Chapter 10

Genetics of Viruses

10.1 Virus Structure and Genetic Composition

- The diversity of viruses with regard to host range, structure, and genomes
- The results of an experiment indicating that the genome of tobacco mosaic virus is RNA

Characteristics of Viruses

- Non-living particles
- Medically important – cause many diseases
- Nucleic acid genomes
- Both prokaryotic and eukaryotic cells are infected
  - **Bacteriophages** – Viruses that infect bacteria
- Rely on living cells to replicate

Viruses are Highly Diverse

- **Host range differences**
  - What species a virus can infect
  - The cells that a virus infects are its **host cells**

- **Structural differences**
  - Size and shape of the **capsid** (protein coat)
  - Presence or absence of **viral envelope**

- **Genome differences**
  - Nucleic acids of a virus are the **viral genome**

Host range differences

- Some viruses have a **broad host range**
    - Ex: Tobacco Mosaic Virus (TMV) can infect >150 species of plants
- Other viruses can infect only a **single species**

- Or a **single cell type**
  - Ex: Influenza specifically infects lung cells

Structural differences

- The electron microscope allowed the first observation of viruses in the 1930s
  - Many are smaller than the wavelength of visible light
- Range from 20-400nm in diameter
  - Typical bacterium = 1000nm
- All viruses have a **capsid** composed of protein subunits called **capsomers**
  - Can be helical or polyhedral
- Some have a **viral envelope**
- Some have **specialized proteins** to help infection
  - Spikes and knobs

A **capsid** is the protein shell of a virus. It consists of several oligomeric structural subunits made of protein called protomers. The observable 3-dimensional morphological subunits, which may or may not correspond to individual proteins, are called **capsomeres**. The capsid encloses the genetic material of the virus.

The **capsomere** is a subunit of the capsid, an outer covering of protein that protects the genetic material of a virus. Capsomeres self-assemble to form the capsid.

Genome differences

- The nucleic acid genome of a virus may be:
  - Circular or linear
  - DNA or RNA
  - Double-stranded (DNA or RNA) or single-stranded (DNA or RNA)
  - A few thousand or more than 100,000 nts

TABLE 10.1

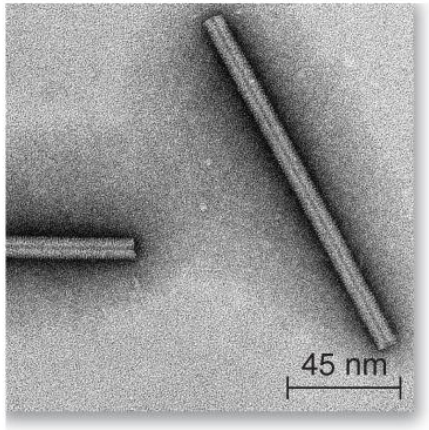
Hosts and Characteristics of Selected Viruses

Virus or Group of Viruses	Host	Effect on Host	Nucleic Acid*	Genome Size (kb)†	Number of Genes†
Phage fd	*E. coli*	Slows growth	ssDNA	6.4	10
Phage λ	*E. coli*	Can exist harmlessly in the host cell or cause lysis	dsDNA	48.5	36
Phage T4	*E. coli*	Causes lysis	dsDNA	169	288
Phage Qß	*E. coli*	Slows growth	ssRNA	4.2	4
Tobacco mosaic virus (TMV)	Many plants	Causes mottling and necrosis of leaves and other plant parts	ssRNA	6.4	6
Baculoviruses	Insects	Most baculoviruses are species-specific; they usually kill the insect.	dsDNA	133.9	154
Parvovirus	Mammals	Causes respiratory, flulike symptoms	ssDNA	5.0	5
Influenza virus	Mammals	Causes classic flu symptoms—fever, cough, sore throat, and headache	ssRNA	13.5	11
Epstein-Barr virus	Humans	Causes mononucleosis, with fever, sore throat, and fatigue	dsDNA	172	80
Adenovirus	Humans	Causes respiratory symptoms and diarrhea	dsDNA	34	35
Herpes simplex type II	Humans	Causes blistering sores around the genital region	dsDNA	158.4	77
HIV	Humans	Causes AIDS, an immunodeficiency syndrome eventually leading to death	ssRNA	9.7	9

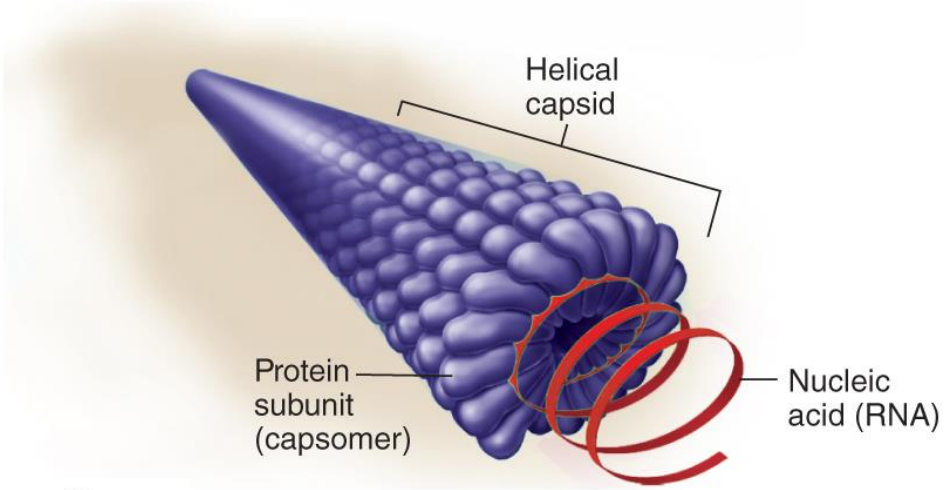
*The abbreviations ss and ds refer to single-stranded and double-stranded, respectively.

†Several of the viruses listed in this table are found in different strains that show variation with regard to genome size and number of genes. The numbers reported in this table are typical values. The abbreviation kb refers to kilobase, which equals 1000 bases.

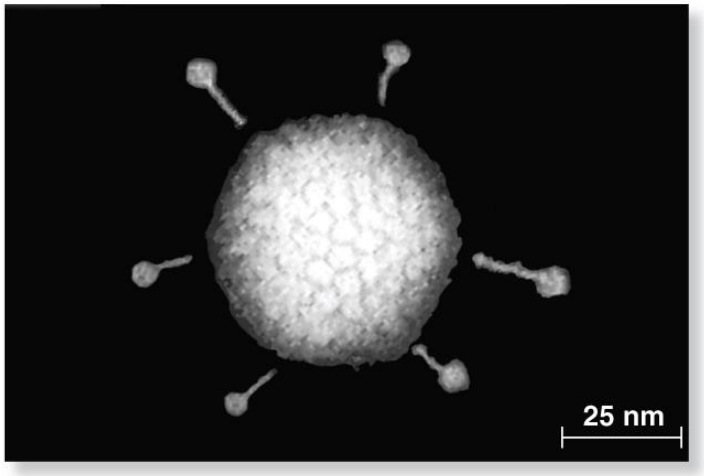
RNA- TLR7 and 8
DNA-TLR9



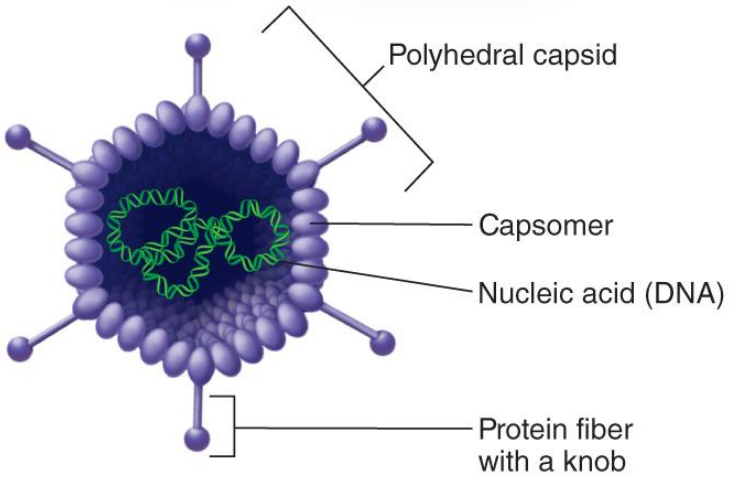
(a) Tobacco mosaic virus, a nonenveloped virus with a helical capsid



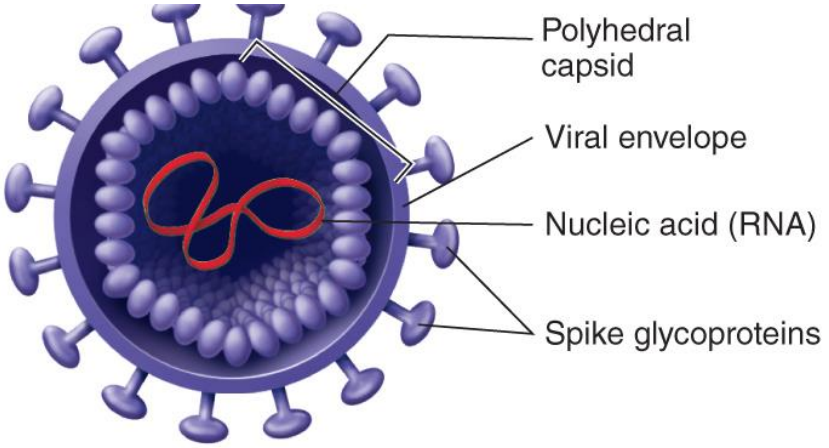
a: © Science Source



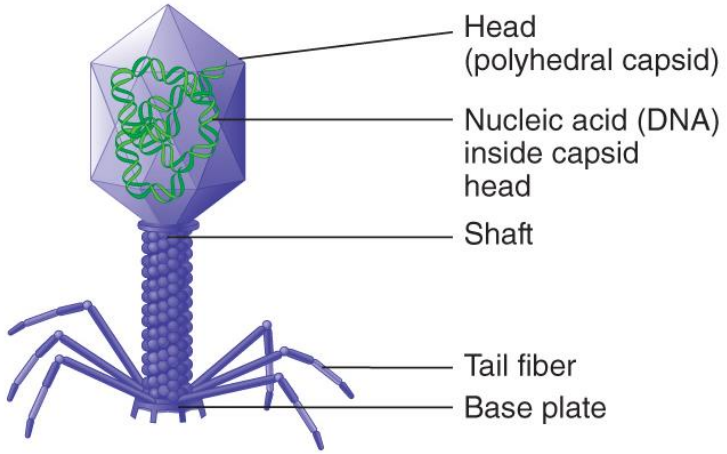
(b) Adenovirus, a nonenveloped virus with a polyhedral capsid and protein fibers with a knob



b: © Dr. Linda M. Stannard, University of Cape Town/SPL/Science



(c) Influenza virus, an enveloped virus with spikes



(d) T4, a bacteriophage

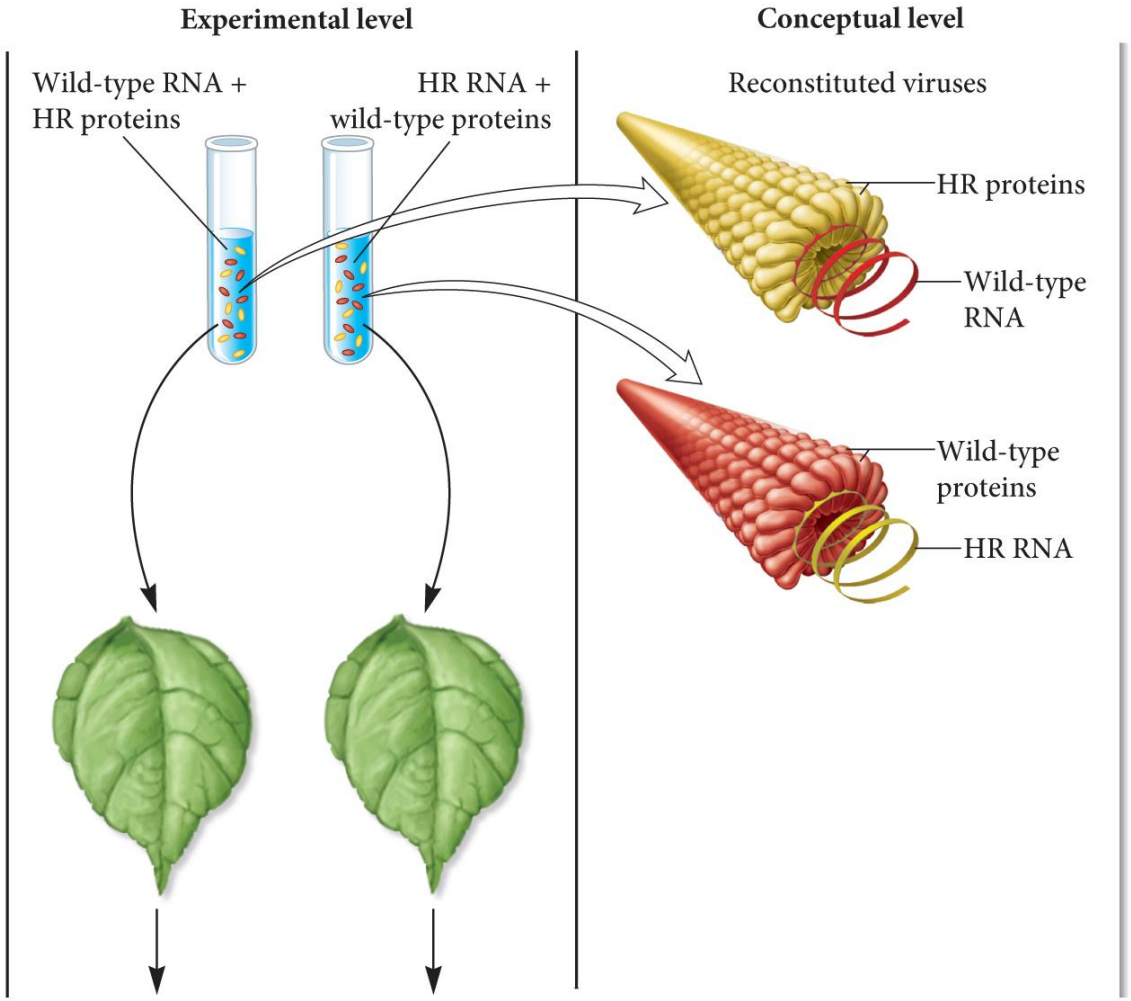
The Genome of TMV is made of RNA

- In 1956, Alfred Gierer and Gerhard Schramm isolated RNA from tobacco mosaic virus
  - This RNA alone could give plants the same lesions as the intact virus
- Then Heinz Fraenkel-Conrat and Beatrice Singer did experiments using wildtype and mutant TMV strains
  - Wildtype TMV
    - Mottled leaves
  - HR mutant TMV
    - Streaks and rings on infected leaves
    - Capsid contained histidine and methionine
- In a **reconstitution experiment**, they could create mixed viruses with one type of RNA and the other type of protein

- *Would the infected phenotype on the leaves depend on the type of RNA or the protein?*

1. Mix together wild-type RNA and HR proteins or HR RNA and wild-type proteins. Allow time for the RNA and proteins to assemble into intact viruses. These are called reconstituted viruses.

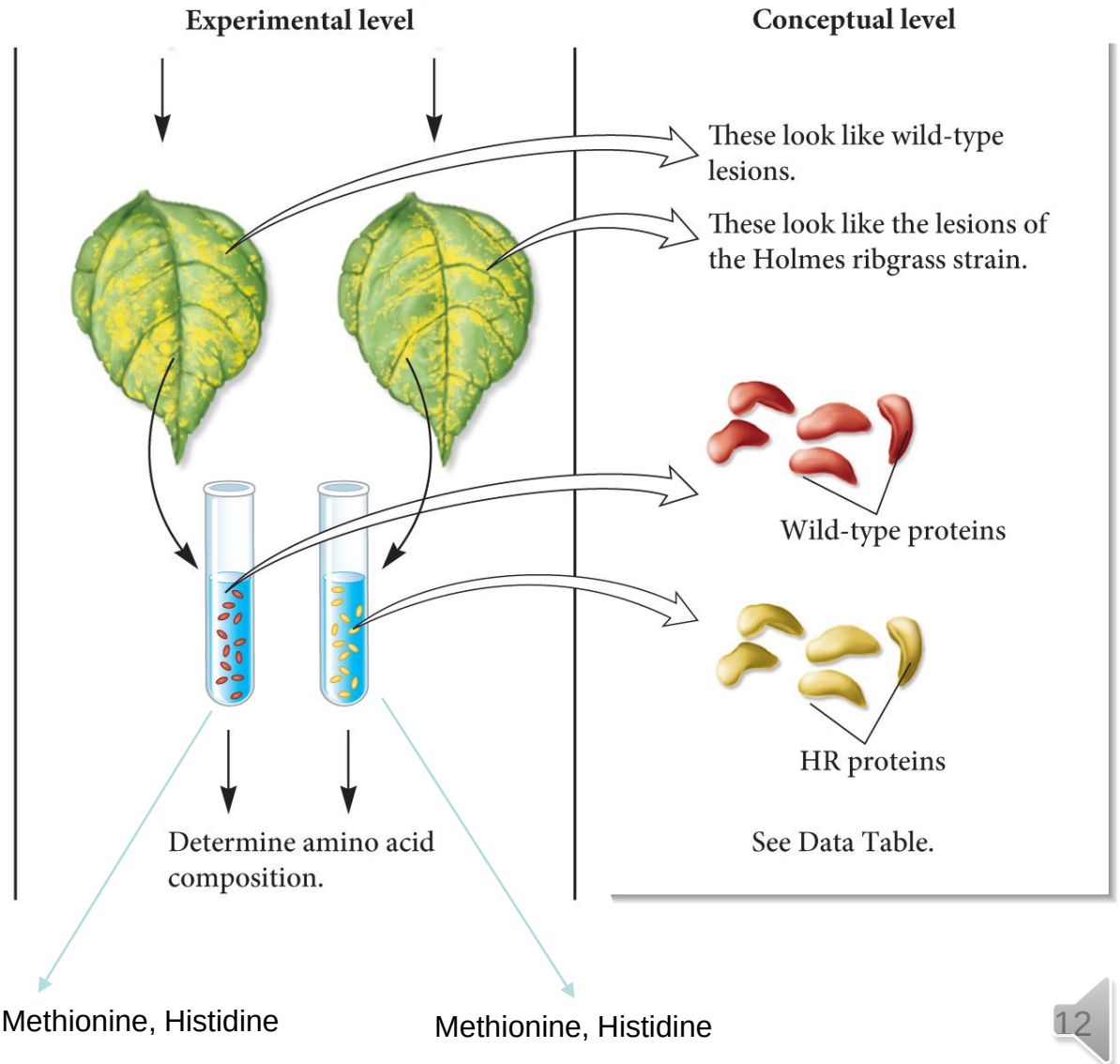
2. Inoculate a small amount of reconstituted viruses onto healthy tobacco leaves. Allow time for infection to occur.



3. Observe the types of lesions that form on the leaves.

4. Take plant tissue containing viral lesions and isolate newly made viral proteins. This is done by extracting the protein with mild alkali.

5. Determine the amino acid composition of the newly made viral proteins. This involves hydrolyzing the proteins into individual amino acids and then separating the amino acids by chromatography.



10.2 Viral Reproductive Cycles

- The reproductive cycles of phage lambda and HIV
- Definition of latency and explain how it occurs for phage lambda and HIV
- The properties of emerging viruses

Reproductive cycles

- Six general steps of **viral reproductive cycle**:

  Step 1. **Attachment**

  Step 2. **Entry**

  Step 3. **Integration**

  Step 4. **Synthesis**

  Step 5. **Viral assembly**

  Step 6. **Release**

- Step 1. **Attachment**
  - Usually specific for only a few cells
  - Proteins on virus interact with specific molecules at cell surface
- Step 2. **Entry**
  - Viral genome enters cell
    - Either viral genome alone
    - or viral genome with associated proteins
  - Some viral proteins immediately produced

- Step 3. **Integration**

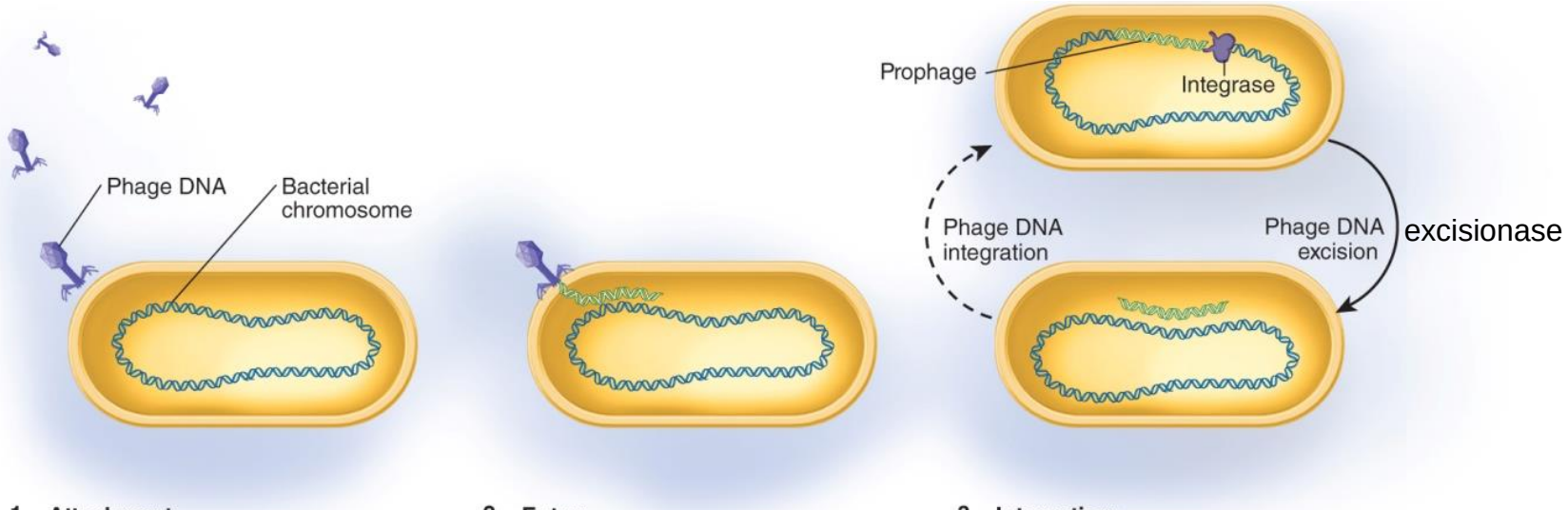
  - Not all viruses integrate into host chromosome
  - **Integrase** – enzyme that mediates integration
  - Once integrated, genome is called a **prophage**
    - This stage is called the **lysogenic cycle**

- Step 4. **Synthesis of viral components**

  - Transcription of viral genes
  - Translation of viral proteins
  - Synthesis of more copies of viral nucleic acid
    - Retroviruses – copies made from provirus
    - DNA viruses – DNA replication

- Step 5. **Viral assembly**
  - Protein and nucleic acid components come together to make infectious particles
  - Some viruses self-assemble
  - Some viruses use proteins to help assembly. These assembly proteins are not found in final infectious particle
- Step 6. **Release**
  - Bacteriophage cause cell to rupture – **lysis**
  - Some eukaryotic viruses bud from cell
    - Results in an envelope of cellular membrane
    - Membrane may also have viral proteins

- Consider the 6 steps of viral reproduction in **Bacteriophage λ**
  - Also known as **phage Lambda**
  - Has a dsDNA genome

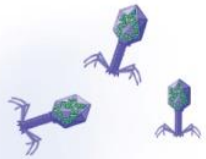


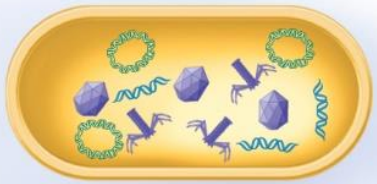
1 **Attachment:** The phage binds specifically to proteins in the outer bacterial cell membrane.

2 **Entry:** The phage injects its DNA into the bacterial cytoplasm.

3 **Integration:** Phage DNA may integrate into the bacterial chromosome via integrase. The host cell carrying a prophage may then undergo repeated divisions, which is called the lysogenic cycle. To end the lysogenic cycle and switch to the lytic cycle, the phage DNA is excised. Alternatively, the reproductive cycle may completely skip the lysogenic cycle and proceed directly to step 4.

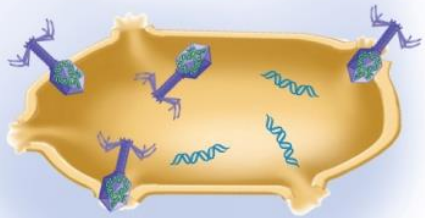
(a) Reproductive cycle of phage λ





4 **Synthesis of viral components:** In the lytic cycle, phage DNA directs the synthesis of viral components. During this process, the phage DNA circularizes, and the host chromosomal DNA is digested into fragments.

5 **Viral assembly:** Phage components are assembled with the help of noncapsid proteins to make many new phages.



6 **Release:** The viral enzyme called lysozyme causes cell lysis, and new phages are released from the broken cell.

- Consider the 6 steps of viral reproduction in **human immunodeficiency virus (HIV)**
  - A **retrovirus**
  - Has a ssRNA genome
  - Uses **reverse transcriptase** to copy RNA into DNA for integration
    - Once integrated, the genome is called a **provirus**

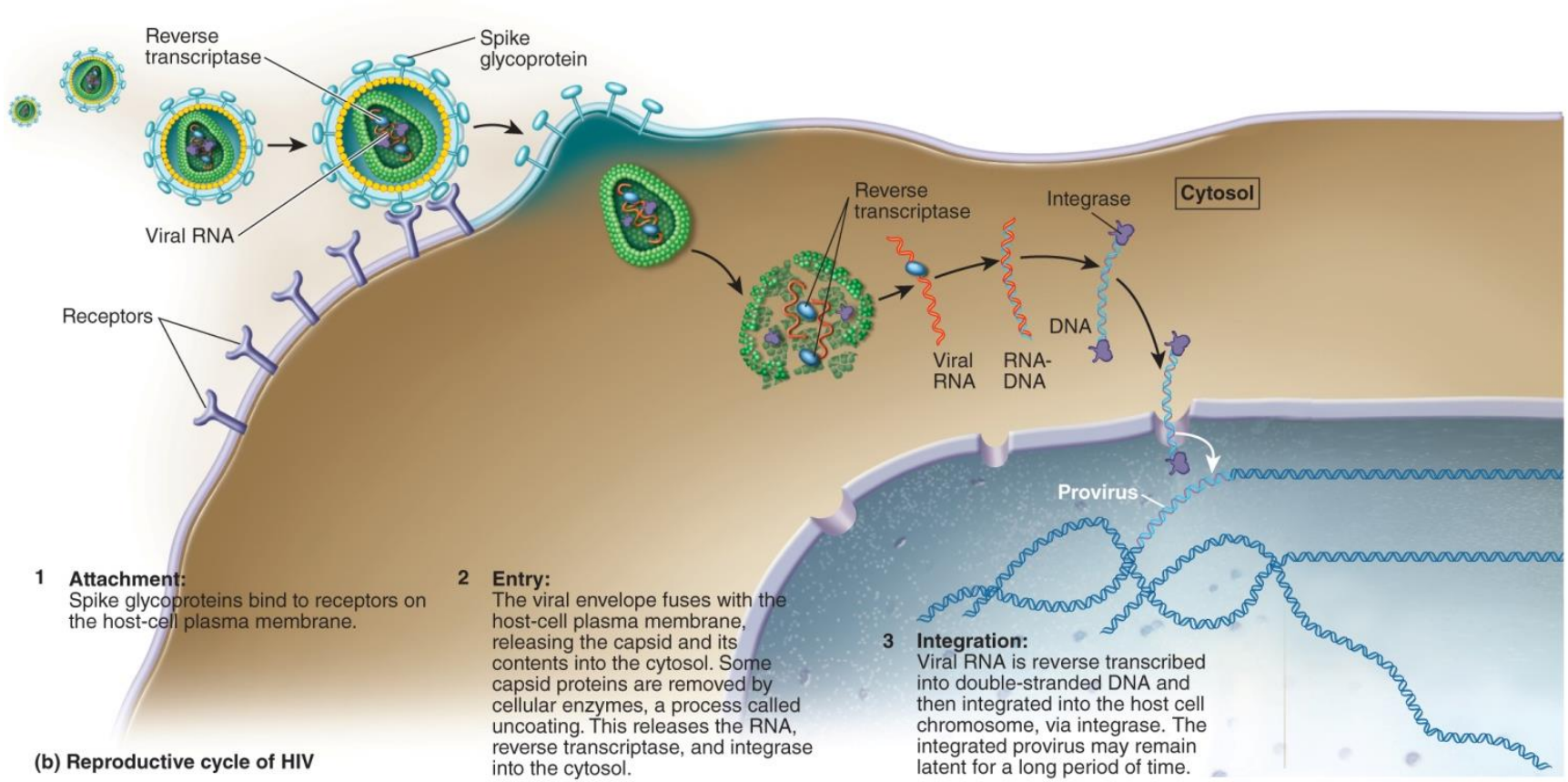
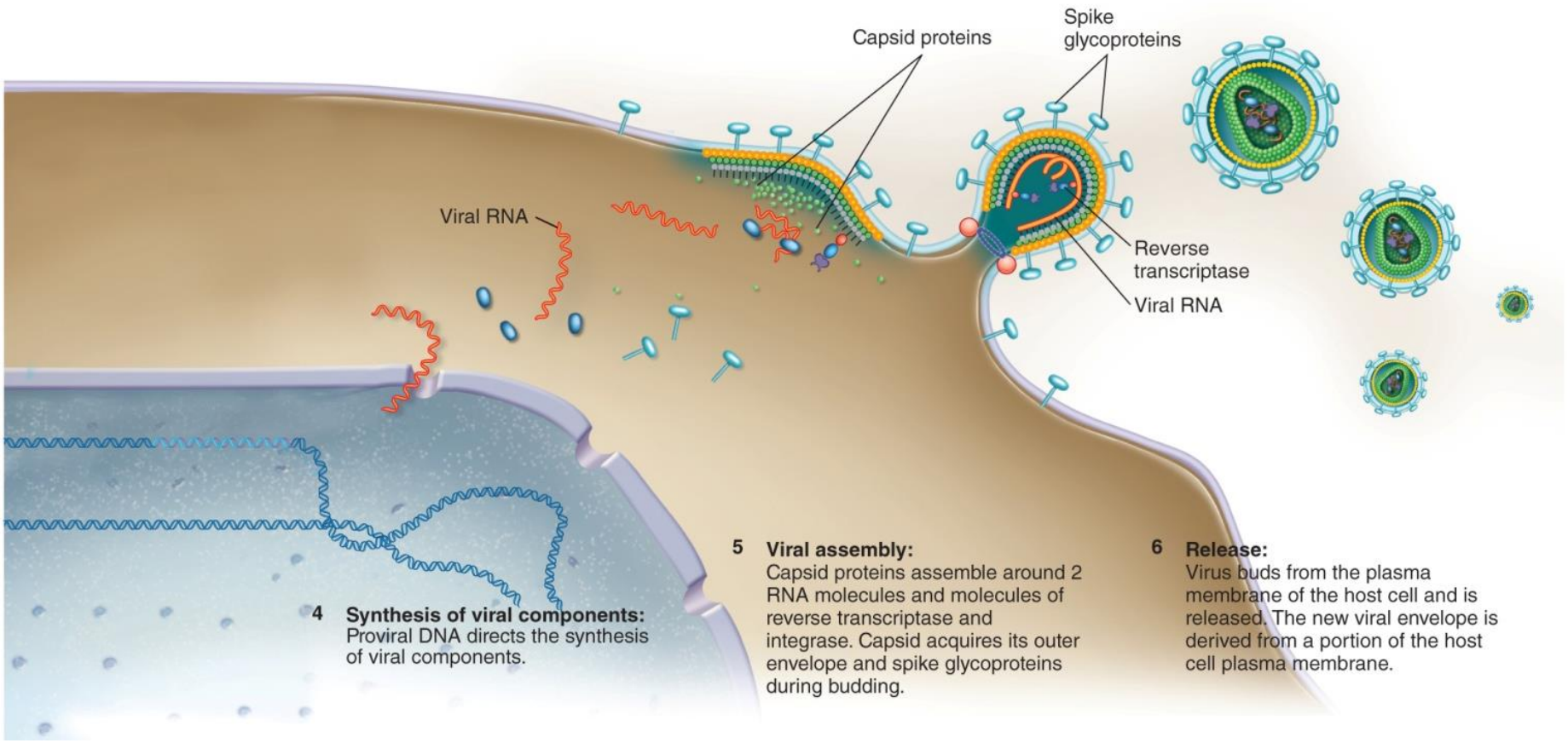

Reverse transcriptase
Spike glycoprotein
Viral RNA
Receptors
Reverse transcriptase
Integrase
Cytosol
DNA
Viral RNA
RNA-DNA
Provirus
1 Attachment:
Spike glycoproteins bind to receptors on the host-cell plasma membrane.
2 Entry:
The viral envelope fuses with the host-cell plasma membrane, releasing the capsid and its contents into the cytosol. Some capsid proteins are removed by cellular enzymes, a process called uncoating. This releases the RNA, reverse transcriptase, and integrase into the cytosol.
3 Integration:
Viral RNA is reverse transcribed into double-stranded DNA and then integrated into the host cell chromosome, via integrase. The integrated provirus may remain latent for a long period of time.
(b) Reproductive cycle of HIV

Figure 10.3


Capsid proteins
Spike glycoproteins
Viral RNA
Reverse transcriptase
Viral RNA
4 Synthesis of viral components: Proviral DNA directs the synthesis of viral components.
5 Viral assembly: Capsid proteins assemble around 2 RNA molecules and molecules of reverse transcriptase and integrase. Capsid acquires its outer envelope and spike glycoproteins during budding.
6 Release: Virus buds from the plasma membrane of the host cell and is released. The new viral envelope is derived from a portion of the host cell plasma membrane.

Latency

- **Latency** – the inactive stage of a virus integrated into the host cell genome
  - Called a **prophage** or **provirus**

- Latency in bacteriophage is called **lysogeny**

- **Temperate phage** – can alternate between lysogenic and lytic cycles (Ex. Bacteriophage)
- **Virulent phage** – has only a lytic cycle (Ex. Phage T4)
  - Not capable of integration into the genome

- Environmental conditions determine exit from latency

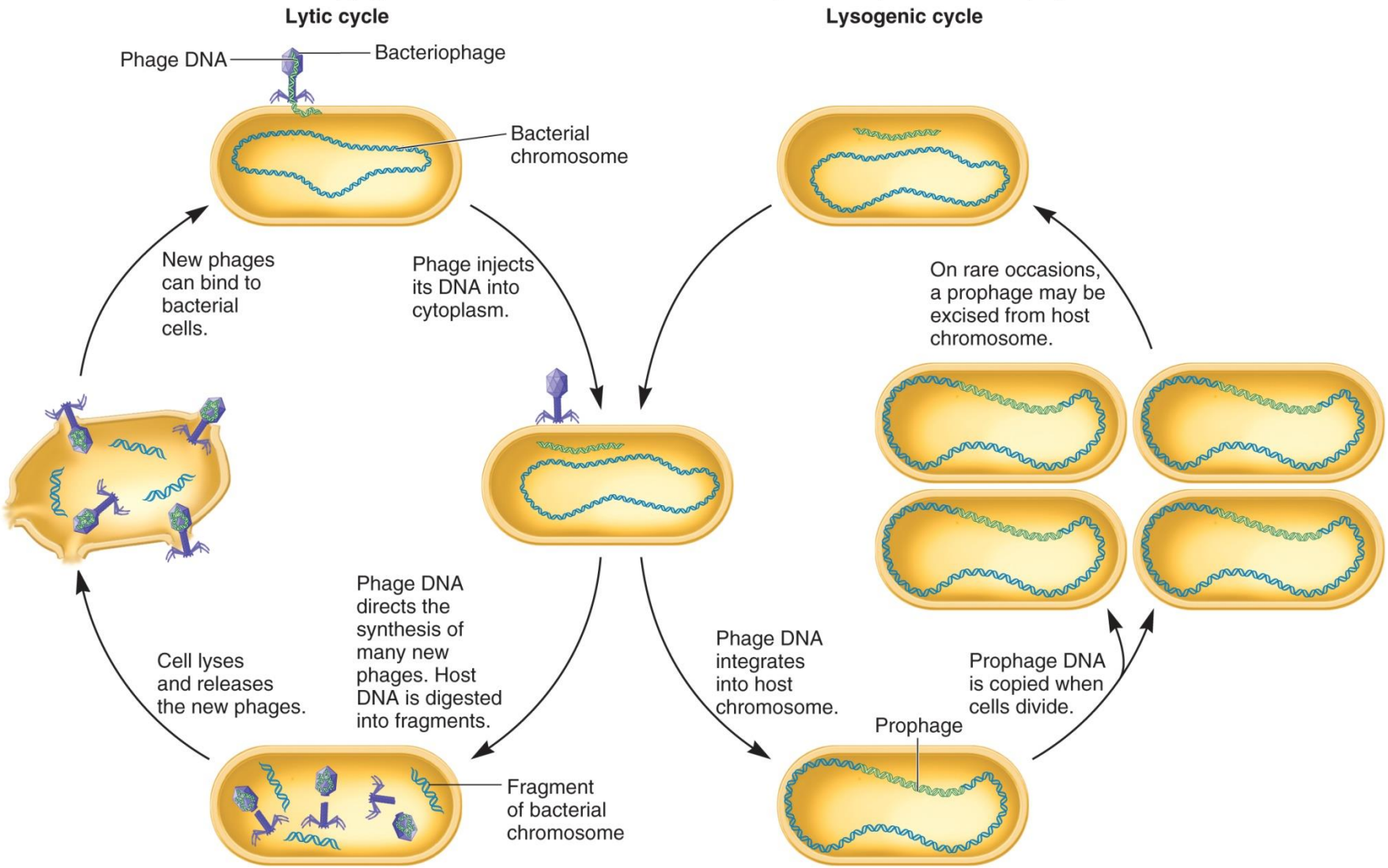


Figure 10.3

Emerging Viruses

- Emerging viruses – Arose recently and are more likely to cause infection than previous strains

- Example: **H1N1 influenza**
  - also known as “swine flu”
  - Over 30,000 people / yr in U.S. die from influenza

- Another emerging virus: **HIV**
  - The cause of AIDS
  - Spread by sexual contact, blood transfusions, shared needles, and from mother to fetus
  - >30 million deaths from 1981-2013
  - Nearly 1 in 100 adults (ages 15-49) are infected in the U.S.
  - In the U.S., about 55,000 new infections a year
  - 70% in men, 30% in women

- Symptoms of AIDS arise from destruction of **helper T cells**
  - Loss of helper T cells seriously compromises the immune system
  - Patient becomes susceptible to **opportunistic infections**
    - Diseases that a healthy person would easily fight off
  - Reverse transcriptase lacks a proofreading function
    - Therefore **mutant strains** arise frequently
      - Difficult for immune system to fight off
      - Resistant to antiviral drugs

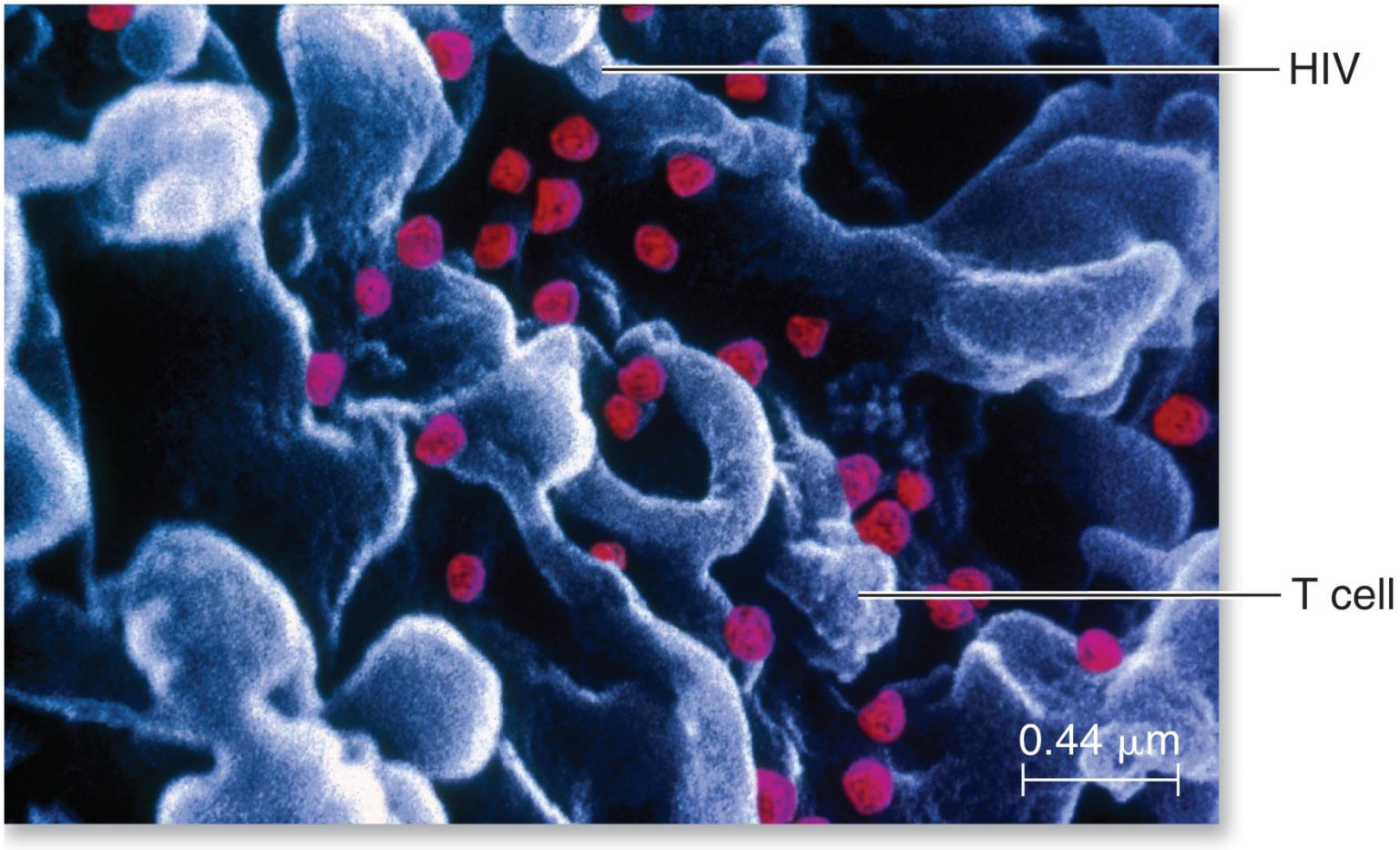
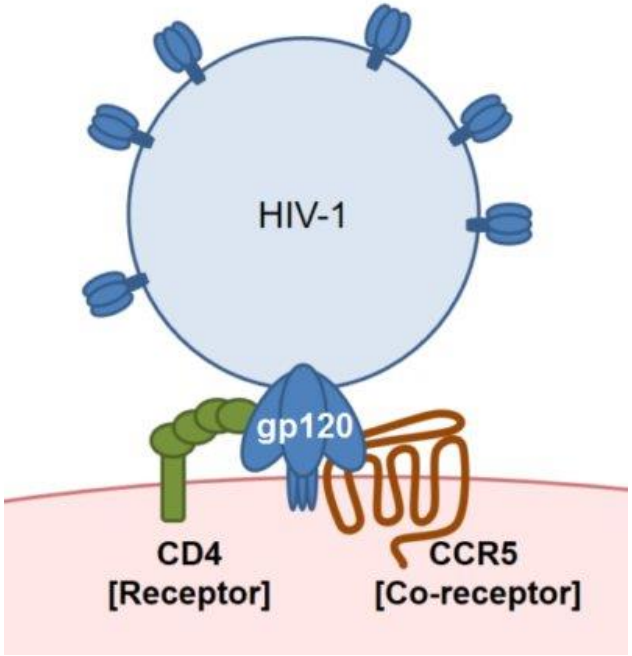
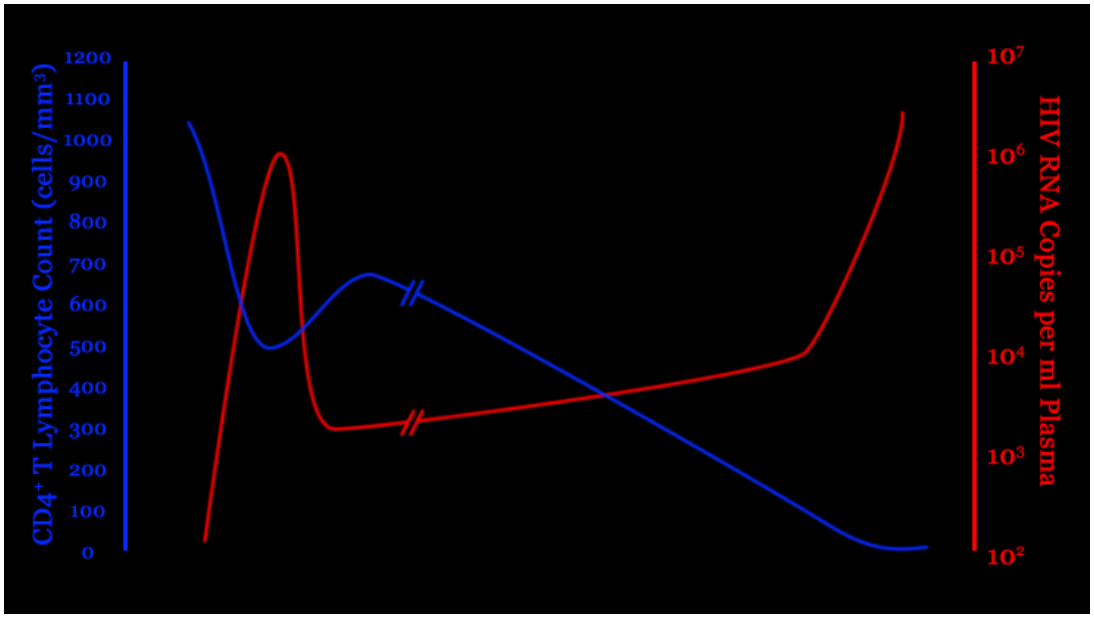


Figure 10.6





https://www.youtube.com/watch?v=vKi95jdJLhs

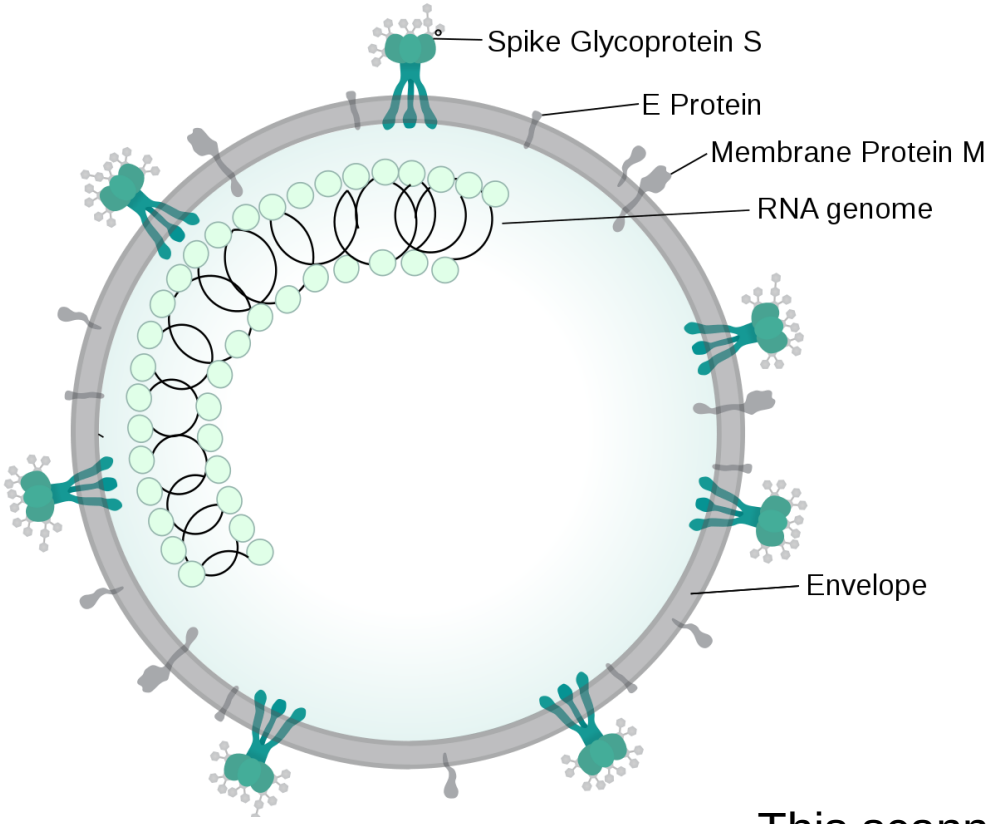
https://www.ibiology.org/human-disease/reverse-transcriptase/#part-2

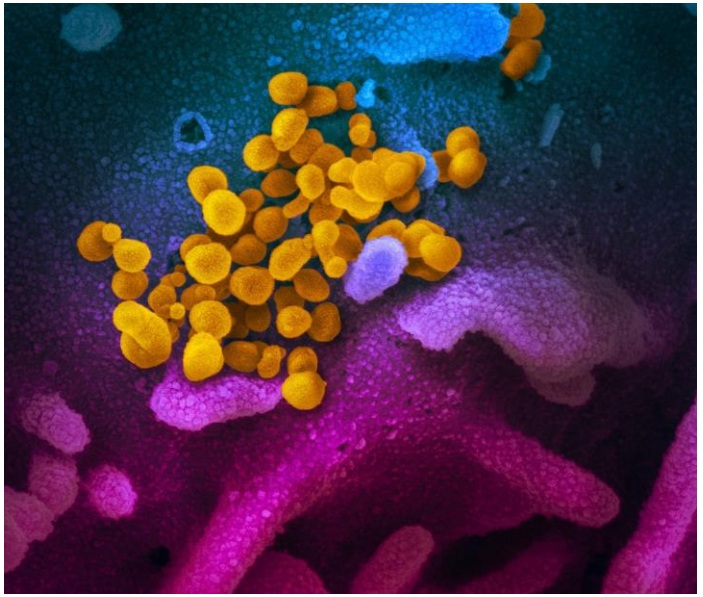
Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) :COVID-19 virus

- 6 Oct 2020, more than 35,366,134 cases of COVID-19 have been reported in 200 countries, approximately 1,039,802 deaths.
- genetic similarity to bat coronaviruses
- close contact and via respiratory droplets produced from coughs or sneezes
- Enters human cells by binding to their angiotensin converting enzyme 2 (ACE2) receptors (alveolar epithelial type II – ACE2 expressing cells)
- belongs to coronaviruses, single-stranded RNA (+ssRNA) virus.
- Other coronaviruses - common cold to more severe diseases such as Middle East respiratory syndrome (MERS)
- RNA sequence - approximately 30,000 bases in length.

High pathogenicity and transmissibility

- coronavirus particles that are inhaled through the nose or mouth have a high chance of attaching to cells in the upper respiratory tract, meaning that relatively few are needed for an infection to gain a foothold.
- SARS-CoV-2 spike protein was predicted to also have a strong binding affinity to human ACE2.
- Multiple cleavage sites on S protein





This scanning electron microscope image shows SARS-CoV-2 (yellow)—also known as 2019-nCoV, the virus that causes COVID-19—isolated from a patient in the U.S., emerging from the surface of cells (blue/pink) cultured in the lab. Credit: NIAID-RML

Life cycle of SARS-CoV