Antibodies of the Mucosal Immune System

Antibodies synthesized by the mucosal immune system include IgA and IgM. Activated B cells differentiate into mucosal plasma cells that synthesize and secrete dimeric IgA, and to a lesser extent, pentameric IgM. Secreted IgA is abundant in tears, saliva, breast milk, and in secretions of the gastrointestinal and respiratory tracts. Antibody secretion results in a local humoral response at epithelial surfaces and prevents infection of the mucosa by binding and neutralizing pathogens.

42.4 Disruptions in the Immune System

By the end of this section, you will be able to do the following:

- Describe hypersensitivity
- Define autoimmunity

A functioning immune system is essential for survival, but even the sophisticated cellular and molecular defenses of the mammalian immune response can be defeated by pathogens at virtually every step. In the competition between immune protection and pathogen evasion, pathogens have the advantage of more rapid evolution because of their shorter generation time and other characteristics. For instance, *Streptococcus pneumoniae* (bacterium that cause pneumonia and meningitis) surrounds itself with a capsule that inhibits phagocytes from engulfing it and displaying antigens to the adaptive immune system. *Staphylococcus aureus* (bacterium that can cause skin infections, abscesses, and meningitis) synthesizes a toxin called leukocidin that kills phagocytes after they engulf the bacterium. Other pathogens can also hinder the adaptive immune system. HIV infects T_H cells via their CD4 surface molecules, gradually depleting the number of T_H cells in the body; this inhibits the adaptive immune system's capacity to generate sufficient responses to infection or tumors. As a result, HIV-infected individuals often suffer from infections that would not cause illness in people with healthy immune systems but which can cause devastating illness to immune-compromised individuals. Maladaptive responses of immune cells and molecules themselves can also disrupt the proper functioning of the entire system, leading to host cell damage that could become fatal.

Immunodeficiency

Failures, insufficiencies, or delays at any level of the immune response can allow pathogens or tumor cells to gain a foothold and replicate or proliferate to high enough levels that the immune system becomes overwhelmed. **Immunodeficiency** is the failure, insufficiency, or delay in the response of the immune system, which may be acquired or inherited. Immunodeficiency can be acquired as a result of infection with certain pathogens (such as HIV), chemical exposure (including certain medical treatments), malnutrition, or possibly by extreme stress. For instance, radiation exposure can destroy populations of lymphocytes and elevate an individual's susceptibility to infections and cancer. Dozens of genetic disorders result in immunodeficiencies, including Severe Combined Immunodeficiency (SCID), Bare lymphocyte syndrome, and MHC II deficiencies. Rarely, primary immunodeficiencies that are present from birth may occur. Neutropenia is one form in which the immune system produces a below-average number of neutrophils, the body's most abundant phagocytes. As a result, bacterial infections may go unrestricted in the blood, causing serious complications.

Hypersensitivities

Maladaptive immune responses toward harmless foreign substances or self antigens that occur after tissue sensitization are termed **hypersensitivities**. The types of hypersensitivities include immediate, delayed, and autoimmunity. A large proportion of the population is affected by one or more types of hypersensitivity.

Allergies

The immune reaction that results from immediate hypersensitivities in which an antibody-mediated immune response occurs within minutes of exposure to a harmless antigen is called an **allergy**. In the United States, 20 percent of the population exhibits symptoms of allergy or asthma, whereas 55 percent test positive against one or more allergens. Upon initial exposure to a potential allergen, an allergic individual synthesizes antibodies of the IgE class via the typical process of APCs presenting processed antigen to T_H cells that stimulate B cells to produce IgE. This class of antibodies also mediates the immune response to parasitic worms. The constant domain of the IgE molecules interact with mast cells embedded in connective tissues. This process primes, or sensitizes, the tissue. Upon subsequent exposure to the same allergen, IgE molecules on mast cells bind the antigen via their variable domains and stimulate the mast cell to release the modified amino acids histamine and serotonin; these chemical mediators then recruit eosinophils which mediate allergic responses. Figure 42.26 shows an example of an allergic response to ragweed pollen. The effects of an allergic reaction range from mild symptoms like sneezing and itchy, watery eyes to more severe or even life-threatening reactions involving intensely itchy welts or hives, airway contraction with severe

respiratory distress, and plummeting blood pressure. This extreme reaction is known as anaphylactic shock. If not treated with epinephrine to counter the blood pressure and breathing effects, this condition can be fatal.

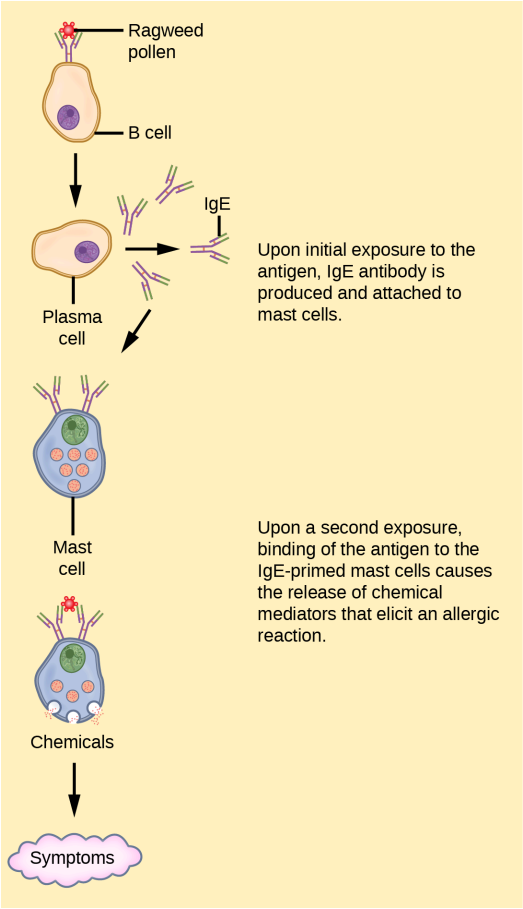

Figure 42.26 On first exposure to an allergen, an IgE antibody is synthesized by plasma cells in response to a harmless antigen. The IgE molecules bind to mast cells, and on secondary exposure, the mast cells release histamines and other modulators that affect the symptoms of allergy. (credit: modification of work by NIH)

Delayed hypersensitivity is a cell-mediated immune response that takes approximately one to two days after secondary exposure for a maximal reaction to be observed. This type of hypersensitivity involves the T_H1 cytokine-mediated inflammatory response and may manifest as local tissue lesions or contact dermatitis (rash or skin irritation). Delayed hypersensitivity occurs in some individuals in response to contact with certain types of jewelry or cosmetics. Delayed hypersensitivity facilitates the immune response to poison ivy and is also the reason why the skin test for tuberculosis results in a small region of inflammation on individuals who were previously exposed to *Mycobacterium tuberculosis*. That is also why cortisone is used to treat such responses: it will inhibit cytokine production.

Autoimmunity

Autoimmunity is a type of hypersensitivity to self antigens that affects approximately five percent of the population. Most types of autoimmunity involve the humoral immune response. Antibodies that inappropriately mark self components as foreign are termed **autoantibodies**. In patients with the autoimmune disease myasthenia gravis, muscle cell receptors that induce contraction in response to acetylcholine are targeted by antibodies. The result is muscle weakness that may include marked difficultly with fine and/or gross motor functions. In systemic lupus erythematosus, a diffuse autoantibody response to the individual's own DNA and proteins results in various systemic diseases. As illustrated in Figure 42.27, systemic lupus erythematosus may affect the heart, joints, lungs, skin, kidneys, central nervous system, or other tissues, causing tissue damage via antibody binding, complement recruitment, lysis, and inflammation.

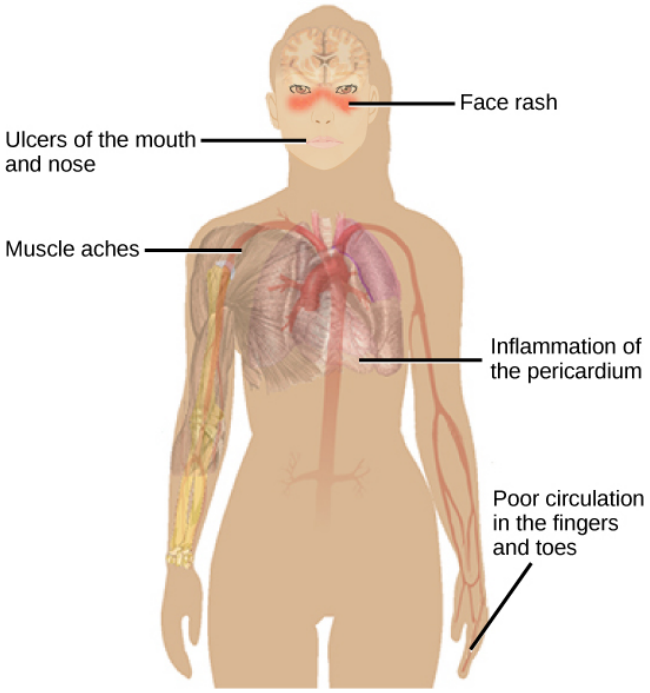

Figure 42.27 Systemic lupus erythematosus is characterized by autoimmunity to the individual's own DNA and/or proteins, which leads to varied dysfunction of the organs. (credit: modification of work by Mikael Häggström)

Autoimmunity can develop with time, and its causes may be rooted in molecular mimicry. Antibodies and TCRs may bind self antigens that are structurally similar to pathogen antigens, which the immune receptors first raised. As an example, infection with *Streptococcus pyogenes* (bacterium that causes strep throat) may generate antibodies or T cells that react with heart muscle, which has a similar structure to the surface of *S. pyogenes*. These antibodies can damage heart muscle with autoimmune attacks, leading to rheumatic fever. Insulin-dependent (Type 1) diabetes mellitus arises from a destructive inflammatory T_H1 response against insulin-producing cells of the pancreas. Patients with this autoimmunity must be injected with insulin that originates from other sources.

KEY TERMS

adaptive immunity immunity that has memory and occurs after exposure to an antigen either from a pathogen or a vaccination

affinity attraction of molecular complementarity between antigen and antibody molecules

allergy immune reaction that results from immediate hypersensitivities in which an antibody-mediated immune response occurs within minutes of exposure to a harmless antigen

antibody protein that is produced by plasma cells after stimulation by an antigen; also known as an immunoglobulin

antigen foreign or "non-self" protein that triggers the immune response

antigen-presenting cell (APC) immune cell that detects, engulfs, and informs the adaptive immune response about an infection by presenting the processed antigen on the cell surface

autoantibody antibody that incorrectly marks "self" components as foreign and stimulates the immune response

autoimmune response inappropriate immune response to host cells or self-antigens

autoimmunity type of hypersensitivity to self antigens

avidity total binding strength of a multivalent antibody with antigen

B cell lymphocyte that matures in the bone marrow and differentiates into antibody-secreting plasma cells

basophil leukocyte that releases chemicals usually involved in the inflammatory response

cell-mediated immune response adaptive immune response that is carried out by T cells

clonal selection activation of B cells corresponding to one specific BCR variant and the dramatic proliferation of that variant

complement system array of approximately 20 soluble proteins of the innate immune system that enhance phagocytosis, bore holes in pathogens, and recruit lymphocytes; enhances the adaptive response when antibodies are produced

cross reactivity binding of an antibody to an epitope corresponding to an antigen that is different from the one the antibody was raised against

cytokine chemical messenger that regulates cell differentiation, proliferation, gene expression, and cell trafficking to effect immune responses

cytotoxic T lymphocyte (CTL) adaptive immune cell that directly kills infected cells via perforin and granzymes, and releases cytokines to enhance the immune response

dendritic cell immune cell that processes antigen material and presents it on the surface of other cells to induce an immune response

effector cell lymphocyte that has differentiated, such as a B cell, plasma cell, or cytotoxic T lymphocyte

eosinophil leukocyte that responds to parasites and is involved in the allergic response

epitope small component of an antigen that is specifically recognized by antibodies, B cells, and T cells; the antigenic determinant

granzyme protease that enters target cells through perforin and induces apoptosis in the target cells; used by NK cells and killer T cells

helper T lymphocyte (T_H) cell of the adaptive immune system that binds APCs via MHC II molecules and stimulates B cells or secretes cytokines to initiate the immune response

host an organism that is invaded by a pathogen or parasite

humoral immune response adaptive immune response that is controlled by activated B cells and antibodies

hypersensitivities spectrum of maladaptive immune responses toward harmless foreign particles or self antigens; occurs after tissue sensitization and includes immediate-type (allergy), delayed-type, and autoimmunity

immune tolerance acquired ability to prevent an unnecessary or harmful immune response to a detected foreign body known not to cause disease or to self-antigens

immunodeficiency failure, insufficiency, or delay at any level of the immune system, which may be acquired or inherited

inflammation localized redness, swelling, heat, and pain that results from the movement of leukocytes and fluid through opened capillaries to a site of infection

innate immunity immunity that occurs naturally because of genetic factors or physiology, and is not induced by infection or vaccination

interferon cytokine that inhibits viral replication and modulates the immune response

lymph watery fluid that bathes tissues and organs with protective white blood cells and does not contain erythrocytes

lymphocyte leukocyte that is histologically identifiable by its large nuclei; it is a small cell with very little cytoplasm

macrophage large phagocytic cell that engulfs foreign particles and pathogens

major histocompatibility class (MHC) I/II molecule protein found on the surface of all nucleated cells (I) or specifically on antigen-presenting cells (II) that signals to immune cells whether the cell is healthy/normal or is infected/cancerous; it provides the appropriate template into which antigens can be loaded for recognition by lymphocytes

mast cell leukocyte that produces inflammatory molecules,

such as histamine, in response to large pathogens and allergens

memory cell antigen-specific B or T lymphocyte that does not differentiate into effector cells during the primary immune response but that can immediately become an effector cell upon reexposure to the same pathogen

monocyte type of white blood cell that circulates in the blood and lymph and differentiates into macrophages after it moves into infected tissue

mucosa-associated lymphoid tissue (MALT) collection of lymphatic tissue that combines with epithelial tissue lining the mucosa throughout the body

natural killer (NK) cell lymphocyte that can kill cells infected with viruses or tumor cells

neutrophil phagocytic leukocyte that engulfs and digests pathogens

opsonization process that enhances phagocytosis using proteins to indicate the presence of a pathogen to phagocytic cells

passive immunity transfer of antibodies from one individual to another to provide temporary protection against pathogens

pathogen an agent, usually a microorganism, that causes disease in the organisms that it invades

pathogen-associated molecular pattern (PAMP) carbohydrate, polypeptide, and nucleic acid "signature" that is expressed by viruses, bacteria, and parasites but differs from molecules on host cells

pattern recognition receptor (PRR) molecule on macrophages and dendritic cells that binds molecular signatures of pathogens and promotes pathogen engulfment and destruction

perforin destructive protein that creates a pore in the target cell; used by NK cells and killer T cells

plasma cell immune cell that secrets antibodies; these cells arise from B cells that were stimulated by antigens

regulatory T (T_{reg}) cell specialized lymphocyte that suppresses local inflammation and inhibits the secretion of cytokines, antibodies, and other stimulatory immune factors; involved in immune tolerance

T cell lymphocyte that matures in the thymus gland; one of the main cells involved in the adaptive immune system

CHAPTER SUMMARY

42.1 Innate Immune Response

The innate immune system serves as a first responder to pathogenic threats that bypass natural physical and chemical barriers of the body. Using a combination of cellular and molecular attacks, the innate immune system identifies the nature of a pathogen and responds with inflammation, phagocytosis, cytokine release, destruction by NK cells, and/or a complement system. When innate mechanisms are insufficient to clear an infection, the adaptive immune response is informed and mobilized.

42.2 Adaptive Immune Response

The adaptive immune response is a slower-acting, longer-lasting, and more specific response than the innate response. However, the adaptive response requires information from the innate immune system to function. APCs display antigens via MHC molecules to complementary naïve T cells. In response, the T cells differentiate and proliferate, becoming T_H cells or CTLs. T_H cells stimulate B cells that have engulfed and presented pathogen-derived antigens. B cells differentiate into plasma cells that secrete antibodies, whereas CTLs induce apoptosis in intracellularly infected or cancerous cells. Memory cells persist after a primary exposure to a pathogen. If reexposure occurs, memory cells differentiate into effector cells without input from the innate immune system. The mucosal immune system is largely independent from the systemic immune system but functions in a parallel fashion to protect the extensive mucosal surfaces of the body.

42.3 Antibodies

Antibodies (immunoglobulins) are the molecules secreted from plasma cells that mediate the humoral immune response. There are five antibody classes; an antibody's class determines its mechanism of action and production site but does not control its binding specificity. Antibodies bind antigens via variable domains and can either neutralize pathogens or mark them for phagocytosis or activate the complement cascade.

42.4 Disruptions in the Immune System

Immune disruptions may involve insufficient immune responses or inappropriate immune targets. Immunodeficiency increases an individual's susceptibility to infections and cancers. Hypersensitivities are misdirected responses either to harmless foreign particles, as in the case of allergies, or to host factors, as in the case of autoimmunity. Reactions to self components may be the result of molecular mimicry.

VISUAL CONNECTION QUESTIONS

1. Figure 42.11 Which of the following statements about T cells is false?
   a. Helper T cells release cytokines while cytotoxic T cells kill the infected cell.
   b. Helper T cells are CD4+, while cytotoxic T cells are $CD8^+$.
   c. MHC II is a receptor found on most body cells, while MHC I is a receptor found on immune cells only.
   d. The T cell receptor is found on both $CD4^+$ and $CD8^+$ T cells.

2. Figure 42.14 Based on what you know about MHC receptors, why do you think an organ transplanted from an incompatible donor to a recipient will be rejected?

3. Figure 42.16 The Rh antigen is found on Rh-positive red blood cells. An Rh-negative female can usually carry an Rh-positive fetus to term without difficulty. However, if she has a second Rh-positive fetus, her body may launch an immune attack that causes hemolytic disease of the newborn. Why do you think hemolytic disease is only a problem during the second or subsequent pregnancies?

REVIEW QUESTIONS

4. Which of the following is a barrier against pathogens provided by the skin?
   a. high pH
   b. mucus
   c. tears
   d. desiccation

5. Although interferons have several effects, they are particularly useful against infections with which type of pathogen?
   a. bacteria
   b. viruses
   c. fungi
   d. helminths

6. Which organelle do phagocytes use to digest engulfed particles?
   a. lysosome
   b. nucleus
   c. endoplasmic reticulum
   d. mitochondria

7. Which innate immune system component uses MHC I molecules directly in its defense strategy?
   a. macrophages
   b. neutrophils
   c. NK cells
   d. interferon

8. Which of the following is both a phagocyte and an antigen-presenting cell?
   a. NK cell
   b. eosinophil
   c. neutrophil
   d. macrophage

9. Which immune cells bind MHC molecules on APCs via CD8 coreceptors on their cell surfaces?
   a. T_H cells
   b. CTLs
   c. mast cells
   d. basophils

10. What "self" pattern is identified by NK cells?
    a. altered self
    b. missing self
    c. normal self
    d. non-self

11. The acquired ability to prevent an unnecessary or destructive immune reaction to a harmless foreign particle, such as a food protein, is called _____.
    a. the T_H2 response
    b. allergy
    c. immune tolerance
    d. autoimmunity

12. Upon reexposure to a pathogen, a memory B cell can differentiate to which cell type?
    a. CTL
    b. naïve B cell
    c. memory T cell
    d. plasma cell

13. Foreign particles circulating in the blood are filtered by the _____.
    a. spleen
    b. lymph nodes
    c. MALT
    d. lymph

14. The structure of an antibody is similar to the extracellular component of which receptor?
   a. MHC I
   b. MHC II
   c. BCR
   d. none of the above

15. The first antibody class to appear in the serum in response to a newly encountered pathogen is _____.
   a. IgM
   b. IgA
   c. IgG
   d. IgE

16. What is the most abundant antibody class detected in the serum upon reexposure to a pathogen or in reaction to a vaccine?
   a. IgM
   b. IgA
   c. IgG
   d. IgE

17. Breastfed infants typically are resistant to disease because of _____.
   a. active immunity
   b. passive immunity
   c. immune tolerance
   d. immune memory

18. Allergy to pollen is classified as:
   a. an autoimmune reaction
   b. immunodeficiency
   c. delayed hypersensitivity
   d. immediate hypersensitivity

19. A potential cause of acquired autoimmunity is _____.
   a. tissue hypersensitivity
   b. molecular mimicry
   c. histamine release
   d. radiation exposure

20. Autoantibodies are probably involved in:
   a. reactions to poison ivy
   b. pollen allergies
   c. systemic lupus erythematosus
   d. HIV/AIDS

21. Which of the following diseases is not due to autoimmunity?
   a. rheumatic fever
   b. systemic lupus erythematosus
   c. diabetes mellitus
   d. HIV/AIDS

CRITICAL THINKING QUESTIONS

22. Different MHC I molecules between donor and recipient cells can lead to rejection of a transplanted organ or tissue. Suggest a reason for this.

23. If a series of genetic mutations prevented some, but not all, of the complement proteins from binding antibodies or pathogens, would the entire complement system be compromised?

24. Explain the difference between an epitope and an antigen.

25. What is a naïve B or T cell?

26. How does the T_H1 response differ from the T_H2 response?

27. In mammalian adaptive immune systems, T cell receptors are extraordinarily diverse. What function of the immune system results from this diversity, and how is this diversity achieved?

28. How do B and T cells differ with respect to antigens that they bind?

29. Why is the immune response after reinfection much faster than the adaptive immune response after the initial infection?

30. What are the benefits and costs of antibody cross reactivity?