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Viral Replication

Viral replication is the formation of biological viruses during the infection process in the target host cells by generating abundant copies of its **genome** and packaging these copies into viruses, the virus is able to continue infecting new hosts. Replication between viruses is greatly varied and depends on the type of genes involved in them. Most DNA viruses assemble in the nucleus while most RNA viruses developed solely in the cytoplasm. Genome of RNA or DNA viruses exist in considerable variety of sizes and shapes, from small molecules of single-stranded RNA or DNA to a large double stranded molecules that may be linear or circular. Whatever their physical nature viral RNA or DNA molecules must be replicated efficiently within an infected cell to provide genomes assembly into progeny virions.

Not all infections lead to new progeny virus. *Productive* infections occur in permissive cells and result in the production of infectious virus. *Abortive* infections fail to produce infectious progeny, either because the cell may be non-permissive and unable to support the expression of all viral genes or because the infecting virus may be defective, lacking some functional viral gene. *A latent* infection may ensue with the persistence of viral genome, the expression of no or few viral genes and the survival of infected cell. So, the pattern of replication may vary for a given virus, depending on the types of host cell infected.

Viral genomes contain information which:

- Ensure replication of viral genomes.
- Ensures packing of genomes into virions.
- Alters the structure and/or function of the host cell to a greater or lesser degree.

Virus Replication Strategy:

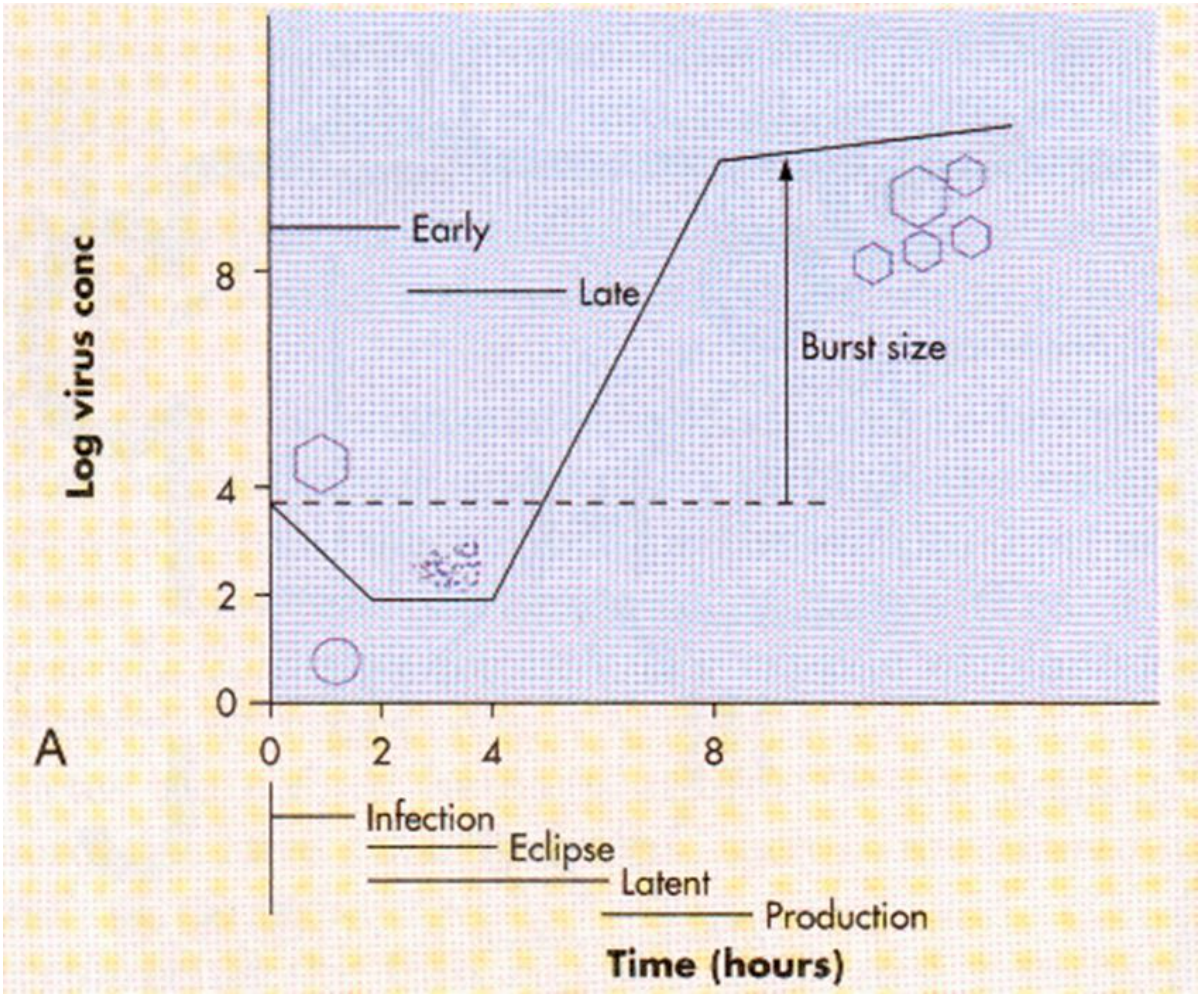
Viral strategy refers to the manner in which each virus carries out the infections. Generally:

- The virus needs to make mRNA that can be translated into protein by the host cell translation machinery.
- The virus needs to replicate its genome.
- Host enzymes for mRNA synthesis and genome replication.

Multiplicity of Infection:

Our understanding of the life cycle of viruses has been developed by studying virus infections under conditions where cell cultures become infected synchronously with virus, infection can be achieved by infecting culture with a high amount of virus such the cells within the culture become infected rapidly. A typical one step growth analysis begins with the addition of virus to cells and can be divided into several phases:

1. Initial phase: adsorption of virus (after 1 hr.).
2. Eclipse phase: No infectious virus can detect during this time, lasts for 10-12 hr. the period during which the input virus becomes uncoated.
3. Synthetic phase: starts around 12 hr. post infection during which new virus particles are assembled.
4. Latent period: during this period production will reach a maximum plateau level, after 18 hr. extracellular virus is detected.



Steps in the **Replication Cycle** of viruses are still composed of sic steps:

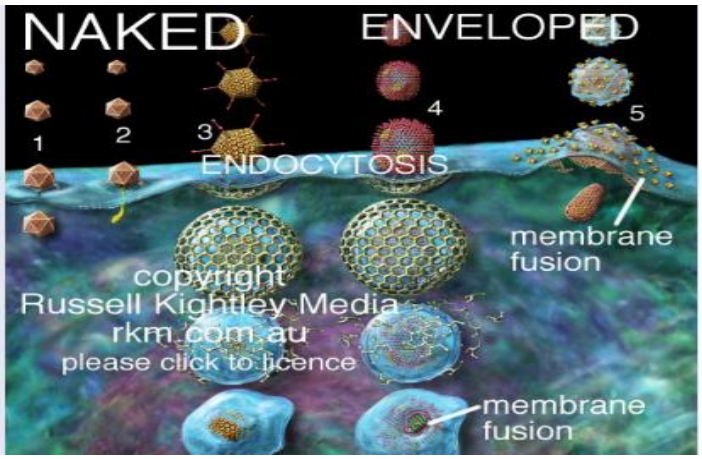
1. **Attachment/**

   It is the interaction of a virion with a specific receptor site on the surface of a cell (adsorption step). Receptor molecules differ for different viruses but are generally glycoproteins (Picornaviruses), in others may be oligosaccharides (Orthomyxoviruses and Paramyxoviruses). The presence or absence of receptors plays an important role in cell tropism and viral pathogenesis. Not all cells in susceptible host will express the necessary receptors for example poliovirus is able to attach only to cells in the central nervous system and intestinal tract. The attachment step may initiate irreversible structural changes in the virion.

Virus	Target cell	Receptor
Epstein Bar virus	B- cell	CD21
Human Immuno-deficiency virus	Helper T cell	CD4
Rhinovirus	Epithelial cell	ICAM-1 Intracellular adhesion molecule
Rabies cell	Neuron cell	Acetylcholine receptor
Influenza virus	Epithelial cell	Sialic acid
B19 Parvovirus	Erythroid precursor	Erythrocyte P antigen (globoside)

2. **Penetration/**

   Or engulfment mean the taken up of virus particle inside the cell. Unlike attachment, viral penetration is an energy- dependent process. The cell must be metabolically active for this to occur. Three mechanisms may be involved: *Translocation* of the entire virion across the cell membrane. *Endocytosis* of the virus into intracellular vacuoles eventually in the cytoplasm. *Fusion* of viral envelope with the cell membrane and this require the presence of a viral fusion protein in the virus envelope ex. Influenza haemagglutinin.



3. **Uncoating/**

   It is the physical separation of the viral nucleic acid from the outer structural components of the virion occurs with or shortly after penetration. The genome may be released as free nucleic acid (picornaviruses) or as a nucleocapsid (reoviruses). The nucleocapsid usually contains polymerases. Uncoating required acidic pH in the endosome. The infectivity of the parental virus is lost at the uncoating stage.

4. **Genome expression and replication (Biosynthesis):**

   i. Early transcription
   ii. Early translation
   iii. Replication of viral nucleic acids (Complementarily)
   iv. Late transcription
   v. Late translation…

   The essential theme in viral replication is that specific mRNAs must be transcribed from the viral nucleic acid for successful expression and duplication of genetic information. This is accomplished; viruses use the components to translate the mRNA. Various classes of viruses use different pathways to synthesize the mRNA depending on the structure of viral nucleic acid. Viruses can be classified into seven (arbitrary) groups:

   - Double-stranded DNA (Adenoviruses, HSV and Poxvirus)
   - Single strand (+) sense DNA (Parvovirus)
   - Double-stranded RNA (Reoviruses)
   - Single strand (+) sense RNA (Picornaviruses)
   - Single strand (-) sense RNA (Orthomyxoviruses, Rhabdoviruses)
   - Single strand (+) sense RNA with DNA intermediate in lifecycle (Retroviruses).
   - Single strand sense DNA with RNA intermediate in lifecycle (Hepadnaviruses).

In the course of viral replication all the virus specific macromolecules are synthesized in a highly organized sequence. In double stranded DNA containing viruses early viral proteins are synthesized soon after infection and late proteins are made only in late infection after viral DNA synthesis. In contrast. Most if not all of the genetic information of RNA containing viruses is expressed at the same time.

The intracellular sites where the different events in viral replication take place vary from group to group. Viral protein is synthesized in the cytoplasm on polyribosomes composed of virus specific mRNA and host cell ribosomes, many viral proteins undergo modifications (glycosylation, acylation, cleavages, etc..). Once viral mRNA of either DNA or RNA is synthesis it's translated by host cell ribosome's in to viral protein which is either early proteins which are enzymes required for replication of the viral genome so this protein produced before replication of genome and the early protein for RNA viruses polymerase that will synthesize many copies of viral NA for progeny virus particles or late proteins which are structural proteins of progeny viruses.

Viral DNA is usually replicate in the nucleus. Viral genomic RNA is generally duplicated in the cell cytoplasm except HIV which replicate in the nucleus of the host cell, though there are exceptions. So, all DNA viruses are dsDNA except Parvovirus and during replication the (+) sense DNA strand act as template and with presence of DNA dependent RNA polymerase mRNA is synthesized.

In RNA viruses eg. (Poliovirus)…the ssRNA (+) sense viruses it act directly as mRNA, while the ssRNA (-) sense viruses need RNA dependent RNA polymerase to synthesized mRNA eg. (Influenza virus).

In RNA positive stranded Retroviruses (tumor viruses HIV) the mechanism is different, HIV tumor virus carry their own Reverse transcription (RNA – dependent DNA polymerase) and replicate in the nucleus of the host cell, and mRNA transcript by host cell polymerase. In double stranded RNA (Reoviruses) viral polymerase transcript the positive polarity strand to mRNA.

5. **Assembly/**

   Involve the assembly of all the components necessary for the formation of the mature virion at a particular site in the cell. During this process, the basic structure of the virus is formed. The site of assembly varies for different viruses…ex. Picornaviruses, Poxviruses and Reoviruses *in the cytoplasm*. Adenoviruses, Parvoviruses *in the nucleus*. Retroviruses on *the inner surface of the cell membrane.*

6. **Release/**

   For lytic viruses non- enveloped viruses release in a simple process, the cell breaks open and releases the virus. Enveloped viruses acquire the lipid membrane as the virus buds out through the cell membrane. Virion envelope proteins are picked up during this process as the virus is extruded. Budding may or may not kill the cell but is controlled by the virus, the physical interaction of the capsid proteins on the inner surface of the cell membrane forces the particle out through the membrane.

7. Maturation/

The stage of the life cycle at which the virus becomes infectious involve structural changes in the particle often resulting from specific cleavage of capsid proteins to form the mature products which lead to conformational change in the capsid or the condensation of nucleoproteins with the genome. For some viruses assembly and maturation are inseparable, whereas for others maturation may occur after the virus particle has left the cell.