CHAPTER 12
THE STRUCTURE AND INFECTION CYCLE
OF VIRUSES

WHY IS THIS IMPORTANT?

- More than 80% of infectious diseases are caused by viruses.
- As a health professional, most infectious disease that you see will be caused by viruses.
- It is important that you have an understanding of viral structure and the infection cycle cause by viruses.

WHY IS THIS IMPORTANT?

- Viruses are defined as obligate intracellular parasites - they cannot live outside a cellular host.
- Viruses have only one goal – a productive infection.
OVERVIEW

VIRUSES

- Viruses can infect:
  - Bacteria (called bacteriophages)
  - Plant cells
  - Animal cells (human cells included in this group).
- They are specific for a certain cell type.
- They are obligate intracellular parasites.

VIRUS STRUCTURE

- An intact viral particle is called a virion.
- Viral nucleic acid is surrounded by a protein coat called a capsid.
  - Each capsid is made up of capsomeres.
Types of Virus

- There are two types of viruses:
  - DNA viruses
  - RNA viruses

Virus Classification

The Virion

- Virion structure must overcome two basic problems:
  - It must be strong enough to protect the viral nucleic acid.
  - It must be able to release the viral nucleic acid for infection.
- Viruses have specific nomenclature.
THE VIRION

<table>
<thead>
<tr>
<th>Term</th>
<th>Synonym</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Capsomere</td>
<td></td>
<td>Protein molecule forming capsid</td>
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<tr>
<td>Capsid</td>
<td>Protein coat</td>
<td>Protein shell surrounding nucleic acid</td>
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<tr>
<td>Nucleocapsid</td>
<td></td>
<td>Nucleic acid plus capsid</td>
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<tr>
<td>Envelope</td>
<td>Viral membrane</td>
<td>Phospholipid bilayer with embedded glycoproteins surrounding capsid in enveloped virus</td>
</tr>
<tr>
<td>Virion</td>
<td>Viral particle</td>
<td>Complete infectious viral structure: nucleic acid plus capsid for non-enveloped virus; nucleic acid plus capsid plus envelope for enveloped virus</td>
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</tbody>
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THE CAPSID

- It is built from identical protein units called capsomeres.
- Capsomeres bond together and give the capsid structural symmetry.
- Viruses possess either helical or icosahedral symmetry.

HELICAL VIRUSES

- There are two shapes of helical viruses:
  - Rod – straight and relatively rigid
  - Filamentous – flexible, curved, or coiled.
HELICAL VIRUSES

ICOSAHEDRAL VIRUSES

Their shape is derived from 20 triangular faces that make up the capsid.
- The capsid suggest insert ‘has’ 12 points of symmetry.
- There are two types of icosahedral viruses:
  - Simple
  - Complex

VIRAL ENVELOPES

Many viruses that infect humans and other animals are enveloped.
- Envelopes form when viral glycoproteins and oligosaccharides associate with the plasma membrane of the host cell.
- All envelopes have a phospholipid bilayer.
ENVELOPE GLYCOPROTEINS

- They are firmly embedded in the envelope bilayer.
  - This is facilitated by domains of host membrane proteins called spanners.
- They can form spikes or other structures on the outside of the virion.
  - These can be used to attach to a host cell.

GENOMIC PACKAGING

- Genome packaging has an important role in the infection.
- Viral genomes are packaged in one of three ways:
  - Directly in the capsid
  - Enclosed in special proteins
  - Enclosed in proteins from the host cell

VIRAL ENVELOPES

- Envelopes vary in:
  - Size
  - Morphology
  - Complexity
  - Composition
THE INFECTION CYCLE

- The infection cycle was first worked out in bacteriophages (bacterial viruses).
- Animal virus infections can be either lytic or lysogenic.

LYTIC VERSUS LYSOGENIC INFECTION

- In a lytic infection, the host cells fills with virions and bursts.
  - The result is cell death.
- Lysogenic infections are also known as latent infections.
  - The viral genome becomes incorporated into the host cell’s DNA.
    - It can remain this way for an extended period.
    - The host cell lives.
LYTIC INFECTION

- For animal viruses, there are six steps in lytic infection:
  - Attachment
  - Penetration
  - Uncoating
  - Biosynthesis
  - Maturation
  - Release

VIRION ATTACHMENT

- Attachment occurs when a virion binds to specific receptors on a host cell.
- Some viruses require a co-receptor to attach.
  - Without the co-receptor, there is no infection.

WHEN VIRUS MEETS HOST CELL

- Viral-host cell interactions occur through random collisions.
  - The number of viruses is extremely important.
  - Lytic infections produce the maximum number of virions.
WHEN VIRUS MEETS HOST CELL

- The host cell must be permissive for the infection to succeed.
  - It must contain all of the components required to make new virions.
- Viral infections at the apical cell surface usually cause acute infection.
- Viral infection at the basolateral cell surface can become systemic.

WHEN VIRUS MEETS HOST CELL

- Many viruses attach only to specific areas of the host cell membrane - lipid rafts.
- Lipid rafts are rich in cholesterol, fatty acids, and other lipids.
  - They are more reliable for stable attachment.
  - They are also the site of release for many viruses.

HOST CELL RECEPTOR BINDING

- Many different host cell molecules can be used as viral receptors.
  - Some viruses use more than one type.
  - Some receptors are shared by many viruses.
  - Receptors can determine host range of virus.
- Virus-receptor binding is high affinity.
  - There are conformational interactions.
TYPES OF RECEPTOR BINDING

- Non-enveloped viruses
  - Binding takes place between viral capsid and receptor.
- Enveloped viruses
  - Binding takes place between viral envelope proteins and receptor.

PENETRATION & UNCOATING

- Once attached, the virus must gain entry to the host cell.
- It must also uncoat or remove the capsid.
- Uncoating can occur in three places:
  - At the plasma membrane
  - In the cytoplasm
  - At the nuclear membrane
PENETRATION & UNCOATING:

Non-enveloped Viruses

- Use receptor mediated endocytosis to gain entry into the host cell
  - Virus is enclosed in a vesicle – the early endosome
  - Early endosomes fuse with or become late endosomes.
  - Late endosomes fuse with the lysosome where uncoating begins.
  - Some viruses form a pore in the host membrane.

PENETRATION & UNCOATING:

Enveloped Viruses

- Envelope fuses with the host cell membrane
  - Fusion is mediated by specialized fusion proteins of the host cell.
  - It results in the formation of a fusion pore – a large opening allowing viral entry.
  - For some viruses, fusion requires the presence of co-receptor molecules.
**CYTOPLASMIC TRANSPORT OF VIRAL COMPONENTS**

- Viral infection requires compartmentalization.
  - Viral genomes, capsids, and other viral proteins are synthesized in specific locations in the host cell.
  - Newly synthesized viral components are moved to other locations for assembly of viral particles.

- Viral components are moved in vesicles, using host cell microtubules.
  - Specialized host cell proteins are sometimes used.

**TRANSPORT OF THE VIRAL GENOME TO THE NUCLEUS**

- DNA viruses use routine host cell import pathways to cross the nuclear membrane.
  - The pathways form pores in the nuclear membrane.
TRANSPORT OF THE VIRAL GENOME TO THE NUCLEUS

- RNA viruses use reverse transcriptase to convert RNA to DNA.
  - Newly converted viral DNA is put into a pre-integration complex.
  - This moves into the host cell nucleus during mitosis when the nuclear membrane is broken down.

BIOSYNTHESIS

- Biosynthesis of new viral components can be complex.
- Viral genomes are either DNA or RNA.
  - Both can be single or double-stranded.

BIOSYNTHESIS: Double-stranded DNA Viruses

- Double-stranded DNA viruses use the same mechanisms as the host cell for biosynthesis.
  - One strand of viral DNA is transcribed into mRNA.
  - It uses either the host cell or viral RNA polymerase.
BIOSYNTHESIS: Double-stranded DNA Viruses

Viruses with dsDNA genome

- Viral strand is used as a template to make a complementary copy of DNA.
- This uses the host cell’s DNA polymerase.
- The complementary copy is transcribed into mRNA.
- It is also used to make new copies of the viral genome.

BIOSYNTHESIS: Single-stranded DNA Viruses

Viral strand is used as a template to make a complementary copy of DNA.
- This uses the host cell’s DNA polymerase.
- The complementary copy is transcribed into mRNA.
- It is also used to make new copies of the viral genome.
**BIOSYNTHESIS:**
**Replication of DNA Virus Genomes**

- The viral genome has the same configuration as host DNA.
- Replication requires:
  - The synthesis of at least one viral protein
  - The expression of several viral genes.

**BIOSYNTHESIS:**
**Replication of DNA Virus Genomes**

- Replication is performed by the host cell machinery.
- Latent DNA viruses require much less DNA replication.
- Host DNA synthesis is inhibited by the virus.
  - All polymerases and proteins concentrate on viral DNA synthesis.

**BIOSYNTHESIS:**
**Replication of DNA Virus Genomes**

- Specialized sites form in the host cell – replication compartments
  - They contain both DNA templates and host cell replication machinery.
  - They are essentially viral factories.
- Compartmentalization allows exponential viral replication.
BIOSYNTHESIS: Replication of Latent DNA Viruses

- Latent viruses do not kill host cells.
- The viral genome is inserted into a host chromosome.
- Maximum replication is not required.
  - A small number of viral genes are expressed.
  - A limited number of viral genomes are replicated.

BIOSYNTHESIS: DNA Virus Transcription

- Newly made viral DNA molecule is used as the template for transcription
  - Transcription is performed by the host cell’s RNA polymerase.
- Viral gene expression begins after DNA synthesis.
  - Genes are expressed in a specific order.

- Transcription with single-stranded DNA viruses is more complicated.
  - The single DNA strands must first be converted to double strands.
- Viral genes are transcribed at very high rates.
  - This maximizes the number of new viruses being produced.
**BIOSYNTHESIS: DNA Virus Transcription**

- Rapid transcription of viral DNA is regulated by host cell proteins.
- Transcription is coordinated with viral DNA synthesis.
- All host cell transcription and protein synthesis is shut down by the virus.

**BIOSYNTHESIS: RNA Viruses**

- Mechanisms of biosynthesis are more complicated than in DNA viruses.
- Host cells do not possess RNA-dependent polymerases.
  - They are required to make viral mRNA and replicate genomes.
  - Viruses must carry one.

**BIOSYNTHESIS: RNA Viruses**

- RNA viruses are classified using a (+) or (−) strand designation for their genomes
  - Double-stranded RNA viruses contain one (+) strand and one (−) strand.
  - Single-stranded RNA viruses are either:
    - (+) single-stranded – contain a (+) strand
    - (−) single-stranded – contain a (−) strand.
**BIOSYNTHESIS: RNA Viruses**

- Replication and transcription are based on:
  - Complementary base pairing
  - The use of templates

**BIOSYNTHESIS: Double-stranded RNA Viruses**

- Genomes contain one (+) strand and one (−) strand.
- During infection, the (−) strand is copied into messenger RNA.
  - This is done by a viral RNA polymerase.
  - The mRNA is used to produce viral proteins.
- Each of the strands is used as a template to make a new double-stranded genome.
**BIOSYNTHESIS:**

*(+) Single-stranded RNA Viruses*

- The *(+) strand is already mRNA.
  - It can be directly translated into viral proteins.
- Genome replication has 2 steps:
  - The *(+) strand is copied into *(−) template
  - The template is used to make more *(+) strands.

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**BIOSYNTHESIS:**

*(+) Single-stranded RNA Viruses*

![Diagram of RNA viruses with (+) ssRNA genome]

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**BIOSYNTHESIS:**

*(−) Single-stranded RNA Viruses*

- The *(−) strand cannot be used as mRNA
  - It must first be copied into a *(+) template strand.
  - This is done using a viral RNA polymerase.
- The new template strand is mRNA:
  - It is used to synthesis viral proteins.
  - It is also used to make new viral genomes.
BIOSYNTHESIS: (-) Single-stranded RNA Viruses

- Viruses with –ssRNA genome
- +RNA → mRNA → capsomer protein
- −RNA → −RNA

Retroviral Transcription & Integration

- Retroviruses are RNA viruses that contain the enzyme reverse transcriptase.
  - Reverse transcriptase converts RNA into DNA.
  - Converted viral DNA can be inserted into the host cell chromosome.
- Retroviruses cause latent infections.

Viral Control of Translation

- Viruses rely on host cell machinery for translation.
  - They often modify this machinery for their purposes.
- Host genes can inhibit RNA binding to ribosomes.
  - Viruses have developed ways to inactivate these genes.
MATURATION

- Involves the movement of newly made viral components to specific sites in the host cell.
- There are two steps in maturation:
  - Intracellular trafficking
  - Assembly

MATURATION: Intracellular Trafficking

- Some viral components are synthesized in the cytoplasm, and some in the nucleus.
- They are transported through the cell by host cell microtubules to assembly sites.
- Assembly sites depend on:
  - The type of genome (DNA or RNA)
  - The mechanism of genome replication
  - The presence or absence of an envelope.

MATURATION: Intracellular Trafficking

- Many enveloped viruses assemble near the host cell membrane
  - Others assemble near membrane bound organelles.
- Non-enveloped viruses assemble in the host cell nucleus.
MATURATION: Intracellular Trafficking

- Viral proteins travel from the assembly site to the cell membrane in vesicles.
- Viral genome transport depends on whether the virus has an envelope.
  - Enveloped viruses – genomes move to sites near the membrane
  - Non-enveloped viruses - genomes move to the host cell nucleus.

MATURATION: Intracellular Trafficking

ASSEMBLY

- All virions must complete a common set of assembly reactions.
- Non-enveloped viruses:
  - Formation of structural subunits for the capsid
  - Assembly of the capsid
  - Association of the viral genome within the capsid.
ASSEMBLY

- Enveloped viruses:
  - Formation of structural subunits for the capsid
  - Assembly of the capsid
  - Association of viral genome within the capsid
  - Assembly of viral envelope glycoproteins.

ASSEMBLY: Capsids

- Capsomeres are assembled first.
  - Assembly is different in DNA viruses and RNA viruses.
  - The number of capsomeres produced is always more than the number required.
    - This maximizes the chances of capsomeres finding each other.
  - Capsid assembly can be assisted by host chaperone proteins.

ASSEMBLY: Viral Genomes

- This is the most important part of assembly.
  - There are two mechanisms:
    - Concerted assembly – the virion is assembled while the viral genome is being synthesized
    - Sequential assembly – the viral genome is inserted into already assembled capsid.
RELEASE

- New virions can be released from the host cell in two ways:
  - Lysis
  - Budding

RELEASE

- Non-enveloped viruses use lysis.
  - This causes death of the host cell.
- Enveloped viruses use budding.
  - This allows the host cell to live for a while.
- In some viral infections, completed virions are non-infectious.
  - Viral enzymes convert them into an infectious form after release.
SPREAD OF VIRUSES

- Viruses can spread from cell to cell.
  - They can use tight junctions between cells.
  - They can also spread through the formation of syncytia.
    - They allow movement through the body without exposure to the immune system.

- Some viruses produce decoy virions.
  - These are empty capsids or non-infectious virions
  - They confuse and distract the host defenses.
  - Some viruses incorporate host proteins as a type of camouflage.

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