Microbiology an Introduction

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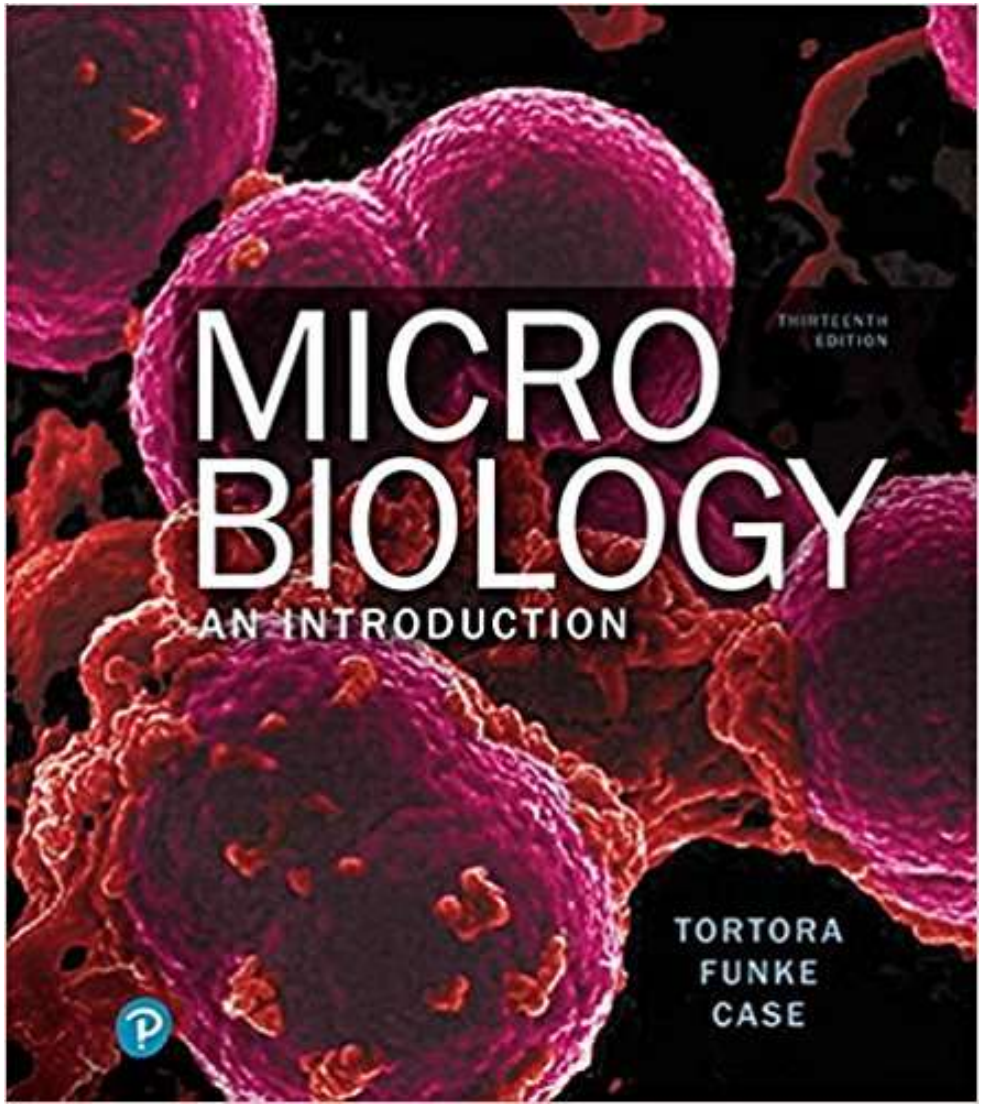


CHAPTER 17

ADAPTIVE IMMUNITY: SPECIFIC DEFENSES OF THE HOST (Adaptive; specific; acquired immunity)

IMMUNITY

- From Latin word "immunis" meaning to exempt
- Immunity is the ability of the body to specifically counteract foreign organisms or substances called antigens.
- Immunity results from the production of the specialized lymphocytes and antibodies.
- Specific antibody and lymphocyte response to an antigen is called specific or adaptive immunity that target a specific pathogen
  - Acquired through infection or vaccination

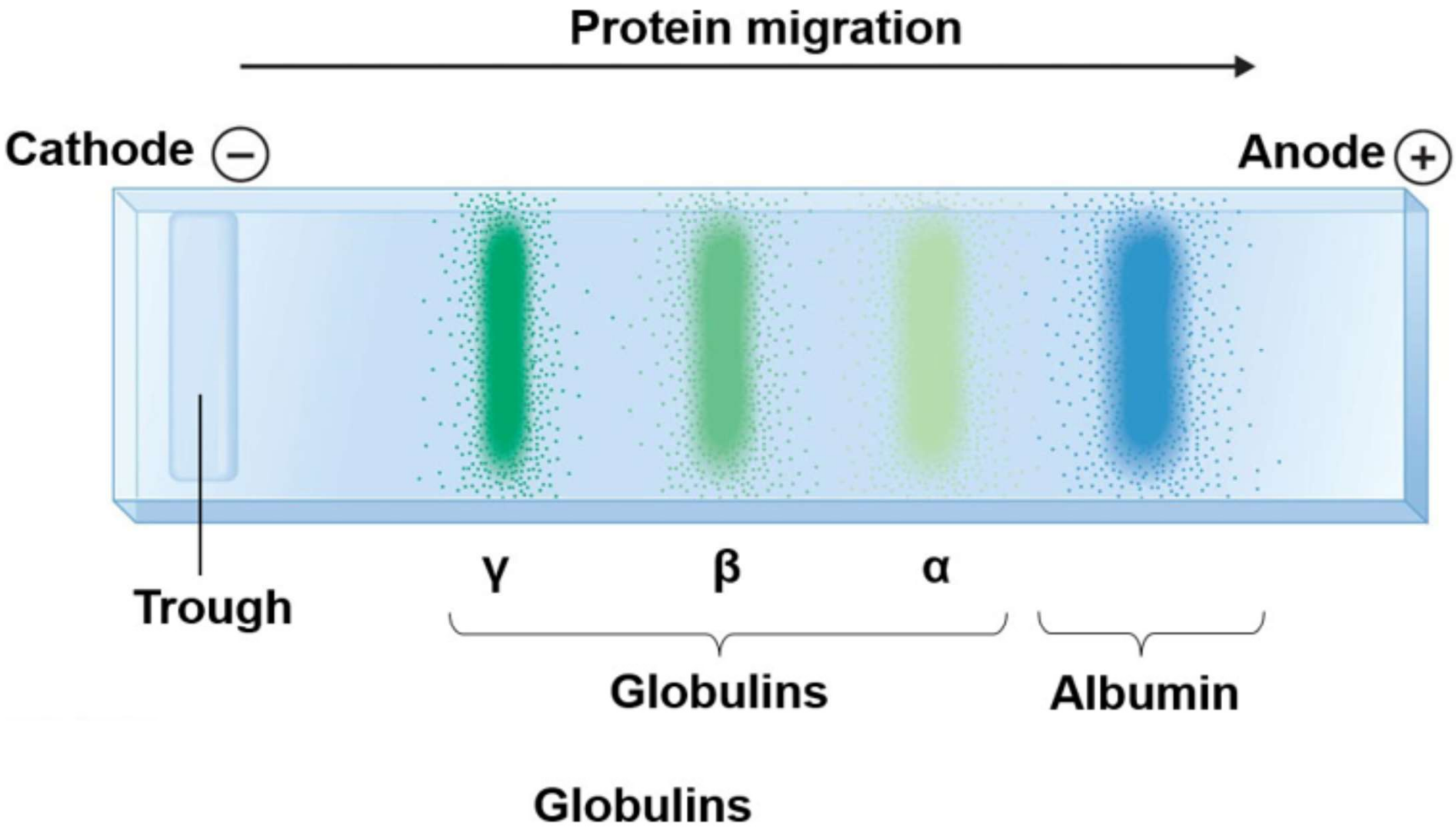
Terminology

- **Innate** (nonspecific) Defenses against any pathogen; has an inherited genetic component
- **Adaptive** Immunity (specific) Is induced; body adapts to a microbial invader or a foreign substance
- **Antigen (Ag)** A substances that is foreign to the body causes the body to trigger an immune response (produce specific antibodies or sensitized T cells
- **Antibody (Ab)** Proteins made in response to an antigen

Terminology

- **Serology** — Study of reactions between antibodies and antigens
- **Antiserum** — blood-derived fluids containing antibodies
- **Globulins** — Serum proteins
- **Gamma (γ) globulin** — Serum fraction containing Ab

The Separation of Serum Proteins by Gel Electrophoresis



Cytokines: Chemical Messengers of Immune Cells

- **Cytokines** are chemical messengers produced by cells in response to a stimulus to deliver message to other cells
  - **Interleukins:** are cytokines that serve as communicators between leukocytes
  - **Chemokines:** cause leukocytes to move to the site of infection
  - **Interferons (IFNs):** interfere with viral infections of host cells
  - **Tumor necrosis factor (TNF):** involved in the inflammation of autoimmune diseases
  - **Hematopoietic cytokines:** control stem cells that develop into red and white blood cells
- Overproduction of cytokines leads to a **cytokine storm**
- **Cytokines** may be useful in treating tumors

The Third Line of Defense

- The human specific immune system recognizes foreign substances as not belonging to the body and develops a specific immune response against them (Immunity)
- The characteristic of specificity and memory distinguish the specific immune response from non- specific resistance
- Substances that provoke a specific response are called **antigens**
- The immune response involves the production of proteins called antibodies and certain specialized lymphocytes.
- The immune system comprises
    * Cells (T – cells and B – cells)
    * Proteins (Antibodies)
    * Lymphatic system

Antigens (*Anti*body *gen*erators)

-Also called as immunogens

-Provoke a highly specific immune response in an organism

-Most antigens are proteins or large polysaccharides

- Lipids and nucleic acids are antigenic when combined with proteins or polysaccharides

-Antigenic compounds are

-Microbial components

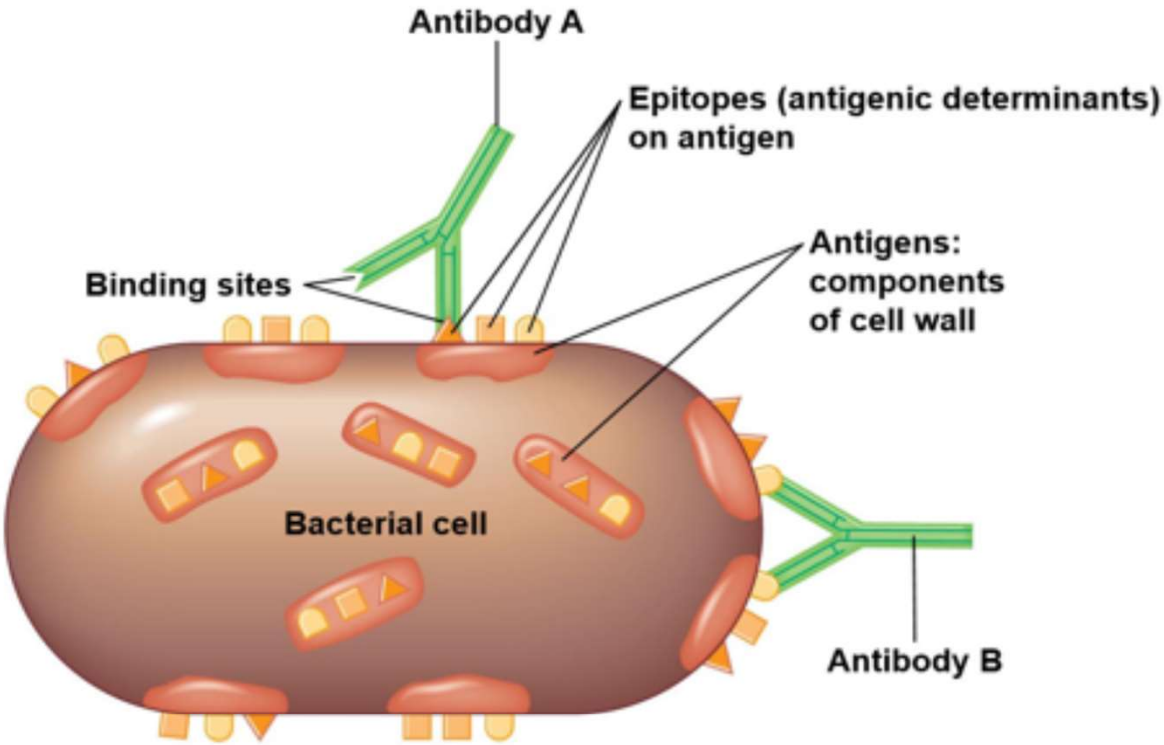
-Capsules, cell wall, flagella, fimbriae, toxins of bacteria, coats of viruses, other types of microbial surfaces

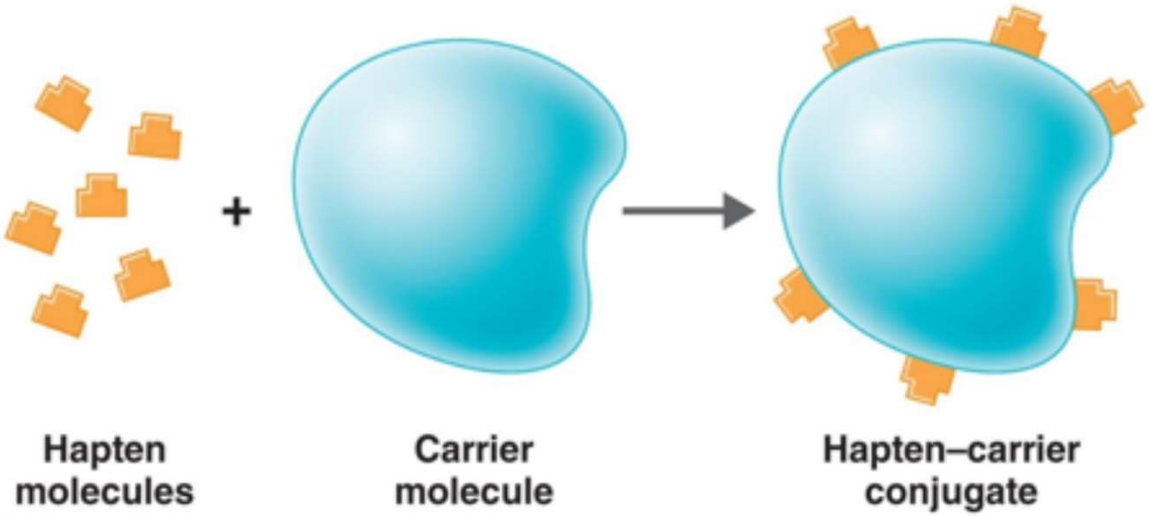
-Non-microbial

- pollens, egg white, blood cell surface molecules, serum proteins from others, surface molecules of transplanted tissue or organs

Antigens

- **Antigens:** substances that cause the production of antibodies
  - Usually components of invading microbes or foreign substances
  - Antibodies interact with **epitopes,** or **antigenic determinants,** on the antigen
- **Haptens:** antigens too small to provoke immune responses; attach to carrier molecules





Lymphocytes and Lymphoid Organs

- Lymphocytes are derived from stem cells in the bone marrow.
- Stem cells produce the specialized blood cells.
- Stem cells replace themselves by cell division so the stem cell population is not depleted.
- Lymphocytes produced by this process seed the thymus, spleen, and lymph nodes.
- Lymphocytes produce self-replacing lymphoid colonies in these organs.
- Since bone marrow and the thymus produce the B and T lymphocytes, they are called Primary lymphoid organs
- Both T and B cells function in specific immunity.

FUNCTIONS OF SPECIFIC IMMUNE RESPONSE

Specific immune response has three major function

1) **Recognize** anything that is non-self
2) **Respond** to this foreign material – involves the recruitment of various defense molecules and cells to either destroy foreign material or render it harmless
3) **Remember** the foreign invader – a more rapid and intense responses to foreign material that occurs upon later encounters with the material

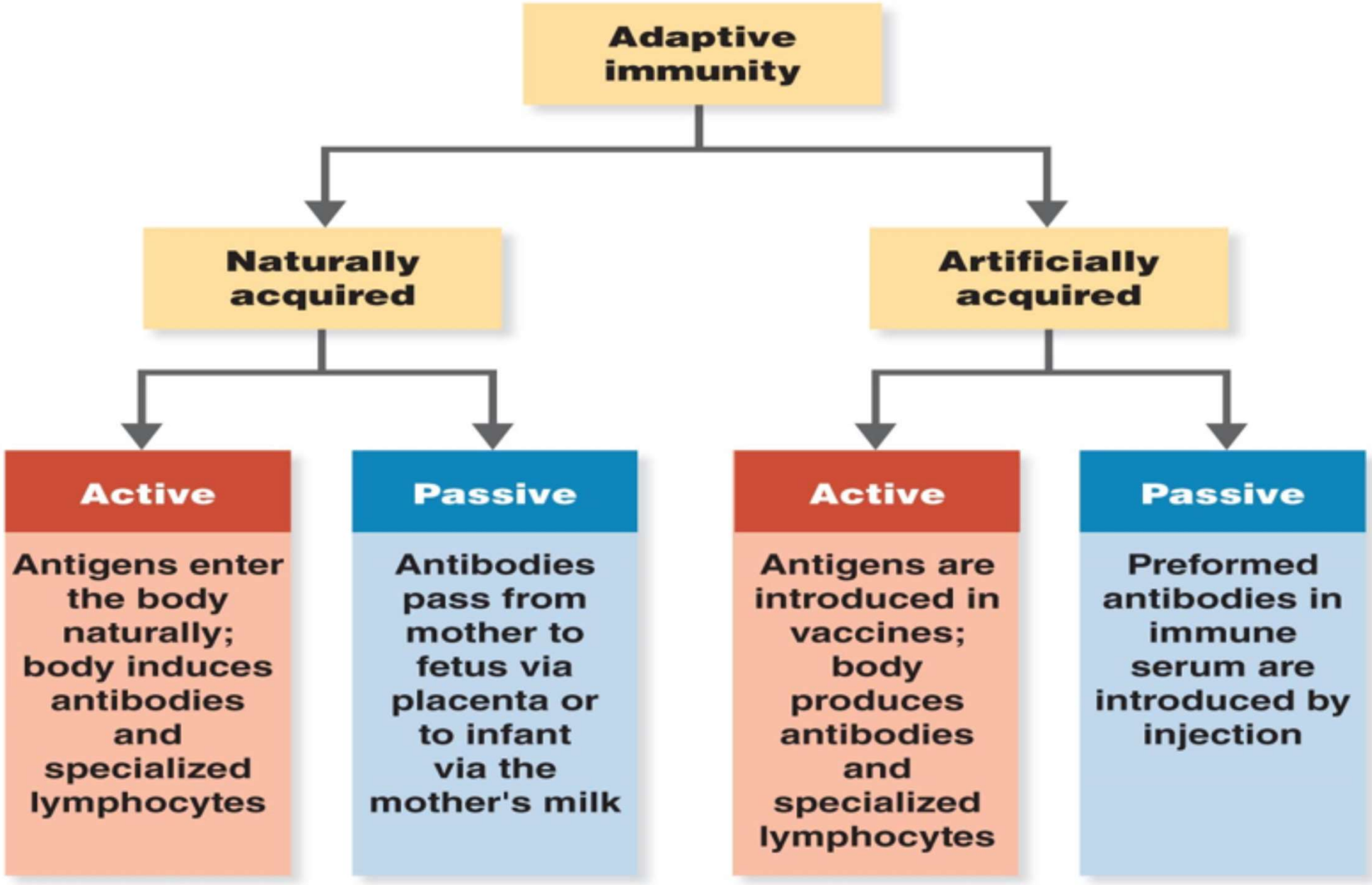
TYPES OF ACQUIRED IMMUNITY

- Acquired immunity is developed during an individual's lifetime

- "**Active**" means exposure to antigen
  - *__Natural__ – via infection
  - *__Artificial__ – via vaccines (solution containing antigen)
  - *(Long lived)
- "**Passive**" means transfer of antibodies
  - *__Natural__ – **transplacental** (across placenta)
    - **Colostrum** (early milk produced by mother) is full of antibodies to develop immunity
  - *__Artificial__ – introduction of antibodies from an immune donor into an individual
  - *(Short lived)

Artificial* = *injection ***Natural* = *natural***

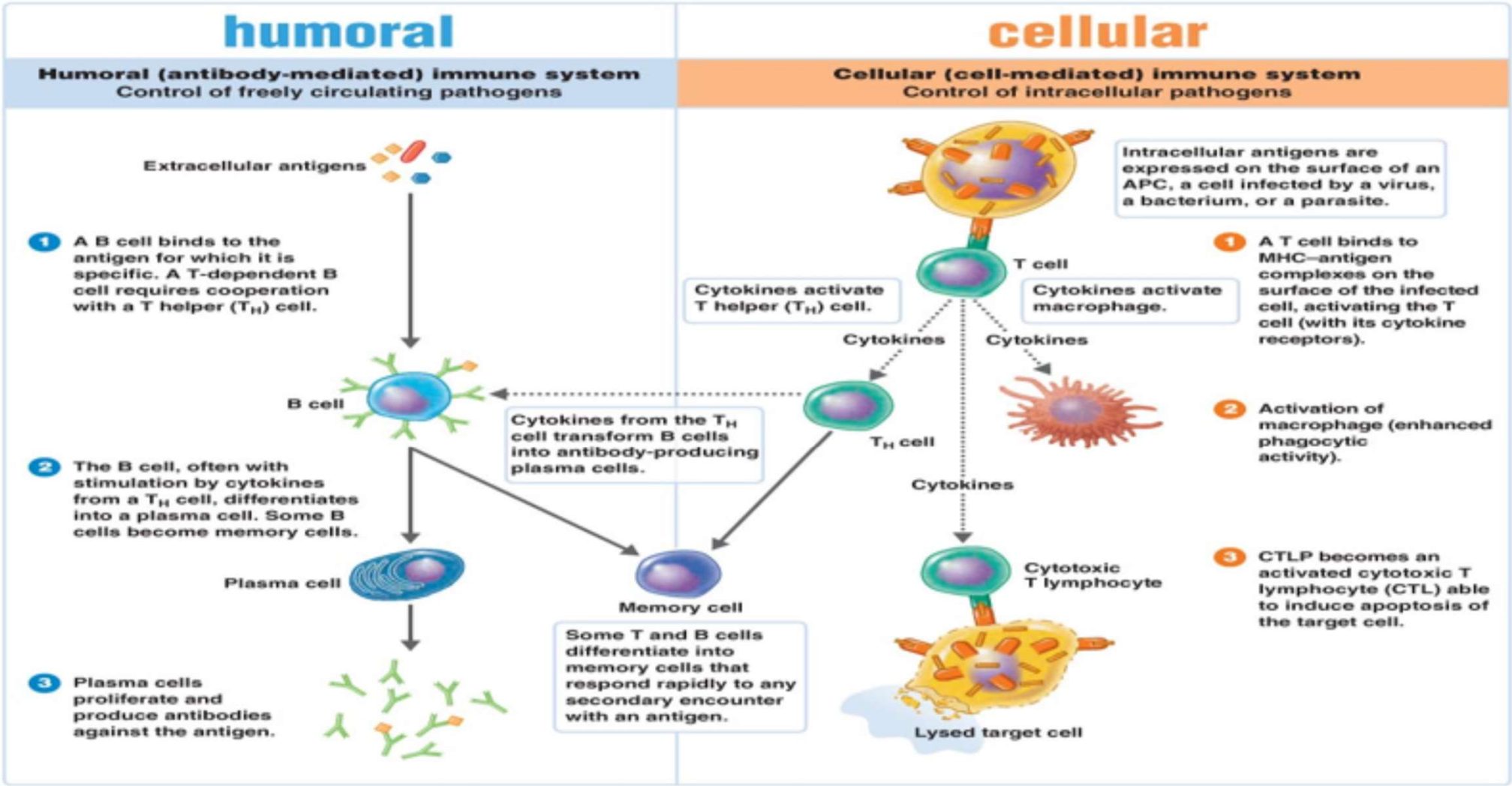
Types of Adaptive Immunity



Passive Immunity is short lived

- When antibodies (immune serum globulins) from a person who has immunity against a disease are injected to another person, it gives the recipient immediate protection against that particular disease. This immunity is short lived because half life of antibodies is very short, and the body keeps no memory of such treatment
- Antibodies of mother are transferred to her baby through placenta or by milk and provide the baby a short-term protection against infections experienced by the mother

The Dual Nature of the Adaptive Immune System



KEY CONCEPTS

The adaptive immune system is divided into two parts, each responsible for dealing with pathogens in different ways. These two systems function interdependently to keep the body free of pathogens.

Humoral immunity, also called antibody-mediated immunity, is directed at freely circulating pathogens and depends on B cells.

Cellular immunity, also called cell-mediated immunity, depends on T cells to eliminate intracellular pathogens, reject foreign tissue recognized as nonself, and destroy tumor cells.

TWO ARMS OF SPECIFIC IMMUNITY

1) **Humoral (antibody-mediated) immunity**
   - based on action of antibody that bind bacteria, toxins, and extracellular viruses, tagging or marking them for destruction. B-cells (B-lymphocytes) are responsible for the production of antibodies

2) **Cellular (cell-mediated) immunity**
   - based on action of T-cells (T-lymphocytes) that directly attack cells infected with viruses or parasites, transplanted cells or organs, and cancer cells.
   - T-cells also regulate the activation and proliferation of macrophages

B Lymphocytes (B cells)

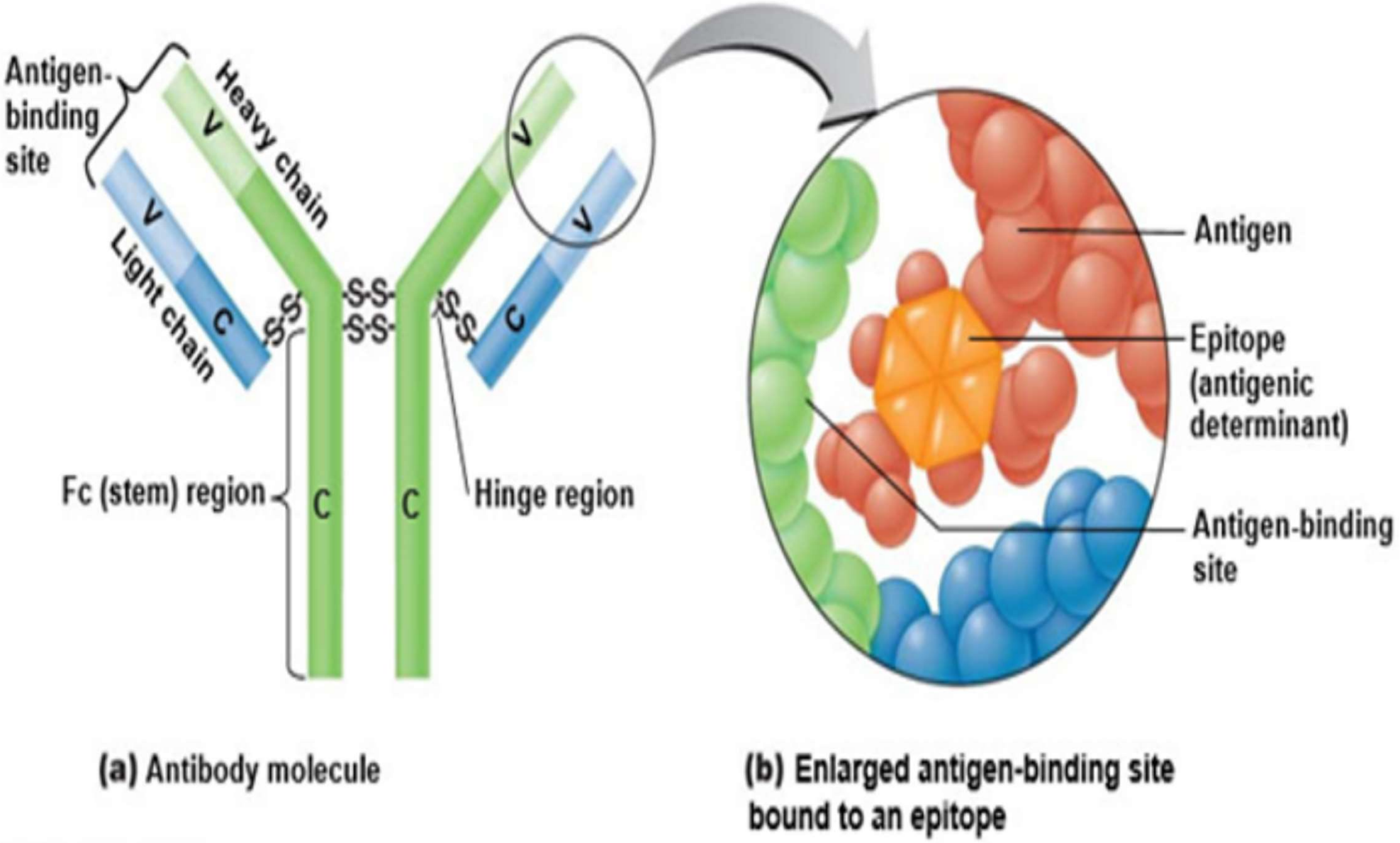
- Provide humoral immunity:
- **B cells** are created and mature in red bone marrow
- Function in specific immunity.
- B cells combat bacterial and some viral infections.
  - Recognize antigens, release antibodies into the blood and lymph.
  - Provide humoral immunity as blood and lymph are body fluids (humors).
- Activated B cell proliferate after activation by an antigen to form
  - Memory cells and
  - Plasma cells
- When Plasma cells are activated by an antigen, they produce ~2000 antibody proteins/second.
  - These antigens may be isolated molecules or may be molecules at the surface of an invading foreign cell.

Antibodies

- Antibodies are globular proteins also called **immunoglobulins (Ig)**
- **Valence** is the number of **antigen-binding sites** on an antibody
  - Bivalent antibodies have two binding sites
- Typical monomer is Y-shaped and has four polypeptide chains
  - Two identical light chains and two identical heavy chains joined by disulfide links
- Within each chain is a variable (V) region where epitope binding occurs
- Constant (Fc) region is the stem, which is identical for a particular Ig class
  - Five classes of Ig (**IgG, IgM, IgA, IgD, IgE**)
- The Fc region can attach to a host cell or complement.

Immunoglobulin Structure

Based on the constant region, antibodies are classified into different types



(a) Antibody molecule

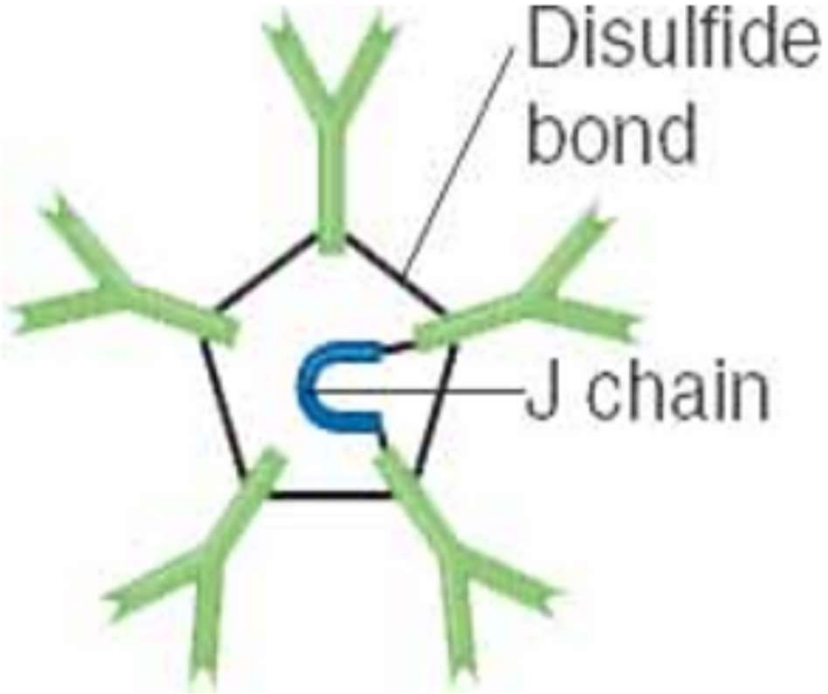
(b) Enlarged antigen-binding site bound to an epitope

IgG antibodies

- Monomer
- Smallest of the five
- 80% of serum antibodies
- In blood, lymph, intestine
- Cross walls of blood vessels, enter tissue fluid
- Only type that can cross placenta
- Enhance phagocytosis; neutralize toxins & viruses; protects fetus & newborn
- Activate the complement system
- Half-life = 23 days

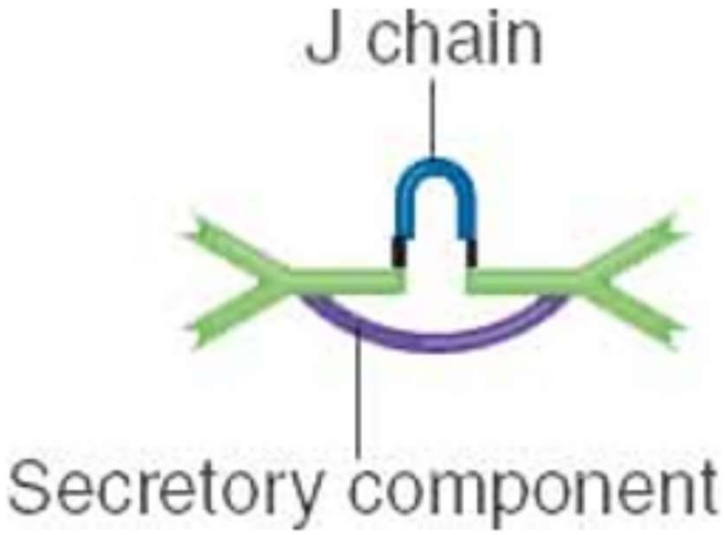
IgM antibodies

- Pentamer
- Largest of the five
- 5-10% of serum antibodies
- Activate complement system
- In blood, lymph, on B cells
- Agglutinates microbes
- First Antibodies (Ab) produced in response to infection
- The primary antibody against A and B antigens on red blood cells
- Half-life = 5 days



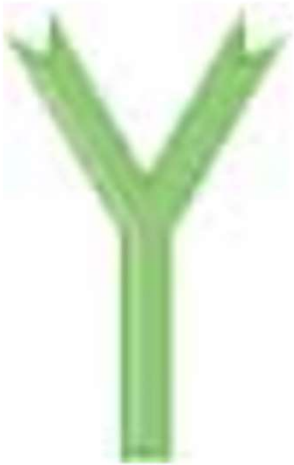
IgA antibodies

- Two types
  - **Dimer (secretory)**
  - **Monomer (non - secretory) in serum (less effective)**
- 10-15% of serum antibodies
- Common in mucous membranes, saliva, tears, and breast milk
- Prevent microbial attachment to mucous membranes
- Half-life = 6 days



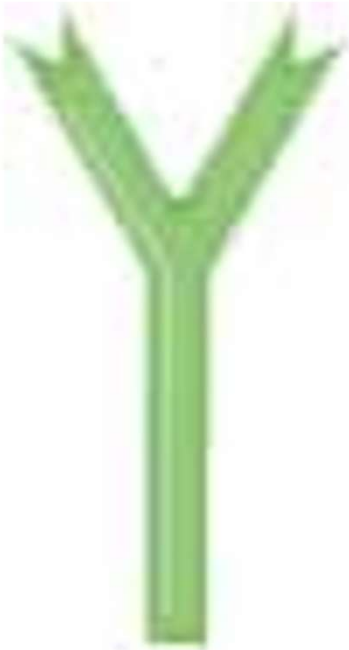
IgD antibodies

- Monomer
- 0.2% of serum antibodies
- In blood, lymph, on B cells
- On B cells, act as antigen receptor, initiate immune response
- Half-life = 3 days

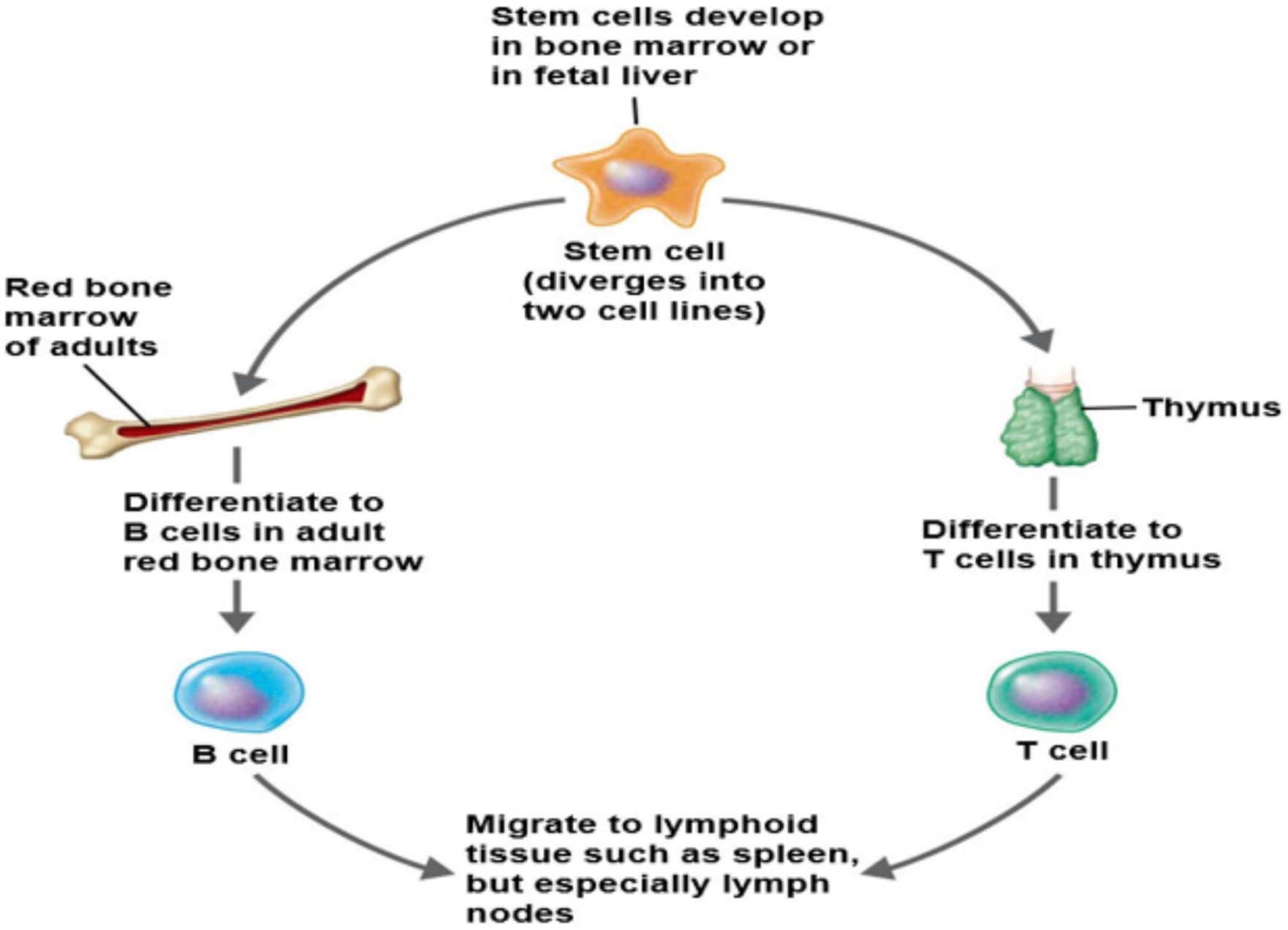


IgE antibodies

- Monomer
- 0.002% (rarest) of serum antibodies
- On mast cells and basophils, in blood
- Cause the release of histamines when bound to antigen
- Participate in allergic reactions
- Lysis of parasitic worms
- Attract IgG, Complement, and phagocytic cells
- Half-life = 2 days

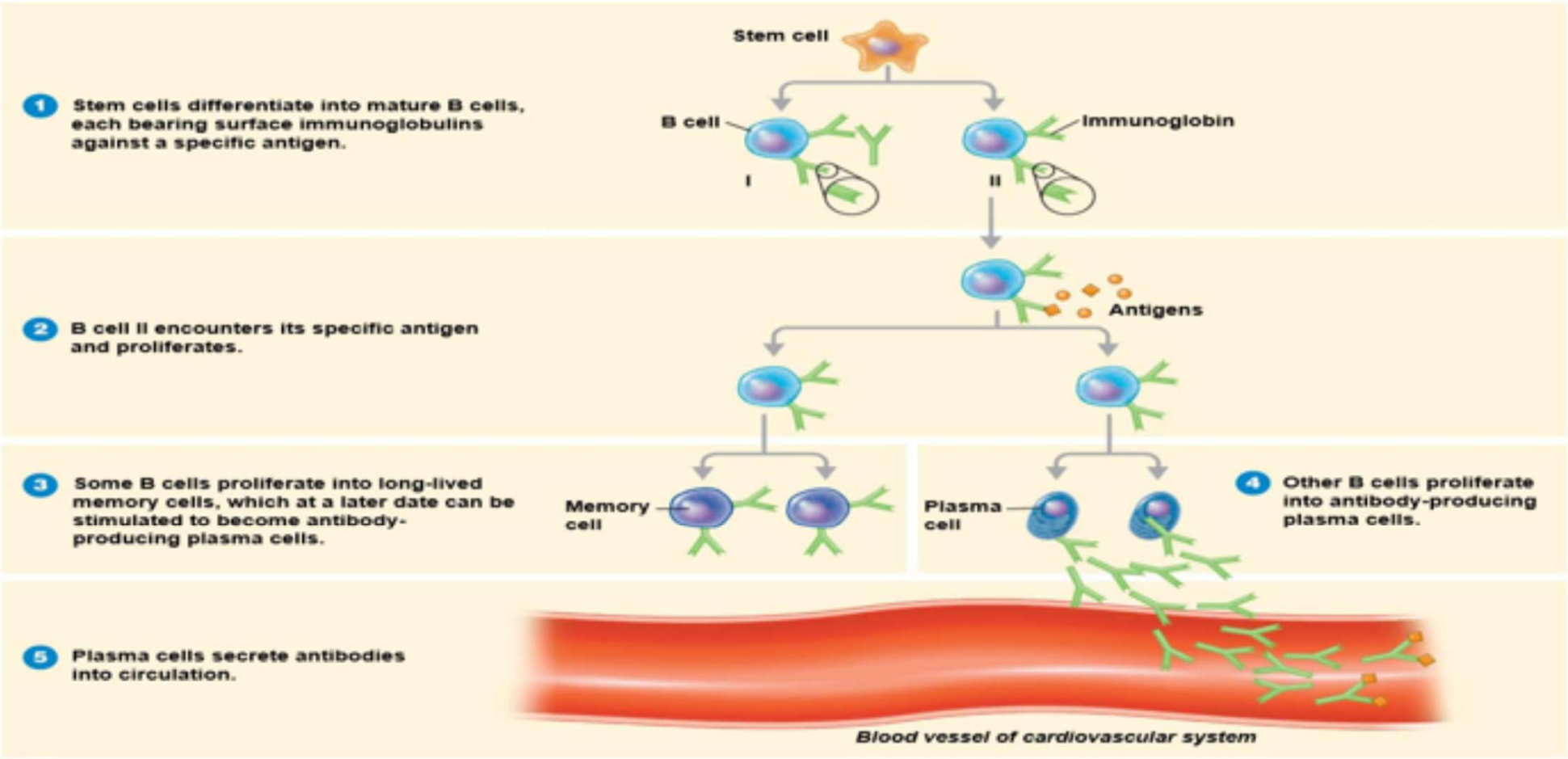


Differentiation of T Cells and B Cells



Clonal Selection

- Bone marrow gives rise to B cells.
- Mature B cells migrate to lymphoid organs.
- A mature B cells recognizes epitopes.



- **ACTIVATION OF ANTIBODY – PRODUCING CELLS BY CLONAL SELECTION**
- A B-cell becomes activated when an antigen reacts with antigen receptors on its surface
- The activated B cell produces a clone of plasma cells and memory cells.
- **The plasma cells secrete antibodies.**
- Memory cells recognize pathogens from previous encounters.
- T cells and B cells that react with self antigens are destroyed during fetal development; this is called clonal deletion.

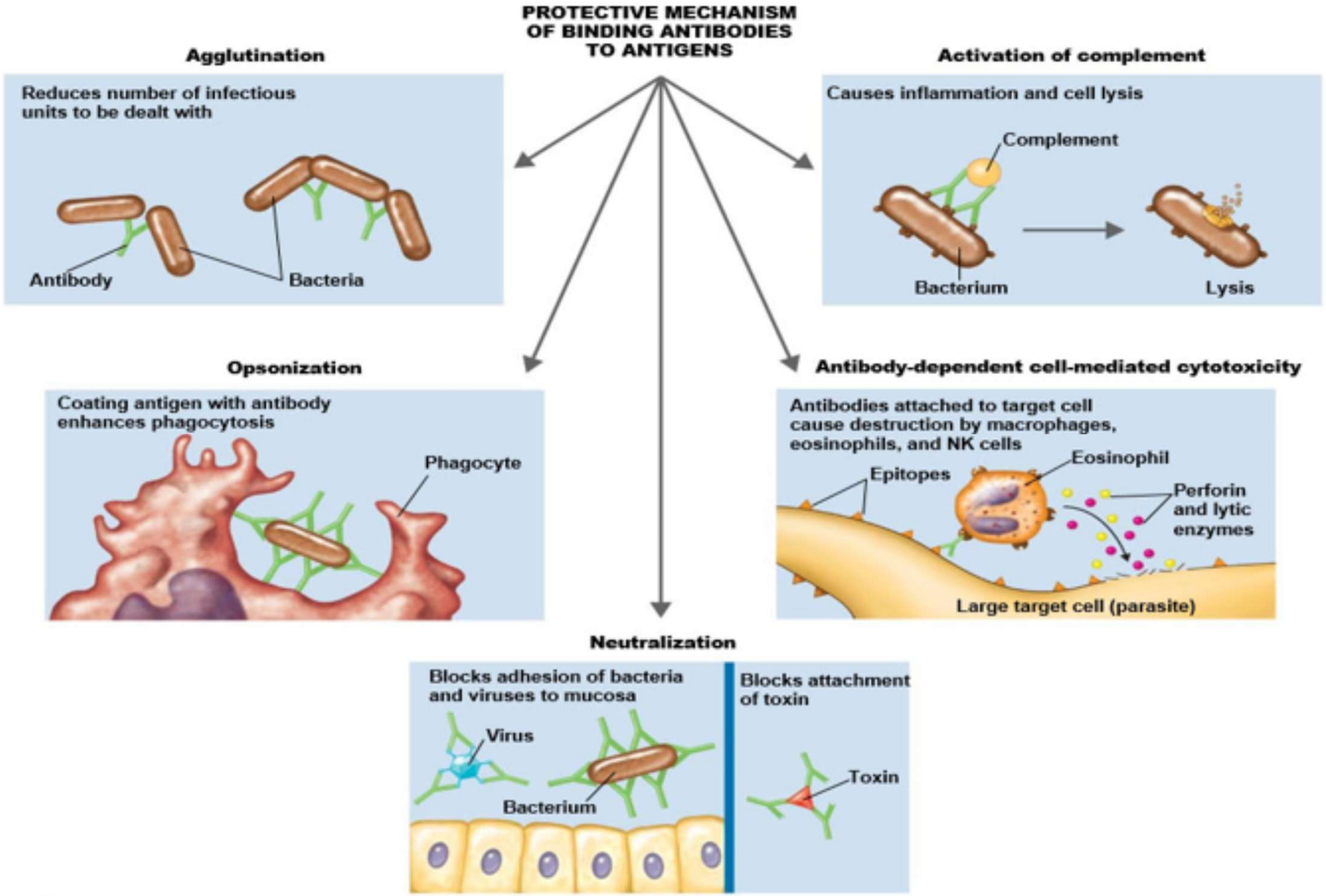
Self-tolerance

- Body doesn't make Antibodies against self antigen
- Clonal deletion
  - The process of destroying B and T cells that react to self antigens

Antigen–Antibody Binding and Its Results

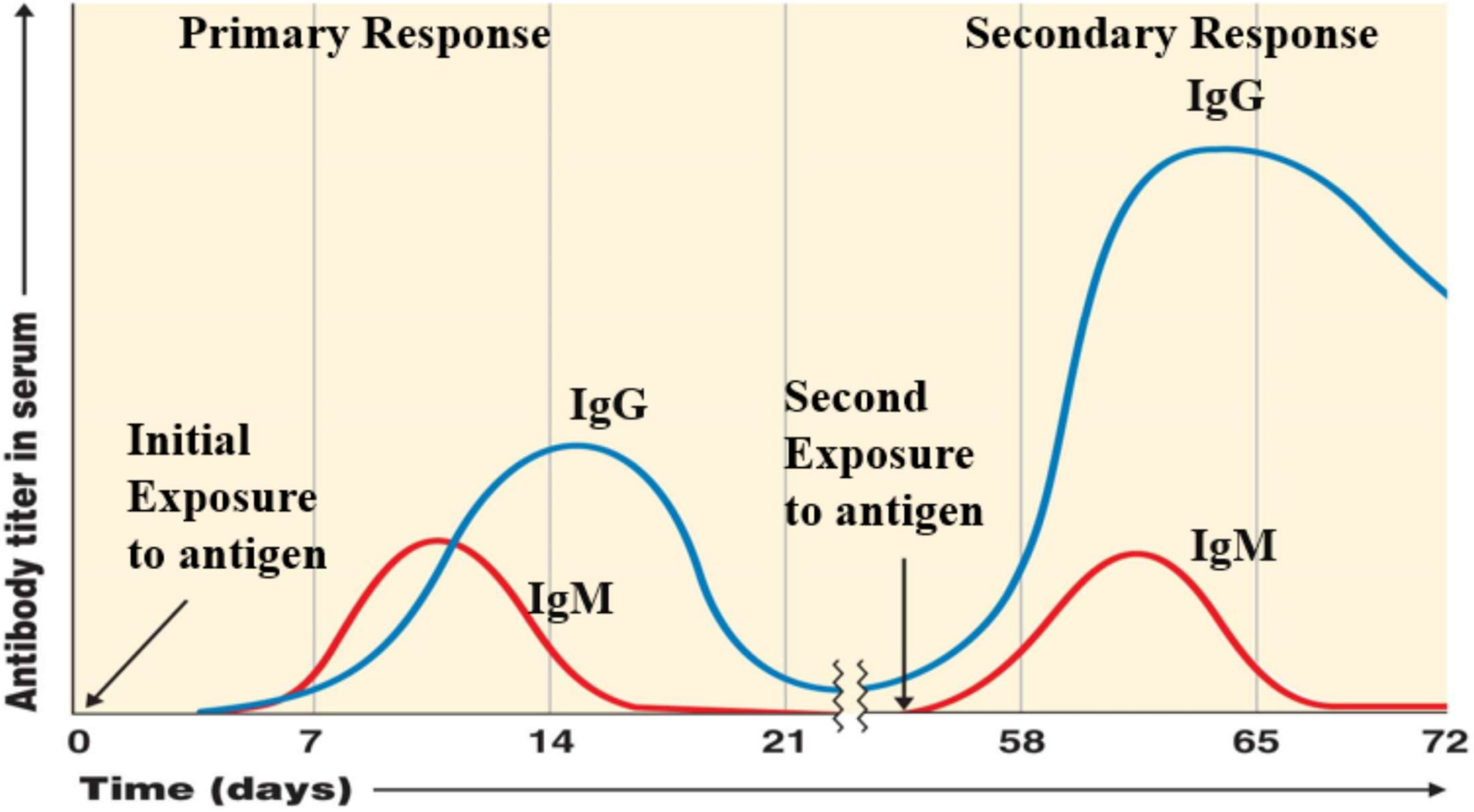
- An **antigen–antibody complex** forms when antibodies bind to antigens
  - Strength of the bond is the **affinity**
  - Antibodies protects the host by tagging foreign molecules or cells for destruction by
    - Agglutination
    - Opsonization
    - Antibody-dependent cell-mediated cytotoxicity
    - Neutralization
    - Activation of the complement system

Antigen–Antibody Binding and Its Results



Immunologic Memory

The Primary and Secondary Immune Responses to an Antigen



IMMUNOLOGICAL MEMMORY

- The response of the body to the first contact with an antigen is called the **primary response**. It is characterized by the appearance IgM followed by IgG.
- **Secondary (memory or anamnestic) response** occurs after the second exposure to an antigen
  - More rapid, lasts many days, greater in magnitude
  - Memory cells produced in response to the initial exposure are activated by the secondary exposure
  - The antibodies produced this time are primarily IgG.
- **Antibody titer** is the relative amount of antibody in the serum
  - Reflects intensity of the humoral response

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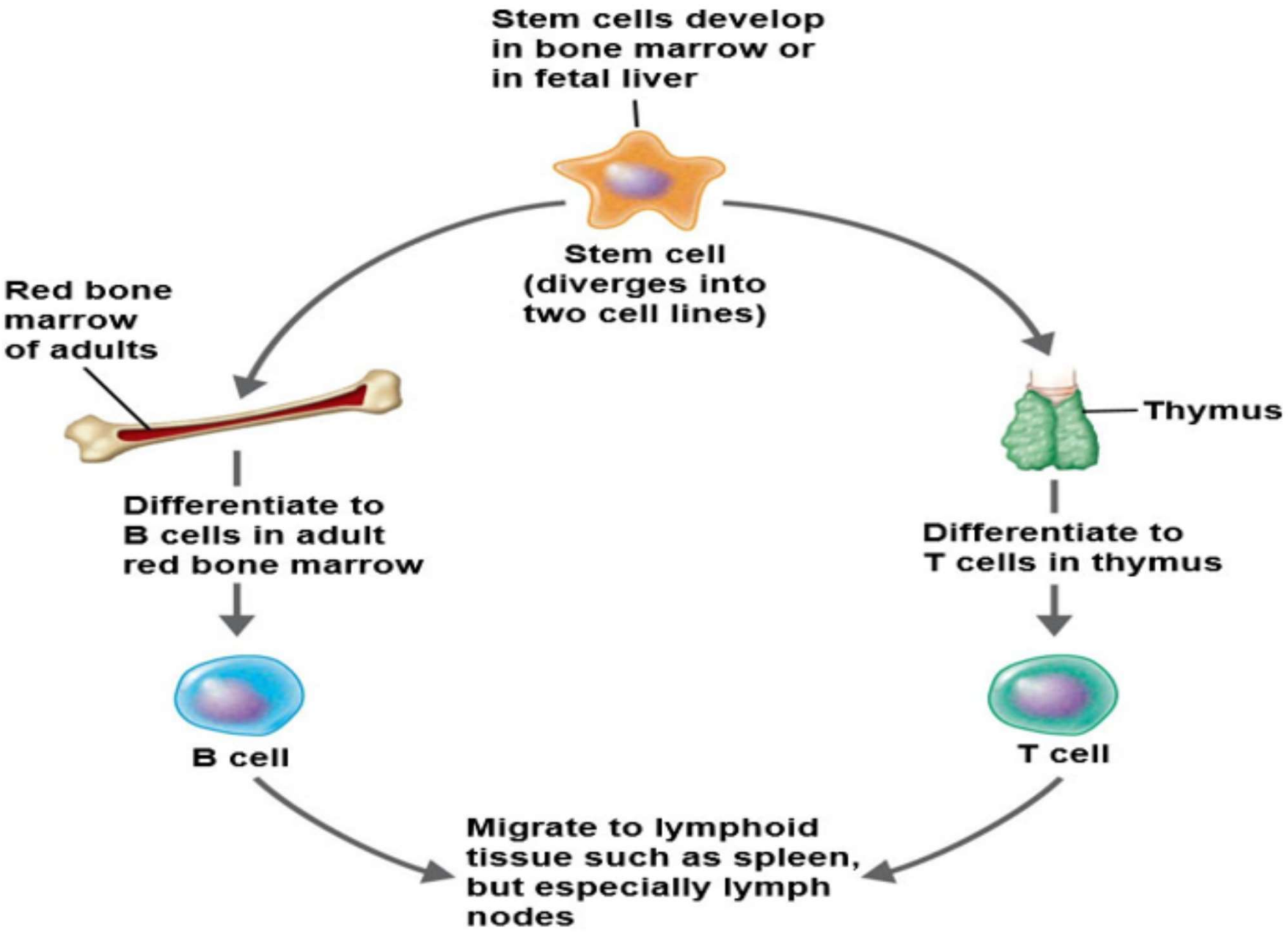


T Cells (T – Lymphocytes)

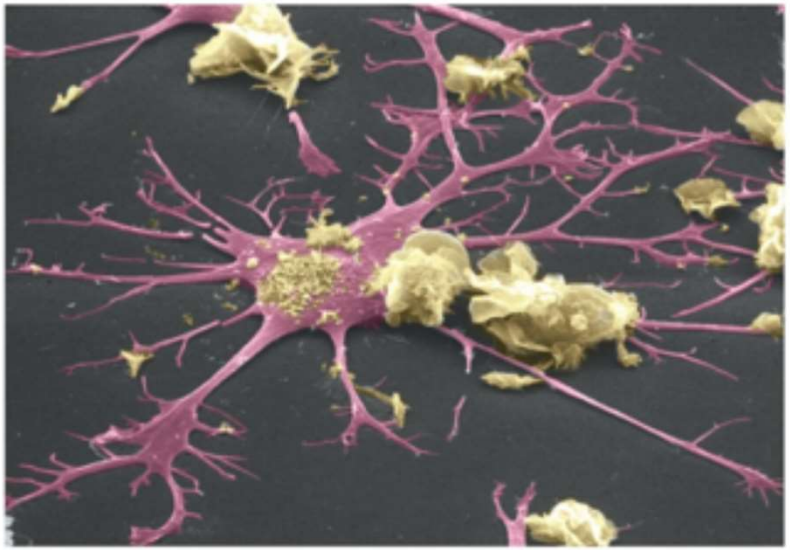
- Develop from stem cells in the bone marrow
- Mature in the Thymus gland
- After maturation in thymus, they migrate to lymphoid tissue
- Differentiate into effector T cells when they are stimulated by an antigen
- Some effector T cells become memory cells
- * Not transferred to fetus via the placenta
- Each T-cell reacts specifically with only one type of antigen.
- Body's ability to make new T-cell decreases with age, beginning with late adolescence

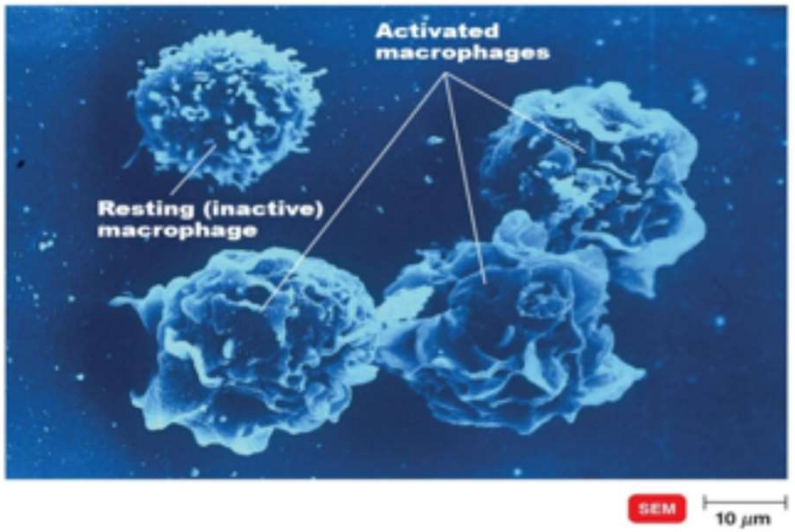
T Cells (T – Lymphocytes)

- Cell mediated immunity primarily involves T-cells that respond to intracellular antigens
- Some attack host cells that have become infected with viruses, fungi, transplanted human cells, and cancerous cells.
- Must come in close or direct contact to destroy the target cells.
- Do not secrete antibodies.
- An antigen must be processed by an APC and position on the surface of the APC on top of MHC (major histocompatibilty complex)

Antigen-Presenting Cells (APCs)

- A T-cell recognizes antigen in association with MHC on APC
- **Dendritic cells (DCs)**
  - Engulf and degrade microbes and display them to T cells
  - Found in the skin, genital tract, lymph nodes, spleen, thymus, and blood
- **Macrophages**
  - Activated by cytokines or the ingestion of antigenic material
  - Migrate to the lymph tissue, presenting antigen to T cells





Types of T-Cells

T-Cells are classified according to their functions and cell surface receptors called CD (Clusters of Differentiation). T – cell are of following types

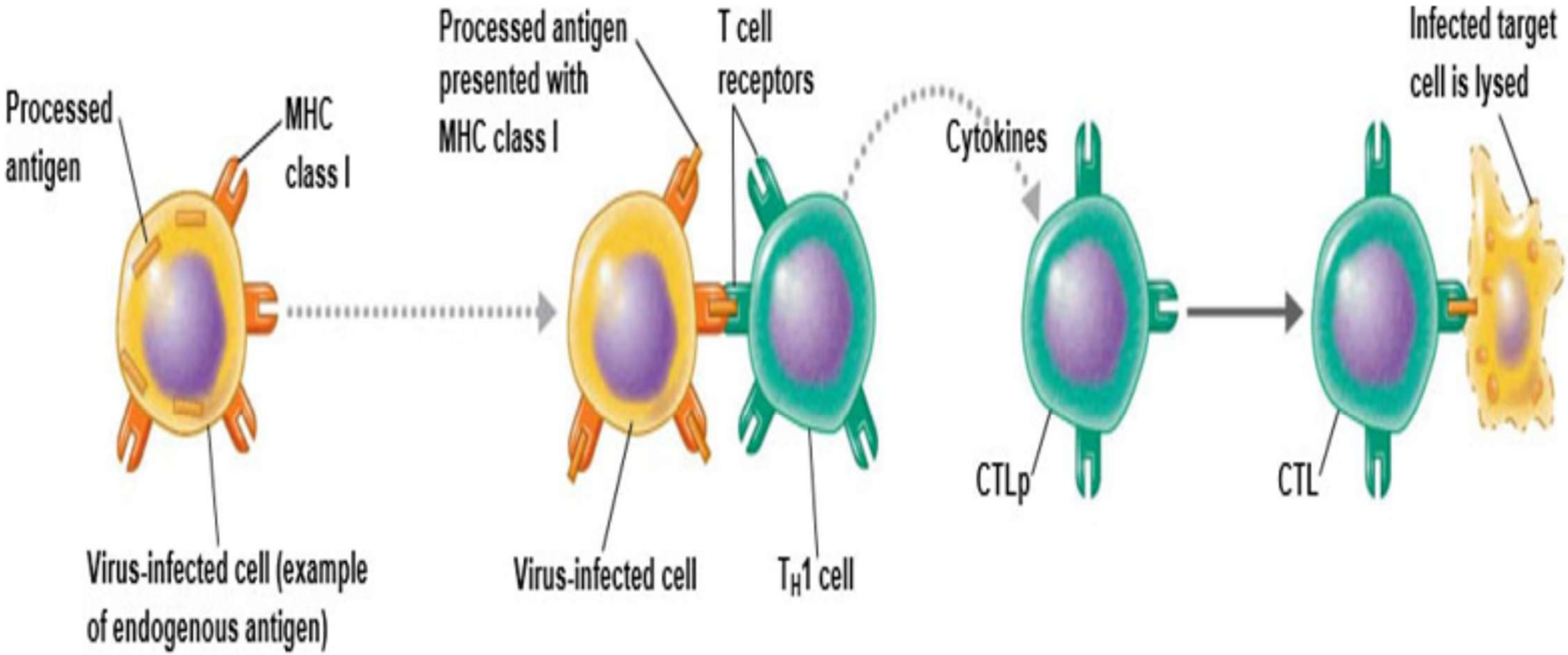
1) **Cytotoxic T-Cells** (Tc) or CD8 destroy target cells by two way

   a) initiation of apoptosis

   b) release of porins that damage the target cell membrane, resulting in cytolysis of target cells

   Cytotoxic T-Lymphocytes (CTL) A Tc can differentiate into an effector cell called CTL. CTL attach by their T-cells receptor to virus infected cells (self-cells) that display class 1 MHC proteins and viral antigens; are then stimulated by T-Helper cells; CTL releases **perforin** and **granzymes** that induce **apoptosis** in the infected cell

Killing of Virus-Infected Target Cell by Cytotoxic T Lymphocyte



1. A normal cell will not trigger a response by a cytotoxic T lymphocyte (CTL), but a virus-infected cell (shown here) or a cancer cell produces abnormal endogenous antigens.
2. The abnormal antigen is presented on the cell surface in association with MHC class I molecules. Binding of a T_H1 cell promotes secretion of cytokines.
3. The cytokines activate a precursor CTL, which produces a clone of CTLs.
4. The CTL induces destruction of the virus-infected cell by apoptosis.

Types of T-Cells

2) <u>Helper T-cells</u> (T_H) or CD4 secrete cytokines (IL-2) that activate other T-cells and B-cells.

* T_H bind to <u>MHC class II</u> molecules on B cell and APCs

3) Delayed Hypersensitivity T (T_D) associated with certain types of allergic reactions

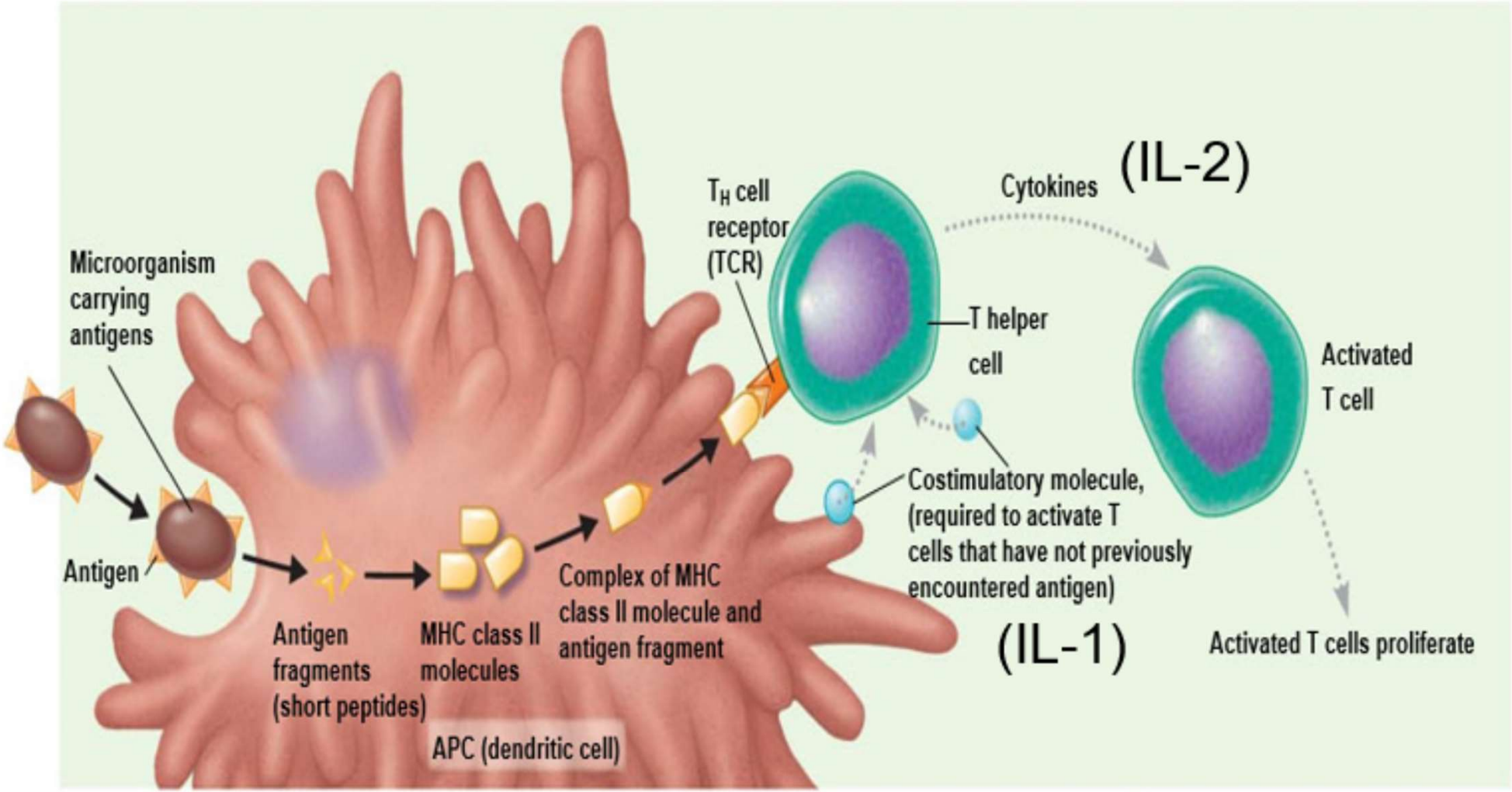
4) T regulatory cells (T_{reg}) formerly called **Suppressor T** (T_S) cells appear to regulate the

immune response (combat autoimmunity by suppressing T cells that escape deletion in thymus

* 5 -10% of T cell population

* They are subset of T helper cells with additional CD25 molecules

Activation of T Helper Cells (CD4+ T Cells)



1. An APC encounters and ingests a microorganism. The antigen is enzymatically processed into short peptides, which combine with MHC class II molecules and are displayed on the surface of the APC.

2. A receptor (TCR) on the surface of the $CD4^+$ T helper cell (T_H cell) binds to the MHC–antigen complex. This includes a Toll-like receptor. The T_H cell or APC is stimulated to secrete a costimulatory molecule. These two signals activate the T_H cell, which produces cytokines.

3. The cytokines cause the T_H cell (which recognizes a dendritic cell that is producing costimulatory molecules) to become activated.

Interrelationship of cell mediated and humoral immunity

- The production of antibodies by

1) T-dependent antigens

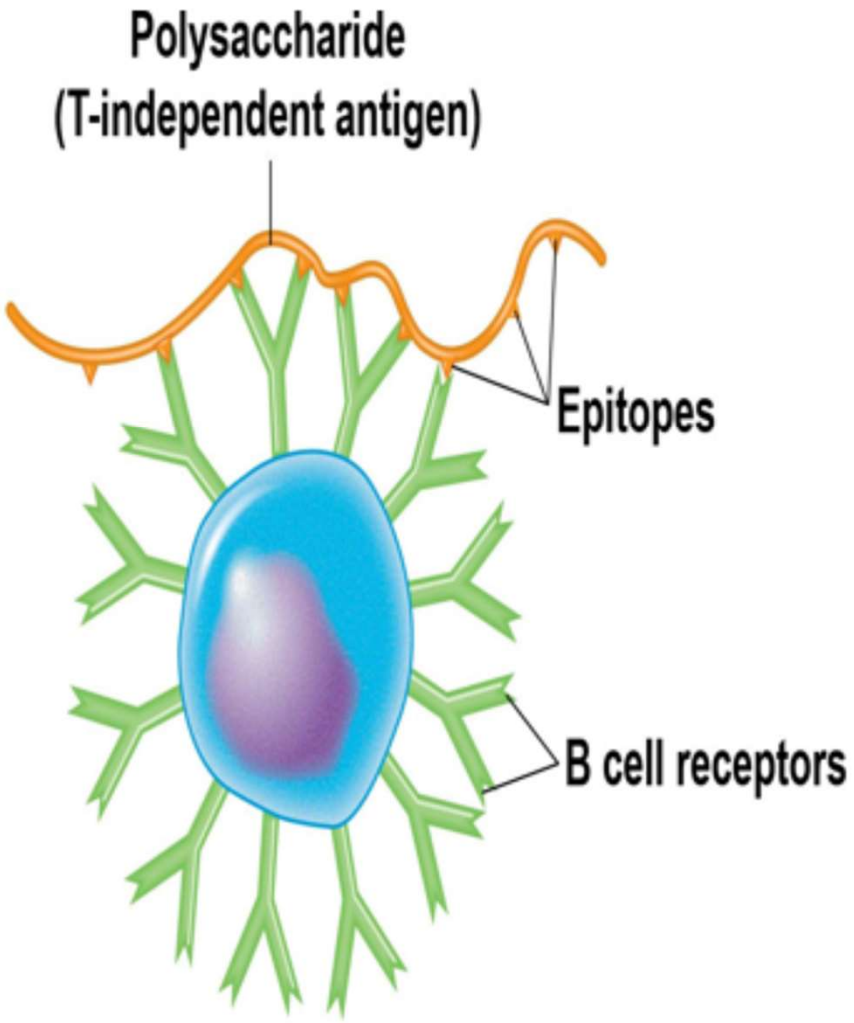
- Require assistance of Helper T-cells
- When T_h bind with MHC-antigen complex produces IL-2 that influence B cells to produce antibodies. T_h also activate B cell directly
- **Mainly proteins** (on viruses, bacteria, foreign RBC etc.

Interrelationship of cell mediated and humoral immunity

- The production of antibodies by

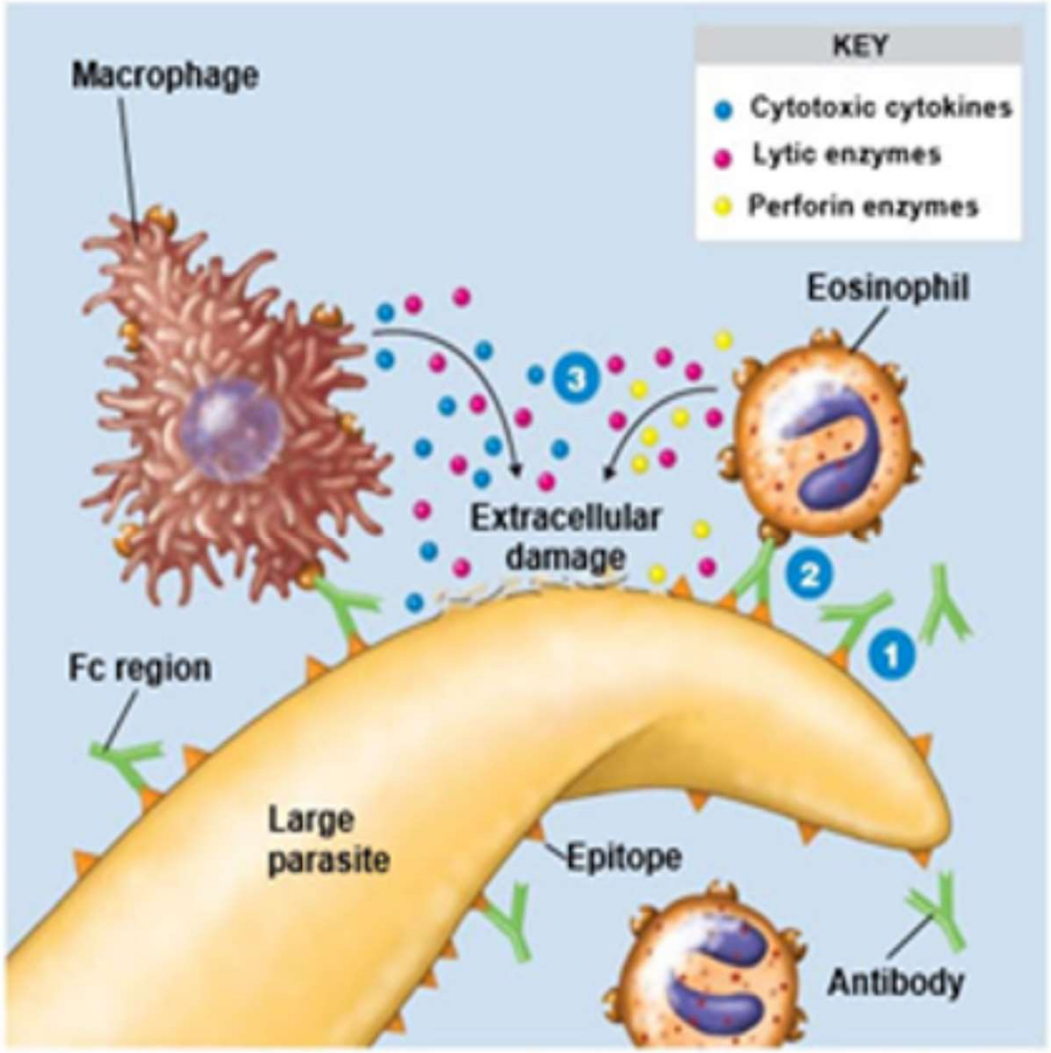
2) **T-independent antigens**

- Do not require assistance of helper T-cells to stimulate B cells
- **Mainly polysaccharides or lipopolysaccharides** (capsules etc.)
  - Provoke a weak immune response, usually producing IgM
  - No memory cells generated



Antibody-Dependent Cell-Mediated Cytotoxicity

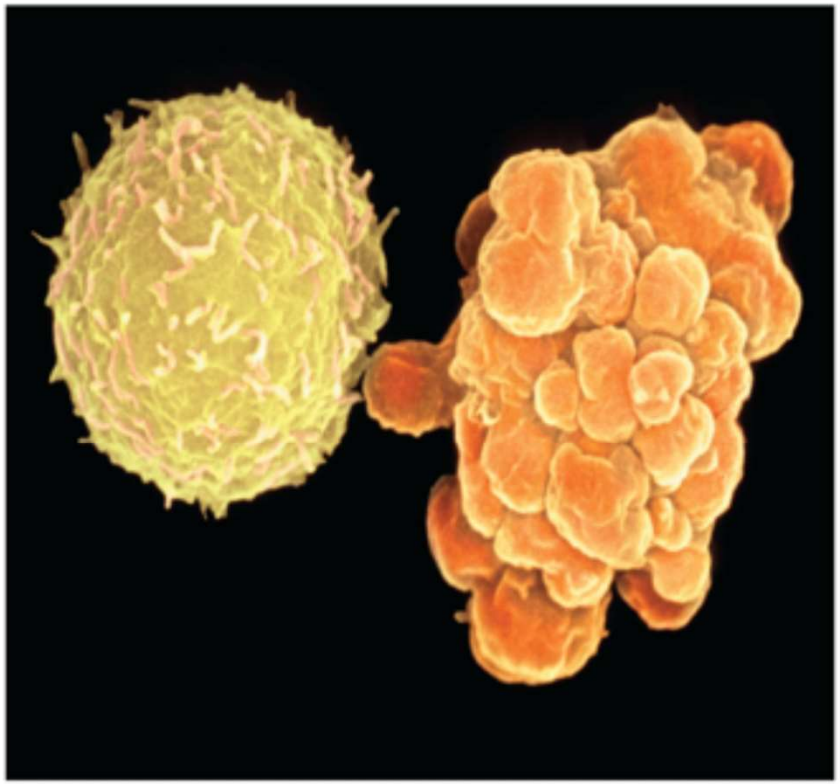
- Protozoans and helminths are too large to be phagocytized
  - Protozoan or helminth target cell is coated with antibodies
  - Immune system cells attach to the Fc regions of antibodies
  - Target cell is lysed by chemicals secreted by the immune system cell



(a) Organisms, such as many parasites, that are too large for ingestion by phagocytic cells must be attacked externally.

Apoptosis

- Lymphocytes that are not needed undergo apoptosis, or programmed cell death, and are destroyed by phagocytes.
- Prevents the spread of infectious viruses into other cells
- Cells cut their genome into fragments, causing the membranes to bulge outward via blebbing

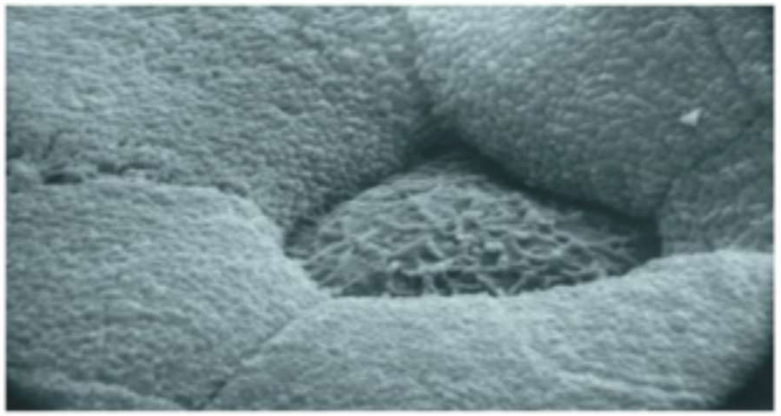


Extracellular Killing by the Immune System

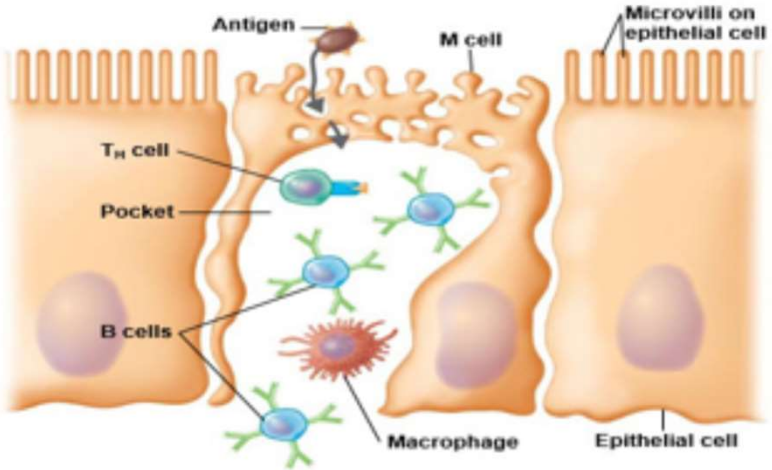
- **Natural killer (NK) cells**
  - Granular leukocytes destroy cells that don't express MHC class I self-antigens
  - Kill virus-infected and tumor cells and attack parasites
  - Not always stimulated by an antigen
  - Form pores in the target cell, leading to lysis or apoptosis

Cellular Immunity Response Process

- T cells combat intracellular pathogens
  - Mature in the thymus
  - **Thymic selection** eliminates immature T cells
  - Migrate from the thymus to lymphoid tissues
  - Attach to antigens via T-cell receptors (TCRs)
- Pathogens entering the gastrointestinal tract pass through **microfold cells (M cells)** located over **Peyer's patches**
  - Transfer antigens to lymphocytes and antigen-presenting cells (APCs)



(a) M cell on Peyer's patch. Note the tips of the closely packed microvilli on the surrounding epithelial cells.



(b) M cells facilitate contact between antigens passing through the intestinal tract and cells of the body's immune system.

Lineage of Effector T Helper Cell Classes and Pathogens Targeted