



UNIVERSITY OF KRAGUJEVAC
FACULTY OF MEDICAL SCIENCES



IMMUNOLOGY, INFECTION, INFLAMMATION

The course is evaluated with 6 ECTS. There are 6 hours of active teaching per week (3 hours of lectures and 3 hours of work in a small group).

EVALUATION:

The grade is based on the number of earned points (maximum 100). Points are earned in two ways: through pre-exam activities and final exam:

PRE-EXAM ACTIVITIES: In this way, the student can earn up to 30 points by actively participating in small group activities and answering questions related to the week's lesson. Based on demonstrated knowledge, the student can earn between 0-2 points per week. To pass the module, student must acquire more than 50% of the total points for that module (see table).

Students who do not earn more than 50% of the points in pre-exam activity will take the exam by answering 2 questions from each module that they have not passed.



MODULE	MAXIMUM POINTS
	Activity during work in a small group
1	16
2	14
Σ	30



FINAL EXAM: In this way, the student can earn up to 70 points. The student takes the test which includes 35 questions that are covering the entire subject material. If the student does not achieve more than 50% correct answers, he/she has not passed the final exam.

LECTURE SCHEDULE

Monday: 12.15-14.15

Internal clinic hall

SCHEDULE OF EXERCISES

Monday: 14.30-16.45

V31/V32/V33

(Institute building)



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Introduction to the immune system

Immunity- resistance to disease

Immune system – cells, tissues and molecules

Immune response- action of the immune system

Immunology- studies the immune system and its response to antigens

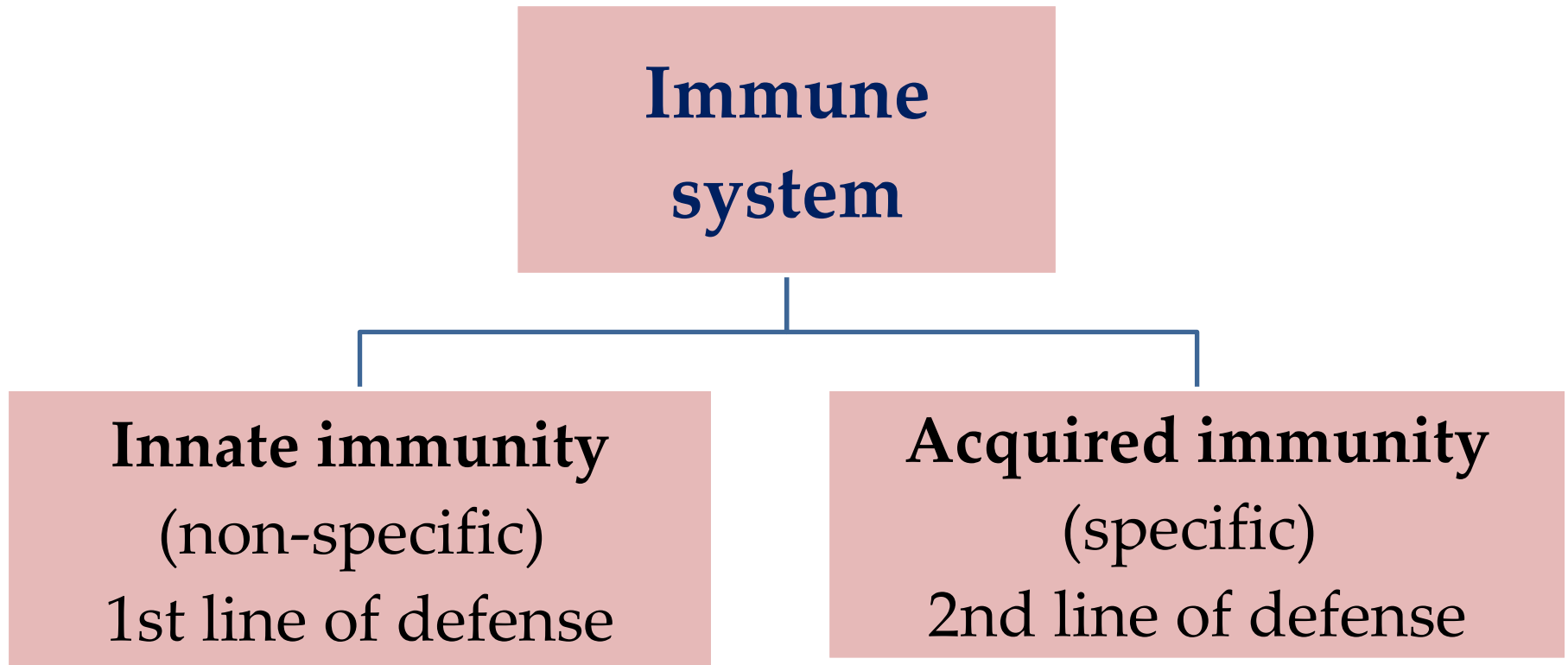
Importance of the immune system in **health** and **disease**

Role of the immune system	Implications
Defense against infections	Deficient immunity results in increased susceptibility to infections; exemplified by AIDS Vaccination boosts immune defenses and protects against infections
Defense against tumors	Potential for immunotherapy of cancer
Control of tissue regeneration and scarring	Repair of damaged tissues
The immune system can injure cells and induce pathologic inflammation	Immune responses are the cause of allergic, autoimmune, and other inflammatory diseases
The immune system recognizes and responds to tissue grafts and newly introduced proteins	Immune responses are barriers to transplantation and gene therapy

This system has a vital role: It protects host body from harmful substances (microbes or their products, chemicals, drugs, pollen, animal hair...), and cell changes that could make disease.

Stimulating immune responses against microbes through **vaccination** is the **most effective method for protecting individuals against infections**; this approach has led to **the worldwide eradication of smallpox**, the only disease that has been eliminated from civilization by human intervention

Disease	Maximum number of cases (year)	Number of cases in 2014
Diphtheria	206,939 (1921)	0
Measles	894,134 (1941)	72
Mumps	152,209 (1968)	40
Pertussis	265,269 (1934)	311
Polio (paralytic)	21,269 (1952)	0
Rubella	57,686 (1969)	0
Tetanus	1,560 (1923)	0
<i>Hemophilus influenzae</i> type B infection	~20,000 (1984)	134
Hepatitis B	26,611 (1985)	58



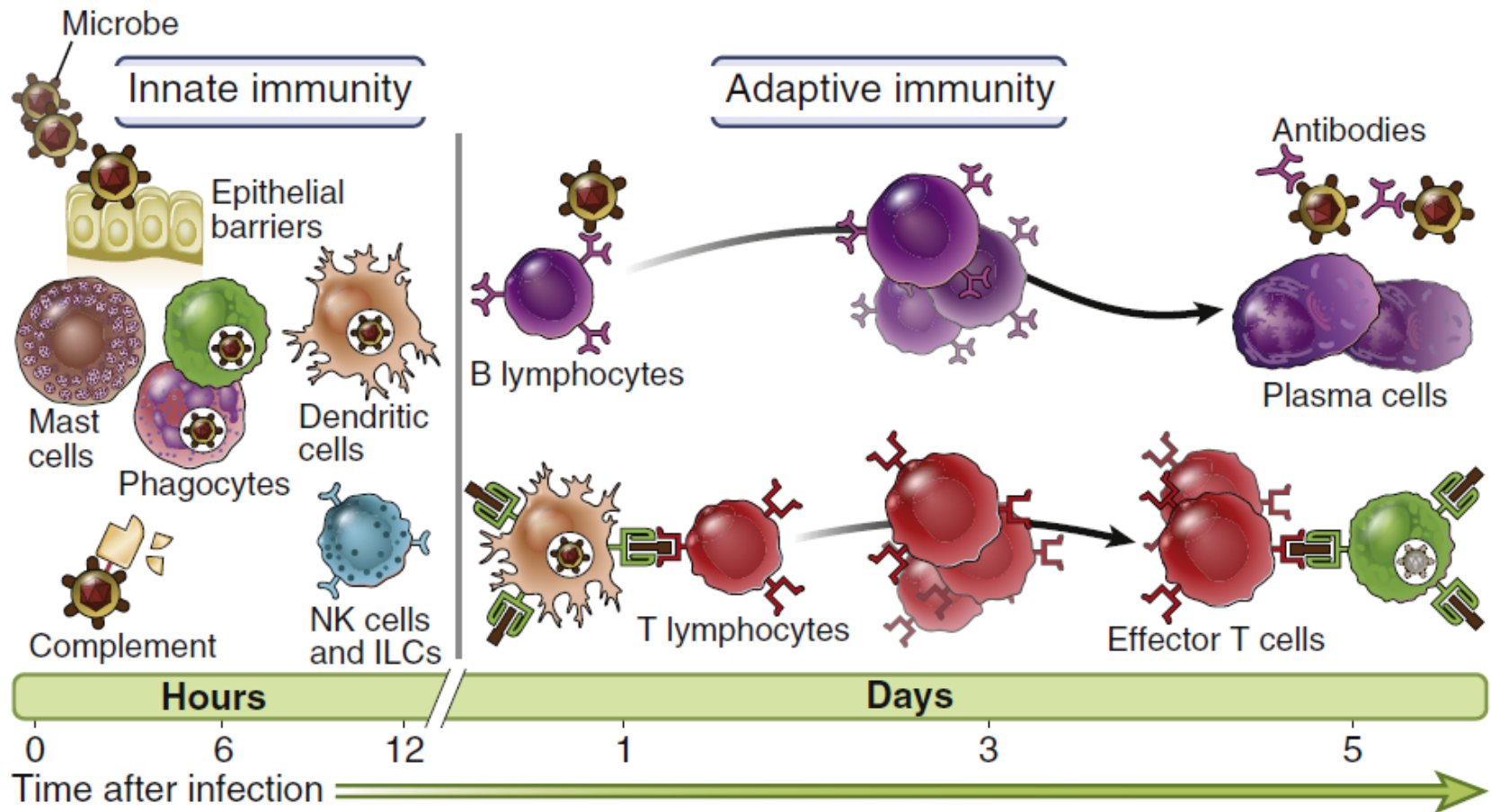
The immune system is made up of two parts: the innate (general) immune system and the acquired (specialized) immune system. Innate and acquired immune system work closely together and take on different tasks whenever a harmful substance (antigens) triggers an immune response.

Innate and acquired immunity

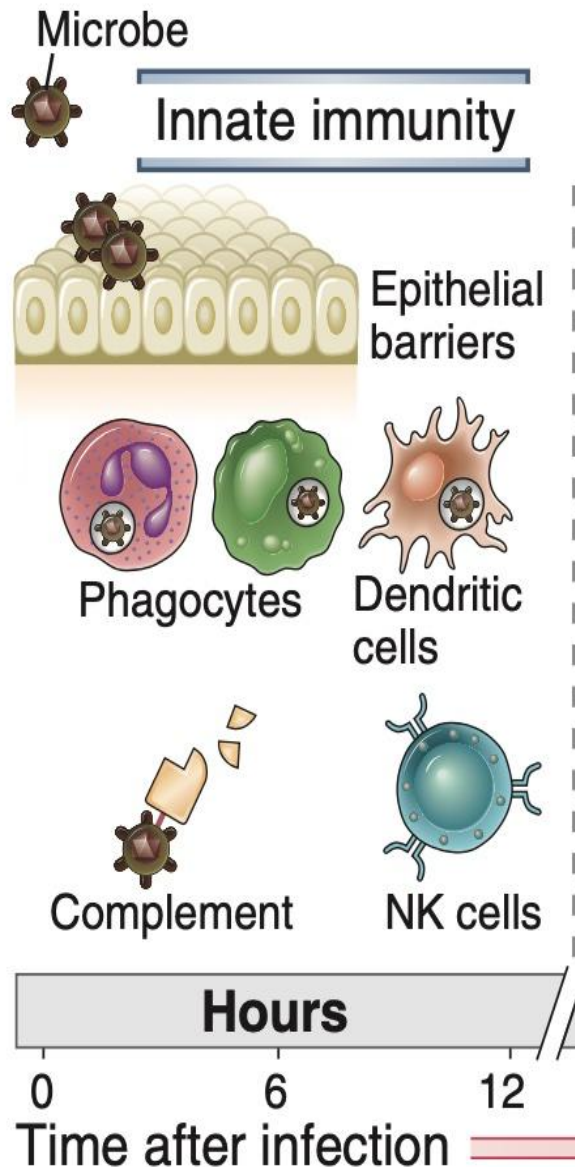
- Innate (also called **non-specific**, **natural** or **native**) immunity provides immediate protection against microbial invasion. It is always present in healthy individuals (hence the term innate), prepared to block the entry of microbes and to rapidly eliminate microbes that do succeed in entering host tissues.
- Acquired (also called **specific** or **adaptive**) immunity develops more slowly and provides more specialized defense against infections. This type immunity can provide more effective defense against infection, and requires proliferation and differentiation of lymphocytes in response to microbes (i.e., it adapts to the presence of microbial invaders). Therefore, adaptive immune system is constantly learning and adapting to microbes.

Innate immunity is phylogenetically older, and the more specialized and powerful adaptive immune response evolved later.

Principal mechanisms of innate and acquired immunity



Innate immunity



Preserved epithelial barrier integrity

Specialized cells

Natural antibiotics

Dendritic cells

Phagocytes

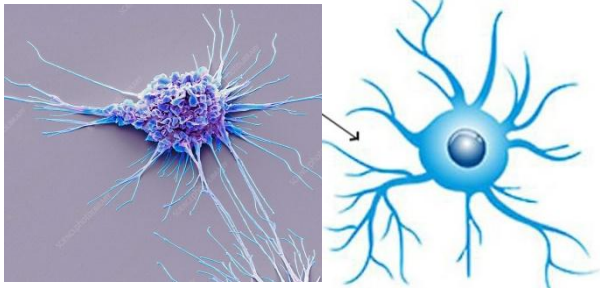
NK cells

Complement system

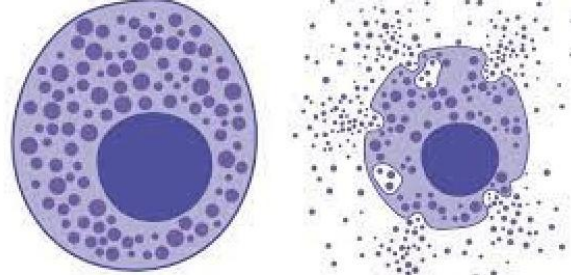
The innate immune system **detects an intruder and sends out a first line of defense and directs the adaptive immune system to create a more specific and effective response.**

If microbes do breach epithelia and enter the tissues or circulation, numerous innate immune cells work to fight off them, including:

- Tissue-resident dendritic cells, macrophages, and mast cells serve as sentinels to detect the presence of microbes in tissues and initiate immune responses. Dendritic cells (DCs), so called because of their many protruding membrane extensions, also have the specialized function of capturing microbial antigens and displaying them to T lymphocytes.



Dendritic cells

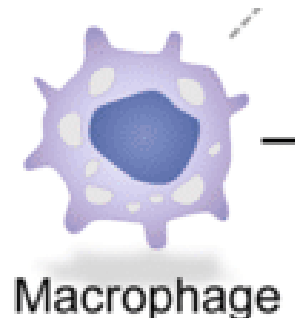
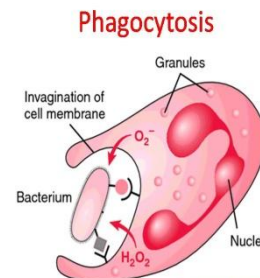


Mast cells

- **Professional phagocytes** or “**eating cells**” are **neutrophils** and **macrophages** that ingest and destroy microbes.



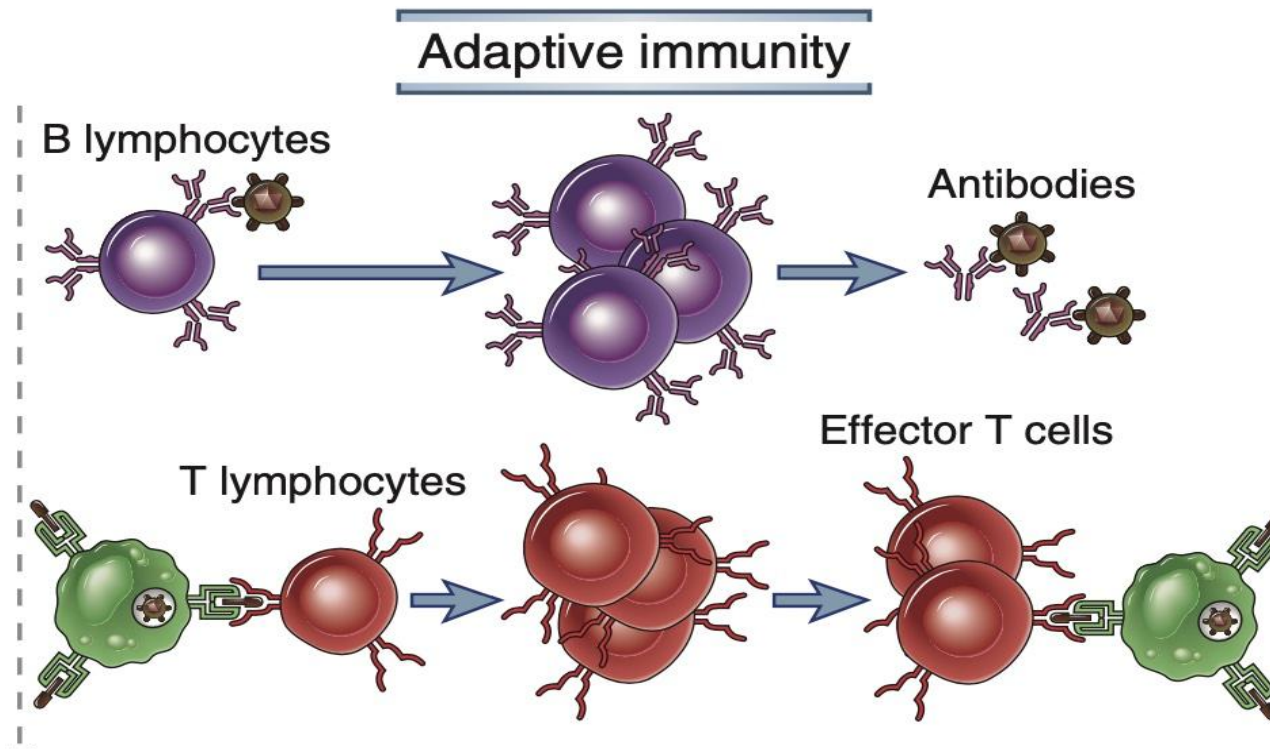
Neutrophil



Macrophage

Types of acquired (adaptive) immunity

Antigen is everything that the immune system has a **specific receptor**, and causes an immune response.



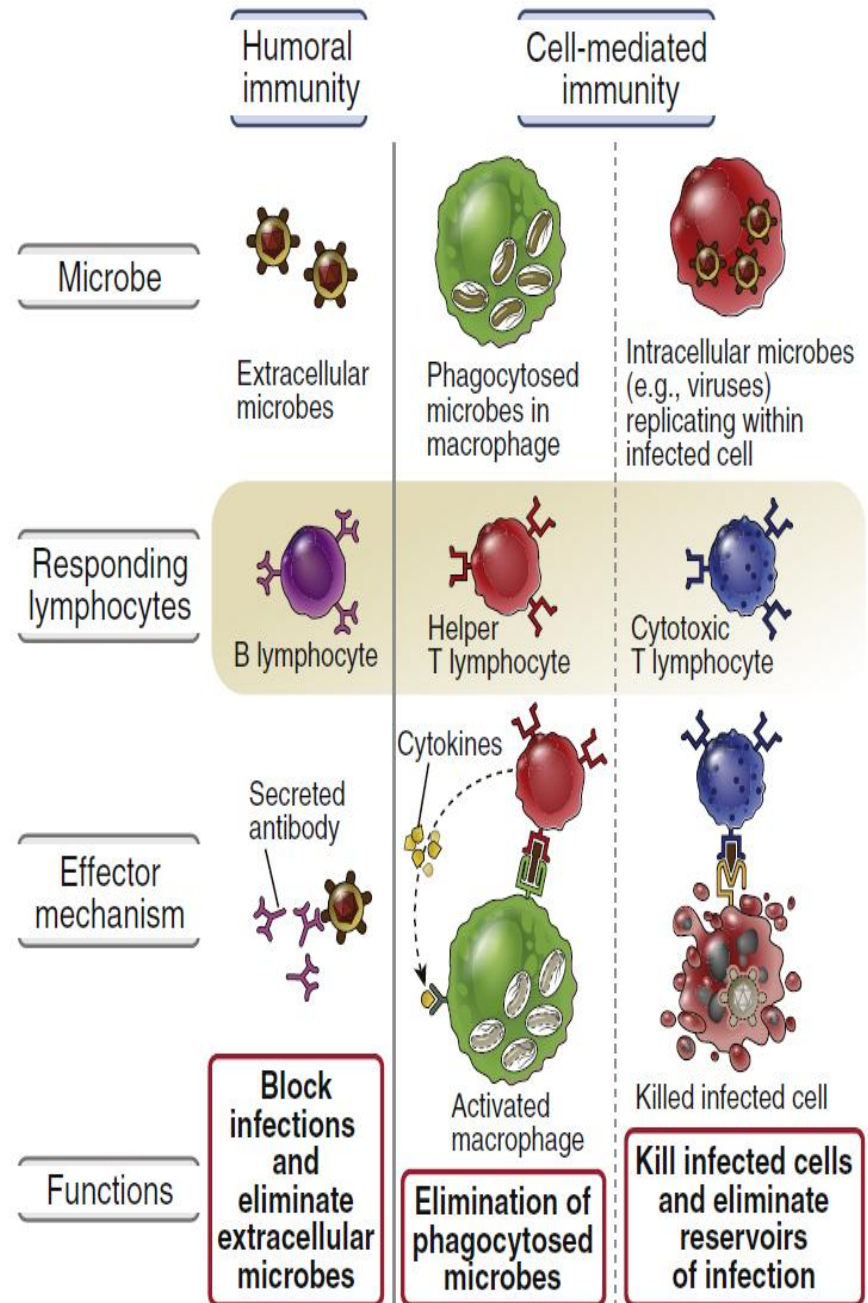
- **Humoral immunity** is mediated by **antibodies**, which are produced by cells called **B lymphocytes**
- **Cell-mediated immunity** it is mediated by cells, which are called **T lymphocytes**.

Microbes that live and divide outside cells are called extracellular microbes.

However, other microbes, often called intracellular microbes, can live and divide inside infected cells, including phagocytes.

In **humoral immunity**, B lymphocytes secrete antibodies that eliminate **extracellular microbes**.

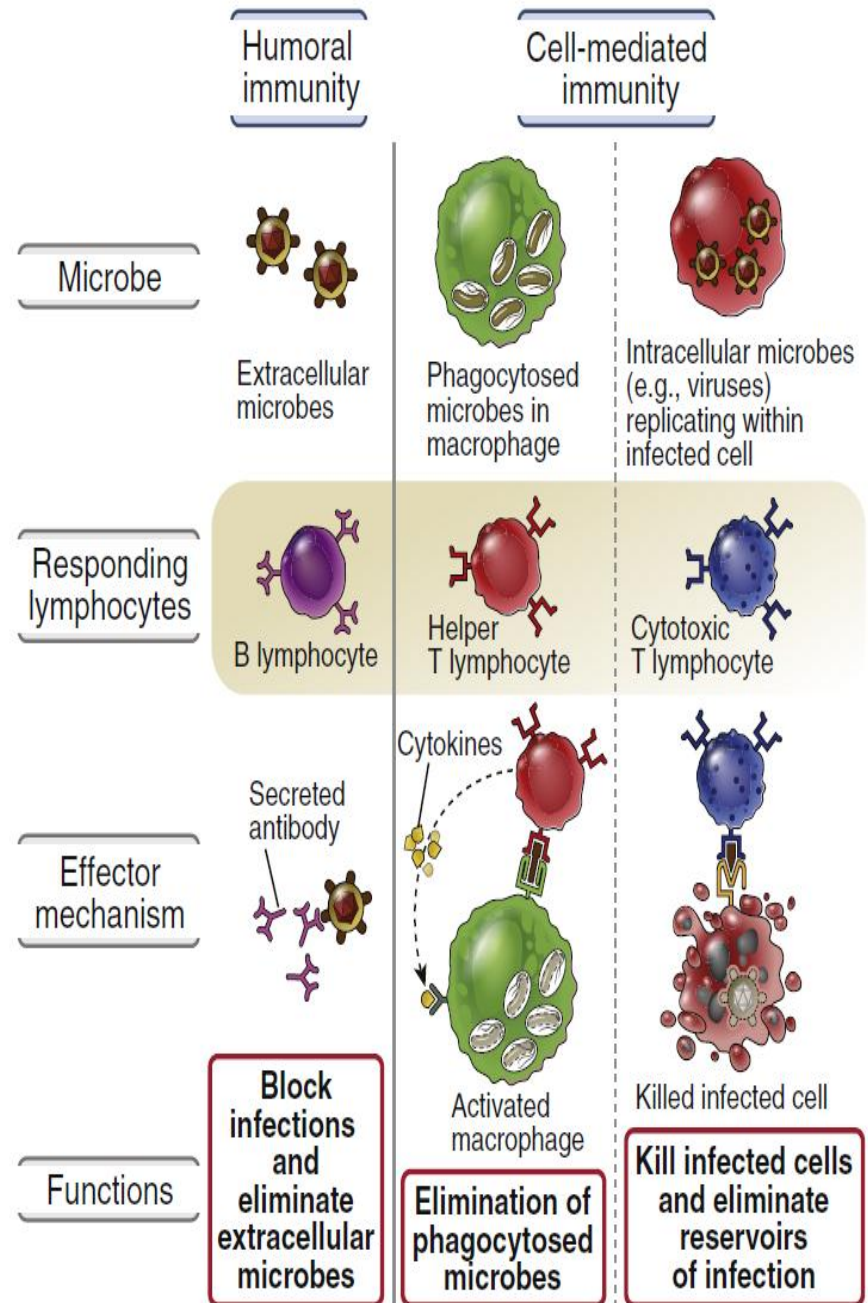
B lymphocytes and antibodies are able to recognize many different types of molecules, including **proteins, carbohydrates, nucleic acids, and lipids**.



Cell-mediated immunity is especially important to defend against **intracellular microbes** that can survive and replicate inside cells.

In cell-mediated immunity, some T lymphocytes secrete soluble proteins called cytokines that recruit and activate phagocytes to destroy ingested microbes, and other T lymphocytes kill infected cells.

Most T cells recognize only **peptide fragments** of protein antigens **presented on cell surfaces**.



Two types of immunity exist — active and passive

Immunity may be induced in an individual by **infection** or **vaccination** (**active immunity**) or conferred on an individual by transfer of antibodies or lymphocytes from an actively immunized individual (**passive immunity**).

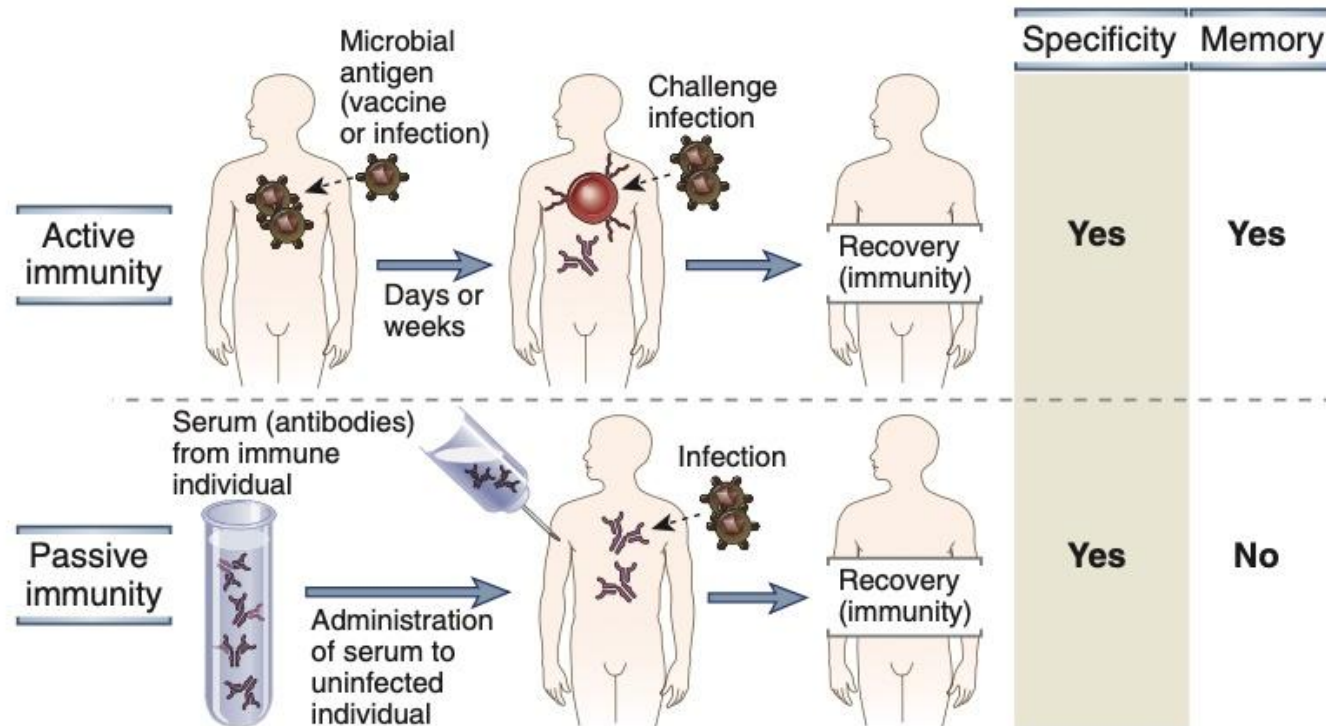
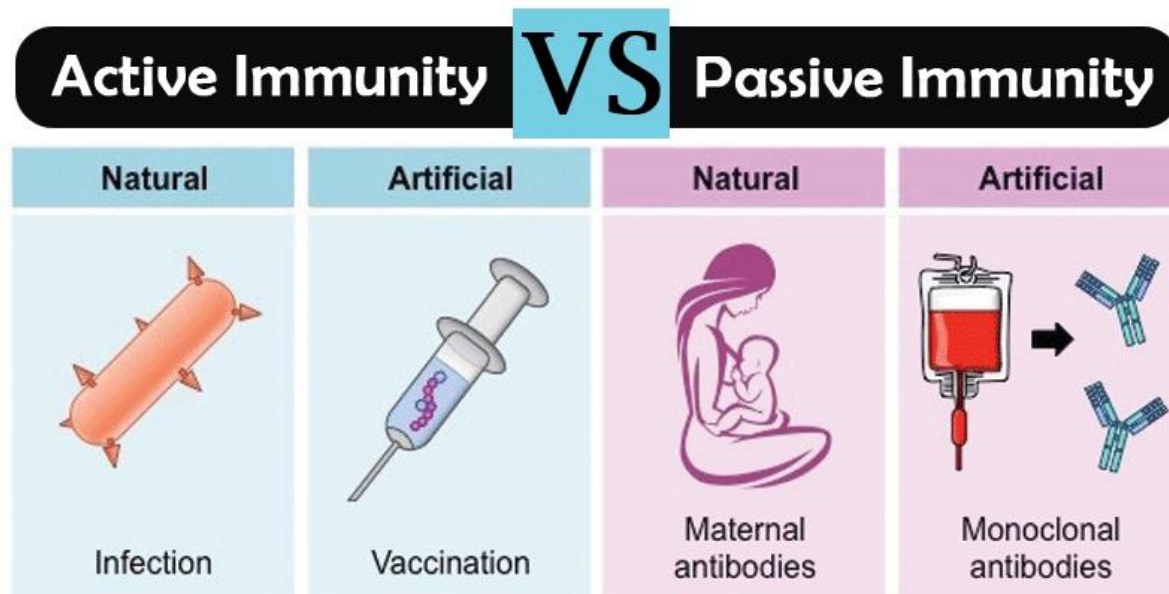


FIGURE 1-3 Active and passive immunity. Active immunity is conferred by a host response to a microbe or microbial antigen, whereas passive immunity is conferred by adoptive transfer of antibodies or T lymphocytes specific for the microbe. Both forms of immunity provide resistance to infection and are specific for microbial antigens, but only active immune responses generate immunologic memory. Cell transfers can be done only between genetically identical donor and recipient (e.g., inbred mice) to avoid rejection of the transferred cells.

Active immunity is immunity to a pathogen that occurs following exposure to all or part of that pathogen. It can occur in one of two ways: **naturally after infection** or via **vaccination as artificial** active immunity. After the infection or immunization, individual develops immune memory for the microbes, conferring immunity against the disease.

Passive immunity is protection from a disease provided by antibodies or cells (e.g., lymphocytes) derived from another individual which already immune to an infection. The example of **natural** passive immunity is seen in **newborns**, who are protected against infections by acquiring antibodies during fetal life from their mothers through the placenta and in the neonatal period from breast milk. **Artificial passive immunity** is useful for treating some diseases with **antibodies pooled from immunized donors**.



Properties of adaptive immune responses

Feature	Functional significance
Specificity	Ensures that immune responses are precisely targeted to microbial pathogens
Diversity	Enables immune system to respond to a large variety of antigens
Memory	Leads to enhanced responses to repeated exposures to the same antigens
Clonal expansion	Increases number of antigen-specific lymphocytes from a small number of naive lymphocytes
Specialization	Generates responses that are optimal for defense against different types of microbes
Contraction and homeostasis	Allows immune system to respond to newly encountered antigens
Nonreactivity to self	Prevents injury to the host during responses to foreign antigens

Specificity and Diversity.

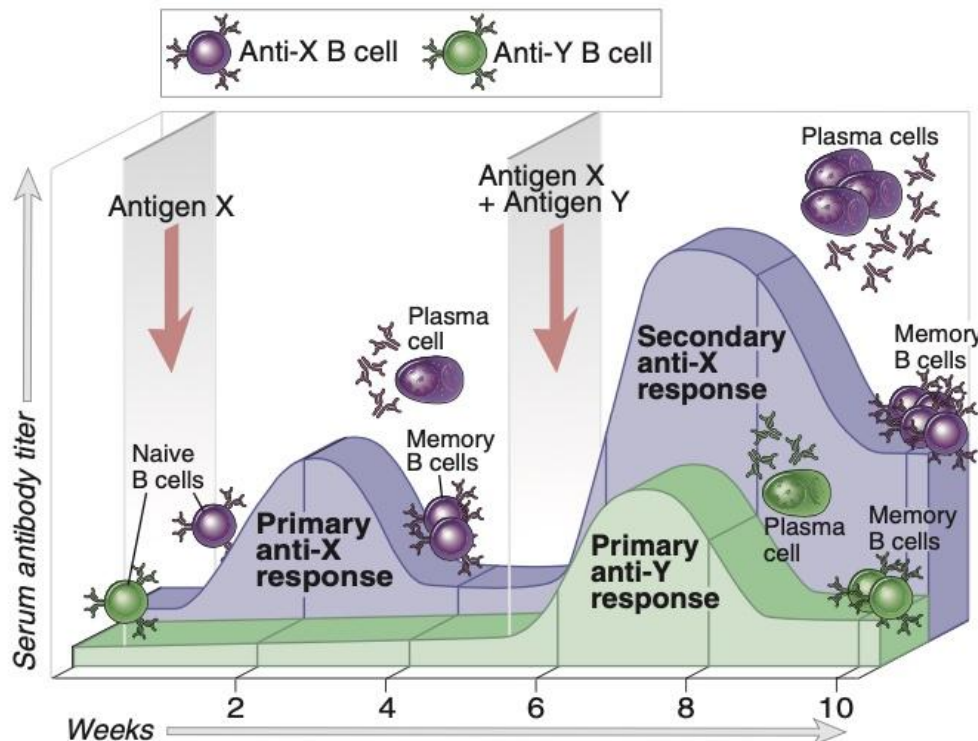
Clonal expansion

- Both B cells and T cells have surface receptors for antigen. **Specificity** of antigen receptors is the ability to distinguish between many different antigens. It implies that the total collection of lymphocyte specificities, sometimes called the lymphocyte repertoire, is **extremely diverse**.
- The total population of B and T lymphocytes consists of **many different clones** (each clone made up of cells all derived from one lymphocyte), and all the cells of one clone express identical antigen receptors, which are different from the receptors of all other clones.

Each antigen selects a preexisting clone of specific lymphocytes and stimulates the proliferation and differentiation of that clone.

Immunologic memory. Primary and secondary immune responses

Immune system **can remember** every encounter with antigen. This property of adaptive immunity is called **immunologic memory**.



The response to the first exposure to antigen is the primary immune response, and it is initiated by lymphocytes called naive lymphocytes that are seeing antigen for the first time.

FIGURE 1-4 Specificity, memory, and contraction of adaptive immune responses. Antigens X and Y induce the production of different antibodies (specificity). The secondary response to antigen X is more rapid and larger than the primary response (memory). Antibody levels decline with time after each immunization (contraction, the process that maintains homeostasis). The same features are seen in cell-mediated immune responses.

Immunologic memory. Primary and secondary immune responses

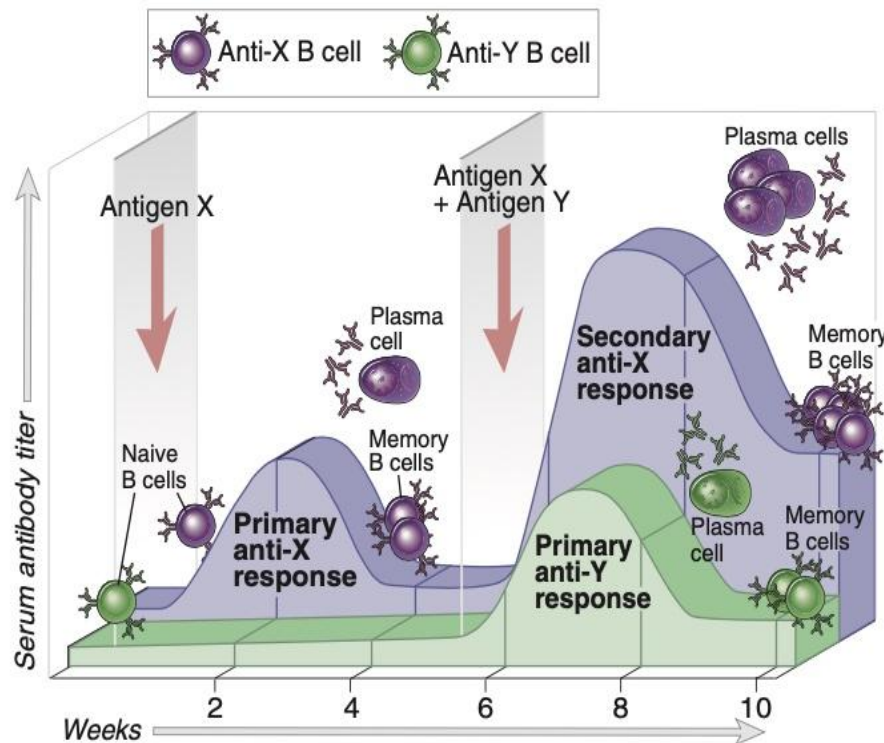


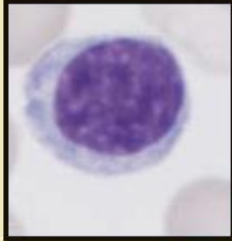

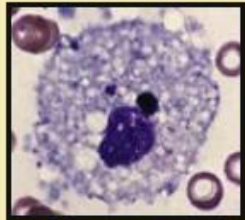
FIGURE 1-4 Specificity, memory, and contraction of adaptive immune responses. Antigens X and Y induce the production of different antibodies (specificity). The secondary response to antigen X is more rapid and larger than the primary response (memory). Antibody levels decline with time after each immunization (contraction, the process that maintains homeostasis). The same features are seen in cell-mediated immune responses.

Subsequent encounters with the same antigen lead to responses called **secondary immune responses**. These are the result of the activation of **memory lymphocytes**, which are long-lived cells that were induced during the primary immune response.

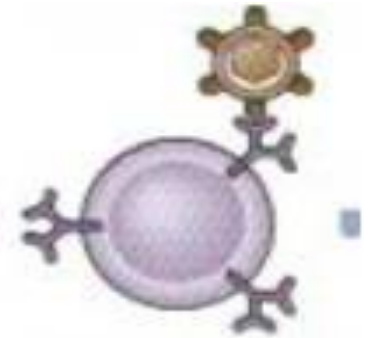
Secondary immune response is:

- faster,
- larger
- more effective than previous response.

Principal cells of the adaptive immune system

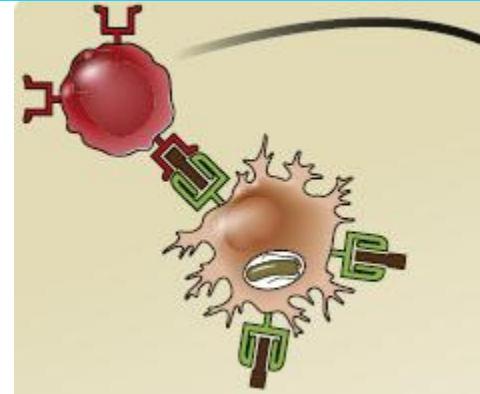
Cell type	Principal function(s)
Lymphocytes: B lymphocytes; T lymphocytes  <i>Blood lymphocyte</i>	Specific recognition of antigens and generation of adaptive immune responses: <ul style="list-style-type: none">• B lymphocytes: mediators of humoral immunity• T lymphocytes: mediators of cell-mediated immunity
Antigen-presenting cells: dendritic cells; macrophages; B cells; follicular dendritic cells  <i>Dendritic cell</i>	Capture of antigens for display to lymphocytes: <ul style="list-style-type: none">• Dendritic cells: initiation of T cell responses• Macrophages: effector phase of cell-mediated immunity• Follicular dendritic cells: display of antigens to B lymphocytes in humoral immune responses
Effector cells: T lymphocytes; macrophages; granulocytes  <i>Macrophage</i>	Elimination of antigens: <ul style="list-style-type: none">• T lymphocytes: activation of phagocytes, killing infected cells• Macrophages: phagocytosis and killing of microbes• Granulocytes: killing microbes

B cells



- They synthesize and express the **membrane form of antibodies (immunoglobulins)** that serve as antigen receptors (**BCR** – from **B Cell Receptor**).
- Since they recognize the antigen, they proliferate and differentiate into effector B cells – a **plasma cells** that synthesizes and secretes the **soluble form of antibodies** of the same specificity.

T cells



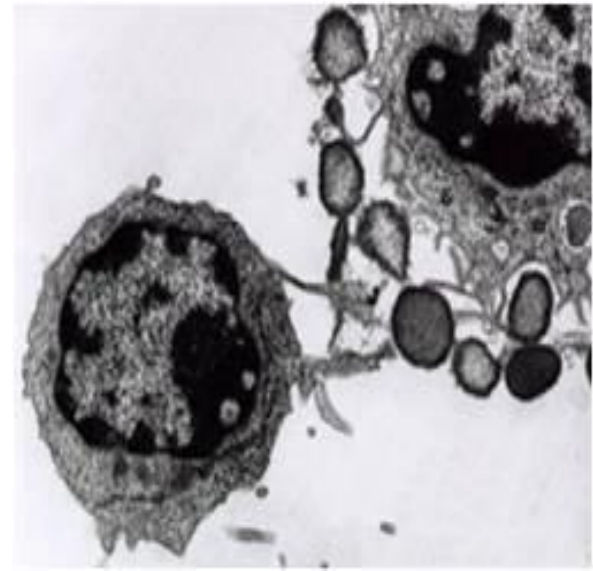
- Synthesize and express the **T cell receptor for antigen (TCR)**.
- The antigen receptors of most T lymphocytes **recognize only peptide fragments** of protein antigens that are bound to specialized peptide display molecules, called **major histocompatibility complex (MHC) molecules**, on the surface of **specialized cells**, called **antigen-presenting cells**

Subpopulation of T cells

- **CD4+T cells:** peptides are recognized in the context of **MHC II class**. By function, they are helpers (helpers-Th) and **produce cytokines**. **They help** B cells in production of antibodies and phagocytes to destroy ingested microbes.
- Some CD4+ T cells are not helpers by function, but are so-called **regulatory cells (Treg)**, whose function is to **prevent or limit the immune response**.
- **CD8+T cells:** they recognize peptides within the products of **MHC I class**. They **are cytotoxic or cytolytic** lymphocytes (CTL). These lymphocytes **kill** our cells that contain intracellular microorganisms or tumor cells.

NK Cells

- NK cells (**Natural Killer cells**) – congenital killers, innate killer cells. They are lymphocytes, although they **do not have specific clone-distributed receptors**, and belong to the innate immunity.



B						
Class	Functions	Antigen receptor and specificity	Selected phenotypic markers	Percentage of total lymphocytes*		
$\alpha\beta$ T Lymphocytes						
CD4 ⁺ helper T lymphocytes	B cell activation (humoral immunity) Macrophage activation (cell-mediated immunity) Stimulation of inflammation	$\alpha\beta$ heterodimers Diverse specificities for peptide–class II MHC complexes	CD3 ⁺ CD4 ⁺ CD8 [–]	Blood	Lymph node	Spleen
				35–60	50–60	50–60
CD8 ⁺ cytotoxic T lymphocytes	Killing of cells infected with intracellular microbes, tumor cells	$\alpha\beta$ heterodimers Diverse specificities for peptide–class I MHC complexes	CD3 ⁺ CD4 [–] CD8 ⁺	15–40	15–20	10–15
Regulatory T cells	Suppress function of other T cells (regulation of immune responses, maintenance of self-tolerance)	$\alpha\beta$ heterodimers Specific for self and some foreign antigens (peptide–class II MHC complexes)	CD3 ⁺ CD4 ⁺ CD25 ⁺ FoxP3 ⁺ (most common)	0.5–2	5–10	5–10
B Lymphocytes						
B cells	Antibody production (humoral immunity)	Surface Ig Diverse specificities for many types of molecules	Fc receptors class II MHC CD19 CD23	Blood	Lymph node	Spleen
				5–20	20–25	40–45

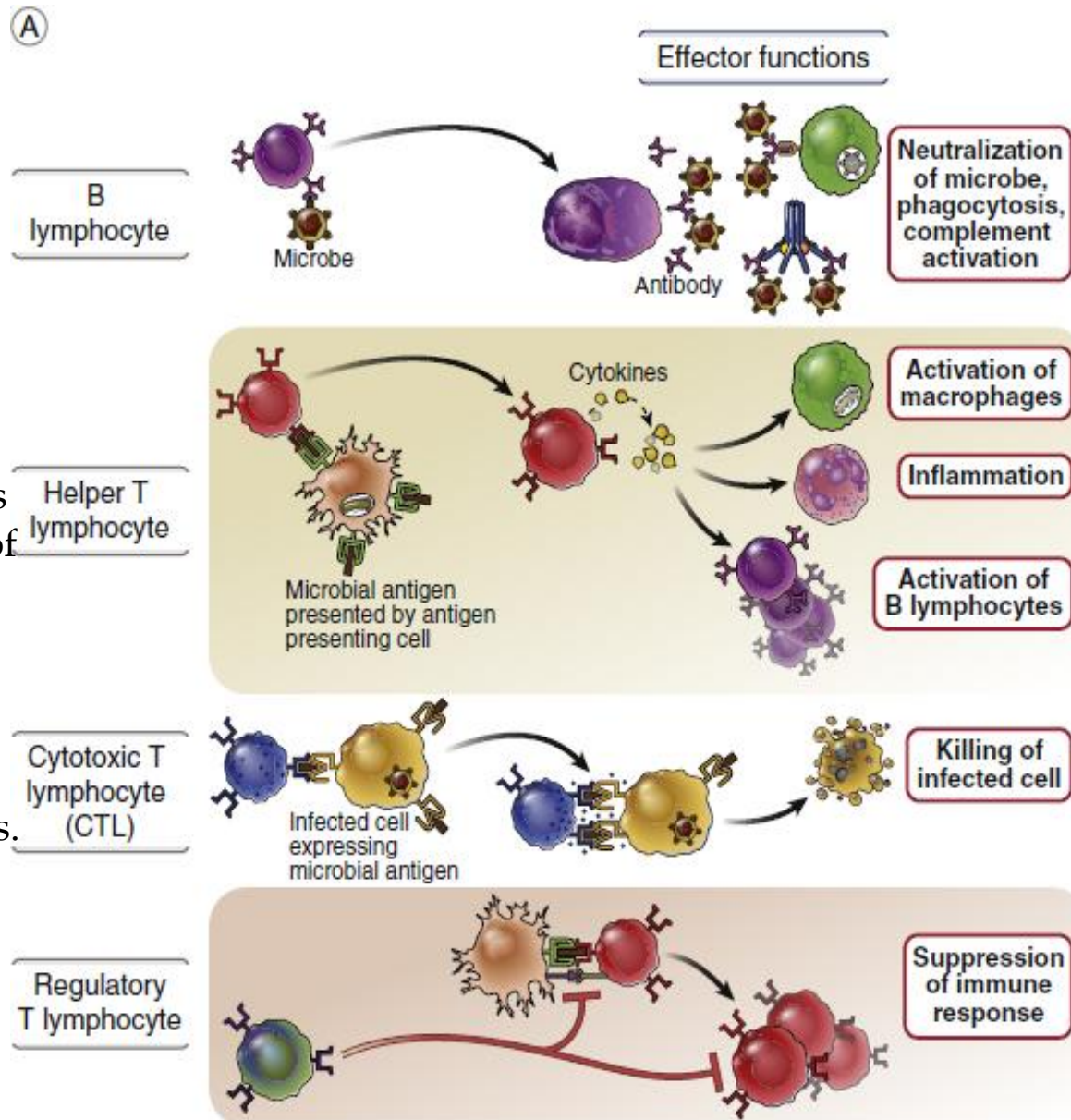
Fig. 1.9, cont'd B. The table summarizes the major properties of the lymphocytes of the adaptive immune system. Not included are $\gamma\delta$ T cells, natural killer cells and other innate lymphoid cells, which are discussed in [Chapter 2](#). *The percentages are approximations, based on data from human peripheral blood and mouse lymphoid organs. Ig, Immunoglobulin; MHC, major histocompatibility complex.

B lymphocytes recognize soluble or microbial surface antigens and differentiate into antibody-secreting cells called plasma cells.

Helper T cells recognize these peptides displayed by MHC II molecules on the surface of macrophages or other antigen presenting cells, and secrete cytokines that stimulate different mechanisms of immunity and inflammation.

Cytotoxic T lymphocytes recognize peptides displayed by MHC I molecules on the surface of infected cells or tumor cells, and kill these cells.

Regulatory T cells limit the activation of other lymphocytes, especially of T cells, and prevent autoimmunity.



Lymphocyte maturation

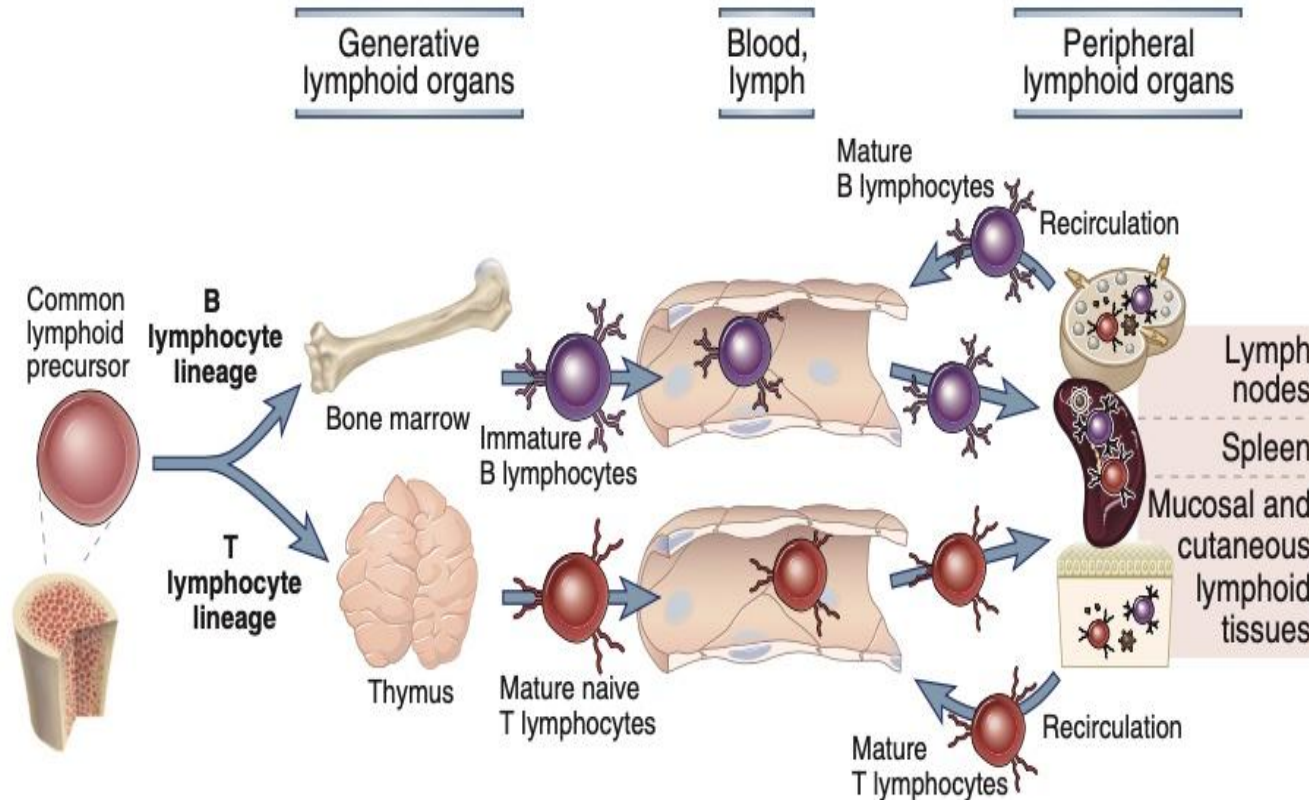


FIGURE 2-5 Maturation of lymphocytes. Lymphocytes develop from bone marrow stem cells and mature in the generative lymphoid organs (bone marrow and thymus for B and T cells, respectively) and then circulate through the blood to secondary lymphoid organs (lymph nodes, spleen, regional lymphoid tissues such as mucosa-associated lymphoid tissues). Fully mature T cells leave the thymus, but immature B cells leave the bone marrow and complete their maturation in secondary lymphoid organs. Naive lymphocytes may respond to foreign antigens in these secondary lymphoid tissues or return by lymphatic drainage to the blood and recirculate through other secondary lymphoid organs.

Lymphocytes

Naive (innocent) lymphocytes – mature immunocompetent lymphocytes. They recognize the antigen but are not functionally able to eliminate it.

Effector lymphocytes – able to recognize and Eliminate the antigen.

Memory lymphocytes are functionally inactive; they do not perform effector functions unless stimulated by antigen. When these cells encounter the same antigen that induced their development, the cells rapidly respond to initiate secondary immune responses.

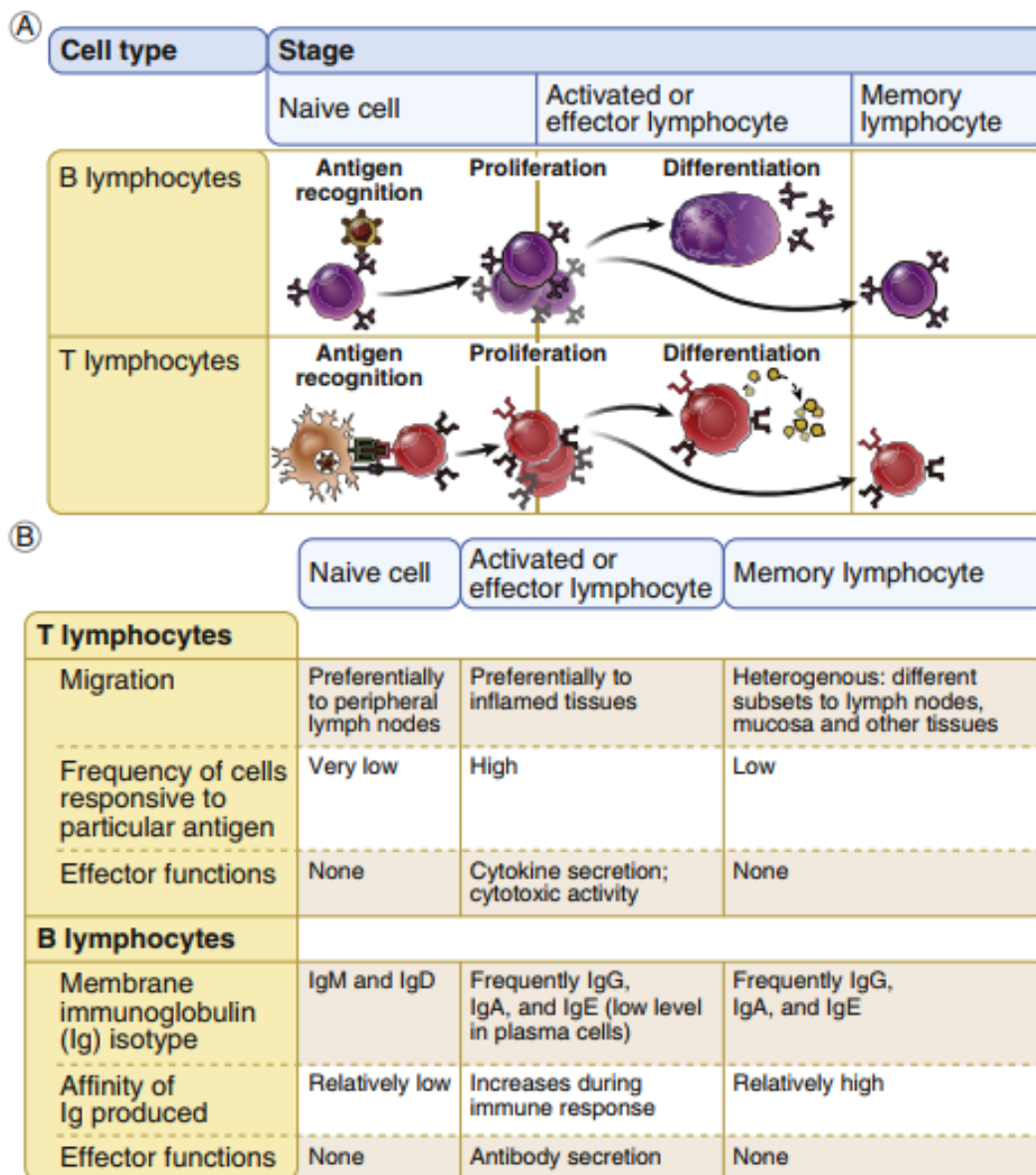


Fig. 1.11 Stages in the life history of lymphocytes. **A**, Naive lymphocytes recognize foreign antigens to initiate adaptive immune responses. Naive lymphocytes need signals in addition to antigens to proliferate and differentiate into effector cells; these additional signals are not shown. Effector cells, which develop from naive cells, function to eliminate antigens. The effector cells of the B lymphocyte lineage are antibody-secreting plasma cells (some of which are long lived). The effector cells of the CD4 T lymphocyte lineage produce cytokines. (The effector cells of the CD8 lineage are CTLs; these are not shown.) Other progeny of the antigen-stimulated lymphocytes differentiate into long-lived memory cells. **B**, The important characteristics of naive, effector, and memory cells in the B and T lymphocyte lineages are summarized. The generation and functions of effector cells, including changes in migration patterns and types of immunoglobulin produced, are described in later chapters.

Lymphocytes

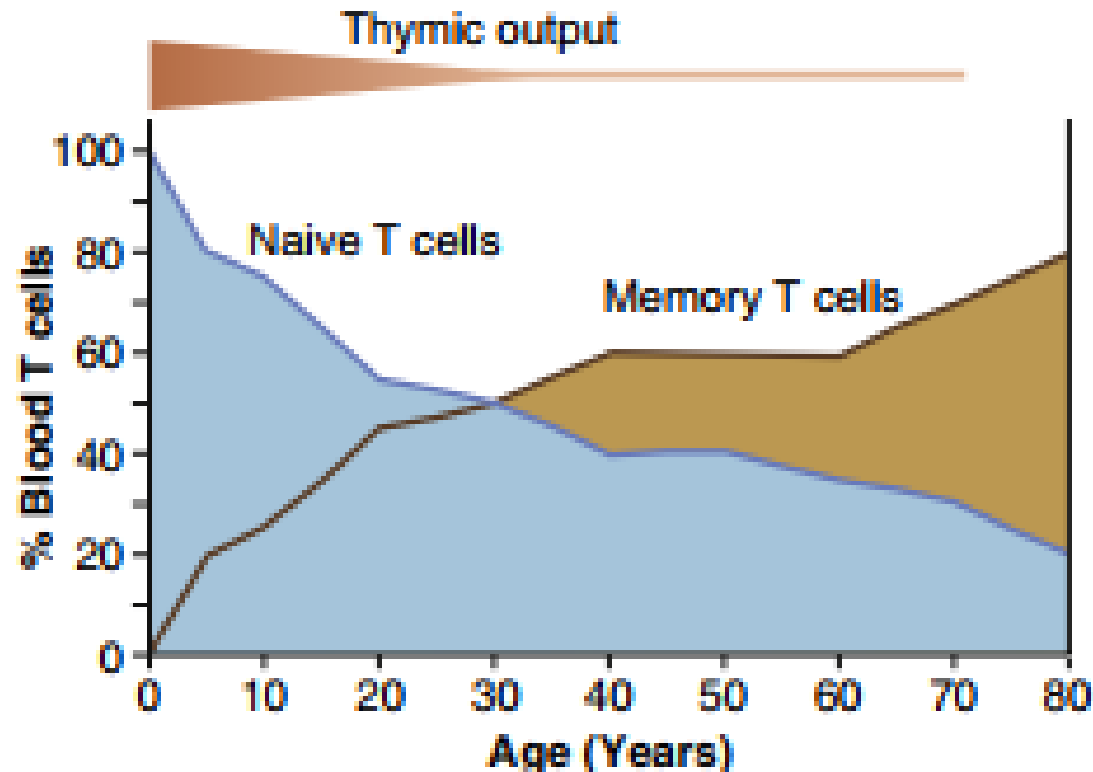


Fig. 1.12 Change in proportions of naive and memory T cells with age. The proportions of naive and memory T cells are based on data from multiple healthy individuals. The estimate of thymic output is an approximation. (Courtesy Dr. Donna L. Farber, Columbia University College of Physicians and Surgeons, New York, NY.)

Antigen-presenting cells (APC)



- **Non-professional APC** (APC in a broad sense) – display peptide antigens, as part of class I MHC molecules, for effector T lymphocytes (CD8+ T = CTL). These are all cells except: erythrocytes, spermatozoid and trophoblast cells.
- **Professional APC** (APC in the narrow sense) – show peptide antigens as part of MHC molecules II class, but also I class MHC, Th lymphocytes (CD4+ T). These are: dendritic cells, Mo/Mf cells, B lymphocytes. They are located in the skin, mucous membranes and connective tissue. That's where they collect antigens, transport them to the lymph nodes, and show them there with lymphocytes. In addition, they provide other contact and soluble signals for the activation of T lymphocytes.

Tissues of the immune system

The central (also called primary) lymphoid organs:

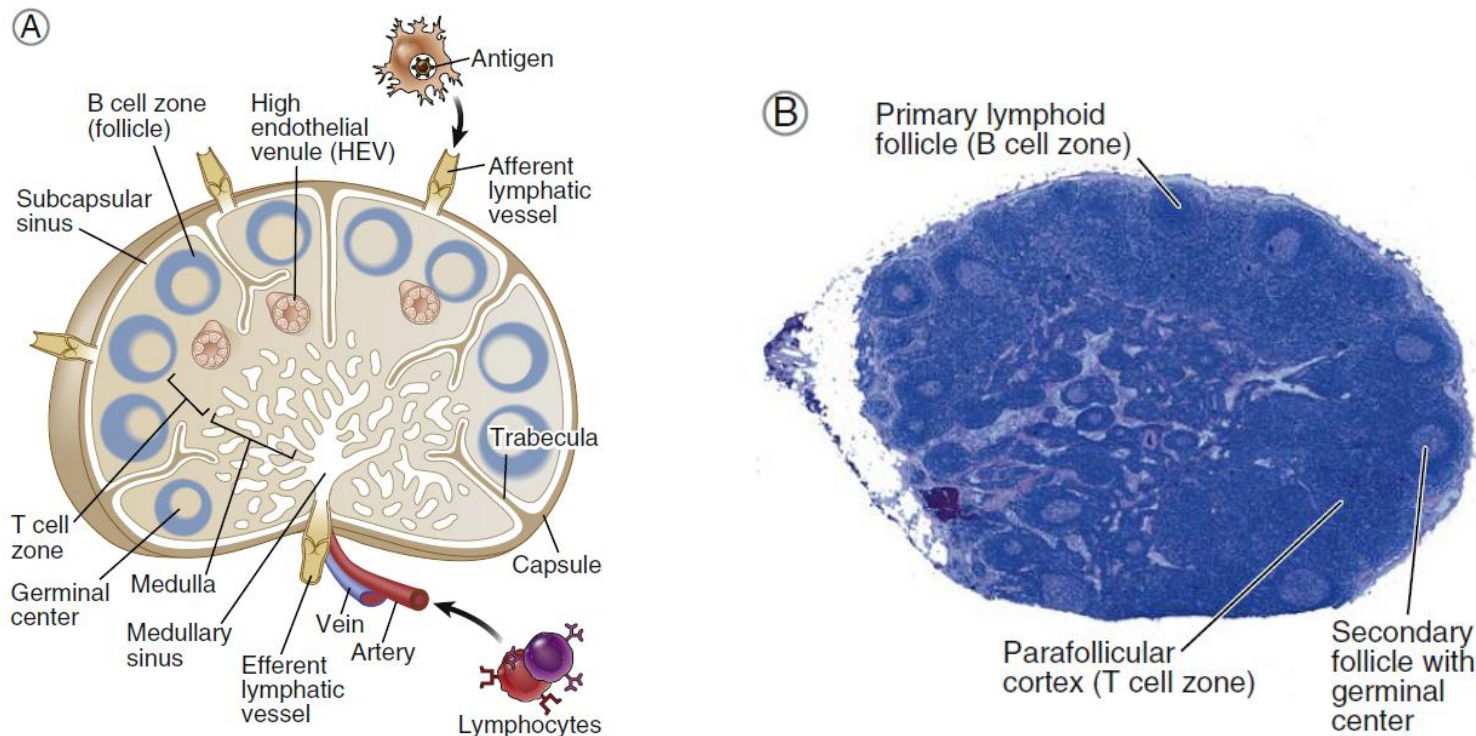
- bone marrow
- thymus, in which T and B lymphocytes mature and become competent to respond to antigens.

Peripheral (secondary) lymphoid organs:

- lymph nodes
- spleen
- mucosal and cutaneous immune systems, in which adaptive immune responses to microbes are initiated. Peripheral lymphatic organs are organized to concentrate antigens, APC and lymphocytes and create conditions for the initiation of the acquired immune response.

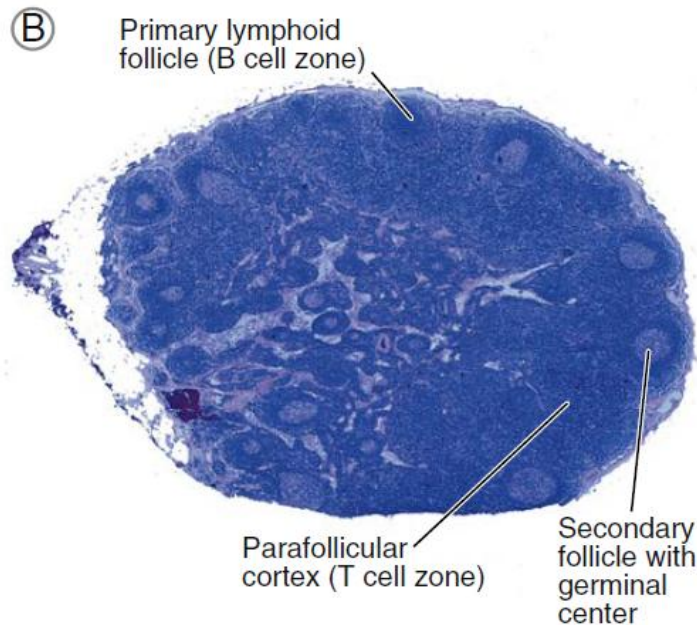
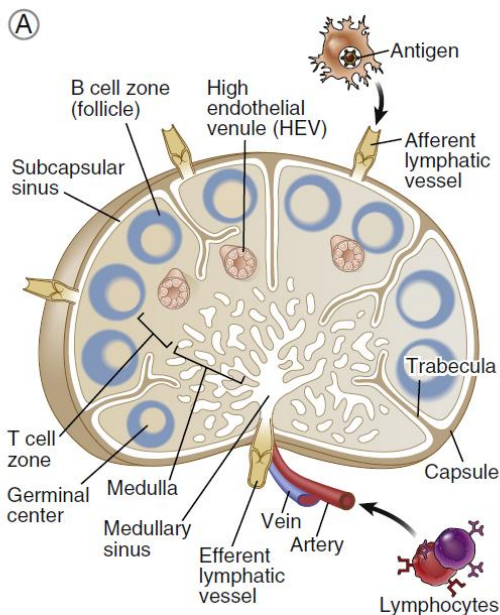
Lymph nodes

They are encapsulated nodular aggregates of lymphoid tissues located along lymphatic channels throughout the body. Fluid, called lymph, constantly leaks out of small blood vessels in all epithelia and connective tissues and most parenchymal organs. Lymph is drained by lymphatic vessels from the tissues to the lymph nodes and eventually back into the blood circulation.



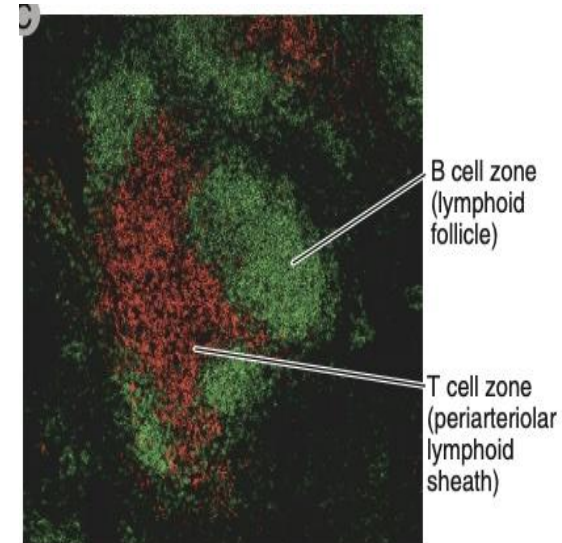
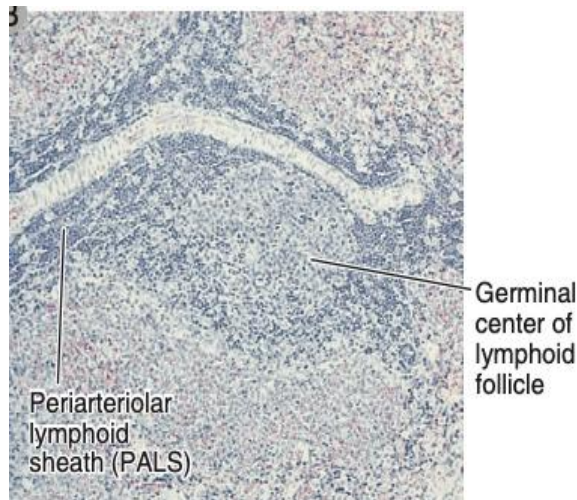
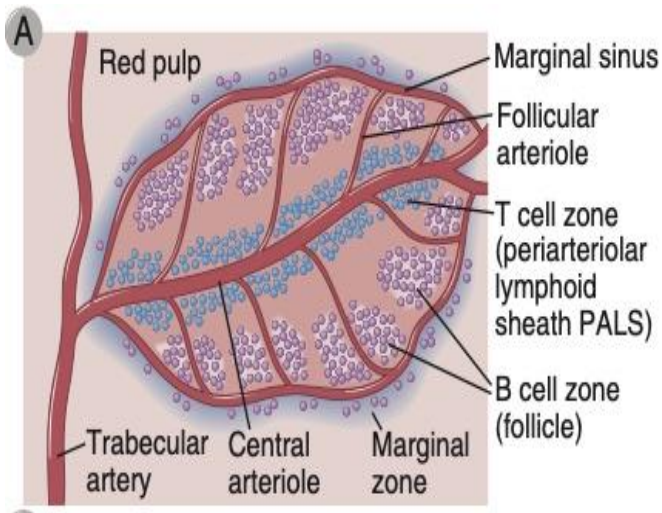
Lymph nodes

As the lymph passes through lymph nodes, APCs in the nodes are able to sample the antigens of microbes that may enter through epithelia into tissues. Dendritic cells also pick up antigens of microbes from epithelia and other tissues and transport these antigens to the lymph nodes. The net result of these processes of antigen capture and transport is that the antigens of microbes entering through epithelia or colonizing tissues become concentrated in draining lymph. Naive T and B lymphocytes preferentially go to the peripheral lymphoid organs and tissues, in which antigen is concentrated



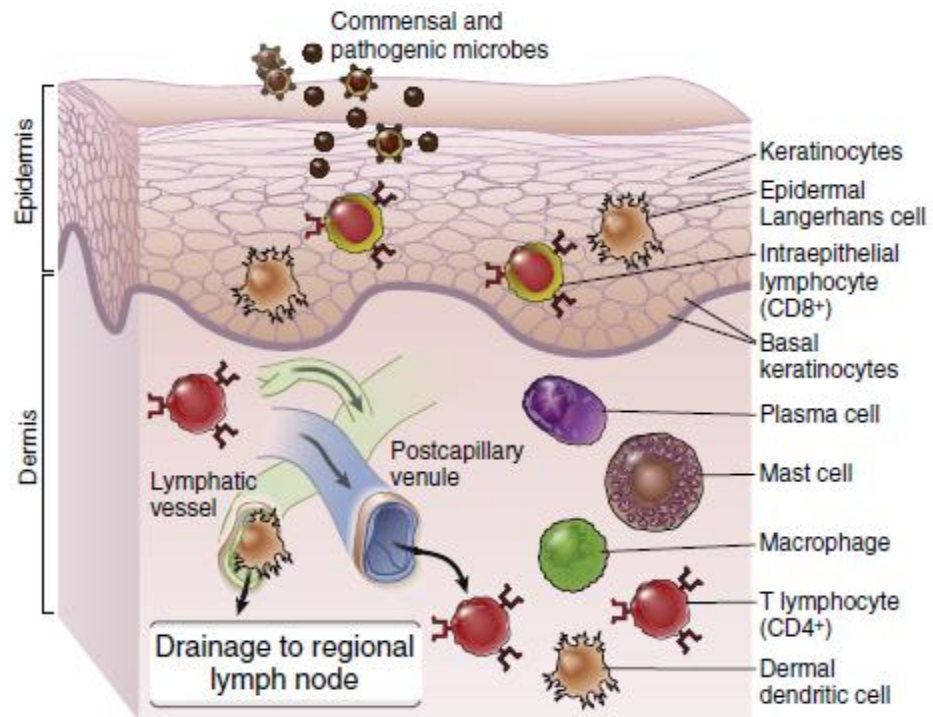
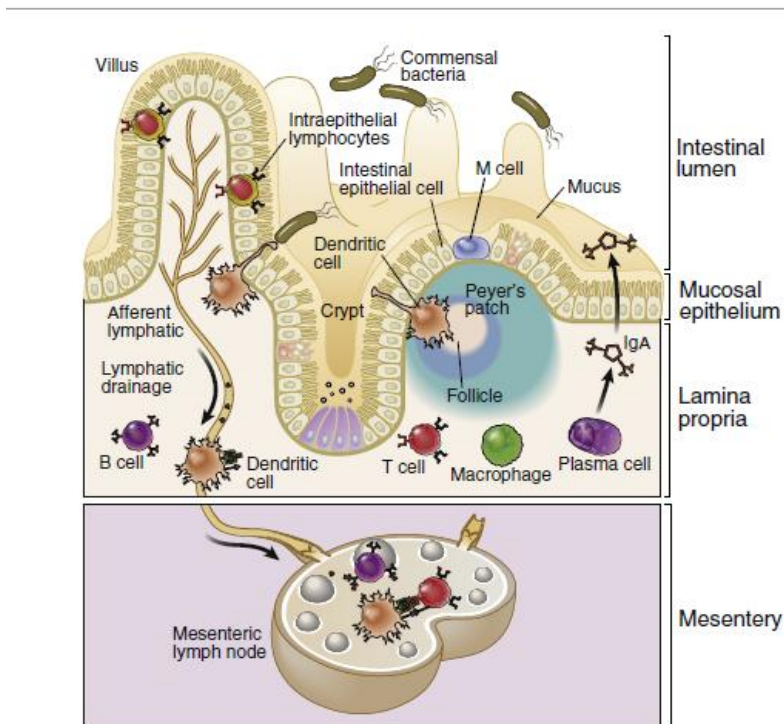
Spleen

The spleen is a highly vascularized organ whose major functions are to remove aging and damaged blood cells and particles (such as immune complexes and opsonized microbes) from the circulation and to initiate adaptive immune responses to bloodborne antigens.



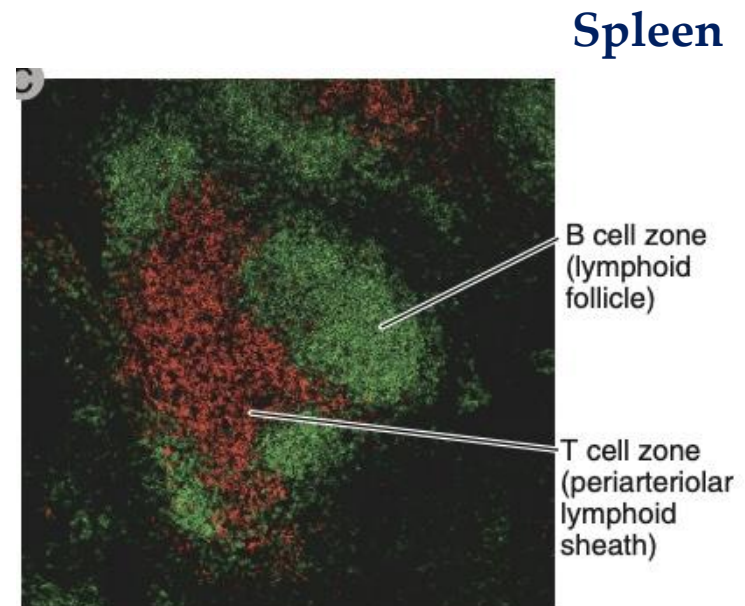
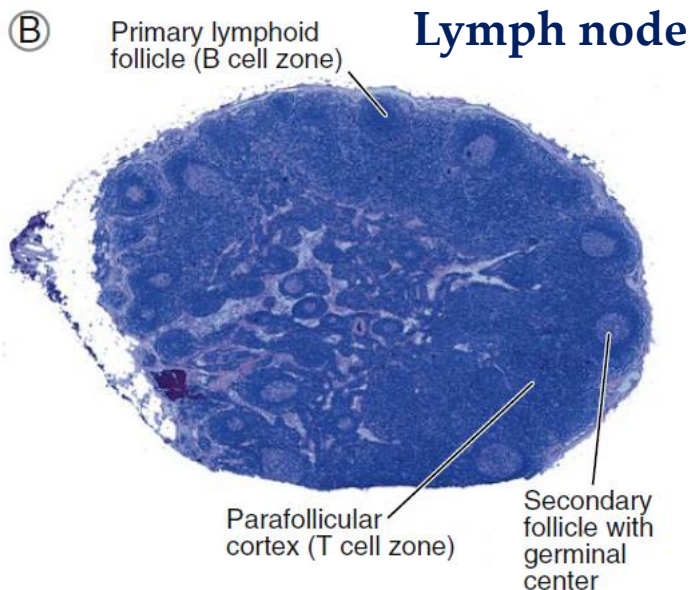
Cutaneous and mucosal immune system

There are specialized collections of lymphoid tissues and APCs located in and under the epithelia of the skin and the gastrointestinal and respiratory tracts, respectively. Although most of the immune cells in these tissues are diffusely scattered beneath the epithelial barriers, there are discrete collections of lymphocytes and APCs. A remarkable property of these systems is that they are able to respond to pathogens but do not react to the enormous numbers of usually harmless commensal microbes present at the epithelial barriers.



Segregation of T and B lymphocytes in different regions of peripheral lymphoid organs

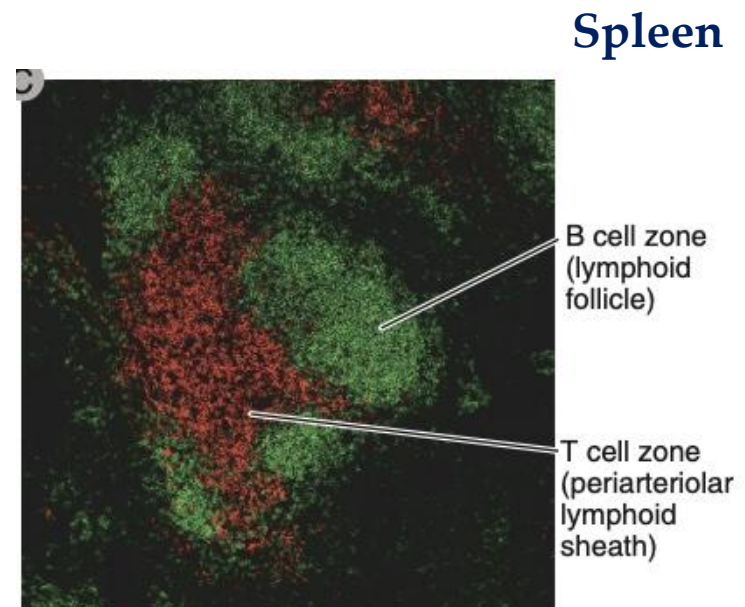
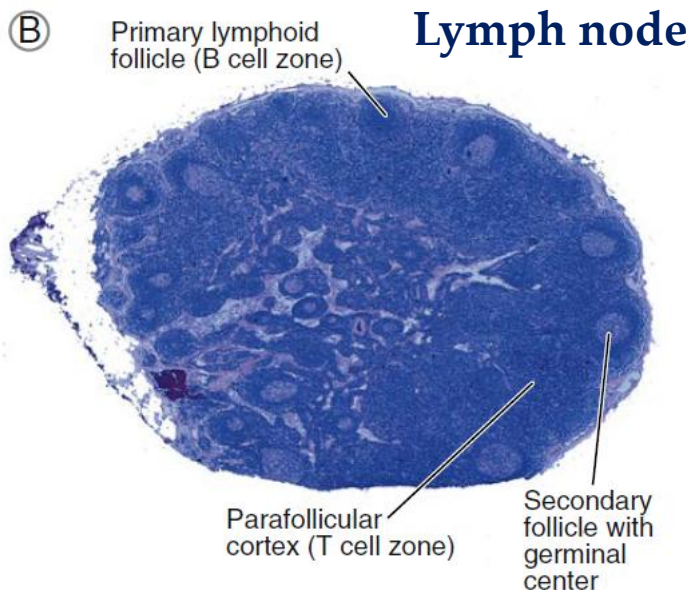
In lymph nodes as other peripheral lymphoid organs, T lymphocytes and B lymphocytes are separated into different anatomical compartments, B cells are concentrated in discrete structures, called **follicles**, located around the periphery, or cortex, of each node. The **T lymphocytes** are concentrated outside but adjacent to the follicles, in the **paracortex**. In the spleen, **T lymphocytes** are concentrated in **periarteriolar lymphoid sheaths** surrounding small arterioles, and B cells reside in **the follicles**.



Segregation of T and B lymphocytes in different regions of peripheral lymphoid organs

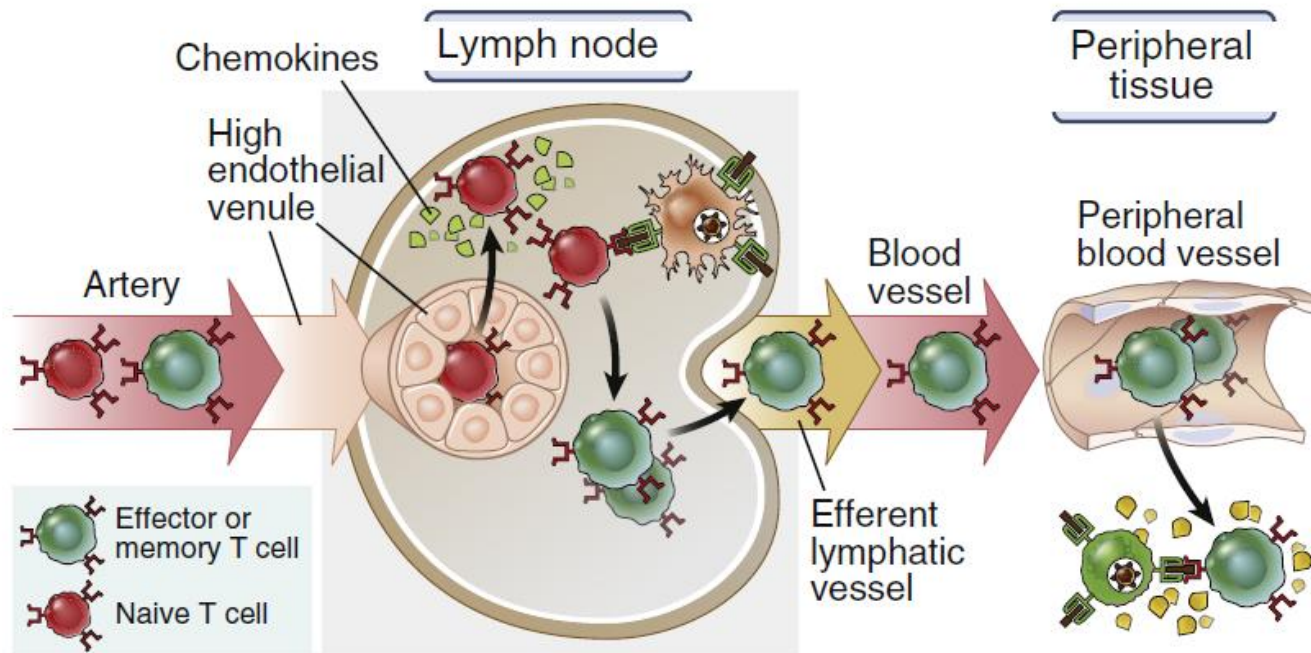
The chemokines induce T and B lymphocyte separation into physically distinct microenvironments such as T and B cell areas where subset-attracting chemokines are expressed.

This anatomic organization of peripheral lymphoid organs is tightly regulated to allow immune responses to develop after stimulation by antigens.



Lymphocyte recirculation and migration into tissues

Naive lymphocytes constantly recirculate between the blood and peripheral lymphoid organs, where they may be activated by antigens to become effector cells, and the effector lymphocytes migrate from lymphoid tissues to sites of infection, where microbes are eliminated.



Recirculation and migration of lymphocytes

Naïve lymphocytes all the time recirculate between blood-peripheral lymphatic organs.

When they become effector lymphocytes (after contact with antigen) they migrate to places of infection where they eliminate microorganisms.

T lymphocytes mainly recirculate and migrate.

(B lymphocytes do not need to recirculate and migrate to function)



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