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 bound 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.

- Tonsils
- Cervical lymph node
- Lymphatic ducts
- Thymus gland
- Axillary lymph node
- Breast lymphatics
- Spleen
- Abdominal lymph node
- Peyer’s patches in intestinal wall
- Appendix
- Red bone marrow
- Inguinal lymph node
- Mucosa-associated lymphatic tissue (MALT)
- Large intestine
- Small intestine
- Intestinal lymphatic tissue

From heart

Tissue cell

Intercellular fluid

Lymph to heart via lymphatic vessels

Gap in wall

Valve

Lymphatic capillary

Blood capillary

To heart

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.

- **Clonal selection**
- **Memory cells**
  - (mitosis & differentiation)
- **Naïve B cells**
- **Effector cells**
  - Apoptosis
Every antibody have this same basic structure:

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

**F\text{ab} (arm)**

**Hinge**

**F\text{c} (stem)**

**Heavy chains**

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

The B cell receptor (BCR) is a protein complex that consists of two heavy chains and two light chains. The variable region of these chains contains the antigen-binding sites, which interact with epitopes on the antigen. The cytoplasmic membrane of a B lymphocyte contains a transmembrane portion of the BCR. Free (soluble) antibodies bind to antigen in the same way as the BCR.
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., H₂O₂)

6) activation of complement (classical pathway)
Adhesin proteins

Bacterium

Toxin

Virus

Neutralization

Neutralization

Agglutination

Opsonization

Perforin allows granzyme to enter, triggers apoptosis and lysis

Bacteria die

F<sub>c</sub> receptor protein

Activation of the Classical Complement Pathway

Oxidation

Antibody-dependent Cellular Cytotoxicity (ADCC)

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

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

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.

NOTE: Same basic process also occurs in T cells to produce unique T cell receptors (TCRs).
Stem cell (in red bone marrow)

B cells

Cell with auto-antigens

BCRs

Blood vessel

To spleen

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>Structure, number of binding sites</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>Type of heavy chain</td>
<td>Gamma (γ)</td>
<td>Alpha (α)</td>
<td>Mu (μ)</td>
<td>Epsilon (ε)</td>
<td>Delta (δ)</td>
</tr>
<tr>
<td>Functions</td>
<td>Complement activation, neutralization, neutralization, opsonization, production of hydrogen peroxide, agglutination, and antibody-dependent cellular toxicity (ADCC); crosses placenta to protect fetus</td>
<td>Neutrinization 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>Locations</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>Approximate half-life (time it takes for concentration to reduce by half) in blood (days)</td>
<td>20</td>
<td>6</td>
<td>10</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Percentage in serum</td>
<td>80</td>
<td>10−15</td>
<td>5−10</td>
<td>&lt;1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Size (mass in kilodaltons)</td>
<td>150</td>
<td>Monomer: 160 Dimer: 385</td>
<td>970</td>
<td>188</td>
<td>184</td>
</tr>
</tbody>
</table>
3. Antigens & Antigen Presentation

Chapter Reading – pp. 476-480
**Epitopes** (antigenic determinants)

- **Cytoplasmic membrane**
- **Epitopes**
- **Cytoplasm**

**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**

Normal (uninfected) cell

Virally infected cell

Intracellular virus

Endogenous antigens

Extraacellular microbes

Exogenous antigens

Copyright © 2009 Pearson Education, Inc., publishing as Pearson Benjamin Cummings.
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
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 ($T_c$)

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
Antigen-binding groove

Cytoplasmic membrane of any nucleated cell

Class I MHC protein

Cytoplasm

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

Class II MHC protein

Cytoplasmic membrane of B cell or other antigen-presenting cell (APC)
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+ T<sub>c</sub> cells
- if the peptide is from a foreign protein, the cell will be killed

Occurrences 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
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 T\(_C\)) recognize peptide antigens ONLY if presented on MHC class I molecules

- CD4\(^+\) T cells (T\(_H\) or T\(_R\)) 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
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
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
- Antigen presented to T cell
- Infected cell
- Death of infected cell
Humoral & Cell-Mediated Immunity

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. Antigen presentation

MHC II protein
Epitope
TCR
Th cell

DC
IL-12

2. Th differentiation

Th1 cell
IL-2

3. Clonal expansion

Active Tc cell
IL-2 receptor (IL-2R)

4. Self-stimulation

Active Tc cell
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 $T_H$ cells activated to become $T_{H2}$ cells

4) $T_{H2}$ 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)

(T_H2 cell help)

4. Plasma cells

5. Memory B cells

Secondary immune response

6. Antigen

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.
Natural vs Artificial Immunity

- **Artificial immunity** results from the injection of antigen (active) or antibodies (passive)

  - **Naturally acquired**
    - **Active**: Antigens enter the body naturally; body induces antibodies and specialized lymphocytes
    - **Passive**: Antibodies pass from mother to fetus via placenta or to infant via the mother’s milk

  - **Artificially acquired**
    - **Active**: Antigens are introduced in vaccines; body produces antibodies and specialized lymphocytes
    - **Passive**: Preformed antibodies in immune serum are introduced by injection

- **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