The Lymphatic and Immunology Systems

- Resistance is the ability to ward off disease
  - lack of resistance is termed susceptibility
- Nonspecific resistance to disease
  - general defensive mechanisms effective on a wide range of pathogens (disease producing microbes)
- Specific resistance or immunity is ability to fight a specific pathogen
  - cell-mediated immunity
  - antibody-mediated immunity

Lymphatic System

- Organs, vessels and a fluid called lymph
  - similar to interstitial fluid
- Organs involved
  - red bone marrow
  - thymus
  - spleen
  - lymph nodes
  - diffuse lymphatic tissue
    - tonsils, adenoids & peyers patches

Functions of the Lymphatic System

- Draining excess interstitial fluid & plasma proteins from tissue spaces
- Transporting dietary lipids & vitamins from GI tract to the blood
- Facilitating immune responses
  - recognize microbes or abnormal cells & responding by killing them directly or secreting antibodies that cause their destruction

Lymphatic Vessels & Circulation

- Capillaries that begin as closed-ended tubes found in spaces between cells
- Combine to form lymphatic vessels
  - resemble veins with thin walls & more valves
- Fluid flows through lymph nodes towards large veins above the heart
  - lymph emptied into bloodstream
Lymphatic Capillaries

- 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)
- In GI tract, known as lacteals -- contain chyle

Lymph Trunks & Ducts

- Vessels unite to form trunks & thoracic ducts

Formation & Flow of Lymph

- Fluid & proteins escaping from vascular capillaries is collected by lymphatic capillaries & returned to the blood
- Respiratory & muscular pumps promote flow of lymphatic fluid
- Lymphatic vessels empty into subclavian veins
Lymphatic Organs & Tissues

- Widely distributed throughout the 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 is site where pre-T cells from red marrow mature
- Secondary lymphatic organs & tissues
  - site where most immune responses occur
    - lymph nodes, spleen & lymphatic nodules

Thymus Gland

- Large organ in infants (70 g) but atrophied as adult (3 g)
- 2 lobed organ located in mediastinum
- Capsule & trabeculae divide it into lobules
- Each lobule has cortex & medulla
- Cortex
  - tightly packed lymphocytes & macrophages
- Medulla
  - reticular epithelial cells produces thymic hormones
  - Hassall’s corpuscles

Lymph Nodes

- Flow is in one direction
  - afferent vessels lead in
  - sinuses lead to efferent vessels that exit at hilus
- Only nodes filter lymph
- Bean-shaped organs, up to 1 inch long, located along lymphatic vessels
  - scattered throughout body but concentrated near mammary glands, axillae & groin
- Stroma is capsule, trabeculae & reticular fibers
- Parenchyma is divided into 2 regions:
  - cortex
    - lymphatic nodules with germinal centers containing dendritic cells
      - antigen-presenting cells and macrophages
    - B cells proliferate into antibody-secreting plasma cells
  - medulla
    - contains B cells & plasma cells in medullary cords
Spleen

- 5 inch organ between stomach & diaphragm
- Hilus contains blood & lymphatic vessels
- Stroma consists of capsule, trabeculae, fibers & fibroblasts
- Parenchyma consists of white pulp and red pulp
  - white is lymphatic tissue (lymphocytes & macrophages) around branches of splenic artery
  - red pulp is venous sinuses filled with blood & splenic tissue (splenic cords)

Lymphatic Nodules

- Concentrations of lymphatic tissue not surrounded by a capsule scattered throughout connective tissue of mucous membranes
  - mucosa-associated lymphoid tissue (MALT)
- Peyer’s patches in the ileum of the small intestine
- Appendix
- Tonsils form ring at top of throat
Nonspecific Resistance to Disease

• Immediate protection against wide variety of pathogens & foreign substances
  – lacks specific responses to specific invaders

• Mechanisms function regardless of type of invader
  – external mechanical & chemical barriers
  – internal nonspecific defenses
    • antimicrobial proteins
    • natural killer cells & phagocytes
    • inflammation & fever

Skin & Mucous Membranes

• Mechanical protection
  – skin (epidermis) closely packed, keratinized cells
    • shedding helps remove microbes
  – mucous membrane secretes viscous mucus
    • cilia & mucus trap & move microbes toward throat
  – washing action of tears, urine and saliva

• Chemical protection
  – sebum inhibits growth bacteria & fungus
  – perspiration lysozymes breakdown bacterial cells
  – acidic pH of gastric juice and vaginal secretions destroys bacteria

Internal Defenses

• Antimicrobial proteins discourage microbial growth
  – interferons
    • produced by virally infected lymphocytes & macrophages
    • diffuse to neighboring cells to induce synthesis of antiviral proteins
  – complement proteins
    • inactive proteins in blood plasma
    • when activated enhance immune, allergic & inflammatory reactions
  – transferrins
    • iron-binding proteins inhibit bacterial growth by reducing available iron

Natural Killer Cells & Phagocytes

• NK cells kill a variety of microbes & tumor cells
  – found in blood, spleen, lymph nodes & red marrow
  – attack cells displaying abnormal MHC antigens

• Phagocytes (neutrophils & macrophages)
  – ingest microbes or particulate matter
  – macrophages developed from monocytes
    • fixed macrophages stand guard in specific tissues
      – histiocytes in the skin, kupffer cells in the liver, alveolar macrophages in the lungs, microglia in the brain & macrophages in spleen, red marrow & lymph nodes
    • wandering macrophages in most tissue
Inflammation

• Damaged cell initiates
• Signs of inflammation
  – redness
  – heat
  – swelling
  – pain
• Function is to trap microbes, toxins or foreign material & begin tissue repair

Stages of Inflammation
• Vasodilation & increased permeability of vessels
  – caused by histamine from mast cells, kinins from precursors in the blood, prostaglandins from damaged cells, and leukotrienes from basophils & mast cells
  – occurs within minutes producing heat, redness & edema
  – pain can result from injury, pressure from edema or irritation by toxic chemicals from organisms
  – blood-clotting factors leak into tissues trapping microbes
• Phagocyte emigration
  – within an hour, neutrophils and then monocytes arrive and leave blood stream (emigration)
• Tissue repair

Abscesses and Ulcers
• Pus is dead phagocytes, damaged tissue cells & fluid
• Abscess is accumulation of pus in a confined space not open to the outside
  – pimples & boils
• Ulcer is an open sore

Fever
• Abnormally high body temperature that occurs because the hypothalamic thermostat is reset
• Occurs during infection & inflammation
  – bacterial toxins trigger release of fever-causing cytokines such as interleukin-1
• Benefits
  – intensifies effects of interferons, inhibits bacterial growth, speeds up tissue repair

Specific Resistance: Immunity
• Immunity is bodies ability to defend itself against specific foreign material or organisms
• bacteria, toxins, viruses, cat dander, etc.

• Differs from nonspecific defense mechanisms
  – specificity----recognize self & non-self
  – memory----2nd encounter produces even more vigorous response

• Immune system is cells and tissues that produce the immune response

• Immunology is the study of those responses

  Maturation of T and B Cells

• T cell mature in thymus
  – cell-mediated response
    • killer cells attack antigens
    • helper cells costimulate T and B cells
  – effective against fungi, viruses, parasites, cancer, and tissue transplants

• B cells in bone marrow
  – antibody-mediated response
    • plasma cells form antibodies
  – effective against bacteria

Antigens
• Molecules or bits of foreign material
  – entire microbes, parts of microbes, bacterial toxins, pollen, transplanted organs, incompatible blood cells

• Required characteristics to be considered an antigen
  – immunogenicity = ability to provoke immune response
  – reactivity = ability to react to cells or antibodies it caused to be formed

• Get past the bodies nonspecific defenses
  – enter the bloodstream to be deposited in spleen
  – penetrate the skin & end up in lymph nodes
  – penetrate mucous membrane & lodge in associated lymphoid tissue

  Chemical Nature of Antigens/Epitopes

• Large, complex molecules, usually proteins
  – if have simple repeating subunits are not usually antigenic (plastics in joint replacements)
  – small part of antigen that triggers the immune response is epitope
    • antigenic determinant

• Hapten is smaller substance that can not trigger an immune response unless attached to body protein
  – lipid of poison ivy
Diversity of Antigen Receptors

- Immune system can recognize and respond to a billion different epitopes — even artificially made molecules
- Explanation for great diversity of receptors is genetic recombination of few hundred small gene segments
- Each B or T cell has its own unique set of gene segments that codes its unique antigen receptor in the cell membrane

Major Histocompatibility Complex Antigens

- All our cells have unique surface markers (1000s molecules)
  - integral membrane proteins called HLA antigens
- MHC-I molecules are built into cell membrane of all cells except red blood cells
- MHC-II markers seen only on membrane of antigen presenting cells (macrophages, B cells, thymus cells)
- Function
  - if cell is infected with virus MHC-I contain bits of virus marking cell so T cells recognize is problem
  - if antigen presenting cells (macrophages or B cells) ingest foreign proteins, they will display as part of their MHC-II

Histocompatibility Testing

- Histocompatibility is a similarity of MHC antigens on body cells of different individuals
  - tissue typing must be done before any organ transplant
  - can help identify biological parents

Pathways of Antigen Processing

- B and T cells must recognize a foreign antigen before beginning their immune response
  - B cells can bind to antigen in extracellular fluid
  - T cells can only recognize fragments of antigens that have been processed and presented to them as part of a MHC molecule
    - Helper T cells “see” antigens if part of MHC-II molecules on surface of antigen presenting cell
    - Cytotoxic T cells “see” antigens if part of MHC-I molecules on surface of body cells

Cytokines & Cytokine Therapy

- Small protein hormones involved in immune responses
  - secreted by lymphocytes and antigen presenting cells
- Cytokine therapy uses cytokines (interferon)
  - alpha-interferon used to treat Kaposi’s sarcoma, genital herpes, hepatitis B and C & some leukemias
  - beta-interferon used to treat multiple sclerosis
  - interleukin-2 used to treat cancer (side effects)
Cell-Mediated Immunity

- Begins with activation of T cell by a specific antigen
- Result is T cell capable of an immune attack
  - elimination of the intruder by a direct attack

Activation, Proliferation & Differentiation of Cytotoxic T Cells

- Receptor on CD8 cell binds to foreign antigen fragment part of MHC-I
- Costimulation from helper T cell
  - prevents accidental immune response
- Proliferates & differentiates into population (clone) of Tc cells and memory Tc cells
- Occurs in secondary lymphatic organs such as lymph node

Activation, Proliferation & Differentiation of Helper T Cells

- Receptor on CD4 cell binds to foreign antigen fragment associated with MHC-II
- Costimulation with interleukin
- Proliferates & differentiates into population (clone) of TH cells and long-lived memory TH cells

Types of Mature T Cells

- Helper T cells
- Cytotoxic (killer) T cells
- Memory T cells

**Helper T Cells**

- Display CD4 on surface so also known as T4 cells or TH cells
- Recognize antigen fragments associated with MHC-II molecules & activated by APCs
- Function is to costimulate all other lymphocytes
  - secrete cytokines (interleukin-2)
    - autocrine function in that it costimulates itself to proliferate and secrete more interleukin (positive feedback effect causes formation of many more helper T cells)

**Cytotoxic T Cells**

- Display CD8 on surface
- Known as T8 or Tc or killer T cells
• Recognize antigen fragments associated with MHC-I molecules
  – cells infected with virus
  – tumor cells
  – tissue transplants
• Costimulation required by cytokine from helper T cell
  Memory T Cells
• T cells from a clone that did not turn into cytotoxic T cells during a cell-mediated response
• Available for swift response if a 2nd exposure should occur

Elimination of Invaders
• Cytotoxic T cells migrate to site of infection or tumor formation
• Recognize, attach & attack
  – secrete granules containing perforin that punch holes in target cell
  – secrete lymphotoxin that activates enzymes in the target cell causing its DNA to fragment
  – secrete gamma-interferon to activate phagocytic cells

Immunological Surveillance
• Cancerous cell displays weird surface antigens (tumor antigens)
• Surveillance = immune system finds, recognizes & destroys cells with tumor antigens
  – done by cytotoxic T cells, macrophages & natural killer cells
  – most effective in finding tumors caused by viruses
• Transplant patients taking immunosuppressive drugs suffer most from viral-induced cancers

Antibody-Mediated Immunity
• Millions of different B cells that can recognize different antigens and respond
• B cells sit still and let antigens be brought to them
  – stay put in lymph nodes, spleen or peyer’s patches
• Once activated, differentiate into plasma cells that secrete antibodies
• Antibodies circulate in lymph and blood
  – combines with epitope on antigen similarly to key fits a specific lock

Activation, Proliferation, & Differentiation of B Cells
• B cell receptors bind to antigen -- response more intense if on APC
• Helper T cell costimulates
• Rapid cell division & differentiation occurs
long-lived memory cells
- clone of plasma cells
  - produce antibody at 2000 molecules/sec for 4-5 days
  - secrete only one kind antibody
- Antibody enters the circulation to attack antigen

Antibody Structure

- Glycoproteins called immunoglobulins
  - 4 polypeptide chains -- 2 heavy & 2 light chains
  - hinged midregion lets assume T or Y shape
  - tips are variable regions -- rest is constant region
    - 5 different classes based on constant region
      - IgG, IgA, IgM, IgD and IgE
    - tips form antigen binding sites

Antibody Actions

- Neutralization of antigen by blocking effects of toxins or preventing its attachment to body cells
- Immobilize bacteria by attacking cilia/flagella
- Agglutinate & precipitate antigens by cross-linking them causing clumping & precipitation
- Complement activation
- Enhancing phagocytosis through precipitation, complement activation or opsonization (coating with special substance)

Monoclonal Antibodies

- Antibodies against a particular antigen can be harvested from blood
  - different antibodies will exist for the different epitopes on that antigen
- Growing a clone of plasma cells to produce identical antibodies difficult
  - fused B cells with tumor cells that will grow in culture producing a hybridoma
  - antibodies produced called monoclonal antibodies
- Used clinically for diagnosis -- strep throat, pregnancy, allergies, hepatitis, rabies, cancer
Role of the Complement System

• Defensive system of plasma proteins that attack and destroy microbes
• System activated by 2 different pathways
• Produce same result
  – inflammation: dilation of arterioles, release of histamine & increased permeability of capillaries
  – opsonization: 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

Pathways of the Complement System

• Classical pathway begins with activation of C1
• Alternate pathway begins with activation of C3
• Lead to inflammation, enhanced phagocytosis or microbe bursting

Immunological Memory

• Primary immune response
  – first exposure to antigen response is steady, slow
  – memory cells may remain for decades
• Secondary immune response with 2nd exposure
  – 1000’s of memory cells proliferate & differentiate into plasma cells & cytotoxic T cells
  • antibody titer is measure of memory (amount serum antibody)
  – recognition & removal occurs so quickly not even sick
Self-Recognition & Immunological Tolerance

- T cells must learn to recognize self (its own MHC molecules) & lack reactivity to own proteins
  - self-recognition & immunological tolerance
- T cells mature in thymus
  - those can’t recognize self or react to it
    - destroyed by programmed cell death (apoptosis or deletion)
    - inactivated (anergy) -- alive but unresponsive
  - only 1 in 100 emerges immunocompetent T cell
- B cells develop in bone marrow same way