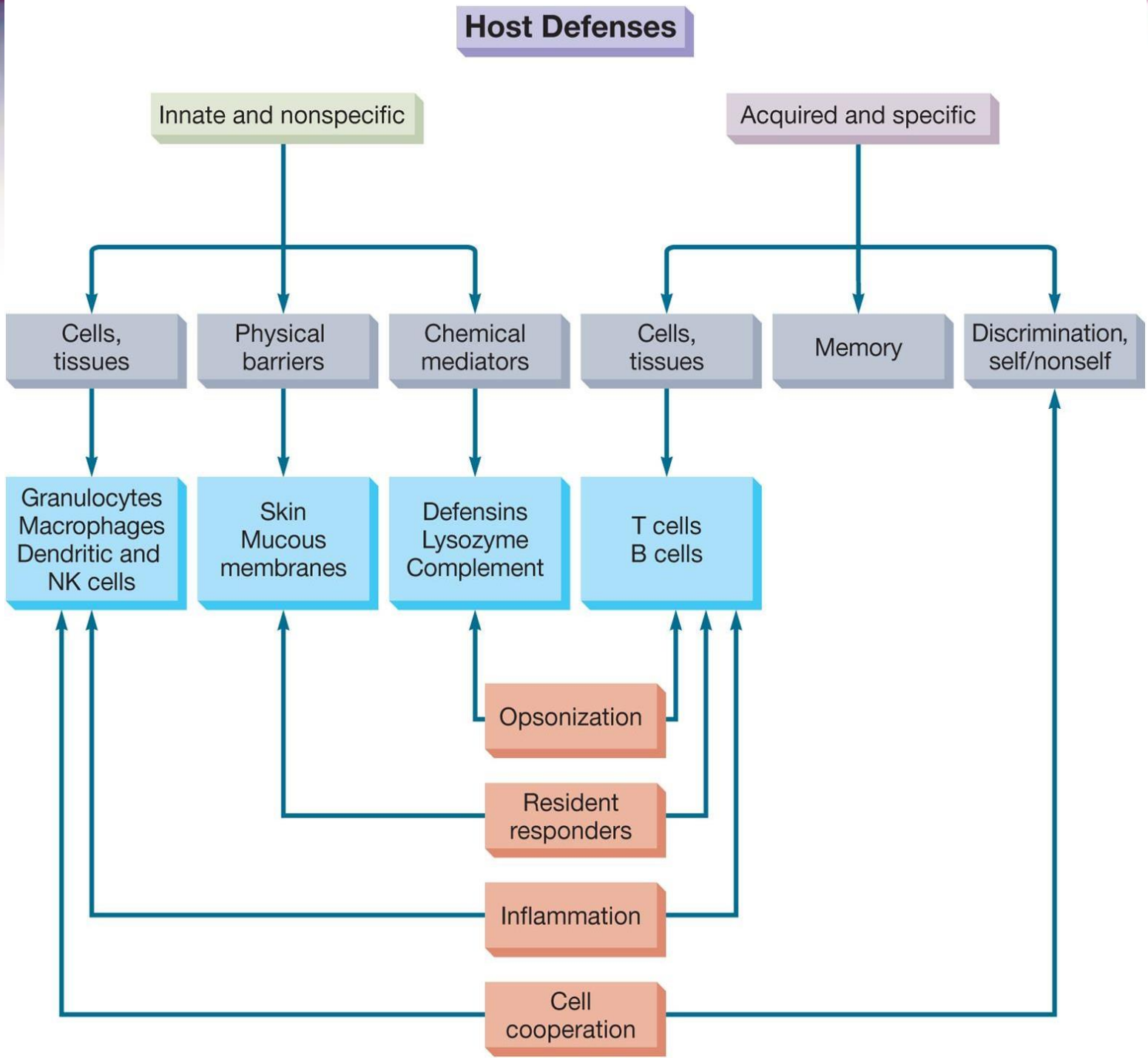
Immunity

- Nonspecific immune response
  - 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
  - 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
Acquired and specific
Cells, tissues
Physical barriers
Chemical mediators
Cells, tissues
Memory
Discrimination, self/nonself
Granulocytes Macrophages Dendritic and NK cells
Skin Mucous membranes
Defensins Lysozyme Complement
T cells B cells
Opsonization
Resident responders
Inflammation
Cell cooperation

Antigens

- Recognized as foreign
- Invoke immune responses
  - presence of antigen in body ultimately results in B cell activation → → production of antibodies
    - antibodies bind to specific antigens, inactivating or eliminating them
    - other immune cells also become activated
- Name comes from antibody generators

White Blood Cells of Innate and Adaptive Immunity

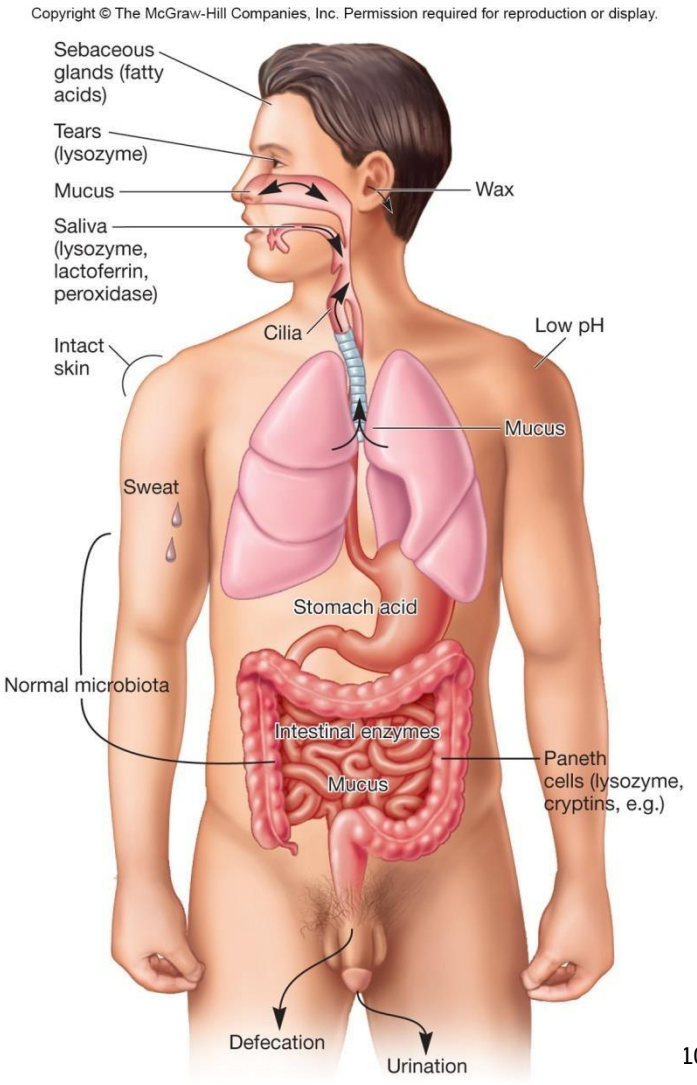
- White blood cells (WBCs) play a major role in the innate and specific responses
- Hematopoesis
  - development of white blood cells in bone marrow of mammals
    - WBCs that mature prior to leaving bone marrow, e.g., macrophages and dendritic cells, become part of innate immune system and will respond 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

33.2 Physical and Mechanical Barrier Defenses of Innate Resistance

1. Identify the barriers that help prevent microbial invasion of the host
2. Explain how the physical and chemical barriers function to prevent microbial invasion of the host
3. Relate host anatomy and secretions to the success of innate resistance strategies

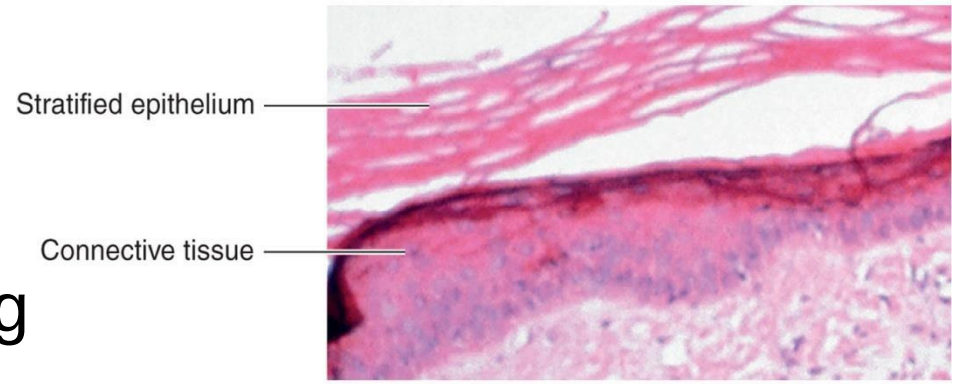
Physical Barriers in Nonspecific (Innate) Resistance

- 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

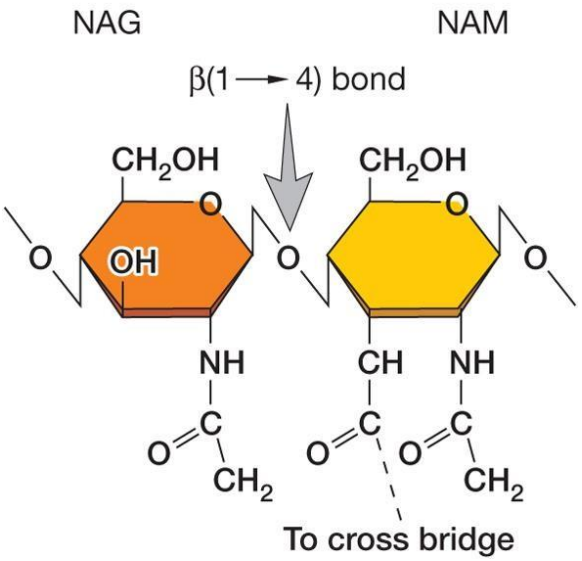
- Strong mechanical barrier to microbial invasion
  - keratin produced by keratinocytes in outer layer
- Inhospitable environment for microbes
  - attached organisms removed by shedding of outer skin cells
  - pH is slightly acidic
  - high NaCl concentration
  - subject to periodic drying



CDC/Dr. Steve Kraus

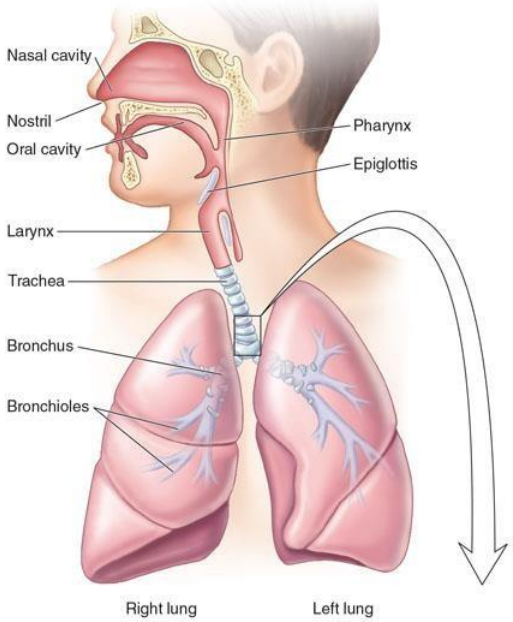
Mucous Membranes

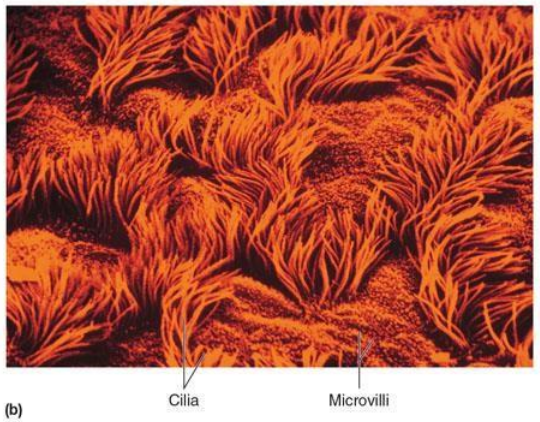
- Form protective covering that resists penetration and traps many microbes
- Are often bathed in antimicrobial secretions which contain a variety of antimicrobial substances
  - lysozyme
    - hydrolyzes bond connecting sugars in peptidoglycan
  - lactoferrin
    - secreted by activated macro-phages and PMNs
    - 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

- Mucus secreting epithelial membrane
- Flushing action of tears
- Lysozyme, lactoferrin, and secretory IgA in tears

33.3 Chemical Mediators in Innate Resistance

1. Discuss host mediators that have antimicrobial actions
2. Describe in general terms the activation of the host complement system and its three outcomes
3. List the four categories of cytokines and discuss their major functions
4. Correlate host protection from microbial invasion with specific mediators

Chemical Mediators in Nonspecific (Innate) Resistance

- Many already noted (e.g., gastric juices, lysozyme, 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
  - highly conserved through evolution
  - 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

Cationic Peptides…

- 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

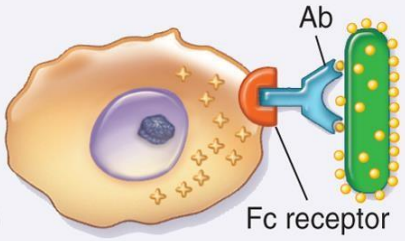
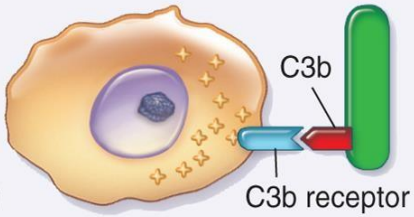
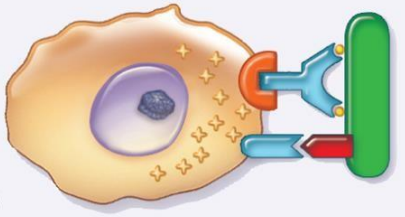
- Peptides produced by normal microbiota
- Lethal to related species
- Produced by Gram-positive and Gram-negative cells
- e.g., colicins produced by *E. coli*
- e.g., lantibiotics produced by Gram-positive bacteria

The Complement System

- Composed of >30 serum proteins
- Augments (or “complements”) the antibacterial activity of antibody
- Three major activities:
  - defending against bacterial infections
  - bridging innate and adaptive immunity
  - disposing of wastes

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

Phagocytic cell	Degree of binding	Opsonin
	+	Antibody
	+ +	Complement C3b
	+ + + +	Antibody and complement C3b

Other Functions of Complement Proteins

- 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

33.4 Cells, Tissues, and Organs of the Immune System

1. Recognize the different types of leukocytes involved with innate resistance
2. Outline the leukocyte response to microbial invasion
3. Integrate leukocyte distribution within the host with host resistance
4. Differentiate between primary and secondary lymphoid organs and tissues in terms of structure and function
5. Predict connections between innate host resistance and specific immune responses

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

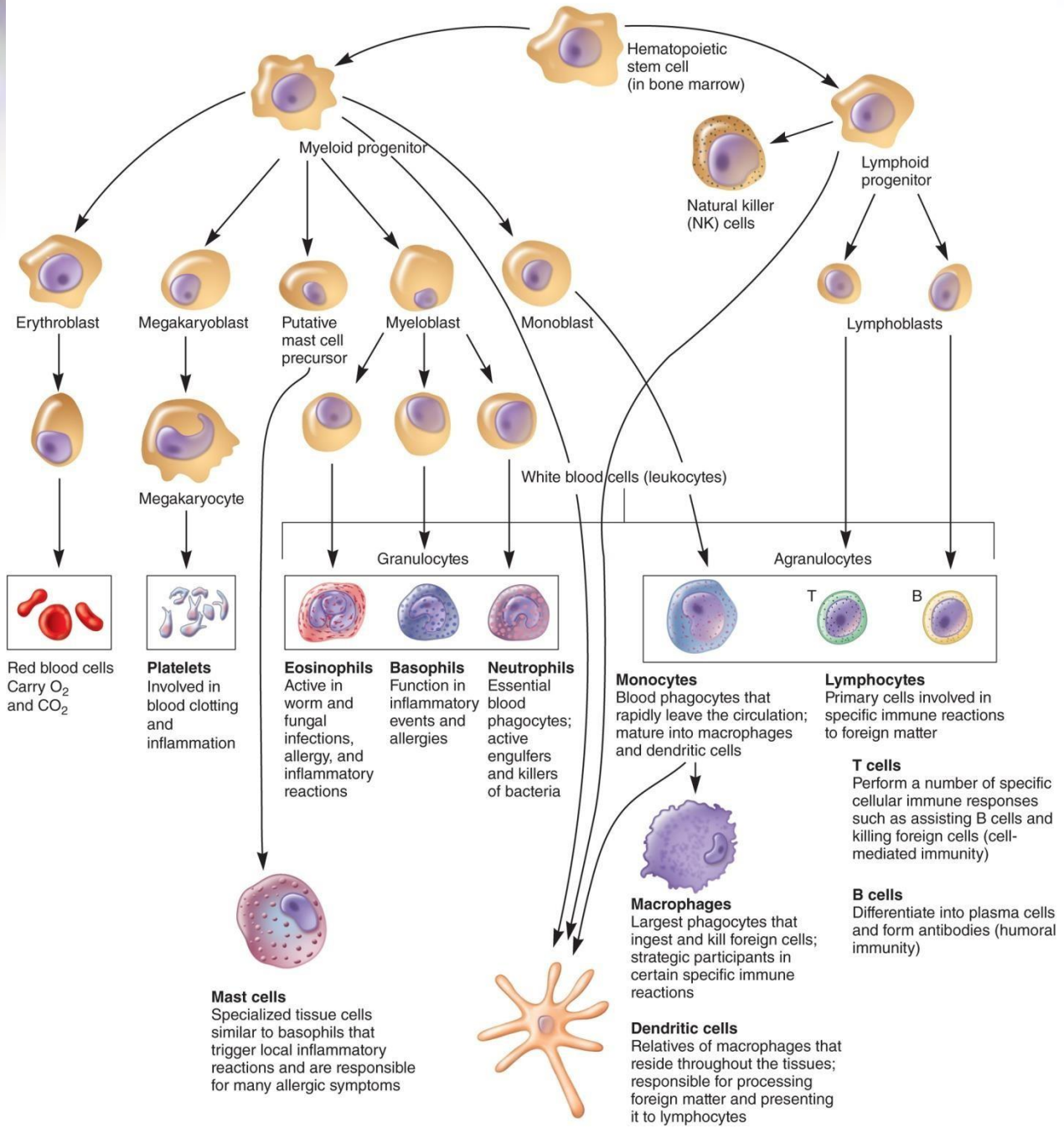


Table 33.4 Normal Adult Blood Count

Cell Type	Cells/mm^3	Percent WBC
Red blood cells	5,000,000	
Platelets	250,000	
White blood cells	7,400	100
Neutrophils	4,320	60
Lymphocytes	2,160	30
Monocytes	430	6
Eosinophils	215	3
Basophils	70	1

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

- Stain bluish-black with basic dyes
- Nonphagocytic
- Release vasoactive mediators
  - e.g., histamine, prostaglandins, serotonin, and leukotrienes from granules
- Play important role in development of allergies and hypersensitivities

Eosinophils

- Stain red with acidic dyes
- Defend against protozoan and helminth parasites
- Release cationic proteins and reactive oxygen metabolites
- May play a role in allergic reactions

Neutrophils

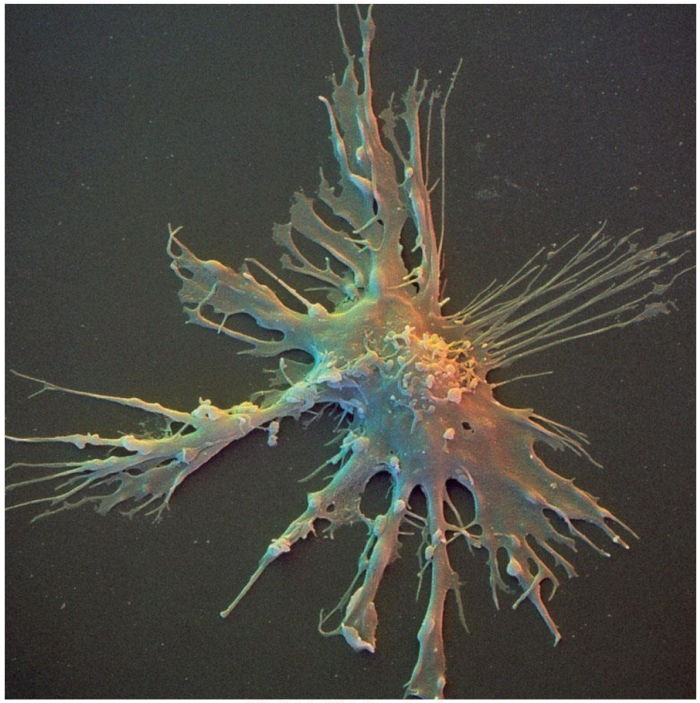
- Stain at neutral pH
- Highly phagocytic
- Circulate in blood then migrate to sites of tissue damage
- Kill ingested microbes with lytic enzymes and reactive oxygen metabolites contained in primary and secondary granules

Monocytes and Macrophages

- Highly phagocytic cells
- Monocytes
  - are mononuclear phagocytic leukocytes
  - 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)
    - bind pathogen associated molecular patterns (PAMPs)
  - named according to tissue in which they reside

Dendritic Cells

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



Lymphocytes

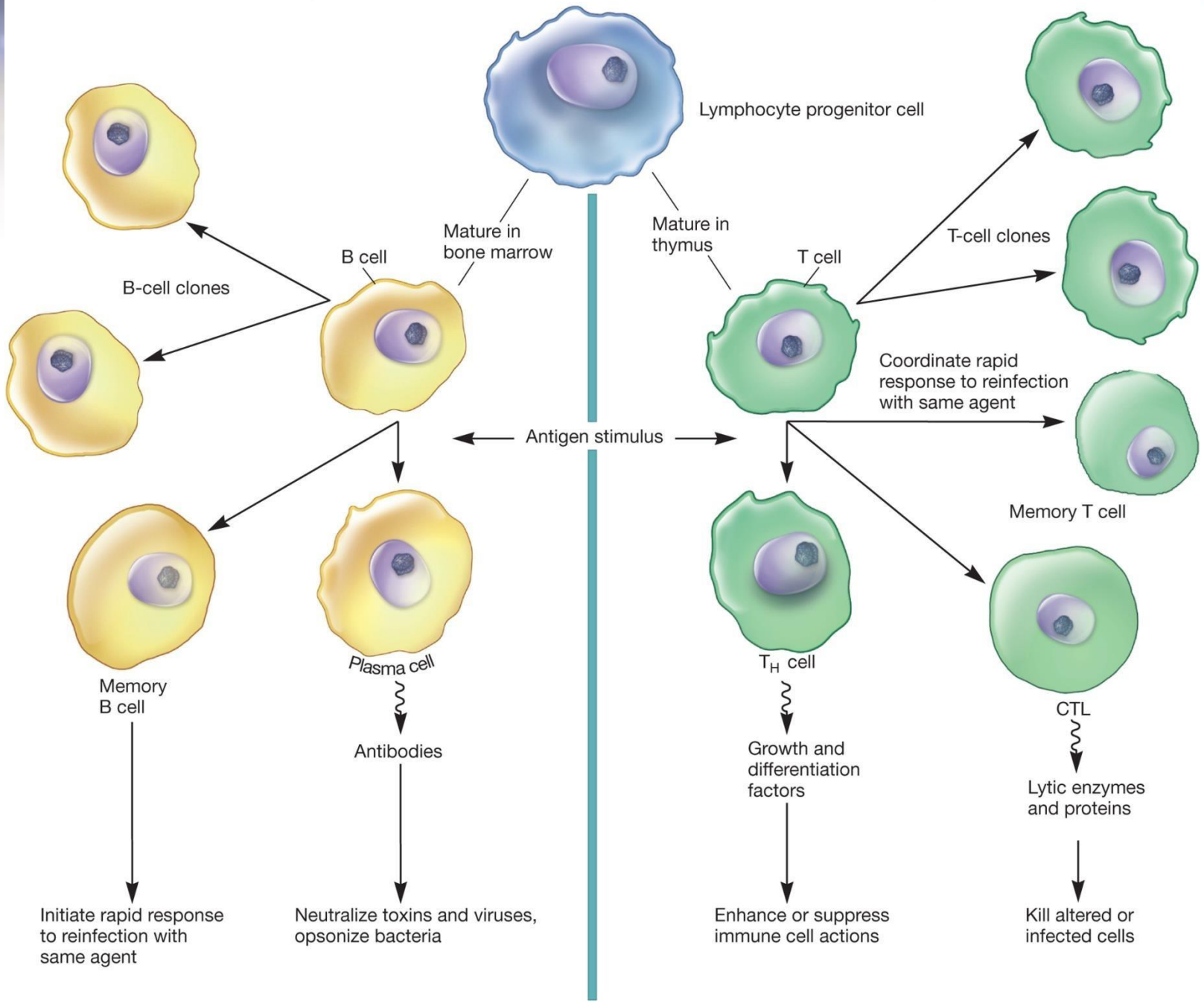
- Major cells of the immune system
- Major populations include T cells, B cells, and natural killer (NK) cells
- B and T lymphocytes differentiate in bone marrow from stem cells
  - are only activated by binding of specific antigen onto lymphocyte surface receptors
  - after activation replication continues 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

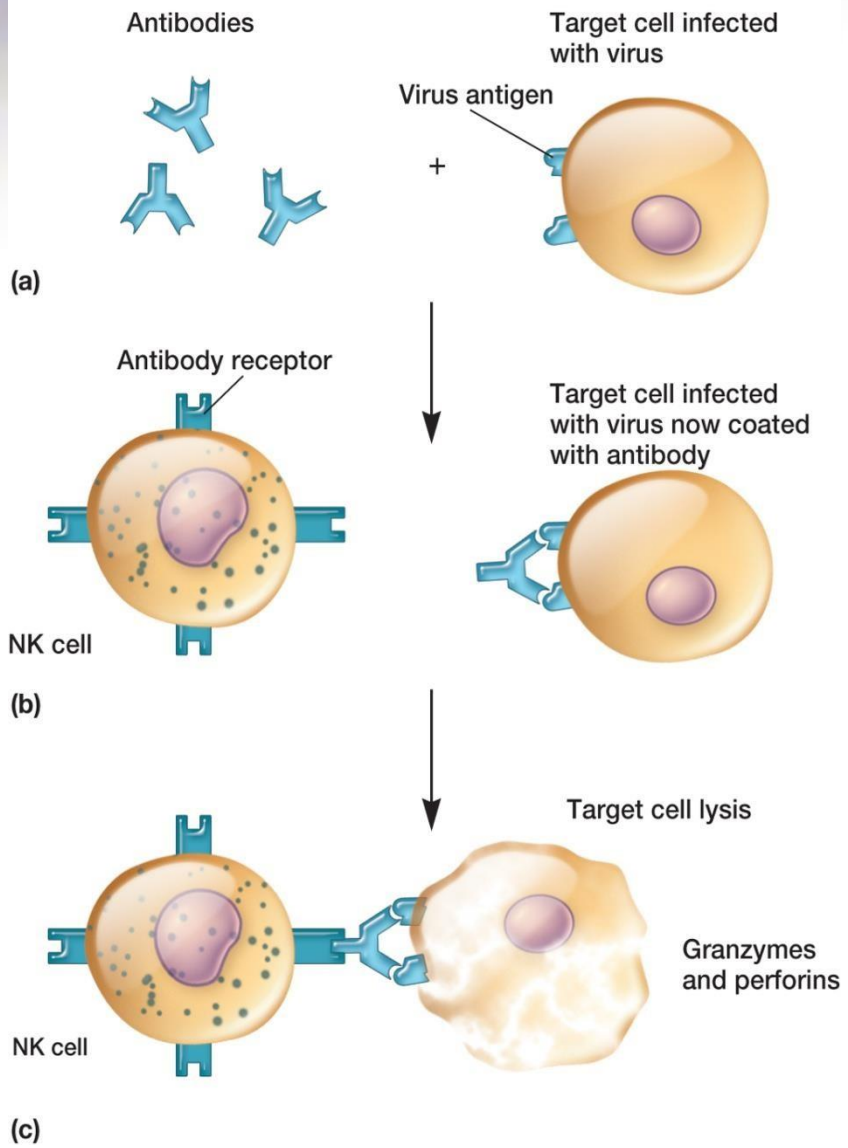
T Lymphocytes (T cells)

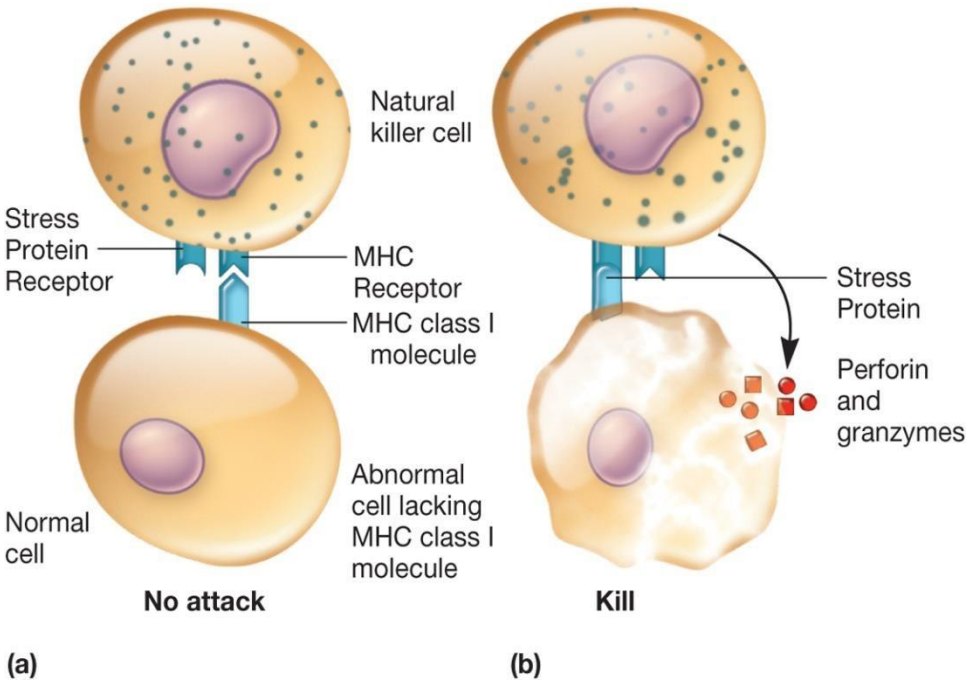
- Mature in thymus
- Can remain in thymus, circulate in blood, or reside in lymphoid tissue
- Like B cells, require antigen binding to surface receptors for activation and continuation of replication
- Activated T cells differentiate into helper T cells (TH) and cytotoxic lymphocytes (CTLs)
- Secrete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



Natural Killer (NK) Cells

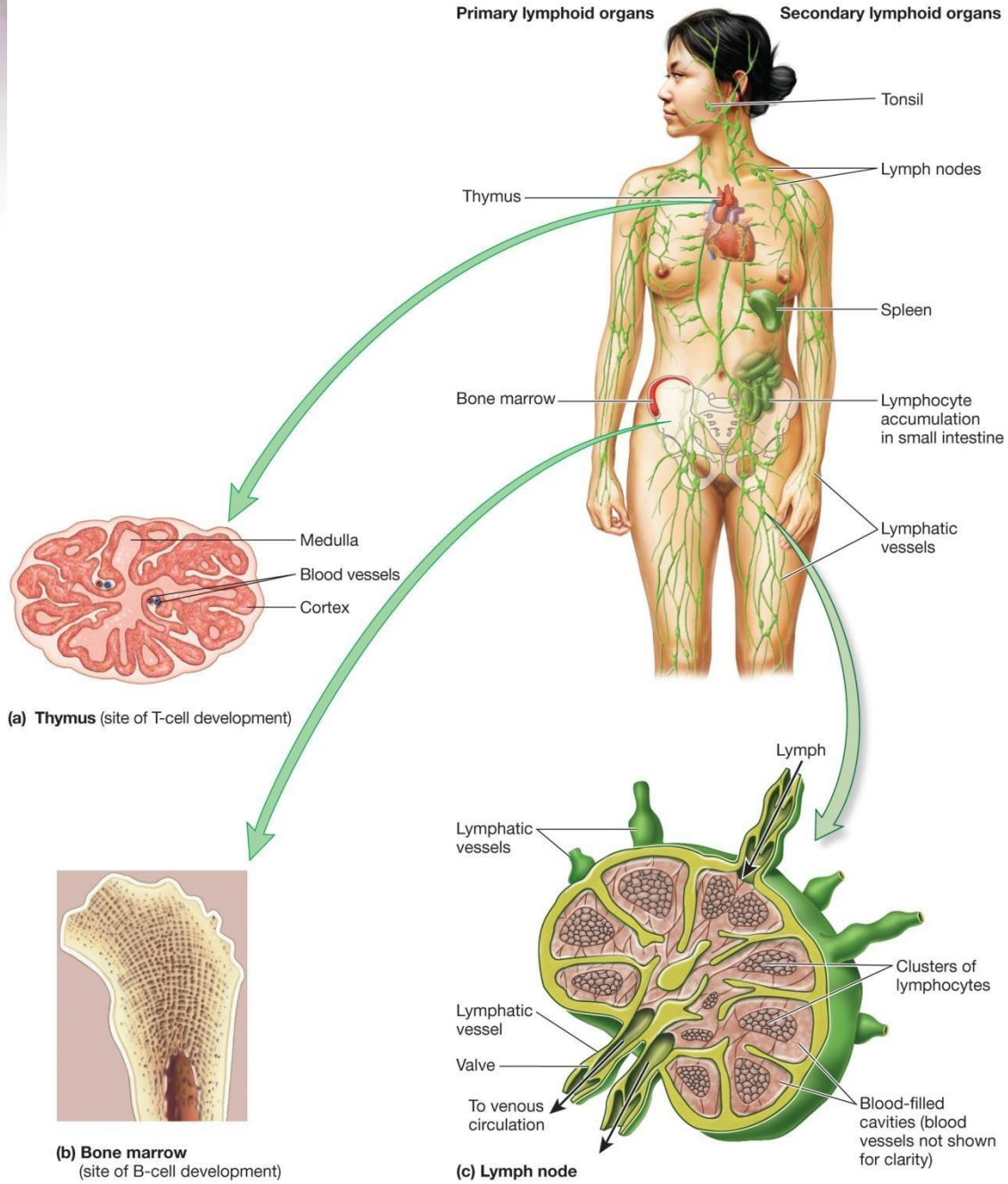
- Small population of large non-phagocytic granular lymphocytes
  - important role in innate immunity
  - kill malignant cells and cells infected with pathogens by releasing granzymes (cytotoxic enzymes)
- Two ways of recognizing target cells
  - bind to antibodies which coat infected or malignant cells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





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

Secondary Lymphoid Organs and Tissues

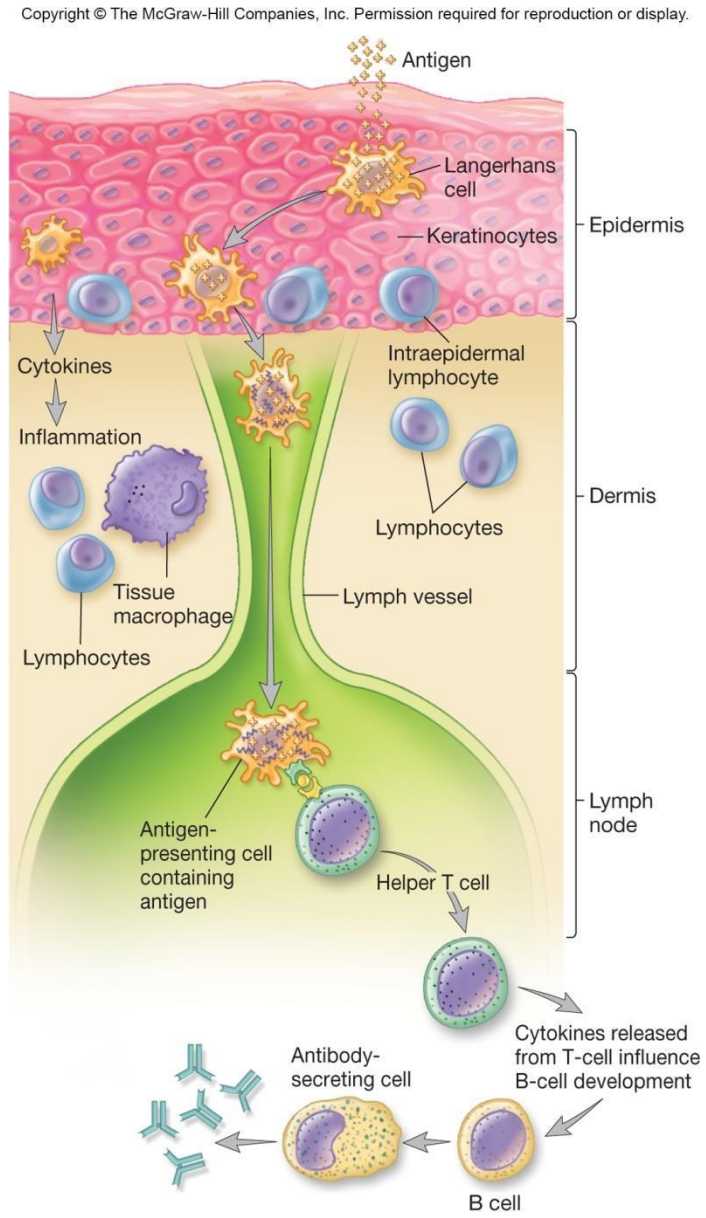
- Lymph nodes
  - most highly organized lymphoid tissue
  - filter lymph
  - microbes and antigens trapped and phagocytosed by macrophages and dendritic cells
  - B cells differentiate into memory and plasma cells within lymph nodes

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)

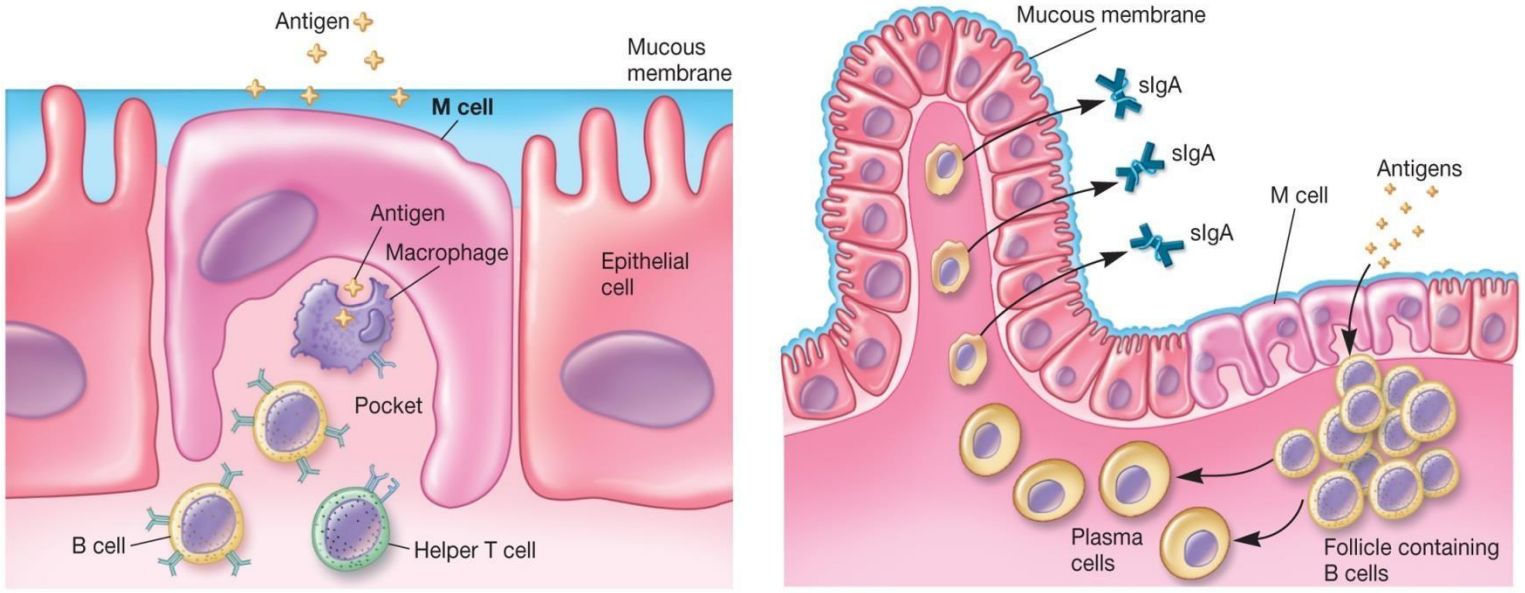
Skin Associated Lymphoid Tissue (SALT)

- 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



33.5 Phagocytosis

1. Explain the methods by which pathogens are recognized by phagocytes
2. Describe the process of autophagy and phagocytosis
3. Forecast how biochemical activities within the phagocyte result in pathogen destruction

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 Recognition

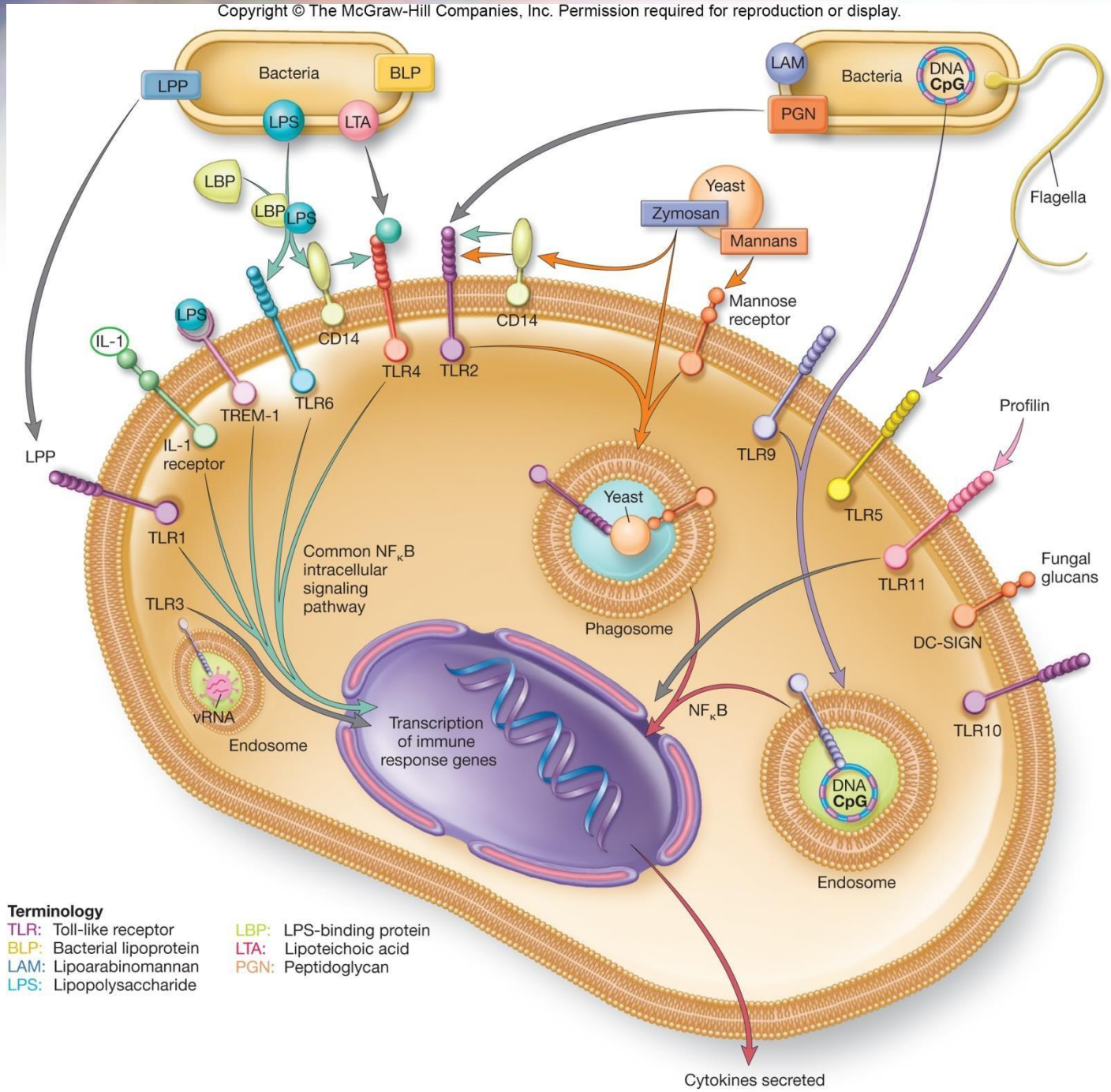
- Opsonin-independent mechanism
  - pathogen recognition
    - common pathogen components are non-specifically recognized to activate phagocytes
      - signaling mechanism involved
  - involves nonspecific/specific receptors on phagocytes
  - four main forms:
    - recognition by lectin-carbohydrate interactions
    - recognition by protein-protein interactions
    - recognition by hydrophobic interactions
    - detection of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs)

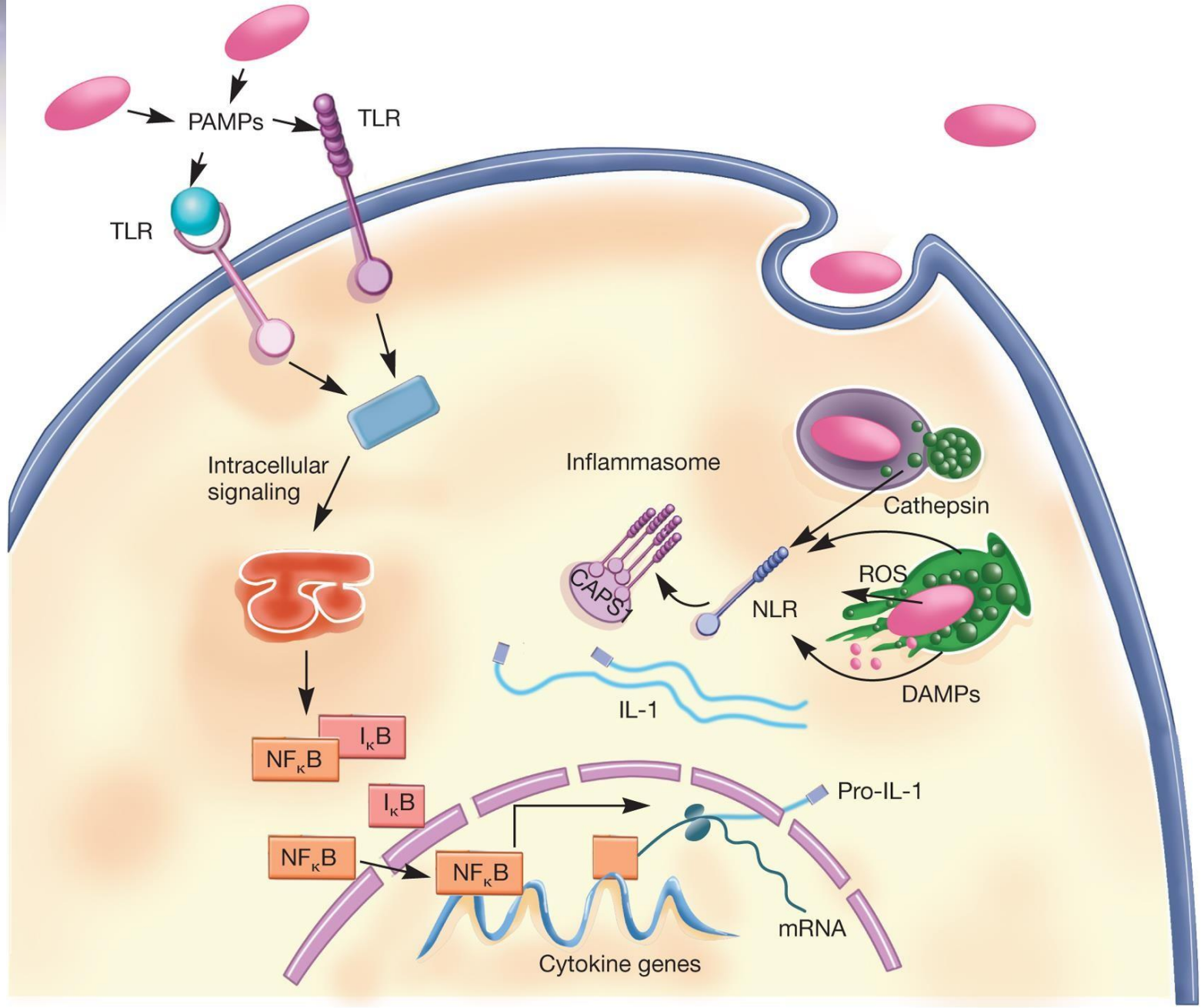
Pathogen-Associated Molecular Patterns (PAMPs)

- 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

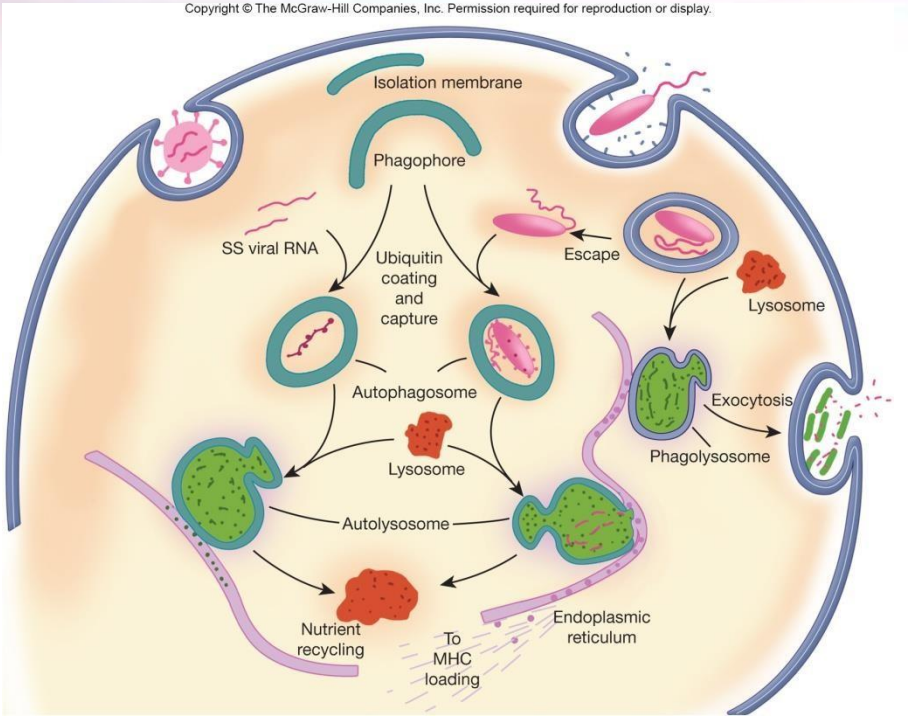
Toll-Like Receptors (TLRs)

- A class of PRRs that function exclusively as signaling receptors
- Recognize and bind unique PAMPs of viruses, bacteria, or fungi
  - the binding triggers an evolutionarily ancient signal and is communicated to the host cell nucleus which initiates the host response





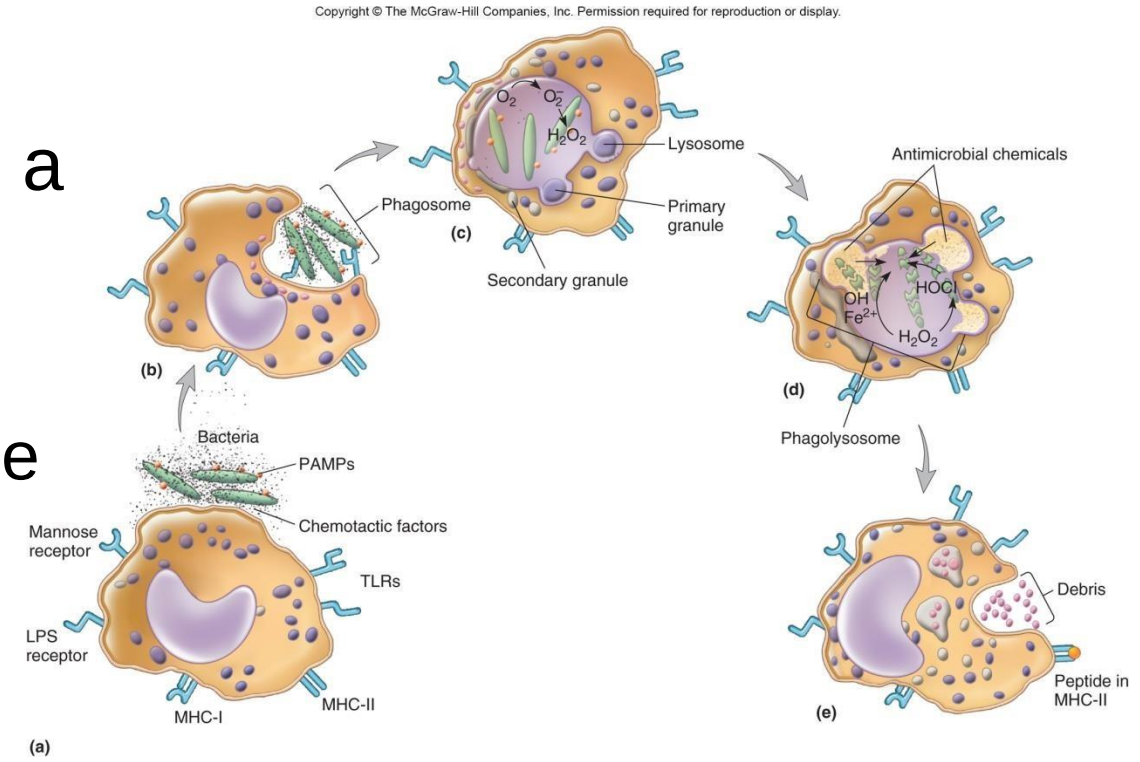
Intracellular digestion



- Autophagy
  - Highly conserved process
  - Tags internal microbes for destruction
    - Ubiquitin protein labels item
    - Phagophore (free-floating, open membrane) encircles item
    - Autophagosome is fused with lysosome to degrade contained items

Intracellular Digestion

- Once bound, microbes can be internalized and delivered to a lysosome to become a phagosome
  - respiratory burst reactions occur once phagosome forms
  - toxic oxygen products are produced which can kill invading microbes



Intracellular Digestion

Table 33.5 Formation of Reactive Oxygen Intermediates

Oxygen Intermediate	Reaction
Superoxide ($O_2^{-}\bullet$)	$NADPH + 2O_2 \xrightarrow{\text{NADPH oxidase}} 2O_2^{-}\bullet + H^+ + NADP^+$
Hydrogen peroxide (H_2O_2)	$2O_2^{-}\bullet + 2H^+ \xrightarrow{\text{Superoxide dismutase}} H_2O_2 + O_2$
Hypochlorous acid (HOCl)	$H_2O_2 + Cl^- \xrightarrow{\text{Myeloperoxidase}} HOCl + OH^+$
Singlet oxygen ($^1O_2$)	$ClO^- + H_2O_2 \xrightarrow{\text{Peroxidase}} {}^1O_2 + Cl^- + H_2O$
Hydroxyl radical ($\bullet OH^-$)	$O_2^{-}\bullet + H_2O_2 \xrightarrow{\text{Peroxidase}} 2\bullet OH^- + O_2$

- phagolysosome
- vacuole which results from fusion of phagosome with lysosome
  - presence of toxic chemicals
    - e.g., degradative enzymes
    - e.g., toxic reactive oxygen intermediates (ROIs)
    - e.g., reactive nitrogen intermediates (RNIs)

Exocytosis

- Process used by neutrophils to expel microbial fragments after they have been digested
- Phagolysosome unites with cell membrane
  - results in extracellular release of microbial fragments
- Macrophages and dendritic cells undergo process called antigen presentation
  - move fragments from phagolysosome to endoplasmic reticulum
  - peptide fragment components combine with glycoproteins, becoming part of cell membrane
    - peptides bound so they are ultimately presented outward from the cell

Antigen Presentation

- Important process because it allows wandering lymphocytes to become activated
- Links nonspecific and specific immune responses

33.6 Inflammation

1. Outline the sequence of innate host responses that result in inflammation
2. Distinguish acute and chronic inflammation in terms of the host responses involved in each
3. Construct a concept map relating host cells and processes that remove pathogens

Inflammation

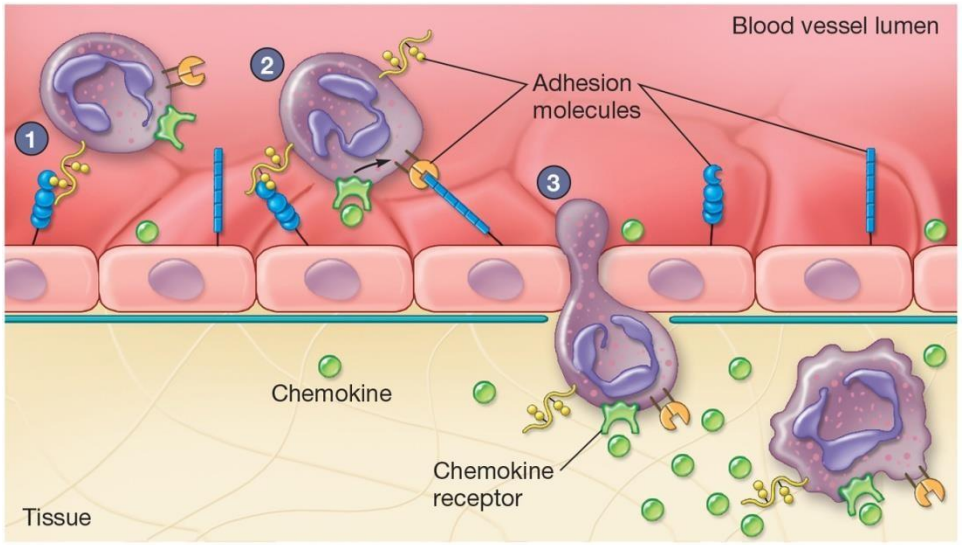
- Nonspecific response to tissue injury
  - can be caused by pathogen or physical trauma
  - acute inflammation is the immediate response of body to injury or cell death
- Cardinal signs
  - redness (rubor)
  - warmth (calor)
  - pain (dolor)
  - swelling (tumor)
  - altered function (functio laesa)

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



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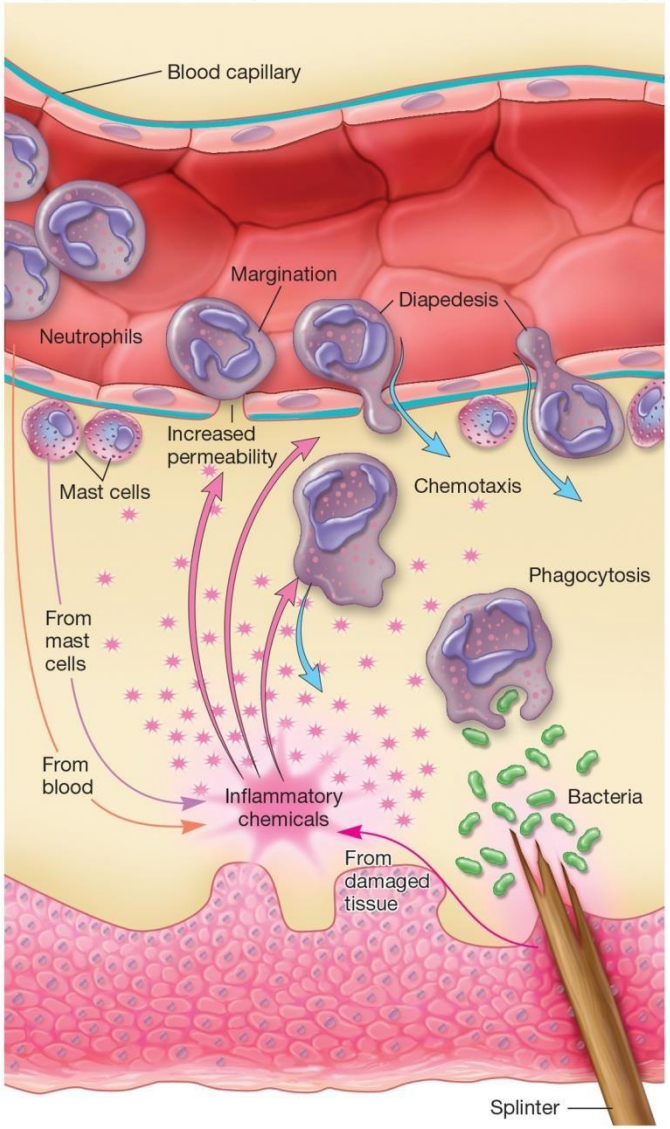
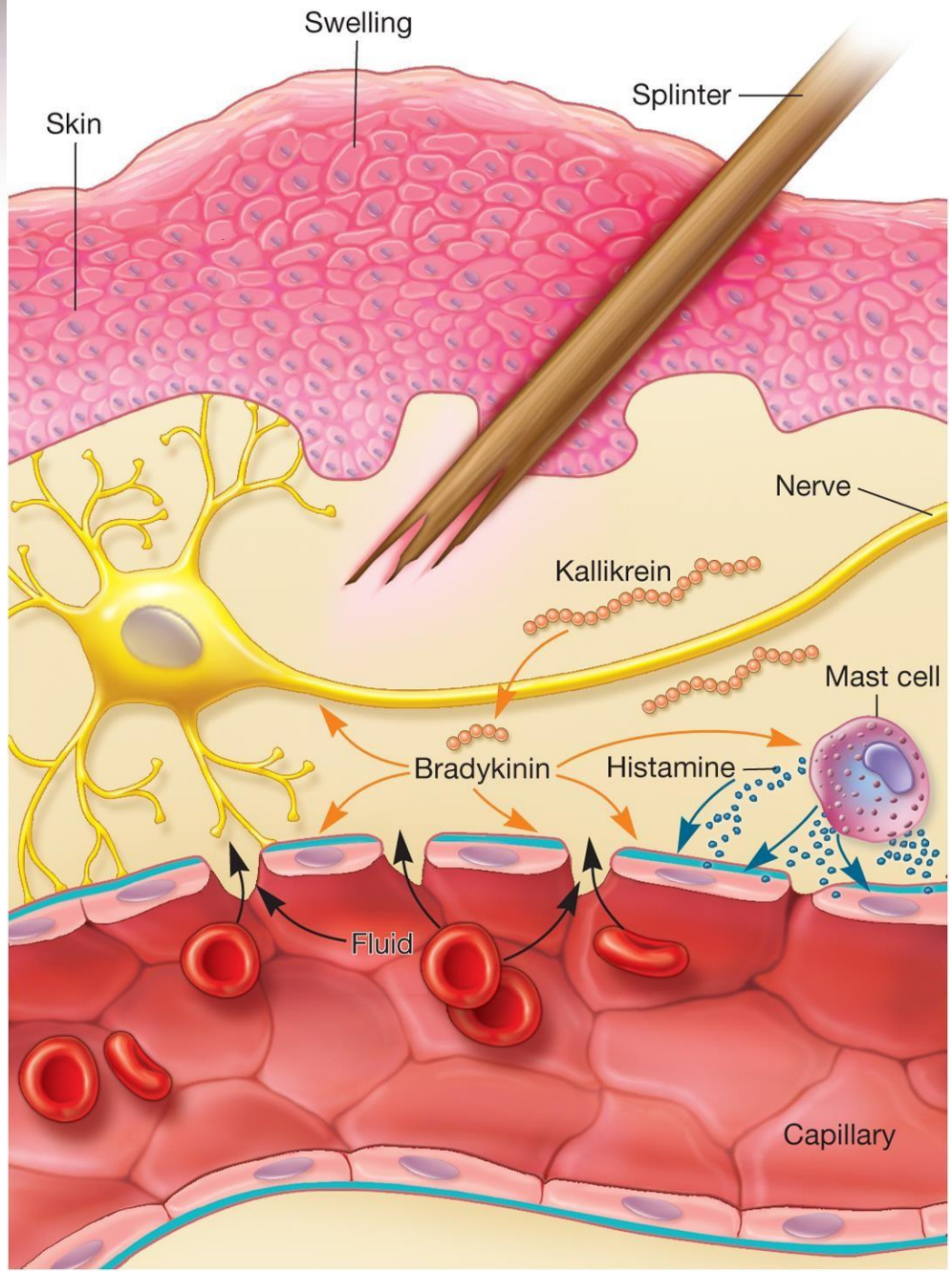


(a)

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