Lecture 27 – Infections Disease II
F. Evasion Mechanisms by Viruses:

**Antigenic Drift:**
- HIV
- Flu (seasonal)

**Antigenic Shift:** Flu Virus:
- A/Fujian/411/2002 (H3N2)
- Neuraminidase → Viral release
- Hemagglutinin → Viral entry

**Latency state:**
- Herpes simplex (cold sores)
- Herpes zoster (chicken pox → shingles)

**HIV**
- Integrates into host cell DNA (Mφ, Th)

**Reduction in Antigen Presentation:**

**MHC II: Measles, HIV**
- Inhibits MHC Peptide Presentation
- Occurs at multiple steps (depends on the virus)

**MHC I:**
- HSV = herpes simplex virus, EBV = Epstein Barr virus (mono), HCMV = Human cytomegalovirus, HHV8 = Kaposi’s sarcoma-associated human herpesvirus 8
**Dengue Virus:**
1. Infection via infected mosquitoes.
2. Four different serotypes of virus, each with a distinct genome and geographical location.
3. Distinct Ab are easily raised against each serotype, and these are effective against the particular serotype.
4. They cross-react with other serotypes, but don't neutralize the virus.

**Dengue Fever:**
Subsequent infection—different serotype
1. Antibodies that recognize one serotype of the virus bind, but do not completely inactivate another serotype.
2. Antibody-virus complex brought into macrophages/dendritic cells via $F_C$ receptor.
3. Cell is now infected and activates $T_C$ and $T_H$-cells via MHC-viral peptides.
4. INF-$\gamma$, secreted by $T_H$ cells recruits more macrophages and activates them. The newly arriving macrophages become infected.
5. TNF-$\alpha$ secreted by macrophages, causes severe local inflammation.
T-cell Subsets & T-cell Based Response to Pathogens:

$T_{H1}$ – cellular immune response:
- IL-2: Activation of $T_{CTL}$
- INFγ:
  - Activation of macrophages
  - Production of IgG3 Ab
- TNFβ (=TNFα) - inflammation

$T_{H2}$ – antibody based immune response:
- IL-5 & IL-4: Activation of B-cells
- IL-4: Class switch to IgE or IgG1

Cross-regulation by cytokines:

Intracellular Pathogens - Leprosy: Mycobacterium leprae

Which T-cell response is more effective against leprosy? Why?

Disease caused by over-reaction of T-cell

Immune Response to Bacterial components (exotoxins). Staphylococcal
Food poisoning & Toxic Shock Syndrome:

Exotoxins produced by bacteria act as "superantigens" that non-specifically activate large numbers of T cells. Toxic shock syndrome occurs with contaminated surgical dressing and long-term use of certain types of feminine hygiene products (tampons).
Chronic debilitating disease transmitted by the bite of the tsetse fly. Caused by a flagellated single celled protozoan parasite e.g. *Trypanosoma brucei*. (medical-dictionary.thefreedictionary.com)

**Disease:**
In the systemic phase, the parasite differentiates in the bloodstream and divides every 4-6 hours. In the neurologic phase, the parasite infects the central nervous system (CNS) causing meningoencephalitis and eventually loss of consciousness and then death.

**Immune response:**
During the systemic phase, antibodies are made against a protein on the surface of the parasite - variant surface glycoprotein (VSG). Antibodies eliminate the parasite by complement-mediated lysis or opsonization followed by phagocytosis.

**Genetics of evasion of immune response:**
1. Each trypanosome carries a large repertoire of VSG genes, each encoding a different VSG primary sequence. A trypanosome expresses only one VSG at a time.
2. Activation of a VSG gene involves duplication of the VSG gene and transposition to a transcriptionally active expression site; the previous gene is displaced.

**Evasion of immune response:**
1. Most of the parasites are cleared by antibody mediated mechanisms. 1% of the parasites escape killing because they bear an antigenically different VSG. These parasites proliferate and cause another wave of parasitemia.
2. In the course of a single infection, each new wave of parasitemia is able to evade the immune response to the preceding variant.

![Image of trypanosome lifecycle and immune response](image-url)
**Response to Multi-cellular Parasites – e.g. Schistosomes**

**TH2 response:**
- Sensitization results in the production of IgE antibodies, via TH2 dominated response due to IL-4 secretion from basophils.
- Activation – crosslinking of IgE on Mast Cells
- Response – degranulation of mast cell, activation of eosinophils.

**Key Cell Types:**
1. Basophils: Initiate response by promoting IgE synthesis.
2. Mast Cells: Immediate response for IgE-Fc-receptor activation.

**Mast cells:** Found in mucosal and epithelial tissues
- Have constitutively expressed high affinity Fc receptors on surface.
- Anti-parasite IgE antibodies bind to surface of mast cell.
- Crosslinking of IgE/Fc receptor complex activates mast cell, releasing:
  i) Proteolytic enzymes:
  ii) Histamine, heparin:
  iii) TNFα:
  & long-term inflammatory mediators.

Histamine binds to histamine receptors causing:
- Increase in permeability of blood vessel, allowing fluid and other immune cells to enter tissue.
- Smooth muscle contractions
- Increase of mucus flow from epithelium
- Fluid flow across epithelium

Result is fluid/mucus flow outside the body + coughing, sneezing, vomiting, diarrhea.

**Eosinophils:** Similar to mast cells in response.
- Fc receptors up-regulated in response to inflammation.
- IgE-antigen interactions cause release of:
  i) Collagenase, ii) Peroxidase, iii) Proteins that are neutrotoxic to parasites.

**TH1 Response – Can be more effective than TH2 response.**
- INFγ production activates macrophages that are effective at killing parasites.
- Evasion - Schistosomes may induce TH2 cells to produce cytokine that suppresses TH1 formation.