Innate Immunity: Inflammation & Wound Healing

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
    • Coughing and sneezing
    • Flushing from urinary system
    • Vomiting
    • Mucus and cilia

Second Line of Defense

• Inflammatory response
  – Caused by a variety of materials
    • Infection, mechanical damage, ischemia, nutrient deprivation, temperature extremes, radiation, etc.
  – Local manifestations
    • ________, ________, ________, __________
  – 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
  – Antimicrobial peptides
  – 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

Mast Cell Degranulation

Plasma Protein Systems

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

Phagocytes

- Neutrophils (PMNs)
  - Predominate in early inflammatory responses
  - arrive _______________
  - Ingest bacteria, dead cells, and cellular debris
  - Cells are short lived and become component of purulent exudate

- Monocytes and macrophages
  - Monocytes - produced in bone marrow → blood → inflammatory site, where they develop into macrophages
  - Macrophages typically arrive at the inflammatory site _______________

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

- Natural killer (NK) cells
  - Function against cells infected with viruses and cancer

- Platelets
  - Activation results in degranulation (release of ________) 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
  - _______ exudate: indicates early inflammation

- Fibrinous exudate
  - _______ exudate: indicates more advanced inflammation

- Purulent exudate
  - _______: indicates a bacterial infection

- Hemorrhagic exudate
  - Exudate contains _______: 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 ____________

- Often related to an unsuccessful acute inflammatory response
Resolution and Repair

- Debridement
  - Cleaning up the dissolved clots, microorganisms, erythrocytes, and dead tissue cells
- Healing
  - 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 Immunity
Chapter 6

Adaptive (specific) Immunity
- state of protection against infectious agents mainly
  __________________
• Antigens – found on infectious agents, environmental substances, cancers
• Specificity – of antigens for antibodies
• Memory – _______________
• 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 foreign protein capable of stimulating immune response in healthy person
   - A foreign protein capable of stimulating immune response in susceptible person
   - A protein that binds with an antibody
   - A protein that is released by the immune system

2. Antibodies are produced by
   - B cells
   - T cells
   - Plasma cells
   - 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 and antigen binds to its appropriate antibody:
   - A. Agglutination may occur
   - B. Phagocytosis may occur
   - C. Antigen neutralization may occur
   - D. All of the above

Infection & Defects in Mechanisms of Defense

Chapter 7

Hypersensitivity

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

Hypersensitivity

- 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)
    - 

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

- Immediate hypersensitivity reactions
- Anaphylaxis
- Delayed hypersensitivity reactions

Type I Hypersensitivity

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

Type I Hypersensitivity

- Manifestations
  - Itching
  - Urticaria
  - Conjunctivitis
  - Rhinitis
  - Hypotension
  - Bronchospasm
  - Dysrhythmias
  - GI cramps and malabs

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
Type II Hypersensitivity

- 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

Type III Hypersensitivity

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

Type III Hypersensitivity

Immune complex disease

- Serum sickness
  - Caused by formation of immune complexes and lodge in tissues (vessels, kidneys, joints)
- Arthus reaction
  - Observed after injection, ingestion, or inhalation
  - Skin reactions after repeated exposure

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 \underline{\text{__________}}, 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
  - 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

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 ___________
  - Atrophy of __________ and other lymphoid structures
  - Development of __________ 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 (______________)
  - 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**
Neuroendocrine Regulation

- Catecholamines
  - Released from chromaffin cells of the adrenal medulla
    - Epinephrine released
  - α-adrenergic receptors
    - $\alpha_1$ and $\alpha_2$
  - β-adrenergic receptors
    - $\beta_1$ and $\beta_2$
    - Mimic direct __________ stimulation

- Cortisol (hydrocortisone)
  - Activated by adrenocorticotropic hormone (ACTH)
  - Stimulates gluconeogenesis
  - Elevates the blood glucose level
  - Powerful anti-inflammatory and immunosuppressive agent

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 (______________)
  - 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
Stress-Induced Hormone Alterations

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

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

Stress-Induced Hormone Alterations

• 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. Eosinophil count
  – C. Lymphocyte count
  – D. Adrenocorticoid levels