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Introduction to Animal Viruses

OUTLINE

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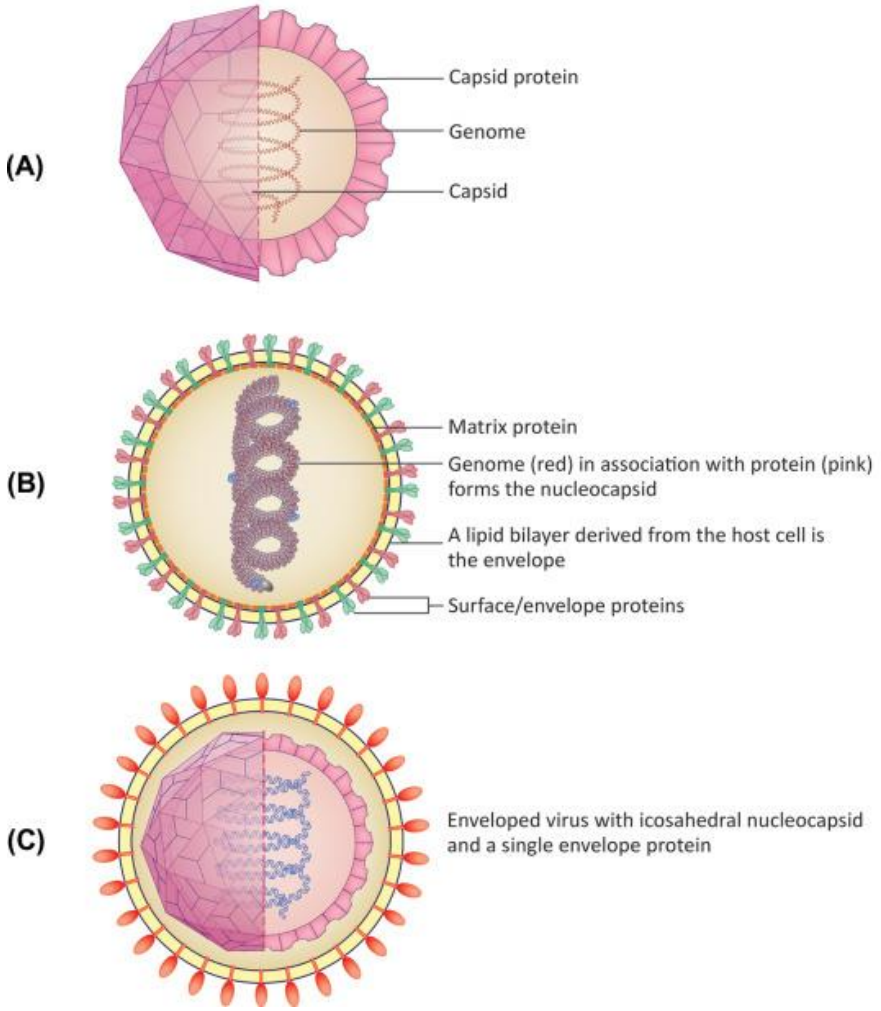
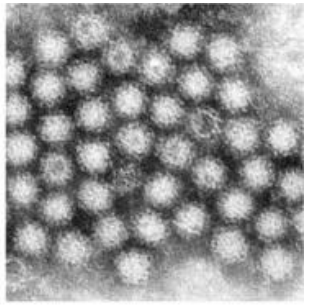
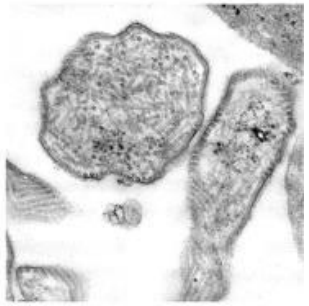
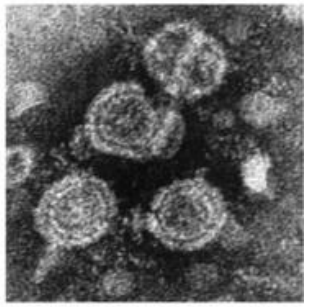
Marika D'Avanzo – University of Naples Federico II

What is a virus?









(A) Diagram of an unenveloped virus with icosahedral symmetry; electron micrograph of calicivirus.
(B) Dagram of enveloped virus with a helical nucleocapsid; electron micrograph of measles virus, a paramyxovirus.
(C) Diagram of an enveloped virus with an icosahedral nucleocapsid; electron micrograph of hepadnavirus.

- Viruses are infectious agents that are not cellular in nature.

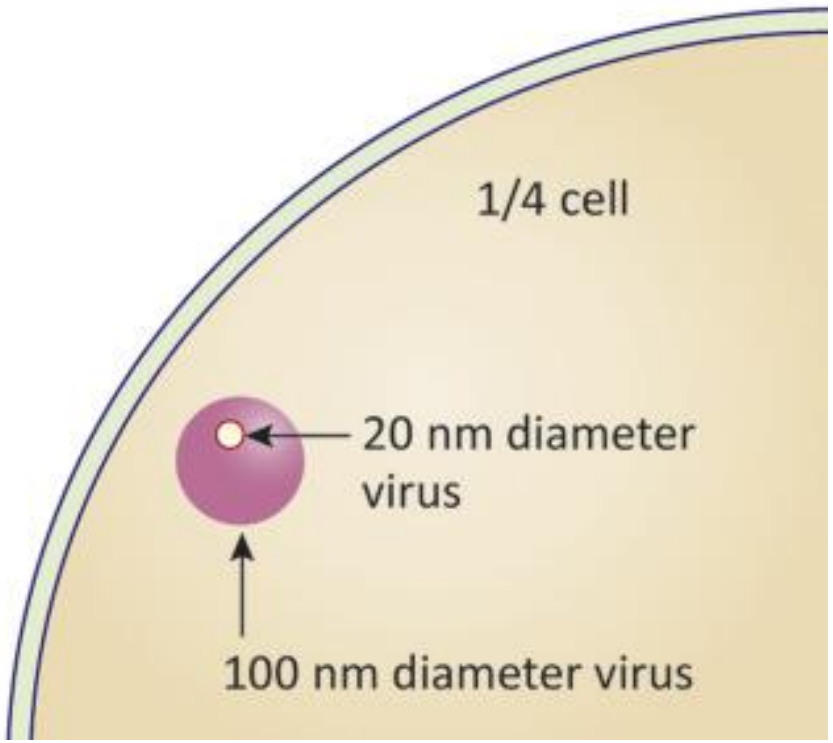
- Viruses must enter a living host cell in order to replicate, thus all viruses are obligate intracellular parasites.
Synthesis of the proteins and nucleic acids (DNA and RNA) for assembly into new virus particles (virions) requires an energy source (ATP), building materials (amino acids and nucleotides), and protein synthesis machinery (ribosomes) supplied by the host cell.
The cell also provides scaffolds (microtubules, filaments, membranes) on which virus particles replicate their genomes and assemble. The cell is a factory providing working machinery and raw materials.

- Viruses have nucleic acid genomes that are surrounded by and protected by protein coats called capsids. Capsids protect genomes from environmental hazards and are needed for efficient delivery of viral genomes into new host cells. Some viruses have lipid membranes, called envelopes that surround the capsid.

- Viruses are structurally much simpler than cells.
Viruses do not increase in number by cell division: they assemble from newly synthesized protein and nucleic acid parts (building blocks).
As viruses are not cells, they have none the organelles associated with cells. A sample of purified virions has no metabolic activity.

- Viruses are packages designed to deliver nucleic acids to cells; they are excellent examples of “selfish genes.”

Diversity in the world of viruses



Relative sizes of an animal cells and virions.

- Nucleic acid genome: some utilize DNA as genetic material, while others have RNA genomes. Viral genomes are not always double-stranded molecules; there are single stranded viral RNA and DNA genomes. There are viral genomes that consist of a single molecule of nucleic acid, but some genomes are segmented (Reoviruses).

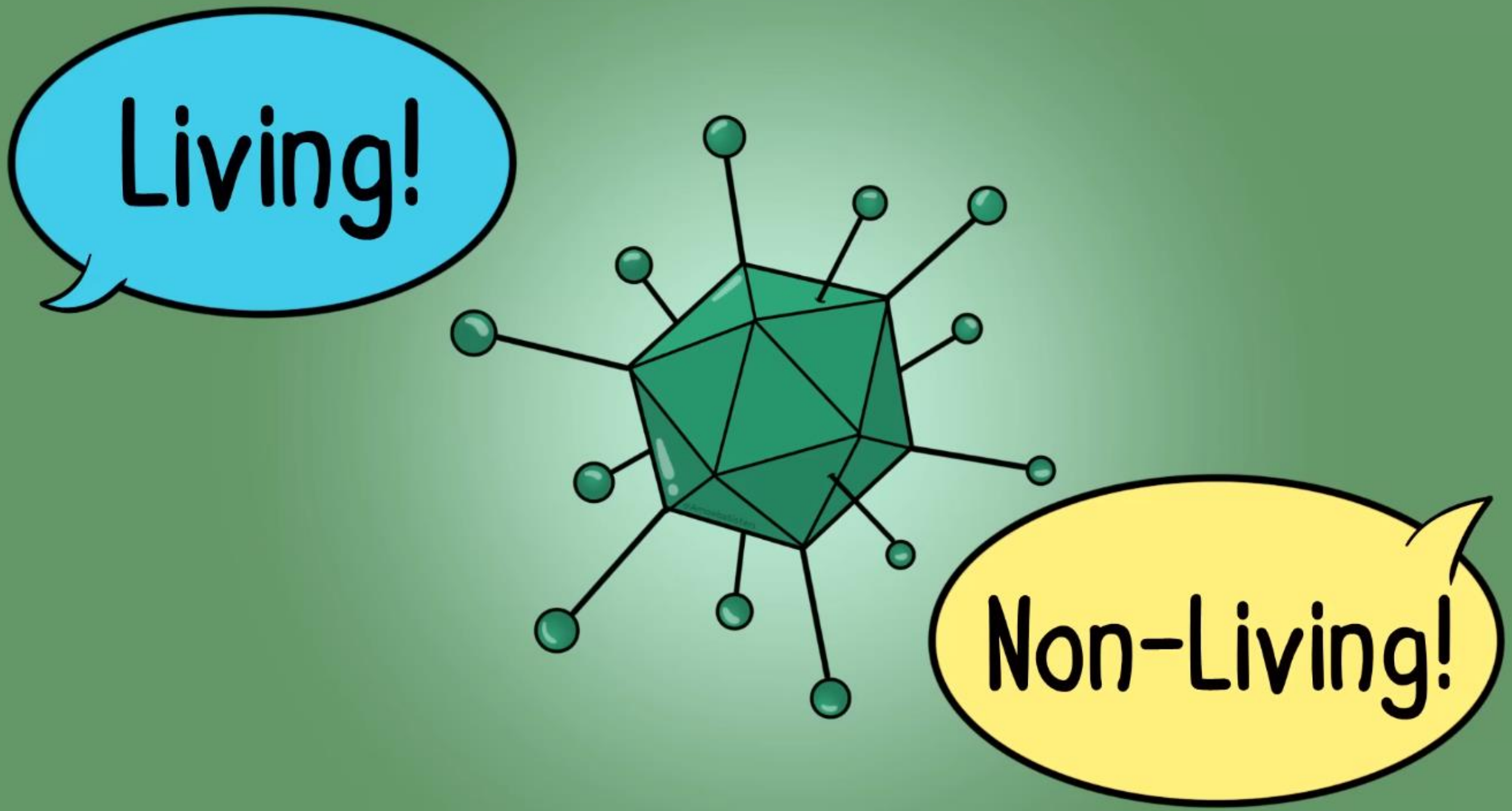
- Some viruses have lipid envelopes in addition to a genome and protein coat. Viral envelopes are not homogenous. Different types of host membranes may be utilized, and their specific lipid and protein components can differ.

- Viruses range in size from 10 to 1000 nm in size. Viral genomes range in size from 3000 nucleotides to over 1,000,000 base pairs.

- Outcomes of viral infections are diverse. Infection does not always result in cell or host death. Some host genes are derived from viruses and have played key roles in evolution. (Some plant viruses are beneficial in extreme environments.)

- Some viruses complete their replication cycles in minutes while others take days. Some viruses are transiently associated with an infected host (days or weeks) while others (herpesviruses) are life-long residents.

- Three general scenarios for virus evolution have been proposed:
  - Retrograde evolution: Intracellular parasites lost the ability for independent metabolism keeping only those genes necessary for replication (Poxviruses).
  - Origins from cellular DNA and RNA components: Some DNA genomes resemble plasmids or episomes. Did these DNAs acquire protein coats and the ability to be transferred from cell to cell efficiently?
  - Descendants of primitive precellular life forms: Viruses originated and evolved along with primitive, self-replicating molecules.


Living!
Non-Living!

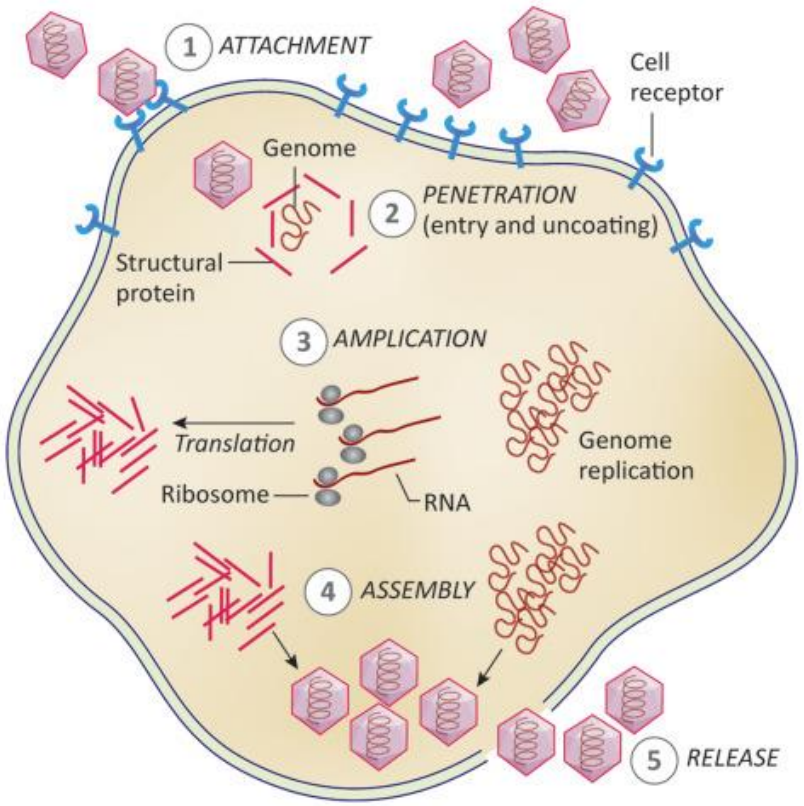
Are viruses alive?

This question is the subject of ongoing debate. They replicate to increase in number and the terms “virus replication-cycle” and “virus lifecycle” are often used interchangeably. Viruses also evolve (change their genomes), sometimes very rapidly. In this manner they adapt to new hosts and environments. In contrast, the virion (the physical package that we view with an electron microscope) has no metabolic activity.

Some viruses can be assembled simply by mixing purified genomes and proteins in a test tube. The genomes may have been synthesized by machine and the viral proteins may have been produced in bacteria. If those component parts combine under suitable conditions, a fully infectious virion can be produced.

To avoid the question of living versus non-living, the term “infectious agent” is both appropriate and descriptive. We can then speak of infectious virions that are capable of entering a cell and initiating a replication-cycle, or inactivated virions that cannot complete a replication-cycle.

Basic steps in the virus replication-cycle

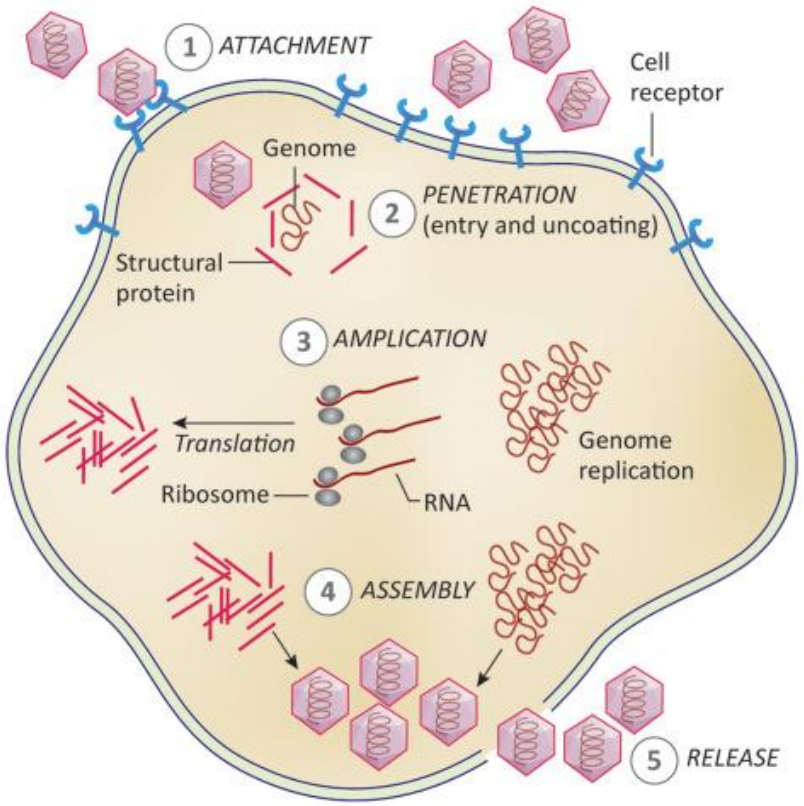


1. **Attachment** results from very specific interactions between viral proteins and molecules on the surface of the host cell. The interactions are usually hydrophobic and ionic. It is influenced by environmental conditions such as pH and salt concentration; becomes stronger as many copies of a viral surface protein interact with multiple copies of the host cell receptor molecules.

2. **Penetration** of the viral genome into the host cell cytoplasm or nucleoplasm. After penetration, there may be a further rearrangement of viral proteins to release the viral genome, a process called uncoating. Penetration and uncoating are two distinct steps for some viruses while for others the viral genome is uncoated during the process of penetration. The processes of penetration and uncoating are irreversible, the infecting virion cannot reassemble.

3. **Synthesis** of the new viral proteins and genomes. This is a complex process that requires transcription (synthesis of mRNA), translation (protein synthesis), and genome replication to generate the parts that will assemble into new virions. Synthesis of viral proteins and genomes occurs in close association with, and depends upon, many host cell proteins and structures. The great diversity among viruses depends on the processes that regulate transcription, translation, genome replication and the specific virus host cell interactions that shape these processes.

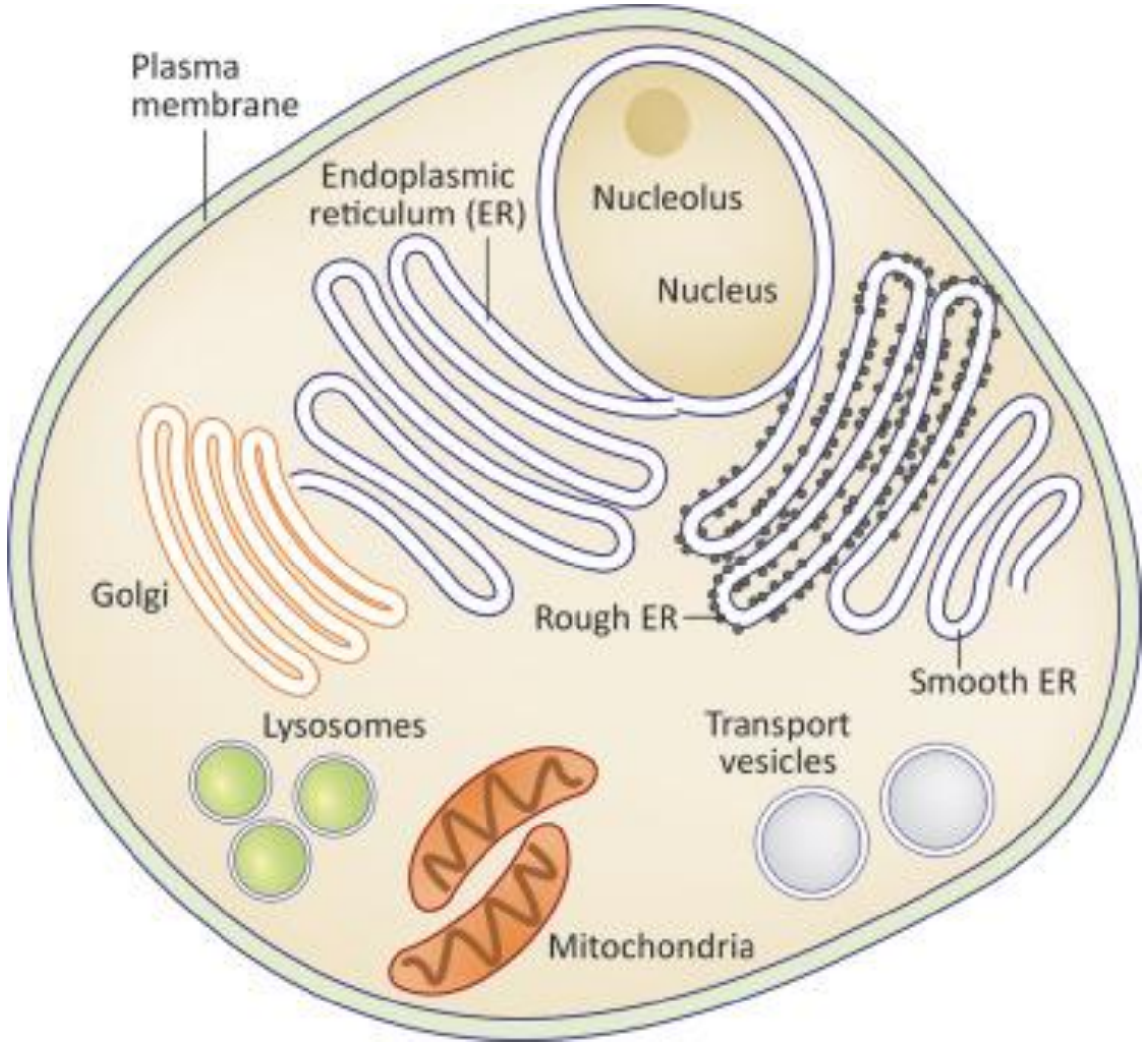
Basic steps in the virus replication-cycle



4. **Assembly** of new virions. New particles assemble from the genome and protein components that accumulate in the infected cell. Viruses are assembled at different sites in host cells; sometime large areas of the cell become virus factories, concentrated regions of viral proteins and genomes from which host cell organelles are excluded.

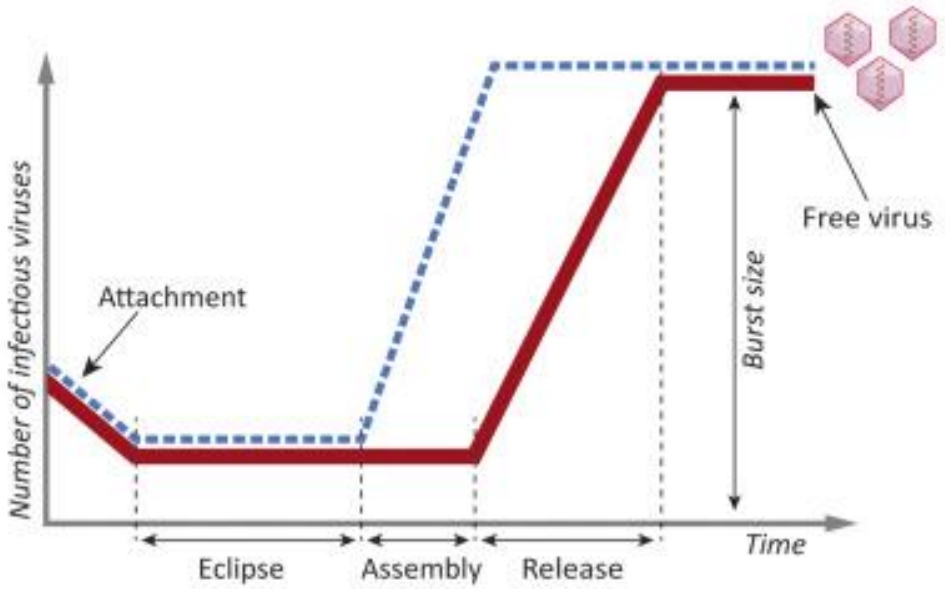
5. **Release** from the host cell and **maturation** of the released virions. Virion release may occur upon **cell rupture** or **lysis**. Enveloped viruses must acquire their envelopes from cellular membranes in a process called **budding**. Some enveloped viruses bud through the plasma membrane, but budding can occur at other, intracellular membranes. The budding process can kill the host cell. Other viruses obtain their lipid enveloped by budding into cellular vesicles. These vesicles then fuse with the plasma membrane to release the virions (exocytosis). Maturation: changes in virus structure that occur after a virus is released from the host cell; it may be required before a virus is able to infect a new cell; may involve cleavage or rearrangement of viral proteins; it sets the stage for a productive encounter with the next cell.

Viruses assemble in the cell (under conditions of favorable energy) but when the released virions encounter new cells they must be able to disassemble (uncoating).



Simple schematic of a eukaryotic cell identifying some major organelles.

Basic steps in the virus replication-cycle



Penetration of a virus into the host cell is not reversible. During the so-called eclipse phase infectious virions cannot be detected, even if cells are broken open (lysed), there are no infectious particles to be found.

The red curve represents infectious virions released from the infected cells. The blue curve represents infectious virions released if the cells are lysed.

Key to understanding the one-step growth curve is to note that after attachment, the number of virions detected in media and within cells decreases. These virions have penetrated cells and their genomes have uncoated, thus they are no longer “infectious.” New virions are detected only after amplification and assembly.

Growing viruses

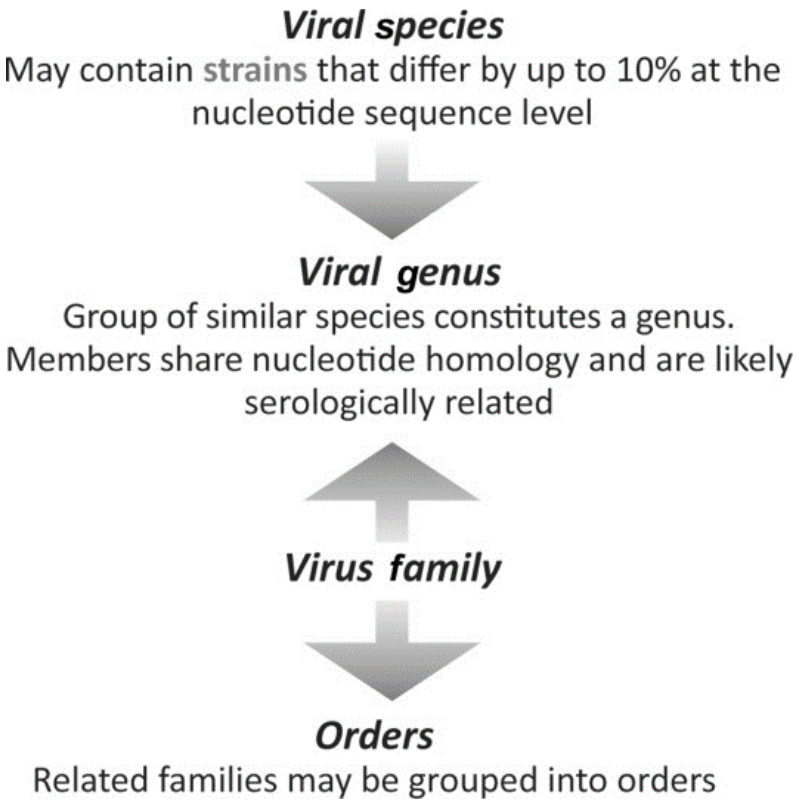
Viruses are obligate intracellular parasites; they replicate only within living cells. Thus in the laboratory, susceptible cells or organisms are required to study virus replication.

For the virologist, ideal host cells are easily grown and maintained in the laboratory. Animal virologists often use cell and (less often) organ cultures. To culture animal cells, tissues or organs are harvested and disrupted (using mechanical and enzymatic methods) to obtain individual cells. Often cells are derived from tumors that grow robustly in culture. Cells circulating in the blood, such as lymphocytes, can be obtained directly from animal blood samples. If cells are provided with the appropriate environment (growth media, temperature, pH, and CO2), they will remain metabolically active and may undergo cell divisions.

Often the best-studied viruses are those that have been adapted for robust growth in a culture system. However, cell or organ cultures may be very different from the natural environment of the human or animal host. The biggest difference is that the cultured cells lack the many antiviral defenses encountered in an organism. Thus it is not uncommon for a virus highly adapted to cell cultures to perform poorly when used to infect an animal. In fact, propagation in culture is a common method for producing attenuated (weakened) live viral vaccines. Attenuated viruses replicate in a host, but do not cause disease.

When considering experiments with viruses, it is very important to understand both the host system and the origins of the virus being studied.

Categorizing viruses (taxonomy)

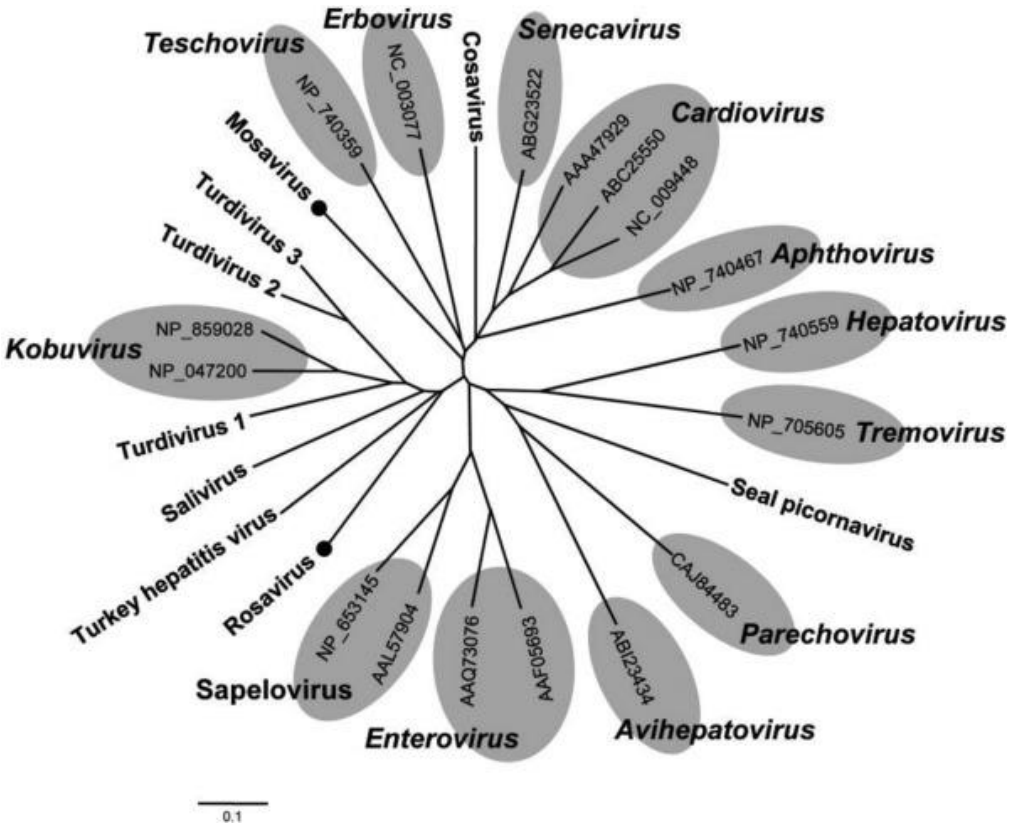


1. By the type of nucleic acid that serves as the viral genome.
• DNA viruses: Package DNA genomes synthesized by a DNA-dependent DNA polymerase.
• RNA viruses: Package RNA genomes synthesized by an RNA-dependent RNA polymerase.
• Viruses that uses the enzyme reverse transcriptase (RT) during the replication-cycle. RT is an RNA-dependent DNA polymerase as it synthesizes a DNA copy of an RNA molecule. Reverse transcribing viruses use both RNA and DNA versions of their genomes (at different times) during their replication cycles.

2. By the physical makeup of their genomes (single stranded, double stranded, unsegmented, segmented, linear, circular), the presence of lipid envelopes (enveloped viruses and naked viruses). Capsids also come in different shapes and sizes. The goal of viral taxonomy is to categorize viruses using groups of traits.

Viruses are grouped into orders, families, genera, and species. Orders contain two or more related families, and families can be subdivided into multiple genera. A genus is further subdivided into species (or strains). The family is often called the fundamental unit of viral taxonomy. Viruses in the same family are considerably more closely related than viruses from different families. Placement of viruses into families is accomplished by examining shared characteristics. All viruses within a family share a core set of properties.

Categorizing viruses (taxonomy)



Phylogeny of the family *Picornaviridae* showing recognized genera.
In some cases a genus contains only one virus isolate or strain.

Genome sequences from many different viruses can be compared to generate "phylogenies" and provide a visual "map" of relationships among viruses. In some cases, many thousands of viral genome sequences are compared in order to generate detailed phylogenies.

Is it useful to generate or understand phylogenies of viruses?
The origins of a disease outbreak can be determined using detailed genetic information. Information from genome sequencing can be used to analyse past outbreaks and track the transmission of viruses from one person or animal to another in order to determine the best methods to curb virus transmission during an epidemic.

Outcomes of a viral infection

• Productive or permissive infection. Viral proteins and nucleic acids are synthesized and virions are assembled and released.

• Non-permissive infection. The cell is completely resistant to infection.

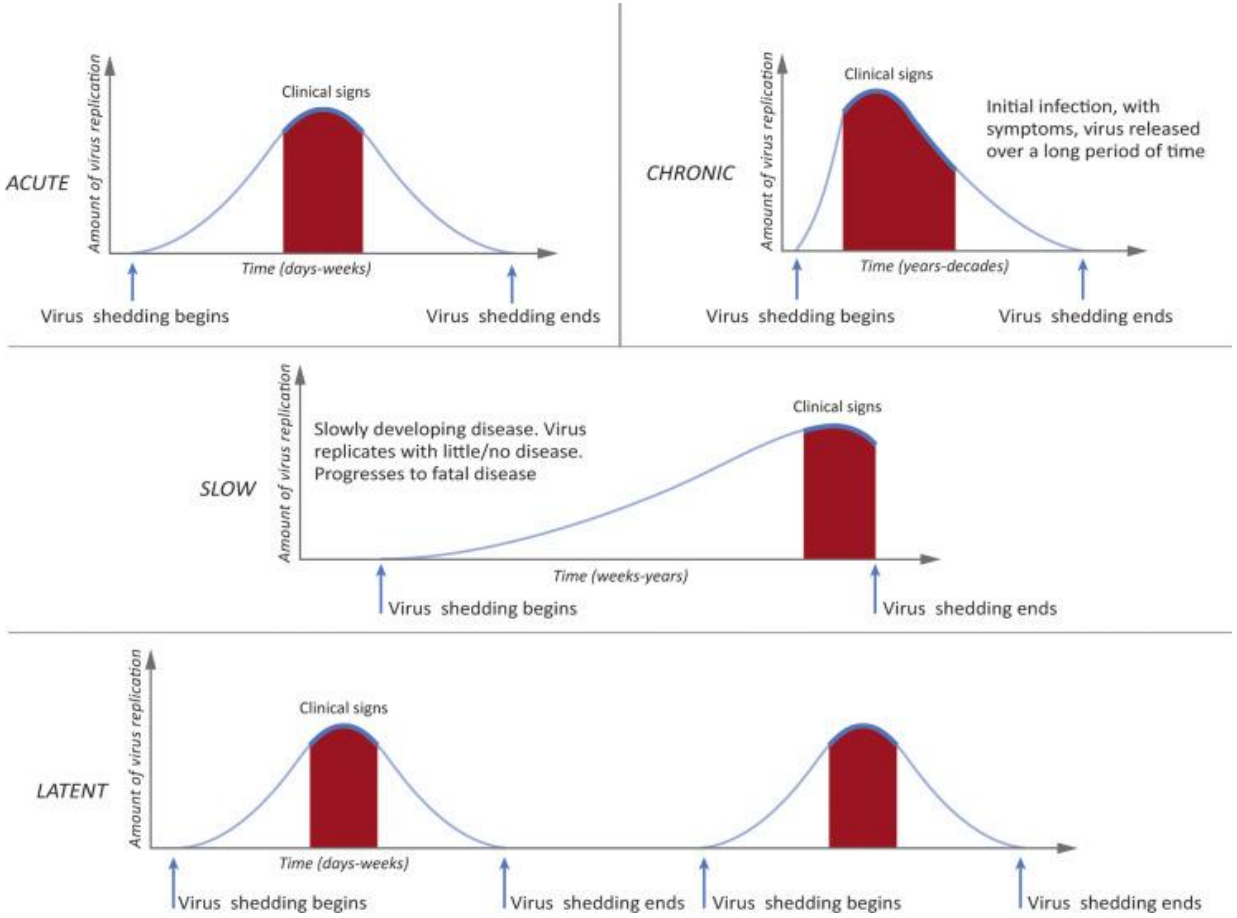
• Abortive or nonproductive infection. The virus enters the cell, but replication becomes irreversibly blocked at some step before particles are produced.

• Latent infection. Describes a situation where a viral genome is present in the cell, but no or only a few viral proteins are produced. Latency implies that the virus can productively replicate given the right conditions.

Both productive and nonproductive infections can impact the cell. The effects of infection can range from no apparent change, to cell death, to transformation (immortalization). Productive infection often results in cell death (lytic or cytopathic infection), but this is not always the case. Some viruses can replicate without damaging the cell, resulting in an inapparent infection. Sometimes an inapparent infection results from latency. A much less frequent outcome of infection is transformation or immortalization that allows the cell to divide without restriction. Immortalized cells may be productively infected (virus is released) or the condition may result from a nonproductive infection. Inapparent infection also occurs at the level of the animal host.

Some viruses replicate in hosts without causing disease. Disease is the result of damage to tissues or organs. Many viral infections cause disease, and diseases can be described as acute, chronic, or latent.

Outcomes of a viral infection



Acute disease has a rapid onset, lasts from days to months, and the virus is either controlled or cleared, or causes death of the host. Example: the common cold. From a public health standpoint, it is important to know that virus replication and spread may begin well before symptoms develop and virus may be shed for days or weeks after symptoms have resolved. The peak of clinical signs and symptoms may or may not correspond to peak virus titers, or the time of maximum transmissibility.

Chronic viral infections have a slower progression and the time to resolution is years to a lifetime. These viral infections may, but do not always, lead to death of the host. Chronic infections are also called persistent infections. Virus is produced and shed continuously (albeit sometimes at very low levels). Examples : hepatitis C virus (HCV), hepatitis B virus (HBV), and human immunodeficiency virus (HIV). A chronic viral infection can be without symptoms (inapparent) for years.

Latent infection describes the maintenance of a viral genome without the production of detectable virus. Examples: Herpesviruses, the chickenpox/shingles virus (varicella-zoster virus),

Introduction to viral pathogenesis

Viral pathogenesis is defined as the mechanism by which viruses cause disease.
A simple view of viral pathogenesis is that viruses replicate and kill cells, thus causing disease. For example, death of liver cells (hepatocytes) causes hepatitis, death of enterocytes may cause diarrhea, death of respiratory epithelial cells may cause severe respiratory tract disease. However loss of cell function, without death, can also produce disease. During HIV infection, immunodeficiency is not simply caused by cell death; the virus also alters the function of some cells needed to maintain a healthy immune system.

Signs and symptoms of disease can also result from tissue damage caused by host immune responses. Inflammation, killing of virus-infected cells by the immune system, or deposition of immune complexes are examples. Of course, like any biological event, disease is often a complex combination of direct damage by virus in concert with host immune responses. Understanding viral pathogenesis, the mechanism by which disease develops, is an important consideration in developing effective treatments.

Introduction to viral transmission

Common routes of infection include:

- fecal-oral: occurs via ingestion of contaminated food or water. Virus enters the body through epithelial cells or lymphoid in the gastrointestinal tract.
- respiratory droplets: viruses in the respiratory tract are expelled as droplets. The transmission may be directly from one individual to another or may occur through fomites. Viruses expelled from the respiratory tract may also be transmitted by contact with mucosal surfaces such as the eye.
- contact with contaminated fomites,
- exchange of infected bodily fluids, tissues, or organs: result from blood transfusions, use of dirty needles, trauma (bleeding), organ or tissue transplantation, sexual contact, or artificial insemination
- airborne: transmitted over long distances through the air. Simply sitting in a room with a measles-infected individual can lead to infection. It should be noted that airborne transmission is distinct from aerosol transmission. In airborne transmission, particle sizes are very small and remain suspended in the air for long periods.
- insect vectors: transmitted from one host to another primarily via an insect intermediary. Bloodfeeding insects such as mosquitos, ticks, and midges are common vectors. Viruses transmitted by insect vectors are collectively called arboviruses.

Take home messages

- Viruses are infectious agents (but are not cells).
- Viruses are obligate intracellular parasites that require host cells for their replication.
- Virions are the packages that contain the viral genome.
- Virions assemble from viral proteins and genomes synthesized within the infected cell.
- In the laboratory viruses are cultured or grown in cell or organ culture.
- Viruses can change or adapt to new growth conditions.
- Viruses have different genome types, capsid types, routes of infection, and diverse interactions with host cells.
- Virus infection may but does not always lead to cell death or host disease.
- Virus infections may be relatively short lived (acute infections) or may be life-long (chronic or persistent).

Thanks for your attention :)

NEXT LECTURES COULD BE ON

Virus Structure

Virus Interaction with the cell

Virus Transmission and Epidemiology

Viral vaccines

Virus evolution and genetics

Viral pathogenesis

Family Coronaviridae and Orthomyxoviridae

OR WHATEVER YOU WANT TO KNOW ABOUT!

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