Lecture 34 Outline

• Cell mediated Immunity:
  o Cytotoxic T cells
  o Helper T cells

• HIV:
  • Epidemiology & History
  • Mechanism
  • The Elusive Cure

Homework Problem:
The process by which the body comes up with the correct antibodies to a given disease is most like?
(a) going to a tailor and having a suit made to fit you.
(b) going to a shoe store and trying on shoes until you find a pair that fits.
(c) picking out a video that you haven’t seen yet.
(d) selecting a lottery prize-winner by means of a random drawing.

Humoral immunity: B cells = if you take sera from someone and inject it into someone else, you can transfer the immunity from the first person to the next because what you are transferring is the antibodies. So B cell mediated.

Cell mediated Immunity: T cells = cannot be transferred by transferring sera. The cells themselves (T cells) have to be transferred. Antibodies can only deal with antigens that are extracellularly located. Virus particles inject themselves into cells where antibodies can’t get to them!

Cytotoxic T cells (=Killer T cells) evolved to deal with viruses masquerading as self

Questions addressed in today’s lecture:
• How does the immune system recognize “disguised” invaders?
• How do cytotoxic T cells get rid of infected cells?
• How do T cells distinguish between infected cells and macrophages?

Self vs Non-Self Distinction Mediated by MHC Class I and II proteins - T cell “Education” in the Thymus
  MHC I: found on all cells of an individual
  MHC II: primarily found on B cells and macrophages

Major Histocompatibility Complex (MHC) binds viral particles and then moves to cell surface, result >> exposed antigen. MHC-antigen complex recognized by T Cell Receptor on Killer T cells.

T Cell Receptor Diversity mechanism is similar to Antibody Diversity mechanism

Cytotoxic T cell Recognition of Virus-Infected Cell triggers destruction of infected cell. Activated Cytotoxic T cell releases preforin, which inserts into membrane of infected cell and forms a huge pore (called lysis). Water rushes in >>> kills infected cell and source of reproducing viral particles.

Specific Immunity: Helper T cells
- [T cell receptor & CD8] on Cytotoxic T cells bind to [MHC II + antigen] - presenting cells >> destroys infected cell (preforin)
- [T cell receptor & CD4] on Helper T cells bind to [MHC II + antigen] - presenting cells >> triggers release of interleukins and cytokines >> stimulate proliferation of T and B cells and antibody production. Helper T cells coordinate and amplify Humoral & Cell-mediated Responses.

(Movie example of binding event.)
HIV & the Immune System

HIV Particles Invade Helper T Cells – we know so much about how helper T cells work because of HIV!

HIV - Epidemiology & History

Demographic of HIV:

- Adults and children estimated to be living with HIV/AIDS as of end 2001
  (2001 World Health Organization data)
- 40 million people with HIV
- 5 million newly infected in 2001
- 3 million deaths in 2001
- Highest increase in infection rate in Eastern Europe and Central Asia
- In Kenya, AIDS has replaced retirement as the leading reason people leave their jobs...

Origin of HIV: probably Zoonosis (= when disease is transferred from animals to man)

HIV-1 - most prevalent form
- traced to SIV in Pan troglodytes troglodytes (chimp)
- food source in west central Africa

HIV-2 - traced to sooty magabey monkey; - also a food source

HIV Anatomy

--Virus capsule contains all elements essential for replication of virus
--Capsule protected (shielded from basic immune defenses) by a membrane coat derived from the host.
--Membrane coat studded with glycoproteins gp120 and gp41
--gp120 and gp41 connected to host membrane by a fragile stalk which can break off >>> produces free-floating gp120 & gp41

Contents of viral capsule:

HIV RNA
Reverse transcriptase – enzyme that makes DNA from RNA
Integrase- enzyme that integrates the HIV DNA into host cell genome
Protease- enzyme that processes (chops up) newly synthesized HIV protein
RNA coding for gp120 & gp41

How HIV Kills Cells & Compromises the Immune System

1. Blocks CD4 Receptors on Helper T Cells:
   - gp120 binds to the CD4 coreceptor on helper T cells. These T cells can not bind MHC complexes anymore and so are non-functional. Weakens immune response.

2. Syncytia Formation:
   - virus membrane coat has many gp140s. Each one can bind another CD4 molecule on a helper T cell.
   - Cause aggregation (clumping) and precipitation of helper T cells.

3. Lysis of helper T cells:
   - when virus replicates and buds off the host cell it takes some of the host cell membrane as its membrane coat. So many buds that T cell membrane comprised >>> lysis of T cell!

Once host cell infected, HIV remains quiescent until Helper T cell is activated. Activation of T Cell causes transcription of viral HIV DNA, proliferation of the HIV virus !!, and lysis of Invaded T Cell

HIV Life Cycle:

HIV enters cell. Virus freed of membrane coat and capsule. Reverse transcriptase synthesizes DNA from RNA. Integrase incorporates viral dna into host genome. Virus quiescent. Once helper T cell activated, viral DNA transcribed into RNA and translated producing a long precursor protein. Precursor protein cutup into individual enzymes that are packaged with the viral RNA into a new capsule. Capsule buds off the host cell membrane, taking membrane along as its new membrane coat. Causes T cell lysis.
HIV Outruns the Immune System:
As it stands our immune systems could probably cope with and win the battle against HIV. The MOST insidious thing about HIV is its high mutation rate:
Normal Mutation rate:
   1 mutation / 1,000,000,000 nucleotide pairs
HIV Mutation Rate:
   1 mutation / 2,000 nucleotide pairs (= 1 million times the mutation rate of cancer cells!)
Everytime a B cell or T cell mounts a successful response (develops an effective antibody or T cell receptor) against gp120 or gp41, gp120 or gp41 have changed their shape because they mutate faster than the B and T cell rate for producing novel antibodies. High virus mutation rate due to the fact that HIV is a retrovirus (info carried by RNA, not DNA). Reverse transcription process generates more mutations.

Elusive Immunization ... >>> antibodies to gp120 (gp120 changes too fast)
Elusive Cures...
- Block Entry: gp120 mutation rate too high
- Block reverse transcriptase: too non-specific so far, also block normal host cell reverse transcriptase
- Block integrase: not absolutely necessary for HIV to integrate (so not a lot of research here)
- Block protease: most used treatment, but not a cure. After initial infection, no additional viral particles make it into bloodstream. Slows progression tremendously, but must stay on drugs!

HIV Progression
Monitored by determining concentration of T cells in blood.
Initial infection = immune system responds normally. But high mutation rate of virus causes some of the virus to remain hidden and proliferate. Eventually HIV takes over.