Viruses

Lectures 16 and 17

Learning Outcomes

- Characteristics of Viruses
- Viral Taxonomy
- Viral Structure
- Viral Replication
- Prions
- Vaccines
  - Chapter 18
Viruses

- First virus isolated 1935 Wendell Stanley
- Are NOT composed of cells
- Do NOT belong in ANY of DOMAINS of Life
- Dependent upon host structures for replication
  - Ribosomes, RNA polymerase, tRNA, amino acids
- 'Virus' derived from Greek root meaning poison

Characteristics of Viruses

- 1. Viruses contain genetic material
  - Either DNA or RNA never both
- 2. Protein coat = Virion
- 3. Multiply inside living cells
- 4. Cause the synthesis of structures for their own transfer
Host Range of Viruses

- Most viruses infect only specific types of cells in one host.
- Host range is determined by specific host attachment receptors.
- Polio
  - Narrow range
- Rabies
  - Broad host range

Bacteriophage Therapy?

- Phages specific to particular serotypes of bacteria.
  - Limited host range
- Cannot infect humans
- Beneficial bacteria not harmed
- Phage population will increase inside of patient
- Role in combating drug-resistant bacteria
Relative Sizes

- Sizes measured in nm (1000 nm in 1 um)
- Small
- Picornaviruses
- Polio 30nm
- Large
- Vaccinia 300nm
- Overlap size of smallest bacteria
  - Chlamydia
  - Rickettsia

Viral Proteins

- ‘Early Proteins’
  - Enzymes
    - DNA or RNA Polymerases
    - Protease
- ‘Late Proteins’ Structural Proteins
  - Capsid proteins
  - Spikes
- Antigenicity due to variations in structural proteins
  - Serotypes
  - Strains of influenza
- Antibodies bind to structural proteins
- **Components**
  - Lipoprotein derived from host cell plasma membrane
  - Viral proteins
- **Protein spikes**
  - Attach to host cell receptors for hormones
  - Glycoproteins
  - Influenza
  - Hemagglutinin
  - HIV
  - Gp 120
- **Less resistant than non-enveloped viruses**

- **Viral Envelope**

- **Virus Shapes**
  - Helical
  - Polyhedral
  - Enveloped
    - Spikes
    - Glycoproteins
  - Complex
    - Bacteriophages
  - All built from repeating protein units capsomeres
Viral Taxonomy

- NOT included in any Domain of life
- Lack cells (cell theory)
- However named according to rules to name organisms

- Family names end in -viridae
- Genus names end in -virus

- Viral species: A group of viruses sharing the same genetic information and ecological niche (host). Common names are used for species
- Subspecies are designated by a number

- Herpesviridae
- Herpesvirus
- Human herpes virus 1
- HHV 2,
- HHV 3

- Retroviridae
- Lentivirus
- Human Immunodeficiency Virus 1, HIV 2
Herpes Viruses

- Greek word herpein ("to creep")
- Many infections both latent and recurring
- HHV-1, HHV-2 - Herpes Simplex Viruses
  - Cold sores, genital herpes
- HHV-3 - Varicella-zoster
  - Chickenpox and shingles
- HHV-4 Epstein-Barr
  - Mononucleosis, Burkitt’s Lymphoma
- HHV-5 - Cytomegalovirus
- HHV-6, HHV-7 - Roseolovirus
- HHV-8 Kaposi’s Sarcoma

Culturing Viruses

- Viruses must be grown in living cells.
- Bacterial lawns
  - Bacterial colonies due to phages lysing bacteria
- Live animals
- Embryonated eggs
  - Vaccine development
- Animal cell cultures
- Primary cell lines
- Continuous cell lines
  - Cancers cells HeLa can be maintained indefinitely
Bacteriophages (Lytic Cycle)

- **Attachment**: Phage attaches by tail fibers to host cell
- **Penetration**: Phage lysozyme opens cell wall, tail sheath contracts to force tail core and DNA into cell
- **Biosynthesis**: Production of phage DNA and proteins
- **Maturation**: Assembly of phage particles
- **Release**: Phage lysozyme breaks cell wall

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The Lysogenic Cycle

1. Phage DNA (coated) enters host cell
2. Phage attaches to host cell and injects DNA
3. Bacterial chromosome
4. Phage DNA circularizes and enters lytic cycle or lysogenic cycle
5. Many cell divisions
6. Phage DNA integrates into the bacterial chromosome by recombination, becoming a prophage
7. New phage DNA and proteins are synthesized and assembled into viruses
8. Lysogenic cycle
9. Lysogenic bacterium reproduces normally
10. Lysogenic bacterium may excise from the bacterial chromosome by another recombination event, initiating a lytic cycle
Specialized Transduction

Prophage exists in galactose-using host (containing the gal gene).

1. Phage genome excises, carrying with it the adjacent gal gene from the host.
2. Phage matures and cell lyises, releasing phage carrying gal gene.
3. Phage infects a cell that cannot utilize galactose (lacking gal gene).
4. Along with the prophage, the bacterial gal gene becomes integrated into the new host's DNA.
5. Lysogenic cell can now metabolize galactose.

Prophage

Bacterial DNA

Galactose-positive donor cell

Galactose-positive recombinant cell

Galactose-negative recipient cell

Galactose-negative recombinant cell

Animal viruses

- Attachment: Viruses attaches to cell membrane receptor
- Penetration: By endocytosis or fusion
- Uncoating: By viral or host enzymes
- Biosynthesis: Production of nucleic acid and proteins
- Maturation: Nucleic acid and capsid proteins assemble
- Release: By budding (enveloped viruses) or rupture
Attachment, Penetration, and Uncoating

Figure 13.14

Replication of DNA Viruses

1. Virion attaches to host cell
2. Virion penetrates cell and its DNA is uncoated
3. Early transcription and translation; enzymes are synthesized
4. Late transcription; DNA is replicated
5. Late translation; capsid proteins are synthesized
6. Virions mature
7. Capsid proteins
8. Virions are released
9. Virions are released
10. Virus generates cell and its DNA is uncoated
11. Late transcription; enzymes are synthesized
12. Early transcription and translation; enzymes are synthesized
DNA Viruses

- Non-enveloped
  - Adenoviridae
    - Mastadenovirus
    - Respiratory diseases
  - Papovaviridae
    - Papillomavirus
    - Warts
    - Polyomavirus

- Enveloped
  - Herpesviridae
    - Simplexvirus (HHV-1 and 2)
    - Varicellovirus (HHV-3)
  - Hepadnaviridae
    - Hep B
  - Poxviridae
    - Pox viruses
    - Smallpox

* RNA or Sense Strand = mRNA

- Viral genome transcribed
  - "early proteins"
    - Enzymes for viral replication
    - RdRp
      - Synthesizes the strand
      - template for making new + strands
  - "late proteins"
    - capsid proteins
Single Strand RNA Virus

- + strand
  - Genome used directly as mRNA
    - can be translated immediately
      - e.g. Common Cold
- - strand
  - mRNA must be transcribed
    - from genome template
  - Must carry RNA dependent
    RNA polymerase enzyme
    - RdRp
  - Measles

- Strand RNA Viruses

- RNA dependent RNA Polymerase
- Uses - strand to make + strand
- + strand (mRNA) transcribed into viral proteins
Single Strand RNA Viruses

- Nonenveloped
  - Picornaviridae
    - Rhinovirus
    - Common cold
    - Poliovirus
    - Echovirus
    - Coxackie Virus
  - Caliciviridae
    - Norovirus
    - Stomach Flu

- Enveloped + strand
  - Togaviridae
    - Rubivirus - rubella
  - Flavivirus
    - Yellow fever

- Enveloped - strand
  - Rhabdoviridae
    - Rabies
  - Filoviridae
    - Ebola
  - Orthomyxoviridae
    - Influenza
    - Multiple segments of single stranded RNA

Retrovirus Replication

1. Retrovirus penetrates host cell.
2. Virion penetrates cell and its DNA is uncoated.
3. DNA of one of the host cell's chromosomes
4. Maternal intron is used to build off and create RNA as it buds out.
5. The new viral DNA is transported into the host cell's nucleus and integrated as a provirus. The provirus may divide independently with the host cell DNA.
6. Mature retrovirus leaves host cell, acquiring an envelope as it buds out.
Release of an enveloped virus by budding

- Activated oncogenes transform normal cells into cancerous cells.
- Transformed cells:
  - increased growth
  - loss of contact inhibition
  - tumor specific transplant antigens
  - T antigens.
- The genetic material of oncogenic viruses becomes integrated into the host cell’s DNA.
Oncogenic Viruses

- Oncogenic DNA Viruses
  - Herpesviridae
    - HHV-4, Burkitt's Lymphoma
    - HHV-8, Kaposi's sarcoma
  - Papillomaviridae
    - HPV 16, HPV 18
    - Cervical cancer
  - Hepadnaviridae
  - Hepatitis B, Liver cancer
- Oncogenic RNA Viruses
  - Flaviviridae
    - Hepatitis C, Liver cancer
  - Retroviridae
    - HTLV-1
    - Human T-Lymphotrophic Virus
    - Leukemia

Latent v Persistent Infections

- Latent Viral Infections
  - Virus remains in asymptomatic host cell for long periods
    - Cold sores, shingles
- Persistent Viral Infections
  - Disease processes occur over a long period, generally fatal
    - Subacute sclerosing panencephalitis (measles virus)
**Common Cold**

- + Single Strand RNA
- Binds to receptor on mucous membrane of nose
  - Lower temperatures 91°F
- Acute Infection
- High virulence 1 virus particle sufficient to cause infection
- Replication within 8 hours producing thousands of infectious particles
- Infection over before immune system able to produce antibodies
- Susceptible to re-infection

**Cytopathic Effects**

- Rhinovirus RNA possesses initiation sequence Rhinovirus protein disrupts normal cap-dependent initiation shutting down protein synthesis of cellular (capped) mRNA
- Ribosomes only synthesize viral proteins
- Cells die
Prions

- Infectious proteins
  - Inherited and transmissible by ingestion, transplant, & surgical instruments
- All are fatal
- Kuru
- Sheep scrapie,
- Creutzfeldt-Jakob disease
- Mad cow disease
  - Bovine Spongiform Encephalopathy
- Fatal familial insomnia

Figure 13.21

PrP

Endosome
Lysosome

PpE
PpE

PrPSc
The UK BSE Outbreak

- Bovine Spongiform Encephalopathy
  - 179,000 cases 1985-89
  - 4.4 million cattle culled
- Cows fed protein supplement containing Sheep spines infected with Scrapie prion
- New variant CJD
- Creutzfeldt-Jakob disease
  - 165 cases in UK
  - Still no evidence for link

Vaccines - Applications of Immunology

- Introduce viral antigen (or bacterial, or toxin) into body
- Muscular
- Oral
- Nasal
- Stimulate formation of antibodies
- Cell mediated immunity
Vaccine History

- Variolation Inoculation of smallpox into vein (18th century)
- 1% mortality
- Inoculation of cowpox (Vaccina) into skin
  - Edward Jenner
- Vaccine named after Jenner (or Blossom, the vaca)

Vaccination

- Prevention better (and cheaper) than cure
- Herd Immunity
- Epidemics
- Eradication
  - Smallpox
  - Polio?
  - Measles?
Attenuated Whole-Antigen Vaccines

- Living, but weakened virus
  - Vaccines require refrigeration
- Lifelong immunity
- 95% effective
- Living virus replicates in body
- Polio - Sabin

Inactivated Whole-Agent Vaccines

- Microbes killed by formalin or phenol
  - Protein structure not altered
- Polio - Salk
- Rabies
- Hepatitis A
- Flu
- Cholera
- Does NOT provide as long lived immunity
- Boosters required
Subunit Vaccines

- Subunit Vaccines
  - Only use antigenic fragments
  - proteins
  - Recombinant bacteria produce antigens of pathogen
- Hepatitis B
  - Yeast synthesizes viral protein

Toxoids

- Toxoids
- Inactivated toxins
- Vaccines → Antibodies to toxin
- Dtap
- Diphtheria
- Tetanus
- Acellular Pertussis
Conjugated Vaccines

- Improves immune response to a poorly antigenic substance such as polysaccharide capsules
  - T-independent antigens
- Capsule fragment + protein such as tetanus toxoid
  - Pneumococcal Conjugate Vaccine
  - Hib vaccine

Development of New Vaccines

- Fear of Litigation
- Allergic reaction
  - Flu vaccines and eggs
- High cost but low Profit
- Culturing Live Viruses
- Recombinant Vaccines
- Edible Vaccines...?
Coxsackie Virus

- **Group A**
  - infect the skin and mucous membranes
  - Hand, Foot and Mouth Disease
- **Group B**
  - infect the heart, pleura, pancreas, and liver
  - myocarditis, pericarditis
  - pericardial effusion
  - Linked with development of autoimmune conditions
  - Type 1 diabetes following Pancreatitis
  - Sjogren’s Syndrome
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<th>Vaccine</th>
<th>Recommendations</th>
<th>Frequency</th>
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<td>Inactivated viruses,</td>
<td>For influenza A, including children over 6 months. Adults over 50 years,</td>
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<td>influenza and</td>
<td>Healthy adults aged 65 years and older, and pregnant women.</td>
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<td>live attenuated</td>
<td>Parents should consider annual influenza vaccine for children 6 months and</td>
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<td>viruses, annual dose</td>
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<td>For infants aged 12 months. Adults 48 years and older, and pregnant women.</td>
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<td>Rubella</td>
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<td>For infants aged 12 months, and for women of childbearing age who are not</td>
<td>Annual</td>
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