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Chapter 7

# Virology

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**Abstract:** Virology is the study of structure and characterization of viruses and this field is a recently emerged as a separate entity and gaining insights in microbiology. Viruses are obligate host dependent and cannot replicate outside the host due to absence of both replicative enzymes and metabolic enzymes. Hence, they depend on the host for replication and survival. Electron microscopes can be used to study the cellular details of viruses and their examination.

**Keywords:** Metabolic enzymes, Obligate host, Virology, Replication, Viruses

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## 1. General Characteristics of viruses:

Viruses consists of nucleic acid material surrounded by a protein coat known as capsid. Capsid is made up of protein sub units known as capsomers. Virus nucleic acid along with capsid is known as nucleocapsid. Some viruses consists of additional membrane surrounding the nucleocapsid known as envelope. Envelope of virus is obtained from the nuclear membrane or plasma membrane of the host during infection. Some viruses contain additional enzymes required for infection encoded with in the viral genome. A complete virus with nucleocapsid and enzymes is referred as Virion.

### 1.1.Virus Genome:

Viruses are highly flexible in their nucleic acid genetic make up and may contain ds DNA, ssDNA, ds RNA or ss RNA as their genetic material. In the case of viruses with ds RNA or ssRNA either +ve sense (similar to sequence in mRNA) or -ve sense (complementary to the sequence of mRNA) can be possible. Some viruses start with one of genetic material while infection and may change their genetic material in to other form during infection.

**1.2. Virus structure:**

Viral nucleocapsid can appear in two shapes and the overall appearance of the virus can be altered by envelope. Helical viruses are made of hollow cylinder with capsomers arranged in a helical manner. Icosahedral viruses show icosahedral symmetry with 20 triangular faces. The simple icosahedral capsid is made up of 3 capsomers with total of 60 capsomers arranged in the head. Some viruses does not possess any of the two symmetries and they show third type of symmetry known as complex symmetry. Examples include pox virus with brick shaped exterior and complicated internal arrangement. T4 bacteriophage also shows complex symmetry with Icosahedral head and helical tail.

**1.3. Virus replication:** Virus replication completes in major 5 steps those include:

1. Attachment: In this step virus contact the bacteria and attach to the bacteria for infection.

2. Penetration or Entry: Virus penetrates and inject the genetic material in to the bacterial cell.

3. Replication or Multiplication of virus: After entry in to the cell the virus under goes replication or multiply in the host to synthesize the proteins and replicate the genetic material.

4. Assembly: The synthesized proteins and Nucleic acid material will be packed in to the nucleocapsid and later on tail filbers and head of the virus are assembled to form a complete virion.

**5.** Lysis or release of virus: The bacterial cells after complete assembly lyses the bacterial cell to release the complete virion and is ready to start infecting the new bacterial cell.

## 2. Differences between bacteria and viruses:

| Contents | Bacteria | Virus |
|---|---|---|
| **Cell wall** | Bacteria cell wall is made up of peptidoglycan | Viruses do not possess cell wall and the nucleic acid is surrounded by capsid termed as Nucleocapsid |
| **Size** | Bacterial cells are larger compared than viruses ranging about 900-1000nm | Viruses are smaller in size ranging about 30-50nm |
| **Non living/Living** | They are living cells | They can replicate only inside the |

| | | |
|---|---|---|
| | | presence of host cell |
| **Mode of reproduction** | They can reproduce asexually by Binary fission | They insert their genome in to the host genome and make multiple copies in the host cell and released through lysis by induction |
| **Host dependence** | They are host independent | They can replicate inside the host itself and hence host dependent |
| **Ribosomes** | Present | Absent |
| **RNA or DNA** | RNA or DNA is present in the cytoplasm | RNA or DNA is enclosed inside protein coat called capsid |
| **Genetic material** | DNA is the genetic material | Either DNA or RNA can act as genetic material but not the both |
| **Infection** | Usually causes localized infection Ex: Pneumonia | Usually causes systemic infection. Ex: Flu |
| **Diseases** | Pneumonia, Meningitis, Typhoid, Food Poisoning | Common cold, Influenza, Hepatitis, AIDS |
| **Treatment** | Antibiotics | Antiviral drugs and vaccines |
| **Examples** | E.coli, K.pneumoniae, Staphylococcus | Influenza virus, Retro Viruses, Hepatitis B |

## 3. Classification of viruses:

Viruses are classified based on morphology, type of symmetry and base composition and mode of replication. Viruses that infects human are grouped currently in to 21 families a narrow range when compared to viruses that can infect vertebrates to protozoa and bacteria and fungi to plants.

### 3.1. **Morphology:**

#### 3.1.1 Helical symmetry:

Viruses with Helical symmetry show protomers arranged helical around the nucleic acid like a helical rods or as filaments spirally. In addition to arrangement as flexible or rigid or helical or elongated the virus can be characterized by their length, width, Pitch of the helix and number of protomers arranged around the nucleic acid. The most extensively studied helical virus is Tobacco mosaic virus.

### 3.1.2 Icosahedral symmetry:

Icosahedral symmetry consists of 20 equilateral triangular faces and 12 vertices. Lines through opposite vertices will define the axes of five fold symmetry - all structural features in polyhedron will repeat about five times at $360^0$ around any axes of five fold symmetry. Line through center of opposite triangular faces of five fold axes show three fold symmetry. Two fold symmetry is shown by lines of mid centers of opposite edges. Icosahedral symmetry with either spherical or polyhedron show five fold, Three fold and Two folds axes of rotational symmetry.

### 3.2. Chemical composition:

### 3.2.1. RNA viruses:

RNA viruses contains either ss RNA or ds RNA as their genome in which more than 20% of RNA viruses can vary in their genomes due to high error rate during the replication. In case of RNA viruses either + strand or sense strand and - ve strand or anti sense strand are present where sense strand is similar to mRNA and can translate in to proteins where as antisense strand is complementary to mRNA and can synthesize the new proteins only after synthesis of sense strand.The genome of the virus can be present as complete whole or in two or more segments referred to as segmented genomes.

dsRNA viral genomes for example reo virus contains 10,11,12 segmented genomes and enzymes required for replication, 3 capsid proteins and many of small structural proteins. The segmented genome with sense strand and anti sense strand are organized as linear ds molecule with hydrogen bonds. The mode of replication is very complex and only sense strand is released for replication.

The retro virus genome is made up of 2 identical plus strand ssRNA composed of 7-11kb in length and the individual segments are connected non covalently at terminal ends. Retroviruses contains 2 enveloped proteins coded by env gene, 4-6 nonglycosylated core proteins and 3 non-functional structural proteins i.e., Reverse transcriptase, Integrase and protease (RT,IN,PR) encoded by gag gene. Retro virus possess Reverse transcriptase enzyme which reverse transcribes DNA from RNA and one of the example of retro virus is HIV.

### 3.2.2. DNA virus genomes:

DNA virus genomes contain a single copy of ds linear DNA. Papova viruses containing Polyoma and papilloma viruses contain genome circular ds DNA comprises of 5.1 and 7.8kb and the DNA is accessible for both transcription and self replication. Two or three structural proteins will make the papova virus capsid and 5- 6 non functional structural proteins are required for Virus transcription, DNA replication and cell transformation.

ss linear DNA of 4-6 kb in size is present in parvo virus and circular ssDNA of only 1.7 to 2.3kb is found in circovirus which is the example of small autonomously propagating viruses. Adeno associated viruses are known as defective phages as they are unable to produce new virions with out the help of helper viruses like Adeno virus or herpes virus.

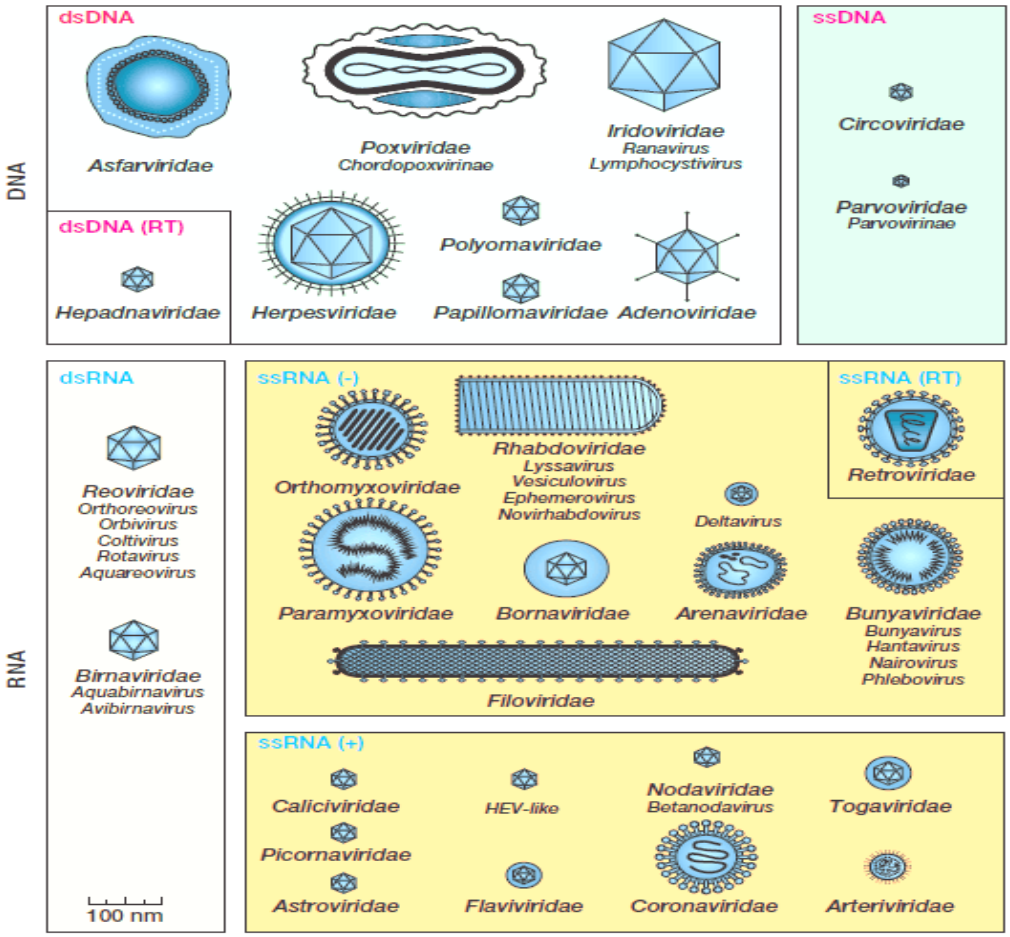


Figure :11 Classification of viruses based on DNA and RNA. [Taken from Claude m. Fauquet (1999).Taxonomy, classification and nomenclature of viruses in encyclopedia of virology (second edition) ].

## 4. Physico chemical structure of TMV:

TMV is a non enveloped filamentous virus with ss positive sense RNA as the genome. It is the causative agent of the tobacco mosaic disease and Franklin et al., was the first person

to study the structure of TMV in 1957. TMV shows helical symmetry with protomers arranged helical around RNA with a size of 18x300 nm and mol. Wt of $39x10^6$ daltons.

**4.1. Components:**

The virion consists of central core of 4nm around which protomers are arranged helical surronding the central core and the total diameter of virion with cental core is around 18nm. Inside the helical capsid, the positive sense ss RNA is spirally coiled to form a helix. The protein coat or capsid is made up of around 2,130 capsomeres arranged in to capsid. Each capsomere comprises of single polypeptide chain with 151 amino acids and having molecular weight of around 17,500 dal. A single capsomere contact about 3 nucleotides of RNA. The pitch of the helix is around 2.3nm and the overall diameter is 18nm including central core of 4nm.

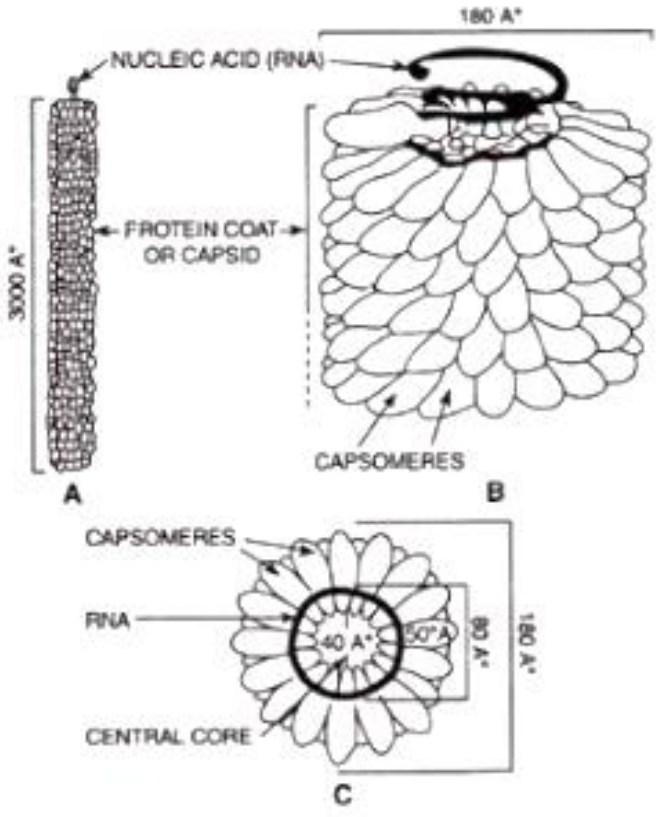


Figure: 12 : Structural organization of TMV [ Taken from Scholthof, K.-B. G. 2004. Tobacco mosaic virus: A model system for plant biology. Annu. Rev. Phytopathol. 42:13 34. http://www.ncbi.nlm.nih.gov/ entrez/query.fcgi? cmd= Retrieve&db=pubmed&dopt=Abstract&list_uids=15283658&query_hl=5].

Denaturation and phase transition studies of TMV reveals the structure to be a stack of piles overlapped with one and another to form a hollow cylinder where as X-ray crystallographic studies confirms the structure as helical turns instead of stack piles arranged inside the hollow cylinder. Total capsomeres will take around 130 helical turns over the ssRNA of the TMV to form the nucleocapsid.

**4.2. Genome:**

Genome of TMV is monopartite with positive sense ssRNA packed inside the protein helices. It comprises around 6,395 nucleotides. The genome of TMV is made up of 4 genes namely MET (Methyl transferase and RNA helicase ), RNA dependent RNA polymerase, Movement protein and coat protein. At 5' end TMV has a cap and hence can be used as mRNA and 3' end of the genome folds in to transfer RNA.

**4.3. Multiplication of the virus:**

1. **Infection or entry in to host:** Enter of TMV in to plant host requires wound incision or abrasion by which virus can enter the systemic circulation easily and transported along with the photosynthates in the pholem and colonize the cells and spread to other cells through cell- cell movements.

2. **Movement to adjacent cell:** Plant cells are interconnected through each other through narrow strands called plasmodesmata and neither RNA nor TMV can pass freely through the strands. Movement proteins coats to the thin ssRNA and make the TMV to pass through plasmodesmata and infect the adjacent cells. TMV moves slowly less than 1mm per day and can spread to the adjacent cells to cause the systemic infection.

**4.4. Genome Replication:**

- Uncoating of virus particle can occur inside the cells where the virus act as infectious particle.
- The TMV of virus can acts as both genome and mRNA and can be used for self replication and translation for the synthesis of new proteins and viral genome.
- The genome of TMV is made up of 4 genes namely MET (Methyl transferase and RNA helicase ), RNA dependent RNA polymerase, Movement protein and coat protein.
- At 5' end TMV has a cap and hence can be used as mRNA and 3' end folds in to transfer RNA.

**4.5. Replication of the virus:**

- Unlike bacteria TMV cannot translate the polycistronic mRNA and hence the replication is different in the case of TMV.

- The replication of TMV begins with synthesis of RNA dependent RNA polymerase which can acts as transcriptase and can direct the replication of the genome.
- The plus strand can itself act as mRNA and can synthesise the new proteins and for replication the positive strand is directed to synthesize the complementary negative strand intermediate forms called replicative forms (RFs) to synthesize the more copies of the genome + strand ssRNA.

**4.6. Assembly:**

- With the help of ribosomes and tRNA ample copies of protomers are synthesised.
- The new virions are synthesized by packing the protomers in to capsid and arrangement of genome around inside the protein helices.

## 5. Physico chemical structure of Herpes Virus:

Herpesviridae family include herpes viruses consists of large and complex double stranded DNA as genomes. Of 100 herpes viruses known 8 are known to cause infection in humans. 8 viruses that cause infection to human are: herpes simplex virus 1, herpes simplex virus 2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, Human herpesvirus-6, Human herpesvirus-7, and Kaposi's sarcoma herpes virus.

**5.1. Classification :**

Herpes viruses are classified in to three major classes:

1. α herpesviruses: These include herpes simplex virus 1, herpes simplex virus 2, varicella-zoster virus that contain short replication cycle and induce cytopathology in single layer cells and the viruses of this class exhibit broad host range.

2. β herpesviruses: Cytomegalovirus, Human herpesvirus-6, Human herpesvirus-7 are included in this class and these viruses possess long replication cycle with narrow host range.

3. γ herpesviruses: Epstein-Barr virus and human herpesvirus 8 comes under this group with a narrow and restricted host range.

**5.2. Transmission:**

Herpes viruses are transmitted to susceptible hosts through direct physical contact with the infected person. The transmission of virus can be possible through air borne and transmission details of human herpes viruses are summarized in the below table.

| Virus | Transmission |
|---|---|
| Herpes simplex virus 1 (HSV-1) | Through Lesions and Body fluids |
| Herpes simplex virus 2 (HSV-2) | Sexual contact, Through Genitally infected mother during birth |
| Herpes simplex virus 3 (VZV) | Direct contact and through Respiratory route |
| Herpes simplex virus 4 (CMV) | Through saliva, Sexual contact (Probably) and Transplacentary |
| Herpes simplex virus 5 (EBV) | Through infected body fluids saliva and urine, Transplacentary,Transplantation and blood transfusion |
| Herpes simplex virus 8 (KSHV) | Through infected fluids like saliva and through sexual contact |

**5.3. Structure of Virion:**

Herpes virus is made up of ds and non segmented DNA approximately 120 to 250bp in length and encode around 70-200 genes.

Herpes virus will possess four layered structure :

1. Core: ds DNA is arranged in the form of torus

2. Capsid : Surronding the DNA the capsid of 100nm in diameter is present and it composes around 162 capsomeres arranged with icosahedral symmetry.

3. Tegument: Present between capsid and envelope asymmetrical and amorphous substance with enzymes required for the virus chemical processes which can be subverted to virion production, enzymes required for immediate defense responses of virus against host defense systems and some others those with unidentified function.

4. Envelope: Surrounding the nucleocapsid, presence of membrane known as envelope and it is acquired either from the nuclear membrane or plasma membrane of the host during infection. Envelope contains unique glycoproteins with 150-200nm in diameter is present in Herpes virus referred as peplomers. Peplomers are usually spherical or pleomorphic with T= 16 icosahedral symmetry.

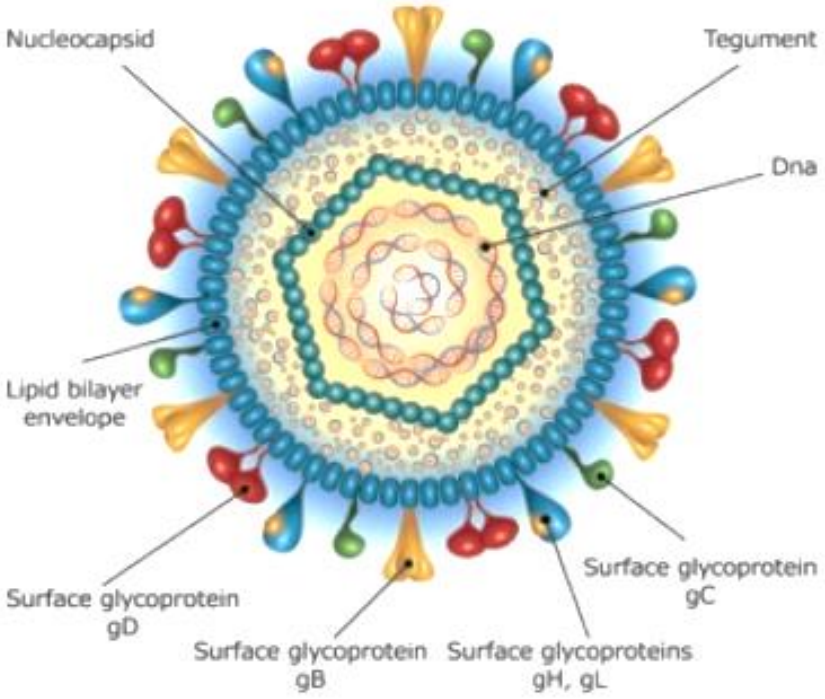


Figure: 13 Structure of Herpes Simplex virus [ Taken from Maximova, Natalia & Pizzol, Antonio & Sonzogni, Aurelio & Gregori, Massimo & Granzotto, Marilena & Tamaro, Paolo. (2015). Polyclonal gammopathy after BKV infection in HSCT recipient: A novel trigger for plasma cells replication?. Virology Journal. 12. 10.1186/s12985-015-0254-z].

**5.4. Multiplication:**

Transcription, Replication of genome and assembly occurs in the nucleus. The expression of genes in the virus occurs in the following order.

1. Immediate early genes: Necessary for regulatory function

2. Early Genes: Required for transcription and replication

3. Late genes: Required for synthesis of structural genes

Tegument and envelope are acquired during budding of the virus from the nucleus or E.R. The host cell will die as the mature virions are released through lysis and some may remain latent and reactivate at any time and the stimulant for reactivation is not known.

## 6. Physico chemical structure of Polyoma virus:

Polyoma viridae is the family where poly means many and oma means tumor formally grouped with Papilloma virus and contains naked , non enveloped capsid with icosahedral symmetry. The diameter of capsid is about 45nm. Genome of polyoma virus is closed circular ds DNA complexed with histones.

Genome of virus encodes 3 genes VP1, VP2 and VP3 that encodes viral capsid. The virus is entirely host dependent and replicates in the nucleus. Examples of polyoma viruses include JC - Virus and BK-Virus that causes Multifocal leukoencephalopathy (JCV) and renal diseases in immunocompromised individuals (BKV).

BK virus is transmitted to host by respiratory route or infected fluids like urine and JK virus is transmitted through respiratory route.

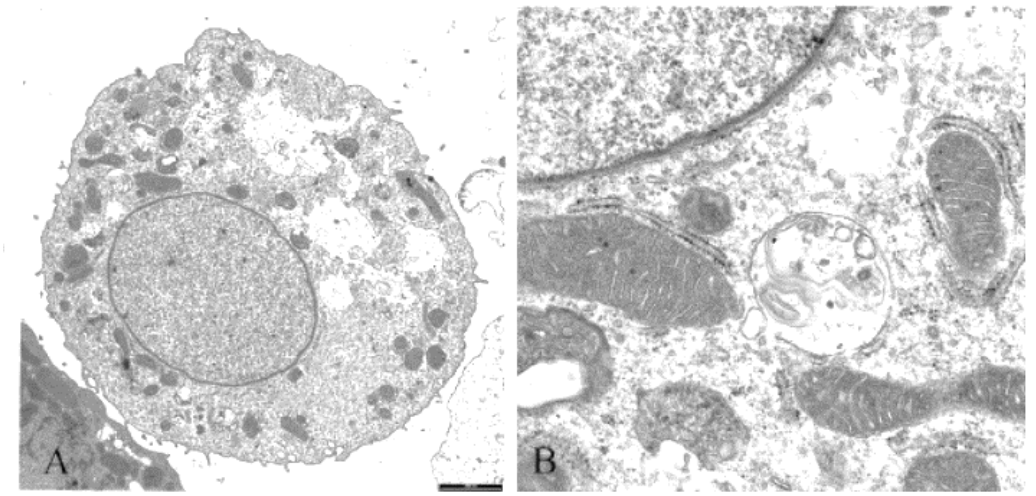


**Figure:14** Polyoma virus infecting the Epithelial cells of the urinary tract [ Taken from Pappo O, Demetris AJ, Raikow RB, et al. Human polyoma virus infection of renal allografts: histopathological diagnosis, clinical significance, and literature review. Mod Pathol 1996;9(2):105-109].

**6.1.Morphology:**

Mature virions measure about 40- 45nm in diameter and contains approximately 88% of protein and 12% of DNA.VP1 is the major capsid protein and contribute around 75% of the total protein in most of the mammalian polyoma viruses and however in bird polyoma viruses additional protein VP4 may be present. The virions contains non enveloped capsid with T=7 dextro icosahedral symmetry and made up of 72 pentameric capsomers. Each pentamer is associated with one VP1 protein and the capsomers are interlinked by VP1 at C-terminal arm.

Capsomers are further stabilized by the Ca+2 ions and disulfide bonds and VP2&3 may form hair pin bonds in the internal cavity of each pentamer. VP4 of the bird polyoma virus is present between VP1 and viral genome and each virion contains single copy of ds DNA. Free lipids and carbohydrates (either in free or attached ) are completely absent in the virion. However covalent linkage of myristic acid to Gly-2 is highly conserved in mouse polyoma viruses and mutation of which in MPyV hampers viral replication that results in less pathogenicity and infectivity in hosts.

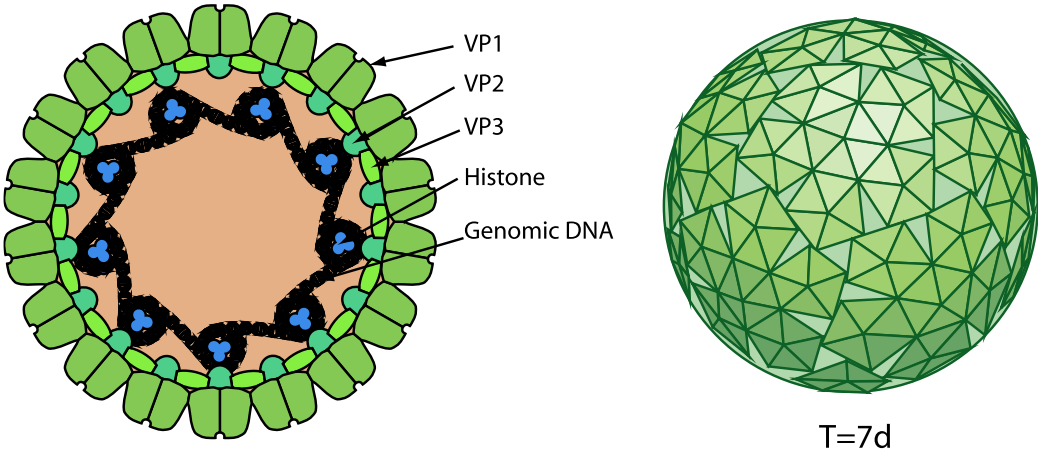


Figure: 15 Figure showing the structure and symmetry of polyoma virus.[ Taken from Pappo O, Demetris AJ, Raikow RB, et al. Human polyoma virus infection of renal allografts: histopathological diagnosis, clinical significance, and literature review. Mod Pathol 1996;9(2):105-109].

**6.2. Synthesis of virions:**

Typical polyoma virus encodes around two major proteins large tumor antigen (LTAg) and small tumor antigen (STAg) and express as early immediate genes and synthesis of three capsid proteins VP1,2 &3 expression onset begins after replication and termed as

late structural genes. A well populated polyoma viruses express a open reading Frame (ORF) as a separate sequence as a part of alternative tumor antigen or ALTAg. It can also be expressed as part of middle tumor antigen (MTAg) during early infection. VP4 encoded by SV40 virus as a additional late protein and may not be included as structural protein.

Putative ORFs for VP4 may be present in JC virus and BK virus and VP4 does not possess similarity to Agnoprotein expressed by other mammalian viruses. This protein may be expected to be involved in genome packaging and capsid formation in other mammalian viruses.

## 7. T4 Bacteriophage:

T4 bacteriophage is one of the bacteriophages that infect E.coli (T1-T7) suggested by Delbruck and his coworkers as models used for studying phage immunityduring the period of 1944. In T- even phages (T2, T4 and T6) are similar in their structure, antigenic nature and genetics. Many early findings in genetics like Genetic code and confirmation of DNA as the genetic material are based on the studies on T even phages. In 1959, Brenner et al. Tried and succeeded in picturisation of T even phages using electron microscope.

Bacteriophage T4 is classified under the family Myoviridae and order Caudovirales due to the presence of contractile tail. The phage head and tail fibers are assembled separately and they are united to form the complete virion. T4 bacteriophage possess dsDNA as its genetic material made up of 168kbp and composed of 289 ORFs. The mature head possess $1150A^0$ long and $850A^0$ wide prolate head which encapsulates the genome. A $925A^0$ in length and $250A^0$ wide contractile tail and is attached to special polar vertex present at one end of the head. The contractile tail is attached to hexagonal base plate at other end of the tail and long tail fibers (LTFs) are attached to hexagonal base plate. LTFs serves as sensors to recognize the receptors on the host for active infection.

Six short TFs unfolds after the host recognition and STFs after unfolding binds irreversibly to the host there by increasing the infection. The contractile tail increase the efficiency of infection by penetrating the tail tube and injecting the phage genome in to the host cell.

T4 bacteriophage can undergo both lytic and lysogenic cycles of infection in host. Lytic cycle results in immediate lysis of the host cell and releasing the phages there by the phages can begin the new round of infection. In some cases the phage can show lysis inhibition where all the phages may not be released outside when the extracellular phage particle concentration is found to be high.

Lysogenic cycle may not lead to immediate lysis of the cell instead the phage genome will integrate in to the host cell and replicates along with the host genome. The integrated phage genome is termed as prophage and when the host cell conditions deteriorate the prophage becomes active and leads to immediate lysis of the host cell. The phages which exhibit lysogeny are known as temperate phages and the phenomenon is termed as lysogeny.

Example of phages that show lysogeny include lambda phage. Lysogeny can add advantage to bacterial cells by the process called lysogenic conversion where the bacterial strains like corynebacterium or vibrio cholerae becomes highly virulent and can produce diphtheria and cholera toxoids in high potent form.

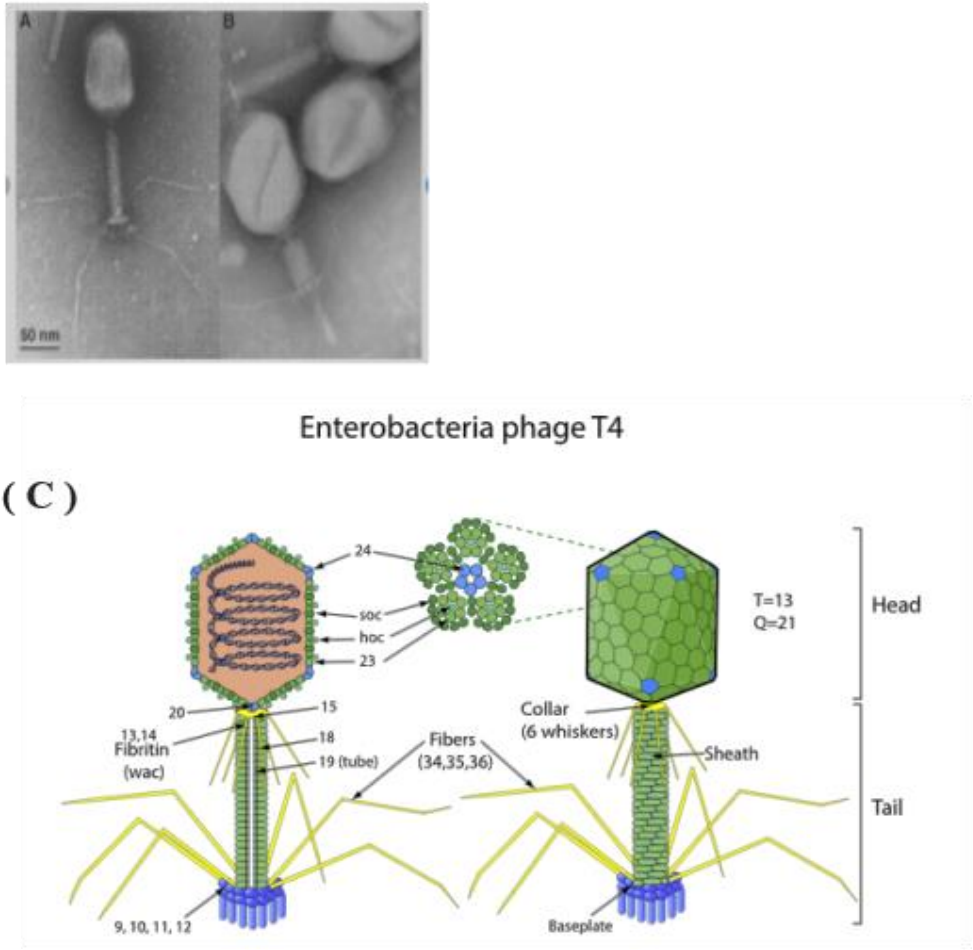


Figure:16 Figure (A) & (B) Electromicrograph showing the structure of T4 Bacteriophage, ( C ) Structure of T4 Bacteriophage [Taken from Miller, Eric & Kutter, Elizabeth & Mosig, Gisela & Arisaka, Fumio & Kunisawa, Takashi & Rüger, Wolfgang.

(2003). Bacteriophage T4 Genome. Microbiology and molecular biology reviews : MMBR. 67. 86-156, table of contents. 10.1128/MMBR.67.1.86-156.2003].

### 7.1. Synthesis of Nucleic acids and proteins:

With in short time period the ribosomes start translating the mRNA and synthesise the proteins required for viral genome duplication. In case of RNA phages RNA polymerase is synthesized first to facilitate the replication. During the new phage synthesis the host cell replication and protein synthesis is arrested and the helper proteins of the phage will help in packaging and phage assembly.

### 7.2. Phage assembly:

Phage base plate will be formed first and the tail fibers are assembled afterward. The capsid heads are assembled separately and the phage heads and tails are attached after packing of Genome in to the phage head. The amount of phage components synthesize will be critical for the successful production of mature T4 bacteriophage virions.

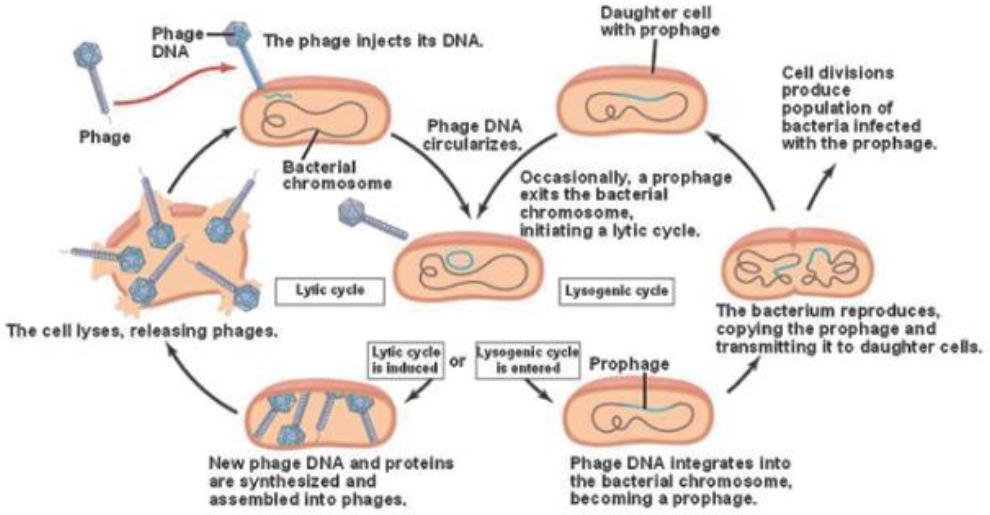


Figure:17 Overview of Lytic and Lysogenic cycle. [Taken from Vander Elst, Niels & Meyer, Evelyne. (2018). Potential therapeutic application of bacteriophages and phage-derived endolysins as alternative treatment of bovine mastitis. Vlaams Diergeneeskundig Tijdschrift. 87. 181-186. 10.21825/ vdt.v87i4.16 065].

### 7.3. Release of virions:

- Phages may be released by lysis or by extrusion or budding. T4 bacteriophages undergo lytic cycle and causes release of phage particles through lysis.

- Filamentous phages secrete new virion particles from the cell surface. One of the example of filamentous phage is M13 phage that releases from host cell through budding process.
- Temperate phage did not lyse the host cell and remains integrated and remains as temporary residents of the host cell.
- Around 15-30 min is required to complete one round of lytic cycle by T4 bacteriophage.

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