

Immuno: AIDS – April 4 and 6

Reading from Abbas and Lichtman: pages 217-223

This reading is not as in depth as the material covered in lecture and in the lecture notes, but is an overview of the material and a good place to start.

The Human Immunodeficiency Virus

- Retrovirus that mainly **infects CD4+ lymphocytes** and causes progressive destruction of these cells
- HIV is made up of two RNA strands, a lipoprotein coat derived from host cells containing viral proteins

HIV life cycle

- Infection by major envelope glycoprotein is **gp120** which binds **CD4** and the chemokine receptors **CXCR4 and CCR5**, after which viral membrane fuses to the host cell using **gp41**
- virus is uncoated by a protease and DNA copy is formed by **reverse transcriptase**
- the DNA copy, or **provirus**, remains latent until the infected cell is turned on by an external stimulus; viral genes are transcribed along with the host's genes
- when the provirus is activated, new virus is made and shed from the host cell
- integrated HIV provirus may remain latent within infected cells for years

Pathogenesis of AIDS

- dendritic cells capture the virus as it enters the epithelia and **transport it to the peripheral lymphoid organs**, where it infects T-cells
- during the course of infection CD4+ T-cell count is depleted, resulting from the death of infected and uninfected cells
 - infected T cells might be killed by viral protein production that interferes with T cell synthetic machinery, which leads to apoptosis
 - the mechanism of death of uninfected cells is poorly understood, but may result from the chronic activation of CD4 cells which culminates in apoptosis
- other cells such as dendritic cells and macrophages can be infected and destroyed, but the most important and reliable indicator is T cells

Clinical features of HIV infection and AIDS

- after HIV infection, patients express mild acute illness with fever and malaise
- virus typically remains latent for 5-10 years, during which T cell count progressively declines; once T cell count declines to 200 cell/cubic mm, patients become susceptible to opportunistic infections and have **full-blown AIDS**
- **opportunistic infections** are typically caused by microbes that are cleared by cell-mediated immunity in normal individuals including *P. Carinii*, mycobacteria, and viruses (recall that T helper cells activate cytotoxic T cells), oncogenic viruses such as Epstein-Barr and herpesvirus, as well as extracellular bacteria
- **infected individuals mount an immune response to HIV** early on, including antibodies and CTLs against the virus, but it does not prevent chronic progression of the disease
- antibodies to gp120 are made ineffective by mutation of the virus, and CTLs are made ineffective because virus reduces expression of MHC class I receptors on infected cells

Therapies and Vaccination Strategies

- **HAART** (highly active antiretroviral therapy): two protease inhibitors and a reverse transcriptase inhibitor aimed controlling the replication of HIV- very expensive
- the control of HIV will require development of vaccines that activate the innate immune system, cause antibody production and confer mucosal immunity

Dr. Macleod's Lecture and Lecture Notes

HIV Types and Subtypes

- HIV-1 and HIV-2 are both related to simian immunodeficiency virus
- HIV-1 is most prevalent in the west, and have two forms: R5 and X5
- Interestingly, SIVs do not cause the profound CD4+ T-cell depletion seen in HIV, this may be because the cellular immune response in monkeys is not as large, providing less host cells for HIV to proliferate in
- **AIDS may result from the aggressive host response seen in humans**

Cellular Tropism and Viral Invasion

- Initially viral invasion occurs in the **peripheral lymph nodes**
HIV can infect a variety of cells, but undergoes initial massive replication in **CD4+/CCR5+ T-cells**
- The virus attaches to CD4 using the **gp120** envelope protein; gp120 is altered and interacts with CCR5 or CXCR4
 - **R5 strain** attaches CCR5; CCR5 is a receptor for **CCL3L** and pro-inflammatory chemokines like MIP-1
 - **X5 strain** attaches CXCR4; CXCR4 is receptor for SDF-1 (stromal cell derived factor – 1)
- HIV then expressed **gp41**, which mediates fusion with host cell membrane and entry of virus into host cell
- The HIV virus makes polyproteins (called Gag → virion core protein, matrix protein, Pol → reverse transcriptase, proteases, integrase, and Env), which are then cleaved to make functional proteins for the viral progeny
- The R5 strain is seen in host to host transmission, while X5 is seen during phenotype switching; X5 causes rapid progression to AIDS
- There are people who are homozygous for a CCR5 deletion and are naturally resistant to HIV, and allelic variation of CCR5 genes can delay or accelerate the progression of HIV to AIDS

AIDS is a Disease of the Mucosal Immune system

- The thing most stressed in lecture is that AIDS, particularly in its early stages, is a disease of the mucosal immune system. The key to finding a vaccine for AIDS is to examine the gut, which is the natural habitat of the virus.
- **Macleod spent almost 30 minutes on the first figure in the AIDS handout, so it is important to understand how the virus gets from the mucosa to the peripheral lymph nodes.**
- The AIDS virus enters the body through the genital mucosa where initial viral replication takes place in CD4+ T-cells in the lamina propria of the genital mucosa
- **M-cells and dendritic cells carry undegraded virus to peripheral lymph nodes** (typically the iliac lymph nodes). The HIV virus exploits the fact that B-cell differentiation cannot occur in the absence of unprocessed antigen. Therefore HIV is brought to the lymph node without attack.
 - Dendritic cells ferry the HIV virus (and other lentiviruses) on DC-SIGN (a membrane protein) to secondary lymphoid tissue; HIV remains infectious for days while being carried by dendritic cells
- In the peripheral lymph nodes, large numbers of infected CD4+ memory T-cells are killed (either by activation induced or autonomous cell death), which leads to regional immunodeficiency, destruction of lymph nodes and chronic activation (because immunodeficiency leads to invasion by opportunistic microbes) and subsequent

destruction of even more CD4+ T-cells (note the figure on page 19 of the handout that shows the absence lymph nodes in the gut due to chronic HIV infection)

- HIV can lead to neurological damage, and the severity of symptoms depends on age, genetics, and the variant of HIV-1

Intracellular Innate Resistance to HIV

- Eukaryotic cells have naturally occurring **RNA editing proteins (APOBEC3G and APOBEC3F)** that are similar to bacterial restriction enzymes; these cause hypermutation in the coding strand of viral DNA
- Cells expressing APOBEC are termed ‘nonpermissive’ and the viral protein Vif increases infectivity of HIV-1 by inhibiting APOBEC activity
- Look at the figure called “**RNA editing in mammals**”

Genetic Resistance to HIV

- Chemokine receptors are coreceptors for HIV, and therefore their increased expression increases susceptibility to HIV infection; **PSC-RANTES** is a vaginal topical agent that reduces expression of CCR5 receptors
- Expression of **CCL3L1**, a ligand for CCR5, influences susceptibility to HIV; if high levels of CCL3L1 are being expressed and taking up the CCR5 receptors, HIV does not have a method of invading host cells
- Other ligands for CCR5 are the pro-inflammatory cytokines MIP- α and MIP- β
- **CCL3L1 is also something Macloed spent some time on, he also brought it up during a review, also check figure called “No vacancy”**

Adaptive Immune Responses to HIV

- During the initial phase of HIV infection, the body mounts a response to HIV: there are increased numbers of CD4+ and CD8+ T-cells, as well as HIV-1 specific antibodies
- After 1-3 months the acute phase subsides and HIV levels decline to a **set point viremia**, this takes 4-6 months
- HIV is about the evade the host response by rapid genetic diversification of gp120, which evades the antibody mediated response
- CTLs against the HIV are also important in resolving the acute stage of the virus, and particular alleles of the B haplotype of HLA (Human Leukocyte Antigen) slow the progression of the disease
- HIV infection causes the progressive loss of both mature effector CD4+ cells and their precursors (a “double blow”)
- Refer to the figured entitled “**schematic diagram of course of HIV-1 infection**”, note the viremia set point and “CD4+ inflection point” (when the symptoms become serious)

Immune Evasion by HIV

- HIV protein **Nef** causes reduced expression of MHC I
- **Nef** also causes expression of **Fas ligand** on the surface of infected cells, when HIV specific cells (like CTLs) bind an infected cell, the ligand binds Fas and causes apoptosis (Fas is the ‘death receptor’)
- HIV also evades killing by NK cells by reducing expression of HLA

Anti-HIV Drug Development

- In the western world, HAART, a three drug cocktail of two protease inhibitors and one retroviral inhibitor, is the treatment for people with full blown AIDS, multiple drugs delay resistance by HIV
- Specifically HAART is AZT (reverse transcriptase inhibitor), 3TC and indinavir
- HAART does not eradicate HIV
- Look at the diagram at second to last page called “**Hypothesized effect of HAART**”

HIV/AIDS Vaccine

- A vaccine must be able to induce mucosal immune responses to HIV, especially in the genital tract
- Live attenuated vaccine with **Nef** eliminated, has been shown to be effective in primates using SIV
- There is also evidence that individuals in the population exposed to a naturally attenuated strain of HIV may have resistance to HIV
- **There is a nice little summary the end of the handout giving 5 reasons why making a protective vaccine is so difficult**

So that's it. Hopefully this is helpful to you, and if you find any mistakes please email me at rshah16@uiuc.edu and I'll repost with corrections.