Non-specific host defenses
Lecture 20 - Chapter 14

Topics
- Defense Mechanisms
- Components of immunity
- Non-specific immunity

Defense Mechanisms

• Innate and nonspecific immunity
  – First line of defense
  – Second line of defense

• Acquired and specific immunity
  – Third line of defense

Immunology

• Study of immunity - the host’s resistance to infectious agents of disease

Immunity

• Involves nonspecific and specific components
• Has fluid-based (humoral) and cellular (white blood cells [wbc] = leukocytes) components
  – Surveillance of the host body
  – Recognition of foreign agents or material
  – Destruction of foreign agents or material

First line of defense

• Barriers of innate immunity
  – Anatomical
  – Chemical
  – Genetic

Anatomical barriers

• Intact Skin
  – Outermost layer
  – Hair follicles
  – Skin glands
• Mucous membrane
  – GI (digestive) tract
  – Urinary tract
  – Respiratory tract (also ciliary escalator)
  – Outer Eye
Chemical barriers

- Sebaceous secretions
- Eyelid glands – meibomian gland
- Tears and saliva – lysozyme
- Menstruation
- Acidic pH
  - Sweat
  - Stomach
  - Skin
  - Semen
  - Vagina

Genetic barriers

- Different level of sensitivity and resistance to infectious agents
  - Malaria (sickle cells)
  - Tuberculosis
  - Leprosy
  - Fungal infections

Second and Third lines of defense

- Involves specific and non-specific contributions to host immunity
- Depends on activity of protective cells

WBC (Leukocyte)

- WBC recognize markers for “self” on the host cell
  - Do not attack or do not respond to host cell
- WBC recognize markers for “non-self” on the invading agent or material
  - Attack or respond to agent
Components of immunity

- All systems are integrated
  - Recticulo-endothelial system (RES)
  - Extracellular fluids system (ECF)
  - Blood, vascular (circulatory) system
  - Lymphatic system

Reticulo-endothelial (RES)

- Network of connective tissue fibers (Reticulum)
- Interconnects cells
- Allows immune cells to bind and move outside the blood and lymphatic system

Extracellular fluid (ECF)

- The spaces surrounding tissue cells and RES
- ECF enables immune cells to move

Blood

- Components
- Stemcells
- Hematopoiesis
The buffy coat layer from unclotted blood contains WBCs.

**Hematopoiesis**

- Production of blood
  - Starts at the embryonic stage
    - Yolk sac and liver
  - Continues throughout adult stage
    - Bone marrow

**Cellular components of blood**

- White blood cells (WBC) or leukocytes
- Red blood cells (RBC)
- Platelets

**Stem cells**

- Hematopoietic stem cells in bone marrow
  - Myeloid stem cells
    - Wbc: neutrophils, eosinophils, basophils; monocytes
    - Rbc: erythrocytes
    - platelets
  - Lymphoid stem cells
    - Agranular wbc: T lymphocytes; B lymphocytes
White blood cell

- Leukocytes
  - Granulocytes (large cytoplasmic granules)
    - Neutrophils
    - Basophils
    - Eosinophils
  - Agranulocytes (very small granules)
    - T cells
    - B cells
    - Monocytes

Neutrophils

- Nuclei - horse shoe or polymorphic nuclei
- Present in high numbers in blood and tissue
- Phagocytizes bacteria – granules are digestive enzymes
- First to arrive during an inflammatory immune response

Eosinophils

- Nuclei – bilobed
- Present in the bone marrow and spleen
- Attach and destroy eukaryotic pathogens
- Associated with inflammation and allergies

Basophils

- Nuclei – constricted
- Present in low in number in the body
- Function is similar to eosinophils
- Localized basophils are called mast cells

Lymphocytes

- Agranular
- Present throughout the body
- Contribute to specific (adaptive) immunity
  - T cells
  - B cells

Monocytes

- Agranular and motile
- Differentiate into macrophages (circulation and lymphatics) and dendritic cells (tissue associated)
- Phagocytosis
**Lymphatic system**

- Network of vessels that extend to most body areas
- Connected to the blood system
- Provides an auxiliary route for the return of extracellular fluid to the circulatory system
- “Drain off” system for inflammatory response
- Contains lymphocytes, phagocytes and antibodies

**Fluids**

- Plasma-like fluid (lymph) - formed from blood components
  - Water
  - Dissolved salts
  - Proteins (antibodies, albumin)
  - White blood cells
  - No red blood cells
- Diffuses into the lymphatic capillaries

**Lymph Vessels**

- Parallels the blood system
- Returns lymph to the blood system
- Movement of lymph depends on (smooth) muscle contractions
- Permeate all parts of the body except the central nervous system, bone, placenta, and thymus.

**Lymph Nodes**

- Exist in clusters
- Located
  - along the lymphatic and blood vessels
  - in the thoracic and abdominal cavity regions, armpit, groin and neck
- Filter for the lymph fluid
- Provide environment for immune reactions

**Spleen**

- Located in the upper left portion of the abdominal cavity
- Filter for lymph fluid and blood
  - traps pathogens
- Adults can survive without spleen
- Asplenic children are severely immunocompromised
**Thymus gland**

- **Embryo**
  - Two lobes in the pharyngeal region
  - High activity (releases mature T cells) until puberty
- **Adult**
  - Gradually shrinks
  - Lymph nodes and spleen supply mature T cells

**Gut-associated lymphoid tissue (GALT)**

- Recognized incoming microbes from food
- Supply lymphocytes for antibody response
- Examples: Appendix, Lacteals, Peyer’s patches

**Non-specific Immunity**

- Inflammation
- Phagocytosis
- Cytokines (i.e., Interferon)
- Complement

**Inflammation**

- Five major symptoms
  - Redness (Rurbor)
  - Warmth (Calor)
  - Swelling (Tumor)
  - Pain (Dolor)
  - Loss of function

**Fig. 14.12** In the thymus gland immature T cells differentiate into mature T cells.

**Fig. 14.13** The response to injury.
Inflammation - Causes

- Trauma
- Tissue injury due to physical or chemical agents
- Specific immune reactions

Inflammation - Function

- Mobilize and attract immune components to the site of injury (second line of defense)
- Localized and remove harmful substances
- Destroy microbes and block their invasion
- Aid in the repair of tissue damage

The major events in inflammation are injury, vascular reactions, edema, and resolution.

- Vascular changes
- Edema
- Fever
- Phagocytosis

Vascular changes

- Blood cells, tissue cells, and platelets release chemical mediators and cytokines, which cause fever, stimulate lymphocytes, prevent virus spread, cause allergic reactions

  • Chemical mediators
    - Vasoactive
      - Affect endothelial cells, smooth muscles of blood vessels
    - Chemotactic (chemokines)
      - Affect WBC

  • Cytokines
    - Interferon, interleukins

Edema

- Leakage of vascular fluid (exudate) into tissue
- Exudate - plasma proteins, white blood cells (WBC), debris, and pus
- Migration of WBC is called diapedesis or transmigration
- Chemotaxis - response Chemokines
The transmigration of WBCs is followed by chemotaxis.

**Fever**

- Fever is caused by pyrogens
- Pyrogens
  - Microbes and their products (ex. LPS)
  - Leukocyte products (called Interleukins)
- Fever:
  - Causes a reset of the hypothalamic thermostat (Hypothalamus) to a higher temperature
  - Causes Vasoconstriction
  - Inhibits microbe and viral multiplication, reduces nutrient availability, increases immune reactions

**Phagocytosis**

- Neutrophils
- Macrophages & Dendritic Cells

**Neutrophils**

- Early responders to inflammation
- Neutrophils are primary responders to bacterial infections and components of pus
- Eosinophils, the primary responders to parasitic infections (eukaryotes), are non-phagocytic and recruited by players in the third line of defense.

**Macrophages & Dendritic Cells**

- Monocytes transform into scavenger cells that can reside in one particular location
  - Alveolar Cells, Kupffer Cells - Macrophages
  - Langerhans Cells - Dendritic cells
  - Drift throughout the Reticuloedothelial System
- Macrophages & Dendritic cells
  - Perform phagocytosis
  - Interact with B and T cells

Fig. 14.16 Diapedesis and chemotaxis of leukocytes.

Fig. 14.17 The development stages of monocytes and macrophages.
Macrophages can take-up permanent residence in the lung (alveolar), liver (Kupffer) and skin (Langerhans).

Fig. 14.18 Sites containing macrophages

A summary of the mechanism of phagocytosis.

Fig. 14.19 The phases in phagocytosis

Mechanism of phagocytosis

- Chemotaxis (Peptidoglycan, LPS, foreign debris)
- Ingestion (Phagocytes enclose the pathogen or foreign material, form a phagosome)
- Phagolysosome (Phagosomes fuse with the Lysosome forming the Phagolysosome, where antimicrobial chemicals are released)
- Destruction (Enzymes: Oxidative burst; Nitrosative burst)

Interferon

- Synthesis: in WBCs & Tissue cells
- Produced in response to viral infections, microbe infections and other antigens, increased nucleic acid contents, immune products

Classes

- Interferon alpha
  – Product of lymphocytes and macrophages
- Interferon beta
  – Product of fibroblasts and epithelial cells
- Interferon gamma
  – Product of T lymphocytes

Activity

- A signal (induced by virus-cell interaction) is sent to the nucleus to synthesize (transcription and translation) interferon
- Interferon is secreted from cell
- Interferon binds to other host cells and induces production antiviral proteins (leads to inhibition of viral multiplication; i.e., by inhibition of translation)
Interferon is produced, released, and taken-up by a near-by cell, where by original cell is not protected but the recipient cell is protected.

Fig. 14.20 The antiviral activity of interferon.

Other Roles of Interferon

- Activates and instructs T and B cell development
- Activates macrophages
- Inhibits tumor cell growth

Complement

- Consist of 26 blood proteins
- Produced by liver hepatocytes, lymphocytes, and monocytes

The three complement pathways, their activators, and the complement proteins involved.

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Activator</th>
<th>Host Components Initially Bound</th>
<th>Complement Proteins Involved</th>
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</thead>
<tbody>
<tr>
<td>Classical (rapid, efficient)</td>
<td>Complement-fixing antibodies (IgG, IgM)</td>
<td>C3 complex</td>
<td>C3, C4, C5</td>
</tr>
<tr>
<td>Lectin</td>
<td>Mannose</td>
<td>Mannose-binding lectin</td>
<td>C3, C5, C6, C7, C8, C9</td>
</tr>
<tr>
<td>Alternative (slower, less efficient)</td>
<td>Bacterial or fungal cell wall</td>
<td>Factor B, Factor D, Properdin</td>
<td></td>
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</tbody>
</table>

Table 14.1 Complement pathways

Pathways

- Classical
  - activated by the presence of antibody bound to microbes
- Lectin
  - activated when a host serum protein binds a particular sugar in the wall of fungi and other microbes
- Alternative
  - activated when complement proteins bind to cell wall or surface components of microbes

Stages

- Initiation
- Amplification and cascade
- Polymerization
- Membrane attack
The classical pathway begins with C1 components binding to antibodies, and ends by puncturing small pores through the membrane, leading to lysis.

**Summary: Complement**

- Different activators
- Different inflammatory mediators
- Formation of membrane attack complex
- Perforation and lysis of cells

Fig. 14.21 Steps in the classical complement pathway at a single site.