Mechanisms of Self-Defense

Inflammation

Chapter 5

Immunity

• First line of defense
  — Innate resistance (or natural immunity)
  — Includes natural barriers
• Second line of defense
  — Inflammation
• Third line of defense
  — Adaptive (acquired) immunity
  — Involves “memory”

First Line of Defense

• Physical and mechanical barriers
  — Skin
  — Mucous Membranes – linings of the GI, genitourinary, and respiratory tracts
    Mechanical removal:
    • Sloughing off of cells (dead skin cells)
    • Coughing and sneezing
    • Flushing from urinary system
    • Vomiting
    • Mucus and cilia (mucus escalator)

Second Line of Defense

• Inflammatory response
  — Caused by a variety of materials
    • Infection, mechanical damage, ischemia, nutrient deprivation, temperature extremes, radiation, etc.
  — Local manifestations
    • Heat, swelling, pain, loss of function
  — Vascular response
    • Vasodilation (VD), blood vessels become leaky, WBCs adhere to inner walls of vessels & migrate through the vessels

First Line of Defense

• Biochemical barriers
  — Enzymes synthesized and secreted in saliva, tears, ear wax, sweat, and mucus (lysozymes)
  — Antimicrobial peptides (acidic)
  — Normal bacterial flora on the skin and in gut
Inflammation

• Goals (Benefits of Inflammation)
  – Limit tissue damage and control the inflammatory process
  – Prevent and limit infection and further damage
  – Initiate adaptive immune response
  – Initiate healing

Cellular Mediators of Inflammation

• Cellular components
  - Granulocytes, platelets, monocytes, lymphocytes
    – Neutrophils & macrophages (mature monocytes) → phagocytic
    – Eosinophils → kill parasites
    – Platelets → clotting sequence & release mediators
    – Lymphocytes (NK cells) → attack virus and cancer infected cells

Mast Cells

• Important activator of inflammatory response
• Contain granules, located in loose CT
• Skin, digestive lining, and respiratory tract
• Release:
  – Histamine → VC of large blood vessels & VD of venules
  – Leukotrienes → SMC contraction, incr. vascular permeability
  – Prostaglandins
    • Similar to leukotrienes; they also induce pain (affect nerves)
    – Platelet-activating factor (PAF)
      • Similar effect to leukotrienes and platelet activation

Plasma Protein Systems

• Protein systems
  – Complement system
    • Circulating proteins that can destroy pathogens directly
  – Coagulation system
    • Forms a clot that stops bleeding
  – Kinin system
    • Bradykinin - causes VD, pain, SMC contraction, vascular permeability, and leukocyte chemotaxis
Phagocytosis

Phagocytes

- Neutrophils (PMNs)
  - Predominate in early inflammatory responses
    - Arrive 6-12 hr after injury
    - Ingest bacteria, dead cells, and cellular debris
    - Cells are short lived and become component of purulent exudate

Phagocytes

- Monocytes and macrophages
  - Monocytes - produced in bone marrow → blood → inflammatory site, where they develop into macrophages
  - Macrophages typically arrive at the inflammatory site 24 hours or later after neutrophils

Monocytes and Macrophages

- Increased cell size and lysosomal granules

Phagocytes

- Eosinophils
  - Mildly phagocytic
  - Duties
    - Main defense against parasites and regulation of vascular mediators from mast cells

Phagocytes

- Natural killer (NK) cells
  - Function against cells infected with viruses and cancer
- Platelets
  - Activation results in degranulation (release of serotonin) and to stop bleeding
Cytokines

- Interleukins (IL)
  - Produced by macrophages and lymphocytes in response to a pathogen or stimulation by other products of inflammation
- Interferon (INF)
  - Protects against viral infections
  - Produced and released by virally infected host cells in response to viral double-stranded RNA

Local Manifestations of Acute Inflammation

- Due to vascular changes & leakage of circulating components into the tissue
  - Heat
  - Redness
  - Swelling
  - Pain

Exudative Fluids

- Serous exudate
  - Watery exudate: indicates early inflammation
- Fibrinous exudate
  - Thick, clotted exudate: indicates more advanced inflammation
- Purulent exudate
  - Pus: indicates a bacterial infection
- Hemorrhagic exudate
  - Exudate contains blood: indicates bleeding

Systemic Changes due to Inflammation

- Fever
  - Caused by exogenous and endogenous pyrogens → act on hypothalamus
- Leukocytosis
  - Increased numbers of circulating leukocytes
- Increased plasma protein synthesis
  - Produced in liver

Chronic Inflammation

- Inflammation lasting 2 weeks or longer
- Often related to an unsuccessful acute inflammatory response
Resolution and Repair

- Debridement
  - Cleaning up the dissolved clots, microorganisms, erythrocytes, and dead tissue cells
- Healing
  - Filling in the wound
  - Sealing the wound (epithelialization)
  - Shrinking the wound (contraction)

Healing

- Primary intention
  - Wounds that heal under conditions of minimal tissue loss
- Secondary intention
  - Wounds that require a great deal more tissue replacement
  - Open wound

Healing

- Reconstructive phase
  - Fibroblast proliferation
  - Collagen synthesis
  - Epithelialization
  - Contraction
  - Cellular differentiation
- Maturation phase
  - Continuation of cellular differentiation
  - Scar tissue formation
  - Scar remodeling

Dysfunctional Wound Healing

- Dysfunction during inflammatory response
  - Hemorrhage
  - Fibrous adhesion
  - Infection
  - Excess scar formation
Dysfunctional Wound Healing
- Keloid (scar) formation

Dysfunctional Wound Healing
• Wound disruption
  — Dehiscence
  • Wound pulls apart at the suture line
    — Excessive strain and obesity are causes
  • Increases risk of wound sepsis

Concept Check
• 1. Inflammation:
  — A. Confines and destroys injurious agents
  — B. Stimulates and enhances immunity
  — C. Promotes healing
  — D. All of the above

• 2. Which of the following is not a local manifestation of inflammation?
  — A. Swelling
  — B. Pain
  — C. Heat and redness
  — D. Leukocytosis

• 3. The inflammatory response:
  — A. Prevents blood from entering injured tissue
  — B. Elevates body temp. to prevent spread of infection
  — C. Prevents formation of abscesses
  — D. Minimizes injury and promotes healing

• 4. Scar tissue is:
  — A. Nonfunctional collagen and fibrous tissue
  — B. Functional tissue that follows wound healing
  — C. Regenerated tissue formed in area of injury
  — D. Fibrinogen with entrapped phagocytes and neurons

Adaptive (specific) Immunity
- state of protection against infectious agents mainly
  - 3rd line of defense
• Antigens – found on infectious agents, environmental substances, cancers
• Specificity – of antigens for antibodies
• Memory – long lived response
• Antibodies – protect individual from infection
• Lymphocytes – mediate immune response
  — B and T cells
Antigen Presentation

- Antigen-presenting cells (APCs)
  - Macrophages and macrophage–like cells (B cells)

- Major histocompatibility complex (MHC)
  - Glycoproteins on the surface of all human cells (except RBCs)
  - Also referred to as human leukocyte antigens (HLAs)

Antibodies

- Also called immunoglobulins (Ig)
- Produced by plasma cells (mature B cells) in response to exposure to antigen

Classes of antibody

- IgG - most abundant class (80-85%), major antibody found in fetus & newborn
- IgA – found in blood and secretions
- IgM – largest, produced 1st in initial response to antigen
- IgE - lowest blood conc., allergic rxn.
- IgD – low conc. in blood, receptor on B cells.

Primary and Secondary Responses

- Primary response
  - Initial exposure
  - Latent period or lag phase
    - B cell differentiation is occurring
  - After 5 to 7 days, an IgM antibody for a specific antigen is detected
  - An IgG response equal or slightly less follows the IgM response

- Secondary response
  - More rapid
  - Larger amounts of antibody are produced
  - Rapidity is caused by the presence of memory cells that do not have to differentiate
  - IgM is produced in similar quantities to the primary response, but IgG is produced in considerably greater numbers
Concept Check

1. An antigen is
   A. A foreign protein capable of stimulating immune response in healthy person
   B. A foreign protein capable of stimulating immune response in susceptible person
   C. A protein that binds with an antibody
   D. A protein that is released by the immune system

2. Antibodies are produced by
   A. B cells
   B. T cells
   C. Plasma cells
   D. Memory cells

3. The antibody with the highest concentration in blood is:
   A. IgA
   B. IgD
   C. IgE
   D. IgG

4. If a child develops measles and acquires immunity to subsequent infections, the immunity is:
   A. Acquired
   B. Active
   C. Natural
   D. A and B are correct

5. Which cells are phagocytic?
   A. B cells
   B. T cells
   C. T killers
   D. Macrophages

6. When an antigen binds to its appropriate antibody:
   A. Agglutination may occur
   B. Phagocytosis may occur
   C. Antigen neutralization may occur
   D. All of the above

Hypersensitivities, Infection, and Immune Deficiencies

Chapter 7

Hypersensitivity

- Excessive immunologic reaction to an antigen that results in disease or damage to the host after reexposure

- Allergy
  - Deleterious effects of hypersensitivity to environmental (exogenous) antigens

- Autoimmunity
  - Disturbance in the immunologic tolerance of self-antigens

- Alloimmunity
  - Immune reaction to tissues of another individual
    - transient neonatal diseases (HDN)
    - transplant rejection and transfusion reaction
Hypersensitivity

• Characterized by the immune mechanism
  – Type I
    • IgE mediated
  – Type II
    • Tissue-specific reactions
  – Type III
    • Immune complex mediated
  – Type IV
    • Cell mediated

Type I Hypersensitivity

• IgE mediated
• Against environmental antigens (allergens)
• IgE binds to Fc receptors on surface of mast cells (cytotropic antibody)
• Histamine release
  – $H_1$ and $H_2$ receptors
  – Antihistamines

Type I Hypersensitivity

• Manifestations
  – Itching
  – Urticaria
  – Conjunctivitis
  – Rhinitis
  – Hypotension
  – Bronchospasm
  – Dysrhythmias
  – GI cramps and malabsorption

Type I Hypersensitivity

• Genetic predisposition
• Tests
  – Food challenges
  – Skin tests
  – Laboratory tests
• Desensitization
  – IgG-blocking antibodies
Type II Hypersensitivity

- Tissue specific
  - Specific cell or tissue (tissue-specific antigens) is the target of an immune response

- Five mechanisms
  - Cell is destroyed by antibodies & complement
  - Cell destruction through phagocytosis
  - Soluble antigen may enter the circulation and deposit on tissues
  - Antibody-dependent cell-mediated cytotoxicity
  - Causes target cell malfunction

Type III Hypersensitivity

- Immune complex mediated
- Antigen-antibody complexes are formed in the circulation and are later deposited in vessel walls or extravascular tissues
- Not organ specific

- Immune complex clearance
  - Large—macrophages
  - Small—renal clearance
  - Intermediate—deposit in tissues

Type IV Hypersensitivity

- Does not involve antibody
- Cytotoxic T-lymphocytes or lymphokine producing Th1 cells
  - Direct killing by Tc or recruitment of phagocytic cells by Th1 cells
- Examples
  - Acute graft rejection, skin test for TB, contact allergic reactions, and some autoimmune diseases
**Allergy**

- Environmental antigens that cause atypical immunologic responses in genetically predisposed individuals
  - Pollens, molds and fungi, foods, animals, etc.
- Allergen is contained within a particle too large to be phagocytosed or is protected by a nonallergenic coat
- Original insult is apparent

**Autoimmunity**

- Breakdown of tolerance
  - Body recognizes self-antigens as foreign
- Sequestered antigen
  - Self-antigens not normally seen by the immune system
- Infectious disease
  - Molecular mimicry
- Neoantigen
  - Haptens become immunogenic when they bind to host proteins

**Autoimmunity**

- Forbidden clone
  - During differentiation, lymphocytes produce receptor that react with self-antigens
- Ineffective peripheral tolerance
  - Defects in regulatory cells
- Original insult
- Genetic factors

**Alloimmunity**

- Immune system reacts with antigens on the tissue of other genetically dissimilar members of the same species
  - Transient neonatal alloimmunity
    - Fetus expresses parental antigens not found in the mother
    - Transplant rejection and transfusion reactions

**Autoimmune Examples**

- Systemic lupus erythematosus (SLE)
  - Chronic multisystem inflammatory disease
  - Autoantibodies against:
    - Nucleic acids, erythrocytes, coagulation proteins, phospholipids, lymphocytes, platelets, etc.

**Autoimmune Examples**

- Systemic lupus erythematosus (SLE)
  - Deposition of circulating immune complexes containing antibody against host DNA
  - More common in females
Systemic Lupus Erythematosus

- Clinical manifestations
  - Arthralgias or arthritis (90% of individuals)
  - Vasculitis and rash (70%-80%)
  - Renal disease (40%-50%)
  - Hematologic changes (50%)
  - Cardiovascular disease (30%-50%)

Countermeasures

- Vaccines
  - Induction of long-lasting protective immune responses that will not result in disease in a healthy recipient
  - Attenuated organism
  - Killed organisms
  - Recombinant viral protein
  - Bacterial antigens
  - Toxins

Countermeasures

- Antimicrobials
  - Inhibit synthesis of cell wall
  - Damage cytoplasmic membrane
  - Alter metabolism of nucleic acid
  - Inhibit protein synthesis
  - Modify energy metabolism

Pathogenic Adaptations

- Suppression of immune response
- Antigenic changes
- Development of resistance

Acquired Immunodeficiency Syndrome (AIDS)

- Syndrome caused by a viral disease
  - Human immunodeficiency virus (HIV)
  - Depletes the body’s Th cells
- Incidence
  - Worldwide
    - 5 million per year
  - United States
    - About 31,000 cases per year

Acquired Immunodeficiency Syndrome (AIDS)

- Effective antiviral therapies have made AIDS a chronic disease
- Epidemiology
  - Blood-borne pathogen
  - Increasing faster in women than men
Acquired Immunodeficiency Syndrome (AIDS)

- Pathogenesis
  - Retrovirus
    - Genetic information is in the form of RNA
    - Contains reverse transcriptase to convert RNA into double-stranded DNA
    - Integrase

Human Immunodeficiency Virus (HIV)

Concept Check

1. What is not characteristic of hypersensitivity?
   - A. Specificity
   - B. Immunologic mechanisms
   - C. Inappropriate or injurious response
   - D. Prior contact not needed to elicit a response

2. Which hypersensitivity is caused by poison ivy?
   - A. Type I
   - B. Type II
   - C. Type III
   - D. Type IV

3. Which is not an autoimmune disease?
   - A. MS
   - B. Pernicious anemia
   - C. Transfusion rxn.
   - D. Ulcerative colitis
   - E. Goodpasture disease

4. An alloimmune disorder is:
   - A. Erythroblastosis fetalis
   - B. IDDM
   - C. Myxedema
   - D. All of the above

5. A positive HIV antibody test signifies that the:
   - A. Individual is infected with HIV and likely so for life
   - B. Asymptomatic individual will progress to AIDS
   - C. Individual is not viremic
   - D. Sexually active individual was infected last weekend

6. The mechanism of hypersensitivity for drugs is:
   - A. Type I
   - B. Type II
   - C. Type III
   - D. Type IV

Stress and Disease

Chapter 8
Stress

- A person experiences stress when a demand exceeds a person’s coping abilities, resulting in reactions such as disturbances of cognition, emotion, and behavior that can adversely affect well-being.

Dr. Hans Selye (1946)

- Worked to discover a new sex hormone
- Injected ovarian extracts into rats
- Witnessed 3 structural changes:
  - Enlargement of the adrenal cortex
  - Atrophy of thymus and other lymphoid structures
  - Development of bleeding ulcers in the stomach and duodenum

Dr. Hans Selye

- Dr. Selye witnessed these changes with many agents (cold, surgery, restraint). He called these stimuli “stressors.”
- Many diverse agents caused same general response:
  - general adaptation syndrome (GAS)

General Adaptation Syndrome (GAS)

- Three stages
  - Alarm stage
    - Arousal of body defenses (fight or flight)
  - Stage of resistance or adaptation
    - Mobilization contributes to fight or flight
  - Stage of exhaustion
    - Progressive breakdown of compensatory mechanisms
    - Onset of disease

GAS Activation

- Alarm stage
  - Stressor triggers the hypothalamic-pituitary-adrenal (HPA) axis
    - Activates sympathetic nervous system (SNS)
- Resistance stage
  - Begins with the actions of adrenal hormones
- Exhaustion stage
  - Occurs if stress continues and adaptation is not successful

Stress Response

- Nervous system
- Endocrine system
- Immune system
**Neuroendocrine Regulation**

- **Catecholamines**
  - Released from chromaffin cells of the adrenal medulla
    - Epinephrine released
    - α-adrenergic receptors
      - α₁ and α₂
    - β-adrenergic receptors
      - β₁ and β₂
    - Mimic direct sympathetic stimulation

**Cortisol and Immune System**

- **Glucocorticoids and catecholamines**
  - Decrease cellular immunity while increasing humoral immunity
  - Increase acute inflammation
  - Th2 shift

**Stress Response**

- **β-Endorphins**
  - Proteins found in the brain that have pain-relieving capabilities
  - Released in response to stressor
  - Inflamed tissue activates endorphin receptors
  - Hemorrhage increases levels, which inhibits blood pressure increases and delay compensatory changes
Stress-Induced Hormone Alterations

• Growth hormone (somatotropin)
  – Produced by the anterior pituitary and by lymphocytes and mononuclear phagocytic cells
  – Affects protein, lipid, and carbohydrate metabolism and counters the effects of insulin
  – Enhances immune function
  – Chronic stress decreases growth hormone

• Prolactin
  – Released from the anterior pituitary
  – Necessary for lactation and breast development
  – Prolactin levels in the plasma increase as a result of stressful stimuli

• Oxytocin
  – Produced by the hypothalamus during childbirth and lactation
  – Produced during orgasm in both sexes
  – May promote reduced anxiety

• Testosterone
  – Secreted by Leydig cells in testes
  – Regulates male secondary sex characteristics and libido
  – Testosterone levels decrease because of stressful stimuli
  – Exhibits immunosuppressive activity

Concept Check

• 1. Which is not characteristic of Selye’s stress syndrome?
  – A. Adrenal atrophy
  – B. Shrinkage of thymus
  – C. Bleeding GI ulcers
  – D. Shrinkage of lymphatic organs

• 2. Which characterizes the alarm stage?
  – A. Increased lymphocytes
  – B. Incr. SNS act.
  – C. Incr. PSN act.
  – D. Incr. eosinophils

• 3. CRF is released by the:
  – A. Adrenal medulla
  – B. Adrenal cortex
  – C. Anterior pituitary
  – D. Hypothalamus

• 4. Stress is defined as any factor that stimulates:
  – A. Posterior pituitary
  – B. Anterior pituitary
  – C. Hypothalamus to release CRF
  – D. Hypothalamus to release ADH
• 5. Which would not occur in response to stress?
   – A. Increased systolic BP
   – B. Increased Epi
   – C. Constriction of pupils
   – D. Increased adrenocorticoids

• 6. Which would not be useful to assess stress?
   – A. Total cholesterol
   – B. Esosinophil count
   – C. Lymphocyte count
   – D. Adrenocorticoid levels