45, 72). As natural predators of cyanobacteria, cyanophages contribute to the decline or even collapse of cyanobacterial blooms (97, 134); thus, cyanophages function as a key factor that determines the seasonal fluctuation of the dominant bloom-forming cyanobacterium *M. aeruginosa* (121). Therefore, cyanophages are promising eco-friendly agents against cyanobacterial blooms.

1.3. Canonical Cyanophage Classification Based on Tail Morphology

Most cyanophages isolated to date belong to the order *Caudovirales* and, as such, are characterized as tailed phages with a dsDNA genome (130). Similar to bacteriophages, the typical cyanophage also possesses an icosahedral capsid that encapsulates its genome and that is linked to a tail and attached fibers. Cyanophages are canonically classified according to their easily distinguishable tail

Table 1 Representative freshwater cyanophages[a]

Family	Cyanophage	Accession number	Genome size (kb)	GC (%)	Host
Myoviridae	Ma-LMM01	NC_008562	162.11	45.9	*Microcystis aeruginosa* NIES-298
	MaMV-DC	NC_029002	169.22	46.3	*Microcystis aeruginosa* FACHB-524
	Pam3	ON014755	54.54	61.8	*Pseudanabaena mucicola* Chao 1806
	PhiMa05	MW495066	27.39	54.2	*Microcystis* SG03/SH12/WIN01
	MaMV-DH01	OP394178	182.37	45.4	*Microcystis aeruginosa* FACHB-524
	S-CRM01	NC_015569	178.56	39.2	*Synechococcus* sp. LC16
	B3	MN695334	244.93	34.8	*Synechococcus* sp.
	B23	MN695335	243.63	34.8	*Synechococcus* sp.
	S-SRM01	MW015081	240.84	35.6	*Synechococcus* sp. SR-C6
	Yong-L2–223	OM868081	65.73	57.7	*Synechococcus* sp. PCC 7002
	MinM2	OQ594354	65.01	67.9	*Synechococcus* sp.
	A1	KU234533	68.30	38.3	*Nostoc* sp. PCC 7120
	YongM	MT426122	65.43	35	*Nostoc* sp. FACHB-596
	N-1	KU234532	64.96	35.4	*Nostoc* sp. PCC 7120
Siphoviridae	PA-SR01	MT234670	137.01	39.5	*Pseudanabaena* KCZY-C8
	Pam2	ON014754	142.86	39.2	*Pseudanabaena mucicola* Chao 1806
	Pam5	ON014757	39.51	61.9	*Pseudanabaena mucicola* Chao 1806
	Pan1	ON968452	72.04	62.5	*Pseudanabaena mucicola* Chao 1811
	Pan2	ON968453	51.03	58.6	*Pseudanabaena mucicola* Chao 1811
	Pan4	ON968455	37.17	63.7	*Pseudanabaena mucicola* Chao 1811
	Pan5	ON968456	46.55	43.7	*Pseudanabaena mucicola* Chao 1811
	Mic1	MN013189	92.63	35	*Microcystis aeruginosa* FACHB-1318/1339
	vB_MelS-Me-ZS1	MK069556	49.67	58.2	*Microcystis elabens* FACHB-916
	MinS1	MZ923504	49.97	70.7	*Microcystis aeruginosa* FACHB-905
	Mae-Yong1326-1	OP028995	48.82	70.7	*Microcystis aeruginosa* FACHB-1326
	Mwe-Yong1112-1	MZ436628	39.68	66.6	*Microcystis wesenbergii* FACHB-1112
	vB_MweS-Yong2	OM681334	44.53	71.6	*Microcystis wesenbergii* FACHB-1112
	S-LBS1	MG271909	34.64	60.2	*Synechococcus* sp. TCC793
	RM-2018a	MH636380	104.36	39	*Cylindrospermopsis raciborskii* Cr2010
	Cr-LKS3	OM373202	46.25	66.3	*Cylindrospermopsis raciborskii* KLL06
	vB_AphaS-CL131	MG209611	112.79	39.7	*Aphanizomenon flos-aquae* KM1, etc.
	S-2L	MW334946	45.09	68.4	*Synechococcus* sp. 698
Podoviridae	Pam1	ON014753	36.04	53.1	*Pseudanabaena mucicola* Chao 1806
	Pam4	ON014756	48.35	72.4	*Pseudanabaena mucicola* Chao 1806
	Pan3	ON968454	37.96	61	*Pseudanabaena mucicola* Chao 1811
	S-EIV1	KJ410740	79.18	46.2	*Synechococcus* sp. PCCC-A2c
	S-SRP01	MW015080	45.02	48.1	*Synechococcus* sp. SR-R4S1
	S-SRP02	MW822601	42.14	63.4	*Synechococcus* sp. SR-C1
	JingP1	ON677538	40.80	51.5	*Plectonema boryanum* FACHB-240
	Pf-WMP4	DQ875742	40.49	46.5	*Plectonema foveolarum*

(*Continued*)

Table 1 (*Continued*)

Family	Cyanophage	Accession number	Genome size (kb)	GC (%)	Host
	Pf-WMP3	NC_009551	43.25	51.8	*Plectonema foveolarum*
	PP	NC_022751	42.48	46.4	*Plectonema boryanum* IU 594/*Phormidium foveolarum* IU 427
	A4	NC_024358	41.75	43.4	*Anabaena* sp. PCC 7120
	TR020	MT457475	44.81	46	*Arthronema africanum* 1980/01
	Lbo240-Yong1	OM897575	39.74	52	*Leptolyngbya boryana* FACHB-240
Tailless	PaV-LD	NC_016564	95.30	41.5	*Planktothrix agardhii* HAB0637
Unassigned	Mea-Yong924-1	MZ447863	40.33	48.3	*Microcystis aeruginosa* FACHB-924

[a]The table includes data through June 2024.
Abbreviation: GC, guanine-cytosine content.

morphology as *Myoviridae*, *Podoviridae*, or *Siphoviridae* (97) and are referred to as cyanomyophages, cyanopodophages, or cyanosiphophages, respectively. Similar in morphology to *Escherichia coli* phage T4, cyanomyophages have a long, contractile tail and include examples such as A1 (124), AS-1 (16), P-SSM4 (101), and MaMV-DC (81), which infect *Anabaena*, *Synechococcus*, *Prochlorococcus*, and *Microcystis*, respectively. Like *E. coli* phage T7, cyanopodophages have a short tail, whereas

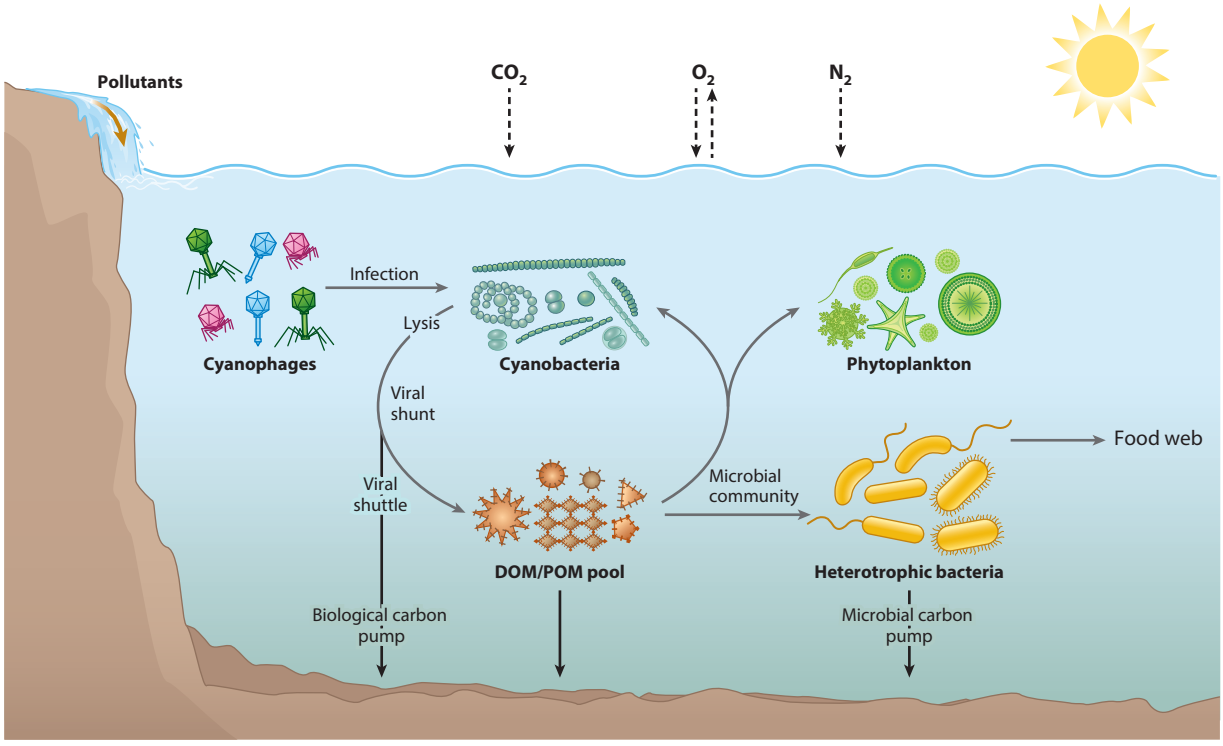

Figure 1

The ecological roles of cyanobacteria and cyanophages in aquatic ecosystems. In these ecosystems, cyanophages contribute to primary production and biogeochemical cycling, usually via the infection and lysis of cyanobacteria. Abbreviations: DOM, dissolved organic matter; POM, particulate organic matter.

cyanosiphophages, similar to *E. coli* phage λ, possess a long but noncontractile tail. For instance, the tail of *Prochlorococcus* cyanopodophage P-SCSP1u is as short as approximately 19 nm (10); in contrast, the *Pseudanabaena* cyanosiphophage Pan2 has a long and flexible tail of approximately 210 nm in length (133).

Beyond these canonical cyanophages, there are notable instances of unusual morphology in tail and capsid. For example, the *Planktothrix* cyanophage PaV-LD has been reported to be tailless (35). The cyanophages Pan1 (133), S-CBS2 (44), and P-SS2 (103) possess a prolate instead of an icosahedral capsid. Similar to filamentous bacteriophages, filamentous cyanophages of *Microcystis*, *Anabaena*, and *Planktothrix* have also been observed (21). These findings indicate that cyanophages should also have highly diverse morphology, comparable to that of bacteriophages.

2. GENOMIC, METAGENOMIC, AND PHYLOGENETIC ANALYSES OF CYANOPHAGES

2.1. Genome Sequences

The first complete genome sequence of a cyanophage was reported in 2002, from the marine cyanophage P60 of *Synechococcus* WH7803 (14). To date, 191 cyanophage genomes have been sequenced (**Figure 2**), the majority of which were isolated from the marine cyanobacteria *Prochlorococcus* and *Synechococcus*, in addition to the 47 genome sequences of freshwater cyanophages. The genome sizes range from 30 to 273 kb, with 35.4–66.3% guanine-cytosine content (97). Cyanophages with a genome greater than 200 kb are classified as jumbo and include PhiMa05 and S-SSM7 (78, 102). Despite the use of deep genome annotation via multiple tools, such as BLASTp (2), HHpred (41), and AlphaFold2 (51), less than 40% of the putative open reading frames can be functionally annotated. The annotated open reading frames are mainly divided into five groups: structural proteins, nucleotide metabolism, DNA replication and packaging, AMGs, and other functions (26, 119, 133).

Systematic analyses revealed that cyanophages possess a series of unique genomic features for survival. In the cyanophage S-2L genome, all adenines are completely replaced by 2-aminoadenines; this substitution confers improved thermal stability and resistance to most restriction enzymes (4, 68, 73, 95). In the S-TIM5 genome, all cytosines following purines are methylated (88); this sequence-dependent methylation mechanism protects the genome from nuclease degradation. In several *Synechococcus* cyanophages, more than 20 tRNA genes may supplement host tRNAs, and this supplementation facilitates efficient protein translation or enables cross-infectivity toward hosts with varied guanine-cytosine content (25, 71, 117, 132). The S-CREM1 genome encodes several regulatory RNAs that may regulate host metabolism (132). In addition, the cyanophage Pan1 encodes a salvage synthase QueD, which, together with other enzymes from the host, is indispensable for the constitution of a complete queuosine modification pathway (133).

Cyanophage AMGs are typically acquired from their cyanobacterial hosts during infection, and most are involved in photosynthesis, carbon metabolism, nutrient acquisition, and nucleotide biosynthesis (61, 97, 134). For example, many marine cyanophages possess *psbA* and *psbD* to maintain the photosynthetic activity of the infected host and provide energy for phage progeny amplification (62, 63, 74). Some freshwater cyanophages instead encode the nonbleaching protein A, which degrades the host's major light-harvesting complex, phycobilisome, and thereby supplies sufficient substrates for cyanophage protein synthesis (35, 122). The cyanophage ribonucleotide reductase could efficiently provide additional substrates for genome replication (39). CP12, a small inhibitor that is widespread among many cyanophages, can shut down the Calvin cycle; redirect the carbon flow toward the pentose phosphate pathway; and, eventually, facilitate

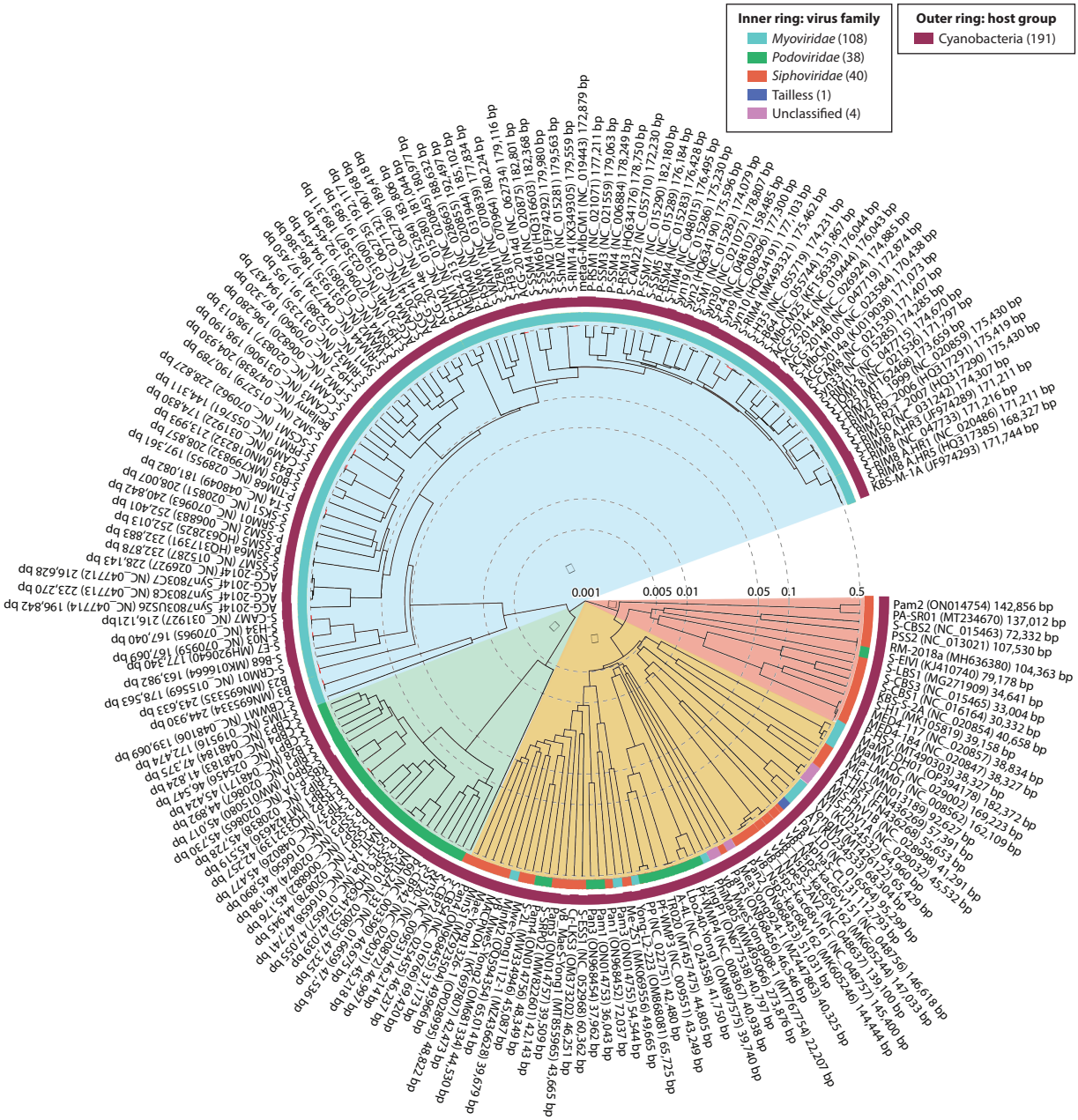

Figure 2

Proteomic tree of the 191 currently available cyanophage genomes, constructed via ViPTree. This analysis incorporates 132 complete genome sequences downloaded from the Virus-Host DB (**https://www.genome.jp/virushostdb**) and 59 additional sequences obtained from the GenBank database (**https://www.ncbi.nlm.nih.gov/genbank/**). The inner ring of the tree represents various virus families, classified according to the tail morphology of cyanophages. Beyond the canonical *Myoviridae*, *Podoviridae*, and *Siphoviridae*, the tailless and unclassified cyanophages are also designated as separate families. The outer ring shows the host group. Cyanophages in the four fan-shaped regions are shaded in different colors: marine *Siphoviridae* (cluster I, red), marine *Myoviridae* (cluster II, blue), marine *Podoviridae* (cluster III, green), and freshwater cyanophages (cluster IV, yellow).

deoxynucleoside triphosphate biosynthesis for phage genome replication (110). Under phosphate starvation conditions, PstS and PhoH, encoded by the cyanophage genome, help the host enhance phosphate uptake (17, 60). Unlike marine cyanophages, whose genomes have a variety of AMGs, freshwater cyanophages generally contain substantially fewer AMGs (76). Freshwater cyanophages and cyanobacteria likely share nutrient metabolisms and substrate pools, whereas marine cyanophages usually take over and redirect host metabolisms toward phage amplification (76).

2.2. Metagenomics

Because of the difficulty in isolating single colonies of a cyanobacterial host and its cyanophage via traditional culture-based methods, the number of bona fide culturable cyanophages remains extremely limited. In contrast to time-consuming and laborious methods, the metagenomic approach enables the analysis of genetic material from environmental samples in a one-pot manner (3); as a result, the distribution and abundance of many more cyanophages, especially uncultured cyanophages across diverse environments, can be quantified.

Through fragment recruitment analyses, we found that five cyanophages, Pam1–Pam5, exhibit varying abundances across different seasons in Lake Chaohu (26). A large-scale analysis revealed the abundance of cyanophage S-TIM5 in the Red Sea and the wide distribution of the cyanophage's homologous genes in oceans (88). The comparative recruitment of metagenomic reads onto the PA-SR01 genome indicated that this abundant freshwater cyanophage is globally prevalent in marine ecosystems as well (128). The high abundance and wide distribution of cyanophages highlight their ecological significance in diverse aquatic environments, particularly in oligotrophic oxygen-deficient zones (34). Furthermore, metagenomics has emerged as an effective tool for discovering novel enzymes, antimicrobials, therapeutic compounds, and various biochemically active compounds in microbes and phages (20, 85, 86), such as the AMG-encoded viral fatty acid desaturase, which modulates the membrane fluidity of the infected host (86). In-depth recruitment analyses of metagenomic data enabled us to mine 98 putative phage contigs of varied lengths (26). Based on the reference genomes, we successfully assigned three complete genomes and seven large fragments to the uncultured cyanophages (26). This metagenomic data–mining method will significantly expand the scope of uncultured cyanophages.

2.3. Phylogenetic Analysis Based on Large Terminase and Beyond

Because of constant gene exchanges and rapid coevolution with their hosts, cyanophages exhibit remarkable genomic diversity and complex phylogenetic relationships (97). While 16S rRNA genes are used in microbial phylogenetic analyses, no universal marker gene has been identified for cyanophages. To date, relatively conserved genes that encode the terminase large subunit (TerL) and structural proteins have been employed for phylogenetic analyses of cyanophages (6, 35, 58, 100). As a key component of the DNA-packaging motor, TerL is responsible for pumping the genome into the capsid (84). Based on the phylogenetic analysis of TerL sequences, tailed dsDNA phages are classified into seven distinct groups corresponding to various DNA-packaging mechanisms (12, 44). For instance, Pam2 belongs to the T7-like terminal repeats group, whereas Pam3, Pam4, and Pam5 are categorized into the λ-like 5′-extended COS (cohesive end site) end, gene transfer agent–like headful, and P22-like headful groups, respectively (26). A phylogenetic analysis of major capsid proteins demonstrated the evolutionary divergence of PA-SR01 from other cyanophages and bacteriophages (128), whereas tail sheath phylogeny revealed that S-SRM01 is evolutionarily close to marine cyanomyophages (127). Additionally, portal-based phylogeny indicated that marine T4-like cyanophages are highly diverse and can be further divided into five

clades (58). Based on core genes of the pan-genome, especially DNA polymerase sequences, the marine cyanopodophages isolated thus far could be clustered into four subgroups (113). Notably, the DNA polymerase γ encoded by the cyanophage shares a common evolutionary origin with the mitochondrion (13, 88, 117, 119). Certain specific AMGs found exclusively in cyanophages may also serve as markers for phylogenetic analysis (1).

Beyond single-marker genes and concatenated core genes, phylogenetic analysis can be performed on whole phage proteomes. Using a proteomic tree constructed by ViPTree (79), we can explore the global genomic heterogeneity and evolutionary relationships among hundreds of cyanophages and even thousands of bacteriophages. The proteomic tree of the currently available 191 cyanophage genomes indicates that marine cyanophages can be classified into marine *Siphoviridae*, *Myoviridae*, and *Podoviridae* clusters (clusters I–III), whereas freshwater cyanophages are grouped into a separate cluster (cluster IV) of various tail morphologies (**Figure 2**). Notably, despite infecting the same host, Pam1–Pam5, as well as Pan1–Pan5, are evolutionarily distinct from each other (**Figure 2**). In contrast, Pan1 and Pan3 share a relatively close evolutionary distance with Pam3 and Pam1, respectively (**Figure 2**). A large-scale proteomic tree based on the genomes of 4,923 dsDNA phages revealed that Pan1 resembles an α-proteobacterial phage (133). Furthermore, phage phylogeny can be visualized in a network representation, with nodes representing phage genomes and edges depicting similarities at the gene, protein, or genome level (22). This network-based phylogeny not only illustrates the complexity of evolutionary relationships but also provides insights into horizontal gene transfer events.

3. DIVERSE STRUCTURES OF CYANOPHAGES

A mature cyanophage primarily consists of two parts: a regular, rigid capsid that encapsulates the genome and a variable tail machine composed of the neck, tail, and attached fibers/spikes. The indispensable structural components are highly conserved among different cyanophages; in contrast, the other structural components are relatively variable. Recent technological breakthroughs in single-particle cryo-electron microscopy (cryo-EM) have facilitated the systematic determination of the intact structures of cyanophages at high resolution. The structure of P-SCSP1u was reported previously (10), and we solved the intact structures of two cyanopodophages and two cyanomyophages (**Figure 3**). These structures elucidate cyanophage self-assembly patterns, provide the structural basis for host recognition, and enhance genome reannotation.

3.1. A Unified Capsid

Despite variations in tail morphology, all known cyanophages encapsulate the genome in either an icosahedral or a prolate capsid, which is a self-assembly of multiple copies of the major capsid protein (MCP), with or without cement proteins. Capsid size is determined by the number of MCP subunits in an asymmetric unit, referred to as the triangulation number (T) (99). For instance, cyanophages P-SSP7, Syn5, Pam1, Pam3, P-SCSP1u, and A4 all exhibit a T of 7, corresponding to six subunits of one hexon and one penton subunit (10, 38, 42, 65, 118, 129). In total, 415 copies of MCPs assemble into two forms of capsomers: 60 hexons at the surface of the isometric capsid shell and 11 pentons at the vertex (10, 38, 65, 118, 129). When $T = 7$, the capsid is approximately 600∼680 Å in diameter, consistent with a relatively small genome size (36.0–54.5 kb). A1 has a genome of 64.6 kb and a capsid of 740 Å in diameter ($T = 9$), while Mic1 possesses a genome of 92.6 kb and a capsid of 880 Å in diameter ($T = 13$) (18, 49). An alternative way to increase capsid packaging capacity involves the conversion of the isometric capsid into an elongated prolate form (94).

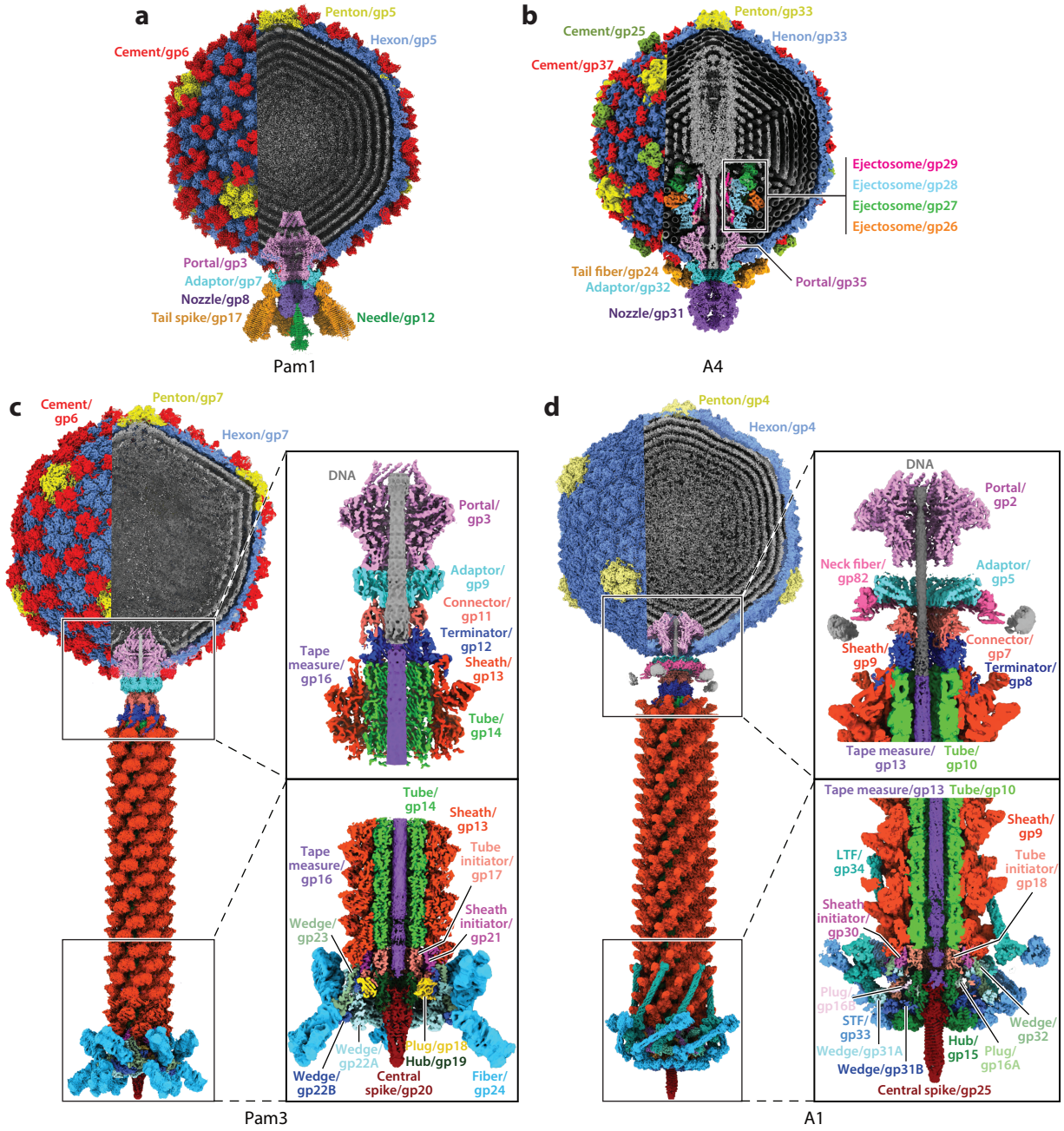

Figure 3

The diverse structures of the cyanopodophages (*a*) Pam1 and (*b*) A4 and the cyanomyophages (*c*) Pam3 and (*d*) A1. For each cyanomyophage, zoomed-in views of the neck and baseplate are also shown in the respective panels. The protein components of the cyanophages are labeled and colored differently in the cryo-electron microscopy map. Abbreviations: LTF, long tail fiber; STF, short tail fiber.

All reported cyanophage MCPs adopt a canonical HK97 fold, which is commonly found in tailed dsDNA bacteriophages and herpesviruses (27). Each MCP subunit consists of four distinct domains: an N-terminal arm, an extended loop, a peripheral domain, and an axial domain. Multiple copies of MCPs assemble into hexons and pentons, mainly via the crossed axial domains at the center, as well as through the head-to-tail interactions between peripheral domains and adjacent extended loops at the periphery (49, 129). These hexons and pentons are further interlocked by gradually increasing curvatures and form the capsid (18).

The genome packaging of cyanophages typically coincides with the maturation of the capsid, as visualized in Syn5-infected *Synechococcus* cells (19). After maturation, the capsid acquires sufficient stability to withstand the internal pressure exerted by the densely packaged DNA. The capsids of cyanophages P-SSP7, P-SCSP1u, and A1 are stabilized solely by diverse inter- and intra-capsomer interactions (10, 18, 65). In contrast, extra cement proteins are recruited to reinforce the capsid stability of cyanophages Mic1, Pam3 (**Figure 3**), and A4 (**Figure 3**). Two cement subunits intertwine to form a dimer, adhering to the twofold axes of the Mic1 capsid (49), whereas the trimeric cement proteins of Pam3 attach to the threefold axes of the capsid (118). Moreover, the A4 capsid is stabilized by two types of cement proteins: gp37 dimers and gp25 trimers at the twofold axes and threefold axes, respectively (**Figure 3**). Conversely, Syn5 features knob-like cement proteins diagonally aligned on the hexons, along with an unusual horn structure at the vertex opposite the tail machine (38).

3.2. The Interlocked Neck

Similar to bacteriophages and herpesviruses (40, 66), cyanophages have 1 of 12 vertices of the capsid connected to the neck that initiates the assembly of a short tail in cyanopodophages or serves as a docking platform for independently assembled tails in cyanomyophages. Typically, for all cyanophages, the neck is composed of a dodecameric portal-adaptor complex surrounded by five hexons, and cyanomyophages have an additional hexameric connector (**Figure 3**).

The portal subunit consists of five domains—the barrel, crown, wing, stem, and clip —arranged from the interior to the exterior. Notably, the barrel domain varies in length or may be absent in some bacteriophages (40). Twelve subunits form a cylindrical portal dodecamer, which has a central channel filled with a rope-like segment of genomic DNA that runs perpendicular to a ring of DNA segment in the circular cleft between the wing domains of the portal and the inner surface of the capsid. Using the 12 clip domains that protrude outside the capsid, the portal first recruits terminase for DNA packaging (106) and then links to the adaptor dodecamer once terminase is released (109). Each adaptor subunit contains a conserved α-helical bundle domain, a C-terminal-embracing tail interacting with the portal, and a lateral domain that connects other structural components. For instance, the Pam1 adaptor possesses a capsid-docking domain that directly interacts with the capsid (129), whereas the adaptors of P-SCSP1u and A4 have a fiber-docking domain for the attachment of tail fibers (10, 42). Besides connecting to the portal, the adaptor also interacts with the connector in the cyanomyophage Pam3 via the β-barrel of the dodecameric adaptor surrounded by six α1 helices of the connector (118). The pairwise interfaces among the portal, adaptor, and connector are complementary in shape and electrostatic potential, and this complementarity facilitates the sequential joining and precise assembly of the interlocked neck.

The cyanomyophage A1 is an exception: Its adaptor exhibits a different fold and a unique 15-fold symmetry (124). Because the α1 helices of the A1 connector are longer than those of Pam3, these helices can hook the loop ring formed by the A1 adaptor and thereby ensure the compatibility of the 15:6 symmetry in the neck. Furthermore, the pentadecameric adaptor is connected to five bead-chain-like neck fibers, which may self-assemble independently (124).

3.3. The Simple Tails of Cyanopodophages

The short and relatively simple tails of cyanopodophages can be classified into two types: the T7-like P-SCSP1u, which consists of only a nozzle protein (10), and the P22-like Pam1, which consists of a nozzle protein and a needle protein (**Figure 3**). The nozzle of P-SCSP1u folds into four distinct domains: a central β-propeller domain and a platform domain (both of which are conserved among podophages), as well as a fiber-docking domain and a tip domain; the latter two domains are absent in the nozzle of Pam1. Six nozzle subunits form a hexameric ring that attaches to the helical bundle of the adaptor dodecamer via the platform domains. Notably, the platform domain of the Pam1 nozzle also functions as a binding site for the suspension of the tail spike.

Compared with that of T7, the P-SCSP1u nozzle hexamer features a central gate composed of 12 negatively charged aspartate residues, which contribute to the sealing of the genome within the capsid via electrostatic repulsive forces (10). In contrast, the Pam1 hexameric nozzle possesses a cavity with an opening of approximately 28 Å in diameter, sufficient for the passage of dsDNA; however, this cavity is sealed by a trimeric needle at the distal end (129). These high-resolution structures offer valuable insights into tail assembly and genome sealing in the relatively simple cyanopodophages.

3.4. The Complicated Tails of Cyanomyophages

Cyanomyophages Pam3 and A1 both have a long and contractile tail, which, from the distal to proximal ends, consists of the multicomponent baseplate, tube initiator, sheath initiator, helically stacked tube and sheath surrounding the tape measure protein (TMP), and terminator (**Figure 3**). The independently assembled tail is docked to the neck via direct interactions between the terminator and the connector. The length of the cyanomyophage tail is determined by the TMP, which also serves as a scaffold for tail assembly. The majority of TMPs in A1 and Pam3 exhibit a sixfold helical bundle structure, with three C-terminal α-helices directly interacting with the baseplate (118, 124).

Along the TMP, the tube and sheath subunits surround into the inner and outer layers, both of which adopt a six-start helical structure (118, 124). The tube subunits of Pam3 and A1 both adopt a conserved structure in which a β-hairpin protrudes toward the next hexamer to mediate interhexamer interactions and thus extend the tube. Similarly, the C-terminal domain of one sheath subunit stabilizes the protruding termini of two subunits in the succeeding hexamer and enables the extension of the sheath.

The growth of the tube and sheath is initiated on the baseplate by the tube initiator and sheath initiator, respectively, but stopped by a shared terminator (**Figure 3**). In Pam3 and A1, the β-barrel domains of six tube initiator subunits form a ringlike structure that is compatible with the first hexamer of the tube; this mimicry initiates tube growth. Additionally, the C-terminal domain of the tube initiator stretches downward to anchor the tube on the baseplate. The sheath initiator adopts a fold like that of the C-terminal domain of the sheath and facilitates the initiation and extension of the sheath through a similar interhexamer interaction pattern. At the end of growth, one terminator subunit simultaneously interacts with two tube subunits and one sheath subunit; disrupts the interhexamer interfaces of the tube and sheath, respectively; and ultimately terminates the extension of the tail (118, 124).

Pam3 and A1 both possess a baseplate composed of five components: a trimeric central spike-hub complex (components 1 and 2) surrounded by six wedge heterotriplexes (component 3 and 4) and a hexameric plug (component 5) (**Figure 3**). The central spike of Pam3 has a much shorter β-helix and a unique α-helical bundle compared with those of the A1 central spike, whereas the hub of A1 possesses three extra enzymatic domains in addition to a conserved barrel domain.

Unlike that of Pam3, the wedge of A1 contains an insertion domain that inserts into a cleft on the hub or stretches outside to hold the tail fiber (118, 124). The hexameric plug of A1 adopts two configurations that alternatingly anchor to the hub and stick the trimeric hub and hexameric wedge. Together, these five components form a highly compact baseplate in a mortise-and-tenon manner at the distal end of the tail but show significant variations in structures, interfaces, and assembly patterns across cyanomyophages.

3.5. Tail Spikes and Fibers

The tails of cyanophages are typically adorned with multiple copies of tail spikes or fibers, which often function as receptor-binding proteins (RBPs) that recognize host receptors on the cell surface (10, 118, 124, 129). In cyanopodophages, the tail spikes or fibers are usually connected to the junction between the adaptor and the nozzle (**Figure 3**). Pam1 possesses six trimeric spikes, the head-binding domains of which are responsible for interactions with the adaptor and the nozzle (129). The receptor-binding domain of its tail spike consists of a right-handed parallel β-helix and a β-sandwich at the distal tip. In contrast, P-SCSP1u employs six trimeric tail fibers that bind to the fiber-docking domains of the adaptor and nozzle (10). Notably, each subunit of the fiber/spike trimer adopts different binding interfaces to the tail (10, 129); this flexible interaction facilitates the recognition of host receptors.

In cyanomyophages, the tail fibers mainly anchor to the baseplate (**Figure 3**). Pam3 carries 12 tail fibers, which are arranged alternatingly in upward and downward configurations around the baseplate wedge (118). Each subunit of the trimeric tail fiber consists of an α-helical domain at the N terminus that facilitates the attachment of the fiber to the wedge. Two cysteine-rich regions in each heterotriplex of the baseplate wedge provide two triangular platforms that each dock an upward fiber and a downward fiber of Pam3 via disulfide bonds. In contrast, A1 possesses two types of tail fibers—six long tail fibers (LTFs) and six short tail fibers (STFs)—which are folded back pairwise with their distal ends oriented toward the capsid (124). Each LTF subunit consists of a shoulder and an arm domain, with the shoulder anchoring to the wedge of the baseplate and the arm lying along the groove on the sheath. Each STF subunit contains four distinct domains: the β-ring, joint, stem, and cell wall–binding domains. Eighteen β-ring domains from six STF trimers form a ring encircling the distal plane of six baseplate wedges, whereas the joint domains adhere to the periphery of six wedges. Notably, the long helical bundle formed by the stem domains of trimeric STFs runs along the groove of the trimeric shoulder domains of the LTFs and composes an LTF-STF pair (**Figure 3**). The fine structural information of different tail spikes and fibers enables us to characterize more host recognition modules that determine host specificity.

3.6. A Proposed Process of Cyanophage Maturation

Based on the present structures, we propose that the assembly of the cyanophage capsid is initiated from the portal and is mainly driven by scaffolding proteins and terminases. Once the scaffolding proteins are expelled and the complete genome is encapsulated within the capsid, the adaptor is recruited to the portal, and then various tails dock. In the case of cyanopodophages, the short tail features a nozzle (and, in some instances, a needle) that usually is surrounded by six tail spikes/fibers. Conversely, in cyanomyophages, the contractile tail and attached fibers are assembled independently and docked to the adaptor-connector complex. We suggest that cyanosiphophages likely adopt a maturation process similar to that of cyanomyophages. Notably, the rapid and precise folding of so many structural proteins, along with the final assembly of a mature cyanophage, is often facilitated by a series of chaperone proteins. Genetic manipulation

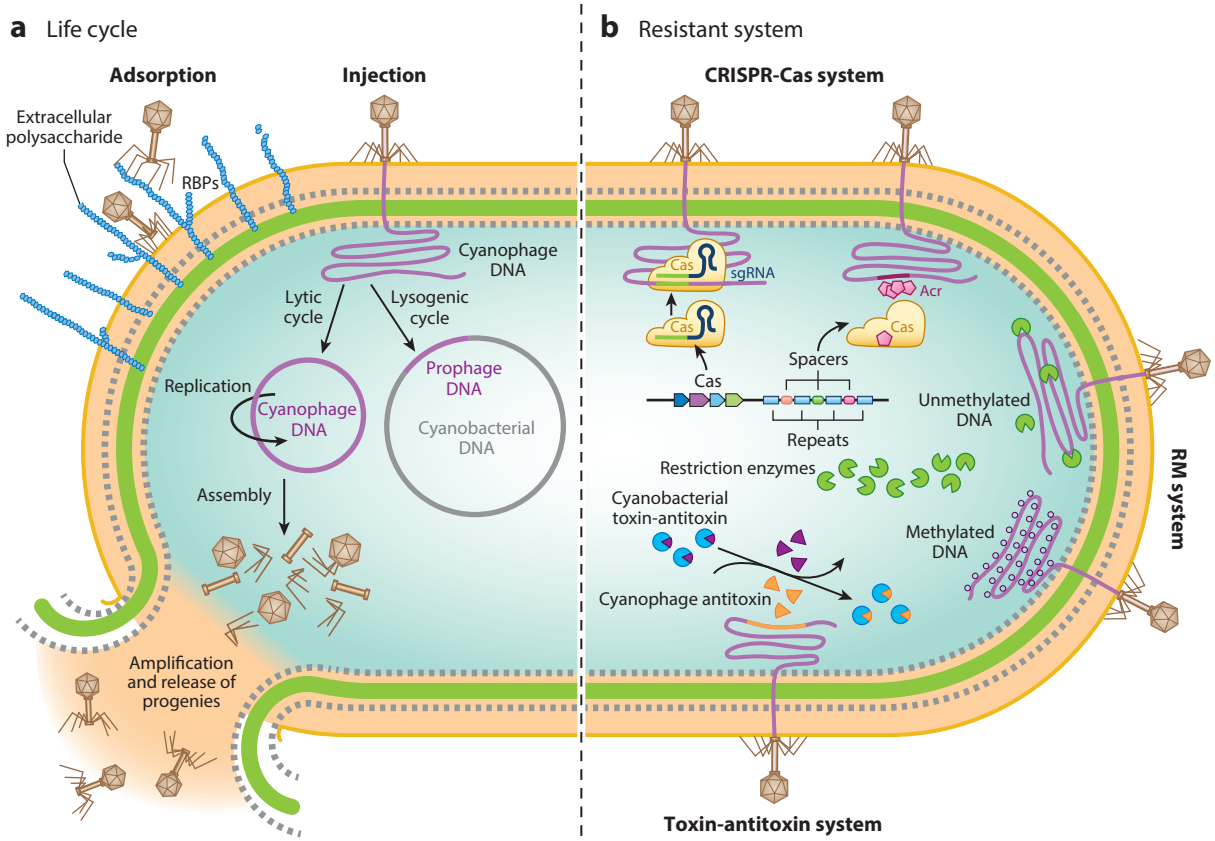

Figure 4

(*a*) The life cycle of a cyanophage upon infection and (*b*) the coevolved infection and anti-infection strategies between cyanophages and cyanobacteria. First, the cyanophage recognizes the extracellular polysaccharides on the surface of the cyanobacterium via receptor-binding proteins (RBPs). Following genome injection into the host cell, the cyanophage can enter the lytic cycle (amplification and release of progenies) or the lysogenic cycle (integration into the host genome as a prophage). The resistant system includes the cyanobacterial CRISPR-Cas, restriction-modification (RM), and toxin-antitoxin systems that respond to cyanophage infection, as well as the anti-CRISPR (Acr) proteins, methyltransferases, and antitoxins produced by cyanophages.

combined with cryo-electron tomography (cryo-ET) might help elucidate the in vivo assembly and maturation processes of cyanophages.

4. INTERACTION WITH THE HOST

4.1. Specific Modules Recognizing the Host

Cyanophage infection of a host begins with the recognition of and binding to receptors on the host cell surface via specific host recognition modules (**Figure 4**). These modules, usually located at the distal end of RBPs, are key determinants of the host spectrum (80). The remarkable genetic and structural diversity of both cyanophage RBPs and cyanobacterial receptors complicates the elucidation of their interaction mechanism. The host recognition modules of various cyanophages usually adopt different structures, which enable them to recognize diverse hosts (124). A series of host receptors in bacteriophages have been identified, including lipopolysaccharide (LPS), flagella, pili, teichoic acids, capsules, and several outer membrane proteins (80). In contrast, the O-antigen

of LPS is the only experimentally proven host receptor for cyanophages to date (116). Nevertheless, based on the structures of cyanophages, several specific host recognition modules have been identified. Additionally, studies using cryo-ET have revealed that RBPs should undergo significant conformational changes for successful adsorption to the host (77).

Because the specific host recognition module of Pam1 is the C-terminal receptor-binding domain of the tail spike, which resembles an α-1,3-glucanase that hydrolyzes bacterial polysaccharides (46, 129), Pam1 probably also possesses glycosyl hydrolase activity toward host extracellular polysaccharides (129). Notably, the cement protein of Pam1 is well-aligned with the distal β-sandwich motif of the tail spike; this alignment indicates that the cement protein might also contribute to host recognition (129). Aided by AlphaFold2 predictions, we found that the host recognition modules of Pam2, Pam3, and Pam5 exhibit structural similarity to the β-sandwich motif of the Pam1 tail spike, and this structural similarity likely enables them to recognize similar extracellular polysaccharides and thus infect the same host as does Pam1 (26).

Structural analyses combined with in vitro binding assays indicated that the arm domain of the LTF and the stem domain and the cell wall–binding domain of the STF are indeed specific host recognition modules of A1, albeit they bind to different host receptors (124). This observation is consistent with the finding that only the LTF specifically binds to the O-antigen of LPS in *Anabaena* sp. PCC 7120 (116). In addition, the distal motif of the A1 neck fiber is also considered to be a carbohydrate-binding module, whereas the baseplate hub of A1 possesses dual hydrolytic activities, indicating that both the neck fiber and the hub are involved in the infection process (124).

4.2. Lytic and Lysogenic Cycles

After injecting its genome into the host, the cyanophage follows two possible fates: the lytic or lysogenic cycle (**Figure 4**). In the lytic cycle, the cyanophage rapidly replicates its genome, synthesizes the necessary proteins, and lyses the host cell; these reactions ultimately result in the production of a substantial number of progenies (**Figure 4**). Virulent cyanophages that follow a lytic cycle can be readily identified and amplified in the laboratory. However, during the lysogenic cycle, the cyanophage integrates its genome into the host genome and remains latent as a prophage (**Figure 4**), replicating alongside the host for generations (43). Lysogenic prophages can be excised from the host genome and can enter the lytic cycle; this switch occurs spontaneously or is triggered by certain environmental stimuli, such as temperature shifts, ultraviolet radiation, heavy metal exposure, or altered nutrient conditions (43, 56). In addition, the life cycle of a cyanophage is also governed by diurnal rhythm control, along with the host's photosynthetic rhythm (64).

Currently, the presence of lysogeny-associated genes in a cyanophage genome is proposed to indicate that a lytic cyanophage could also enter a lysogenic cycle. In the Mic1 genome, the discovery of the ParABS plasmid partitioning system and a prophage antirepressor suggested that the cyanophage might also possess a lysogenic cycle under unknown conditions; this suggestion was further supported by the observation of bull's-eye plaques on the infection plate (119). Genome analysis showed that Pam1 and Pam5 also possess genes encoding the lysogenic-lytic cycle regulators and corresponding site-specific recombinases (26). Additionally, the presence of three prophage antirepressors, coupled with the absence of lysogeny-associated genes, suggested that the currently lytic cyanophage vB_AphaS-CL131 was originally a lysogenic cyanophage (100).

4.3. Infection and Anti-Infection Strategies

Upon infection, lytic cyanophages utilize the host's metabolic pathways to amplify progenies; simultaneously, cyanobacteria employ a variety of anti-infection strategies that they have evolved.

For example, marine *Prochlorococcus* and *Synechococcus* modify their cyanophage receptors by mutations (98), whereas freshwater cyanobacteria usually activate various antiviral defense systems, such as CRISPR-Cas, restriction-modification (RM), and toxin-antitoxin systems (**Figure 4**). *M. aeruginosa* possesses many putative antiviral defense genes that are expressed during cyanophage infection (69, 112). Hosts degrade cyanophage genomes via CRISPR-Cas and RM systems (126); in response, cyanophages acquire anti-CRISPR and methyltransferase genes to evade these defenses (50, 55, 70). The presence of CRISPR spacers and putative anti-CRISPR genes in the Pam2 genome indicates that Pam2 and its host adopt anti-CRISPR and CRISPR mechanisms, respectively (26). The expression of two Mic1 methyltransferases in the host suggests that the nascent Mic1 genome is methylated, thereby enabling Mic1 to resist the host's RM system (114). In addition, cyanophage infection can induce the dissociation of toxin from the toxin-antitoxin complex, lead to the death of the host cell, and interrupt the production of more progenies (57). In some cases, an extra antitoxin encoded by the cyanophage can rescue the lytic cycle (100, 132).

From a global perspective, transcriptomics significantly enhances our understanding of viral infection strategies and host anti-infection responses. During the lytic cycle, cyanophage genes exhibit a temporal expression pattern with three phases (75, 114): early (host takeover), middle (DNA replication and nucleotide metabolism), and late (phage assembly and host lysis). Comparisons of global transcriptomic profiles indicated that cyanophages might adopt either a constant or a suddenly increased mode of gene expression (114). Upon infection, the host triggers various transcriptional responses, including significant upregulation of the CRISPR-Cas and toxin-antitoxin systems (32, 75, 114). In contrast, genes involved in photosynthesis and other key metabolic pathways are downregulated (24, 114). Notably, a transcriptomic study revealed that the cyanophage Syn9 displays a nearly identical infection pattern across three host strains; this finding suggests that the broad host spectrum is attributable to a shared host defense system (24).

4.4. Mutual Adaptation Between Cyanobacteria and Cyanophages

The long-term coexistence of cyanophages and cyanobacteria fosters their mutual adaptation and rapid coevolution, which are driven by repetitive cycles of infection and anti-infection. Cyanobacteria provide a platform for cyanophage amplification, whereas cyanophages act as gene shuttles for the host to gain new traits via lysogenic conversion and/or horizontal gene transfer (93, 108). The CRISPR array in the cyanophage N-1 genome is similar to the CRISPR DR5 family commonly found in cyanobacteria; this observation suggests that the cyanophage can transfer genes among host strains (15). In turn, the AMGs acquired by the cyanophage from previous hosts can assist subsequent hosts in adapting to various stresses (17, 48, 87). Moreover, the photosynthesis genes *psbA* and *psbD* are frequently shuttled among cyanophages and their hosts (104).

The cyanophage P-SSP7 expresses four host-derived AMGs to produce energy and substrates for its amplification in resource-poor oceans (61). We identified a less-infective Mic1 variant of the *Microcystis* host; in the cyanophage's genome, an early gene encoding a TnpB-like endonuclease was interrupted by the insertion of a host gene (119). Additionally, cyanophage resistance can evolve in the host because of repetitive cycles of infection and anti-infection (114). Altogether, the cross talk between cyanobacteria and cyanophages represents a fascinating model for the investigation of mutual adaptation through coevolution.

5. CONCLUSION AND PERSPECTIVE

In the post-COVID-19 pandemic era, basic research on viruses has garnered increasing attention. A series of high-resolution structures of diverse intact cyanophages offer profound insights into their assembly patterns. Concurrently, omics technologies allow for the mining of more virtual

cyanophages with various genome types and morphologies across diverse environments. The domestication and amplification of these cyanophages in the laboratory will facilitate the engineering of chassis cyanophages for synthetic biology and promote their future applications in a wide range of scenarios.

During the past century of molecular biology, bacteriophages have emerged as a rich platform for the discovery of various genetic and biotechnological tools (90). Given their similarities to bacteriophages, both from genomic and structural perspectives, we hypothesize that much more diverse cyanophages should also exist. To date, however, only tailed dsDNA cyanophages have been reported, and the existence of cyanophages with ssDNA, dsRNA, or ssRNA genomes, similar to bacteriophages M13, Φ6, and MS2, respectively, remains a mystery (22). Furthermore, cyanophages with nontailed morphology, such as polyhedral, filamentous, and pleomorphic capsids, have yet to be identified—if they exist (22). The challenges associated with the sampling and isolation of culturable cyanobacterial hosts, particularly those living in extreme habitats, largely impede the identification of cyanophages with unusual genome types and morphologies. Fortunately, powerful omics technologies, combined with artificial intelligence (AI), will enable us to mine many more metagenome-assembled genomes (MAGs) of unknown cyanophages, even if most of these cyanophages remain virtual and unculturable in the laboratory.

Although many MAGs have been uncovered at an unprecedented rate from metagenomic and metatranscriptomic data (82), a universal molecular marker that distinguishes cyanophage MAGs from their bacteriophage counterparts is lacking. The current approach involves searching for homologous genes or DNA segments between MAGs and complete cyanobacterial genomes. Although most AMGs and tRNAs of cyanophages are derived from their hosts via gene transfer (5, 36), none are specific and universal. While CRISPR spacers provide in silico evidence to pair hosts with their phages (23), these spacers are present in only a small fraction of host genomes (7, 96). Sequence composition features, such as co-occurrence profiling, *k*-mer frequency, and codon usage profile, have also been utilized to pair phages and hosts (29, 30). In addition, a couple of deep learning algorithms have been employed to extract embedded features from genome sequences independently of biological knowledge (31, 47) and may offer an ideal approach for predicting the pairing of cyanophages with their hosts.

The continuous accumulation of structural information and vast metagenomic data on cyanophages enables us to assign the indispensable structural modules of a cyanophage. Beyond these structural components, a cyanophage usually possesses extra functional modules for better adaptation, such as those that confer resistance to host defense systems, accelerate DNA replication and nucleotide metabolism, or facilitate host lysis. However, the identification of these functional modules remains a big challenge, mostly because of the lack of a well-established genetic manipulation platform. The recent application of the CRISPR-Cas12a system to systematically knock out nonessential genes in cyanophages A4 and A1 (125) indicated the potential for manipulating the genomes of desired cyanophages.

Given the limitation of the capsid's DNA encapsulation capacity, the identification of indispensable structural and functional modules is critical for constructing chassis cyanophages. In the recombinant cyanophage designed for a given purpose, nonessential genes can be replaced with exogenous genes. For example, cyanophages with an altered or expanded host spectrum could be applied as eco-friendly agents to control cyanobacterial blooms. In fact, evidence that exchanging recognition modules or mutating tail fibers can alter host spectrum has been validated in bacteriophages (28, 120). Moreover, AI-assisted protein design might provide more efficient methods for expanding host spectrum and/or improving the stability and lytic activity of cyanophages; these advancements are necessary for their large-scale application in environmental control. Given the circumstances of the current postindustrial era, combined with the eutrophication of urban

water bodies and the abuse of antibiotics, the development of customized cyanophages specifically targeting unwanted cyanobacteria has become imperative.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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