# 16 Specific Defense: Adaptive Immunity

## CHAPTER SUMMARY

### Elements of Specific Immunity (pp. 462–472)

The body augments the mechanisms of nonspecific defense with another line of defense that destroys invaders while "learning" in the process. This third line of defense retains a memory of specific pathogens so that when it encounters them a second time, it responds rapidly and effectively. This response is called adaptive immunity or **specific immunity**.

#### Antigens

**Antigens** are substances that trigger specific immune responses. The three-dimensional shape of a region of an antigen that is recognized by the immune system is the **antigenic determinant** (or *epitope*). Effective antigen molecules are large, complex, stable, degradable, and foreign to their host. The most effective antigens therefore are large foreign macromolecules such as proteins, glycoproteins, and phospholipids, but complex carbohydrates and lipids, as well as some bacterial DNA, can be antigenic.

Although immunologists characterize antigens in various ways, one clinically important way is to group them according to their relationship to the body:

- Exogenous antigens include toxins and other secretions and components of microbial cell walls, membranes, flagella, and pili.
- Protozoa, fungi, bacteria, and viruses that reproduce inside a body's cells produce **endogenous antigens**. The immune system can only "see" and respond to these antigens if they are incorporated into the cell's cytoplasmic membrane.
- **Autoantigens** (or self antigens) are antigenic molecules found on an individual's normal (uninfected) cells. Immune cells that recognize autoantigens as foreign are normally eliminated during the development of the immune system. This phenomenon, called *self-tolerance*, prevents the body from mounting an immune response against itself.

#### The Cells, Tissues, and Organs of the Lymphatic System

The **lymphatic system** is composed of **lymphatic vessels**, which conduct the flow of *lymph*—a colorless, watery liquid similar in composition to blood plasma—from local tissues and returns it to the circulatory system. It also includes *lymphoid tissues and organs* that are directly involved in specific immunity, including lymph nodes, the thymus, the spleen, the tonsils, and mucosa-associated lymphoid tissue (MALT). Cells with a central role in specific immunity, called **lymphocytes**, migrate to and persist in various lymphoid organs, where they are available to encounter foreign invaders in the blood and lymph.

The red bone marrow contains stem cells which give rise to lymphocytes, which are distinguished according to the glycoproteins on their cell surfaces with

*cluster of differentiation* numbers, such as CD4, CD95, etc. After their production in the bone marrow, lymphocytes must undergo a maturation process. B lymphocytes mature in the bone marrow, and T lymphocytes mature in lymphatic organs where they are influenced by chemical signals from the thymus. After maturation, they migrate to secondary lymphoid organs and tissues, including the **lymph nodes** in the neck, groin, and armpit, the spleen, and other accumulations of lymphoid tissue.

## B Lymphocytes (B Cells) and Immunoglobulins

**B lymphocytes**, also called **B cells**, arise and mature in the bone marrow. Those that are actively fighting against exogenous antigens are called **plasma cells**, and secrete soluble, antigen-binding proteins called **antibodies** or **immunoglobulins** (Ig) into the blood or lymph. Historically, bodily fluids were called *humors*, and thus the activity of B cells is said to be part of a **humoral immune response**.

A basic antibody molecule is formed of four polypeptide chains—two *heavy chains* and two *light chains*—linked with disulfide bonds in such a way that a basic antibody molecule looks like the letter Y with three regions: a *stem* and two *arms* connected by a flexible *hinge region*. The antibody stem is called the **$F_C$ region**. Among all B cells, there are five basic types of heavy chains, and these give their names to five classes of antibodies: IgG, IgM, IgA, IgE, and IgD.

The arms of each heavy and light chain vary in amino acid sequence, and thus each is called a *variable region*. The **antigen-binding site** is formed by the variable regions of a heavy and light chain of an antibody. Antigen-binding sites are complementary to antigenic determinants. Once antibodies are bound to antigens, they function in several ways. These include:

- **Activation of complement** (discussed in Chapter 15)
- **Stimulation of inflammation** (discussed in Chapter 15)
- **Neutralization** of toxins by binding to critical portions, or of bacteria or viruses by blocking attachment molecules on their surfaces
- **Opsonization**, or enhanced phagocytosis, whereby antibodies act as **opsonins**, molecules that stimulate phagocytosis
- **Agglutination**, the clumping of antibody molecules bound with two microbial cells each, which hinders the activity of pathogens and increases the chance that they will be phagocytized

The class involved in any given humoral immune response depends on the type of invading antigen, the portal of entry involved, and the antibody function required:

- **Immunoglobulin G (IgG)** is the predominant antibody class found in the bloodstream and the primary defender against invading bacteria.
- **Immunoglobulin A (IgA)** is the antibody class most commonly associated with various body secretions, including tears and milk. IgA pairs with a secretory component to form *secretory IgA*.
- **Immunoglobulin M (IgM)** is the third most common antibody class and the predominant antibody produced first during a primary humoral immune response.
- **Immunoglobulin E (IgE)** is the signal antibody molecule that triggers the release of cell-damaging molecules onto parasites, particularly parasitic worms.
- **Immunoglobulin D (IgD)** is a membrane-bound antibody molecule found in some animals as a B cell receptor.

The surface of each B cell is covered with about 500,000 identical copies of **B cell receptor (BCR)**, an antibody that is not secreted but instead remains integral to the cytoplasmic membrane. BCRs are antibody-like proteins that are complementary

to antigens. A BCR has the same shaped binding sites as do the antibodies that can be synthesized by that cell.

### T Lymphocytes (T Cells)

An adult's red bone marrow produces lymphocytes that leave the bone marrow to mature under the influence of the thymus. These **T lymphocytes**, or **T cells**, generate about half a million copies of **T cell receptor** (**TCR**) in the cytoplasmic membrane. Because T cells act directly against antigens, their activity is considered to be part of a **cell-mediated immune response**.

Immunologists recognize two types of T cells:

- **Cytotoxic T cells** are distinguished by the presence of the CD8 cell-surface glycoprotein. They directly kill infected cells, as well as abnormal body cells such as cancer cells.
- **Helper T cells** have CD4 glycoprotein. They help to regulate the activity of B cells and cytotoxic T cells during an immune response. There are two subpopulations: $T_H1$ cells activate cytotoxic T cells to secrete perforins and granzymes that destroy infected or abnormal cells, and $T_H2$ cells function in conjunction with B cells.

### Immune System Cytokines

**Cytokines** are soluble regulatory proteins that act as intercellular signals when released by certain body cells including kidney cells, skin cells, and immune cells. Cytokines of the immune system include:

- **Interleukins** (**ILs**) which signal among leukocytes
- **Interferons** (**IFNs**) which, as discussed in Chapter 15, are antiviral proteins that also act as cytokines
- **Growth factors**, which stimulate stem cells to divide
- **Tumor necrosis factor** (**TNF**), which is secreted by macrophages and T cells to kill tumor cells and to regulate immune responses
- **Chemokines**, which signal leukocytes to rush to a site of inflammation or infection and activate other leukocytes

## The Body's Preparations for a Specific Immune Response (pp. 472–476)

The body prepares for specific immune responses by killng lymphocytes with receptors complementary to autoantigens, making *major histocompatibility complex* proteins, and processing antigens so that they can be recognized by lymphocytes.

### Lymphocyte Editing by Clonal Deletion

Cells with receptors that respond to autoantigens are selectively killed via **apoptosis** in a process known as **clonal deletion** (because daughter cells—clones—are deleted). Surviving lymphocytes and their descendents respond only to foreign antigens. When self-tolerance is impaired, the result is an *autoimmune disease*.

### The Roles of the Major Histocompatibility Complex

The **major histocompatibility complex** is a cluster of genes located on each copy of chromosome 6 (in humans), which codes for *major histocompatibility antigens*. These antigens, which are present in the cell membranes of leukocytes, hold and

position antigenic determinants for presentation to T cells. Class I MHC molecules are found on the cytoplasmic membranes of all nucleated cells. Class II MHC proteins are found only on B lymphocytes and special cells called **antigen presenting** cells (APCs). These include monocytes, macrophages, and their close relatives, such as dendritic cells. Antigens are captured, ingested, and degraded into antigenic determinants by APCs. They are then bound to MHC molecules, and inserted to present the antigenic determinant on the outer surface of the APCs cytoplasmic membrane.

### Antigen Processing

Since large antigens with repeating antigenic determinants can be processed by B cells without the help of T cells, they are called **T-independent antigens**. Most antigens are smaller and B cells targeted against them cannot function without assistance from helper T cells. These antigens are therefore called **T-dependent antigens**.

## The Humoral Immune Response (pp. 476–478)

### B Cell Activation and Clonal Selection

Humoral immunity can be viewed as consisting of the following series of cellular interactions, which are mediated by membrane-bound proteins as well as cytokines:

1. Antigen presentation (discussed earlier)
2. Differentiation of $T_H$ into $T_H2$ cells
3. Clonal selection, in which only the B cell with BCRs complementary to the antigenic determinant will be recognized
4. Activation of B cell by the $T_H2$ cell such that it proliferates rapidly

### Memory B Cells and the Establishment of Immunologic Memory

A small percentage of the cells produced by B cell proliferation do not secrete antibodies but survive as **memory B cells**, long-lived cells with BCRs complementary to the specific antigen that triggered their production. In a **primary immune response**, relatively small amounts of antibodies are produced slowly and are of limited effectiveness. When an antigen is encountered a second time, the activation of memory cells in the **secondary immune response** ensures that the immune response is rapid and strong. Enhanced immune responses to subsequent exposures are called **memory responses**.

## The Cell-Mediated Immune Response (pp. 478–481)

The body uses cell-mediated immune responses to fight intracellular pathogens such as viruses that have invaded body cells, as well as abnormal body cells such as cancer cells. Cytotoxic T cells recognize abnormal molecules expressed on the surface of an infected, cancerous, or foreign cell. Cytotoxic T cells function only in the presence of cytokines from $T_H1$ cells.

### The Perforin-Granzyme Cytotoxic Pathway

In the **perforin-granzyme pathway**, cytotoxic T cells destroy their targeted cells by secreting **perforins** and **granzymes**, toxic protein molecules. Perforins perforate cell membranes and granzymes activate apoptotic enzymes in the target cell, thereby forcing the cell to commit suicide.

### The CD95 Cytotoxic Pathway

In the CD95 **cytotoxic pathway**, when cytotoxic T cells contact their target cells, the binding of their CD95 protein with CD95 on the target cell activates enzymes that trigger apoptosis.

### Memory T Cells

Some activated T cells become **memory T cells**, and can persist for months or even years in lymphoid tissues. Contact with an antigenic determinant matching its TCR prompts the memory T cell to immediately produce cytotoxic T cells. As with humoral immunity, a memory response is more rapid and more effective than a primary response.

### T Cell Regulation

The body carefully regulates cell-mediated immunity so that T cells do not respond to autoantigens. To prevent autoimmunity, T cells require additional signals from an APC. If they do not receive these signals, they will not respond.

## Types of Acquired Immunity (pp. 481–482)

Immunologists categorize specific immunity as either naturally or artificially acquired, and as either active or passive.

### Naturally Acquired Active Immunity

**Naturally acquired active immunity** occurs when the body responds to exposure to antigens by mounting specific immune responses.

### Naturally Acquired Passive Immunity

**Naturally acquired passive immunity** occurs when a fetus, newborn, or child receives antibodies across the placenta or within breastmilk.

### Artificially Acquired Active Immunity

**Artificially acquired active immunity** occurs when the body receives antigens by injection, as with vaccinations, and mounts a specific immune response.

### Artificially Acquired Passive Immunity

**Artificially acquired passive immunity** occurs when the body receives, via injection, preformed antibodies in antitoxins or antisera, which can destroy fast-acting and potentially fatal pathogens such as rabies virus.

# KEY THEMES

Once past the first and second lines of defense, pathogens are faced with the last, and best, line of defense we have—the immune system. The complex association of cells, tissues, and chemicals that make up the immune system are responsible for specifically "seeing" antigens and disposing of them. As you study this chapter, focus on the following:

- *Active immunity is necessary for full protection against disease-causing microorganisms:* Nonspecific defenses protect us against the majority of

invaders, but if they are breached, the immune system has to be able to respond decisively to the challenge.

- *B cells are involved in tagging:* One of the primary roles of B cells and antibodies is to tag foreign cells and infected cells for destruction. This is one method of controlling immune damage.
- *T cells are involved in killing:* Once labeled for destruction, T cells clear the body of free pathogens as well as microbially infected cells.

## QUESTIONS FOR FURTHER REVIEW

*Answers to these questions can be found in the answer section at the back of this study guide. Refer to the answers only after you have attempted to solve the questions on your own.*

### *Multiple Choice*

1. Acquired immunity is most beneficial because it provides:
   a. Immediate responses to all foreign invaders
   b. Specific responses geared to specific invaders
   c. Passive barrier protection against all invaders
   d. None of the above
2. Which of the molecules listed below would make the best antigens?
   a. Molecules with stable, defined shapes
   b. Large molecules rather than small molecules
   c. Visible molecules rather than hidden molecules
   d. All of the above
3. The main function of B cells is to:
   a. Circulate in the blood and phagocytize microbes
   b. Secrete protective antigens
   c. Secrete protective antibodies
   d. Lyse infected cells
4. Which of the following activities of antibodies would prevent the attachment of a virus to a host cell?
   a. Agglutination
   b. Neutralization
   c. Opsonization
   d. All of the above would prevent attachment
5. A microbially infected cell would most likely be killed by a:
   a. CD8 expressing T cell
   b. Helper T cell
   c. Cytotoxic T cell
   d. Both a and c
6. B cells work in conjunction with which T lymphocyte?
   a. Cytotoxic T cell
   b. Type 1 helper T cell
   c. Type 2 helper T cell
   d. B cells do not work with T cells of any type
7. Which of the following is not an immune system cytokine?
   a. Growth factor
   b. Interferon
   c. Interleukin
   d. Antibody

8. Which of the following cells would possess MHC I antigens?
   a. B cell
   b. T cell
   c. Skin cell
   d. All of the above
9. The best example of a T-independent antigen would be a:
   a. Viral capsid protein
   b. Bacterial plasma membrane protein
   c. Bacterial capsule polysaccharide
   d. Fungal DNA fragment
10. Antigen presenting cells present antigens to:
    a. Type 1 helper T cells
    b. B cells
    c. Memory cells
    d. All of the above
11. Which of the following statements is true about both the Perforin-Granzyme cytotoxic pathway and the CD95 cytotoxic pathway?
    a. Both stimulate apoptosis in the target cell
    b. Both involve specific interaction of type 1 helper T cells with infected cells
    c. Both involve specific interactions with cytotoxic T cells and specific receptors on the infected host cells
    d. None of the above are true
12. Secondary immune responses involve:
    a. Memory B cells
    b. Memory T cells
    c. Immediate responses without the need for activation of immune cells
    d. All of the above

### *Fill in the Blanks*

1. Adaptive immunity is _____ over the course of one's lifetime. This is in contrast to nonspecific defenses which are the same since birth.
2. _____ are molecules that trigger specific immune responses. These molecules can further be broken down into _____ which are the specific, three-dimensional regions recognized by the immune system.
3. The two major types of lymphocytes are _____ and _____.
4. Plasma cells are _____ (B/T) cells that secrete _____. These plasma cells are part of the _____ (humoral/cell-mediated) immune response.

5. For each statement presented, indicate which antibody (or antibodies) best fits the description. Answer IgG, IgM, IgA, IgE, or IgD. You may use each answer more than once and some statements may fit more than one antibody.

   a. The most common antibody in the blood: _____

   b. Involved in response to parasitic worms: _____

   c. Activates complement: _____

   d. Pentameric antibodies in serum: _____

   e. Found in body secretions: _____

   f. Function remains unknown; this antibody is not present in all animals: _____

6. The term used to describe the process of cell suicide is _____. During clonal deletion, the process named prevents lymphocytes that recognize _____ from becoming part of the circulating immune cells.

7. MHC I molecules are found on _____ cells while MHC II molecules are found on _____ and _____ cells (in each case, name the cell type). The only cells that do not express either MHC I or MHC II antigens are _____.

8. For an infected cell to be killed, APCs stimulate _____ cells into becoming _____ cells. These cells then activate _____ cells which bind the infected cell to kill it through one of two pathways: _____ or _____.

9. Acquired immune responses can be either an _____ or _____ process. Antibodies that cross the placenta from mother to child is an example of _____ immunity.

10. Immune memory can only be achieved through _____ (active/passive) immune responses.

### *Short-Answer Questions for Thought and Review*

1. Describe the difference between the three major types of antigens. Which type of antigen will lead to the best immune response?

2. Sketch the structure of an antibody and indicate which part designates antibody class, where antigenic determinants are bound, which parts are constant, and which parts vary.

3. Explain the absolute necessity for the process of clonal deletion.

4. Explain why clonal selection is necessary in a humoral immune response.

5. Compare and contrast a primary immune response and a secondary immune response to the same antigen.

### *Critical Thinking*

1. Based on the structure of the lymphatic system, its tissues, vessels, and cells, explain why the immune system does not actively patrol the brain or spinal cord.
2. For someone born with a genetic disease where B cells are not produced, what types of immune responses would be missing?
3. Follow the fate of an exogenous pathogenic bacterium through the immune system. Assume it is phagocytized by a macrophage but that the bacterium cannot infect the macrophage.

### *Concept Building Questions*

1. Explain why bacterial DNA is a good antigen but would not be useful in actually producing protective immunity against bacterial infection. Answer in terms of what you know about the immune system and the structure of various microbes. What other types of structures would also be antigenic but not protective?
2. Some microbes are classified partly by serotype—that is, by the antigens they display and the antibodies they elicit. Even though antigens are derived from fairly constant proteins, glycoproteins and polysaccharides on the microbial surface, why are specific antigens a better or more useful classification parameter than the whole structural element itself?