Physiology

The Immune System

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Defense Mechanisms

- The Immune System
  - All structure and process that provide a defense against pathogens.
    - Pathogen: a disease-causing agent
  - Is a functional system
    - Includes cells that carry out immune defense
      - Trillions of cells
      - Inhabit lymphatic tissue
      - Circulate in the body fluid
    - Most Important
      - Lymphocyte
      - Macrophage

Defense Mechanisms

- Immune defenses identify self from non-self
  - Protect against microbes
    - Viruses
    - Bacteria
    - Fungi
    - Parasites
  - Isolate or remove nonmicrobial foreign substances
  - Destroy cancer cells
- Function is called Immune surveillance

Defense Mechanisms

- Immunology
  - Study of physiological defenses by which the host destroys or neutralizes foreign matter
    - Both dead and living foreign matter
- Immunity: also called immune defenses
  - Nonspecific or innate:
    - Inherited defense mechanisms.
  - Specific or acquired:
    - Prior exposure (lymphocytes).

Immunity

- Nonspecific immunity
  - Characteristics
    - Can respond immediately to protect against any foreign substance or cell
    - Does not have to recognize specific identity
    - Is genetic
- Specific Immunity
  - Characteristics:
    - Depends upon specific recognition
      - By lymphocytes
    - Attack is unique to the substance or cell
- Work together:
  - Nonspecific "sets the stage for specific

The Players

- Cells
  - All leukocytes
  - Notable derivatives or relations
    - Plasma cells
    - Macrophages
    - Macrophage-like cells (not descended from macrophages)
    - Mast cells

The Players

- Chemicals
  - Cytokines
    - Protein messengers released from cells
      - Regulate cell growth and development in both nonspecific and specific defenses
    - Act as paracrine agents mostly
    - Sometimes have hormone effects
      - Circulate in blood
    - Physiology is complex

Nonspecific Immunity

- General information:
  - Also called nonspecific body defenses
  - Includes:
    - Membrane barriers
    - Array of cells and chemicals on initial "battlefronts"
  - Species resistance: inherited nonspecific resistance

Nonspecific Immunity: MB

- Surface Membrane Barriers
- First Line of Defense
  - Intact epithelial barriers
  - Are physical barriers
- External: epithelial membranes
  - Skin. (cutaneous membrane)
    - Keratin
      - Resist weak acids and bases
      - Resist bacterial enzymes and toxins
  - Mucous membranes:
    - Outer surface of eye
    - Lines exterior-exposed body cavities
      - GI tract.
      - Respiratory tract.
      - Urinary tract.
      - Reproductive tract.

Nonspecific Immunity: MB

- Protective Chemicals
  - Acid pH of skin secretions
    - Decrease bacterial growth
    - SEBUM: contains chemicals toxic to bacteria
    - Vaginal secretion: very acidic
  - Stomach mucosa: secretions kill pathogens
    - HCL
    - Pepsin
  - Saliva: washes oral cavity and teeth
    - Contains LYSOZYME: kills bacteria
  - Lacrimal fluid: washes external eye surface
    - Contains LYSOZYME
  - Mucus
    - Traps microorganisms (sticky)
- Other Protective devices
  - cilia

Nonspecific Immunity: cells and chemicals

- OVERVIEW
- Enormous number of cellular and chemical defenses
  - Need way to distinguish self from nonself
  - Need general characteristic marking an invader
- Most common IDENTIY TAGS
  - Classes of carbohydrate and lipid in bacterial cell walls
  - Can be recognized by immune cells and defense plasma proteins (eg: complement)
    - Bind to invaders
  - Key difference between specific and nonspecific defense

Nonspecific Immunity: cells and chemicals

- OVERVIEW: continued
- Most significant methods:
  - Phagocytosis and Natural killer cells
  - Inflammatory Response
    - Cells enlisted:
      - Macrophages
      - Mast cells
      - WBCs in general
    - Many kinds of chemicals
      - Some help kill pathogens
      - Some help repair tissues

Nonspecific Immunity: cells and chemicals

- OVERVIEW: continued
  - Antimicrobial Substances
    - Antibacterial proteins
      - Called COMPLEMENT: mostly made by hepatocytes
      - in blood
    - Antiviral proteins
      - Called INTERFERON
      - Released by virus-infected cells
  - Fever:
    - Systemic response.
    - High temperature:
      - Inhibits microbial replication.
      - Enhances body repair.

Nonspecific Immunity: cells and chemicals

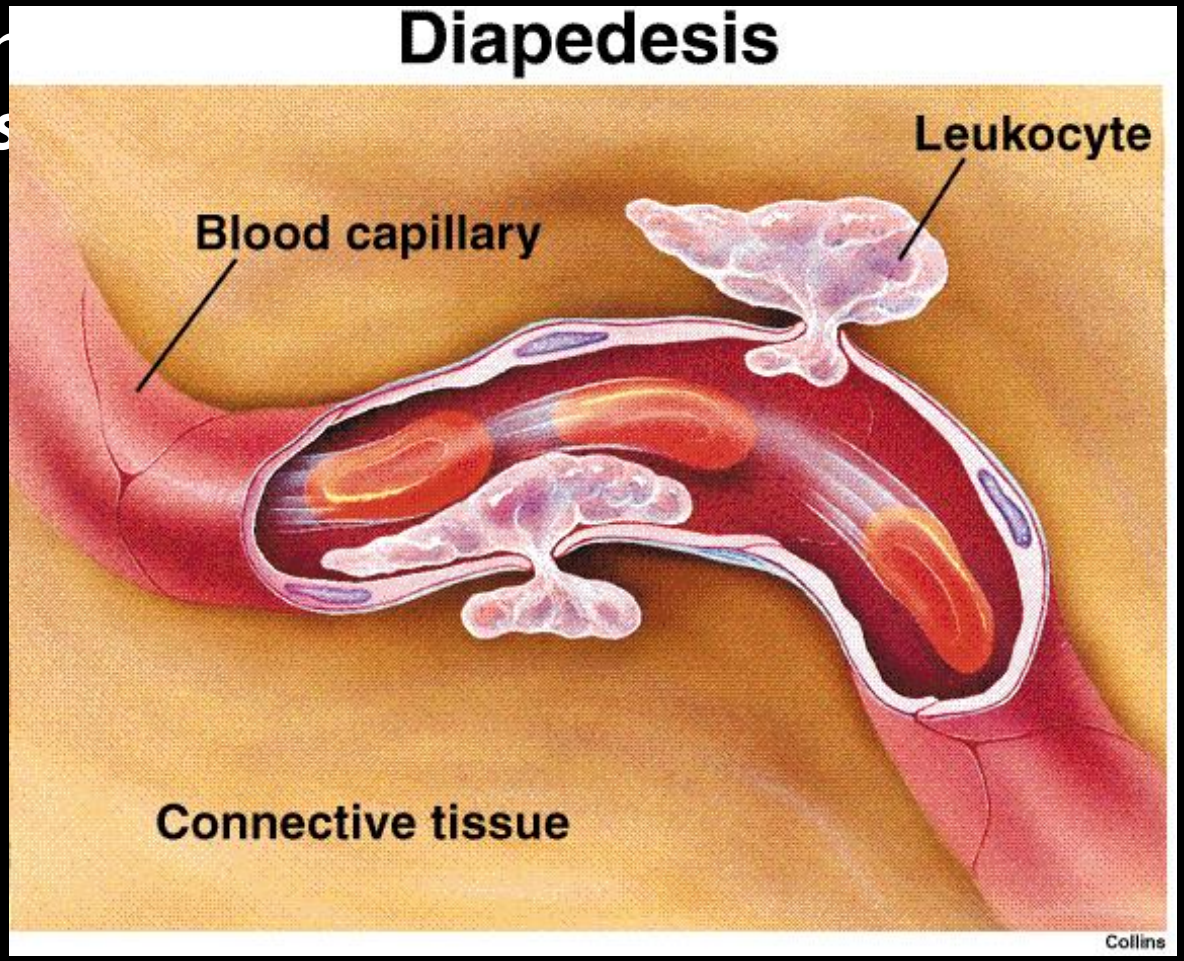
- Phagocytosis: ingestion and destruction of particulate matter
  - One of most important nonspecific defenses
- Based on ability to distinguish between the kinds of carbohydrates that are produced by mammalian cells and those produced by bacteria.
  - Bacterial carbohydrates flag the cell for phagocytic attack.
- 3 major groups of phagocytic cells:
  - Neutrophils: 1st to arrive at infection.
  - Mononuclear phagocyte system:
    - Macrophages and monocytes.
  - Organ-specific phagocytes.
    - Kupffer cells
    - Langerhans cells
    - Histocytes

Phagocytosis

- Method of Action
  - Ingestion
    - Form PHAGOSOME
    - Fuse with lysosome
    - NOT ALWAYS SUCCESSFUL
      - Must adhere first
      - "Rougher" the surface the better
      - "Roughened" by:
        - Complement proteins
        - antibodies

Phagocytosis

- Neutrophils and m
through tiny gaps
cells.

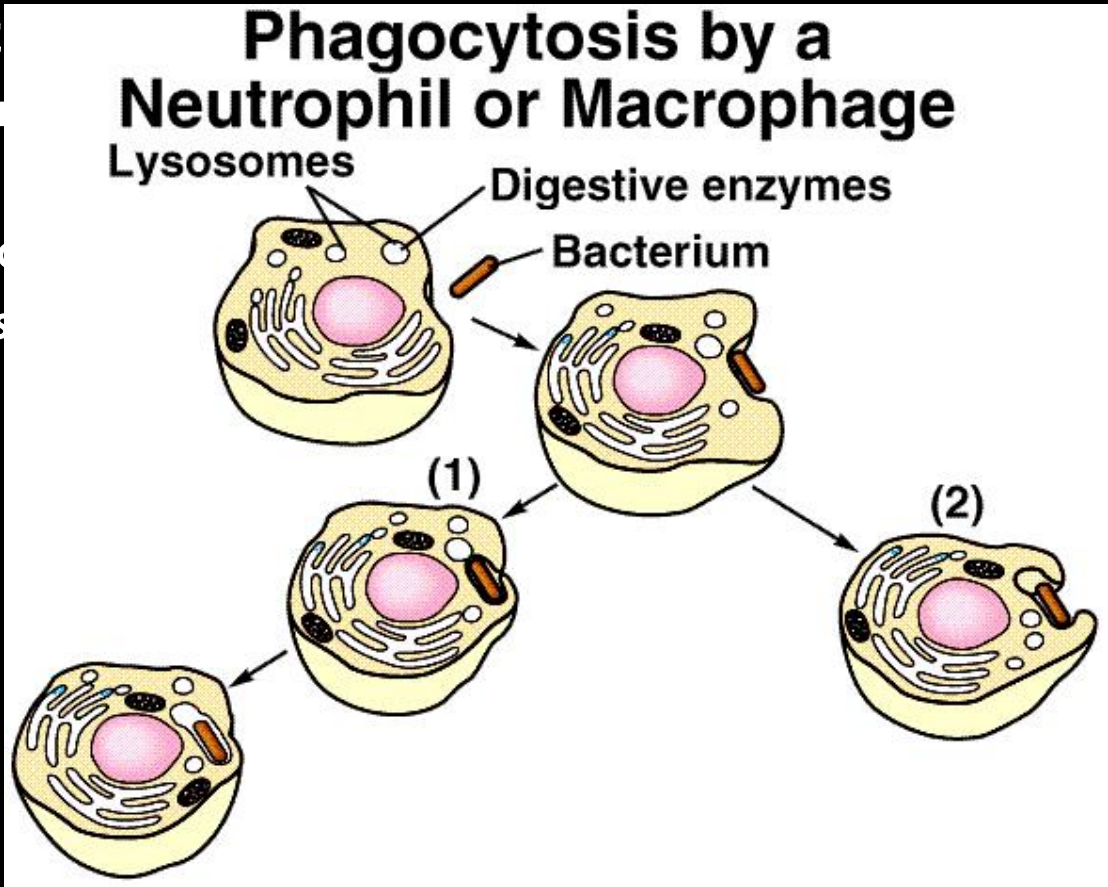


Phagocytosis

- Destruction
  - By macrophages and neutrophils
  - Intracellular digestion
    - Activate lysosomal enzymes
    - Produce RESPIRATORY BURST
      - Liberates free radicals
      - Potent cell-killing abilities
  - Extracellular Destruction
    - Neutrophils
    - Release oxidizing substances
    - Effectively kills cells
      - Also kills neutrophils
      - May damage tissue cells

Phagocytosis

- Phagocytes engulf part
  - Particle becomes surrou
  - Forms vacuole.
  - Vacuole fuses with lysos
  - Lysosomes can be releas



Phagocytes

Intracellular killing of microbes

Chemical secretion

Regulate inflammation
Extracellular killing
Activation of clotting or anti-clotting
Hormonal regulation

Natural Killer (NK) Cells

- Lymphocytes that are related to T cells.
- Do not need specific antigen recognition
  - Do not require prior exposure for sensitization to the tumor antigens
  - NK cells destroy tumors in a nonspecific fashion.
- Roam body in blood and lymph
- Method of action:
  - Lysis of cancer cells
  - Lysis of viras-infected body cells
- Act before Immune Response
  - Provide first line of cell-mediated defense.
  - Stimulated by interferon.

Inflammatory Response

- Second major kind of nonspecific cellular and chemical defense
  - Considered second line of defense
    - Involves interaction of cells, chemicals and tissue fluid
  - Occurs when:
    - Surface barriers are breached
    - Tissues are injured by physical factors
      - Heat/cold
      - UV radiation
      - Ionizing radiation (x-rays)
      - Physical trauma

Inflammatory Response

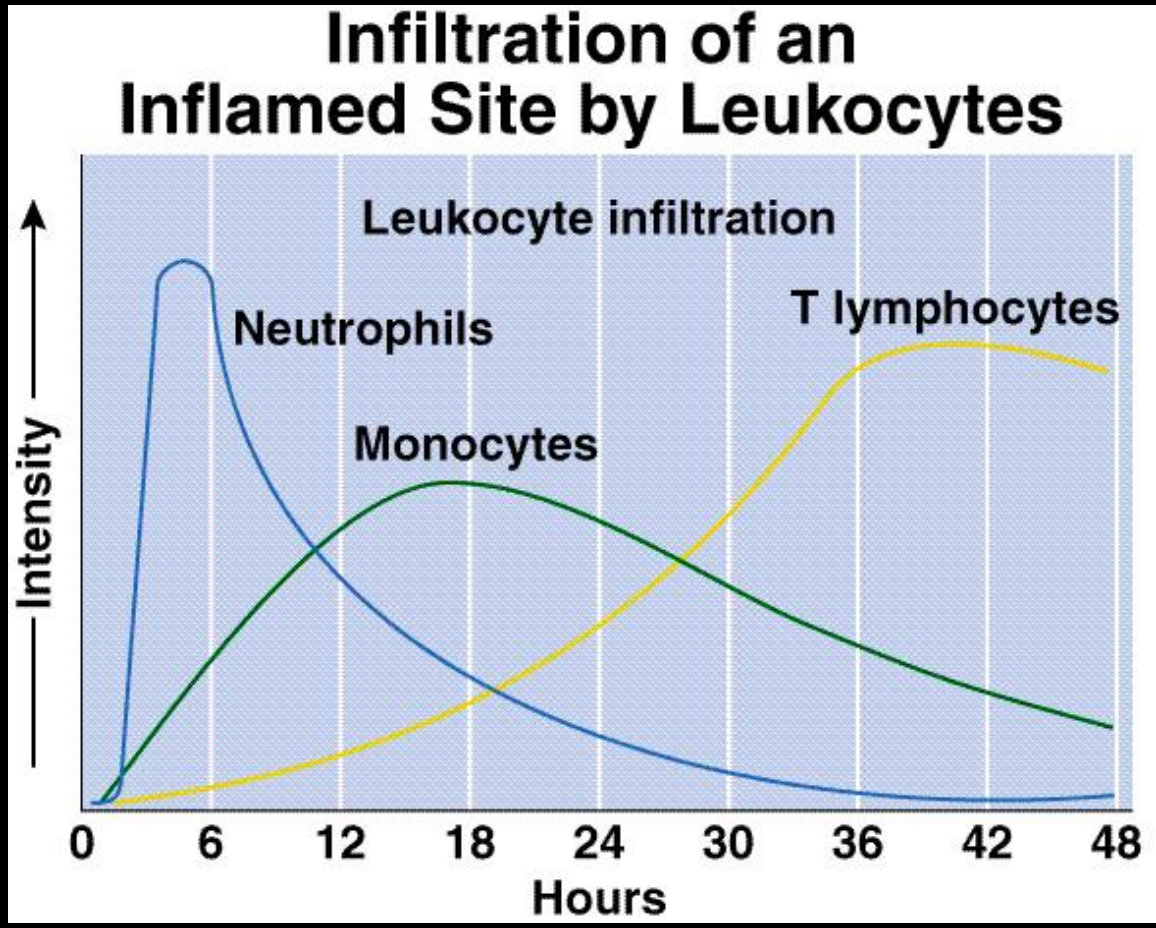
- Principle effects
  - Prevents spread of injurious agent
  - Disposes of cellular debris and pathogens
  - Sets stage for repair
- Acute inflammation
  - Short term
  - 4 cardinal signs
    - Swelling
    - Redness
    - Heat
    - pain

Local Inflammation

- Inflammatory reaction initiated by phagocytosis and complement activation.
- Complement activation attracts new phagocytes to the area.
- B lymphocytes are stimulated to produce antibodies against specific antigens.
  - Activates complement.
  - Antibodies promote phagocytic activity.

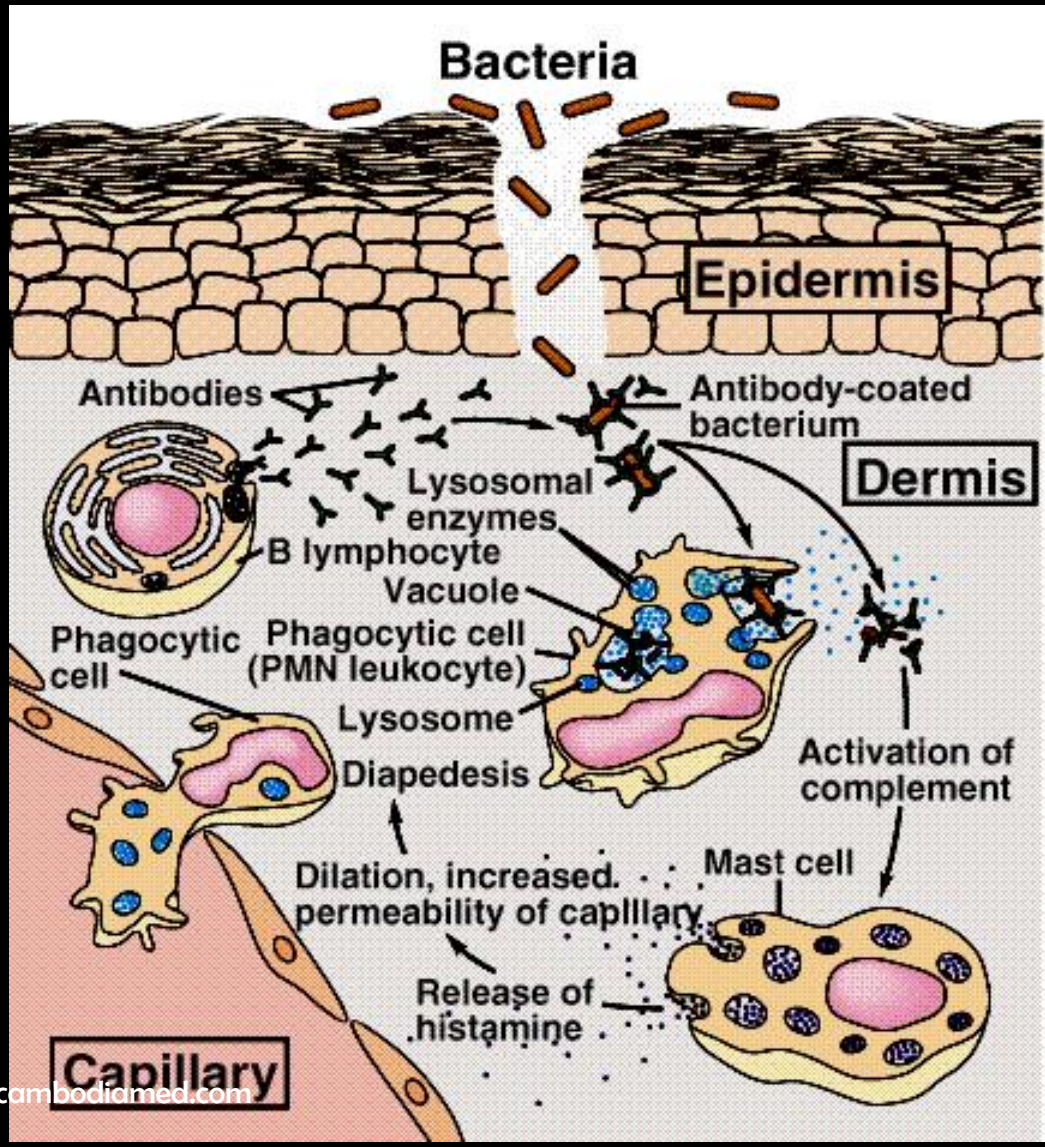
Local Inflammation

- Leukocytes interact with adhesion molecules in endothelial cell.
- Chemotaxis attracts leukocytes.
- Via diapedesis, leukocytes guide more leukocytes to site of infection.
- First to arrive are neutrophils, then monocytes, and T lymphocytes.



Local Inflammation

- Mast cells release histamine and secrete TNF-alpha.
  - Increases membrane permeability.
  - Vasodilation.
  - Recruit neutrophils.



Local Inflammation

- Characteristic effects of inflammation:
  - Redness and warmth.
  - Swelling (edema).
  - Pus (dead leukocytes).
  - Pain.
  - Endogenous pyrogens.

Antimicrobial Substances

- Third major kind of nonspecific cellular and chemical defense
- Includes complement and interferon
- Considered a second line of defense

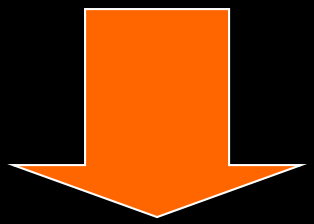
Complement

- Also called the complement system
- General points
  - Group of ~ 20 plasma proteins
  - Usually inactive
  - Major system to destroy foreign substances
  - Nonspecific
  - Works with and overlays other methods of defense

Complement Proteins

- Complements (or enhances) nonspecific and specific defenses.
- The combination of antibodies with antigens does not cause destruction of the antigens or pathogen.
- Antibodies serve to identify the targets for immunological attack.
- Identified antibodies activate the complement against specific invaders.

Activated Complement Proteins



Direct destruction by MAC
(membrane attack complex)
Vasodilation
Increased capillary permeability
Chemotaxis
Opsinization
(antibodies stimulate phagocytosis)

Complement Types

- Two major pathways.
- **Classical**:
  - 11 proteins
    - C1 – C9
      - C1 actually 3 protein
  - Initiation
    - Antibodies bind to pathogen
    - C1 binds to AP complex
    - Complement activated in sequence.
- Alternate Pathway
  - Triggered by interaction of 3 plasma proteins
    - Factors B, D, and P
    - These interact with carbos on cell surface of
      - Bacteria
      - Parasites
      - fungi

Complement Types

- Classical
- 11 complement proteins, designated C-1 to C-9.
- Complement proteins can be subdivided into 3 components:
  - C1: recognization.
  - C4, C2, C3: activation.
  - C5-C9: attack (complement fixation).

Complement Fixation

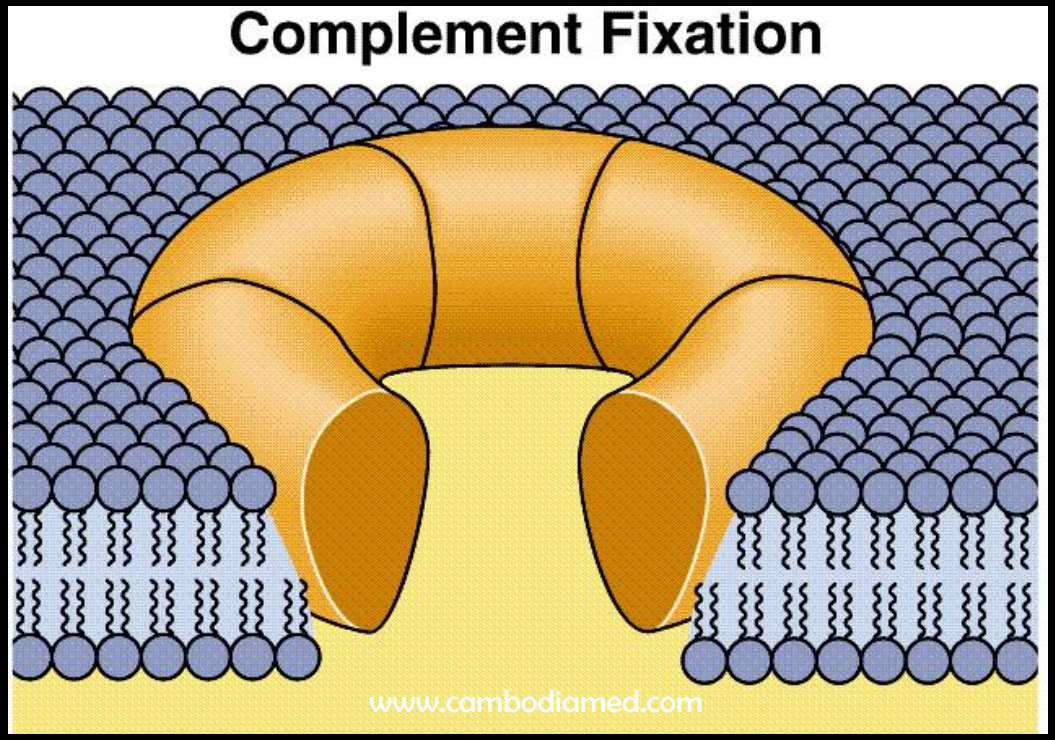
- Complement proteins attach to the cell membrane and destroy it.
- Antibodies of IgG and IgM attach to antigens on invading cell membranes, bind to C1 activating the process.
- Activated C1 hydrolyzes C4 into $C4_a$ and $C4_b$.
- $C4_b$ binds to the cell membrane.
- $C4_b$ splits C2 into $C2_a$ and $C2_b$.

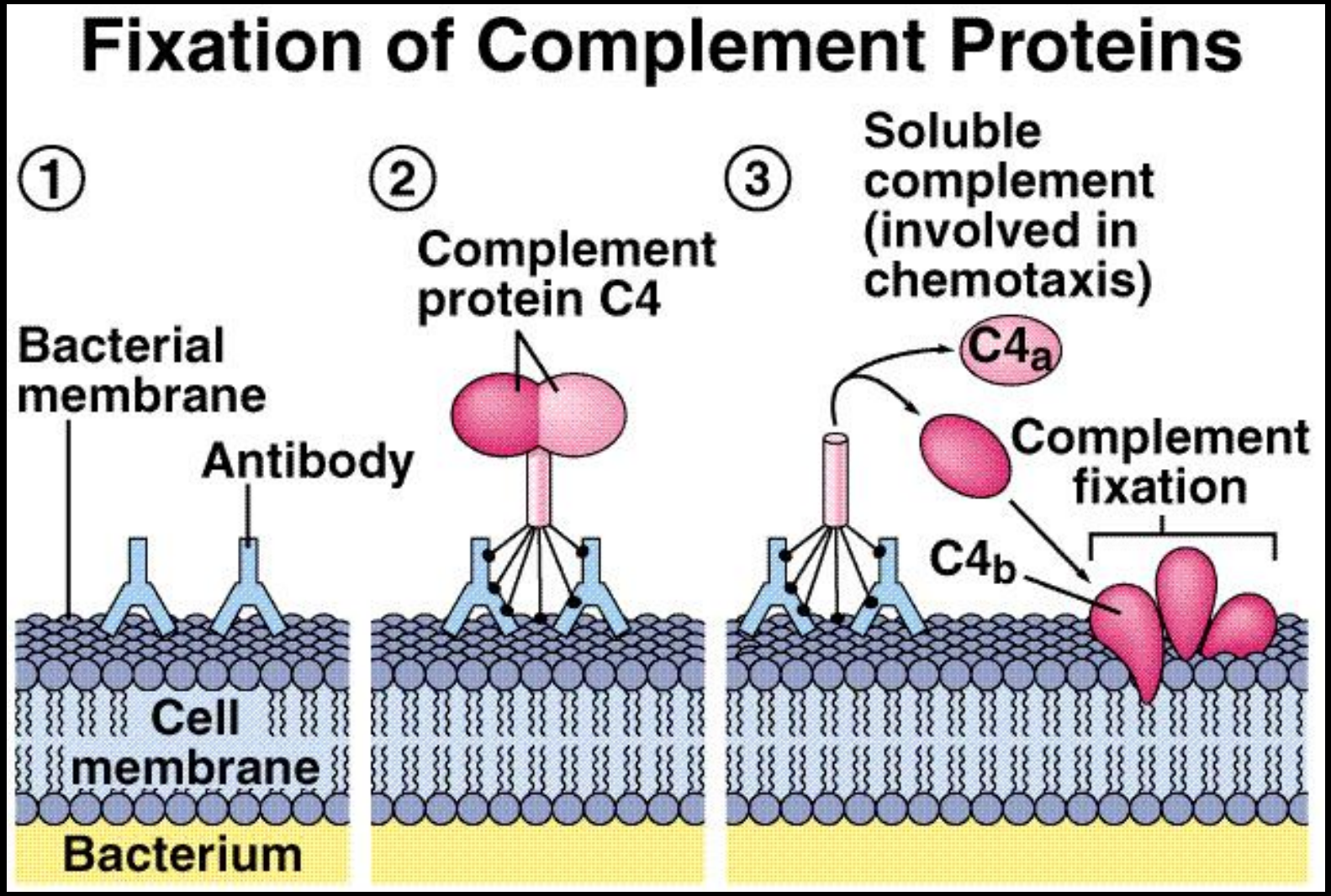
Complement Fixation

- $C2_a$ attaches to $C4_b$ and cleaves C3 into $C3_a$ and $C3_b$.
- Fragment $C3_b$ becomes attached to the complex in the cell membrane.
- $C3_b$ converts C5 to $C5_a$ and $C5_b$.
- $C5_b$ and C6 through C9 become fixed to the cell membrane.

Complement Fixation

- Complement proteins C5 to C9 create large pores in membrane, causing osmotic influx of H_2O.
- Complement proteins kill the cell.





Complement Fragments

- Complement fragments:
  - Chemotaxis:
    - Attract phagocytes.
  - Opsinization:
    - Phagocytes have receptors for $C3_b$.
    - Form bridges between phagocyte and victim cell.
  - Histamine release:
    - Increase blood flow and capillary permeability.
    - Bring in more phagocytes.

Interferon

- **Interferons (cytokines)**
  - Nonspecific, short-acting resistance to viruses.
  - Act as messengers that protect other cells in the vicinity from viral infection.
  - Produced by most body cells
    - α inhibit viral replication, increases NK cells, induces MHC-I antigens.
    - β inhibit viral replication, increases NK cells, induces MHC-I antigens.
  - Produced by certain lymphocytes, NK cells
    - γ activates macrophages, induces MHC-II antigens.
    - Defense against infection and cancer

Fever

- Third major kind of nonspecific cellular and chemical defense.
- Hypothalamus regulates body temp
  - Thermoregulatory center.
- Reset upward by endogenous pyrogen
  - May be interleukin-1 beta
    - First produced as a cytokine by WBCs
    - Then produced by the brain.

Nonspecific Immunity

- **Endogenous pyrogens:**
- Cell wall of gram – bacteria contains endotoxin.
- Endotoxin stimulates monocytes and macrophages to release cytokines:
  - Interleukin-1, interleukin-2, TNF (tumor necrosis factor):
  - Increased activity of neutrophils.
  - Increased production of interferon.
  - Produce fever, increase sleepiness, and decrease plasma iron.

Adaptive (Specific) Immunity

- General Information
  - Third line of defense: the immune response
  - Functions:
    - Amplify the inflammatory response
    - Activate complement
    - Specific defense against specific antigens
    - Adaptive defense
    - Has memory

Adaptive (Specific) Immunity

- Two aspects:
  - Humoral and Cell-mediated
  - Humoral Immunity
    - Involves B-cells
      - Produce antibodies
      - Kinds
        - Plasma cells
        - Memory cells
    - Attack:
      - Bacteria
      - Free viruses

Adaptive (Specific) Immunity

- Two aspects: continued
  - Cell-mediated immunity
    - Involves T-cells
      - Direct cellular attack
      - Also release chemical mediators
    - Kinds
      - Regulatory cells
        - Helper T (2 kinds)
        - Suppressor T
      - Effector cell
        - Cytotoxic T
      - Memory T
    - Attack
      - Cells infected with viruses, intracellular parasites

Adaptive (Specific) Immunity

- Requires prior exposure
  - Can be through immunization
- Results in the production of antibodies
  - Responsible for the immunity
  - Are specific in action
  - Produced by B-lymphocytes
  - Produced in response to antigens

Antigens

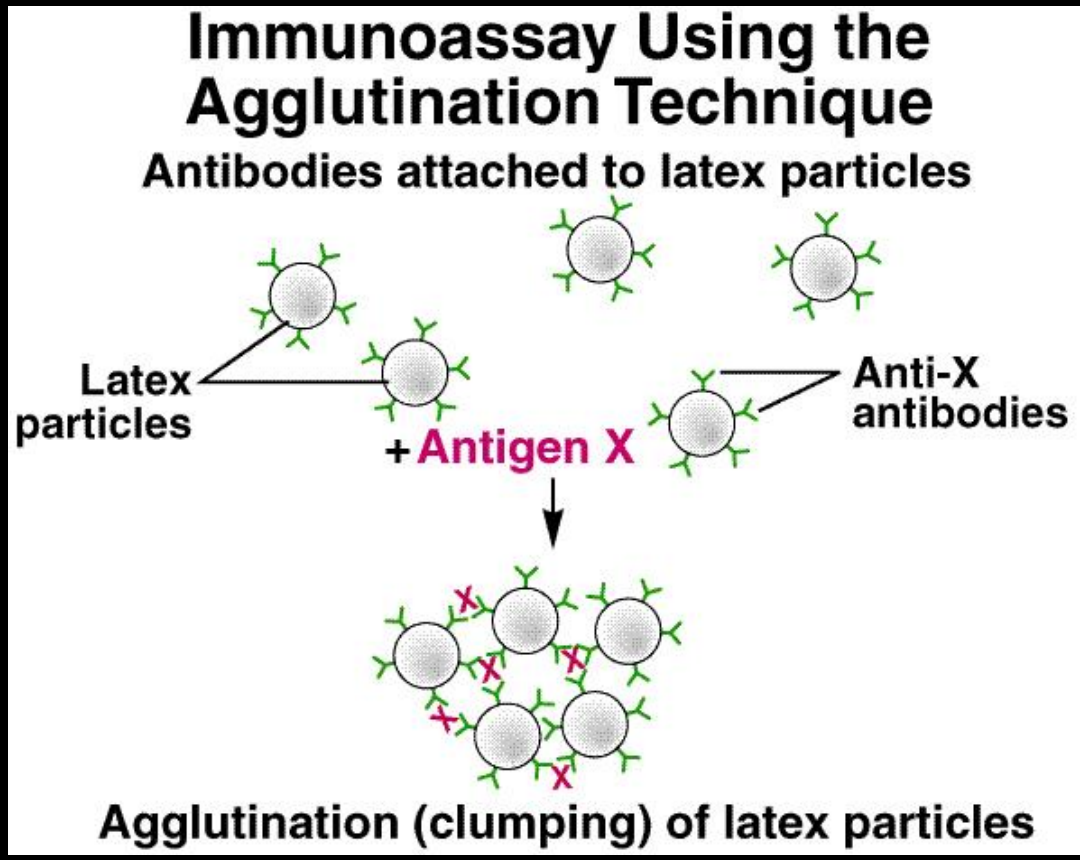
- Molecules that stimulate the production of antibodies.
- Combine specifically with antibodies produced.
- Foreign to blood and other body fluids.
- Immune system can distinguish “self” molecules from nonself antigens.
- Large, complex molecules can have different antigenic determinant sites.

Haptens

- Small organic molecules can become antigens if they bind to proteins.
- Become antigenic determinant sites on the proteins.

Immunoassays

- Antigen-antibody complex reaction can produce clumping (agglutination).
- Agglutinated particles can be used to assay a variety of antigens.



Lymphocytes

- Derived from stem cells in the bone marrow.
- Stem cells produce the specialized blood cells.
- Replace themselves by cell division so the stem cell population is not depleted.
- Lymphocytes seed the thymus, spleen, and lymph nodes.

Lymphocytes

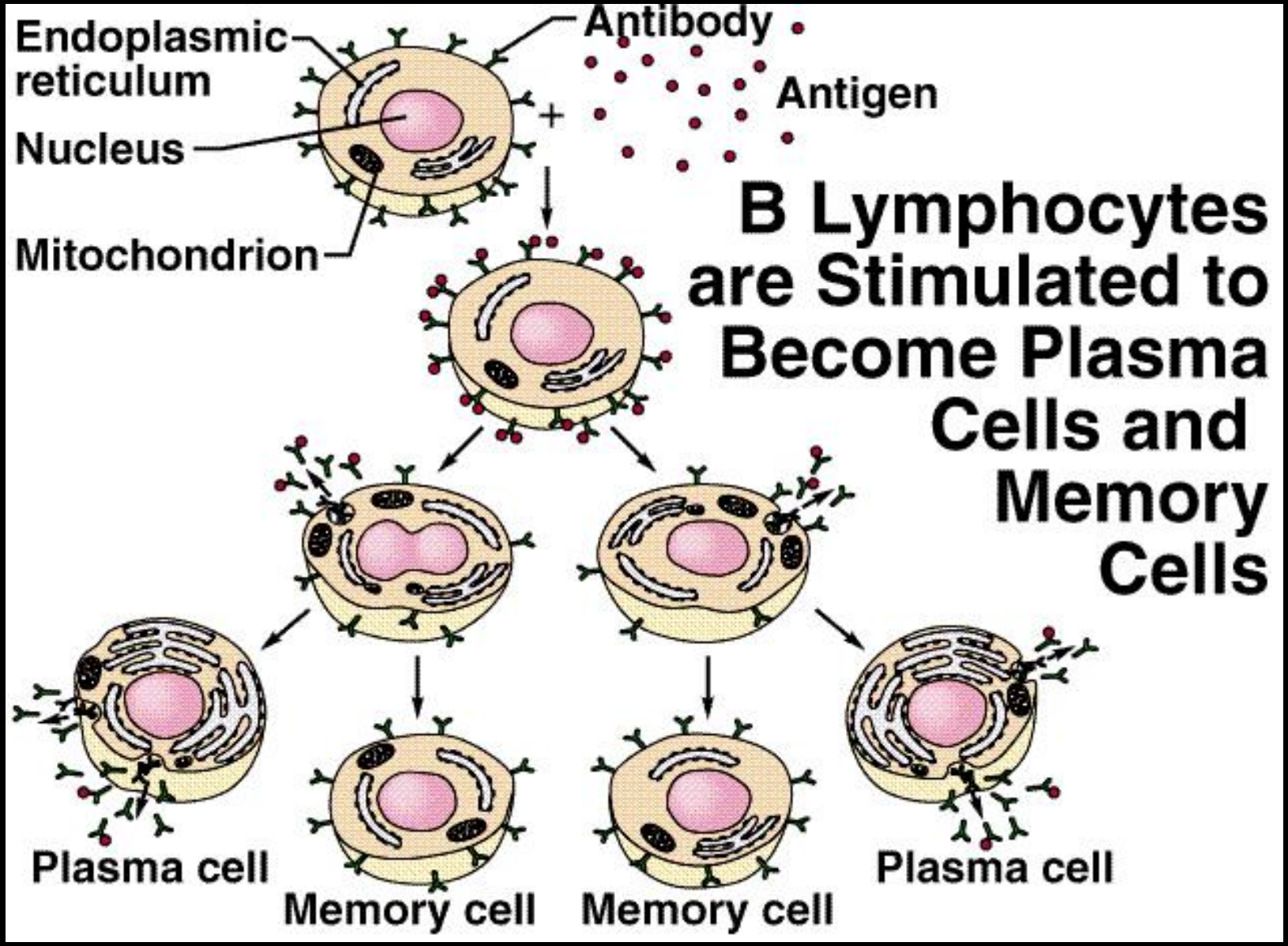
- Lymphocytes that seed the thymus become T lymphocytes (T cells).
- Have surface characteristics and immunological function that differ from other lymphocytes.
- Do not secrete antibodies.
- Must come in close or direct contact to destroy them.
- T cells are 65 – 85% of the lymphocytes in blood and most in the germinal centers of lymph nodes and spleen.

Lymphocytes

- Most of the lymphocytes that are not T cells are B lymphocytes (B cells).
- Processed in the bone marrow.
- Function in specific immunity.
- B cells combat bacterial infections as well as some viral infections by secreting antibodies into the blood and lymph.
- Provide humoral immunity (blood and lymph are body fluids (humors).

B Lymphocytes

- Secrete antibodies that bind to antigens.
- Stimulate production of memory cells:
  - Important in active immunity.
- Others are transformed into plasma cells:
  - Produce 2000 antibody proteins/sec when exposed to antigen.
  - These antigens may be isolated molecules or may be molecules at the surface of an invading foreign cell.



Antibodies

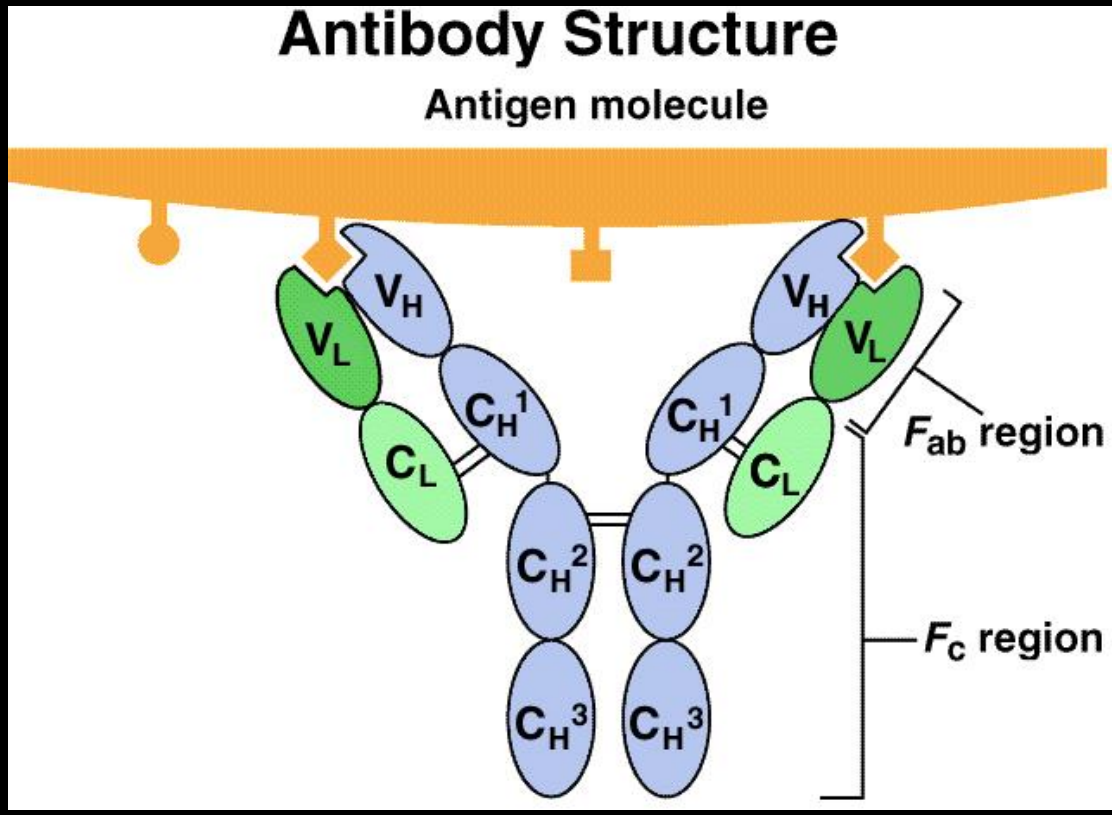
- Antibody proteins are also known as immunoglobulins.
- Found in the gamma globulin class of plasma proteins.
- Different antibodies have different structure, as the antibodies have specific actions.

Antibodies

Immunoglobulin	Functions
lgG	Main form of antibodies in circulation: production increased after immunization; secreted during secondary response
lgA	Main antibody type in external secretions, such as saliva and mother's milk
lgE	Responsible for allergic symptoms in immediate hypersensitivity reactions
lgM	Function as antigen receptors on lymphocyte surface prior to immunization; secreted during primary response
lgD	Function as antigen receptors on lymphocyte surface prior to immunization; other functions unknown

Antibody Structure

- 100 million trillion antibody molecules that contain 4 polypeptide chains.
- F_{ab} regions are variable, provide a specific bonding site for antigen.
- B lymphocytes have antibodies that serve as receptors for antigens
- Provides active immunity.

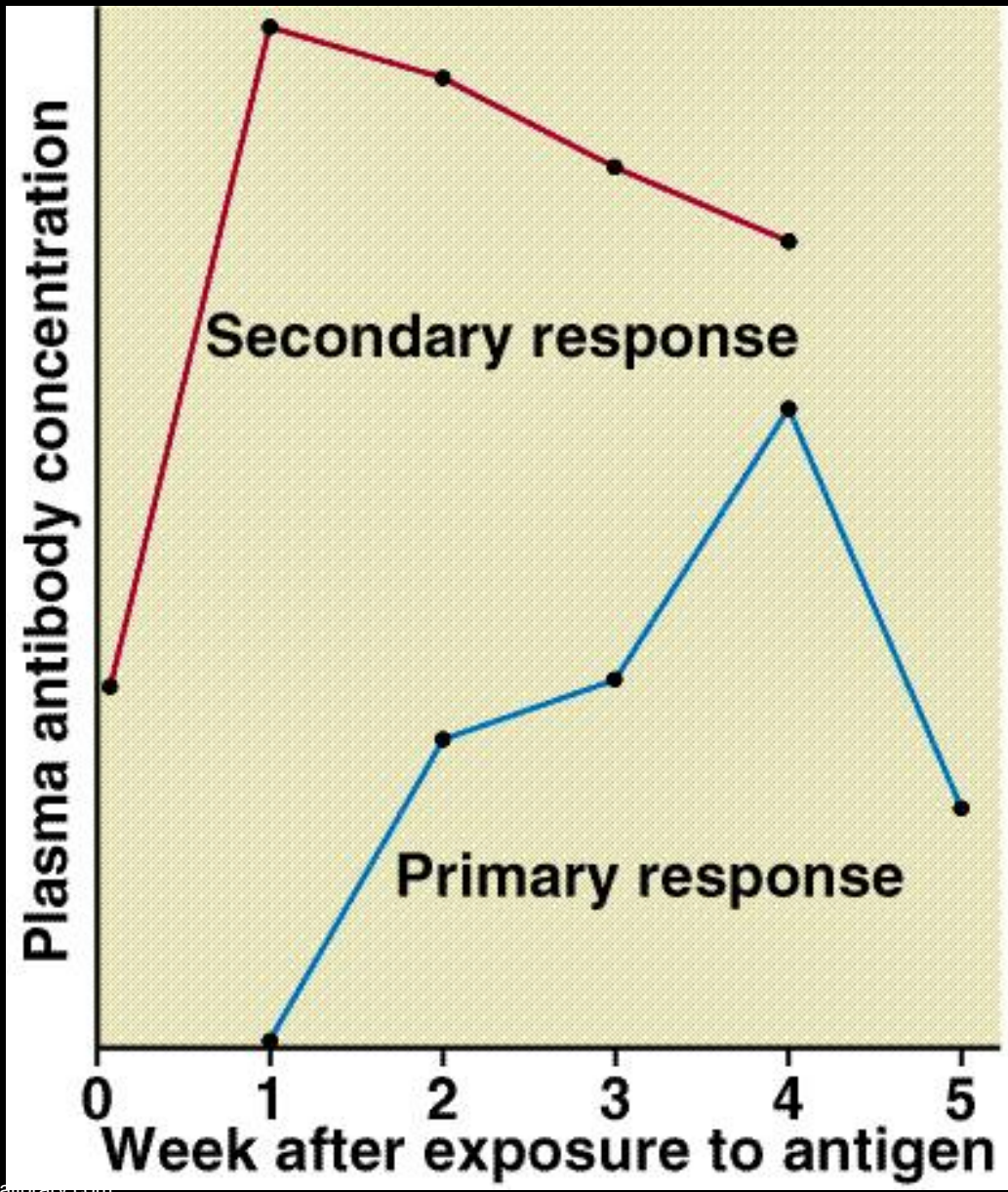


Active Immunity

- Primary response:
  - First exposure to pathogen, immune response insufficient to combat disease.
  - Latent period of 5-10 days before measurable amounts of specific antibodies appear in blood.

Active Immunity

- Secondary response:
- Subsequent exposure to same antigen.
- Antibody production is much more rapid.
  - Maximum antibody concentration reached in < 2 hrs.
  - Maintained longer period of time.



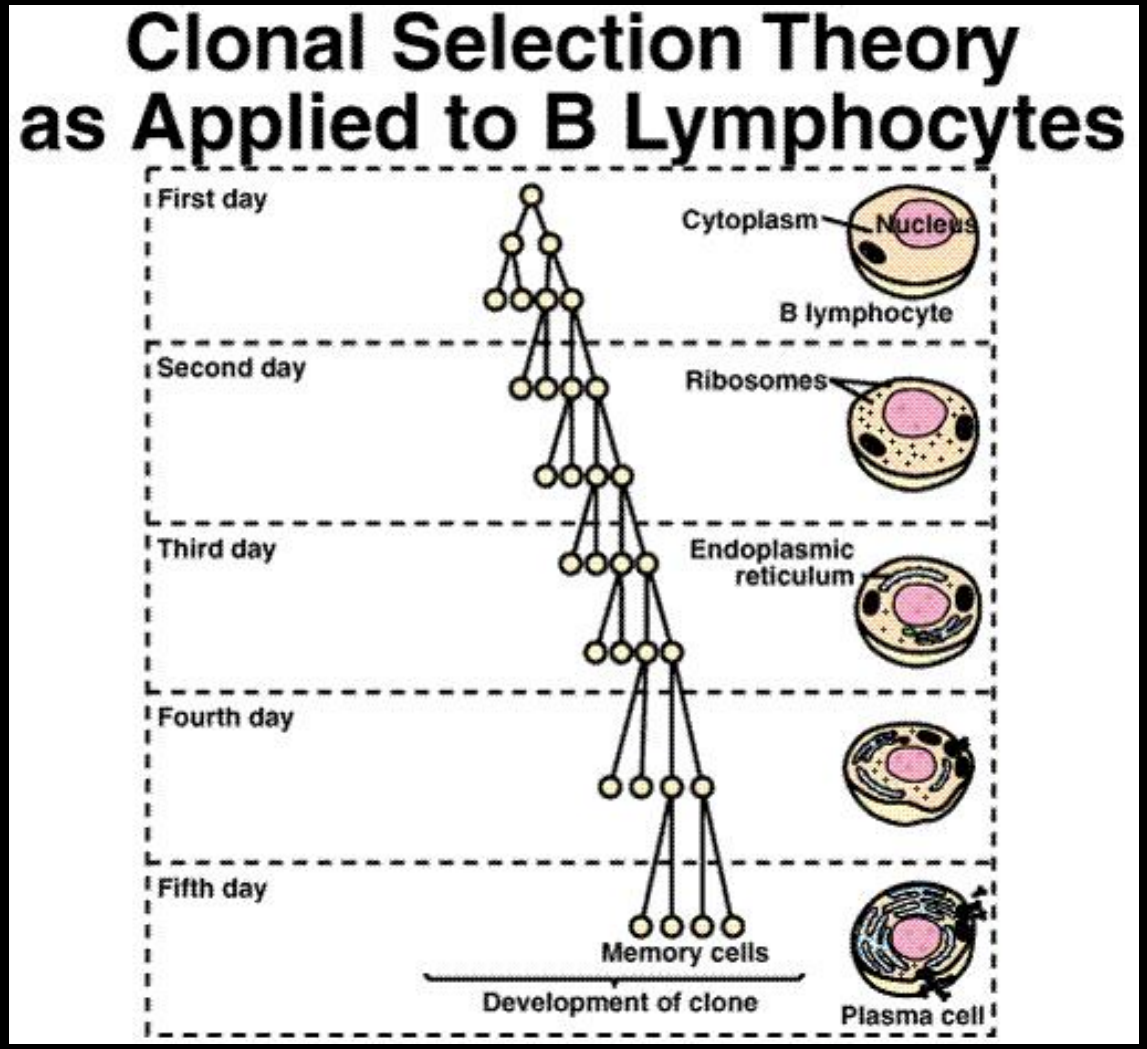
Primary and Secondary Immune Responses

Clonal Selection Theory

- B lymphocytes inherit the ability to produce a particular antibody.
- T lymphocytes inherit the ability to respond to particular antigens.
- Inherited specificity reflected in antigen receptor proteins on surface of lymphocytes.

Clonal Selection Theory

- Exposure stimulates specific lymphocytes to divide many times until a large population of genetically identical cells (clone) is produced.
- Antigens select lymphocytes that are already able to make antibodies.



Passive Immunity

- Immune protection produced by the transfer of antibodies to a recipient from a donor.
- Donor has been actively immunized.
- Occurs naturally in mother to fetus during pregnancy and mother to infant during nursing.

Passive Immunity

- Immunological competence:
  - Ability to mount a specific immune response.
  - Does not develop until 1 month after birth.
  - Passive immunity disappears when infant is 1 month old.
    - Infant did not itself produce lymphocyte clones.

Monoclonal Antibodies

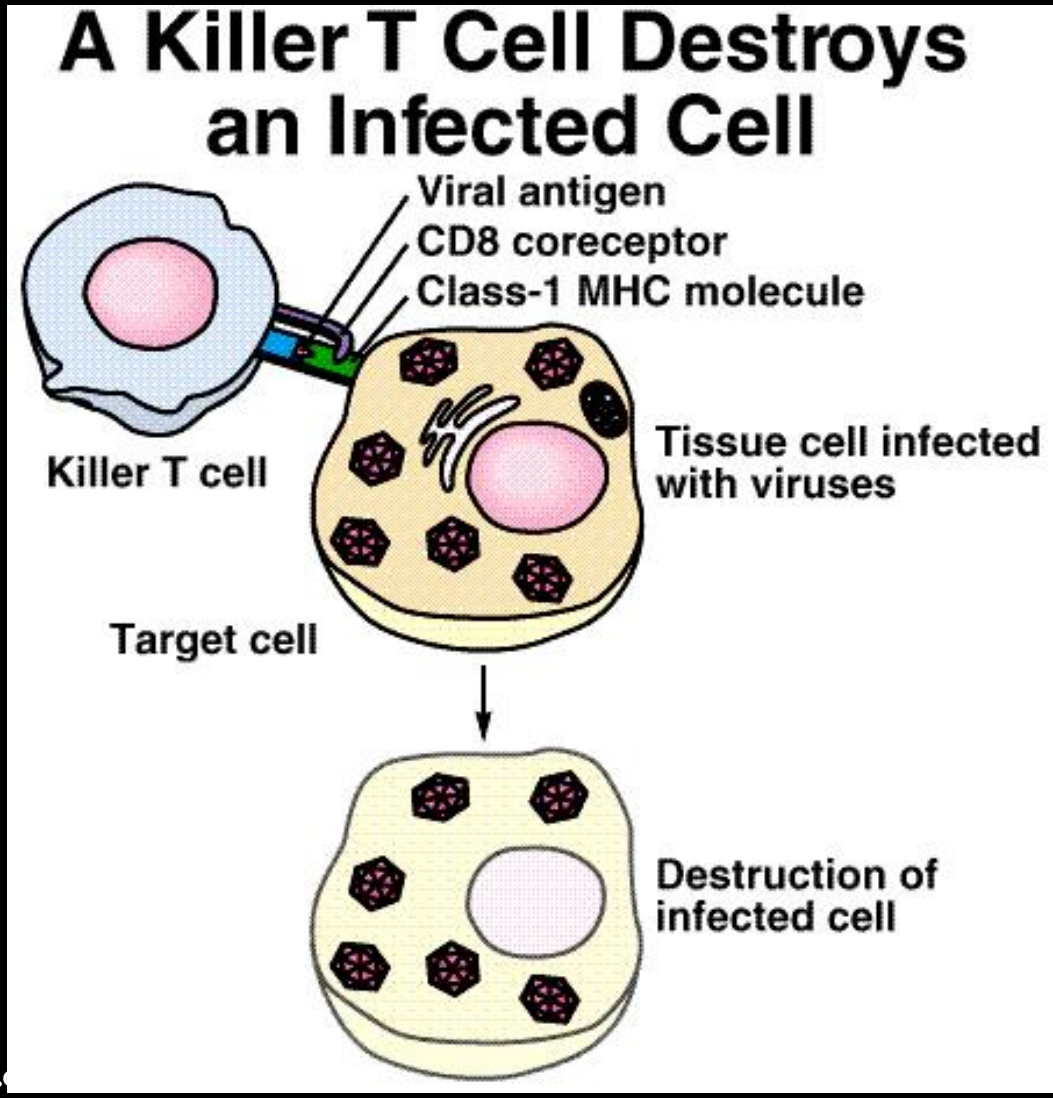
- Commercially prepared.
- Exhibit specificity for one antigenic determinant only.
- Results in more sophisticated clinical laboratory tests.
- May aid in the diagnosis of cancer.

T Lymphocytes

- Thymus atrophies after puberty.
- Colonies of T cells in lymph nodes and other organs produce T cells under stimulation of thymus hormones.
- Thymus secretes:
  - Thymopoietin I and thymopoietin II
    - Promote transformation of lymphocytes into T cells.

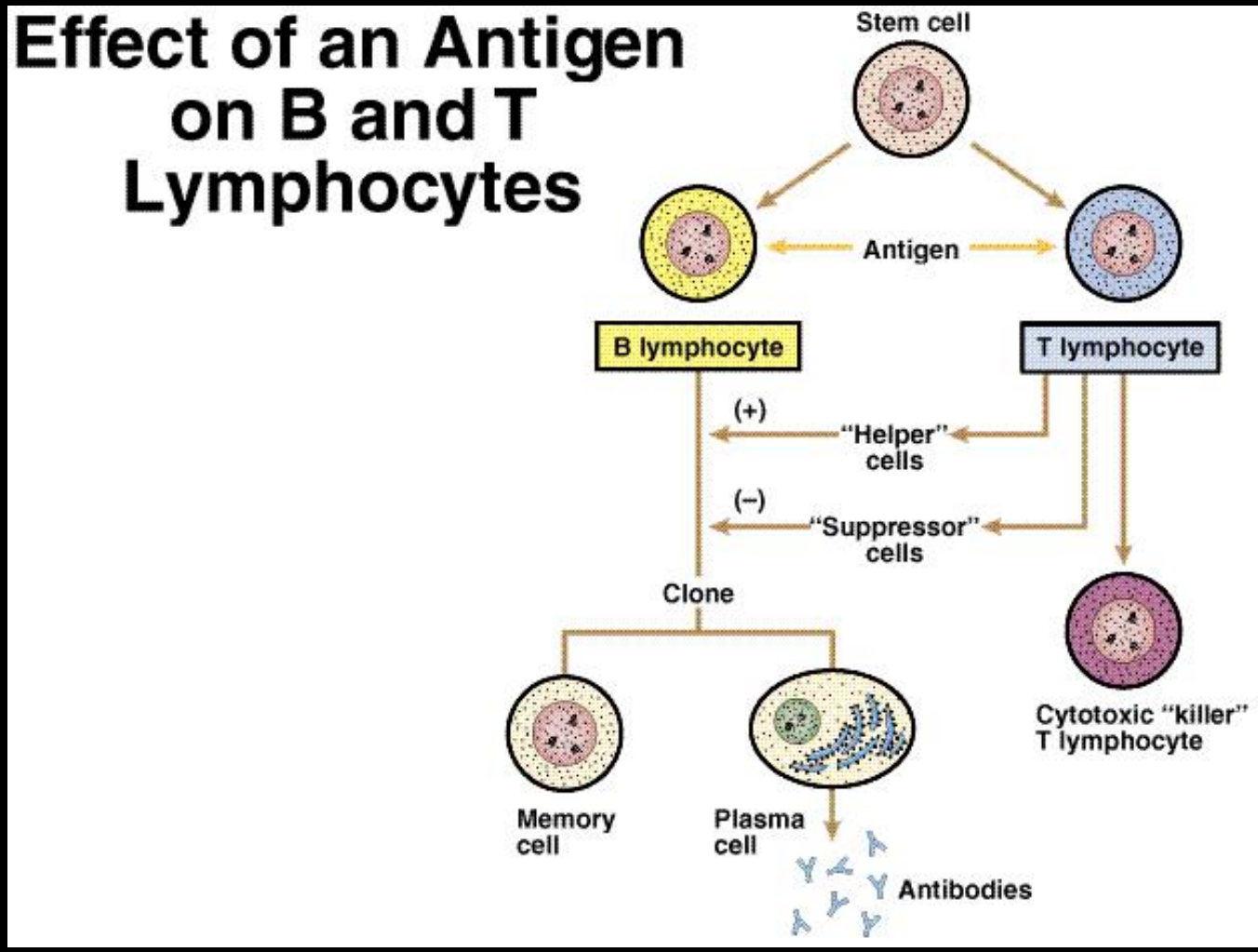
Killer (cytotoxic) T Cells

- Cell mediated destruction.
- Destroy specific cells with antigens on their surface.
- Must be in actual contact with their victim cells.
- Defend against viral and fungal infections.
- Secrete perforins:
  - Perforins polymerize in the cell membrane and form cylindrical channels through the membrane.

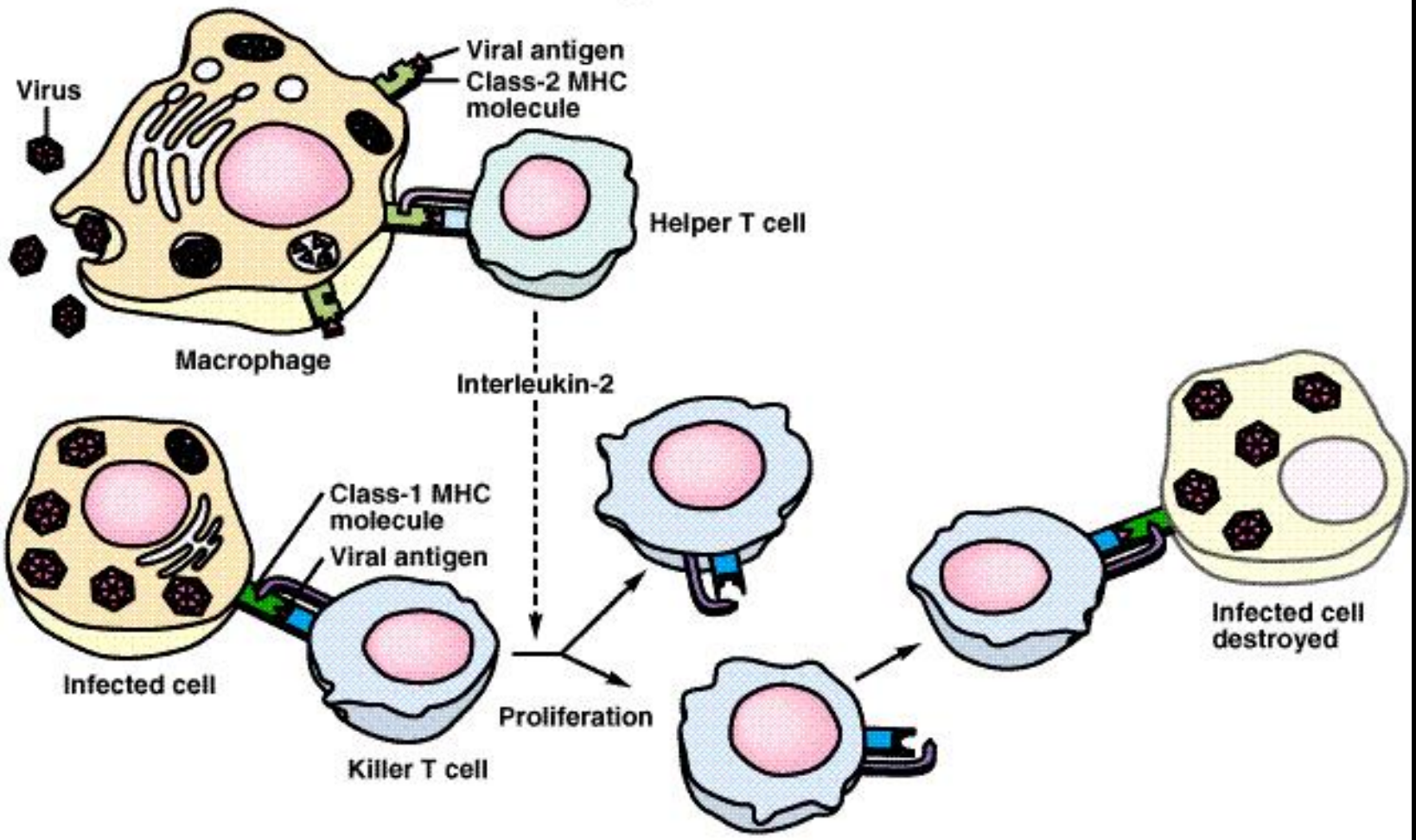


Helper T Cells

- Indirectly participate by regulating the response of both T killer cells and B cells.
- B cells must be activated by helper T cells before they produce antibodies.



Interaction of Macrophages, Helper T Cells, and Killer T Cells



Suppressor T Cells

- Indirectly participate in the specific immune response.
- Inhibit T cell and B cell activities.
- Affects the amount of antibodies secreted.
- Moderate immune response.

Lymphokines

- Interleukin-1:
  - Secreted by macrophages and other cells.
  - Activates T cells.
- Interleukin-2:
  - Released by helper T cells.
  - Activates killer T cells.
- Interleukin-3:
  - Serves as a growth factor.
  - Activates killer T cells.
- Interleukin-4:
  - Secreted by T cells.
  - Required for proliferation and clone development of B cells.

Subtypes of Helper T Cells

- T_H1:
  - Produce interleukin 2 and gamma interferon.
    - Activate killer T cells.
- T_H2:
  - Secrete interleukin-4 and interleukin-5.
    - Stimulate B lymphocytes.

Major Histocompatability Complexes (MHC)

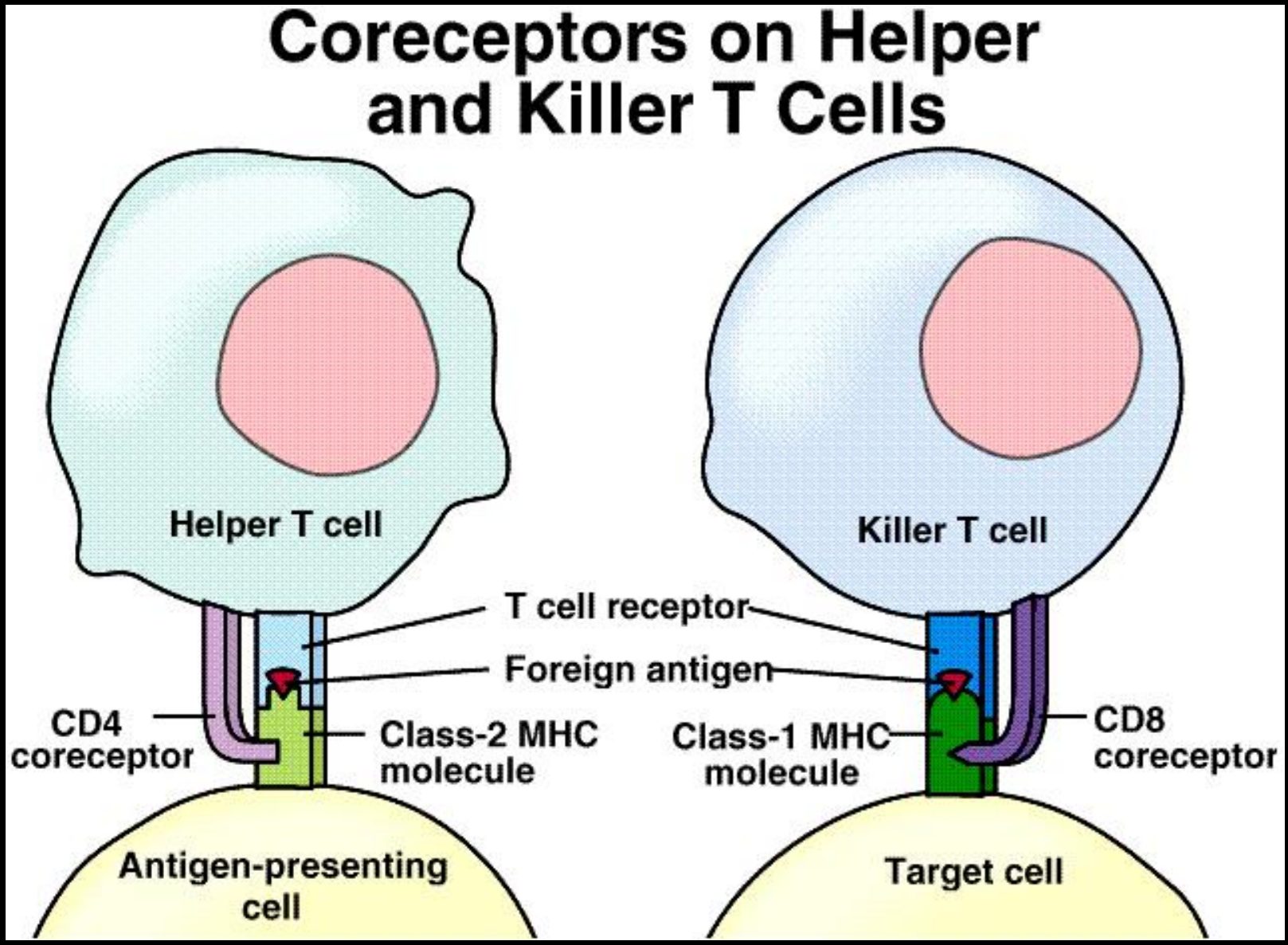
- All cells except mature RBCs are genetically marked with histocompatability antigens on the membrane surface.
- Also called human leukocyte antigens (HLAs).
- The histocompatability antigens are coded for a group of genes called MHC located on chromosome 6.
- MHC of genes produces 2 classes of MHC molecules:
  - Class-1
  - Class-2

Major Histocompatability Complexes

- MHC-class-1:
  - Produced by all cells but RBCs.
  - Picks up cytoplasmic peptides and transports to membrane.
  - Killer T cells (cytotoxic) interact with antigens.
  - Coreceptor CD8 permits each type of T cell to interact only with a specific class of MHC molecules.

Major Histocompatability Complexes

- MHC-class-2:
  - Produced only on antigen-presenting cells and B cells
  - Appear only on cell membrane when cell is processing antigens.
  - Activate T cells.
  - Helper T cells react with antigens.
  - Coreceptor CD4 interact with only a specific class of MHC molecule.



Destruction of T Lymphocytes

- Activated T cells must be destroyed after the infection has cleared.
- T cells produce a surface receptor called FAS.
- Production of FAS increases during the infection.
- Activated T cells begin to produce FAS ligand.
- FAS binds to FAS ligand and triggers apoptosis (cell suicide).

Tumor Immunology

- Tumors are interrelated with the functions of the immune system.
- Division of tumor cells is not effectively controlled by normal inhibitory mechanisms.
- Tumor cells also dedifferentiate (become similar to less specialized cells of an embryo).
- As tumor cells dedifferentiate, they reveal surface antigens that can stimulate the immune destruction of the tumor.

Immunotherapy for Cancer

- Interleukin-2 activates both killer T cells and B lymphocytes.
- Gamma interferon are also used to treat cancer.
- Preliminary results promising.

Diseases Caused by the Immune System

- Ability of immune system to tolerate self-antigens while it identifies and attacks foreign antigens that can be deranged.
- Diseases caused by the immune system can be grouped into 3 categories:
  - Autoimmune disease.
  - Immune complex diseases.
  - Allergy or hypersensitivity.

Autoimmunity

- Those produced by failure in the immune system to recognize and tolerate self-antigens.
- Failure due to:
  - An antigen that does not normally circulate in the blood may be exposed to the immune system.
    - Thyroglobulin.
  - A self-antigen that is otherwise tolerated may be altered by combining with a foreign hapten.
    - Thrombocytopenia.

Autoimmunity

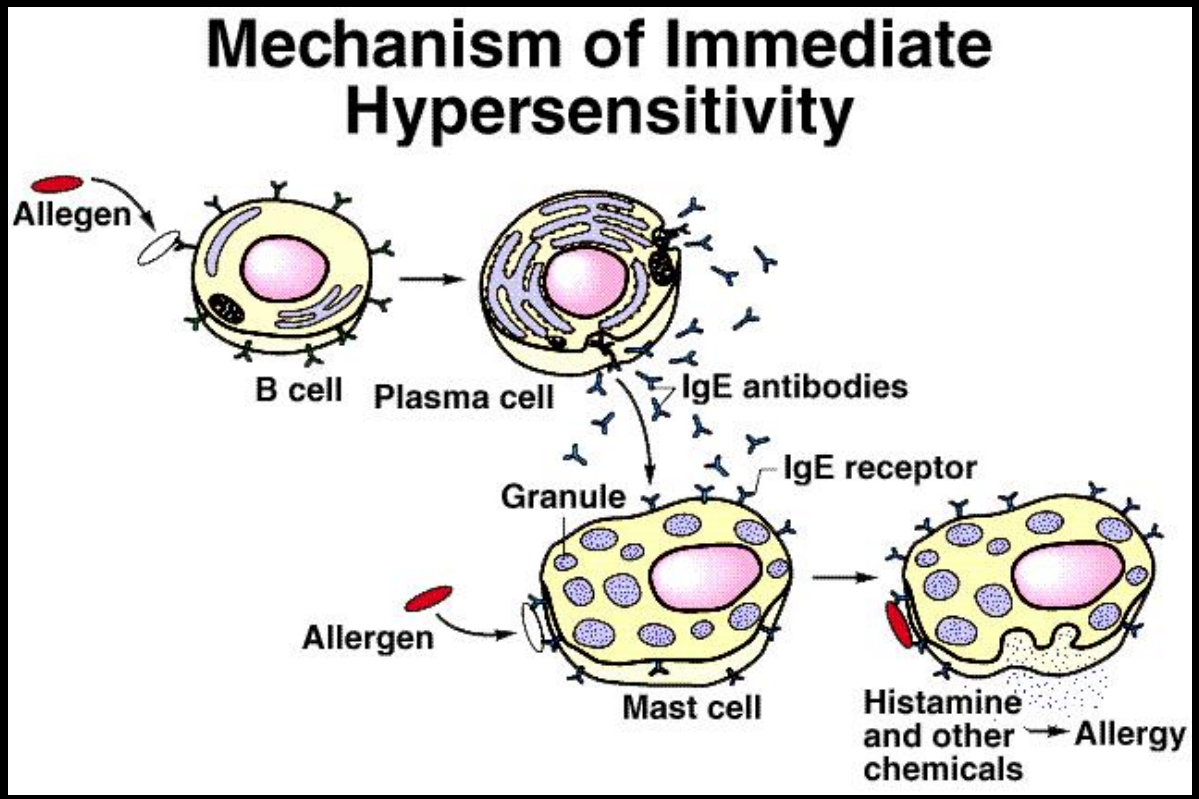
- Antibodies may be produced that are directed against other antibodies.
  - Rheumatoid arthritis.
- Antibodies produced against foreign antigens may cross-react with self-antigens.
  - Rheumatic fever.
- Self-antigens may be presented to the helper T cells together with class-2 MHC molecules.
  - Type I diabetes.

Immune Complex Diseases

- Antigen-antibody combinations that are free rather than attached to bacterial or other cells.
- Activates complement proteins and promotes inflammation.
  - Hepatitis B.

Immediate Hypersensitivity

- Production of IgE antibodies.
- Do not circulate in the blood.
- Attach to mast cells and basophils.
- When exposed again to same allergen, histamine and prostaglandin D are secreted.
- Produce symptoms.



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