Virus Classification and Virus Replication

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VIRUS CLASSIFICATION AND TAXONOMY

- One classification scheme was developed in the 1970s by Nobel laureate David Baltimore.
- The **Baltimore classification system** categorizes viruses based on the **type of nucleic acid** genome and **replication strategy** of the virus.
- **Positive-strand** (also positive-sense or plus-strand) RNA is able to be immediately translated into proteins; as such, messenger RNA (mRNA) in the cell is positive strand.
- **Negative-strand** (also negative-sense or minus- strand) RNA is not translatable into proteins; it first has to be transcribed into positive-strand RNA.
- Viruses are only classified using order, family, genus, and species (Table 1)

Table 1 Taxa Used to Classify Viruses

Taxon	Notes	Example
Order	▪ Ends in -virales suffix; only about half of viruses are currently classified in orders.	Picornavirales
Family	▪ Ends in -viridae suffix; sub- families are indicated with -virinae suffix.	Picornaviridae
Genus	▪ Ends in -virus suffix.	Enterovirus
Species	▪ Generally the "common name" of the virus. Classifying and cataloging anything below the species classification.	Rhinovirus A (Serotypes include Human rhinovirus 1, which includes strains human rhino- virus 1A and human rhinovirus 1B)

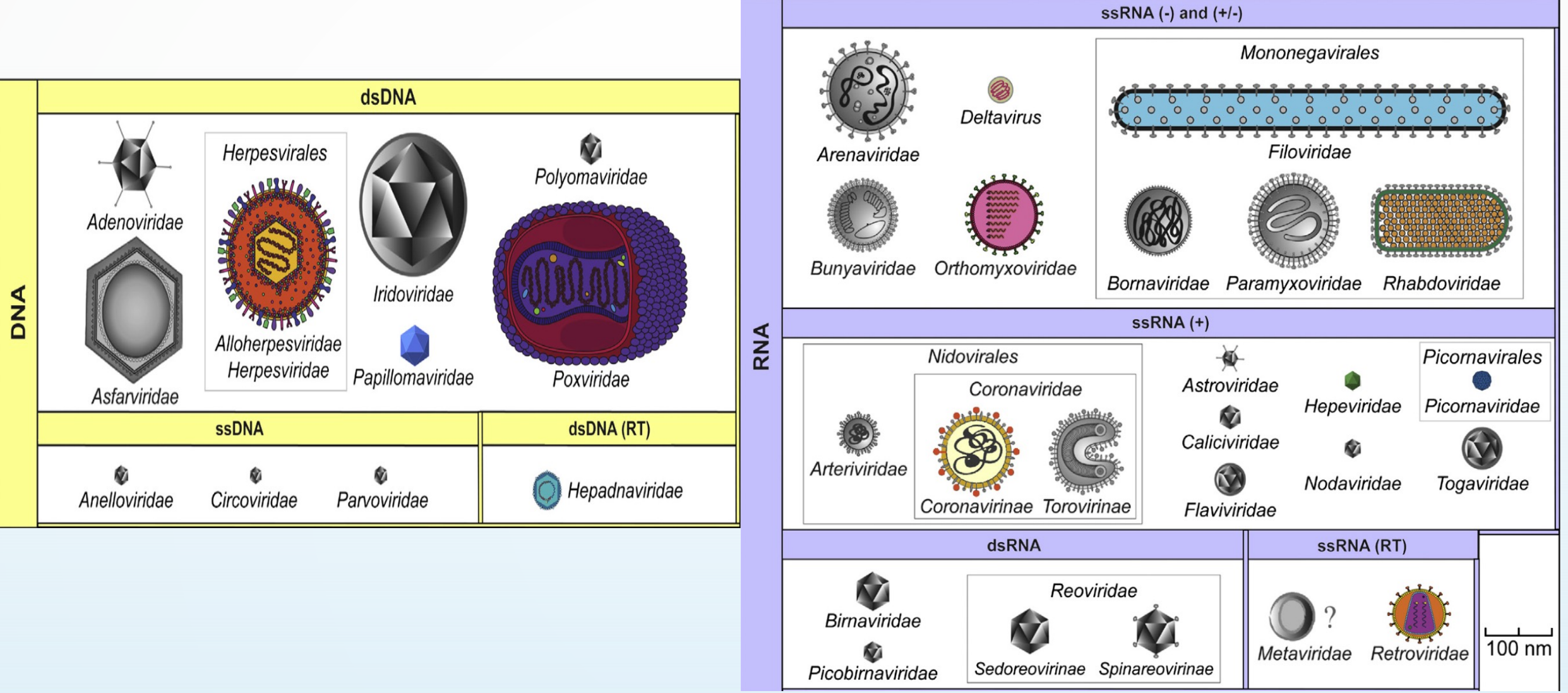


Figure1 Taxa of viruses that infect vertebrates. Viruses are categorized based upon their type of nucleic acid (DNA viruses in yellow boxes and RNA viruses in blue boxes)

Name Origins of Viruses

- **Viruses named after the clinical conditions they cause**
- **Human immunodeficiency virus (HIV)**

Causes the decline of the immune system, leading to immunodeficiency

- **Hepatitis virus;** All hepatitis viruses cause liver inflammation (hepatitis)
- **Poxviruses;** From pockes meaning “sac,” referring to the blistery rash observed
- **Rabies virus**

From Latin *rabies*, meaning “madness,” describing the symptoms seen with disease progression

Viruses named after their properties

- **Coronavirus**

From Latin *corona*, meaning crown, referring to the crown-like appearance of the virions when viewed with an electron microscope

- **Herpesviruses**

From Greek *herpein*, "to creep," referring to the lesions that slowly spread across the skin

- **Viruses named after their location of discovery**
- **Ebola virus**
- Named after the Ebola River in northern Democratic Republic of the Congo (formerly Zaire), where the virus first emerged in 1976.
- **Viruses named after people**
- **Epstein–Barr virus**
- Named after Michael Anthony Epstein and Yvonne Barr, who discovered the virus

Virus Replication

- A virus must undergo the process of replication to create new, infectious virions.
- After gaining entry into the body, a virus makes physical contact with and crosses the plasma membrane of a target cell.
- Inside, it releases and replicates its genome while facilitating the manufacture of its proteins by host ribosomes.
- Virus particles are assembled from these newly synthesized biological molecules and become infectious virions.
- Finally, the virions are released from the cell to continue the process of infection.

The seven stages of virus replication are categorized as follows:

1. Attachment
2. Penetration
3. Uncoating
4. Replication
5. Assembly
6. Maturation
7. Release

1. ATTACHMENT

- Virus 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 (Table 2).

1- Rhinovirus binds a protein known as intercellular adhesion molecule 1 (ICAM-1), involved in the attachment of one cell to another.

2- Influenza A virus strains bind to the sialic acid sugars found at the ends of cellular carbohydrate chains (Fig.2).

3- Coreceptors; HIV initially binds to a protein known as CD4 on the surface of T lymphocytes with one of two coreceptor proteins (CCR5 and CXCR4).

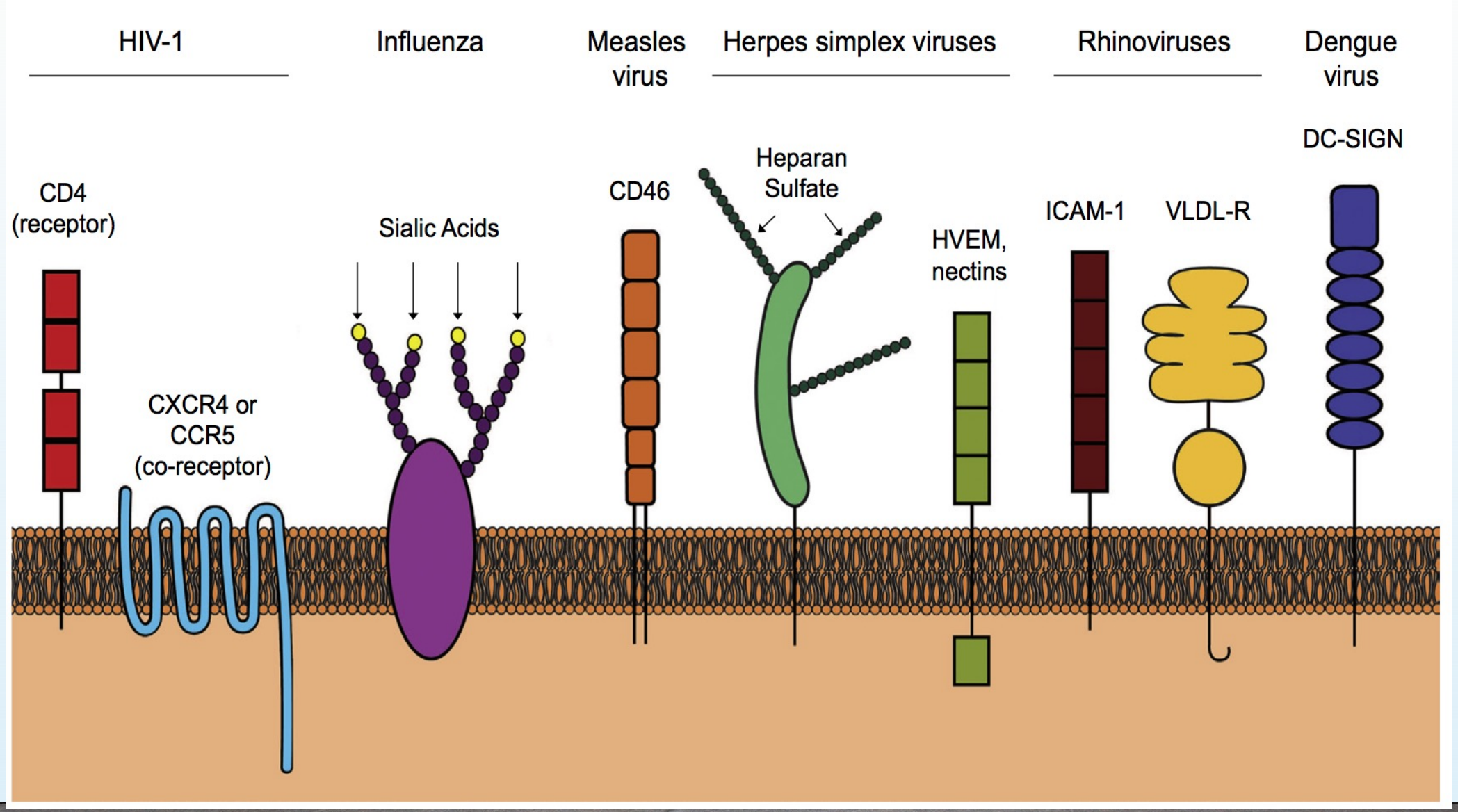


Figure 2 Cell surface receptors

Different viruses use specific cell surface receptors for attachment.

Virus	Cell surface receptor(s)
Rhinoviruses	Intercellular adhesion molecule 1 (ICAM-1) (90%), low-density lipoprotein receptor (10%)
Poliovirus	Poliovirus receptor (PVR) CD155
Human immunodeficiency virus	CD4 (receptor); CCR5 or CXCR4 (coreceptors)
Influenza A virus	Sialic acid
Measles virus	CD46, CD150
Herpes simplex virus-1	Heparan sulfate, HVEM, Nectin-1
Dengue virus	DC-SIGN
Hepatitis B virus	Sodium taurocholate– cotransporting polypeptide
Human papillomavirus	Heparan sulfate, integrins

2. PENETRATION

Penetration refers to the crossing of the plasma membrane by the virus, following attachment.

Enveloped and nonenveloped viruses

1. Receptor- mediated endocytosis

a) Most types of viruses use **clathrin-mediated endocytosis** to enter the cell, including **dengue virus**, and **hepatitis C virus** (**Fig 3**). .

b) papillomaviruses (that cause warts or cervical cancer), use **caveolae-mediated endocytosis**.

2. PENETRATION

2. Other forms of endocytosis, such as:

-**Bulk-phase endocytosis**, the cell forms a vesicle that engulfs whatever molecules are present in the extracellular fluid, including viruses.

-**Phagocytosis** is a form of receptor-mediated endocytosis that is used by specialized cells to engulf entire cells.

- **Large DNA viruses, Herpes simplex virus type 1 (HSV-1).**

penetration method of **enveloped** viruses by **fusion**.

- Fusion of the viral envelope can occur at the cell membrane or within endocytosed vesicles, such as the endosome
- Is mediated by the same viral protein that is used by the virus for attachment or by a different viral protein, depending upon the virus.

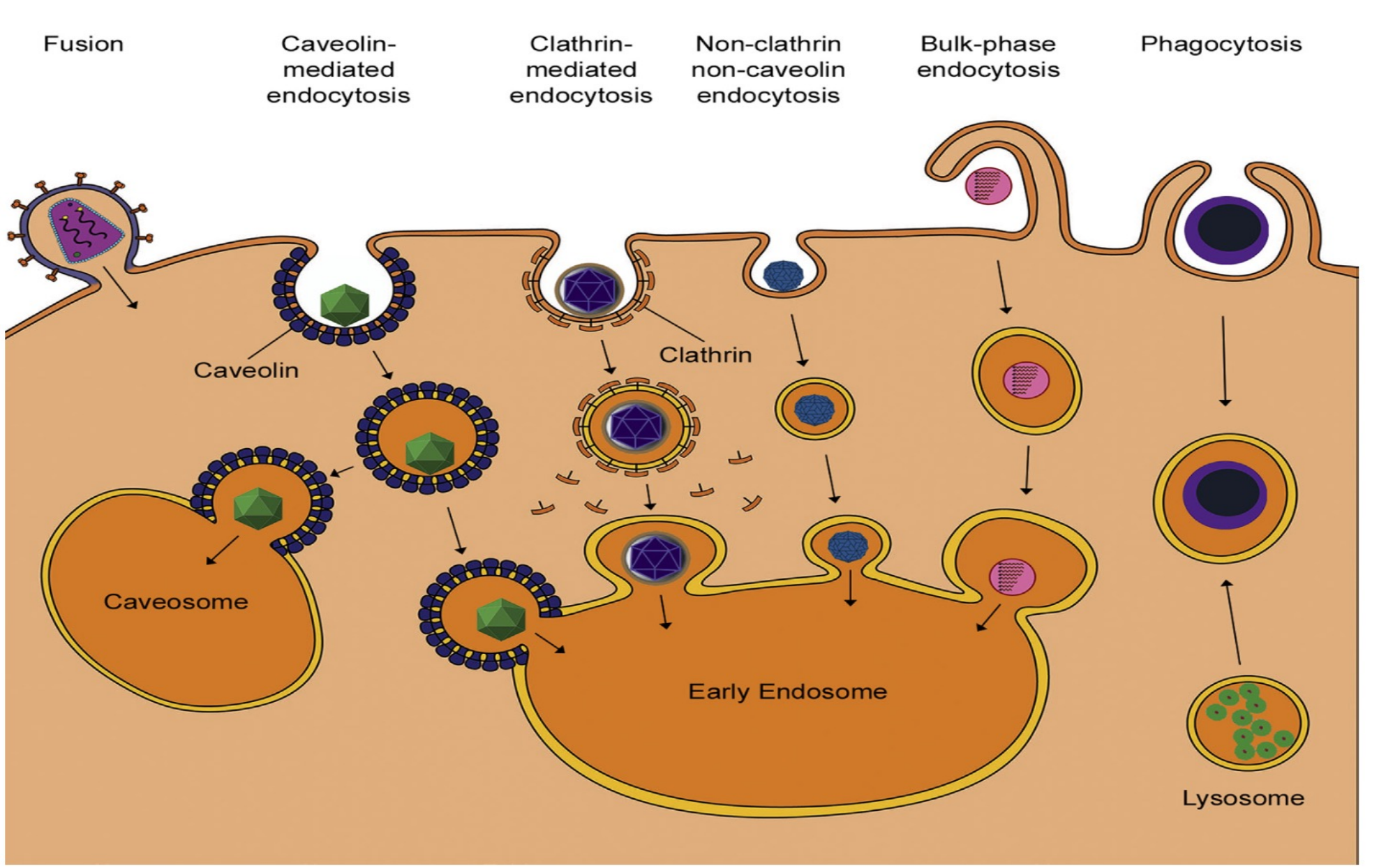


Fig.3 Viral penetration into the cell. Different viruses take advantage of various cellular mechanisms to gain entry into the cell.

Table 3 Methods of Penetration for Select Human Viruses	
Type of penetration (entry)	Virus examples
Clathrin-mediated endocytosis	Dengue virus, hepatitis C virus, reovirus, adenovirus.
Caveolin-mediated endocytosis	Human papillomavirus, hepatitis B virus
Fusion	HIV, influenza, respiratory syncytial virus, herpes simplex viruses, dengue virus, Ebola virus

3. UNCOATING

- Refers to the breakdown or removal of the capsid, causing the release of the virus genome into the cell (fig.4)
- Can be separated from or tightly linked with penetration.
- **1. Rhinoviruses** are taken into the cell by receptor-mediated endocytosis in clathrin-coated vesicles. Within the acidic endosome, the virus expands in size about 4%, and one of the capsid proteins, VP1 (viral protein 1), forms pores in the endosome that allow the release of the rhinovirus RNA genome.

3. UNCOATING

- **2. Poliovirus;** they have been thought to not enter the cell at all, the binding of the poliovirus capsid to the cell surface receptor causes a conformational change in the virion that creates a pore in the **cell membrane** through which the viral RNA is released into the cytoplasm.

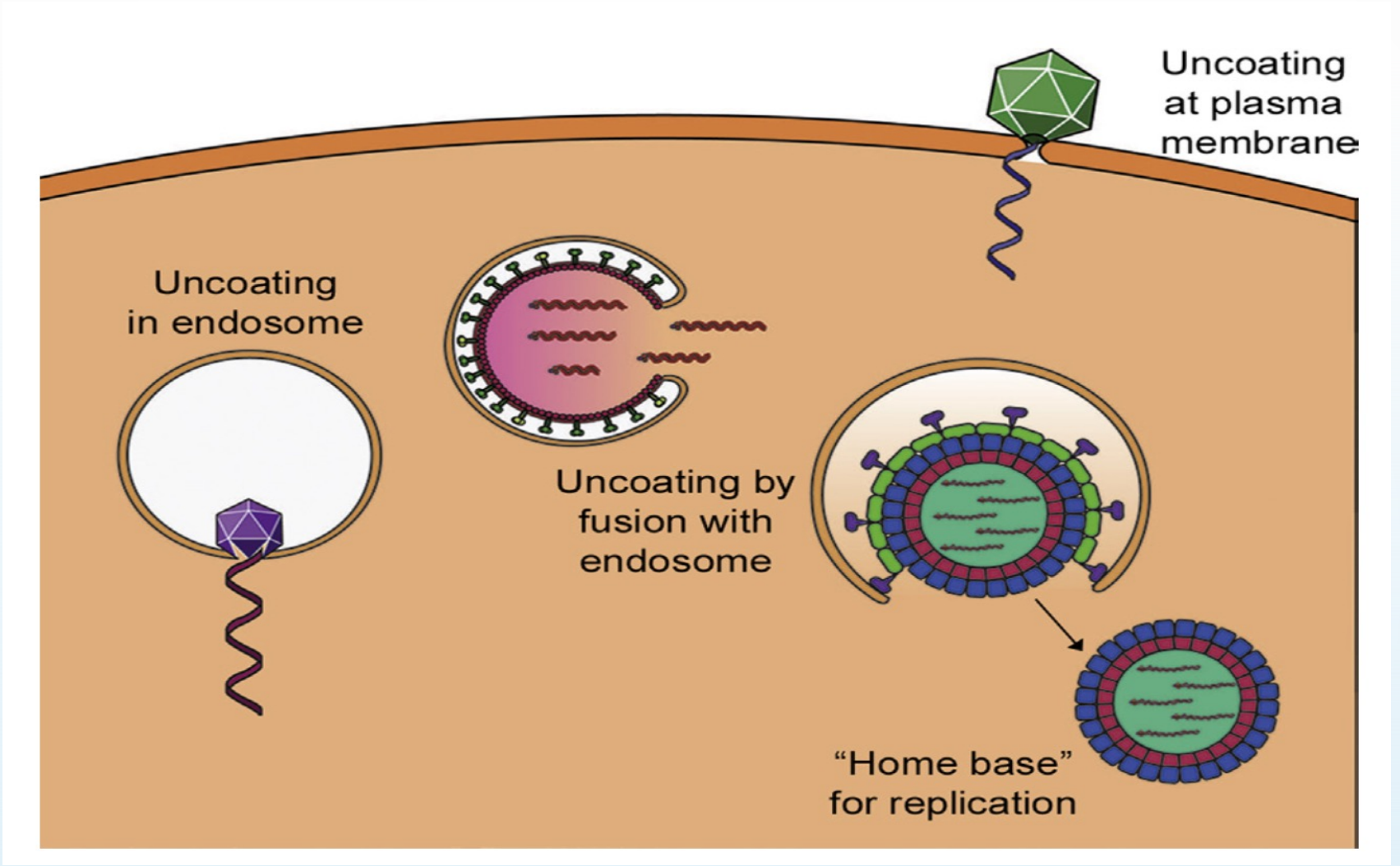


Figure 4 Uncoating of virion capsids

4. REPLICATION

- Virus's genome acts as the instructions for the synthesis of virus proteins.
- Virus genome is copied by replication → protein synthesis → create new virion's particles
- The **replication strategy** of a virus is generally dependent upon the type of **nucleic acid genome** it contains.

4. REPLICATION

- The Baltimore classification system categorizes the viruses into seven classes based upon their type of genome:

1. Double-stranded DNA viruses
2. Single-stranded DNA viruses
3. Double-stranded RNA viruses
4. Positive-sense RNA viruses
5. Negative-sense RNA viruses
6. RNA viruses that reverse transcribe
7. DNA viruses that reverse transcribe

TABLE 4 Families of Human Viruses Within Each Replication Class	
Family	**Virus examples**
Class I: dsDNA viruses	
Adenoviridae	Adenovirus
Herpesviridae	Herpes simplex virus, Epstein–Barr virus, varicella zoster virus
Poxviridae	Variola, vaccinia
Class II: ssDNA viruses	
Parvoviridae	Parvovirus B19
Class III: dsRNA viruses	
Reoviridae	Rotavirus
Class IV: +ssRNA viruses	
Coronaviridae	Human coronavirus
Hepeviridae	Hepatitis E virus
Picornaviridae	Poliovirus, rhinovirus, enterovirus, hepatitis A virus
Class V: −ssRNA viruses	
Filoviridae	Ebola virus, Marburg virus
Orthomyxoviridae	Influenza A virus, influenza B virus
Paramyxoviridae	Nipah virus, Hendra virus, measles virus, mumps virus
Rhabdoviridae	Rabies virus
Class VI: RNA viruses that reverse transcribe	
Retroviridae	Human immunodeficiency virus-1 and -2
Class VII: DNA viruses that reverse transcribe	
Hepadnaviridae	Hepatitis B virus

- Viruses with **dsDNA genomes** have similar nucleic acid to living organisms and often use the enzymes and proteins that the cell normally uses including its **DNA polymerases and RNA polymerases;** are located in the nucleus.
- So all dsDNA viruses that infect humans enter the nucleus of the cell, while **RNA genomes** do not .
- During replication, the **ssDNA genome** enters the nucleus of the host cell, where the ssDNA is converted to dsDNA by **DNA polymerase.**
- **dsRNA** viruses contain an RdRp that is carried into the cell within the virion.

- The genomes of **+ssRNA** viruses are infectious, since positive-sense RNA is able to be directly translated by ribosomes.
- **−ssRNA** viruses are not infectious and must be transcribed into vmRNA before translation can occur.
- Therefore, −ssRNA viruses must also carry an RNA-dependent RNA polymerase (RdRp) into the cell.

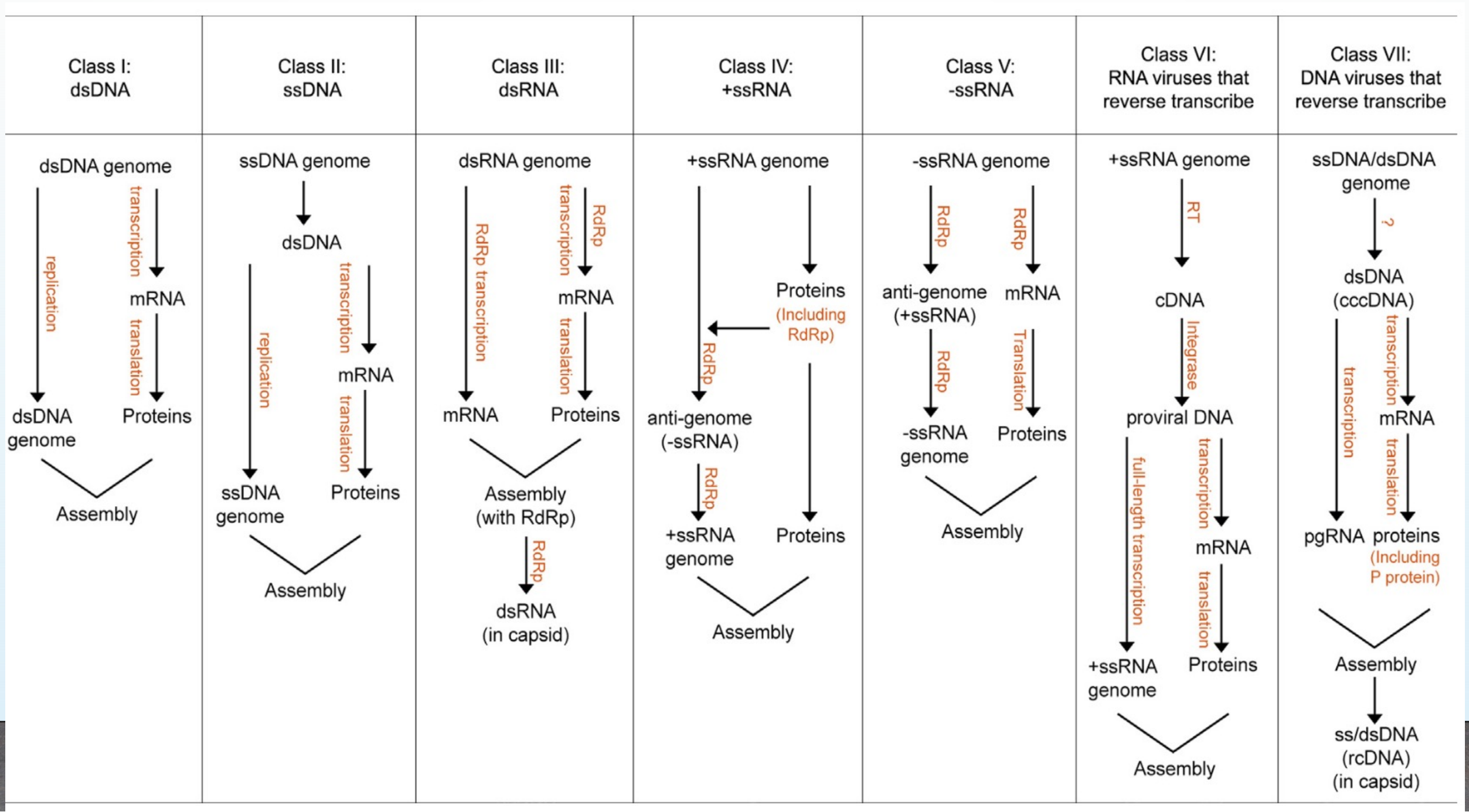
- **Retroviruses** are viruses that **reverse transcribe an RNA genome into cDNA.**
- **Reverse transcriptase (RT)** is the enzyme that carries this out and has the activity of an RNA- dependent DNA polymerase, DNA-dependent DNA polymerase, and RNase H.
- Transcription and genome replication is carried out by host enzymes.

- Hepatitis B virus is also a **retroid virus** but instead reverse transcribes in order to create its DNA genome, which is partially single-stranded and partially double- stranded and known as rcDNA.
- This is repaired to a completely double-stranded episome (cccDNA) in the nucleus of the cell.
- **RNA polymerase II** transcribes an RNA pregenome that is reverse transcribed, after being packaged into the capsid, into the rcDNA genome.

4. REPLICATION

- Viral nucleic acids are found in a variety of configurations.
- They can be **linear** or **circular**, and they can be **segmented** into several smaller pieces within the virion, as occurs with **influenza viruses**, or **nonsegmented** like **rabies virus**, containing one molecule of nucleic acid that encodes all necessary genes.
- Regardless of the structure of their nucleic acid, all viruses need to express their viral proteins and replicate their genome within the cell in order to create new virions.

- New strains of virus can occur when two different strains infect one cell.
- **Recombination** occurs when the genome of an RNA virus is being replicated and the RdRp jumps from the template of one strain to the template of the other strain, creating a **hybrid** genome.
- **Reassortment** occurs when the genome segments of segmented viruses are mixed while being packaged into new capsids.


Class I: dsDNA
dsDNA genome
replication
transcription
mRNA
translation
dsDNA genome
Proteins
Assembly
Class II: ssDNA
ssDNA genome
dsDNA
replication
transcription
mRNA
translation
ssDNA genome
Proteins
Assembly
Class III: dsRNA
dsRNA genome
RdRp transcription
RdRp
transcription
mRNA
translation
mRNA
Proteins
Assembly (with RdRp)
RdRp
dsRNA (in capsid)
Class IV: +ssRNA
+ssRNA genome
Proteins (Including RdRp)
RdRp
anti-genome (-ssRNA)
RdRp
+ssRNA genome
Proteins
Assembly
Class V: -ssRNA
-ssRNA genome
RdRp
RdRp
anti-genome (+ssRNA)
mRNA
RdRp
Translation
-ssRNA genome
Proteins
Assembly
Class VI: RNA viruses that reverse transcribe
+ssRNA genome
RT
cDNA
Integrase
proviral DNA
full-length transcription
transcription
mRNA
translation
+ssRNA genome
Proteins
Assembly
Class VII: DNA viruses that reverse transcribe
ssDNA/dsDNA genome
?
dsDNA (cccDNA)
transcription
transcription
mRNA
translation
pgRNA
proteins (Including P protein)
Assembly
ss/dsDNA (rcDNA) (in capsid)

5. ASSEMBLY

- Viruses components must be collected at a particular site of the cell and undergo assembly to form an immature virus particle, 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**.

1. Most **nonenveloped DNA viruses** assemble their nucleocapsid in the **nucleus**, since that is the site of genome replication.
2. Viruses with **envelopes** derived from **the plasma membrane** usually assemble there.

6. MATURATION

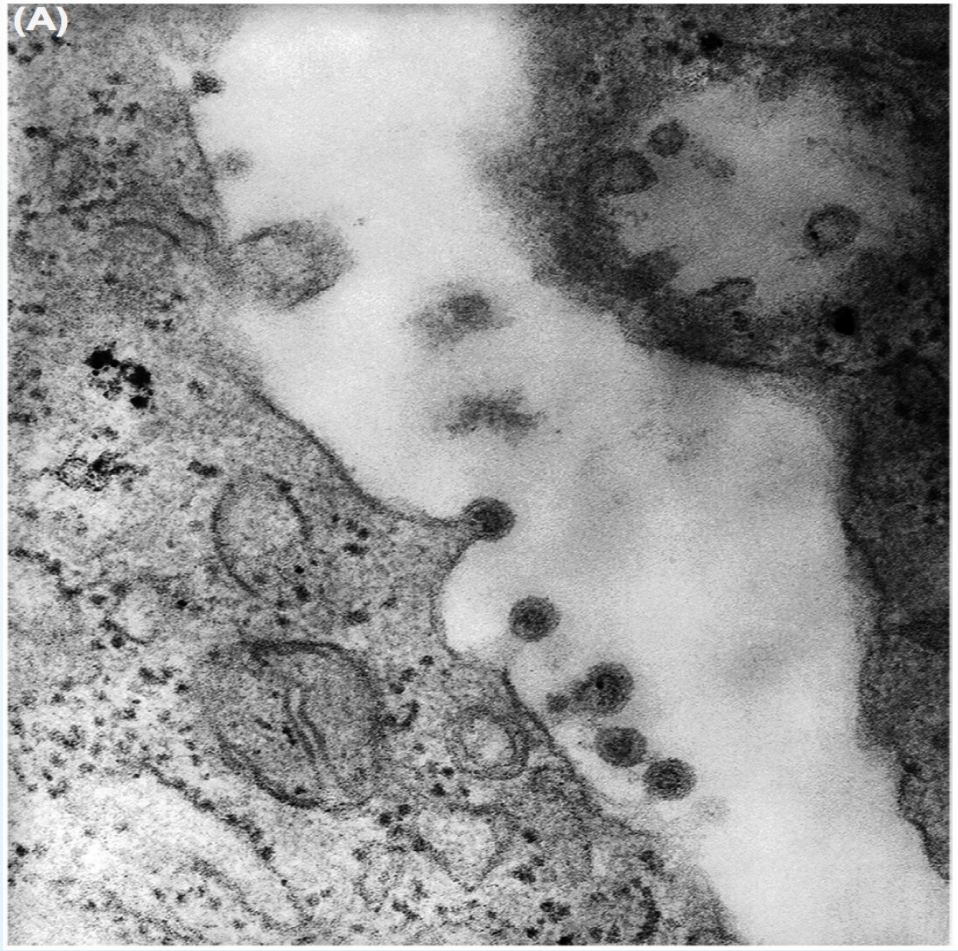
- Maturation refers to the final changes within an immature virion.
- Structural capsid changes are often involved
- Example; **influenza HA protein** (involved in attachment to the cell's sialic acid).
- **HA protein** must be cleaved into two portions by cell **proteases; HA1** and **HA2** to become infectious
- HA1 portion binds the cell surface receptor, the HA2 portion is what fuses the viral envelope to the endosomal membrane to release the virus into the cytoplasm.

7. RELEASE

- Final step
- First: for **enveloped virus**
- 1. Viruses that obtain their envelope from the plasma membrane generally assemble on the inside layer of the **plasma membrane**; The plasma membrane is completely wrapped around the virus, which leaves the cell. This process is known as **budding** (Figure 6).
- 2. Viruses can bud from any of the membrane systems **within the cell**, including the rER, Golgi complex, or even the nuclear envelope. Then, undergoes **exocytosis** to leave the cell.

7. RELEASE

- **Second:** for **Nonenveloped** viruses can also exit the cell via **exocytosis**. Lytic viruses, however, disrupt the plasma membrane and cause the **lysis**, or bursting, of the cell.
- This releases the nascent virions to infect new cells. Many nonenveloped human viruses are released through cell lysis.



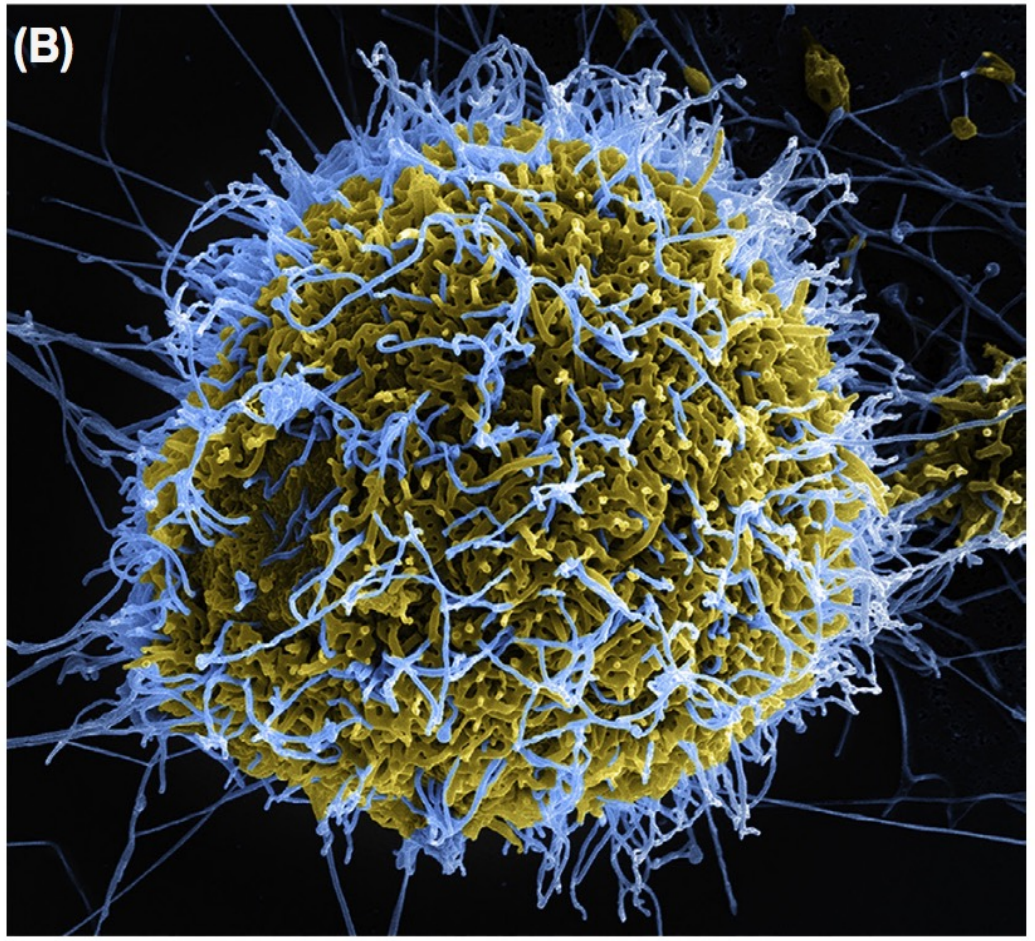


Figure 6 Virion budding. (A) Rubella virus virions are observed budding from the host plasma membrane in this transmission electron micrograph.
(B)helical Ebolavirus virions (blue) are budding from an infected cell (yellow).