L12: Viral Pathogenesis I

Most infections do not have any consequence:

- Many particles do not find a living cell to infect
- Many particles are destroyed or inactivated as they enter the host
- Many infections never go further than one or two cells at the site of infection

If you do get infected, many infections are inapparent (asymptomatic). There are no symptoms, but immune defences are activated (eg. antibodies made). We can use this serology to detect inapparent infections - The virus may still be replicating and transmitted even in asymptomatic infection, so this is important.

To cause infection, the virus must:

- Enter body
- Multiply and spread
- Target the appropriate organ
    - Eg. Hepatitis - Liver

To be maintained in nature, viruses must either be:

- Shed into the environment
- Taken up by an arthropod vector or needle
- Passed congenitally

Viral replication can be:

- Local (confined to the organ of entry)
- Systemic (involving many organs).

After initial acute infection, the course of infection is determined largely by the **immune response** of the host. You encounter passive barriers, then you have the innate immunity and the adaptive immune response. **This will either cause clearance or persistence.**

Tropism is the anatomical localisation of infection. Eg. Norovirus has tropism for the gut. This is initially determined by the receptor specificity of the virus.

Routes of Entry

Routes of entry are limited due to the physical barrier – skin.
Entry points include the mouth, respiratory tract, alimentary tract, urogenital tract, conjunctiva, insect bites, wounds etc.

Most viruses enter via the epithelial cells of the mucosal layer because the epidermis of the skin is covered by drying cells covered with keratin, which provides a hostile environment. Sweat also decreases infection.

Viruses in many different families, with different structure, have evolved to use the same mode of entry.

The Respiratory Tract

- **Most common site of entry**
- Through transmission of infected nasal secretions or aerosol inhalation
- Droplet size determines initial site of virus deposition
    - If >10uM, adheres to nasal cavity (prevents subsequent infection)
    - If 5-10uM, limited to airways
    - <5uM, limited to alveoli of lower resp tract
- Barriers to infection:
    - Mucus, cilia, temp gradient, IgA
        - Mucous is not found in the alveoli sacs. This site is protected by alveolar macrophages
    - Temp:
        - In URT - 31-32C
            - Rhinovirus only replicates here – is confined to URT
        - In LRT - 37C

Viruses attach to specific receptors on epithelial cells and can remain localised or spread further to underlying tissues.

Ciliated cells move material throughout the resp tract.
Epithelial cells line the mucosal layer.
Mucosal layer is facilitated by goblet cells which make the mucous
Basement membrane is a thick lining which virus need to invade to get to underlining tissues.

In the URT, passive defence systems including mucous and ciliated cells.
Deeper in alveoli, macrophages perform surveillance and can clear infections in the lung.

Systemic Respiratory Infections

Mumps

- Spreads from site of replication
- Primary replication in **epithelial cells** of URT
- Sialic acid promotes uptake and entry
- Infects all organs
    - Even CNS
- Mild meningitis common (10-20% cases)
    - Encephalitis uncommon
- Salivary glands swell
    - Virus infects salivary glands
    - Macrophages and immune response infiltrate, causing swelling

Measles

- Infects resp tract then spreads
- Primary replication in **epithelial cells** of URT
- CD150 and CD46 are receptors for entry.
- Infects **local macrophages, lymphocytes, and D cells**
    - Drains to LN

    - Enters circulation
    - Amplified in the lymphoid tissue
- Then returns to epithelial cells in cell and mouth
- Highly contagious
- Downregulates CD46
    - Causes immunosuppression
- Can delete envelope protein and transmit only with nucleocapsid so can avoid the immune system (SSPE)

The Alimentary Tract

Ingested viruses can either be swallowed or infect the oropharynx, and then get carried elsewhere.

Barriers to infection:

- Sequestration in intestinal contents
    - Constant movement of contents can allow contact with receptor, though
- Mucus
- Stomach acid
- Intestinal alkalinity
    - Denatures proteins
- Proteolytic enzymes
    - Secreted by pancreas
- Lipolytic activity of bile
- IgA
- Scavenging macrophages

Viruses that infect the intestinal tract are normally acid and bile resistant and *do not have an envelope.*

- Some enveloped viruses, such as coronaviruses, are protected when ingested in milk or food so cause enteric infection

Some viruses cause diarrhoea, due to local infection. Others do not cause disease in the intestinal tract but instead spread there to cause systemic infection.

If viruses do not have receptors for epithelial cells, they need to enter via a breach in the epithelial surface. Eg. HIV and Hep B can be sexually transmitted through abrasions in the rectal route

Entry via the GI tract may involve:

- Local infection
    - Rotavirus, coronavirus, adenovirus
- Invasion to produce systemic infection
    - Gain access via the alimentary tract then spread
        - Due to invasion of tissues underlying the mucosal layer
    - Enteroviruses, Hep A

The virus survival depends on:

- **Acid stability**
  - Protein shell is resistant
- Resistance to **bile salts**
  - Norovirus needs bile salts for infection
- Inactivation by **proteolytic enzymes**
  - Poliovirus is activated by proteolytic enzymes
  - Rhinoviruses are inactivated by proteolytic enzymes.

The small intestine is a selectively permeable barrier, with polarised epithelial cells which are in direct contact with both the outside world AND the immune system and the nervous system.

Enterocytes are interspersed with Tuft cells (norovirus infection) and M cells, which deliver material from the gut lumen to immune cells in the Peyer's Patches. This is a surveillance mechanism. Many viruses can utilise this mechanism to be passed through the M cell into the underlying cells to initiate infection. The virus can be transcytosed through M cells.

Local vs Systemic spread

Many viruses multiply in epithelial cells at the site of entry and produce a spreading infection and then shed into the exterior directly. Failure to spread to deeper tissues leads to transmission back through the resp tract.

- Respiratory infections – Influenza, rhinoviruses and RSV
- GI infections – rotaviruses
- Dermatologic infections – papillomaviruses (HPV)

To undergo systemic spread - Polarised infection of epithelial cells and spread can also occur.
Viral budding is targeted to **apical or basal surfaces** of the polarised cells by embedded motifs in the surface glycoproteins.

Viraemia

Viraemia is the presence of infectious virus particles in the blood. It can be free in the blood or contained within infected cells such as lymphocytes.

Two types:

- **Active viraemia**
  - **Produced by replication**
    - **In epithelial cells**
  - Then newly made virions released in the blood
- **Passive viraemia**
  - **Straight introduction without replication**
  - Eg. Injection by a needle or mosquito at site of entry

Passive, Primary and Secondary Viraemia

- Initial input of passive viraemia through injection/bite
- Virus exits blood because it infects epithelial cells.
- Gets released from these, causing primary viraemia.
- Will go into secondary LN Tissues (liver and spleen) and amplify
- Released again, causing secondary viraemia.
    - Cleared by Ab response etc

Viruses may be free in plasma

- Produced by infected vascular endothelium or
- Released in large amounts from, liver and spleen.
- Can be neutralised and removed by antibodies and macrophages over 1-2 weeks.
    - Disadvantage for virus – **can be recognised by immune system**

Viruses may be cell-associated

- Can persist for long periods in latency
    - Advantage as it **Avoid CTL attack**
    - **Protected from Ab** (the virus is IC)
        - Ab can't access virus
- Eg. Measles, Dengue – spread by monocytes
- Eg. HIV – spread in CD4 T cells

Viraemia Process: Poxvirus

- Skin invasion
- Multiplication in epithelia of skin
- Virus drains to regional LNs
- Multiplies here
- Goes back into blood (Primary)
- Travels to liver and spleen
- Multiplies to high levels, causing necrosis.
- Released back into the blood (Secondary)
- Goes back to skin epithelia
- Causes focal infections.

Modes of Spread

Haematogenous Spread

Viruses can spread in the blood and lymphatics. Can facilitate dispersion and spread.

The capillary endothelial cells are barriers to entering the tissues, but viruses can overcome this:

- Some viruses can replicate in endothelial cells, then progeny is released into tissues
    - eg. Ebola

    - This can promote haemorrhaging.
- Some viruses can pass between the tight junctions
    - eg. Mumps can get through choroid plexus of brain.
- Some viruses cross to tissues in monocytes and lymphocytes as part of normal cell trafficking
    - eg. Dengue, HIV can pass within infected cells in capillary.
- Some viruses are transported across these cells by **transcytosis** to the underlying tissue.
    - Whole virus particle passes
    - They are not destroyed and doesn't infect those cells.

Neural spread

Viruses can spread via peripheral nerves, such as herpes, rabies and varicella.

- Uncoated NC is passively carried along axons or dendrites.
- Multiplication occurs in body of nerve
- Released progeny cross the synaptic junction
    - Enter the CNS.
    - Infection is hard to clear after this
- Viruses are protected from CD8 because nerve cells don't have MHC I molecules
- Other viruses enter the CNS directly from the blood stream.

Rabies

- Replicates at site of infection (bite) in myocytes
- Enters axons (they are unmyelinated)
- Travels towards nucleus (retrograde axoplasmic flow)
- Reaches spinal cord and travels to brain

Louis Pasteur found transmission is **very slow** (10-20mm/day). So, you can immunise people with antibodies **(passive immunisation)** to treat rabies infection with a vaccine.

- **Transport along nerves can be in a forward (anterograde) or backward direction (retrograde)**
- This can be from **site of infection** to other sites in the body (rabies, polio), or from **reservoir sites** to epithelium (herpes)
- **Motor proteins direct/carry vesicles along the axons -** NC is bound to the motor proteins to facilitate anterograde or retrograde movement.

Varicella-zoster

- Utilises **both hematogenous and neural spread.**
- Infects the conjunctiva and/or mucosa of the URT.
- Drains to the LN
    - Does primary replication
- Released into blood - primary viraemia
- Further replication in the liver and spleen (secondary LN)
- Released into blood - secondary viraemia