Immunology and AIDS

- Human Immunodeficiency Virus type 1 (HIV-1)
- The etiologic agent of acquired immunodeficiency syndrome (AIDS)
- Probably originated in Sub-saharan Africa after crossing species barrier from Chimpanzees
- Three major groups for HIV-1
  - M = main
  - O = outlier
  - N = non-M and non-O
- Three independent crossings from chimps to humans

Immunology and AIDS

- HIV-1
  - Group M subtypes all originated from a common ancestor virus which is believed to have existed before 1940
    - A,B,C,D,F1,F2,G,H,I,J,K
  - These organisms form a CLADE
    - Share common features and are derived from a common ancestor
- HIV-2
  - is most closely related to a type of simian immunodeficiency virus (SIV) that occurs in sooty mangabey monkeys
  - Probably crossed to humans from these primates
  - Similar disease as HIV-1 but milder course and this isolate has only a limited spread in the population

HIV viral structure

- Family Retroviridae
- Viruses that have and use reverse transcriptase
- Genus Lentiviridae
- A protein bullet shaped capsid
  - P24 gag protein
  - Two duplicate strands of RNA
  - Nucleocapsid proteins p7 and p9, reverse transcriptase enzyme, Ntase H, integrase enzyme, and protease enzyme

- surrounded by a spherical envelope of host derived membrane and membrane components
  - Envelope glycoproteins gp41 and gp120
HIV viral structure

Life Cycle of HIV

- Infection by binding CD4 and gp120
- Host chemokine receptor CXCR4 or CCR5
- Virion host cell fusion
- Viral capsid entry into host cell
- Freeing of viral genome
- RNA to cDNA via RT
- Viral DNA replication by host cell
- Integration of viral ds DNA into host genome

HIV Activation and Replication

- Transcription and translation of viral genes using host cell machinery
- Some packaged into new virions some transpoated to cell surface
- New virions can emerge from cell or directly infect neighboring cell without forming a viral particle

Animal models of HIV

- No really good animal model for disease
- HIV-1 only infects and causes AIDS in human cells
- HIV can cause infection in Chimps but not disease
- SIV can infect and cause disease in rhesus monkeys
- Not natural hosts and so develop an AIDS-like illness with similar pathogenesis (natural hosts are not harmed)
- Hybrid strains of SIV and HIV have been developed (SHIV) that cause disease and AIDS-like illness in monkeys
- Developing transgenic mice that express human CD4 and coreceptors for HIV infection
HIV-1 structural genes

HIV Pathogenesis

- No longer thought to be a long period of viral latency
- The entire course of infection is the interplay of continuous dynamic viral replication and host responses
- Course of infection may be considered several stages based on the evolution of virologic and host parameters
  - the concentration of virus in the blood,
  - the CD4+ T cell counts,
  - and antiviral immune responses.

Pathogenesis: Acute Phase

- Exposure to HIV-1
- Mucosal exposure leads to infection of DCs (CD4+)
- but no viral replication occurs in DCs
- DCs move to lymph nodes and expose T cells (CD4+)
- CD4+ T cells are infected and activated
- Vigorous HIV-1 replication in activated T cells
- Infection spreads systemically
- Explosive rate of infection and plasma viremia is due to lack of immune response
- Mononucleosis-like illness
- No antibodies to HIV-1 but HIV-1 DNA/RNA can be detected
- Illness symptoms are self limited and often go undiagnosed
Pathogenesis:
Chronic Asymptomatic Infection
- Marked by ~stable levels of viremia and almost normal CD4+ T cell counts
- CD4+ T cell counts slowly decline but patient is relatively asymptomatic
- Essentially a dynamic equilibrium between virus and immune system
- PCR based detection shows that the majority of individuals have stable viremia
- Result of vigorous ongoing production and destruction of virus
- CD4+ T cells are produced and killed in large numbers
- Estimated 1X10^{10} viral particles are produced and cleared DAILY
  - 10,000,000,000 = 10 BILLION viral particles

Pathogenesis: Late Infection
- Rapid and progressive decline in CD4+ T cells
- Rapid and progressive increase in viral load (viremia)
- Accelerated phase usually begins after the CD4+ T cell count has dropped to ~ 500 cells per cubic millimeter (mm³)
- Clinical symptoms often develop at this phase
- Fevers, sweats, enlarged lymph nodes, weight loss
- Risk of opportunistic infections increases
- At ~200 CD4+ T cells per mm³ AIDS ensues
- The cause for the progressive failure of the immune system is unclear
- Loss of HIV-1 containment leads to loss of CD4+ T cells
- TH1 bias in early infection switches to TH2 bias in Late infection
- Cause or effect of Late phase?
Immune Defects Due to HIV-1 Infection

- Almost all aspects of immunity are affected as the disease progresses
- Loss of CMI and increased susceptibility to intracellular pathogens
- Loss of Humoral immunity = no specific antibody responses
- Innate immune system is also damaged

Table 22.1 Mechanisms of leukopenia caused by chronic HIV-1 infection

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Cellular effect</th>
<th>Molecular bases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct infection</td>
<td>Necrosis</td>
<td>Aberrant signaling by gp120</td>
</tr>
<tr>
<td></td>
<td>Apoptosis</td>
<td>Viral protein (Tat, Vpr?)</td>
</tr>
<tr>
<td></td>
<td>Immune clearance</td>
<td>Cytotoxic T cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antibody-mediated</td>
</tr>
<tr>
<td>Bystander cell loss</td>
<td>Synctium formation</td>
<td>Aberrant signaling</td>
</tr>
<tr>
<td></td>
<td>Free gp120 binding</td>
<td>Immune clearance (antibody)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased production</td>
<td>Superantigen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stem cell infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thymocyte gp120 binding</td>
<td></td>
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<tr>
<td></td>
<td>Loss of antigen-presenting cells</td>
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</tbody>
</table>

Immune Defects Due to HIV-1 Infection

Antigen Presenting Cells (APCs)

- APCs = monocytes/macrophages and Dendritic cells (DCs) can be infected
- Numbers decrease during infection
- Loss of DCs probably contributes to loss of CMI
- Loss of Macrophage presentation probably contributes to loss of humoral immunity
Immune Defects Due to HIV-1 Infection

B cells

• B cell hyperreactivity

• Polyclonal hypergammaglobulinemia
  – Too many antibodies of all specificities

• Terminal differentiation to plasma cells seems to occur without appropriate signals
  – Nonspecific polyclonal antibody production

• Consequences include autoimmunity, impaired switching, increased incidence of B cell lymphomas due to chronic activation

Immune Defects Due to HIV-1 Infection

CD8+ T cells

• Loss of CD8+ cell functions (CTL function) and consequent loss of CMI

• Dependent on CD4+ helper T cells that are no longer around in significant numbers

• Loss of DCs also may contribute to nonresponsiveness of CD8+ T cells

Immune Defects Due to HIV-1 Infection

Other Cell Types

• Pluripotent Stem cells can be infected with HIV-1 in vitro

• In vivo role is unclear

• Loss of stem cells could contribute to depletion of all immune cell types

• Natural killer cells have decreased cytolytic activity although numbers remain stable.
  – Loss of IFN-gamma stimulation?

• Neutrophils exhibit defective phagocytosis and chemotaxis

Immune Responses to HIV-1 Infection

• CD4+ T cells that respond specifically to HIV-1 antigens

• CD8+ CTLs that respond specifically to HIV-1 antigens
  – Up to 14 different viral antigens in a single individual
    • Many more than other chronic viral infections
  – Some Multiply exposed but uninfected individuals have detectable CTL responses to HIV-1 but no circulating Antibodies
    • Suggests that CMI cleared infection before advent of humoral response

• Antiviral Cytokines produced by CD8+ T cells
  – See next figure

• Antiviral Antibodies have activity against replication in vitro are called neutralizing antibodies
  – In vivo affects on HIV infection are unknown
Antiviral Cytokines Produced by CD8+ T Cells

<table>
<thead>
<tr>
<th>Table 22.2</th>
<th>Secreted factors that inhibit HIV-1 infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
<td><strong>Example</strong></td>
</tr>
<tr>
<td>Chemokines</td>
<td>RANTES, MIP-1α, MIP-1β, MCP-2</td>
</tr>
<tr>
<td></td>
<td>SDF-1α, SDF-1β</td>
</tr>
<tr>
<td>Other secreted factors</td>
<td>CAF</td>
</tr>
</tbody>
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Evasion of Immune Responses by HIV-1:

- **Escape from Antiviral Cytokines?**
  - Observed in vitro, but not known whether HIV-1 can escape effects in vivo
- **Escape from Neutralizing Antibodies?**
  - Gp120 CD4+ binding site is hidden in vivo
  - Gp120 is highly glycosylated - reducing immunogenicity
  - Virions hiding in follicular Dendritic Cells in lymph nodes
    - Site for latent reservoir of virus?
- **Escape from CTLs**
  - See next slide

Pharmacologic Therapy for HIV-1 Infection

- **Nucleoside RT inhibitors**
  - First class of drugs, AZT, nucleoside analogs
  - Chain termination occurs when RT incorporates these
    - Prevent production of viral DNA
    - When used individually, resistance occurs rapidly
- **Non-nucleoside RT inhibitors**
  - Bind and inactivate RT enzyme
  - When used individually, resistance occurs rapidly
- **Protease inhibitors**
  - Bind and inactivate viral protease needed for processing of precursor proteins to functional proteins
  - Forms nonviable virions without viral protease
- **Viral-host cell fusion inhibitors**
  - Peptides that block viral entry into cells via gp41