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!!

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 MHC
- 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

- Category A: Acquirement or initial establishment
  - 3 weeks following exposure to virus, rapid replication
  - Delayed immune response
- Category B: Symptomatic
  - Early indications of severe failure
  - 5 months after exposure
  - HIV population in blood
  - 3 weeks after appearance of CD4 lymphocytes
- Category C: AIDS-indicator conditions
  - Rapid decrease in CD4 lymphocytes
  - HIV population in blood

Global Burden of HIV/AIDS

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<th>New infections 2005</th>
<th>AIDS deaths 2005</th>
<th>Adult prevalence</th>
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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.