Chapter 13
Viral Genetics

Viral Diseases
- Measles
- Polio
- Hepatitis
- Chicken pox

Influenza: 1918 Epidemic
- 30-40 million deaths world-wide

Smallpox
- Eradicated in 1976
  - vaccinations ceased in 1980
  - at risk population?

Emerging Viruses
- Viruses that “jump” host
  - switch species
  - Ebola, SARS, bird flu, hantavirus
  - The Coming Plague by Laurie Garrett

A Sense of Size
- Comparing size
  - eukaryotic cell
  - bacterium
  - virus
What is a virus? Is it alive?

- DNA or RNA enclosed in a protein coat
- Viruses are not cells
- Extremely tiny
  - need an electron microscope to see
  - smaller than ribosomes
  - ~20–50 nm

1st discovered in plants (1800s)
- tobacco mosaic virus
- couldn’t filter out
- couldn’t reproduce on media like bacteria

Variation in Viruses

- Parasites
  - lack enzymes for metabolism
  - lack ribosomes for protein synthesis
  - need host “machinery”

Viruses are not cells

- Extremely tiny
  - need an electron microscope to see
  - smaller than ribosomes
  - ~20–50 nm

Variation in Viruses

- A package of genes in transit from one host cell to another

“A piece of bad news wrapped in protein”
  – Peter Medawar

Viral Genomes

- Viral nucleic acids
  - DNA
    - double-stranded
    - single-stranded
  - RNA
    - double-stranded
    - single-stranded
  - Linear or circular
    - smallest viruses have only 4 genes, while largest have several hundred

Viral Protein Coat

- Capsid
  - crystal-like protein shell
  - 1-2 types of proteins
  - many copies of same protein

Viral Envelope

- Lipid bilayer membranes cloaking viral capsid
  - envelopes are derived from host cell membrane
  - glycoproteins on surface

<table>
<thead>
<tr>
<th>Classes of Animal Viruses, Grouped by Type of Nucleic Acid</th>
<th>Complex/Double-stranded</th>
<th>Single-stranded</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>Complex</td>
<td>Double-stranded</td>
</tr>
<tr>
<td>RNA</td>
<td>Double-stranded</td>
<td>Single-stranded</td>
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Viral Envelope

- Lipid bilayer membranes cloaking viral capsid
  - envelopes are derived from host cell membrane
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HIV
Generalized Viral Lifecycle

- **Entry**
  - virus DNA/RNA enters host cell

- **Assimilation**
  - viral DNA/RNA takes over host
  - reprograms host cell to copy viral nucleic acid & build viral proteins

- **Self assembly**
  - nucleic acid molecules & capsomeres then self-assemble into viral particles
  - exit cell

Symptoms of Viral Infection

- **Link between infection & symptoms varies**
  - kills cells by lysis
  - cause infected cell to produce toxins
    - fever, aches, bleeding...
  - viral components may be toxic
    - envelope proteins

- **Damage?**
  - depends...
    - lung epithelium after the flu is repaired
    - nerve cell damage from polio is permanent

Viral Hosts

- **Host range**
  - most types of virus can infect & parasitize only a limited range of host cells
    - identify host cells via “lock & key” fit
    - between proteins on viral coat & receptors on host cell surface
  - broad host range
    - rabies = can infect all mammals
  - narrow host range
    - human cold virus = only cells lining upper respiratory tract of humans
    - HIV = binds only to specific white blood cells

Bacteriophages

- **Viruses that infect bacteria**
  - ex. phages that infect *E. coli*
  - lambda phage
  - 20-sided capsid head encloses DNA
  - protein tail attaches phage to host & injects phage DNA inside

Bacteriophage Lifecycles

- **Lytic**
  - reproduce virus in bacteria
  - release virus by rupturing bacterial host

- **Lysogenic**
  - integrate viral DNA into bacterial DNA
  - reproduce with bacteria

Lytic Lifecycle of Phages

1. The T4 phage uses its tail fibers to attach to the bacterial cell. The tail fiber enters the bacterial cell.
2. The phage injects its DNA into the cell.
3. The infected bacterial cell produces new phage particles. Phage assembly occurs in the bacterial cell.
4. The empty bacterial cell is lysed, releasing the phage particles that can infect other bacterial cells.
5. The new phages are released from the lysed bacterial cell.
6. The cycle repeats with new bacterial cells.
Lysogenic Lifecycle of Phages

Defense Against Viruses
- Bacteria have defenses against phages
  - bacterial mutants with receptors that are no longer recognized by a phage
    - natural selection favors these mutants
  - bacteria produce restriction enzymes
    - recognize & cut up foreign DNA
- It’s an escalating war!
  - natural selection favors phage mutants resistant to bacterial defenses

RNA Viruses
- Retroviruses
  - have to copy viral RNA into host DNA
    - enzyme = reverse transcriptase
    - RNA → DNA → mRNA
  - host’s RNA polymerase now transcribes viral DNA into viral mRNA
  - mRNA codes for viral components
  - host’s ribosomes produce new viral proteins

Retroviruses
- HIV
  - Human ImmunoDeficiency Virus
  - causes AIDS
    - Acquired ImmunoDeficiency Syndrome
  - opportunistic diseases
  - envelope with glycoproteins for binding to specific WBC
  - capsid containing 2 RNA strands & 2 copies of reverse transcriptase

HIV Infection
- HIV enters host cell
  - macrophage & CD4 WBCs
  - cell-surface receptor
  - reverse transcriptase synthesizes double stranded DNA from viral RNA
  - high mutation rate
- Transcription produces more copies of viral RNA
  - translated into viral proteins
  - proteins & vRNA self-assemble into virus particles
  - released from cell by “budding” or by lysis

HIV Treatments
- inhibit vRNA replication
  - AZT
    - thymine mimic
  - protease inhibitors
    - stops cleavage of polyprotein into capsid & enzyme proteins

RNA Viruses
- Retroviruses
- HIV
- HIV Infection
- HIV Treatments
Potential HIV treatments

- Block receptors
  - chemokines
  - bind to & block cell-surface receptors
    - 11% of Caucasians have mutant receptor allele
- Block vRNA replication
  - CAF replication factor

Cancer Viruses

- Viruses appear to cause certain human cancers
  - hepatitis B virus
    - linked to liver cancer
  - Epstein-Barr virus = infectious mono
    - linked to lymphoma
  - papilloma viruses
    - linked with cervical cancers
  - HTLV-1 retrovirus
    - linked to adult leukemia

Cancer Viruses

- Transform cells into cancer cells after integration of viral DNA into host DNA
  - carry oncogenes that trigger cancerous characteristics in cells
  - version of human gene that normally controls cell cycle or cell growth
- Most tumor viruses probably cause cancer only in combination with other mutagenic events

Prions

- Misfolded proteins
  - infectious
  - make plaques (clumps) & holes in brain as neurons die
- Creutzfeldt-Jakob disease
  - "mad cow" disease
- Proteinaceous infectious molecule

Protein as Information Molecule?!

- Prions challenge Central Dogma
  - transmit information to other proteins

Stanley Prusiner
UC School of Medicine
1982 | 1997