Immune System

• Functional system rather than organ system
  – Removes pathogenic cells, infected cells, or abnormal cells

• Immunity = ability to ward off microorganisms

• divisions
  – Innate (non-specific) immunity
    • Response: fast, non-specific
  – Adaptive (acquired) immunity
    • Response: slow, specific
Innate immunity

• 1ˢᵗ line of defense: barriers
• 2ⁿᵈ line of defense: Cells and chemicals
  – Recognizes and destroys
  – Response does NOT change
  – Inflammation
    • Primary response of the innate system
    • Inhibits the spreading of pathogens
physical and chemical barriers

• Cutaneous secretion
  – Sweat
  – Sebum

• Mucosal secretion
  – Acidic secretion (gastric and vaginal)
  – Mucus

• Mucociliary escalator
physical and chemical barriers

• Body Fluids: Tears, saliva, and urine
  – wash away microorganisms
  – Lysozyme

• Normal flora vs. pathogenic microorganisms
Internal Defenses

Innate defenses

Surface barriers
• Skin
• Mucous membranes

Internal defenses
• Phagocytes
• Natural killer cells
• Inflammation
• Antimicrobial proteins
• Fever
Phagocytes

- Neutrophils & Macrophages
- Events of phagocytosis
  - Phagocyte adheres to pathogens
    - opsonins
  - Phagosome
  - phagolysosome
  - digestion
  - Exocytosis of vesicle
    - removes indigestible and residual material
opsonization
Natural Killer Cells

- Non-phagocytic lymphocytes
  - No memory
- Response: rapid
  - apoptosis in cancer and virus-infected cells
- Perforin
- granzymes
- INF-alpha & beta
  - Anti-viral replication
  - Activates NK
- INF-gamma
  - Activates macrophage & NK
Interferons (INF)

- Secreted by lymphocytes
- INF-alpha & beta
  - Anti-viral replication
    - block viral reproduction and degrade viral RNA
  - Activates NK lymphocytes
- INF-gamma (immune INF)
  - Activates macrophage & NK lymphocytes
complement proteins

- 20-25 blood proteins
  - inactive form
- Complement cascade
  - Complement activation
- Result
  - Lysis
Complement System

• Compliment activated
  – By direct interaction with a pathogen or by antibodies

• Activated complements results in
  – Chemotaxis
  – Opsonization
  – Inflammation
    • Basophils & mast cells
  – Lysis
Inflammation

• occurs whenever tissues are damaged

• Objectives
  – Chemotaxis to prevents the spread of infection
  – Disposes of pathogens & debris
  – promote tissue repair once the infection is under control
signs of acute inflammation

• damaged tissues releasing
  – histamine, prostaglandins, kinins, leukotrienes
  – Heat & Redness
    • local vasodilation: ↑blood flow to the area (local hyperemia)
  – Swelling
    • ↑local capillary permeability: edema
      – dilution of harmful substances
      – delivery of clotting factors, oxygen, & nutrients for tissue repair
      – Diapedesis => chemotaxis
  – Pain => Impairment of function
    • Bradykinin: stimulate pain-sensitive neurons
Inflammation: flowchart of events.

**Initial stimulus**
- Tissue injury

**Physiological response**
- Arterioles dilate
- Increased capillary permeability
- Leaked protein-rich fluid (exudate formation)
- Leaked clotting proteins form interstitial clots that wall off area to prevent injury to surrounding tissue

**Signs of inflammation**
- Heat
- Redness
- Pain
- Swelling
- Possible temporary impairment of function
- Temporary fibrin patch forms scaffolding for repair
- Pus may form

**Result**
- Area cleared of debris
- Leukocytes migrate to injured area
- Margination (leukocytes cling to capillary walls)
- Diapedesis (leukocytes pass through capillary walls)
- Phagocytosis of pathogens and dead tissue cells (by neutrophils, short-term; by macrophages, long-term)
- Leukocytes in bloodstream (leukocytosis)
- Local hyperemia (increased blood flow to area)
- Increased temperature increases metabolic rate of cells

**Innate defenses → Internal defenses**
Innate defenses

**Chemotaxis**

Inflammarory chemicals diffusing from the inflamed site act as chemotactic agents.

1. **Leukocytosis.** Neutrophils enter blood from bone marrow.
2. **Margination.** Neutrophils cling to capillary wall.
3. **Diapedesis.** Neutrophils emigration
4. **Chemotaxis**

Capillary wall
Basement membrane
Endothelium
Fever

• Systemic response to infection
  – Leukocytes and macrophages: pyrogens

• When is it good? Mild fever
  – liver and spleen: sequester iron and zinc (needed by microorganisms)
  – ↑metabolic rate => faster repair

• When is it bad? High fever
  – Hallucinations, Confusion, Irritability, Convulsions, Dehydration
Adaptive (acquired) immunity

- **3rd line of defense**
  - Specific and improves efficiency each time it encounters the same pathogen
    - Slow onset on initial exposure
    - Quick response on 2nd exposure – memory cells

- **Divisions**
  - Cell-mediated immunity
  - Humoral immunity
Lymphocytes

- 2 main classes ______
- Development
- Maturation
  - Immunocompetency
    - Lymphocyte can recognize one specific antigen
    - Clone = group of lymphocytes
    - Clonal expansion => Naïve cells
    - Clonal deletion => no autoimmune dz
  - Self-tolerance: Lymphocytes unresponsive to self-antigens
- Lymphocyte Activation
  - Antigen challenge: naive cells => activated cells
Adaptive defenses

Humoral immunity

Cellular immunity

Primary lymphoid organs
(red bone marrow and thymus)

Secondary lymphoid organs
(lymph nodes, spleen, etc.)

Origin
• Both B and T lymphocyte precursors originate in red bone marrow.

Maturation
• Lymphocyte precursors destined to become T cells migrate (in blood) to the thymus and mature there.
• B cells mature in the bone marrow.
• During maturation lymphocytes develop immunocompetence and self-tolerance.

Seeding secondary lymphoid organs and circulation
• Immunocompetent but still naive lymphocytes leave the thymus and bone marrow.
• They “seed” the secondary lymphoid organs and circulate through blood and lymph.

Antigen encounter and activation
• When a lymphocyte’s antigen receptors bind its antigen, that lymphocyte can be activated.

Proliferation and differentiation
• Activated lymphocytes proliferate (multiply) and then differentiate into effector cells and memory cells.
• Memory cells and effector T cells circulate continuously in the blood and lymph and throughout the secondary lymphoid organs.
Clones

• Small groups of identical lymphocytes

• Each clone has many copies of the SAME RECEPTOR to a specific ANTIGEN
  – Antigen: foreign molecules provoking acquired immune response

• > 1 million different varieties of clones
  – Result: Diverse lymphocytic responses
antigen-presenting cells (APCs)

• Dendritic cells, macrophages, and activated B-cells
  – Do not respond to specific antigens
  – Objective: Present antigen fragments on the surface as a signal to Helper T-cells
  • “ID the invading antigens”
Acquired immunity

- **Humoral Immunity**
  - Deals with extracellular antigens
  - B lymphocytes and plasma cells

- **cell-mediated immunity**
  - deals with microorganisms inside the cells
  - Cytotoxic T-cells

- **Helper T Cells**
  - Control Adaptive Immunity
    - via regulating activities of B-cells & cytotoxic T-cells
MHC proteins

• major histocompatibility complex proteins
  – AKA: Human Leukocyte Antigen (HLA)
    • International HLA system: ID compatibility in organ transplant
  – Glycoproteins found on cell surfaces
  – Coded by MHC genes (millions of different combinations)

• 2 classes
  – MHC-I: found on all nucleated cells
  – MHC-II: found on APCs
APCs and MHC II Proteins

- **APC**
  - Antigens displayed on class-II MHC protein

- **Costimulation**
  - confirmation signal between APC & Helper T-cells

- **Clone formation**
  - Activated Helper T-Cells
    - activate B cells and cytotoxic T cells
B-Cell Primary Response

- APC
  - class-II MHC protein
- Costimulation
- Activated Helper T-Cells
  - activate B cells => plasma cells + memory cells
antibodies

• AKA immunoglobulins or gamma globulins
• Y-shaped structure
  – 4 polypeptide chains
  – variable regions
  – Constant region
    • binds to other immune cells and determines the mechanism the bound antigen will be destroyed
    • determine the antibody class
antibody class

- IgM = associated with primary responses
  - Potent agglutinating agent
- IgG = produced in secondary immune responses
  - Crosses placental barrier
- IgA = in external secretions
  - Prevent entry of pathogens
- IgE = target parasites & associated with allergic responses
- IgD = appear on the surface of B cells, role unclear (possibly as B cell receptor)
Antibody Action (PLAN)

- **Precipitation**
  - Antibodies bind soluble antigens into clumps

- **Lysis**
  - Antibodies bound to a bacterium activate complement

- **Agglutination**
  - Antibodies bind cell surface antigens into clumps

- **Neutralization**
  - Antibodies bind to and mask the dangerous portions of antigens, toxins, and viruses
Adaptive defenses → Humoral immunity

**Antigen-antibody complex**

- **Inactivates by**
  - **Neutralization** (masks dangerous parts of bacterial exotoxins; viruses)
  - **Agglutination** (cell-bound antigens)
  - **Precipitation** (soluble antigens)

- **Fixes and activates**
  - **Complement**

**Enhances**
- **Phagocytosis**
- **Inflammation** (Histamine release, Chemotaxis)
- **Cell lysis**

Figure 21.15  Mechanisms of antibody action.
Antigen-antibody complexes

• do not destroy antigens
• prepare them for destruction by innate defenses
B-Cell Response

Primary Response
• Lag period: longer
  – clonal selection
  – antibody production

Secondary Response
• Lag time: shorter
  – Plasma cells remain alive and functioning for a longer time
Adaptive defenses → Humoral immunity

Primary response
(initial encounter with antigen)

- Antigen binding to a receptor on a specific B lymphocyte (B lymphocytes with noncomplementary receptors remain inactive)
- Proliferation to form a clone
- Activated B cells
- Plasma cells (effector B cells)
  - Secreted antibody molecules
- Memory B cell—primed to respond to same antigen

Secondary response (can be years later)
- Clone of cells identical to ancestral cells
- Subsequent challenge by same antigen results in more rapid response
- Plasma cells
  - Secreted antibody molecules
- Memory B cells
Primary immune response to antigen A occurs after a delay.

Secondary immune response to antigen A is faster and larger.

- Antibody titer (antibody concentration in plasma (arbitrary units))
- Time (days)

First exposure to antigen A

Second exposure to antigen A; first exposure to antigen B
B-Cell Immunity

• Classified in 2 separate ways
  – Active immunity: memory cell produced in response to foreign antigen
    • Natural adaptive: infection
    • Artificial adaptive: vaccination
  – Passive immunity: antibodies from another person (animal) are transferred to a non-immune individual
    • Natural: IgG from mother to fetus or IgA from milk
    • Artificial: injection of serum (gamma globulin = anti-venom)
Figure 21.13 Active and passive humoral immunity.

**Humoral immunity**

- **Active**
  - Naturally acquired
    - Infection; contact with pathogen
  - Artificially acquired
    - Vaccine; dead or attenuated pathogens

- **Passive**
  - Naturally acquired
    - Antibodies passed from mother to fetus via placenta; or to infant in her milk
  - Artificially acquired
    - Injection of exogenous antibodies (gamma globulin)
Cell-Mediated Immunity

• What is the big limitation of antibodies?
• Cell-mediated immunity
  – deals with intracellular pathogens (& cancerous cells)
  – cytotoxic T-cells
Activating Killer T Lymphocytes

- Infected host cell
  - MHC-I
- Cytotoxic T-cells
T Lymphocyte Memory

• How would the response of a memory Helper T cell or a memory cytotoxic T cell differ from the primary response?
  – Secondary Response:
Other T-cells

- **Suppressor T cells**
  - suppress the activity of B cells and T cells
  - Prevent unnecessary immune activity

- **Regulatory T Lymphocytes**
  - Prevents B & T-cells from going overboard
ABO Compatibility

• RBC membranes
  – Lack MHC proteins
  – ABO blood group antigens
    • blood types: A, B, AB, and O
  – Rh antigens

<table>
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<th>Blood Group</th>
<th>U.S. Population (%)</th>
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<td>B</td>
<td>9</td>
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<td>AB</td>
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Table 24.2

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Each person inherits one allele for ABO blood groups from each parent. A and B are dominant to O but equal if they occur together (blood type AB).
Organ Transplants

• Ideal
  – Autografts: from one body site to another in same person
  – Isografts: between identical twins

• Most common
  – Allografts: between individuals who are not identical twins
    – ABO, other blood antigens, MHC antigens matched as closely as possible

• Rare
  – Xenografts: from another animal species
Hypersensitivities

• Immune responses to perceived (otherwise harmless) threat cause tissue damage

• Different types distinguished by
  – Their time course
  – Whether antibodies or T cells involved

• Antibodies cause immediate and subacute hypersensitivities

• T cells cause delayed hypersensitivity
Subacute Hypersensitivities

• Caused by IgM and IgG transferred via blood plasma or serum
• Slow onset (1–3 hours) and long duration (10–15 hours)
• Cytotoxic (type II) reactions
  – Antibodies bind to antigens on specific body cells, stimulate phagocytosis and complement-mediated lysis of cellular antigens
  – Example: mismatched blood transfusion reaction
Subacute Hypersensitivities

- **Immune complex (type III) hypersensitivity**
  - Antigens widely distributed in body or blood
  - Insoluble antigen-antibody complexes form
  - Complexes cannot be cleared from particular area of body
  - Intense inflammation, local cell lysis, and cell killing by neutrophils
  - Example: systemic lupus erythematosus (SLE)
Prevention of Rejection

• After surgery
  – Patient treated with immunosuppressive therapy
    • Corticosteroid drugs to suppress inflammation
    • Antiproliferative drugs
    • Immunosuppressant drugs

• Many of these have severe side effects
Severe Combined Immunodeficiency (SCID) Syndrome - Bubble Boy disease

• Marked deficit in B and T cells
• Fatal if untreated; treated with bone marrow transplants