RAISON D’ETRE OF THE IMMUNE SYSTEM:

To Distinguish Self from Non-Self Thereby Protecting Us From Our Hostile Environment.

Innate Immunity

Adaptive Immunity
Innate immunity:

(Antigen nonspecific) defense mechanisms that are used by the host immediately or within several hours of encountering antigen.
lysozyme in tears and other secretions

commensals

skin

physical barrier

fatty acids

commensals

removal of particles by rapid passage of air over turbinate bones

mucus, cilia

acid

rapid pH change

commensals

flushing of urinary tract

low pH and commensals of vagina
Cellular Components of the Innate Immune Response

- NK cells
-Granulocytes

**Antigen Presenting Cells:**
- Dendritic cells
- Macrophages
Acquired Immunity
Is adaptive and displays four characteristic attributes:

• Antigen specific
• Diversity
• Immunologic Memory
• Self/nonself recognition
Adaptive Immunity

Involves two major types of cells:

Lymphocytes:
a. T cells
b. B cells

Antigen presenting cells: (APC)
a. Macrophages
b. B cells
c. Dendritic cells
Antigen Presenting Cells

These specialized cells internalize antigen by phagocytosis or endocytosis and then express parts of the antigen on the cell surface. These cells are distinguished by two properties:

1. Express class II MHC molecules

2. Provide co-stimulatory signals necessary for activation of T-cells.
Lymphocyte Functions

B-cells (CD19 and CD20):

- Can present antigens. Not the primary function.
- B cells secrete their antigen receptors: antibodies.
Antibodies cont.

• Antibodies can work at distal sites. Are in interstitial fluids, blood and lymph fluids.

• Antibodies can help elicit clearance of an antigen, or can prevent proper functioning of the antigen: neutralization.

• Antibodies are effective against extracellular pathogens, such as bacteria, or virus that has budded from the cell.
Lymphocyte Functions

T-cells (CD3): Their antigen receptor is surface bound.

1. Cytotoxic T cells (CTL) kill infected cells.
   • Control intracellular pathogens such as viruses.
   • Require cell to cell contact to recognize antigen.
   • Are identified by the surface marker CD8.
Lymphocyte Functions

T-cells cont.:

2. Helper T cells (Th) provide “help” for cytotoxic T cells and B cells.
   • Also require cell to cell contact to recognize antigen.
   • Secrete cytokines and chemokines.
   • Are identified by the surface marker CD4.
Antigen: ag

APC

CD4+ T-cell

CD8+ T-cell

Death signals:
Perforin
Granzyme etc.

Cytokines
And
Interferon

B-cell

Lysis

Clearance,
Neutralization
Lymphocyte Receptors

T and B cells use specialized receptors to make physical contact with non-self.

Although the structure of these receptors are similar, they embrace non-self in very different ways.

<table>
<thead>
<tr>
<th>Cell</th>
<th>Antigen receptor</th>
<th>Binding specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>B cell</td>
<td>Immunoglobulin (Ig)</td>
<td>Soluble antigen</td>
</tr>
<tr>
<td>T cell</td>
<td>T cell receptor (TCR)</td>
<td>Processed antigen</td>
</tr>
</tbody>
</table>
The T-cell Receptor

\[ \text{α chain} \quad \text{β chain} \]

\[ V_\alpha \quad V_\beta \]

\[ C_\alpha \quad C_\beta \]

Hinge

http://bioweb.wku.edu/courses/biol328/TcR.png
The T-cell Receptor Complex

http://www-immuno.path.cam.ac.uk/~immuno/part1/lec08/TCRcomplex.gif
Antibody Structure

http://www.kensbiorefs.com/humphy.html
Antigen Specificity:

Is determined by interactions between cellular receptors (T-cell receptor and B-cell receptor complex), antigen and human leukocyte antigens (HLA).
Human Leukocyte Antigens:

Are encoded by the major histocompatibility complex (MHC) on chromosome 6 in humans.

**Class I antigens** are found on all nucleated cells.
- \( = A, B, C \)
  - CD8+ T cells recognize antigen plus MHC Class I

**Class II antigens** are primarily on antigen presenting cells (macrophages, dendritic cells and B cells).
- \( = DR, DP, DQ \)
  - CD4+ T cells recognize antigen plus MHC Class II
Processing and presentation of antigens

And David S. Goodsell for: Molecule of the Month

http://www.rcsb.org/pdb/molecules/pdb63_3.html
T-cell recognition of antigen

- Infected cell
- MHC molecule presents peptide
- Antigen peptide bound to MHC molecule
- T-cell receptor recognizes MHC and peptide
Diversity of the adaptive immune response is due to the diversity of the T-cell and B-cell receptor complexes.
Signal joint (sj) and coding joint (cj) TREC production from the $\alpha/\delta$ locus

MHC - peptide binding

T-cell recognition sequences

Anchor sequences bind to the MHC.
Peptide sequences effect MHC binding and TCR recognition:

- **Binds MHC And TCR**
  - [Diagram showing binding of multiple peptides]

- **Loss or decrease In MHC binding**
  - [Diagram showing decreased binding for a subset of peptides]

- **Loss or decrease in TCR binding**
  - [Diagram showing decreased binding for a different subset of peptides]
Antibody – antigen recognition

Antibodies recognize either linear epitopes or epitopes in secondary structures. A change is the amino acid sequence or secondary structure can eliminate or diminish the antibody binding.
Activation of T-cells requires signaling through the TCR and co-stimulatory molecules.
Memory

Is established through the clonal expansion of activated T or B cells:
Self/nonself recognition:

Is achieved through the interaction of antigen receptors, HLA, and antigen.

Responses to this complex are controlled through a process of “education.”
Tolerance:
The inability to react with self.

Autoimmunity:
The state in which tolerance to self is lost.
Immune responses are most efficient in tissue parenchyma.

Lymph nodes and the spleen provide architectural support for cell-to-cell interactions, and serve as “filters” for fluids draining other tissues.
Immune Response To HIV Infection
HOW THE IMMUNE SYSTEM Responds TO HIV

1. Macrophages ingest viral particles and break them down into small peptides (epitopes).

2. Selected epitopes are displayed on the surface; helper T cells bind to them.

3. Helper T cells secrete proteins that activate other immune cells.

4. B cells release antibodies, which bind to virus.

5. Macrophages ingest and destroy antibody-bound particles.

4a. Killer T cells attack infected cells bearing specific epitopes.

5a. Infected cell dies.
Infection Levels (Separate Scales)

- **CD4+ T-cell**
- **CD8+ T-cell**
- **HIV**
- **Antibodies**

Acute

- 4 – 8 weeks

Asymptomatic

AIDS and Death

Levels (Separate Scales)

Years
Immune Response to HIV

• **CD4:** Helper T-cell responses
• **CTL:** Cytotoxic T-cell responses
• **B-cell:** Antibody responses
• **APC:** Antigen Presenting Cells
CD4 Responses To HIV

CD4+ T-cell responses to antigens are usually indirectly measured by proliferation (cell division).

- $^3$H-Thy uptake
- CFSE

- Cytokine production is another measure of activation
  - Eliza
  - ELISpot
CD4+ T-cell responses are predictive of disease progression.

In most individuals, the following pattern is observed:

**CD4+ T-cell responses decline at various stages:**

- **response to HIV and recall antigens** (early)
- **response to alloantigens** (mid)
- **response to mitogens** (late)
- **expression of IL-2 receptor (CD25)**

In addition, there is aberrant cytokine production

- **production of IFN-γ, IL-2**
- **production of IL-4, IL-10**
HIV SPECIFIC CTL

CTL responses are made to various epitopes on:
- Gag, RT, Env, Pol, Nef, Vif, Vpr

- Inverse correlation between viral load and levels of circulating HIV-specific CTL.

- Emergence of CTL escape mutants over time.

- Depletion of CD8+ T cells from macaques prior to infection with SIV, leads to higher viral loads and more profound immunosuppression.

- Absence of detectable HIV-specific CTL, or oligoclonal CTL responses are associated with poor clinical outcome.
CTL Responses To HIV

CTL responses are measured by
• $^{51}$Cr release assay (Killing)
• ELISpot (Cytokine release)

Antigen specific CD8+ T-cells can be quantified by tetramer staining. (Number of specific cells)
CTL fail to eliminate HIV-1

- Many chronically infected individuals have vigorous HIV-1-specific CTL responses yet they almost always fail to adequately suppress the virus. Why?

  - Epitope escape?
  - CTL Exhaustion?
  - Suboptimal CTL?
Donor A: CD8 response to SL9

![Graph showing the proportion of SLYNTVATL GAG tetramer, Gamma-INF, and SLYNTVATL over time from 01/85 to 01/95.](image-url)
1 Original population of HIV replicates well

2 Immune cells able to recognize original epitope reduce viral population

3 Escape mutant carrying unrecognized version of epitope appears and replicates unopposed for a time

4 Immune system eventually gains control over mutant, but another emerges

5 Repeated production of mutant viruses leads to great viral diversity
Antibody Responses
General Properties of Anti-viral Antibodies

• Can be generated to any accessible portion of the virus.

• Effective in blocking entry (neutralizing) if directed to viral receptors such as gp120 of HIV.

• Can block fusion (neutralizing) if antibody (Ab) binds to fusion protein such as gp41 of HIV.

• Can effect clearance of virus if it binds the virus and then binds Fc receptors on monocytes and macrophages.

• Can also bind complement and kill enveloped viruses.

• Most effective if they are present at the site of viral entry.
Gp120 and Gp41-mediated fusion

Gp120 is presented as a trimer. The monomer does not present the proper epitopes.

CD4 binding site is devoid of glycosylation and relatively conserved between isolates but is masked by V1V2 loops and is in a depression.
Escape from Nab by epitope mutation

![Graph showing viral infectivity (%) against plasma dilutions]

- Normal human plasma
- WEAU day 16 plasma
- WEAU day 72 plasma
- WEAU day 136 plasma
- WEAU day 212 plasma
- WEAU day 391 plasma
- WEAU day 772 plasma

Legend: 16-2 env
HIV and APC’s

• APC’s may exhibit altered:
  chemotaxis
  IL-1 production
  antigen presentation
  oxidative burst response
  antimycobacterial activity

• Antigen presenting cells can act as trojan horses.
Dendritic Cells and DC-SIGN

DC-Specific, ICAM-3 Grabbing, Nonintegrin.

Interaction of DC-SIGN with ICAM-3 establishes the initial contact of the DC with a resting T-cell.

This is important because of the low number (100-1000 copies/cell) of MHC-peptide ligands on the DC. This enhanced binding allows the T-cell to scan the surface of the DC.

DC-SIGN also binds the glycan-rich HIV-1 envelope in the absence of CD4.
Proposed pathways for the transmission of HIV-1 to T-cells.
Why does the immune response fail to clear HIV?

• HIV integrates into the host genome. Therefore, to eliminate HIV, infected cells must be killed.

• Host factors can paradoxically enhance HIV replication. Therefore, by responding to HIV, CD4+ T-cells can be destroyed.
Why does the immune response fail to clear HIV?

• HIV can mutate and escape immune mediated opposition.

• Suboptimal CTL responses can be elicited.
Why does the immune response fail to clear HIV?

• Sugar coating (glycosylation) and folding of gp120 protects against Ab recognition.

• Critical binding sites on gp41 are revealed for only a short period of time.
Why does the immune response fail to clear HIV?

• APC's may exhibit altered functions diminishing their ability to elicit immune responses.

• Antigen presenting cells can act as trojan horses, spreading HIV to CD4+ T-cells as they begin to respond to antigen.
Why does the immune response fail to clear HIV?

**Role of viral genes:**

**Tat:** Extracellular Tat stimulates CD4+ and CD8+ T-cells.

**Nef:** Intracellular Nef appears to activate cells to promote viral replication. Affect on cellular function?

Intracellular Nef downregulates CD4 and MHC class I molecules. In vivo significance?