Chapter 16: Adaptive Immunity

1. Overview of Adaptive Immunity
2. B cells & Antibodies
3. Antigens and Antigen Presentation
4. T cells
5. Humoral & Cell-Mediated IRs
1. Overview of Adaptive Immunity

Chapter Reading – pp. 473-476
The Nature of Adaptive Immunity

Unlike innate immunity, adaptive (acquired) immunity is highly specific and depends on exposure to foreign (non-self) material.

- depends on the actions of T and B lymphocytes (i.e., T cells & B cells) activated by exposure to specific antigens (Ag):

**Antigen** = any substance that is recognized by an antibody or the antigen receptor of a T or B cell

**Only antigenic material that is “foreign” should trigger an immune response, although “self antigens” can trigger autoimmune responses.**
Adaptive Immune Responses occur in a variety of lymphatic tissues throughout the body.

T cells, B cells & APCs aggregate in these tissues to coordinate adaptive responses to foreign antigens.
From the Bone Marrow…

Immature T cells 1st go to the thymus (via blood)

• in the thymus T cells undergo a maturation process referred to as “education”

• basically, this is where T cells that would react to “self antigens” are eliminated
  • essential for preventing autoimmunity

• eventually end up in lymph nodes, skin, gut or spleen

B cells end up in lymph nodes, skin, gut or spleen

• here they await foreign antigen they bind to
Antigen Receptors

Each T or B cell that survives development in the bone marrow or thymus has its own unique antigen receptor.

These “naïve” T and B cells do not become active unless they encounter antigen that binds their receptors…
2. B Cells & Antibodies

Chapter Reading – pp. 482-489
B cells

Have a B cell receptor (BCR) that can be released as antibody.
Antibody Structure

Every antibody have this same basic structure:

- **Light chain**
  - Antigen-binding sites
  - Variable region of heavy chain
  - Variable region of light chain

- **Hinge**
  - Constant region of light chain

- **F<sub>ab</sub> (arm)**
  - Constant region of heavy chain

- **F<sub>c</sub> (stem)**
  - Heavy chains

**variable regions** bind Ag & are unique for ea B cell
BCR bound to Antigen

Epitope

Antigen-binding sites

Variable region

Heavy chain

Light chain

B cell receptor (BCR)

Cytoplasmic membrane of B lymphocyte

Trans-membrane portion of BCR

Cytoplasm

Free (soluble) antibody binds antigen in the same way.
The Roles of Antibodies

Antibodies bind to antigens resulting in 6 general outcomes:

1) neutralization
   • prevents antigen (e.g., virus, toxin) from functioning

2) agglutination
   • the “cross-linking” of antigens into a large complex

3) opsonization (enhancing phagocytosis)

4) antibody-dependent cell-mediated cytotoxicity
   • facilitating destruction of eukaryotic pathogens

5) oxidation (catalyze production of oxidants – e.g., \( \text{H}_2\text{O}_2 \))

6) activation of complement (classical pathway)
Neutralization

Agglutination

Opsonization

Antibody-dependent Cellular Cytotoxicity (ADCC)

Oxidation

Activation of the Classical Complement Pathway
Generation of B cell Receptors

Since there are millions of different B cells and each produces a unique antigen receptor, how could this be encoded in the genome?

- the antibody (immunoglobulin) genes in each B cell undergo a somewhat random DNA recombination process that is unique for each B cell

- in this way, the antigen receptor produced by each B cell is unique (has nothing to do with foreign Ag)
  - cells that produce a non-functional receptor die
  - cells with a “self-reactive” receptor are eliminated

Surviving B cells should only bind to foreign antigen!
Antigen Receptor Gene Recombination

Heavy chain locus

V_H1  V_H2  V_H3  V_H65  D_H1 D_H2 D_H3  D_H27  J_H1 J_H2 J_H3  J_H6

1. RAG randomly combines one D segment with one J segment.

2. RAG randomly combines DJ with one V segment.

3. Transcription and translation of polypeptide completed.

Occurs in immunoglobulin heavy chain & light chain genes to generate a unique antigen receptor in each B cell.

NOTE: Same basic process also occurs in T cells to produce unique T cell receptors (TCRs)
Clonal Deletion of B cells

Of the B cells that produce a functional BCR, those that are “self-reactive” (bind self antigens) undergo apoptosis.

apoptosis = programmed cell death (i.e., cell suicide)
The Different Classes of Antibody

All antibodies fall into 5 general classes based on their constant regions (which are the same for all antibodies in a given class) and other features:

**IgM (Immunoglobulin type “M”)**
- a pentameric structure consisting of 5 antibodies connected by disulfide bonds and a J chain polypeptide
- the first class of antibody produced by a B cell after its initial exposure to antigen that binds its B cell receptor
- most effective at agglutination, activating complement

**IgD**
- only used as BCR, *never* secreted, function unclear
**IgG**

- a **monomeric** class comprising ~80% of serum antibodies and also found throughout the lymph
- good for opsonization, activating complement
- only class of antibody to cross the placenta to fetus

**IgA**

- **monomeric** (serum), **dimeric** (2 Ab’s, J chain & secretory component) when secreted (protected from digestion)
- present in saliva, mucus, breast milk & other external secretions, and is the most abundant of all Ab’s

**IgE**

- a **monomeric** class that binds to IgE receptors on mast cells, eosinophils & basophils to trigger allergic reactions
**Table 16.1 Characteristics of the Five Classes of Antibodies**

<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>IgE</th>
<th>IgD</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Antigen-binding site" /> <img src="image2" alt="Disulfide bond" /> <img src="image3" alt="Carbohydrate" /></td>
<td><img src="image4" alt="Monomer" /> <img src="image5" alt="α" /> <img src="image6" alt="Secretory component" /> <img src="image7" alt="Secretory (dimer)" /></td>
<td><img src="image8" alt="Pentamer" /> <img src="image9" alt="μ" /> <img src="image10" alt="J Chain" /> <img src="image11" alt="α" /></td>
<td><img src="image12" alt="Monomer" /> <img src="image13" alt="ε" /></td>
<td><img src="image14" alt="Monomer" /> <img src="image15" alt="δ" /></td>
<td></td>
</tr>
<tr>
<td><strong>Structure, number of binding sites</strong></td>
<td>Monomer, 2</td>
<td>Monomer, 2 Dimer, 4</td>
<td>Pentamer, 10</td>
<td>Monomer, 2</td>
<td>Monomer, 2</td>
</tr>
<tr>
<td><strong>Type of heavy chain</strong></td>
<td>Gamma (γ)</td>
<td>Alpha (α)</td>
<td>Mu (μ)</td>
<td>Epsilon (ε)</td>
<td>Delta (δ)</td>
</tr>
<tr>
<td><strong>Functions</strong></td>
<td>Complement activation, neutralization, opsonization, production of hydrogen peroxide, agglutination, and antibody-dependent cellular toxicity (ADCC); crosses placenta to protect fetus</td>
<td>Neutralization and agglutination; dimer is secretory antibody</td>
<td>Monomer can act as BCR; pentamer acts in complement activation, neutralization, agglutination</td>
<td>Triggers release of antiparasitic molecules from eosinophils and of histamines from basophils and mast cells</td>
<td>Unknown, but perhaps acts as BCR</td>
</tr>
<tr>
<td><strong>Locations</strong></td>
<td>Serum, mast cell surfaces</td>
<td>Monomer: serum Dimer: mucous membrane secretions; milk</td>
<td>Serum</td>
<td>Serum, mast cell surfaces</td>
<td>B cell surface</td>
</tr>
<tr>
<td><strong>Approximate half-life (time it takes for concentration to reduce by half) in blood (days)</strong></td>
<td>20</td>
<td>6</td>
<td>10</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Percentage in serum</strong></td>
<td>80</td>
<td>10–15</td>
<td>5–10</td>
<td>&lt;1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Size (mass in kilodaltons)</strong></td>
<td>150</td>
<td>Monomer: 160 Dimer: 385</td>
<td>970</td>
<td>188</td>
<td>184</td>
</tr>
</tbody>
</table>

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3. Antigens & Antigen Presentation

Chapter Reading – pp. 476-480
**ANTIGENS**

Anything capable of binding a BCR (Ab) or TCR & inducing an adaptive IR.

(a) Epitopes (antigenic determinants)

(b) Exogenous antigens

(c) Endogenous antigens

(d) Autoantigens

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Native vs Processed Antigen (Ag)

Native Antigen:

- antigen that is in its natural state or structure
  - e.g., proteins that are folded “properly” (i.e., not denatured or broken down)
- antibodies (soluble or as a B cell receptor) bind to native antigens

Processed Antigen:

- antigen (usually protein) digested within an APC (phagocyte) & presented in “pieces” on its surface
- the T cell receptor binds to processed antigen
Antibodies recognize Native Antigen

- Antibody A
- Epitopes (antigenic determinants) on antigen
- Binding sites
- Antigens: components of cell wall
- Antibody B

Bacterial cell
Epitopes on Native Antigens

An antigen can be a cell, a virus or a type of macromolecule (usually a protein or polysaccharide).

The portion of an antigen that physically contacts a given antibody is called the epitope (aka “antigenic determinant”).

In other words, each antibody recognizes (i.e., binds to) a unique epitope on the native antigen it is specific for.
Processed Antigens

Processed antigens are of 2 types:

1) proteins produced within a cell (endogenous) are digested into peptides which are presented on the cell surface by MHC class I molecules
   - occurs in almost all cells of the body
   - provides a “sample” of intracellular material to cytotoxic T lymphocytes (T<sub>c</sub>)

2) peptides derived from material ingested by phagocytosis (exogenous) are presented on the cell surface by MHC class II molecules
   - occurs only in certain phagocytes (APCs) to present samples of extracellular antigen to helper T cells
Human MHC molecules are referred to as HLAs (Human Leukocyte Antigens)

**MHC Class I**
- presents pieces of *endogenous* antigen
- happens in almost all cells

**MHC Class II**
- presents pieces of *exogenous* antigen
- only in APCs
MHC Class I Antigen Presentation

- Endogenous proteins are “chopped up” into short peptides which fit into a groove in MHC class I molecules in the endoplasmic reticulum (ER).

- These complexes are presented on the cell surface to CD8+ Tc cells.

- If the peptide is from a foreign protein, the cell will be killed.

Occurs in all cells!
MHC Class II Antigen Presentation

- exogenous proteins from material obtained by phagocytosis are “chopped up” into short peptides
- peptides are “loaded” onto MHC II when vesicles from Golgi (w/MHC II) fuse with a phagolysosome
- MHC II/peptide complexes are presented on the cell surface to CD4+ T_H cells

Occurs only in APCs!
4. T Cells

Chapter Reading – pp. 480-482, 488-492
T cells

Recognize “processed” antigen via T cell receptor:

**CD8⁺**: cytotoxic T cells (T<sub>c</sub> or CTLs) that kill infected or cancerous cells

**CD4⁺**: helper T cells (T<sub>H</sub>) that activate other immune cells, regulatory T cells (T<sub>R</sub>) that suppress IRs
MHC-mediated Antigen Binding

- **CD8⁺ T cells** (CTLs or Tₐ) recognize peptide antigens **ONLY** if presented on MHC class I molecules.
- **CD4⁺ T cells** (Tₜ or Tᵣ) recognize peptide antigens **ONLY** if presented on MHC class II molecules.
- A T cell will only become activated if its TCR “fits” the MHC/peptide complex.

Specificity of T cell activation depends on the peptide!
Clonal Deletion of T cells

Of the T cells that produce a functional TCR, those that recognize processed self-antigens (presented by APCs) undergo apoptosis

- eliminates self-reactive T cells and thus protects the body from autoimmunity
Cytotoxic T cells

Kill infected cells by inducing apoptosis in 2 ways:

1) perforin and granzymes

2) Fas–ligand (CD95L) binds to Fas (CD95) on target

Active cytotoxic T (Tc) cell

- TCR
- CD8
- Viral epitope
- MHC I protein
- Virally infected cell
- Intracellular virus

Intracellular virus

Virally infected cell

- Active apoptotic enzymes
- Inactive apoptotic enzymes
- Enzymatic portion of CD95 becomes active
- Active apoptotic enzymes induce apoptosis
- Fas–ligand (CD95L) binds to Fas (CD95) on target

Active apoptotic enzymes induce apoptosis

Granzymes activate apoptotic enzymes

Perforin complex (pore)

Inactive apoptotic enzymes

Perforin

Granzyme

Cytotoxic T cells

Kill infected cells by inducing apoptosis in 2 ways:

1) perforin and granzymes

2) Fas–ligand (CD95L) binds to Fas (CD95) on target
What do Helper T Cells do?

As we’ve learned, adaptive immunity involves the following:

1) the production of antibody by B cells
2) the killing of infected cells by cytotoxic T cells

However, neither B cells nor cytotoxic T cells take action unless they receive specific signals from helper T cells ($T_H$):

- via cytokines such as the interleukins (e.g., IL-2) and interaction with cell surface proteins
**Activation of T\(_H\) Cells**

\( T_H \) cells become activated upon binding exogenous Ag
- presented in MHC class II by an APC

\( T_H \) cells then secrete cytokines, etc, activating B cells, \( T_C \) cells & several other cell types

1. Microbe
2. Phagocyte
3. APC
4. Interleukins
5. IL-2
6. IL-2 activates other B and T cells
7. TCR

B cell → humoral immunity

T cell → cellular immunity

TCR

**Diagram:**
- Microbe
- Phagocyte
- APC
- Interleukins
- TCR
- IL-2
- T cell
- B cell
- Humoral immunity
- Cellular immunity
Two Types of Helper T Cells

Type 1 helper T cells ($T_{H1}$):

- secrete cytokines to activate CTLs, NK cells and macrophages
- trigger cell-mediated immune response to deal with intracellular pathogens (e.g., viruses)

Type 2 helper T cells ($T_{H2}$):

- secrete cytokines to activate B cells, eosinophils
- trigger humoral immune response to deal with extracellular pathogens (e.g., most bacteria)
The APC determines whether a naïve $T_H$ cell will become a $T_{H1}$ or $T_{H2}$ based on pathogen.

- via cytokines, cell-cell interactions
How does APC know the pathogen?

APCs and other cell types express a variety of receptors that recognize Pathogen-Associated Molecular Patterns (PAMPs).

- Toll-like Receptors (TLRs) are an important class of PAMP receptor proteins
  - e.g., TLR3 binds dsRNA, TLR5 binds flagellin

PAMP receptors such as TLRs reveal the type of pathogen present so that the appropriate innate and adaptive IRs are triggered.
Summary of Helper T Cell Function

1) APC (e.g., dendritic cell or macrophage) presents peptide antigens from what it “ate” on MHC class II molecules & releases cytokines reflecting the type of pathogen consumed

2) Any CD4\(^+\) \(T_H\) cells with a T cell receptor that recognizes MHC class II presented peptides are activated to become \(T_{H1}\) or \(T_{H2}\) cells

3) \(T_{H1}\) cells activate cells associated with cellular immunity (e.g., CD8\(^+\) CTLs), \(T_{H2}\) cells activate cells associated with humoral immunity (e.g., B cells)
5. Humoral & Cell-Mediated Immune Responses

Chapter Reading – pp. 489-497
Humoral vs Cell-Mediated Immunity

Humoral Immunity

B cell → antibodies → antibody/antigen complex

Cell-Mediated Immunity

T cell → infected cell → death of infected cell

antigen presented to T cell
There are 2 basic types of adaptive immune response (IR):

1) humoral IR
   • involves antibodies made by B cells & released into the extracellular fluids (blood, lymph, saliva, etc…)
   • deals with extracellular pathogens (or any extracellular foreign material)

2) cell-mediated IR
   • involves special cytotoxic T cells (CTLs) that kill cells containing intracellular pathogens (e.g., viruses)

*both types of IR depend on helper T cells*
Antigen presentation

1. DC
   - MHC II protein
   - Epitope
   - TCR
   - Th cell
   - IL-12
   - Inactive Tc cell
   - IL-2 receptor (IL-2R)

2. Th differentiation
   - Th1 cell
   - IL-2
   - Active Tc cells
   - IL-2R

3. Clonal expansion
   - Memory T cell

4. Self-stimulation
   - Active Tc cells
   - IL-2R

A Cell-mediated Immune Response

Results in the activation of $T_C$ cells specific for a particular pathogen
Summary of Primary Cell-Mediated IR

The initial activation of cytotoxic T cells due to an intracellular pathogen occurs as follows:

1) a dendritic cell or macrophage ingests or is infected by an intracellular pathogen

2) peptides fr. pathogen presented on MHC class II and MHC class I molecules

3) specific $T_H$ cells activated to become $T_{H1}$ cells

4) $T_{H1}$ cells activate specific $T_C$ cells to:
   - undergo mitosis to produce more of that T cell clone
   - differentiate into active CTLs OR memory T cells
T Cell Memory

T cells (whether \( T_H \) or \( T_C \)) produce extremely long-lived memory cells:

- activated directly upon subsequent exposure
  
  **No need for activation signals from other T cells or APCs!**

- secondary responses are much more rapid and much more intense than primary responses
  
  - this is the basis for immunizations
  
  - the enhanced secondary response is so much more effective that the individual is largely protected from re-infection with the same pathogen
Superantigens

Superantigens (such as those produced by certain bacterial pathogens) are rare molecules capable of stimulating T cells non-specifically by bridging MHC class II with the T cell receptor.

- regardless of peptide on MHC class II
- results in “wholesale” activation of helper T cells, intense & dangerous IR
A Humoral Immune Response

Results in the activation of B cells specific for particular native antigen
Summary of Primary Humoral IR

The initial exposure of a B cell to its specific antigen results in its activation as follows:

1) dendritic cell or macrophage ingests extracellular antigen by phagocytosis

2) peptides fr. antigen presented on MHC class II

3) specific T<sub>H</sub> cells activated to become T<sub>H2</sub> cells

4) T<sub>H2</sub> cells in turn activate specific B cells to:
   • undergo mitosis to produce more of that B cell clone
   • differentiate into antibody secreting plasma cells OR memory B cells
Antibody Class Switching

Following the first exposure to its specific antigen, an activated B cell will generate IgM producing plasma cells.

Various cytokines produced by $T_H$ and other cells in the vicinity can induce plasma cells to switch the antibody class to IgG, IgA or IgE:

- usually switch to IgG and possibly later to IgA or IgE
- involves DNA recombination in the gene encoding the antibody
B Cell Memory

Memory B cells remaining after the initial activation of a B cell have the following characteristics:

- they are extremely long-lived (years!)
- their BCRs are of the IgG, IgA or IgE class
- activated directly upon subsequent exposure
  - generate more plasma cells & memory cells
  - No need for T cell help!
- such secondary responses are much more rapid and much more intense than primary responses
  - generate more plasma cells & memory cells
Primary immune response

1. BCR
2. Antigen
3. Proliferation (mitosis)
4. Plasma cells
5. Memory B cells
6. Antigen

Secondary immune response

- (Th2 cell help)

- Plasma cells
- Memory B cells
Secondary Humoral Immune Response

- response is more rapid
- greater amount of antibody is produced for the antigen
T-independent B Cell Activation

Some antigens (e.g. bacterial polysaccharides) can activate B cells to secrete antibody without the help of T cells:

• due to repeating molecular units that bind and “cross-link” many BCRs on the same cell

• results in much more rapid antibody production

Memory B cells are NOT produced, thus no immunological memory is generated.
• artificial immunity results from the injection of antigen (active) or antibodies (passive)

• natural immunity results from natural exposure to antigen (active) or transfer of antibodies from mother to child (passive)
Key Terms for Chapter 16

- T cell receptor, B cell receptor
- native vs processed antigen, epitope
- MHC class I & MHC class II
- humoral vs cellular immunity
- cytokines, $T_{H1}$ vs $T_{H2}$ cells
- clonal selection, clonal deletion
- PAMPs, TLRs
- antibody: heavy & light chains, variable, constant
...more Key Terms for Chapter 16

- plasma cell, memory B and T cells
- class switching
- apoptosis, Fas-ligand, perforin
- agglutination
- natural vs artificial immunity
- active vs passive immunity

Relevant Chapter Questions
MC: 1-5, 7-10    TF: 1-5    Matching: all
“Visualize It”    SA: 1, 2