Foundations of Public Health

Immunology

Cell Mediated Immunity:
Antigens, T cells & Cytokines
Objectives

• Describe the cell mediated immune response and characteristics of T cells
• Identify the characteristics of antigens, haptens, & mitogens
• Describe the process of positive & negative selection of T cells in the thymus
• Identify the similarities & differences of CD4 vs. CD8 cells
• Identify the similarities & differences of Th1 and Th2 cells
• Identify the characteristics and functions of cytokines
Cell Mediated Immunity (CMI)

- **Second brand** of acquired immune response (Block 3 covered AMI)
- **T lymphocytes** strongly influence & regulate an immune response
- T cells stimulate other immune cells to fight an infection by **cytokine** production
- T cells can kill other cells!!
Cell Mediated Immunity

- Important defense against **intracellular** organisms
- Antibodies cannot reach inside cells
- T cells critical to bridge the gap
- Directly **target & attack** infected cells (specificity)
Important Concepts for Block IV

• T cells must be able to “see” both self & foreign antigens

• T cells have the power to directly attack Ag
  • Must keep them in control!

• T cells can help B cells
  • Improves antibody mediated immune response
What is self?  Answer: MHC

• How does a B or T cell know that it is bumping into one of our cells or into a bacteria or virus (foreign antigen)??

• The immune system first needs to know what is foreign vs. what is self

• Major Histocompatibility Complex (MHC) molecules are the “self” identifiers.
Major Histocompatibility Complex

- Two classes of membrane proteins encoded by the MHC genetic locus
- (MHC I & MHC II)
- These genes are **found in all mammals**, not microorganisms (i.e. self!)
- Function to display antigen peptides to T cells
What is foreign? Answer: Antigens

- Substances foreign to the host which are capable of inducing an immune response and of reacting specifically with the products (cells / antibodies) of that response.
- These substances are more accurately called immunogens.
Potent Antigen Characteristics

- **Proteins** > Polysaccharide > Lipid
- **Chemical complexity**: bacterium > homopolymer
- **Molecular size** – macromolecules (MW > 10 Kb)
- **Immunodominant** epitopes: exposed & flexible
- **Rigidity** – particular Ags taken up by cells of RES (phagocytes)
- **Foreign** – degree of difference from host
- **Host factors** also play a role, including physiological conditions, genetic make-up (MHC)
Definitions:

• **Antigenic determinants** (Epitope): actual portion of Ag molecule that determines specificity and binds to product of immune response

• **Lock & key theory** – binding of the epitope (via MHC & the TcR) is the key that opens the locked T cell, priming it for action
Antigen does not necessarily = Immunogen

• An antigen simply can be a molecule that binds to an antibody or to the TcR
• However, not all antigens are capable of eliciting an immune response (immunogen)
• Haptens & mitogens are 2 examples
**Hapten**

- **Incomplete antigen**
- Small molecule that *cannot elicit* an immune response without a larger “carrier”
- Can react *specifically* with the product of an immune response

**Mitogens**

- Substances which can activate T & B cells *non–specifically*
- Cells multiply in response to the correct mitogen
- Used as an *indicator of cell type and function*
**Thymus**

- Primary lymphoid organ, **site of T cell maturation**
- Contains epithelial cells, dendritic cells, macrophages, & T cells (of course)
- T cell **precursors** are at different stages
- **Final synthesis** of T cell receptors (TcR), also called the antigen receptor, occurs here
**Thymus: The Policeman**

- All maturing T cells undergo selection:
  - Positive selection
    - TcR **weakly** recognizes **self** MHC
    - T cell can now “see” you antigen presenting cell
    - **Passes inspection** & continues into circulation!
  - Negative selection
    - TcR **strongly** recognizes **self** MHC
    - T cell can strongly “see” both your APC and your self antigens
    - **Fails inspection** – these cells would attack self!!
T Cell Selection

Stem cell → Double negative (CD4⁻CD8⁻) Pro-T cell → Double positive (CD4⁺CD8⁺) immature T cell → Pre-T cell

- Weak recognition of class II MHC + peptide → Positive selection
- Weak recognition of class I MHC + peptide → Positive selection
- No recognition of MHC + peptide → Apoptosis
- Strong recognition of either class I or class II MHC + peptide → Apoptosis
- Failure of positive selection ("death by neglect")

Negative selection

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Two Types of T cells

- **CD8+ class**, the cytotoxic cells
  - Have CD8 co-receptor
  - **CD8+ cells only recognize MHC I**
  - Have cytolytic ability to kill other cells
  - Essential for **cell mediated immunity** & control of intracellular pathogens

- **CD4+ class**, the helper cells
  - Have CD4 co-receptor
  - **CD4+ cells only recognize MHC II**
  - Two subsets of helpers: Th1 and Th2
  - Essential for **antibody mediated immunity** & help B cells to control extracellular pathogens
T Cell Molecules Needed for Ag Recognition

- **T cell Receptor (TcR)**
  - Heterodimeric protein expressed that **recognizes antigen**
  - **Tremendous diversity** as coded by variable gene segments V, D, J & C
  - Does **not** undergo somatic hypermutation

- **Co-receptors (CD4, CD8) recognize MCH**

- Additional **accessory molecules** have important signal transduction & adhesion functions (CD28 costimulation)
Refer to page 87 in the textbook for an additional diagram that clearly shows the interactions between T cells and APCs.
Note the **structural similarities** between the TcR and Antibodies!

Additionally, T cells have co-receptors (CD4 & CD8 depending on type) that restrict their recognition of antigens to specific MHC classes.
Human Immunodeficiency Virus (HIV)

- A **retrovirus** (lentivirus, “slow virus”)
  - Reverse transcription of viral RNA into DNA
- RNA surrounded by a protein capsid (p24)
- **Embedded viral proteins** (Env: cap of gp120, stem of gp41)
- **Enveloped virus** (from host cell)
CD4 Cells & HIV

- HIV enters the body & is taken up by dendritic cells
- Later, CD4+ cells come to the rescue and also become infected
- HIV (gp120) binds to the CD4 co-receptor (CXCR-4) to enter the T cell
- CD4 cells are depleted over time as the virus begins to kill more T cells that are produced
CD4 Cells & HIV

- **Reduced # of CD4** cells cannot fully activate CD8 T cells
- Then **CD8 T cells cannot kill HIV infected cells** & the virus continues to infect new cells
- **Memory T cells** express the most CD4 co-receptors & consequently are **most vulnerable to HIV**
- HIV depletes memory cells & now the immune system loses its ability to quickly respond to known antigens
- **Immunodeficiency results!!**
- Infections with other organisms can no longer be controlled
HIV Course of Infection

1. 1–2 months following initial exposure, HIV in blood peaks.
2. 1–2 months after exposure, CD4 T-cell numbers plunge.
3. Immune response reduces viral load.
4. Levels of HIV in blood remain low.
5. CD4 T-cell population declines steadily.
6. Huge but indefinite numbers of latent HIV in lymphatic tissue. (Color below line indicates viral load in lymphatic tissue.)
8. Rise of HIV in blood as immune system breaks down.
GLOBAL TOTALS

- People living with HIV/AIDS, December 2000: 36.1 million
- New infections in 2000: 5.3 million
- Deaths due to HIV/AIDS: In 2000: 3.0 million
  Cumulative: 21.8 million

In 2005:

- Estimated **38.6 million** [33.4 – 46.0 million] living with HIV worldwide
- 4.1 million [3.4 – 6.2 million] newly infected in 2005
- 2.8 million [2.4 to 3.3 million] died of AIDS in 2005
Global Burden of HIV/AIDS

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<th>Region</th>
<th>People living with HIV 2005</th>
<th>New infections 2005</th>
<th>AIDS deaths 2005</th>
<th>Adult prevalence %</th>
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<td>Sub-Saharan Africa</td>
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<td>4.1 million</td>
<td>2.8 million</td>
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Cytokines: They’re Back!

- Mediators which act as signals between cells
- Also known as lymphokines, monokines interleukins (IL), interferons, chemokines, colony stimulating factors (CSF)
Cytokines: Characteristics

- **Low** molecular weight glycoproteins
- **Functionally related** families – not chemically related
- Same cytokine can be produced by several cell types
Cytokines: Characteristics

• **Actively** synthesized & secreted (not stored)
• **High affinity** – great potency at low concentrations
• May act locally by binding to cell receptors
• May be **multifunctional**
• Rarely exert effect alone (words in a sentence)
• Involved in the **regulation of all biological processes** (not just immune response)
Cytokines & Regulation

• Cytokine production is transient and tightly regulated
• Act synergistically or antagonistically
• Regulate expression of receptors, self & other cells
  • Cytokine receptors shed and bind soluble cytokine molecules
  • Receptor antagonists bind to specific receptor, don’t transmit signal
  • Cytokine Inhibitory Proteins may bind to receptor or cytokine
Cytokine World
Cytokines are extremely important to maintain the immune system and other physiological functions.
In Summary

- Cell mediated immune response & intracellular organisms
- Self vs. foreign
- MHC restriction for T cells (e.g. CD4 recognizes MHC II)

- Different types of antigens – immunogen, hapten, mitogen
- T cell selection is thymus
- Types of T cells
- Cytokines
Self-Test Questions

• How is cell mediated immunity different from humoral immunity?
• How can the immune system recognize self? What is foreign?
• What happens if the T cell receptor (TcR) strongly recognizes self MHC?
• What are the 2 types of T cells?
• What MHC does each type recognize?
• What type influences CMI? AMI?
• How does HIV deplete the immune system & memory?
• Name 3 characteristics of cytokines.