

Chapter 49 The Immune System in Animals**I. Innate Immunity****A. Early Observations of Immunity**

1. Three observations in determining how immunity works:
 - a. Wounds usually heal even if they become infected.
 - b. People infected with a virus or bacteria usually recover even without drugs.
 - c. People who have been infected with a disease rarely get the disease again.
2. E. Jenner (1700s) had a key insight.
 - a. Jenner hypothesis: Milkmaids did not get smallpox because exposure to cow's milk exposed them to cowpox, which was providing immunity.
 - b. Experiment: Inoculate a boy with fluid from a cowpox pustule, then later inoculate with fluid from a smallpox pustule.
 - c. Result: The boy did not get smallpox.
 - d. Jenner's technique, vaccination, was adopted throughout Europe.

B. Cells that are always ready to respond to foreign invaders confer innate immunity.

1. Antigens are any foreign molecule.
 - a. Most are proteins or glycoproteins from bacteria or viruses.
 - b. Foreign carbohydrates or lipids can also act as antigens.
2. Cells involved in innate immunity are nonspecific in their response to antigens.
3. Innate response is the same regardless of the species of organism that invades.

C. Barriers to Entry

1. Human skin provides a physical and chemical barrier.
 - a. Lactic acid and fatty acids lower the pH of the surface and inhibit bacteria.
 - b. Protective mucus on the skin surface prevents contact of pathogens with skin cells.
2. Breaks occur in the skin barrier.
 - a. Breaks in the barrier occur at openings of the digestive, reproductive tracts, respiratory tracts, and sense organs.
 - b. Some viruses have an enzyme that breaks down the mucus barrier.
 - c. Eyes are protected by tears, which have lysozyme that will break down bacterial cell walls.

D. The Innate Immune Response

1. Leukocytes implement the innate response when infection occurs.
2. Pattern recognition receptors on immune cells detect molecules unique to invaders:
 - a. *N*-formylmethionine on bacterial proteins
 - b. Lipopolysaccharide in walls of gram-negative bacteria
 - c. Cell-wall components that terminate in mannose
3. The inflammatory response is activated:
 - a. Platelets form clots in places where skin has broken and bleeding occurs.
 - b. Mast-cell leukocytes release chemicals that cause blood vessels near the wound to constrict.
 - c. Other mast-cell secretions cause vessels farther from the wound to dilate.
 - d. Blood delivery to the wound area increases.
 - e. Cells in nearby tissues release chemokines.

- f. Chemokines create a chemotactic gradient that neutrophils and other leukocytes use to find the wound site.
- g. Neutrophils phagocytose bacteria and secrete lysozyme, which degrades bacterial cell walls.
- h. Neutrophils also release a variety of reactive oxygen intermediates (ROI) such as nitric oxide and hydrogen peroxide, which attack bacteria and fungi.
- i. Macrophages arrive at the wound site and phagocytose bacteria.
- j. Macrophages also secrete cytokines, which perform a variety of functions:

II. The Acquired Immune Response: Recognition

- A. The acquired immune response is specific for each antigen.
 - 1. Every animal is exposed to an enormous number of different antigens.
 - 2. How can the immune system respond to so many different antigens?
 - 3. Researchers in the 1920s injected rabbits with organic compounds that do not exist in nature.
 - a. The rabbit immune systems produced antibodies in response.
 - b. Conclusion: The immune system can produce an almost limitless array of antibodies.
- B. An Introduction to Lymphocytes and the Immune System
 - 1. Lymphocytes are involved in the acquired immune response.
 - a. Lymphocytes form and mature in the bone marrow and thymus gland.
 - b. Lymphocytes circulate through the blood, lymph nodes, spleen, and lymphatic ducts in lymph fluid.
 - c. Lymphocytes mostly encounter antigens in the lymph nodes and spleen.
 - d. The lymph nodes, spleen, and lymphatic ducts make up the secondary organs of the immune system.
 - 2. Circulating lymphocytes are in an inactive state in which they have:
 - a. A large nucleus
 - b. Relatively little cytoplasm and few mitochondria
 - c. A ruffled membrane
 - 3. If a resting lymphocyte encounters an antigen to which it can respond, it becomes activated.
 - a. The cytoplasm increases, and many mitochondria appear.
 - b. A massive amount of rough endoplasmic reticulum is formed.
 - c. Conclusion: The lymphocyte begins active production and secretion of molecules.
- C. The Discovery of B Cells and T Cells
 - 1. Experiments in chickens identified an organ important for antibody production.
 - a. Chickens were injected with *Salmonella* toxin.
 - b. Chickens that lacked an organ, called the bursa, either died or did not produce any antibodies.
 - c. All chickens with intact bursa produced abundant antibodies.
 - d. Hypothesis: The bursa is required for antibody production, and antibodies are important for neutralizing antigens.
 - e. Later experiments showed that lymphocytes from the bursa (B cells) produce antibodies.
 - f. Organisms that lack a bursa produce B cells in bone marrow.
 - 2. A related experiment in mice identified an organ important for T-cell production.
 - a. Mice lacking a thymus had defective immune systems.

- b. Skin grafts placed on the mice were not rejected.
 - c. Mice with intact immune systems rejected the foreign tissue.
 - d. Lymphocytes from the thymus (T cells) perform many immune functions, including recognizing and killing foreign cells.
3. T cells come in two major types, distinguished by proteins on their membrane:
- a. CD8⁺ cells have the CD8 protein on their membrane.
 - b. CD4⁺ cells have the CD4 protein on their membrane.
- D. Antigen Recognition and Clonal Selection
1. By the 1950s several general observations of the immune system had been made:
 - a. Antibodies could be produced to a seemingly limitless number of antigens.
 - b. Each antibody is specific to one antigen.
 - c. The immune response increases over time after an infection occurs.
 - d. The immune response is remembered; individuals fight off a subsequent infection by the same antigen.
 2. The clonal selection theory
 - a. Each lymphocyte formed in the bone marrow or thymus was hypothesized to have a unique receptor in its membrane.
 - b. When an antigen binds the receptor, the lymphocyte is activated.
 - c. Some of the cloned cells persist after the infection has been cleared, which enables a quick response if the invader returns.
 3. The discovery of B-cell receptors and T-cell receptors
 - a. The presence of unique receptors on B and T cells has been confirmed.
 - b. The B-cell receptor (BCR)
 - c. The T-cell receptor (TCR)
 - d. Antibodies, BCRs, and TCRs bind to epitopes on the antigen.
 4. What is the molecular basis of antigen specificity?
 - a. B-cell myelomas were used to produce large amounts of different antibodies and BCRs for structural studies.
 - b. Results of analyzing the structure of different antibodies and BCRs
 - c. The TCR also has a variable region at the amino terminus of both the alpha and beta chains.
 5. The discovery of gene recombination
 - a. Dryer and Bennett (1965) hypothesis: Immunoglobulins are shuffled together by combining a gene for the constant (C) region with a gene for the variable (V) region.
 - b. Hozumi and Tonegawa (1976) confirmed the Dryer and Bennet hypothesis.
 - c. Later work produced a model for how gene recombination occurs during light-chain production.
- E. How Does the Immune System Distinguish Self from Non-self?
1. Autoimmunity occurs when a B-cell or T-cell reacts to antigens on "self" molecules; then an immune reaction occurs.
 2. Experiments have shown that young B-cells and T-cells that are self-reactive are eliminated before leaving the bone marrow or thymus.
 3. The autoimmune disease known as multiple sclerosis results from T cells that attack the myelin sheath.

III. The Acquired Immune Response: Activation

A. Antigen Presentation by MHC Proteins: Activating T Cells

1. Dendritic cells, which are leukocytes, are recruited to areas where bacteria are multiplying rapidly.
 2. Dendritic cells take up some antigen and migrate to a lymph node.
 3. Dendritic cells process the antigen they have ingested.
 - a. Enzymes degrade the antigen into fragments.
 - b. Antigen fragments become bound to Class I and Class II major histocompatibility (MHC) proteins.
 - c. The MHC-antigen complex migrates to the plasma membrane, and the antigen is presented on the surface of the cell.
 4. $CD4^+$ T cells that have the complementary receptors interact with an epitope on the antigen being presented.
 5. Binding to an epitope presented on an MHC protein activates the T cell.
 - a. The activation process involves many steps.
 - b. Two signals must occur before the T cell is activated.
 6. The T cell undergoes clonal expansion; that is, it divides to form a large population of lymphocytes, all of which recognize the same antigen.
 7. If the T cell is $CD8^+$, its daughter cells develop into cytotoxic T lymphocytes (CTLs).
 8. If the T cell is $CD4^+$, its daughter cells develop into two types of helper T cells, T_H1 and T_H2 , which have different functions.
 9. CTLs and helper T cells are called effector T cells because they leave the lymphatic ducts, enter the bloodstream, and travel to the site of infection.
- B. B-Cell Activation and Antibody Secretion
1. B-cell receptors interact directly with antigen and internalize it.
 2. The antigen is processed by the same pathway as occurs in dendritic cells.
 3. The B cell displays an epitope of the antigen on its surface in a Class II MHC protein.
 4. A T_H2 $CD4^+$ helper T cell that has a complementary receptor binds to the antigen-MHC complex on the B cell.
 5. Binding supplies an initial activation signal, and a second co-stimulatory activation signal follows.
 6. The B cell begins to divide.
 - a. Some daughter cells differentiate into plasma cells, which produce antibodies.
 - b. Antibodies, secreted from the plasma cells, circulate in the blood.
 - c. Antibodies bind to the antigen and mark it for destruction.
- C. Antigen Presentation by Infected Cells: A Signal for Action by $CD8^+$ T Cells
1. Viruses enter cells when they infect them.
 2. The infected cell processes antigens from the invader.
 3. Viral antigens are bound to MHC I proteins and presented on the surface of the infected cell.
 4. All nucleated cells in the body can express MHC I proteins and present antigen on their surface, effectively targeting themselves for destruction.

IV. The Acquired Immune Response: Culmination

A. Killing Bacteria

1. During the innate response, macrophages will phagocytose many bacteria.
2. Macrophages also present antigen of the bacteria on their surface on MHC II proteins.
3. An activated T_H1 helper T cell that recognizes the same antigen binds to the MHC II-antigen complex on the macrophage.

- a. Binding enhances the phagocytotic activity of the macrophage.
 - b. The T_H1 cell releases cytokines that kill bacteria and viruses, bring additional leukocytes to the area, and activate the inflammatory response.
 - c. Antibodies begin to bind the bacteria.
 - d. Macrophages destroy bacteria to which antibodies are bound.
 - e. Complement proteins from the bloodstream assemble on antibody-antigen complexes, become activated, and lyse the bacterial cell.
- B. Destroying Viruses
1. Cell-mediated response
 - a. Activated $CD8^+$ cells (CTLs) recognize and bind the virus antigen-MHC I complexes on the surface of infected cells.
 - b. The CTL releases molecules that form a ring that tightly binds the CTL to the surface of the infected cell.
 - c. A hole forms in the membrane of the infected cell inside the ring of molecules.
 - d. The CTL releases granules that cause the cell to self-destruct.
 - e. The CTL disengages and seeks out other infected cells.
 2. Humoral response
 - a. Occurs in fluid—that is, in the blood and lymph—and involves antibodies.
 - b. Antibodies bind to viruses that are outside cells.
- C. Why Does the Immune System Reject Foreign Tissues and Organs?
1. Just as the immune system recognizes and attacks foreign antigens on bacteria and viruses, it will attack transplanted tissue and organs.
 - a. Blood transfusions can be dangerous if blood type is not attended to.
 - b. Similar problems will arise with organ transplants.
- D. Responding to Future Infections: Immunological Memory
1. B cells and T cells undergoing clonal expansion produce memory cells.
 2. Memory cells do not participate in the primary immune response.
 3. Memory cells circulate through the blood and tissue for years or decades.
 4. If the same antigen enters the body, memory cells trigger a secondary acquired immune response.
 - a. The secondary response is faster and more efficient.
 - b. Some memory cells that respond migrate to the germinal center of lymph nodes. antibodies that bind more tightly to the antigen than the originals did.
 - c. The secondary immune response produces antibody at a much faster rate than the primary immune response.

Chapter Vocabulary

immune
immunity
vaccination/immunization
inoculated

innate immunity
inflammatory response
lactic acid
fatty acids
leukocytes
pattern-recognition
receptors
neutrophils
platelets
mast cells
histamine
reactive oxygen
intermediates
macrophages
chemokines
chemotactic gradient
phagocytosis
commensal
proteoglycans
mucus
lysozyme
nitric oxide
hydrogen peroxide
reactive oxygen
intermediates (ROI)
pattern recognition
receptors
N-formylmethionine
gram negative
lipopolysaccharide
mannose
platelets
vasodilation
vasoconstriction
fever

acquired immunity
antigen

epitope
antibody
lymphocytes
B cells
T cells
CD8⁺ cells
CD4⁺ cells
bursa
bone marrow
thymus
lymph
lymph nodes
lymphatic ducts
spleen

clonal selection theory
clonal expansion

B-cell receptor (BCR)
gamma globulin
immunoglobulin
light chain
heavy chain
transmembrane domain
variable regions
constant regions
gene recombination
V segments
C segment
J segments
D segments
junctional diversity

T-cell receptor (TCR)
presented
alpha chain
beta chain

myeloma
hybridoma
polyclonal antibodies
monoclonal antibodies

dendritic cells
major histocompatibility
proteins (MHC)

Class I MHC
Class II MHC
MHC-antigen complex
helper T cells
T_H1 cells
T_H2 cells
cytotoxic T lymphocytes
(CTLs)
effector T cells
plasma cells
memory cells
primary immune response
immunological memory
secondary acquired immune
response
germinal center
somatic hypermutation

complement protein
humoral response
cell-mediated response

autoimmunity
anti-self receptor
negative selection
multiple sclerosis
myelin sheath
rheumatoid arthritis
type 1 diabetes mellitus
myasthenia gravis
lupus

IgE
allergens
hypersensitive reaction
basophils
histamine
hives
asthma
anaphylactic shock
epinephrine
antihistamines
corticosteroids