Trends in Peptide and Protein Sciences
2016, Vol. 1, No. 1, 7-13

Review Article

A Short Introduction to Bacteriophages

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Article history:
Received: 7 August 2016
Accepted: 27 August 2016

Keyword:
Bacteriophages
Bacteria
Transduction
Lysogeny
Lysis

HIGHLIGHTS

- Bacteriophages or phages are bacterial viruses with prokaryotes invasion ablility.
- Bacteriophage genes include lysis, replication, regulation, packaging, structural, antimicrobial resistance and housekeeping genes.
- Bacteriophages are important agents in transduction of mobile genetic elements to bacteria.
- One of the most interesting areas of the phage research can be its treatment application.

ABSTRACT

First discovered in the 19th century, bacteriophages (phages) are bacterial viruses and the most widespread entities on earth. Phages have multiple important roles in maintaining the bacterial population, carbon cycling, bacterial pathogenicity, and bacterial evolution. They can be used to develop DNA and protein vaccines, novel antibiotics and antiviral drugs, and phage therapy. The International Committee on Taxonomy of Viruses categorizes phages in two major orders of *Caudovirales* and *Ligamenvirales*, including five families, nine subfamilies, 145 genera, and 684 species. The most widespread families in nature are *Siphoviridae*, *Myoviridae*, *Podoviridae*, and *Inoviridae*. Phages are morphologically categorized in two major categories of tailed and polyhedral, filamentous, or pleomorphic phages. They can have either a single- or double-strand DNA or RNA genome. Phages are important for transferring mobile genetic elements, such as virulence genes and antimicrobial resistance determinants to bacteria by transduction, and have been used to treat bacterial infections. In conclusion, phages are important entities because of their roles in bacterial metabolism and surveillance in nature. Further studies can help us obtain a better understanding of the phage mechanism in bacterial evolution.

Introduction

History

Bacteriophages or phages are bacterial viruses that are able to invade prokaryotes (Mihara et al., 2016). The approximate population of phages is suggested to be 10^{31}, which is 10 times greater than the bacterial population (Canchaya et al., 2004; Pedulla et al., 2003; Hendrix, 2002). Bacteriophages play a significant role in maintaining the bacterial population and are important for adopting pathogens to their hosts, which is termed as a 'host-pathogen-phage interaction' (Ventura et al., 2007; Boyd and Brussow, 2002). Furthermore, they can play roles in carbon cycling, bacterial pathogenicity, and bacterial evolution. Bacteriophages can be used to develop DNA vaccines, protein vaccines, novel antibiotics, novel antiviral drugs, gene therapy, and phage therapy (Turton et al., 2012; Serwer et al., 2007).

Bacteriophages were first discovered in the 19th century. In 1896, Ernest Hankin, an English bacteriologist, inactivated *Vibrio cholerae* using water filtrates from the

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Table 1. Classification of phages.

Order	Family	Specifications
No order	*Corticoviridae*	Non-enveloped, icosahedral capsid with lipid layer, circular supercoiled dsDNA
No order	*Cystoviridae*	Enveloped, icosahedral capsid, lipids, three molecules of linear dsRNA
No order	*Guttaviridae*	Pleomorphic, envelope, protrusions, beard of long fibers, circular dsDNA
No order	*Fuselloviridae*	Pleomorphic, envelope, lipids, capsid, protrusions, short tail-like fibers, circular supercoiled dsDNA
No order	*Inoviridae, genus Inovirus*	Non-enveloped, long filaments with helical symmetry, circular ssDNA
No order	*Inoviridae, genus Plectrovirus*	Non-enveloped, short rods with helical symmetry, circular ssDNA
No order	*Leviviridae*	Non-enveloped, quasi-icosahedral capsid, one molecule of linear ssRNA
Ligamenvirales	*Lipothrixviridae*	Enveloped filaments, lipids, linear dsDNA
No order	*Microviridae*	Non-enveloped, icosahedral capsid, circular ssDNA
Caudovirales	*Myoviridae,* A1	Non-enveloped, tail contractile, head isometric, linear dsDNA
Caudovirales	*Myoviridae,* A2, A3	Non-enveloped, tail contractile, head elongated, linear dsDNA
No order	*Plasmaviridae*	Pleomorphic, envelope, lipids, no capsid, circular supercoiled dsDNA
Caudovirales	*Podoviridae,* C1	Non-enveloped, tail short and noncontractile, head isometric, linear dsDNA
Caudovirales	*Podoviridae,* C2, C3	Non-enveloped, tail short and noncontractile, head elongated, linear dsDNA
Ligamenvirales	*Rudiviridae*	Non-enveloped, helical rods, linear dsDNA
Caudovirales	*Siphoviridae,* B1	Non-enveloped, tail long and noncontractile, head isometric, linear dsDNA
Caudovirales	*Siphoviridae,* B2, B3	Non-enveloped, tail long and noncontractile, head elongated, linear dsDNA
No order	*Tectiviridae*	Non-enveloped, icosahedral capsid with inner lipoprotein vesicle, linear dsDNA, tail produced for DNA injection, linear dsDwNA
Unassigned	*Salterprovirus*	Pleomorphic, envelope, capsid, short tail-like fibers, linear dsDNA

From ICTV, 2015

Ganges and Jamuna rivers. This was repeated in 1898 by Nikolay Gamaleya, a Russian bacteriologist, using *Bacillus subtilis*. In 1915, Frederick Twort, an English bacteriologist, proposed that the inactivator possibly was a bacterial virus. Later, in 1917, Felix d'Herelle, a French-Canadian microbiologist, reported the first bacterial lysis and named the lysis agent a bacteriophage. Since then, phage study has been continued by many researchers such as Clark and Clark (1927), Evans (1934), Rakieten and Tiffany (1938), Tiffany and Rakieten (1939), Evans (1941), Kjems (1955), Bleiweis and Zimmerman (1961), Brock et al. (1963), and Brock (1964).

Taxonomy

Currently, the International Committee on Taxonomy of Viruses (ICTV) categorizes phages in two major orders (*Caudovirales* and *Ligamenvirales*), five families, nine subfamilies, 145 genera, and 684 species. Unassigned families mostly belong to archaea (Table 1) (Krupovic et al., 2016; ICTV, 2015). Of the phage families, four main families are widespread in nature: *Siphoviridae*

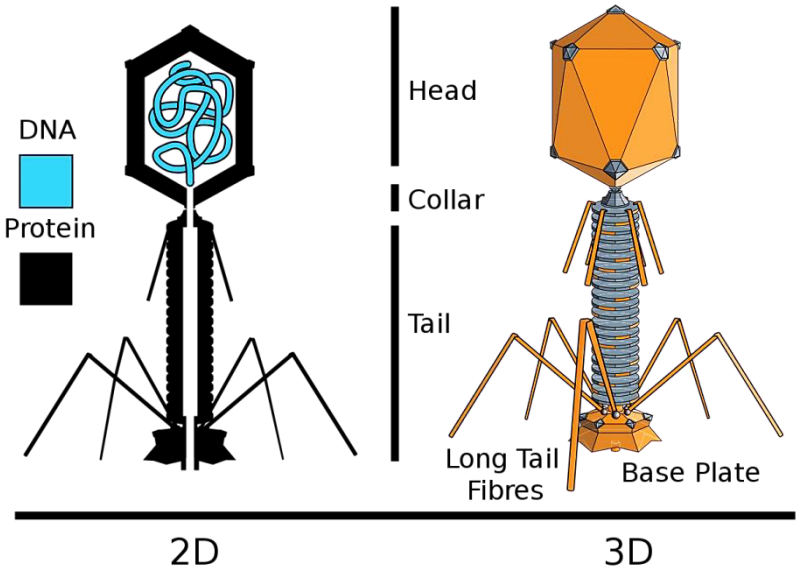


Figure 1. Graphic of a tailed phage (from Wikimedia Commons).

(order: *Caudovirales*), *Myoviridae* (order: *Caudovirales*), *Podoviridae* (order: *Caudovirales*), and *Inoviridae* (unassigned family) (Nelson, 2004; Lawrence et al., 2002).

Morphology

Bacteriophages are morphologically categorized in two major categories: tailed (head-tail) and PFP (polyhedral, filamentous or pleomorphic) phages. The classic structure of tailed phages represents an icosahedral head containing capsid and genome, a neck or collar, one tail or more, and a base plate (Figure 1) (Fokine and Rossmann, 2014; Yap and Rossmann, 2014). The phage tail includes a core covered by a helical sheath. The helical sheath ends at the base plate with long- and short-tail fibres or pins. The phage genome is composed of single- or double-strand DNA or RNA, and includes from a few to several hundred kilobases (Clokie et al., 2011; Frost et al., 2005). The bacteriophage genes include lysis, replication, regulation, packaging, structural, antimicrobial resistance, and housekeeping genes. These genes encode various proteins, such as head-tail-joining proteins, head-tail adaptor proteins, host specificity proteins, portal proteins, prohead protease, tail component, tail major proteins, tape measure proteins, large and small terminase subunits, amidase, holing, HNH endonuclease, and DNA primase (Son et al., 2010).

Morphologically, a majority (96%) of phages have tails; mostly a single tail. Other phages are PFP (Ackermann, 2001, 2007). More than half of all tailed phages have long, flexible, non-contractile tails, and they are classified in the *Siphoviridae* family, followed by the *Myoviridae* (long, non-flexible, contractile tails) and *Podoviridae* (long, non-flexible, non-contractile tails) families. Moreover, filamentous phages are classified into three families: *Inoviridae* (unassigned family), *Lipothrixviridae* (order: *Ligamenvirales*), and *Rudiviridae* (order: *Ligamenvirales*) (Ackermann, 2003) found in eubacteria (*Inoviridae*) (Campos et al., 2003) and archaea (*Lipothrixviridae* and *Rudiviridae*) (Geslin et al., 2003). *Inoviridae* are long-tube or short-rod phages with a total length of up to 2 μm, including a circular single-stranded DNA (ssDNA) genome (Klieve et al., 2004). They are broadly distributed in nature, isolated from a variety of bacteria, such as enterobacteria, *Vibrio* spp., *Pseudomonas* spp., *Xanthomonas* spp., *Acholeplasma* spp., *Spiroplasma* spp., and *Enterococcus* spp. (Fauquet and Pringle, 2000). The *Leviviridae* family includes polyhedral phages and contains a linear single-stranded RNA (ssRNA) genome (Vinje et al., 2004). Usually, ssRNA phages are found in mammalian bacteria but not in avian bacteria (Bollback and Huelsenbeck, 2001). The *Leviviridae* family members are small phages with a size of 23–30 nm (Love et al., 2008; Klovins et al., 2002). Another PFP phage, the *Guttaviridae* family, is a droplet-shaped phage. It was introduced by Zillig et al. (1998) and Arnold et al. (2000) in archae, and later by Mazaheri Nezhad Fard et al. (2010) in eubacteria (Liu et al., 2009; Lipps, 2006; Vestergaard et al., 2005). Morphology of the phage shows long thin filaments at one end and a teardrop cell containing a highly methylated circular double-stranded DNA (dsDNA) genome with an approximate size of 20 kb (Sau and Deb, 2008; Prangishvili and Garrett, 2004;

Rice et al., 2001). The *Fuselloviridae* family contains a lemon-shaped phage with peripheral projections and short fibres attached to one pole and a circular, super-coiled dsDNA genome (Kraft et al., 2004; Wiedenheft et al., 2004; Prangishvili et al., 2001). *Fuselloviridae* phages have mostly been isolated from archaea but were first reported in eubacteria by Mazaheri Nezhad Fard et al. in 2010 (Xiang et al., 2005; Rice et al., 2004; Geslin et al., 2003; Stedman et al., 2003).

Ecology

Bacteriophages are important agents in transferring mobile genetic elements (MGEs) to bacteria by transduction. Transduction occurs in three main steps: 1) phage binding to bacterial specific receptors such as surface protein, carbohydrate, or lipopolysaccharide molecule; 2) genome injecting into the bacterial cell; and 3) phage protein synthesis, using bacterial replication machinery (Heineman and Bull, 2007). Bacteria-specific receptors can be located in the outer membrane of Gram-negative bacteria, the cell wall of Gram-positive bacteria, the capsule or slime layer, and in association with flagella or pili (Lindberg, 1973). Blocking each of these steps may result in bacterial resistance to phages (Clokie et al., 2011). Another resistance mechanism includes clustered, regularly interspaced, short palindromic repeats or CRISPR within the bacterial genome (Hegstad et al., 2010). Generally, transduction contributes greatly to indirect horizontal gene transfer (HGT) (Weinbauer, 2004; Weinbauer and Rassoulzadegan, 2004). Furthermore, transduction may help transfer R plasmids between Gram-positive bacteria. Transduction has widely been used in studies on Gram-positive bacteria such as enterococci, streptococci, staphylococci, *Listeria* spp., *Bacillus* spp., and *Lactobacillus* spp. This includes studies in the fields of mutagenesis, packaging, and replicating (Mazaheri Nezhad Fard et al., 2011; Lindsay and Holden, 2006; Chandry et al., 2002; Hodgson, 2000).

Two functional groups of lysogenic and lytic phages have already been described (Drulis-Kawa et al., 2015; Canchaya et al., 2003). Lysogenic phages (also known as temperate or mild phages) infect bacteria and integrate their genome into the host genome, which is called a prophage (Lindsay et al., 2009). Prophages can be found in gammaproteobacteria and low-GC Gram-positive bacteria, and they shift to a lytic phase (Weaver et al., 2009; Brussow et al., 2004). This process or lysogenic induction is mediated by ultraviolet (UVC) or some antibiotics, such as mitomycin C and norfloxacin (Rokney et al., 2008; Aertsen et al., 2005). In bacteria, prophages encode outer membrane proteins (OMPs), pathogenicity islands, and virulence factors such as toxins (e.g. cytotoxic, enterotoxic, and neurotoxic), leukocidins, and superantigens (Stevens et al., 2009; Maiques et al, 2007; Ubeda et al., 2007; Baba et al., 2002; Ruzin et al., 2001). Examples of the common toxins include diphtheria, botulism, pertussis or whooping cough, yersiniosis, spirochetosis, scarlet fever, food poisoning, and verotoxins (Frank et al., 2013; Novick, 2003; Krylov, 2003; Boyd and Brussow, 2002). Examples of other proteins and virulence factors include auxiliary metabolic enzymes, ADP-ribosyltransferase toxins, LPS-modifying enzymes, type III effector proteins, detoxifying enzymes, hydrolytic enzymes, pore-forming lysins, serum resistance-associated proteins, and antibiotic resistance genes.

Applications

Nowadays, many global studies are being carried out on phages by international researchers and there are regional studies by Iranian researchers as well (Sabouri Ghannad et al., 2012; Khajeh Karamoddini et al., 2011a, b). In addition to the broad genetic research on phages, one of the most interesting areas of phage research can be its treatment application. The potential of phage treatment was first suggested by d'Herelle at the Pasteur Institute in Paris (Wittebole et al., 2014). However, the idea of a phage therapy centre was first expressed by the Georgian physician and bacteriologist, George Eliava, who founded the Eliava Institute in Tbilisi in 1923 (www.eliava-institute.org). This was later followed by the foundation of the Institute of Immunology and Experimental Therapy by the Polish immunologist and microbiologist, Ludwik Hirszfeld, in Wroclaw in 1952 (www.iitd.pan.wroc.pl) and Phage Therapy Center in Tbilisi (www.phagetherapycenter.com). In general, phages are used to treat different infections, such as dysentery, salmonellosis, and gastroenteritis, most commonly in East European countries and countries of the former Soviet Union (Sarkar, 2002; Sulakvelidze et al., 2001). They are used to treat skin, mucosa, and wound infections (Taylor et al., 2002; Sulakvelidze et al., 2001). However, phage therapy may include some undesirable disadvantages alongside its life-saving advantages. Some of the advantages include effectiveness against multiple drug resistant (MDR) bacteria, high specificity for target bacteria, no selective resistance, rapid response to resistant mutants, no chemical residues, uncommon side effects (e.g. Jarisch-Herxheimer reaction, toxic shock syndrome), and cheaper development costs. Some of the undesirable disadvantages include low public acceptance, limited accessibility, serum phage neutralization, and bacterial phage resistance. In conclusion, phages are important entities on earth due to their multiple roles in bacterial metabolism and surveillance in nature. However, further studies are needed to explore unknown features of the phages that can improve human lifestyle.

Acknowledgments

I wish to thank Prof. Mary Barton from University of South Australia and A/Prof. Michael Heuzenroeder from University of Adelaide, Australia.

Competing Interests

The authors declare no competing interest.

References

Ackermann, H. W. (2001). "Frequency of morphological phage descriptions in the year 2000." *Archives of Virology*, **146**(5): 843-857.

Ackermann, H. W. (2003). "Bacteriophage observations and evolution." *Research in Microbiology*, **154**(4): 245-251.

Ackermann, H. W. (2007). "5500 Phages examined in the electron microscope." *Archives of Virology*, **152**(2): 227-243.

Aertsen, A., Faster, D. and C. W. Michiels, (2005). "Induction of Shiga toxin-converting prophage in Escherichia coli by high hydrostatic pressure. "*Applied and Environmental Microbiology*, **71**(3): 1155-1162.

Arnold, H. P., Ziese, U. and W. Zillig, (2000). "SNDV, a novel virus of the extremely thermophilic and acidophilic archaeon Sulfolobus." *Virology*, **272**(2): 409-416.

Baba, T., F. Baba, T., Takeuchi, F., Kuroda, M., Yuzawa, H., Aoki, K.I., Oguchi, A., Nagai, Y., Iwama, N., Asano, K., Naimi, T. and H. Kuroda, (2002). "Genome and virulence determinants of high virulence community-acquired MRSA." *The Lancet*, **359**(9320): 1819-1827.

Bleiweis, A. S. and L. N. Zimmerman, (1961). "Formation of two types of osmotically fragile bodies from Streptococcus faecalis var. liquefaciens." *Canadian Journal of Microbiology*, **7**(3): 363-373.

Bollback, J. P. and J. P. Huelsenbeck, (2001). "Phylogeny, genome evolution, and host specificity of single-stranded RNA bacteriophage (family Leviviridae)." *Journal of Molecular Evolution*, **52**(2): 117-128.

Boyd, E. F. and H. Brüssow, (2002). "Common themes among bacteriophage-encoded virulence factors and diversity among the bacteriophages involved." *Trends in Microbiology*, **10**(11): 521-529.

Brock, T. D. (1964). "Host range of certain virulent and temperate bacteriophages attacking group D streptococci." *Journal of Bacteriology*, **88**(1): 165-171.

Brock, T. D., Peacher, B. and D. Pierson, (1963). "Survey of the bacteriocines of enterococci." *Journal of Bacteriology*, **86**(4): 702-707.

Brüssow, H., Canchaya, C. and W. D. Hardt, (2004). "Phages and the evolution of bacterial pathogens: from genomic rearrangements to lysogenic conversion." *Microbiology and Molecular Biology Reviews*, **68**(3): 560-602.

Campos, J., Martínez, E., Suzarte, E., Rodríguez, B. L., Marrero, K., Silva, Y., Ledón, T., del Sol, R. and R. Fando, (2003). "VGJΦ, a novel filamentous phage of Vibrio cholerae, integrates into the same chromosomal site as CTXΦ." *Journal of Bacteriology*, **185**(19): 5685-5696.

Canchaya, C., Fournous, G. and H. Brüssow, (2004). "The impact of prophages on bacterial chromosomes." *Molecular Microbiology*, **53**(1): 9-18.

Canchaya, C., Fournous, G., Chibani-Chennoufi, S., Dillmann, M. L. and H. Brüssow, (2003). "Phage as agents of lateral gene transfer." *Current Opinion in Microbiology*, **6**(4): 417-424.

Chandry, P. S., Moore, S. C., Davidson, B. E. and A. J. Hillier, (2002). "Transduction of concatemeric plasmids containing the cos site of Lactococcus lactis bacteriophage sk1." *FEMS Microbiology Letters*, **216**(1): 85-90.

Clark, P. F. and A. S. Clark, (1927). "A Bacteriophage Active Against a Virulent Hemolytic Streptococcus." *Experimental Biology and Medicine*, **24**(7), 635-639.

Clokie, M. R., Millard, A. D., Letarov, A. V. and S. Heaphy, (2011). "Phages in nature." *Bacteriophage*, **1**(1): 31-45.

d'Hérelle, F. (1917). "Sur un microbe invisible antagoniste des bacilles dysentériques." *Comptes Rendus de l'Académie des Sciences—Series D*, **165:** 373–375.

Drulis-Kawa, Z., Majkowska-Skrobek, G. and B. Maciejewska, (2015). "Bacteriophages and Phage-Derived Proteins–Application Approaches." *Current Medicinal Chemistry*, **22**(14): 1757-1773.

Evans, Alice C. (1934). "The prevalence of Streptococcus bacteriophage." *Science,* **80**: 40-41.

Evans, A. C. (1942). "Technique for the Determination of the Sensitivity of a Strain of Streptococcus to Bacteriophage of Type A, B, C or D." *Journal of Bacteriology*, **44**(2): 207.

Fokine, A. and M. G. Rossmann, (2014). "Molecular architecture of tailed double-stranded DNA phages." *Bacteriophage*, **4**(2): e28281.

Frank J. A., Lorimer, D., Youle, M., Witte, P., Craig, T., Abendroth, J., Rohwer, F., Edwards, R. A., Segall A. M. and A. B. Jr. Burgin, (2013). "Structure and function of a cyanophage-encoded peptide deformylase." *The ISME Journal*, **7**: 1150−60.

Frost, L. S., Leplae, R., Summers A. O. and A. Toussaint, (2005). "Mobile genetic elements: the agents of open source evolution." *Nature,* **3**(9): 722−32.

Geslin, C., Le Romancer, M., Erauso, G., Gaillard, M., Perrot, G. and D. Prieur, (2003). "PAV1, the first virus-like particle isolated from a hyperthermophilic euryarchaeote,"Pyrococcus abyssi"." *Journal of Bacteriology*, **185**(13): 3888-3894.

Hankin, E. H. (1896). "L'action bactericide des eaux de la Jumna et du Gange sur le vibrion du cholera." *Annales de l'Institut Pasteur*, **10:** 511-523.

Hegstad, K., Mikalsen, T., Coque, T. M., Werner, G. and A. Sundsfjord, (2010). "Mobile genetic elements and their contribution to the emergence of antimicrobial resistant *Enterococcus Faecalis* and *Enterococcus Faecium*." *Clinical Microbiology and Infection*, **16**(6): 541-554.

Heineman, R. H. and J. J. Bull, (2007). "Testing optimality with experimental evolution: lysis time in a bacteriophage." *Evolution*, **61**(7), 1695-1709.

Hendrix, R. W. (2002). "Bacteriophages: evolution of the majority." *Theoretical Population Biology*, **61**(4): 471-480.

Hodgson, D. A. (2000). "Generalized transduction of serotype 1/2 and serotype 4b strains of *Listeria Monocytogenes*." *Molecular Microbiology*, **35**(2): 312-323.

ICTV, International Committee on Taxonomy of Viruses (2015). Virus Taxonomy, Available at: http://www.ictvonline.org/virusTaxonomy.asp, (last accessed August 2016).

Khajeh Karamoddini, M., Fazli-Bazzaz, B. S., Emamipour, F., Ghannad, M. S., Jahanshahi, A. R., Saed, N. and A. Sahebkar, (2011). "Antibacterial

efficacy of lytic bacteriophages against antibiotic-resistant *Klebsiella* species." *The Scientific World Journal*, **11:** 1332-1340.

Khajeh Karamoddini, M. (2011a). "Antiviral activities of aerial subsets of Artemisia species against Herpes Simplex virus type 1 (HSV1) in vitro." *Asian Biomedicine*, **5**(1): 63-68.

Kjems, E. (1955). "Studies on streptococcal bacteriophages; I. Techniques of isolating phage-producing strains." *Acta Pathologica Microbiologica Scandinavica*, **36**(5): 433-440.

Klieve, A. V., Bain, P. A., Yokoyama, M. T., Ouwerkerk, D., Forster, R. J. and A. F. Turner, (2004). " Bacteriophages that infect the cellulolytic ruminal bacterium Ruminococcus albus AR67." *Letters in Applied Microbiology*, **38**(4): 333-338.

Klovins, J., Overbeek, G. P., Van den Worm, S. H. E., Ackermann, H. W. and J. Van Duin, (2002). "Nucleotide sequence of a ssRNA phage from Acinetobacter: kinship to coliphages." *Journal of General Virology*, **83**(6): 1523-1533.

Kraft, P., Oeckinghaus, A., Kummel, D., Gauss, G. H., Gilmore, J., Wiedenheft, B., Young, M. and C. M. Lawrence (2004). "Crystal structure of F-93 from Sulfolobus spindle-shaped virus 1, a winged-helix DNA binding protein." *Journal of Virology*, **78**(21): 11544-11550.

Krupovic, M., Dutilh, B. E., Adriaenssens, E. M., Wittmann, J., Vogensen, F. K., Sullivan, M. B., Rumnieks, J., Prangishvili, D., Lavigne, R., Kropinski, A. M. and J. Klumpp, (2016). "Taxonomy of prokaryotic viruses: update from the ICTV bacterial and archaeal viruses subcommittee." *Archives of Virology*, **161**(4): 1095-1099.

Krylov, V. N. (2003). "The role of horizontal gene transfer by bacteriophages in the origin of pathogenic bacteria." *Russian Journal of Genetics*, **39**(5): 483-504.

Lawrence, J. G., Hatfull, G. F. and R. W. Hendrix, (2002). "Imbroglios of viral taxonomy: genetic exchange and failings of phenetic approaches." *Journal of Bacteriology*, **184**(17): 4891-4905.

Lindberg, A. A. (1973). "Bacteriophage receptors." *Annual Reviews in Microbiology*, **27**(1): 205-241.

Lindsay, A. M., Zhang, M., Mitchell, Z., Holden, M. T., Waller, A. S., Sutcliffe, I. C. and G. W. Black, (2009). "The Streptococcus equi prophage-encoded protein SEQ2045 is a hyaluronan-specific hyaluronate lyase that is produced during equine infection." *Microbiology*, **155**(2): 443-449.

Lindsay, J. A. and M. T. Holden, (2006). "Understanding the rise of the superbug: investigation of the evolution and genomic variation of Staphylococcus aureus." *Functional & Integrative Genomics*, **6**(3): 186-201.

Lipps, G. (2006). "Plasmids and viruses of the thermoacidophilic crenarchaeote *Sulfolobus*." *Extremophiles*, **10**(1): 17-28.

Liu, B., Zhou, F., Wu, S., Xu, Y. and X. Zhang, (2009). "Genomic and proteomic characterization of a thermophilic *Geobacillus* bacteriophage GBSV1." *Research in Microbiology*, **160**(2): 166-171.

Love, D. C., Vinje, J., Khalil, S. M., Murphy, J., Lovelace, G. L. and M. D. Sobsey, (2008). "Evaluation of RT-PCR and reverse line blot hybridization for detection and genotyping F+ RNA coliphages from estuarine waters and molluscan shellfish." *Journal of Applied Microbiology*, **104**(4): 1203-1212.

Maiques, E., Ubeda, C., Tormo, M. Á., Ferrer, M. D., Lasa, Í., Novick, R. P. and J. R. Penadés, (2007). "Role of staphylococcal phage and SaPI integrase in intra-and interspecies SaPI transfer." *Journal of Bacteriology*, **189**(15): 5608-5616.

Mathur, S. and R. Singh, (2005). "Antibiotic resistance in food lactic acid bacteria—a review." *International Journal of Food Microbiology*, **105**(3): 281-295.

Mazaheri Nejad Fard, R., Barton, M. D. and M. W. Heuzenroeder, (2010). "Novel bacteriophages in *Enterococcus* spp." *Current Microbiology*, **60**(6): 400-406.

Mazaheri Nezhad Fard, R., Barton, M. D. and M. W. Heuzenroeder, (2011). "Bacteriophage-mediated transduction of antibiotic resistance in *enterococci*." *Letters in Applied Microbiology*, **52**(6): 559-564.

Mihara, T., Nishimura, Y., Shimizu, Y., Nishiyama, H., Yoshikawa, G., Uehara, H., Hingamp, P., Goto, S. and H. Ogata, (2016). "Linking Virus Genomes with Host Taxonomy." *Viruses*, **8**(3): 66. DOI: 10.3390/v8030066.

Nelson, D. (2004). "Phage taxonomy: we agree to disagree." *Journal of Bacteriology*, **186**(21): 7029-7031.

Novick, R. P. (2003). "Mobile genetic elements and bacterial toxinoses: the superantigen-encoding pathogenicity islands of *Staphylococcus Aureus*." *Plasmid*, **49**(2): 93-105.

Pedulla, M. L., Ford, M. E., Houtz, J. M., Karthikeyan, T., Wadsworth, C., Lewis, J. A., Jacobs-Sera, D., Falbo, J., Gross, J., Pannunzio, N. R. and W. Brucker, (2003). "Origins of highly mosaic mycobacteriophage genomes." *Cell*, **113**(2): 171-182.

Prangishvili, D. and R. A. Garrett, (2004). "Exceptionally diverse morphotypes and genomes of crenarchaeal hyperthermophilic viruses." *Biochemical Society Transactions*, **32**(2): 204-208.

Prangishvili, D., Arnold, H. P., Götz, D., Ziese, U., Holz, I., Kristjansson, J. K. and W. Zillig, (1999). "A novel virus family, the *Rudiviridae*: structure, virus-host interactions and genome variability of the *Sulfolobus* viruses SIRV1 and SIRV2." *Genetics*, **152**(4): 1387-1396.

Prangishvili, D., Stedman, K. and W. Zillig, (2001). "Viruses of the extremely thermophilic archaeon *Sulfolobus*." *Trends in Microbiology*, **9**(1): 39-43.

Rakieten, M. L. and E. J. Tiffany, (1938). "The absorption of staphylococcus bacteriophages by *Enterococci*." *Journal of Bacteriology*, **36**(2): 155-173.

Rice, G., Stedman, K., Snyder, J., Wiedenheft, B., Willits, D., Brumfield, S., McDermott, T. and M. J. Young, (2001). "Viruses from extreme thermal environments." *Proceedings of the National Academy of Sciences*, **98**(23): 13341-13345.

Rokney, A., Kobiler, O., Amir, A., Court, D. L., Stavans, J., Adhya, S. and A. B. Oppenheim, (2008). "Host responses influence on the induction of lambda prophage." *Molecular Microbiology*, **68**(1): 29-36.

Ruzin, A., Lindsay, J. and R. P. Novick, (2001). "Molecular genetics of SaPI1–a mobile pathogenicity island in *Staphylococcus Aureus*." *Molecular Microbiology*, **41**(2): 365-377.

Sabouri Ghannad, M., Majzoobi, M. M., Ghavimi, M. and M. Mirzaei, (2012). "Needlestick and sharp object injuries among health care workers in Hamadan Province, Iran." *Journal of Emergency Nursing*, **38**(2): 171-175.

Sarkar, B. L. (2002). "Cholera bacteriophages revisited." *ICMR Bull*, **32**: 33-7.

Sau, K. and A. Deb, (2009). "Temperature influences synonymous codon and amino acid usage biases in the phages infecting extremely thermophilic prokaryotes." *In Silico Biology*, **9**(1, 2): 1-9.

Serwer, P., Hayes, S. J., Thomas, J. A., Griess, G. A. and S. C. Hardies, (2007). "Rapid determination of genomic DNA length for new bacteriophages." *Electrophoresis*, **28**(12): 1896-1902.

Son, J. S., Jun, S. Y., Kim, E. B., Park, J. E., Paik, H. R., Yoon, S. J., Kang, S. H. and Y. J. Choi, (2010). "Complete genome sequence of a newly isolated lytic bacteriophage, EFAP-1 of *Enterococcus Faecalis*, and antibacterial activity of its endolysin EFAL-1." *Journal of Applied Microbiology*, **108**(5): 1769-1779.

Stedman, K. M., She, Q., Phan, H., Arnold, H. P., Holz, I., Garrett, R. A. and W. Zillig, (2003). "Relationships between fuselloviruses infecting the extremely thermophilic archaeon *Sulfolobus*: SSV1 and SSV2." *Research in Microbiology*, **154**(4): 295-302.

Stevens, R. H., Porras, O. D. and A. L. Delisle, (2009). "Bacteriophages induced from lysogenic root canal isolates of *Enterococcus Faecalis*." *Oral Microbiology and Immunology*, **24**(4): 278-284.

Sulakvelidze, A., Alavidze, Z. and J. G. Morris, (2001). "Bacteriophage therapy." *Antimicrobial Agents and Chemotherapy*, **45**(3): 649-659.

Taylor, P. W., Stapleton, P. D. and J. P. Luzio, (2002). "New ways to treat bacterial infections." *Drug Discovery Today*, **7**(21): 1086-1091.

Tiffany, E. J. and M. L. Rakieten, (1939). "The Absorption of Bacteriophage by Sensitized *Enterococci*." *Journal of Bacteriology*, **37**(3): 333.

Turton, J. F., Perry, C. and M. J. Hannah, (2012). "Isolation of Bacteriophage against Currently Circulating Strains of *Acinetobacter Baumannii*." *Journal of Medical Microbiology & Diagnosis*, **1**:109. DOI:10.4172/2161-0703.1000109.

Ubeda, C., Barry, P., Penadés, J. R. and R. P. Novick, (2007). "A pathogenicity island replicon in *Staphylococcus aureus* replicates as an unstable plasmid." *Proceedings of the National Academy of Sciences*, **104**(36): 14182-14188.

Ventura, M., Canchaya, C., Tauch, A., Chandra, G., Fitzgerald, G. F., Chater, K. F. and D. van Sinderen, (2007). "Genomics of *Actinobacteria*: tracing the evolutionary history of an ancient phylum." *Microbiology and Molecular Biology Reviews*, **71**(3): 495-548.

Vestergaard, G., Häring, M., Peng, X., Rachel, R., Garrett, R. A. and D. Prangishvili, (2005). "A novel rudivirus, ARV1, of the hyperthermophilic archaeal genus *Acidianus*." *Virology*, **336**(1): 83-92.

Vinjé, J., Oudejans, S. J., Stewart, J. R., Sobsey, M. D. and S. C. Long, (2004). " Molecular detection and genotyping of male-specific coliphages by reverse transcription-PCR and reverse line blot hybridization." *Applied and Environmental Microbiology*, **70**(10): 5996-6004.

Weaver, K. E., Kwong, S. M., Firth, N. and M. V. Francia, (2009). "The RepA_N replicons of Gram-positive bacteria: a family of broadly distributed but narrow host range plasmids." *Plasmid*, **61**(2): 94-109.

Weinbauer, M. G. and F. Rassoulzadegan, (2004). "Are viruses driving microbial diversification and diversity?." *Environmental Microbiology*, **6**(1): 1-11.

Weinbauer, M. G. (2004). "Ecology of prokaryotic viruses." *FEMS Microbiology Reviews*, **28**(2): 127-181.

Wiedenheft, B., Stedman, K., Roberto, F., Willits, D., Gleske, A.K., Zoeller, L., Snyder, J., Douglas, T. and M. Young, (2004). "Comparative genomic analysis of hyperthermophilic archaeal *Fuselloviridae* viruses." *Journal of Virology*, **78**(4): 1954-1961.

Wittebole, X., De Roock, S. and S. M. Opal, (2014). "A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens." *Virulence*, **5**(1): 226-235.

Xiang, X., Chen, L., Huang, X., Luo, Y., She, Q. and L. Huang, (2005). "*Sulfolobus Tengchongensis* spindle-shaped virus STSV1: virus-host interactions and genomic features." *Journal of Virology*, **79**(14): 8677-8686.

Yap, M. L. and M. G. Rossmann, (2014). "Structure and function of bacteriophage T4." *Future Microbiology*, **9**(12): 1319-1327.

Zillig, W., Arnold, H. P., Holz, I., Prangishvili, D., Schweier, A., Stedman, K., She, Q., Phan, H., Garrett, R. and J. K. Kristjansson, (1998). "Genetic elements in the extremely thermophilic archaeon *Sulfolobus*." *Extremophiles*, **2**(3): 131-140.