

Lecture 3

Viral genetics , Molecular and Viral replication

Viruses are simple entities, lacking an energy-generating system and having very limited biosynthetic capabilities.

- The smallest viruses **have only a few genes**; the largest viruses **have as many as 200**.
- Genetically, however, viruses have many features in common with cells.
- Viruses undergo genetic changes through **mutation** and major genetic changes through **recombination**.
- **Mutation** occurs when an error is incorporated in the viral genome.
- **Recombination** occurs when co-infecting viruses exchange genetic information, creating a novel virus.
- **Replication of viruses:**
- Is the formation of viruses during the infection process in the target host cells.
- Viruses must first get into the cell before viral replication can occur.
- **Most DNA viruses assemble in the nucleus while most RNA viruses develop solely in cytoplasm.**

Viral genetics:

Viruses grow rapidly, there are usually a large number of progeny virions per cell.

- There is, therefore, more chance of mutations occurring over a short time period.

The nature of the viral genome (RNA or DNA; segmented or non-segmented) plays an important role in the genetics of the virus. however,

Viruses may change genetically due to **mutation or recombination**.

- DNA viruses tend to more genetically stable than RNA viruses.

There are error correction mechanisms in the host cell for DNA repair, but probably not for RNA.

Figure (1) Tautomerization changes the base pairing abilities of the base

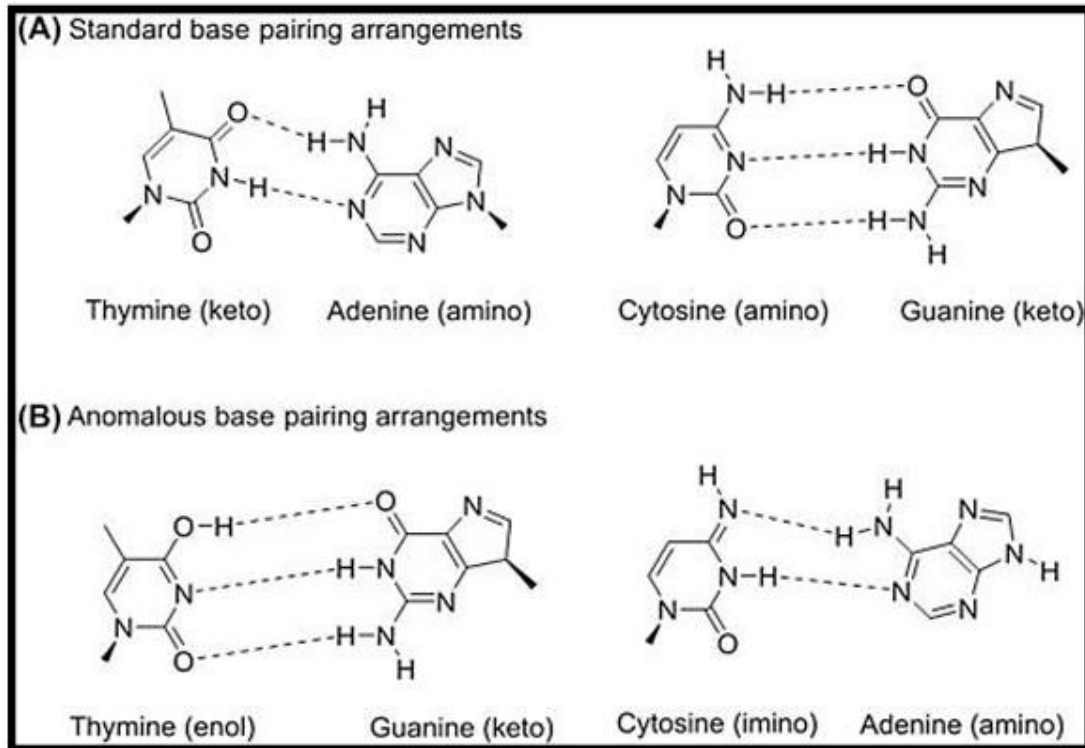


Figure (1) Tautomerization changes the base pairing abilities of the base

Mutation in viruses:

1- Spontaneous mutations:

These arise naturally during viral replication: e.g. due to errors by the genome replicating polymerase or a result of the incorporation of tautomeric forms of the bases (resonance from keto to enol and from amino to imino forms).

2- Mutations that are induced by physical or chemical means

a- Chemical:

Agents acting directly on bases, e.g. **nitrous acid**.

Agents acting indirectly, e.g. **base analogs** which mispair more frequently than normal bases thus generating mutations.

b- Physical:

Agents such as **UV light** or **X-rays** can induce mutation in viruses.

Types of mutation:

- 1 • Point mutation
- 2 • Insertion mutation
- 3 • Deletion mutation

Recombination:

Exchange of genetic information occurs when viruses of two different parent strains coinfect the same host cell and interact during replication to generate virus progeny that have some genes from both parents. Recombination generally occurs between members of the same virus type (e.g., between two influenza viruses or between two herpes simplex viruses).

"Classic" recombination:

This involves breaking of covalent bonds within the nucleic acid, exchange of genetic information, and reforming of covalent bonds. **This kind of break/join recombination is common in DNA viruses or those RNA viruses which have a DNA phase (retroviruses). The host cell has recombination systems for DNA.**

Recombination of this type is very rare in RNA viruses (**there are probably no host enzymes for RNA recombination**).

Reassortments:

- **Form of recombination (non classical)**
- **Very efficient**
- **Segmented viruses only.**
- **Can occur naturally.**
- **Used in some new vaccines:** e.g for influenza and rotaviruses.

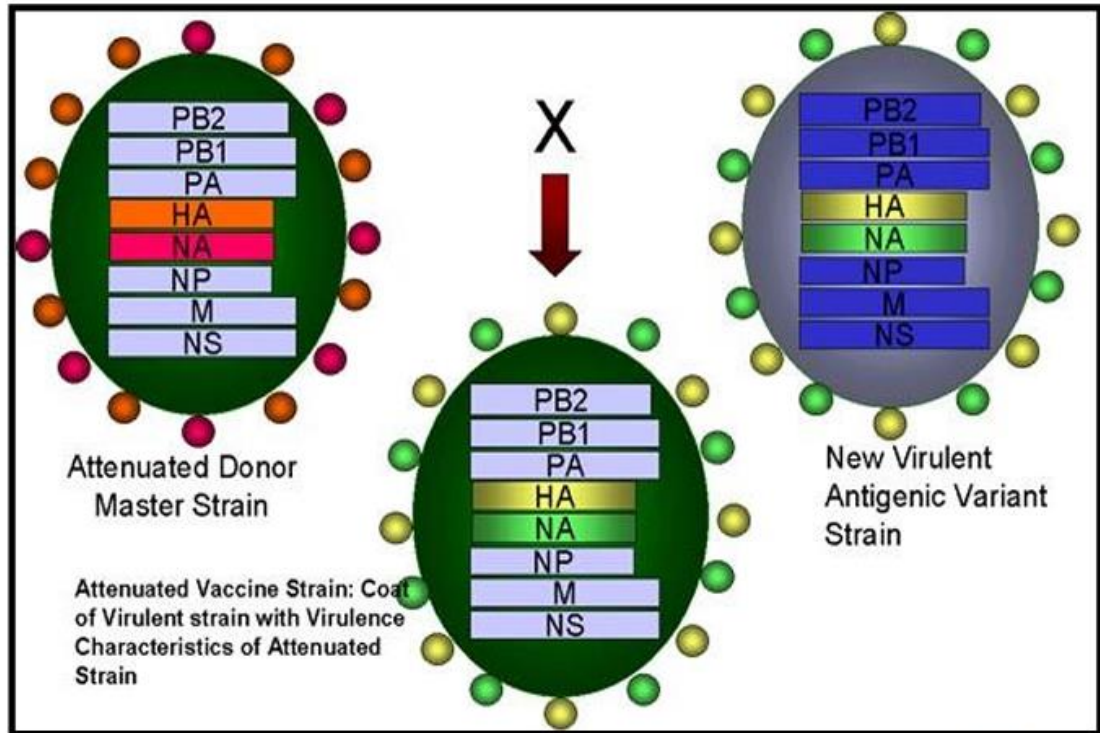
If a virus has a segmented genome and if two variants of that virus infect a single cell, **progeny virions can result with some segments from one parent, some from the other.**

This is an efficient process - **but is limited to viruses with segmented genomes** - so far the only human viruses characterized with segmented genomes are RNA viruses e.g. orthomyxoviruses, reoviruses, arenaviruses, bunya viruses.

Reassortment may play an important role in nature in generating novel reassortants and has also been useful in laboratory experiments.

(figure 2). For example, in a reassorted virus if one segment comes from virus A and the rest from virus B, we can see which properties resemble virus A and which virus B.

Figure 2:-Reassortment of genes between the attenuated strain of influenza virus and a new virulent strain in the formation of an attenuated influenza



Replication of viruses:

- Is the formation of viruses during the infection process in the target host cells.
- Viruses must first get into the cell before viral replication can occur.
- Most DNA viruses assemble in the nucleus while most RNA viruses develop solely in cytoplasm.

- Steps of viral replication:

A. Attachment & adsorption:

This is the first step in viral replication. Surface proteins of the virus interact with specific receptors on the target cell surface.

B. Penetration (Uptake):

After binding of virus, virus is taken up inside the cell which is referred as penetration or engulfment.

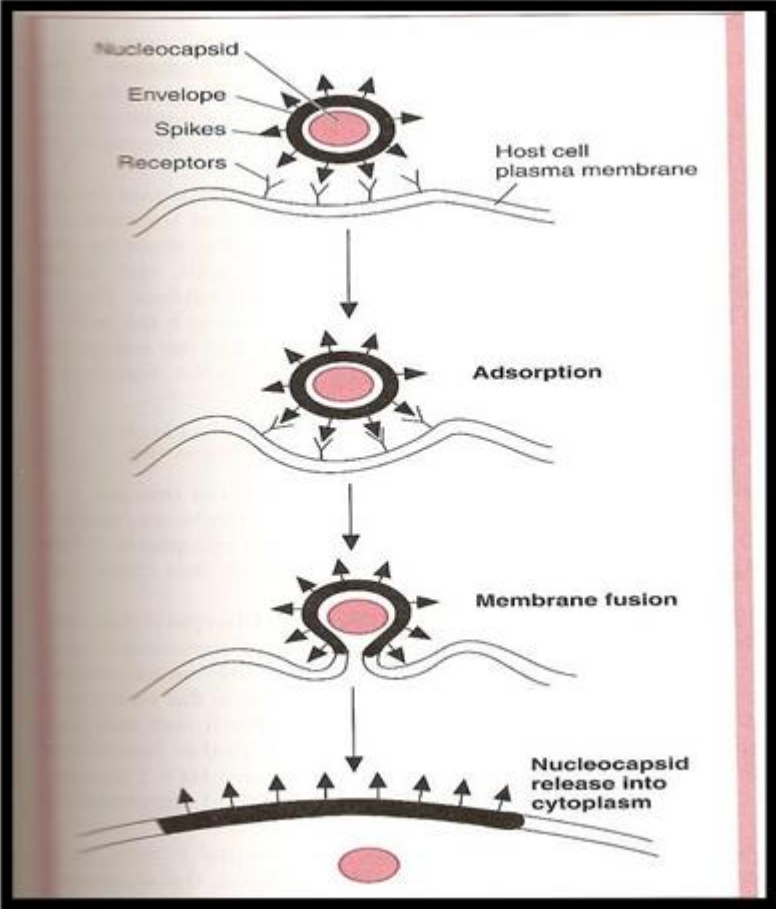
penetration in viruses by :-

A) Direct translocation across cell membrane :

B) Fusion of viral envelope and cell membrane: as in some enveloped viruses for example:- paramyxoviruses (measles) , retroviruses (HIV).

C) Receptor mediated endocytosis or Engulfed in a pinocytotic vesicle (viropexis) as in naked viruses and other enveloped viruses:

in which the cell engulfs virus by invagination of the cell membrane then vesicles formation in the cell cytoplasm. Low PH made the virus



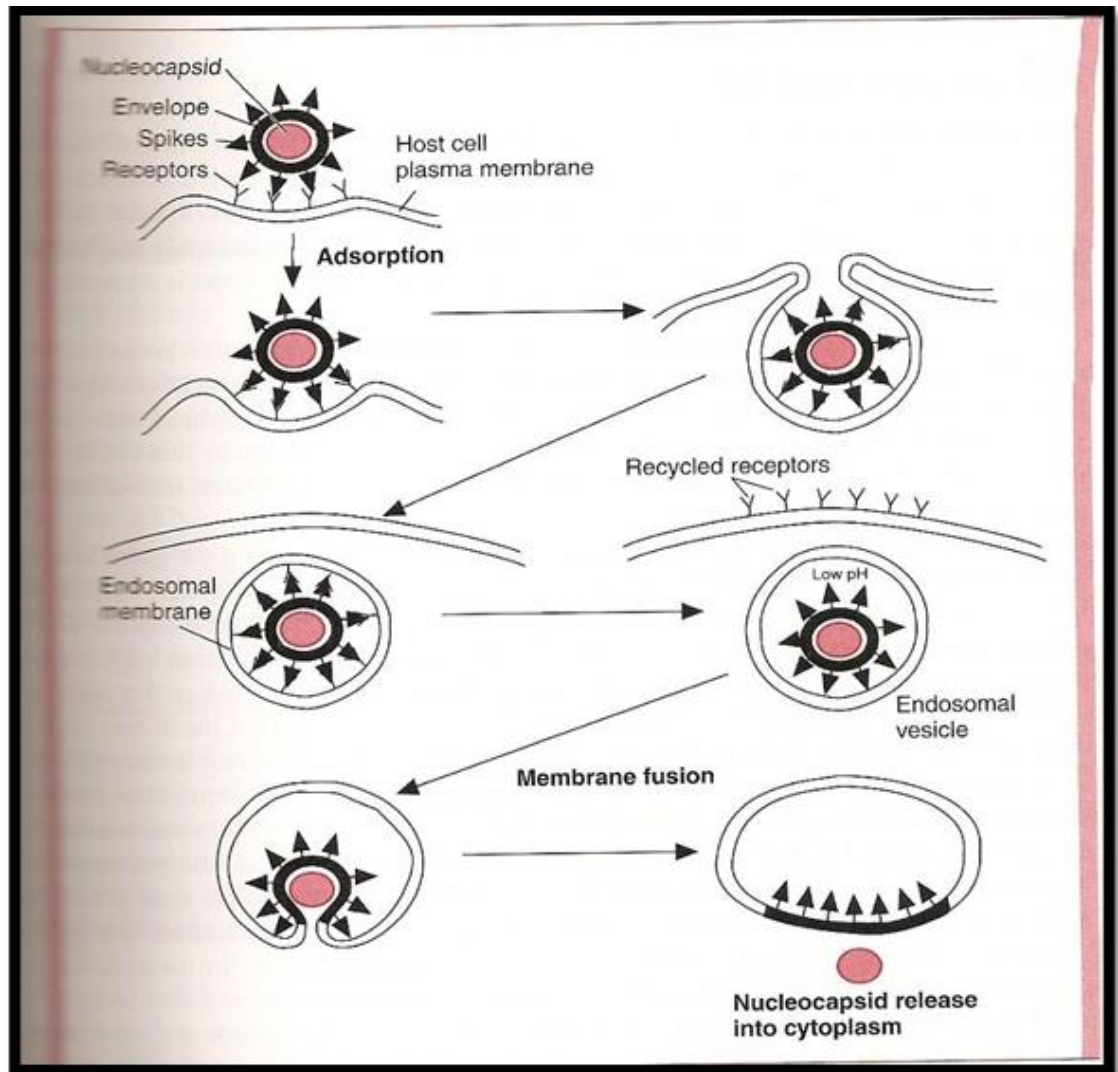


Figure (3) :- Entry of some enveloped viruses by fusion of the viral envelope.

Figure (4) :- Uneveloped and some enveloped viruses enter the cell by endocytosis (viropexis).

C. Uncoating

This process include release of the viral genome from its protective capsid to enable the viral nucleic acid to replicate. The period of the replication cycle between the end of the uncoating stage and maturation of new viral particles is termed the Eclipse period . No virus is found inside the cell during this period .

D- Gene expression and genome replication: -

1-Early viral mRNA synthesis (transcription)

A. DNA viruses:

Replicate in the nucleus and use the host cell DNA dependent RNA polymerase to synthesize their mRNA. The poxviruses are the exception because they replicate in the cytoplasm. They carry their own polymerase within the virus particle. The genome of all DNA viruses consists of double-stranded (ds) DNA, except for the parvoviruses, which have a single-stranded (ss) DNA genome.

B. RNA viruses:

Fall into four groups with quite different strategies for synthesizing mRNA include:

1. Single- stranded RNA of positive polarity. These viruses use their RNA genome directly as mRNA (e.g. Poliovirus).

2. Single- stranded RNA of negative polarity:- An mRNA must be transcribed by using the negative strand as a template. The virus carries its own RNA- dependent RNA polymerase (e.g. Influenza virus).

3. Double-stranded-RNA :- The virus carries its own polymerase for transcribing into mRNA (e.g. Reovirus).

4. Single- stranded RNA of positive polarity with DNA intermediate :- The RNA transcribed into double- stranded DNA by the RNA dependent DNA polymerase (reverse transcriptase), carried by the virus. This DNA copy is then transcribed into viral mRNA by the

regular host cell RNA polymerase.(e.g Retroviruses). Most RNA viruses undergo their entire replication cycle in cytoplasm. The two principle exceptions are retroviruses and influenza viruses, both of which have an important replication step in the nucleus.

2- Early viral proteins synthesis (Translation):

Once the viral mRNA of either DNA or RNA viruses is synthesized, it is translated by host cell ribosomes into viral proteins. Some of which are early proteins, i.e. enzymes required for replication of viral genome, and others of which are late proteins, i.e. structural proteins of the progeny viruses. Early proteins: occurring before the replication of the genome. Late proteins: occurring after genome replication.

E- Assembly New virus genomes and proteins are assembled to form new virus particles.

The assembly occurs in nucleus or cytoplasm of host cell depending upon types of virus. DNA virus assembled in nucleus except Poxvirus and RNA viruses assembled in cytoplasm except Influenza virus and Reo virus.

F- Release Release of mature virus from host cell:

is the final event in virus replication. enveloped viruses are released by budding from the infected cells. Unenveloped viruses are released by rupture or lysis of the infected cells.