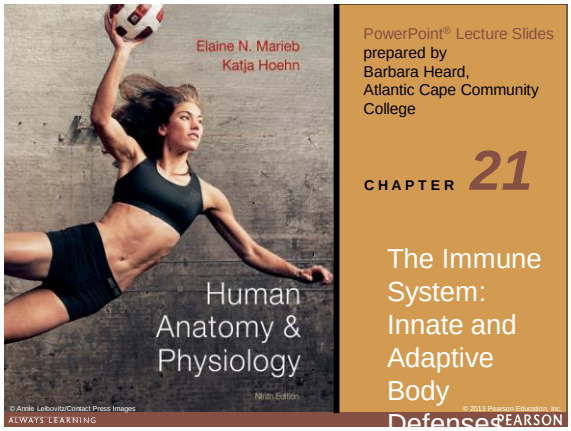

PowerPoint® Lecture Slides
prepared by
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CHAPTER 21

The Immune System: Innate and Adaptive Body Defenses

Immunity

- Resistance to disease
- Immune system
  - Two intrinsic systems
    - **Innate** (nonspecific) defense system
    - **Adaptive** (specific) defense system

Immune System

- Functional system rather than organ system
- Innate and adaptive defenses intertwined
- Release and recognize many of same defensive molecules
- Innate defenses do have specific pathways for certain substances
- Innate responses release proteins that alert cells of adaptive system to foreign molecules

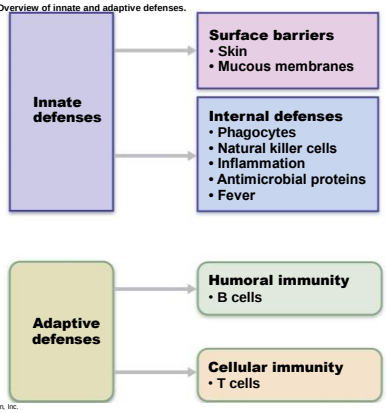
Immunity

- Innate defense system has two lines of defense
  - First - external body membranes (skin and mucosae)
  - Second - antimicrobial proteins, phagocytes, and other cells
    - Inhibit spread of invaders
    - Inflammation most important mechanism

Immunity

- Adaptive defense system
  - Third line of defense attacks *particular* foreign substances
    - Takes longer to react than innate system

Figure 21.1 Overview of innate and adaptive defenses.



Innate Defenses

- Surface barriers ward off invading pathogens
  - Skin, mucous membranes, and their secretions
    - Physical barrier to most microorganisms
    - Keratin resistant to weak acids and bases, bacterial enzymes, and toxins
    - Mucosae provide similar mechanical barriers

Surface Barriers

- Protective chemicals inhibit or destroy microorganisms
  - Acidity of skin and secretions – acid mantle – inhibits growth
  - Enzymes - lysozyme of saliva, respiratory mucus, and lacrimal fluid – kill many microorganisms
  - Defensins – antimicrobial peptides – inhibit growth
  - Other chemicals - lipids in sebum, dermcidin in sweat – toxic

Surface Barriers

- Respiratory system modifications
  - Mucus-coated hairs in nose
  - Cilia of upper respiratory tract sweep dust- and bacteria-laden mucus toward mouth
- Surface barriers breached by nicks or cuts - second line of defense must protect deeper tissues

Internal Defenses: Cells and Chemicals

- Necessary if microorganisms invade deeper tissues
  - **Phagocytes**
  - **Natural killer** (NK) **cells**
  - Antimicrobial proteins (interferons and complement proteins)
  - Fever
  - **Inflammatory response** (macrophages, mast cells, WBCs, and inflammatory chemicals)

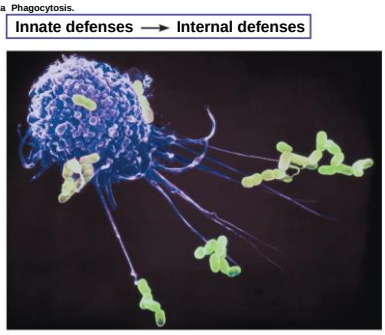
Phagocytes

- **Neutrophils** most abundant but die fighting
  - Become phagocytic on exposure to infectious material
- **Macrophages** develop from monocytes – chief phagocytic cells – robust cells
  - Free macrophages wander through tissue spaces, e.g., alveolar macrophages
  - Fixed macrophages permanent residents of some organs; e.g., stellate macrophages (liver) and microglia (brain)

Mechanism of Phagocytosis

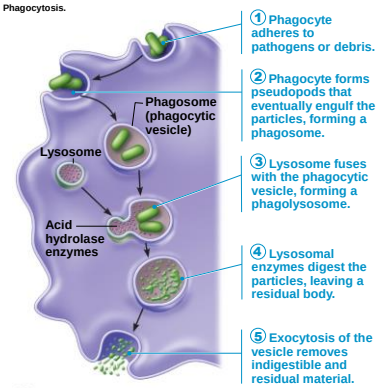
- Phagocyte must adhere to particle
  - Some microorganisms evade adherence with capsule
    - **Opsonization** marks pathogens—coating by complement proteins or antibodies
- Cytoplasmic extensions bind to and engulf particle in vesicle called **phagosome**
- Phagosome fuses with lysosome → **phagolysosome**

Figure 21.2a Phagocytosis.



(a) A macrophage (purple) uses its cytoplasmic extensions to pull rod-shaped bacteria (green) toward it. Scanning electron micrograph (4800x).

Figure 21.2b Phagocytosis.



(b) Events of phagocytosis.

Mechanism of Phagocytosis

- Pathogens killed by acidifying and digesting with lysosomal enzymes
- Helper T cells cause release of enzymes of **respiratory burst,** which kill pathogens resistant to lysosomal enzymes by
  - Releasing cell-killing free radicals
  - Producing oxidizing chemicals (e.g., H_2O_2)
  - Increasing pH and osmolarity of phagolysosome
- Defensins (in neutrophils) pierce membrane

Natural Killer (NK) Cells

- Nonphagocytic large granular lymphocytes
- Attack cells that lack "self" cell-surface receptors
  - Induce **apoptosis** in cancer cells and virus-infected cells
- Secrete potent chemicals that enhance inflammatory response

Inflammatory Response

- Triggered whenever body tissues injured
- Prevents spread of damaging agents
- Disposes of cell debris and pathogens
- Alerts adaptive immune system
- Sets the stage for repair

Inflammatory Response

- Cardinal signs of acute inflammation:
  1. Redness
  2. Heat
  3. Swelling
  4. Pain

  (Sometimes 5. Impairment of function)

Inflammatory Response

- Begins with chemicals released into ECF by injured tissues, immune cells, blood proteins
- Macrophages and epithelial cells of boundary tissues bear Toll-like receptors (TLRs)
- 11 types of TLRs recognize specific classes of infecting microbes
- Activated TLRs trigger release of cytokines that promote inflammation

Inflammatory Response

- Inflammatory mediators
  - Kinins, prostaglandins (PGs), and complement
    - Dilate local arterioles (**hyperemia**)
      - Causes redness and heat of inflamed region
    - Make capillaries leaky
    - Many attract leukocytes to area
    - Some have inflammatory roles

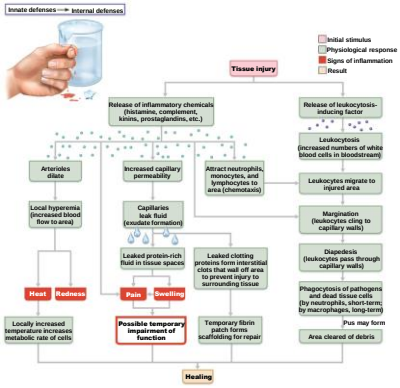
Inflammatory Response: Edema

- ↑ Capillary permeability → **exudate** to tissues
  - Fluid containing clotting factors and antibodies
  - Causes local swelling (**edema**)
  - Swelling pushes on nerve endings → pain
    - Pain also from bacterial toxins, prostaglandins, and kinins
  - Moves foreign material into lymphatic vessels
  - Delivers clotting proteins and complement

Inflammatory Response

- Clotting factors form fibrin mesh
  - Scaffold for repair
  - Isolates injured area so invaders cannot spread

Figure 21.3 Inflammation: flowchart of events.



Phagocyte Mobilization

- Neutrophils lead; macrophages follow
  - As attack continues, monocytes arrive
    - 12 hours after leaving bloodstream → macrophages
    - These "late-arrivers" replace dying neutrophils and remain for clean up prior to repair
- If inflammation due to pathogens, complement activated; adaptive immunity elements arrive

Phagocyte Mobilization

- Steps for phagocyte mobilization
  1. **Leukocytosis:** release of neutrophils from bone marrow in response to **leukocytosis-inducing factors** from injured cells
  2. **Margination:** neutrophils cling to walls of capillaries in inflamed area in response to CAMs
  3. **Diapedesis** of neutrophils
  4. **Chemotaxis:** inflammatory chemicals (**chemotactic agent**) promote positive chemotaxis of neutrophils

Figure 21.4 Phagocyte mobilization.

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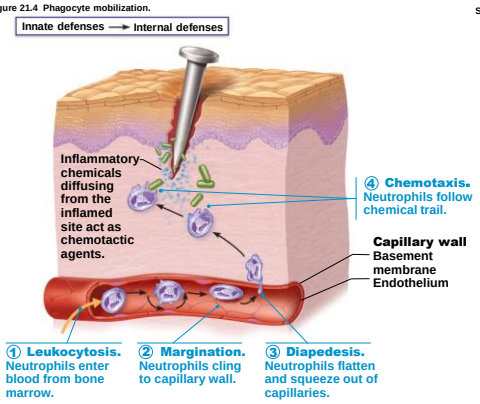


Antimicrobial Proteins

- Include interferons and complement proteins
- Some attack microorganisms directly
- Some hinder microorganisms' ability to reproduce

Interferons

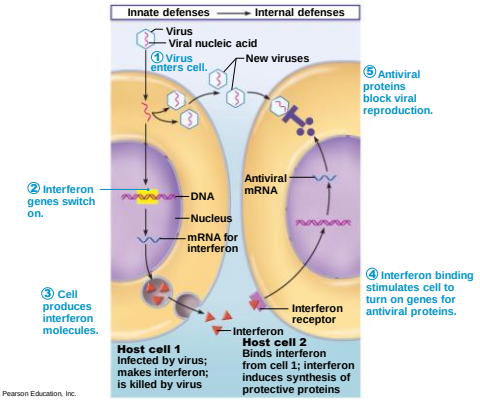
- Family of immune modulating proteins
  - Have slightly different physiological effects
- Viral-infected cells secrete IFNs (e.g., IFN alpha and beta) to "warn" neighboring cells
  - IFNs enter neighboring cells → produce proteins that block viral reproduction and degrade viral RNA
  - IFN alpha and beta also activate NK cells

Interferons

- IFN gamma (immune interferon)
  - Secreted by lymphocytes
  - Widespread immune mobilizing effects
  - Activates macrophages
- Since IFNs activate NK cells and macrophages, indirectly & directly fight cancer. HOW- Neighboring cells make anitiviral when IF stimulated ..after formed IF can activate NK cells to attack cancer cells .
- Artificial IFNs used to treat hepatitis C, genital warts, multiple sclerosis, hairy cell leukemia

Figure 21.5 The interferon mechanism against viruses.

Slide 1



Complement System (Complement)

- ~20 blood proteins that circulate in inactive form
- Include C1–C9, factors B, D, and P, and regulatory proteins
- Major mechanism for destroying foreign substances
- Our cells contain complement activation inhibitors

Complement

- Unleashes inflammatory chemicals that amplify all aspects of inflammatory response
- Kills bacteria and certain other cell types by cell lysis
- Enhances both innate and adaptive defenses

Complement Activation

- Three pathways to activation
  - **Classical pathway**
    - Antibodies bind to invading organisms and to complement components
    - Called complement fixation
    - First step in activation; more details later

Complement

- **Lectin pathway**
  - **Lectins** - produced by innate system to recognize foreign invaders
  - When bound to foreign invaders can also bind and activate complement
- **Alternative pathway**
  - Activated spontaneously, lack of inhibitors on microorganism's surface allows process to proceed

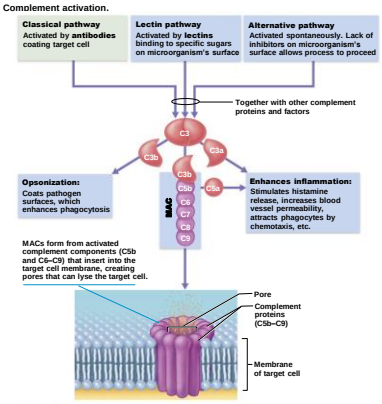
Complement Activation

- Each pathway involves activation of proteins in an orderly sequence
- Each step catalyzes the next
- Each pathway converges on C3, which cleaves into C3a and C3b
- Common terminal pathway initiated that
  - Enhances inflammation, promotes phagocytosis, causes cell lysis

Complement Activation

- Cell lysis begins when
  - C3b binds to target cell → insertion of complement proteins called **membrane attack complex** (MAC) into cell's membrane
  - MAC forms and stabilizes hole in membrane → influx of water → lysis of cell
- C3b also causes opsonization
- C3a and other cleavage products amplify inflammation
  - Stimulate mast cells and basophils to release histamine
  - Attract neutrophils and other inflammatory cells

Figure 21.6 Complement activation.



Fever

- Abnormally high body temperature
- Systemic response to invading microorganisms
- Leukocytes and macrophages exposed to foreign substances secrete **pyrogens**
- Pyrogens act on body's thermostat in hypothalamus, raising body temperature

Fever

- Benefits of moderate fever
  - Causes liver and spleen to sequester iron and zinc (needed by microorganisms)
  - Increases metabolic rate → faster repair

Adaptive Defenses

- Adaptive immune (specific defense) system
  - Protects against infectious agents and abnormal body cells
  - Amplifies inflammatory response
  - Activates complement
  - Must be primed by initial exposure to specific foreign substance
    - Priming takes time

Adaptive Defenses

- **Specific** – recognizes and targets specific antigens
- **Systemic** – not restricted to initial site
- Have **memory** – stronger attacks to "known" antigens
- Two separate, overlapping arms
  - Humoral (antibody-mediated) immunity
  - Cellular (cell-mediated) immunity

Humoral Immunity

- Antibodies, produced by lymphocytes, circulating freely in body fluids
- Bind temporarily to target cell
  - Temporarily inactivate
  - Mark for destruction by phagocytes or complement
- *Humoral immunity has extracellular targets*

Cellular Immunity

- Lymphocytes act against target cell
  - Directly – by killing infected cells
  - Indirectly – by releasing chemicals that enhance inflammatory response; or activating other lymphocytes or macrophages
- *Cellular immunity has cellular targets*

Antigens

- Substances that can mobilize adaptive defenses and provoke an immune response
- Targets of all adaptive immune responses
- Most are large, complex molecules not normally found in body (nonself)

Complete Antigens

- Important functional properties
  - **Immunogenicity:** ability to stimulate proliferation of specific lymphocytes
  - **Reactivity:** ability to react with activated lymphocytes and antibodies released by immunogenic reactions
- Examples: foreign protein, polysaccharides, lipids, and nucleic acids

Haptens (Incomplete Antigens)

- Small molecules (**haptens**) not immunogenic by themselves
  - E.g., peptides, nucleotides, some hormones
- May be immunogenic if attached to body proteins and combination is marked foreign
- Cause immune system to mount harmful attack
- Examples: poison ivy, animal dander, detergents, and cosmetics

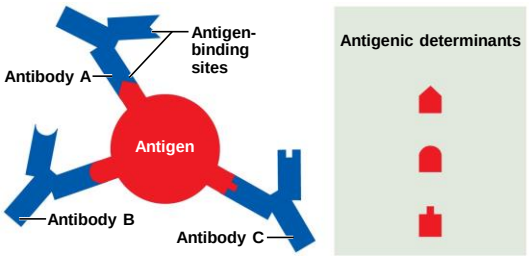
Antigenic Determinants

- Only certain parts (**antigenic determinants**) of entire antigen are immunogenic
- Antibodies and lymphocyte receptors bind to them as enzyme binds substrate

Antigenic Determinants

- Most naturally occurring antigens have numerous antigenic determinants that
  - Mobilize several different lymphocyte populations
  - Form different kinds of antibodies against them
- Large, chemically simple molecules (e.g., plastics) have little or no immunogenicity

Figure 21.7 Most antigens have several different antigenic determinants.



Self-antigens: MHC Proteins

- Protein molecules (**self-antigens**) on surface of cells not antigenic to self but antigenic to others in transfusions or grafts
- Example: MHC glycoproteins
  - Coded by genes of major histocompatibility complex (MHC) and unique to individual
  - Have groove holding self- or foreign antigen
    - T lymphocytes can only recognize antigens that are presented on MHC proteins

Cells of the Adaptive Immune System

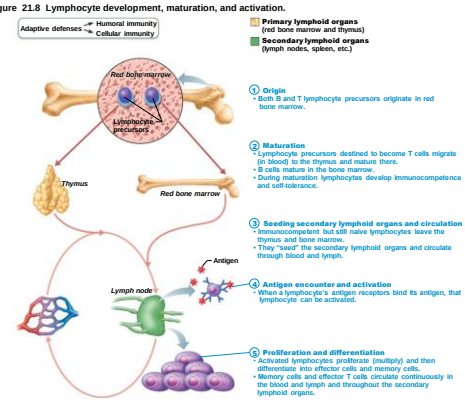
- Three types of cells
  - Two types of lymphocytes
    - B lymphocytes (B cells)—humoral immunity
    - T lymphocytes (T cells)—cellular immunity
  - Antigen-presenting cells (APCs)
    - Do not respond to specific antigens
    - Play essential auxiliary roles in immunity

Lymphocyte Development, Maturation, and Activation

- Five general steps
  - **Origin** – all originate in red bone marrow
  - **Maturation**
  - **Seeding secondary lymphoid organs and circulation**
  - **Antigen encounter and activation**
  - **Proliferation and differentiation**

Figure 21.8 Lymphocyte development, maturation, and activation.

Slide 1



Maturation

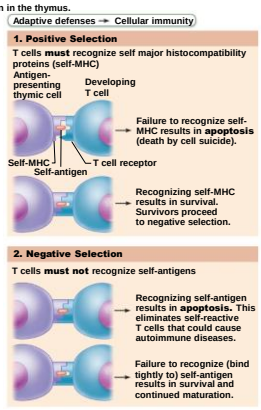
- "Educated" to become mature; B cells in bone marrow, T cells in thymus
  - **Immunocompetence** – lymphocyte can recognize one specific antigen by binding to it
    - B or T cells display only one unique type of antigen receptor on surface when achieve maturity – bind only one antigen
  - **Self-tolerance**
    - Lymphocytes unresponsive to own antigens

- START THURSDAY

T cells

- T cells mature in thymus under negative and positive selection pressures ("tests")
  - Positive selection
    - Selects T cells capable of recognizing self-MHC proteins (MHC restriction); failures destroyed by apoptosis
  - Negative selection
    - Prompts apoptosis of T cells that bind to self-antigens displayed by self-MHC
    - Ensures self-tolerance

Figure 21.9 T cell education in the thymus.



B cells

- B cells mature in red bone marrow
- Positively selected if successfully make antigen receptors
- Those that are self-reactive
  - Eliminated by apoptosis (clonal deletion)

Antigen Encounter and Activation

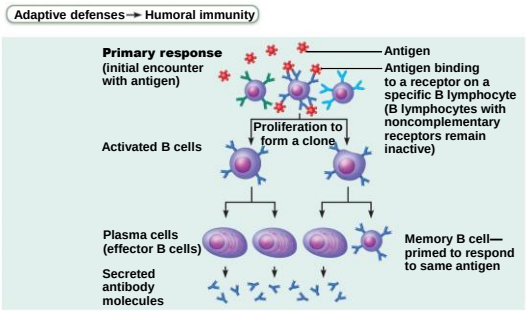
- **Clonal selection**
  - Naive lymphocyte's first encounter with antigen → selected for further development
  - If correct signals present, lymphocyte will complete its differentiation

Table 21.3 Overview of B and T Lymphocytes

Table 21.3 Overview of B and T Lymphocytes

	B LYMPHOCYTES	T LYMPHOCYTES
Type of immune response	Humoral	Cellular
Antibody secretion	Yes	No
Primary targets	Extracellular pathogens (e.g., bacteria, fungi, parasites, some viruses in extracellular fluid)	Intracellular pathogens (e.g., virus-infected cells) and cancer cells
Site of origin	Red bone marrow	Red bone marrow
Site of maturation	Red bone marrow	Thymus
Effector cells	Plasma cells	Cytotoxic T (T_C) cells Helper T (T_H) cells Regulatory T (T_{Reg}) cells
Memory cell formation	Yes	Yes

Figure 21.11a Clonal selection of a B cell.



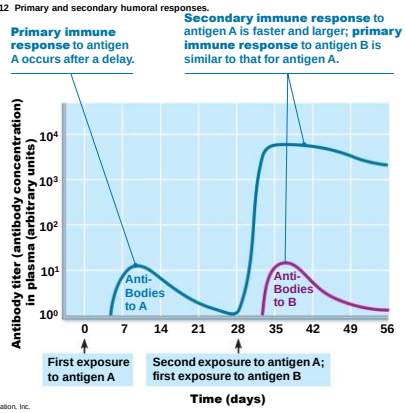
Immunological Memory

- **Primary immune response**
  - Cell proliferation and differentiation upon first antigen exposure
  - Lag period: three to six days
  - Peak levels of plasma antibody are reached in 10 days
  - Antibody levels then decline

Immunological Memory

- **Secondary immune response**
  - Re-exposure to same antigen gives faster, more prolonged, more effective response
    - Sensitized memory cells respond within hours
    - Antibody levels peak in two to three days at much higher levels
    - Antibodies bind with greater affinity
    - Antibody level can remain high for weeks to months

Figure 21.12 Primary and secondary humoral responses.



Active Humoral Immunity

- When B cells encounter antigens and produce specific antibodies against them
- Two types of active humoral immunity:
  - **Naturally acquired**—response to bacterial or viral infection
  - **Artificially acquired**—response to vaccine of dead or attenuated pathogens

Active Humoral Immunity

- Vaccines
  - Most of dead or attenuated pathogens
  - Spare us symptoms of primary response
  - Provide antigenic determinants that are immunogenic and reactive

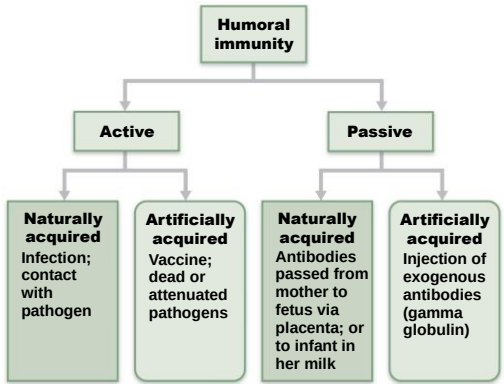
Passive Humoral Immunity

- Readymade antibodies introduced into body
- B cells are not challenged by antigens
- Immunological memory does not occur
- Protection ends when antibodies degrade

Passive Humoral Immunity

- Two types
  1. Naturally acquired—antibodies delivered to fetus via placenta or to infant through milk
  2. Artificially acquired—injection of serum, such as gamma globulin
     - Protection immediate but ends when antibodies naturally degrade in body

Figure 21.13 Active and passive humoral immunity.



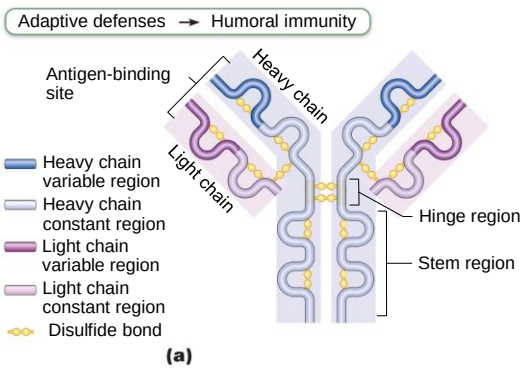
Antibodies

- Immunoglobulins—gamma globulin portion of blood
- Proteins secreted by plasma cells
- Capable of binding specifically with antigen detected by B cells
- Grouped into one of five Ig classes

Basic Antibody Structure

- Constant (C) regions of stem
  - Determine antibody class (**IgM, IgA, IgD, IgG, or IgE**)
  - Serve common functions in all antibodies by dictating
    - Cells and chemicals that antibody can bind
    - How antibody class functions to eliminate antigens

Figure 21.14a Antibody structure.



Classes of Antibodies

- IgM
  - Pentamer (larger than others); first antibody released
  - Potent agglutinating agent
  - Readily fixes and activates complement
- IgA (secretory IgA)
  - Monomer or dimer; in mucus and other secretions
  - Helps prevent entry of pathogens

Table 21.4 Immunoglobulin Classes (1 of 2)

Table 21.4 Immunoglobulin Classes*

 IgM (pentamer)	▪ The first immunoglobulin class-se creted by plasma cells during the primary response. (This fact is diag-nostically useful because presence of IgM in plasma usually indicates current infection by the pathogen eliciting IgM's formation.) ▪ Readily fixes and activates complement. ▪ Exists in monomer and pentamer (five united monomers) forms. ▪ The monomer serves as an antigen receptor on the B cell surface. ▪ The pentamer (illustrated) circulates in blood plasma. ▪ Numerous antigen-binding sites make it a potent agglutinating agent.
 IgA (dimer)	▪ The dimer (illustrated), referred to as **secretory IgA** is found in body secretions such as saliva, sweat, in-testinal juice, and milk. ▪ Secretory IgA helps stop pathogens from attaching to epithelial cell sur-faces (including mucous membranes and the epidermis). ▪ The monomer exists in limited amounts in plasma.

*Key characteristics are listed in blue type.

Classes of Antibodies

- IgD
  - Monomer attached to surface of B cells
  - Functions as B cell receptor
- IgG
  - Monomer; 75–85% of antibodies in plasma
  - From secondary and late primary responses
  - Crosses placental barrier

Classes of Antibodies

- IgE
  - Monomer active in some allergies and parasitic infections (EEEK !)
  - Causes mast cells and basophils to release histamine
- B cells can switch antibody classes but retain antigen specificity
  - IgM at first; then IgG
  - Almost all secondary responses are IgG

Table 21.4 Immunoglobulin Classes (2 of 2)

Table 21.4 Immunoglobulin Classes* (continued)

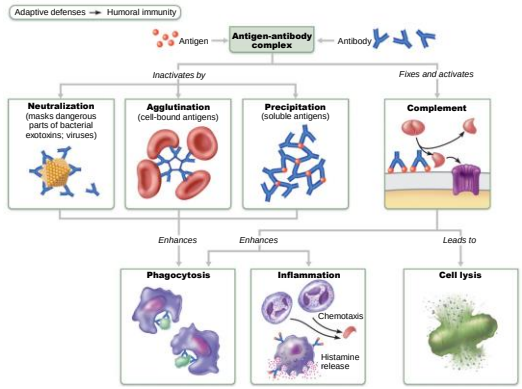
 IgD (monomer)	▪ Found on the B cell surface. ▪ Functions as a B cell antigen recep-tor (as does IgM).
 IgG (monomer)	▪ The most abundant antibody in plasma, accounting for 75–85% of circulating antibodies. ▪ The main antibody of both second-ary and late primary responses. ▪ Readily fixes and activates complement. ▪ Protects against bacteria, viruses, and toxins circulating in blood and lymph. ▪ Crosses the placenta and confers passive immunity from the mother to the fetus.
 IgE (monomer)	▪ Stem end binds to mast cells or basophils. Antigen binding to its receptor end triggers these cells to release histamine and other chemi-cals that mediate inflammation and an allergic reaction. ▪ Secreted by plasma cells in skin, mucosae of the gastrointestinal and respiratory tracts, and tonsils. ▪ Only traces of IgE are found in plasma. ▪ Levels rise during severe allergic at-tacks or chronic parasitic infections of the gastrointestinal tract.

*Key characteristics are listed in blue type.

Antibody Targets and Functions

- Antibodies inactivate and tag antigens; do not destroy them
  - Form **antigen-antibody** (immune) **complexes**
- Defensive mechanisms used by antibodies
  - Neutralization and agglutination (the two most important)
  - Precipitation and complement fixation

Figure 21.15 Mechanisms of antibody action.



T cell Activation: Proliferation and Differentiation

- Primary T cell response peaks within a week
- T cell apoptosis occurs between days 7 and 30
  - Benefit of apoptosis: activated T cells are a hazard – produce large amount inflammatory cytokines → hyperplasia, cancer
- Effector activity wanes as amount of antigen declines
- Memory T cells remain and mediate secondary responses

Cytokines

- Chemical messengers of immune system
- Mediate cell development, differentiation, and responses in immune system
- Include interferons and interleukins
- Interleukin 1 (IL-1) released by macrophages co-stimulates bound T cells to
  - Release interleukin 2 (IL-2)
  - Synthesize more IL-2 receptors

Cytokines

- IL-2 key growth factor, acting on cells that release it and other T cells
  - Encourages activated T cells to divide rapidly
- Other cytokines amplify and regulate innate and adaptive responses
  - E.g., tumor necrosis factor – cell toxin
  - E.g., gamma interferon – enhances killing power of macrophages

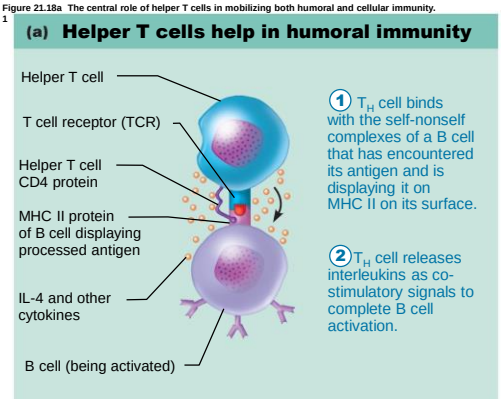
Roles of Helper T (T_H) cells

- Play central role in adaptive immune response
  - Activate both humoral and cellular arms
  - Once primed by APC presentation of antigen, they
    - Help activate T and B cells
    - Induce T and B cell proliferation
    - Their cytokines recruit other immune cells
- Without T_H, there is no immune response

Helper T cells: Activation of B cells

- Interact directly with B cells displaying antigen fragments bound to MHC II receptors
- Stimulate B cells to divide more rapidly and begin antibody formation
- B cells may be activated without T_H cells by binding to **T cell–independent antigens**
  - Response weak and short-lived
- Most antigens require T_H co-stimulation to activate B cells: **T cell–dependent antigens**

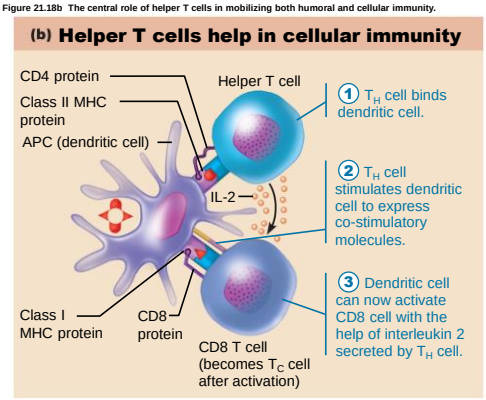
Figure 21.18a The central role of helper T cells in mobilizing both humoral and cellular immunity. Slide 1



Helper T cells: Activation of CD8 cells

- CD8 cells require T_H cell activation into destructive cytotoxic T cells
- Cause dendritic cells to express co-stimulatory molecules required for CD8 cell activation

Figure 21.18b The central role of helper T cells in mobilizing both humoral and cellular immunity. Slide 1



Helper T cells: Amplification of Innate Defenses

- Amplify responses of innate immune system
- Activate macrophages → more potent killers
- Mobilize lymphocytes and macrophages and attract other types of WBCs

Helper T cells: Subsets of T_H cells

- T_H1 – mediate most aspects of cellular immunity
- T_H2 – defend against parasitic worms; mobilize eosinophils; promote allergies
- T_H17 – link adaptive and innate immunity by releasing IL-17; may play role in autoimmune disease

Cytotoxic T (T_C) cells

- Directly attack and kill other cells
- Activated T_C cells circulate in blood and lymph and lymphoid organs in search of body cells displaying antigen they recognize

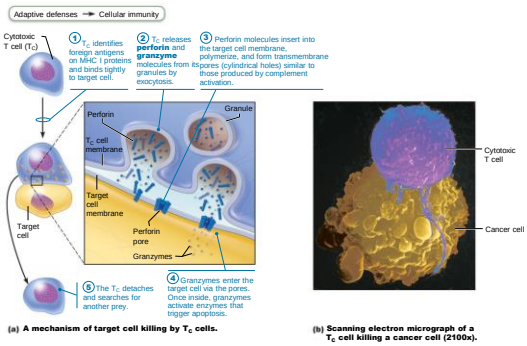
Roles of Cytotoxic T (T_C) cells

- Targets
  - Virus-infected cells
  - Cells with intracellular bacteria or parasites
  - Cancer cells
  - Foreign cells (transfusions or transplants)

Cytotoxic T cells

- Lethal hit – two methods:
  - T_C cell releases **perforins** and **granzymes** by exocytosis
    - Perforins create pores through which granzymes enter target cell
    - Granzymes stimulate apoptosis
  - T_C cell binds specific membrane receptor on target cell, and stimulates apoptosis

Figure 21.19 Cytotoxic T cells attack infected and cancerous cells.



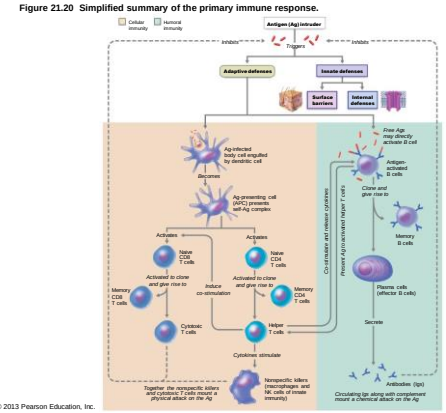
(a) A mechanism of target cell killing by T_C cells.

(b) Scanning electron micrograph of a T_C cell killing a cancer cell (2100x).

Natural Killer cells

- Recognize other signs of abnormality
  - Lack of class I MHC
  - Antibody coating target cell
  - Different surface markers of stressed cells
- Use same key mechanisms as T_C cells for killing their target cells
- Immune surveillance—NK and T_C cells prowl for markers they recognize

Figure 21.20 Simplified summary of the primary immune response.



Organ Transplants

- Four varieties
  - **Autografts**: from one body site to another in same person
  - **Isografts**: between identical twins
  - **Allografts**: between individuals who are not identical twins
  - **Xenografts**: from another animal species

Organ Transplants

- Success depends on similarity of tissues
  - Autografts and isografts ideal donor tissues
    - Almost always successful if good blood supply and no infection
  - Research into successful xenografts from genetically engineered animals
  - Most common is allograft
    - ABO, other blood antigens, MHC antigens matched as closely as possible

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

Immunosuppressive Therapy Problems

- Patient's immune system suppressed
  - Cannot protect from foreign agents
  - Bacterial and viral infections → death
  - Must balance drugs for graft survival but no toxicity
  - Use antibiotics to control infections
  - Best circumstances – rejection after 10 years in 50% of patients

Immunosuppressive Therapy Problems

- Research to induce tolerance
  - Chimeric immune system
    - Suppress recipient's bone marrow
    - Douse recipient's bone marrow with bone marrow from donor of new organ
    - "Combined" immune system may treat transplanted organ as self
  - Harness regulatory T cell to suppress immune reactions

Immunodeficiencies

- Congenital or acquired conditions that impair function or production of immune cells or molecules such as complement or antibodies

Congenital Immunodeficiencies

- Severe Combined Immunodeficiency (SCID) Syndrome - genetic defect
  - Marked deficit in B and T cells
  - Defective adenosine deaminase (ADA) enzyme
    - Metabolites lethal to T cells accumulate
  - Fatal if untreated; treated with bone marrow transplants

Hodgkin's Disease

- Acquired immunodeficiency
- Cancer of B cells
- Leads to immunodeficiency by depressing lymph node cells

Acquired Immune Deficiency Syndrome (AIDS)

- Cripples immune system by interfering with activity of helper T cells
- Characterized by severe weight loss, night sweats, and swollen lymph nodes
- Opportunistic infections occur, including pneumocystis pneumonia and Kaposi's sarcoma

Acquired Immune Deficiency Syndrome (AIDS)

- Caused by human immunodeficiency virus (HIV) transmitted via body fluids—blood, semen, and vaginal secretions
- HIV enters the body via
  - Blood transfusions; blood-contaminated needles; sexual intercourse and oral sex; mother to fetus
- HIV
  - Destroys T_H cells → depresses cellular immunity

Treatment of Autoimmune Diseases

- Suppress entire immune system
  - Anti-inflammatory drugs, e.g., corticosteroids
  - Blocking cytokine action
  - Blocking co-stimulatory molecules
- Research
  - Activating regulatory T cells; inducing self-tolerance using vaccines; directing antibodies against self-reactive immune cells

Immediate Hypersensitivity

- Acute (type I) hypersensitivities (allergies) begin in seconds after contact with allergen
- Initial contact is asymptomatic but sensitizes person
- Reaction may be local or systemic

Anaphylactic Shock

- Systemic response to allergen that directly enters blood and circulates rapidly
- Basophils and mast cells enlisted throughout body
- Systemic histamine release may cause
  - Constriction of bronchioles; tongue may swell
  - Sudden vasodilation and fluid loss from bloodstream may →
  - Circulatory collapse (hypotensive shock) and death
- Treatment: epinephrine

- Just extra outline from TEXT not covered in class

Class I MHC Proteins

- Bind with fragment of protein synthesized in the cell (**endogenous antigen**)
- Endogenous antigen is self-antigen in normal cell; a nonself antigen in infected or abnormal cell
- Crucial for CD8 cell activation
- Inform cytotoxic T cells of microorganisms hiding in cells (cytotoxic T cells ignore displayed self-antigens)
- Act as antigen holders; form "self" part that T cells recognize

Class II MHC Proteins

- Bind with fragments of exogenous antigens that have been engulfed and broken down in a phagolysosome
- Recognized by helper T cells
- Signal CD4 cells that help is required

MHC Restriction

- CD4 and CD8 cells have different requirements for MHC protein that presents antigens to them
  - CD4 cells that become T_H – bind only class II MHC proteins typically on APC surfaces
  - CD8 cells that become cytotoxic T cells – bind only class I MHC proteins on APC surfaces
    - Once activated, cytotoxic T cells seek same antigen on class I MHC proteins on any cell

MHC Restriction

- CD8 cells activated by class I MHC proteins
- How do APCs get endogenous antigens from another cell and display them on class I MHCs?
  - Dendritic cells engulf dying virus-infected or tumor cells, or import antigens via temporary gap junctions with infected cells—then display both class I and class II MHCs

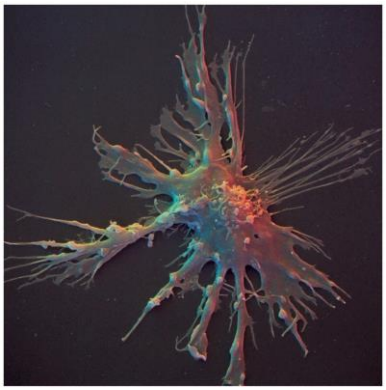
Antigen-presenting Cells (APCs)

- Engulf antigens
- Present fragments of antigens to T cells for recognition
- Major types
  - **Dendritic cells** in connective tissues and epidermis
  - **Macrophages** in connective tissues and lymphoid organs
  - **B cells**

Dendritic Cells and Macrophages

- Dendritic cells phagocytize pathogens, enter lymphatics to present antigens to T cells in lymph node
  - Most effective antigen presenter known
  - Key link between innate and adaptive immunity
- Macrophages widespread in lymphoid organs and connective tissues
  - Present antigens to T cells to activate themselves into voracious phagocytes that secrete bactericidal chemicals

Figure 21.10 Dendritic cell. Scanning electron micrograph (1050x).



B lymphocytes

- Do not activate naive T cells
- Present antigens to helper T cell to assist own activation

Adaptive Immunity: Summary

- Uses lymphocytes, APCs, and specific molecules to identify and destroy nonself substances
- Depends upon ability of its cells to
  - Recognize antigens by binding to them
  - Communicate with one another so that whole system mounts specific response

Activation and Differentiation of B Cells

- B cell activated when antigens bind to its surface receptors and cross-link them →
- Receptor-mediated endocytosis of cross-linked antigen-receptor complexes (clonal selection) →
- Proliferation and differentiation into effector cells

Fate of the Clones

- Most clone cells become plasma cells
  - Secrete specific antibodies at rate of 2000 molecules per second for four to five days, then die
  - Antibodies circulate in blood or lymph
    - Bind to free antigens and mark for destruction by innate or adaptive mechanisms

Fate of the Clones

- Clone cells that do not become plasma cells become **memory cells**
  - Provide immunological memory
  - Mount an immediate response to future exposures to same antigen

Neutralization

- Simplest defensive mechanism
- Antibodies block specific sites on viruses or bacterial exotoxins
- Prevent these antigens from binding to receptors on tissue cells
- Antigen-antibody complexes undergo phagocytosis

Agglutination

- Antibodies bind same determinant on more than one cell-bound antigen
- Cross-linked antigen-antibody complexes agglutinate
  - Example: clumping of mismatched blood cells

Precipitation

- Soluble molecules are cross-linked
- Complexes precipitate and are subject to phagocytosis

Complement Fixation and Activation

- Main antibody defense against cellular antigens (bacteria, mismatched RBCs)
- Several antibodies bind close together on a cellular antigen → complement-binding sites on stem regions align
  - Triggers complement fixation into cell's surface
  - → Cell lysis

Complement Fixation and Activation

- Activated complement functions
  - Amplifies inflammatory response
  - Promotes phagocytosis via opsonization
  - → Positive feedback cycle that enlists more and more defensive elements

Basic Antibody Structure

- T- or Y-shaped **antibody monomer** of four looping polypeptide chains linked by disulfide bonds
- Two identical heavy (H) chains with hinge region at "middles"
- Two identical light (L) chains
- Variable (V) regions at one end of each arm combine to form two identical **antigen-binding sites**

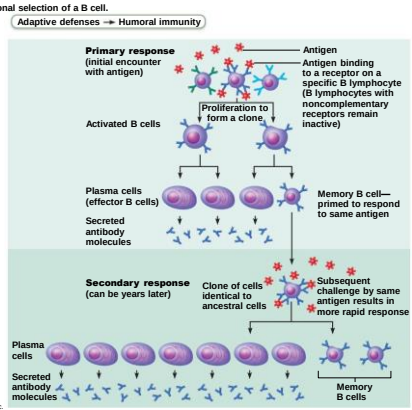
Cytotoxic T cells

- Bind to a self-nonself complex
- Can destroy all infected or abnormal cells

Seeding Secondary Lymphoid Organs and Circulation

- Immunocompetent B and T cells not yet exposed to antigen called **naive**
- Exported from primary lymphoid organs (bone marrow and thymus) to "seed" secondary lymphoid organs (lymph nodes, spleen, etc.)
  - Increases chance of encounter with antigen

Figure 21.11 Clonal selection of a B cell.



Monoclonal Antibodies as Clinical and Research Tools

- Commercially prepared pure antibody
  - Specific for single antigenic determinant
- Produced by **hybridomas**
  - Cell hybrids: fusion of tumor cell and B cell
- Proliferate indefinitely and have ability to produce single type of antibody
- Used in research, clinical testing, and cancer treatment

Summary of Antibody Actions

- Antigen-antibody complexes do not destroy antigens; prepare them for destruction by innate defenses
- Antibodies do not invade solid tissue unless lesion present
- Can act intracellularly if attached to virus before it enters cell
  - Activate mechanisms that destroy virus

Cellular Immune Response

- T cells provide defense against intracellular antigens
- Some T cells directly kill cells; others release chemicals that regulate immune response

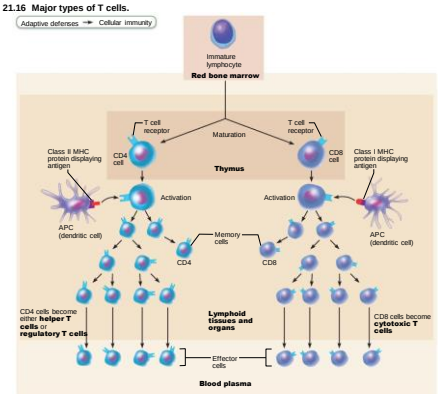
Cellular Immune Response

- Two populations of T cells based on which glycoprotein surface receptors displayed
  - CD4 cells usually become **helper T cells** (T_H); activate B cells, other T cells, macrophages, and direct adaptive immune response
    - Some become **regulatory T cells** – which moderate immune response
  - Can also become memory T cells

Cellular Immune Response

  - CD8 cells become **cytotoxic T cells** (T_C)
    - Destroy cells harboring foreign antigens
    - Also become memory T cells
  - Helper, cytotoxic, and regulatory T cells are *activated* T cells
  - Naive T cells simply termed CD4 or CD8 cells

Figure 21.16 Major types of T cells.



MHC Proteins and Antigen Presentation

- T cells respond only to processed fragments of antigens displayed on surfaces of cells
- Antigen presentation vital for activation of naive T cells and normal functioning of effector T cells

MHC Proteins

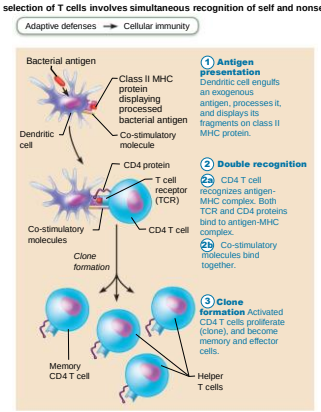
- Two types of MHC proteins important to T cell activation
  - Class I MHC proteins – displayed by all cells except RBCs
  - Class II MHC proteins – displayed by APCs (dendritic cells, macrophages, and B cells)
- Both types are synthesized at ER and bind to peptide fragments

Table 21.5 Role of MHC Proteins in Cellular Immunity

Table 21.5 Role of MHC Proteins in Cellular Immunity	CLASS I	CLASS II
Displayed by	All nucleated cells	APCs (dendritic cells, macrophages, B cells)
Recognized by	Naive CD8 cells and cytotoxic T cells	Naive CD4 cells and helper T cells
Foreign antigens on MHC are	Endogenous (intracellular pathogens or proteins made by cancerous cells)*	Exogenous (phagocytized extracellular pathogens)
Foreign antigens on MHC send this message	**If displayed by an APC:** "I belong to self, but have captured a foreign invader. This is what it looks like. Kill any cell that displays it." **If displayed by any other body cell:** "I belong to self, but have been invaded or become cancerous. Kill me!"	"I belong to self, but have captured a foreign invader. This is what it looks like. Help me mount a defense against it."

*Dendritic cells are an exception because they can present another cell's endogenous antigens on their class I MHC proteins to activate CD8 cells.

Figure 21.17 Clonal selection of T cells involves simultaneous recognition of self and nonself.



Acquired Immune Deficiency Syndrome (AIDS)

- HIV multiplies in lymph nodes throughout asymptomatic period, ~10 years if untreated
- Symptoms when immune system collapses
- Virus also invades brain → dementia
- HIV-coated glycoprotein complex attaches to CD4 receptor
- HIV enters cell and uses reverse transcriptase to produce DNA from its viral RNA
- The DNA copy (a **provirus**) directs host cell to make viral RNA and proteins, enabling virus to reproduce

Acquired Immune Deficiency Syndrome (AIDS)

- HIV reverse transcriptase → frequent errors; high mutation rate and resistance to drugs
- Treatment with antiviral drugs
  - **Fusion inhibitors** block HIV's entry into cell
  - **Integrase inhibitors** block viral RNA integration into host's DNA
  - **Reverse transcriptase and protease inhibitors** inhibit viral replication enzymes
  - Antiretroviral vaginal gel reduces risk by 50%

Autoimmune Diseases

- Immune system loses ability to distinguish self from foreign
- Production of autoantibodies and sensitized T_C cells that destroy body tissues
- Examples include multiple sclerosis, myasthenia gravis, Graves' disease, type 1 diabetes mellitus, systemic lupus erythematosus (SLE), glomerulonephritis, and rheumatoid arthritis