Advanced Medical virology

Viruses Replication

Lecture 2

BY

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Viral Replication

- As a virus is an intracellular pathogen, it cannot replicate without any metabolism and machinery of a host cell. Hence a virus must first invade a cell before viral replication can occur.

-The process of infection begins with the coming together of a virus particle and a susceptible host cell.

-Susceptibility defines the capacity of a cell or an animal to become infected.

- To infect a cell, the virion must attach to the cell surface, penetrate the cell, and become sufficiently uncoated to make its genome accessible to viral or host machinery for transcription or translation.

- **Infection of a cell must be Productive (permissive).**
- Virus replication can be divided into eight stages:

These stages can be divided into three phases

I -Initiation phase

- Attachment
- Penetration
- Uncoating

II - Replication phase

- DNA Synthesis
- RNA Synthesis
- Protein synthesis

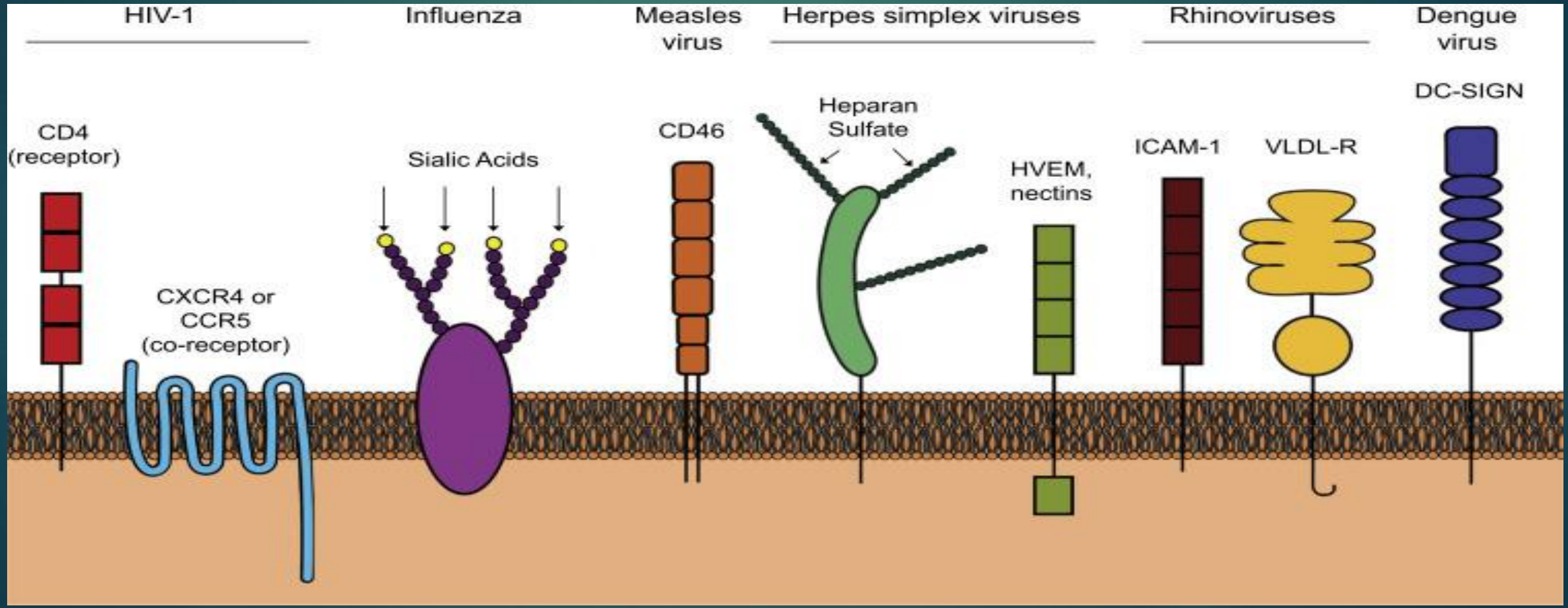
III - Release phase

- Assembly
- Maturation
- Releas

Attachment

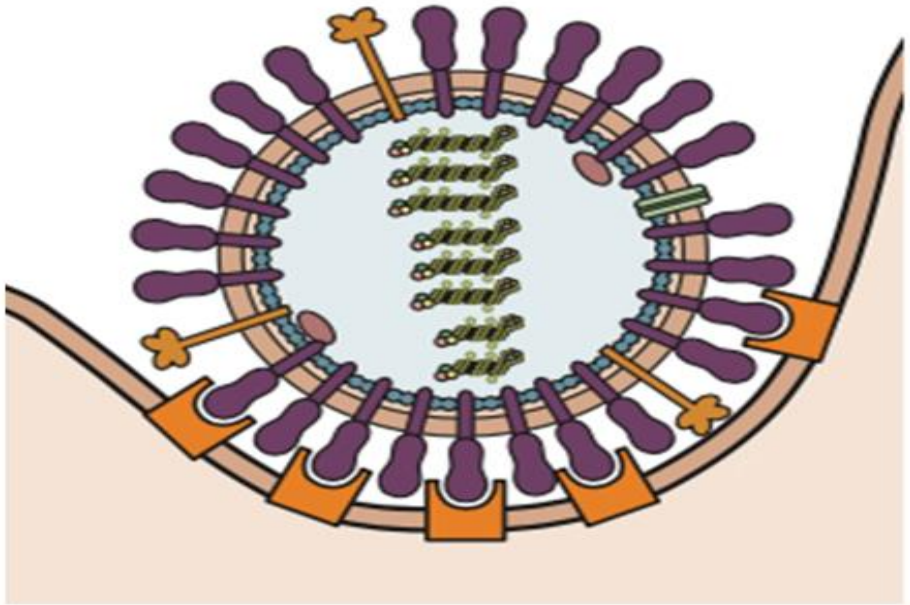
- Surface protein on virus attaches to **specific receptor(s)** on cell surface
- May be specialized proteins with limited tissue distribution or more widely distributed
- **Virus specific receptor is necessary but not sufficient for viruses to infect cells and complete replicative cycle**
- Attachment constitutes the specific binding of a viral protein VAP to a constituent of the cell surface (receptor/ anti-receptor).
- Complex viruses may **have more than one species of antireceptor** molecules.
- Anti receptor molecules may have several domains, each of which may react with a different receptor.
- Mutations in the genes specifying anti-receptors may cause loss of the capacity to interact with certain receptors.

- To infect a cell, it is critical that a virus initiates **attachment**—the binding of the virus to the host cell. This interaction is specific: the virus contains a **virus attachment protein** that adsorbs to a **cell surface receptor** on the cell.



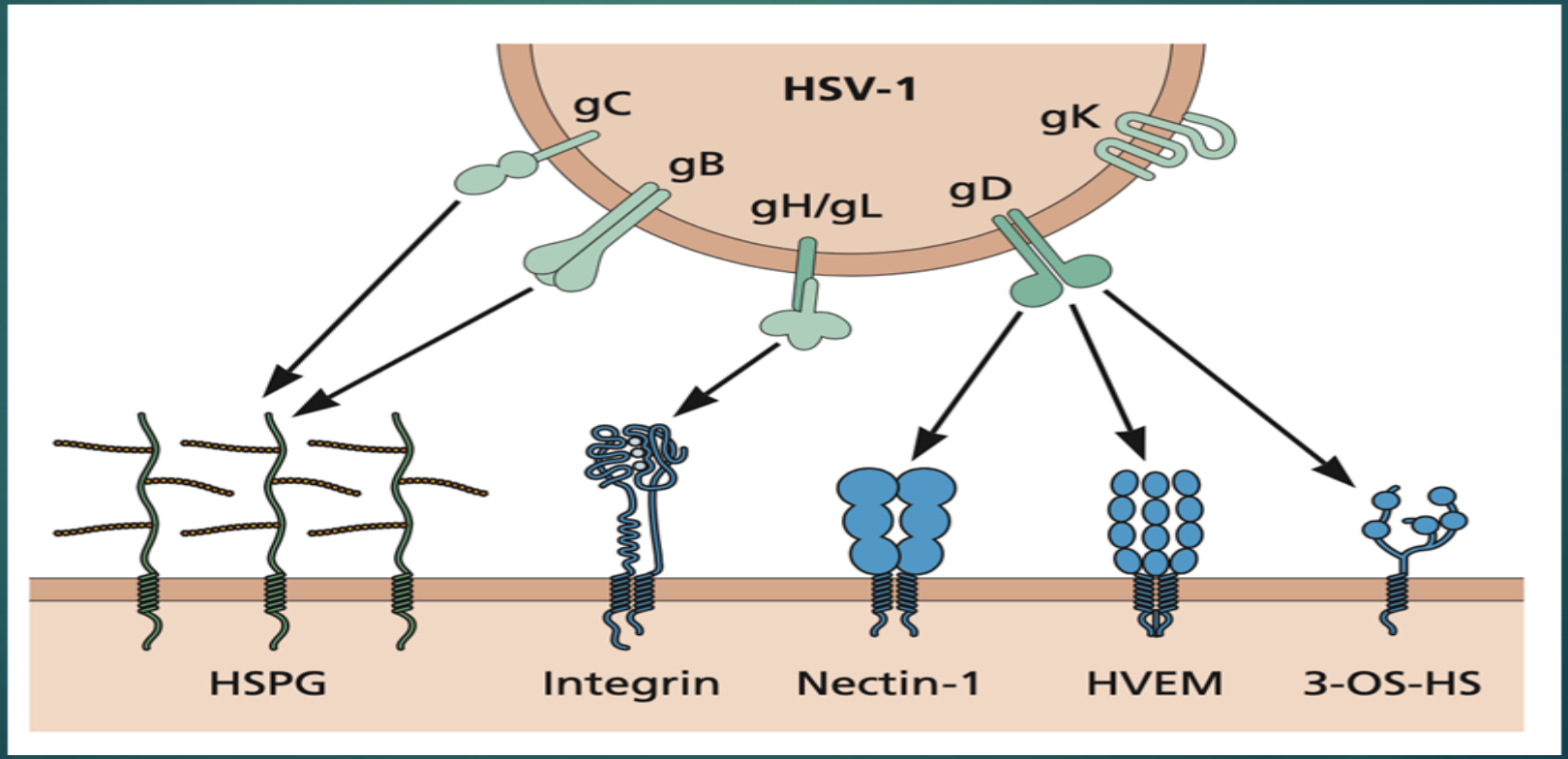
Cellular receptors for viruses

- Essential for all viruses except those of fungi (no extracellular phases) and plants (enter cells by mechanical damage)
- 1985: one receptor known, sialic acid for influenza virus



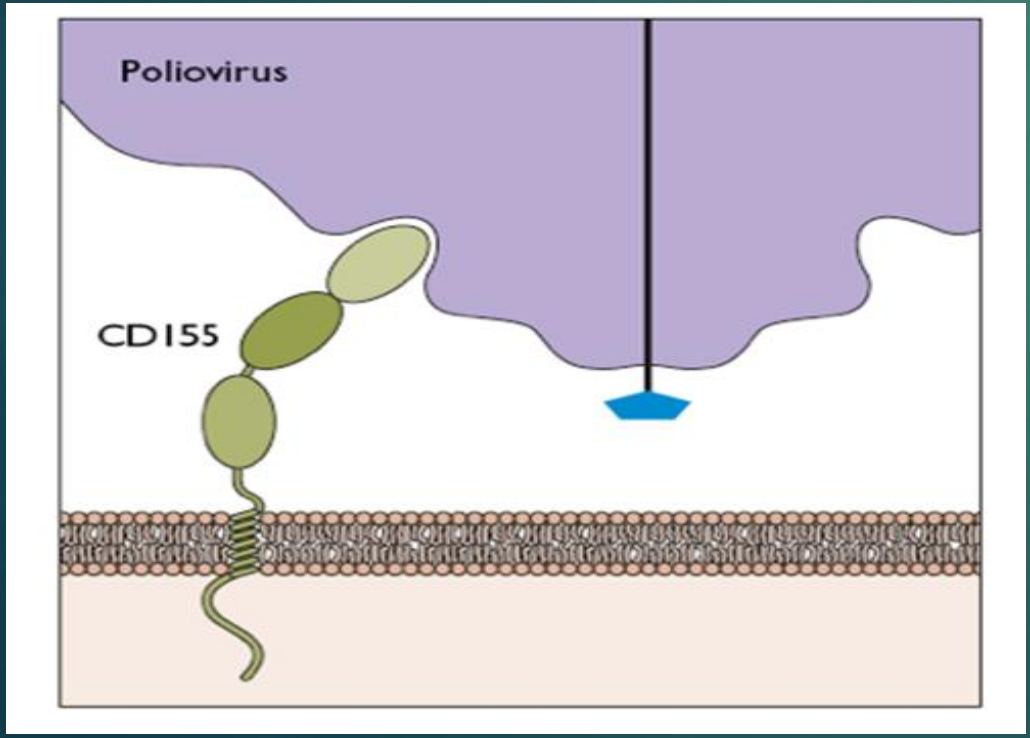
Viruses of the same family may bind different receptors

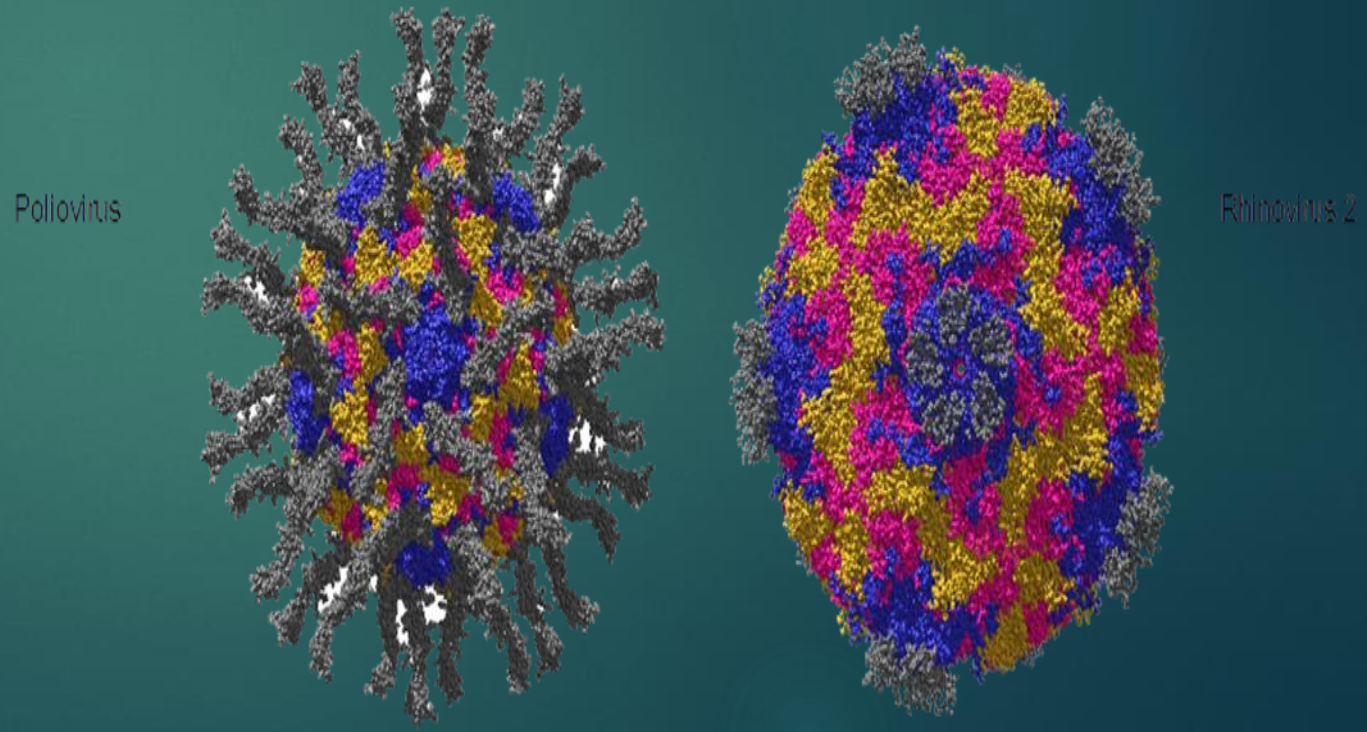
- Rhinoviruses (3), retroviruses (16)
- One virus may bind multiple receptors



Virus attachment sites

- Each virion has multiple sites that can bind to receptors, and each site is made up of regions of one or more protein molecules.
- The virus attachment sites of naked viruses are on the capsid surface, sometimes within depressions (e.g. poliovirus) and sometimes on ridges (e.g. foot and mouth disease virus).

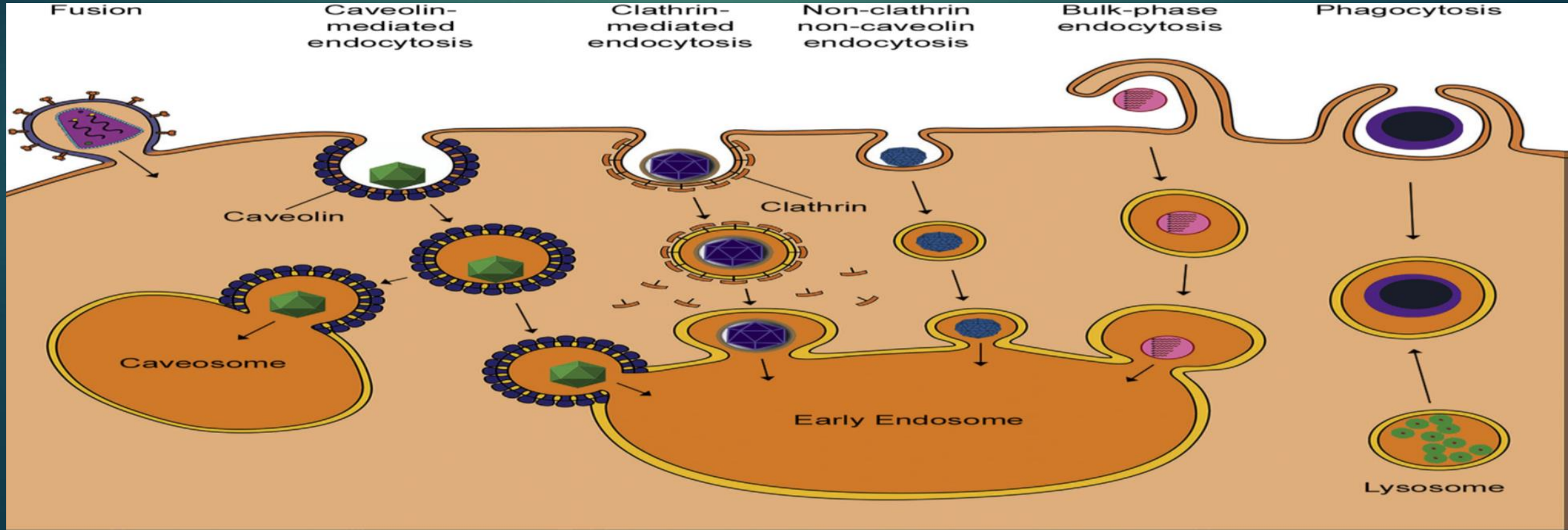


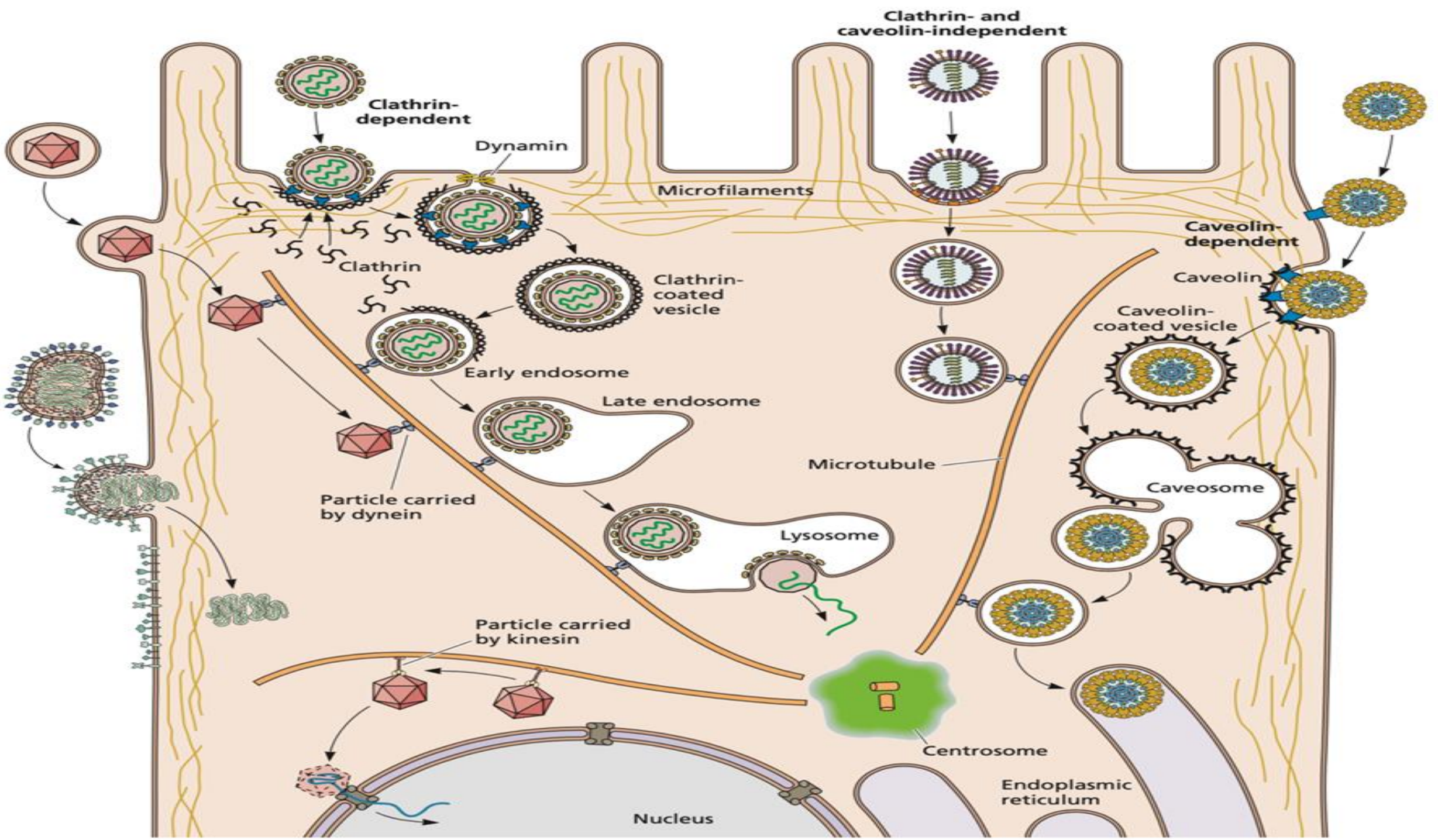


2) Penetration [entry]:

- Penetration is energy dependent process
- Virus may penetrate into host by:

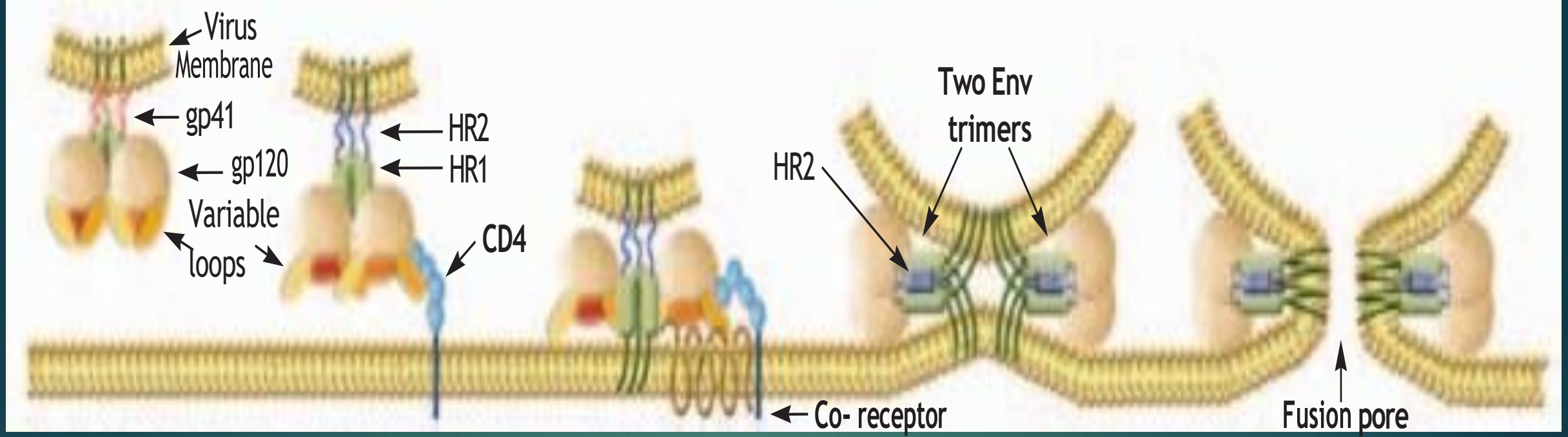
1. Endocytosis
2. Fusion




Clathrin- and caveolin-independent
Clathrin-dependent
Dynamin
Microfilaments
Caveolin-dependent
Caveolin
Clathrin
Clathrin-coated vesicle
Caveolin-coated vesicle
Early endosome
Late endosome
Microtubule
Particle carried by dynein
Caveosome
Lysosome
Particle carried by kinesin
Centrosome
Endoplasmic reticulum
Nucleus

Methods of Penetration for Select Human Viruses

Type of penetration (entry)	Virus examples
Clathrin-mediated endocytosis	Dengue virus, hepatitis C virus, reovirus, adenovirus, parvovirus B19, West Nile virus
Caveolin-mediated endocytosis	Human papillomavirus, SV40, hepatitis B virus
Fusion	HIV, influenza, respiratory syncytial virus, herpes simplex viruses, dengue virus, Ebola virus



1.An HIV-1 virion approaches a target cell. A native envelope trimer (gp120-gp41)3 is shown here

2.Gp120 binds the CD4 primary receptor, resulting in exposure of the coreceptor binding site, and conformational changes in gp41 (HR1, HR2). HIV may need to bind several CD4 molecules for successful fusion

3.Gp120 changes conformation, allowing another region of gp120 to bind the coreceptor, thus drawing the membranes closer together;
the hydrophobic N-terminus of gp41 is exposed and inserts into the cell membrane lipid bilayer

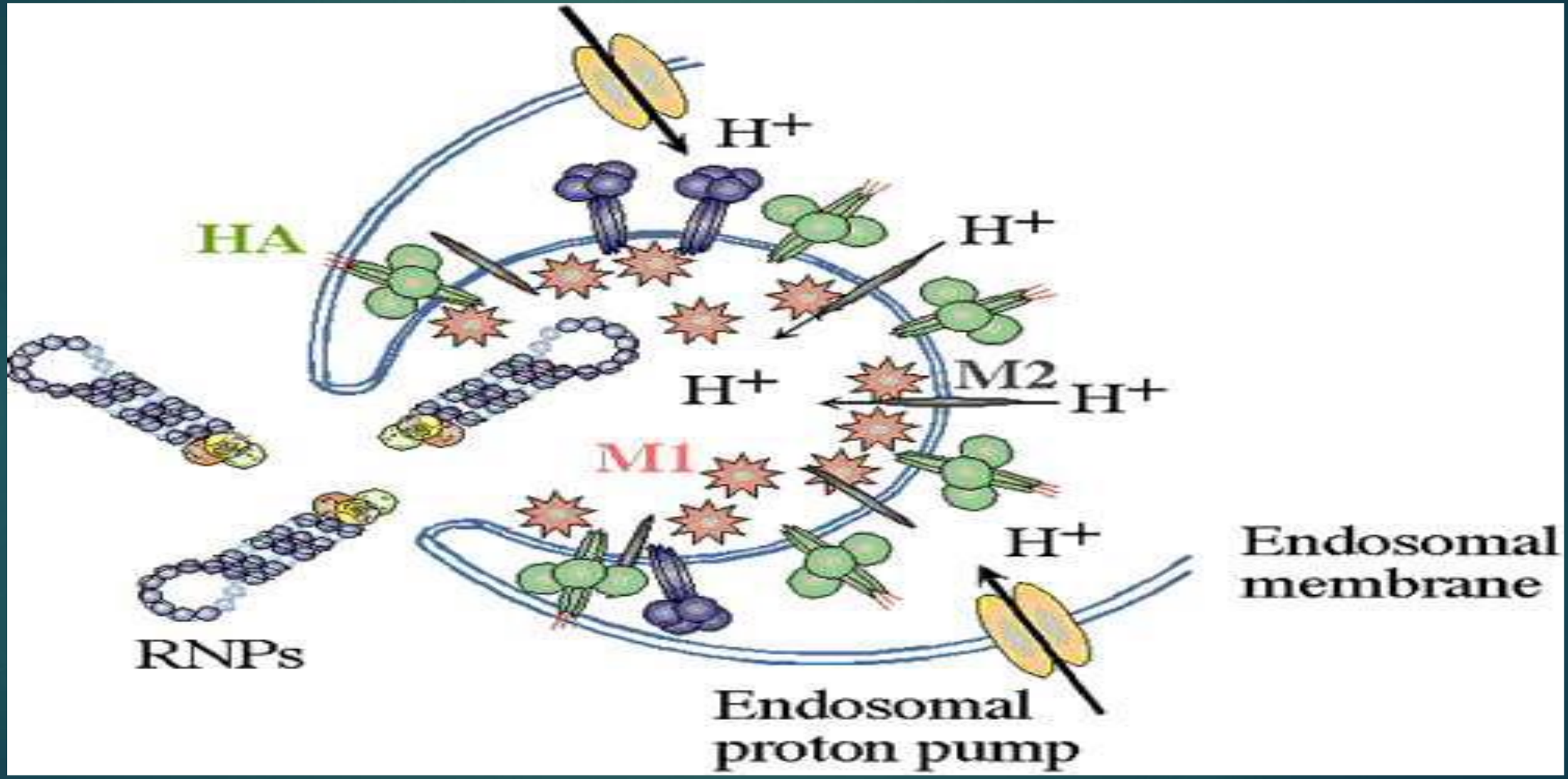
4. Further conformational changes in gp41 (HR2) bring its C- and N-terminal hydrophobic domains close together, and with another Env trimer forms a hydrophobic channel

5. Viral and cell bilayer lipids flow down the hydrophobic channel and fuse together, forming a fusion pore. The viral genome enters the cell when the pore enlarges

The fusion of other enveloped viruses, such as **influenza A virus**, is not triggered solely by protein–protein interactions but also **requires exposure to an acid pH.** The virus particle attaches to a cell and is then engulfed into a vesicle by receptor-mediated endocytosis. Strictly speaking, the virus in the vesicle is still on the *outside* the cell and not in the cytoplasm, as it is contained in what was plasma membrane.

The release of the genome into the cytoplasm is dependent upon the internal environment of the endocytic vesicle becoming acidic (pH 5–6). This is achieved by fusion of **the endocytic vesicle with an intracellular vesicle called an endosome.** A membrane-bound endosomal protein then pumps protons into the lumen of the vesicle. The low pH initiates conformational changes in the viral envelope proteins (the influenza virus hemagglutinin) which release the hidden hydrophobic N-terminus of the membrane anchoring part of the membrane (HA2). Fusion of the viral lipid bilayer with the bilayer of the vesicle then proceeds exactly as described above for HIV-1.

influenza A virus

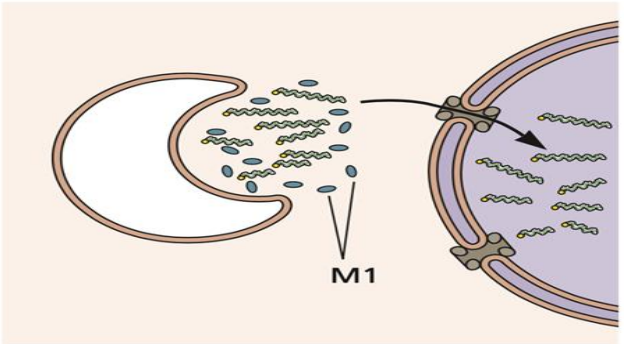


3- Uncoating: refers to the breakdown or removal of the capsid, causing the release of the virus genome into the cell to wherever genome replication and transcription will take place.

Uncoating can be separated from or tightly linked with penetration, and viruses achieve uncoating in a variety of different ways.

- at the cell surface, the capsid remaining on the exterior surface of the cell like poliovirus
- within the cytoplasm;
- at a nuclear pore;
- within the nucleus.

Influenza virus



Herpesviru
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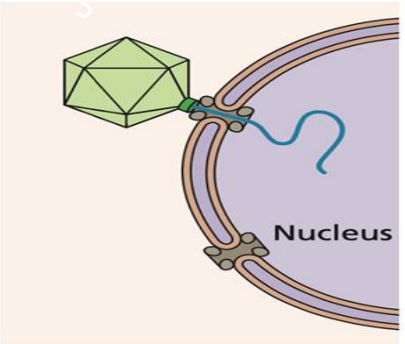
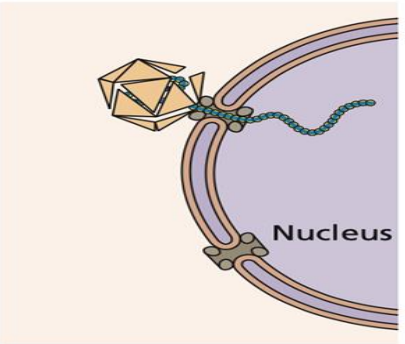
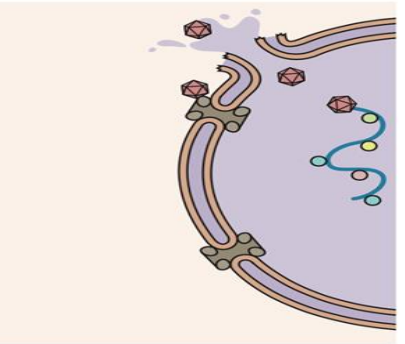
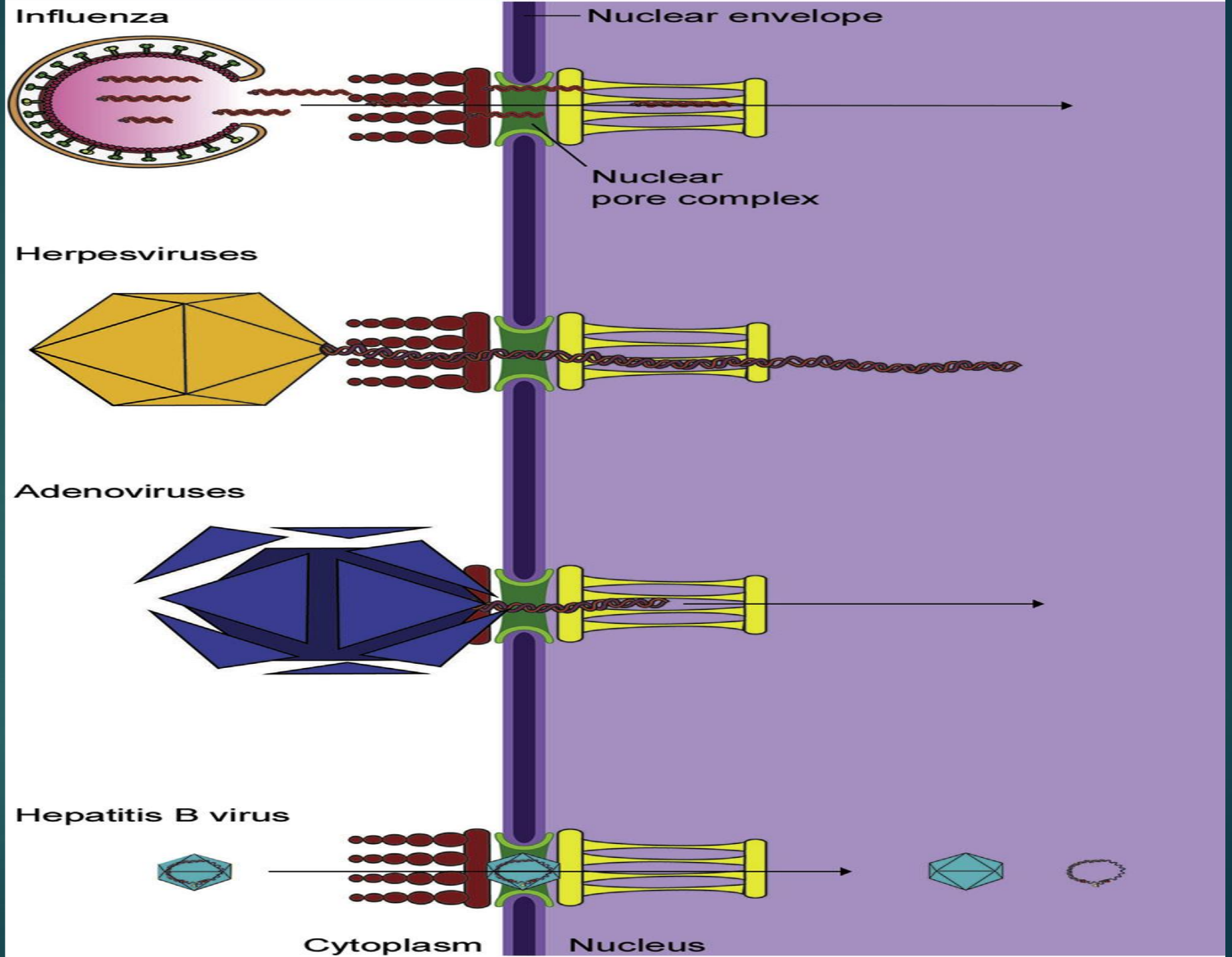


Adenovirus



Parvovirus

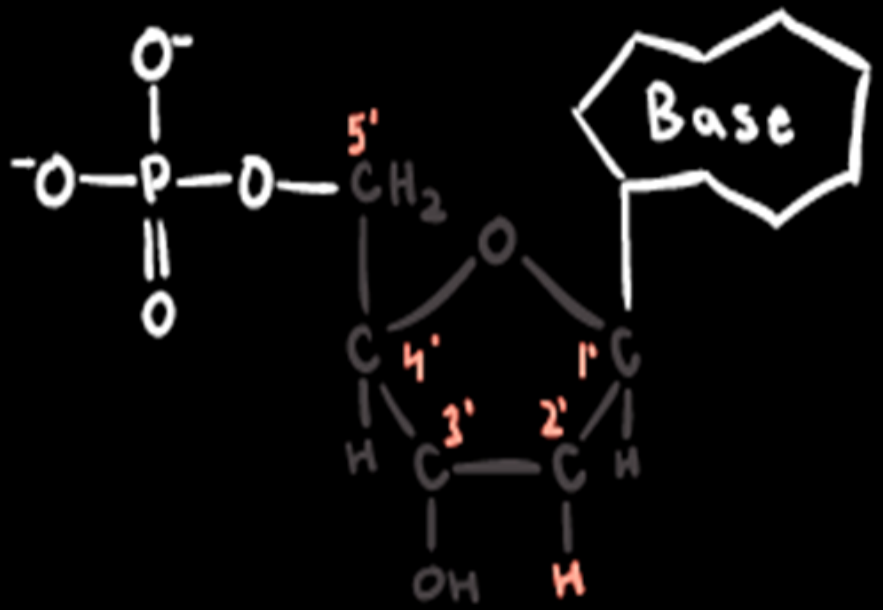



Influenza
Nuclear envelope
Nuclear
pore complex
Herpesviruses
Adenoviruses
Hepatitis B virus
Cytoplasm
Nucleus

4-Transcription and Genome Replication

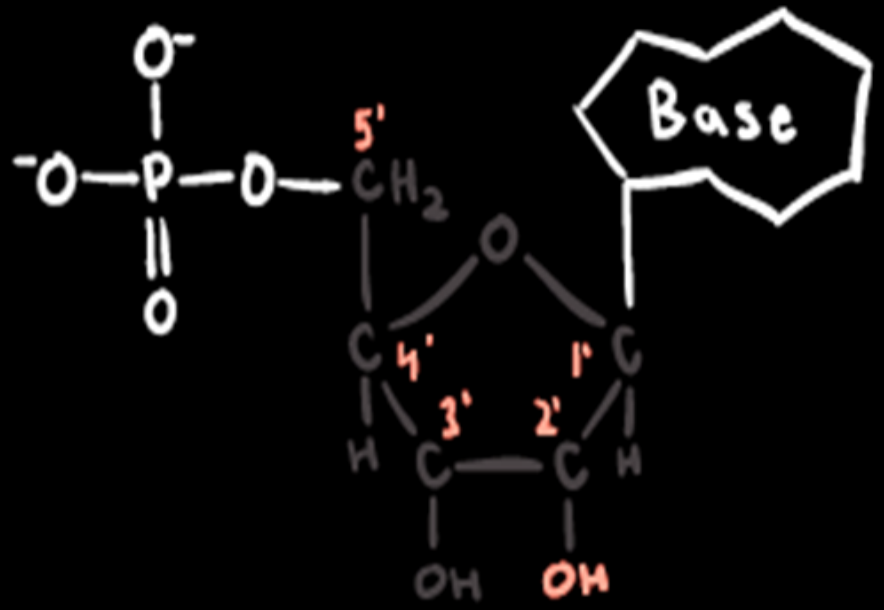
Transcription of viral mRNA (vmRNA) must occur before genome replication if viral proteins are involved in replicating the virus genome. In addition, certain translated viral proteins act as **transcription factors** to direct the transcription of other genes.

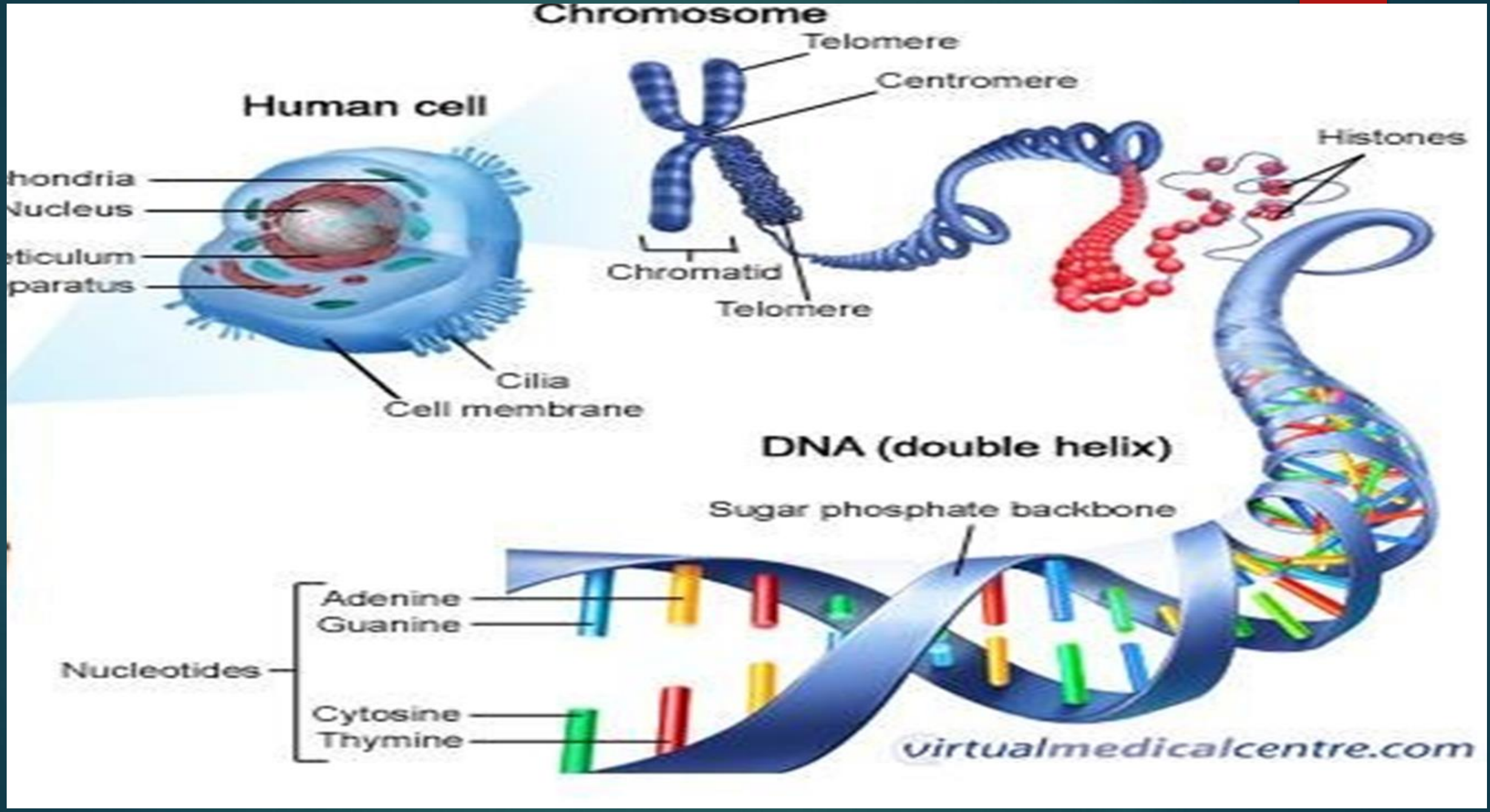
DNA



RNA

RNA




Chromosome
Telomere
Centromere
Human cell
Histones
hondria
Nucleus
ticulum
paratus
Chromatid
Telomere
Cilia
Cell membrane
DNA (double helix)
Sugar phosphate backbone
Adenine
Guanine
Nucleotides
Cytosine
Thymine
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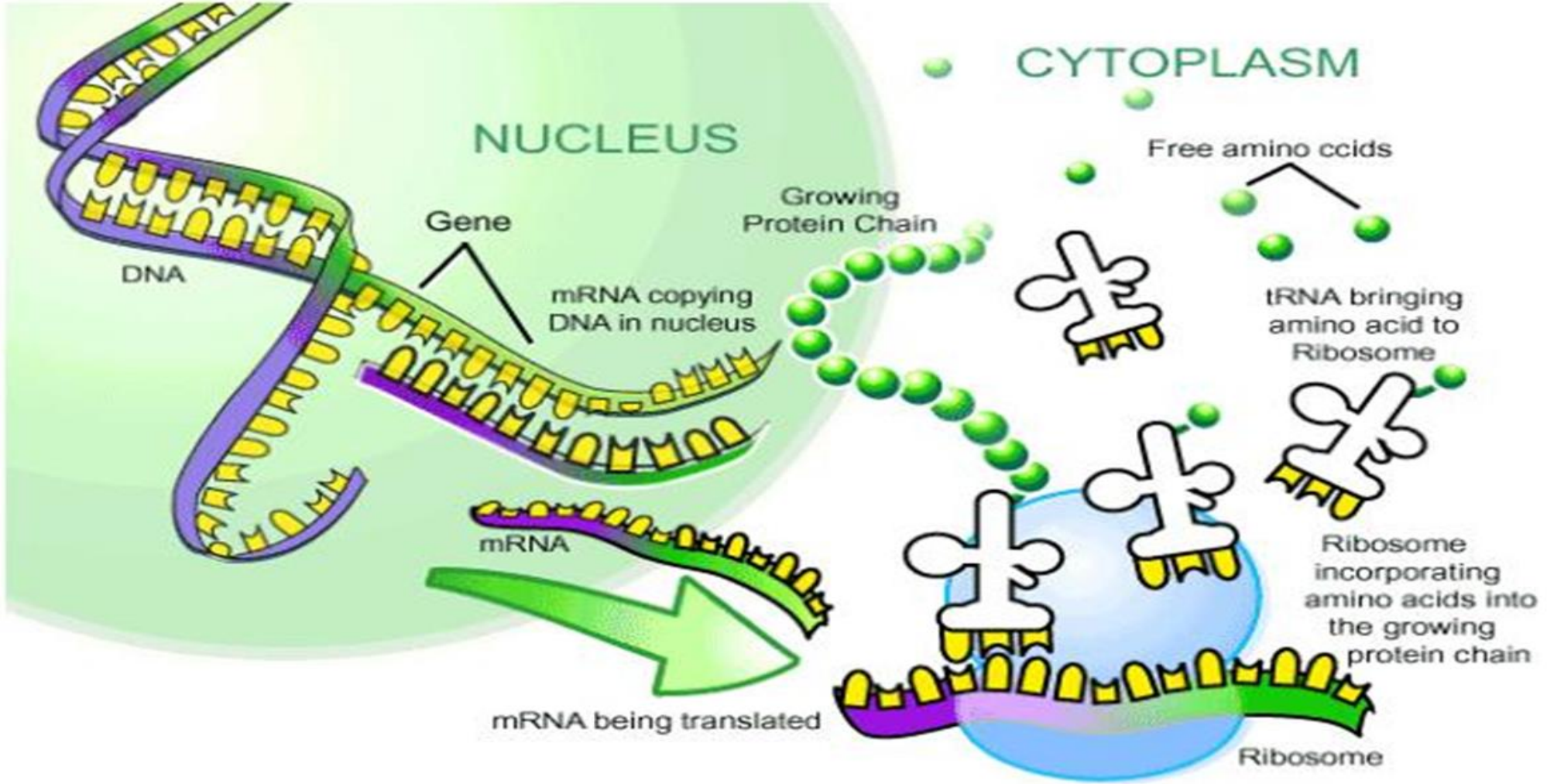
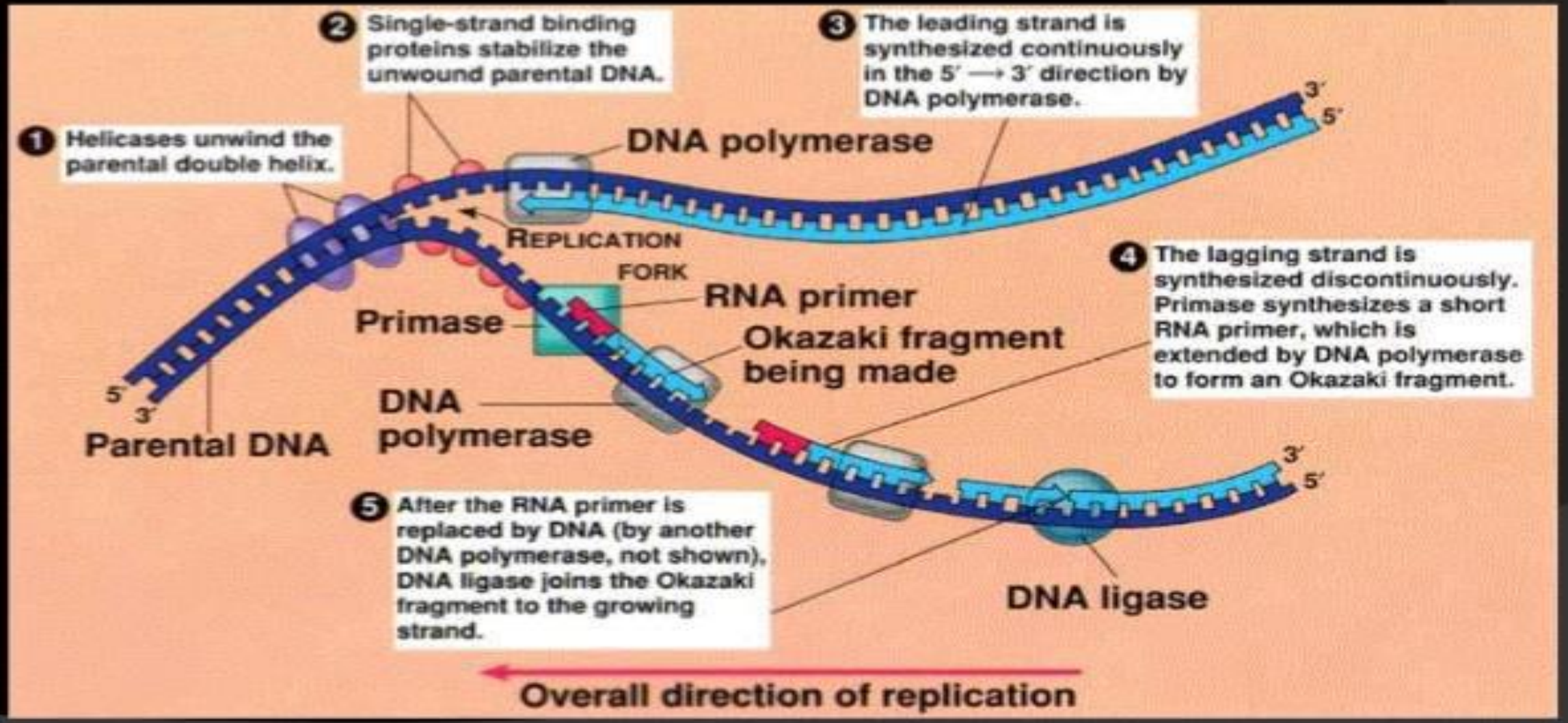
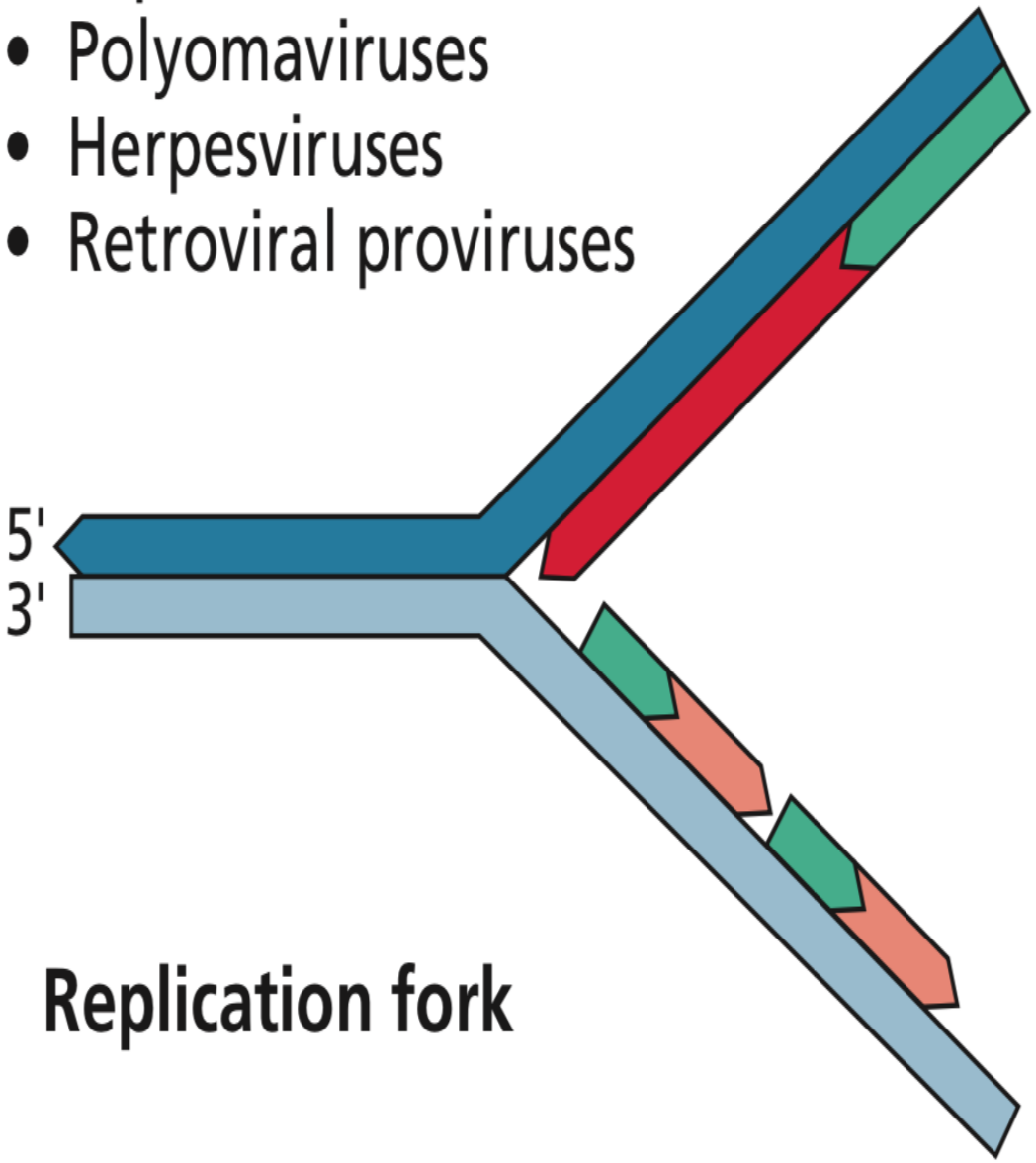
Protein Synthesis-Transcription



Replication Fork

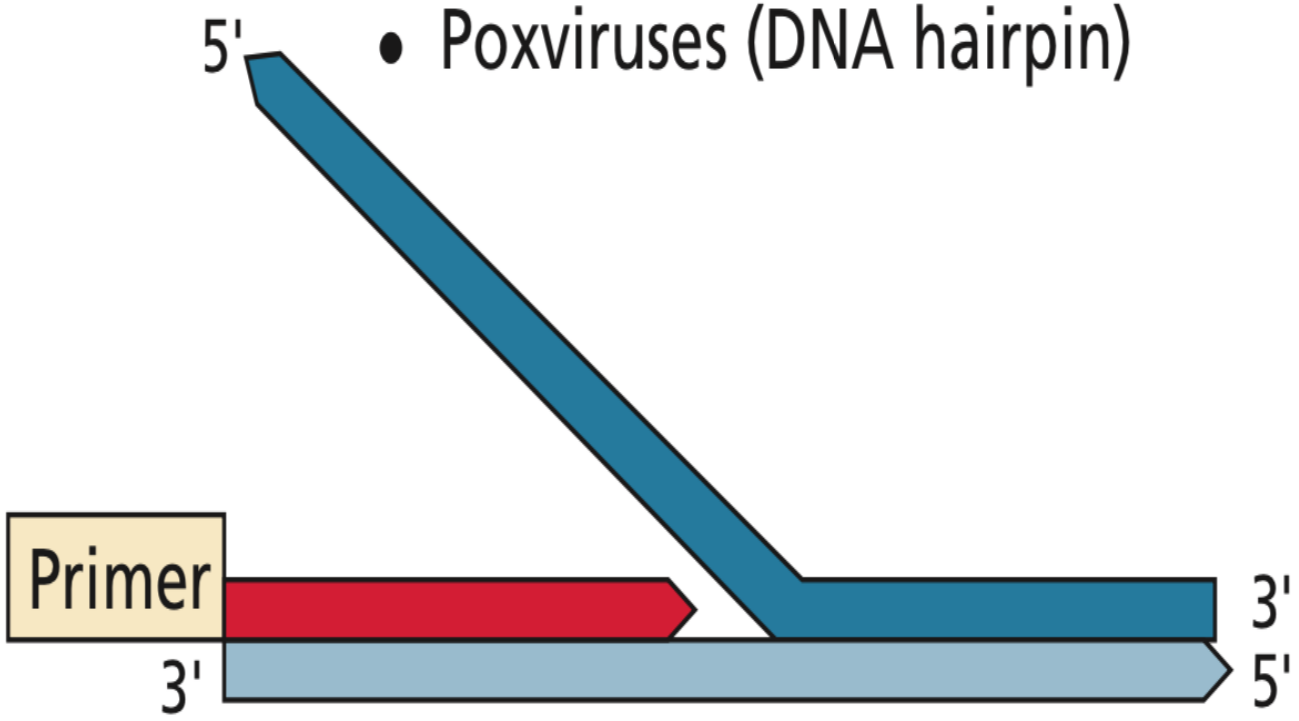


- Papillomaviruses
- Polyomaviruses
- Herpesviruses
- Retroviral proviruses



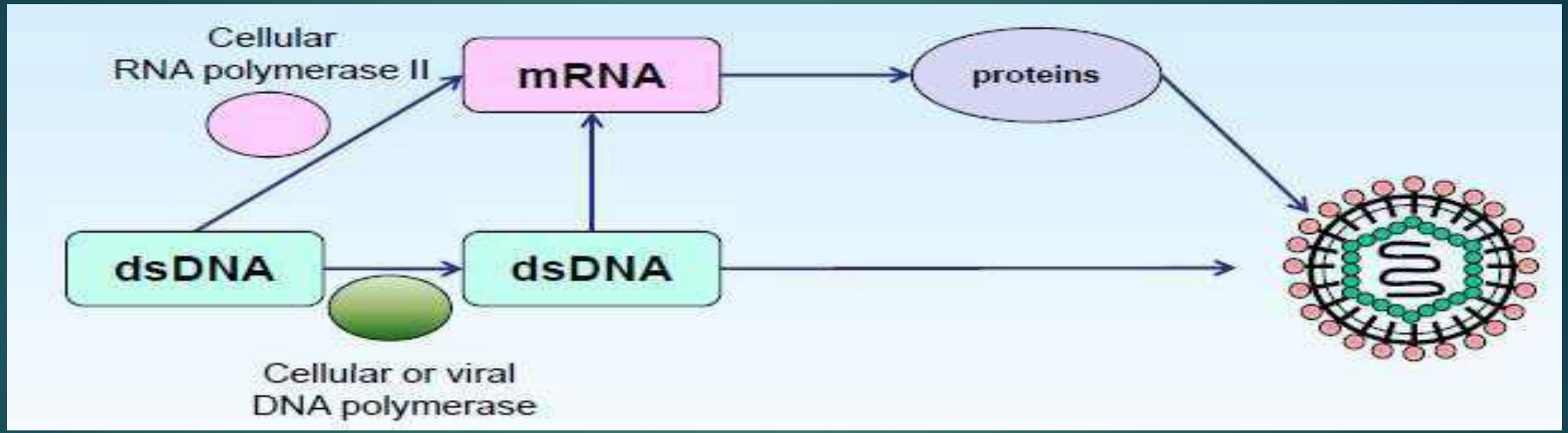
Replication fork

- Adenoviruses (protein)
- Parvoviruses (DNA hairpin)
- Poxviruses (DNA hairpin)



Strand displacement (primer)

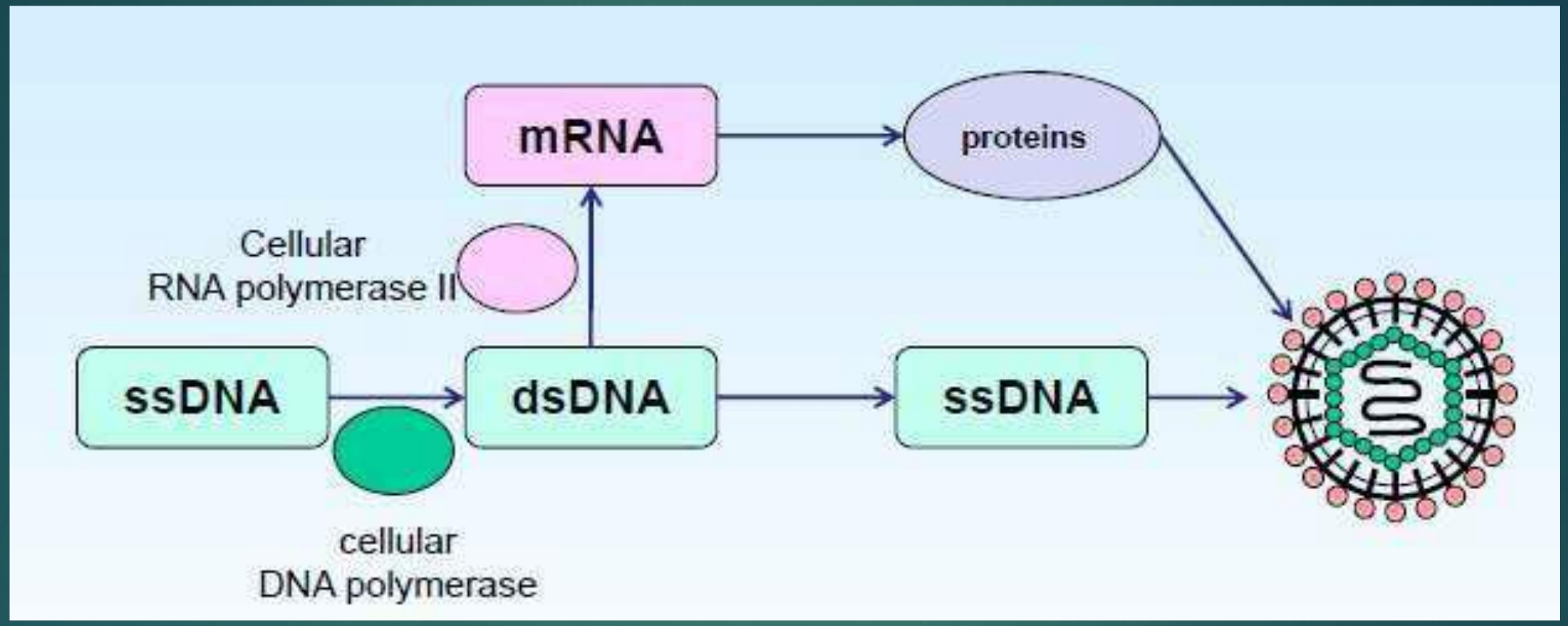
1.Double stranded DNA:



Replication of genome of double stranded DNA virus

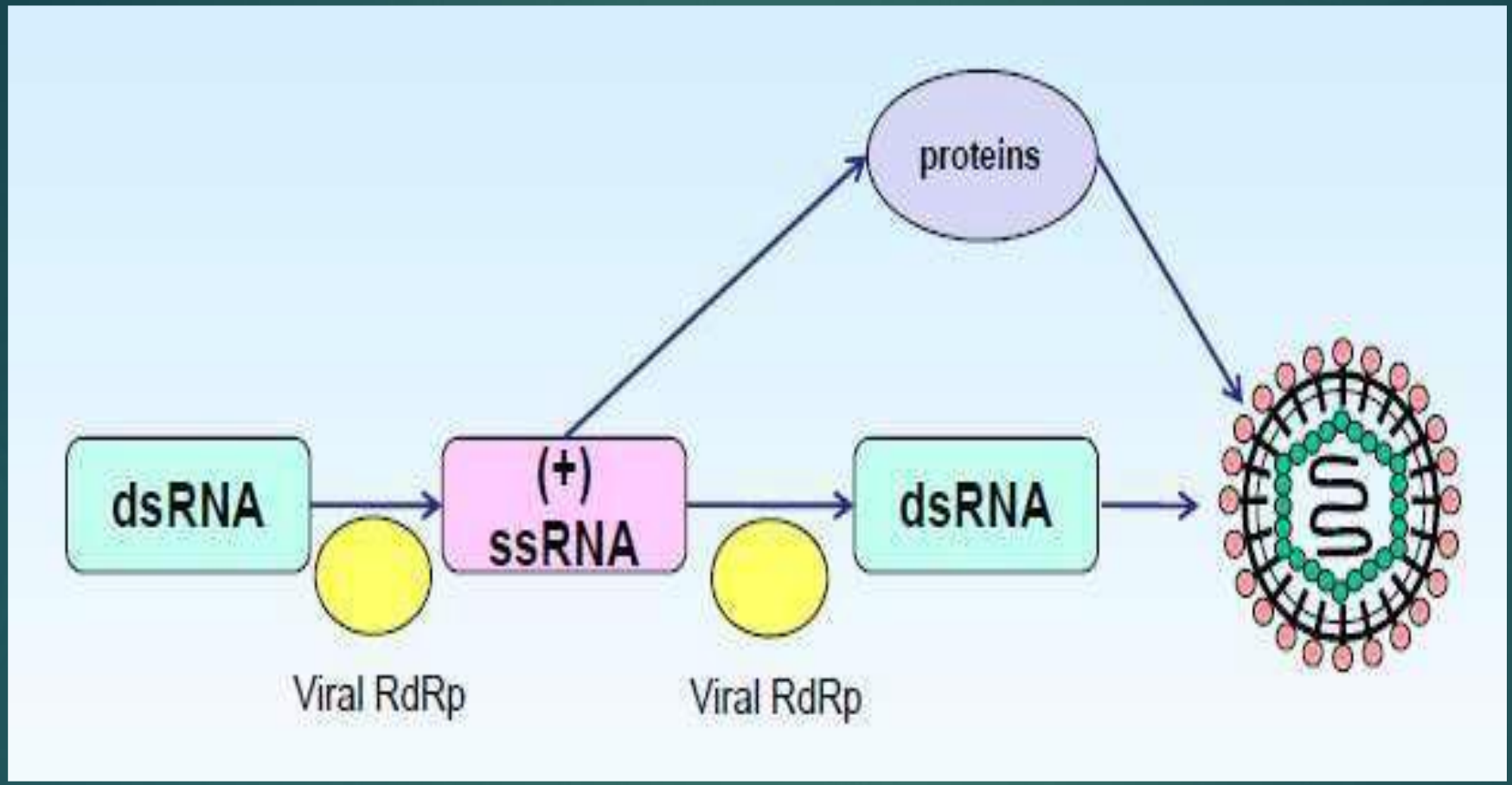
Example: *Poxvirus, Herpes virus*

II. Single stranded DNA:



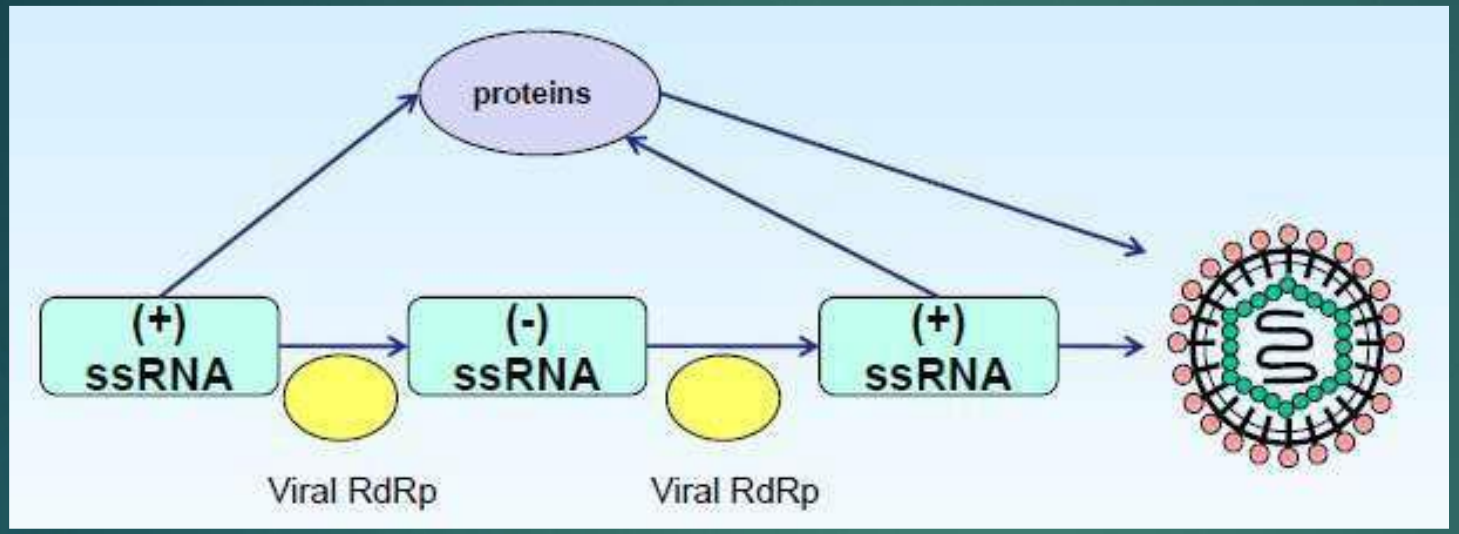
Replication of genome of single stranded DNA virusExample: Parvovirus

III. Double stranded RNA:



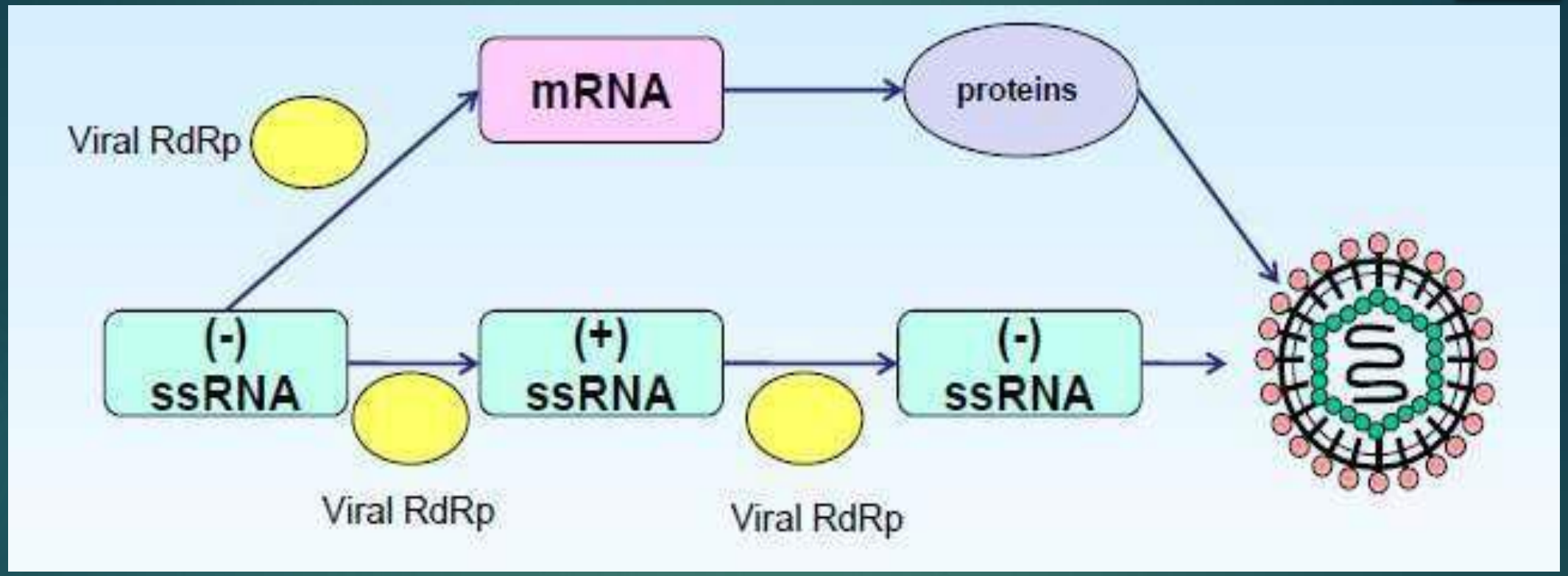
Replication of genome of double stranded RNA virus
RNA-dependent RNA polymerase (RdRp)
Example: Reoviruses

IV. Single stranded (+)ve sense RNA



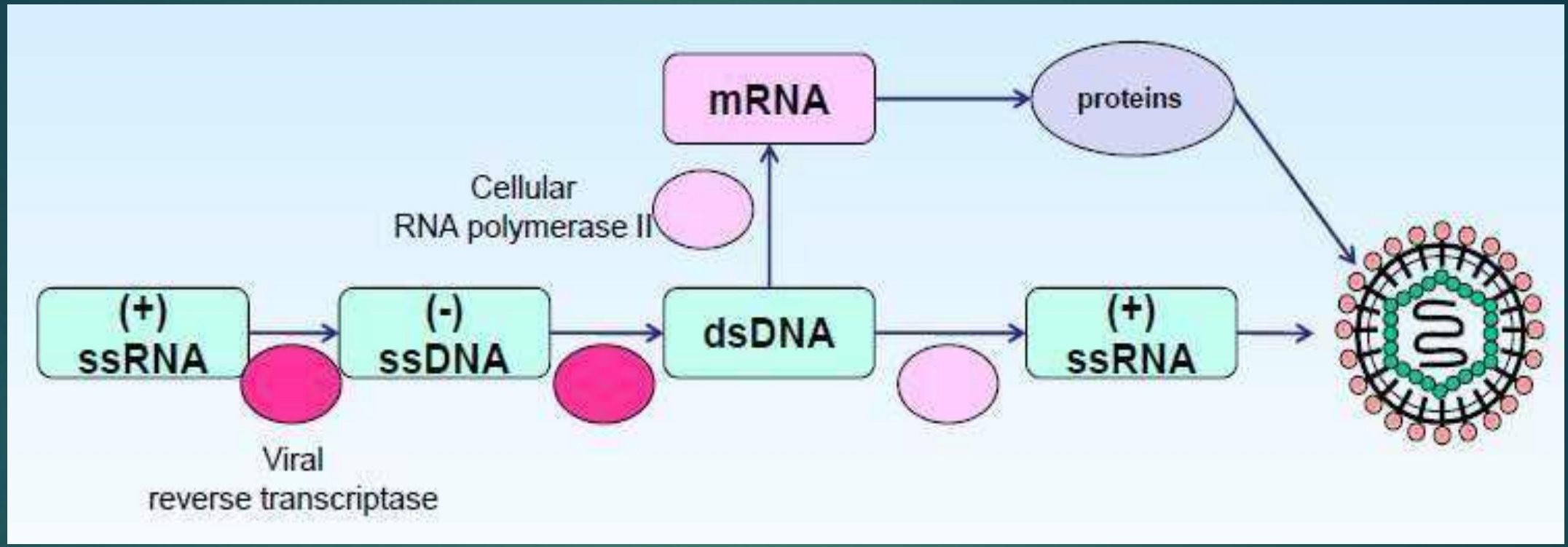
Replication of genome of +sense single stranded RNA virus
Example: Toga virus & Hepatitis E virus

V. Single stranded (-)ve sense RNA:



Replication of genome of -sense single stranded RNA virus
Example: Rabis, Paramyxoviruse etc.

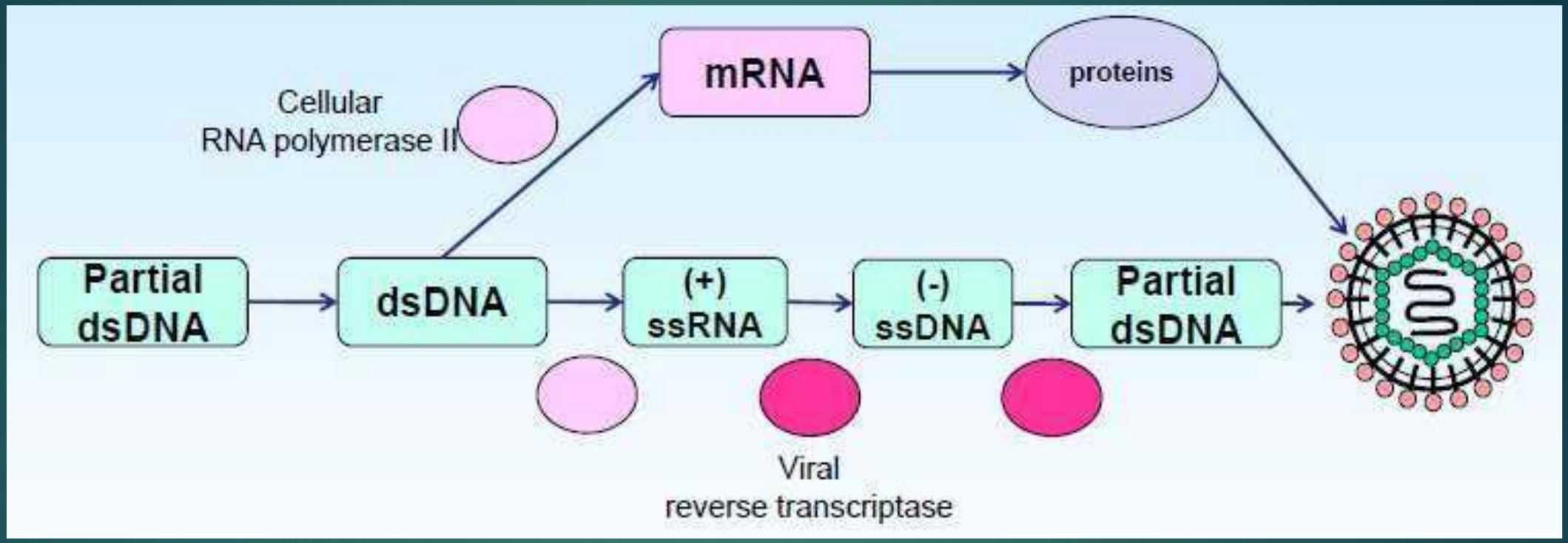
vi. Single stranded (+)ve sense RNA with DNA intermediate:



Replication of genome of single stranded (+)ve sense RNA virus with DNA intermediate

Example: Retrovirus

VII.Double stranded DNA with RNA intermediate:



Replication of genome of double stranded DNA virus with RNA intermediate

Example: Hepadnaviruses

5-ASSEMBLY

Viruses are created from newly synthesized components, and to be released from the cell, those components must be collected at a particular site of the cell and undergo assembly to form an immature virus particle. In the same way that penetration and uncoating are difficult to separate in the cycle of some viruses, assembly can often occur alongside maturation and release. The location of virion assembly will depend upon the particular virus. **It can take place within the nucleus of the cell, at the plasma membrane, or at a variety of intracellular membranes, such as the Golgi complex. Most nonenveloped DNA viruses assemble their nucleocapsid in the nucleus, since that is the site of genome replication.**

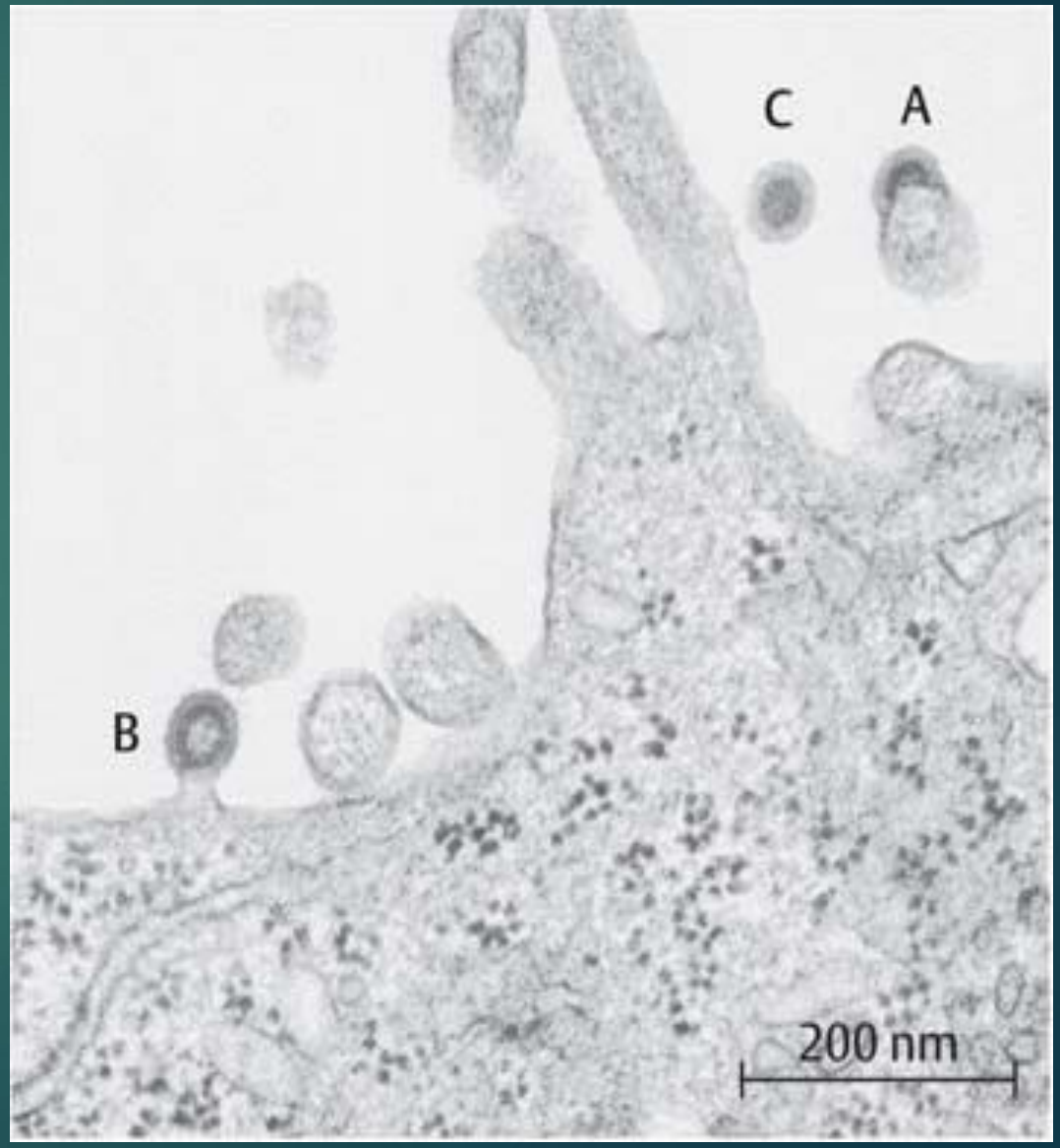
Viral proteins are imported through nuclear pores to reach the site of assembly. When assembled, most DNA viruses are too large to fit through nuclear pores, however. **At this point, some viruses are able to traverse the double-membraned nuclear envelope, while others induce cell lysis or apoptosis to escape the nucleus**. On the other hand, viruses with envelopes derived from the plasma membrane usually assemble there. **The nucleic acid genome of a helical virus is protected by repeating capsid proteins. Because of this, capsid proteins can begin wrapping the genome as soon as it is copied.**

The genome can be wrapped around capsid proteins;. **In contrast, some icosahedral viruses nearly complete the assembly of their capsids before the nucleic acid genome is inserted.** Spontaneous assembly of the capsid, termed "selfassembly," occurs with the capsid proteins of simple icosahedral viruses, such as the picornaviruses and parvoviruses.

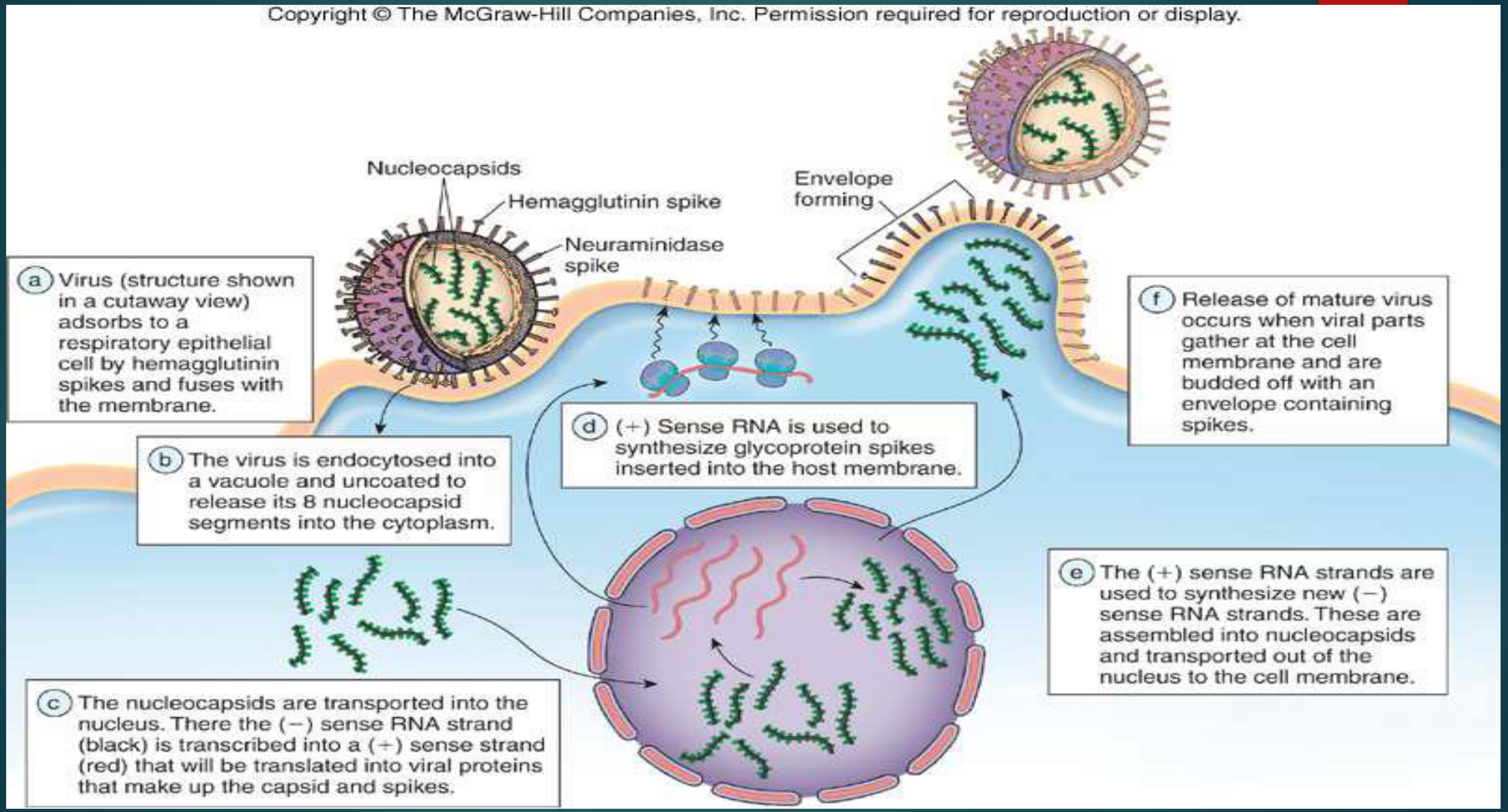
The assembly of viruses with more complex architecture is orchestrated by a variety of viral chaperone proteins called scaffolding proteins. Herpesviruses and adenoviruses are examples of large icosahedral viruses that assemble with scaffolding protein assistance.

6- Release

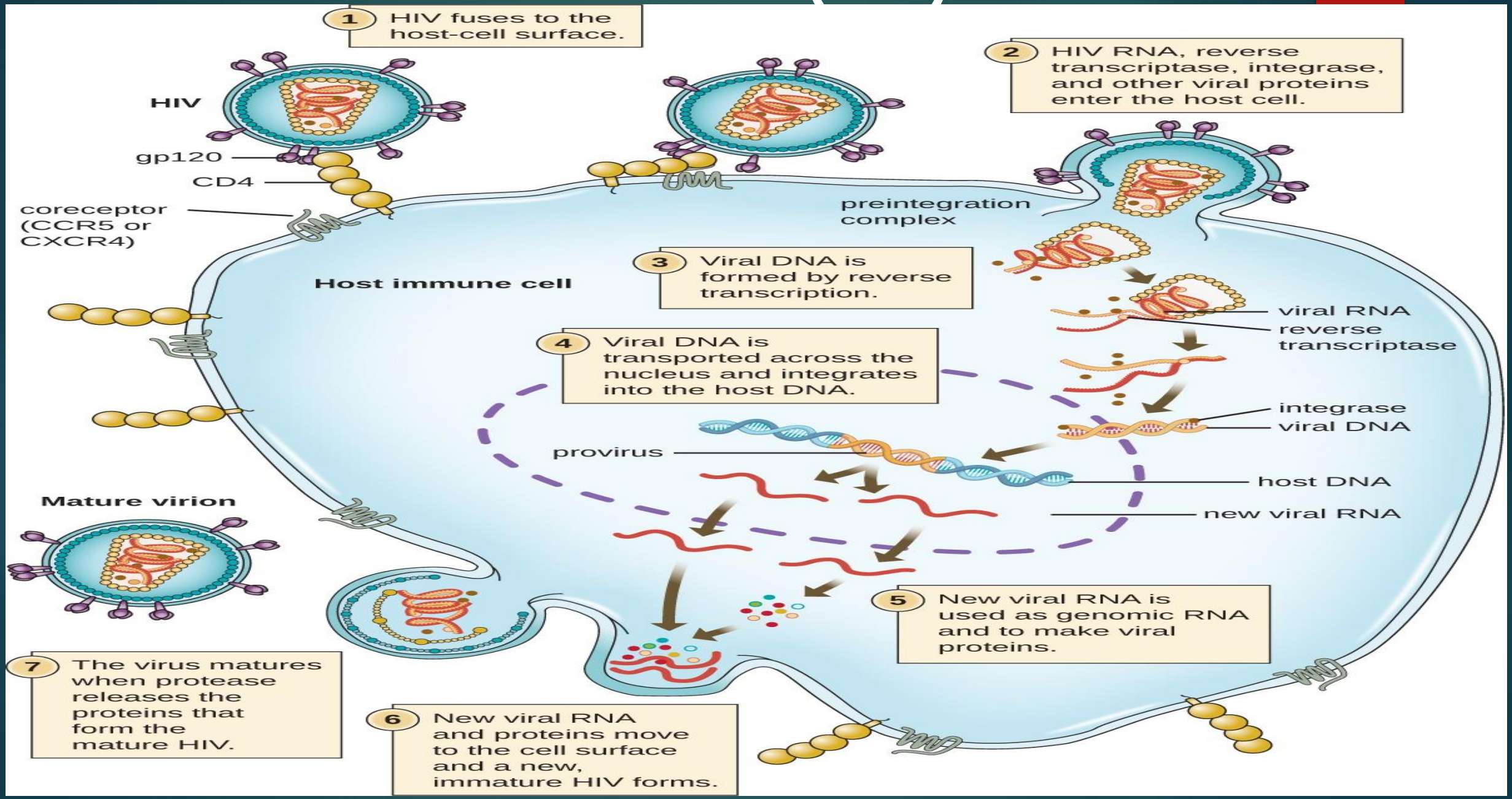
The release of viral progeny in some cases correlates closely with viral maturation, whereby envelopes or components of them are acquired when the particles **“bud off”** of the cytoplasmic membrane and are expelled from the cell. In nonenveloped viruses, release of viral progeny is realized either by means **of lysis of the infected cell.**



influenza A virus



Retrovirus(HIV)



Entry of bacteriophages into cells

• Like animal viruses, phages bind specifically to cell surface molecules that function as receptors and co-receptors.