

Retroviruses & Human Immunodeficiency Virus (HIV)

Reading: Schaechter's Mechanisms of Microbial Disease, Fourth Edition, Chapter 38.

I. **Overview.** The Retroviridae comprise 3 subfamilies: *Oncovirinae* (HTLV-1, HTLV-2 and HTLV-5); *Lentivirinae* (HIV-1 and HIV-2) and the *Spumavirinae* (Human Foamy Virus -- not associated with human disease).

II. Key Features

- A. Human viruses are associated with tumors, leukemias, and immunodeficiencies.
- B. Common genetic organization and strategy - major differences lie in regulatory complexity.
- C. Genome consists of 2 copies of (+) stranded RNA.
- D. RNA converted to DNA (reverse transcription) by a bizarre mechanism followed by chromosomal integration.
- E. Integrated DNA co-linear with viral DNA.
- F. Only *Oncovirinae* can immortalize and transform cells. They are fast acting and cause sarcomas and leukemias through incorporated cellular genes (protooncogenes which cause dis-regulation of cell growth. They can transform cells *in vitro*. At least 35 different protooncogenes have been identified which include growth hormones, growth hormone receptors, protein kinases, GTP-binding proteins and nuclear DNA binding proteins.
- G. The Lentiviruses, such as HIV, can not transform cells *in vitro* -- they are typically associated with slow and immunosuppressive diseases.
- H. HIV is a slow cytocidal virus with exquisite tropism for CD4+ expressing cells and macrophages which kills cells rather immortalizes them. It is the loss of CD4+ cells which destroys helper and delayed type hypersensitivity functions of the immune response.

II. Structure and composition of virion; simple vs. complex RNA genomes.

- A. Enveloped virus with nucleocapsid surrounding RNA, capsid and envelope with glycoproteins (gp120 and gp 41).
- B. Diploid, positive sense RNA genome, gene map of a simple virus - gag-pol-env.
 - 1. gag - group specific antigens, internal components p24, p18, p15.
 - 2. pol - polymerase gene, reverse transcriptase (RT); integrase (int) and protease.
 - 3. env - envelope proteins, i.e. gp120 and gp41 for HIV.
- C. Provirus - double stranded DNA copy of the RNA genome, contains the LTR- Long Terminal Repeat which contains the regulatory sequences for

replication.

- D. HIV, HTLV – possess complex gene structure with sequences for other regulatory proteins; tat, rev, vpu, vpr, vif and nef.

III. Reproductive cycle

- A. Adsorption and penetration.
- B. Reverse transcription - reverse transcriptase (RT) synthesizes a double stranded DNA copy of the genome RNA (provirus).
 - 1. Synthesis of a DNA copy of the virion RNA by RT (RNA -dependent DNA polymerase).
 - 2. Degradation of the RNA by a ribonuclease activity (RNase H) of RT.
 - 3. Synthesis off the second DNA strand by RT (DNA dependent DNA polymerase activity).
- C. Integration of the proviral DNA into the chromosomal DNA by viral integrase protein, requires the LTR. The DNA can integrate anywhere in DNA.
- D. Genome RNA synthesis and mRNA synthesis by the host cell RNA polymerase II and splicing.
- E. Protein synthesis of long precursors and processing by viral protease to individual viral proteins.
- F. Assembly and packaging of the virion by budding through plasma membrane of cell.

IV. HIV glycoproteins and regulatory proteins.

- A. Glycoproteins.
 - 1. gp160 is a polyprotein, cleaved by host protease to gp120 and gp41.
 - 2. gp120 is the protein that binds the virus to the CD4 receptor on T helper cells.
 - 3. Neutralizing antibody is made to gp120.
 - 4. High antigenic variability of virus due to changes primarily in gp120 due to variable regions (V1-5). The constant regions do not vary.
- B. Regulatory proteins - tat, rev, nef, vif, vpr, vpu.

V. HIV Infection -clinical disease - potential for blocking infection

- A. Most clinical syndromes associated with HIV are linked to opportunistic infections by fungi, bacteria and other viruses
- B. Potential sites for interfering with infections take advantage of the unique biology of the viruses and/or virus encoded enzymes.
- C. There are drugs which interfere with both viral replication (nucleoside analog and non-nucleoside analog reverse Transcriptase inhibitors and virus assembly (protease inhibitors).

VI. The CDC -National Center for HIV prevention

<http://www.cdc.gov/nchstp/od/nchstp.html>

VII. Additional Reference

Interesting reading but not required:

1. A fascinating study of long term survivors of HIV, the CCR5 chemokine receptor and the deletion $\lambda 32$ CCR5 allele. McNicholl JM, Smith DK, Qari SH, Hodge T., (1997) Emerg Infect Dis **3**, 261-71 Host genes and HIV: the role of the chemokine receptor gene CCR5 and its allele.

Question: Prior to AIDS, what might have been the selective pressure to accumulate the $\lambda 32$ mutation in human populations?