IMMUNE RESPONSE TO VIRAL INFECTION

Dr Mere Kende

MBBS, MMED (Path), MACTM, MAACB, MACRRM

Senior Lecturer: SMHS, UPNG
Outline

- Introduction to Immune system
  - Immune system
  - Examples of Virus infection

- Immune response to viral infection
  - Important elements controlling virus infection
  - Examples of influenza infection
  - Summary
Eterovirus (coxsackie, echo/rhinoviruses)
Influenza Viruses A & B

Symptoms of Influenza

Central
- Headache

Systemic
- Fever
  (usually high)

Muscular
- (Extreme) tiredness

Joints
- Aches

Nasopharynx
- Runny or stuffy nose
- Sore throat
- Aches

Respiratory
- Coughing

Gastric
- Vomiting
Foot & Mouth Disease (Coxsackie Virus)
Fifth disease/Erytherma Infectiosum (Parvovirus B19)

‘Slapped Cheek Sign’
Rotavirus

**DISEASE KILLED 78,000 KIDS IN 2014**

Around 8.53 lakh children less than one-year age will be given the rotavirus vaccine annually at 6, 10 and 14 weeks

- Rotavirus alone is responsible for up to 40% of all cases of severe diarrhoea in India
- Of the overall child mortality in India, diarrhoea is responsible for 10% deaths
- In 2014, about 78,000 children died due to rotavirus
- About 8.7 lakh children were hospitalised due to rotavirus in 2014

- Mexico recorded a 46% drop in diarrhoea-related deaths in under-5 children after rotavirus vaccine was introduced in 2007
- Brazil recorded 22% drop in deaths after the introduction of vaccine
Epstein-Barr Virus Infection/Mumps

The kiss of cancer

- Named after its discoverers, Epstein–Barr virus (EBV) was first isolated in 1964 from patients with hematologic pathology. It is a lymphocytic human herpesvirus that is carried, like some other pathogenic herpesviruses, by the majority of the world’s population as a persistent, latent contagious agent.
The tissues of the immune system

- A large collection of organs and tissues are involved in the immune system of animals.

- Some of these tissues create and or educate the immune system, bone marrow and thymus, while other parts are involved in fighting infections, lymph systems, lymph nodes, spleen and MALT.

- The thoracic duct collects liquid from the lymph system and returns it to the circulatory system at the left subclavian vein near the heart.

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Main symptoms of Infectious mononucleosis:

**Central**
- Fatigue
- Malaise
- Loss of appetite
- Headache

**Visual**
- Photophobia

**Tonsils**
- Reddening
- Swelling
- White patches

**Throat**
- Soreness
- Reddening

**Respiratory**
- Cough

**Systemic**
- Chills
- Fever
- Aches

**Lymph nodes**
- Swelling

**Spleen**
- Enlargement
- Abdominal pain

**Gastric**
- Nausea
Mosquito Transmitted Viruses

- Dengue
- Ross River Virus
- Bahmar Forest Virus
- Chikungunya Infection
- Zika Virus
# Hepatitis viruses

<table>
<thead>
<tr>
<th>Name of Virus</th>
<th>Viral genome</th>
<th>Transmission</th>
<th>Incubation period</th>
<th>Chronic Hepatitis</th>
<th>Cure?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A Virus (HAV)</td>
<td>ssRNA</td>
<td>Enteric</td>
<td>15-45 days</td>
<td>No.</td>
<td>No cure. Treatments usually tackle the symptoms.</td>
</tr>
<tr>
<td>Hepatitis B Virus (HBV)</td>
<td>dsDNA</td>
<td>Parental</td>
<td>45-160 days</td>
<td>Yes. 10% chance</td>
<td>No cure. Treatments usually tackle the symptoms.</td>
</tr>
<tr>
<td>Hepatitis C Virus (HCV)</td>
<td>ssRNA</td>
<td>Parental</td>
<td>15-150 days</td>
<td>Yes. &gt;50% chance</td>
<td>No cure. Treatments usually tackle the symptoms.</td>
</tr>
<tr>
<td>Hepatitis D Virus (HDV)</td>
<td>-ssRNA (-ve)</td>
<td>Parental</td>
<td>30-60 days</td>
<td>Yes. &lt;5% of coinfectious &gt;80% of superinfectious</td>
<td>No cure. Treatment: Alpha interferon for 12 months.</td>
</tr>
<tr>
<td>Hepatitis E Virus (HEV)</td>
<td>ssRNA</td>
<td>Enteric</td>
<td>15-60 days</td>
<td>No.</td>
<td>No cure. Treatments usually tackle the symptoms.</td>
</tr>
</tbody>
</table>
Herpes Simplex 1 & 2 (Mouth, lips, genitals)
Herpes Zoster / Shingles
Chicken Pox
Measles
HPV / Cervix Cancer

Human Papilloma Virus and Warts

Genital warts: Found on shaft of penis (male), vagina, vulva, cervix (female) and around anus
Portal of entry

- Respiratory Droplets
- Direct Contact
- Blood Transfusion/Needle Stick Injury
- Mosquito Bite
- Sexual Activity
- Mother to Child
Prevention

- Hand Washing
- Hygiene Practice
- Vaccination
- Masks
- Isolation from crowd
- No contact
Virus

- DNA versus RNA virus

- Need to survive so infect & multiply intracellular

- Virus has tropism/has preference to difference cells/tissues/organs

- Intracellular so immune cells must have method to detect them

- MHC I important for recognition on infection

- Can remain in tissues without recognition for months/years (HBV, HCV, HSV)
Barriers to Virus Infection

- Innate
- Physical/Chemical
- Non-specific Immune cells (NK, WBC, Complements, Acute Phase Proteins, CRP)
- Specific Immune Cells
Anatomical immunity.

- Parts of the body are designed to prevent the passage of unwanted microorganisms.

- Some examples of structures that inhibit the advance of pathogens include the skin, hair, blinking eyelids, nose hairs, cilia in the lungs and the peristaltic action of the digestive track.

http://www.microbiologytext.com INNATE/NON-SPECIFIC
### The Innate Immune System

<table>
<thead>
<tr>
<th>Defense</th>
<th>Mode of Antagonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical structures (skin, hair, blinking, nose hairs, cilia in the lungs and the peristaltic action of the digestive track)</td>
<td>Provide physical barriers or motion that sweeps microbes out of areas of the body</td>
</tr>
<tr>
<td>Tissue bactericidies</td>
<td>Many proteins and chemicals are created by the body that kill or inhibit the growth of microbes (FFAs, pH, protease)</td>
</tr>
<tr>
<td>Microbial antagonism</td>
<td>The normal flora of the body prevent pathogens from colonizing and causing disease. (competition)</td>
</tr>
<tr>
<td>Complement proteins</td>
<td>These proteins can be triggered by microbial secretions or by antibodies. They alert the immune system and can cause cell lysis. (non-specific)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>A reaction to tissue damage that involves a large collection of cells, proteins and chemicals.</td>
</tr>
<tr>
<td>Phagocytes</td>
<td>Cells that attack microorganisms, engulf them and kill them. They are a major defense of the body.</td>
</tr>
<tr>
<td>Natural killer cells</td>
<td>Cells that roam the body and attack cells coated in IgG.</td>
</tr>
<tr>
<td>Substance</td>
<td>Common sources</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Serum, saliva, sweat, tears</td>
</tr>
<tr>
<td>Basic proteins and polypeptides (histones, β-lysins and other cationic proteins, tissue polypeptides)</td>
<td>Serum or organized tissues</td>
</tr>
<tr>
<td>Lactoferrin and transferrin</td>
<td>Body secretions, serum, organized tissue spaces</td>
</tr>
<tr>
<td>Peroxidase</td>
<td>Saliva, tissues, cells (neutrophils)</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>Serum and mucosal surfaces</td>
</tr>
</tbody>
</table>
Phagocytes, Neutrophils, Macrophages and Monocytes

Phagocytes are the cellular sentries of the immune system, detecting, engulfing and killing pathogens in our bodies.

They also destroy dead or dying cells and cancerous cells.

http://www.microbiologytext.com
Killing Mechanisms of Phagocytes.

- The figure shows the many different techniques used by phagocytes to kill pathogens.
- Some require oxygen while others do not.

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Cytokines

- Interferons - destroy Viruses
Immune Cells are activated if they bypass non-Specific Barriers

- APCs
- Dendritic Cells
- Mucosal Epithelial Cells (M-cells)
- Antibody Bound Viruses
Organization of O-MALT

LUMEN

M-Cell

Follicle-associated epithelium

Dome region

Germinal Center

Parafollicular region

Lymphoid Follicle
Antigen Adherence to M-Cells

- Adherence favors endocytosis and transcytosis
- Adherent materials tend to evoke strong immune responses
- Wide variety of pathogens adhere to M-cells
- Mechanism of adherence is unclear
- Many commensal microorganisms avoid adherence to M-cells
Dendritic Cell.

- Are found in most tissues of the body, projecting their branches throughout the immediate area.
- Monitor foreign antigens that may exist.
- If an antigen is found, it is taken up by the dendritic cell and presented to the immune system.

http://www.microbiologytext.com
Dendrites

http://www.transferpoint.net/assets/images/macrophage.jpg
Different Antibody Types. There are five different antibodies classes that are formed in the cell.

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Antibody Agglutination.

- Antibodies have two identical variable regions that can interact with antigen. If the antibody binds to antigens on two separate microbes, it can cause them to stick together.

- As more antibody attacks the antigen, large clumps of antigen-antibody complexes form and this is called agglutination.

- Note in this figure the antibodies are drawn much larger than in reality for clarity.

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<table>
<thead>
<tr>
<th>Cytokine or Chemokine</th>
<th>Producing cell</th>
<th>Target cell</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin-1 (IL-1)</td>
<td>Macrophages, monocytes and B cells</td>
<td>T cells, B cells</td>
<td>Acts as a growth regulator of T cells and B cells. Induces other cells such as hepatocytes to produce proteins relevant to host defense. Serves as an endogenous pyrogen, which produces fever.</td>
</tr>
<tr>
<td>Interleukin-2 (IL-2)</td>
<td>T cells</td>
<td>T cells</td>
<td>Stimulates the proliferation of T cells and activates natural killer cells.</td>
</tr>
<tr>
<td>Interleukin-3 (IL-3)</td>
<td>Stem cells, Mast cells</td>
<td></td>
<td>Regulates the proliferation of stem cells and the differentiation of mast cells.</td>
</tr>
<tr>
<td>Interleukin-4 (IL-4)</td>
<td>T\textsubscript{H}2</td>
<td>B cells</td>
<td>B cell proliferation and enhanced antibody synthesis.</td>
</tr>
<tr>
<td>Interleukin-5 (IL-5)</td>
<td>T\textsubscript{H}2</td>
<td>B cells</td>
<td>B cell differentiation and IgA synthesis</td>
</tr>
<tr>
<td>Interleukin-6 (IL-6)</td>
<td>T\textsubscript{H}2, monocytes, macrophages</td>
<td>B cells, plasma cells, stem cells</td>
<td>B cell differentiation and antibody production. T cell activation, growth and differentiation. Has a major role in the mediation of the inflammatory and immune responses initiated by infection or injury.</td>
</tr>
<tr>
<td>CXCL-8</td>
<td>Many host cells</td>
<td>T cells, neutrophils, macrophages</td>
<td>Chemoattractant for neutrophils</td>
</tr>
<tr>
<td>Cytokine or Chemokine</td>
<td>Producing cell</td>
<td>Target cell</td>
<td>Effect</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-----------------------------------------------------</td>
<td>------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>α-Interferon (IFN-α)</td>
<td>Leucocytes, tissue cells</td>
<td>Tissue cells</td>
<td>Inhibition of viruses</td>
</tr>
<tr>
<td>γ-Interferon (IFN-γ)</td>
<td>T cells</td>
<td>Tissue cells, macrophages, natural killer cells</td>
<td>Inhibition of protein synthesis in virally infected cells. Activation of macrophages and natural killer cells. Stimulates IL-1, IL-2 and antibody production.</td>
</tr>
<tr>
<td>Tumor Necrosis Factor-α (TNF-α)</td>
<td>T cells</td>
<td>Tissue cells (tumors)</td>
<td>Kills cells, including tumor cells</td>
</tr>
<tr>
<td>Tumor Necrosis Factor-β (TNF-β)</td>
<td>T cells</td>
<td>Tissue cells (tumors)</td>
<td>Kills cells, including tumor cells</td>
</tr>
<tr>
<td>Colony Stimulating Factors (CSF)</td>
<td>T\textsubscript{H}1, macrophages</td>
<td>Phagocytes</td>
<td>Causes phagocytic white cells of all types to differentiate and divide.</td>
</tr>
<tr>
<td>Macrophage chemoattractant and activating factor (MCAF)</td>
<td>Monocytes, macrophages, fibroblasts (connective tissue cells) and keratinocytes (skin cells)</td>
<td>Macrophages, T cells</td>
<td>Attract and activate macrophages and T cells.</td>
</tr>
<tr>
<td>B cell growth factors</td>
<td>T cells</td>
<td>B cells</td>
<td>Multiplication of B cells</td>
</tr>
</tbody>
</table>
The T-Cell Receptor.

- The structure of the T cell receptor (TCR) is reminiscent of antibody structure.

- However, T cell receptors are found anchored in the membrane of T cells, while the majority of antibodies float free in various fluids of the body.

- (Left panel) a cartoon showing the constant and variable regions of the TCR. (Right panel) A molecular model of a TCR. (Source: L. Kjer-Nielsen, et al. 2003. Immunity 18:53–64)

http://www.microbiologytext.com
MHC Complex proteins are found on most cells of the body.

They function to display proteins to T cells.

MHC I molecules display proteins that originate in the cytoplasm of the displaying cell (endogenous).

A) A cartoon of the domains of an MHC I molecule. B) Top and side views showing the binding of an antigen (in this case, an influenza peptide) to mouse MHC I molecule. The anchor domain is not shown in the molecular model. (Source: R. Meijers, et al., 2005. J. Molec. Biol. 345:1099–1110)

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Viral Immune Response

- With intracellular parasites, viruses and some microorganisms, cytotoxic T cells are particularly important.

- After activation, cytotoxic T cells must destroy host cells to eliminate virus.

- Therefore must have ability to see infected from healthy cells
CMI and Viral Infection

- Cell-mediated Immunity is much more important and effective in curing viral infection

  - T-cell responses,
  - cytotoxic responses,
  - NK cell responses, and
  - antibody dependant cytotoxicity ADCC
Cytotoxic CD8 CELLS

- Recognise virus infected cells displaying MHC I – antigen complex via it’s TCR
- SOME VIRUSES DONOT ALLOW MHC I-ANTIGEN COMPLEX ON SURFACE- ESCAPE DETECTION
- Punch holes in infected cells (PREFORMED perforin)
- Create holes for movement of STORED granzymes, fluid, Electrolytes to kill infected cell,-speed up apoptosis
- Granulysin- lysis of outer membrane of infected cell
Immune response to (influenza) virus infection.

An immune defense against a viral infection is more dependent on T cells and less dependent on antibodies.

Figure 34–6

Activation of T cells requires interaction of T-cell receptors with an antigen (foreign protein) that is transported to the surface of the antigen-presenting cell by a major histocompatibility complex (MHC) protein. Cell-to-cell adhesion proteins enable the T cell to bind to the antigen-presenting cell long enough to become activated.
Cytotoxic T-cells

Virus, transplant, cancer

Perforins- punch holes in infected cells
Interferon- alpha & gamma

- Secreted by infected cells, T-cells & macrophages – inhibit viral replication, sends signal nearby cells to increase MHC I so T cells surveying can recognise infected cells
Antibodies

- Preformed can remove viruses before infecting cells
- Binds virus; neutralise, agglutinate, easy target for immune cells
- Antibody-virus complex—easy target for phagocytosis via Fc receptor
- Antibody-virus complex---activate complement (classical pathway, c1) —
  - opsonise promote phagocytosis, lysis complex to destroy virus infected cells, or attack membranes of certain types of viruses
Antibody Protection of the Host

Neutralization

- Antibody prevents bacterial adherence

Opsonization

- Antibody promotes phagocytosis

Complement activation

- Antibody activates complement, which enhances opsonization and lyses some bacteria

Figure 34–7

Regulation of the immune system, emphasizing a pivotal role of the helper T cells. MHC, major histocompatibility complex.
TH1

Cytotoxic T cell

IL-2 receptor

Activation of cytotoxic T cell

Viral epitope

Cytotoxins

Cell death

Class I MHC protein

Virus-infected cell

TH2

Helper T cell

IL-2

CD4

IL-2 receptor

Activation of B cell

IL-4 (BCGF)

IL-5 (BCDF)

B cell

IgM monomer

Differentiation

Plasma cell

Antibody

Source: Levinson W: Review of Medical Microbiology and Immunology, 10th Edition: http://www.accessmedicine.com
Example of Influenza Infection

- very contagious disease
- Easily spreads through respiratory droplets expelled (∼1m) by infected individuals.

- For this example, imagine that an influenza sufferer has just sneezed on their hand and then opened a door, contaminating the door handle. Another person touching the handle can picked up droplets containing 100,000,000 flu viruses and a subsequent touch can transfer 1,000,000 to the nasal or oral cavity.
Entry- respiratory droplets ----retro pharynx area.

Majority of viruses inactivated (low pH, normal flora & salivary/mucous secretions)

Few survive & enter epithelial cells by binding to sialic acid-containing proteins or lipids on the surface of throat epithelial cells (receptor-mediated endocytosis.) —(Tropism)

The virus genome is internalized and 8 Genomic fragments of influenza virus are released into the cell.

Up until this point, the immune system has no indication that anything is amiss (wrong).
New virus is synthesized, repeatedly→ multiply

Some of these proteins are degraded by host cell machinery and the unique peptide fragments are transported into the endoplasmic reticulum, where they combine with newly synthesized MHC I molecules. (viral antigen processing)

The MHC I molecules loaded with foreign viral antigens now find their way to the surface of the cell (antigen presentation)

The infected cell also begins to produce and secrete α-interferon.

IFN signals invasion of virus --------- induces neighboring cells to produce compounds that interfere with viral replication making further infection more difficult. (cytokine paracrine signalling)
Some virally infected cells begin to release flu virus particles into the surrounding tissues—**Invasion & local**—*hematogenous spread.* (viraemia)

Death viral particles & cytokines & macrophages secretions → **inflammation.**
RESULTS: Symptoms of viraemia & inflammation

- (redness, soreness and swelling in the back of the throat & fever)

- Mucous secretion from the intensifying inflammation begins to cause a **runny nose and coughing**.

- INF & interleukin 1 release---------→ aches & fever
Control of Infection

- Inhibition of further viral replication (INF)
- Production of specific CD8, CD4, b-cells
- Synthesis of antibodies - further destruction of virus
- Control of viremia & infection by CD8, antibodies, phagocytosis, IFN
- Resolution of symptoms
- Activation of memory cells (no repeat infection/infection mild)
Free virus in the body is eliminated by the action of antibodies and phagocytes and the activated \( T_c \) cells destroy any virally infected cells.

As the load of virus present in the body decreases, T suppressor cells help the immune response abate.

After infection, subsequent attack by this strain of influenza virus is prevented by the action of T and B memory cells.
Summary Viral Infection

- **Steps:**
  - (1) influenza virus enters the cell
  - and begins to replicate (2)
  - Viral proteins fill the cytoplasm (3)
  - Most go on to form influenza virus and escape (4).
  - The presence of viral proteins in the cytoplasm also causes the production of α-IFN (5) effect on neighboring cells

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Some viral proteins are degraded and end up being displayed in MHC I molecules.

(6). Passing Tc cells (Th1) will test the MHC I molecule presenting foreign antigen and a fraction will be activated by it.
Activated $T_c$ cells are directed to differentiate into cytotoxic T cells by $T_H^1$ cells (7).

Activated cytotoxic T cells then attack other virally infected cells displaying viral antigens in the MHC I molecules that the T cells react to (8).

Viral antigens are also presented to B cells producing antibodies in a similar fashion to that Bacterial antigens.

These antibodies attack free virus, agglutinating it and making it available for phagocytosis (9).

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Influenza virus is a good example to study because it illustrates many of the salient points of viral infection and is also an important human pathogen.

However, remember that the specific response of the immune system is dependent upon the particular pathogen.

Many of the mechanisms that we describe here come into play in other viral infections, but the exact response is always unique to the particular viral agent.
Memory cells..IMMUNITY

- Some activated lymphocytes become memory cells (T/B-cells)
- Over population of specific clone of cells than original
- Subsequent reaction to infection is fast
- Primary exposure — slow, less sustained Ig production
- Secondary exposure - fast, more potent & sustained Ig production

Note: Concept of repeated injection on immunization

Guyton. Text Book of Medical Physiology; 11th
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