ADAPTIVE IMMUNITY

The Specific Immune Response
In Physiology Today

**Diagram:**

- **Infected cell**
  - Viral antigen
  - Class I MHC protein
  - T-cell receptor

- **Cytotoxic T cell**
  - Activation

- **Macrophage**
  - Viral antigen
  - Class II MHC protein

- **Helper T cell**
  - IL-1
  - TNF
  - IL-2
  - and other cytokines

- **Channels**
  - Water moves in, cell swells and dies; virus cannot replicate and is released

- **Infected cells**
  - Perforin

**Flow:**

1. Begin
2. Viral antigen activates Cytotoxic T cell
3. Activated Cytotoxic T cell releases perforin
4. Perforin enters infected cell
5. Infected cell swells and dies
6. Virus cannot replicate and is released
The Adaptive Arm of the Immune System

• Specific Immune Response
• Internal defense against a specific *pathogen*
• Acquired as you are exposed to diseases
  – The immune system “learns”
  – Memory cells remain for every pathogen you are exposed to
• My adaptive immunity is not the same as yours!
Once a lymphocyte has recognised a foreign antigen it expands to eliminate the infection. Some cells then become long lasting >20 years ‘memory’ cells. Memory cells respond very quickly to subsequent exposure to antigen.
The Adaptive Arm of the Immune System

- Controlled by the lymphatic system
- A coordinated mechanism involving a link between APC’s and lymphocytes
  - APC’s are non-specific
  - Lymphocytes are specific
- Identifies **specific** foreign antigens
Lymphocytes

• Lymphocytes must recognize the specific pathogen to be attacked
• Any antigen that the host immune cell does not recognize as self
  – Lymphocytes recognize antigens
    • Proteins or large carbohydrates
    • Protein coats of virions
    • Antigens on foreign cells
    • Cancer cells
    • Transplanted cells
• Lymphocyte trafficking increases the likelihood that they will contact their specific antigen
  • Lymphocytes are circulating through lymph, lymph organs and the blood all the time
B Lymphocytes

- Mature in Bone marrow
- B-cell activation occurs in the spleen or lymph nodes
- APC to helper T-cells
- Produce plasma cells which secrete antibodies
T Lymphocytes

• Migrate and mature in the Thymus gland
  – Helper T cells
    • Necessary for amplification of the immune response
    • Activate B-cells and Killer T-cells and other Helper T-cells
  – Killer (Cytotoxic) T cells
    • Attack and kill your own cells that have become cancerous or infected or damaged
Roles of Lymphocytes

**Encounter and recognition**
- Begin
- Antigen
  - B cell
  - Helper T cell
  - Cytotoxic T cell

**Activation**
- (Cytokines)
  - Plasma cells
  - Antibodies
  - (Cytokines)

**Attack**
- Guide phagocytes, complement, and NK cells to attack antigen-bearing cells
- Directly attack antigen-bearing cells
Encounter and Recognition

• Encounter and recognition of antigen by lymphocytes
  – Each lymphocyte is specific for just one type of antigen
  – ≈ 100 million distinct antigen receptors
  – Progeny of lymphocytes are called clones
Stages of Specific Immune Response

*Lymphocyte Activation*

- Lymphocyte activation
  - Binding of antigen to receptor on lymphocyte
  - Triggers the lymphocyte to undergo multiple rounds of mitosis to produce clones – *clonal expansion*
  - Some lymphocytes will be *effector cells* and be part of the attack response
  - Some lymphocytes will be set aside as *memory cells* for quicker subsequent responses in the future
Stages of Specific Immune Response

The Attack

• The attack launched against specific antigen by the activated lymphocytes
  ◆ Activated B cells differentiate into plasma cells and secrete antibodies into the blood (but themselves remain in lymph nodes or spleen)
  ◆ Activated Killer T cells directly attack and kill cells
  ◆ Activated Helper T cells release IL-2 which amplify the immune response

• Plasma cells, helper T cells, killer T cells that participated in the attack die by apoptosis
  – Prevents the immune response from becoming excessive and potentially destroying its own tissues
The 5 classes of Antibodies Produced By Plasma Cells

• Immunoglobulins

• 5 classes based on the amino acid sequence of constant ends

• Classes
  – IgA
  – IgD
  – IgE
  – IgG
  – IgM
IgA
Immunoglobulin A

• Mucosal immunity
  – Secreted by mucus membranes lining digestive, respiratory, UG tract and prostate
  – Found in body secretions
    • Breast milk
    • Sweat
    • Tears
  – Provides protection against microbes that multiply in mucus secretions
IgD

Immunoglobulin D

• Little known regarding function
IgE
Immunoglobulin E

- Defense against multicellular parasites
- Implicated in allergic responses
  - Activates mast cells and/or basophils to secrete histamine
- Found in lungs, skin, mucus membranes
IgG
Immunoglobulin G

- Most abundant antibody in blood and ECF
  - Binds to many kinds of pathogens (bacteria, virions, fungi)
  - Causes agglutination
  - Neutralizes toxins
  - Activates the complement pathway
  - Opsonization for phagocytosis
  - Directs marked virions to the proteosomes
- Crosses the placenta for fetal immunity
IgM
Immunoglobulin M

- Produced primarily by B-cells in the spleen
- Found in plasma and lymph
  - Too large to move into ECF
- Most abundant upon first exposure to an infection
  - Natural antibody
- Causes agglutination
- Activates the complement pathway
Function of Helper T Cells

• Helper T Cells
  – Express **CD4** proteins in their plasma membranes
  – Amplify the response of B-cells and other helper T-cells
  – Activated by binding to antigen
    • Once activated, the Helper T-cell secretes **IL-2**
      • **IL-2** is a *cytokine* that acts on B-cells and other T-cells
    • B-cells cannot function adequately unless they are stimulated by **IL-2**
Function of Killer T Cells

• Cytotoxic T cells
  – Express **CD8** proteins in their plasma membranes
  – Must travel through the blood and lymph to seek out their targets
  – Attack and directly kill cells by secreting chemicals
  – Attack host cells (your own cells):
    • Cancer cells
      – Any damaged or dysfunctional cell
    • Infected cells
      – Cells infected with any pathogen
CD Classification of T Cells

- CD proteins are in the plasma membrane of T cells
- CD4:
  - Helper T cells
  - Macrophages
- CD8:
  - Cytotoxic T cells
- CD4 populations decimated by HIV
B Cell Receptors

- The receptor on B cells for its specific antigen is the antibody it secretes
- Constant ends
  - Determine antibody class
    - IgA, IgD, IgE, IgG, IgM
  - Bind to macrophage
- Variable ends
  - Bind antigens
  - A near infinite variety!
T Cell Receptors

• T cell receptors for antigens are integral membrane proteins
  – Stay bound to the membrane of T cells
• T cell receptors can not bind antigen unless the antigen is first complexed with MHC proteins
  – 2 classes of “self” plasma membrane proteins
• T cell receptor then combines with the entire complex of antigen and MHC protein
MHC Proteins

- Different from person to person
- Act as cellular ID tags – markers of biological self
- Binding to MHC proteins
  - **Class I MHC** proteins
    - Bind to the CD8 protein on killer T cells
  - **Class II MHC** proteins
    - Bind to the CD4 protein on helper T cells

- A group of proteins: the *major histocompatibility complex* are called MHC proteins

- Also called human leukocyte-associated antigens or *HLA antigens*
Antigen Presenting Cells (APC)

• T cells can bind antigen *only* when the antigen appears on the plasma membrane of a host cell complexed with the MHC proteins

• Host cells bearing these complexes are called *antigen presenting cells (APC’s)*
  – Macrophage
  – Dendritic cells
  – B-Cells

• Produce the MHC Class 2 proteins
Presentation to Helper T cells

1. After an antigen has been phagocytized by an APC (non-specific response) it is broken down into smaller peptides.

2. The digested epitopes (fragments) bind to the MHC Class 2 proteins within an endosome of the APC.

3. The epitope-MHC complex is transported to the cells surface and displayed in the plasma membrane.
Dendritic Cells

- Most likely derived from monocytes
- Made in bone marrow
- Found in tissues in contact with the outside world
  - Skin
  - Linings of:
    - Nose
    - Lungs
    - Stomach
    - Intestines
- Migrate to lymph nodes and the spleen to present to T-Cells
Antigen Presentation to Helper T Cells

(a) Macrophage
- Class II MHC protein
- Antigen fragment
- Helper T-cell receptor
- Class II MHC protein
- Nucleus

(b) B Cell
- Immunoglobulin (B-cell receptor)
- Antigen
- Class II MHC protein
- Helper T-cell receptor
- Nucleus

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.
Lymphokines

- APC binding to the helper T cell triggers the APC to secrete large amounts of **lymphokines**
  1. **IL-1** and tumor necrosis factor (**TNF**) secreted by APCs
  2. Stimulate helper T cells to secrete **IL-2**
  3. **IL-2** activates more T-cells and B-cells
Presentation to Cytotoxic T cells

- **Any host cell** can act as an APC to a cytotoxic T cell
  1. Any host cell that is cancerous
  2. Any host cell that has become infected
  3. Any host cell that has been damaged
- APCs for Cytotoxic T cells express the **MHC Class 1** protein
- Host cells synthesize the antigen that complexes with the MHC Class 1 protein
Perforin

- Activated Killer T cells secrete **perforin**
- Perforin causes holes (perforations) to form in the cell membrane
- Cell destruction results in the release of virions into the ECF where they can be directly neutralized by antibodies
Antibody-Mediated Response
Humoral Response

• Humoral responses are the major defenses against
  – Bacteria *in the extracellular fluid*
  – Virions *in the extracellular fluid*
  – Other microorganisms *in the extracellular fluid*
  – Toxins *in the extracellular fluid*

• *Once bound to an antibody, antigen cannot infect other body cells or reproduce*
  – Becomes immobilized and is tagged for destruction
Antibody-Mediated Response
Humoral Response

• Communication by antibodies in the blood and lymph with other immune cells
  • Antibodies inactivate antigens in plasma
  • Antibodies bind to bacteria for complement activation
  • Antibodies recruit and guide other cells to perform the attack
    – Phagocytic cells
Antibodies Allow Phagocytes to Bind to Pathogens
Active Immunity

- Immunity develops over time as a result of the body’s contact with antigens
- Causes B cells to secrete the antibodies for the antigen
- **Memory Cells** provide long lasting immunity
- **Natural Active Immunity**
  - Occurs when you are naturally exposed to antigen
- **Acquired Active Immunity**
  - Occurs when you are injected with the antigen

HepA, TDAP vaccines
Passive Immunity

• You receive preformed antibodies
• Provides instant, temporary immunity
• **Natural Passive Immunity**
  – Maternal transfer of antibodies to baby
  – Breast feeding (IgA)
  – Transplacental transfer (IgG)
• **Acquired Passive Immunity**
  – Occurs when you receive preformed antibodies (IgG) in an injection
  • HepB, Rabies, Tetanus, Varicella-Zoster (chicken pox, shingles) vaccines
Acute Phase Response

• Many systemic responses to infection
• Initiated by lymphokines released by monocytes and macrophage
  • IL-1, IL-6, TNF
• Stimulates actions of the
  • Brain, hypothalamus
  • Liver
  • Bone marrow
  • Adipocytes
  • Muscle
Acute Phase Response

Monocytes and macrophages
Secrete IL-1, TNF, and IL-6

↑ Plasma IL-1, TNF, and IL-6

Liver
Retains Fe, Zn
 Secretes acute phase proteins

↓ Plasma Fe, Zn
↑ Plasma acute phase proteins

Brain
Fever
↓ Appetite
↓ Food intake
Sleepiness
Fatigue

Bone marrow
↑ Production and release of leukocytes

Bone
↑ Lipolysis

Adipose tissue
↑ Lipolysis

Muscle
↑ Protein breakdown
↑ Amino acid release

Hypothalamus
Anterior pituitary
↑ ACTH secretion

↑ Plasma ACTH

Adrenal cortex
↑ Cortisol secretion

↑ Plasma cortisol
Disorders of the Immune System

Immunodeficiency

• *Immunodeficiency*

• May be caused by aging, stress, or viral infection

• May lead to “opportunistic” diseases or cancer (*pneumonia, bronchitis*)

• Manifested by a failure of the immune system to protect from these diseases
Disorders of the Immune System

Autoimmune disorder

• **Autoimmunity**
  – an immune response is mounted against “self” antigens

• Host antigens that are transformed or previously hidden

• Include
  – Diabetes mellitus Type I
  – Systemic Lupus
  – Rheumatoid Arthritis
Hypersensitivities

• Immune responses to environmental agents cause inflammation

• Immediate hypersensitivities (allergies)
  – Antibody (IgE) production and mast cell secretion of histamine
  – Hay fever, allergies, penicillin, bee sting

• Delayed hypersensitivities
  – Overstimulation of lymphocytes and macrophages
  – Take 2-3 days to develop
  – Chronic inflammation and cytokine release
  – Against tuberculin, transplant rejection