Innate Immunity: Nonspecific Defenses of the Host (Chapter 16)

Lecture Materials for

Amy Warennda Czura, Ph.D.
Suffolk County Community College
Eastern Campus

Primary Source for figures and content:

Susceptibility = lack of resistance
Resistance = ability of host to ward off disease

1. Nonspecific resistance / Innate Immunity
   - defenses that protect against any pathogen, immediate, no memory

2. Specific resistance / Adaptive Immunity
   - defense against a particular pathogen, requires time to develop, involves specialized cells, has memory

Body defense
   (on handout)

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Nonspecific Defenses / Innate Immunity
First line of defense: keep microbes out
1). Skin & Mucous Membranes
   A. Physical factors: barriers or removal
      1. Skin
         (cutaneous membrane = dermis+epidermis)
         epidermis:
         - top layer = dead cells,
           keratin filled, cells tightly linked
         - dry, unfavorable, constantly shed
         - impermeable unless damaged or moist
2. Mucous membranes  
-thick, moist epithelium  
-less protective than keratinized  
-has goblet cells for mucus production

3. Ciliary escalator  
-ciliated epithelium of respiratory tract  
-cilia beat in wave motion: clear microbes in mucus out of respiratory tract

4. Lacrimal apparatus  
(lacrimal gland & lacrimal canals)  
-constant tears over eye  
-washes microbes off
5. Salivary glands
   -washing of teeth and mouth to reduce colonization
6. Vomiting & diarrhea
   -rapid contractions of gastrointestinal tract to rapidly flush out microbes and toxins

B. Chemical factors
1. mucus
   -glycoproteins + water
   -thick, inhibits colonization
2. sebum
   -oily, from sebaceous glands
   -fatty acids & lactic acids
      make skin pH 3-5
   -acid pH inhibits microbe growth
3. perspiration
   -water + salts
   -water flushes microbes off skin
   -salt accumulates inhibiting microbe growth
4. lysozyme
   - enzyme in most body secretions
   - breaks down peptidoglycan cell walls
5. gastric juice
   - HCl + enzymes + mucus
   - pH 1-3 destroys most bacteria and toxins

2). Normal Microbiota
-microbial antagonism:
   - compete for nutrients or space
   - alter environment (pH, oxygen)
   - produce toxins (e.g. bacteriocins)

Second line of defense: if microbes enter, attack and defend

3). Leukocytes = White Blood Cells
-usually low #s in blood, ↑ during infection
leukocytosis = increase in WBC % in blood
(leukopenia = ↓ in WBCs due to damage by some pathogens)
When activated, most leukocytes will produce cytokines: intercellular signaling molecules/hormones that will function to trigger, enhance, and coordinate various defense mechanisms.

Types of leukocytes:

A. Granulocytes (visible granules)
   1. Neutrophils
      - aka PMNs (polymorphonuclear leukocytes)
      - 3 to 5 lobed nuclei
      - highly mobile and phagocytic
      - first to arrive at injury or infection
      - dominate during initial stages of infection or injury
      - often dominate during bacterial infection
   2. Basophils (blood) = Mast cells (tissue)
      - not phagocytic
      - release histamine: triggers inflammation and allergy
3. Eosinophils
- motile
- slightly phagocytic
- produce toxins to fight multicellular parasite infections

B. Agranulocytes (granules not visible)
1. Monocytes (blood) =
   - Macrophage (activated, in tissues)
   - highly phagocytic
A. Fixed macrophages / histiocytes
   - remain in certain tissue/organs to screen for pathogens & remove damaged cells
   (e.g. Kupffer cell (liver), microglia (CNS), Alveolar macrophages (lung))
B. Wandering/Free Macrophage
-move from blood to injury or infection
-arrive after neutrophils
-phagocytose dead cell debris
-dominate in later stages of infection or injury repair
-dominate during fungal or viral infection
C. Dendritic cells
-located in epidermis, mucous membranes & lymphoid tissues
-initiate adaptive immune responses

2. Lymphocytes = T, B, & NK cells
T cells: cell mediated immunity
B cells: antibody mediated immunity
NK cells: non-specific, target infected or cancerous cells
release perforin & granzymes
- specialized cells
- not phagocytic
- in lymphoid tissues and blood
- B & T cells involved in specific resistance
- B & T cells respond to specific antigens

phagocytes = leukocytes specialized to endocytose microbes & cell debris
neutrophils, macrophages, eosinophils

Mechanism of phagocytosis (on handout)
1. **Chemotaxis and Adherence**
   - Chemotaxis = chemical attraction of phagocyte to microbe; attracted by microbial products, damaged cells, cytokines, and/or complement
   - Adherence = attachment of plasma membrane of phagocyte to microbe; Toll-like receptors (TLRs) on phagocyte membrane bind to pathogen-associated molecular patterns (PAMPs) on microbe
   - Adherence made easier by opsonization
   - Opsonization = coating of the microbe with antibodies or complement proteins

2. **Ingestion**: phagocyte extends pseudopods around microbe

3. **Phagosome formation**: fusion of pseudopods around the microbe encloses it in a phagocytic vesicle called a phagosome which now floats in the cytoplasm

4. **Phagolysosome formation**: the phagosome fuses with a lysosome creating a phagolysosome putting the microbe in contact with digestive enzymes and bacteriocidal substances

5. **Digestion**: most microbes are killed and hydrolyzed in 10-30 min
   - Oxidative burst kills the microbe: toxic oxygen radicals (superoxide, hydrogen peroxide)
   - Enzymes and acids hydrolyze the microbe into component organic molecules

6. **Formation of the residual body**: useful small organic molecules are absorbed into the cytoplasm and the acids and enzymes are neutralized. Residual body = all remaining undigested material in a vesicle

7. **Exocytosis**: residual body contents are discharged outside the cell
Microbial Evasion of Phagocytosis:
1. Inhibit adherence or engulfment
   - M protein: *Streptococcus pyogenes*
   - Capsules: *Streptococcus pneumoniae*
   - Biofilms: prevent detachment
2. Survive phagocytosis
   - Leukocidins: *Staphylococcus aureus*
     lyse phagocyte before lysosome fusion
   - Membrane attack complexes: *Listeria*
     lyse phagosome to release bacteria into cytoplasm to grow
   - Prevent lysosome fusion and grow in phagosome: *Plasmodium*
   - Inactivate digestive enzymes in lysosome: HIV
   - Resist digestion: *Mycobacterium*
4). Inflammation
-process triggered by damage to body
-results in: redness (erythema), pain, heat, swelling (edema), and sometimes loss of function
-purpose:
  1. destroy injurious agent & remove byproducts of injury
  2. limit spread of injury
  3. repair or replace damaged tissue
-damage and/or infection causes production or release of signaling molecules which will coordinate events for inflammation:
  -histamine: from mast cells, causes vasodilation and increased vascular permeability
  -TNFα: cytokine from macrophages, amplifies response
  -prostaglandins: from damaged cells, intensifies histamine action and attracts phagocytes
-leukotrienes: from mast cells, increases vessel permeability and promotes phagocytosis

Stages of inflammation (on handout)
5.) Fever = elevated body temp
- triggered by microbial substance (e.g. LPS) or cytokines from activated phagocytes which reset thermostat in hypothalamus
- accelerates defense mechanisms & repair
- enhances activity of antiviral & antibacterial enzymes
6.) Antimicrobial substances

A. Complement fixation

- complement cascade consists of ~30 proteins in blood (made by liver)
- activation and fixation of complement proteins will aid destruction of microbes
- complement cascade can be activated by:
  1. Classical Pathway
     - antibodies bound to the surface of the microbe

![Complement cascade diagram](image-url)
2. Alternate Pathway
Factors P, B & D bind to microbe

Any of the three will result in activation of the complement cascade and fixation of complement to the microbe (on handout)

3. Lectin Pathway
Lectin binds to microbe
Complement System

Complement Fixation

Activated by:
1. Antibody binding to microbe
2. Complement proteins binding to microbe
3. Lectins binding to microbe

Cascade is triggered in blood: one complement protein turns on the next

Three Antimicrobial Results of Complement Fixation:
1. MAC formation = Cytolysis
   C5-C9 form the Membrane Attack Complex: the proteins assemble into a pore on the microbe membrane resulting in cell lysis
2. Opsonization = Phagocytosis
   C3b opsonizes bacteria to enhance phagocytosis
3. Inflammation = Phagocytosis
   C3a + C5a triggers histamine release from Mast cells thus triggering inflammation
B. Interferons
-special cytokines: antiviral signaling proteins used between cells to initiate antiviral activities
1. IFNβ:
-produced by virus infected cells
-trigger neighboring uninfected cells to produce AVPs (antiviral proteins)
-AVPs block viral replication in the cell
2. IFNα:
-produced by leukocytes
-trigger AVP production in body cells
-activates defense cells (e.g. NK cells) to kill virus infected cells
3. IFNγ:
-produced by lymphocytes
-activate defense cells for phagocytosis (e.g. macrophages & neutrophils)
C. Iron binding proteins
   1. Transferrin: blood, lymph, interstitial fluid
   2. Lactoferrin: mucus, saliva, milk
   3. Ferritin: liver, spleen, red bone marrow

D. Antimicrobial peptides (AMPs)
   - 12-50 amino acids long
   - produced in response to detection of microbial surface molecules
   - carry out a wide variety of antimicrobial effects:
     * inhibit wall synthesis
     * create pores in membrane
     * destroy DNA or RNA
     * recruit dendritic cells (phagocytosis)
     * recruit mast cells (inflammation)