HIV/AIDS

Pr Coscoy
MCB150

AIDS

◆ Human Immunodeficiency Virus
◆ Acquired ImmunoDeficiency Syndrome.
◆ AIDS results from CD4+ T cell depletion causing severe immunosuppression and an increase in opportunistic infections.

Opportunistic Infections

Kaposi's Sarcoma

Kaposi's sarcoma is a classic opportunistic infection which is only seen in AIDS patients in the U.S.
Caused by Kaposi's Sarcoma herpesvirus OR Human Herpes Virus-8.

HIV Classification

◆ Family: Retroviridae
◆ Genus: lentiviruses
◆ Cytopathic retroviruses
  - Human immunodeficiency virus-1 (HIV-1)
  - Human immunodeficiency virus-1 (HIV-2)
  - Simian immunodeficiency virus (SIV)
  - Feline immunodeficiency virus (FIV)
◆ Transforming retroviruses.
  - Human T cell lymphotropic virus (HTLV)-1 can cause T cell leukemia.

HIV Classification

HIV-1 and HIV-2 (50% homology) cause similar immunodeficiency disease in humans.
HIV-1 found in 80% of cases in the world.
HIV-1 is broken up into "clades".
Worldwide HIV Infections

- 42 millions of infected
- 3 millions died in 2003
- 14000 infected per day
- 29 millions in Africa
- 10 millions between 15-24 years old
- 1/50 have access to a treatment
- 1% of pregnant women are treated
- 5 millions contaminated in 2003
- 3 millions died

HIV Structure

- Enveloped RNA virus
- Feb, 1983

HIV Genome

- env gene encodes envelope glycoprotein (gp160) (precursor protein split into gp120 and gp41).

HIV Regulatory/accessory genes

- Tat (transcriptional activation domain) and Rev promote viral replication
- The HIV promoter is located in the 5' LTR and contains an enhancer with two NF-kB binding sites and the transactivation response element (where Tat binds).
**HIV Envelope Proteins**

- Glycoprotein (gp) 120 molecule is noncovalently bound to gp41, which is embedded in the envelope membrane.
- Gp120 is the viral attachment receptor for host cell entry and target for neutralizing antibodies.

**HIV Life cycle**

- HIV infects:
  - CD4+ T cells: activated and naive
  - Macrophages
  - Dendritic cells.

**Resistance to HIV Entry**

- Individuals with a 32 bp deletion in their CCR5 gene appear to be resistant to HIV.
- Individuals with increased levels of the chemokines that bind to CCR5 (MIP1-α, MIP1-β, and RANTES) have reduced levels of viral replication and may have greater resistance to infection.

**HIV Life Cycle**

**HIV entry**

The two primary co-receptors are CXCR4 and CCR5.

**Replication or Integration**

Once viral RNA in cytoplasm-----
- ssRNA uses RT to make cDNA copy and then double-stranded viral DNA.
- dsDNA can make mRNA and viral RNA to initiate replication ------- lytic infection
  **OR**
- dsDNA migrates to nucleus and integrates into the genome using a viral integrase ---- latent infection
HIV Life Cycle
Integration establishes Latency

- Once integrated, the virus can remain latent for long periods.
- Provirus is the integrated DNA copy of the viral RNA.

HIV Life Cycle
Activation of Latently Infected Cell

Transcription factors (such as NF-κB) can act on the HIV enhancer regions to initiate transcription of viral DNA into RNA.
- mRNA transcripts are used for protein
- Genomic ssRNA transcripts are made for inclusion in viral particles that initiate lytic infection.

Clinical Aspects
Transmission

- HIV is transmitted through contact with blood or body fluids.
- Routes of transmission
  - Contact with rectal or genital mucosa with infected semen or vaginal secretions.
  - By injections of HIV-infected blood.
  - During pregnancy, childbirth, or nursing (vertical transmission).

DC-SIGN Captures HIV-1

DC-SIGN Captures HIV-1 and Retains Long-Term Infectivity

<table>
<thead>
<tr>
<th>DC-SIGN binds HIV-1</th>
<th>DC-SIGN binds HIV-1 and retains long-term infectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial HIV-1 exposure</td>
<td>Productive HIV-1 infection in lymphoid organs</td>
</tr>
<tr>
<td>Migration</td>
<td>Production of viral particles</td>
</tr>
</tbody>
</table>
Transmission - acute infection

Immune response to HIV

Humoral immune response
◆ Neutralizing antibodies to gp120.
  – Most important epitopes are found in the third hypervariable region of gp120 termed the V3 loop.
  – These antibodies may play an important role in vivo especially during resolution of primary infection.
  – However the antibody titer does not decrease as immunodeficiency occurs.

Humoral immune response
◆ Neutralizing antibodies to gp120.
  – Most important epitopes are found in the third hypervariable region of gp120 termed the V3 loop.
  – These antibodies may play an important role in vivo especially during resolution of primary infection.
  – However the antibody titer does not decrease as immunodeficiency occurs.

CMI response to HIV
During the prolonged period of asymptomatic infection there is a vigorous CMI that is initially effective at eliminating virally infected cells but as CMI begins to decline immunodeficiency begins.

Immune response to HIV
CD4+ Th
◆ CD4+ cells are the primary HIV infected cells.
◆ Uninfected HIV-specific CD4+ T cells found during long asymptomatic phase help eliminate virus.
  – Increased proliferation of HIV-specific CD4+ Th cells from infected individuals correlates with reduced viral loads.

Immune response to HIV
CD4+ Th
◆ CD4+ cells are the primary HIV infected cells.
◆ Uninfected HIV-specific CD4+ T cells found during long asymptomatic phase help eliminate virus.
  – Increased proliferation of HIV-specific CD4+ Th cells from infected individuals correlates with reduced viral loads.

Immune response to HIV
CD4+ Th
◆ CD4+ cells are the primary HIV infected cells.
◆ Uninfected HIV-specific CD4+ T cells found during long asymptomatic phase help eliminate virus.
  – Increased proliferation of HIV-specific CD4+ Th cells from infected individuals correlates with reduced viral loads.

CTLs crucial for anti-HIV CMI
Why?
◆ The emergence of HIV-specific CTL during primary infection correlates with acute viral load reduction.
◆ Inverse correlation between CTL activity and plasma viral RNA load.
◆ HIV specific CTLs have been found with activity against Env, gag, nef, pol.
◆ CTL escape mutants of HIV have been identified.
◆ CTLs produce high levels of MIP-1α, MIP-1β, and RANTES.

CTLs crucial for anti-HIV CMI
Why?
◆ The emergence of HIV-specific CTL during primary infection correlates with acute viral load reduction.
◆ Inverse correlation between CTL activity and plasma viral RNA load.
◆ HIV specific CTLs have been found with activity against Env, gag, nef, pol.
◆ CTL escape mutants of HIV have been identified.
◆ CTLs produce high levels of MIP-1α, MIP-1β, and RANTES.

CTLs crucial for anti-HIV CMI
Why?
◆ The emergence of HIV-specific CTL during primary infection correlates with acute viral load reduction.
◆ Inverse correlation between CTL activity and plasma viral RNA load.
◆ HIV specific CTLs have been found with activity against Env, gag, nef, pol.
◆ CTL escape mutants of HIV have been identified.
◆ CTLs produce high levels of MIP-1α, MIP-1β, and RANTES.

CTLs crucial for anti-HIV CMI
Why?
◆ The emergence of HIV-specific CTL during primary infection correlates with acute viral load reduction.
◆ Inverse correlation between CTL activity and plasma viral RNA load.
◆ HIV specific CTLs have been found with activity against Env, gag, nef, pol.
◆ CTL escape mutants of HIV have been identified.
◆ CTLs produce high levels of MIP-1α, MIP-1β, and RANTES.

CTLs crucial for anti-HIV CMI
Why?
◆ The emergence of HIV-specific CTL during primary infection correlates with acute viral load reduction.
◆ Inverse correlation between CTL activity and plasma viral RNA load.
◆ HIV specific CTLs have been found with activity against Env, gag, nef, pol.
◆ CTL escape mutants of HIV have been identified.
◆ CTLs produce high levels of MIP-1α, MIP-1β, and RANTES.
CD4+ T cell Depletion

Why are there low numbers of infected CD4+ T cells in peripheral blood?

- Few infected CD4+ T cells detected in blood during the clinically latent period.
- However HIV found in lymph nodes.
  - Keep in mind that 98% of lymphocytes are in immune organs and tissues not in peripheral blood.

CD4+ T cell Depletion

Pathogenic Process in Lymph Nodes

- HIV remains active in the lymph nodes, and large numbers of viral particles can be detected in lymphoid follicles.
  - Activity of the virus in these sites eventually leads to loss of follicular dendritic cells and disruption of lymphoid architecture.

CD4+ T cell Depletion

Why are there low numbers of infected CD4+ T cells in peripheral blood?

Steady State Model of Infection

- CD4 T cell decline is a gradual losing of long immune struggle involving a cycle of
  - CD4+ T cell infection
  - CD4+ T cell death
  - CD4+ T cell replacement.

Steady State Model of Infection

Constant battles
HIV vs Immune System

- Constant turnover of CD4+ T cells drives the pathogenic process and constant viral replication contributes to development of HIV genetic variation.
- Finally the CD4+ T cell regeneration is exhausted, CD4+ T cell number declines, and AIDS develops.
Potential Mechanisms of CD4+ T cell depletion

- Infected CD4+ T cells killed directly by HIV, or by virus-specific CD8+ CTL.
- Uninfected CD4 cells
- Cross-linking of CD4 by gp120 can cause T cells to undergo apoptosis.
- Gp120 may bind CD4+ T cells in the thymus and interfere with positive selection.

HIV May Infect Thymus Lead to Lytic Infection or Latency

Clinical aspects of HIV Infection Diagnostics

- Detection of exposure to HIV determined by ELISA measuring antibodies to gp120.
  - Confirmed by Western Blot measuring antibody response to all viral proteins.
- HIV Viral RNA detected by PCR.

Drug Therapy Antivirals

- Nucleoside analogs. Nucleoside chain terminators
  - AZT (3'-azidothymidine), ddI (dideoxy-inosine), ddC (dideoxy-cytidine), D4T, 3TC.
- Reverse transcriptase inhibitors
  - nevirapine.
- Protease inhibitors which inhibit protein processing of large polyproteins.
  - ritonavir, saquinavir - many more.
- Combination drug therapy is most beneficial.

Mechanism for antivirals

Effect of Antivirals on AIDS Deaths

AIDS Cases and deaths in U.S.A. 1985 - 1999
Clinical aspects of HIV Infection

- Monitoring Infection
  - Amount or viral particles measured in plasma by PCR test detecting viral RNA. Known as "viral load".
  - CD4 T cell counts measured by flow cytometry.

Effect of Antivirals

- Viral Load
  - After antiviral therapy, viral load goes down and CD4 T cells up.

HIV Vaccine Issues

- Animal model not reproducible.
- HIV protein sequence variation.
  - High mutation rate of HIV allows rapid antigenic variation.
- What immune response will provide protection?
- Need to identify good immunogens.
- Stimulate immunity on mucosal surfaces.

Original HIV Vaccines

- Various preparations of gp120 injected with adjuvant.
- Good for antibody responses but poor for CTLs.
Canarypox virus with gp160 gene (and other genes) followed by immunization with recombinant gp120 and or gp41 proteins as a booster.

Thus the canarypox vaccine primes eliciting both CTL and some ab responses followed by boost with recombinant protein to elicit increased ab responses.