

Antibodies

- Also called immunoglobulins
 - 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 that 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
- 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

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
- C 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

Mechanisms of Antibody Diversity

- Plasma cells make over a billion different types of antibodies
- Each cell, however, only contains 100,000 genes that code for these polypeptides
- 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

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

Complement Fixation and Activation

- Complement fixation is the main mechanism used against cellular antigens
- Antibodies bound to cells change shape and expose complement binding sites
- This triggers complement fixation and cell lysis
- Complement activation:
 - Enhances the inflammatory response
 - Uses a positive feedback cycle to promote phagocytosis
 - Enlists more and more defensive elements

Other Mechanisms of Antibody Action

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

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
 - Cell-bound antigens are cross-linked, causing clumping (agglutination)
- Precipitation – soluble molecules are cross-linked into large insoluble complexes

Mechanisms of Antibody Action

Monoclonal Antibodies

- Commercially prepared antibodies are used:
 - To provide passive immunity
 - In research, clinical testing, and treatment of certain cancers
- Monoclonal antibodies are pure antibody preparations
 - Specific for a single antigenic determinant
 - Produced from descendants of a single cell

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 (T_H cells) are primarily helper T cells (T_H)
 - CD8 cells (T_C cells) are cytotoxic T cells (T_C) that destroy cells harboring foreign antigens
- Other types of T cells are:
 - Suppressor T cells (T_S)
 - Memory T cells

Importance of Humoral Response

- Soluble antibodies
 - The simplest ammunition of the immune response
 - Interact in extracellular environments such as body secretions, tissue fluid, blood, and lymph

Importance of Cellular Response

- 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

Class I MHC Proteins

- Endogenous antigens are:
 - Degraded by proteases and enter the endoplasmic reticulum
 - Transported via TAP (transporter associated with antigen processing)
 - Loaded onto class I MHC molecules
 - Displayed on the cell surface in association with a class I MHC molecule

Class I MHC Proteins

Class II MHC Proteins

- Class II MHC proteins are found only on mature B cells, some T cells, and antigen-presenting cells
- A phagosome containing pathogens (with exogenous antigens) merges with a lysosome
- Invariant protein prevents class II MHC proteins from binding to peptides in the endoplasmic reticulum

Class II MHC Proteins

- Class II MHC proteins migrate into the phagosomes 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

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-antigen 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 that acts to recognize the self-antigen 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

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 may require binding to other surface receptors on an APC
 - Macrophages produce surface B7 proteins when nonspecific defenses are mobilized
 - B7 binding with the CD₂₈ 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 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

- IL-2 is a key growth factor, which sets up a positive feedback cycle that encourages activated T cells to divide
 - It is used therapeutically to enhance the body's defenses against cancer
- Other cytokines amplify and regulate immune and nonspecific responses

Cytokines

- Examples include:
 - Perforin and lymphotoxin – cell toxins
 - Gamma interferon – enhances the killing power of macrophages
 - Inflammatory factors

Helper T Cells (T_H)

- Regulatory cells that play a central role in the immune response
- 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
- Without T_H, there is no immune response

Helper T Cells (T_H)

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

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

- Bind to self-antigen complexes on all body cells
- Infected or abnormal cells can be destroyed as long as appropriate antigen and co-stimulatory stimuli (e.g., IL-2) are present
- Natural killer cells activate their killing machinery when they bind to MICA receptor
- MICA receptor – MHC-related cell surface protein in cancer cells, virus-infected cells, and cells of transplanted organs

Mechanisms of T_C Action

- In some cases, T_C cells:
 - Bind to the target cell and release perforin into its membrane
 - In the presence of Ca²⁺ perforin causes cell lysis by creating transmembrane pores
- Other T_C cells induce cell death by:
 - Secreting lymphotoxin, which fragments the target cell's DNA
 - Secreting gamma interferon, which stimulates phagocytosis by macrophages

Mechanisms of T_C Action

Other T Cells

- Suppressor T cells (T_S) – regulatory cells that release cytokines,

which suppress the activity of both T cells and B cells

- Gamma delta T cells (T_{gd}) – 10% of all T cells found in the intestines that are triggered by binding to MICA receptors

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 lymph nodes leads to immunodeficiency by depressing lymph node cells
- Acquired immune deficiency syndrome (AIDS) – cripples the immune system by interfering with the activity of helper T (CD4) cells
 - Characterized by severe weight loss, night sweats, and swollen lymph nodes
 - 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
- Attachment
 - HIV's coat protein (gp120) attaches to the CD4 receptor
 - A nearby 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 and 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_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, and 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 haptten attachment or as a result of infectious damage

Mechanisms of Autoimmune Diseases

- If the determinants on foreign antigens resemble self-antigens:
 - Antibodies made against foreign antigens cross-react with self-antigens

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

- 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, resulting in a flood of histamine release and inducing the inflammatory response

Acute Allergic Response

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

Subacute Hypersensitivities

- Caused by IgM and IgG, and transferred via blood plasma or serum
 - Onset is slow (1–3 hours) after antigen exposure
 - Duration is long lasting (10–15 hours)
- Cytotoxic (type II) reactions
 - Antibodies bind to antigens on specific body cells, stimulating phagocytosis and complement-mediated lysis of the cellular antigens
 - Example: mismatched blood transfusion reaction

Subacute Hypersensitivities

- Immune complex (type III) hypersensitivity
 - Antigens are widely distributed through the body or blood
 - Insoluble antigen-antibody complexes form
 - Complexes cannot be cleared from a particular area of the body
 - Intense inflammation, local cell lysis, and death may result
 - Example: systemic lupus erythematosus (SLE)

Delayed Hypersensitivities (Type IV)

- Onset is slow (1–3 days)
- Mediated by mechanisms involving delayed hypersensitivity T cells and cytotoxic T cells
- Cytokines from activated T_C are the mediators of the inflammatory response
- Antihistamines are ineffective and corticosteroid drugs are used to provide relief

Delayed Hypersensitivities (Type IV)

- Example: allergic contact dermatitis (e.g., poison ivy)
- Involved in protective reactions against viruses, bacteria, fungi, protozoa, cancer, and rejection of foreign grafts or transplants