REPLICATION OF VIRUSES

Viruses rely completely on living host cells for their replication. The small genome size put them at disadvantage. Also, they lack organelles and other machineries required for protein synthesis. Although some viruses enter the host cell with few virus-encoded enzymes, others do not possess any protein of their own and therefore depend completely on those produced by the host cell. Virus replication is facilitated by the host cell which provides the required energy and synthetic machinery and sometimes essential enzymes for replication and also by the viral nucleic acid which carries the genetic information required for the synthesis of viral components.

The replicative cycle of a virus can be divided into a number of stages:

1. Attachment to surface receptors on a susceptible host cell
2. Entry into the cell
3. Uncoating of the viral nucleic acid
4. Transcription of the viral nucleic acid and translation of mRNA for synthesis of virus-encoded proteins
5. Replication of the viral nucleic acid into progeny/daughter nucleic acid
6. Assembly of newly formed virus particles
7. Release of the daughter virions from the host cell

The duration of the replicative cycle ranges from 6 to 40 hours. Infection of a susceptible host c ell is usually followed by an eclipse phase.

Eclipse phase: this is the initial stage of virus replication whereby the infecting virus loses its physical identity and most or all of its infectivity. At this time, no virus is detectable in the infected host. The eclipse phase is followed by the productive stage as new virus particles are formed and released from the cell.

Steps in virus replication

Attachment: viruses have evolved to the point where they can utilize a wide range of essential host cell surface protein as receptors. They bind with their own receptor-binding proteins (ligands) to the receptors on the host cell plasma membrane. Virus receptors on cells could be glycoproteins or glycolipids. The interaction between the virus receptor-binding proteins and the corresponding receptor on the host cell contributes to host specificity.

Entry: following attachment, the virus gains access to the host cell internal environment where replication takes place. Viruses employ three different mechanisms for this internalization:

I. Receptor-mediated endocytosis (viropexis): The site of virus attachment to the plasma membrane is coated internally with the protein clathrin and the virus-receptor complex is taken into the cell in a manner similar to phagocytosis. A cage-like lattice, in form of endosome (vesicle) is then formed after internalization. Fusion of the endosome with lysome degrades the membrane and the nucleocapsid of the virus is released (seen in rhabdoviruses, orthomyxoviruses and flaviviruses). Acidification of the clathrin coated cage-like structure within the host cell cytoplasm also leads to breakdown of the viral structures in certain viruses.

II. Fusion of viral envelope with the plasma membrane of the host cell (seen in retroviruses, herpesviruses and paramyxoviruses)

III. Direct introduction of viral genome into the cytoplasm (injection) through channels in the plasma membrane. This is seen in some non-envelope viruses such as picornaviruses.

Uncoating: this implies the release of viral genome from the nucleocapsid for transcription to take place. However, in certain viruses, transcription may proceed without complete release of the viral genome. The genome of reoviruses may be fully expressed without being fully uncoated. The mechanism involved in the process of uncoating is not fully understood.

Uncoating may occur on the cell membrane, cytoplasm, or nucleus and is facilitated by celluar enzymes in some viruses. In poxviruses, uncoating takes place in two stages. The initial stage is facilitated by host cell enzymes while the later stage is mediated by virus-specified proteins. In non-envelope viruses, uncoating may be due to proteolytic activity of lysosomal enzymes. Uncoating leads to loss of virus infectivity.

Replication of viral nucleic acid and synthesis of viral proteins: there is synthesis of viral nucleic acid using the viral genome as template. The nucleic acid may be messenger RNA or replicative intermediates. Proteins including enzymes (non-structural proteins) and capsids (structural proteins) are also produced. Regulatory proteins which shut down the normal cellular metabolic processes and direct sequential production of viral molecules are also synthesized. Replication of DNA viruses takes place in the nucleus of the host cell except poxviruses in which case replication takes place in the cytoplasm. The RNA viruses replicate in the cytoplasm except orthomyxoviruses which require host hoost DNA transcription, paramyxoviruses which have a non-obligatory nuclear pahse of replication and retroviruses which replicate via a DNA intermediate (provirus).

Major activities occurring at this stage include:

- Transcription of mRNA from viral genome
- Translation of mRNA into early protein which initiate and maintain the synthesis of virus components and shut down the host protein and nucleic acid sunthesis
- Replication of viral nucleic acid destined for encapsidation
- Synthesis of late proteins which are the components of daughter virion capsid

Transcription: the mechanisms of transcription and nucleic acid synthesis differ in different types of viruses. In single stranded (ss) nucleic acid, complimentary strand is first synthesized

producing double stranded (ds) replicative intermediates. In picornaviruses, ssRNA acts directly as mRNA because of their positive polarity. The parental positive-sense strand acts as template for production of complimentary strand with negative sense. The negative sense complimentary strand then acts as the template for the synthesis of the positive sense progeny viral nucleic acid. In single stranded negative sense RNA viruses (rhabdoviruses), a complimentary positive sense RNA is produced from the parental negative sense RNA. The complimentary positive sense RNA then acts both as mRNA for protein synthesis and as the template for the synthesis of negative sense progeny viral RNA destined for encapsidation. Retroviruses exhibit a unique replicative process. The virus ssRNA genome is first converted into a RNA-DNA hybrid by the action of the viral enzyme reverse transcriptase (an RNA-dependent DNA polymerase). The RNA strand of the RNA-DNA hybrid is removed after the synthesis of a DNA strand complimentary to the DNA strand of the RNA-DNA hybrid. This results in the formation of a dsDNA. The dsDNA (provirus) is then integrated into the host cell genome where it acts as the template for the synthesis of progeny viral RNA. The integration of the provirus into the host cell genome may cause transformation of the cell and development of neoplasm.

Translation: this is the synthesis of viral proteins. It involves the attachment of the mRNA to ribosomes in the cytoplasm of the host cell. The genetic information contained in the mRNA is used to order specific amino acid for protein synthesis including capsid protein and enzymes.

Assembly/maturation: Assembly of daughter virion may take place in the nucleus (DNA viruses) or in the cytoplasm (RNA viruses). The progeny nucleic acid is incorporated into the capsids which are preformed (spontaneously produced capsid referred to as procasids). Non-envelope viruses are afterwards present in the host cell as fully developed virion while envelope viruses acquire their envelope from plasma membrane during their release.

Release: envelope viruses are usually released by budding from the plasma membrane of the host cell. In non-envelope viruses, release is by cytolysis (disintegration) of the host cell.