Pathogenesis of viral infection

Lecturer
Dr Ashraf Khasawneh
Department of Biomedical Sciences
Viral epidemiology

• **Endemic:** Disease present at fairly low but constant level
• **Epidemic:** Infection greater than usually found in a population
• **Pandemic:** Infections that are spread worldwide
• **Infectivity:** The frequency with which an infection is transmitted when contact between a virus and host occurs
• **Disease index:** # persons develop disease/ total infected
• **Virulence:** # fatal cases/ total # of cases
• **Incidence:** # of new cases within a specific period of time %
• **Prevalence:** # of cases of a disease that are present in a particular population at a given time
What does a pathogen have to do?

- Infect (infest) a host
- Reproduce (replicate) itself
- Ensure that its progeny are transmitted to another host
Virus route of entry

1. Horizontal: (person to person)
   a) **Inhalation** - via the respiratory tract ex. RSV, MMR, VZV, Rhinovirus
   b) **Ingestion** - via the gastrointestinal tract ex. Hep A, Rota, Astroviruses, Caliciviruses
   c) **Inoculation** - through skin abrasions; mucous membranes (e.g. sexual transmission); transfusion; injections (e.g. by doctors or via shared syringes in drug abuse); transplants

2. Vertical : i.e. from mother to fetus
   a) **Transplacental** ex. CMV, rubella, HIV
   b) **Delivery** ex. Hep B, Hep C, HSV, HIV, HPV
   c) **Breast feeding** ex. CMV, Hep B, HIV

3. Zoonotic (animal to human)
   a) **Animal bite** ex. Rabies
   b) **Insect bite** ex. Dengue, West Nile
   c) **Animal excreta** ex. Hanta, Arena
Sites of virus entry

- Eyes (conjunctiva)
- Mouth
- Respiratory tract: ciliated epithelium, mucus secretion, lower temperature
- Alimentary canal: gastric acid, bile salts
- Skin: abrasion
- Arthropod vectors
- Urogenital tract
- Anus
## Terminology

- **Incubation period**: Time between exposure and first symptom

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incubation Period</th>
<th>Disease</th>
<th>Incubation Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>1-2d</td>
<td>Chickenpox</td>
<td>13-17d</td>
</tr>
<tr>
<td>Common cold</td>
<td>1-3d</td>
<td>Mumps</td>
<td>16-20d</td>
</tr>
<tr>
<td>Bronchiolitis, croup</td>
<td>3-5d</td>
<td>Rubella</td>
<td>17-20d</td>
</tr>
<tr>
<td>Acute respiratory disease</td>
<td>5-7d</td>
<td>Mononucleosis</td>
<td>30-50d</td>
</tr>
<tr>
<td>Dengue</td>
<td>5-8d</td>
<td>Hepatitis A</td>
<td>15-40d</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>5-8d</td>
<td>Hepatitis B</td>
<td>50-150d</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>6-12d</td>
<td>Rabies</td>
<td>30-100d</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>5-20d</td>
<td>Papilloma</td>
<td>50-150d</td>
</tr>
<tr>
<td>Measles</td>
<td>9-12d</td>
<td>HIV</td>
<td>1-10y</td>
</tr>
<tr>
<td>Measles</td>
<td>9-12d</td>
<td>HIV</td>
<td>1-10y</td>
</tr>
</tbody>
</table>
Terminology

- **Communicability**: Ability of virus to shed into secretions
- **Localized infection**: infection limited to site of entry
- **Disseminated infection**: spread throughout the body
- **Primary viremia**: site of entry > regional LN > blood
- **Secondary viremia**: site of entry > regional LN > blood > organs (liver, spleen) > blood
Having gained entry to a potential host, the virus must initiate an infection by entering a susceptible cell. This frequently determines whether the infection will remain localized at the site of entry or spread to become a systemic infection.
Secondary Replication

• Occurs in systemic infections when a virus reaches other tissues in which it is capable of replication, e.g. Poliovirus (gut epithelium - neurons in brain & spinal cord) or Lentiviruses (macrophages - CNS + many other tissues). If a virus can be prevented from reaching tissues where secondary replication can occur, generally no disease results.
## Localized Infections:

<table>
<thead>
<tr>
<th>Virus:</th>
<th>Primary Replication:</th>
<th>Secondary Replication:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinoviruses</td>
<td>U.R.T.</td>
<td></td>
</tr>
<tr>
<td>Rotaviruses</td>
<td>Intestinal epithelium</td>
<td></td>
</tr>
<tr>
<td>Papillomaviruses</td>
<td>Epidermis</td>
<td></td>
</tr>
</tbody>
</table>

## Systemic Infections:

<table>
<thead>
<tr>
<th>Virus:</th>
<th>Primary Replication:</th>
<th>Secondary Replication:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteroviruses</td>
<td>Intestinal epithelium</td>
<td>Lymphoid tissues, C.N.S.</td>
</tr>
<tr>
<td>Herpesviruses</td>
<td>Oropharynx or G.U.tract</td>
<td>Lymphoid cells, C.N.S.</td>
</tr>
</tbody>
</table>
Spread Throughout the Host

• Apart from direct cell-cell contact, there are 2 main mechanisms for spread throughout the host:
  • via the bloodstream
  • via the nervous system
via the bloodstream

- Virus may get into the bloodstream by direct inoculation - e.g. Arthropod vectors, blood transfusion or I.V. drug abuse. The virus may travel free in the plasma (Togaviruses, Enteroviruses), or in association with red cells (Orbiviruses), platelets (HSV), lymphocytes (EBV, CMV) or monocytes (Lentiviruses). Primary viraemia usually proceeds and is necessary for spread to the blood stream, followed by more generalized, higher titre secondary viraemia as the virus reaches other target tissues or replicates directly in blood cells.
via the nervous system

• spread to nervous system is preceded by primary viraemia. In some cases, spread occurs directly by contact with neurons at the primary site of infection, in other cases via the bloodstream. Once in peripheral nerves, the virus can spread to the CNS by axonal transport along neurons (classic - HSV). Viruses can cross synaptic junctions since these frequently contain virus receptors, allowing the virus to jump from one cell to another
Virulence and cytopathogenicity

• **Virulence**: the ability of the virus to cause disease in infected cell

• **Persistent infection**
  – Latent infection, lysogeny
  – Chronic infection

• **Permissive cells** allow production of virions and/or transformation

• **Virulent viruses** Kill target cell and cause disease (productive response)

• **Nonpermissive cells** permits cell transformation only

• **Abortive infection** no virus replication, early viral proteins cause cell death

• **Cytopathic effect**
Cytopathic effects- virus-induced damage to cells

1. Changes in size & shape
2. Cytoplasmic inclusion bodies
3. Nuclear inclusion bodies
4. Cells fuse to form multinucleated cells
5. Cell lysis
6. Alter DNA
7. Transform cells into cancerous cells
8. Virokines and viroreceptors: DNA viruses; cell proliferate and avoid host defenses
Cytopathic changes in cells

- Normal cell
- Giant cell
- Multiple nuclei
- Inclusion bodies
<table>
<thead>
<tr>
<th>Virus</th>
<th>Response in Animal Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox virus</td>
<td>Cells round up; inclusions appear in cytoplasm</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Cells fuse to form multinucleated giant cells; nuclear inclusions</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Clumping of cells; nuclear inclusions</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>Cell lysis; no inclusions</td>
</tr>
<tr>
<td>Reovirus</td>
<td>Cell enlargement; vacuoles and inclusions in cytoplasm</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Cells round up; no inclusions</td>
</tr>
<tr>
<td>Rabies virus</td>
<td>No change in cell shape; cytoplasmic inclusions (Negri bodies)</td>
</tr>
<tr>
<td>HIV</td>
<td>Giant cells with numerous nuclei (multinucleate)</td>
</tr>
</tbody>
</table>
Patterns of viral infection

• Inapparent infection (Subclinical infection).
• Apparent infection:
  • Acute infection
  • Persistent Infection
    • Chronic infections
    • Latent Infection
  • Slow virus infections
Patterns of viral infection

Acute followed by clearing

Chronic Infection

Acute followed by persistent infection and virus overproduction

Slow chronic infection

Acute infection
- Rhinovirus
- Rotavirus
- Influenza virus

Persistent infection
- Lymphocytic choriomeningitis virus

Latent, reactivating infection
- Herpes simplex virus

Slow virus infection
- Measles virus SSPE
- Human immunodeficiency virus
Chronic Infection

- Virus can be continuously detected; mild or no clinical symptoms may be evident.
Latent infection

The Virus persists in an occult, or cryptic, from most of the time. There will be intermittent flare-ups of clinical disease, Infectious virus can be recovered during flare-ups. Latent virus infections typically persist for the entire life of the host.
Slow virus infection

• A prolonged incubation period, lasting months or years, during which virus continues to multiply. Clinical symptoms are usually not evident during the long incubation period.
Overall fate of the cell

• The cell dies in **cytocidal** infections this may be **acute** (when infection is brief and self-limiting) or **chronic** (drawn out, only a few cells infected while the rest proliferate) - Cytocidal effect

• The cell lives in **persistent** infections this may be **productive** or **nonproductive** (refers to whether or not virions are produced) or it may alternate between the two by way of **latency** and **reactivation** - Steady state infection
• **Transformation**-Integrated infection (Viruses and Tumor)
  – RNA tumor viruses usually transform cells to a malignant phenotype by integrating their own genetic material into the cellular genome and may also produce infectious progeny.
  – Retroviruses:
    • Acute transforming viruses: \( v-src \) oncogene mimic cellular genes (proto-oncogene)
    • Insertional mutagenesis: inappropriate expression of a proto-oncogene adjacent to integrated viral genome
    • Transactivating factors: *tax* gene in HTLV-1; *turns on cellular genes causing cellular proliferation*
  – DNA tumor virus infections are often cytocidal; thus transformation is associated with abortive or restrictive infections in which few viral genes are expressed. The persistence of at least part of the viral genome within the cell is required for cell transformation. This is accompanied by the continual expression from a number of viral genes.
  – P53: regulates the cell cycle; functions as a tumor suppressor that is involved in preventing cancer. HPV
  – pRb: prevent excessive cell growth by inhibiting cell cycle progression until a cell is ready to divide. HPV

• **Apoptosis**
  – P53: initiate apoptosis, programmed cell death, if DNA damage proves to be irreparable
<table>
<thead>
<tr>
<th>Type</th>
<th>Virus production</th>
<th>Fate of cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortive</td>
<td>-</td>
<td>No effect</td>
</tr>
<tr>
<td>Cytolytic</td>
<td>+</td>
<td>Death</td>
</tr>
<tr>
<td>Persistent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Productive</td>
<td>+</td>
<td>Senescence</td>
</tr>
<tr>
<td>Latent</td>
<td>-</td>
<td>No effect</td>
</tr>
<tr>
<td>Transforming</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA viruses</td>
<td>-</td>
<td>Immortalization</td>
</tr>
<tr>
<td>RNA viruses</td>
<td>+</td>
<td>Immortalization</td>
</tr>
</tbody>
</table>
# Mechanisms of viral cytopathogenesis

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Viruses/Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of cellular protein synthesis</td>
<td>Polioviruses, HSV, poxviruses, togaviruses</td>
</tr>
<tr>
<td>Inhibition and degradation of cellular DNA</td>
<td>herpesviruses</td>
</tr>
<tr>
<td>Alteration of cell membrane structure</td>
<td>All enveloped viruses</td>
</tr>
<tr>
<td>Glycoprotein insertion</td>
<td>HSV, VZ virus, HIV</td>
</tr>
<tr>
<td>Syncytia formation</td>
<td>HSV, HIV, RSV</td>
</tr>
<tr>
<td>Disruption of cytoskeleton permeability</td>
<td>Togaviruses, herpesviruses</td>
</tr>
<tr>
<td>Inclusion bodies</td>
<td>Rabies</td>
</tr>
<tr>
<td>Toxicity of Virion components</td>
<td>Adenovirus fibers</td>
</tr>
</tbody>
</table>
Possible consequences to a cell that is infected by a virus

• **Lytic infections**: Result in the destruction of the host cell; are caused by virulent viruses, which inherently bring about the death of the cells that they infect.

• **Persistent infections**: Infections that occur over relatively long periods of time, where the release of the viral particles may be slow and the host cell may not be lysed.

• **Latent infections**: Delay between the infection by the virus and the appearance of symptoms.

• **Transformation**: Some animal viruses have the potential to change a cell from a normal cell into a tumor cell which grows without restraint.
The diagram illustrates the process of viral transformation leading to tumor cell division. It shows the following stages:

1. **Adsorption**: The virus attaches to the cell.
2. **Penetration**: The virus enters the cell.
3. **Multiplication**: The virus replicates within the cell.
4. **Death of cell and release of virus**: The infected cell eventually dies, releasing the replicated virus.
5. **Transformation of normal cells to tumor cells**: The released virus can transform normal cells into tumor cells.

The diagram also highlights different types of infections:

- **Lytic infection**: The cell dies quickly upon viral replication.
- **Persistent infection**: The virus replicates slowly without causing cell death.
- **Latent infection**: The virus remains inactive within the cell, waiting to be reactivated.

These processes are crucial in understanding the mechanisms of cancer development and the role of viruses in tumor formation.