Replication of Viruses

- Viral infection occurs at the level of cells and molecules.
- The majority of viruses don't cause clinical manifestation.
- The viruses that infect plants are harmless to animals, and most viruses that infect other animals are harmless to humans.

Viruses cause infection by:
- modifying host cell’s gene so that it will start producing abnormal amino acids and other components that have toxic effect on the host cell.
- force the cell’s components to express viral genome which cause several deformities in the host cell.
- Modification of host gene expression (which affects the mechanism not the genes) by structural or functional interactions.

In other words, viruses modify the host cell's genes so that the immune cells of the body will recognize infected cells as foreign bodies.

Host Range, Susceptibility, and Permissiveness:

Host range: the tissues that can be affected by the virus (either animal tissues or plant tissues).
- For infection to occur (meaning that both virus and host cell contact with each other):
  1- tissue should be from the host range of the virus
  2- host cell is susceptible for the virus.
• e.g. : when influenza virus gets to respiratory tract, it will cause infection but when hepatitis virus get to the tract it will not cause infection because it's not from its host range.
  e.g : skin is from the host range of pox virus .
* virus that can infect many kinds of tissues is said to be "wide ranged virus" like herpes simplex virus which affect brain, skin, liver and other, otherwise it's "narrowed-range virus" usually infect only one tissue .

** Susceptibility :** it is the ability of a cell to be infected. It's determined by the kinds of receptor on the host cell.

E.g. hepatitis virus have many receptor on the liver so the liver cells are susceptible for hepatitis.

**Permissiveness** : the ability of the virus to replicate inside the host cell. So if the host cell contain the essential components required for replication then the cell is said to be permissive cell.

So even if the cell is infected and the virus enters the cell, it might not replicate and the virus will be aborted if the cell is not permissive.

• Some viruses are simple and highly dependent on the host cell in their replication "takes the enzymes and precursors and other" and other contain all components for replication and use the cell as a space for the replication only.

** Burst mass :** number of viruses produced by a single cells .

Only 1-10% percent of the burst viruses are able to cause infection, others are defective viruses and unable to cause diseases. This defection caused by inefficient assembly between parts of viruses.
Replication cycle produces:

- Functional components, enzymes, RNA (like mRNA) and other proteins.
- Structural components, RNA (like rRNA) or DNA, capsid, glycoprotein, matrix protein, envelope.

Development of viruses inside host cells:

* **Eclipse phase**: begins by attachment "infection" to cell and end when detecting the virus *intracellularly* which marks the assembly of the virus, during this phase the virus is undetectable and in the form of genome.

  **Latent period**: from infection until first detection of the virus *extracellularly*.

* **Maturation and releasing phase**.
  this study Important in the area of antiviral chemotherapy where it is needed to determine what stages are essential in the development of the drug to target these stages with the drugs.

* So if a virus infected a cell then for a short time the virus is undetectable "eclipse phase" because the virus is in the form of genome only, after that we will see a burst mass of 100,000 virus getting out by either lyses "naked" or budding out "enveloped" but only 1000 to 10,000 are able to cause infection and others are defective.

Types of Infection:

- Productive (permissive): here the cell is susceptible and permissive and from the host range of the virus, so the virus can infect and replicate inside the cell.
• **Abortive** (non-permissive): here the cell is susceptible but not permissive so the virus can infect the cell but can't replicate inside the cell so the virus will be aborted.

• **Stringent or restrictive**: it's transient permissive so it allows for the replication of viruses for short period then it stops.

• **Transforming**: when incomplete replication occurs. Genome of virus may activate oncogene "by modifying host cell's genes" forming malignant tumor and the viruses are called "oncogenic viruses".

  e.g. for DNA viruses: hepatitis B, polyomaviruses, human papillomavirus (HPV) "which cause cervical carcinoma", papovavirus and adenoviruses. Human herpes virus A.

  for RNA viruses like hepatitis C and retroviruses "like HIV".

**Replication process**:  
We have 8 stages of viral replication but some of them happens simultaneously:

Attachment, penetration, uncoating, genome replication, gene expression, assembly, maturation and release.

So this order is theoretic and the stages can't be recognized, so we have another category:

I— **Initiation phase**

  - Attachment - Penetration - Uncoating

II— **Replication phase**

  - DNA Synthesis-RNA Synthesis-Protein synthesis
III- Release phase

- Assembly - Maturation- Exit from cell

* note that replication might be more than one step "if –ve ssRNA then we need to transcribe it into mRNA then forming +ve ssRNA then translation"

Attachment :
As we mentioned before, the host cell must be susceptible for the virus, that is, having a specific receptor for the virus for the attachment to occur.

A protein called (Viral Attachment Protein) on the capside of naked viruses and on the envelope of enveloped viruses function as "anti-receptor" to bind with the receptor on the surface of host cell.

- Recall that wide-range viruses can affect many kinds of tissues because it have many kinds of VAP on their surface Complex viruses may have more than one species of anti-receptor molecules.

  e.g. VAP of EPV herpes virus utilize CD21 receptors present on B-lymphocyte and epithelial cells. But influenza and other herpes viruses utilize glycoprotein receptors that are widely spread.

  * some mutations may disable some anti-receptor or might just change its shape so that the immune cells will not recognize these viruses and it will still infect the body continuously. e.g. influenza virus.

Repulsion between virus and cell membrane impedes attachment because both are negatively charged. Attachment, therefore, requires ions to reduce electrostatic repulsion.

- Energy and temperature don’t influence or even don’t affect the attachment, so the only way is to reduce repulsion forces. So unless there is ions, repulsion will not occur.
Early attachment results from random collision between virions and cell surface and it’s easily detach.

Early binding is reversible because it’s not specific, but firm binding which is specific binding requires specific receptor anti-receptor interaction.

If the virus attach with the host cell by firm binding "receptor anti-receptor interaction" then the virus:

1- Either penetrate into the cell and continue replication
2- Or it detach from the cell causing irreversible damage to VAP thus reducing the ability of the virus to attach to another receptors.

- An exception of that is the influenza virus which release an enzyme called "neuraminidase" which allow the influenza virus to elute from the host cell by breaking the bonds between them without damage.

**Penetration:**

Requires energy, occur coincidently with attachment process and has 3 mechanisms:

1- **Endocytosis (viriopexis)** of the virus particle resulting in accumulation of virus particles inside cytoplasmic vesicles "phagosome", most common

- Phagosome: is a vesicle formed around a particle absorbed by phagocytosis. The vacuole is formed by the fusion of the cell membrane around the particle.
- The fusion between the host cell membrane and the envelope of the virus "in enveloped viruses" must be mediated by some structure "like matrix protein" because
both structure have the same nature “phospholipid bilayer”.

2- **Fusion of the virion envelope with the cellular membrane** and then releasing of the viral genome inside the host cell. Requires fusion protein in viral envelope, e.g. GP41 protein in HIV is responsible for the fusion.

3- **Translocation of the entire virus across the plasma membrane.**

Endocytosis of Non-enveloped RNA Viruses:
phH dependent

- Cell Receptor (IgG super family) for the anti-receptor of the virus.
- At low pH, virus becomes lipophilic and forms a pore in the cell membrane.
- RNA genome is then ejected through the hydrophobic pore.

  e.g. Rhinovirus

  - Can be inhibited by use of weak bases such as ammonium chloride & chloroquine, because these bases can neutralize the viruses.

Endocytosis of Enveloped RNA Viruses:
Influenza Virus as an example

  Endosome is acidic (pH 5-6)

  Exposed hydrophobic fusion domain

  Differ from non-enveloped viruses in that their envelopes fuse with the membranes of the endosomes and they don't form pores.
Penetration – Fusion :
Direct FUSION of the virion envelope with the surface membrane of the cells may also take place with some viruses.

Virion envelope glycoproteins with fusion activity mediate the melding of the two phospholipids bilayers and mixing of the aqueous compartments previously separated by them.

In some viruses a specialized glycoprotein is responsible for fusion (e.g. gp41 of HIV)

**Uncoating:**

Makes viral nucleic acid available for transcription to permit multiplication to proceed.

Uncoating can occur partially or completely depending on the kind of the virus.

E.g. icosahedral viruses can be uncoated only by removing the vertices and mRNA moves through these openings.

Mechanism variably understood depending upon the virus kind.

Uncoating usually occurs after penetration.

Capsid is removed and genome is exposed usually as a nucleoprotein complex.

Process is poorly understood and variable.

In reoviruses which is icosahedral, the capsid only ever partially disintegrates and replication takes place in a structured particle.

In poxviruses, host factors induce the disruption of the virus, and the uncoating is partial.
The release of DNA from the core depends upon viral factors made after entry.

Orthomyxo, paramyxovirus and picornavirus all lose the protective envelope or capsid upon entry into the cytoplasm.

In the influenza virus, the M2 envelope viral protein allowed osomal protons into the virion particle resulting in its partial dissolution. and they can increase the acidity inside the cell “forming acidic environment” which will cause uncoating of the virus.

In herpesviruses, adenoviruses and papovaviruses, the capsid is eventually routed along the cytoskeleton to nuclear membrane.

Now the Virus is ready to be expressed ...

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