Classification and identification of bacteriophage receptors

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The chapter presents a retrospective survey of bacterial virus receptors classification concepts, current state-of-the art of the nature and structure of host receptors, and overview of related problems and possible solution pathways. This review is mainly focused on structures governing phage recognition of host cell and mechanisms of phage adsorption and penetration into microbial cell.

Keywords: bacteriophage receptors; classification and identification; application; phage adsorption

1. Introduction: Presence of phage receptors on the surface of bacterial cells

Bacteriophages are represented by viral particles specifically infecting bacterial species. These infectious agents are widely distributed in nature. Total viral abundance across aquatic systems typically varies within the range of 10^4 to 10^8 virions per ml and tends to rise with the increased productivity of the system. The number of phages ranges from 0.65 to 2.9×10^9 virions per g in freshwater sediments and from 0.03 to 11.71×10^9 virions per g in marine systems. Total phage abundance in the soil constitutes about 1.5×10^8 viral particles per g [1].

Bacteriophages were discovered in 1915 and 1917 independently by Frederick Twort and Felix d'Herelle, respectively [2, 3]. However, real or presumptive "bacteriophage" references have been described approximately 20 years prior to the actual discovery of bacterial viruses [4]. Since that moment, bacterial viruses have been considered as potential antimicrobial drugs. Nevertheless, debatable therapeutic results, lack of knowledge on basic phage biology, the discovery and the convenience of antibiotics led to decreased medical interest in bacterial viruses. Studies and application of bacteriophages continued in the eastern countries, mostly at the territory of Poland and Georgia. The emergence and spread of antibiotic-resistant bacteria in the latest decades triggered the search of alternative ways of fighting pathogenic microorganisms, such as the use of bacteriophages [5].

Life cycle of bacteriophages includes several stages: attachment to surface of the host cell and injection of nucleic acid, reorientation of cell metabolism, synthesis of virion components, assembly of viral particles and release of formed phages with lysis of the infected cell. Virulent phages pass through all these steps (lytic cycle), while temperate phages are distinguished by additional stage - integration of nucleic acid into the host genome (lysogenic cycle). In the latter case when cell divides, prophage DNA is also transferred on to daughter cells. Some phages display chronic infection lifestyle characterized by release of virions over long intervals without substantial disruption of host cells. Chronic viruses could be of both virulent and temperate types [6].

Adsorption is the initial and crucial step in phage infection. The susceptibility of bacteria to bacteriophages is primarily dependent on presence of specific attachment sites, or receptors. Bacterial viruses are able to target various receptors of different chemical nature on the cell surface. Many phages need one specific kind of molecule present in high concentration to be properly positioned for surface penetration. However, some phages make use of receptor present in a few copies per cell or recognize multiple receptors. Adsorption rate and efficiency depend on external factors and host physiological state. Phages may require specific cofactors for attachment to receptors. Their loss or alteration lead to appearance of bacterial resistance to certain virus, but provide no protection against other kinds of phages using different attachment sites. The molecules serving as receptors could be crucial to the bacterial cell, so that their loss can affect important functions and diminish bacterial competitive ability [7].

2. Current classification of bacteriophage receptors: Protein and lipopolysaccharide receptors

Phage infection begins with viral attachment to a specific receptor. Bacteriophages have been shown to bind to receptors in various locations of cell surface. The following structures could be used as attachment sites for virus: cell wall, flagella, pili/fimbriae or capsule.

Composition of cell wall in Gram-positive and Gram-negative bacteria significantly differs, so that phages attach to completely different sites of envelope. Cell wall of Gram-positive bacteria is represented by a thick layer mostly consisting of peptidoglycan, or murein. This polymer is composed of amino acids and sugar derivatives. The latter are connected through glycosidic bonds, forming glycan tetrapeptide sheets cross-linking by amino acids. Teichoic acids are other main components of cell wall of Gram-positive bacteria. These polymers contain glycerol phosphate or ribitol phosphate and amino acids. Peptidoglycan and teichoic acids often serve as receptors for Gram-positive bacteria,

although protein receptors also have been described. However, phage attachments sites in cell wall of Gram-negative bacteria are better studied due to complexity of cell walls of Gram-positive bacteria [8, 9].

In contrast, Gram-negative bacteria include a thin peptidoglycan layer and additional outer membrane. The latter is composed of lipopolysaccharides (LPS), proteins, and phospholipids. Proteins localized in membrane and LPS sites can be used as receptors for bacteriophages. Usually LPS have three domains: a lipophilic moiety termed lipid A, a hydrophilic glycan called O-specific polysaccharide (O-chain or O-antigen), and a joining core oligosaccharide (OS). The latter can be separated into two regions, one proximal to lipid A (inner core OS), and proximal to O-antigen (outer core OS). LPS possessing all three domains are called "smooth" LPS. The lack of O-chain and/or portions of core OS is typical for "rough" LPS. Depending on the region of adsorption, phages can demonstrate a narrow or a broad host range. Because of a more conservative nature of OS, phages recognizing this region are able to infect more bacterial hosts, while O-antigen shows a large variability, hence phages attaching to it are limited in host range. In turn, proteins of outer membrane can be divided into five groups: 1) structural proteins interacting with peptidoglycan layer; 2) porins forming membrane channels; 3) enzymes; 4) substrate receptors with high affinity; 5) transport proteins [8, 10, 11].

3. Receptors localized in cell wall of bacteria

As mentioned above, composition of cell wall of Gram-positive and Gram-negative bacteria is different, so that their bacteriophages recognize and attach to quite varied receptors on cell surface. *Salmonella* phage g341 adsorbs to bacteria containing mannosyl-rhamnosyl-O-acetylgalactose repeating sequence in LPS. The virus isn't able to attach to mutant or lysogenic bacteria with altered LPS. The phage baseplate deacetylase takes part in adsorption via the formation of enzyme-substrate complex with the receptor [12]. Temperate *Salmonella* phage ε15 changes receptor D-Mannosyl-β1→4-L-Rhamnosyl-α1→3-D-O-Acetyl-Galactose repeat units joined together by α1→6 glycosidic linkages, with a non-acetylated polymer of the same repeat unit held together by β1→6 glycosidic bonds. The phage blocks the activity of the host cell O-polysaccharide alpha polymerase enzyme, replacing it with O-polysaccharide beta polymerase enzyme and thereby inhibiting acetylation of galactose residues [13, 14]. Phage 2 receptors in LPS of *Pseudomonas aeruginosa* strain BI contain L-rhamnose, D-glucosamine, and D-glucose, or a structurally related molecule. Either one of the latter two could be located at a terminal position alpha-linked to the adjacent residue, or located internally in the polysaccharide chain linked through its C-4 position [15]. Temperate phage D3 is able to convert side chain of *P. aeruginosa* PAO1 LPS. The virus introduces acetyl group into position 4 of the fucosamine residue and changes the bonding between trisaccharide repeating units from α1→4 to β1→4 [16]. The terminal galactose in LPS core of *E. coli* C takes part in phage øX174 adsorption. The loss of this monosaccharide leads to bacterial resistance, while loss of the branch heptose or glucose does not produce the same effect [17]. Phage NM8 recognizes *Rhizobium meliloti* M11S cells via specific attachment to the sialic acids of LPS, wherein acetyl groups play a major role [18]. G segment in phage Mu DNA is a genetic element controlling gene expression by DNA rearrangement. This segment is capable of inversion which leads to appearance of two types of viral particles recognizing quite different bacteria. Mu G(+) type infects *E. coli*, while Mu G(-) virions affect such bacteria as *Enterobacter cloacae*, *Citrobacter freundii*, *Serratia marcescens* and *Erwinia carotovora*. Two phage types recognize different cell wall receptors, which in both cases are located in LPS [19]. Mu phage particles differ in the type of glycosidic linkage of a terminal glucose residue: αl,2 for G(+) and βl,6 for G(-) [20].

The LamB protein is a well-characterized porin taking part in maltose transport and serving as a receptor for several phages, like λ, K10 and TP1. The porin consists of 3 identical subunits formed by 18-stranded antiparallel β-barrel, which constitute a wide channel with a diameter of about 2.5 nm. Loops are found at the end of the barrel. Studies demonstrated that only about half of the phage λ resistant *E. coli* variants are surface exposed mutants. The remaining mutations might have indirect effect by inducing structural change on the surface or the dynamic behavior of the loops [21]. Protein FhuA (earlier TonA) is an *Escherichia coli* outer membrane protein transporting the ferric siderophore ferrichrome. Similar to the porin proteins, FhuA consists of a β barrel, but additionally contains a plug which fills the lumen of the barrel. The plug is a globular N-terminal domain that enters the β barrel from the periplasmic side and tightly closes the pore in the β barrel. The β barrel extends well above the lipid bilayer. Phages T1, T5, φ80, and UC-1 use this protein as a receptor. Studies with phage T5 resulted in the following scenario of cell infection. Phage T5 binds reversibly using pb1 of the L-shaped tail fibers to the polymannose O antigen. Protein pb2 of the straight tail fiber contacts and is inserted into the bacterial surface until pb5 contacts FhuA, which triggers the release of DNA from the phage head. DNA passes through a channel formed by pb2 across the outer membrane, the periplasm, and the cytoplasmic membrane [22]. Infection by phage T5 occurs independently of TonB, ExbB and ExbD, compared to other phages attaching to FhuA [23]. Phage H8 is similar in morphology and genomic structure to T5 and is able to infect *Salmonella, E. coli*, *Shigella*, *Citrobacter*, and *Serratia* species. The phage adsorbs to the outer membrane protein FepA and requires TonB for infection. Receptor-phage interaction first involves residues distributed over outer surface of FepA and then narrows to the charged or aromatic residues that participate in the binding and transport of ferric enterobactin and colicins B and D [24]. Outer membrane protein Tsx of *E. coli* is engaged in transport of nucleosides and serves as T6 receptor [25]. Deletion of 8 amino acids between residues 198 and 207 of Tsx in *E. coli* results in phage resistance, but protein is still functioning as colicin K receptor and as a substrate-specific channel [26]. Two

membrane proteins, BactA and BactB, with molecular weights of 65±5 kDa and 35±5 kDa and unidentified functions, are involved in the adsorption of bacteriophage B40-8 to the surface of *Bacteroides fragilis* [27].

Bacterial viruses can utilize both types of receptors for attachment. Phage T4 of *E. coli* is adsorbed using six long and six short tail fibres. The long tail fibres recognize the outer membrane protein C (OmpC) or LPS and take part in the initial reversible attachment of the virion, while short tail fibres extend and bind irreversibly to the core region of LPS, serving as inextensible stays during penetration of the tail tube the into cell envelope [28]. The above-mentioned phage T5 uses LPS as initial receptor [22]. Phage Ox2 (*E. coli* and *Salmonella typhimurium*) requires, in addition to the OmpA protein, a certain type of rough LPS. However, isolated OmpA protein could bind the phage without supply of LPS. It is presumed that LPS might change the conformation of the OmpA protein, reduce the amount of porin proteins in the outer membrane or probably cause other disturbances of protein integrity [29]. Single mutations in a gene encoding a tail fiber component (protein 38) of phage Ox2 provoked alteration of attachment sites. Studied phage Ox2 recognized the outer membrane protein OmpA as a receptor, while its mutants utilize other outer membrane proteins or shift attachment site to LPS [30]. Both bacteriophages TLS (*E. coli*) and VP3 (*Vibrio cholerae*) depend on outer membrane protein TolC and core oligosaccharide for development of viral infection [31, 32]. Bacteriophage TuIb also requires LPS in addition to the OmpC as receptor components [33]. This phage is able to adapt to other outer membrane proteins via mutation [34]. Phage T4 usually demands both LPS and protein OmpC for *E. coli* infection. Glucose residue of LPS is masked by an additional sugar chain preventing its interaction with the tail fiber of T4. OmpC may interact with LPS to overcome this prevention. However, the research demonstrated that glucose residue is not essential for receptor activity when OmpC protein is present. It is likely that OmpC protein and the glucose residue of LPS can replace each other [35]. Phage Yep-phi specific to *Yersinia pestis*, in addition to the rough LPS, uses outer membrane proteins Ail and OmpF for attachment [36].

In some cases receptors are enzymatically degraded by phage particles during the normal process of infection. O-polysaccharide of *Salmonella johannesburg* 5.58 (R^-) is the receptor for phage φ 1 (40) and is enzymatically degraded via endo-N-acetylgalactosaminidase activity of phage particles. The end groups generated by this cleavage are N-acetyl-D-galactosamines [37]. Coliphage Ω8 enzymatically degrades the polysaccharide moiety of *E. coli* O8 : K^- LPS. The products of the action are oligosaccharides represented by the trisaccharide repeating unit α-mannosyl-1,2-α-mannosyl-l,2-mannose and multiples of it. The virus also splits the LPS of *E. coli* O93 and *Klebsiella* O5 in the same way [38]. Phage ε34 of *Salmonella newington* cleaves its receptor represented by O polysaccharide. It consists of mannosyl-rhamnosyl-galactose repeating units joined together by β-galactosyl linkages. Generated end-group was galactose, indicating the cleavage was caused by the specific breakage of β-galactosyl l-6 mannose linkages [39].

Phage J-I needs both L-rhamnose in the cell wall and D-galactosamine in the cytoplasmic membrane as the receptor material for infection of *Lactobacillus casei* s-I [40]. The polysaccharide located outside the peptidoglycan layer in *Lb. casei* was found to inhibit the adsorption of PL-1 phage. Further research demonstrated that L-rhamnosyl residues are the main determinants of PL-1 phage receptor sites, while D-glucosyl residues may be involved indirectly [41]. In some case, receptors in cell wall could be hidden. *Lactococcus lactis* subsp. *cremoris* SK112 is sensitive to phage Sk11G, while the strain of the same species SK110 is resistant to the virus due to galactose-containing component from the cell wall [42]. Broad-host-range virulent phage A511 uses the listerial peptidoglycan as a primary receptor [43]. The adsorption of phages CYM (*Streptococcus thermophilus* YSD10) and 0BJ (*S. thermophilus* BJ15) to cell walls is a fast process, mediated by receptors of carbohydrate nature. It was demonstrated that glucosamine and rhamnose influenced CYM infection, while glucosamine and ribose interfered with the adsorption of phage 0BJ [44].

Pre-incubation with lectin Concanavalin A decreases adsorption of bacteriophage K to *Staphylococcus aureus* 3528 and SP-50 to *Bacillus subtilis* 3610. Lectin interacts with α-N-acetyl-glucosaminyl substituents of the cell wall teichoic acid, but exerts no effect on adsorption of phages to microorganisms with the substituents of β-configuration [45]. Temperate phage A118 uses teichoic acids in general and rhamnose and glucosamine in particular for adsorption to *Listeria monocytogenes* serovars 1/2. Phage A500 predominantly lysing *L. monocytogenes* serovars 4b is also dependent on cell wall teichoic acids [43. The surface glucose-substituted lipoteichoic acids are required for the specific reversible adsorption as well as free, non-substituted glycerol residues for the irreversible adsorption of wild-type phage LL-H to *Lactobacillus delbrueckii* ssp. *lactis*. In turn, mutant LL-H uses both surface glucose-substituted and glucose-free lipoteichoic acids as the receptors [46]. Phage Dp-1 of *Streptococcus pneumoniae* chooses choline residues of the teichoic acid as attachment sites [47]. Siphoviruses (ϕ47, ϕSa2mw, ϕ13, ϕ77) and myoviruses (ϕK, ϕ812) of *S. aureus* prefer wall teichoic acid rather than lipoteichoic acid as the receptors. Siphoviruses need the N-acetylglucosamine on wall teichoic acid for adsorption, while myoviruses seem to adsorb to its backbone [48].

S-layer, or surface layer, is the component of the cell envelope identified in different species of almost every taxonomic group of bacteria. S-layer proteins account for approximately ten percent of cellular proteins and can act as receptors. *Lactobacillus helveticus* CNRZ 892 strain is covered by the protein of S-layer type. The central region of the protein plays a role of receptor for the virulent phage CNRZ 832-B1 [49].

Both protein and carbohydrate are essential to promote receptor activity of *Streptococcus faecium* phage during P3 infection [50]. Further research of lactococcal bacteriophages c2, m13, kh, 1, h, 5, and 13 demonstrated that viruses initially adsorbed to cell wall carbohydrate and subsequently to cell membrane protein PIP, which provoked ejection of

the phage genome [51]. Bacteriophage SPP1 reversibly binds to glucosylated poly(glycerolphosphate) cell wall teichoic acids of *B. subtilis*. This interaction strongly accelerates irreversible binding to main receptor YueB [52].

4. Capsular polysaccharides, pili, fimbriae and flagella as potential phage receptors

Besides cell wall, phages are able to recruit other cell structures as attachment sites. Pili, or fimbriae, are appendages on cell surface engaged in biofilm formation, phage transduction, DNA uptake and a special form of bacterial cell movement, known as "twitching motility". Names "pili" and "fimbriae" are usually synonymous, but in some case "pili" is used in regard to bacterial conjugation. The pili of Gram-negative bacteria can be divided into four distinct groups based on their assembly pathways: a) pili assembled by the chaperone-usher pathway; b) the Type IV pili; c) pili assembled by the extracellular nucleation/precipitation pathway (curli pili); and d) pili assembled by the alternative chaperone-usher pathway (CS1 pilus family). Pili of Gram-positive bacteria are less studied compared to the other group. Two types of pili in Gram-positive bacteria were identified by electron microscopy: short, thin rods extending 70 to 500 nm in length, 1–2 nm in diameter and much longer flexible pili (0.3 – 3 mm) with diameter of 3–10 nm. Type IV pilus structure conferring gliding motility was also found in Gram-positive bacteria [53].

Type IV pili are among the *P. aeruginosa* surface molecules that function as phage receptors. Phages PO4 [54], PP7 [55], Pf [56], F116 [57], D3112 [58], DMS3 [59], B3 [60] and ϕKMV [61] use this type of pili as an attachment site. Some strains of *P. aeruginosa* express type IV pilin glycosylated with either lipopolysaccharide O-antigen units or polymers of D-arabinofuranose and blocking phage infection. Phages DMS3 and JBD68 are able to partially overcome specific forms of pilus glycosylation [62]. Siphophages Sano and Salvo and podophages Prado and Paz use type IV pili for infection of both *Xylella fastidiosa* and *Xanthomonas* species [63]. Bacteriophage Pf3 infects *P. aeruginosa* strain O via the conjugative pilus [64]. Phages MS-2 and f1 use F pili found in male strains of *E. coli* as the receptors, but they have completely different attachment sites. RNA phage MS-2 adsorbs laterally along the entire length of the pilus, while DNA virus f1 is attached to one of the two free ends of F pilus fragment [65]. RNA phage f2 of *E. coli* blocks the penetration of DNA phage fI into host cell. Lumen of the pilus is used by both fI and f2 for nucleic acid transport [66]. The average number of F pili with attached fl decreases as phage DNA enters the cell. Concomitant with this loss, the remaining F pili become shorter [67]. Reduction in pilus length has been observed for other bacterial species [68]. Phage R17 attaches to F pili of *E. coli* via A protein leading to the cleavage of this protein into two smaller components that are transferred into the cell along with the phage RNA [69].

Flagella are appendages involved in cell motility. The flagellum has three parts: the basal body, the hook and the filament. The basal body is embedded within the cell membranes and acts as a rotary motor. The hook and filament extend outwards in the cell exterior. The filament works as a helical propeller. The hook connects the basal body and filament and functions as a universal joint to smoothly transmit torque produced by the motor to the filament [70]. Phage WOT8 is flagellum-dependent and able to infect both *Serratia* and *Pantoea* species [71]. Phage PV22 from *Proteus vulgaris* has been shown to interact with *Campylobacter jejuni* by attachment to flagella followed by translocation of the phage to the polar region of the bacterium up to the point of DNA injection. However, the phage failed to inject its DNA into *C. jejuni*. Nevertheless, adsorption of the phage could influence bacterial replication since the cultures had retarded growth within the areas of phage application [72]. *Salmonella* phage χ attaches to the filament of a bacterial flagellum, but its injection site is located at the base of the flagellum. The virus slides along the filament of the flagellum to the base, owing to the movement of the flagellum [73]. Two phages of *Asticcacaulis biprosthecum* (ϕAcS_2 and ϕAcM_4) attach to flagella at the region where head and tail of the phage are joined, while the distal end of the tail is free for adsorption to receptor sites at the cell surface [74]. Phage iEPS5 could infect *Salmonella enterica* only when the flagellum was rotating counterclockwise. The phage can inject its DNA through the flagellar filaments into the bacteria [75]. *Vibrio parahaemolyticus* possesses both polar and lateral flagella. Deletion of polar flagella, but not the lateral ones, can dramatically promote the adsorption of phage to the bacteria and enhance the phage infectivity. The rotation itself, not the physical presence, of polar flagella reduces the adsorption to the bacterial cells [76]. Flagella are used for adsorption by phages χ (genera *Escherichia*, *Salmonella*, and *Serratia*) [77], F341 (*C. jejuni*) [78], SSP002 (*Vibrio vulnificus*) [79], PBS1 (*B. subtilis*) [80], GS2 and GS6 (*Agrobacterium tumefaciens*) [81], ϕCp34 (*Caulobacter crescentus* and *Caulobacter vibrioides*) [82], ϕAT1 (*Erwinia carotovora* ssp. *atroseptica*) [83], 7-7-1 (*Rhizobium lupini*) [84], PM3 (*Aeromonas hydrophila*) [85], etc.

The capsules look like a viscous substance covering cell envelope. They usually consist of polysaccharides and can be found in both Gram-negative and Gram-positive bacteria. Capsules also act as receptors for bacteriophages. A set of seven bacteriophages targets the Vi capsular antigen of *S. enterica* serovar Typhi. These phages are genetically and morphologically diverse, however, they all share a domain linked to the tail spike which is required for recognition and deacetylation of the Vi exopolysaccharide [86]. Both phages K1E and K1-5 penetrate the capsule and infect *E. coli* K1, using a specific glycosidase. K1-5 additionally carries a second enzyme allowing to infect *E. coli* K5 with capsule chemically different from that of K1 [87]. Bacteriophage F336 demands O-methyl phosphoramidate moiety attached to the 2-acetamido-2-deoxy-β-D-galactofuranose of the capsular polysaccharide for efficient *Campylobacter jejuni* infection [88]. Phage K29 initially adsorbs on the capsule and then paves its way to outer membrane of *E. coli*. A virus particle reaching the outer membrane might subsequently move along the surface of the cell or turn back into the

capsule [89]. The capsular phage 29 of *E. coli* catalyzes the hydrolysis of β-D-glucosido-(1-3)-D-glucuronic acid bonds in the receptor polymer. Virus glucanase subunits move along the polymer strands and the cleavage of glycosidic bonds opens a path for the phage head and provides the energy for the movement to the host surface [90]. Two *Klebsiella* bacteriophages, K5-2 and K5-4, are able to infect and grow on capsular types K30, K69 and K5 or K8 and K5 strains. Each phage encodes two different capsule depolymerases. One is a putative tail fiber protein that allows the phage to attach and degrade either the K30/K69 or K8 capsular polysaccharide. The other protein allows to adsorb and degrade the K5 capsular polysaccharide. Capsule K5 deletion mutants were not lysed by either phage, suggesting that the capsule was essential for phage infection [91].

Bacterial plasma membrane is covered by cell wall and cannot be used as a primary receptor for phage attachment. However, it still may take part in phage infection. Phage-resistant mutants of *Lactococcus lactis* subsp. *lactis* C2 infected with phage c2 did not form plaques but bound the virus normally. Carbohydrate analyses of cell walls revealed no significant differences in saccharide composition between the wild-type and phage-resistant strains, but interactions of the phage with the cytoplasmic membranes were diverse [92]. The above-mentioned studies of lactococcal bacteriophages c2, m13, kh, 1, h, 5, and 13 showed that these viruses demand cell membrane protein PIP [51]. Spheroplasts (cells with removed cell wall) of the genera *Escherichia*, *Salmonella*, *Aerobacter*, *Proteus*, and *Serratia* can be infected by T4 phage exposed to urea. The interaction between the phage and the bacteria does not require either phage tail fibers or the specific receptors of the bacteria [93] Further research demonstrated that exposed phage T4 may be inactivated by cell membrane preparations [94].

5. Significance of bacteriophage receptors governing phage recognition of host cell.

Adsorption to specific receptor is the initial and crucial step in development of phage infection. The lack, modification or hiding of the receptor lead to appearance of cell resistance to certain bacterial viruses. However, even in this case cell remains susceptible to other phages and viruses themselves are able to adapt and overcome adsorption inhibition. Phages use various surface structures as attachment sites. Receptors of Gram-negative bacteria are more thoroughly studied as compared to the other bacterial group. Nevertheless, the data on structure, mechanisms and interactions of phage receptors are piling up due to ongoing research.

The studies of bacteriophage receptors and the viral adsorption mechanisms are indispensable in many areas. The research of phage-host interactions allows to minimize negative influence of the phage on beneficial bacteria generating valuable compounds and improve quality and yield of products in biotechnology. On the other hand, the gained knowledge may find use in medicine and food industry to control pathogenic microorganisms, so that the detailed information concerning biology of phages and their hosts is required.

6. Mechanisms of phage adsorption and penetration into microbial cell

Bacteriophage adsorption determines the following progress of infection. The attachment to specific receptor depends on many characteristics, like physical-chemical factors (temperature, pH, presence of ions and certain compounds), and the physiology of the host cell. The adsorption includes two steps: reversible binding to cell surface and irreversible attachment followed by penetration of viral nucleic acid in host cell.

The tailed phages represent the most numerous and well-studied group of bacterial viruses [95]. Thus, many known mechanisms, kinetics and phage-cell interaction primarily concern these bacteriophages. Adsorption kinetics of bacteriophage binding can be described by relatively simple equations governed by the laws of mass-action. Despite multiple changes and modifications of equations like consideration of presence of defective phage particles, there is no universal method of kinetic description. In each case physical-chemical properties, host cell condition and adsorption mechanism can provide accurate prediction of binding dynamics [96].

T7, member of the *Podoviridae* infecting *E. coli*, is icosahedral phage with short, noncontractile tail and six fibers. Each fiber has an N-terminal domain that attaches the fiber to the tail, followed by proximal and distal half-fibers. The latter interact with the cell surface. Inside phage, 40-kb genome and internal core, consisting of three proteins, are located. The core is essential for both virion morphogenesis and ejection of the genome. Tail fibers of T7 could be in free and capsid-bound state. After initial reversible binding T7 particle “walks” on the cell surface via fiber detachment and binding to the cell. After finding the certain receptor for the tail, all fibers rotate downward to contact the outer membrane. Internal core proteins are injected into the cell envelope and the extended tail is formed, creating trans-envelope channel used for DNA transport [97]. Podophage P22 of *Salmonella* binds to LPS O-polysaccharide via 6 trimeric tailspike proteins. The phage particle descends towards the outer membrane surface, cleaving O-antigen by tailspike proteins until encountering a barrier made of LPS core and lipid A regions. Then plug protein gp26 extending from the bottom of the tail structure penetrates the core structure and undergoes conformational change. Together, tailspike proteins and gp26 are suggested to serve as a surface pressure sensor to initiate DNA release [98]. Phage Ø29 is characterized by two steps of DNA penetration. At the first step about 65% of the genome is pumped into the cell by the pressure built up inside the viral capsid. It allows to synthesize viral proteins from the right early operon. At the

second step at least one of the viral early proteins participates in the molecular machinery that pulls the remaining DNA inside the cell [99].

Phage p2 of *L. lactis* from family *Siphoviridae* bears icosahedral capsid connected to a long noncontractile tail. Tail tip carries the baseplate, comprising receptor-binding protein (RBP). Its primary role is recognition of specific host receptor. Tail tube adhesion domains interact with host cell wall to maintain the phage close to its target. Then the external RBP sites in the nonactivated conformation may scan the surface in search of specific pellicle phosphohexasaccharide motifs. If the number of specific binding events is large enough and Ca^{2+} is available, the mechanical pull induced by this binding may destabilize the rest conformation of the baseplate and disrupt the interaction between the second distal tail protein (another part of baseplate) and RBP head domain. The RBP undergoes a 200° downward rotation to orient their 18 saccharide binding sites toward the host surface, concomitantly with the opening of tail-associated lysin to form a central channel. It allows to eject the tape measure protein from the tail tube followed by genome release from the capsid, which passes through the tail tube and enters the cytoplasm [100]. The *Siphoviridae* coliphage T5 carries 250-nm tail phage ends with three L-shaped fibres attached to a conical baseplate and a straight central fibre [101]. As mentioned in previous chapters, T5 infection begins with reversible binding by pb1 of the L-shaped tail fibers to the LPS, then pb2 of the straight tail fiber is inserted into the bacterial surface until pb5 contacts FhuA [22]. Upon binding to FhuA, pb5 undergoes conformational changes, at the secondary and tertiary structural level, leading to the transmission of the signal through the tail to the capsid and triggering DNA release into cell [102]. Phage SPP1 infection of *B. subtilis* begins with reversible adsorption to glucosylated cell wall teichoic acids culminating in irreversible binding to YueB. This interaction results in a very fast depolarization of the cytoplasmic membrane, opening a transmembrane channel followed by DNA injection. Sub-millimolar concentrations of Ca^{2+} are necessary and sufficient for SPP1 reversible binding to the host envelope and membrane depolarization, while DNA delivery to the cytoplasm depends on millimolar concentrations of this divalent cation [103]. Phage LL-H uses lipoteichoic acids as the receptor. Binding of the virus arranges its tail fibers into ring conformation attached to the end of the tail base and releases tape measure protein homolog with peptidoglycan activity in restricted area. This homolog produces additional space for creation of the stable Ca-lipoteichoic acid channel between the end of the tail base and the cytoplasmic membrane. The channel provides a gateway for other proteins to interact with the cytoplasmic membrane and further as a guide for phage DNA [46].

Bacteriophage T4 and related viruses from family *Myoviridae* are characterized by availability of contractile tail as compared to other tailed phages. The tail of T4 consists of the tail tube surrounded by a helical sheath. Both tube and sheath are attached to the dome-shaped baseplate at the end distant from the head. Six long tail fibers are attached to the periphery of the baseplate, while the six short tail fibers are folded beneath this structure. Infection is initiated with the reversible binding of long tail fibers to the cell outer layer of LPS. It induces the release of short tail fibers from beneath the baseplate, causing the baseplate to switch to a stellar shape. Conformational change leads to exertion of radially directed force onto the bottom layer of the sheath and initiation of contraction of the latter. The head, attached via the neck to the sheath, also undergoes rotation by almost a full turn. It might help to dislodge the baseplate hub at the end of the tail tube from the baseplate and help the cell-puncturing device to penetrate the cell by combining pressure with rotation. This device additionally contains three lysozyme domains for digesting the peptidoglycan layer within the periplasmic space. The contraction occurs by sliding of the individual domains of tail sheath protein gp18 over each other. The domains of the neck protein gp15 also alter their conformation removing the knobs from inside of the neck's channel and opening the iris for DNA passage [104, 105]. The research of *B. subtilis* phage SBP8a showing the similar mechanism of contraction suggests that once contraction is initiated, it always goes to completion, and tail is unable to return to the extended state [106].

The majority of studied phages possesses tail used in host cell recognition, adsorption, and penetration into bacterial cell walls. However, some bacterial viruses are devoid of this structure and thus their mechanisms of adsorption differ from tail phages. ΦX174 is a small icosahedral, tailless bacteriophage from family *Microviridae*. 60 F proteins form the capsid decorated by 12 spikes on the vertices, each containing five G proteins. F proteins bind to G proteins through loops EF and FG. The initial contact with the host cell is performed by one of the 12 spikes leading to spike dissociation from the capsid and change of F protein structure. Alteration of the EF loop enables to maintain a stable contact between the capsid and the host cell membrane, while the change in the FG loop opens the gate at the special vertex and prepares the phage for DNA translocation. Inside the capsid changes in the conformation of DNA pilot proteins H and the nucleic acid occur to facilitate genome ejection through the vertex [107].

Bacteriophage PM2 is member of the *Corticoviridae* family infecting *Pseudoalteromonas* species. It is tailless phage with icosahedral capsid which outer protein shell composed of the major capsid protein P2 and the pentameric RBP P1 at the vertices of the capsid. This phage is characterized by presence of additional inner membrane. Infection takes several steps. The virus adsorbs to the receptor in a competent conformation depending on the intracellular ATP concentration. The interaction triggers dissociation of the protein shell, and leads to the fusion of the viral membrane with the host outer membrane. As the result the genome enters the periplasm and faces the peptidoglycan layer. The following step require Ca^{2+} ion as the promoter. The virus induces opening of a pore in the cytoplasmic membrane and releases the cellular lytic factor into the periplasm, where it locally digests the peptidoglycan layer. The same pore is

used for PM2 genome penetration into the cytoplasm. Virus replication begins, when outer membrane is stabilized by divalent cations, otherwise osmotic lysis takes place [108].

Phage φ6 from family *Cystoviridae* is represented by nucleocapsid enveloped by lipid-containing membrane composed of phospholipids and protein. The vurus adsorbs to a type IV pilus of *P. syringae*. The phage is forced into contact with the bacterial outer membrane by pilus retraction, and membrane of the phage fuses with the host outer membrane, driving nucleocapsid in the periplasmic space. Protein P5 located on the outside of the nucleocapsid expresses endopeptidase activity allowing the particle to enter the host cell, whereupon it loses the shell [109]. Phage φ13 of the same family possesses similar mechanism, but the virus attaches directly to the LPS [110, 111].

The icosahedral membrane-containing bacteriophage PRD1 from *Tectiviridae* family infects cells with only IncP-, IncN-, or IncW-type multiple drug resistance conjugative plasmids. Upon infection, the internal phage membrane transforms into a tubular structure that protrudes through a vertex and penetrates the cell envelope for DNA injection [112]. Bam35 penetration differs considerably from that of PRD1, although their virion architectures are very similar and both viruses form a tail-like structure during genomic-DNA release. PRD1 entry does not cause plasma membrane depolarization, compared to Bam35 [113].

Mechanism of filamentous bacteriophage infection has been mostly studied on Ff phages (M13, fd, f1) of *E. coli* possessing F pili. The infection is specifically mediated by viral coat protein 3 (g3p) located at one end of the phage particle and consisting of three functionally distinct domains. The C terminus of g3p anchors the protein in the phage coat, while the two distal domains N1 and N2 interact with each other to form a di-domain. Infection begins upon N2 interaction with F-pilus of the bacteria. After F-pilus retraction, N1 binds to the C-terminal domain of primary receptor TolA. The retracting pilus brings g3p domains in closer contact with TolA domains. The latter can assume a more compact state of assembly, bringing the outer and inner membranes of the bacteria closer together. At this stage, the central domain of TolA is capable to interact with N2. The phage g3p is inserted into the inner membrane, and the cap of the phage head is opened to allow phage DNA to enter the bacteria [114].

7. Historical background of application of bacteriophage receptors

Since the discovery bacteriophages have been considered and studied as the promising antimicrobial agents. However, early phage studies were characterized by lack of appropriate control and reproducibility as well as conflicting results. During era of antibiotics bacteriophages have been used and studied mainly in USSR and Poland. Appearance of antibiotic resistant bacteria resumed interest in bacteriophages as alternative antimicrobial agents [5]. Moreover, apart from medicine phages may be applied in agriculture, food industry and biotechnology.

In contrast, phage separate components are less useful, however, a few studies have been reported. In turn, protein phage receptors are applied in bacterial surface display presenting recombinant proteins or peptides on the surface of bacterial cells. The outer membrane proteins FhuA, LamB, and BtuB of *E. coli* demonstrated the platform facilitating presentation of single polypeptides for recombinant vaccines and whole-cell adsorbents, or generation of comprehensive libraries of peptide sequences by combining two or three proteins [115]. LPS are also attractive agents for agriculture, medicine, food and cosmetic industries [116]. Teichoic acids can find applications as antigens for the generation of novel vaccines to combat Gram-positive bacterial infections [117].

RBP evident potential is in bacterial detection and identification. The application of RBP shows some advantages over whole phages as detection probes for bacterial infections. The smaller size of RBPs promotes a more uniform surface coverage of biosensor elements used in different diagnostic platforms. RBPs can be easily engineered for increased affinity and specificity. They recognize and bind to the host bacteria, not inducing the lytic cycle and preventing the destruction of bacterial DNA and specific marker antigens. Lysins, enzymes degrading the bacterial cell wall, may also be engineered as a tool for bacterial detection. Cell wall binding domains (CBDs) of endolysins recognize and noncovalently bind to certain ligands within the bacterial cell wall, thereby bringing the catalytic domains in proximity to their substrate. The binding spectra of CBDs range from entire bacterial genera to the serovar or even strain level [118, 119].

The representatives of genus *Mycobacterium* include pathogens able to cause grave diseases in mammals. Phage L5 minor tail protein Gp6 and lysin Gp10 can be used for the rapid detection of mycobacteria. Immobilized Gp10 was able to bind both *Mycobacterium avium* subsp. *paratuberculosis* and *M. smegmatis* cells whereas Gp6 was *M. smegmatis* specific [119]. Real time PCR accompanied by magnetic separation with RBP (phage Gp48) instead of antibodies was able to detect *C. jejuni* cells at levels of 10^2 CFU/mL in less than 3 hours [120]. The use of paramagnetic beads coated with recombinant phage endolysin-derived CBD molecules allows to immobilize and recover more than 90% of the viable *Listeria monocytogenes* cells from diluted suspensions within 20 to 40 min. Recovery rates were similar for different species and serovars of the bacterium and were not affected by the presence of other microorganisms [121]. Paramagnetic beads coated with recombinant gp37-gp38 long tail fiber (phage S16) complexes captured over 95% of *S. enterica* typhimurium cells from suspensions containing 10 to 10^5 CFU/ml within 45 min, and they yielded equivalent recovery rates for other tested strains of the genus. The novel enzyme-linked long tail fiber assay uses horseradish peroxidase-conjugated long tail fibers to label *Salmonella* cells for subsequent identification by peroxidase-catalyzed

conversion of chromogenic 3,3′,5,5′-tetramethylbenzidine substrate. The color development was proportional for *Salmonella* concentrations between 10^2 and 10^7 CFU/ml. The assay took 2 hours to complete [122].

Phage components can be used in molecular techniques and control processes. Oral administration of lyophilized leaves of *Nicotiana benthamiana* expressing tailspike protein Gp9 from the P22 to newly hatched chickens showed approximately 1-log reduction in *Salmonella* typhimurium colonization as compared to the untreated control fowl [123]. Endolysin ClyH more rapidly degraded peptidoglycan *of S. aureus*, shortening the DNA sample preparation for real time PCR [124].

8. Development of an assay for the identification of receptors

Phages recognize their hosts through RBP binding to the receptor on the host cell surface. Due to high specificity, RBPs are regarded as promising agents for control and detection of bacteria. However, there is no rapid method for identifying phage RBPs, since the latter may bind to quite distinct receptors. *E. coli* gene libraries expressing randomly sheared fragments of phage DNA allow to rapidly identify RBPs in the absence of sequence information. Phage DNA is extracted, fragmented, ligated into an expression vector, transformed into *E. coli* and then transferred to a nitrocellulose membrane where recombinant proteins are overexpressed. The membrane is probed for binding to the phage host bacterium. The tailspike or putative tail fibre of phages P22 and phage 1 was successfully identified using this method [125]. One of the more widely applied methods for RBP identification makes use *in silico* analysis via homology comparison with proteins of other phages. G17-g20 and g15-g17 proteins of *Listeria* phages A118 and P35, respectively, have significant similarity to phage related proteins, including RBPs. However, further investigation revealed that both A118 gp19 and A118 gp20 in addition to P35 gp16 were able to absorb to *Listeria* SV 1/2 cells [126]. Homology comparison was carried out for P793 and ϕLN04 sharing 80.1% nucleotide sequence identity, but preferring different strains of *Leuconostoc pseudomesenteroides* as hosts. Further construction of chimeric phages leading to the switch in host range has been used. Genes ORF21 (P793) and ORF23 (ϕLN04) were identified as RBP encoding tail structural module [127].

Separate receptor-binding domain of RBP also can be detected, using *E. coli* transformed by glutathione-S-transferase fused protein expression vector with ampicillin resistance. Bacterial derivatives with different RBP fragments were immobilized onto solid surfaces and were tested for their ability to capture *C. jejuni*. The binding domains were localized in the C-terminal quarter of RBP [128].

9. Study of the structure of the receptor-binding domains of bacteriophage

Detailed research of phage-host interactions demands knowledge about structure of RBPs and their separate domains directly taking part in adsorption mechanisms. X-ray crystallography is currently the most favored technique for structural analysis of proteins, including phage sources. A purified sample at high concentration is crystallised and the crystals are exposed to an x-ray beam. The resulting diffraction patterns can then be processed, initially to yield information about the crystal packing symmetry and the size of the repeating unit that forms the crystal. The data were collected by distribution of diffraction spots [129].

Crystallography was successfully applied in research of RBPs and their domains, for example, of T7. Gp17 of phage T7 encodes tail fibers taking part in reversible attachment to *E. coli*. They comprise an N-terminal tail-attachment domain, a slender shaft, and a C-terminal domain composed of several nodules. Detailed structure of the latter part has been described after crystallization process. Amino acids 371-447 form a tapered pyramid with a triangular cross-section composed of interlocked β-sheets from each of the three chains. The triangular pyramid domain has three α-helices at its narrow end, which are connected to a C-terminal three-blade β-propeller tip domain by flexible loops. The monomers of this tip domain each contain an eight-stranded β-sandwich. Loops located on the top of the tip domain are suggested to interact with host cell receptors [130]. RBP of phage p2 infecting *L. lactis* strains is a homotrimeric protein composed of three domains: the shoulders, a β-sandwich attached to the phage; the neck, an interlaced β-prism; and the receptor-recognition head, a seven-stranded β-barrel. The structure of the p2 RBP trimer has been investigated at 2.3-Å resolution after crystallization process. The receptor-binding site has been additionally studied with a neutralizing antibody llama VHH domain. The recognition-head domain of phage p2 demonstrated structural similarity to those of adenoviruses and reoviruses invading mammalian cells [131].

Another method of phage structural study is cryo-electron microscopy. X-ray crystallography demands preliminary crystallization of proteins, but the latter cannot always be subjected to this procedure. Imaging by cryo-electron microscopy is performed using frozen specimens maintained either in liquid nitrogen or in liquid helium temperatures. Cryogenic temperatures could reduce the effects of radiation damage as compared to room temperatures [132]. The cryo-electron microscopic investigation of the 1358 virion revealed capsid with *dextro* handedness and protruding decorations on capsid and tail. The baseplate of the phage gathers six trimeric RBPs partly resembling those of phage p2. The microscopy even allows to observe large baseplate conformational change, the ∼180° rotation of the RBPs reminiscent of 200° rotation in phage p2 baseplate activation [133].

10. Problems related to identification of bacteriophage receptors: Conclusions

Phage infection begins as the specific adsorption of the phage to the bacterial receptor on the host surface. The interaction between the host receptor and the phage RBP still requires additional studies. Phage receptors of several groups of bacteria, like *E. coli* are sufficiently studied, while the others are known superficially [134]. A similar case is observed in regard to different phage families. Tailed phages consisting of three families (*Podoviridae*, *Siphoviridae* and *Myoviridae*) are the most wide-spread types of bacterial viruses. Thus, their structure, including composition of RBPs, and mechanisms of adsorption are better studied as compared to other phages. Nevertheless, new data about receptor structure and host-phage interactions are gradually collected and novel methods allowing to overcome limitations of prior techniques have been developed.

Bacteriophages are able to attach to receptors of different chemical nature. Bacterial viruses use cell wall, flagella, pili or capsule as attachment sites. Therefore, composition of cell wall of Gram-positive and Gram-negative bacteria is quite different, so that viruses adsorb to diverse sites. Gram-positive bacteria use peptidoglycan and teichoic acids, while Gram-negative species adhere to LPS and proteins. Often phages use two different receptors for irreversible and reversible adsorption and even change their composition. Bacterial viruses themselves demand special agent – RBP, to adsorb on cell surface. Tailed phages carry RBPs on the baseplate of the tail, while other viruses bear this structure on capsid surface. Modification of RBP composition may lead to change of recognition sites on cell surface, even quite different in chemical nature. Investigation of phage structure usually is carried out with x-ray crystallography, although recently new methods came to the fore.

The knowledge of mechanisms and structures taking part in phage-cell interactions is important for practical purposes. It may allow to decrease negative influence of phages on beneficial bacteria as well as help in detection, identification and control of pathogenic microorganisms.

References

[1] Weinbauer MG. Ecology of prokaryotic viruses. FEMS Microbiology Reviews. 2004;28(2):127-81. DOI: 10.1016/j.femsre.2003.08.001

[2] Twort FW. An investigation on the nature of ultramicroscopic viruses. The Lancet. 1915; 186(4814):1241-3. DOI: 10.1016/S0140-6736(01)20383-3.

[3] d'Hérelle F. Sur un microbe invisible antagoniste des bacilles dysentériques. Comptes Rendus de l'Académie des Sciences Series D. 1917; 165:373-5.

[4] Abedon ST, Thomas-Abedon C, Thomas A, Mazure H. Bacteriophage prehistory: Is or is not Hankin, 1896, a phage reference? Bacteriophage. 2011;1(3):174-8. DOI: 10.4161/bact.1.3.16591

[5] Wittebole X, De Roock S, Opal SM. A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens. Virulence. 2014;5(1):226-35. DOI:10.4161/viru.25991

[6] Hobbs Z, Abedon ST. Diversity of phage infection types and associated terminology: the problem with 'Lytic or lysogenic'. FEMS Microbiology Letters. 2016;363(7):fnw047. DOI: 10.1093/femsle/fnw047

[7] Guttman B, Raya R, Kutter E. Basic phage biology. In: Kutter E, Sulakvelidze A, editors. Bacteriophages: biology and applications. Boca Raton, Florida: CRC Press; 2005. p. 29-66.

[8] Rakhuba DV, Kolomiets EI, Dey ES, Novik GI. Bacteriophage receptors, mechanisms of phage adsorption and penetration into host cell. Polish Journal of Microbiology. 2010;59(3):145-55. DOI: 10.1016/j.micres.2015.01.008.1.94

[9] Bertozzi Silva J, Storms Z, Sauvageau D. Host receptors for bacteriophage adsorption. FEMS Microbiology Letters. 2016;363(4):fnw002. DOI: 10.1093/femsle/fnw002

[10] Lindberg AA. Bacteriophage receptors. Annual Review of Microbiology. 1973;27:205-41. DOI: 10.1146/annurev.mi.27.100173.001225

[11] Silipo A., Molinaro A. Lipid A Structure. In: Knirel Y, Valvano M, editors. Bacterial Lipopolysaccharides. Springer, Vienna; 2011. p. 1-20. DOI: 10.1007/978-3-7091-0733-1_1

[12] Iwashita S, Kanegasaki S. Deacetylation reaction catalyzed by *Salmonella* phage c341 and its baseplate parts. The Journal of Biological Chemistry. 1976;251(17):5361-5.

[13] Robbins PW, Uchida T. Studies on the chemical basis of the phage conversion of O-antigens in the E-group *Salmonellae*. Biochemistry. 1962;1(2):323-35. DOI: 10.1021/bi00908a020

[14] Losick R, Robbins PW. The receptor site for a bacterial virus. Scientific American. 1969;221(5):120-4.

[15] Castillo FJ. Partial characterization of *Pseudomonas* phage 2 receptor. Canadian Journal of Microbiology. 1980;26(8):1015-7. DOI: 10.1139/m80-172

[16] Kuzio J, Kropinski AM. O-antigen conversion in *Pseudomonas aeruginosa* PAO1 by bacteriophage D3. Journal of Bacteriology. 1983;155(1):203-12.

[17] Feige U, Stirm S. On the structure of the *Escherichia coli* C cell wall lipopolysaccharide core and on its øX174 receptor region. Biochemical and Biophysical Research Communications. 1976;71(2), 566-73. DOI: 10.1016/0006-291X(76)90824-X

[18] Defives C, Werquin M, Mary P, Hornez JP. Roles of exopolysaccharides and lipopolysaccharides in the adsorption of the siphovirus phage NM8 to *Rhizobium meliloti* M11S cells. Current Microbiology. 1996;33(6):371-6. DOI: 10.1007/s002849900130

[19] Kamp D, Sandulache R. Recognition of cell surface receptors is controlled by invertible DNA of phage Mu. FEMS Microbiology Letters. 1983;16(1):131-5. DOI: 10.1111/j.1574-6968.1983.tb00273.x

[20] Sandulache R, Prehm P, Expert D, Toussaint A, Kamp D. The cell wall receptor for bacteriophage Mu G (−) in *Erwinia* and *Escherichia coli* C. FEMS Microbiology Letters. 1985;28(3):307-10. DOI: 10.1111/j.1574-6968.1985.tb00811.x

[21] Chatterjee S, Rothenberg E. Interaction of bacteriophage l with its *E. coli* receptor, LamB. Viruses. 2012;4(11):3162-78. DOI: 10.3390/v4113162
[22] Braun V. FhuA (TonA), the career of a protein. Journal of Bacteriology. 2009;191(11):3431-6. DOI: 10.1128/JB.00106-09
[23] Killmann H, Braun V. Energy-dependent receptor activities of *Escherichia coli* K-12: mutated TonB proteins alter FhuA receptor activities to phages T5, T1, phi 80 and to colicin M. FEMS microbiology letters. 1994;119(1-2):71-6. DOI: 10.1111/j.1574-6968.1994.tb06869.x
[24] Rabsch W, Ma L, Wiley G, Najar FZ, Kaserer W, Schuerch DW, Klebba JE, Roe BA, Laverde Gomez JA, Schallmey M, Newton SM, Klebba PE. FepA- and TonB-dependent bacteriophage H8: receptor binding and genomic sequence. Journal of Bacteriology. 2007;189(15):5658-74. DOI: 10.1128/JB.00437-07
[25] Hantke K. Phage T6-colicin K receptor and nucleoside transport in *Escherichia coli*. FEBS Letters. 1976;70(1):109-12. DOI: 10.1016/0014-5793(76)80737-5
[26] Nieweg A, Bremer E. The nucleoside-specific Tsx channel from the outer membrane of *Salmonella typhimurium*, *Klebsiella pneumoniae* and *Enterobacter aerogenes*: functional characterization and DNA sequence analysis of the tsx genes. Microbiology. 1997;143(Pt 2):603-15. DOI: 10.1099/00221287-143-2-603
[27] Puig A, Araujo R, Jofre J, Frias-Lopez J. Identification of cell wall proteins of *Bacteroides fragilis* to which bacteriophage B40-8 binds specifically. Microbiology. 2001;147(Pt 2):281-8. DOI: 10.1099/00221287-147-2-281
[28] Thomassen E, Gielen G, Schütz M, Schoehn G, Abrahams JP, Miller S, van Raaij MJ. The structure of the receptor-binding domain of the bacteriophage T4 short tail fibre reveals a knitted trimeric metal-binding fold. Journal of Molecular Biology. 2003;331(2):361-73. DOI: 10.1016/S0022-2836(03)00755-1
[29] Sukupolvi S. Role of lipopolysaccharide in the receptor function for bacteriophage Ox2. FEMS Microbiology Letters. 1984;21(1):83-7. DOI: 10.1111/j.1574-6968.1984.tb00190.x
[30] Drexler K, Dannull J, Hindennach I, Mutschler B, Henning U. Single mutations in a gene for a tail fiber component of an *Escherichia coli* phage can cause an extension from a protein to a carbohydrate as a receptor. Journal of Molecular Biology. 1991;219(4):655-63. DOI: 10.1016/0022-2836(91)90662-P
[31] German GJ, Misra R. The TolC protein of *Escherichia coli* serves as a cell-surface receptor for the newly characterized TLS bacteriophage. Journal of molecular biology. 2001;308(4):579-85. DOI: 10.1006/jmbi.2001.4578
[32] Fan F, Li X, Pang B, Zhang C, Li Z, Zhang L, Li J, Zhang J, Yan M, Liang W, Kan B. The outer-membrane protein TolC of *Vibrio cholerae* serves as a second cell-surface receptor for the VP3 phage. Journal of Biological Chemistry. 2018;293(11):4000-13. DOI: 10.1074/jbc.M117.805689
[33] Yu F, Yamada H, Mizushima S. Role of lipopolysaccharide in the receptor function for bacteriophage TuIb in *Escherichia coli*. Journal of Bacteriology. 1981;148(2):712-5.
[34] Moreno F, Wandersman C. OmpC and LamB proteins can serve as substitute receptors for host range mutants of coliphage TuIa. Journal of Bacteriology. 1980;144(3):1182-5.
[35] Yu F, Mizushima S. Roles of lipopolysaccharide and outer membrane protein OmpC of *Escherichia coli* K-12 in the receptor function for bacteriophage T4. Journal of Bacteriology. 1982;151(2):718-22.
[36] Zhao X, Cui Y, Yan Y, Du Z, Tan Y, Yang H, Bi Y, Zhang P, Zhou L, Zhou D, Han Y, Song Y, Wang X, Yang R. Outer membrane proteins ail and OmpF of *Yersinia pestis* are involved in the adsorption of T7-related bacteriophage Yep-phi. Journal of Virology. 2013;87(22):12260-9. DOI: 10.1128/JVI.01948-13
[37] Chaby R, Girard R. Adsorption and endo-glycosidase activity of phage φ 1 (40) on *Salmonella johannesburg* O-polysaccharide. Virology. 1980;105(1):136-47. DOI: 10.1016/0042-6822(80)90162-2
[38] Reske K, Wallenfels B, Jann K. Enzymatic degradation of O-Antigenic lipopolysaccharides by coliphage Ω8. European Journal of Biochemistry. 1973;36(1):167-71. DOI: 10.1111/j.1432-1033.1973.tb02897.x
[39] Iwashita S, Kanegasaki S. Release of O antigen polysaccharide from *Salmonella newington* by phage ϵ34. Virology. 1975;68(1):27-34. DOI: 10.1016/0042-6822(75)90144-0
[40] Yokokura T. Phage receptor material in *Lactobacillus casei*. Journal of General Microbiology. 1977;100(1):139-45. DOI: 10.1099/00221287-100-1-139
[41] Ishibashi K, Takesue S, Watanabe K, Oishi K. Use of lectins to characterize the receptor sites for bacteriophage PL-1 of *Lactobacillus casei*. Microbiology. 1982;128(10):2251-9. DOI: 10.1099/00221287-128-10-2251
[42] Sijtsma L, Sterkenburg A, Wouters JT. Properties of the cell walls of *Lactococcus lactis* subsp. *cremoris* SK110 and SK112 and their relation to bacteriophage resistance. Applied and Environmental Microbiology. 1988;54(11):2808-11.
[43] Wendlinger G, Loessner MJ, Scherer S. Bacteriophage receptors on *Listeria monocytogenes* cells are the N-acetylglucosamine and rhamnose substituents of teichoic acids or the peptidoglycan itself. Microbiology. 1996;142(Pt 4):985-92. DOI: 10.1099/00221287-142-4-985
[44] Quiberoni A, Stiefel JI, Reinheimer JA. Characterization of phage receptors in *Streptococcus thermophilus* using purified cell walls obtained by a simple protocol. Journal of Applied Microbiology. 2000;89(6):1059-65. DOI: 10.1046/j.1365-2672.2000.01214.x
[45] Archibald AR, Coapes HE. Blocking of bacteriophage receptor sites by Concanavalin A. Journal of General Microbiology. 1972;73(3):581-5. DOI: 10.1099/00221287-73-3-581
[46] Munsch-Alatossava P, Alatossava T. The extracellular phage-host interactions involved in the bacteriophage LL-H infection of *Lactobacillus delbrueckii* ssp. *lactis* ATCC 15808. Frontiers in Microbiology. 2013;4:408. DOI: 10.3389/fmicb.2013.00408
[47] Lopez R, Garcia E, Garcia P, Ronda C, Tomasz A. Choline-containing bacteriophage receptors in *Streptococcus pneumoniae*. Journal of Bacteriology. 1982;151(3):1581-90.
[48] Xia G, Corrigan RM, Winstel V, Goerke C, Gründling A, Peschel A. Wall teichoic acid-dependent adsorption of staphylococcal siphovirus and myovirus. Journal of Bacteriology. 2011;193(15):4006-9. DOI: 10.1128/JB.01412-10
[49] Ventura M, Callegari ML, Morelli L. Surface layer variations affecting phage adsorption on seven *Lactobacillus helveticus* strains. Annali di Microbiologia ed Enzimologia. 1999;49(1):45-54.

[50] Vidaver AK, Brock TD. Purification and properties of a bacteriophage receptor material from *Streptococcus faecium*. Biochimica et Biophysica Acta (BBA)-General Subjects. 1966;121(2):298-314. DOI: 10.1016/0304-4165(66)90119-X
[51] Monteville MR, Ardestani B, Geller BL. Lactococcal bacteriophages require a host cell wall carbohydrate and a plasma membrane protein for adsorption and ejection of DNA. Applied and Environmental Microbiology. 1994;60(9):3204-11.
[52] Baptista C, Santos MA, São-José C. Phage SPP1 reversible adsorption to *Bacillus subtilis* cell wall teichoic acids accelerates virus recognition of membrane receptor YueB. Journal of Bacteriology. 2008;190(14):4989-96. DOI: 10.1128/JB.00349-08
[53] Proft T, Baker EN. Pili in Gram-negative and Gram-positive bacteria - structure, assembly and their role in disease. Cellular and Molecular Life Sciences. 2009;66(4):613-35. DOI: 10.1007/s00018-008-8477-4
[54] Bradley DE. Basic characterization of a *Pseudomonas aeruginosa* pilus-dependent bacteriophage with a long noncontractile tail. Journal of Virology. 1973;12:1139-48.
[55] Bradley DE. The structure and infective process of a *Pseudomonas aeruginosa* bacteriophage containing ribonucleic acid. Journal of General Microbiology. 1966;45:83-96. DOI: 10.1099/00221287-45-1-83
[56] Bradley DE. The adsorption of the *Pseudomonas aeruginosa filamentous* bacteriophage Pf to its host. Canadian Journal of Microbiology. 1973;19:623-31. DOI: 10.1139/m73-103
[57] Byrne M, Kropinski AM. The genome of the *Pseudomonas aeruginosa* generalized transducing bacteriophage F116. Gene. 2005;346:187-94. DOI: 10.1016/j.gene.2004.11.001
[58] Wang PW, Chu L, Guttman DS. Complete sequence and evolutionary genomic analysis of the *Pseudomonas aeruginosa* transposable bacteriophage D3112. Journal of Bacteriology. 2004;186:400-10. DOI: 10.1128/JB.186.2.400-410.2004
[59] Budzik JM, RoscheWA, Rietsch A, O'Toole GA. Isolation and characterization of a generalized transducing phage for *Pseudomonas aeruginosa* strains PAO1 and PA14. Journal of Bacteriology. 2004;186(10):3270-3. DOI: 10.1128/JB.186.10.3270-3273.2004
[60] Roncero C, Darzins A, Casadaban MJ. *Pseudomonas aeruginosa* transposable bacteriophages D3112 and B3 require pili and surface growth for adsorption. Journal of Bacteriology. 1990;172(4):1899-904. DOI: 10.1128/jb.172.4.1899-1904.1990
[61] Chibeu A, Ceyssens PJ, Hertveldt K, Volckaert G, Cornelis P, Matthijs S, Lavigne R. The adsorption of *Pseudomonas aeruginosa* bacteriophage phiKMV is dependent on expression regulation of type IV pili genes. FEMS Microbiology Letters. 2009;296(2):210-8. DOI: 10.1111/j.1574-6968.2009.01640.x
[62] Harvey H, Bondy-Denomy J, Marquis H, Sztanko KM, Davidson AR, Burrows LL. *Pseudomonas aeruginosa* defends against phages through type IV pilus glycosylation. Nature Microbiology. 2017;3(1):47-52. DOI: 10.1038/s41564-017-0061-y
[63] Ahern SJ, Das M, Bhowmick TS, Young R, Gonzalez CF. Characterization of novel virulent broad-host-range phages of *Xylella fastidiosa* and *Xanthomonas*. Journal of Bacteriology. 2014;196(2):459-71. DOI: 10.1128/JB.01080-13
[64] Holland SJ, Sanz C, Perham RN. Identification and specificity of pilus adsorption proteins of filamentous bacteriophages infecting *Pseudomonas aeruginosa*. Virology. 2006;345(2):540-8. DOI: 10.1016/j.virol.2005.10.020
[65] Caro LG, Schnös M. The attachment of the male-specific bacteriophage F1 to sensitive strains of *Escherichia coli*. Proceedings of the National Academy of Sciences of the United States of America. 1966;56(1):126-32. DOI: 10.1073/pnas.56.1.126
[66] Silverman PM, Valentine RC. The RNA injection step of bacteriophage f2 infection. Journal of General Virology. 1969;4(1):111-24. DOI: 10.1099/0022-1317-4-1-111
[67] Jacobson A. Role of F pili in the penetration of bacteriophage fl. Journal of Virology. 1972;10(4):835-43.
[68] Bradley DE. Shortening of *Pseudomonas aeruginosa* pili after RNA-phage adsorption. Journal of General Microbiology. 1972;72(2):303-19. DOI: 10.1099/00221287-72-2-303
[69] Krahn PM, O'Callaghan RJ, Paranchych W. Stages in phage R17 infection. VI. Injection of A protein and RNA into the host cell. Virology. 1972;47(3):628-37. DOI: 10.1016/0042-6822(72)90552-1
[70] Terashima H, Kawamoto A, Morimoto YV, Imada K, Minamino T. Structural differences in the bacterial flagellar motor among bacterial species. Biophysics and Physicobiology. 2017;14:191-8. DOI: 10.2142/biophysico.14.0_191
[71] Evans TJ, Crow MA, Williamson NR, Orme W, Thomson NR, Komitopoulou E, Salmond GP. Characterization of a broad-host-range flagellum-dependent phage that mediates high-efficiency generalized transduction in, and between, *Serratia* and *Pantoea*. Microbiology. 2010;156(Pt 1):240-7. DOI: 10.1099/mic.0.032797-0
[72] Zhilenkov EL, Popova VM, Popov DV, Zavalsky LY, Svetoch EA, Stern NJ, Seal BS. The ability of flagellum-specific *Proteus vulgaris* bacteriophage PV22 to interact with *Campylobacter jejuni* flagella in culture. Virology journal. 2006;3:50. DOI: 10.1186/1743-422X-3-50
[73] Schade SZ, Adler J, Ris H. How bacteriophage chi attacks motile bacteria. Journal of Virology. 1967;1(3):599-609.
[74] Pate JL, Petzold SJ, Umbreit TH. Two flagellotropic phages and one pilus-specific phage active against *Asticcacaulis biprosthecum*. Virology. 1979;94(1):24-37. DOI: 10.1016/0042-6822(79)90435-5
[75] Choi Y, Shin H, Lee JH, Ryu S. Identification and characterization of a novel flagellum-dependent *Salmonella*-infecting bacteriophage, iEPS5. Applied and Environmental Microbiology. 2013;79(16):4829-37. DOI: 10.1128/AEM.00706-13
[76] Zhang H, Li L, Zhao Z, Peng D, Zhou X. Polar flagella rotation in *Vibrio parahaemolyticus* confers resistance to bacteriophage infection. Scientific Reports. 2016;6:26147. DOI: 10.1038/srep26147
[77] Samuel AD, Pitta TP, Ryu WS, Danese PN, Leung EC, Berg HC. Flagellar determinants of bacterial sensitivity to chi-phage. Proceedings of the National Academy of Sciences of the United States of America. 1999;96(17):9863-6.
[78] Baldvinsson SB, Sørensen MC, Vegge CS, Clokie MR, Brøndsted L. *Campylobacter jejuni* motility is required for infection of the flagellotropic bacteriophage F341. Applied and Environmental Microbiology. 2014;80(22):7096-106. DOI: 10.1128/AEM.02057-14
[79] Lee HS, Choi S, Shin H, Lee JH, Choi SH. *Vibrio vulnificus* bacteriophage SSP002 as a possible biocontrol agent. Applied and Environmental Microbiology. 2014;80(2):515-24. DOI: 10.1128/AEM.02675-13
[80] Joys TM. Correlation between susceptibility to bacteriophage PBS1 and motility in *Bacillus subtilis*. Journal of Bacteriology. 1965;90(6):1575-7.
[81] Bradley DE, Douglas CJ, Peschon J. Flagella-specific bacteriophages of *Agrobacterium tumefaciens*: demonstration of virulence of nonmotile mutants. Canadian Journal of Microbiology. 1984;30(5):676-81. DOI: 10.1139/m84-101

[82] Fukuda A, Miyakawa K, Iba H, Okada Y. A flagellotropic bacteriophage and flagella formation in *Caulobacter*. Virology. 1976;71(2):583-92. DOI: 10.1016/0042-6822(76)90383-4
[83] Evans TJ, Trauner A, Komitopoulou E, Salmond GP. Exploitation of a new flagellatropic phage of *Erwinia* for positive selection of bacterial mutants attenuated in plant virulence: towards phage therapy. Journal of Applied Microbiology. 2010;108(2):676-85. DOI: 10.1111/j.1365-2672.2009.04462.x
[84] Lotz W, Acker G, Schmitt R. Bacteriophage 7-7-1 adsorbs to the complex flagella of *Rhizobium lupini* H13-3. The Journal of General Virology. 1977;34(1):9-17. DOI: 10.1099/0022-1317-34-1-9
[85] Merino S, Camprubi S, Tomás JM. Isolation and characterization of bacteriophage PM3 from *Aeromonas hydrophila* the bacterial receptor for which is the monopolar flagellum. FEMS Microbiology Letters. 1990;57(3):277-82. DOI: 10.1016/0378-1097(90)90080-A
[86] Pickard D, Toribio AL, Petty NK, van Tonder A, Yu L, Goulding D, Barrell B, Rance R, Harris D, Wetter M, Wain J, Choudhary J, Thomson N, Dougan G. A conserved acetyl esterase domain targets diverse bacteriophages to the Vi capsular receptor of *Salmonella enterica* serovar Typhi. Journal of Bacteriology. 2010;192(21):5746-54. DOI: 10.1128/JB.00659-10
[87] Leiman PG, Battisti AJ, Bowman VD, Stummeyer K, Mühlenhoff M, Gerardy-Schahn R, Scholl D, Molineux IJ. The structures of bacteriophages K1E and K1-5 explain processive degradation of polysaccharide capsules and evolution of new host specificities. Journal of Molecular Biology. 2007;371(3):836-49. DOI: 10.1016/j.jmb.2007.05.083
[88] Sørensen MC, van Alphen LB, Harboe A, Li J, Christensen BB, Szymanski CM, Brøndsted L. Bacteriophage F336 recognizes the capsular phosphoramidate modification of *Campylobacter jejuni* NCTC11168. Journal of Bacteriology. 2011;193(23):6742-9. DOI: 10.1128/JB.05276-11
[89] Bayer ME, Thurow H, Bayer MH. Penetration of the polysaccharide capsule of *Escherichia coli* (Bi161/42) by bacteriophage K29. Virology. 1979;94(1):95-118. DOI: 10.1016/0042-6822(79)90441-0
[90] Fehmel F, Feige U, Niemann H, Stirm S. *Escherichia coli* capsule bacteriophages. VII. Bacteriophage 29-host capsular polysaccharide interactions. Journal of Virology. 1975;16(3):591-601.
[91] Hsieh PF, Lin HH, Lin TL, Chen YY, Wang JT. Two T7-like bacteriophages, K5-2 and K5-4, each encodes two capsule depolymerases: isolation and functional characterization. Scientific reports. 2017;7(1):4624. DOI: 10.1038/s41598-017-04644-2
[92] Valyasevi R, Sandine WE, Geller BL. A membrane protein is required for bacteriophage c2 infection of *Lactococcus lactis* subsp. *lactis* C2. Journal of Bacteriology. 1991;173(19):6095-100. DOI: 10.1128/jb.173.19.6095-6100.1991
[93] Wais AC, Goldberg EB. Growth and transformation of phage T4 in *Escherichia coli* B-4, *Salmonella*, *Aerobacter*, *Proteus*, and *Serratia*. Virology. 1969;39(2):153-61. DOI: 10.1016/0042-6822(69)90035-X
[94] Benz WC, Goldberg EB. Interactions between modified phage T4 particles and spheroplasts. Virology. 1973;53(1):225-35. DOI: 10.1016/0042-6822(73)90481-9
[95] Ackermann HW, Prangishvili D. Prokaryote viruses studied by electron microscopy. Archives of Virology. 2012;157(10):1843-9. DOI: 10.1007/s00705-012-1383-y
[96] Storms ZJ, Sauvageau D. Modeling tailed bacteriophage adsorption: insight into mechanisms. Virology. 2015;485:355-62. DOI: 10.1016/j.virol.2015.08.007
[97] Hu B, Margolin W, Molineux IJ, Liu J. The bacteriophage t7 virion undergoes extensive structural remodeling during infection. Science. 2013;339(6119):576-9. DOI: 10.1126/science.1231887
[98] Andres D, Hanke C, Baxa U, Seul A, Barbirz S, Seckler R. Tailspike interactions with lipopolysaccharide effect DNA ejection from phage P22 particles in vitro. The Journal of Biological Chemistry. 2010;285(47):36768-75. DOI: 10.1074/jbc.M110.169003
[99] González-Huici V, Salas M, Hermoso JM. The push-pull mechanism of bacteriophage Ø29 DNA injection. Molecular Microbiology. 2004;52(2):529-40. DOI: 10.1111/j.1365-2958.2004.03993.x
[100] Bebeacua C, Tremblay D, Farenc C, Chapot-Chartier MP, Sadovskaya I, van Heel M, Veesler D, Moineau S, Cambillau C. Structure, adsorption to host, and infection mechanism of virulent lactococcal phage p2. Journal of Virology. 2013;87(22):12302-12. DOI: 10.1128/JVI.02033-13
[101] Saigo K. Isolation of high-density mutants and identification of nonessential structural proteins in bacteriophage T5; dispensability of L-shaped tail fibers and a secondary major head protein. Virology. 1978;85(2):422-433. DOI: 10.1016/0042-6822(78)90449-X
[102] Flayhan A, Wien F, Paternostre M, Boulanger P, Breyton C. New insights into pb5, the receptor binding protein of bacteriophage T5, and its interaction with its *Escherichia coli* receptor FhuA. Biochimie. 2012;94(9):1982-9. DOI: 10.1016/j.biochi.2012.05.021
[103] Jakutytė L, Lurz R, Baptista C, Carballido-Lopez R, São-José C, Tavares P, Daugelavičius R. First steps of bacteriophage SPP1 entry into *Bacillus subtilis*. Virology. 2012;422(2):425-34. DOI: 10.1016/j.virol.2011.11.010
[104] Kostyuchenko VA, Chipman PR, Leiman PG, Arisaka F, Mesyanzhinov VV, Rossmann MG. The tail structure of bacteriophage T4 and its mechanism of contraction. Nature Structural and Molecular Biology. 2005;12(9):810-3. DOI: 10.1038/nsmb975
[105] Yap ML, Rossmann MG. Structure and function of bacteriophage T4. Future Microbiology. 2014;9(12):1319-27. DOI: 10.2217/fmb.14.91
[106] Fu X, Walter MH, Paredes A, Morais MC, Liu J. The mechanism of DNA ejection in the *Bacillus anthracis* spore-binding phage 8a revealed by cryo-electron tomography. Virology. 2011;421(2):141-8. DOI: 10.1016/j.virol.2011.08.028
[107] Sun Y, Roznowski AP, Tokuda JM, Klose T, Mauney A, Pollack L, Fane BA, Rossmann MG. Structural changes of tailless bacteriophage ΦX174 during penetration of bacterial cell walls. Proceedings of the National Academy of Sciences of the United States of America. 2017;114(52):13708-13. DOI: 10.1073/pnas.1716614114
[108] Cvirkaite-Krupovic V, Krupovic M, Daugelavicius R, Bamford DH. Calcium ion-dependent entry of the membrane-containing bacteriophage PM2 into its *Pseudoalteromonas* host. Virology. 2010;405(1):120-8. DOI: 10.1016/j.virol.2010.05.021

[109] Mindich L. Precise packaging of the three genomic segments of the double-stranded-RNA bacteriophage phi6. Microbiology and Molecular Biology Reviews. 1999;63(1):149-60.
[110] Qiao X, Qiao J, Onodera S, Mindich L. Characterization of phi 13, a bacteriophage related to phi 6 and containing three dsRNA genomic segments. Virology. 2000;275(1):218-24. DOI: 10.1006/viro.2000.0501
[111] Daugelavicius R, Cvirkaite V, Gaidelyte A, Bakiene E, Gabrenaite-Verkhovskaya R, Bamford DH. Penetration of enveloped double-stranded RNA bacteriophages phi13 and phi6 into *Pseudomonas syringae* cells. Journal of Virology. 2005;79(8):5017-26. DOI: 10.1128/JVI.79.8.5017-5026.2005
[112] Grahn AM, Butcher SJ, Bamford JKH, Bamford DH. PRD1 - dissecting the genome, structure and entry. In: Calendar R, editor. The bacteriophages. 2nd ed. New York: Oxford University Press; 2006. p. 161-170.
[113] Gaidelyte A, Cvirkaite-Krupovic V, Daugelavicius R, Bamford JK, Bamford DH. The entry mechanism of membrane-containing phage Bam35 infecting *Bacillus thuringiensis*. Journal of Bacteriology. 2006;188(16):5925-34. DOI: 10.1128/JB.00107-06
[114] Karlsson F, Borrebaeck CA, Nilsson N, Malmborg-Hager AC. The mechanism of bacterial infection by filamentous phages involves molecular interactions between TolA and phage protein 3 domains. Journal of Bacteriology. 2003;185(8):2628-34. DOI: 10.1128/JB.185.8.2628-2634.2003
[115] Etz H, Minh DB, Schellack C, Nagy E, Meinke A. Bacterial phage receptors, versatile tools for display of polypeptides on the cell surface. Journal of Bacteriology. 2001;183(23):6924-35. DOI: 10.1128/JB.183.23.6924-6935.2001
[116] Kohchi C, Inagawa H, Nishizawa T, Yamaguchi T, Nagai S, Soma G. Applications of lipopolysaccharide derived from *Pantoea agglomerans* (IP-PA1) for health care based on macrophage network theory. Journal of Bioscience and Bioengineering. 2006;102(6):485-96. DOI: 10.1263/jbb.102.485
[117] van der Es D, Hogendorf WF, Overkleeft HS, van der Marel GA, Codée JD. Teichoic acids: synthesis and applications. Chemical Society Reviews. 2017;46(5):1464-82. DOI: 10.1039/c6cs00270f
[118] Schmelcher M, Loessner MJ. Application of bacteriophages for detection of foodborne pathogens. Bacteriophage. 2014;4(1):e28137. DOI: 10.4161/bact.28137
[119] Arutyunov D, Singh U, El-Hawiet A, Seckler HD, Nikjah S, Joe M, Bai Y, Lowary TL, Klassen JS, Evoy S, Szymanski CM. Mycobacteriophage cell binding proteins for the capture of mycobacteria. Bacteriophage. 2014;4(4):e960346. DOI: 10.4161/21597073.2014.960346
[120] Poshtiban S, Javed MA, Arutyunov D, Singh A, Banting G, Szymanski CM, Evoy S. Phage receptor binding protein-based magnetic enrichment method as an aid for real time PCR detection of foodborne bacteria. The Analyst. 2013;138(19):5619-26. DOI: 10.1039/c3an01100c
[121] Kretzer JW, Lehmann R, Schmelcher M, Banz M, Kim KP, Korn C, Loessner MJ. Use of high-affinity cell wall-binding domains of bacteriophage endolysins for immobilization and separation of bacterial cells. Applied and Environmental Microbiology. 2007;73(6):1992-2000. DOI: 10.1128/AEM.02402-06
[122] Denyes JM, Dunne M, Steiner S, Mittelviefhaus M, Weiss A, Schmidt H, Klumpp J, Loessner MJ. (2017). Modified bacteriophage S16 long tail fiber proteins for rapid and specific immobilization and detection of *Salmonella* cells. Applied and Environmental Microbiology, 2017;83(12):e00277-e00317. DOI: 10.1128/AEM.00277-17
[123] Miletic S, Simpson DJ, Szymanski CM, Deyholos MK, Menassa R. A plant-produced bacteriophage tailspike protein for the control of *Salmonella*. Frontiers in Plant Science. 2016;6:1221. DOI: 10.3389/fpls.2015.01221
[124] Hu Y, Yang H, Wang J, Zhang Y, Yu J, Wei H. Comparison between a chimeric lysin ClyH and other enzymes for extracting DNA to detect methicillin resistant *Staphylococcus aureus* by quantitative PCR. World Journal of Microbiology and Biotechnology. 2016;32(1):1. DOI: 10.1007/s11274-015-1971-6
[125] Simpson DJ, Sacher JC, Szymanski CM. Development of an assay for the identification of receptor binding proteins from bacteriophages. Viruses. 2016;8(1):17. DOI: 10.3390/v8010017
[126] Bielmann R, Habann M, Eugster MR, Lurz R, Calendar R, Klumpp J, Loessner MJ. Receptor binding proteins of *Listeria monocytogenes* bacteriophages A118 and P35 recognize serovar-specific teichoic acids. Virology. 2015;477:110-8. DOI: 10.1016/j.virol.2014.12.035
[127] Kot W, Hammer K, Neve H, Vogensen FK. Identification of the receptor-binding protein in lytic *Leuconostoc pseudomesenteroides* bacteriophages. Applied and Environmental Microbiology. 2013;79(10):3311-4. DOI: 10.1128/AEM.00012-13
[128] Javed MA, Poshtiban S, Arutyunov D, Evoy S, Szymanski CM. Bacteriophage receptor binding protein based assays for the simultaneous detection of *Campylobacter jejuni* and *Campylobacter coli*. PLoS One. 2013;8(7):e69770. DOI: 10.1371/journal.pone.0069770
[129] Smyth MS, Martin JH. x ray crystallography. Molecular pathology. 2000;53(1):8-14. DOI: 10.1136/mp.53.1.8
[130] Garcia-Doval C, van Raaij MJ. Structure of the receptor-binding carboxy-terminal domain of bacteriophage T7 tail fibers. Proceedings of the National Academy of Sciences of the United States of America. 2012;109(24):9390-5. DOI: 10.1073/pnas.1119719109
[131] Spinelli S, Desmyter A, Verrips CT, de Haard HJ, Moineau S, Cambillau C. Lactococcal bacteriophage p2 receptor-binding protein structure suggests a common ancestor gene with bacterial and mammalian viruses. Nature Structural and Molecular Biology. 2006;13(1):85-9. DOI: 10.1038/nsmb1029
[132] Milne JL, Borgnia MJ, Bartesaghi A, Tran EE, Earl LA, Schauder DM, Lengyel J, Pierson J, Patwardhan A, Subramaniam S. Cryo-electron microscopy - a primer for the non-microscopist. The FEBS Journal. 2013;280(1):28-45. DOI: 10.1111/febs.12078
[133] Spinelli S, Bebeacua C, Orlov I, Tremblay D, Klaholz BP, Moineau S, Cambillau C. Cryo-electron microscopy structure of lactococcal siphophage 1358 virion. Journal of Virology. 2014;88(16):8900-10. DOI: 10.1128/JVI.01040-14
[134] Labrie SJ, Samson JE, Moineau S. Bacteriophage resistance mechanisms. Nature Reviews. Microbiology. 2010;8(5):317-27. DOI: 10.1038/nrmicro2315