

Chapter 43: Immune System

1. Briefly explain the six steps to ingestion and destruction of a microbe by a phagocytic cell.

First, pseudopodia surround the microbes. Second, the microbes are engulfed into a cell. Third, a vacuole containing the microbes forms. Fourth, the vacuole fuses with a lysosome. Fifth, toxic compounds and lysosomal enzymes destroy microbes. Finally, microbial debris is released by the exocytosis.

2. Explain the role of the Toll receptor in producing antimicrobial peptides.

Each mammalian Toll-like receptor, or TLR, recognizes fragments of molecules characteristic of a set of pathogens. Lipopolysaccharide, flagellin, CpG DNA (DNA containing unmethylated CG sequences) and double-stranded (ds) RNA are all found in microorganisms or viruses, but not in animal cells. Together with other recognition and response factors, TLR proteins trigger internal innate immune defenses.

3. List three innate defenses vertebrates share with invertebrates and the two defenses unique to vertebrates.

Pathogen recognition in mammals triggers the production and release of a variety of peptides and proteins that attack microbes or impede their reproduction. Some of these defense molecules function like the antimicrobial peptides of insects, damaging broad groups of pathogens by disrupting membrane integrity. Others, including the interferons and complement proteins, are unique to vertebrate immune systems. Interferons are proteins that provide innate defense against viral infections. The complement system consists of roughly 30 proteins in blood plasma that function together to fight infections.

4. List five examples of barrier defenses.

barrier defense	how the barrier repels pathogens
mucus membranes	mucus traps microbes and other particles
saliva, tears	bathe various exposed epithelia, providing washing action that also inhibits colonization by fungi and bacteria
stomach acid	kills most microbes in food and water before they can enter the intestines
secretions from oil and sweat glands	gives human skin a 3–5 pH range, acidic enough to prevent the growth of many bacteria
skin	blocks entry of many pathogens

5. Explain how Toll-like receptors are used in cellular innate defenses, using TLR3 and TLR4 as examples.

TLR4, located on immune cell plasma membranes, recognizes lipopolysaccharide, a type of molecule found on the surface of many bacteria. TLR3, on the inner surface of vesicles formed by endocytosis, is the sensor for double-stranded RNA, a form of nucleic acid characteristic of certain viruses.

6. In the chart below, explain the role of the four phagocytic cells.

phagocytic cell type	role in innate defense
neutrophils	most abundant phagocytic cells in the mammalian body; signals from infected tissues attract neutrophils, which then engulf and destroy molecules
macrophages	large phagocytic cells; some migrate throughout body, while others reside permanently in various organs, tissues; macrophages in spleen, lymph nodes, other tissues of lymphatic system particularly well positioned to combat pathogens
eosinophils	have low phagocytic activity but are important in defending against multicellular invaders, such as parasitic worms; rather than engulfing parasites, position themselves against parasite's body, then discharge destructive enzymes that damage invader
dendritic cells	populate tissues that are in contact with environment; mainly stimulate development of acquired immunity against microbes they encounter

7. Trace the flow of lymph in four stages. For each stage, explain the role of the lymphatic system in innate defense. 

First, interstitial fluid bathing the tissues, along with the white blood cells in it, continually enters the lymphatic vessels. Second, fluid inside the lymphatic system, called lymph, flows through lymphatic vessels throughout the body. Third, within lymph nodes, microbes and foreign particles present in the circulating lymph encounter macrophages and other cells that carry out defensive actions. Fourth, lymphatic vessels return lymph to the blood via two large ducts that drain into veins near the shoulders.

8. Explain the role of the antimicrobial compounds interferon and complement.

Interferons are proteins that provide innate defense against viral infections. Virus-infected body cells secrete interferons, inducing nearby uninfected cells to produce substances that inhibit viral reproduction. In this way, interferons limit the cell-to-cell spread of viruses in the body, helping control viral infections such as colds and influenza. Some white blood cells secrete a different type of interferon that helps activate macrophages, enhancing their phagocytic ability. Pharmaceutical companies now mass-produce interferons by recombinant DNA technology for treating certain viral infections, such as hepatitis C.

The complement system consists of roughly 30 proteins in blood plasma. These proteins circulate in an inactive state and are activated by substances on the surface of many microbes. Activation results in a cascade of biochemical reactions that can lead to lysis of invading cells. The complement system also functions in the inflammatory response and in adaptive defenses.

9. Explain the three steps of an inflammatory response.

At the injury site, mast cells release histamines, and macrophages secrete cytokines. These signaling molecules cause nearby capillaries to dilate. Capillaries widen and become more permeable, allowing fluid containing antimicrobial peptides to enter the tissue. Signals released by immune cells attract neutrophils. Neutrophils digest pathogens and cell debris at the site, and the tissue heals.

10. What role do natural killer cells play in the immune system?

Cellular innate defenses in vertebrates involve natural killer cells, which circulate through the body and detect the abnormal array of surface proteins characteristic of some virus-infected and cancerous cells. Natural killer cells do not engulf stricken cells. Instead, they release chemicals that lead to cell death, inhibiting further spread of the virus or cancer.

11. How do the pathogens that cause pneumonia and tuberculosis avoid our immune responses?

The outer capsule that surrounds certain bacteria, such as *Streptococcus pneumoniae*, interferes with molecular recognition and phagocytosis. Some bacteria, after being engulfed by a host cell, resist breakdown within lysosomes. Rather than being destroyed within host cells, the bacterium that causes TB grows and reproduces, effectively hidden from the body's innate immune defenses.

12. Summarize where T cells and B cells develop and give an overview of their functions.

Like all blood cells, lymphocytes originate from stem cells in the bone marrow. Some lymphocytes migrate from the bone marrow to the thymus, an organ in the thoracic cavity above the heart. These lymphocytes mature into T cells. Lymphocytes that remain and mature in the bone marrow develop as B cells. (Lymphocytes of a third type remain in the blood and become the natural killer cells active in innate immunity.)

13. What is immunological memory and why is it important?

Prior exposure to an antigen alters the speed, strength, and duration of the immune response. If an individual is exposed again to the same antigen, the response is faster, of greater magnitude, and more prolonged.

14. Explain how cytokines help coordinate the innate and acquired immune responses.

Activated macrophages and neutrophils discharge cytokines, signaling molecules that enhance an immune response. These cytokines, signaling molecules that enhance an immune response. These cytokines promote blood flow to the site of injury or infection. The increase in local blood supply causes the redness and increased skin temperature typical of the inflammatory response. Enhanced blood flow helps deliver antimicrobial peptides.

15. What are antigens and epitopes? What is the relationship between an antigen receptor and an antibody or immunoglobulin?

Any substance that elicits a response from a B cell or T cell is called an antigen. In adaptive immunity, recognition occurs when a B cell or T cell binds to an antigen, such as a bacterial or viral protein, via a protein called an antigen receptor. All of the antigen receptors made by a single B or T cell are identical. Infection triggers activation of B and T cells with antigen receptors specific for parts of that pathogen. The small, accessible portion of an antigen that binds to an antigen receptor is called an epitope. An antigen receptor of a B cell binds to an epitope. Following binding, the B cell gives rise to cells that secrete a soluble form of the antigen receptor. This soluble receptor, called an antibody, or immunoglobulin (Ig), is specific for the same epitope as the original B cell. Different antibodies can recognize distinct epitopes on the same antigen. It is the antibodies, rather than the B cells themselves, that actually help defend against pathogens. The antigen receptors of T cells function differently.

17. What forms the specific antigen-binding site?

Parts of a heavy-chain V region and a light-chain V region form an asymmetrical binding site for an antigen.

19. T cells display only one type of antigen receptor on the surface of the cell. Compare and contrast a T cell with a B cell.

Whereas the antigen receptors of B cells bind to epitopes of intact antigens circulating in body fluids, those of T cells bind only to fragments of antigens that are displayed, or presented, on the surface of host cells.

20. Explain the role of the major histocompatibility complex (MHC) to T-cell receptor binding.

The host protein that displays the antigen fragment on the host cell surface is called an MHC (major histocompatibility complex) molecule. If the cell displaying an antigen fragment encounters a T cell with the right specificity, the antigen receptor on the T cell can bind to both the antigen fragment and the MHC molecule.

21. Explain how an infected host cell uses the MHC molecule to display an antigen.

Recognition of protein antigens by T cells begins when a pathogen or part of a pathogen either infects or is taken in by a host cell. Inside the host cell, enzymes in the cell cleave the antigen into smaller peptides. Each peptide, called an antigen fragment, then binds to an MHC molecule inside the cell. Movement of the MHC molecule and bound antigen fragment to the cell surface results in antigen presentation, the display of the antigen fragment in an exposed groove of the MHC protein.

22. Explain the differences between Class I and Class II MHC molecules.

MHC class	type of cells displayed by	T cells by which recognized
I	most body cells & antigen-presenting cells	helper T cells
II	antigen-presenting cells	cytotoxic T cells

24. List four properties of the acquired immune system.

There is an immense diversity of lymphocytes and receptors, enabling the immune system to detect pathogens never before encountered. Adaptive immunity normally has self-tolerance, the lack of reactivity against an animal's own molecules and cells. Cell proliferation triggered by activation greatly increases the number of B and T cells specific for an antigen. Immunological memory allows for a stronger and more rapid response to an antigen encountered previously.

25. Explain the four steps involved in producing genetically unique B-cell receptors. ↗

The capacity to generate diversity is built into the structure of Ig genes. A receptor light chain is encoded by three gene segments: a variable (V) segment, a joining (J) segment, and a constant (C) segment. The V and J segments together encode the variable region of the receptor chain, while the C segment encodes the constant region. Alternative copies of the V and J segments are arranged within the gene in a series. A functional gene is built from one copy of each type of segment. Early in B cell development, an enzyme complex called recombinase randomly links one light-chain V segment to one J gene segment.

This recombination event eliminates the long stretch of DNA between the segments, forming a single exon that is part V and part J. Because there is only an intron between the J and C DNA segments, no further DNA rearrangement is required. Instead, the J and C segments of the RNA transcript will be joined when splicing removes the intervening RNA. The rearrangements are permanent and passed on to the daughter cells when the lymphocyte divides. In any given cell, only one allele of a light-chain gene and one allele of a heavy-chain gene are rearranged. Following translation, Each pair of randomly rearranged heavy and light chains results in a different antigen-binding site.

26. Explain how the body develops self-tolerance in the immune system.

Because antigen receptor genes are randomly rearranged, some immature lymphocytes produce receptors specific for epitopes on the organism's own molecules. If these self-reactive lymphocytes were not eliminated or inactivated, the immune system could not distinguish self from nonself. Instead, as lymphocytes mature in the bone marrow or thymus, their antigen receptors are tested for self-reactivity. Some B and T cells with receptors specific for the body's own molecules are destroyed by apoptosis (programmed cell death). The remaining self-reactive lymphocytes react to foreign molecules.

27. *What are effector cells, memory cells, and clonal selection?*

Once activated, a B cell or T cell undergoes multiple cell divisions. For each activated cell, the result of this proliferation is a clone, a population of cells that are identical to the original cell. Some cells from this clone become effector cells, short-lived cells that take effect immediately against the antigen and any pathogens producing that antigen. The effector forms of B cells are plasma cells, which secrete antibodies. The effector forms of T cells are helper cells and cytotoxic cells. The remaining cells in the clone become memory cells, long-lived cells that can give rise to effector cells if the same antigen is encountered later in the animal's life. T cells also undergo clonal selection, generating memory T cells and effector T cells.

28. *What are the four key events in clonal selection?*

First, antigens bind to the antigen receptors of a B cell. Second, The selected B cell proliferates, forming a clone of identical cells bearing receptors for the antigen. Third, some daughter cells develop into long-lived memory cells that can respond rapidly upon subsequent exposure to the same antigen and other daughter cells develop into short-lived plasma cells that secrete antibodies specific for the antigen. This process is called clonal selection because an encounter with an antigen *selects* which lymphocyte will divide to produce a *clonal* population of thousands of cells specific for a particular epitope.

29. *Explain the difference between a primary and secondary immune response.* 

The production of effector cells from a clone of lymphocytes during the first exposure to an antigen is the basis for the primary immune response. The primary response peaks about 10–17 days after the initial exposure. During this time, selected B cells and T cells give rise to their effector forms. If an individual is exposed again to the same antigen, the response is faster (typically peaking only 2–7 days after exposure), of greater magnitude, and more prolonged. This is the secondary immune response, which relies on the reservoir of T and B memory cells generated following initial exposure to an antigen. Because these cells are long-lived, they provide the basis for immunological memory, which can span many decades.

30. *Explain the humoral and cell-mediated immune responses.*

In the humoral immune response, antibodies help neutralize or eliminate toxins and pathogens in the blood and lymph. In the cell-mediated immune response, specialized T cells destroy infected host cells. Both responses include a primary immune response and a secondary immune response enabled by memory cells.

31. *Explain how helper T cells help activate both T cells and B cells.* 

A type of T cell called a helper T cell triggers both the humoral and cell-mediated immune responses. Helper T cells themselves do not carry out those responses. Instead, signals from helper T cells initiate production of antibodies that neutralize pathogens and activate T cells that kill infected cells. After an antigen-presenting cell engulfs and degrades a pathogen, it displays antigen fragments complexed with class II MHC molecules on the cell surface. A specific helper T cell binds to a displayed complex via its antigen receptor and an accessory protein. This interaction promotes secretion of cytokines by the antigen-presenting cell. Proliferation of the helper T cell, stimulated by cytokines from both the antigen-presenting cell and the helper T cell itself, gives rise to a clone of activated helper T cells, all with receptors for the same MHC–antigen fragment complex. Following proliferation, helper T cells secrete other cytokines, which help activate B cells and cytotoxic T cells.

32. *Explain the role of dendritic cells and macrophages in starting a primary and secondary immune response.*

Antigen presentation by a dendritic cell or a macrophage activates a helper T cell. The helper T cell then proliferates, forming a clone of activated helper T cells. The B cells present antigens to already activated helper T cells, which in turn activate the B cells themselves. Activated helper T cells also help stimulate cytotoxic T cells.

33. *What are the effector cells in cell-mediated immunity?*

In the cell-mediated immune response, cytotoxic T cells are the effector cells.

34. What must occur for a cytotoxic T cell to become activated?

Antigen presentation by a dendritic cell or a macrophage activates a helper T cell.

35. Explain the three primary steps that occur as a cytotoxic T cell destroys a target cell. 

An activated cytotoxic T cell binds to a class I MHC–antigen fragment complex on an infected cell via its antigen receptor and an accessory protein. The T cell releases perforin molecules, which form pores in the infected cell membrane, and granzymes, enzymes that break down proteins. Granzymes enter the infected cell by endocytosis. The granzymes initiate apoptosis within the infected cell, leading to fragmentation of the nucleus and cytoplasm and eventual cell death. The released cytotoxic T cell can attack other infected cells.

36. How is B-cell antigen presentation unique?

A macrophage or dendritic cell can present fragments from a wide variety of protein antigens, whereas a B cell presents only the antigen to which it specifically binds. When an antigen first binds to receptors on the surface of a B cell, the cell takes in a few foreign molecules by receptor-mediated endocytosis. The class II MHC protein of the B cell then presents an antigen fragment to a helper T cell.

37. Explain the three primary steps that occur in B cell activation. 

After an antigen-presenting cell engulfs and degrades a pathogen, it displays an antigen fragment complexed with a class II MHC molecule. A helper T cell that recognizes the complex is activated with the aid of cytokines secreted from the antigen-presenting cell. When a B cell with receptors for the same epitope internalizes the antigen, it displays an antigen fragment on the cell surface in a complex with a class II MHC molecule. An activated helper T cell bearing receptors specific for the displayed fragment binds to the B cell. This interaction, with the aid of cytokines from the T cell, activates the B cell. The activated B cell proliferates and differentiates into memory B cells and antibody-secreting plasma cells. The secreted antibodies are specific for the same antigen that initiated the response.

38. What is the difference between plasma cells and memory cells produced from the activation of B cells?

B cell activation by an antigen is aided by cytokines secreted from helper T cells that have encountered the same antigen. Stimulated by both an antigen and cytokines, the B cell proliferates and differentiates into memory B cells and antibody-screening effector cells called plasma cells.

39. Explain how monoclonal antibodies are used in home pregnancy kits.

Antibodies that an animal produces after exposure to a microbial antigen are polyclonal. In contrast, other antibody tools are monoclonal, prepared from a single clone of B cells grown in culture. Home pregnancy kits use monoclonal antibodies to detect human chorionic gonadotropin (hCG). Because hCG is produced as soon as an embryo implants in the uterus, the presence of this hormone in a woman's urine is a reliable indicator for a very early stage of pregnancy.

40. Why is the antibody response to a microbial infection polyclonal?

Polyclonal antibody tools are the products of many different clones of plasma cells, each specific for a different epitope.

41. Explain how antibodies can dispose of antigens through viral neutralization, opsonization, and activation of complement.

Antibodies do not kill pathogens, but by binding to antigens, they mark pathogens in various ways for inactivation or destruction. In the simplest of these activities, neutralization, antibodies bind to viral surface proteins. The bound antibodies prevent infection of a host cell, thus neutralizing the virus. Similarly, antibodies sometimes bind to toxins released in body fluids, preventing the toxins from entering body cells. In another process, called opsonization, antibodies bound to antigens on bacteria present a readily recognized structure for macrophages or neutrophils and therefore increase phagocytosis. Because each antibody has two antigen-binding sites, antibodies sometimes also facilitate phagocytosis by linking bacterial cells, virus particles, or other foreign substances into aggregates.

Antibodies sometimes work together with the proteins of the complement system to dispose of pathogens. Binding of a complement protein to an antigen-antibody complex on a foreign cell triggers a cascade in which each protein of the complement system activates the next protein. Ultimately, activated complement proteins generate a membrane attack complex that forms a pore in the membrane of the foreign cell. Ions and water rush into the cell, causing it to swell and lyse. Whether activated as part of innate or adaptive defenses, this cascade of complement protein activity results in the lysis of foreign cells and produces factors that promote inflammation or stimulate phagocytosis.

42. Explain the difference between active and passive immunity. Give examples.

Active immunity includes the defenses that arise when a pathogen infects the body and prompts a primary or secondary immune response. In contrast, a different type of immunity results when the IgG antibodies in the blood of a pregnant female cross the placenta to her fetus. The transferred antibodies can immediately react with any pathogen for which they are specific. This protection is called passive immunity because the antibodies provided by the mother guard against pathogens that have never infected the newborn. Because passive immunity does not involve the recipient's B and T cells, it persists only as long as the transferred antibodies last (a few weeks to a few months).

43. Describe how immunizations can serve as an example of active immunity.

Active immunity can develop from the introduction of antigens into the body through immunization. In the first documented case of immunization, Jenner used the cowpox virus to induce adaptive immunity against the closely related smallpox virus. An encounter with the pathogen from which the vaccine was derived triggers a rapid and strong secondary immune response.

44. Why is immune rejection an example of a healthy immune system?

The body's rejection of transplanted tissues or organs or of an incompatible blood transfusion is the expected reaction of a healthy immune system exposed to foreign antibodies, indicating that it can distinguish effectively between self and nonself. It remains a largely unanswered question why a pregnant woman does not reject her fetus as nonself tissue.

45. Explain how antibodies against blood types are present. What is the role of MHC in tissue and organ transplants? Why are bone marrow transplants medically unique?

If a person with type A blood receives a transfusion of type B blood, that person's anti-B antibodies cause an immediate and devastating transfusion reaction. The transfused red blood cells undergo lysis, which can lead to chills, fever, shock, and kidney malfunction. Anti-A antibodies in the donated type B blood will also act against the recipient's type A red blood cells. In the case of tissue and organ transplants, or grafts, MHC molecules stimulate the immune response that leads to rejection. Each vertebrate species has many alleles for each MHC gene, enabling presentation of antigen fragments that vary in shape and net electrical charge.

Transplants of bone marrow from one person to another can also cause an immune reaction, but for a different reason. Bone marrow transplants are used to treat cancers and various blood cell diseases. Prior to receiving transplanted bone marrow, the recipient is typically treated with radiation to eliminate his or her own bone marrow cells, thus destroying the source of abnormal cells. This treatment effectively obliterates the recipient's immune system, leaving little chance of graft rejection. However, lymphocytes in the donated marrow may react against the recipient. This graft versus host reaction is limited if the MHC molecules of the donor and recipient are well matched.

46. What are allergies?

Allergies are exaggerated responses to certain antigens called allergens.

47. Explain a typical allergic response. 

IgE antibodies produced in response to initial exposure to an allergen bind to receptors on mast cells. On subsequent exposure to the same allergen, IgE molecules attached to a mast cell recognize and bind the allergen. Cross-linking of adjacent IgE molecules triggers release of histamine and other chemicals, leading to allergy symptoms.

48. Explain what happens if a person experiences anaphylactic shock.

An acute allergic response sometimes leads to anaphylactic shock, a whole-body, life-threatening reaction that can occur within seconds of exposure to an allergen. Anaphylactic shock develops when widespread release of mast cell contents triggers abrupt dilation of peripheral blood vessels, causing a precipitous drop in blood pressure, as well as constriction of bronchioles. Death may occur within minutes due to lack of blood flow and inability to breathe.

49. Describe the causes and symptoms of lupus, rheumatoid arthritis, Type 1 diabetes mellitus, and multiple sclerosis.

Autoimmune diseases cause the immune system to lose self-tolerance. In systemic lupus erythematosus, the immune system generates antibodies against histones and DNA released by the normal breakdown of body cells. These self-reactive antibodies cause skin rashes and kidney dysfunction. Rheumatoid arthritis leads to damage and painful inflammation of the cartilage and bone of joints. In type 1 diabetes mellitus, the insulin-producing beta cells of the pancreas are the targets of autoimmune cytotoxic cells. The most common chronic neurological disorder in developed countries is the autoimmune disease multiple sclerosis. In this disease, T cells infiltrate the central nervous system. The result is destruction of the myelin sheath that surrounds parts of many neurons, leading to muscle paralysis through a disruption in neuron function.

50. Explain how immunodeficiency diseases are different from autoimmune diseases.

A disorder in which an immune system response to antigens is defective or absent is called an immunodeficiency. An inborn immunodeficiency results from a genetic or developmental defect in the immune system. An acquired immunodeficiency develops later in life following exposure to chemical or biological agents. Exposure to certain agents can cause immunodeficiencies that develop later in life. In contrast, the immune system attacks itself in an autoimmune disease.

51. Describe the pathogen strategies of antigenic variation, latency, and attack on the immune system (HIV).

Immunological memory is a record of the foreign epitopes an animal has encountered. If the pathogen that expressed those epitopes no longer does so, it can reinfect or remain in a host without triggering the rapid and robust response that memory cells provide. Such changes in epitope expression, called antigenic variation, are the major reason the influenza virus remains a major health problem.

After infecting a host, some viruses enter a largely inactive state called latency. Because such dormant viruses cease making most viral proteins and typically produce no free virus particles, they do not trigger an adaptive immune response. Nevertheless, the viral genome persists in the nuclei of infected cells, either as a separate small DNA molecule or as a copy integrated into the host genome. Latency typically persists until conditions arise that are favorable for viral transmission or unfavorable for host survival, such as when the host is infected by another pathogen.

The human immunodeficiency virus (HIV), the pathogen that causes AIDS, both escapes and attacks the adaptive immune response. Once introduced into the body, HIV rapidly infects helper T cells. In the cell, the HIV RNA genome is reverse-transcribed, and the product DNA is integrated into the host cell's genome. In this form, the viral genome can direct production of new virus particles.

HIV mutates at a very high rate during replication, so some HIV invariably escapes the body's immune response. Altered proteins on the surface of some mutated viruses reduce interaction with antibodies and cytotoxic T cells. The virus thus *evolves within the body*. When the viral DNA integrates into the chromosome of a host cell but does not produce new virus proteins or particles, it is shielded from the immune system by the host cell. This latent viral DNA is also protected from antiviral agents currently used against HIV because they attack only actively replicating viruses. Over time, an untreated HIV infection not only avoids the adaptive immune response but also abolishes it. Viral reproduction and cell death triggered by the virus lead to loss of helper T cells, impairing both humoral and cell-mediated immune responses. The result is a progression to AIDS.

52. Explain how the high mutation rate in surface antigen genes in HIV has hampered development of an AIDS vaccine.

Mutations that occur in each round of viral reproduction can generate strains of HIV that are drug resistant. The impact of such viral drug resistance can be reduced by the use of a combination of drugs. However, the appearance of strains resistant to multiple drugs reduces the effectiveness of such multidrug "cocktails" in some patients. Frequent mutations in genes for HIV surface antigens have also hampered efforts to develop an effective vaccine. Viruses are involved in about 15–20% of all human cancers.