

The Immune System: Innate and Adaptive Body Defenses

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Immunity: Two Intrinsic Defense Systems

- **Innate (nonspecific)** system responds quickly and consists of:
 - **First line of defense** – intact **skin** and mucosae prevent entry of microorganisms
 - **Second line of defense** – **antimicrobial proteins**, **phagocytes**, and other cells
 - Inhibit spread of invaders throughout the body
 - Inflammation is its hallmark and most important mechanism

Immunity: Two Intrinsic Defense Systems

- Adaptive (specific) defense system
 - Third line of defense – mounts attack against particular foreign substances
 - Takes longer to react than the innate system
 - Works in conjunction with the innate system

Surface Barriers (*First Line of Defense*)

- Skin, mucous membranes, and their secretions make up the first line of defense
- Keratin in the skin:
 - Presents a formidable physical barrier to most microorganisms
 - Is resistant to weak acids and bases, bacterial enzymes, and toxins
- Mucosae provide similar mechanical barriers

Epithelial Chemical Barriers

- Epithelial membranes produce protective chemicals that destroy microorganisms
 - **Skin acidity** (pH of 3 to 5) inhibits bacterial growth
 - **Sebum** contains chemicals toxic to bacteria
 - Stomach mucosae secrete concentrated **HCl** and protein-digesting enzymes
 - **Saliva** and **lacrimal** fluid contain lysozyme
 - **Mucus** traps microorganisms that enter the digestive and respiratory systems

Respiratory Tract Mucosae

- Mucus-coated **hairs** in the nose trap inhaled particles
- Mucosa of the upper respiratory tract is **ciliated**
 - Cilia sweep dust- and bacteria-laden mucus away from lower respiratory passages

Internal Defenses (*Second Line of Defense*)

- The body uses **nonspecific** cellular and chemical devices to protect itself
 1. Phagocytes
 2. natural killer (NK) cells
 3. Inflammatory response enlists macrophages, mast cells, WBCs, and chemicals
 4. Antimicrobial proteins in blood and tissue fluid
- Harmful substances are identified by surface carbohydrates unique to infectious organisms

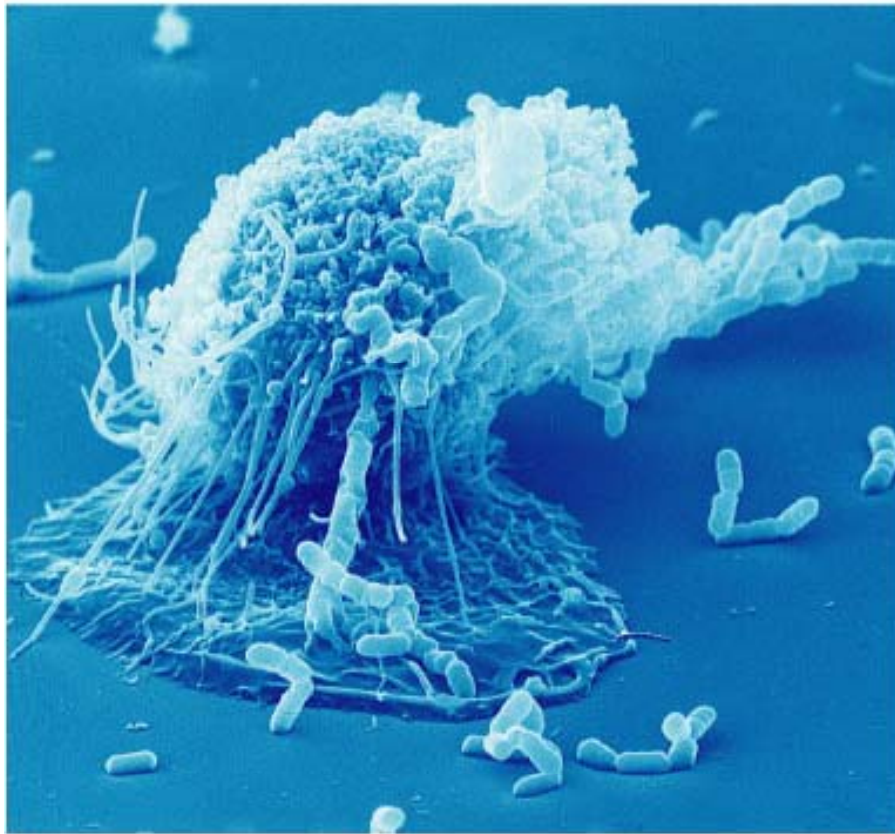
1. Phagocytes

- **Macrophages** are the chief phagocytic cells
- Free macrophages wander throughout a region in search of cellular debris
- **Kupffer cells (liver)** and **microglia (brain)** are fixed macrophages
- **Neutrophils** become phagocytic when encountering infectious material
- **Eosinophils** are weakly phagocytic against parasitic worms
- Mast cells bind and ingest a wide range of bacteria

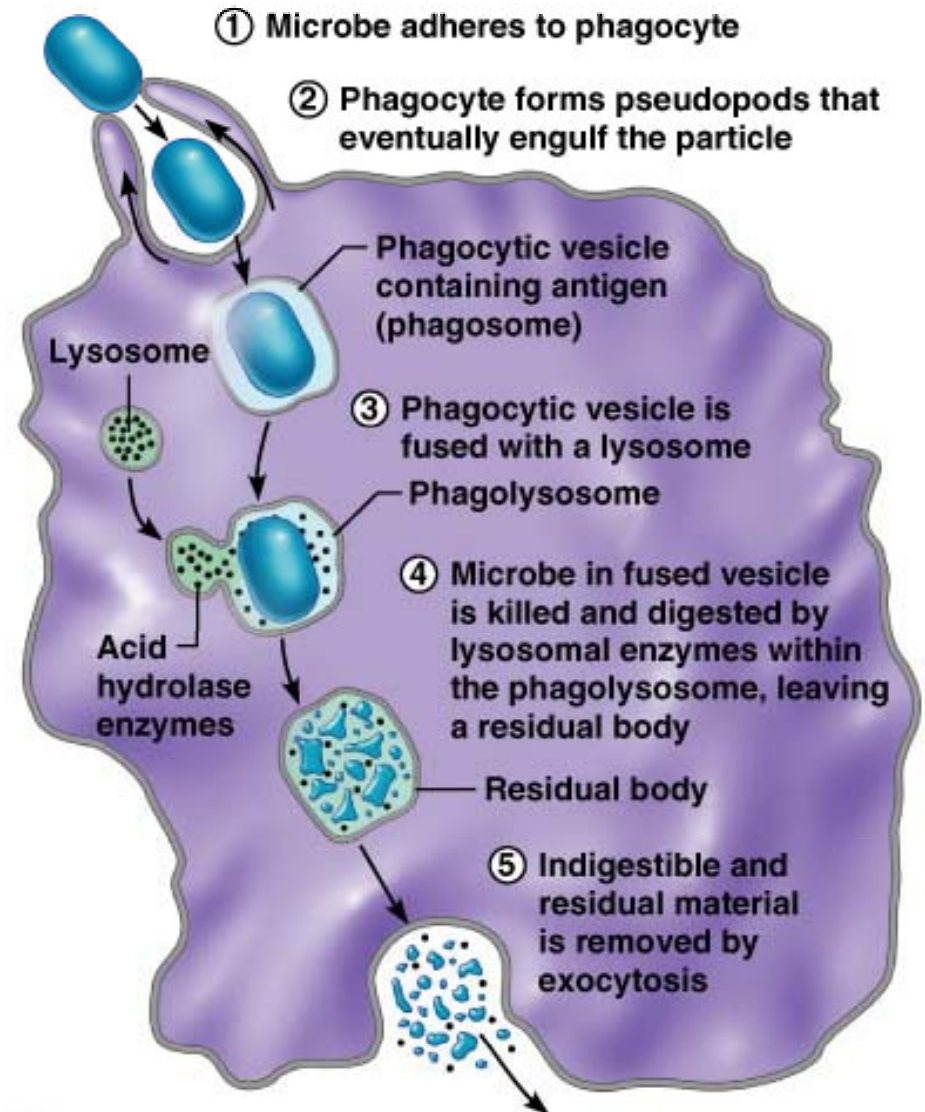
Mechanism of Phagocytosis

- Microbes adhere to the phagocyte
- Pseudopods engulf the particle (antigen) into a phagosome
- Phagosomes fuse with a lysosome to form a phagolysosome
- Invaders in the phagolysosome are digested by proteolytic enzymes
- Indigestible and residual material is removed by exocytosis

Mechanism of Phagocytosis



(a)



(b)

2. Natural Killer (NK) Cells

- Cells that can lyse and kill cancer cells and virus-infected cells
- Natural killer cells:
 - Are a **small**, distinct group of large **granular lymphocytes**
 - React nonspecifically and eliminate **cancerous and virus-infected** cells
 - Kill their target cells by releasing perforins and other cytolytic chemicals
 - Secrete potent chemicals that **enhance the inflammatory response**

3. Inflammation: Tissue Response to Injury

- The inflammatory response is triggered whenever body tissues are injured
 - Prevents the spread of damaging agents to nearby tissues
 - Disposes of cell debris and pathogens
 - Sets the stage for repair processes
- The four cardinal signs of acute inflammation are redness, heat, swelling, and pain

Inflammation Response

- Begins with a flood of inflammatory chemicals released into the extracellular fluid
- Inflammatory mediators (chemicals) :
 - Include kinins, prostaglandins (PGs), complement, and cytokines
 - Are released by injured tissue, phagocytes, lymphocytes, and mast cells
 - Cause local small blood vessels to dilate, resulting in hyperemia

Toll-like Receptors (TLRs)

- Macrophages and cells lining the gastrointestinal and respiratory tracts bear TLRs
- TLRs recognize specific classes of infecting microbes
- Activated TLRs trigger the release of cytokines that promote inflammation

Inflammatory Response: Vascular Permeability

- Chemicals liberated by the inflammatory response **increase the permeability** of local capillaries
- Exudate (fluid containing proteins, clotting factors, and antibodies):
 - Seeps into tissue spaces **causing local edema (swelling)**, which contributes to the sensation of **pain**

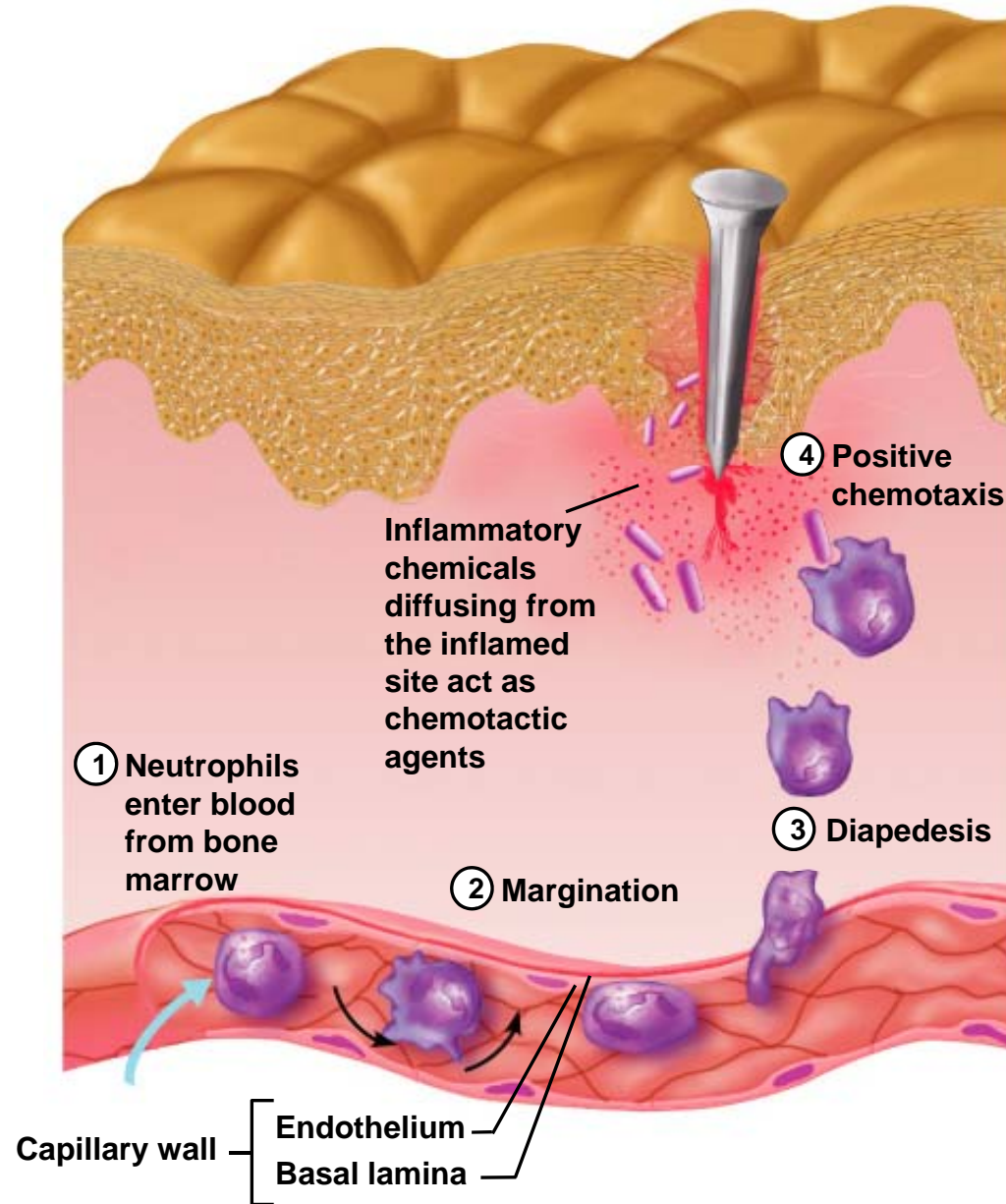
Inflammatory Response: Edema

- The surge of protein-rich fluids into tissue spaces (edema):
 - Helps to dilute harmful substances
 - Brings in large quantities of oxygen and nutrients needed for repair
 - Allows entry of clotting proteins, which prevents the spread of bacteria

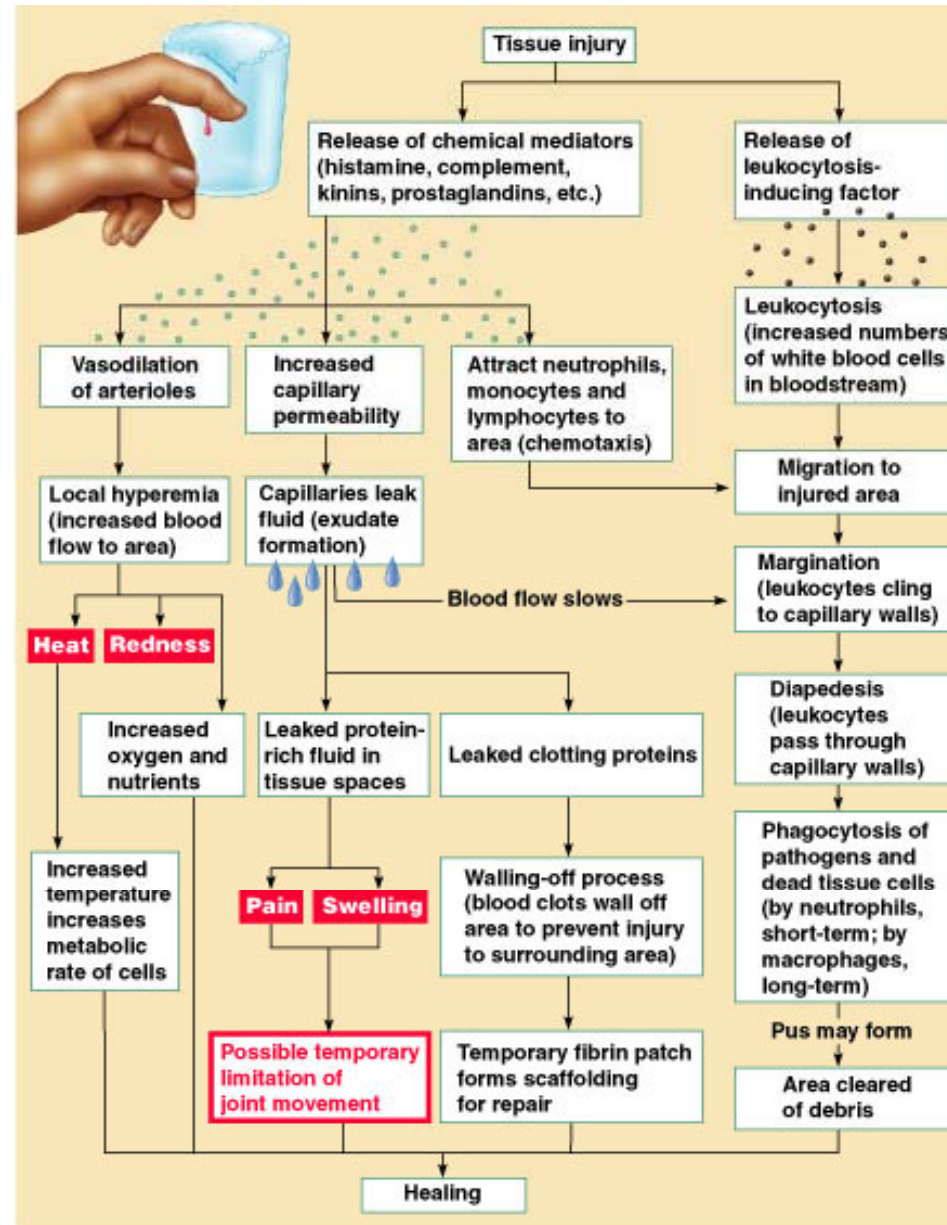
Inflammatory Response: Phagocytic Mobilization

- Occurs in four main phases:
 - **Leukocytosis** – neutrophils are released from the bone marrow in response to leukocytosis-inducing factors released by injured cells
 - **Margination** – neutrophils cling to the walls of capillaries in the injured area
 - **Diapedesis** – neutrophils squeeze through capillary walls and begin phagocytosis
 - **Chemotaxis** – inflammatory chemicals attract neutrophils to the injury site

Inflammatory Response: Phagocytic Mobilization



Flowchart of Events in Inflammation



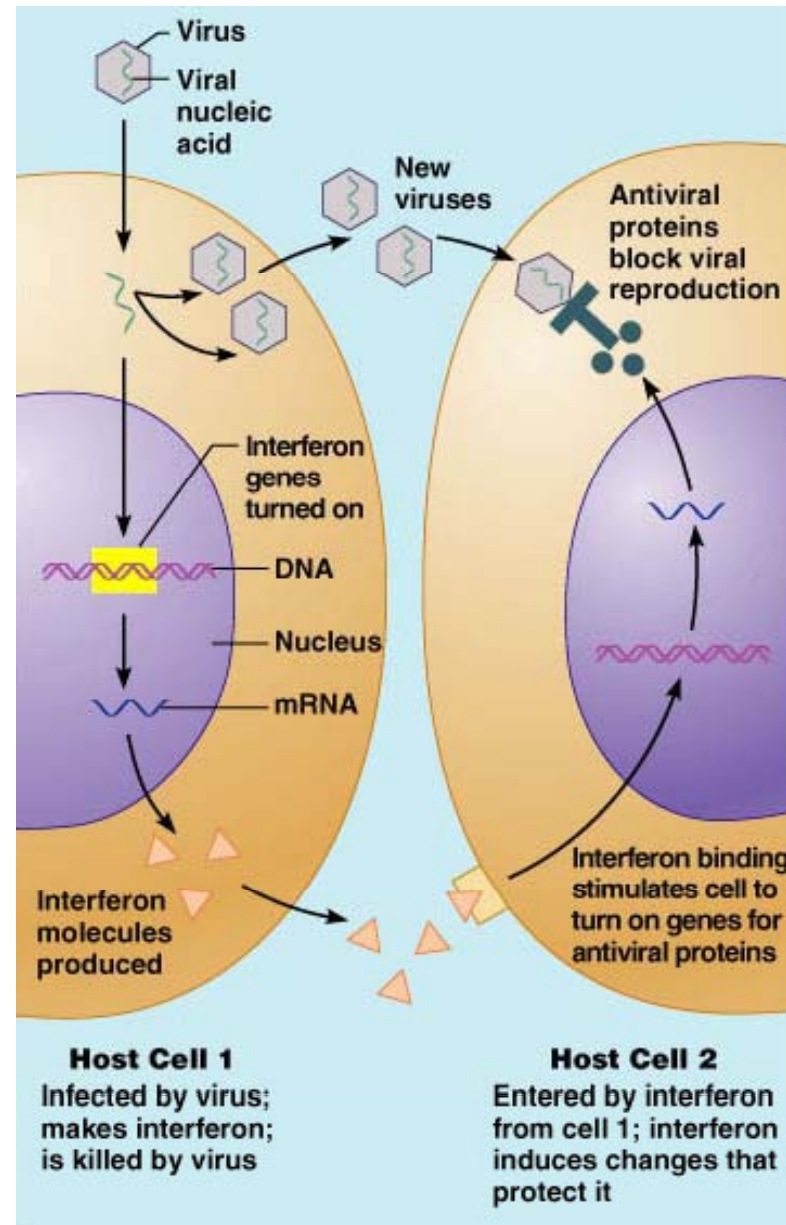
4. Antimicrobial Proteins

- Enhance the innate defenses by:
 - **Attacking microorganisms** directly
 - Hindering microorganisms' ability to reproduce
- The most important antimicrobial proteins are:
 - **Interferon**
 - **Complement proteins**

4 a. Interferon (IFN)

- Genes that synthesize IFN are activated when a host cell is invaded by a virus
- Interferon molecules leave the infected cell and enter neighboring cells
 - Interferon stimulates the neighboring cells to activate genes for PKR (an antiviral protein)
 - PKR nonspecifically blocks viral reproduction in the neighboring cell

Interferon (IFN)



Interferon Family

- Interferons are a family of related proteins each with slightly different physiological effects
- Lymphocytes secrete gamma (γ) interferon, but most other WBCs secrete alpha (α) interferon
- Fibroblasts secrete beta (β) interferon
- Interferons also activate macrophages and mobilize NKs
- FDA-approved alpha IFN is used:
 - As an antiviral drug against hepatitis C virus
 - To treat genital warts caused by the herpes virus

4 b. Complement

- 20 or so proteins that circulate in the blood in an inactive form
- Proteins include C1 through C9, factors B, D, and P, and regulatory proteins
- Provides a major mechanism for destroying foreign substances in the body

Complement

- Amplifies all aspects of the inflammatory response
- Kills bacteria and certain other cell types (our cells are immune to complement)
- Enhances the effectiveness of both nonspecific and specific defenses

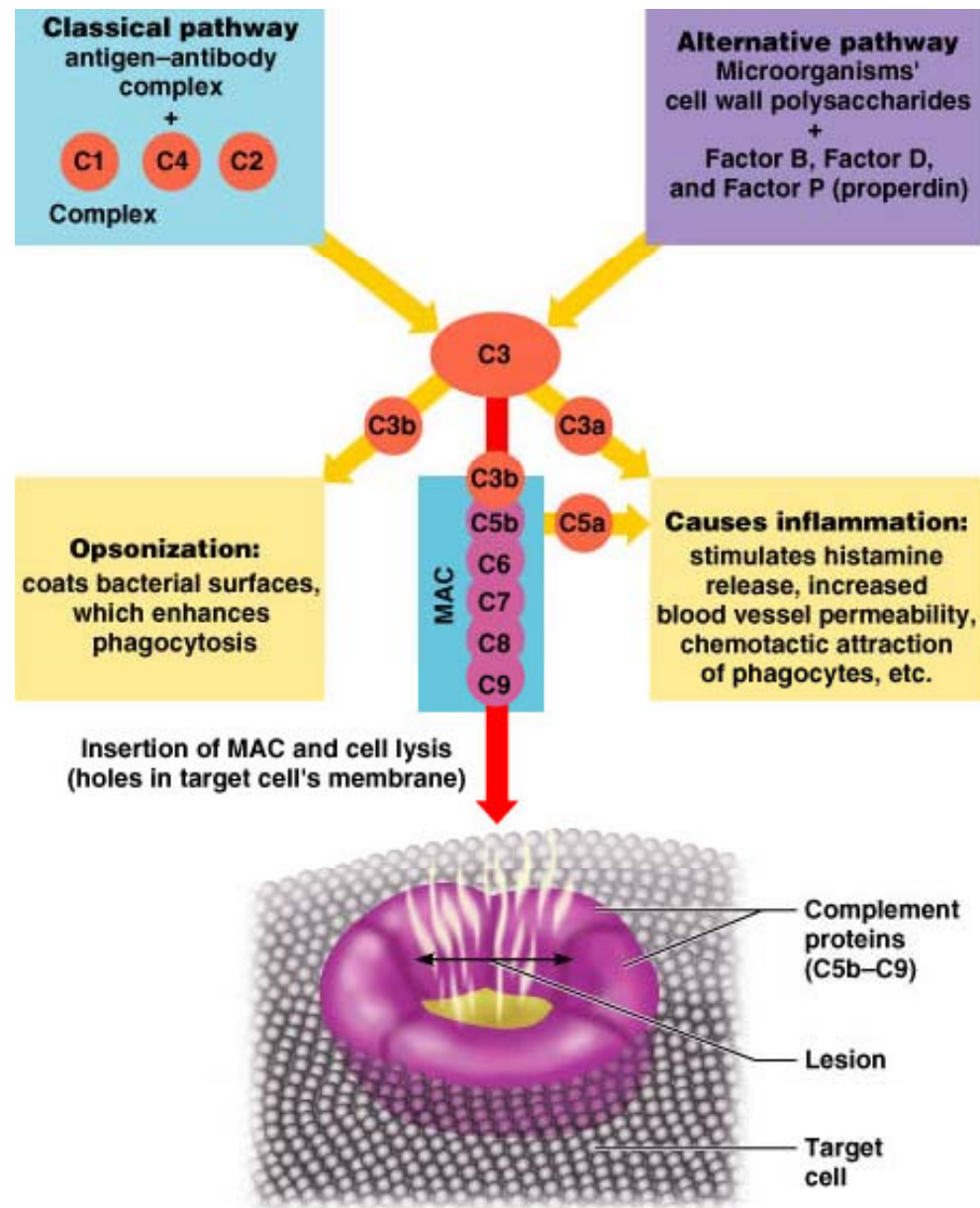
Complement Pathways

- Complement can be activated by two pathways: classical and alternative
- Classical pathway is linked to the immune system
 - Depends on the binding of antibodies to invading organisms
 - Subsequent binding of C1 to the antigen-antibody complexes (complement fixation)
- Alternative pathway is triggered by interaction among factors B, D, and P, and polysaccharide molecules present on microorganisms

Complement Pathways

- Each pathway involves a cascade in which complement proteins are activated in an orderly sequence and where each step catalyzes the next
- Both pathways converge on C3, which cleaves into C3a and C3b
- C3b initiates formation of a membrane attack complex (MAC)
- MAC causes cell lysis by interfering with a cell's ability to eject Ca^{2+}
- C3b also causes opsonization, and C3a causes inflammation

Complement Pathways



C-reactive Protein (CRP)

- CRP is produced by the liver in response to inflammatory molecules
- CRP is a clinical marker used to assess for:
 - The presence of an acute infection
 - An inflammatory condition and its response to treatment

Functions of C-reactive Protein

- Binds to PC receptor of pathogens and exposed self-antigens
- Plays a surveillance role in targeting damaged cells for disposal
- Activates complement

Fever

- Abnormally high body temperature in response to invading microorganisms
- The body's thermostat is reset upwards in response to pyrogens, chemicals secreted by leukocytes and macrophages exposed to bacteria and other foreign substances

Fever

- High fevers are dangerous as they can **denature enzymes**
- Moderate fever can be beneficial, as it causes:
 - The liver and spleen to sequester iron and zinc (needed by microorganisms)
 - An **increase in the metabolic rate**, which speeds up tissue repair

Adaptive (Specific) Defenses (*Third Line of Defense*)

- The adaptive immune system is a functional system that:
 - Recognizes specific foreign substances
 - Acts to immobilize, neutralize, or destroy foreign substances
 - Amplifies inflammatory response and activates complement

Adaptive Immune Defenses

- The adaptive immune system is antigen-specific, systemic, and has memory
- It has two separate but overlapping arms
 - Humoral, or antibody-mediated (B Cell) immunity
 - Cellular, or cell-mediated (T Cell) immunity

Antigens

- Substances that can mobilize the immune system and provoke an immune response
- The ultimate targets of all immune responses are mostly large, complex molecules not normally found in the body (nonself)

Complete Antigens

- Important functional properties:
 - **Immunogenicity** – the ability to stimulate proliferation of specific lymphocytes and antibody production
 - **Reactivity** – the ability to react with the products of the activated lymphocytes and the antibodies released in response to them
- Complete antigens include foreign protein, nucleic acid, some lipids, and large polysaccharides

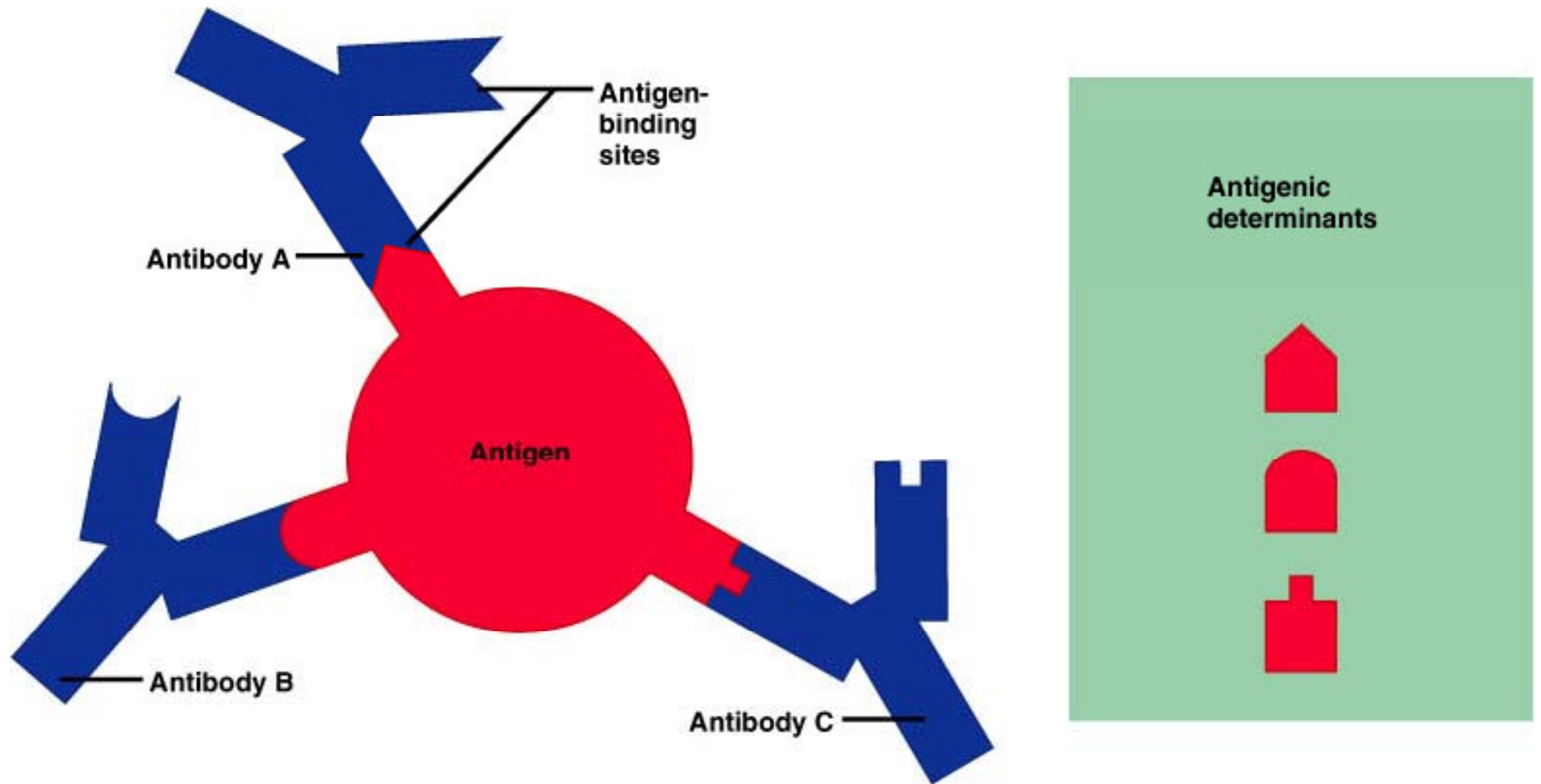
Haptens (Incomplete Antigens)

- Small molecules, such as peptides, nucleotides, and many hormones,
 - not immunogenic (*does not stimulate a response*)
 - reactive when attached to protein carriers
- If they link up with the body's proteins, the adaptive immune system may recognize them as foreign and mount a harmful attack (allergy)
- Haptens are found in poison ivy, dander, some detergents, and cosmetics

Antigenic Determinants

- Only certain parts of an entire antigen are immunogenic
- Antibodies and activated lymphocytes bind to these antigenic determinants
- Most naturally occurring antigens have numerous antigenic determinants that:
 - Mobilize several different lymphocyte populations
 - Form different kinds of antibodies against it
- Large, chemically simple molecules (e.g., plastics) have little or no immunogenicity

Antigenic Determinants



Self-Antigens: MHC Proteins

- Our cells are dotted with protein molecules (self-antigens) that are not antigenic to us but are strongly antigenic to others (*reason for transplant rejection*)
- One type of these, MHC proteins, mark a cell as self
- The two classes of MHC proteins are:
 - Class I MHC proteins – found on virtually all body cells
 - Class II MHC proteins – found on certain cells in the immune response

MHC Proteins

- Are **coded for by genes** of the major histocompatibility complex (MHC) and are unique to an individual
- Each MHC molecule has a deep groove that displays a peptide, which is a normal cellular product of protein recycling
- **In infected cells, MHC proteins bind to fragments of foreign antigens**, which play a crucial role in mobilizing the immune system

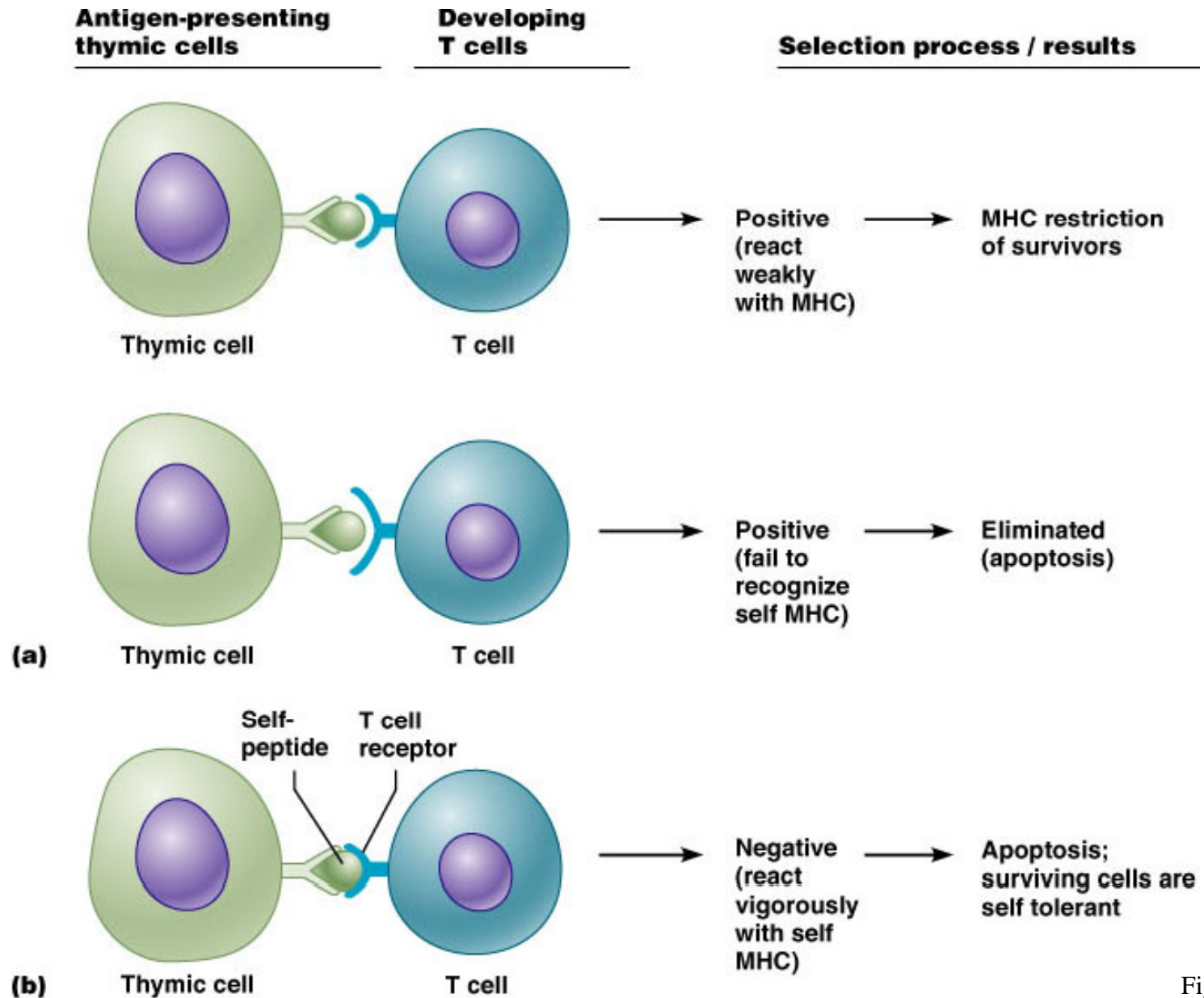
Cells of the Adaptive Immune System

- Two types of lymphocytes
 - B lymphocytes – oversee humoral immunity
 - T lymphocytes – non-antibody-producing cells that constitute the cell-mediated arm of immunity
- Antigen-presenting cells (APCs):
 - Do not respond to specific antigens
 - Play essential auxiliary roles in immunity

Lymphocytes

- Immature lymphocytes released from bone marrow are essentially identical
- Whether a lymphocyte matures into a B cell or a T cell depends on where in the body it becomes immunocompetent
 - B cells mature in the bone marrow
 - T cells mature in the thymus

T Cell Selection in the Thymus



T Cells

- T cells **mature in the thymus** under negative and positive selection pressures
 - Negative selection – eliminates T cells that are strongly anti-self
 - Positive selection – selects T cells with a weak response to self-antigens, which thus become both immunocompetent and self-tolerant

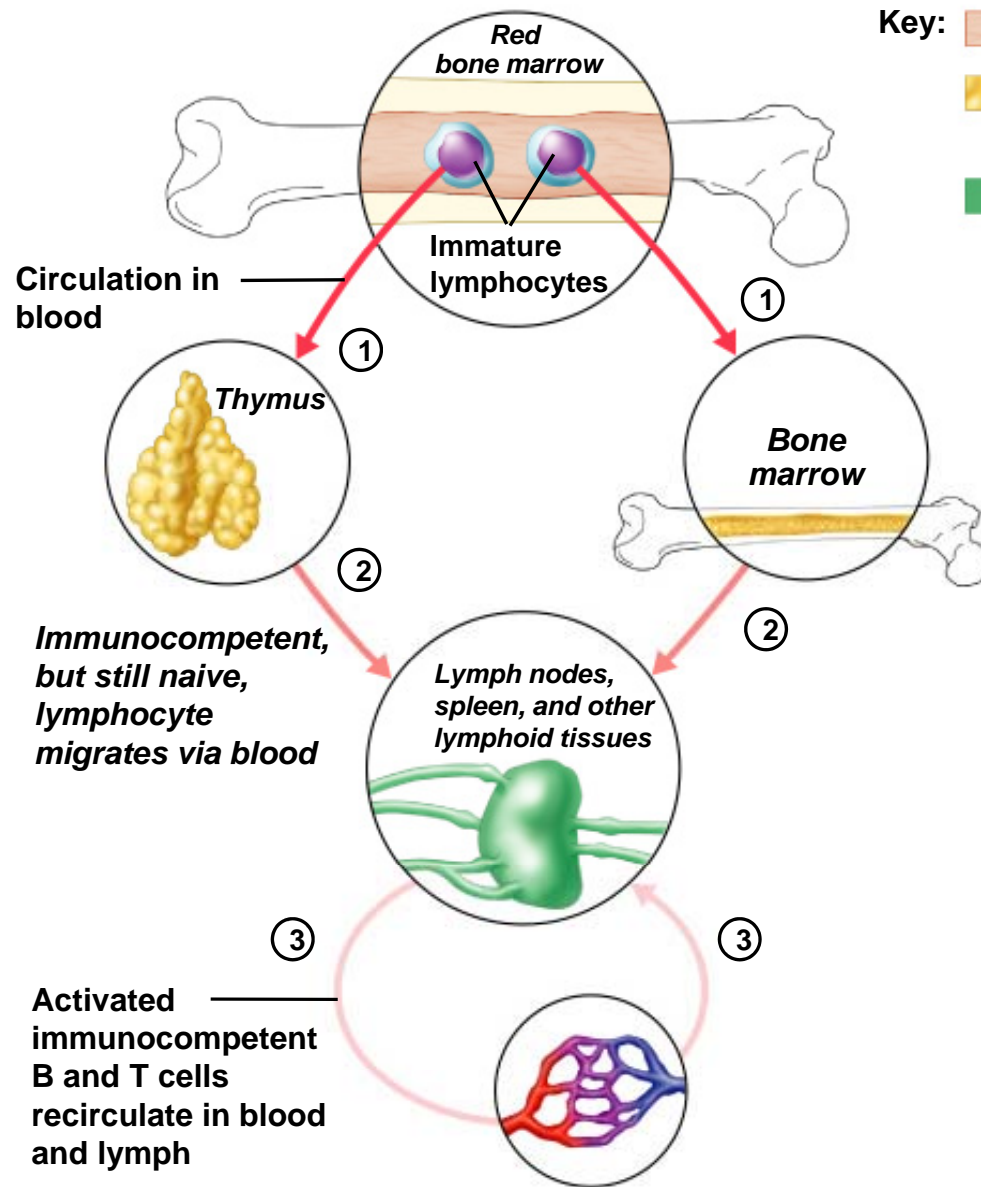
B Cells

- B cells become immunocompetent and self-tolerant in **bone marrow**
- Some self-reactive B cells are inactivated (anergy) while others are killed
- Other B cells undergo receptor editing in which there is a rearrangement of their receptors

Immunocompetent B or T cells

- Display a unique type of receptor that responds to a distinct antigen
- Become immunocompetent before they encounter antigens they may later attack
- Are exported to secondary lymphoid tissue where encounters with antigens occur
- Mature into fully functional antigen-activated cells upon binding with their recognized antigen
- It is genes, not antigens, that determine which foreign substances our immune system will recognize and resist

Immunocompetent B or T cells



Key: = Site of lymphocyte origin

= Site of development of immunocompetence as B or T cells; primary lymphoid organs

= Site of antigen challenge and final differentiation to activated B and T cells

① Lymphocytes destined to become T cells migrate to the thymus and develop immunocompetence there. B cells develop immunocompetence in red bone marrow.

② After leaving the thymus or bone marrow as naive immunocompetent cells, lymphocytes “seed” the lymph nodes, spleen, and other lymphoid tissues where the antigen challenge occurs.

③ Mature (antigen-activated) immunocompetent lymphocytes circulate continuously in the bloodstream and lymph and throughout the lymphoid organs of the body.

Antigen-Presenting Cells (APCs)

- Major roles in immunity are:
 - To engulf foreign particles
 - To present fragments of antigens on their own surfaces, to be recognized by T cells
- Major APCs are dendritic cells (DCs), macrophages, and activated B cells
- The major initiators of adaptive immunity are DCs, which actively migrate to the lymph nodes and secondary lymphoid organs and present antigens to T and B cells

Macrophages and Dendritic Cells

- Secrete soluble proteins that activate T cells
- Activated T cells in turn release chemicals that:
 - Rev up the maturation and mobilization of DCs
 - Prod macrophages to become activated macrophages, which are insatiable phagocytes that secrete bactericidal chemicals

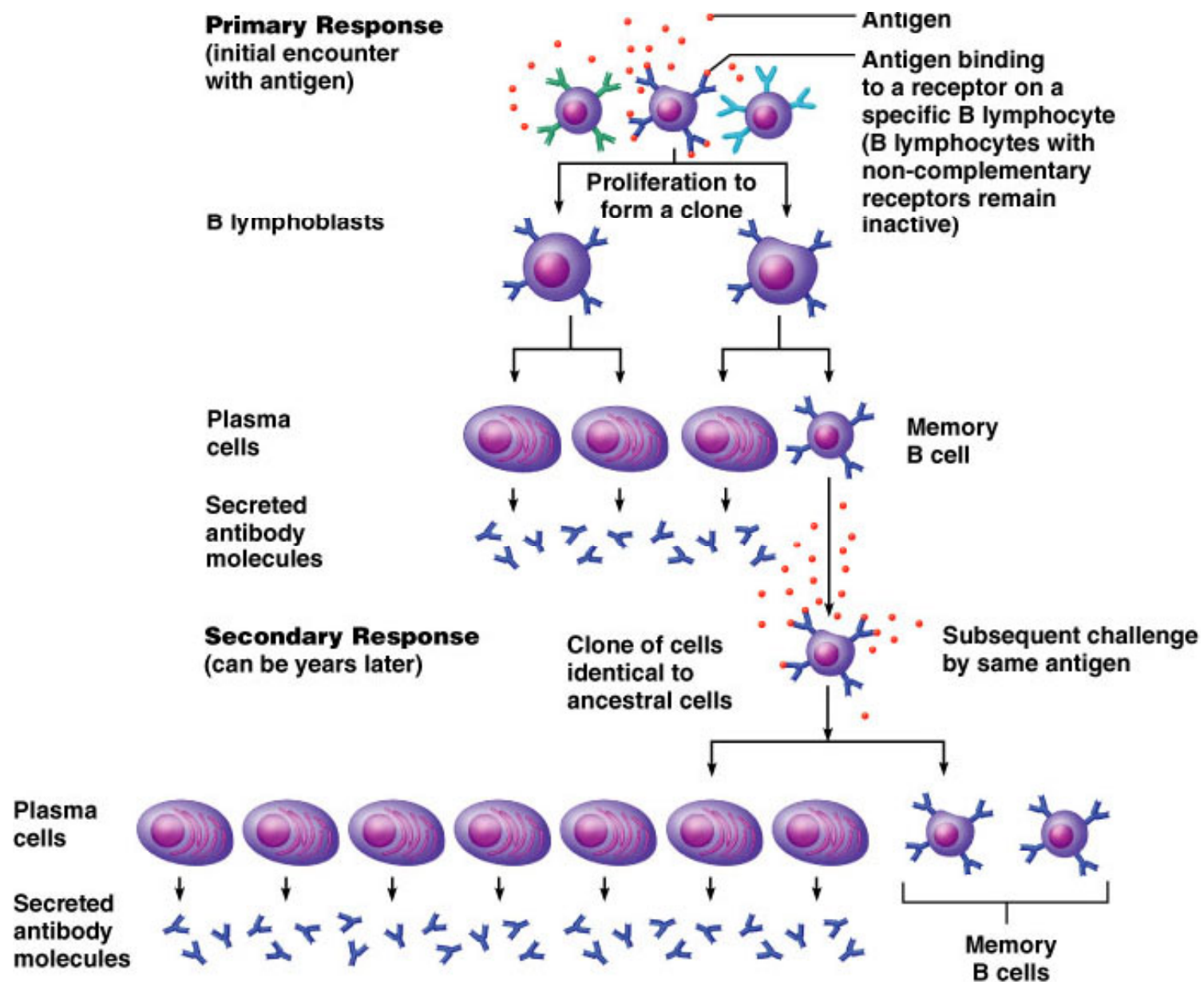
Humoral Immunity Response

- Antigen challenge – first encounter between an antigen and a naive immunocompetent cell
- Takes place in the spleen or other lymphoid organ
- If the lymphocyte is a B cell:
 - The challenging antigen provokes a humoral immune response
 - Antibodies are produced against the challenger

Clonal Selection

- **Stimulated B cell** growth forms clones bearing the same antigen-specific receptors
- A naive, immunocompetent B cell is activated when antigens bind to its surface receptors and cross-link adjacent receptors
- Antigen binding is followed by receptor-mediated endocytosis of the cross-linked antigen-receptor complexes
- These activating events, plus T cell interactions, trigger clonal selection

Clonal Selection



Fate of the Clones

- Most clone cells become antibody-secreting plasma cells
- Plasma cells secrete specific antibody at the rate of 2000 molecules per second

Fate of the Clones

- Secreted **antibodies**:
 - Bind to free antigens
 - **Mark the antigens for destruction** by specific or nonspecific mechanisms
- Clones that do not become plasma cells become **memory cells** that can **mount an immediate response** to subsequent exposures of the same antigen

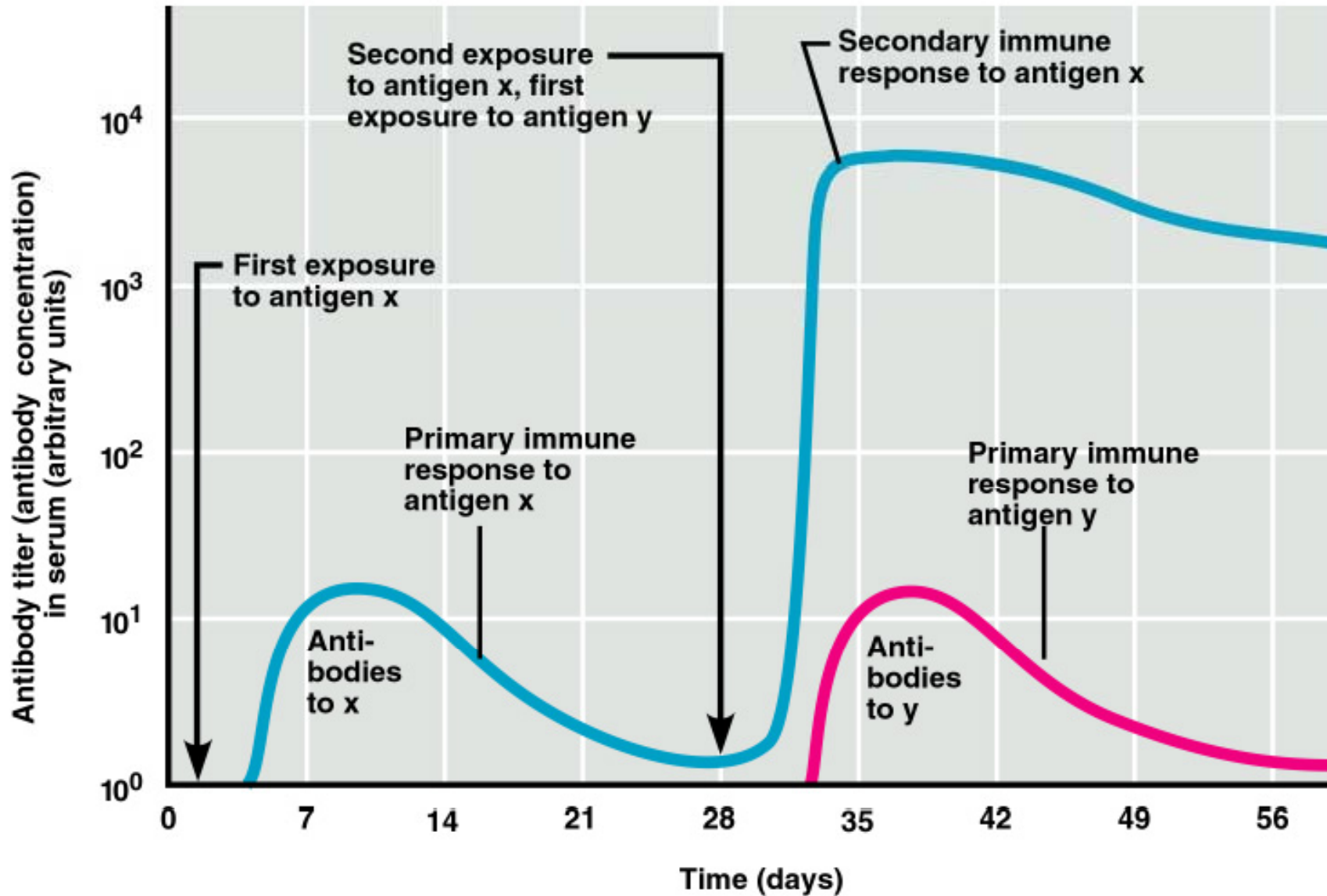
Immunological Memory

- **Primary immune response** – cellular differentiation and proliferation, which occurs on the first exposure to a specific antigen
 - Lag period: **3 to 6 days** after antigen challenge
 - Peak levels of plasma antibody are achieved in **10 days**
 - Antibody levels then decline

Immunological Memory

- Secondary immune response – re-exposure to the same antigen
 - Sensitized memory cells respond within hours
 - Antibody levels peak in 2 to 3 days at much higher levels than in the primary response
 - Antibodies bind with greater affinity, and their levels in the blood can remain high for weeks to months

Primary and Secondary Humoral Responses



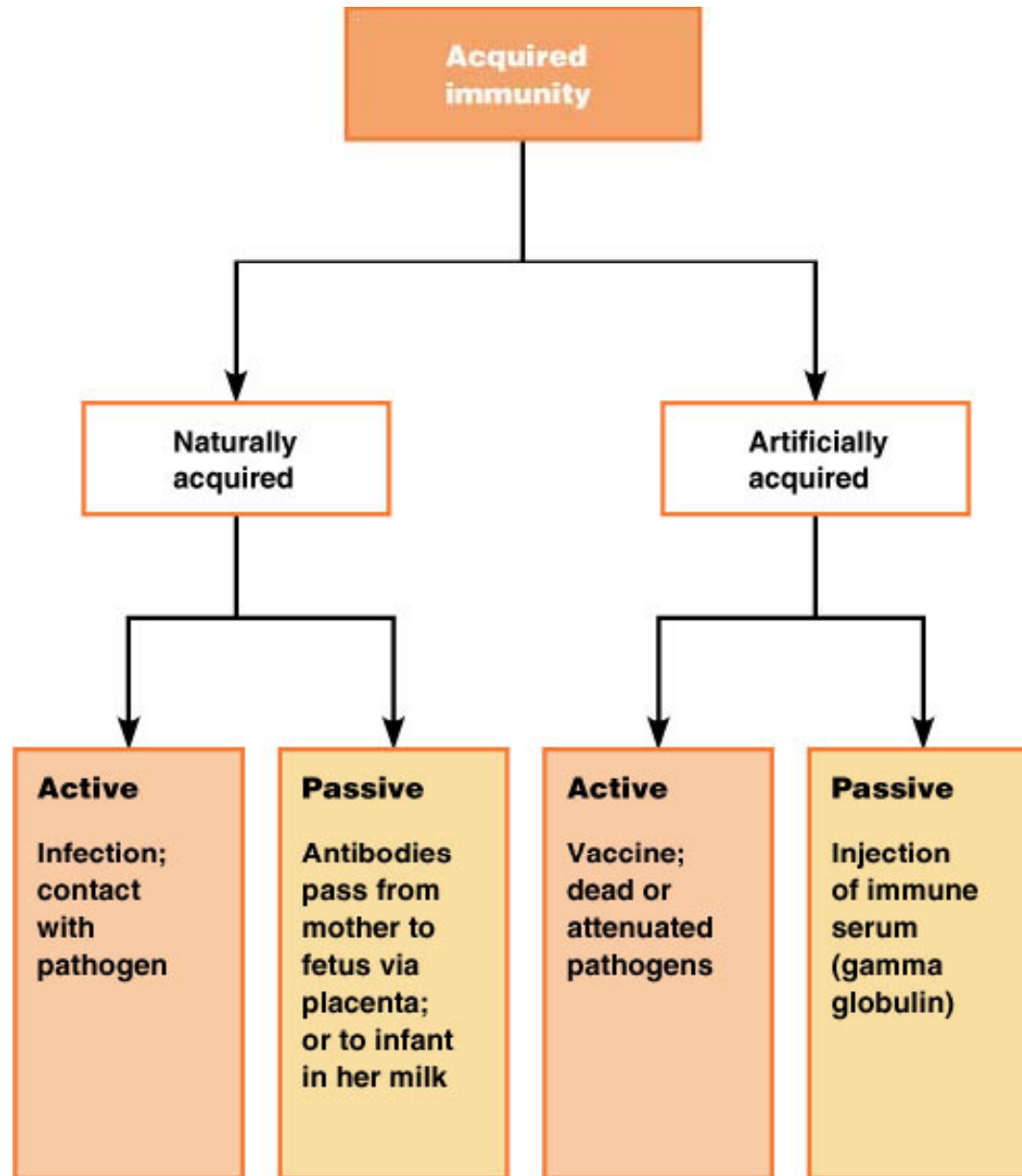
Active Humoral Immunity

- B cells encounter antigens and produce antibodies against them
 - Naturally acquired – response to a bacterial or viral infection
 - Artificially acquired – response to a vaccine of dead or attenuated pathogens
 - Vaccines – spare us the symptoms of disease, and their weakened antigens provide antigenic determinants that are immunogenic and reactive

Passive Humoral Immunity

- Differs from active immunity in the antibody source and the degree of protection
 - B cells are **not challenged by antigens**
 - **Immunological memory does not occur**
 - Protection ends when antigens naturally degrade in the body
- **Naturally acquired** – from the mother to her fetus via the placenta
- **Artificially acquired** – from the injection of serum, such as gamma globulin

Types of Acquired Immunity



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

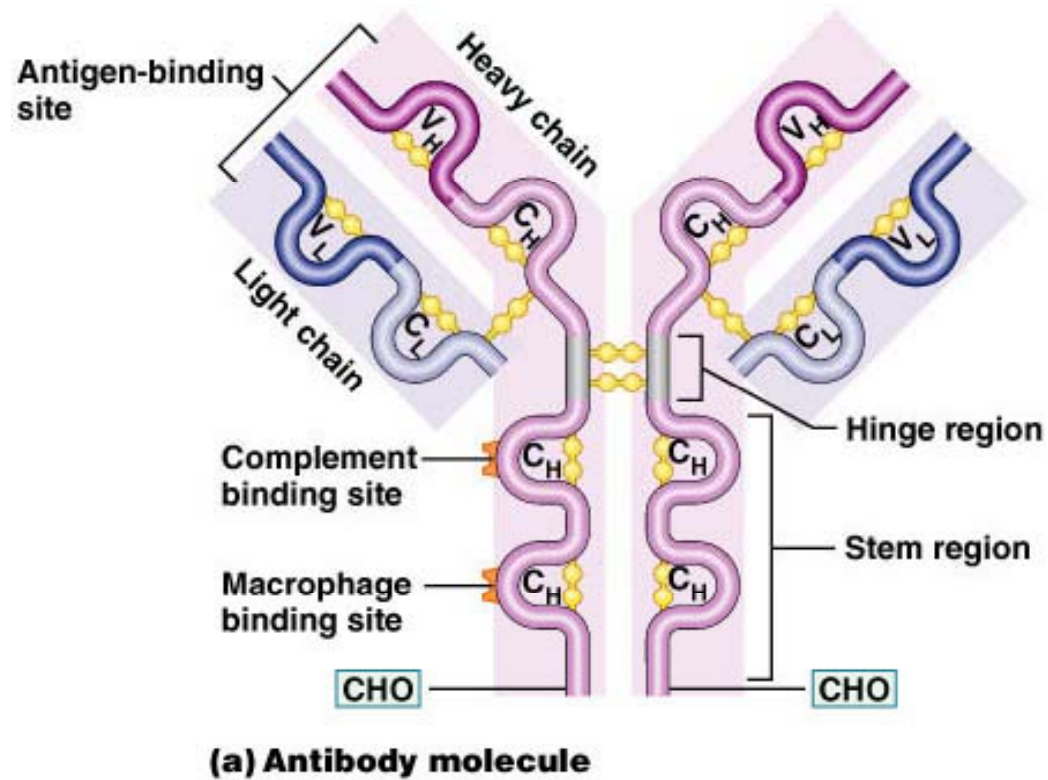
Classes of Antibodies

- 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

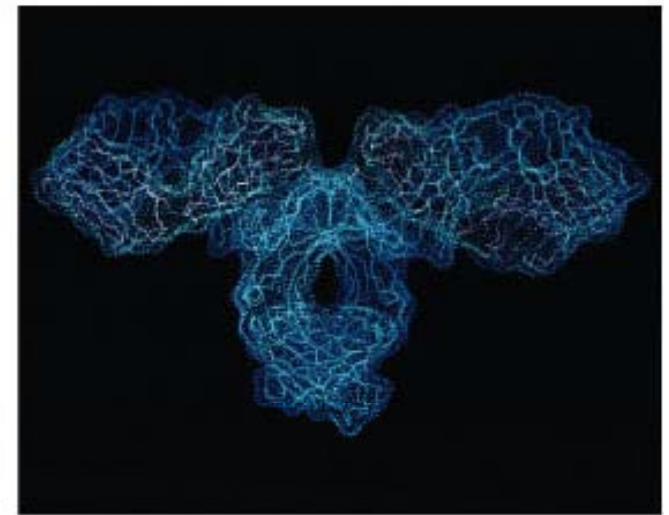
Basic Antibody Structure



Key:

 = Disulfide bond

 = Carbohydrate side chain



(b)

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

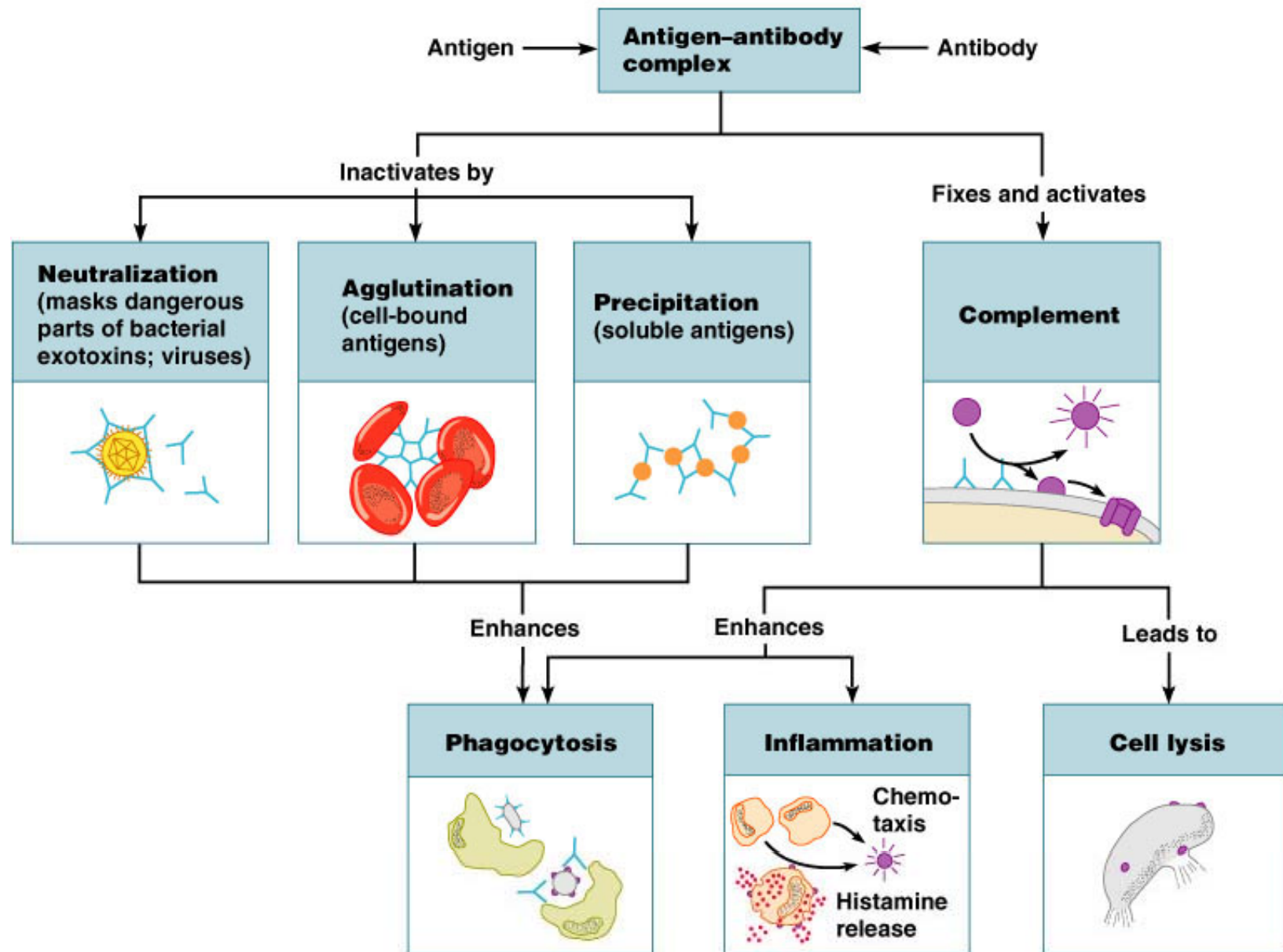
Other Mechanisms of Antibody Action

- 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

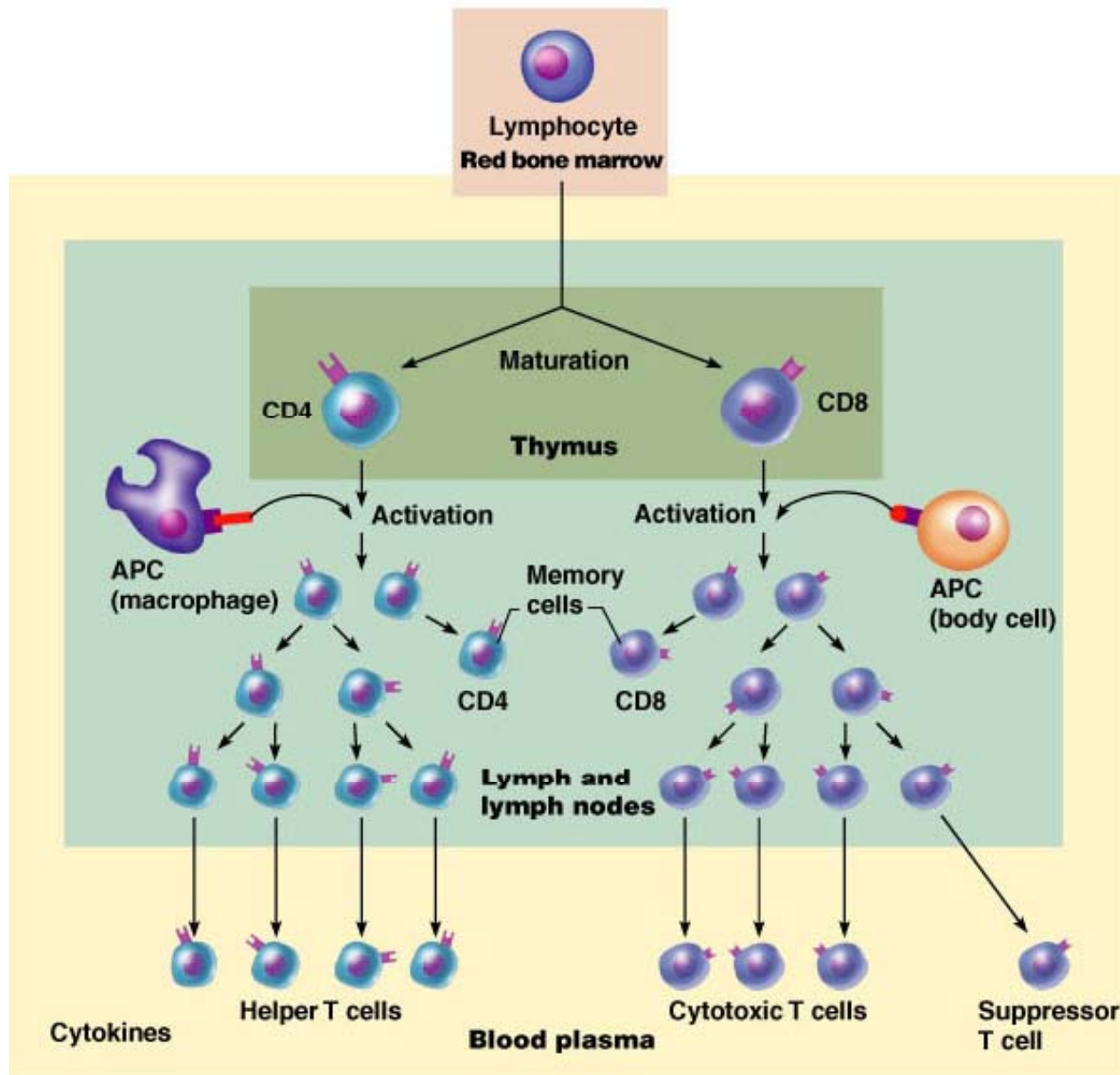
Monoclonal Antibodies

- Hybridomas – cell hybrids made from a fusion of a tumor cell and a B cell
 - Have desirable properties of both parent cells – indefinite proliferation as well as the ability to produce a single type of antibody

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_H)
 - **CD8 cells** (T8 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**

Major Types of 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)

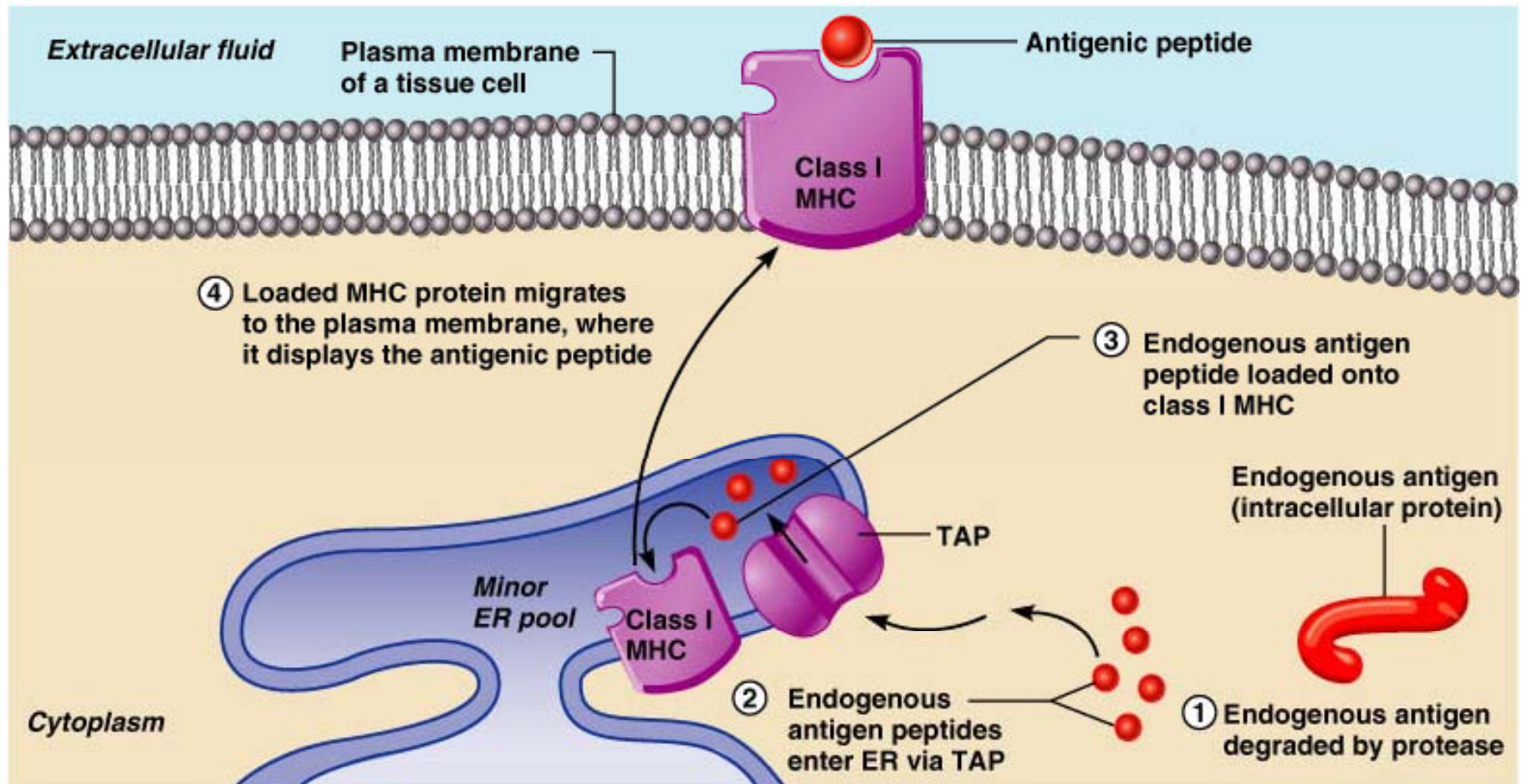
MHC Proteins

- 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



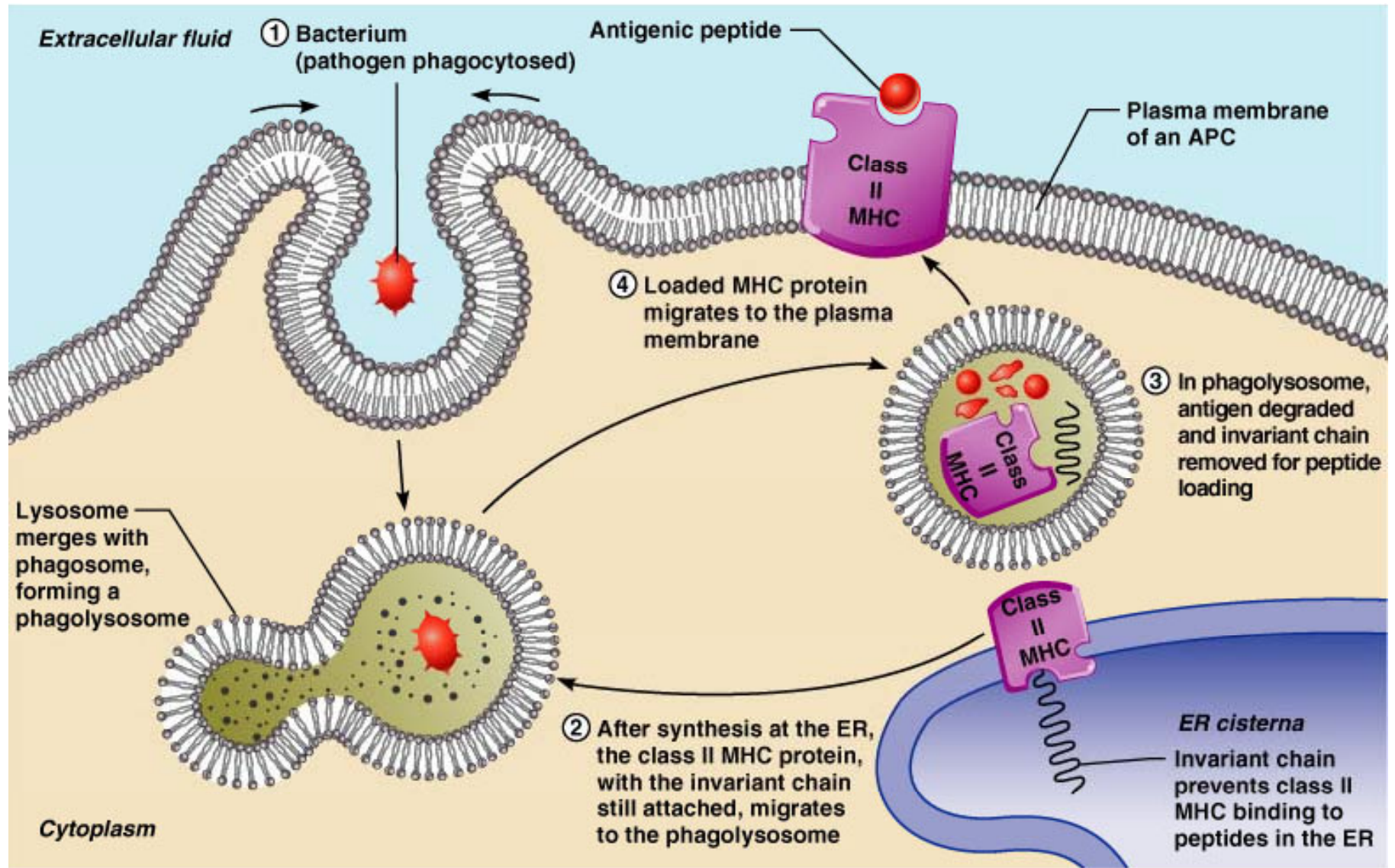
Class II MHC Proteins

- 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-antself 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)

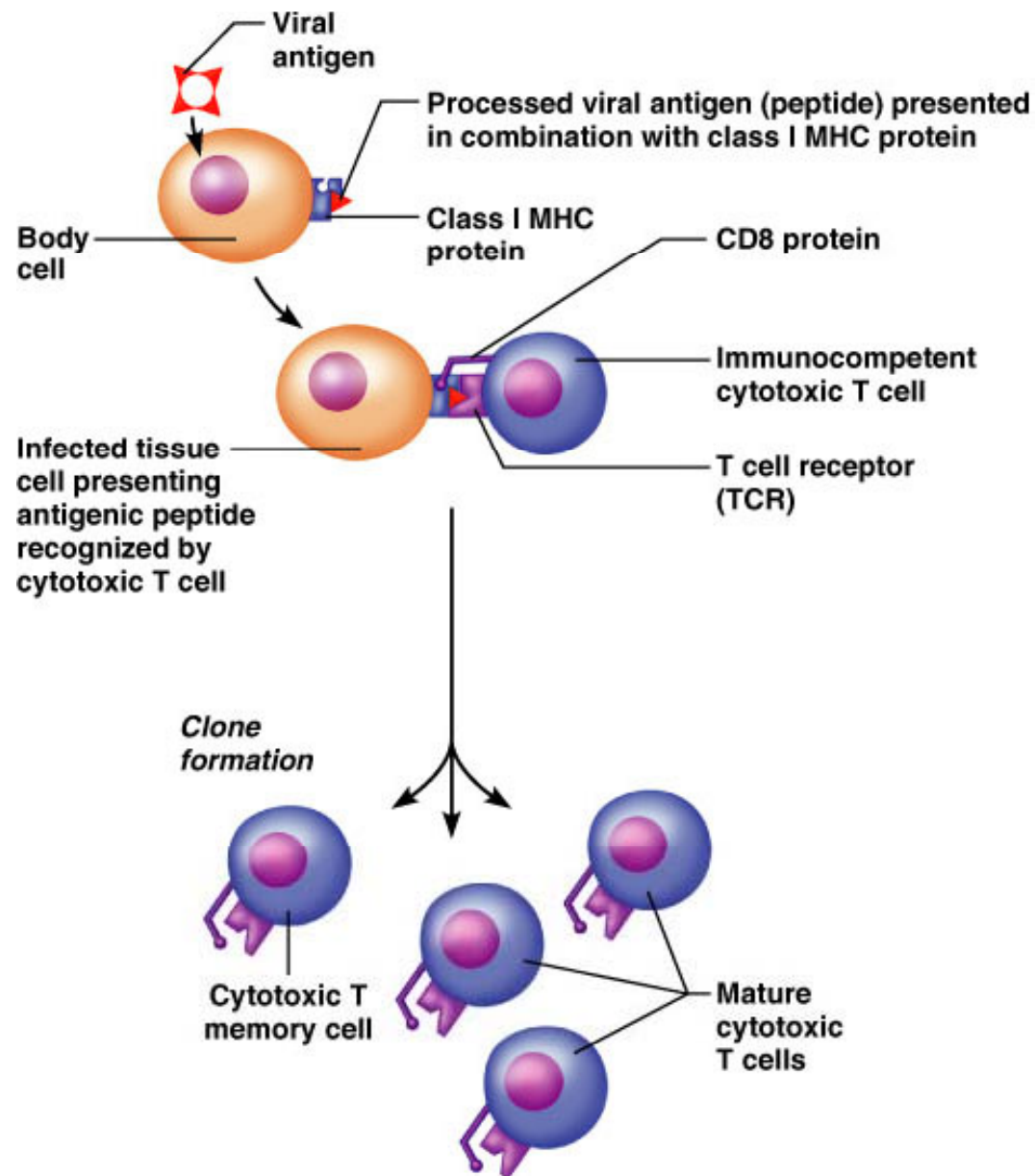
T Cell Activation: Step One – Antigen Binding

- 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

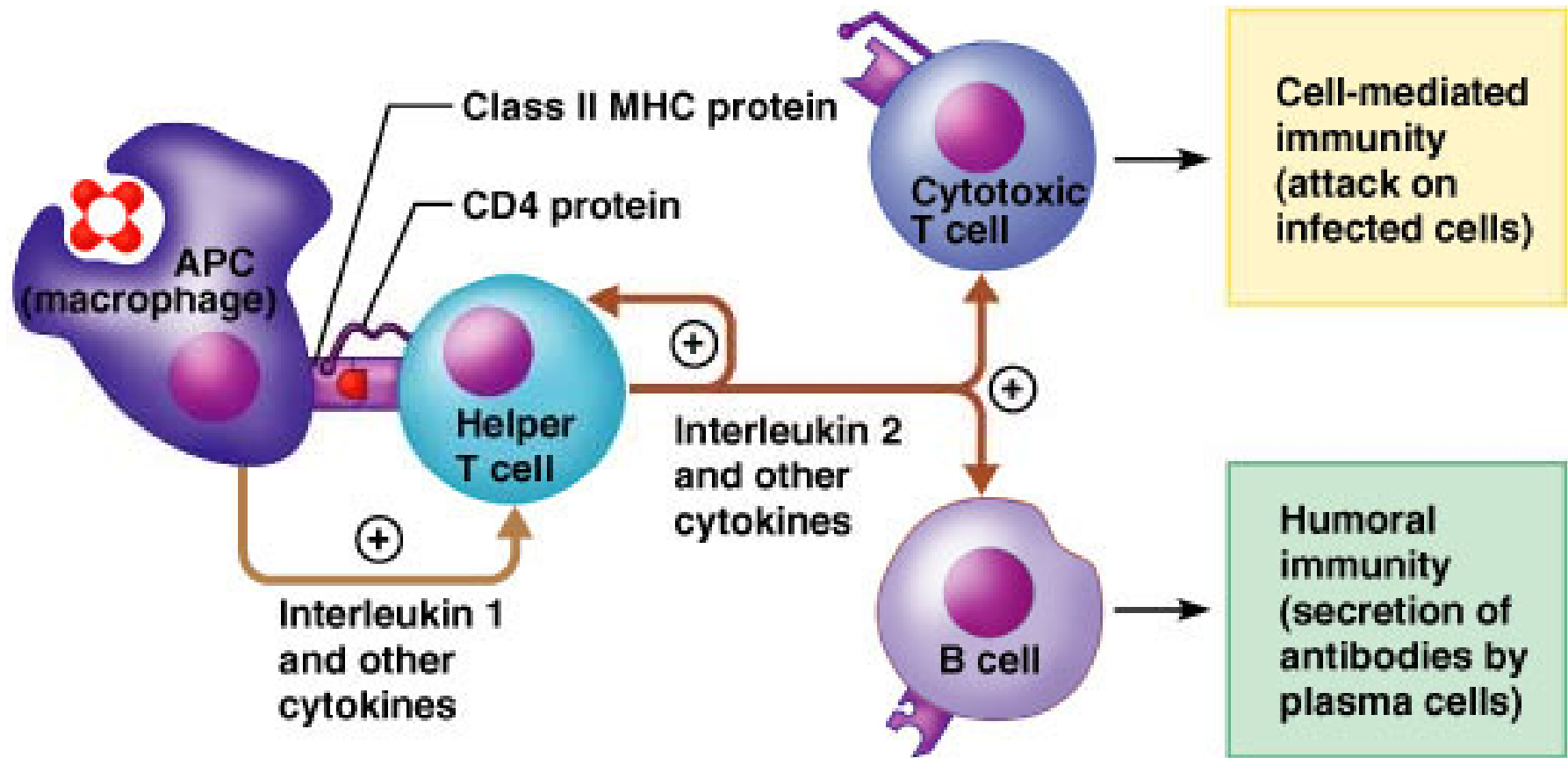
Cytokines

- 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 adaptive 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

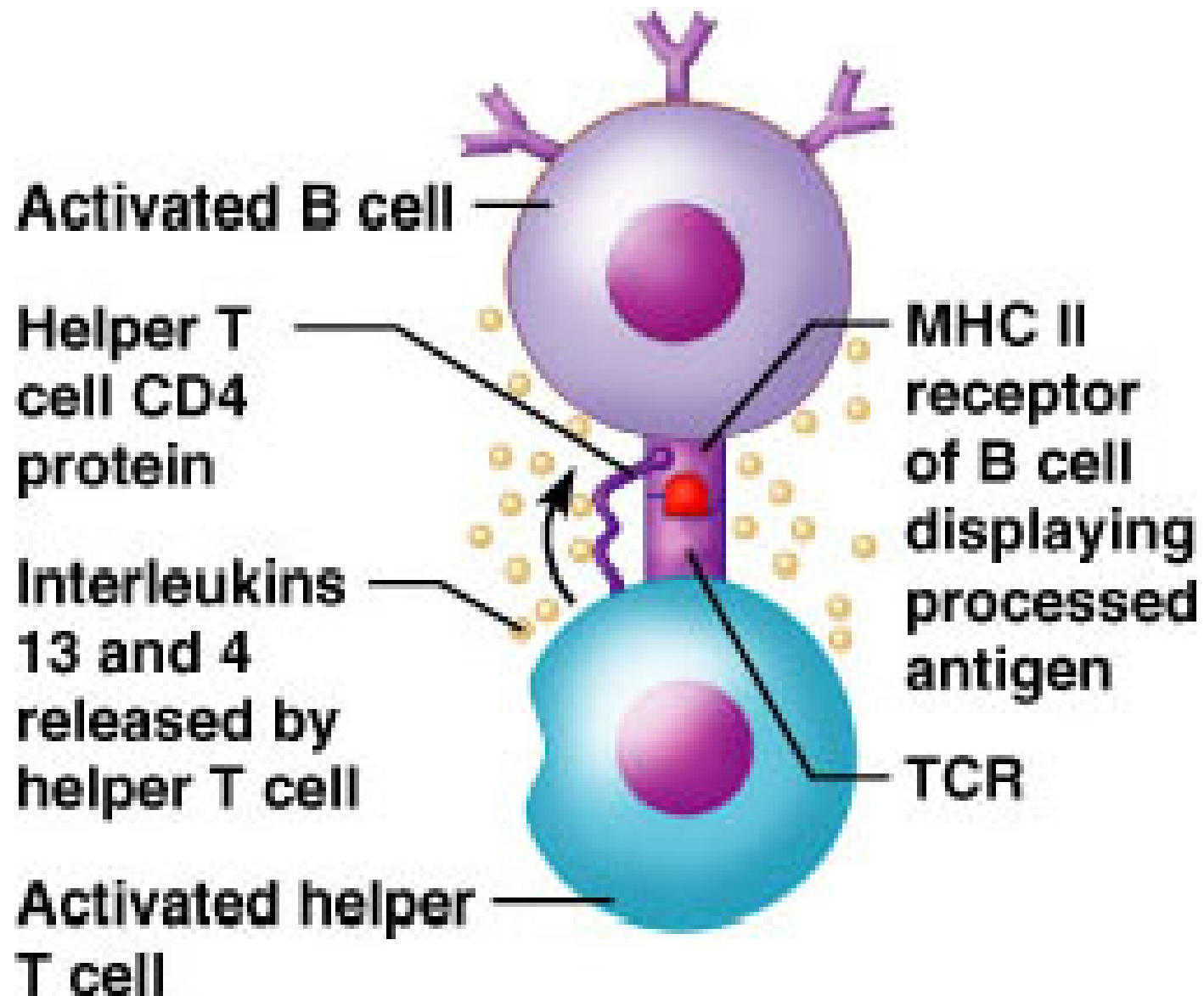
Helper T Cells (T_H)



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**

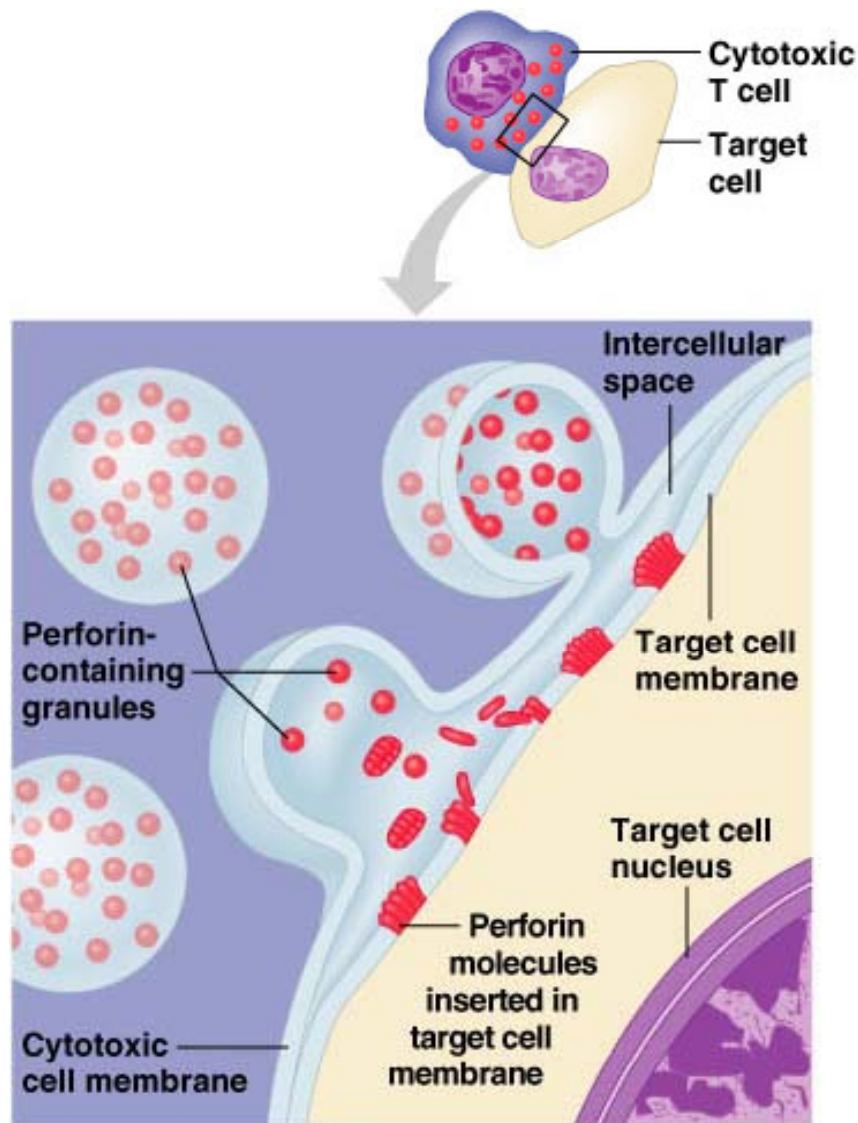
Cytotoxic T Cells

- 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

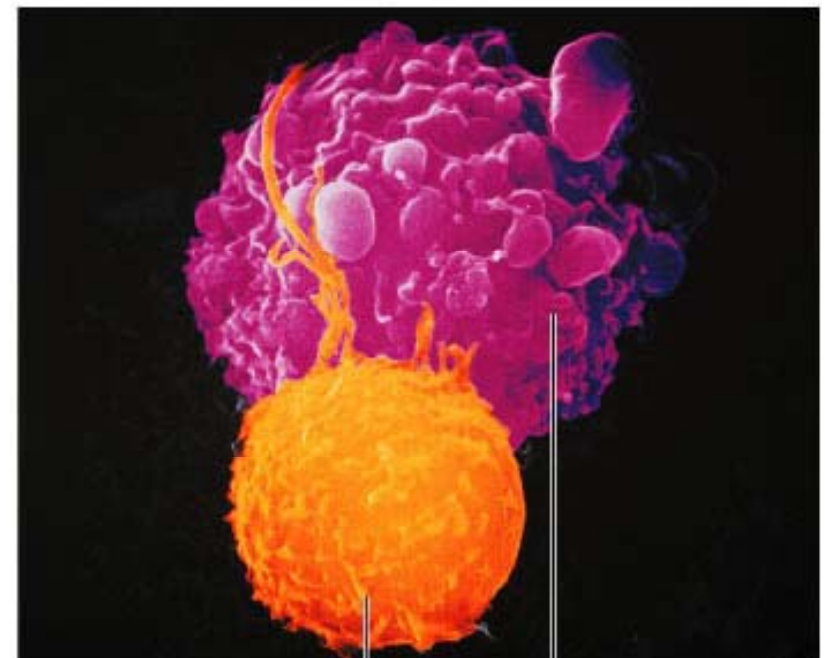
Mechanisms of T_c Action

- 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



(a)



(b)

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

Summary of the Primary Immune Response

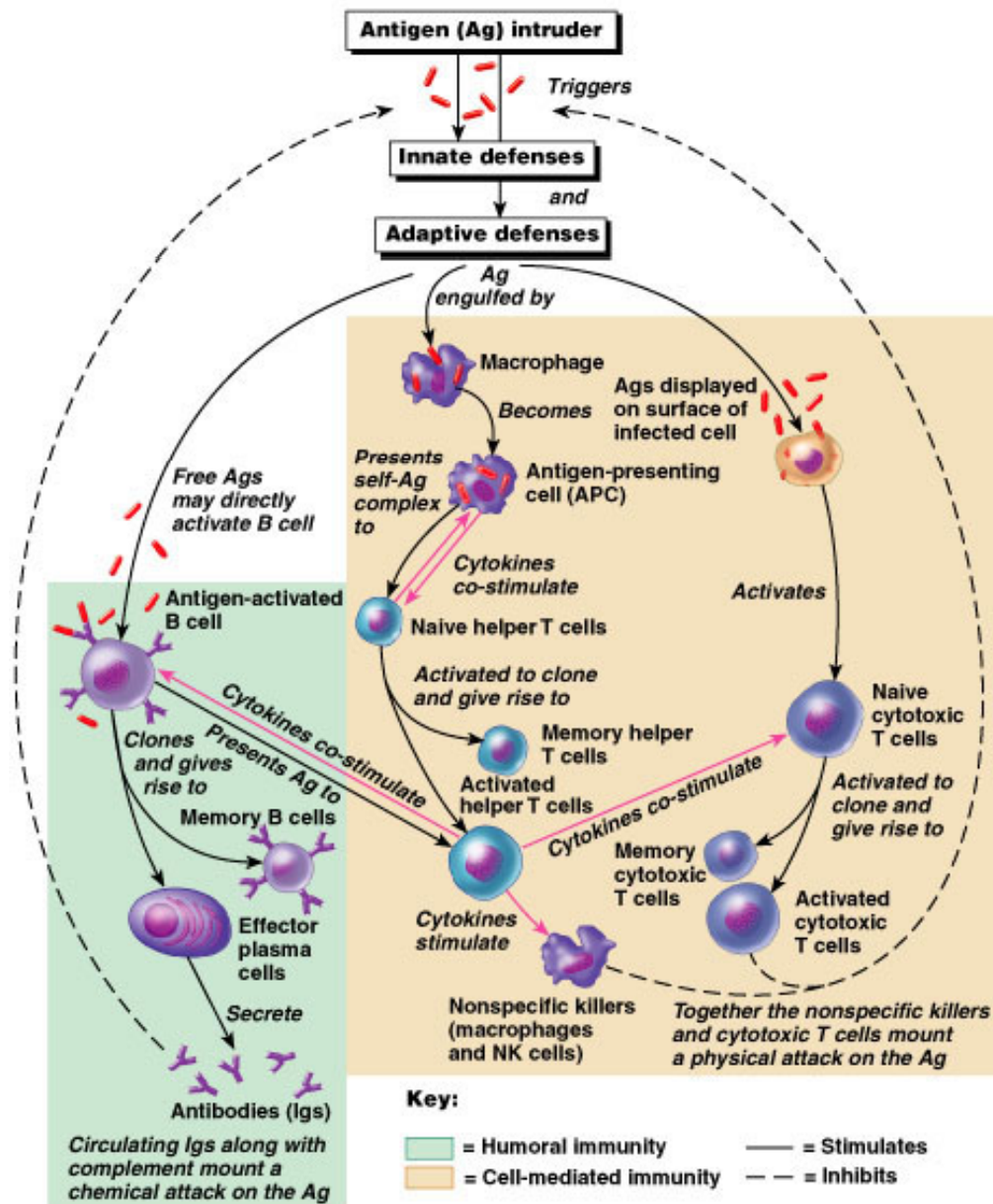


Figure 21.19

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

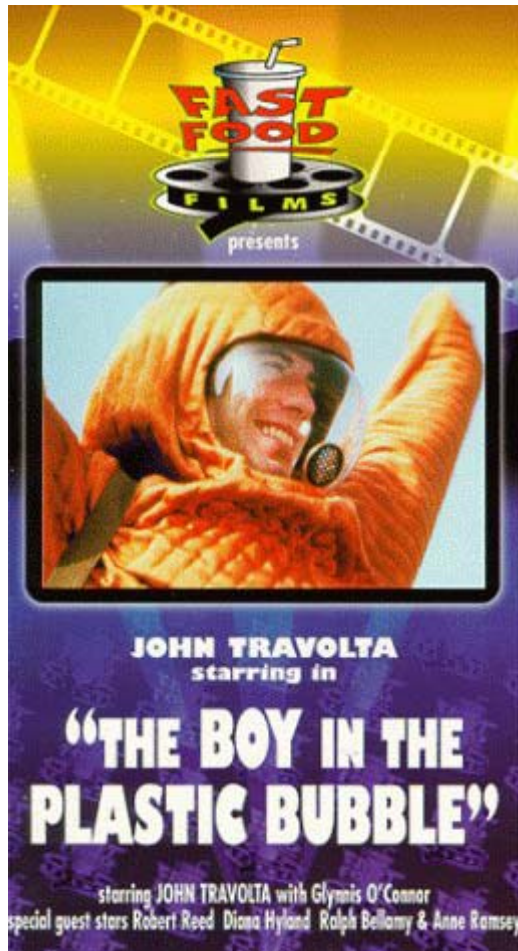
Immunodeficiencies

- Congenital or acquired conditions in which the function or production of immune cells, phagocytes, or complement is abnormal

Severe Combined Immunodeficiency (SCID)

- 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

Severe Combined Immunodeficiency (SCID)



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
 - 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

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

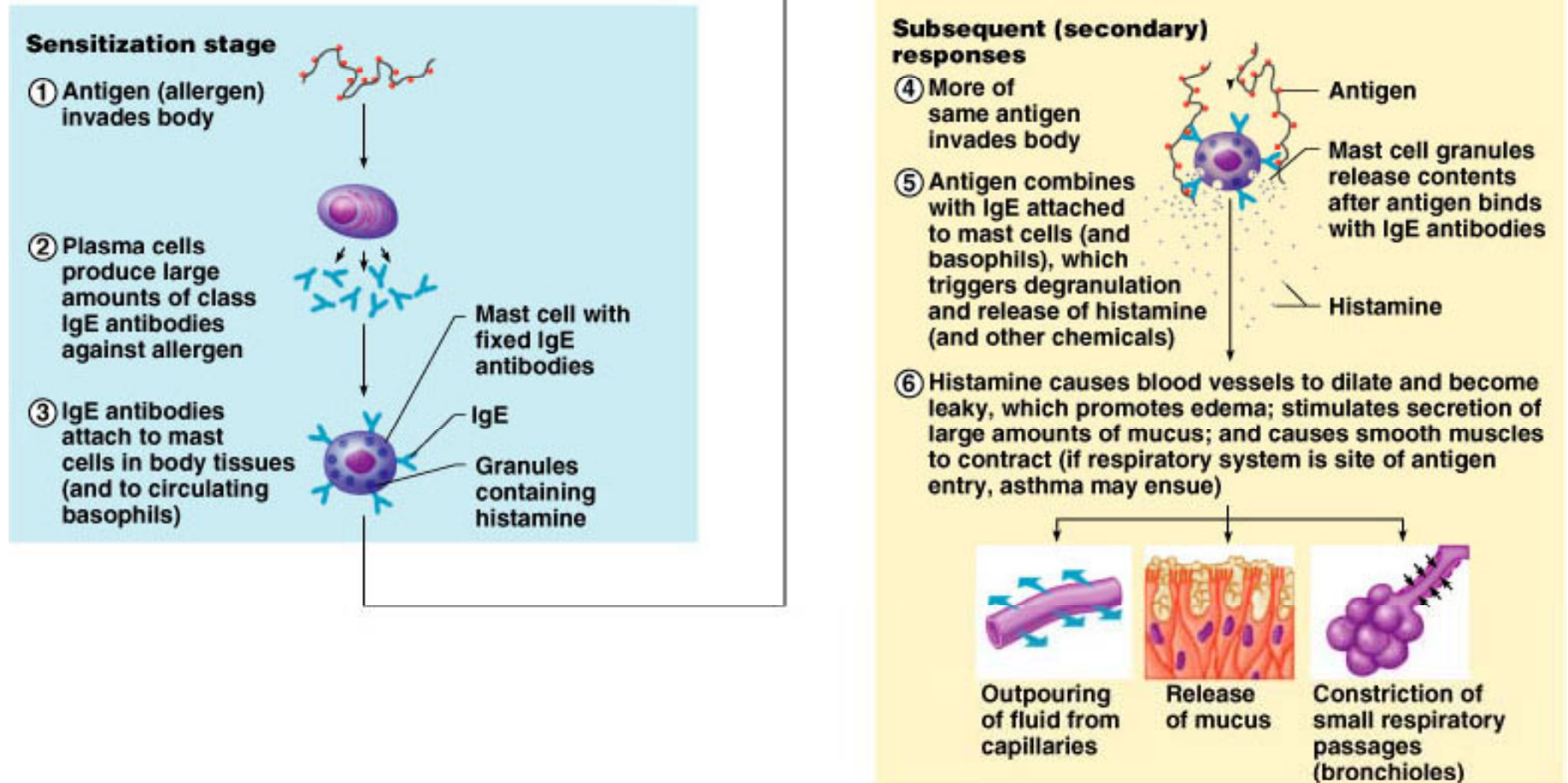
Immediate Hypersensitivity

- 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