REVIEW ARTICLE

Bacteriophages

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Abstract

Bacteriophages, viruses that invade bacterial cells, are the most abundant organisms in the biosphere. Phages include viruses with double-stranded DNA (most common), single-stranded DNA, single-stranded RNA, and double-stranded RNA (least common). Most virions (96%) are tailed; other types are cubic, filamentous, or pleomorphic. Phage genomes are diverse and pervasively mosaic owing to a high frequency of horizontal genetic exchange and recombinations. Phages may have lytic or lysogenic life cycles. They attach to specific bacteria and achieve killing by enzymes endolysins and holins, without affecting the commensal microflora because of host specificity. There is a constant "evolutionary arms race" which leads to competitive bacteria phage coevolution. Numerous diverse and sophisticated bacterial defense mechanisms are being developed to inhibit various stages of the phage life cycle. At the same time, phages have also evolved to overcome these bacterial defenses. Phage-based treatments are being developed where single phages, phage cocktails, phage-derived enzymes, phages in combination with antibiotics, and genetically modified phages might be useful. This can be useful in the treatment of infection with multidrug resistant (MDR) pathogens and also for biofilm removal.

Keywords: Abi-associated enzymes, Abortive infection, Adsorption block, Bacteriophage, Bacteriophage exclusion system, Biofilms, Bradley's classification, *Carjivirus communis*, Caudovirales, Chromosomal islands, Contractile tails, Cosmids, CrAssphage, CRISPER-cas bacterial immune system, Darwinian principles, Double-stranded DNA, Destruction of phage DNA after injection, Diversity-generating retroelements, dsDNA, Endolysin, Enterobacteria P4-like prophages, ESKAPE, Evolutionary arms race, Glucosyl-hydroxymethylcytosine, Helper proteins, Human phageome, Hydroxymethylcytosine, Infant, *Lactococcus* phage c2, Lit activator gol peptide, Long non-contractile tails, Lytic cycle, Lysogenic cycle, Metagenomics, Mosaicism, MS2 coat, *Mycoplasma* phage P1, Myoviridae, Neonate, Newborn, P2-like prophages, *Pasteurella* phage F108, Penetration block, Phage display, Phagemid, Phage coevolution, Phage cocktail, Phage terminase small subunit, Phage anti-restriction-induced system, Phage ecology, Podoviridae, Polyphage, Prophage, Prokaryote viruses, Prokaryotic argonautes, Pseudolysogenic cycle, Receptor, Receptor-binding proteins, Restriction-modification systems, RexAB system, Retrons, Short tails, Siphoviridae, ssRNA, Temperate phage, Toxin-antitoxin systems, Transduction, Virulent phage.

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Key Points

- Bacteriophages are viruses that invade bacterial cells.
- These viruses can be double-stranded DNA (most common), single-stranded DNA, single-stranded RNA, and double-stranded RNA (least common).
- Most virions (96%) are tailed; other types are cubic, filamentous, or pleomorphic. Phage genomes are diverse and pervasively mosaic owing to a high frequency of horizontal genetic exchange and recombinations. Phages may have lytic or lysogenic life cycles.
- These virions attach to specific bacteria and achieve killing by enzymes endolysins and holins, without affecting the commensal microflora because of host specificity.
- Phage-based treatments of bacterial infections are being developed where single phages, phage cocktails, phage-derived enzymes, phages in combination with antibiotics, and genetically modified phages might be useful.

Introduction

Bacteriophages are viruses that invade bacterial cells. Bacteriophage is derived from "bacteria" and the Greek word *phagein*, signifying "to devor." The term "Prokaryote viruses" is a better term because it also includes viruses, mostly of hyperthermophiles, which do not resemble any conventional bacteriophages. They are the most abundant organisms in biosphere.[1]

Bacteriophages were the first type of viruses to be discovered. Many elemental discoveries of molecular biology—the proof that DNA was the molecule transmitting genetic information, the basic mechanisms of gene regulation, and the genetic code, were made using bacteriophages.[2] In 1972, Walter Fiers reported the first complete nucleotide sequence of a gene (gene encoding bacteriophage MS2 coat protein) and in 1976, of the viral genome of phage MS2.[3–5]

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Table 1: Classification of prokaryote viruses[6]

Shape	*Nucleic acid*	*Family*	*Examples*
Tailed	dsDNA	*Myoviridae* (Tail contractile)	T4
		Siphoviridae (Tail long, non-contractile)	λ
		Podoviridae (Tail short)	T7
Polyhedral	ssDNA	*Microviridaae*	φX174
	dsDNA	*Corticoviridae, Tectiviridae,* SH1, STIV	PM2, PRD1
	ssRNA	*Leviviridae*	MS2
	dsRNA	*Cystoviridae*	φ6
Filamentous	ssDNA	*Inoviridae*	*MI3*
	dsDNA	*Lipothrixviridae, Rudiviridae*	*TTV1, SIRV-1*
Pleomorphic	dsDNA	*Plasmaviridae, Fuselloviridae, Guttaviridae, Ampullaviridae, Bicaudaviridae, Globuloviridae*	*L2, SSV-1, His-1*

In 1896, Ernest Hankin, a British bacteriologist noted marked antibacterial activity (against *Vibrio cholerae*) in the Ganga and Yamuna rivers in India, and attributed it to an unknown heat labile substance (with ability to pass through fine porcelain filters) and could limit the spread of cholera epidemics.[7]

Bacteriophages were discovered independently by FW Twort in 1915 and by Félix d'Herelle in 1917; hence, it is also known as BTwort-d'Herelle phenomenon or Bacteriophage phenomenon. D'Herelle's commercial laboratory in Paris synthesized five phage preparations against different bacteria, namely, Bacte´-coliphage, Bacte´-rhinophage, Bacte´-intesti-phage, Bacte´-pyo-phage, and Bacte´-staphy-phage, and were marketed by the French company L'Ore´al.[8]

Viral Structure

Bacteriophage genomes exhibit some unique features, namely, diversity, mosaicism, and differential gene mobility.

Diversity of the Bacteriophage Population

Phage genomes are enormously diverse,[9] accounting for 15% of all viruses with known unique sequences. There are around 750 unique, sequenced bacteriophage genomes, comprising of numerous virion morphologies and nucleic acid compositions. Most are double-stranded DNA (dsDNA) tailed phages (*Caudovirales*). There are around 50 each of completely sequenced RNA phages and single-stranded (ssDNA) phages, and 500 sequenced dsDNA tailed phages. Among the dsDNA tailed phages, 55% are morphologically *Siphoviridae* with long flexible non-contractile tails, 25% are *Myoviridae* with contractile tails and 20% are *Podoviridae* with short stubby tails.

Phage genome can be made up of 3,300 nucleotide ssRNA viruses of *Escherichia coli*[10] to the 500 kbp genome of *Bacillus megaterium* phage G. The smallest of the dsDNA tailed phages genomes are ~11.5 kbp such as *Mycoplasma* phage P1,[11] ~21 kbp such as *Lactococcus* phage c2,[12] and ~30 kbp *Pasteurella* phage F108[13] for the *Podoviridae, Siphoviridae*, and *Myoviridae* families, respectively. Further variation in size has been observed.

Phage viruses can contain dsDNA, which is most common ssDNA, ssRNA, and dsRNA. Most virions (96%) are tailed; other types are cubic, filamentous, or pleomorphic. The CFP categories include nearly 200 types, which comprise about 4% of all viruses. The term "cubic" refers to cubic symmetry and icosahedral shape. Table 1 denotes the classification of phages.

Phages with DNA genomes have the lowest per-nucleotide mutation rates and maximum genetic stability thereby having the ability to maintain larger genomes. Phages with ssRNA genomes have the maximum per-nucleotide mutations rates and smallest genomes.[14,15] Tailed phage genomes can range up to over 500 kb,[16,17] whereas the genomes of tailless phages are generally shorter than 15 kb.[15,18]

The term *polyphage* refers to filamentous phages, which are typically genomic multimers of phages with multiple viral particles encapsulated in the same set of coat proteins.[19]

Phage infectivity and stability is decided by the DNA content of capsid, which plays a role in evolutionary natural selection process, wherein, DNA is gained or lost to achieve virion stability. Being non-motile, phages require Brownian motion to reach their targets.[2]

Mosaicism

Mosaicism is the hallmark feature of bacteriophage genomes. Genome architecture of phages is pervasively mosaic, different segments have distinct evolutionary histories,[20] owing to horizontal genetic exchange. This is exemplified in Mycobacteriophages, where genetic assortment may be the result of repeated site-specific recombination and illegitimate recombination (genome acquisition of bacterial host genetic sequences).[21]

Differential Gene Mobility

Phage genomes are mosaic with a widespread non-homologous recombination across the genome with genes having differential mobility. Core gene recombinations that allow a more stable arrangement are selected during evolution; although promiscuous reassortments of the non-core genes are allowed.

Drivers of Bacteriophage Evolution

Phage evolution follows Darwinian principles. Their genomes bear the maximum genetic novelty among all organisms; with 80% of their encoded genes being unrelated to known proteins, and have unknown functions. This is relevant in the context of phage resistance; it helps in the evolution of phage variants that overcome resistant strains of bacteria. Simultaneously, there are host-mediated protection systems in play like restriction-modification,[22] CRISPR's,[23] tRNA cleavage,[24] and toxin-antitoxin systems.[25] In contrast, there are also phage-encoded mechanisms that enable variants with genome diversity to develop rapidly[26] along with genes that counteract host protection systems, such as

anti-restriction,[27] and RNA repair enzymes,[28] and those providing protection from other viruses.

There is a wide variability in phage length, ranging from 24 to 200 nm,[29] with T4 phages being largest measuring 200 nm in length and 80–100 nm in width. Phages may have an icosahedral shape or a shape with 20 sides and filaments.[30] Figure 1 shows the diagrammatic representation of a bacteriophage. The head or capsid is made up of protein subunits called protomers. The tail is composed of a hollow tube through which the nucleic acid passes into the bacterial host cell upon infection by a phage. Some phages do not possess a tail. The T4 phage has additional structures like baseplate and tail fibers attached to the tail which help attaching it to a bacterial host.[31] Table 2 summarizes the information of the major viral components. Figure 2 shows the transmission electron micrographs of phages.

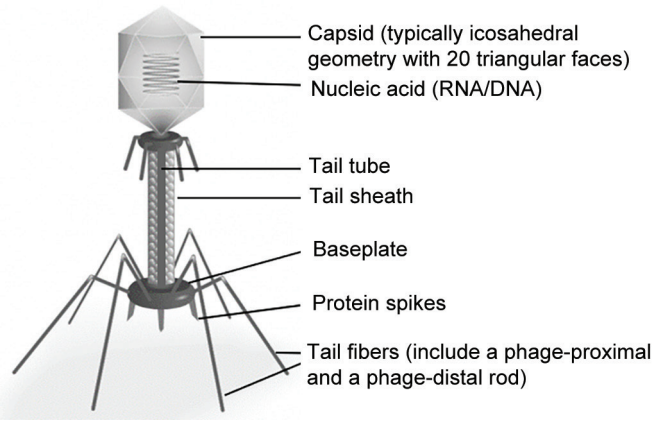


Fig. 1: Diagrammatic representation of a bacteriophage

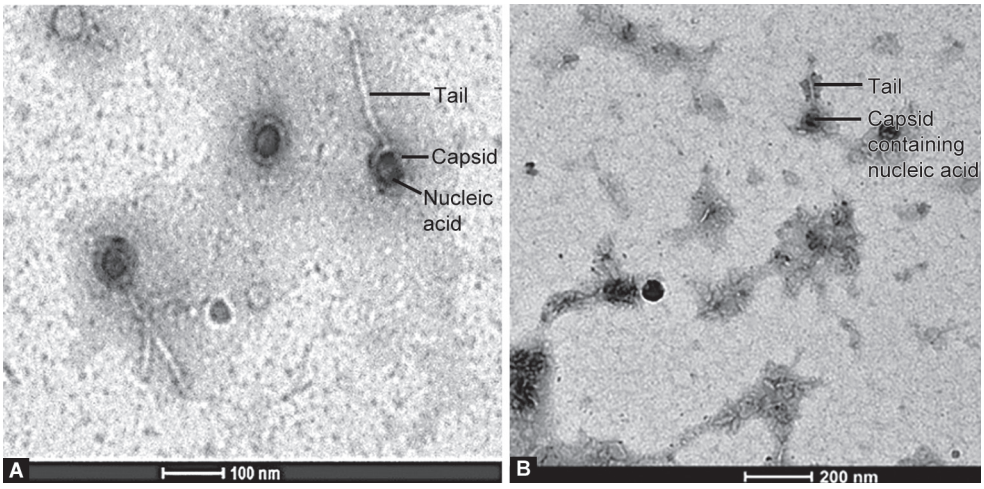
Table 2: Major structural components of bacteriophages

Structure	*Available information*
Lipid envelope	The lipoprotein envelope is derived from the nuclear membrane of an infected host cell[32] and covers the nucleocapsid. The only bacteriophages known to have a lipid envelope around their protein capsids are the members of the *Cystoviridae* family[33] which includes *Pseudomonas* phage phi6. It has three double-stranded RNA genome segments (S, M, and L) and a nucleocapsid surface shell formed by protein P8. Five viral membrane proteins are present—the major envelope protein P9, fusogenic protein P6, spike protein P3, putative holin protein P10, and minor membrane protein P13.[34]
Glycoproteins	Glycoproteins form membrane spikes on the virion surface. They are present in bacteriophages PM2, MX-1, P4, etc.[35–37]
Receptor-binding motifs	Receptor-binding motifs are involved in virion attachment to host cell surface receptors during the process of infection and endocytosis. Receptor-binding proteins (RBPs) of phages initiate infection of their bacterial host and act as the primary determinant for host specificity.[38]
Envelope protein	Envelope proteins facilitate attachment to cell surfaces and viral entry into the cells.[34,39,40]
Membrane protein	Holins and spanins are bacteriophage-encoded membrane proteins which control bacterial cell lysis in the final stage of their reproductive cycle. They accumulate in the membrane to disrupt the inner membrane and outer membrane of the bacteria.[41]
MHC or HLA proteins	Either not expressed or relevance unclear fetal/infantile disease.
Spike protein	Spike proteins allow phages to penetrate host cells and cause infection. Phage tail-spike proteins enable detection of pseudaminic acid-coated pathogenic bacteria and guide the development of antiglycan antibodies with cross-species antibacterial activity.
Surface tubules	Either not expressed or relevance unclear fetal/infantile disease.
Palisade layer	Either not expressed or relevance unclear fetal/infantile disease.
Viral tegument	Either not expressed or relevance unclear fetal/infantile disease.
Lateral bodies	Either not expressed or relevance unclear fetal/infantile disease.
Capsid	The capsid is a highly ordered proteinaceous structure which encloses the viral genomic RNA in nucleocapsid cores.[42]
Capsomeres	Structural subunits of the capsid are known as capsomeres and can be seen in electron micrographs. The head consists of numerous capsomeres with double-stranded DNA enclosed within.[43]
Core membrane	Either not expressed or relevance unclear fetal/infantile disease.
Protein core	Either not expressed or relevance unclear fetal/infantile disease.
Core fibrils	Either not expressed or relevance unclear fetal/infantile disease.
Matrix	Either not expressed or relevance unclear fetal/infantile disease.
Enzymes	Bacteriophage killing is achieved by two enzymes—endolysin and holin. Endolysins are phage-encoded peptidoglycan hydrolases produced at the end of the lytic cycle. Holin forms membrane lesions, through which endolysins cleave the peptidoglycan and cause host cell lysis and release of progeny phages.[44–46]
RNA elements	A transient double-stranded replicative RNA intermediate consisting of viral plus- and minus- strand RNAs is synthesized by a replicase complex formed by the non-structural proteins.[47,48]

(Contd...)

Table 2: *(Contd...)*

Structure	*Available information*
Nucleus	Bacteriophages φKZ and φPA3 encode a proteinaceous shell which assembles a nucleus-like structure to compartmentalize proteins and DNA during viral infection.[49]
Nucleosome	The genomes of some viruses (nuclear DNA viruses and retroviruses) requires evasion of host DNA damage recognition machinery. These genomes are organized into nucleosomes by annexing eukaryotic histones and the host nucleosome assembly machinery during latent and early lytic phase.
DNA	Bacteriophages may have ssDNA or dsDNA genome.[6]
RNA	Bacteriophages may have ssRNA or dsRNA genome.[6]
Genome-associated polyprotein	Protein-primed genome replication is a strategy to initiate DNA or RNA synthesis in linear genomes. Bacteriophage terminal proteins (TPs) are covalently attached to viral genomes to prime DNA replication. TPs are DNA-binding proteins and target phage genomes to the host nucleoid.[50]
DNA polymerase	Bacteriophage-encoded DNA polymerases are quite different from other known enzymes catalyzing DNA synthesis.[51] They can show activities unusual for the members of the family they belong to,[52] display unique structures,[53] or disobey canonical rules of base pairing during DNA synthesis adopted by all living organisms.[54]
RNA polymerase	The single subunit DNA-dependent RNA polymerase (RNAP), encoded by bacteriophage T7, is the prototype of a class of simple RNAPs (present in T3 and SP6, and the mitochondrial RNAPs). Phage-like RNAPs are related to other nucleotide polymerases such as DNA polymerases, RNA-dependent RNA polymerases, and RT.[55]
Reverse transcriptase	DNA synthesis is catalyzed by RNA-directed DNA polymerase (reverse transcriptase) in some phages.[56]
Head	Head is made of proteins and an inner core of nucleic acid. It is assembled as an empty capsid and thereafter, packaged with DNA by an ATP-dependent packaging machine, which binds to the same special pentameric vertex that is later occupied by the phage tail.
Baseplate	It is the most distal part of the tail of *Myoviridae* and *Siphoviridae,* and acts as a multiprotein molecular machine which binds to the host cell entry receptor that controls tail sheath contraction and initiates genome ejection by a change in the baseplate conformation.[57,58]
Integrase	Phage integrases are enzymes that mediate unidirectional site-specific recombination between two DNA recognition sequences, the phage attachment site, attP, and the bacterial attachment site, attB. They have two major families- the tyrosine recombinases and the serine recombinases, based on their mode of catalysis. Tyrosine family integrases, such as lambda integrase, utilize a catalytic tyrosine to mediate strand cleavage, recognize longer attP sequences, and require other proteins encoded by the phage or the host bacteria. Serine family integrases are larger, use a catalytic serine for strand cleavage, recognize shorter attP sequences, and do not require host cofactors.[59]
Tail	The phage tail is a complex, multiprotein structure that mediates attachment, digestion and penetration of the cell wall and genome ejection.[60,61]
Tail fiber	The host range of a phage is determined by phage tail fibers (or spikes), which mediate recognition and adsorption by specific bacteria.[62–64]
Neck	The neck of some bacteriophages (e/g T4) has "collar" and "whiskers", composed of fibritin molecules. Fibritin acts as a chaperone to facilitate attachment of long tail fibers to the virus during the assembly process.[65,66]



Figs 2A and B: Transmission electron micrographs of bacteriophages of the myoviridae family

Table 3: Differences between virulent and temperate phages

	Virulent phages	*Temperate phages*
Definition	Replicate by lytic cycle only	Replicate by both lytic and lysogenic cycle
Prophage stage	Not formed	Formed
Killing the host bacterium	Kill the host after each infection cycle	Do not kill the host immediately after infection
Transduction	Generalized transduction	Specialized transduction

Virus Taxonomy

Bradley's classification suggested six basic morphological types of tailed phages which were further divided on the basis of morphotypes (contractile tails, long and non-contractile tails, and short tails). Virus taxonomy is decided by the International Committee on the Taxonomy of Viruses (ICTV),[67] which published its first report in 1971. The Bacterial and Archaeal Viruses Subcommittee (BAVS) within ICTV holds the responsibility of classifying new prokaryotic viruses.[68] It considers numerous parameters like host range, physical characteristics (such as structure, capsid size, and shape), type of genomic material (single or double-stranded DNA or RNA), genome size, and resistance to organic solvents.[69]

In its report of March 2021–March 2022, Bacterial Viruses Subcommittee of the International Committee on Taxonomy of Viruses made drastic changes in bacteriophage taxonomy. Morphology-based families *Podoviridae*, *Siphoviridae*, and *Myoviridae* and the order *Caudovirales* were abolished, and a binomial system of nomenclature for species was established. One order, 22 families, 30 subfamilies, 321 genera, and 862 species were newly created.[70] The order *Caudovirales* was replaced by the class *Caudoviricetes* to encompass all tailed bacterial and archaeal viruses with icosahedral capsids and a dsDNA genome.

In 2020, ICTV endorsed binomial format for the naming of viruses, in which the genus name and a species epithet form a unique species name. For example, *Escherichia virus T4* was renamed *Tequatrovirus T4*, crAssphage was assigned to the species *Carjivirus communis*. The class *Caudoviricetes* now contains 14 families assigned to four orders, of which three orders include viruses infecting archaea.[71,72]

Mechanism of Proliferation

Bacteriophages exhibit host selectivity on account of requirement of specific receptors (lipopolysaccharides, teichoic acids, proteins, and flagella) on the bacterial surface for infection. External lipopolysaccharide (LPS) layer and embedded outer membrane proteins (OMPs) of Gram-negative bacteria are required for transport and diffusion of nutrients. These act as phage receptors, and are instrumental for adsorption of phage particles.[73] Teichoic acids of Gram-positive bacteria cell wall also work as phage receptors.[74,75]

There are different ways of insertion of genetic material in different phage groups. In the Myoviridae phage, after receptor recognition, the baseplate is attached with the bacterial surface by the flexing activity of tail fiber and inserts its genetic material by its tail contraction. Podoviridae phage is devoid of the tail part and inserts its genetic material after enzymatically degrading a portion of the bacterial cell membrane by small, tooth-like tail fibers.[73–75]

Replication of Phages

There are two types of life cycles of bacteriophages—lytic and lysogenic cycles.

Lytic Cycle

The lytic phase phages are also called as virulent phages. Following the multiplication of phages in the host, lysis and rupture of host bacteria occurs to release new phage particles. Host chromosome may be packed in to the capsid during phage replication which leads to horizontal gene transfer by transduction. Virulent phages may be used to counter the menace of antibiotic resistant pathogenic bacteria.

Lysogenic Cycle

Temperate phages undergo lysogenic phase in their life cycle wherein viral genetic material is integrated with the bacterial genome (called prophage), thereby ensuring continued replication of the viral genetic material without any fatal consequences to the infected host.[76] Phenotype of the infected bacteria changes; thereby bringing about its pathogenicity.[77,78] Prevention of lysogenic conversion can be done by hydrogen peroxide by production of a reactive oxygen species, glutathione, and overexpression of transcriptional repressors.[78–80]

Pseudolysogenic Cycle

Psuedolysogenic life cycle maybe shown by some phages. A phage enters a bacterial cell, does not integrate in a stable fashion and stays in this mode until there is a trigger for a lytic or lysogenic life cycle.[1]

Table 3 shows the differences between virulent and temperate phages.

Transduction

Phages are also a critical component of the human microbiome owing to being a mediator of genetic exchange between pathogenic and non-pathogenic bacteria.[81,82] Transduction is the transfer of genes from one bacterial strain to another by a bacteriophage and is of two types—generalized or specific. In "generalized" transduction, bacterial genomic DNA gets packaged inside phage capsids instead of phage genomic DNA during lytic cycle. This phage then infects a healthy host cell, integrates into its chromosome and alters the genome of the host as well as progeny. In "specialized" transduction, lysogenic phages excise parts of the bacterial DNA with their genome when initiating a lytic replication cycle. All progeny phages transduce the same bacterial gene to their hosts.[2]

Epidemiology

Bacteriophages are the most common organisms in the biosphere. Ganga water is an abundant natural source of diverse bacteriophages, which has the potential for the development of a phage bank, for the purpose of bacteriophage therapy in the future.[47]

Table 4: Antiphage defenses[83]

Bacterial defense mechanism	*Description*
Encounter blocks	Extracellular polymeric substances blocking virion approach to bacterial surfaces, e.g., capsules
Adsorption resistance (envelope-level resistance)	Binding failure due to absence of requisite receptor molecules on bacterial surfaces
Penetration blocks (exclusion; superinfection exclusion)	Blocks on phage movement during association with host, preventing entrance into host cytoplasm during adsorption
Immunity to superinfection (homoimmunity)	Blocks on phage replication due to recognition of specific phage-associated motifs
Abortive infection	Killing of phages but at cost of death of individual, phage-exposed bacteria
Restriction-modification	Generic features of organisms are targeted (recognition sequences found in DNA); equivalent host features are protected
Phage growth limitation system	Tagging of phages for elimination by clonally related cells
Opsonization	CRISPR phage resistance via acquisition of novel-to-host DNA sequence

Pathogenesis

Bacteriophage killing is attributed to two enzymes, endolysin and holin. Endolysins are phage-encoded peptidoglycan hydrolases, generated at the end of the lytic cycle. Holin forms membrane lesions, through which endolysins cleave the peptidoglycan, leading to host cell lysis and release of progeny phages.[47–49]

Phages do not affect the commensal microflora because of host specificity. Natural interactions among microbes boost phage generation which is exemplified by the Kumbh Mela community bath in Ganga river giving rise to high frequency of diversified bacteriophages.[47]

Interaction with mammalian hosts induces antiphages neutralizing antibodies, which peaks by the end of third week. Therefore, bacteriophages can be effectively used in acute cases with duration below 2 weeks. In chronic cases requiring prolonged therapy, phage cocktail of different antigenicities may be effective.[84]

Attachment and Penetration

Phages attach to specific receptors on the bacterial cell surface, including lipopolysaccharides, teichoic acids, proteins or flagella; hence, they infect only certain hosts which harbor those receptors. Attachment requires disintegration of the capsular outer layer of the hosts which is aided by polysaccharide-degrading enzymes of the virus. Phages are incapable of independent movements, hence require random encounters with the correct receptors in solution, such as blood, and lymphatic circulation.

Penetration of genetic material in the cell is done by a hypodermic syringe-like motion by Myovirus bacteriophages. Upon contact with the specific receptor, reversible binding is initiated wherein the tail fibers of bacteriophages flex to bring the baseplate closer to the surface of the cell. Thereafter, irreversible binding occurs by tail contraction to injecting genetic material through the bacterial membrane. Podoviruses enzymatically degrade bacterial membranes by small, tooth-like tail fibers to insert genetic material.[85]

Synthesis of Proteins and Nucleic Acid

After penetration of the genetic material, viral mRNA is translated to proteins by bacterial ribosomes. Bacterial RNA polymerase is modified by phages to preferentially transcribe viral mRNA, thereby disrupting synthesis of proteins and nucleic acids of the host. Virions are formed and assembled with the help of helper proteins.

Virion Assembly

Virion assembly is aided enzymatically by helper proteins. In T4 phage, morphogenesis starts initially with baseplate assembly followed by tails and subsequently, packaging of DNA in the head. An appropriate balance of morphogenetic proteins is mandatory for proper virion assembly which takes about 15 minutes.

Release of Virions

Virion release is followed by infection of a new host bacterium by the progeny phages. Tailed phages accomplish virion release by enzymatic breakdown of the peptidoglycan cell wall by endolysins, filamentous phages make the host secrete new virus particles and *Mycoplasma* phages achieve virion release by budding.

Communication

Bacteriophage Φ3T has been shown to signal other phages by Arbitrium protein.[86,87]

Antiphage Defense Mechanisms

Antiphage defense mechanisms have been developed by the prokaryotes to halt phage invasion and replication. The red queen hypothesis states that an organism must constantly evolve to maintain its relative fitness in the face of a predator.[88] There is a constant ''evolutionary arms race'' which leads to competitive bacteria phage coevolution.[89] Numerous diverse and sophisticated bacterial defense mechanisms are developed to inhibit every stage of the phage life cycle, whereas phages also evolve to overcome these bacterial defenses (Table 4).[90]

Adsorption Block

Bacteria develop strategies to decrease adsorption of phages to their specific bacterial receptors (protein, polysaccharide, or lipopolysaccharide LPS) by introducing mutations in the receptor structure and introducing physical barriers to camouflage receptors. This is seen in LamB, the phage lambda receptor, in *E. coli*-resistant cells.[91]

Penetration Block

Superinfection exclusion (SIE) is a bacterial defense in which intracellular phages, including prophages, block the infection of the same (homotypic SIE) or a different (heterotypic SIE) phage. Superinfection exclusion systems are phage-encoded

membrane-anchored or membrane-associated proteins and act to prevent phage DNA injection into bacterial hosts. They protect a lysogenized host from infection by other phages, thereby giving a strong selective advantage to the bacterium because they help protect the surrounding bacteria also since the infecting phage is rendered non-infectious after DNA ejection. The *E. coli* prophage HK97 confers both homotypic as well as heterotypic SIE thorough the expression of gp15.[92]

Restriction-modification Systems

Restriction-modification (R-M) systems include a restriction endonuclease (REase) and a cognate methyltransferase (MTase)[93] and halt replication and release of phages by destroying their DNA. The MTase methylates self-DNA at specific recognition sites, whereas foreign DNA stays unmodified, hence recognized by R-M REases and split into harmless fragments. The restriction endonuclease recognizes short DNA motifs of 4- to 8-base-pairs long, and cuts the phage DNA. These DNA motifs of the bacterial host are protected by methyltransferase to modify its own DNA to avoid recognition by the restriction enzyme.

Restriction-modification systems are of four types according to their subunit composition, recognition site, and mechanism of action.[93,94] Both type I and III systems translocate along DNA and cleave away from the recognition sites. Type II, used in molecular cloning, cleave within or near the recognition site. Type IV systems have a restriction endonuclease and lack a methylase, which cleaves only modified DNA. RM systems and DNA modifications exemplify an elaborate ''arms race'' between *E. coli* and phage T4. T4 contains hydroxymethylcytosine (HMC) in place of cytosine, inhibiting types I–III RM systems that recognize sites containing cytosine.[95] To counter this, *E. coli* uses McrBC, a type IV system specific for HMC-containing DNA.[96] In response, T4 can glycosylate its DNA, which impairs McrBC activity.[97] Against this, *E. coli* has evolved an additional type IV system, the GmrS-GmrD system, that can cleave glycosylated DNA.[98]

CRISPR-Cas bacterial immune systems[99] are present in approximately 50% of sequenced bacteria and 90% of sequenced archaea.[100] They are a part of adaptive immunity and provide resistance against invading phages[101] and plasmids.[102] Types I, II, and V use the crRNA guide to recognize the complementary target sequence in the DNA of the invader, known as the protospacer. In addition to this complementarity, cleavage requires the presence of a conserved protospacer-adjacent motif (PAM) in one flank of the target.[103–105] As a consequence of this targeting requirement, phages harboring mutations that eliminate the PAM or the complementarity between the protospacer and the crRNA can escape targeting.[106,107]

Prokaryotic Argonautes

Prokaryotic Argonautes (pAgos) are a bacterial innate defense mechanism in 9% of bacterial and 32% of archaeal genomes.[108] They are encoded within defense islands, regions enriched for phage resistance systems, and have undergone extensive horizontal gene transfer[109] defense mechanisms employed are DNA guided DNA silencing and RNA-guided DNA silencing. The apo form of pAgo can degrade invader DNA sequence and subsequent degradation products can serve as guide DNAs, which allows sequence-specific interference against the same target.[110,111]

Abortive Infection

Abi is a process to prevent the release of functional phage virions to prevent the predation of the surrounding clonal bacterial population at the expense of host cell survival. It is an altruistic action or a ''programmed cell death'' by disruption of essential cellular processes including translation, transcription, and replication or by inducing membrane leakage. Abi systems are encoded by mobile genetic elements, including prophages and plasmids[61] and are mechanistically diverse. The RexAB system in phage lambda protects lysogenized cells from infection by coliphages by inducing a loss of membrane potential, leading to decreased ATP levels.[112] Toxin-antitoxin (TA) systems have also been known to mediate abortive infection.[25]

Toxin-antitoxin Systems

TA gene pair consists of a toxin causing stress and antitoxin inhibiting the toxin's catalytic activity. They work as antiviral systems by disrupting phage life cycle and preventing virion release. Antitoxin is labile and requires continuous expression to remain at appropriate stoichiometric ratios with and neutralize the toxin.[113] Toxins possess catalytic activities, including DNase and RNase and can inhibit DNA replication, ATP synthesis and cell division machinery. There are six TA types, categorized based on the nature of the toxin and antitoxin (protein or RNA) and the mechanism of toxin neutralization.[113] TA systems have been implicated in phage defense, stress responses, plasmid maintenance, and persister cell formation.

Retrons

Retrons are bacterial genetic elements composed of a reverse transcriptase (RT) and a noncoding RNA (ncRNA) and protect against phage infection via abortive infection.[114,115] The Thoeris defense system is another mechanism which deploys a unique strategy for bacterial antiphage resistance via NAD^+degradation.[116]

Assembly Interference

Phage-inducible chromosomal islands (PICIs) are genetic elements that parasitize phages for replication and transmission.[117] PICIs are integrated into bacterial chromosomes and excise in the presence of a specific ''helper phage.'' PICI genomes are small (15 kb), encoding genes required for excision and integration, and a repressor that inhibits their expression. In *Staphylococcus aureus*, PICIs are named ''SaPIs'' (*S. aureus* pathogenicity islands), induced when their repressor, Stl, is sequestered away by an antirepressor expressed early during the helper phage lytic cycle.[118] They disseminate critical virulence factors.[119] They are induced to excise, replicate, and package themselves after infection by "helper" phages and allow the intracellular phage program to progress for the production of mature phage particles loaded with SaPI DNA.[120] Infected cell dies but phage reproduction is halted and SaPIs are spread to neighboring cells. They can also remodel the phage capsid proteins to generate small capsids that are tailored to the smaller SaPI genome and exclude the larger helper phage genome.[121,122] SaPIs encode phage packaging interference (Ppi) proteins, to block the phage terminase small subunit (required for recognition of phage DNA and initiation of packaging)[122] and also interrupt phage late gene activation, which is essential for phage packaging and cell lysis.[85]

Recently Discovered Antiphage Mechanisms

Enterobacteria P4- and P2-like prophages possess genetic hotspots that encode bacterial immune mechanisms[123] such as phage anti-restriction-induced system (PARIS). This system triggers an Abi response after sensing a phage-encoded anti-restriction

protein, Ocr, which inhibits R-M systems and bacteriophage exclusion (BREX).[123] The BREX system mediates methylation of a non-palindromic, six-nucleotide motif to achieve self-/non-self-discrimination,[124,125] aiding in the destruction of phage DNA after injection.

The DISARM mechanism[126] provides broad antiphage immunity by a novel RM-like mechanism that includes a methyltransferase modifying a five-nucleotide motif and a multicomponent restriction element to cleave phage DNA early in the phage life cycle.

Phage Counterattack Strategies

In response to diverse bacterial defenses, phages have developed novel counterattack mechanisms. To overcome variations in the bacterial cell surface receptors, phages vary their tropism through mutations in their RBPs. Receptor binding protein genes and genes mediating host recognition are prone to mutations, due to the activity of diversity-generating retroelements (DGRs).[127] These are prone to targeted mutation by exchange of two variable repeats by an error-prone RT.[128]

To overcome the barrier imposed by capsules and extracellular layers, some phages develop the ability to bind to these structures,[129] and degrade them using depolymerases. These enzymes may be either expressed as part of tail-spike or tail-fiber proteins or released in a soluble form following lysis of infected bacteria.[130]

Phages can counter RM systems in the following ways: (i) Removal of restriction sites from their genome (palindrome avoidance) to prevent recognition by REases;[131,132] (ii) modification of sequences recognized by REases (e.g. the glucosyl-hydroxymethylcytosine of T4 that is used instead of cytosine;[133] (iii) changing of distance and orientation of restriction sites to avoid restriction by REases;[134] (iv) occlusion of restriction sites with proteins;[135] (v) sequesteration of REases with proteins;[136] and (vi) acquisition of genes encoding an MTase that modifies the phage genome.[137]

CRISPR-Cas systems can be evaded[138] by acquisition of point mutations or deletions in the PAM sequences.[139] Anti-CRISPR (Acr) proteins avert recruitment of the crRNA-Cas complex to target DNA by binding the complex or occluding the PAM sequence, glucosylation of phage genetic material, or by inhibiting the endonuclease domain to prevent cleavage.[140]

Phages avert toxin–antitoxin systems by inhibiting the protease that degrades the antitoxin, expressing their own antitoxin analogue[141,142] or mutations in genes involved in the metabolism of nucleic acids.[143]

Mutations in phage genes which operate Abi-associated enzymes, such as the Lit activator Gol peptide in T4, obstructs Abi mechanism.[144] The Ocr protein of phage T7 sabotages the BREX system by binding the methyltransferase BrxX.[145]

Bacteriophage-host Symbiosis

Temperate phages integrate their genetic material as extrachromosomal episomes or as prophage during a lysogenic cycle which helps in achieving antibiotic resistance through the transfer or introduction of antibiotic resistance genes protecting hosts from phagocytosis, protecting hosts from secondary infection through superinfection exclusion, increasing host pathogenicity, or enhancing bacterial metabolism or growth. It provides selective advantages to bacteria with simultaneous passive replication of the phage genome.

Phage population in humans is known as human phageome (DHP) and comprises of healthy gut phageome (HGP) and the DHP. The active phageome of a healthy human (i.e., actively replicating as opposed to nonreplicating, integrated prophage) has been estimated to comprise dozens to thousands of different viruses.[146] Bacteriophages are found in 62% of healthy individuals but are reduced in those with inflammatory bowel diseases and in elderly. CrAssphages, most common phages in the human intestine, may be vertically transmitted with unique crAssphage clusters present in all humans.

Phage Ecology

Phage ecology is the study of the interaction of bacteriophages with their environment. It encompasses the study of impact of the abiotic environment on organisms (organismal ecology), impact of individuals of the same species on each other (population ecology), interactions between different species (community ecology), and the interaction and impact of biotic entities on abiotic aspects of environments (ecosystem ecology).[14]

Metagenomics is a concept that refers to the examination of genetic data from environmental samples in order to identify microbial communities.[147] A high-throughput sequence (HTS) based functional metagenomics technique is useful for identifying resistance mechanisms[148,149] and genomic content.

Phage Therapy

Phage-based treatments comprise of phage therapy with single phages or phage cocktails, phage-derived enzymes, phages in combination with antibiotics, and genetically modified phages.[150] These focus on lytic phages because they lack integrases and other enzymes involved in horizontal gene transfer.

Lysins and depolymerases are phage degradation enzymes useful in the removal of biofilms. Lysins are peptidoglycan hydrolases with a bactericidal effect on susceptible bacteria. They break peptidoglycan bonds, degrading the bacterial cell wall and biofilm structure, hence useful for gram-positive bacteria. Depolymerases are enzymes which degrade extracellular substances of encapsulated bacteria to reach phage receptors. They can degrade the chains of capsular polysaccharides, exopolysaccharides, and O-polysaccharides from lipopolysaccharides and peptidoglycan, which are components of the biofilm matrix. Bacteriophage recombinant lytic proteins (lysins and depolymerases) can be used as enzybiotics.[151]

The most common cause of opportunistic infections is the ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus, Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) group of organisms, most of which are MDR isolates.[152] A sub-lethal dose of antibiotics can stimulate phage virulence under certain conditions known as phage-antibiotic synergy (PAS).[153,154] The combination of phage with antibiotics could have a variety of outcomes, including additive, synergistic, ineffective, or antagonistic effects.[155,156] Principi et al.[157] suggested that bacteriophages reduce the minimum inhibitory concentration of AR bacteria to the level of sensitive bacteria.

Temperate phages with phenotypic characteristics useful for biofilm removal can be turned into virulent phages by genetic engineering. Lytic phages are used to destroy bacteria and temperate phages are useful in delivering programmable DNA

Table 5: Definitions associated with bacteriophages

Virulent phage	Phages which display only lytic cycles (no chronic or lysogenic cycles)
Temperate phage	Phages which can undergo either virion productive or lysogenic cycles
Induction	Viral infection changes from a lysogenic cycle to a productive cycle
Chronic cycle/infection	Non- bactericidal phage infection, where virions are produced and continuously released
Productive cycle/infection	Virus reproduction with production of virion particles
Prophage	Phage genome that replicates with its host cell while not generating virion progeny
Cryptic prophage	Prophage that has mutationally lost its ability to enter a virion-productive cycle
Lysogen	Bacterial cell that harbors at least one prophage
Polylysogen	Bacterial cell that harbors more than one prophage
Transduction	Virion-mediated transfer of bacterial DNA to new bacteria either with associated temperate phage genome (specialized transduction) or not in association with phage genome (generalized transduction)
Virome	Metagenomic sequence of viral communities
Phagemid	Phasmid or phagemids are DNA-based cloning vectors possessing both bacteriophages and plasmid traits
Polyphage	Genomic multimers of phages with multiple viral particles being encapsulated in the same set of coat proteins, seen in filamentous phages
Superinfection exclusion	A bacterial defense in which intracellular phages, including prophages, block the infection of the same (homotypic SIE) or a different (heterotypic SIE) phage
Phage display	A molecular biology technique in which phage genomes are modified resulting in coat proteins of the assembled virions being fused to other proteins of interest, thereby displaying them to the external milieu
Phage ecology	Study of interaction of bacteriophages with their environment
Metagenomics	Examination of genetic data from environmental samples to identify microbial communities
Human phageome	Phage population in humans. It includes the "healthy gut phageome" (HGP) and the "diseased human phageome" (DHP)
Restriction-modification (R-M) systems	Restriction endonuclease (REase) and a cognate methyltransferase (MTase) present in some bacteria that halt replication and release of phages by destroying their DNA

nucleases associated with CRISPR to reverse antibiotic resistance and destruction of plasmids that confer antibiotic resistance.

Phage display is a molecular biology technique in which phage genomes are modified resulting in coat proteins of the assembled virions being fused to other proteins of interest, thereby displaying them to the external milieu. It aids isolation of proteins with desired affinity, specificity, stability, and enzymatic activity.[158]

Phagemid

Phasmid or phagemids are DNA-based cloning vectors possessing both bacteriophages and plasmid traits. They carry an origin of replication obtained from the bacteriophage along with origin of replication of the plasmid. Phagemids have the ability to be packaged into the capsid of bacteriophage as they contain a genetic sequence for packaging, unlike plasmids. Hence, they are useful in phage display and generating templates for site directed mutagenesis.[159] Cosmids are hybrid plasmids containing a lambda phage cos sequence and have 37–52 kb of DNA. They are used as cloning vectors and can be used to build genomic libraries.[160]

Table 5 presents the common definitions associated with bacteriophages.

Future Directions

Currently, no framework[161] exists to define phage as a medicinal product for human use, although institutes in Georgia, Poland, provide customized phage cocktails to chronically ill patients after exhaustion of conventional treatment options.[162] The need of the hour is good quality placebo-controlled randomized controlled trials along with a monitoring system for bacterial resistance to phages.[163–165] Good manufacturing practice level facilities are necessary for phage production and research[166,167] in order to ensure phage stability and effectiveness.

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