Introduction to Virology

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Landmarks in Virology

• Introduction of concept of ‘filterable agents’ for plant pathogens (Mayer, Ivanofsky, Beijerinck in late 1880’s)
• First filterable agent from animals described – foot and mouth disease virus (Loeffler and Frosch in 1898)
• First human filterable agent described - yellow fever virus (Reed in 1901)
• Linkage of viruses with cancer (Ellerman, Bang 1908; Rous 1911)
Landmarks in Virology

- Description of bacteriophages (Twort and D’Herelle in 1915)
- Visualization of viruses by EM and x-ray crystallography (1939, 1941)
- Development of tissue culture systems (Sanford, Enders, Gay, Eagle 1948-1955); growth of poliovirus in culture
- Discovery of many agents; explosion in molecular biology (past 45-50 years)

‘Virus’

Latin for ‘slimy liquid’ or ‘poison’
Definitions

• Virus particle or virion
  - Infectious agent composed of nucleic acid (RNA or DNA), a protein shell (capsid) and, in some cases, a lipid envelope

• Capsid
  - Protein coat that surrounds the viral nucleic acid
  - Composed of repeating subunits called capsomeres
  - Have either icosahedral or helical symmetry

• Nucleocapsid
  - Complete protein-nucleic acid complex

Definitions

• Satellite or defective viruses
  - Viruses which require a second (helper) virus for replication
    » Example: hepatitis delta virus requires hepatitis B

• Viroids
  - Small, autonomously replicating molecules
  - Single stranded circular RNA, 240-375 residues in length
  - Plant pathogens

• Prions
  - Not viruses
  - Infectious protein molecules responsible for transmissible and familial spongiform encephalopathies
    » e.g., Creutzfeldt-Jakob disease, bovine spongiform encephalopathy (vCJD in humans)
  - Pathogenic prion protein PrPSc formed from normal human protein, PrPSc, through post-translational processing
Virus Classification

• Older based on
  - Host, target organ or vector

• Modern based on
  - Type of viral nucleic acid
    » RNA or DNA
    » Single stranded (SS) or double stranded (DS)
    » Replication strategy
  - Capsid symmetry
    » Icosahedral or helical
  - Presence or absence of lipid envelope
• Governed by International Committee on Taxonomy of Viruses

Capsid Symmetry

Icosahedral

Helical
Virion Morphology

Virus Classification

Table 18-1 Classification of Viruses

<table>
<thead>
<tr>
<th>Family</th>
<th>Example</th>
<th>Type of Nucleic Acid</th>
<th>Generic Size (Diameter of Virus)</th>
<th>Envelope</th>
<th>Capsid Symmetry</th>
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<tr>
<td>DNA-containing Viruses</td>
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<tr>
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<td>SS + RNA</td>
<td>7-8-9</td>
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<td>9-15</td>
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<td>Roweiridae</td>
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<tr>
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<td>SS + RNA</td>
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<td>Yes</td>
<td>H</td>
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<tr>
<td>Poxviridae</td>
<td>Herring virus</td>
<td>2 ssDNA segments</td>
<td>16-18</td>
<td>Yes</td>
<td>H</td>
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<td>Influenzaviridae</td>
<td>Human immunodeficiency virus type 1</td>
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<td>H</td>
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<tr>
<td>RNA-containing Viruses</td>
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<td>Hepadnaviridae</td>
<td>Hepatitis B virus</td>
<td>Circular B DNA with 6 ssDNA</td>
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<td>Poxviridae</td>
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</tr>
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From Principles and Practice of Infectious Diseases
Coronavirus

Family: Coronaviridae
(+) SS RNA, enveloped, helical

Paramyxovirus

Family: Paramyxoviridae
(-) SS RNA, enveloped, helical
Measles

- Measles virus is a member of the Paramyxoviridae family, genus Morbillivirus
  - Primates are the only natural hosts
- Classically a childhood illness, spread by the respiratory route
  - Primary and secondary viremia
- Incubation period is 10-14 days, followed by 2-3 day prodrome of fever, cough, coryza and conjunctivitis
  - Koplik spots in pharynx may appear
- Maculopapular rash follows
  - Temporally associated with beginning of viral clearance
  - Starts on face and behind ears; moves centrifugally
  - Typically, clinical improvement as rash resolves

Measles

- Complications
  - Pneumonia (giant cell)
  - Encephalitis
  - Subacute sclerosing panencephalitis (SSPE)
    - Rare in vaccine era, but seen years after measles acquired at an early age
    - High titers of anti-measles Ab
  - Ocular
  - Atypical measles
    - Seen in persons exposed to natural measles virus following vaccination with killed vaccine years earlier
- Mortality can be high in malnourished and immuno-compromised populations
- Despite presence of an effective vaccine, 30 million cases reported worldwide in 2003 with 530,000 deaths
  - >95% in countries with per capita income <$1000/yr
  - Seen in US by importation
- Vaccine preventable
  - Live attenuated vaccine
Measles

Rash

Koplik spots

Giant cell pneumonia

Influenza Virus

Family: Orthomyxoviridae

(-) SS RNA segmented, enveloped, helical
Ebola Virus

Family: Filoviridae
(-) SS RNA, enveloped, helical

Rotavirus

Double Capsid  Inner Capsid

Family: Reoviridae
DS RNA segmented, nonenveloped, icosahedral
Retroviruses

Family: Retroviridae
2 identical (+) RNA strands, enveloped, icosahedral capsid, helical nucleoprotein

Hepatitis B Virus

Family: Hepadnaviridae
Circular DS DNA with SS portions, enveloped, icosahedral
**Hepatitis B Virus**

Family: Hepadnaviridae  
Circular DS DNA with SS portions,  
enveloped, icosahedral

**Parvovirus**

Family: Parvoviridae  
SS DNA, nonenveloped, icosahedral
B19 Parvovirus: Erythema Infectiosum

From Clinical Virology

Papillomavirus

Family: Papovaviridae
Circular DS DNA, nonenveloped, icosahedral
Papillomavirus

Family: Papovaviridae
Circular DS DNA, nonenveloped, icosahedral

Cutaneous Wart

From Clinical Virology
Cervical Wart

From Clinical Virology
Plate 27.8

Genital Warts

From Clinical Virology
Plate 8.1
Adenovirus

Family: Adenoviridae
Linear DS DNA, nonenveloped, icosahedral

Adenovirus

Family: Adenoviridae
Linear DS DNA, nonenveloped, icosahedral
Adenovirus Conjunctivitis

From *Clinical Virology*

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Adenovirus Tonsillitis

From *Clinical Virology*
Herpesvirus

Family: Herpesviridae
Linear DS DNA, enveloped, icosahedral

Herpes Simplex Virus Keratitis

From Clinical Virology
Cytomegalovirus Retinitis

From Clinical Virology

Poxvirus

Family: Poxviridae
Linear DS DNA, enveloped, complex
Smallpox

Viral Pathogenesis: Elements of Virus-Host Interaction

- Viral strain
- Inoculum size
- Route of exposure
- Susceptibility of host
  - Is there pre-existent immunity from past exposure or vaccination?
  - Host genetic factors
- Immune status and age of host
Viral Pathogenesis: Net Result of Virus-Host Interaction

- No infection
- Abortive infection with limited viral replication
- Asymptomatic infection
- Symptomatic infection
- Persistent, latent or self-limited infection
  - Depending upon the agent and immune competence of host
- Influenced by availability of effective prophylaxis or therapy

Pathogenetic Steps in Human Viral Infection

- Virus may enter through skin, mucous membranes, respiratory tract, GI tract, via transfusion, needle-stick, or maternal-fetal transmission
- Local replication at site of inoculation
  - Certain agents may cause pathology here
- Neurotropic agents may travel along nerve routes or reach CNS by viremic spread
Pathogenetic Steps in Human Viral Infection

• For many agents, there is replication in regional lymph nodes with subsequent viremia and spread to target organs
  - Some travel free in plasma (e.g., picornaviruses); some are cell associated (e.g., cytomegalovirus)
• Replication in target organs may lead to local damage and further viremia
• Non-specific and virus-specific host immune responses come into play to downregulate viral replication

Immune Response to Viral Infections

• Non-specific immunity
  - Phagocytic cells (neutrophils and monocyte-macrophages)
  - Cytokines (e.g., interferons) and chemokines
  - Natural killer cells
  - Other 'antiviral' factors
• Specific immunity
  - Antigen specific B and T cell responses
    » Antibodies
    » Cytotoxic T cells
    » Antibody dependent cellular cytotoxicity
• Immunopathologic injury
Viral Persistence

- Viruses may cause chronic, persistent infection in the face of an immune response
  - HIV, hepatitis B, hepatitis C

- Immune compromise may result in persistent infection where latency or elimination may have otherwise occurred
  - Herpesviruses, papillomaviruses, rubella virus

Viral Persistence

- Some viruses cause latent infection
- Latency is characterized by a quiescent or minimally transcriptionally active viral genome with potential periods of reactivation
  - Herpesviruses
  - Human retroviruses
  - Human papillomaviruses

- Viruses which exhibit latency may also exhibit chronic, persistent infection in the setting of immune compromise
Viral Persistence

• Mechanisms
  - Persistent/chronic infection
    » Antigenic variation to escape antibody or CTL responses
    » Downregulation of class I major histocompatibility antigens
    » Modulation of apoptosis
    » Privileged sites
  - Latency
    » Decreased viral antigen expression and presentation to the immune system

• Sites
  - Nervous system
    » Herpes simplex virus, varicella-zoster virus
    » JC virus
    » Measles virus
  - Liver
    » Hepatitis B virus, hepatitis C virus, hepatitis D virus
  - Leukocytes
    » HIV, cytomegalovirus, Epstein-Barr virus
  - Epithelial tissue
    » Papillomaviruses
Oncogenesis: Associations

- Epstein-Barr virus with lymphoma, nasopharyngeal carcinoma and leiomyosarcoma
- Herpesvirus 8 with Kaposi’s sarcoma and body cavity B-cell lymphoma
- Hepatitis B and C viruses with hepatocellular carcinoma
- Human papillomavirus with cervical cancer and anogenital carcinoma
- HIV with Kaposi’s sarcoma and lymphoma via immunosuppression

Diagnosis of Viral Infections

- Clinical suspicion
  - Is syndrome diagnostic of a specific entity?
  - Is viral disease in the differential diagnosis of a presenting syndrome?
- Knowledge of appropriate specimen(s) to send
  - Blood
  - Body fluids
  - Lesion scraping
  - Tissue
  - Proper transport is essential
Diagnosis of Viral Infections

- Isolation of virus in tissue culture, animals, embryonated eggs
- Antigen detection in body fluids, blood, lesion scrapings, or tissue
- Nucleic acid detection in body fluids, blood or tissues
- Antibody detection
  - Presence of IgM or 4-fold rise in IgG titer
- Tissue biopsy for light microscopy supplemented by antigen and/or nucleic acid detection
- Electron microscopy of body fluids or tissues

Viral Infections: Prevention and Therapy

- Vaccines
  - One of the most significant advances in human health
    » Eradication of smallpox is prime example
  - Effective vaccines exist for polio, mumps, measles, rubella, influenza, hepatitis A, hepatitis B, varicella-zoster, rabies, adenovirus, Japanese B encephalitis, yellow fever, smallpox
- Immune globulin for prevention or amelioration of clinical disease
  - Varicella-zoster immune globulin, rabies immune globulin, cytomegalovirus immune globulin, respiratory syncytial virus immune globulin (and monoclonal Ab), immune serum globulin for hepatitis A
Viral Infections: Prevention and Therapy

• Blood screening
  - HIV, hepatitis B, hepatitis C, CMV (in certain settings)
• Safe sexual practices
  - HIV, hepatitis B, HSV, and human papillomavirus infections
• Specific antiviral therapy
  - Herpes simplex virus, varicella-zoster virus, cytomegalovirus, HIV, influenza virus, respiratory syncytial virus, hepatitis B and hepatitis C