Viruses causing Immunodeficiency (HIV)

Mechanisms of Human Disease

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HIV (and HTLV): Virus and viral replication

Retrovirus particles have a distinctive morphology

EM of a thin section through a set of retrovirus (HIV-1) particles. The dark nucleocapsid core is surrounded by the lipid envelope (a double layer of dark-light-dark membranes) from which the env gene products project around the virion.
Four enzyme activities in cores: RT, RNase H, integrase and protease. RT activity signifies presence of retro-viruses.

1. People who do not express co-receptor (CCR5-/-) do not get infected by HIV

2. The HIV gp120 / gp41 is the best immunogen for an HIV vaccine

Doms and Trono, Genes Dev, 2000
1. Virion RNAs are templates for cDNA synthesis.
2. There are numerous anti-HIV drugs that block reverse transcription.
Possible sequelae of proviral cDNA integration into the host cell

1. If there is proviral DNA integration, but no transcription of the DNA, then cell will stay latently-infected.
2. If there is proviral DNA integration in germ line cells, then provirus may be endogenously (vertically) transmitted.
3. If integration is into an essential cellular gene, then cell may die (rare because cells are diploid).
4. If integration is near a cellular oncogene, then cell may become transformed; cancer development.
5. If integration is followed by proviral DNA transcription, then cell will produce progeny viruses.
1. "Highly-Active Anti-Retroviral Therapy" (HAART) uses protease inhibitors.
2. Protease inhibitors prevent capsid maturation.

Recapitulation

"Step 1": Entry, reverse transcription, provirus integration. Cells with integrated proviral DNA are "latently infected" (note gene therapy vectors)

"Step 2": Proviral transcription, viral protein production, virus budding and egress. Cells are "productively infected"

HIV transmission
**Retrovirus Transmission: Historical Perspective**

Current HIV-1 is related to HIV-cpz, a chimpanzee lentivirus

Note the transition from rare zoonotic infection to worldwide epidemic

1959: Sample from adult male, DR Congo, HIV+

1960: Lymph node sample, adult female, DR Congo, HIV+

1969: US teenager, died 1969, HIV+

1976: Norwegian sailor, HIV+

1981: US, Los Angeles, Pneumocystis carinii+, adult males, 3/5 died, first recognition of AIDS

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**Probability of HIV Transmission per Coital Act in Monogamous, Heterosexual, HIV-Discordant Couples in Rakai, Uganda**

![Graph showing probability of HIV transmission per coital act.](image)

Source: Gray et al., Lancet 2001;357:1149

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**Transmission**

- HIV is not a particularly infectious virus, not contagious like measles virus
- Not spread by respiratory, alimentary, or vector routes

![Graph showing transmission routes.](image)

HIV is found in plasma, semen, vaginal/cervical fluid, but not in saliva, sweat, tears, breast milk, bronchial fluid, urine, feces.
Transmission

- HIV-1 infectivity reduced by air drying (99%/24 hr)
- By heating (56°C/30 min)
- By 10% bleach or 70% alcohol
- By pH extremes (<6 or >10)
  By detergents

HIV / AIDS is #3 on the mortality and morbidity list of infections

HIV strain variation
HIV has evolved into groups (M; main and O; outlier); the M group has evolved into clades

- Clade B predominates in US and Europe
- Clade E is dominant in Thailand
- Clades change with time; i.e., clade C is spreading in Africa
- Vaccines and antivirals have to be capable of limiting all clades

Evolution of variability is largely in the surface glycoproteins: gp120/gp41

Evolution / Variability in HIV gp120 determines virus tropism for macrophages and CD4+ T cells
HIV pathogenesis:
Immunosuppression

HIV additional genes are involved in virus pathogenesis

HIV infection is robust and cytotoxic

CD4+ T cell culture

Syncytia in lymph node.
CD4+ T cells regulate the immune system

Targeting CD4+ T cells for destruction allows virus to evade / modify immune responses
Virus becomes relatively free from immune surveillance, this increases growth of virus

Prolonged infection disrupts lymph node architecture:
Permanent immunosuppression

Course of HIV disease
Three stages to HIV-induced disease

ACUTE
- Mononucleosis-like syndrome
  - Observed ~3 weeks after initial infection
  - Fever, fatigue, swollen lymph nodes
    - Symptoms can be worse, but vary considerably
    - Majority of infected individuals do not seek medical care in response to these symptoms
- T cell levels drop, may rebound slightly, but rarely reach preinfection levels

LATENT
- Typically lasts 8-12 years following primary infection
- Few if any clinical manifestations
- NOT virologic latency
  - Continued, high levels of viral replication
  - Live, infectious virus easily detectable in blood of patients

AIDS
- Death
Clinical Disease (AIDS)

- When CD4 T cell counts fall below 350 cells/μl, AIDS-related symptoms appear
  - Oral lesions
  - Basal cell carcinomas
  - Activation of latent herpes, mycobacteria infections

- When CD4 T cell counts fall below 200 cells/μl, more severe symptoms occur
  - Protozoal infections
  - Bacterial infections
  - Fungal infections
  - Viral infections and malignancies
    - Kaposi’s Sarcoma
    - Neurological disorders
    - AIDS dementia

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A. Pneumonia (PCP) (Pneumocystis carinii)
B. Kaposi sarcoma (Human herpesvirus 8)
C. CMV retinitis (Cytomegalovirus)
A. Oral leukoplakia (Candida)

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HIV therapy
The goal of HAART is to lower the virologic set-point. Lower viremia correlates with slower disease progression.

**Indication to start HAART:** HIV+ and history of an AIDS-defining illness and/or CD4 T cell < 350 per microliter. Definitive laboratory evidence of HIV.

**“Highly-Active Anti-Retroviral Therapy” (HAART)** uses RT and protease inhibitors concomitantly.

- The protease inhibitors prevent virion capsid morphogenesis.
- The RT inhibitors block reverse transcription.


**HAART**

- Long term HAART treatment associated with:
  - Heart disease
  - Diabetes
  - Liver disease
  - Certain cancers
  - Anemia (! from AZT)

Clinical side effects are diarrhea, nausea, vomiting, weakness, lipodystrophy

- Not, HAART must be prolonged:
  1. HIV is mutable and drug-resistant viruses are easily formed.
  2. HIV provirus can stay in latently-infected cells for a long time.
HIV lentivirus: 
Comparison with HTLV lymphotropic retrovirus

Medical relevance of retroviruses: 
Disease-causing human retroviruses (HIV and HTLV)

HTLV and HIV: 
Similar transmission patterns 
Both common 
--- (~20 million HTLV-infected individuals)

HTLV has lower disease penetrance than HIV 
--- only ~1% of HTLV infected individuals get disease 
HTLV clinical latency period is longer than HIV 
--- over 20 years from infection to clinical disease 

HTLV causes T cell leukemias, 
while HIV causes T cell death and immunosuppression

Countries with endemic HTLV-I, defined as prevalence between 1 and 5% in some populations, are shown in dark brown. Countries with reports of low prevalence (less than 1% in some groups), due mainly to immigration from endemic areas, are shown in tan color. It should be noted that HTLV-I endemic areas do not correspond exactly to the country boundaries shown in the map, for example, Brazil, Japan and Iran, where HTLV-I is limited to residents of certain areas of each country.
HTLV encodes tax, an accessory protein, which induces cell proliferation

A 30-year old man infected with HIV begins to have difficulty with activities of daily living. He has memory problems and decreased ability to perform functions that require fine motor control, such as writing and painting. His CD4+ lymphocyte count is 150 cells per microliter. Which of the following cell types is most important for disseminating HIV into the central nervous system?

A. Natural killer cell  
B. Macrophage  
C. Neutrophil  
D. CD8+ lymphocyte  
E. Langerhans cell