Molecular Biology and Pathogenesis of HIV

Acquired Immune Deficiency Syndrome (AIDS)

- 1981 – first reported cases (pneumocystic pneumonia in gay men)
- indications are that the disease had been spreading silently for several years prior to ID
- 1983 – isolated and identified as HIV (Luc Montagnier)
- Over 600,000 cases reported in the US since 1981
- World pandemic
- Characterized by susceptibility to infection w/ opportunistic pathogens

HIV Genome

Lentivirus – 'slow virus'
Enveloped
Retrovirus
+-strand RNA genome
Encodes 9 gene products
Gag, Pol, Env, Tat, Rev, Nef, Vif, Vpr, Vpu

Life Cycle

Binding to permissive cell

CD4 receptor
CD4 present on monocytes, macrophages, dendritic cells
Coreceptor CCR5 and/or CXCR4
G-protein coupled 7 transmembrane receptor family

Fusion

Viral membrane actually fuses with host cell membrane
Not fully described mechanistically
Release of viral contents into the cellular interior

Reverse Transcription

RNA genome converted to DNA genome via viral RT

Nuclear Transport and Integration into Host Genome

dsDNA copies migrate to nucleus as part of a pre-integration complex (PIC)
Integrase protein cleaves the host genome and then inserts and ligates the viral and host DNA
PROVIRUS
From this point on, HIV becomes a genetic disease
The viral genome is integrated and becomes a permanent component of the host genome

Transcription of viral transcripts

Stimulated by Tat and cellular transcription factors
Tat (Trans-acting activator of transcription)
Enhances viral mRNA xcription by binding to the RNA

Nuclear export of viral mRNA

Rev (Regulator of virion protein expression) cont'd.

Stabilizes the mRNA by direct interaction during transport

Without Rev – no Gag, Env, Pol proteins are translated

Assembly of virion particles

Complete process not mechanistically derived

Gag protein precursor (Pr55gag) produced in the cytoplasm and then moves to the inner plasma membrane for assembly

Other viral proteins, two ssRNA copies, and some cellular proteins

Viral Budding

Individual virions bud from the cell surface and diffuse outward

Virions mature and become infectious

Gag polyprotein cleaved into individual proteins

Structural changes within the virion; core formation

Pathogenesis

HIV breaks down the body's immune system, its natural defense system against foreign substances and invading organisms, such as bacteria that cause disease

Hallmark: Destruction of CD4+ T cells

Time course

Acute infection

infectious mononucleosis-like illness

headache, rash, lymphadenopathy

Many people do not develop any symptoms when they first become infected with HIV.

These symptoms usually disappear within a week to a month and are often mistaken for those of another viral infection. People are very infectious during this period, and HIV is present in large quantities in genital secretions

Seroconversion

Window period

ab production & activation of T cells that attempt to eradicate HIV

As soon as 1 month after infection

As late as 6 months after infection

Asymptomatic infection

Clinical latency but not virologic latency

Some people may begin to have symptoms in as soon as a few months, whereas others may be symptom-free for more than 10 years

Early manifestations of disease

Clinical immunodeficiency: AIDS

The term AIDS applies to the most advanced stages of HIV infection. Official criteria for the definition of AIDS are developed by the CDC in Atlanta, Ga., which is responsible for tracking the spread of AIDS in the United States.

In 1993, CDC revised its definition of AIDS to include all HIV-infected people who have fewer than 200 CD4+ T cells. (Healthy adults usually have CD4+ T-cell counts of 1,000 or more.) In addition, the definition

includes 26 clinical conditions that affect people with advanced HIV disease.

- Infections rare in immunocompetent individuals – 'opportunistic'
  - pneumocystis carinii pneumonia; recurrent bacterial infections; Tuberculosis; invasive fungal infections such as esophageal candidiases; neoplasma including Kaposi's sarcoma, polyclonal B-cell lymphoma, and cervical carcinoma; diarrhea; CMV; Hepatitis A/B; HSV; idioiopathic thrombocytopenic purpura; *Nocardia* infections of lung
- Neurologic illnesses and wasting
  - *Toxoplasma gondii* in the brain
  - *Toxoplasmic* encephalitis

Testing

ELISA + Western Blot

- Serologic diagnosis
  - Takes 6 months for body to produce measurable quantities of ab
- ELISA – 'enzyme linked immunosrbent assay'
  - Detection of immune response to invading pathogen
  - very sensitive and detects almost all persons infected except for first few weeks of infection
- Western Blot – detects HIV proteins
  - Hardly ever gives a false positive result

Nucleic acid detection

- Viral load testing
  - Measurement of the HIV levels in your blood
  - ? 10, 000 viruses/mL blood are considered high

CD4 lymphocyte cell count

- CD4 cells are a type of white blood cell
- Typically around 1000 cells/mm^3
  - ?200 cells/mm^3 denotes immunodeficiency

Therapeutics

- HAART
  - 'Highly Active Antiretroviral Therapy'
  - Drugs used to slow down the growth of the virus
  - Drugs work by affecting different steps of the life cycle
- Therapy During Pregnancy
  - Multiple Studies
    - ?20% transmission to fetus reduced to ~7%
    - Prenatal treatment throughout pregnancy
    - Treatment during labor less effective and must be followed by a multi-week treatment of the infant

Nucleoside reverse transcriptase inhibitors

- **AZT** (ZDV, zidovudine, Retrovir?)
- ddI (didanosine, Videx?)
- ddc (zalcitabine, Hivid?)
- 3TC (lamivudine, Epivir?)
- Combivir? (AZT/3TC combo)

Trizivir? (AZT/3TC/Abacavir combo)

Non-nucleoside reverse transcriptase inhibitors

Nevirapine (Viramune?)
Delavirdine (Rescriptor?)
Efavirenz (Sustiva?)

Protease inhibitors

Saquinavir (Invirase? and Fortovase?)
Indinavir (Crixivan?)
Ritonavir (Norvir?)
Nelfinavir (Viracept?)
Amprenavir (Agenerase?)
Lopinavir (Kaletra?)

Complications

LT effectiveness

Side effects of drugs making up cocktail

Resistance

Do not work for all patients

Compliance

Skipping doses
'Drug holidays' for days/weeks

Reservoir populations

CDC National AIDS Hotline
1-800-342-AIDS
CDC National Prevention Information Network
800-458-5231
http://www.cdc.gov/nchstp/od/nchstp.html
http://www.cdc.gov/nchstp/hiv_aids/dhap.htm
http://www.cdcnpin.org