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MINIREVIEW

Bacteriophage Receptors, Mechanisms of Phage Adsorption and Penetration into Host Cell

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Abstract

Bacteriophages are an attractive tool for application in the therapy of bacterial infections, for biological control of bacterial contamination of foodstuffs in the alimentary industry, in plant protection, for control of water-borne pathogens, and control of environmental microflora. This review is mainly focused on structures governing phage recognition of host cell and mechanisms of phage adsorption and penetration into microbial cell.

K e y w o r d s: bacteriophage receptors, phage penetration mechanism

Introduction

Currently, the bacteriophage phenomenon may be regarded from different viewpoints. On one hand, bacterial viruses pose a grave challenge to industries based on bacterial agents applied in dairy processing, production of enzymes, antibiotics, solvents, insecticides, lactic and acetic acid, and various bacterial preparations when massive concentrations of biomass at active growth phase create favorable conditions for propagation of phages often responsible for lysis of industrial cultures. On the other hand, bacteriophages are objects that are attractive for application in medicine and veterinary practice for therapy of bacterial infections in humans and domestic animals. Bacterial viruses may also be used for biological control of bacterial contamination of foodstuffs in alimentary industry, agriculture; for control of water-borne pathogens, clinical pathogens causing aerogenic infections; control of environmental microflora, *etc.*

Solution of industrial bacteriophage problems and search for practical virus application require fundamental studies to analyze interactions between bacteriophage and host cell and to elucidate correlations of viral infection process in bacterial cell. Such interactions are rather complicated and do not always result in cell lysis. Now phage-cell relations are considered as process consisting of several sequential stages: phage adsorption on host cell surface and penetration of phage nucleic acid into cell, intracellular synthesis of virus components and assembly of virions, lysis of bacterial cell and phage release.

Adsorption is a key stage in virus recognition of sensitive host cell, *i.e.* specificity of phage infection is defined at this moment. Since bacteriophages, like any other viruses are obligate intracellular parasites, successful penetration into bacterial cell is an essential condition for continuation of their life cycle. This review is mainly focused on structures governing phage recognition of host cell and mechanisms of phage adsorption and penetration into microbial cell.

Bacteriophage receptors on cell surface

A specific bacteriophage strain is known to be able to infect a narrow host range or a concrete microbial species or strain. Such specificity in interaction of phage with bacterial cell is determined by specificity of adsorption, which in turn is dependent on the nature and structural peculiarities of receptors on bacterial cell surface (Braun and Hantke, 1997). In addition, a vital role is attributed to receptor localization on cell surface, their amount and density at various cell wall sites.

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The nature of receptors contacting bacteriophages is different for representatives of diverse taxonomic groups and is largely defined by composition of host cell wall and surface structures.

Receptors localized in cell wall of gram-negative bacteria. The outer membrane of gram-negative bacteria differs in structure from the inner membrane and from the plasma membrane of gram-positive microorganisms. One of the distinctive features is its high permeability caused by increased levels of integral proteins forming transport channels – up to 20 000 per cell (Nikaido, 2003). Another distinction is the presence in external lipid layer of a unique glycolipid – lipopolysaccharide (LPS) – typically exclusive for gram-negative bacteria. Proteins localized in membrane and various LPS sites may serve as bacteriophage receptors. In many cases phages require molecules of both types for adsorption (Lindberg, 1973).

Protein receptors. Proteins of outer membrane may be subdivided into 5 classes: 1) structural proteins interacting with peptidoglycan layer; 2) specific and non-specific porins forming membrane channels; 3) enzymes; 4) substrate receptors with high affinity; 5) transport proteins responsible for secretion.

Among structural proteins serving as receptors for virus adsorption, transmembrane protein OmpA was characterized. This protein comprises 8 antiparallel β-structures fixed inside membrane by non-covalent link to peptidoglycan layer with the free C-terminal vertex (Koebnik, 1999a; 1999b; Vogel and Jahnig, 1986). Mutants lacking the protein are distinguished by spherical shape and labile outer membrane. It was also shown that OmpA is involved in process of bacterial conjugation (Schweizer and Henning, 1977).

OmpA protein-LPS complex is capable to inhibit phage Tulb (coliphage isolated from effluents). Binding of bacteriophage with protein-LPS complex occurs reversibly, and precipitation of this complex with Mg^{+2} leads to irreversible phage attachment. Apart from protein, the LPS molecule is not able to inhibit phage particles (Datta *et al*., 1977). OmpA protein inhibits bacteriophage K3 in the solution, while mutants defective in this protein are resistant to phage infection (Van Alpen *et al*., 1977; Scurray *et al*., 1974). Such findings testify to the receptor role of the protein with respect to Tulb and K3, yet phage-recognising sites are located at different areas of the molecule. This assumption is supported by the existence of mutants producing sufficient amount of OmpA protein and sensitive to phage K3 but showing resistance to phage Tulb (Henning *et al*., 1978).

Porins were one of the first outer membrane proteins of gram-negative microorganisms to be characterized in detail (Nakae, 1976). These protein complexes are composed of 3 subunits forming the channel in bacterial membrane. Major proteins of this type in *E. coli* cells are OmpC and OmpF.

OmpC serves as a receptor for phages Hy2, ss4, Tulb and T4 (Scurray *et al*., 1974; Yu and Mizushima, 1982). Phage T4 utilized the protein as a receptor in combination with cell wall LPS. It was shown in experiments with LPS and OmpC mutants that absence of at least one receptor resulted in reduced efficiency of infection, whereas loss of both receptors induced bacteriophage resistance. Protein gp37 shaping tail fibers governs receptor recognition in phage T4 (Montag *et al*., 1990; Heller, 1990). The region is made up by approximately 14 amino acid residues and contains a large amount of histidine residues, responsible for OmpC recognition.

OmpF is a receptor for phage T2 (Riede *et al*., 1985; Hantke, 1978). In contrast to T4 phage, the receptor recognizing site is located within the hypervariable region of protein gp38 attached to terminal part of protein gp37. Instead of hystidine bases, gp38 includes glycine sequences (up to 9 residues) at terminal and internal loci. Protein receptors in the cell wall of *Shigella* and *E. coli* were revealed for bacteriophage T6 (Jesaitis and Goebel, 1952; Michael, 1968). Manning and Reeves demonstrated that *E. coli* with *tsx* gene mutation displayed resistance to bacteriophage T6 infection and in subsequent papers they isolated and purified protein Tsx (product of tsx gene) controlling the transport of nucleotides and proved its receptor function (Manning and Reeves, 1976; 1978).

Selective transport protein LamB is the receptor for phage λ (Randall-Hazelbauer and Schwartz, 1973). Unlike non-selective porins OmpC and OmpF, this protein forms a narrow channel specific for transport of maltose and derived polymers, using aromatic positively charged aminoacid residues (Charbit *et al.*, 1998). Bacteriophage λ recognizes LamB *via* protein gpJ – the factor defining host range of this phage.

Among enzymes localized in the outer membrane are proteases OmpT and OmpX which may serve as receptors for T-like phages with host range mutations M1 and Ox2, respectively (Hashemolhosseini *et al*., 1994a; 1994 b). Proteins TonA (later renamed FhuA) and TonB serve as receptors for phages T7, T5 and φ80.

Receptors with high substrate affinity are components of active transport system. Their function is to carry out solid binding of substances below demand by passive transport system, namely vitamin B12 and iron ions as chelating agents (Frost and Rosenberg, 1975; Hancock *et al*., 1976; Bassford *et al*., 1976).

Secretory transport proteins accomplish the function similar to substrate receptors, but in opposite direction, *i.e.* they transport diverse compounds out of the cell. So far phages using this protein type as receptors have not been detected.

Lipopolysaccharide receptors. In addition to proteins, LPS is another constituent of the outer membrane in gram-negative bacteria serving as a receptor for

bacteriophage adsorption. LPS is a complex polymer made up of monosaccharides and fatty acids. Structurally, it incorporates 3 parts – lipid A, core and O-chain (side chain, O-antigen). Lipid A usually is a disaccharide composed of two D-glycosamine moieties linked by β-1,6-bond with attached fatty acids (up to 8 residues) mediated by ester or amide group. Lipid A performs the role of hydrophobic anchor fixing in plasmatic membrane the whole construction bound *via* short oligosaccharide core to O-chain consisting of polymeric carbohydrate links (Wilkinson, 1996).

There are two types of LPS: Smooth (S) type is characterized by typical LPS structure, *i.e.* comprising lipid A, core and side chain.

Rough (R) type lacks O-chain but contains lipid A and the core.

Some bacteriophages might adsorb to both LPS types. Phages specific to S-type LPS display an extremely narrow host range specificity determined by large variability of O-antigen structure in bacteria of different taxonomic groups. Bacteriophages recognizing R-type and *vice versa* show a broader host range since the structure of LPS core is rather conservative in various species and genera of gram-negative bacteria.

A common feature of bacteriophages fixing to LPS O-chain is that their adsorption results in specific enzymatic cleavage of polysaccharide chain. ε^{15} and P22 may be referred to such phages possesing endorhamnosidase activity and ability to lyse the bond Rha-1 → 3-Gal in O-antigen of *Salmonella anatum* and *Salmonella typhimirium*, respectively (Takeda and Uetake, 1973; Kanegasaki and Wright, 1973; Iwashita and Kanegasaki, 1973; 1976; Eriksson and Lindberg, 1977; Eriksson *et al*., 1979). Bacteriophage φ1 (Reske *et al*., 1973) infecting *Salmonella johannesbury* is characterized by endo-1,3-N-galactoseaminidase activity (Chaby and Girard, 1980; Girard and Chaby, 1981).

Bacteriophage Ω8 adsorbed on the surface of *E. coli* O8 shows endomannosidase activity, breaking down Man-1 → 3-Man link between repeating oligosaccharides and releases prevailing levels of hexa- and nonasaccharides (Reske *et al*., 1973; Prehm and Jann, 1976; Wallenfels and Jann, 1974). It was demonstrated for bacteriophage Sf6 isolated from strain *Salmonella flexneri* serotype 3a that its adsorption is associated with hydrolysis of Rha-1 → 3-Rha bond in O-chain of LPS (Lindberg *et al*., 1978). Virus H-F6S is able to bind to *S. flexneri* strains containing O-chain in LPS. Mutant strains lacking O-antigen are resistant to phage H-F6S but they are sensitive to other phages, like T3, T4, T7, with the respective receptors lying in the area of LPS core. It seems in wild-type strains these areas are hidden by O-chain complicating access for bacteriophages.

In common, bacterial viruses adsorbing to O-antigen chain of LPS in gram negative bacteria recognize it *via* enzyme localized at the tail end, which upon recognition and attachment hydrolyzes one of the bonds in polysaccharide chain of O-antigen. Besides, described bacteriophages have a similar morphology – hexagonal head, short tail with base plate where spikes are localized. According to Bradley classification they are referred to group C (Bradley, 1967), and to *podoviridae* family according to modern classification.

Position of a receptor in O-chain of S-type of LPS is described for phage 2. This bacteriophage infecting wild type strain of *Pseudomonas aeruginosa* B1 is affiliated to group B according to Bradley classification and to *siphoviridae* family according to modern classification because it has a long expanded tail (Bartell *et al*., 1971). This phage displays depolymerase activity owing to the constituent enzyme. After treatment of bacterial cells with purified enzyme isolated from virion, bacteria *P. aerurinosa* lose phage sensitivity (Castillo and Bartell, 1976).

As mentioned above, structure of R-type LPS is limited by lipid A and the core region. In some mutant strains the structure of LPS core could be incomplete which according to a series of reports may result from disruption in core biosynthesis process occurring at different stages. Such structural aberrations could severely affect bacteriophage adsorption. For instance, phage F0 lysing wild-type *Salmonella* strains containing LPS with complete core. N-acetylglucosamine residue linked to the rest of the chain with α-1,2-bond is located at its terminal position. Mutants lacking this terminal glucosamine moiety are resistant to viral infection, and LPS isolated from such strains would not inactivate bacteriophage F0 (Lindberg, 1967; Lindberg and Hellerovist, 1971).

Phages ΦX174, S13 and 6SR also require full LPS core for *Salmonella* and *Shigella* adsorption, with certain distinctions. Phage ΦX174 infects *S. typhimirium* strains showing on outer membrane surface LPS with complete core not protected by O-antigen. Mutants lacking terminal N-acetylglucosamine are still able to bind virus, although at lesser degree. On the other hand, absence of terminal glucosamine residue does not influence adsorption of phage S13 (Jazwinski *et al*., 1975). Whole core terminating in glucosamine is essential for optimal adsorption of phage 6SR to cells of *S. typhimirium* and *S. flexneri*. Yet, mutants of *S. typhimirium* defective in core biosynthesis or mutants of *S. flexneri* containing LPS with disaccharide composed of glucose and heptose moieties at its terminal position are also sensitive to phage infection, but at a lower rate (Lindberg and Hellerovist, 1971).

The afore-mentioned phages behave in different way with respect to *E. coli*. Bacteriophage ΦX174 lysing *E. coli* C loses ability to adsorb to LPS lacking in its core terminal galactose residue (Feige and Stirm, 1976). Similarly, strain *E. coli* K12 sensitive to phage

6SR contains glucose moiety in the terminal position of LPS core (Picken and Beacham, 1977).

It is well known that receptors for T-phages, specifically T3, T4 and T7 are components of R-type LPS of *Shigella* and *Esherichia* (Jesaitis and Goebel, 1952; Michael, 1968; Weidel, 1958). Phage T3 is adsorbed on the surface of *S. flexneri* mutants harboring core terminated with glucose linked to heptose by glycoside bond. The LPS isolated from these strains possesses the highest inactivating capacity towards this virus. Phage T7 adsorbs best on *S. flexneri* mutants with core terminated with galactose residue bound to glucose. Mutant strains *E. coli* K12 with core ending up in heptose and glucose are able to adsorb phages T3 and T7 (Picken and Beacham, 1977). The highest inactivating potential for phage T4 was displayed by LPS isolated from *S. flexneri* possesing in the core terminal disaccharide glucose-heptose. Mutants with complete core are also sensitive to phage T4 infection but inactivating ability of their LPS is lower. In *E. coli* B cells the optimal receptor proved to be LPS containing Glu-1→3-Glu-1→3-Hep in core terminal position (Prehm *et al*., 1976).

Summing up, structure of LPS core responsible for recognition of the same bacteriophage may differ in bacteria of various microbial species and genera as demonstrated above by phages ΦX174, 6SR, T3, T4 and T7. It appears that major role in the receptor formation is played by spatial configuration around terminal glycosidic bond rather than terminal residue in polysaccharide chain of the core (Feige and Stirm, 1976).

Receptors localized in cell wall of gram-positive bacteria. Cell wall of gram-positive bacteria significantly differs from the gram-negative species both in structure and chemical composition. The main component is peptidoglycan making up from 40 to 90% of the cell dry weight. Peptidoglycan is a heteropolymer composed of disaccharide monomer formed by N-acetylglucosamine and N-acetylmuramic acid. A tetrapeptide most often having the following structure: L-alanine – D-glutamic acid – L-diaminopimelic acid – D-alanine is attached to a hydroxy group of N-acetylmuramic acid. This tetrapeptide mediates covalent links between peptidoglycan fibers so that cell wall represents a solid cover adjacent to the cell plasma membrane.

Teichoic acids are the other vital constituents of gram-positive microorganisms. They are water-soluble polymers comprising glycerol or ribitol moieties linked together by phosphodiester bond and traversing peptidoglycan layer in direction perpendicular to the surface of plasmatic membrane. Most teichoic acids contain large ratio of D-alanine bound to free hydroxy groups, but other substitutes, like N-acetyl-D-glucosamine or D-glucose are found more often. Teichoic acids constitute the bulk of bacterial surface antigens.

Examined bacteriophages specific to *Staphylococcus aureus*, namely phages 3C, 52A, 71, 77, 79 and 80 are irreversibly inactivated by a complex of peptidoglycan and teichoic acids supplemented in addition by tetrapeptide attached to muramic acid. Reversible adsorption may be achieved during phage binding with teichoic acids connected with glycan fibers but irreversible procedure requires presence of tetrapeptide in the complex. Presence of N-acetylglucosamine in teichoic acid formula and O-acetyl groups in muramic acid residue is also essential for phage adsorption (Lindberg, 1973; Coyettl and Gheysen, 1968; Chatterjee, 1969; Gheysen *et al*., 1968; Murayama *et al*., 1968; Shaw and Chatterjee, 1971).

Microorganisms of the genus *Bacillus* have the structure of peptidoglycan and teichoic acids similar to that of *S. aureus*. The only distinction is that N-acetylglucosamine as component of teichoic acids is substituted for D-glucose (Jazwinski *et al*., 1975). Due to this structural resemblance phages specific for *S. aureus* may adsorb on the surface of *B. subtilis* (Rakieten and Rakieten, 1937). D-glucose moiety plays a key role for adsorption of bacteriophages specific for *B. subtilis*. Phages Φ1, Φ25, Φ29, SP3, SP10, SP02 and μ were not able to adsorb on the surface of *B. subtilis* mutants lacking D-glucose in teichoic acid composition (Glacer *et al*., 1966; Hemphill and Whiteley, 1975; Young, 1968; Lindberg, 1973). Yet, some phages could infect bacterial cell without glycosylated teichoic acids in case growth occurred on the surface of solid nutrient media rather than in submerged culture (Yasbin *et al*., 1976).

Protein GamR involved in adsorption of phage γ was identified in cell wall of *B. anthracis*. This protein is probably the component of cobalt transport system. *B. cereus* and *B. thuringiensis* also display on the surface GamR-like proteins. Only *B. cereus* is sensitive to phage γ infection although electron microscope studies have shown adsorption of phage particles to cells of both microbial species. It appears, missing additional surface structures in *B. thuringiensis* cells are indispensable for cell penetration and further phage propagation (Davison *et al*., 2005).

Bacteriophages specific for *Lactobacillus delbrueskii* are inactivated by lipoteichoic acids isolated from cell wall of this microbial species. Inactivation degree depends on available D-alanine and L-glucose residues bound to fee hydroxyl groups of teichoic acids. An increase in D-alanine level results in reduced inactivating ability of lipoteichoic acids and their preliminary incubation with glucose-specific lectin ConA leads to complete inhibition of phage adsorption (Raisanen *et al*., 2007).

Bacteriophages infecting *Lactococcus lactis* initially adsorb to polysaccharide cell wall. For some phages this step is irreversible (Monteville *et al*., 1994;

Schafer *et al*., 1991; Valyasevi *et al*., 1990; Valyasevi *et al*., 1994). Rhamnose, glucose and galactose moieties, as a part of extracellular polysaccharides are responsible for primary recognition and attachment of phage virions. Phage eb7 is characterized by adsorption to glucosamine or galactosamine residues (Keogh and Pettingill, 1983). Viruses of lactic acid streptococci belonging to group 2c and phage kh require specific protein (a phage infection protein) for irreversible secondary binding with bacterial cell wall (Monteville *et al*., 1994; Babu *et al*., 1995; Geller *et al*., 1993; Valyasevi *et al*., 1991).

Receptors localized in capsular polysaccharides, pili and flagella. Many bacteriophages are attracted to bacterial pili, flagella, capsular and slime polysaccharides as receptors. Among viruses adsorbing to flagella several agents have been reported including phage χ infecting representatives of Enterobacteriacae family – *Salmonella*, *Serratia*, and *E. coli*, phage PBS7 attached to *B. subtilis*, *B. pumilus*, *B. licheniformis*, phage PBP7 specific to *B. pumilis*, phage 7–7–1 infects *R. lupine* (Shade *et al*., 1967; Lovett, 1972; Lotz *et al*., 1977). The phages have the same mechanism of adsorption, where the virion is fixed to the distal part of flagella *via* tail fibers. This adsorption stage is reversible; electron microscopic photos show that phage attachment does not result in release of nucleic acid from capside. Further on the virion moves closer to cell surface ultimately binding irreversibly to the baseplate of flagella.

Phages ΦAcM4 and ΦAcS2 infecting *Asticcacaulis biprosthecum* also specifically adsorb to flagella *via* site connecting head and tail of the phage whereas distal part of the tail remains free for adsorption to the surface of bacterial cell (Pate *et al*., 1973). The attached virion is able to move along flagella towards cell and also may adsorb to the surface of neighbor cell.

Many bacteria have external protective layers in the form of capsules or slime. Such layer may block access of bacteriophage to receptor localized in the cell wall or may be used for adsorption of phages, particularly those which fail to attach to bacteria devoid of capsules (Chakrabarty *et al*., 1967; Park, 1956).

One of the bacteriophage receptors located in capsules of gram-negative bacteria is Vi-antigen typical for representatives of *Salmonella*, *Citrobacter* and *E. coli*. The polymer consists of residues of N-acetyl-D-galactosaminuronic acid linked by α1,4-bond and partially O-acetylated (Luderitz *et al*., 1968). Studies on interaction of phage II with isolated Vi-antigen demonstrated that virion adsorption was accompanied by enzymatic cleavage of side acetyl groups while total chain depolymerisation did not occur (Taylor, 1965; 1966). The enzyme catalytically governing this reaction is localized in phage tail. Deacetylated Vi-polysaccharide loses capacity of further phage binding, but this property is recovered after reverse acetylation. It should be noted that such interaction is reversible, while components of bacterial cell wall are essential for irreversible binding.

Adsorption of other phages to capsular polysaccharides is also associated with enzymatic activity but in this case it is aimed at depolymerisation of main chain. Enzymes displaying endoglucosidase activity were characterized for phages of *E. coli* K29 and phage of Klebsiella K11 (Stirm *et al*., 1971a; 1971b). Virus K2 hydrolyzes capsule of *Aerobacter aerogenesis* using glucane hydrolase (Yurewicz *et al*., 1971) splitting α1, 3-bond between galactose residues. A common feature of these phages is their similar virion morphology and the interaction of phages with capsular polysaccharides is a reversible process. The capsule acts as a receptor for initial phage attachment whereas cell wall components are essential for irreversible binding (Taylor, 1966; Stirm *et al.* 1971b).

Viruses of 2 types are present among bacteriophages that are able to adsorb to pili of RNA-containing viruses with isometric capsid and DNA-containing viruses in the form of filaments. A peculiarity of such phages is that they use as receptors only sex pili of bacteria, able to adsorb several hundred phage virions. Phages P17, M12, fr, Qβ, f2, f4 infecting *E. coli* are most thoroughly studied among RNA-containing viruses. All above-mentioned phages composed of vast amount of identical subunits are about 27 nm in diameter (Hohn and Hohn, 1970). The second capside component is protein A responsible for recognition and adsorption of virion to pili (Roberts and Steitz, 1967). This protein is available in virion as one copy and upon RNA injection it penetrates into host cell with nucleic acid (Steitz, 1968a; 1968b; Krahn *et al*., 1972).

DNA-containing filamentous phages recognizing pili as receptors may be subdivided into 2 groups: Ff and If phages adsorbing to terminal parts of F and I pili, respectively (Meynell and Lawn, 1968; Schlesinger, 1932). Unlike RNA-containing phages, only few virions may adsorb to one pilus. Binding is also mediated by protein A, similar to RNA phage case (Meynell and Lawn, 1968).

Mechanisms of phage adsorption and penetration

Rate of adsorption is the value characteristic of each phage-host pair and it may vary depending on concentration of phage/host. Since bacteriophages do not have specific structures responsible for virion motion and, consequently, they cannot move independently, the adsorption process is the result of random phage-cell collision described by active mass law (Schlesinger, 1932). It appears therefore that as concentration of virions and bacterial cells grows, the number of random

collisions tends to rise which, in turn, leads to higher adsorption rate.

Rate of adsorption is also determined by a series of diverse non-specific physical-chemical factors (pH, temperature, presence in the media of certain substances and ions) and depends on host physiological state and cultural conditions (Hershey *et al*., 1994; Delbruck, 1940; Quiberoni and Reinheimer, 1998; Sillankorva *et al*., 2004).

Virion adsorption on host cell surface is usually illustrated as the process consisting of 2 stages: reversible and irreversible binding. It should be noted that molecular mechanisms of interaction at both stages of adsorption are specific for different phage-host systems and they may vary significantly in representatives of diverse taxonomic groups.

As a rule, penetration of nucleic acid takes place after irreversible adsorption phase. Mechanisms of this process are specific for each phage, or phage group. Electrochemical membrane potential, ATP molecules, enzymatic splitting of peptidoglycan layer or all three factors may be vital for penetration of genetic material inside the bacterial cell.

Processes of adsorption and phage penetration into cells are investigated in most detail for viruses of *E. coli*, namely T4, T5, T7 (Letellier *et al*., 2004). Some findings are available on processes of adsorption and penetration of viruses incorporating plasmatic membrane. Below these mechanisms will be considered separately for each virus.

T4-like phages. Initial stage of adsorption for T4-like bacteriophages consists in reversible attachment of long tail fibers to specific receptors on the surface of outer membrane. It is necessary for successful infection that 3 or more of tail fibers could adsorb to cell surface since they play a critical role in triggering conformational changes of phage tail essential for DNA penetration into the cell (Crawford and Goldberg, 1977; 1980; Arscott and Goldberg, 1976).

After phage gets attached to the cell *via* long fibers, baseplate changes its shape and as a result it takes stellar conformation. Finally 6 short fibers are generated and they irreversibly adsorb to heptose moiety in LPS core (Riede *et al*., 1985, Montag *et al*., 1987). Conformational alteration of baseplate simultaneously launches contraction of tail sheaths so that inner hollow tube punctures bacterial outer membrane (Moody, 1973). To facilitate penetration through peptidoglycan layer, enzyme lysozyme – an integral part of baseplate protein gp5 is localized at the end of the tube. X-ray spatial analysis of the complex has revealed that domain responsible for peptidoglycan degradation is located at C-terminal part of spike-form structure (Kanamaru *et al*., 2002). Contact of this site with phosphatidylglycerol of the inner membrane is a signal for DNA transport along tail tube and its introduction into the cell. Specific mechanism of DNA penetration *via* inner membrane remains to be elucidated, yet it is clear that phage tail does not penetrate through inner membrane and the process requires electrochemical potential on the inner membrane (Labedan and Goldberg, 1979).

Bacteriophage T7. Phage T7 infection results in restructuring of tail proteins making up a cylinder shape inside phage head. This structure consists of 3 protein gp16 copies, 12 protein gp15 copies and 18 protein gp 14 copies. In addition, phage head contains 2 other proteins playing a key role in DNA transport into the cell – gp13 and gp7.3. DNA molecule is spiraled onto the cylinder formed within the capsid.

Initially, phage T7 interacts with bacterial LPSs *via* tail fibers. As soon as such contact occurs, the signal triggering irreversible virion binding is transmitted into phage capsid. Phage tail, tail fibers and protein gp13 are involved in signal transfer. Irreversible binding is associated with degradation of proteins gp13 and gp7.3 while proteins gp14–16 pass through phage tail channel and shape the pathway across bacterial cell wall (Molineux, 2001; 2005). N-terminal part of gp16 is homologous to bacterial lytic enzyme transglycosylase making a major contribution in the restructuring of the peptidoglycan layer. Perhaps this domain is responsible for penetration of formed tubular structure through peptidoglycan to the inner membrane.

DNA transport *via* the channel slows down when the first 850 base pairs get into the cell. The reason is protein gp16 serves as a special clip retarding rate of DNA penetration. The essence of this mechanism is that partial DNA uptake initiates transcription process and produces inhibitor of cell restrictases. Slow penetration of nucleic acid allows to synthesize this inhibiting factor earlier than DNA sites sensitive to restrictases appear inside the cell (Molineux, 2001; 2005).

T5 and similar phages. Bacteriophage T5 includes hexagonal head 90 nm in size and long flexible tail around 200 nm. Protein FhuA localized in cellular outer membrane and engaged in transport of iron into the cell acts as a receptor for this phage. Adsorption to such protein is energy-sparing and irreversible, leading to DNA release in absence of other factors (Letellier *et al*., 2004).

It was shown that besides irreversible adsorption, T5 is able to bind reversibly to O-antigen of bacterial LPS (Heller and Braun, 1979; 1982). Irreversible binding accelerates DNA introduction into host cell but it is not a crucial factor in adsorption process. This conclusion was made after it was proven that loss of tail fibers by the phage and lack of LPS O-chain in bacteria would not affect plating efficiency.

The precise mechanism of DNA cellular uptake has not been established so far. It is known that injection of genetic material proceeds in 2 stages. Introduc-

tion of 8% DNA into cytoplasm causes a pause lasting 4 minutes (Lanni, 1965; 1968). Entered viral DNA controls synthesis of proteins responsible for degradation of bacterial DNA and switching off its transcription. Later DNA transport is resumed and the rest of nucleic acid is transferred inside bacterial cell.

Phages T1 and φ80 use the same transport protein FhuA as a receptor, although adsorption to it requires energy. Electrochemical proton gradient generated on inner membrane of bacterial cell by electron transport chain is applied as energy source. Electrochemical potential is transmitted to outer membrane *via* mediation of protein TonB. Its N-terminal part is anchored to cell inner membrane, while C-terminal interacts with FhuA receptor. Specific mechanism of energy transfer and mechanism of DNA transport into bacterial cell remains to be decoded.

Bacteriophages incorporating plasmatic membrane. Bacterial viruses structurally comprising lipid bilayer attract vivid interest due to large diversity of mechanisms engaged in viral infection of host cell. For instance, morphologically identical DNA-containing phages PRD1 and PM2 use different receptors for adsorption, have distinct cell penetration mechanisms and infect different hosts. Bacteriophage PRD1 is characterized by a relatively broad host range, including *E. coli*, *P. aeruginosa*, *S. enteric*, but it can infect only strains carrying conjugative plasmids of N, P or W type (Olsen *et al*., 1974). These plasmids encode bacteriophage receptor (Lyra *et al*., 1991). Capsid in the form of an icosahedron is constituted from 24 copies of protein P3, and each vertex is crowned with spikes consisting of proteins P2, P5 and P31 (Benson *et al*., 1999; Butcher *et al*., 1995; Mindich *et al*., 1982; Grahn *et al*., 1999; Rydman *et al*., 1999). Membrane vesicle surrounding double-stranded DNA is inside the capsid. Protein content in the membrane is approximately 50%.

At the first stage of adsorption the phage is reversibly bound to cell receptor *via* protein P2 and as a result spiky protein complex (P2, P5, P31) and a part of capsid proteins (P3) are released. Such modifications produce a hole in capsid envelope (Rydman *et al*., 1999). Further on phage membrane within the capsid is subjected to structural regrouping, yielding tubular tail penetrating into the bacterial cell *via* outer membrane and peptidoglycan layer (Lundstrom *et al*., 1979; Bamford and Mindich, 1982). Two proteins possessing lytic activity – P7 and P15 are localized in the newly generated membrane tube. These proteins acting concertedly break down peptidoglycan at the penetration site, generating small holes (Rydman and Bamford, 2000). Reaching internal membrane, bacteriophage-derived tube fuses with it, releasing DNA into cytoplasm. The process is accompanied by massive extracellular secretion of potassium ions and ATP molecules (Daugelavicius *et al*., 1997).

Phage PM2 also includes intracapsid membrane vesicle surrounding double-stranded DNA molecule (Espejo and Canelo, 1968). Penetration mechanism of genetic material in host cell is not thoroughly investigated but available data indicate that it differs significantly from that in phage PRD1. Adsorption to host cell surface is followed by capsid dissociation into protein constituents. Increased membrane permeability for lipophylic molecules of gramicidine B is also observed, pointing to potential fusion with bacteriophage membrane (Kivela *et al*., 2004). Protein P7 possessing lytic activity and probably playing an important role in the process of penetration through peptidoglycan layer was identified in membrane vesicle (Kivela *et al*., 2004). Penetration of genetic material inside the cell is associated with depolymerisation of the microbial inner membrane.

RNA-containing bacteriophage φ6 entering *P. syringae* cell, apart from nucleic acid, should inject RNA-dependent-RNA-polymerase because the host cell does not contain enzymes able to transcribe viral RNA. Structural peculiarity of this phage is the presence of outer lipid-protein envelope surrounding a capsid with confined complex – RNA plus RNA-polymerase (Bamford *et al*., 1976; Butcher *et al*., 1997; Kenney *et al*., 1992; Vidaver *et al*., 1973; Daugelavicius *et al*., 2005). Main receptors for phage φ6 are type IV pili (Bamford *et al*., 1976; Vidaver *et al*., 1973) where phage is attached *via* protein P3 (Daugelavicius *et al*., 2005; Romantschuk and Bamford, 1985). Integral protein P6 localized in plasmatic membrane of the virion initiates fusion of host outer membrane and phage lipid envelope (Daugelavicius *et al*., 2005; Bamford *et al*., 1987). As a result of such membrane integration the virus capsid with contained nucleic acid floods into the periplasmic space. Endopeptidase P5 localized in the capsid envelope splits the peptidoglycan layer at the point of attack and the virus nucleocapsid reaches the internal membrane of the bacteria, (Daugelavicius *et al*., 2005., Caldentey and Bamford, 1992; Mindich and Lehman, 1979). According to electron microscopy observations, the final stage of virus penetration into bacterial cell envisages generation of membrane vesicle incorporating phage nucleocapsid (Peisajovich and Shai, 2002). The process is similar to viral endocytosis in humans and animals (Smith and Helenius. 2004). Mechanisms of disclosing vesicle in host cytoplasm and virion decoating are not well established to date.

DNA-containing phage Bam35 infects cells of gram-positive bacteria *B. thuringiensis* and contains plasmatic membrane located within the capsid. The mechanism of phage penetration into the cell is not fully investigated. It is known that N-acetylmuramic acid residue – a cell wall component – serves as a receptor. Penetration through the peptidoglycan layer

is related to enzymes gp26 and gp30 localized in the capsid envelope. The transport of genetic material across the plasmatic membrane depends on presence of bivalent cations in the media, whereas phage adsorption and degradation of peptidoglycan are not dependent (Gaidelyte *et al.*, 2006).

Conclusions

The process of bacteriophage adsorption to a receptor on cell surface is the first stage in virus-host interaction. Adsorption phase defines phage-host specificity and mechanisms governing resistance of bacteria to virus infection. The nature of receptor, aspects of its chemical composition and spatial configuration, structure of viral receptor-binding protein and specific interaction mechanisms – all these factors play a key role in shaping stable bacteriophage-host population.

In early studies on phage-host interactions it was assumed to regard processes of adsorption and penetration of nucleic acid into bacterial cell separately from each other as different stages of a virus life cycle. The massive amount of data collected so far evidences a deep correlation between virus adsorption and penetration into bacterial cell. Irreversible adsorption stage virtually always initiates penetration of genetic material inside host cell. It appears desirable therefore to consider the first phase of interaction between virus and bacterial cell as a complex process comprising adsorption, structural alterations of virus and host cell wall and transport of nucleic acid into the cell.

It should be stated that analysis of literature findings indicates a large diversity of bacteriophage-host populations with respect to nature and structure of the receptor, virus antireceptor and molecular mechanisms of virion-cell interactions. It supports the conclusion that investigation of structural-functional aspects and interaction mechanisms for specific phage-host population is indispensable and doubts feasibility of creating general model embracing the whole spectrum of existing bacterial viruses and their hosts.

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