Chapter 13: Viruses

1. Viral Structure
2. The Viral Life Cycle
3. Bacteriophages
4. Animal Viruses
5. Prions
1. Viral Structure

Chapter Reading – pp. 387-393
What exactly is a Virus?

Viruses are extremely small entities that are **obligate intracellular parasites** with no metabolic capacity of their own.

- have none of the characteristics of living cells
  - do NOT reproduce or metabolize on their own
  - do NOT respond to their environment or maintain homeostasis in any way

**It’s hard to “kill” something that’s not really *alive*, so antibiotics that kill bacteria, fungi, etc, do NOT harm viruses**

- depend on host cells for their reproduction (which are typically destroyed in the process)
Size of Viruses

- almost all viruses are smaller than the smallest prokaryotic cells
- pass through filters that trap cells (non-filterable)
What’s a Virus made of?

All viruses consist of at least 2 components:

**Genetic Material**
- usually a single DNA or RNA molecule
- can be single or double stranded, linear or circular
- contains the viral genes

**A Capsid**
- a hollow protein capsule which houses the genetic material

Some viruses also contain:

**An Envelope**
- membrane from host cell with viral proteins (spikes) that surrounds the capsid
Capsids are hollow, protein “shells” that:

- are an array of protein subunits called capsomeres
- consist of ≥1 type of protein
- house the genetic material (DNA/RNA)
- are frequently involved in host recognition & entry
- vary in shape, size among viruses
The Viral Envelope

The capsid of some viruses is enclosed in a phospholipid membrane called an envelope containing viral proteins called “spikes”:

- Membrane comes from host cell
- “Spike” proteins involved in attachment and entry into host cell
Viral Genetic Material

Viral genomes range from ~4000 to 250,000 bp (or nt) and can be:

DNA or RNA

Double- (ds) or single-stranded (ss)

• if single-stranded, it is referred to as “+” or “−”

+ strand = sense or coding strand

− strand = antisense or template strand
Viruses come in 4 basic morphological types:

1. **Polyhedral Viruses**
   - capsomeres in capsid have a “polyhedral” arrangement

2. **Helical Viruses**
   - capsomeres in capsid have a “helical” arrangement

3. **Enveloped Viruses**

4. **Complex Viruses**
   - consist of multiple types of structures
Viral Taxonomy & Nomenclature

ICTV classification is by *Order, Family, Genus & Species* based on morphology, type of nucleic acid, mode of replication, host range:

**Viral Families**
- have the suffix –*viridae* (e.g., Retroviridae)

**Viral Genera**
- have the suffix –*virus* (e.g., *Lentivirus*)

**Viral Species**
- have a descriptive common name & possibly a number to distinguish subspecies (e.g. human immunodeficiency virus)
How are Viruses Identified?

Despite their small size, bacteriophages and other viruses can be detected and identified in a number of ways:

• by the host cells they can infect and kill

• by serological methods
  • i.e., using antibodies that bind to specific viral proteins (western blot, ELISA, fluorescence microscopy, etc)

• by methods that detect viral DNA or RNA
  • i.e., PCR, DNA hybridization, etc

• by electron microscopy
2. The Viral Life Cycle

Chapter Reading – pp. 394-397
Basic Stages of the Viral Reproductive Cycle

1. Attachment
2. Entry
3. Synthesis
4. Assembly
5. Release

- Bacterial chromosome
- Viral DNA
- Viral proteins
Step 1 – Attachment

Also referred to as adsorption, this is where a virus attaches to the surface of a host cell:

- involves very specific interactions between viral & host cell molecules (usually proteins)
  - viral molecules in “outer layer” (i.e., capsid or envelope)
  - molecules in host cell wall (bacteria) or plasma membrane (animal cells)

**These molecular interactions determine the host range of a virus, and thus limit infection to very specific species and cell types**
Step 2 – **Entry**

Method of getting viral DNA or RNA into the host cell depends on the type of virus & host cell:

- **bacteriophages** (viruses that infect bacteria) puncture the cell wall & inject DNA/RNA

- animal viruses typically enter cells by endocytosis or fusion with the membrane
Step 3 – Synthesis

The expression of viral genes...

• transcription & translation of viral genes to produce viral proteins
  • capsid proteins, transcription factors, etc...

• requires host cell gene expression machinery
  • polymerases, ribosomes, tRNA, nucleotides, AA’s...

...and copying of the viral genetic material

• whether DNA or RNA
• requires host enzymes, nucleotides, etc...
Viral Gene Expression

The expression of viral genes typically occurs in multiple waves:

1) early gene expression
   • select viral genes that are expressed right away
   • transcription is driven by viral promoters that require host factors (or viral factors present in capsid)
   • e.g., *viral* transcription factor, replication factor genes

2) late or delayed gene expression
   • typically viral genes that require *viral* transcription factors produced from “early genes”
   • e.g., capsid, “spike” protein genes
Step 4 – Assembly

Assembly refers to the self-assembly of viral proteins and genetic material (DNA or RNA) into intact viral particles:

- capsid & other structural proteins self-assemble
- genetic material is packaged into capsid
- enveloped viruses do not acquire envelope until exiting the host cell
Step 5 – Release

When complete viral particles are assembled they can be released from the host cell in 2 basic ways:

1) cell lysis
   - specific viral proteins cause disruption of the plasma membrane (& cell wall in bacteria)
   - destroys host cell while releasing new viruses

2) budding, exocytosis
   - many enveloped viruses “bud” from host cell, acquiring the viral envelope in the process
   - other animal viruses are released by exocytosis

**Once released, a complete virus is called a virion**
3. Bacteriophages

Chapter Reading – pp. 229, 394-397, 404-405
What’s a Bacteriophage?

A bacteriophage is a virus that infects and destroys bacterial cells.

Bacteriophages are of many different types (some w/DNA or RNA, etc), however 2 types are of particular interest due to decades of study:

“T-even” bacteriophages (T2, T4, T6)
bacteriophage lambda (λ)

***More is known about the biology of these viruses than any other type of virus!***
Growing & Counting Phages

Phages can be “grown” by simply incubating them with host bacteria.

When spread on agar plates, the phages will cause visible regions of clearing to form (plaques)

- due to killing of bacteria
- ea plaque originated with a single virion or plaque-forming unit (PFU)

PFUs, give rise to plaques just as CFUs give rise to bacterial colonies!
“T-even” Bacteriophages

Bacteriophages T2, T4 & T6 are the “T-even” phages that have been studied for decades:

- genetic material is a linear double-stranded DNA molecule (~170 kbp long)
- host cell is *E. coli* (Gram-)
- life cycle is exclusively lytic
  - lyses (bursts & kills) host cell
- a complex virus
  - structures in addition to capsid
“T-even” Phage Structure

Capsid (head)
• polyhedral, houses DNA

Tail
• helical sheath surrounds tail core
• tail fibers & baseplate are involved in attachment to host cell
**T-even Phage Life Cycle**

- **lysozyme** in the capsid digests a hole in the cell wall allowing entry of viral DNA.

- **expression of viral lysozyme** in host cell facilitates lysis of cell and release of new phages.

**T-even life cycle takes ~25 minutes!**
Bacteriophage Lambda (λ)

Bacteriophage λ is another well-known complex phage with the following features:

- linear double-stranded DNA genome of ~50 kbp
- can be lytic or lysogenic
- host cell is *E. coli*
**Lytic vs Lysogenic Cycle**

1. Attachment Lambda phage
2. Entry
3. Prophage in chromosome
4. Replication of chromosome and cell division
5. Induction
6. Synthesis
7. Assembly
8. Release

**Lytic cycle**

**Lysogenic Cycle**

Further replications and cell divisions
Lytic growth is favored in healthy, nutrient-rich hosts.

- Lytic growth involves synthesis, assembly & release much like the T-even phages.
Lysogeny is favored in unhealthy, “starved” hosts

- instead of producing more phages and lysing the cell, the phage DNA is inserted into the host chromosome where it stays “latent” until induced to become lytic

5 Occasionally, the prophage may excise from the bacterial chromosome by another recombination event, initiating a lytic cycle.

Many cell divisions

2 Phage DNA circularizes and enters lytic cycle or lysogenic cycle.

4B Lysogenic bacterium reproduces normally.

3B Phage DNA integrates within the bacterial chromosome by recombination, becoming a prophage.
More on the Lysogeny

Integration of $\lambda$ DNA into host chromosome:

- due to a different set of “early” viral genes that facilitate recombination with host chromosome
- inserted $\lambda$ DNA is called a prophage
- host cell is called a lysogen

Prophage is “passed on” when host divides

- it’s copied along with the host chromosome since it’s part of the same DNA molecule

Various conditions are known to induce prophage to excise from host DNA & become “lytic”…
What induces a Prophage to re-enter the Lytic Cycle?

Exposure to DNA damage (e.g., UV light):
  • when the host cell is in danger, the prophage becomes lytic to avoid “going down with the ship”!

Spontaneous excision:
  • prophages can also become active without any specific inducing event

Lysogens are immune to “superinfection”
  • presence of a prophage prevents any other λ phages from infecting the cell
Specialized Transduction

Excision of a prophage from host DNA can be “imprecise” and take a piece of host DNA along with the phage DNA

- results in packaging of host DNA along with phage DNA in new virions

- differs from “regular” transduction in which random pieces of host DNA are packaged into capsids
4. Animal Viruses

Chapter Reading – pp. 397-403

A. Overview

B. DNA Viruses

C. RNA Viruses
A. Overview
Reproductive Cycle of Animal Viruses

The reproductive stages of animal viruses differ from bacteriophages in some key ways:

1) attachment
   - requires specific interactions between host cell membrane proteins & viral “spike” proteins (enveloped) or capsid proteins (non-enveloped)

2) entry
   - by direct penetration, endocytosis or fusion of the envelope with the cytoplasmic membrane
   - involves uncoating of the virus (release of DNA, RNA)
3) synthesis
   • replication of viral RNA occurs in cytoplasm
   • replication of viral DNA occurs in nucleus

4) assembly
   • RNA viruses typically assemble in cytoplasm
   • DNA viruses typically assemble in nucleus

5) release
   • via lysis (rupture of plasma membrane), budding or exocytosis
   • host cell is not necessarily killed
Entry by Direct Penetration

1. Receptors on cytoplasmic membrane
2. Capsid
3. Viral genome

Direct penetration

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Entry by Fusion

1. Receptors on cytoplasmic membrane of host
2. Viral glycoproteins
3. Viral glycoproteins remain in cytoplasmic membrane
4. Membrane fusion

(b) Membrane fusion
Entry by Endocytosis

Cytoplasmic membrane of host engulfs virus (endocytosis)

1. Cytoplasmic membrane
2. Viral genome
3. Uncoating capsid
4. Endocytosis
5. Uncoating capsid
6. Viral genome
Uncoating of Animal Viruses

Unlike bacteriophages, in which only the DNA or RNA enters the host cell, the capsid of most animal viruses enters the host cell.

This requires the uncoating of the viral genetic material before biosynthesis can occur:

- dissociation of the capsid to allow viral DNA or RNA to be copied, viral genes to be expressed

- can occur in cytoplasm or in a lysosome via host or viral enzymes
Release through Budding

Viruses can also acquire envelope via the nuclear envelope or endoplasmic reticulum.
B. DNA Viruses
Types of DNA Viruses

The genetic material of DNA viruses can be in 2 basic forms:

- single-stranded DNA (+ or – strand)
- double-stranded DNA

A 3rd type involves producing viral DNA from an RNA template:

\[
\text{DNA } \xrightarrow{\text{RNA polymerase}} \text{RNA } \xrightarrow{\text{Reverse Transcriptase}} \text{DNA}
\]
Life Cycle of a DNA Virus

A. The host cell membrane fuses with the viral envelope, thereby permitting entry of the nucleocapsid to the cytoplasm.

B. The viral capsid is uncoated by cell enzymes and the DNA of the viral genome enters the cell’s nucleus.

C. New viral DNA is synthesized in the nucleus resulting in new genomes. Transcription produces mRNAs that are translated on cytoplasmic ribosomes.

D. Capsid proteins are synthesized in the cell’s cytoplasm.

E. Capsid proteins enter the nucleus and combine with viral genomes to form new nucleocapsids.

F. The viruses bud through the nuclear envelope, endomembranes, or plasma membrane to acquire their envelope before the mature virions are released.
Latent Viral Infections

Some DNA viruses integrate the viral DNA into the chromosomal DNA of the host cell:

- analogous to the lysogeny of bacteriophage \( \lambda \)
- the inserted viral DNA is considered a provirus which can remain dormant or latent indefinitely

Other DNA viruses leave behind a dormant, extrachromosomal piece of DNA – an episome.

Latent viruses can become active due to various conditions of stress in the cell and re-enter the standard lytic viral life cycle.
## Examples of DNA Viruses

### Table 13.2 Families of Human Viruses

<table>
<thead>
<tr>
<th>Family</th>
<th>Strand Type</th>
<th>Representative Genera (Diseases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA Viruses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poxviridae</td>
<td>Double</td>
<td><em>Orthopoxivirus</em> (smallpox)</td>
</tr>
<tr>
<td>Herpesviridae</td>
<td>Double</td>
<td><em>Simplexvirus</em>, Herpes type 1 (fever blisters, respiratory infections), Herpes type 2 (genital infections); <em>Varicellovirus</em> (chickenpox); <em>Lymphocryptovirus</em>, Epstein-Barr virus (infectious mononucleosis, Burkitt’s lymphoma); <em>Cytomegalovirus</em> (birth defects); <em>Roseolavirus</em> (roseola)</td>
</tr>
<tr>
<td>Papillomaviridae</td>
<td>Double</td>
<td><em>Papillomavirus</em> (benign tumors, warts, cervical and penile cancers)</td>
</tr>
<tr>
<td>Polyomaviridae</td>
<td>Double</td>
<td><em>Polyomavirus</em> (progressive multifocal leukoencephalopathy)</td>
</tr>
<tr>
<td>Adenoviridae</td>
<td>Double</td>
<td><em>Mastadenovirus</em> (conjunctivitis, respiratory infections)</td>
</tr>
<tr>
<td>Hepadnaviridae</td>
<td>Partial single and partial double</td>
<td><em>Orthohepadnavirus</em> (hepatitis B)</td>
</tr>
<tr>
<td>Parvoviridae</td>
<td>Single</td>
<td><em>Erythrovirus</em> (erythema infectiosum)</td>
</tr>
</tbody>
</table>

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C. RNA Viruses
Types of RNA Viruses

The genetic material of RNA viruses comes in 3 basic forms:

• double-stranded RNA
• + strand RNA (single coding or sense strand)
• - strand RNA (single noncoding or template strand)

RNA virus life cycles (except retroviruses) can be carried out exclusively in the cell cytosol.

A 4th type are the retroviruses which copy ssRNA into DNA (reverse transcriptase) after uncoating:

• can be single-stranded (+ or -) or double-stranded
Unique Features of RNA Viruses

Copying of viral RNA poses a unique problem:

1) viral RNA must be converted to DNA which can then be transcribed to produce more RNA

OR

2) viral RNA must somehow serve as a template to produce more RNA

In reality, RNA viruses use both approaches:

• retroviruses use reverse transcriptase to make DNA from an RNA template

• all other RNA viruses use RNA-dependent RNA transcriptase to transcribe from an RNA template
RNA +strand Viruses

Copying of Genetic Material

- original + strand is used directly to express (translate)
  \textit{RNA-dependent RNA transcriptase}

- the enzyme may also be prepackaged in the viral capsid

- \textit{RNA-dependent RNA transcriptase} uses + strand as a template to produce – strands which are used to produce more + strands
RNA –strand Viruses

Copying of Genetic Material

- *RNA-dependent RNA transcriptase* already present in the capsid proceeds to produce + strands following uncoating.

- *RNA-dependent RNA transcriptase* uses + strand as a template to produce – strands (which are also used to produce more + strands to be translated).
dsRNA Viruses

Copying of Genetic Material

- original + strand is used directly to express (translate) *RNA-dependent RNA transcriptase*
- the enzyme may also be prepackaged in the viral capsid
- *RNA-dependent RNA transcriptase* uses + strand as a template to produce – strands and vice versa
Unique Features of Retroviruses

Viral RNA must first be copied to DNA which is then inserted into host DNA:

- requires the enzyme reverse transcriptase which is present in the viral capsid
- produces DNA from an RNA template

Are frequently lysogenic (i.e., latent):

- DNA copy of viral RNA that is inserted into host chromosomal DNA can remain “quiet” indefinitely
- viral genes can become active due to various “cellular stressors”
Life Cycle of a Retrovirus

- viral RNA is copied into DNA by reverse transcriptase
- once provirus is generated, synthesis, assembly & release occur as with other viruses
# Examples of RNA Viruses

## Table 13.2 Families of Human Viruses (continued)

<table>
<thead>
<tr>
<th>Family</th>
<th>Strand Type</th>
<th>Representative Genera (Diseases)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RNA Viruses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Picornaviridae</td>
<td>Single, +&lt;sup&gt;a&lt;/sup&gt;</td>
<td><em>Enterovirus</em> (polio); <em>Hepatovirus</em> (hepatitis A); <em>Rhinovirus</em> (common cold)</td>
</tr>
<tr>
<td>Caliciviridae</td>
<td>Single, +</td>
<td><em>Norovirus</em> (gastroenteritis)</td>
</tr>
<tr>
<td>Astroviridae</td>
<td>Single, +</td>
<td><em>Astrovirus</em> (gastroenteritis)</td>
</tr>
<tr>
<td>Hepeviridae</td>
<td>Single, +</td>
<td><em>Hepevirus</em> (hepatitis E)</td>
</tr>
<tr>
<td>Togaviridae</td>
<td>Single, +</td>
<td><em>Alphavirus</em> (encephalitis); <em>Rubivirus</em> (rubella)</td>
</tr>
<tr>
<td>Flaviviridae</td>
<td>Single, +</td>
<td><em>Flavivirus</em> (yellow fever); <em>Japanese encephalitis virus</em> (encephalitis); <em>Hepacivirus</em> (hepatitis C)</td>
</tr>
<tr>
<td>Coronaviridae</td>
<td>Single, +</td>
<td><em>Coronavirus</em> (common cold, severe acute respiratory syndrome)</td>
</tr>
<tr>
<td>Retroviridae</td>
<td>Single, +, segmented</td>
<td><em>Human T cell leukemia virus</em> (leukemia); <em>Lentivirus</em> (AIDS)</td>
</tr>
<tr>
<td>Orthomyxoviridae</td>
<td>Single, −&lt;sup&gt;b&lt;/sup&gt;, segmented</td>
<td><em>Influenzavirus</em> (flu)</td>
</tr>
<tr>
<td>Paramyxoviridae</td>
<td>Single, −</td>
<td><em>Paramyxovirus</em> (common cold, respiratory infections); <em>Pneumovirus</em> (pneumonia, common cold); <em>Morbillivirus</em> (measles); <em>Rubulavirus</em> (mumps)</td>
</tr>
<tr>
<td>Rhabdoviridae</td>
<td>Single, −</td>
<td><em>Lyssavirus</em> (rabies)</td>
</tr>
<tr>
<td>Bunyaviridae</td>
<td>Single, −, segmented</td>
<td><em>Bunyavirus</em> (California encephalitis virus); <em>Hantavirus</em> (pneumonia)</td>
</tr>
<tr>
<td>Filoviridae</td>
<td>Single, −</td>
<td><em>Filovirus</em> (Ebola hemorrhagic fever); <em>Marburg virus</em> (hemorrhagic fever)</td>
</tr>
<tr>
<td>Arenaviridae</td>
<td>Single, −, segmented</td>
<td><em>Lassavirus</em> (hemorrhagic fever)</td>
</tr>
<tr>
<td>Reoviridae</td>
<td>Double, segmented</td>
<td><em>Orbivirus</em> (encephalitis); <em>Rotavirus</em> (diarrhea); <em>Coltivirus</em> (Colorado tick fever)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Positive-sense (+RNA) is equivalent to mRNA; i.e., it instructs ribosomes in protein translations.

<sup>b</sup>Negative-sense (−RNA) is complementary to mRNA; it cannot be directly translated.

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5. Prions

Chapter Reading – pp. 407-408
What is a Prion?

Prions are unique, infectious proteins that cause spongiform encephalopathies:

- e.g., “mad cow” disease, kuru, Creutzfeldt-Jacob disease (CJD), scrapie

- involves NO nucleic acid (DNA or RNA)

- involves aberrant folding of a normal protein (PrP) expressed in neural tissue

  - normal = PrP\(^C\); aberrant & infectious = PrP\(^{SC}\)
  - PrP\(^{SC}\) is extremely stable, forms insoluble aggregates
  - consumed PrP\(^{SC}\) induces host PrP\(^C\) to become PrP\(^{SC}\)
Model of Prion based Illness

1. PrP\textsubscript{C} produced by cells is secreted to the cell surface.
2. PrP\textsubscript{Sc} may be acquired or produced by an altered PrP\textsubscript{C} gene.
3. PrP\textsubscript{Sc} reacts with PrP\textsubscript{C} on the cell surface.
4. PrP\textsubscript{Sc} converts the PrP\textsubscript{C} to PrP\textsubscript{Sc}.
5. The new PrP\textsubscript{Sc} converts more PrP\textsubscript{C}.
6. The new PrP\textsubscript{Sc} is taken in by endocytosis.
7. PrP\textsubscript{Sc} accumulates in endosomes.
8. PrP\textsubscript{Sc} continues to accumulate as the endosome contents are transferred to lysosomes. The result is cell death.

- Contact between PrP\textsubscript{C} & PrP\textsubscript{Sc} induces PrP\textsubscript{Sc}
- Insoluble PrP\textsubscript{Sc} accumulates, kills cells
Prion Pathology

Normal vs Aberrant Prp

(a) Cellular PrP

(b) Prion PrP

Spongiform Encephalopathy

Vacuole
Key Terms for Chapter 13

- capsid, capsomere, envelope, spikes
- polyhedral, helical, enveloped, complex viruses
- assembly, cell lysis, budding, virion
- bacteriophage, plaques, lytic vs lysogenic
- prophage, lysogen, lysozyme, specialized transduction
- uncoating, latent, episome, prion
- RNA-dependent RNA transcriptase
- reverse transcriptase, retrovirus

Relevant Chapter Questions
MC: 1-10   M: 1-10   SA: 1-9