Chapter 22: The Lymphatic System and Immunity

Chapter Objectives

LYMPHATIC SYSTEM ANATOMY

1. Describe the organization of lymph vessels.
2. Describe the general cellular structure, distribution, and operation of lymphatic capillaries; then note the special location and duty of lacteals.
3. Identify the primary and secondary lymphatic organs and their distributions and general functions.
4. Specify the names and locations of the different mucosa-associated lymphoid tissues.

INNATE IMMUNITY

5. List the primary mechanisms that are responsible for innate immunity.
6. List the major means by which the skin and mucous membranes act as the first line of defense against pathogens.
7. List and describe the effects of the antimicrobial substances.
8. List the phases of phagocytosis and describe what is occurring in each step.
9. Discuss Natural Killer cells locations and functions.
10. Describe the symptoms and basic stages of inflammation.
11. Discuss the initiating factors and benefits of fever.

ADAPTIVE IMMUNITY AND ANTIGENS

12. Define adaptive (specific) immunity and discuss its properties of specificity and memory.
13. Distinguish the difference between cell-mediated and antibody-mediated immunity and which uses T cells and which uses B cells.
14. Discuss the characteristics of antigens, epitopes and haptens and give some examples of each.
15. Describe the roles of the major histocompatibility complex (MHC) in foreign antigen recognition and the type of cells in the body that possess the two different classes of MHCs.
16. Give the details in the sequence of processing of exogenous antigens by antigen-presenting cells (APCs) from endocytosis to MHC-antigen display on the cell membrane.
17. Describe the processing of endogenous antigens
18. List the names of some cytokines and give their general functions.

CELL-MEDIATED IMMUNITY

19. Describe the components needed to achieve co-stimulation of a T cell.
20. Determine which T cell displays CD4 and which displays CD8.
21. Discuss the activation and activity of helper T cells, including memory helper T cells
22. Discuss the activation and activity of cytotoxic T cells.
23. Describe the mechanisms used by cytotoxic T cells to destroy body cells that have been invaded by pathogens.

ANTIBODY-MEDIATED IMMUNITY

24. Discuss the general locations and response of specific B cells to specific antigens.
25. Describe how B cells are activated and co-stimulated to increase the number of B cells and output of antibodies.
26. Define an antibody.
27. Describe the five functional classes of antibodies.
28. Discuss the five actions provided by antibodies in the elimination of pathogenic antigens.
29. Describe the three ways that the complement system may be activated and the results of the complement system activation.
30. Describe the four different types of acquired immunity.

Chapter Lecture Notes

Introduction

The lymphatic system is comprised of

- a network of vessels that transport body fluids
- the organs and glands involved in immune responses
- the cells and chemicals in those vessels

Lymphatic vessels

- collect and carry away excess fluid from interstitial spaces
Lacteals - special lymphatic capillaries that transport fats from the digestive system to the circulatory system

Organs of the lymphatic system - help defend against disease (Fig 22.1)

red bone marrow
thymus
lymph nodes
spleen
mucosa-associated lymphoid tissue (MALT)

Lymphatic cells and chemicals

white blood cells
cytokines - small cell-signaling protein molecules that are secreted by numerous cells and regulate immune system function

Lymphatic Vessels & Circulation

Lymphatic vessels begin as blind-ended lymph capillaries in tissue spaces between cells

Lymphatic capillaries have a slightly larger diameter than blood capillaries (Fig 22.2)

Found throughout the body except in avascular tissue (cartilage, epidermis & cornea)

Structure is designed to let tissue fluid in but not out

anchoring filaments keep tube from collapsing under outside pressure

overlapping endothelial cells open when tissue pressure is high (one-way valve)

Lymphatic capillaries combine to form lymphatic vessels

resemble veins with thin walls & more valves

Fluid flows through lymph vessels and lymph nodes towards large veins above the heart (Fig 22.4)
The same forces that move blood in veins will also propel lymph through lymphatic vessels.

A condition that interferes with the flow of lymph will result in edema (swelling).

Lymph vessels unite to form trunks

Lymph trunks unite to form lymph ducts which drain lymph into venous blood via the subclavian veins (Fig 22.3)

Right lymphatic duct - right side of head, right arm & right chest (Fig 22.1)

Thoracic duct – the rest of body

Primary lymphatic organs

Provide environment for stem cells to divide & mature into B and T lymphocytes

Red bone marrow gives rise to mature B cells

Thymus (Fig 22.5)

pre-T cells from red marrow mature

large organ in infants (70 g) but atrophied as adult (3 g)

Secondary lymphatic organs & tissues

Site where most immune responses occur

Lymph nodes (Fig 22.6)

bean-shaped organs, up to 1 inch long, located along lymphatic vessels

scattered throughout body but concentrated near mammary glands, axillae & groin

location where B lymphocytes proliferate into antibody-secreting plasma cells

Spleen (Fig 22.7)

5 inch organ between stomach & diaphragm
Interior contains RBCs, WBCs (macrophages, lymphocytes, plasma cells, granulocytes), and platelets.

Macrophages remove worn-out or defective RBCs, WBCs, and platelets.

The spleen stores blood platelets.

The spleen is involved in the production of blood cells during the second trimester of fetal development.

Mucosa-associated lymphoid tissue (MALT) - lymphatic nodules

Tonsils form ring at top of throat

- adenoids (pharyngeal tonsil)
- palatine tonsils (on each side wall)
- lingual tonsil in the back of the tongue

Appendix

Lymphatic nodules (Peyer’s patches) in the small intestine

Function of the Lymphatic System

Immunity or resistance is the ability to ward off disease and can be grouped into two broad areas.

**Innate (nonspecific) immunity**

- general defensive mechanisms effective on a wide range of pathogens (disease producing microbes)

**Adaptive (specific) immunity** refers to defenses that involve specific recognition of a microbe once it has breached the innate defenses.

- cell-mediated immunity
- antibody-mediated immunity (humoral)

**Innate Immunity**
Skin and the mucous membranes - the first line of defense (Table 22.1)

Mechanical protection

skin (epidermis) - closely packed, keratinized cells

shedding helps remove microbes

mucus – sticky substance produced by mucous membrane

cilia & mucus trap & move microbes toward throat

washing action of tears, urine and saliva

defecation and vomiting also may be considered mechanical processes

Chemical protection

The skin produces sebum, which has a low pH that inhibits the growth of bacteria & fungus

Lysozyme is an enzyme component of sweat that also has antimicrobial properties

Gastric juice renders the stomach nearly sterile because its low pH (1.5-3.0) kills many bacteria and destroys most of their toxins

Vaginal secretions also are slightly acidic

Antimicrobial substances, phagocytic and natural killer cells, inflammation, and fever - the second line of defense (Table 22.1)

Antimicrobial substances discourage microbial growth

Interferons (IFNs) - proteins produced by body cells infected with viruses

IFN interfere with or inhibit viral replication, enhance the activity of phagocytes and natural killer (NK) cells, inhibit cell growth, and suppress tumor formation

The complement system - a group of about 30 proteins present in blood plasma and on cell membranes
when activated, these proteins “complement” or enhance certain immune, allergic, and inflammatory reactions.

Iron binding proteins limit available iron, which inhibits certain bacterial growth

- transferrin – blood
- lactoferrin – milk, saliva and mucus
- ferritin – liver, spleen, red bone marrow
- hemoglobin – red blood cells

Antimicrobial proteins (AMPs) are short peptides that have broad spectrum of antimicrobial activity.

Phagocytic cells/phagocytes

- neutrophils
- macrophages developed from monocytes
  - fixed macrophages stand guard in specific tissues
    - histiocytes - skin
    - stellate reticuloendothelial cells (kupffer cells) - liver
    - alveolar macrophages - lungs
    - microglia - brain
    - macrophages in spleen, red marrow & lymph nodes
  - wandering macrophages in most tissues

Phagocytosis – method of attacking the pathogen (Fig 22.9)

Chemotaxis

- attraction to chemicals from damaged tissues, complement proteins, or microbial products
Adherence

attachment to plasma membrane of phagocyte

Ingestion

engulf by pseudopods to form phagosome

Digestion & killing

merge with lysosome containing digestive enzymes

exocytosis residual body

Some of the reasons why a microbe may evade phagocytosis include:

capsule formation

toxin production

interference with lysozyme secretion

the microbe’s ability to counter oxidants produced by the phagocytes

Natural Killer cells kill a variety of microbes & tumor cells

found in blood, spleen, lymph nodes & red bone marrow

attack cells displaying abnormal MHC antigens

sends chemicals at an infected cell causing the cell to burst (cytolysis) or commit programmed cell death (apoptosis)

Inflammation – initiated by damaged cells

Signs of inflammation

redness

heat

swelling

pain
Loss of function may be a fifth symptom, depending on the site and extent of the injury.

Function is to trap microbes, toxins or foreign material & begin tissue repair.

The three basic stages of inflammation:

- Vasodilation & increased permeability of vessels
  - histamine from mast cells
  - kinins from precursors in the blood
  - prostaglandins from damaged cells
  - leukotrienes from basophils & mast cells
- Phagocyte emigration (Diapedesis) (Fig 22.10)
  - within an hour, neutrophils and then monocytes arrive and leave blood stream

Tissue repair

Fever is abnormally high body temperature that occurs because the hypothalamic thermostat is reset.

Occurs during infection & inflammation

- bacterial toxins trigger release of fever-causing cytokines (interleukin-1)

Benefits

- intensifies effects of interferons
- inhibits bacterial growth
- speeds up tissue repair

Adaptive Immunity

Adaptive (specific) Immunity - the ability of the body to defend itself against specific invading agents.
Properties of Adaptive Immunity

Specificity - recognize self vs. non-self

Memory - 2nd encounter produces even more vigorous response

Types of Adaptive Immunity (Fig 22.11)

Cell-mediated immunity (CMI) - destruction of invading or infected cells by T lymphocytes

CMI always involves cells attacking cells

Antibody-mediated (humoral) immunity (AMI) - destruction of pathogen by antibody action

Often a pathogen provokes both types of immune response and they will work together to better destroy the pathogen

Cells involved in Adaptive Immunity

B lymphocytes

become plasma cells that produce and secrete antibodies

Cytotoxic T lymphocytes – T<sub>8</sub> cells, T<sub>c</sub> cells or killer T cells

CD8 on surface

attack and destroy other infected cells

Helper T lymphocytes - T<sub>4</sub> cells or T<sub>H</sub> cells

CD4 on surface

produce and secrete cytokines that “help” the actions of the B lymphocytes and the cytotoxic T lymphocytes

Antigens

Antigen - parts of foreign material that provoke an immune response (Fig 22.12)
large, complex molecules, usually proteins
  entire microbes or parts of microbes
  bacterial toxins
  pollen
  transplanted organs
  incompatible blood cells

simple repeating subunits (plastics) are not usually antigenic

epitope - small part of antigen that triggers the immune response
  immune system can recognize and respond to a billion different epitopes - even
  artificially made molecules

hapten - smaller substance that cannot trigger an immune response unless attached to body protein
  lipid of poison ivy

Required characteristics to be considered an antigen

  immunogenicity - ability to provoke immune response
  reactivity - ability of the antigen to react specifically with the antibodies or cells it provoked

Major Histocompatibility Complex Antigens (human leukocyte antigens (HLA)) – unique set of integral membrane proteins (1000s molecules) found on most of our cells

MHC-I antigens
  built into cell membrane of all cells except red blood cells

MHC-II antigens
  on cell membrane of macrophages, B lymphocytes, and dendritic cells

Pathways of Antigen Processing
B and T lymphocytes must recognize a foreign antigen before beginning their immune response

B lymphocytes can bind to antigen in extracellular fluid
response is better if antigen is processed

T lymphocytes can only recognize fragments of antigens that have been processed and
presented to them combined with a MHC molecule

Processing of Exogenous Antigens (Fig 22.13)

Done by antigen-presenting cells (APCs)
macrophages
B lymphocytes
dendritic cells
encounter extracellular antigens in body fluid and phagocytize them
bacteria
bacterial toxins
parasitic worms
pollen
dust
viruses that have not infected a cell
APC migrates to lymphatic tissue to find T or B lymphocytes
the presentation of exogenous antigens together with MHCII molecules on antigen presenting
cells alerts T or B lymphocytes that “intruders are present”

Helper T lymphocytes “see” antigens if they are combined with MHC-II molecules

Processing of Endogenous Antigens (Fig 22.14)

most of the cells of the body can process endogenous antigens
endogenous antigens are synthesized within the body (intracellular)

viral proteins

proteins produced by cancer cells

fragments of endogenous antigen are associated with MHC-I molecules inside the cell

the antigen/MHC-I complex moves to the cell’s surface where it alerts T or B lymphocytes that have migrated to the cell

Cytotoxic T lymphocytes “see” antigens if they are combined with MHC-I molecules

Cytokines

Cytokines - chemicals released by cells that promote the function of immune system cells

Interleukin-1 (Il-1) (Table 22.2)

produced by macrophages

proliferation of Helper T lymphocytes

Interleukin-2 (Il-2)

produced by Helper T lymphocytes

co-stimulation of T and B lymphocytes, proliferation of T and B lymphocytes, activates natural killer cells

Interleukin-4 (Il-4)

produced by Helper T lymphocytes

co-stimulation of B lymphocytes

Tumor necrosis factor (TNF)

produced by macrophages

stimulates phagocyte accumulation (chemotaxis) and digestion

Cell-Mediated Immunity
Cell-mediated immunity (CMI) uses T lymphocytes to destroy pathogens.

T lymphocytes have two sets of proteins on their surface required for CMI:

- T cell receptors - recognize antigen fragments associated with MHC molecules on the surface of a body cell
- each different receptor recognizes a different antigen/epitope
- great diversity of receptors is due to genetic recombination of few hundred small gene segments

CD proteins – recognize the MHC molecules on the surface of a body cell:

- CD4 – helper T lymphocytes
- CD8 – cytotoxic T lymphocytes

Co-stimulation - activation and proliferation of T lymphocytes:

- MHC-CD pair
- T cell receptor (TCR)-antigen pair
- Cytokines prevent accidental immune response

Co-stimulation of Helper T lymphocytes (Fig 22.15):

- APC processes an antigen and presents it on its surface with MHC-II
- MHC-II on APC surface interacts with CD4 on surface of Helper T lymphocyte
- TCR interacts with processed antigen
- cytokines from the APC or surrounding cells permit the co-stimulation process
- upon co-stimulation, the Helper T lymphocyte produces exact copies of itself (clone)
- copies secrete cytokines (interleukin-2 & 4)
  - contributes to co-stimulation of other T and B lymphocytes
it will co-stimulate itself to proliferate and secrete more interleukin (positive feedback effect causes formation of many more helper T lymphocytes)

some of the copies will become Memory Helper T lymphocytes
clones that are available for swift response if a 2nd exposure should occur
reside in lymphatic tissues

Co-stimulation of Cytotoxic T lymphocytes (Fig 22.16)

any cell (except RBCs) processes an antigen and presents it on its surface with MHC-I
could possibly be an APC that is also presenting same antigen with MHC-II

MHC-I on cell surface interacts with CD8 on surface of Cytotoxic T lymphocyte

TCR interacts with processed antigen
cytokines from activated Helper T lymphocyte permit the co-stimulation process

Helper T lymphocyte may possibly be activated by APC presenting same antigen

upon co-stimulation the cytotoxic T lymphocyte produces exact copies of itself (clone)

that are all able to recognize the antigen that initiated the response

some of the copies will become Memory Cytotoxic T cells

Elimination of Invaders by Cytotoxic T lymphocytes (Fig 22.17)

Cytotoxic T lymphocytes migrate to site of infection or tumor formation
recognize and attach to the pathogen by TCR-antigen interaction
the cytotoxic T lymphocyte is co-stimulated
the Cytotoxic T lymphocyte clones launch a chemical attack

secrete granzymes, protein-digesting enzymes that trigger programmed cell death

(apoptosis)
secrete granules containing perforin that punch holes in target cell which leads to
cytolysis
secrete granulysin, which punches holes in microbe’s cell membranes
secrete lymphotoxin that activates enzymes in the target cell causing its DNA to fragment
secrete gamma-interferon to activate phagocytic cells

Antibody-Mediated Immunity

Antibody-mediated immunity uses B lymphocytes and their products, antibodies, to destroy
pathogens
works mainly against extracellular pathogens and other pathogenic substances dissolved in
body fluids
bacteria
toxins
B lymphocytes sit still in lymph nodes, spleen or peyer’s patches and let antigens be brought
to them
B lymphocyte function (Fig 22.18)

B cell receptors (BCRs) bind to antigen
can bind to unprocessed antigens in fluids but respond more intensely if antigen is
processed by an APC
each different receptor recognizes a different antigen
great diversity of receptors is due to genetic recombination of few hundred small gene
segments
receptors are chemically similar to the antibodies secreted by their progeny
some antigen is taken into the B lymphocyte by receptor-mediated endocytosis, broken down into peptide fragments, combined with MHC-II and moved to the B lymphocyte surface

antigen presented with MHC-II leads to co-stimulation of Helper T lymphocytes
cytokines secreted by Helper T cells co-stimulate B lymphocytes

rapid cell division occurs and clones become plasma cells
produce antibody at 2000 molecules/sec for 4-5 days
secrete only one kind antibody
long-lived memory cells

Antibodies enters the circulation to attack antigen

Antibodies

Antibody (Immunoglobulin) - a glycoprotein that can recognize the specific epitope of an antigen that triggered its production

Based on chemistry and structure, antibodies are grouped into five principal classes

IgG (Table 22.3)

IgA

IgM

IgD

IgE

Antibody Structure (Fig 22.19)

4 polypeptide chains - 2 heavy & 2 light chains with variable and constant portions
tips are variable regions
form antigen binding sites

remainder is constant region

5 different classes based on constant region

hinged mid-region lets the molecule assume T or Y shape

Antibody Actions

Neutralization of antigen by preventing its attachment to body cells or blocking effects of toxins

Immobilize bacteria by attacking cilia/flagella

Agglutinate & precipitate antigens by cross-linking them

Enhance phagocytosis

Complement activation

Complement System in Immunity

The complement system is an innate immunity mechanism that can be activated by antibody-mediated immunity (Fig 22.20)

Made up of over 30 proteins

Complement may be activated by the

Classical pathway - antibodies bind to antigens and activate C1 which leads to activation of C3

Alternate pathway - microbial lipid-carbohydrate complexes interact with complement factors B, D and P leading to activation of C3

Lectin pathway - Liver produced proteins bind to carbohydrates on microbes leading to activation of C3

Activated complement acts in a cascade that causes
inflammation: dilation of arterioles, release of histamine & increased permeability of capillaries

opsonization/phagocytosis: protein binds to microbe making it easier to phagocytize
cytolysis: a complex of several proteins can form holes in microbe membranes causing leakiness and cell rupture

Immunological Memory

Immunological memory - due to the presence of long-lived antibodies and memory B and T lymphocytes

The secondary response (immunological memory) provides protection should the same microbe enter the body again. There is rapid proliferation of memory cells, resulting in a far greater antibody titer (amount of antibody in serum) than during a primary response. (Fig 22.21)

Ways to acquire specific resistance (Table 22.4)
naturally acquired active immunity
   an active response to exposure to an antigen
naturally acquired passive immunity
   passage of antibodies from a mother to an infant
artificially acquired active immunity
   an active response to exposure to an antigen injected during a vaccination
artificially acquired passive immunity
   IV injection of antibodies