Lecture 30 – Immunodeficiencies I

Acquired Immunodeficiency - HIV

A. Virus Structure. HIV (human immunodeficiency virus) is an enveloped (membrane coated) virus that uses RNA as its genetic material. Packaged within the virus are several enzymes:
- reverse transcriptase
- Integrase
- HIV protease.

B. Life Cycle of HIV:

The steps in its lifecycle are as follows:
1. Binding to a specific protein (CD4) on the surface.
   A co-receptor is required:
   - macrophages - CCR5 (mΦ have CD4 too)
   - T-helper cells - CXCR4.
2. Fusion and entry into the cell.
3. Conversion of its RNA into double stranded DNA by an enzyme called reverse transcriptase (RT). This step introduces many errors into the genetic code of the virus because this polymerase lacks a proofreading activity, giving rise to a large number of mutant viruses. Antigenic drift.
4. The viral DNA is integrated into the host DNA by the enzyme integrase.
5. The viral DNA is replicated along with the host DNA.
6. High levels of transcription of the viral DNA sequences only occurs in activated T-cells. Viral RNA and viral messenger RNA are produced.
7. Translation of the viral mRNA generates immature viral proteins.
8. HIV protease converts the immature viral proteins to mature ones by cleavage.
9. New viral particles assemble on the surface of the cell. Therefore viral coat proteins are found on the surface of the infected cell.
10. Mature virus is released to infect other cells.
C. Stages of HIV Infection:

1. Pre-clinical (1-2 weeks)
   - Infection of macrophages and dendritic cells by M-tropic HIV via CD4/CCR5 co-receptor at site of virus entry (mucosal membranes).
   - Gradual transition to T-tropic virus, which infects T\(_H\) via CD4/CXCR4 co-receptor.

2. Acute infection
   - Symptoms typical of viral infection occur – flu like symptoms.
   - T\(_H\) cells die because:
     a) anti-HIV antibody on surface of T\(_H\) (recognizing HIV proteins in host membrane.

     \[ T_H < 300 \rightarrow 120 \]

   b) presentation of viral peptides on MHC I.  

   c) **death due to viral replication**

3. Chronic Latent phase:
   - T\(_H\) cell count continues to decrease, CD4\(^+\)/CD8\(^+\) ratio drops from normal 2/1 level.
   - Lymph node damage accumulates due to inflammatory activity in response to infected T-cells.

4. Crisis Phase, T\(_H\) count <200 cells/ul
   - Rapid viral replication in remaining activated T-cells.
   - Lymph nodes become ineffectual as sites for antigen presentation.
   - General failure of immune system, resulting in:
     1. unusual malignancies
     2. opportunistic infections
     3. neurological syndromes.
D. HIV Treatment:
- Current treatments can extend life such that under ideal conditions the patient is more likely to die of natural causes.
- Numerous issues are associated with HIV drug treatment.
  - Side effects
  - Compliance

Current drugs:
1. Reverse transcriptase inhibitors (inhibit vRNA to DNA):
   - Nucleoside reverse transcriptase inhibitors.
     - Prodrugs have to be phosphorylated to triphosphate to become active.
     - Lack 3'OH group so after they are incorporated they terminate the growing DNA chain.
   - Non-nucleoside reverse transcriptase inhibitors.
     - Bind outside the active site, causing an allosteric change that inhibits reverse transcriptase.
2. HIV Protease Inhibitors (competitive inhibitors)

Viral resistance to any one of these drugs occurs rapidly due to lack of proofreading in RT. Error rate in reverse transcriptase is ~1/10^6, typical viral production is 10^9/day.

HAART treatment (highly active antiretroviral therapy) employs all three of these drug classes, greatly reducing the risk of obtaining viral particles that can replicate (dark lines = with treatment (left panel, treatment+mutation, right panel)).

[Graphs and diagrams showing T-cell levels and viral load changes with and without HAART treatment.]
Lecture 31 – Primary Immunodeficiencies

A. Innate immune system, e.g. Complement system defects.
   - C3 defects are the most severe:
     - Individuals lacking C9 have no clinical symptoms

B. SCID - Severe Combined Immunodeficiency
   T/B⁺: No functional B- or T-Cells:
   1. Adenine deaminase (ADA)
   2. Purine nucleoside phosphorylase (PNP)
   3. RAG1/RAG2 deficiencies.

   T/B⁻: No functional T-cells develop:
   1. Loss of IL-2 receptor γ-chain. This chain is found in the IL-2 cytokine receptor.
   2. Loss of JAK-3 Kinase: required for signal transduction via IL2-γ chain.
   3. Thymic aplasia: thymus does not develop properly.
      - Nude mice are athymic.

C. Antibody Production Disorders:
   1. Common Variable immunodeficiency Disease (CVID).
      Mature naive B-cells do not undergo differentiation to plasma cells and do not class switch to IgG or IgA. (~1:50,000).
   2. Hyper IgM Syndrome: Disorder in B-cell T⁺-cell communication (~1:10,000)
      - No MHC II on B-cells.
      - No CD40 on B-cells.
      - No CD40L expression on T-cells
      - Defective kinase in T-cells.
   3. IgA deficiency (~1:800)
      - Recurrent ear, respiratory, and genital-urinary tract infection.