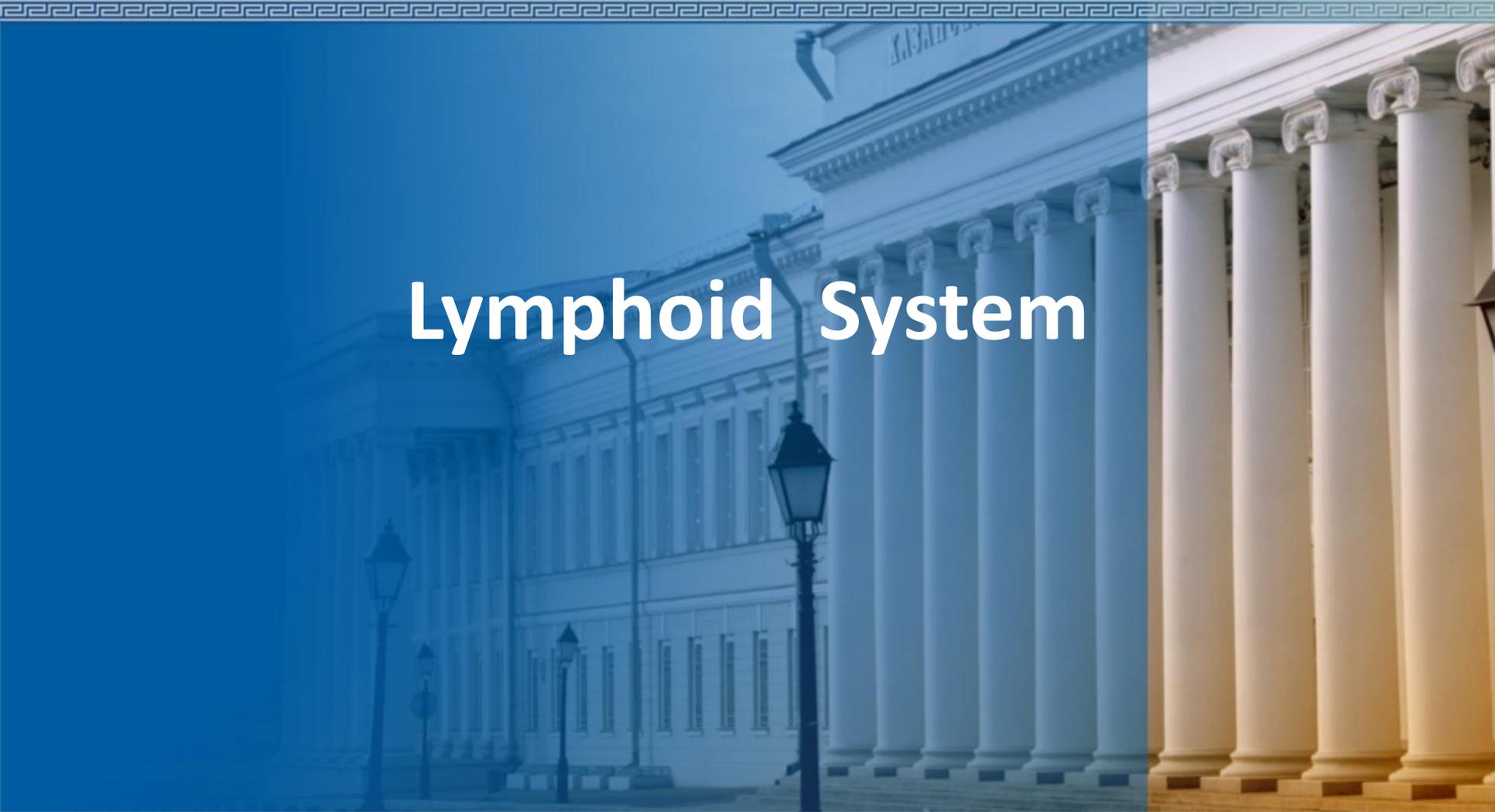




КАЗАНСКИЙ (ПРИВОЛЖСКИЙ) ФЕДЕРАЛЬНЫЙ УНИВЕРСИТЕТ

Lymphoid System



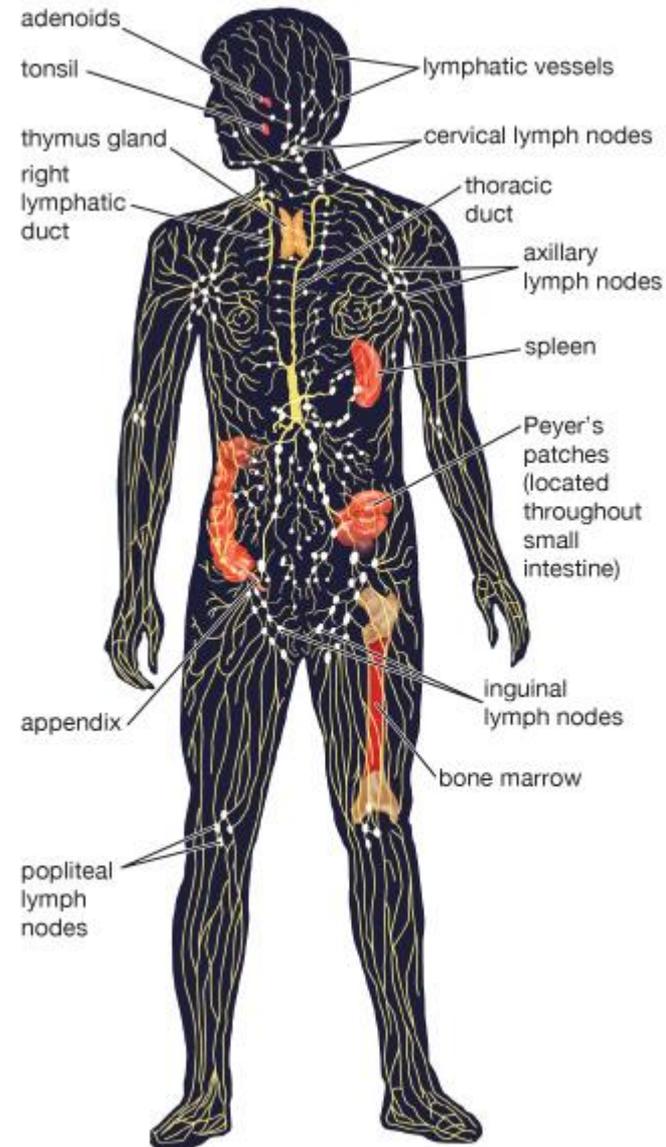
Lymphoid System

- a system of cells that has the ability to distinguish "self" (the organism's own molecules) from "non-self" (foreign substances).
- this system has the ability to neutralize or inactivate foreign molecules and to destroy microorganisms or other cells (such as virus-infected cells, cells of transplanted organs, and cancer cells)
- On occasion, the immune system of an individual reacts against its own normal body tissues or molecules, causing **autoimmune diseases**.

Lymphoid System

- **cells** distributed throughout the body in the blood, lymph, and epithelial and connective tissues
- **lymphoid nodules** found in the mucosa of the digestive system (including the tonsils, Peyer's patches, and appendix), the respiratory system, the reproductive system, and the urinary system are collectively known as **mucosa-associated lymphoid tissue (MALT)**
- **lymphoid organs**—the bone marrow, the thymus, the lymph nodes, the spleen

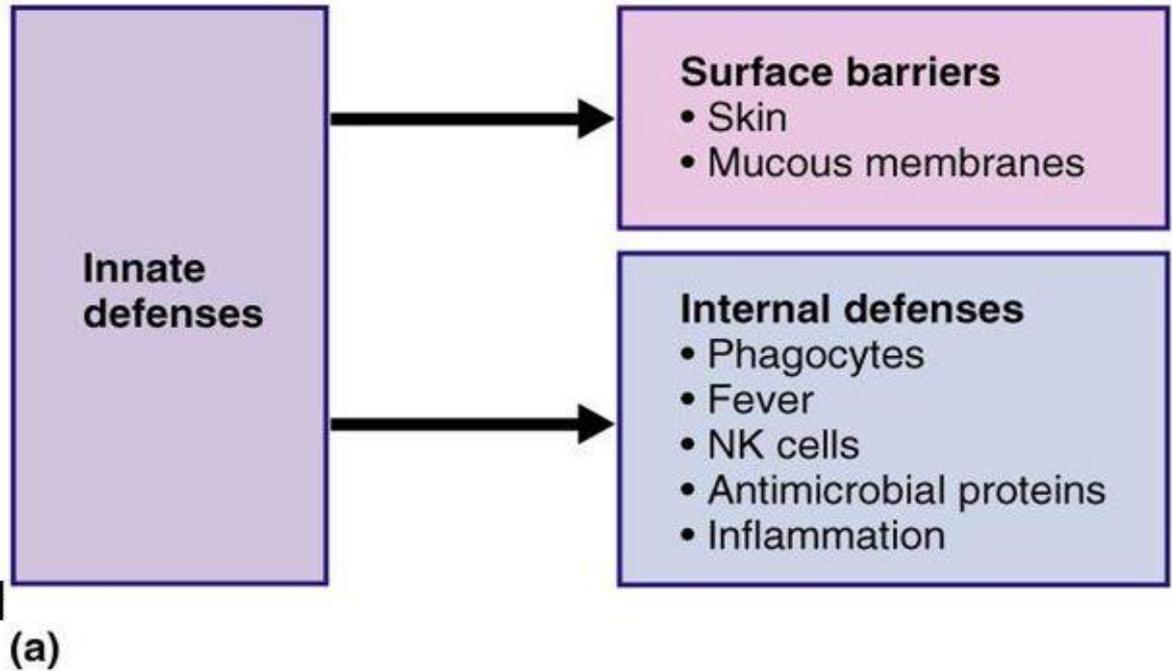
The wide distribution of immune system cells and the constant traffic of lymphocytes through the blood, lymph, connective tissues, and lymphoid organs provide the body with an efficient system of defense



Defense Systems

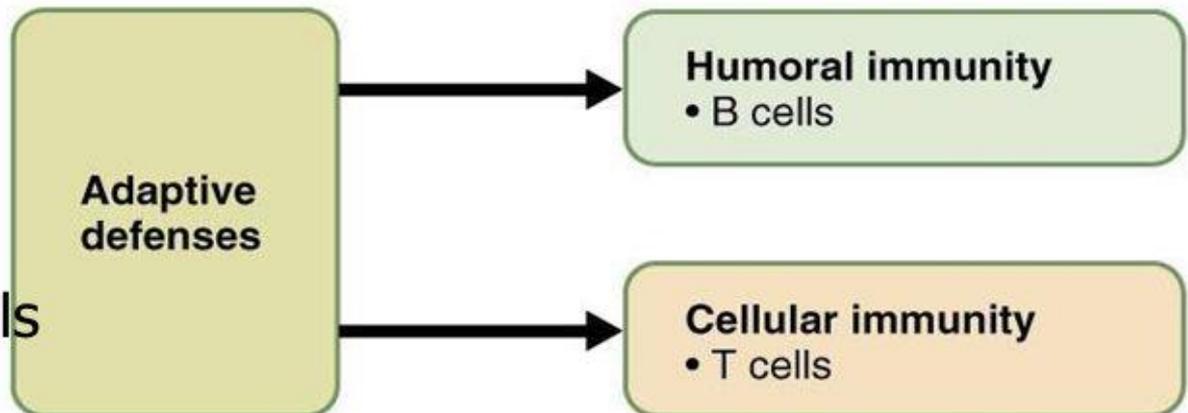
1. Innate (nonspecific) defenses

- External body membranes
- Inflammation
 - Antimicrobial proteins, phagocytes and other cells

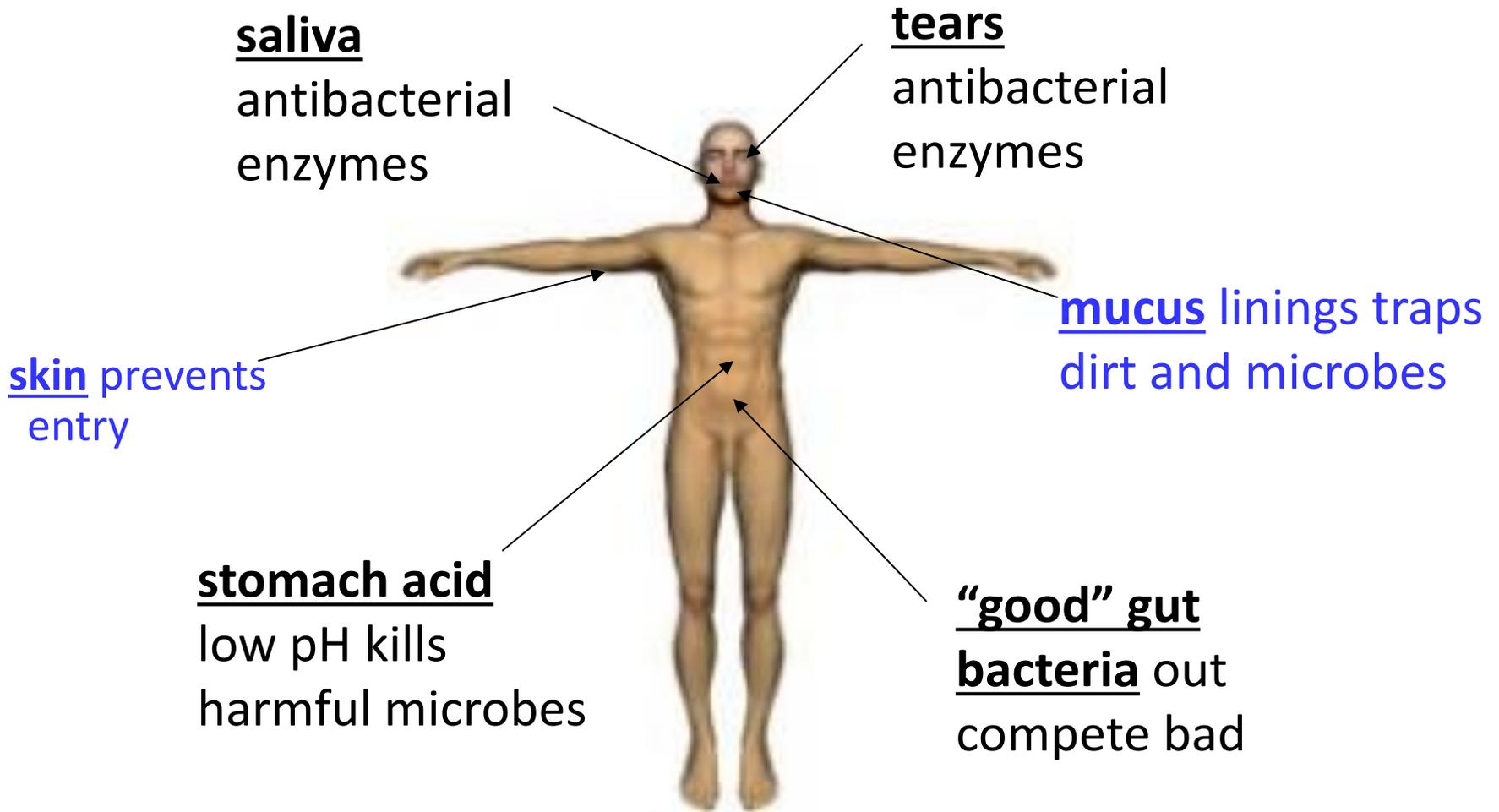


2. Adaptive (specific) defenses

- T cells and B cells

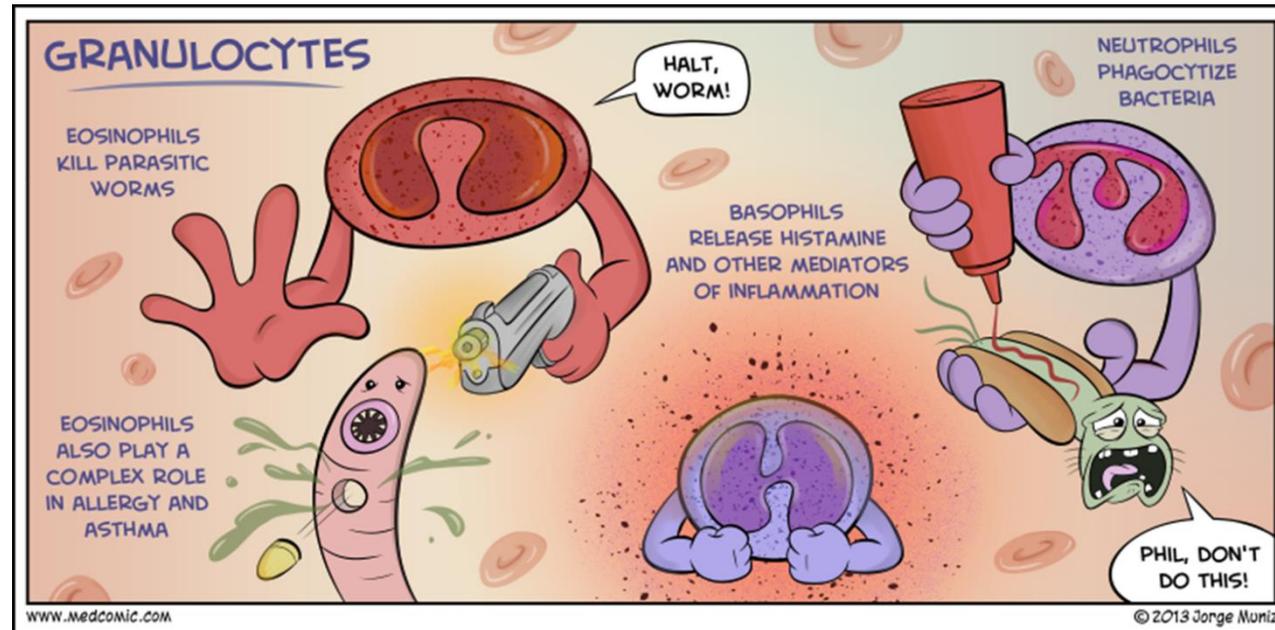


First line of defence

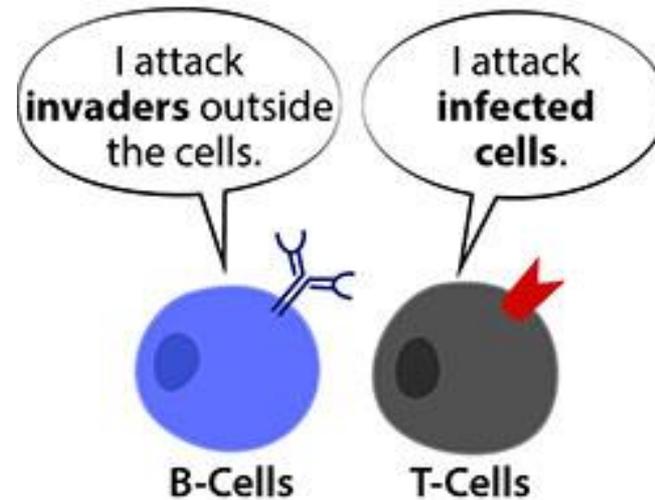


Second line of defence

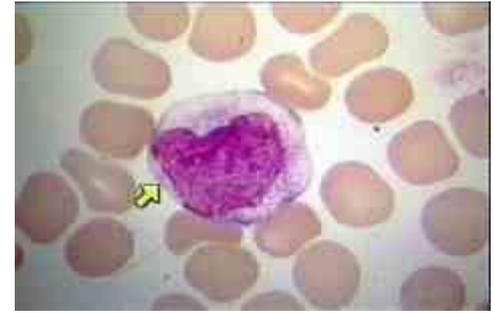
- **Non-specific response**
 - invading pathogens are targeted by leukocytes



- **Specific response**
 - lymphocytes produce antibodies and kill infected cells



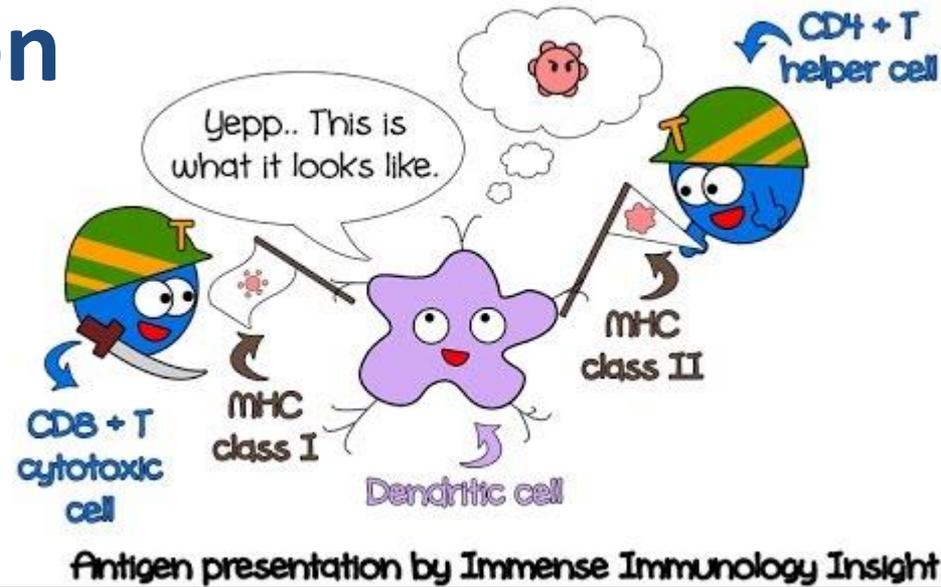
Macrophages



- Larger than neutrophils.
- Found in the tissues, not the blood.
- Made in bone marrow as monocytes, called macrophages once they reach organs.
- Long lived
- Can be **antigen presenting cells**
- **Initiate** immune responses as they display antigens from the pathogens to the lymphocytes.

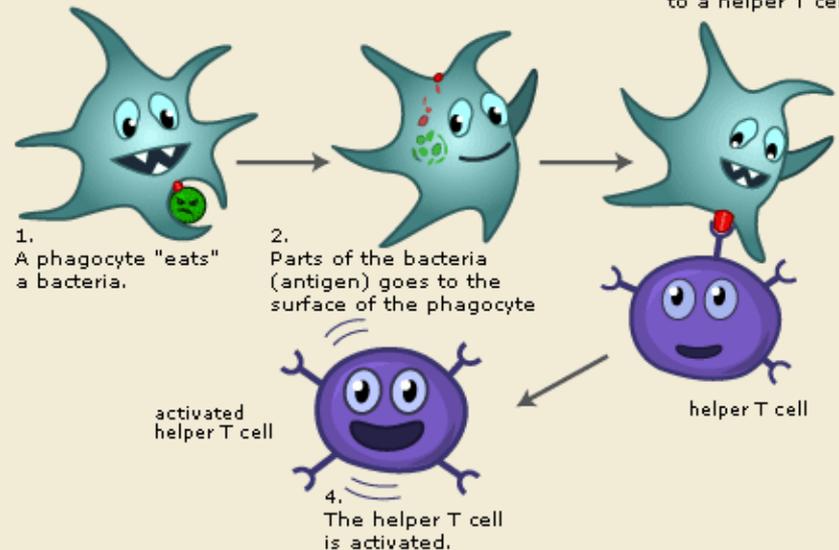
Antigen Presentation

- All pathogens that made their way to our body should be presented to T lymphocytes since they can not directly recognize them
- **Macrophages, Dendritic Cells** and **B lymphocytes** are types of **Antigen Presenting Cells**
- They engulf the evaded pathogen, break it down and present part of it in complex with MHC II molecule on the surface
- Now T lymphocytes can bind to these complexes and begin the immune response



Antigen Presentation

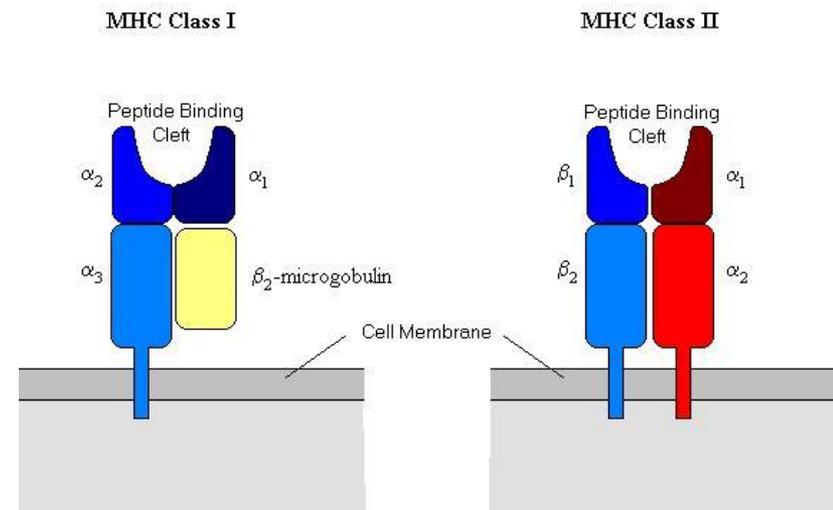
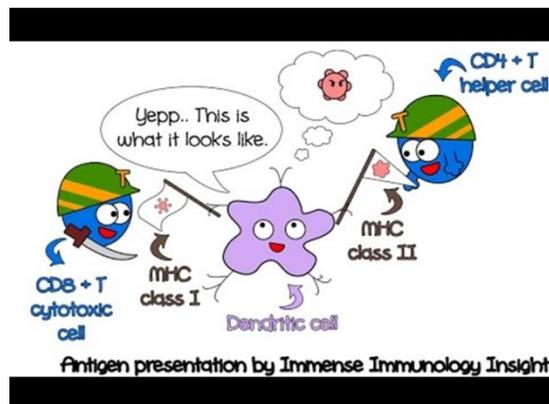
dendritic cell



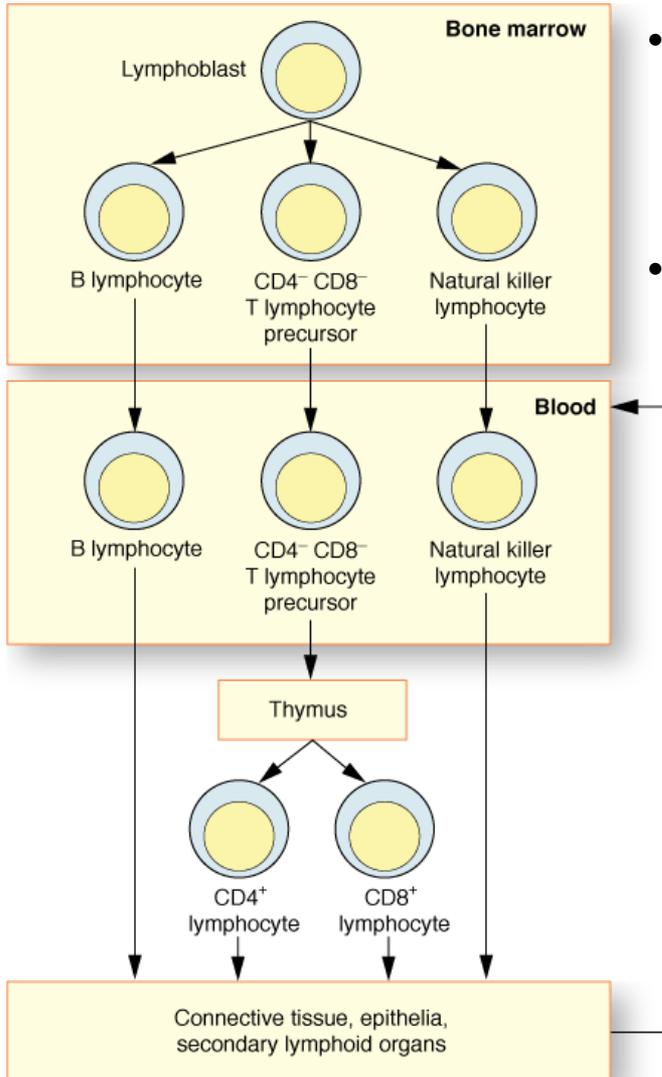
Major Histocompatibility Complex (MHC)

- A complex of chromosomal loci encoding several proteins known as class I and class II MHC molecules
- There is great variation of these molecules among the general population
- One individual, however, expresses only one set of class I proteins and one set of class II proteins; these proteins are unique to that person
- MHC molecules are integral membrane proteins present on the cell surface. They are synthesized by the RER like regular membrane proteins. However, on their way to the cell surface, they couple with small peptides of 10–30 amino acids whose origin differs depending on whether class I or class II molecules are involved
- MHC class I proteins - all nucleated cells
- MHC class II proteins - exist on only a small group of cells called **antigen-presenting cells (APCs)**

(APCs)



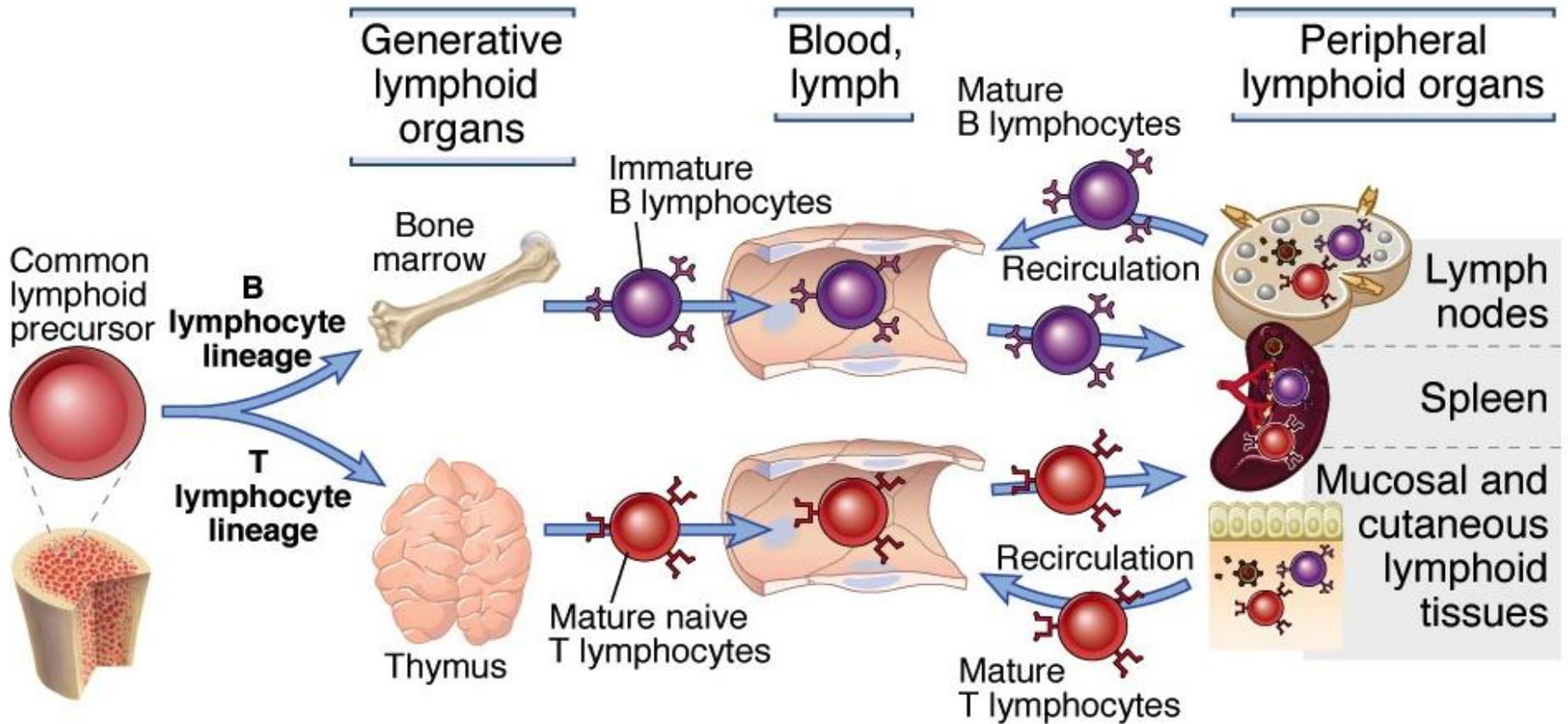
Lymphocytes



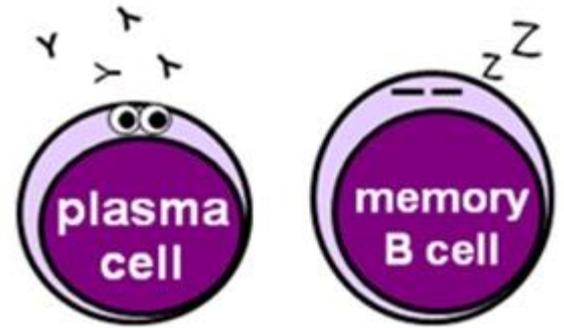
- B and T lymphocytes have receptors on their surface. These receptors are fundamental for recognition of antigens and, thus, for triggering an immune response.
- Each B lymphocyte that leaves the bone marrow or each T lymphocyte that leaves the thymus has just one type of surface receptor that recognizes one specific antigen.

Lymphoid Organ	T Lymphocytes (%)	B Lymphocytes (%)
Thymus	100	0
Bone marrow	10	90
Spleen	45	55
Lymph nodes	60	40
Blood	70	30

T and B lymphocytes



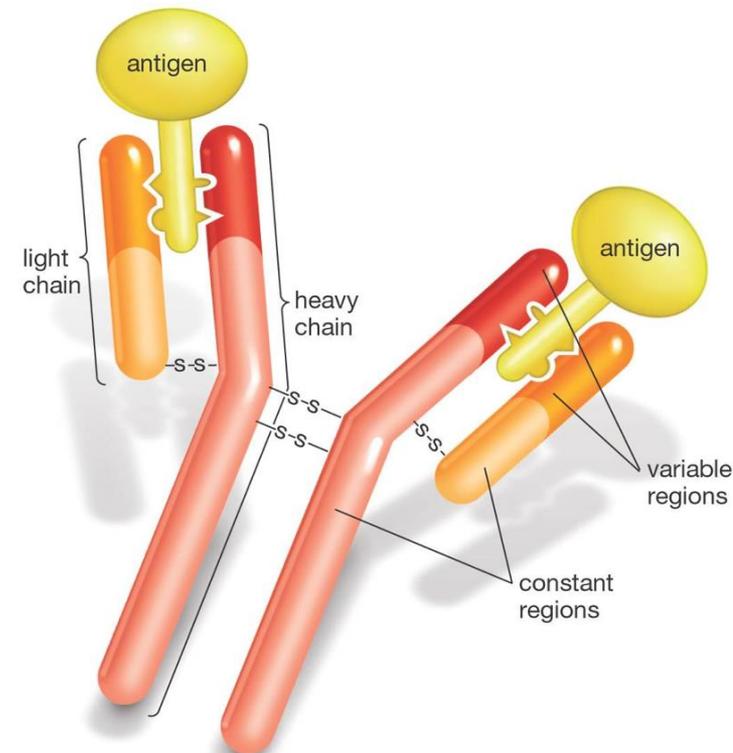
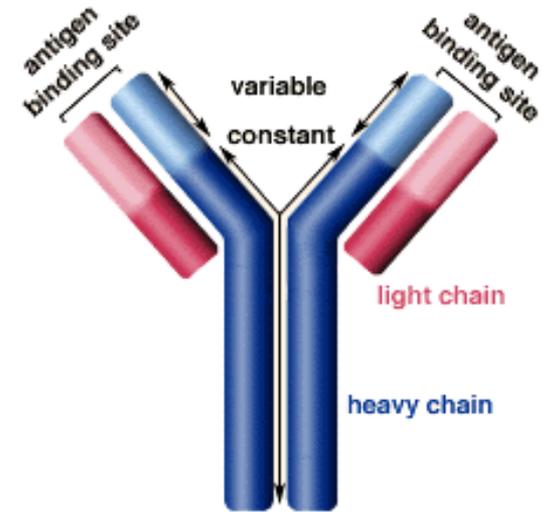
B-lymphocytes

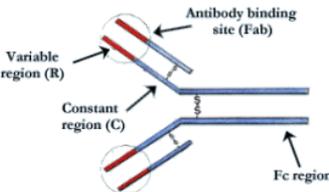
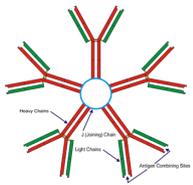
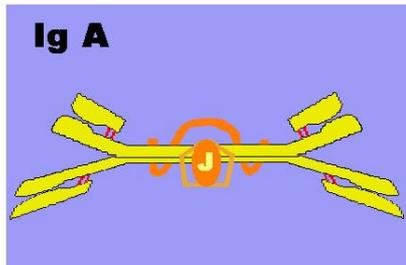
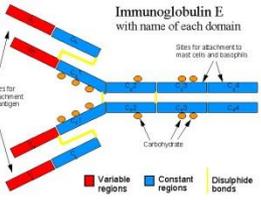


- The surface receptors able to recognize antigens are molecules of IgM
- Each B cell is covered by about 150,000 molecules of IgM
- The encounter of a B lymphocyte with the epitope it recognizes leads to several cycles of cell proliferation forming plenty of **plasma cells**
- This population of plasma cells secretes antibodies against the same epitope as that recognized by the B cell from which it arose.
- Not all activated B cells, however, become plasma cells; some remain as long-lived **B memory cells**, which are able to react very rapidly to a second exposure to the same epitope.

Antibodies

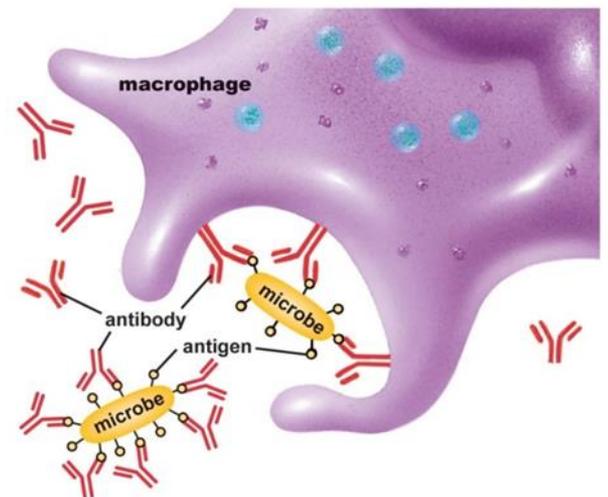
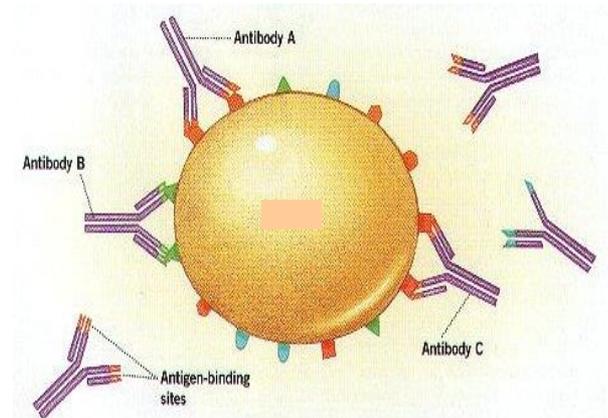
- Also known as immunoglobulins
- The heavy and light chains are polypeptides
- The chains are held together by disulphide bridges
- 2 identical antigen binding sites – **variable regions** and one cell binding – **constant region**
- The order of amino acids in the variable region determines the shape of the binding site



Type	Number of ag binding sites	Site of action	Functions
<p>IgG</p> 	<p>2</p>	<ul style="list-style-type: none"> •Blood •Tissue fluid •CAN CROSS PLACENTA 	<ul style="list-style-type: none"> •Increase macrophage activity •Antitoxins •Agglutination
<p>IgM</p> 	<p>10</p>	<ul style="list-style-type: none"> •Blood •Tissue fluid 	<p>Agglutination</p>
<p>IgA</p> 	<p>2 or 4</p>	<ul style="list-style-type: none"> •Secretions (saliva, tears, small intestine, vaginal, prostate, nasal, breast milk) 	<ul style="list-style-type: none"> •Stop bacteria adhering to host cells •Prevents bacteria forming colonies on mucous membranes
<p>IgE</p> 	<p>2</p>	<p>Tissues</p>	<ul style="list-style-type: none"> •Activate mast cells → HISTAMINE

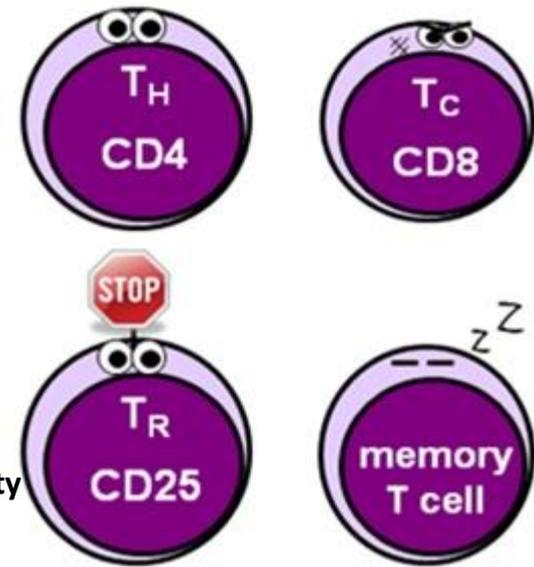
Role of antibodies

- Antibodies released into the blood stream will bind to the antigens that they are specific for - **opsonization**
- Antibodies may disable some microbes, or cause them to stick together - **agglutination**. They “tag” microbes so that the microbes are quickly recognized by various white blood cells.



(b) Antibody effector function

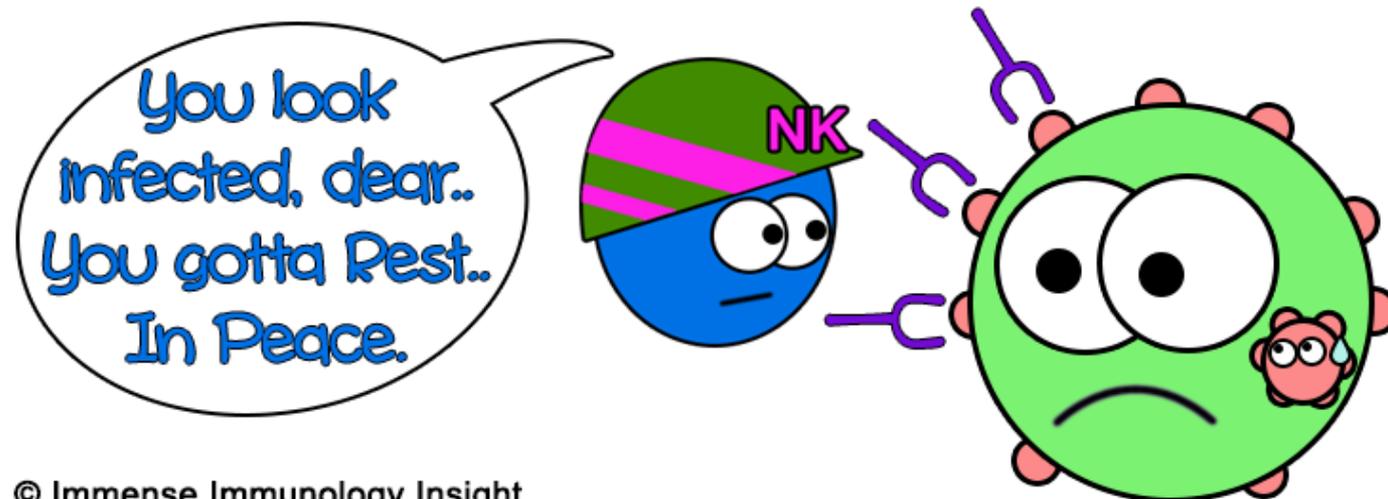
T lymphocytes



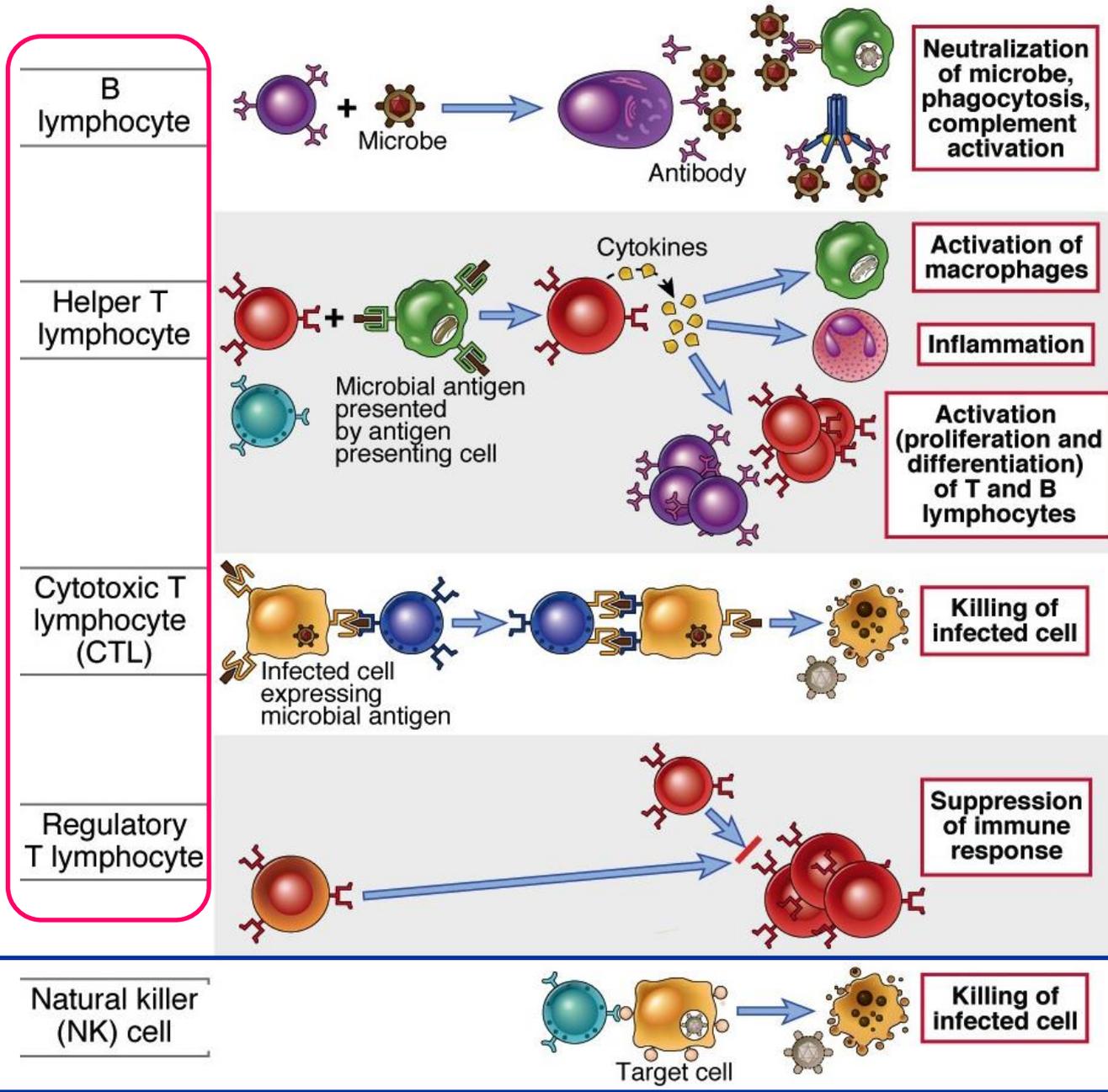
- Constitute 65–75% of blood lymphocytes
 - T cells have a molecule called a **T cell receptor (TCR)** on their surfaces which recognize only epitopes (mostly small peptides) that form complexes with special proteins on the cell surface of other cells (proteins of **the major histocompatibility complex**)
 - Three important subpopulations of T cells are the following:
 - **Helper cells**, which produce cytokines that promote differentiation of B cells into plasma cells, activate macrophages to become phagocytic, activate cytotoxic T lymphocytes, and induce many parts of an inflammatory reaction. Helper cells have a marker called CD4 on their surfaces and are, hence, called **CD4⁺ T cells**.
 - **Cytotoxic T cells** are **CD8⁺** and act directly against foreign cells or virus-infected cells by two main mechanisms. First, they attach to the cells to be killed and release proteins called **perforins** that create holes in the cell membrane of the target cell, with consequent cell lysis. Second, they attach to a cell and kill it by triggering mechanisms that induce programmed cell death, or **apoptosis**.
 - **Regulatory T cells** are CD4⁺CD25⁺ and play crucial roles in allowing immune tolerance, maintaining unresponsiveness to self-antigens and suppressing excessive immune responses.
 - The first encounter of a CD4 or CD8 T cell with its specific epitope is followed by amplification of that clone; some of the cells of this increased population become effector cells, doing the job for which they are specialized, and some remain memory helper or memory cytotoxic T cells, reacting rapidly to the next presentation of the same epitope
- *One of the primary causes of the immunodeficiency syndrome known as **AIDS** involves the killing of helper T cells by the infecting retrovirus. This cripples the patients' immune system rendering them susceptible to opportunistic infections by microorganisms that usually do not cause disease in immunocompetent individuals.*

NK cells

- The **natural killer** lymphocytes lack the markers characteristic of B and T cells.
- They comprise about 10–15% of the lymphocytes of circulating blood.
- Their name derives from the fact that they attack virus-infected cells, transplanted cells, and cancer cells without previous stimulation; for this reason they are involved in what is called an **innate immune response**.
- Do not require activation to kill cells that are missing "self" markers of MHC class I, allowing for a much faster immune reaction.



Types of lymphocyte



Lymphoid organs



- **Primary organs** - where **lymphocytes** are **formed and mature:**

- **Bone Marrow**

(see “Blood and Hematopoiesis”)

- **Thymus**

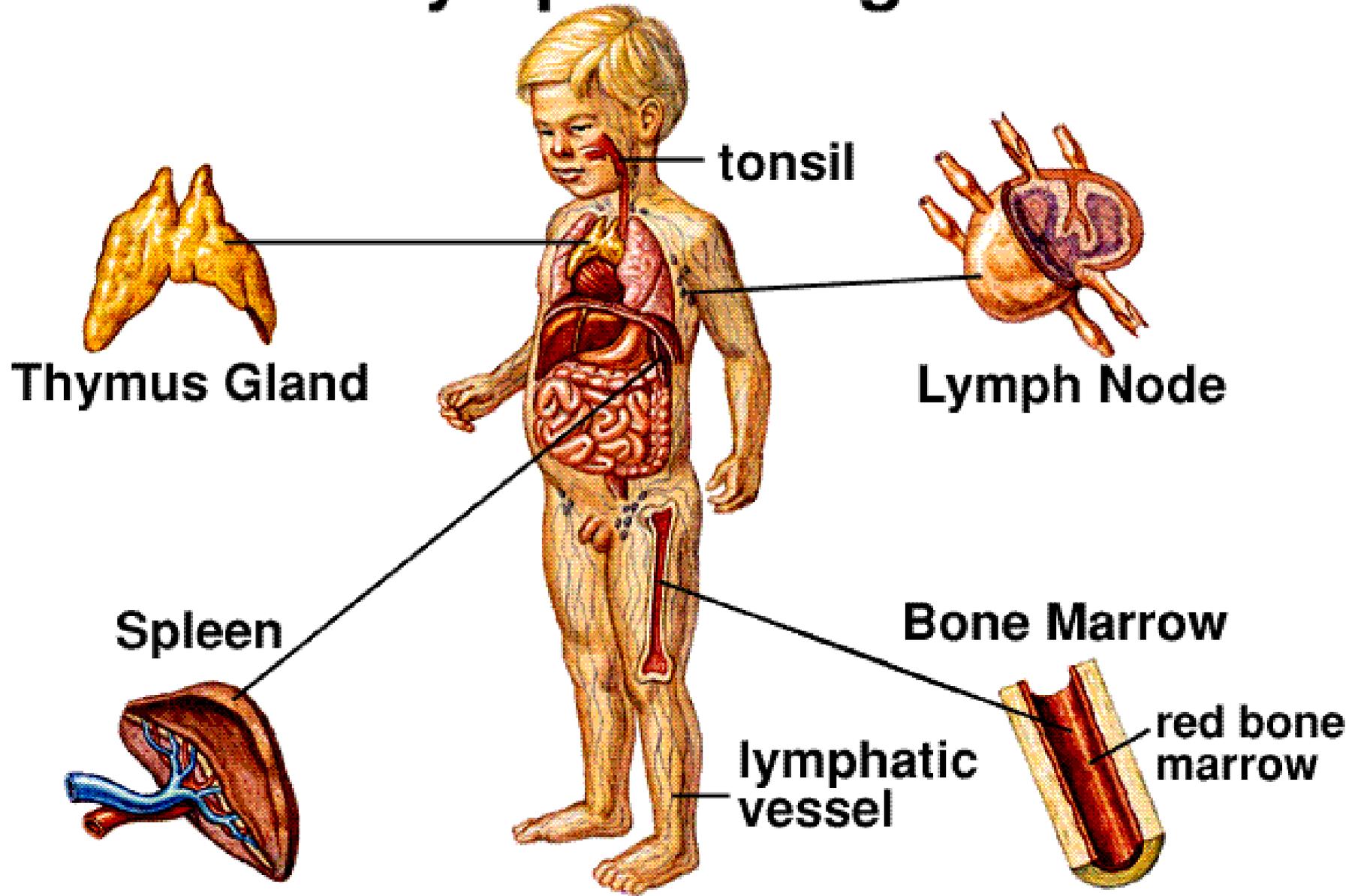
- **Secondary organs** - where lymphocytes are **activated:**

- **Lymph nodes**

- **Spleen**

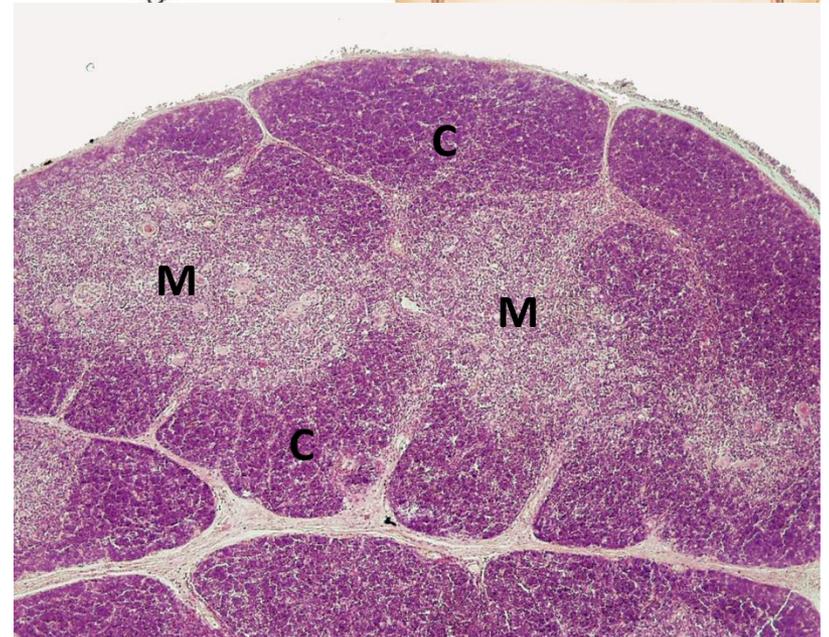
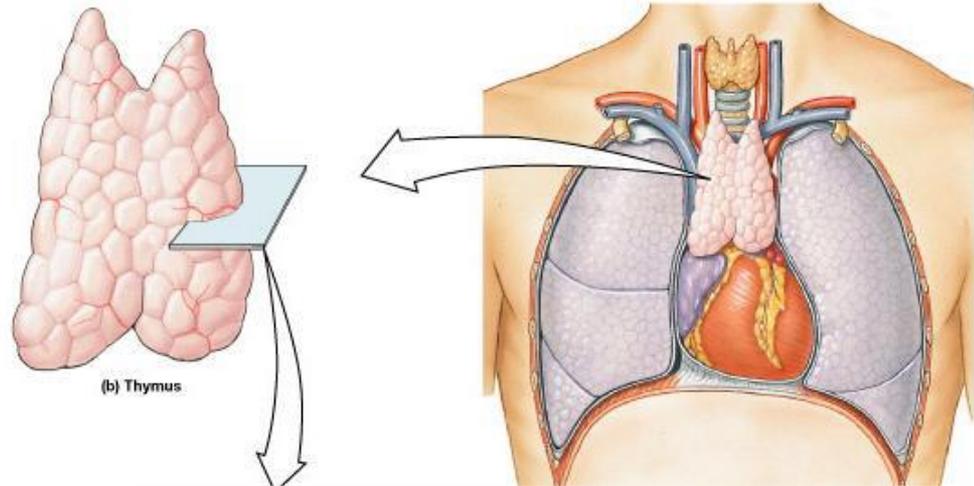
- **Mucosal associated lymphoid tissues** (tonsils, Payers patches and etc.)

Lymphoid Organs



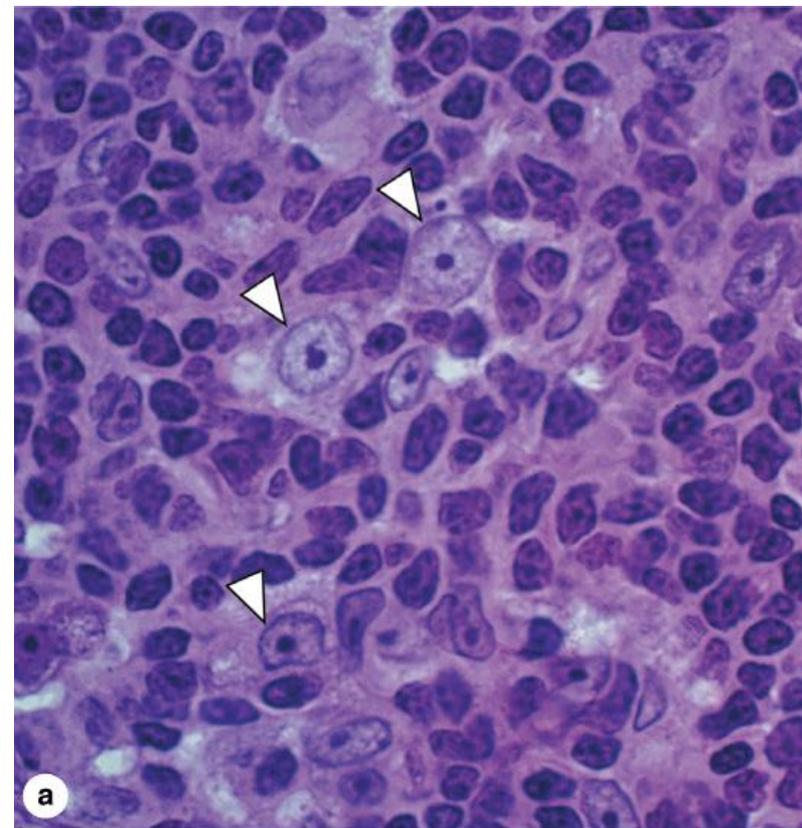
The Thymus

- The thymus is a primary lymphoid organ located in the superior mediastinum
- The thymus is the site of T lymphocyte differentiation and removal of T lymphocytes reactive against self-antigens
- Connective tissue surrounds the thymus and subdivides it into thymic lobules
- Each lobule has a peripheral darkly stained zone known as the **cortex** and a central light zone called the **medulla**.
- The cortex is richer in small lymphocytes than the medulla and therefore it stains more darkly
- The thymus reaches its maximum development in relation to body weight immediately after birth; it undergoes involution after attaining its greatest size in puberty, but continues to produce lymphocytes until old age



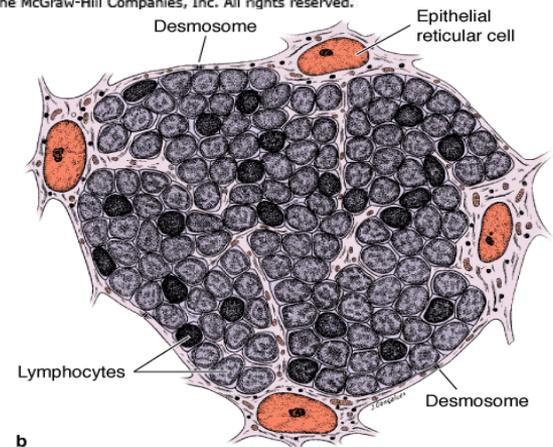
The Thymic Cortex

- The thymic cortex is composed of an extensive population of T lymphoblasts (also called **thymocytes**) and macrophages in a stroma of **epithelial reticular cells**.
- The epithelial reticular cells usually have large nuclei and are diverse morphologically, but generally either squamous or stellate with long processes.
- They are typically joined to similar adjacent cells by desmosomes forming an unusual **cytoreticulum**.
- Arterioles and capillaries in the thymic cortex are sheathed by flattened epithelial reticular cells with tight junctions. The capillary endothelium is continuous and has a thick basal lamina. These features create a **blood-thymus barrier** and prevent most circulating antigens from entering the thymus cortex



Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition*: <http://www.accessmedicine.com>

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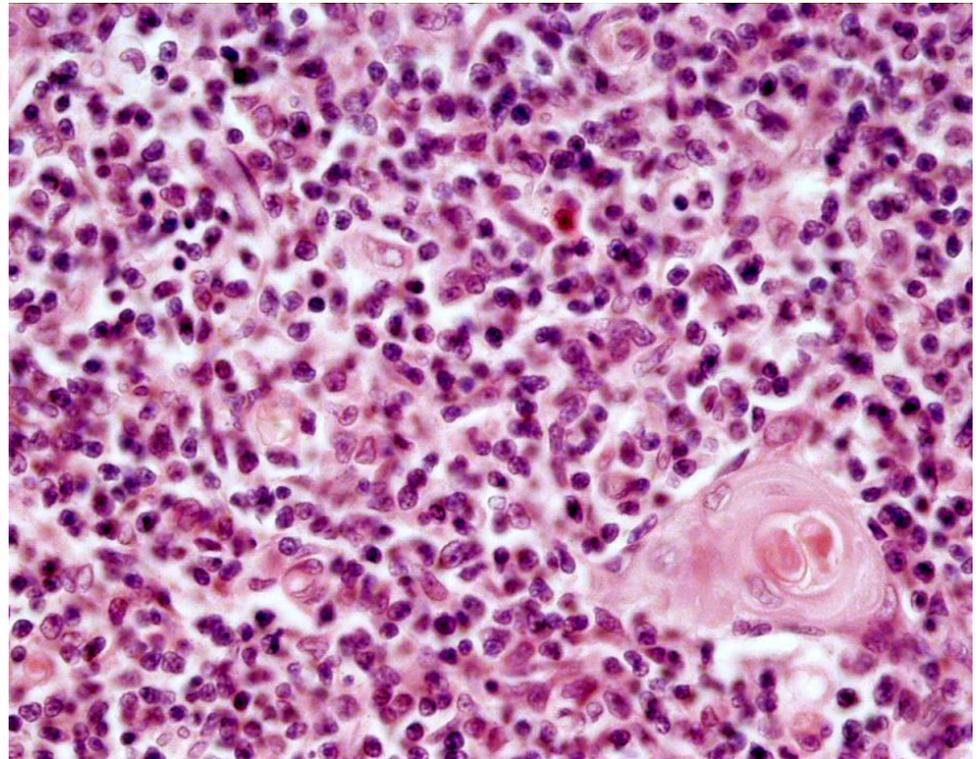


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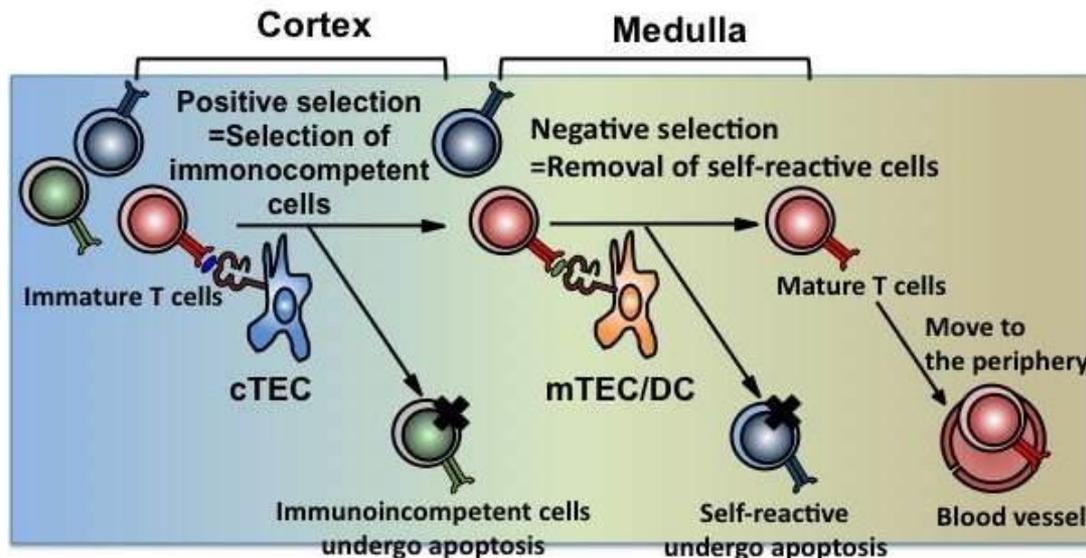
The Thymic Medulla

- Contains epithelial reticular cells, many less densely packed differentiated T lymphocytes, and structures called **thymic (Hassall's) corpuscles**, which are characteristic of this region
- Thymic corpuscles consist of epithelial reticular cells arranged concentrically, filled with keratin filaments, and sometimes calcified.
- No **blood-thymus barrier** is present in the medulla and mature T lymphocytes exit the thymus via venules in this zone.

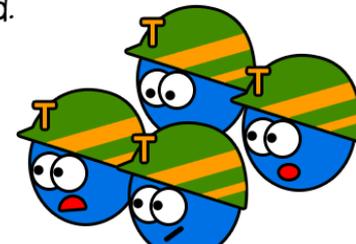


Role of the Thymus in T Cell Maturation

- T lymphoblasts populate the cortex where they proliferate extensively, but do not yet exhibit the T cell receptor or the CD4 and CD8 markers.
- As thymocytes mature and express T cell markers, they undergo **thymic selection**
- Thymocytes whose TCRs cannot bind MHC molecules on epithelial cells at all are nonfunctional and have no future as T cells; these cells (as many as 80% of the total) are induced to undergo apoptosis (**positive selection**).
- Thymocytes that strongly bind MHCs containing self-peptides are also deleted since such T cells could cause a damaging autoimmune response (**negative selection**).
- Only 2–3% of the thymocytes pass both these positive and negative selection tests and survive to migrate into the thymic medulla.
- Besides their structural roles, the epithelial reticular cells produce a number of paracrine factors required for differentiation, selection and migration of mature T lymphocytes, notably **thymopoietin** and **thymosins**



If you are not properly educated, you will be negatively selected.

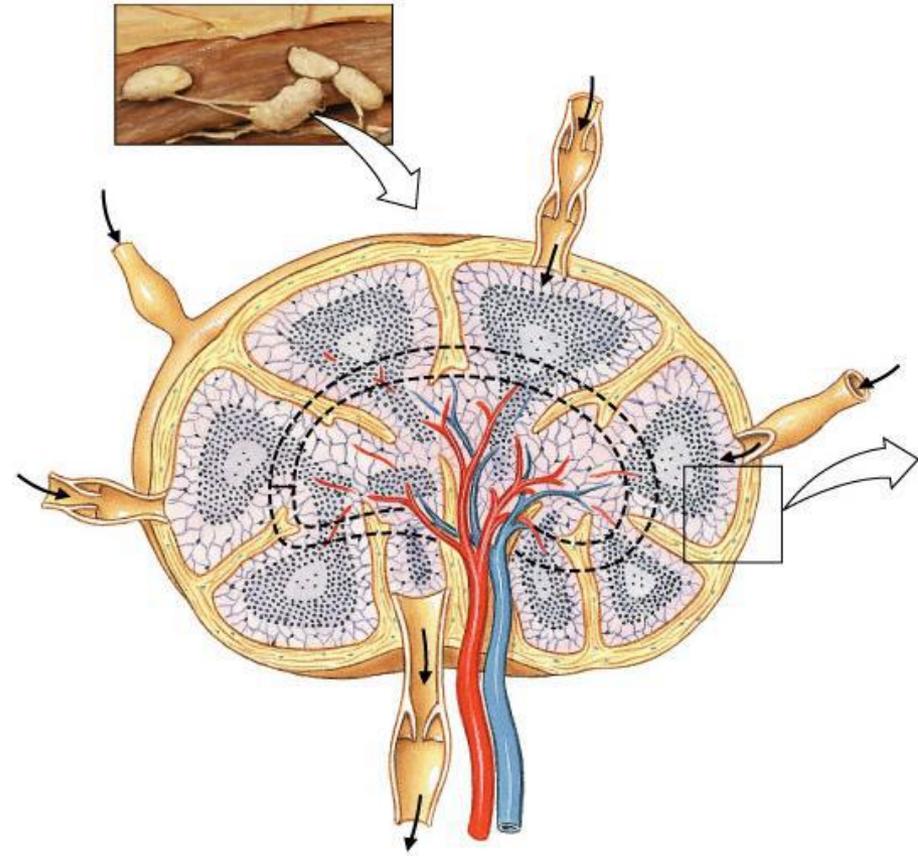


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Education of T lymphocytes

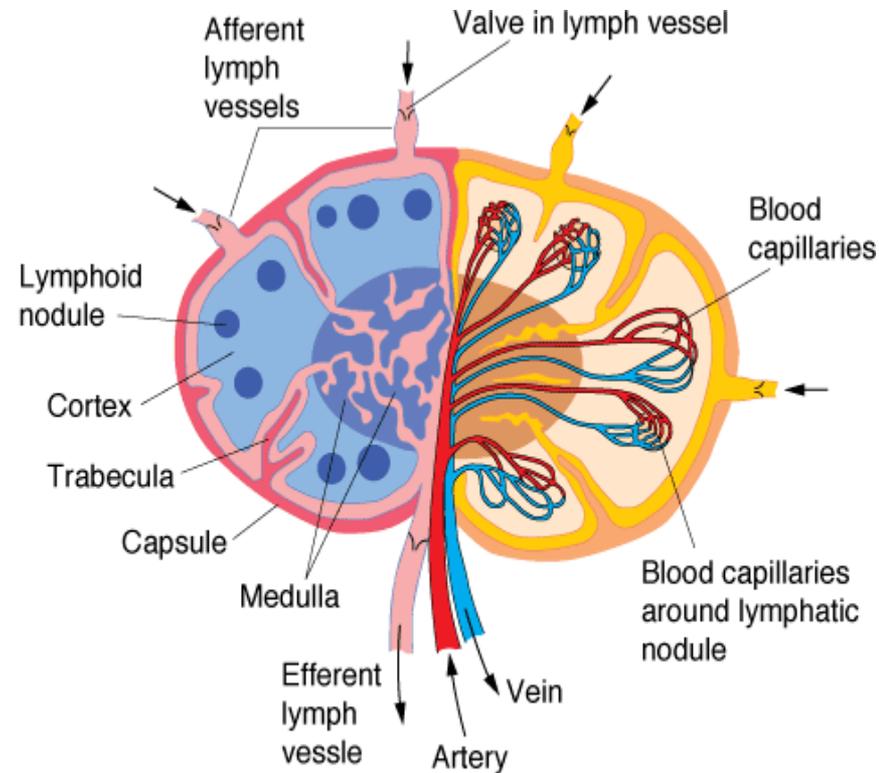
Lymph nodes

- Lymph nodes are bean-shaped, encapsulated structures, generally 2–10 mm in diameter, distributed throughout the body along the course of the lymphatic vessels
- The nodes are found in the axillae (armpits) and groin, along the great vessels of the neck, and in large numbers in the thorax and abdomen, especially in mesenteries
- Lymph nodes constitute a series of in-line filters that are important in the body's defense against microorganisms and the spread of tumor cells.
- A convex surface that is the entrance site of lymphatic vessels and a concave depression, the **hilum**, through which arteries and nerves enter and veins and lymphatics leave the organ
- A connective tissue **capsule** surrounds the lymph node, sending trabeculae into its interior



Lymph nodes

- The most common cells of lymph nodes are lymphocytes, macrophages, plasma cells, and reticular cells
- The different arrangement of the cells and of the reticular fiber stroma supporting the cells creates a **cortex**, a **medulla**, and an intervening **paracortex**



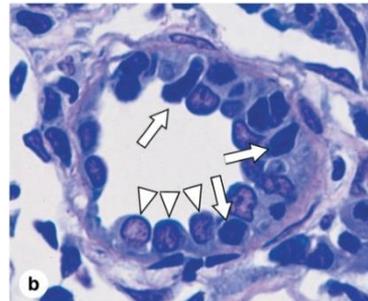
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The cortex of the Lymph node

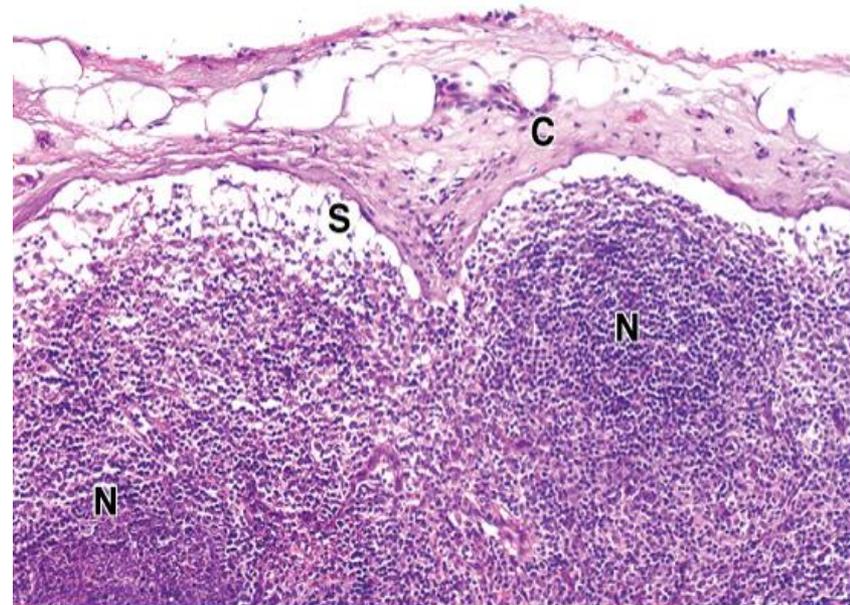
Situated under the capsule, consists of the following components:

- Many reticular cells, macrophages, APCs, and lymphocytes
- **Lymphoid nodules**, with or without germinal centers, formed mainly of B lymphocytes, embedded within the diffuse population of other cells
- **Subcapsular sinuses**, where the lymphoid tissue has wide reticular fiber meshes. Lymph containing antigens, lymphocytes, and APCs drains here after being delivered by the afferent lymphatic vessels
- **Cortical sinuses**, running between the lymphoid nodules, which arise from the subcapsular sinuses

✓ The **paracortex** does not have precise boundaries with the cortex and medulla. It can be distinguished from the outer cortex by its lack of B cell lymphoid nodules and its accumulation of T cells, which can be determined only by immunohistochemistry. Vessels have an unusual endothelial lining of tall cuboidal cells - **high endothelial venules (HEVs)**, whose apical surface glycoproteins and integrins facilitate rapid diapedesis of lymphocytes out of the blood into the paracortex of the lymph node. That's where 90% of lymphocytes return to a lymph node.

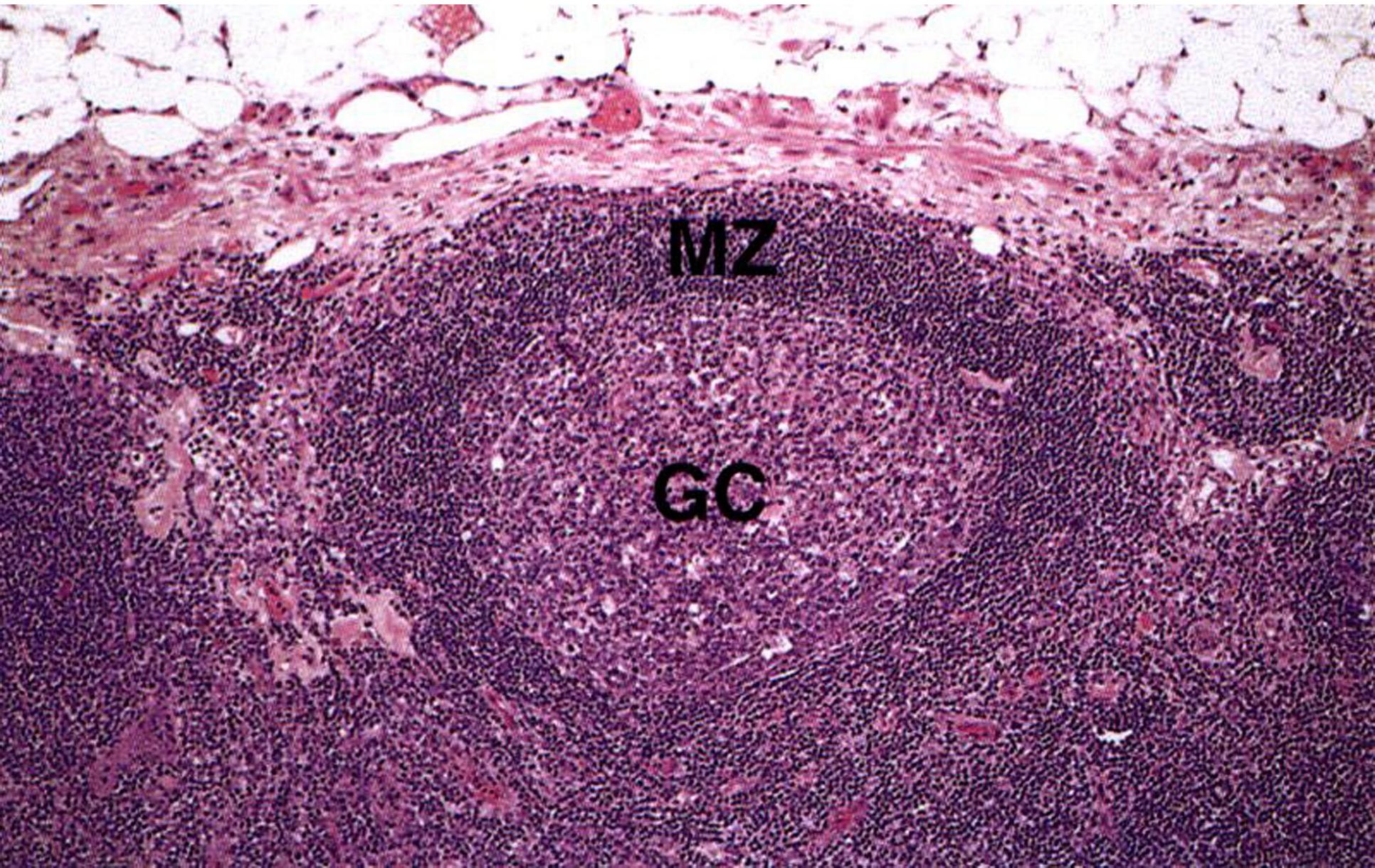


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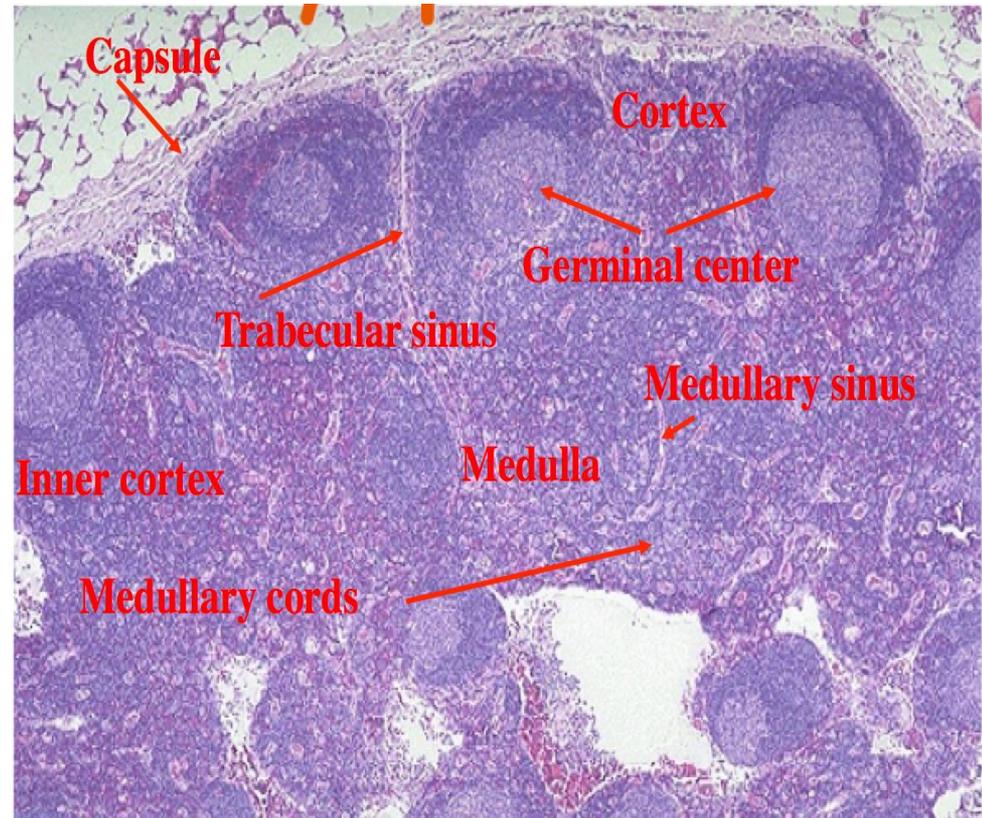
A lymphatic nodule with germinal center (GC)



The medulla of the lymph node

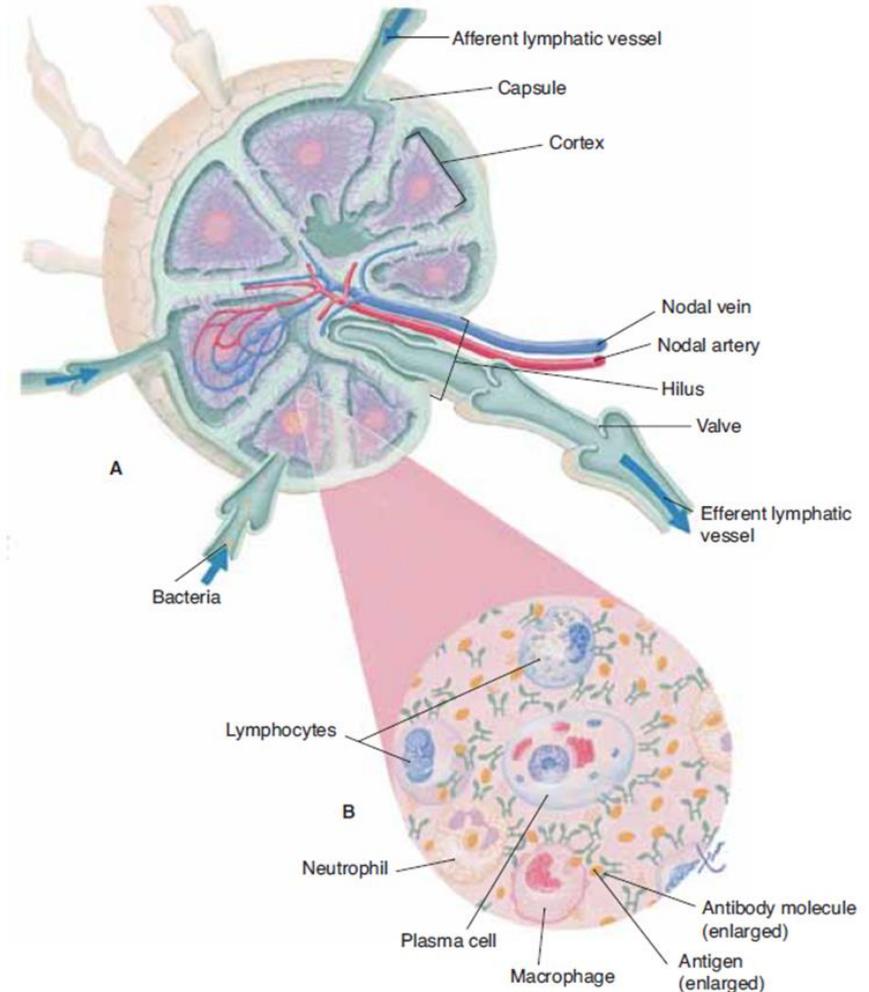
The **medulla** has two major components:

- **Medullary cords** are branched cordlike extensions of lymphoid tissue arising from the paracortex. They contain primarily B lymphocytes and often plasma cells and macrophages.
- Medullary cords are separated by dilated spaces called **medullary sinuses**. They contain lymph, lymphocytes, often many macrophages. These sinuses are continuous with the cortical sinuses and join at the hilum to deliver lymph to the efferent lymph vessel of the lymph node



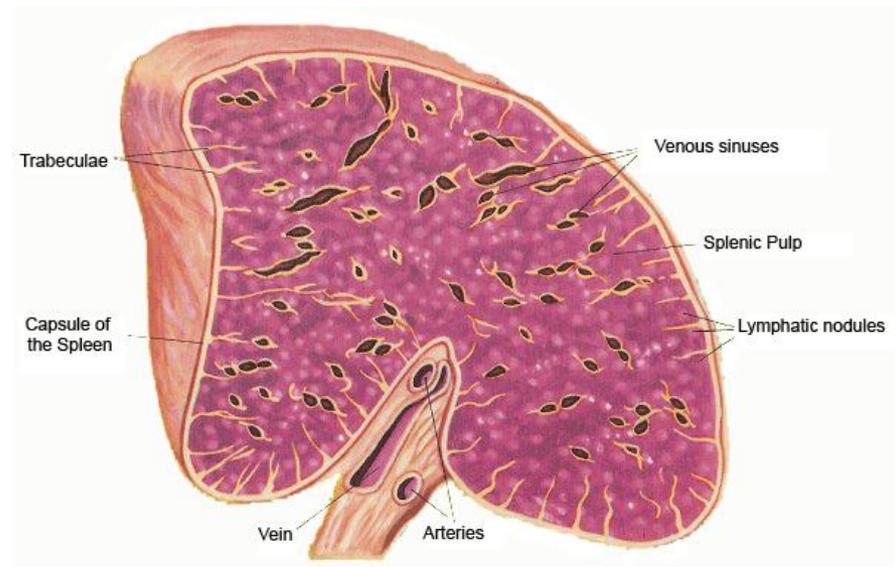
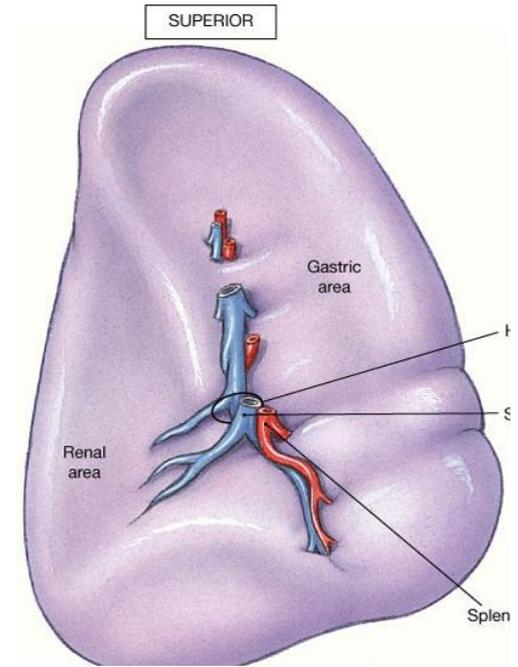
Role of Lymph Nodes in the Immune Response

- Lymph nodes are distributed throughout the body and lymph formed in tissues must pass through at least one node before entering the bloodstream.
- The lymph that arrives at a lymph node contains antigens as soluble molecules, portions of destroyed microorganisms, or antigens already internalized and being transported by macrophages and other APCs. It may also contain microorganisms and cytokines, particularly if it is coming from a region with an infection or inflammation.
- All antigens are presented to B lymphocytes, to T helper cells, and to T cytotoxic lymphocytes to initiate an immune response.
- The lymph node is an important site of lymphocyte proliferation (especially of B cells in the germinal centers) as well as of transformation of B lymphocytes into plasma cells. Because of this, the lymph that leaves a lymph node may be enriched in antibodies. When the lymph is returned to the blood circulation, these antibodies will be delivered to the entire body.
- ✓ Malignant tumor cells often reach lymph nodes and are distributed to other parts of the body via the efferent lymph vessels and blood vessels, a process known as **metastasis**.
- ✓ Infection and antigenic stimulation often cause lymph nodes to enlarge. These swollen nodules, which may be palpated under the skin as indicators of inflammation, have multiple germinal centers with active cell proliferation.



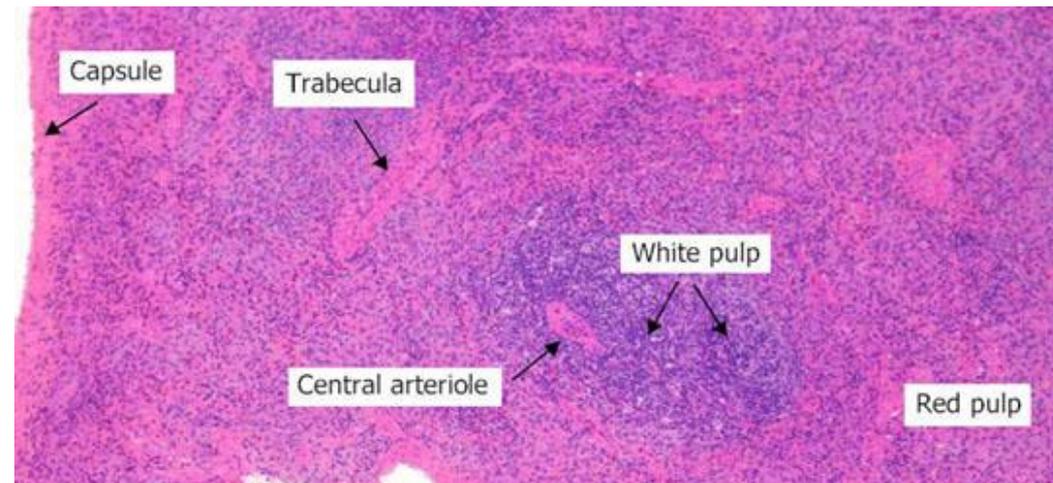
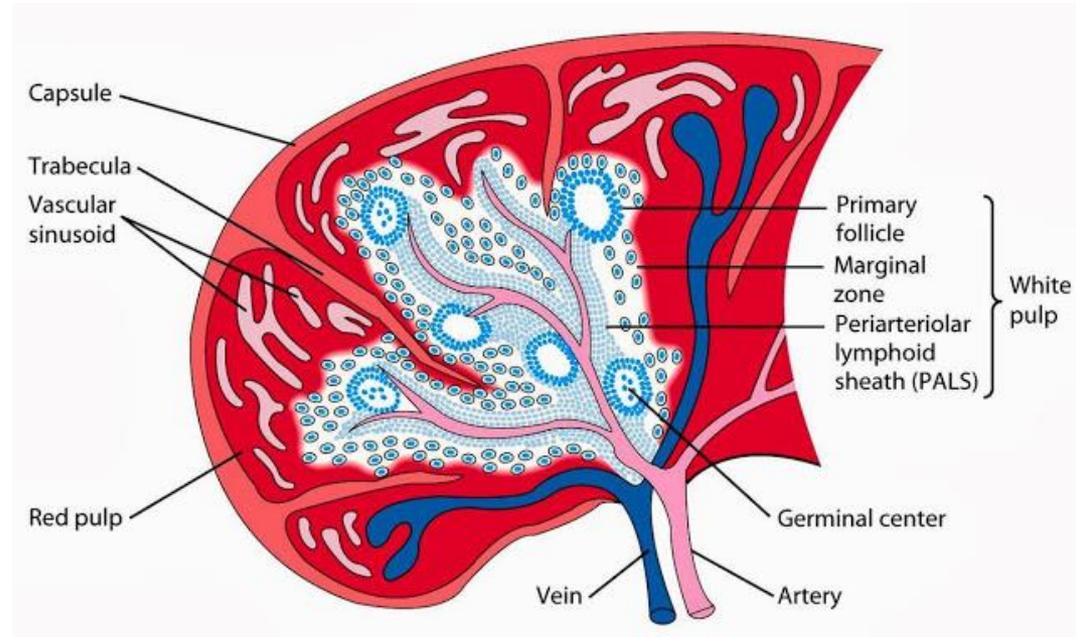
The Spleen

- Involved in **filtration of blood**, making it an important organ in defense against blood circulating antigens.
- The main site of **destruction of aged erythrocytes**.
- Is a **production site of antibodies and activated lymphocytes**, which are delivered to the blood.
- Surrounded by a **capsule** of dense connective tissue from which emerge **trabeculae**, which partially subdivide the parenchyma or **splenic pulp**.



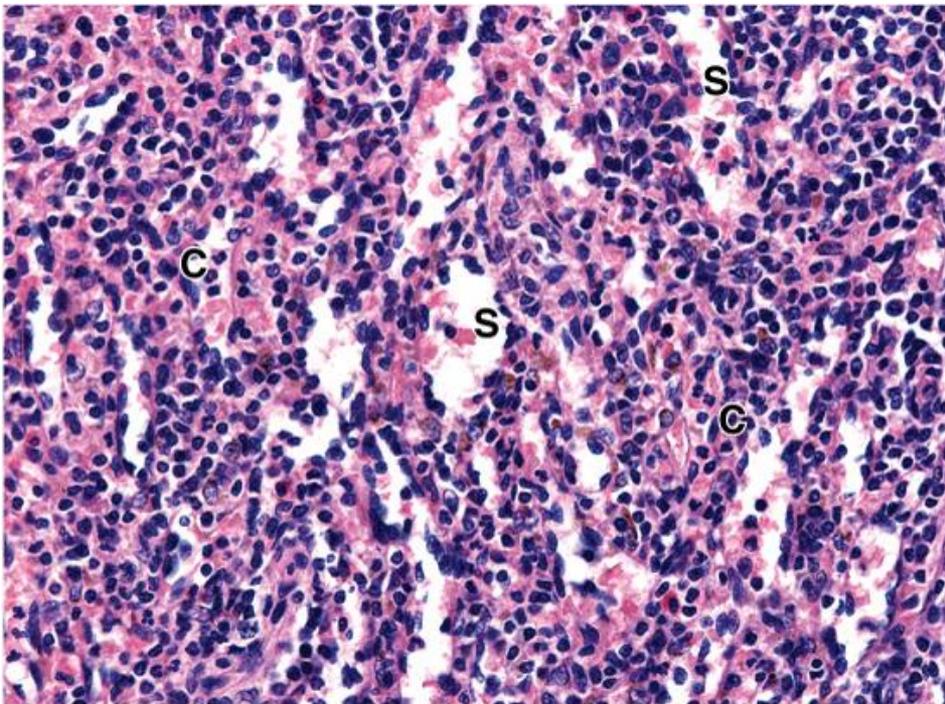
The White Pulp of the Spleen

- Consists of **lymphoid nodules** and the **periarteriolar lymphoid sheathes (PALS)**
- **Lymphoid nodules – B lymphocytes**, germinal centers
- **PALS – T lymphocytes**
- **Marginal zone** - surrounds the lymphoid nodules, consists of many blood sinuses, lymphocytes, many macrophages, and an abundance of blood antigens, plays an important role in the immunological activities of the spleen.

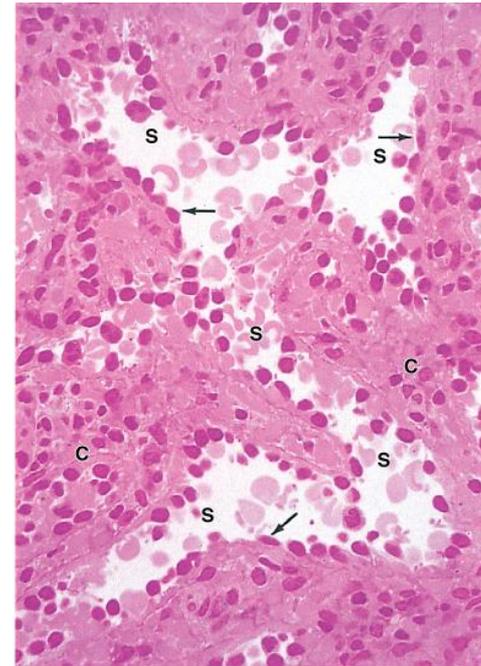


The Red Pulp of the Spleen

- **Red pulp** contains blood-filled **sinusoids** and **splenic cords**
- The splenic cords contain a network of reticular cells or reticular fibers that support T and B lymphocytes, macrophages, plasma cells, and many blood cells (erythrocytes, platelets, and granulocytes)
- Cords are separated by wide, irregularly shaped sinusoids



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Immune system functions of the spleen include:

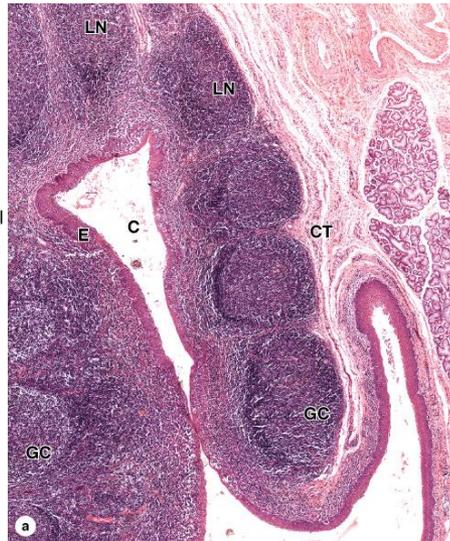
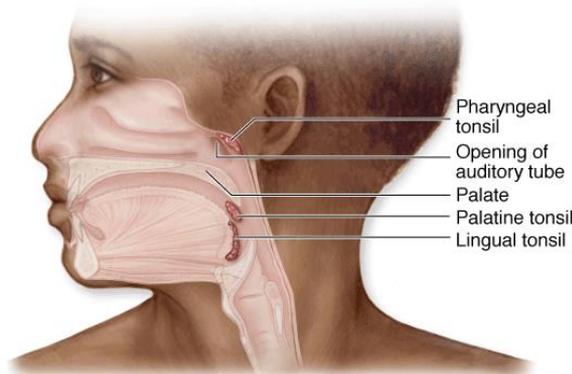
- ✓ antigen presentation by APCs (mostly dendritic cells and macrophages) and initiation of immune response;
- ✓ activation and proliferation of B and T lymphocytes;
- ✓ production of antibodies against antigen present in circulating blood; and removal of macromolecular antigens from the blood.

Hemopoietic functions of the spleen include:

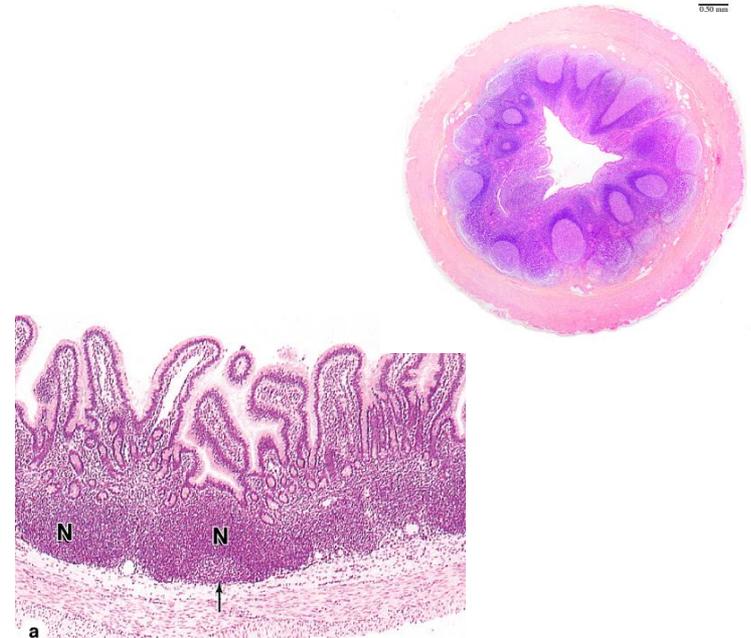
- ✓ removal and destruction of senescent, damaged, and abnormal erythrocytes and platelets;
- ✓ retrieval of iron from erythrocyte hemoglobin;
- ✓ formation of erythrocytes during early fetal life and storage of blood

Mucosa-Associated Lymphoid Tissue (MALT)

- Organs of the digestive, respiratory, genital and urinary systems are common sites of invasion by pathogens because their lumens are open to the external environment.
- Collectively MALT is one of the largest lymphoid organs, containing up to 70% of all the body's immune cells.
- To protect the organism, the mucosal connective tissue of these tracts contains large and diffuse collections of dendritic cells, lymphocytes, IgA-secreting plasma cells, APCs, and lymphoid nodules.
- In some places, these aggregates form structures such as the **tonsils** and the **Peyer patches** in the ileum, aggregates with lymphoid follicles are found in the **appendix**.

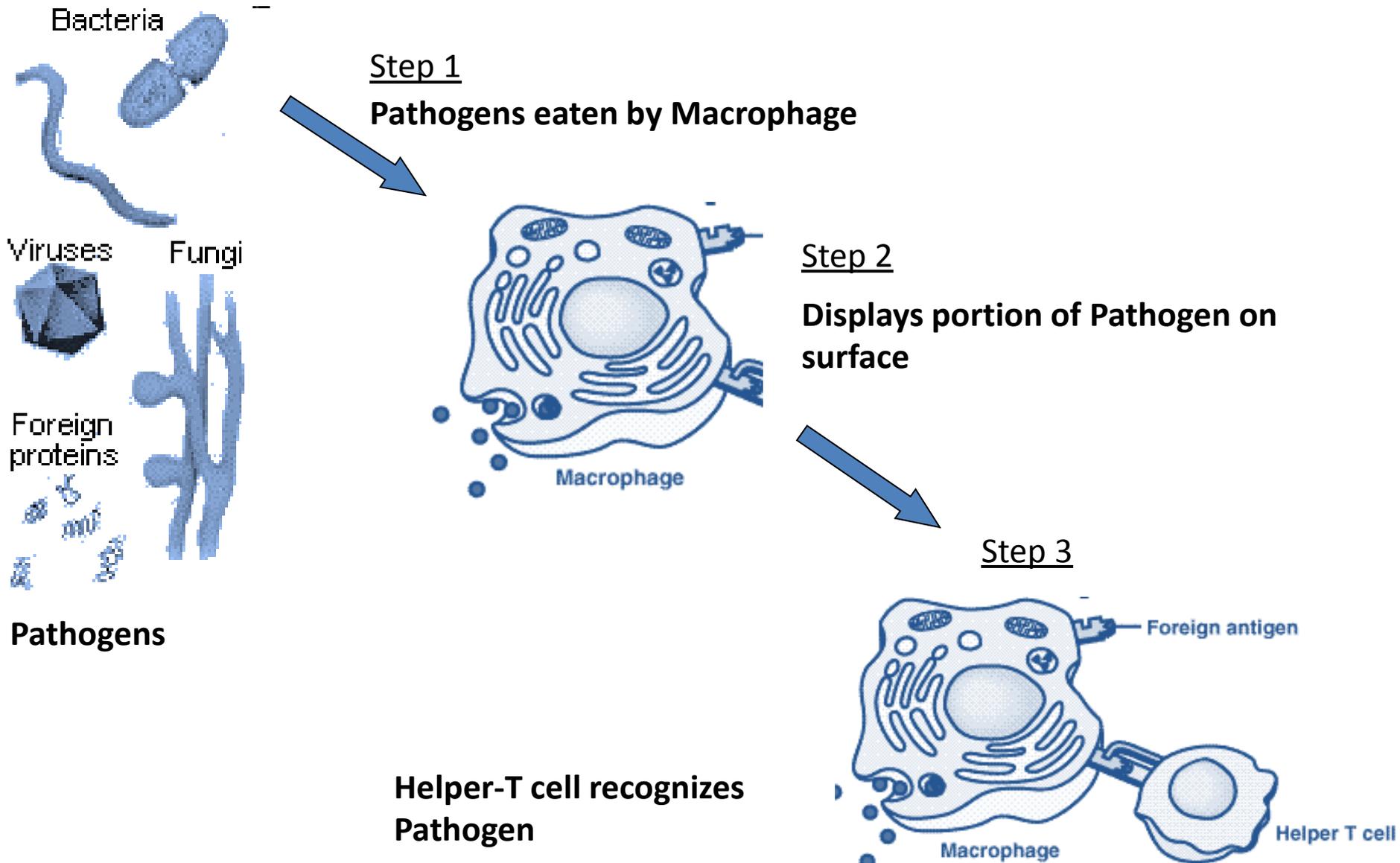


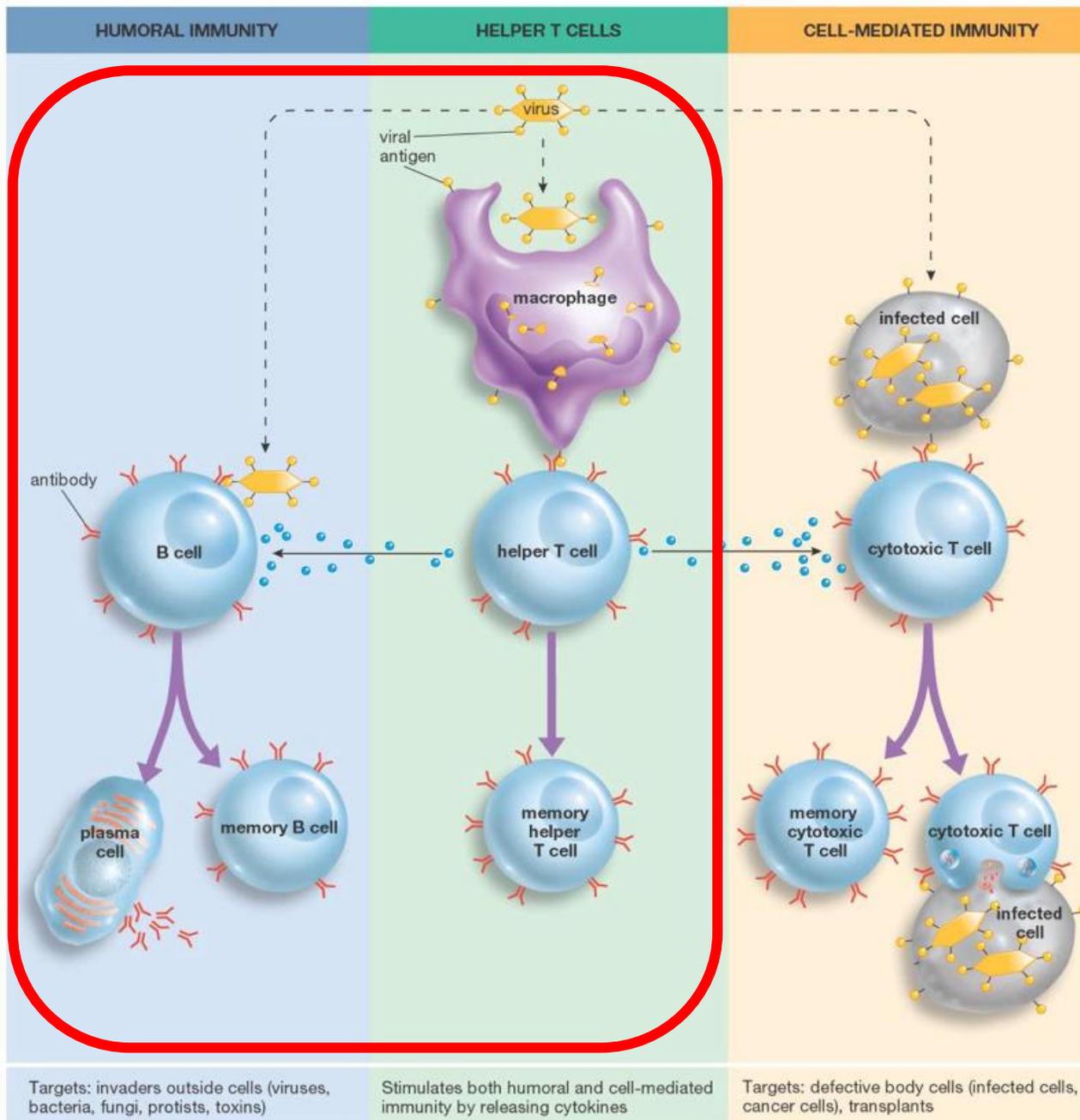
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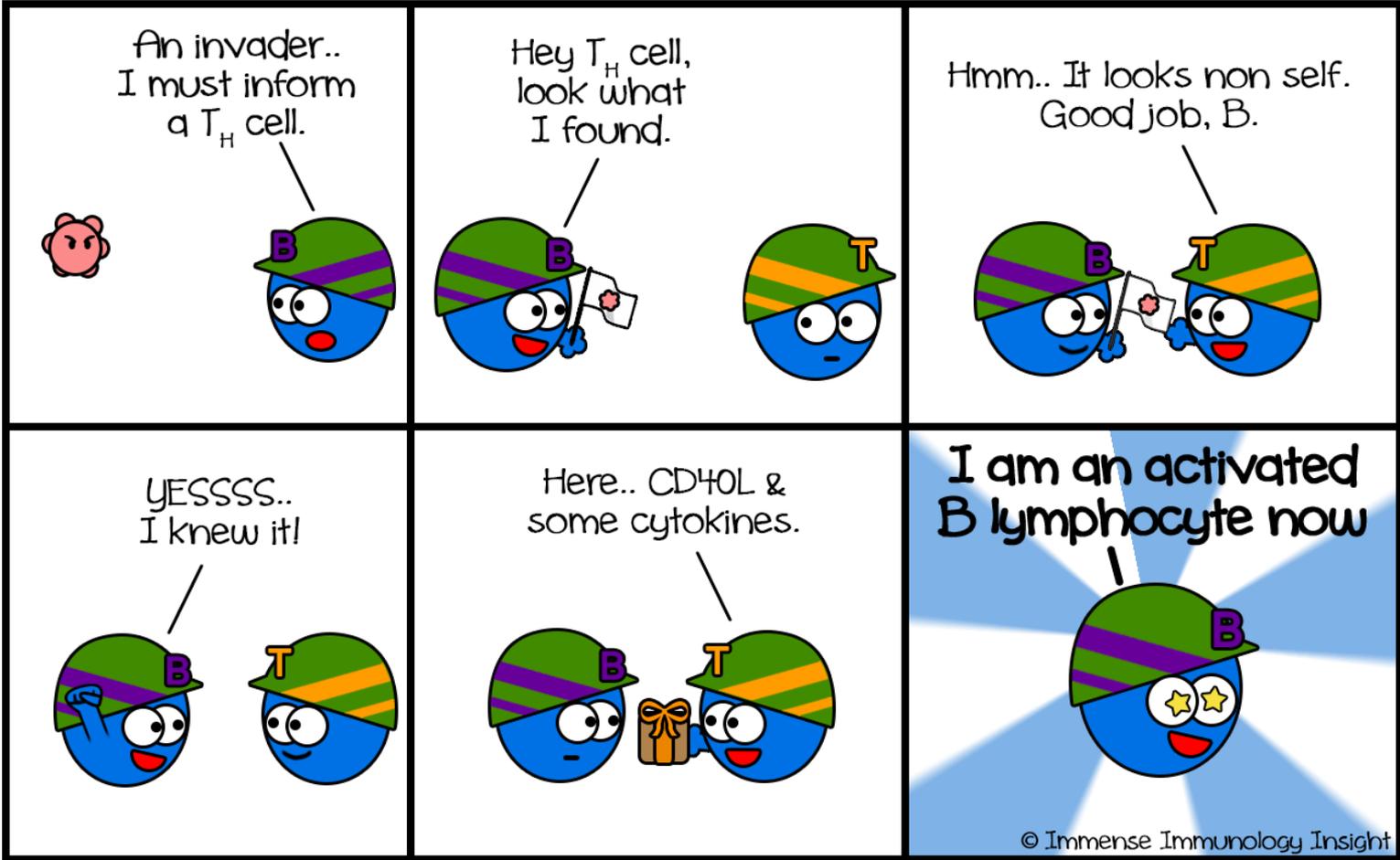


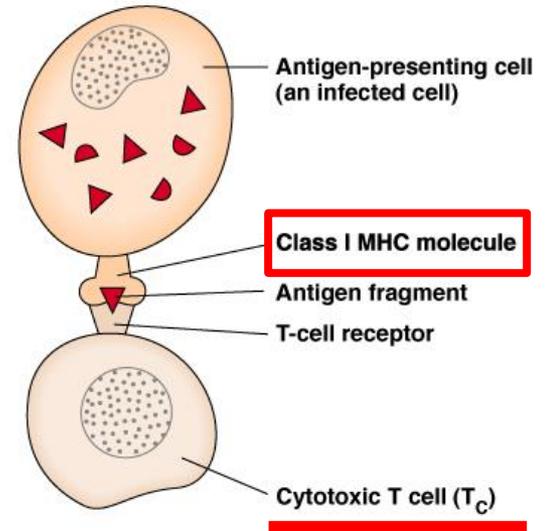
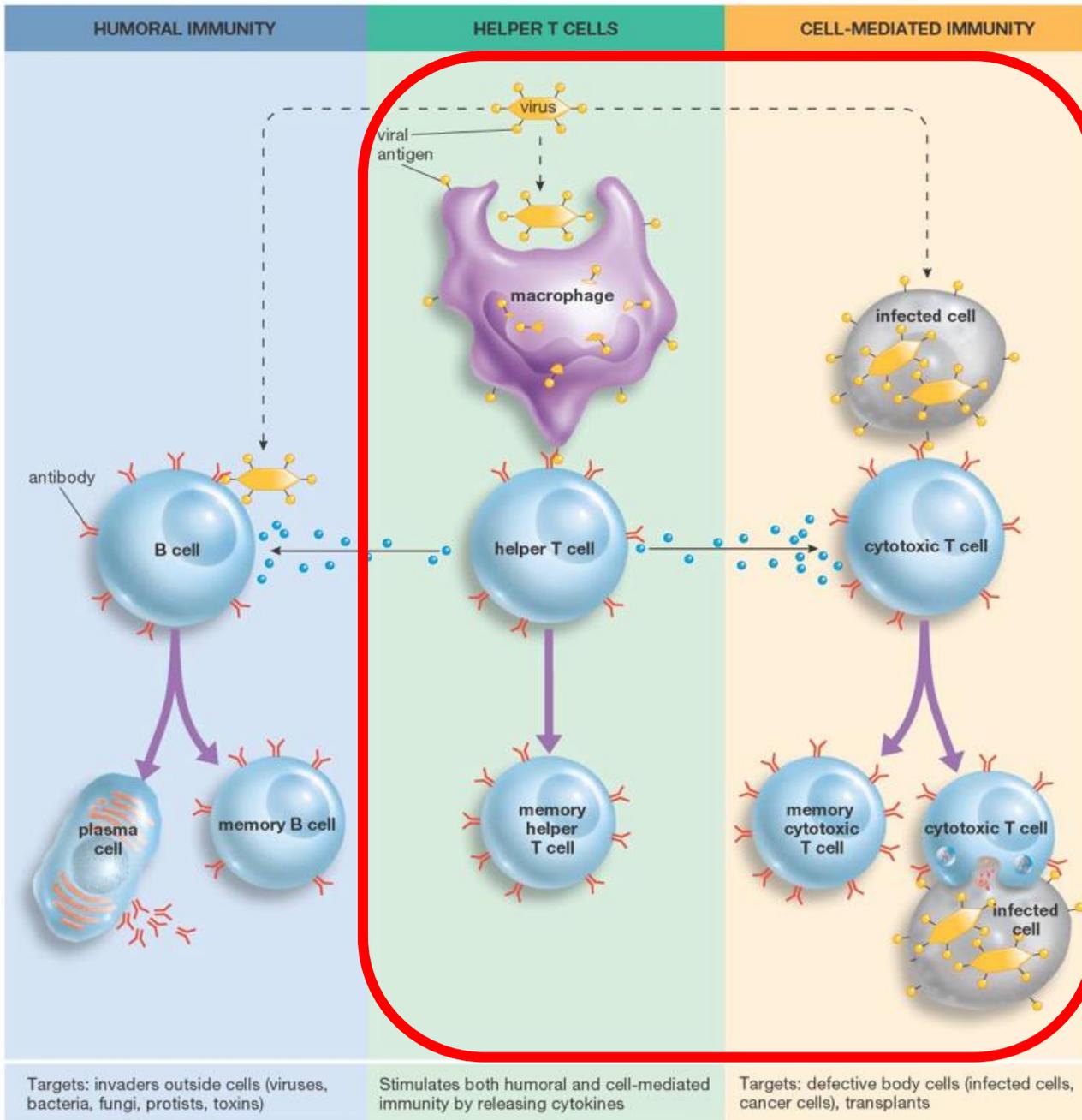
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The Pathway of Specific Immune Response

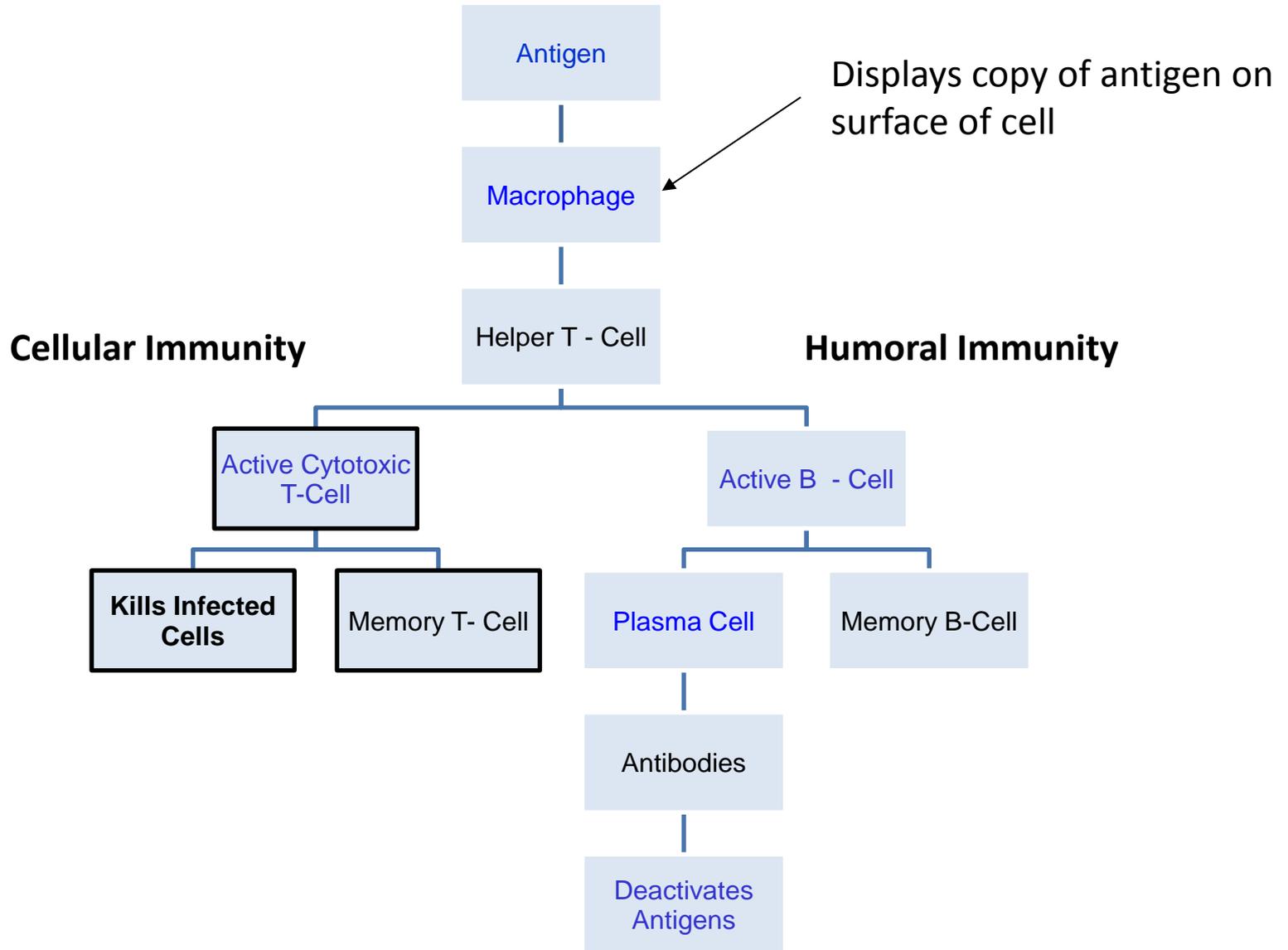








Immune Response Summary



Thank You for Attention