# Virology

## Post-Graduate Course
## M.Sc. 2018-2019
## Lecture 1

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# In This Lecture:

- What are viruses?
- Theories of Viral Origin
- Viral Structure
- Viral Classification
- Viral Replication
- Viral Pathogenesis

# Virion

- A virus is a set of genes, composed of either DNA or RNA, packaged in a protein-containing coat. Some viruses also have an outer lipid bilayer membrane external to the coat called an envelope. The resulting complete virus particle is called a **virion.**

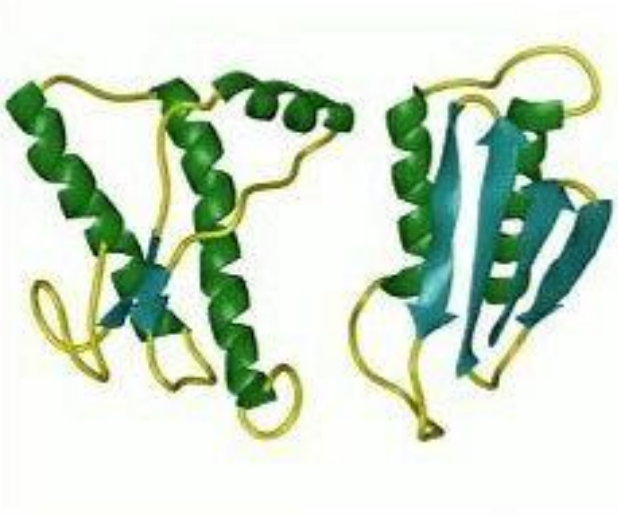
- Two classes of infectious agents exist that are structurally simpler than viruses, namely, viroids and prions.
- **Viroids** are infectious circular RNA molecules that lack protein shells; they are responsible for a variety of plant diseases.
- **Prions,** which apparently lack any genes and are composed only of protein, are agents that appear to be responsible for some transmissible and inherited spongiform encephalopathies such as scrapie in sheep; bovine spongiform encephalopathy in cattle; and kuru, Creutzfeldt-Jakob disease.

# Viroids & Prions

**Viroids**

- Infectious RNA molecules
  - Plant diseases (interfere with metabolism)
- Transmitted like viruses

- **Prions**
  - Infectious protein molecules
  - Animal/human diseases
    - Insomnia, mad cow disease



# What are viruses?

- **Small obligate intracellular parasites**
- **Virion**
  - Complete virus particle : nucleic acid + protein coat, which **may** be surrounded by an envelope
  - It is the form in which the virus moves between cells or hosts
- **Viral Genome**
  - EITHER RNA or DNA genome surrounded by a protective virus-coded protein coat (Capsid)
- Propagation depends on specialized host cells supplying the machinery for replication, metabolism and biosynthesis

- **The DNA or RNA genome** may be:
  - ss – single stranded or
  - ds – double stranded
- **Genomes** may be either:
  - (**+**) sense: Positive-sense viral RNA is identical to viral mRNA and thus can be immediately translated into protein by the host cell.

    OR
  - (**-**) sense: Negative-sense viral RNA is complementary to mRNA and thus must be converted to positive-sense RNA by an RNA polymerase before translation.

# Theories of Viral Origin


- **Regressive theory**
  - Degenerate forms of parasites
  - Mitochondria and chloroplasts?
- **Progressive theory**
  - Normal cellular nucleic acid have ability to replicate autonomously.
  - DNA viruses = plasmids or transposable elements.
  - Retroviruses = retrotransposons (What??)
  - RNA virus = mRNA.
- **Co-evolution theory:**
  - Viruses coevolved with life

# Definitions

- **Bacteriophage**
  - Virus that infects prokaryotic (bacterial) cells.
- **Nucleocapsid:**
  - viral nucleic acid + the protein coat that encloses it.
  - Represents the packaged form of the viral genome.

# Viral Structure - Overview

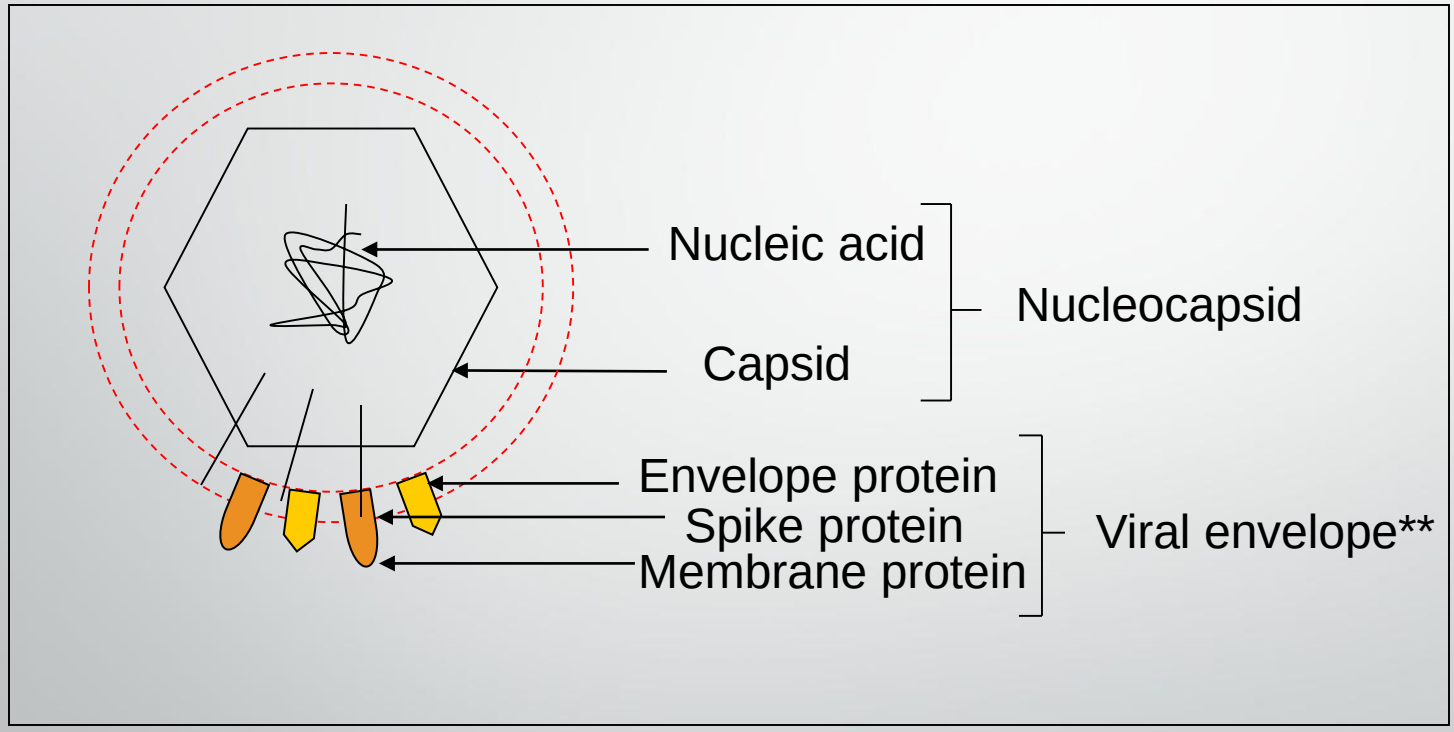
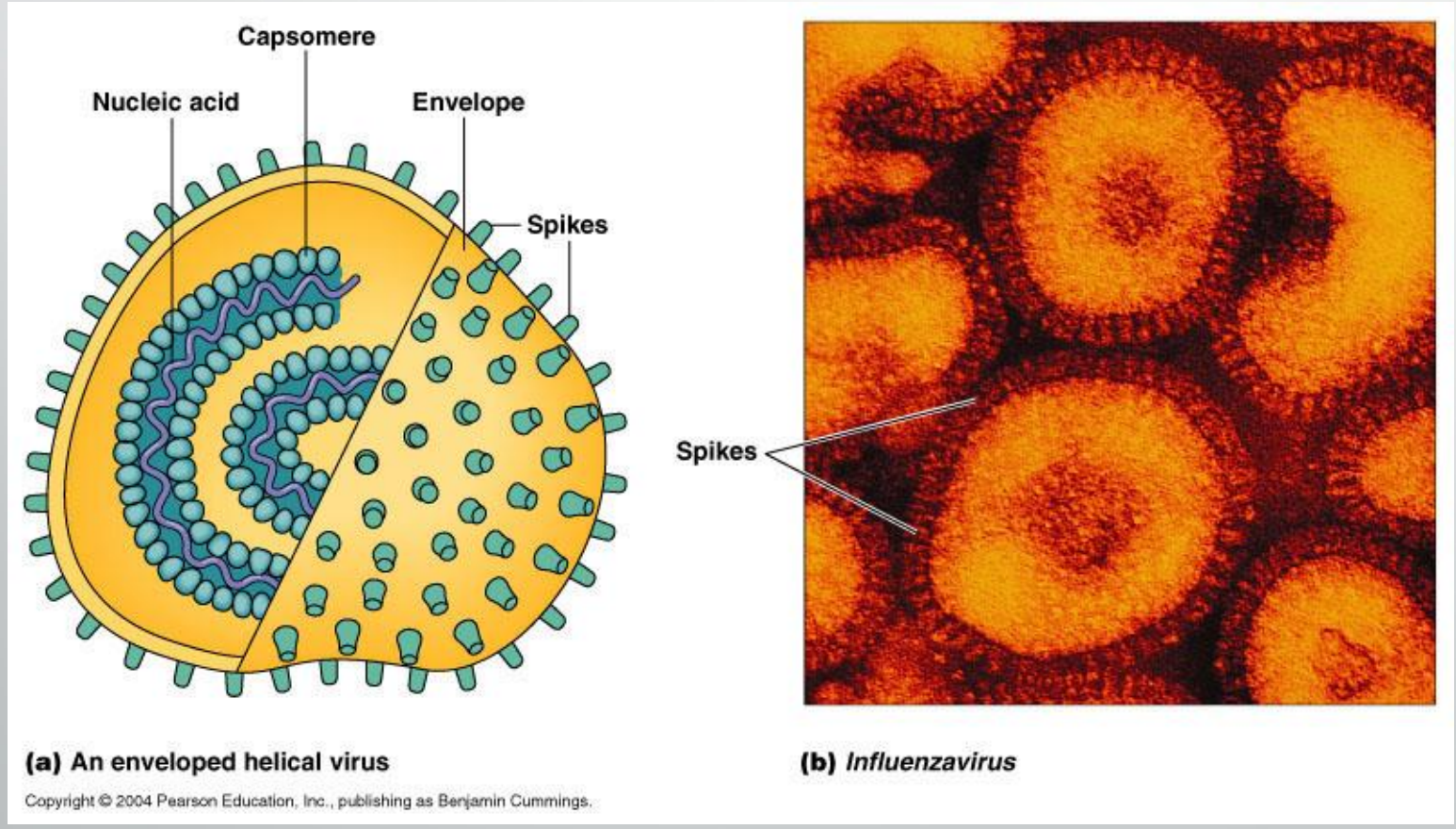



**Fig 1. Schematic overview of the structure of animal viruses**

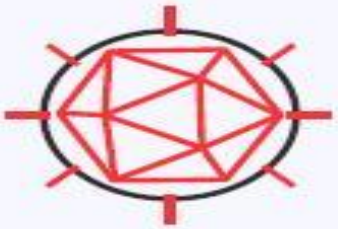
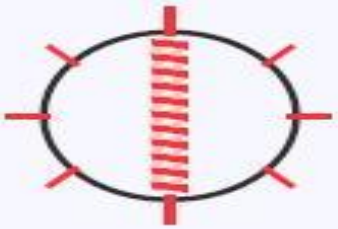
** does not exist in all viruses

# Enveloped viruses

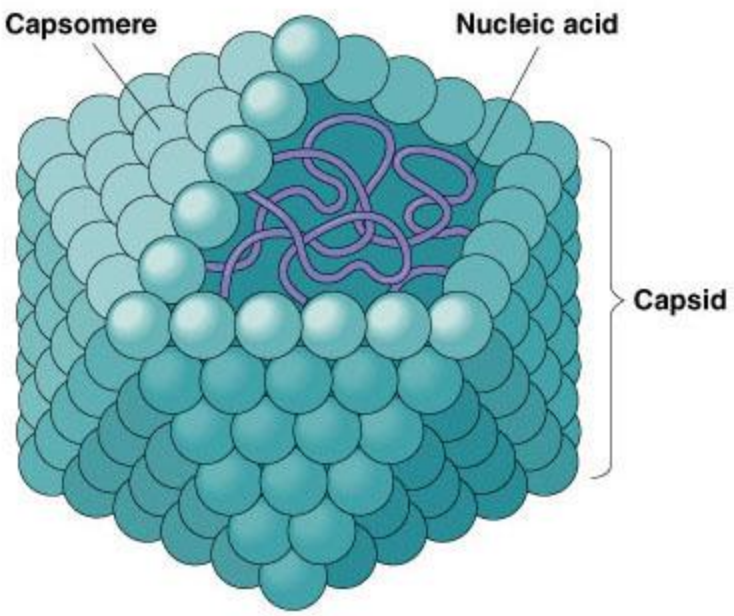


# Viral Structure

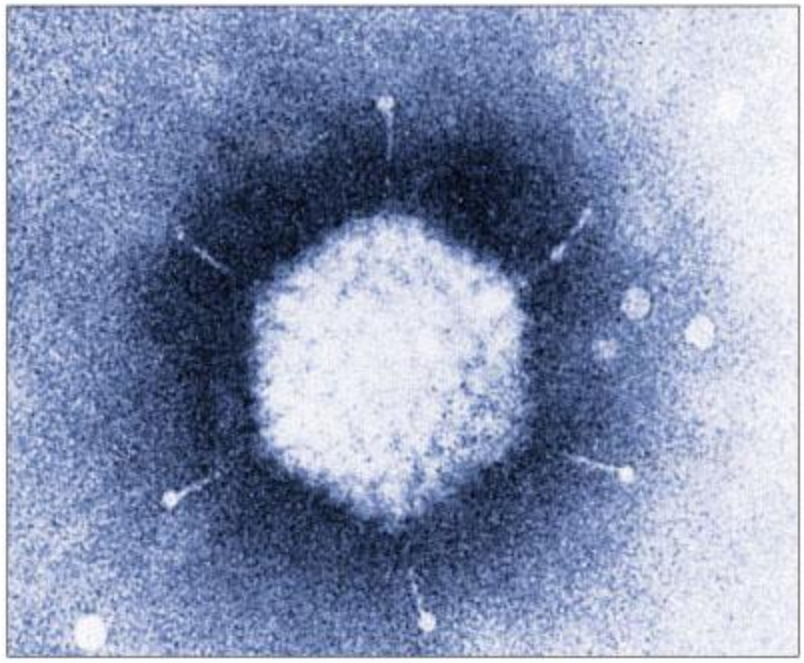
- Varies in size, shape and symmetry
- 3 types of capsid symmetry:
  - Cubic (icosahedral)
    - Has 20 faces, each an equilateral triangle. Eg. adenovirus
  - Helical
    - Protein binds around DNA/RNA in a helical fashion eg. Coronavirus
  - Complex
    - Is neither cubic nor helical eg. poxvirus

| Main types of virion structure | | Genomes | | | |
|---|---|---|---|---|---|
| | | dsDNA | ssDNA | dsRNA | ssRNA |
| Icosahedral, naked |  | ✓ | ✓ | ✓ | ✓ |
| Icosahedral, enveloped |  | ✓ | | ✓ | ✓ |
| Helical, naked |  | ✓ | ✓ | | ✓ |
| Helical, enveloped |  | | | | ✓ |

# Icosahedral symmetry

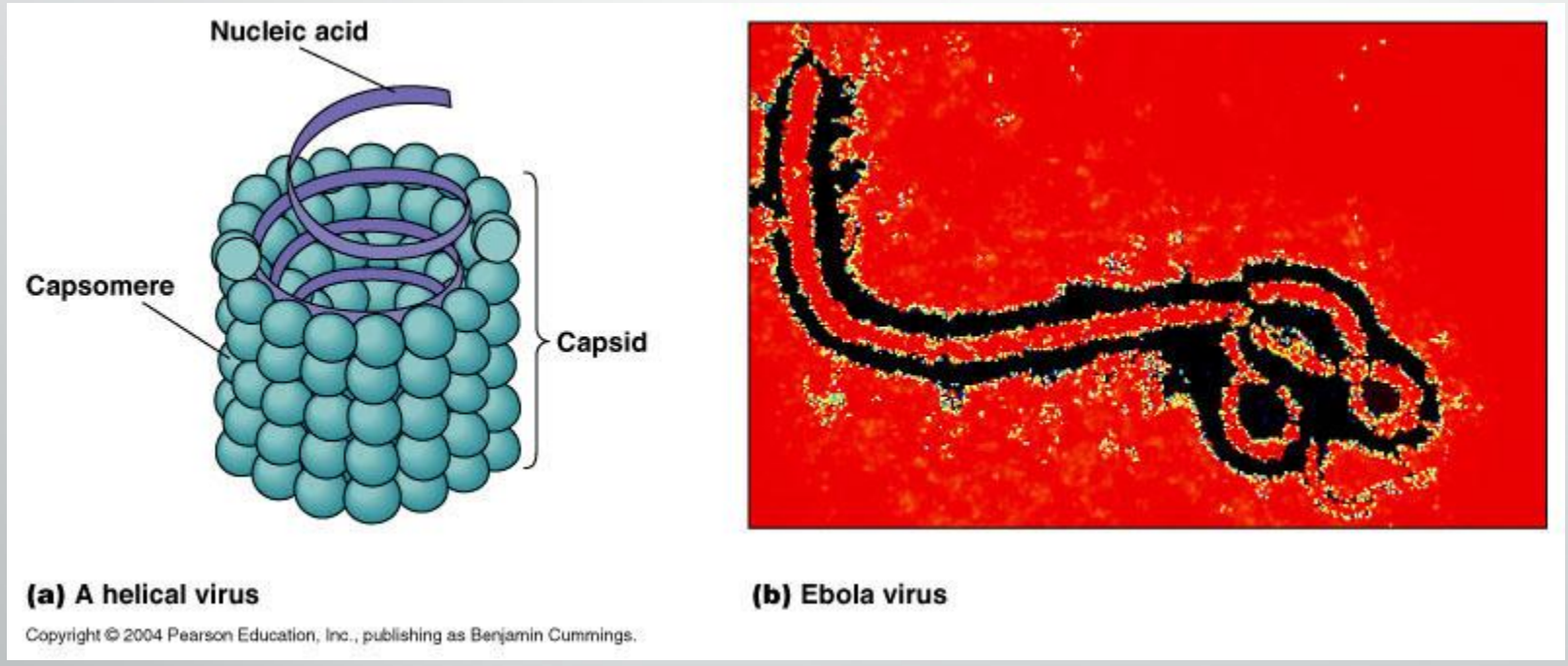


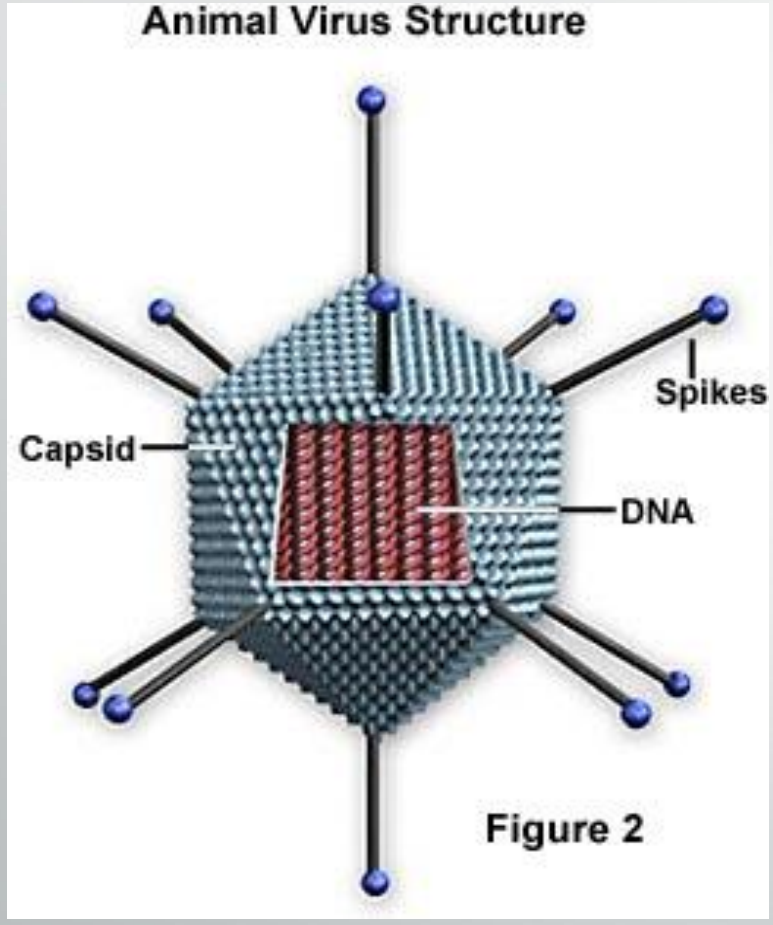

(a) A polyhedral virus

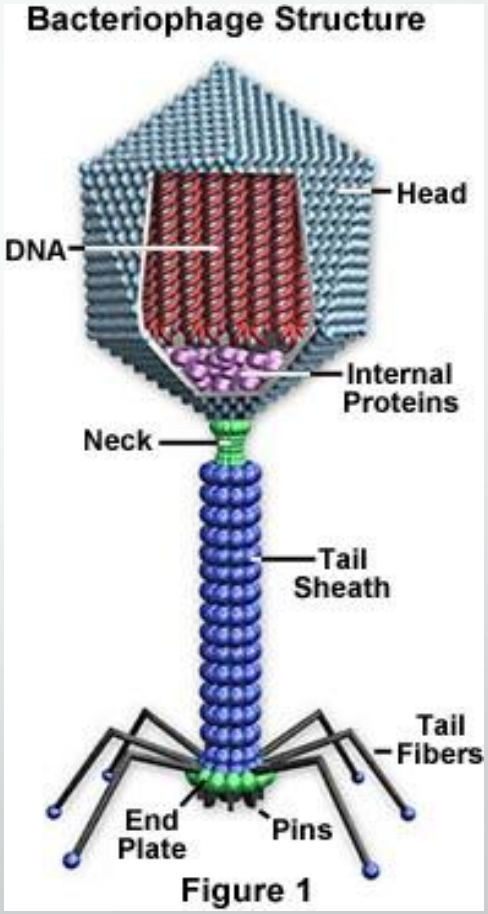


(b) A *Mastadenovirus*

# Helical symmetry






http://micro.magnet.fsu.edu/cells/virus.html

# Baltimore Scheme of Viral Classification

- Scheme that encompass all viruses, based on the:
  - Nature of genomes (type of nucleic acids)
  - Modes of replication and gene expression
- May not be of a common origin
- Used by International Committee on Taxonomy of Viruses (ICTV) with other parameters
- Revised Baltimore scheme based on fundamental importance of mRNA in the replication cycle of viruses
- Viruses do not contain the molecules necessary to translate mRNA, rely on host cell machinery

# Baltimore Scheme of Viral Classification

- They must make mRNA that can be recognized by host cell ribosomes
- Either the genes are stored in the 5'→3' direction (positive or + polarity), analogous to the direction in which genes are represented in mRNA in cells,

# Baltimore Scheme of Viral Classification

- or the genes are stored in the opposite, 3'→5' direction (negative or - polarity).
- In other words: + or - polarity of RNA:
  - "**+**" is able to serve as mRNA.
  - "**-**" is the complement of "+", must function as template to make a complementary strand of + RNA before any translation can occur.

# DNA Viruses

- Group I - dsDNA viruses (double stranded DNA)
  - **mRNA may come from either strand and transcription similar to host's**
- Group II - ssDNA viruses (single stranded DNA)
  - **DNA + or – depending on virus studied**
  - **DNA converted to ds before synthesis of mRNA**

# RNA Viruses: Group III

- **RNA viruses**
  - Group III - dsRNA viruses (double stranded RNA)
    - **Most of these viruses have segmented genomes**
    - **mRNA from one template of each segment**
    - **Mechanism similar to transcription from dsDNA genome**
    - **Enzymes needed not in uninfected cells**
    - **Enzymes encoded by virus, packaged in virion, carried into cell**

# Group IV

- Group IV - **(+)ssRNA viruses** (positive single stranded RNA or mRNA like)
  - **Same sense as mRNA (+), can be translated**
  - **Enzymes for RNA synthesis virus encoded, made after infection initiated**

# Group V

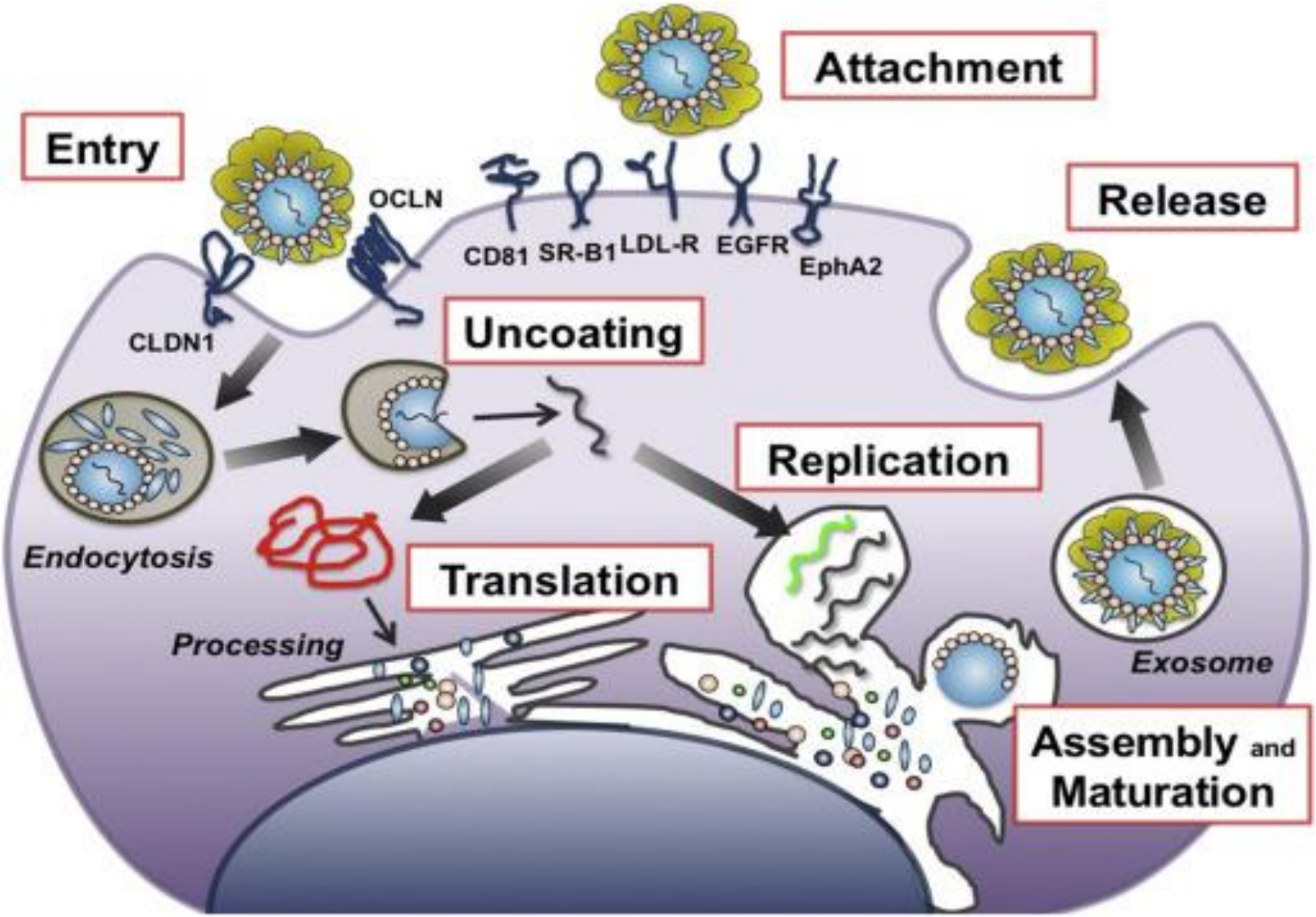
- Group V - **(-)ssRNA viruses** (negative single-stranded RNA)
  - **Genomes complimentary to mRNA (- sense)**
  - **Synthesis of mRNA by transcription from genome strand**
  - **Requires novel virus encoded enzymes**
  - **Some Group V viruses are known as 'ambisense' viruses**
  - **These use newly made 'antigenome' RNA strand as template for mRNA production and Enzymes needed also virus encoded**

# Reverse Transcribing Viruses: Groups VI and VII

- **DNA and RNA Reverse Transcribing viruses**
  - Group VI - **ssRNA-RT viruses** (single stranded RNA)
    - Generate dsDNA intermediate before replication
    - Carried out by reverse transcriptase enzyme; carried in virion
  - Group VII - **dsDNA-RT viruses** (double stranded DNA)
    - Also known as “reversiviruses”
    - Replication strategy via positive-sense ssRNA intermediate and RT enzyme
    - Inverse, but similar to VI

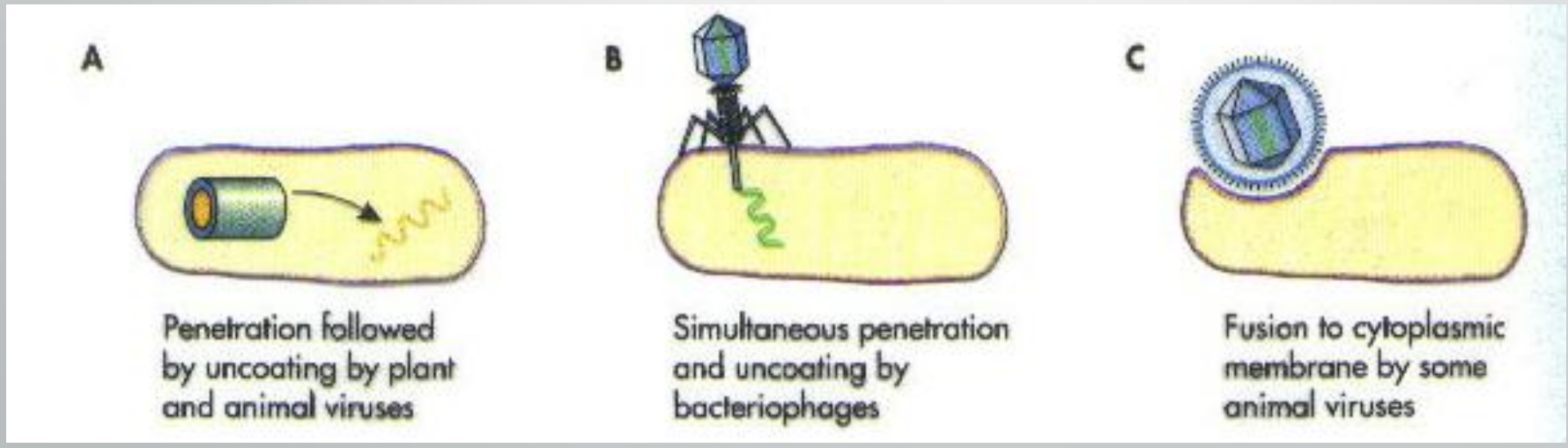
# Viral Replication

- When a virus infects a cell, nucleic acid must be uncoated and gain access to metabolic machinery of cell.
- Virus life cycle is characterized by:
  - **attachment**
  - **penetration**, with entry of nucleic acid into cell
  - **early expression of virus genes** (either directly by translation, if virus contains "+" RNA, or indirectly after transcription and then translation)
  - **replication of virus nucleic acid**
  - **synthesis of new virion components**
  - **packaging and assembly of new virions**
  - **exit** from cell


Attachment
Entry
OCLN
CD81
SR-B1
LDL-R
EGFR
EphA2
Release
CLDN1
Uncoating
Endocytosis
Replication
Translation
Processing
Exosome
Assembly and Maturation

- Attachment
  - specific binding of a virion protein (the anti-receptor) to a constituent of the cell surface (the receptor)
    - *e.g*. hemagglutinin of influenza virus
    - some complex viruses (HSV) may have more than one species of anti-receptor molecule
- Penetration
  - energy-dependent step
  - occurs almost instantaneously after attachment

- **After the virus attaches to the host cell, it can enter the cell by several mechanisms:**
  - Transfer of the entire viral particle across the cell membrane by endocytosis
  - Transfer of only the viral genome through the cell membrane
  - Fusion of the viral envelope with the host cell membrane

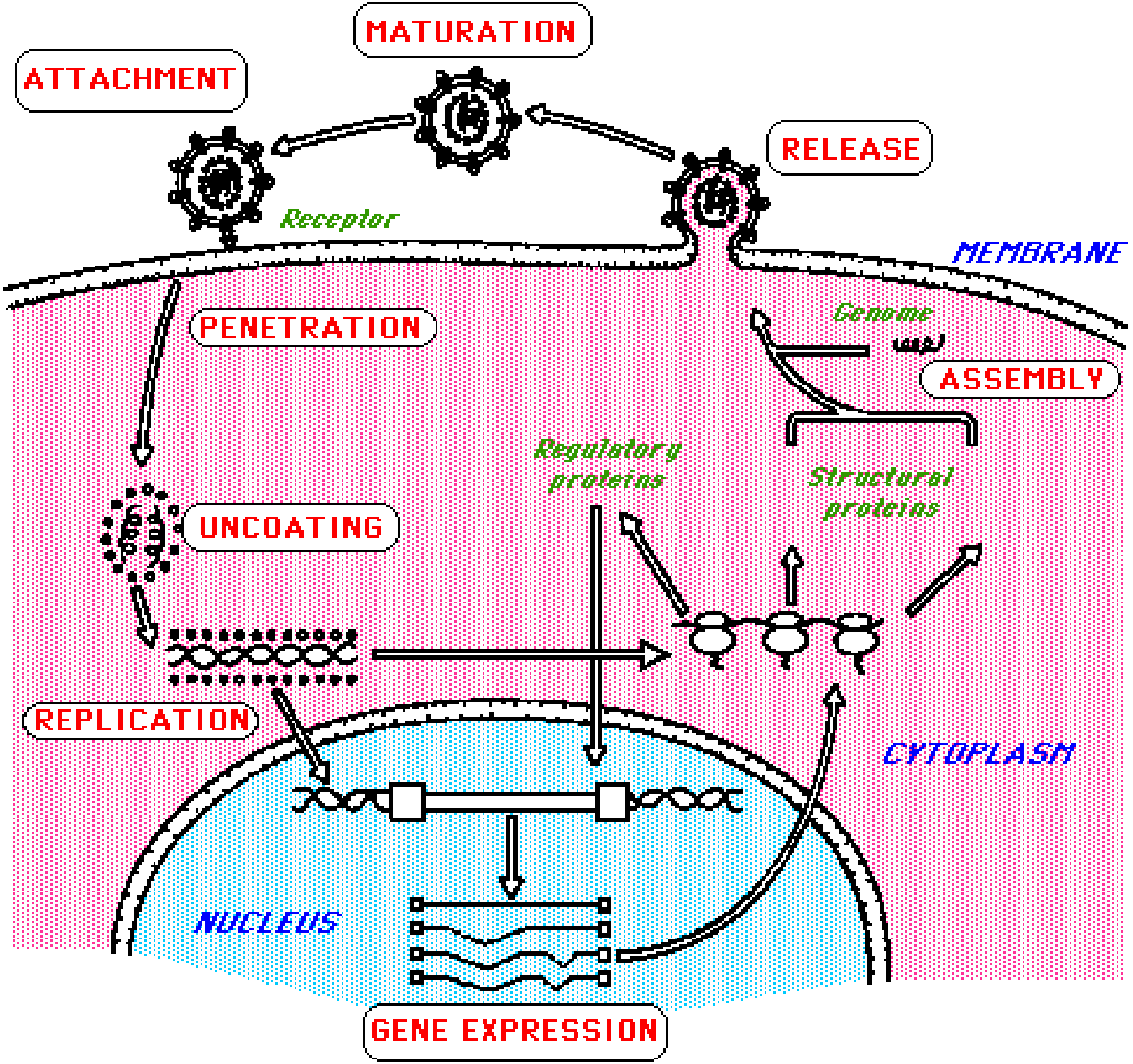


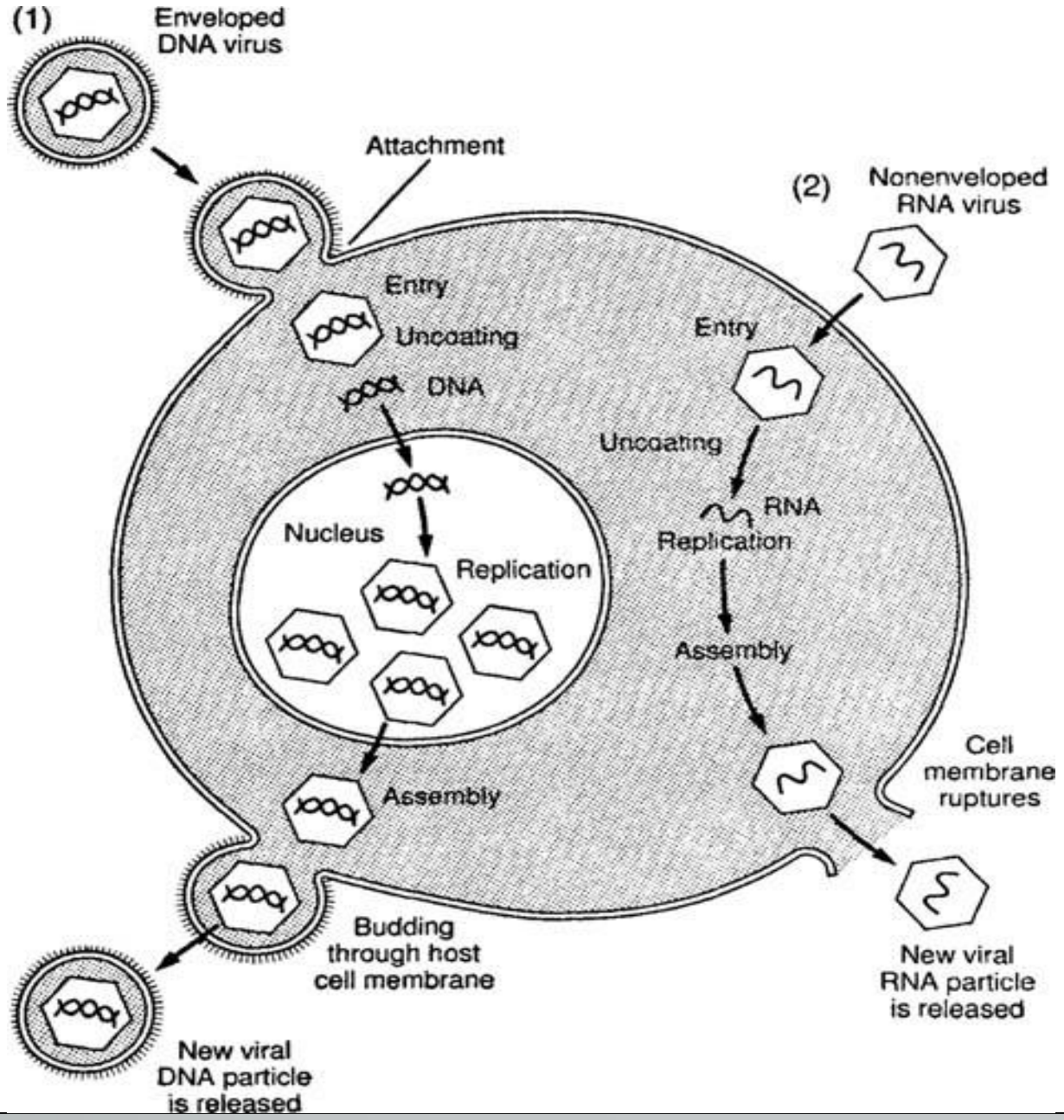
- **Uncoating**
  - at same time as penetration or shortly after
  - separation of viral nucleic acid (n.a.) from outer structural components
    - Released as:
      - free nucleic acid (picornaviruses)
      - as nucleocapsid (reoviruses) = may need acidic pH in endosome
  - viruses only infectious agent for which dissolution of infecting agent obligatory step in replicative pathway
- **Expression of viral genome and synthesis of viral components**

- **After the viral nucleic acid is released inside the host cell:**
  - The transcription and translation processes of the host cell are redirected for the production of viral proteins and nucleic acids
  - The different types of nucleic acid genomes are expressed and replicated in several ways:
    - DNA genomes undergo replication-using processes similar to cellular replication
    - RNA genomes may be +*ssRNA;* Can be read directly as an mRNA or reverse transcribed by reverse transcriptase into DNA
    - RNA genomes may also be -ssRNA; The RNA must first be used as a template to form +mRNAs

# Assembly and Release

- Components of capsid synthesis directed by late genes
- Assembly of enveloped viruses needs interaction with plasma membrane which has been modified
- Final stage of infection
- Enveloped viruses released gradually by budding or exocytosis
- Naked viruses accumulate in cytoplasm and released during lysis


MATURATION
ATTACHMENT
RELEASE
Receptor
MEMBRANE
PENETRATION
Genome
ASSEMBLY
Regulatory proteins
Structural proteins
UNCOATING
REPLICATION
CYTOPLASM
NUCLEUS
GENE EXPRESSION


(1)
Enveloped DNA virus
Attachment
(2)
Nonenveloped RNA virus
Entry
Uncoating
DNA
Nucleus
Replication
Assembly
Budding through host cell membrane
New viral DNA particle is released
Entry
Uncoating
RNA
Replication
Assembly
Cell membrane ruptures
New viral RNA particle is released

# Pathogenesis of Viral Infection

- Viral pathogenesis is the process by which viruses produce disease in the host.
- The factors that determine the viral transmission, multiplication, and development of disease in the host involve complex and dynamic interactions between the virus and the susceptible host.
- Viruses cause disease when they breach the host's primary physical and natural protective barriers; evade local, tissue, and immune defenses; spread in the body; and destroy cells either directly or via bystander immune and inflammatory responses.

- Viral pathogenesis can be divided into several stages, including

(1) transmission and entry of the virus into the host,

(2) spread in the host,

(3) tropism,

(4) virulence,

(5) patterns of viral infection and disease,

(6) host factors,

(7) host defense.

# Epidemiological terms

- The factors that influence acquisition and spread of infectious disease are essential for developing methods of prevention and control. Infection in a population can be
- **endemic** (disease present at fairly low but constant level),
- **epidemic** (infection greater than usually found in the population)
- **pandemic** (infections that are spread worldwide). Infection can be direct (respiratory spread of influenza virus) or indirect (involves a vector).

- Several quantitative measures are expressed as infectivity, disease index, virulence, incidence, and prevalence in terms of epidemiology.
- **Infectivity** is the rate of attack and is measured as the frequency with which an infection is transmitted when there is contact between the virus and a susceptible host.
- **Disease index** is the number of persons who develop the disease divided by total number infected.
- **Virulence** is the number of fatal or severe cases per total number of cases.
- **Incidence** is the number of new cases of a disease within a specified period; it usually reflects a percentage of the population that is affected.
- **Prevalence** is the rate of cases existing in a population at risk during a defined period.

# Transmission and Entry

- Viruses are transmitted via horizontal (common route of transmission; person to person) and vertical (mother-to-child transmission) routes.
- Human viruses cause either systemic or localized infections by entering the host through a variety of routes, including direct inoculation, respiratory, conjunctiva, gastrointestinal and genitourinary routes.
- Zoonotic (animal-to-human) transmission of viral infections can occur from the bite of animals (eg, rabies) or insects (eg, dengue, yellow fever, West Nile) or from inhalation of animal excreta (eg, hantavirus, arenavirus). In some cases, avian flu virus (bird flu) can be transmitted from birds or poultry to humans and swine flu virus can also be transmitted to humans.

- After virus entry into the host, viruses have variable incubation periods. **Incubation period** is the time between exposure to the organism and appearance of the first symptoms of the disease. Some viruses have short incubation periods (influenza—2 to 4 days), whereas others have long incubation periods (eg, hepatitis B virus—weeks to several months).

# Spread in the Host

- Viral infections produce either **localized infection** at the site of entry or **disseminated infection** spread throughout the body.
- Several viruses that cause systemic disease in the host spread from the site of entry to the target tissue, where they cause cell injury after multiplication. Viruses use two major routes to spread and cause systemic infection, namely, hematogenous (via the bloodstream) and neural (via nerves) spread.

# Tropism

- Tropism is the capability of viruses to infect discrete population of cells within an organ. Cellular or tissue tropism is determined by the specific interaction of viral surface proteins (spikes) and cellular receptors on the host cells.

# Virulence and Cytopathogenicity

- The ability of a virus to cause disease in an infected host is called **virulence** or **pathogenicity.**
- The ability of a virus to cause degenerative changes in cells or cell death is called cytopathogenicity

- Three major outcomes can be attributed to a viral infection:
- **abortive infection**, in which no progeny virus particles are produced, but the cell may die because early viral functions can occur;
- **lytic infection,** in which active virus production is followed by cell death; and
- **persistent infection,** in which small numbers of virus particles are produced with little or no CPE.

- Persistent infections include **latent infection,** in which viral genetic material remains in host cell without production of virus and may be activated at a later time to produce virus and/or transform the host cell; **chronic infection,** which involves low level of virus production with little or no CPE; and **viral transformation,** in which viral infection or viral gene product induces unregulated cellular growth and cells form tumors in the host.

- The features of CPE include the following

1. Nucleus: Inclusion bodies, thickening of the nucleus, swelling, nucleolar changes, margination of chromatin
2. Cytoplasm: Inclusion bodies, vacuoles
3. Membranes: Cells round up, loss of adherence, cell fusion (syncytia)
4. Cellular: Lysis (disintegration)

# Patterns of Viral Infection and Disease

- Not every viral infection results in a disease. **Infection** involves multiplication of the virus in the host, whereas **disease** represents a clinically **apparent** response. Infections are much more common than disease; **unapparent** infections are termed **subclinical,** and the individual is referred to as a **carrier.**

# Host Factors

- Several of the host factors, including immune status, genetic background, age, and nutrition, play important roles in determining the outcome of viral infection. Several innate immune responses (interferons alpha and beta, natural killer cells, mucocilliary responses, and others) and adaptive immune responses (antibody and T-cell responses) influence the outcome of viral infections.
- Host genetics is one of the most important factors that influence the outcome of viral infections.

- Age-related correlation between the host and several viral infections has been observed. Several viruses such as varicella-zooster virus (VZV), mumps, polio, and Epstein-Barr virus (EBV) cause less severe infection in infants, whereas others (rotaviruses, respiratory syncytial virus) result in severe disease in infants.
- Production of hormones may also influence the outcome of some viral infections.
- Nutritional state and personal habits of the hosts can also have an effect on viral pathogenesis.

# Host Defenses

- The two major types of host defenses are nonspecific (**innate**) and specific (**adaptive**) immune responses. The innate immune response includes interferons ( α, β ), natural killer cells, macrophages (phagocytosis), defensins, mucociliary clearance, apolipoprotein B RNA editing enzyme (APOBEC3G, an anti HIV enzyme) and fever, whereas the adaptive immune response involves humoral and cell-mediated immunity

# Interferons

- Interferons are host-encoded proteins that provide the first line of defense against viral infections.
- They belong to the class of molecules called **chemokines,** which are proteins or glycoproteins that are involved in cell-to-cell communication.
- There are three types of interferon, interferon-α (leukocyte), interferon-β (fibroblast) and interferon- γ (lymphocyte).

- Virus infection of all types of cells stimulates the production and secretion of either interferon-α or interferon-β, which acts on other cells to induce what is called the **antiviral state.**

- The machinery to inhibit virus production is mobilized only on infection. Interferon has multiple effects on cells, but only three systems have been extensively studied.
- The first system involves a protein called Mx, which is induced by interferon and specifically blocks influenza infections by interfering with viral transcription.
- The second system involves the up-regulation of protein kinase, which is dependent on double-stranded RNA and protein kinase and which phosphorylates and thereby inactivates one of the subunits of an initiation factor (eIF-2) necessary for protein synthesis. In some cases, viruses have evolved specific mechanisms to block the action of this protein kinase.
- The third system involves the induction of an enzyme called 2', 5'-oligoadenylate synthetase, which synthesizes chains of 2', 5'-oligo (A) up to 10 residues in length. In turn, the 2', 5'-oligo (A) activates a constitutive ribonuclease, called RNase L, which degrades mRNA.

# Thank You