ADAPTIVE IMMUNITY
The Specific Immune Response
Physiology
Unit 3
The Adaptive Immune System

- Exposure to antigen triggers the specific immune response
  - *The response “adapts” to different antigen as you are exposed to them*
  - You acquire immunity as you are exposed to different antigens throughout your life
- The immune system “learns”
  - Memory cells are produced and remain for antigens you have been exposed to
  - You are then “immune” to that antigen
- Lymphocytes are involved in your specific immune response to antigen
  - B Lymphocytes
  - T Lymphocytes

- My adaptive immunity is not the same as yours!
Antigen

- Antigen is a molecule that binds to an antibody
  - Any molecule (or fragment) that kind bind to a T-cell receptor (TCR)
  - Any molecule that can bind to a B-cell receptor (BCR)
- Antigens are usually
  - Peptides
  - Proteins
  - Carbohydrates
Specific Immune Response

• Amplified immune response to an *antigen*
• Lymphocytes *must* be activated
  • Mediated by lymphokines released from activated lymphocytes
  • Activated lymphocytes undergo proliferation
  • Progeny of activated lymphocytes are called *clones*
    • *Some will be* effector cells
    • *Some will be* memory cells
Specific Immune Response

• The specific immune response begins with the activation of Helper T cells by Antigen Presenting Cells (APC’s).

• Activated Helper T cells release Interleukin 2 (IL-2) that activates other lymphocytes (amplification).
Lymphocytes

- Lymphocytes must recognize/verify antigen
  - Virus, bacteria, cancer cells, transplanted cells, other infectious agents
- Lymphocytes have a receptor for antigen
  - B cell receptors (BCR’s)
  - T cell receptors (TCR’s)
    - ≈ 100 million distinct antigen receptors on lymphocytes
    - Created by genetic recombination
    - The antigen receptors on lymphocytes are verified during the maturation process to ensure the lymphocytes are NOT self reactive
B Lymphocytes

• Naïve (mature) B-cells are found primarily in lymph nodes and the spleen where they will encounter antigen

• Upon activation, produce plasma cells which secrete **antibodies** against an antigen
  
  • *Some* plasma cells will remain as Memory B cells

• Also act as an APC to Helper T-cells

The “B” stands for Bursa of Fabricius (a lymph organ) – that is where B Cells mature in birds
B Cell Receptors/Antibodies

- The B cell receptor (BCR) is the antibody it secretes.
- Antibodies are produced by genetic recombination, producing a near infinite variety of antibodies for antigen.
The 5 classes of Antibodies Produced By Plasma Cells

• 5 antibody classes
• Constant ends
  • Bind to macrophage, C1 proteins
• Variable ends
  • Bind antigen
• Classification of antibodies is determined by the sequence of amino acids forming the constant ends

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Characteristics</th>
<th>Distribution in the body</th>
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<tbody>
<tr>
<td>IgG</td>
<td>• Highest opsonization and neutralization activities. • Classified into four subclasses (IgG1, IgG2, IgG3, and IgG4).</td>
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<tr>
<td>IgM</td>
<td>• Produced first upon antigen invasion. Increases transiently.</td>
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<tr>
<td>IgA</td>
<td>• Expressed in mucosal tissues. Forms dimers after secretion.</td>
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<tr>
<td>IgD</td>
<td>• Unknown function.</td>
<td></td>
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<tr>
<td>IgE</td>
<td>• Involved in allergy.</td>
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</tbody>
</table>
IgG
Immunoglobulin G

- Generated after class switching
  - Involved in secondary immune response
- Most abundant antibody in the body
  - Binds to many kinds of pathogens (bacteria, virus, fungi)
  - Causes agglutination
  - Neutralizes toxins
  - Activates the complement pathway
  - Opsonization for phagocytosis
  - Directs bound virus to proteosomes for destruction
- Crosses the placenta for fetal immunity
- 4 subclasses
IgM
Immunoglobulin M

- First antibody produced upon initial exposure to antigen
  - Natural antibody
- Found in plasma and lymph
  - Too large to move into IF
- Binds to complement protein C1 and activates the complement pathway (*classical pathway*).
- Causes agglutination
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
IgE
Immunoglobulin E

- Defense against multicellular parasites
  - Helminths, protozoans
- IgE activation of mast cells in allergic responses
  - Asthma, sinusitis, food allergies
  - Activates mast cells and/or basophils to secrete histamine
- Found in lungs, skin, mucus membranes
T Lymphocytes

• Naïve (mature) T cells
  • Some will be in circulation in plasma and lymph
  • Most will be seeded in lymph nodes and the spleen

• Different types of T cells
  • Helper T cells
  • Cytotoxic T cells
  • Regulatory T cells

Mature in the Thymus Gland
T Cell Receptors

TCR

• T cell receptors (TCR) for antigen are integral membrane proteins

• Helper T cells
  • TCR bind to antigen only when it is presented by APC’s

• Killer T cells
  • TCR bind to antigen only when it is presented by host cells that need to be destroyed
Helper T Cells

- Helper T cell activation is required for a maximal immune response
- Helper T cells are activated by Antigen Presenting Cells (APC’s)
- Activated Helper T cells signal for an amplified immune response against a specific antigen
- Activated Helper T cells release IL-2 that activate:
  - B cells
  - Cytotoxic T cells
  - Itself (Helper T cell)

Remember......activated lymphocytes undergo clonal expansion (proliferation)
Antigen Presenting Cells

• There are 3 types of cells that can present antigen to Helper T cells
  1. Macrophage
  2. Dendritic Cells
  3. B cells
Activation of Helper T cells

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

2. The **epitopes** (fragments) complex with 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.

4. The epitope that is presented by APC’s then binds to the TCR.
   - The Helper T cell goes through a 2 step verification process.

5. Once the 2 step verification is complete, the Helper T cell is now activated.
Stages of Specific Immune Response

Encounter and Verification

**Encounter**

- APC’s will present antigen to a Helper T cell in a lymph node

**Verification**

- *Memory T cells*
  
  - Memory cells only have to go through step 1 to activate
  
  - Have already gone through the confirmation step
  
  - Faster response upon reinfection
Stages of Specific Immune Response

*Lymphocyte Activation*

• Activated Helper T cells release a growth factor called **IL-2**

• **IL-2** acts as an autocrine agent which triggers proliferation of the Helper T cell.
  • This results in *clonal expansion*

• **IL-2** also signals the activation of B cells and Cytotoxic T cells (more clonal expansion)
Lymphocyte Activation

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

**Activation**
- (Cytokines)
  - Plasma cells
  - Antibodies
  - Guide phagocytes, complement, and NK cells to attack antigen-bearing cells or to neutralize free antigen
  - (Cytokines)
  - Antibodies
  - Directly attack antigen-bearing cells
Stages of Specific Immune Response

The Attack

• The attack launched against antigen by the activated lymphocytes
  ◆ Activated B cells differentiate into Plasma cells and secrete antibodies for the antigen
  ◆ Activated Cytotoxic T cells destroy host cells
  ◆ Activated Helper T cells secrete IL-2 which amplifies the immune response

• Effector lymphocytes die by apoptosis
  • Prevents the immune response from becoming excessive and potentially destroying host tissues
Killer T cells

• Activated Killer T cells kill host cells that have become:
  • Cancerous
  • Infected
  • Damaged

• Travel through the blood and lymph to seek out target cells
• Bind to and kill host cells by secreting chemicals
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
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 Presentation to Helper T Cells
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

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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