Antibodies

- Also called immunoglobulins (Igs)
  - Constitute the gamma globulin portion of blood proteins
  - Are soluble proteins secreted by activated B cells and plasma cells in response to an antigen
  - Are capable of binding specifically with a specific antigen
- There are five classes of antibodies: IgD, IgM, IgG, IgA, and IgE
Classes of Antibodies

- IgD – monomer attached to the surface of B cells, important in B cell activation
- IgM – pentamer released by plasma cells during the primary immune response
- IgG – monomer that is the most abundant and diverse antibody in primary and secondary response
  - crosses the placenta and confers passive immunity
Classes of Antibodies

- IgA – dimer that helps prevent attachment of pathogens to epithelial cell surfaces
- IgE – monomer that binds to mast cells and basophils, causing histamine release when activated
Basic Antibody Structure

- Consists of four looping polypeptide chains linked together with disulfide bonds
  - Two identical heavy (H) chains and two identical light (L) chains
- The four chains bound together form an antibody monomer
- Each chain has a variable (V) region at one end and a constant (C) region at the other
- Variable regions of the heavy and light chains combine to form the antigen-binding site
Basic Antibody Structure

Adaptive defenses → Humoral immunity

Antigen-binding site

Key:
- = Heavy chain variable region
- = Heavy chain constant region
= = Light chain variable region
= = Light chain constant region
- = Disulfide bond

Heavy chain

Light chain

Complement binding site

Macrophage binding site

Hinge region

Stem region

(a) Antibody molecule
Antibody Structure

- Antibodies responding to different antigens have different V regions…
- but the C region is the same for all antibodies in a given class
Antibody Structure

- C regions (effector regions) form the stem of the Y-shaped antibody and:
  - Determine the class of the antibody
  - Serve common functions in all antibodies
  - Dictate the cells and chemicals that the antibody can bind to
  - Determine how the antibody class will function in elimination of antigens
Plasma cells make over a billion different types of antibodies. However, human cells only contains 25,000 genes. To code for this many antibodies, somatic recombination takes place: Gene segments are shuffled and combined in different ways by each B cell as it becomes immunocompetent. Information of the newly assembled genes is expressed as B cell receptors and as antibodies.
Antibody Diversity

- Random mixing of gene segments makes unique antibody genes that:
  - Code for H and L chains
  - Account for part of the variability in antibodies
- V gene segments, called hypervariable regions, mutate and increase antibody variation
- Plasma cells can switch H chains, making two or more classes with the same V region
  - E.g. IgM switches to an IgG
Antibody Targets

- Antibodies themselves do not destroy antigen; they inactivate and tag it for destruction
- All antibodies form an antigen-antibody (immune) complex
- Defensive mechanisms used by antibodies are neutralization, agglutination, precipitation, and complement fixation
Other Mechanisms of Antibody Action

- Neutralization – antibodies bind to and block specific sites on viruses and bacteria, thus preventing these antigens from binding to receptors on tissue cells

- Later destroyed by phagocytes
Other Mechanisms of Antibody Action

- Agglutination – antibodies bind the same determinant on more than one antigen
  - Makes antigen-antibody complexes that are cross-linked into large lattices (agglutination)
  - IgMs are good at this with mismatched blood
- Precipitation – soluble molecules are cross-linked into large insoluble complexes, fall out of solution, and are phagocytized
Complement Fixation and Activation

- Complement fixation:
  - Main mechanism used against cellular antigens
  - Antibodies bound to cells change shape and expose complement binding sites
  - This triggers complement fixation on the antigenic cell surface resulting in cell lysis
Mechanisms of Antibody Action

Adaptive defenses → Humoral immunity → Antigen-antibody complex → Antigen → Antibody → Inactivates by Neutralization (masks dangerous parts of bacterial exotoxins; viruses) → Agglutination (cell-bound antigens) → Precipitation (soluble antigens) → Complement → Fixes and activates Enhances Phagocytosis Enhances Inflammation Leads to Cell lysis

Figure 21.14
Cell-Mediated Immune Response

- Since antibodies are useless against intracellular antigens, cell-mediated immunity is needed
- Two major populations of T cells mediate cellular immunity:
  - CD4 cells (T4 cells) are primarily helper T cells (T\textsubscript{H})
  - CD8 cells (T8 cells) are cytotoxic T cells (T\textsubscript{C}) that destroy cells harboring foreign antigens
Major Types of T Cells

Adaptive defenses → Cellular immunity

Figure 21.15
Importance of Cellular Response

- T cells cannot “see” free antigens
- T cells recognize and respond only to processed fragments of antigen displayed on the surface of body cells
- T cells are best suited for cell-to-cell interactions, and target:
  - Cells infected with viruses, bacteria, or intracellular parasites
  - Abnormal or cancerous cells
  - Cells of infused or transplanted foreign tissue
Antigen Recognition and MHC Restriction

- Immunocompetent T cells are activated when the V regions of their surface receptors bind to a recognized antigen.

- T cells must simultaneously recognize:
  - Nonself (the antigen)
  - Self (a MHC protein of a body cell)
MHC Proteins

- Both types of MHC proteins are important to T cell activation

- Class I MHC proteins
  - Always recognized by CD8 T cells
  - Display peptides from endogenous antigens (antigens in the cytosol)
Class I MHC Proteins

- Endogenous antigens are:
  - antigens that have been generated within the cell, as a result of normal cell metabolism, or because of viral or intracellular bacterial infection.
  - The fragments are then presented on the cell surface in the complex with MHC class I molecules
    - Non-self fragment signals T cells that a microorganism is in the body
    - Self fragment does not initiate a response from T cells
Class I MHC Proteins

4 Loaded MHC protein migrates to the plasma membrane, where it displays the antigenic peptide.

3 Endogenous antigen peptide loaded onto class I MHC.

2 Endogenous antigen peptides enter ER via TAP.

1 Endogenous antigen degraded by protease.

Fig. 21.16a
Class II MHC Proteins

- Class II MHC proteins are found only on surfaces of cells that present antigens to helper T cells, e.g. dendritic cells, macrophages, and B cells
- Bind longer peptides from exogenous antigens that have been engulfed and broken down in the phagolysosome (see below)
- A phagosome containing pathogens (with exogenous antigens) merges with a lysosome (phagolysosome)
- Invariant protein prevents class II MHC proteins from binding to peptides in the endoplasmic reticulum
Class II MHC Proteins

- Class II MHC proteins migrate to phagolysosomes where the antigen is degraded and the invariant chain is removed for peptide loading

- Loaded Class II MHC molecules then migrate to the cell membrane and display antigenic peptide for recognition by CD4 cells
Class II MHC Proteins

Extracellular fluid

1. Extracellular antigen (bacterium) phagocytized

2. Lysosome merges with phagosome, forming a phagolysosome; antigen degraded

3. After synthesis at the ER, the class II MHC protein migrates in a vesicle, which fuses with the phagolysosome; invariant chain removed, antigen loaded

4. Loaded MHC protein migrates to the plasma membrane

Antigenic peptide

Plasma membrane of an APC

Cytoplasm of APC

Invariant chain prevents class II MHC binding to peptides in the ER

Endoplasmic reticulum (ER)
Antigen Recognition

- Provides the key for the immune system to recognize the presence of intracellular microorganisms

- MHC proteins are ignored by T cells if they are complexed with self protein fragments
Antigen Recognition

- If MHC proteins are complexed with endogenous or exogenous antigenic peptides, they:
  - Indicate the presence of intracellular infectious microorganisms
  - Act as antigen holders
  - Form the self part of the self-antiself complexes recognized by T cells
T Cell Activation: Step One – Antigen Binding

- T cell antigen receptors (TCRs):
  - Bind to an antigen-MHC protein complex
  - Have variable and constant regions consisting of two chains (alpha and beta)
T Cell Activation: Step One – Antigen Binding

- MHC restriction – $T_H$ and $T_C$ bind to different classes of MHC proteins

- $T_H$ cells bind to antigen linked to class II MHC proteins

- Mobile APCs (Langerhans’ cells) quickly alert the body to the presence of antigen by migrating to the lymph nodes and presenting antigen
T Cell Activation: Step One – Antigen Binding

- $T_C$ cells are activated by antigen fragments complexed with class I MHC proteins
- APCs produce co-stimulatory molecules that are required for $T_C$ activation
- TCR (T cell antigen receptors) that acts to recognize the self-nonself complex is linked to multiple intracellular signaling pathways
- Other T cell surface proteins are involved in antigen binding (e.g., CD4 and CD8 help maintain coupling during antigen recognition)
T Cell Activation: Step One – Antigen Binding

Adaptive defenses → Cellular immunity

- Viral antigen internalized by APC
- Processed viral antigen (peptide) presented in combination with class II MHC protein
- Dendritic cell
- Class II MHC protein
- CD4 protein
- Dendritic cell presenting antigenic peptide recognized by helper T cell
- Immunocompetent helper T cell
- T cell receptor (TCR)

Clone formation

- Helper T memory cell
- Activated helper T cells

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Figure 21.17
T Cell Activation: Step Two – Co-stimulation

- Before a T cell can undergo clonal expansion, it must recognize one or more co-stimulatory signals.
- This recognition requires binding to other surface receptors on an APC.
  - Macrophages produce surface B7 proteins when nonspecific defenses are mobilized.
  - B7 binding with the CD\textsubscript{28} receptor on the surface of T cells is a crucial co-stimulatory signal.
- Other co-stimulatory signals include cytokines and interleukin 1 and 2.
T Cell Activation: Step Two – Co-stimulation

- Depending on receptor type, co-stimulators can cause T cells to complete their activation or abort activation

- Without co-stimulation, T cells:
  - Become tolerant to that antigen
  - Are unable to divide
  - Do not secrete cytokines
T Cell Activation: Step Two – Co-stimulation

- T cells that are activated:
  - Enlarge, proliferate, and form clones
  - Differentiate and perform functions according to their T cell class
T Cell Activation: Step Two – Co-stimulation

- Primary T cell response peaks within a week after signal exposure
- T cells then undergo apoptosis between days 7 and 30
- Effector activity wanes as the amount of antigen declines
- The disposal of activated effector cells is a protective mechanism for the body
- Memory T cells remain (sometimes for a lifetime) and mediate secondary responses to the same antigen
Cytokines

- Mediators involved in cellular immunity, including hormonelike glycoproteins released by activated T cells and macrophages

- Some are co-stimulators of T cells and T cell proliferation

- Interleukin 1 (IL-1) released by macrophages co-stimulates bound T cells to:
  - Release interleukin 2 (IL-2)
  - Synthesize more IL-2 receptors
Cytokines

- Examples include:
  - Perforin and lymphotoxin – cell toxins (see later)
  - Gamma interferon – enhances the killing power of macrophages
  - Inflammatory factors
Specific T cell Roles: Helper T Cells ($T_H$)

- Regulatory cells that play a central role in adaptive immunity

- Once primed by APC presentation of antigen, they:
  - Chemically or directly stimulate proliferation of other T cells
  - Stimulate B cells that have already become bound to antigen
  - Activate macrophages

- Without $T_H$, there is no immune response
Helper T Cells (TH)

Adaptive defenses ↔ Humoral immunity
          ↔ Cellular immunity

TH cell help in cell-mediated immunity

1. Dendritic cell activates TH cell.
2. Activated TH cell stimulates dendritic cell to express additional co-stimulatory molecules on its surface.
3. Dendritic cell with expressed co-stimulatory molecules activates TC cell.
**Helper T Cell**

- $T_H$ cells interact directly with B cells that have antigen fragments on their surfaces bound to MHC II receptors

- $T_H$ cells 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
  - Most antigens, however, require $T_H$ co-stimulation to activate B cells

- Cytokines released by $T_H$ amplify nonspecific defenses
Helper T Cells

$T_H$ cell help in humoral immunity

- Activated B cell
- Helper T cell
  - CD4 protein
- MHC II receptor of B cell displaying processed antigen
- Interleukin 4 and other cytokines released by helper T cell
- Activated helper T cell

Figure 21.18b
Specific T Cell Roles: Cytotoxic T Cell ($T_c$)

- $T_c$ cells, or killer T cells, are the only T cells that can directly attack and kill other cells.
- They circulate throughout the body in search of body cells that display the antigen to which they have been sensitized.
- Their targets include:
  - Virus-infected cells
  - Cells with intracellular bacteria or parasites
  - Cancer cells
  - Foreign cells from blood transfusions or transplants
Cytotoxic T Cells

- Before they attack, Tc cells must first “dock” on the target cell by binding to a self-nonself complex.

- Infected or abnormal cells can be destroyed as long as appropriate antigen and co-stimulatory stimuli (e.g., IL-2) are present.
Mechanisms of $T_c$ Action

- Lethal hits are accomplished by one of two mechanisms:
  - **Mechanism One**: $T_c$ cell releases perforin and granzymes from cytoplasmic granules
    - In the presence of $Ca^{2+}$ perforin causes cell lysis by creating transmembrane pores
    - Granzymes (protease) enter target cell thru these pores and degrade cellular contents stimulating apoptosis in the target cell
    - $T_c$ cell then detaches and looks for new prey
Mechanisms of Tc Action

(a)

- Adaptive defenses → Cellular Immunity
- Cytotoxic T cell
- Target cell
- Granules
- Granzymes
- Perforins
- Intercellular space
- Target cell membrane
- Perforin molecules inserted in target cell membrane
- Cytotoxic T cell membrane

Figure 21.19a
Mechanisms of $T_c$ Action

- Mechanism Two:
  - Involves the Tc cell binding the Fas receptor on the target cell resulting in apoptosis of the target cell
Figure 21.20

Innate defenses

Adaptive defenses

Surface barriers and Internal defenses

Antigen (Ag) Intruder

Triggers

Ag-infected body cell engulfed by dendritic cell

Ag-presenting cell (APC) presents self-Ag complex

Activation

Activated to clone and give rise to

Induces costimulation

Activated cytotoxic T cells

Memory cytotoxic T cells

Naive cytotoxic T cells

Activated helper T cells

Memory helper T cells

Activated to clone and give rise to

T helper cells

Activated helper T cells

Cytokine stimulus

Cytokine stimulus

Nonspecific killers (macrophages and NK cells)

Together the nonspecific killers and cytotoxic T cells mount a physical attack on the Ag

Antigen-activated B cells

Clone and give rise to

Effector plasma cells

Secretes

Circulating IgG along with complement mount a chemical attack on the Ag

Key:
- Humoral immunity
- Cell-mediated immunity
- Stimulates
- Inhibits

Free Ags may directly activate B cell

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Organ Transplants

- The four major types of grafts are:
  - Autografts – graft transplanted from one site on the body to another in the same person
  - Isografts – grafts between identical twins
  - Allografts – transplants between individuals that are not identical twins, but belong to same species
  - Xenografts – grafts taken from another animal species
Prevention of Rejection

- Prevention of tissue rejection is accomplished by using immunosuppressive drugs
  - However, these drugs depress patient’s immune system so it cannot fight off foreign agents
Immunodeficiencies

- Congenital and acquired conditions in which the function or production of immune cells, phagocytes, or complement is abnormal
  - **SCID** – severe combined immunodeficiency (SCID) syndromes; genetic defects that produce:
    - A marked deficit in B and T cells
    - Abnormalities in interleukin receptors
    - Defective adenosine deaminase (ADA) enzyme
      - Metabolites lethal to T cells accumulate
  - SCID is fatal if untreated; treatment is with bone marrow transplants
Acquired Immunodeficiencies

- Hodgkin’s disease – cancer of the B cells
- Acquired immune deficiency syndrome (AIDS) – cripples the immune system by interfering with the activity of helper T (CD4) cells
  - Opportunistic infections occur, including pneumocystis pneumonia and Kaposi’s sarcoma
AIDS

- Caused by human immunodeficiency virus (HIV) transmitted via body fluids – blood, semen, and vaginal secretions

- HIV enters the body via:
  - Blood transfusions
  - Contaminated needles
  - Intimate sexual contact, including oral sex

- HIV:
  - Destroys $T_H$ cells
  - Depresses cell-mediated immunity
AIDS

- HIV multiplies in lymph nodes throughout the asymptomatic period
- Symptoms appear in a few months to 10 years
- Mechanism of Attachment
  - CD4 protein on $T_H$ cells provides avenue of attack
  - HIV’s coat protein (gp120) attaches to the CD4 receptor
  - A nearby HIV protein (gp41) fuses the virus to the target cell
AIDS

- HIV enters the cell and uses reverse transcriptase to produce DNA from viral RNA
- This DNA (provirus) directs the host cell to make viral RNA (and proteins), enabling the virus to reproduce, lyse the host cell, and go on to infect other cells
AIDS

- HIV reverse transcriptase is not accurate and produces frequent transcription errors
  - This high mutation rate causes resistance to drugs
- Treatments include:
  - Reverse transcriptase inhibitors (AZT)
  - Protease inhibitors (saquinavir and ritonavir)
  - New drugs currently being developed that block HIV’s entry to helper T cells
Autoimmune Diseases

- Loss of the immune system’s ability to distinguish self from nonself
- The body produces autoantibodies and sensitized T\textsubscript{C} cells that destroy its own tissues
- Examples include:
  - multiple sclerosis
  - myasthenia gravis
  - Graves’ disease
  - Type I (juvenile) diabetes mellitus
  - systemic lupus erythematosus (SLE)
  - Glomerulonephritis
  - rheumatoid arthritis
Mechanisms of Autoimmune Diseases

- Ineffective lymphocyte programming – self-reactive T and B cells that should have been eliminated in the thymus and bone marrow escape into the circulation

- New self-antigens appear, generated by:
  - Gene mutations that cause new proteins to appear
  - Changes in self-antigens by hapten attachment or as a result of infectious damage
Hypersensitivity

- Immune responses that cause tissue damage
- Different types of hypersensitivity reactions are distinguished by:
  - Their time course
  - Whether antibodies or T cells are the principle immune elements involved
- Antibody-mediated allergies are immediate and subacute hypersensitivities
- The most important cell-mediated allergic condition is delayed hypersensitivity
Immediate Hypersensitivity (Allergies)

- Acute (type I) hypersensitivities begin in seconds after contact with allergen

- Anaphylaxis – initial allergen contact is asymptomatic but sensitizes the person
  - Subsequent exposures to allergen cause:
    - Release of histamine and inflammatory chemicals
    - Systemic or local responses
Immediate Hypersensitivity

- The mechanism involves IL-4 secreted by T cells
  - IL-4 stimulates B cells to produce IgE
  - IgE binds to mast cells and basophils causing them to degranulate
  - results in a flood of histamine release and inducing the inflammatory response
Adaptive defenses → Humoral immunity

Sensitization stage

1. Antigen (allergen) invades body.

2. Plasma cells produce large amounts of class IgE antibodies against allergen.

3. IgE antibodies attach to mast cells in body tissues (and to circulating basophils).

<table>
<thead>
<tr>
<th>Mast cell with fixed IgE antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
</tr>
<tr>
<td>Granules containing histamine</td>
</tr>
</tbody>
</table>

Subsequent (secondary) responses

4. More of same antigen invades body.

5. Antigen combines with IgE attached to mast cells (and basophils), which triggers degranulation and release of histamine (and other chemicals).

6. Histamine causes blood vessels to dilate and become leaky, which promotes edema; stimulates secretion of large amounts of mucus; and causes smooth muscles to contract (if respiratory system is site of antigen entry, asthma may ensue).

<table>
<thead>
<tr>
<th>Outpouring of fluid from capillaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Release of mucus</td>
</tr>
<tr>
<td>Constriction of small respiratory passages (bronchioles)</td>
</tr>
</tbody>
</table>
Anaphylaxis

- Reactions include runny nose, itching reddened skin, and watery eyes

- If allergen is inhaled, asthmatic symptoms appear—constriction of bronchioles and restricted airflow

- If allergen is ingested, cramping, vomiting, or diarrhea occur

- Antihistamines counteract these effects
Anaphylactic Shock

- Response to allergen that directly enters the blood (e.g., insect bite, injection)

- Basophils and mast cells are enlisted throughout the body

- Systemic histamine releases may result in:
  - Constriction of bronchioles
  - Sudden vasodilation and fluid loss from the bloodstream
  - Hypotensive shock and death

- Treatment – epinephrine is the drug of choice