Innate Host Resistance
Immunity

• Nonspecific immune response – Ch 33
  – Aka nonspecific resistance, innate, or natural immunity
  – acts as a first line of defense
  – offers resistance to any microbe or foreign material
  – lacks immunological memory

• Specific immune response – Ch 34
  – Aka acquired, adaptive, or specific immunity
  – resistance to a particular foreign agent
  – has “memory”
    • effectiveness increases on repeated exposure to agent
Host Defenses

Innate and nonspecific

- Cells, tissues
  - Granulocytes
  - Macrophages
  - Dendritic and NK cells

- Physical barriers
  - Skin mucous membranes

- Chemical mediators
  - Defensins
  - Lysozyme
  - Complement

Acquired and specific

- Cells, tissues
  - T cells
  - B cells

- Memory

- Discrimination, self/nonself

Opsonization

Resident responders

Inflammation

Cell cooperation
White Blood Cells of Innate and Adaptive Immunity

• White blood cells (WBCs) play a major role in the innate and specific responses

• Hematopoiesis
  – development of white blood cells in bone marrow of mammals
    • WBCs that mature prior to leaving bone marrow, e.g., macrophages and dendritic cells, become part of innate immune system and will respond to all antigens
    • WBCs that are mature but not yet activated after leaving bone marrow become part of the adaptive immune response, e.g., B and T cells and could differentiate in response to specific antigens
Physical Barriers in Nonspecific (Innate) Resistance

- Effectiveness impacted by:
  - direct factors
    - nutrition, physiology, fever, age, and genetics
  - indirect factors
    - personal hygiene, socioeconomic status, and living conditions
- Along with host’s secretions (flushing), barriers = first line of defense against microbes
Skin

- Strong mechanical barrier to microbial invasion
  - keratin produced by keratinocytes in outer layer
- Inhospitable environment for microbes
  - attached organisms removed by shedding of outer skin cells
  - pH is slightly acidic
  - high NaCl concentration
  - subject to periodic drying
Mucous Membranes

- Form protective covering that resists penetration and traps many microbes
- Are often bathed in antimicrobial secretions which contain a variety of antimicrobial substances (chemical mediators)
  - **lysozyme**
    - hydrolyzes bond connecting sugars in peptidoglycan
  - **lactoferrin**
    - secreted by activated macrophages
    - sequesters iron from plasma
  - **lactoperoxidase**
    - produces superoxide radicals
Respiratory System

- Turbulent air flow deposits microbes onto mucosal surfaces
- Mucociliary blanket
  - mucous secretions trap microbes
  - once trapped, microbes transported away from the lungs (mucociliary escalator)
    - expelled by coughing or sneezing
    - salivation washes microbes to stomach
- Alveolar macrophages
  - phagocytic cells in alveoli of lungs
Gastrointestinal Tract

• **Stomach**
  – gastric acid

• **Intestines**
  – pancreatic enzymes
  – bile
  – intestinal enzymes
  – GALT
  – peristalsis

• **Intestines**
  – shedding of columnar epithelial cells
  – secretory IgA
  – normal microbiota
  – Paneth cells
    • produce lysozyme
    • produce cryptins
Genitourinary Tract

- Unfavorable environment for foreign microbes
  - low pH of urine and vagina
  - vagina has lactobacilli
  - urea and other toxic metabolic end products in urine
    - hypertonic nature of kidney medulla
- Flushing with urine and mucus
- Distance barrier of male urethra
The Eye

• Physical protection from the eye lid and eye lashes
• Mucus secreting epithelial membrane
• Flushing action of tears
• Lysozyme, lactoferrin, and secretory IgA in tears
Chemical Mediators in Nonspecific (Innate) Resistance

- Many already noted (e.g., gastric juices, lysozyme, lactoferrin, urea)
- A variety of defensive chemicals such as defensins and other polypeptides are also found in blood, lymph, and other body fluids
Antimicrobial Peptides

- Cationic peptides - three classes whose biological activity is related to their ability to damage bacterial plasma membranes
  - First class: linear, alpha-helical peptides that lack cysteine amino acid residues
    - e.g., cathelicidin, produced by a variety of cells
  - Second class: defensins
    - peptides that are open-ended, rich in arginine and cysteine, and disulfide linked
    - found in neutrophils, intestinal Paneth cells and intestinal and respiratory epithelial cells
  - Third class: larger peptides that are enriched for specific amino acids and exhibit regular structural repeats
    - e.g., histatin, present in human saliva and has anti-fungal activity
Bacteriocins

- Peptides produced by normal microbiota
- Lethal to related species
- Produced by Gram-positive and Gram-negative cells
  - e.g., colicins produced by *E. coli*
  - e.g., lantibiotics produced by Gram-positive bacteria
The Complement System

• Composed of >30 serum proteins
• Augments (or “complements”) the antibacterial activity of antibody (works with the adaptive immune system)
• Three major activities:
  – defending against bacterial infections
  – bridging innate and adaptive immunity
  – disposing of wastes
• Other activities:
  – Function as chemotactic signals that recruit phagocytes to their activation site
  – Puncture cell membranes causing cell lysis
  – Many complement activities unite the nonspecific and specific arms of the immune system to destroy and remove invading pathogens
Opsonization

• Process in which microbes are coated by serum components (opsonins) in preparation for recognition/ingestion by phagocytic cells

• Some complement proteins are opsonins
  – bind to microbial cells, coating them for phagocyte recognition
Cytokines

• Soluble proteins or glycoproteins that are released by one cell population that act as intercellular mediators or signaling molecules

• Three proposed groups based on function
  – regulators of innate resistance mechanisms
  – regulators of adaptive immunity
  – stimulators of hematopoiesis
<table>
<thead>
<tr>
<th>Cytokine¹</th>
<th>Source</th>
<th>Role</th>
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<tbody>
<tr>
<td><strong>Innate Resistance</strong></td>
<td></td>
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<tr>
<td>IL-1</td>
<td>Macrophages, endothelial and epithelial cells</td>
<td>Upregulates inflammatory response, including fever</td>
</tr>
<tr>
<td>IL-6</td>
<td>Macrophages, T cells, endothelial cells, and adipocytes</td>
<td>Upregulates acute phase response, including fever; stimulates neutrophil differentiation</td>
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<tr>
<td>IL-23</td>
<td>Macrophages and dendritic cells</td>
<td>Upregulates inflammatory response via IL-17 from T cells; stimulates IL-1, IL-6, TNF, and chemokine production; enhances T-cell activation and memory response</td>
</tr>
<tr>
<td>IL-27</td>
<td>Macrophages and dendritic cells</td>
<td>Enhances antigen recognition by T and B cells</td>
</tr>
<tr>
<td>IFN-α</td>
<td>All somatic cells, especially macrophages</td>
<td>Upregulates RNAse activity to control viral infection and tumor formation; upregulates inflammatory response, including antigen presentation</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Monocytes/Macrophages</td>
<td>Upregulates inflammatory response, including fever; stimulates acute-phase protein synthesis; induces tumor regression; mediates septic shock</td>
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<tr>
<td><strong>Adaptive Immunity</strong></td>
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<tr>
<td>IL-2</td>
<td>T cells (autocrine process)</td>
<td>Stimulates growth and differentiation of T cells and NK cells; promotes antibody secretion from B cells</td>
</tr>
<tr>
<td>IL-4</td>
<td>T-cell subset (and putatively basophils)</td>
<td>Induces differentiation of a T-cell subset; stimulates production of antibody, especially antibody associated with allergies; inhibits IL-12 production</td>
</tr>
<tr>
<td>IL-5</td>
<td>T-cell subset and mast cells</td>
<td>Stimulates growth of B cells; enhances antibody secretion; activates eosinophils</td>
</tr>
<tr>
<td>IL-12</td>
<td>Macrophages, dendritic cells, and a T-cell subset</td>
<td>Stimulates growth and function of T-cell subsets, stimulates killing functions of NK cells and cytotoxic lymphocytes</td>
</tr>
<tr>
<td>IL-17</td>
<td>T-cell subset</td>
<td>Monocyte and neutrophil chemokine; induces pro-inflammatory cytokines IL-6, TNF-α, IL-1, chemokines, and prostaglandins from various cells</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>T-cell subset and NK cells</td>
<td>Enhances phagocytic functions of macrophages; upregulates cytolytic function of NK cells; stimulates antiviral functions</td>
</tr>
<tr>
<td>TNF-β</td>
<td>Numerous somatic cells</td>
<td>Upregulates T- and B-cell development; activates neutrophils; lyases tumor cells; upregulates CSF-2 and CSF-3</td>
</tr>
<tr>
<td><strong>Hematopoiesis</strong></td>
<td></td>
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<tr>
<td>IL-3</td>
<td>Basophils and activated T cells</td>
<td>Stimulates pluripotent hematopoietic stem cells to become myeloid progenitor cells; stimulates myeloid cell proliferation</td>
</tr>
<tr>
<td>IL-7</td>
<td>Bone marrow and thymic stromal cells, dendritic and epithelial cells, and hepatocytes</td>
<td>Stimulates pluripotent hematopoietic stem cells to become lymphoid progenitor cells; stimulates lymphoid cell proliferation</td>
</tr>
<tr>
<td>CSF-1</td>
<td>Osteoblasts</td>
<td>Induces hematopoietic stem cells to proliferate and differentiate into monocytes/macrophages; promotes monocyte survival</td>
</tr>
<tr>
<td>CSF-2</td>
<td>Macrophages, T cells, endothelial and mast cells, and fibroblasts</td>
<td>Induces hematopoietic stem cells to proliferate and differentiate into granulocytes and monocytes</td>
</tr>
<tr>
<td>CSF-3</td>
<td>Numerous cells and tissues</td>
<td>Induces hematopoietic stem cells to proliferate and differentiate into neutrophils; stimulates neutrophil function and survival</td>
</tr>
</tbody>
</table>

¹ Cytokine: IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; CSF, colony-stimulating factor
Cells of the Immune System

- Granulocytes
- Mast cells
- Monocytes and macrophages
- Dendritic cells
- Lymphocytes
- Each has specialized role in defending host
- Leukocytes
  - white blood cells
  - involved in both specific and nonspecific immunity
  - all arise from pluripotent stem cells
Hematopoietic stem cell
(in bone marrow)

Myeloid progenitor

Putative mast cell precursor

Myeloblast

Monoblast

Lymphoid progenitor

Natural killer (NK) cells

Lymphoblasts

Erythroblast

Megakaryoblast

Megakaryocyte

Red blood cells
Carry O₂ and CO₂

Platelets
Involved in blood clotting and inflammation

Eosinophils
Active in worm and fungal infections, allergy, and inflammatory reactions

Basophils
Function in inflammatory events and allergies

Neutrophils
Essential blood phagocytes; active engulfers and killers of bacteria

Granulocytes

Agranulocytes

Monocytes
Blood phagocytes that rapidly leave the circulation; mature into macrophages and dendritic cells

Lymphocytes
Primary cells involved in specific immune reactions to foreign matter

T cells
Perform a number of specific cellular immune responses such as assisting B cells and killing foreign cells (cell-mediated immunity)

B cells
Differentiate into plasma cells and form antibodies (humoral immunity)

Mast cells
Specialized tissue cells similar to basophils that trigger local inflammatory reactions and are responsible for many allergic symptoms

Macrophages
Largest phagocytes that ingest and kill foreign cells; strategic participants in certain specific immune reactions

Dendritic cells
Relatives of macrophages that reside throughout the tissues, responsible for processing foreign matter and presenting it to lymphocytes
Mast Cells

• Bone marrow-derived cells
• Differentiate in blood and connective tissue
• Contain granules containing histamine and other pharmacologically active chemicals
• Play important role in development of allergies and hypersensitivities

Granulocytes

• Irregularly-shaped nuclei with two to five lobes
• Cytoplasm has granules with reactive substances
  – kill microbes, enhance inflammation
• Three types
  – basophils, eosinophils, neutrophils (polymorphonuclear neutrophil (PMN))
Basophils

• Nonphagocytic
• Release vasoactive mediators
  – e.g., histamine, prostaglandins, serotonin, and leukotrienes from granules
• Play important role in development of allergies and hypersensitivities

Eosinophils

• Defend against protozoan and helminth parasites
• Release cationic proteins and reactive oxygen metabolites
• May play a role in allergic reactions
Neutrophils

• Highly phagocytic
• Circulate in blood then migrate to sites of tissue damage
• Kill ingested microbes with lytic enzymes and reactive oxygen metabolites contained in primary and secondary granules

Monocytes and Macrophages

• Highly phagocytic cells
• Monocytes
  – after circulating for ~8 hours, mature into macrophages
• Macrophages
  – larger than monocytes, reside in specific tissues, highly phagocytic
  – have a variety of surface receptors (including pattern recognition receptors)
  – named according to tissue in which they reside
Dendritic Cells

- Heterogeneous group of cells with neuron-like appendages
- Present in small numbers in blood, skin, and mucous membranes of nose, lungs, and intestines
  - contact, phagocytose, and process antigens → display foreign antigens on their surfaces (antigen presentation)

Natural Killer (NK) Cells

- Small population of large non-phagocytic granular lymphocytes
  - important role in innate immunity
  - kill malignant cells and cells infected with pathogens by releasing granzymes (cytotoxic enzymes)
- Two ways of recognizing target cells
  - bind to antibodies which coat infected or malignant cells (antibody-dependent cell-mediated cytotoxicity (ADCC))
  - recognizes cells that have lost their class I major histocompatibility antigen due to presence of virus or cancer
Lymphocytes

• Major cells of the immune system
• Major populations include T cells, B cells, and natural killer (NK) cells
• B and T lymphocytes differentiate in bone marrow from stem cells
  – are only activated by binding of specific antigen onto lymphocyte surface receptors
  – after activation replication continues as lymphocytes circulate and enter lymphoid tissue
  – memory cells are activated lymphocytes that do not immediately replicate, but will do so later in host’s life when antigen is again present
B Lymphocytes

- B cells (B lymphocytes)
  - mature in bone marrow
  - circulate in blood
  - can settle in lymphoid organs
  - after maturation and activation are called plasma cells and produce antibodies

T Lymphocytes (T cells)

- Mature in thymus
- Can remain in thymus, circulate in blood, or reside in lymphoid tissue
- Like B cells, require antigen binding to surface receptors for activation and continuation of replication
- Activated T cells differentiate into helper T cells (TH) and cytotoxic lymphocytes (CTLs)
- Secrete cytokines, chemicals that have effects on other cells, are produced and secreted by activated T cells
Organs and Tissues of the Immune System

• Primary organs and tissues
  – sites where lymphocytes mature and differentiate into antigen-sensitive mature B and T cells

• Secondary organs and tissues
  – areas where lymphocytes may encounter and bind antigen
    • followed by proliferation and differentiation into fully mature effector cells
Primary Lymphoid Organs and Tissues

- **Thymus**
  - precursor cells move enter from bone marrow and proliferate
  - thymic deletion removes T cells recognizing self antigens
  - remaining cells become mature T cells
  - enter bloodstream and recognize nonself antigens

- **Bone marrow**
  - site of B cell maturation in mammals
  - maturation involves removal of nonfunctioning and self-reactive cells
Secondary Lymphoid Organs and Tissues

• Spleen
  – most highly organized lymphoid organ
  – filters blood
  – macrophages and dendritic cells trap microbes and antigens
    • present antigens to B and T cells
      – most common way that lymphocytes become activated to carry out their immune functions

• Lymph nodes
  – most highly organized lymphoid tissue
  – filter lymph
  – microbes and antigens trapped and phagocytosed by macrophages and dendritic cells
  – B cells differentiate into memory and plasma cells within lymph nodes
Secondary Lymphoid Organs and Tissues

• Lymphoid tissue
  – located throughout the body
  – serve as interface between innate and acquired host immunity
  – act as areas of antigen sampling and processing
  – some lymphoid cells are found closely associated with specific tissues
    • e.g., skin-associated lymphoid tissue (SALT)
    • e.g., mucous-associated lymphoid tissue (MALT)
Skin Associated Lymphoid Tissue (SALT)

- Contains specialized cells
  - Langerhans cell
    - dendritic cell that can phagocytose antigens
    - differentiates into interdigitating dendritic cell – presents antigen to and activates T cells
  - intraepidermal lymphocyte
    - function as T cells
Mucosal-Associated Lymphoid Tissue (MALT)

- Specialized immune barrier
  - gut-associated lymphoid tissue (GALT)
  - bronchial-associated lymphoid tissue (BALT)
  - urogenital system MALT
Phagocytosis

- Process by which phagocytic cells (monocytes, tissue macrophages, dendritic cells, and neutrophils) recognize, ingest, and kill extracellular microbes

- Two mechanisms for recognition of microbe by phagocyte
  - opsonin-independent (nonopsonic) recognition
  - opsonin-dependent (opsonic) recognition

- Phagocytosis can be greatly increased by opsonization
Pathogen-Associated Molecular Patterns (PAMPs)

- Based on detection, by phagocytes, of conserved microbial molecular structures that occur in patterns

- PAMPs are unique to microbes, not present in host
  - e.g., lipopolysaccharide (LPS) of Gram-negative bacteria
  - e.g., peptidoglycan of Gram-positive bacteria

- PAMPs recognized by pattern recognition receptors (PRRs) on/in phagocytic cells
  - PRRs can work alone or together to trigger phagocytes
Inflammation

• Nonspecific response to tissue injury
  – can be caused by pathogen or physical trauma
  – acute inflammation is the immediate response of body to injury or cell death

• Cardinal signs
  – redness (rubor)
  – warmth (calor)
  – pain (dolor)
  – swelling (tumor)
  – altered function (functio laesa)
Acute Inflammatory Response

- The release of inflammatory mediators from injured tissue cells initiates a cascade of events which result in the signs of inflammation

- Involves chemical mediators
  - selectins
    - cell adhesion molecules on activated capillary endothelial cells
  - integrins
    - adhesion receptors on neutrophils
  - chemotaxins
    - chemotactic factors released by injured cells
Acute Inflammatory Response

- Various processes occur
  - margination
  - diapedesis
  - extravasion
More about Acute Inflammation…

• Tissue injury releases kalikrein and other mediators
  – increases capillary dilation and blood flow
  – brings more antimicrobial factors and leukocytes that kill pathogens

• Fibrin clot may restrict pathogen movement

• Phagocytes accumulate in inflamed area and destroy pathogens

• Bone marrow stimulated to release neutrophils and increase rate of granulocyte production
Chronic Inflammation

- Slow process
- Involves formation of new connective tissue
- Usually causes permanent tissue damage
- Dense infiltration of lymphocytes and macrophages at site of inflammation
  - granuloma
    - walled off area
    - formed when phagocytic cells can’t destroy pathogen