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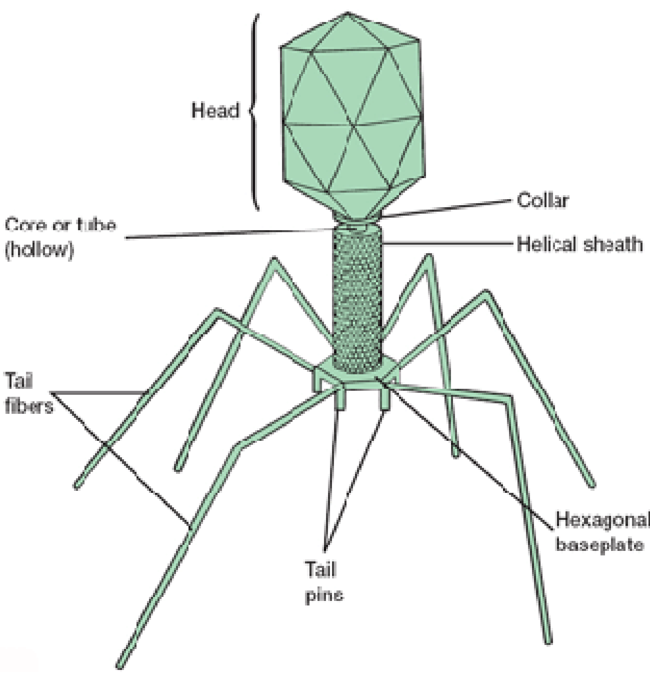
BACTERIOPHAGE

Bacteriophages are viruses that parasitize bacteria. Bacteriophages were jointly discovered by Frederick Twort (1915) in England and by Felix d'Herelle (1917) at the Pasteur Institute in France. Felix d'Herelle coined the term “Bacteriophage”. Bacteriophage means to eat bacteria, and are called so because virulent bacteriophage can cause the compete lysis of a susceptible bacterial culture. They are commonly referred as “phage”. Phages are obligate intracellular parasites that multiply inside bacteria by making use of some or all of the host biosynthetic machinery. They occur widely in nature and can readily be isolated from feces and sewage. There are at least 12 distinct groups of bacteriophages, which are very diverse structurally and genetically.

Examples of phages:

- T-even phages such as T2, T4 and T6 that infect *E.coli*
- Temperate phages such as lambda and mu
- Spherical phages with single stranded DNA such as PhiX174
- Filamentous phages with single stranded DNA such as M13
- RNA phages such as Qbeta

Composition:
Depending upon the phage, the nucleic acid can be either DNA or RNA but not both. The nucleic acids of phages often contain unusual or modified bases, which protect phage nucleic acid from nucleases that break down host nucleic acids during phage infection. Simple phages may have only 3-5 genes while complex phages may have over 100 genes. Certain phages are known have single stranded DNA as their nucleic acid.

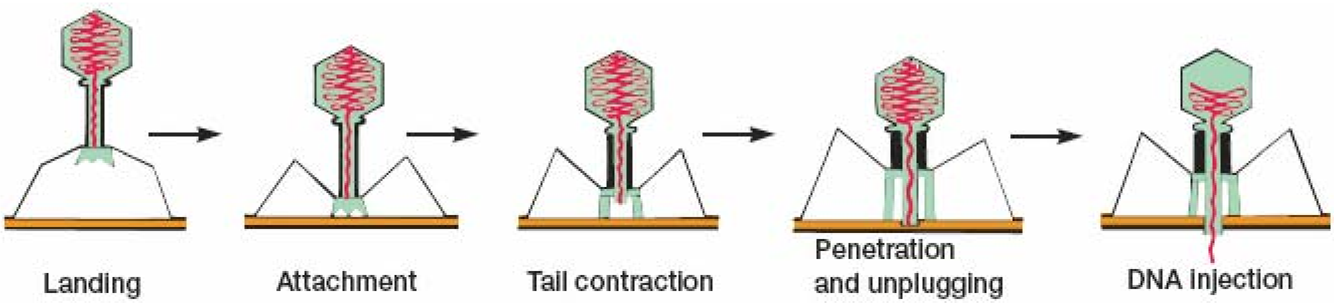


Morphology:
Most phages range in size from 24-200 nm in length. T4 is among the largest phages; it is approximately 200 nm long and 80-100 nm wide. All phages contain a head structure, which can vary in size and shape. Some are icosahedral (20 sides) others are filamentous.
The head encloses nucleic acid and acts as the protective covering. Some phages have tails attached to the phage head. The tail is a hollow tube through which the nucleic acid passes during infection. T4 tail is surrounded by a contractile sheath, which contracts during infection of the bacterium. At the end of the tail, phages like T4 have a base plate and one or more tail fibers attached to it.
The base plate and tail fibers are involved in the binding of the phage to the bacterial cell. Not all phages have base plates and tail fibers.

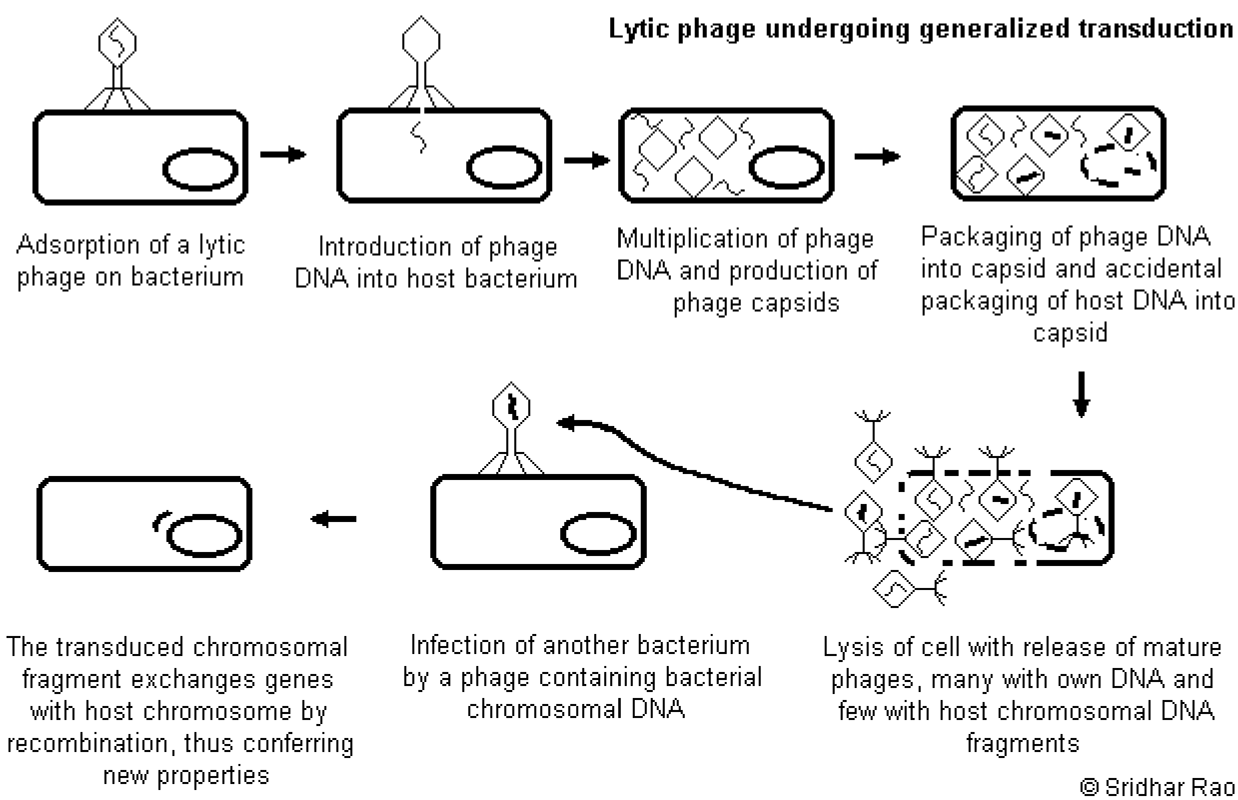
Life cycle:

Adsorption: The first step in the infection process is the adsorption of the phage to the bacterial cell. This step is mediated by the tail fibers or by some analogous structure on those phages that lack tail fibers. Phages attach to specific receptors on the bacterial cell such as proteins on the outer surface of the bacterium, LPS, pili, and lipoprotein. This process is reversible. One or more of the components of the base plate mediates irreversible binding of phage to a bacterium.

Penetration: The irreversible binding of the phage to the bacterium results in the contraction of the sheath (for those phages which have a sheath) and the hollow tail fiber is pushed through the bacterial envelope. Some phages have enzymes that digest various components of the bacterial envelope. Nucleic acid from the head passes through the hollow tail and enters the bacterial cell. The remainder of the phage remains on the outside of the bacterium as "ghost". Even a non-susceptible bacterium can be artificially infected by injecting phage DNA by a process known as transfection.



Depending on the life cycle, phages can either by lytic (virulent) or lysogenic (temperate). While lytic phages kill the cells they infect, temperate phages establish a persistent infection of the cell without killing it. In lytic cycle the subsequent steps are synthesis of phage components, assembly, maturation and release.



Lytic cycle:
Lytic or virulent phages are phages, which multiply in bacteria and kill the cell by lysis at the end of the life cycle. Soon after the nucleic acid is injected, the phage cycle is said to be in eclipse period. During the eclipse phase, no infectious phage particles can be found either inside or outside the bacterial cell. Eclipse phase represents the interval between the entry of phage nucleic acid into bacterial cell and release of mature phage from the infected cell. This phase is devoted to synthesis of phage components and their assembly into mature phage particles.

The phage nucleic acid takes over the host biosynthetic machinery and phage specified m-RNA's and proteins are made. In some cases the early phage proteins actually degrade the host chromosome. Structural proteins (head, tail) that comprise the phage as well as the proteins needed for lysis of the bacterial cell are separately synthesized. Nucleic acid is then packaged inside the head and then tail is added to the head. The assembly of phage components into mature infective phage particle is known as maturation. In Lysis and Release Phase the bacteria begin to lyse due to the accumulation of the phage lysis protein and intracellular phage are released into the medium. It is believed that phage enzymes weaken the cell wall of bacteria. The number of particles released per infected bacteria may be as high as 1000. The average yield of phages per infected bacterial cell is known as burst size.

Lysogenic cycle:
Lysogenic or temperate phages are those that can either multiply via the lytic cycle or enter a dormant state in the cell. In most cases the phage DNA actually integrates into the host chromosome and is replicated along with the host chromosome and passed on to the daughter cells. This integrated state of phage DNA is termed prophage. This process is known as lysogeny and the bacteria harboring prophage are called lysogenic bacteria. Since the prophage contains genes, it can confer new properties to the bacteria. When a cell becomes lysogenized, occasionally extra genes carried by the phage get expressed in the cell. These genes can change the properties of the bacterial cell. This process is known as lysogenic conversion or phage conversion.

Significance of lysogenic conversion includes:

- Lysogenic phages have been shown to carry genes that can modify the Salmonella O antigen.
- Toxin production by *Corynebacterium diphtheriae* is mediated by a gene carried by a beta phage. Only those strains that have been converted by lysogeny are pathogenic.
- *Clostridium botulinum*, a causative agent of food poisoning, makes several different toxins, 2 of which are actually encoded by prophage genomes.
- Lysogenised bacteria are resistant to superinfection by same or related phages. This is known as superinfection immunity.

The lysogenic state of a bacterium can get terminated anytime when it exposed to adverse conditions. This process is called induction. Conditions that favor the termination of the lysogenic state include: desiccation, exposure to UV or ionizing radiation, exposure to mutagenic chemicals, etc. The separated phage DNA then initiates lytic cycle resulting in cell lysis and releases of phages. Such phages are then capable of infecting new susceptible cells and render them lysogenic.

Phage Genetics:
The transfer of genetic elements from one bacterium to another by a bacteriophage is termed as transduction. Transduction can be generalized or specialized. The generalized transduction is seen in lytic cycle where segments of bacterial DNA are packaged inside phage capsid instead of phage DNA. When such phages infect new bacterial cells, the bacterial DNA is injected inside. This piece of DNA may then transfer genes to the host chromosome by recombination. Any bacterial gene may be transferred in generalized transduction. Generalized transduction is usually seen in temperate phages that undergo lytic cycle. Only those genes that are adjacent to the prophage are transferred in specialized transduction.

Significance of bacteriophages:

- Transduction is responsible for transfer of drug resistance, especially in Staphylococci
- Lysogenic conversion is responsible for acquisition of new characteristics
- Random insertion into bacterial chromosome can induce insertional mutation
- Epidemiological typing of bacteria (phage typing)
- Lambda phage is a model system for the study of latent infection of mammalian cells by retroviruses
- Phages are used extensively in genetic engineering where they serve as cloning vectors.
- Libraries of genes and monoclonal antibodies are maintained in phages
- They are responsible for natural removal of bacteria from water bodies

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