General Immunology Course

I- The Components of the Immune System

The immune system is composed of a complex network of distinct organs and tissues, through which innate and adaptive immune cells constantly circulate. This communication network provides the immune system with three essential properties:

➔ A significant capacity for information exchange, either through direct membrane contacts between cells or by the release of soluble mediators. These exchanges occur between different components of the immune system.

➔ A highly effective effector arm capable of protecting the body's integrity.

➔ A strong regulatory mechanism, which is crucial for maintaining immune system balance (homeostasis) at all times and in all locations, ensuring an appropriate immune response.

Disruptions in any of these systems can lead to pathological disorders, such as immune deficiencies, autoimmune diseases, or hypersensitivity conditions.

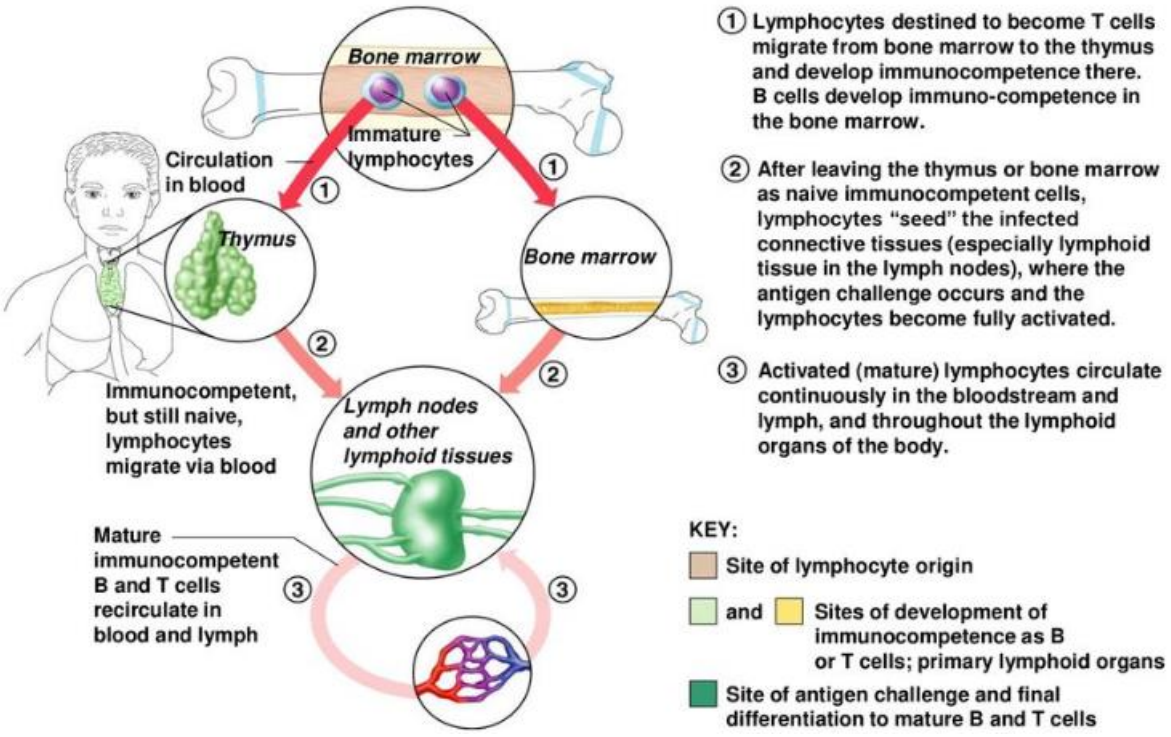

Figure 1: Lymphocytes maturation

I-1 The Organs and Tissues of the Immune System

The immune system consists of primary (or central) lymphoid organs and tissues, where T and B lymphocytes mature and acquire the ability to respond to antigens. It also includes secondary (or peripheral) lymphoid organs, where adaptive immune responses against microbes take place (see Figure 1).

I-1-1 Primary (or Central) Lymphoid Organs

A- Bone Marrow

Bone marrow is the tissue located in the central part of bones. However, in adults, only the bone marrow found in short and flat bones (such as the sternum, vertebrae, ribs, clavicle, pelvis, and skull) retains hematopoietic activity, meaning the ability to produce various blood cell lineages.

Indeed, only these bones still contain red bone marrow, which consists of multipotent hematopoietic stem cells (HSCs) (Figure 2.a) in contrast to yellow bone marrow, which is primarily composed of fat cells (adipocytes).

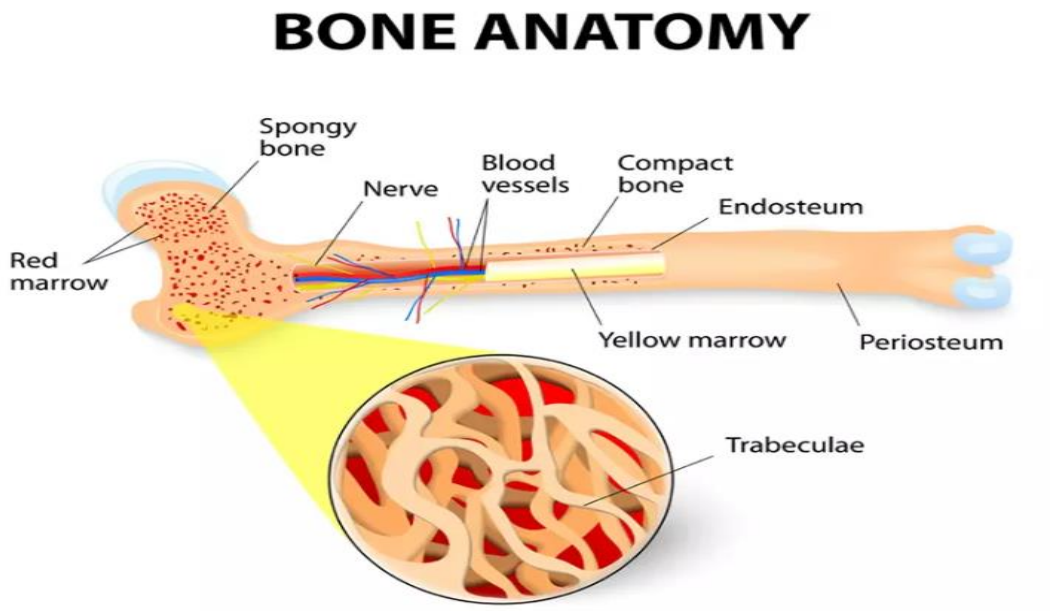

Figure 2.a: Bone marrow Structure

These multipotent stem cells have the ability to self-renew indefinitely and differentiate into a wide range of cell types (see Figure 2.b).

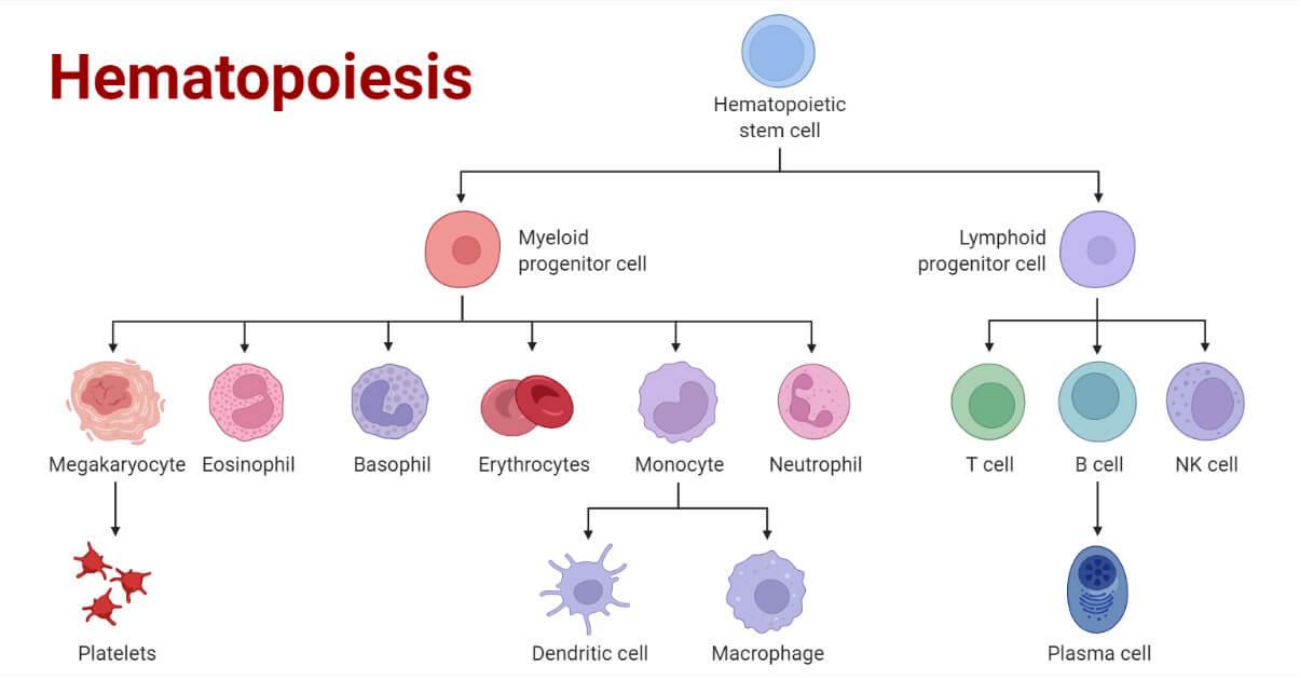

Figure 2.b: Differentiation of hematopoietic stem cells. From a hematopoietic stem cell (HSC) lymphoid stem cells and myeloid stem cells are generated. The former give rise to B lymphocytes, T lymphocytes and NK cells. The latter are at the origin of the three types of granulocytes: neutrophils, eosinophils and basophils, as well as dendritic cells and monocytes which subsequently differentiate into macrophages

Bone marrow also contains stromal cells, which form a supportive tissue that enables the proliferation and differentiation of hematopoietic stem cells.

Note: In birds, the bursa of Fabricius is the primary lymphoid organ responsible for B lymphocyte differentiation. Its equivalent in mammals is the bone marrow.

B- The Thymus

The thymus is the site where T lymphocytes mature and undergo selection (a process known as "education"). It is a bilobed organ located in the anterior mediastinum. From a histological perspective, each thymic lobe is organized into functional units called lobules, which are separated by invaginations of the surrounding capsule. Within these lobules, two distinct regions can be identified: an outer region called the **cortex** and a more central region called the **medulla (Figure 3.a)**.

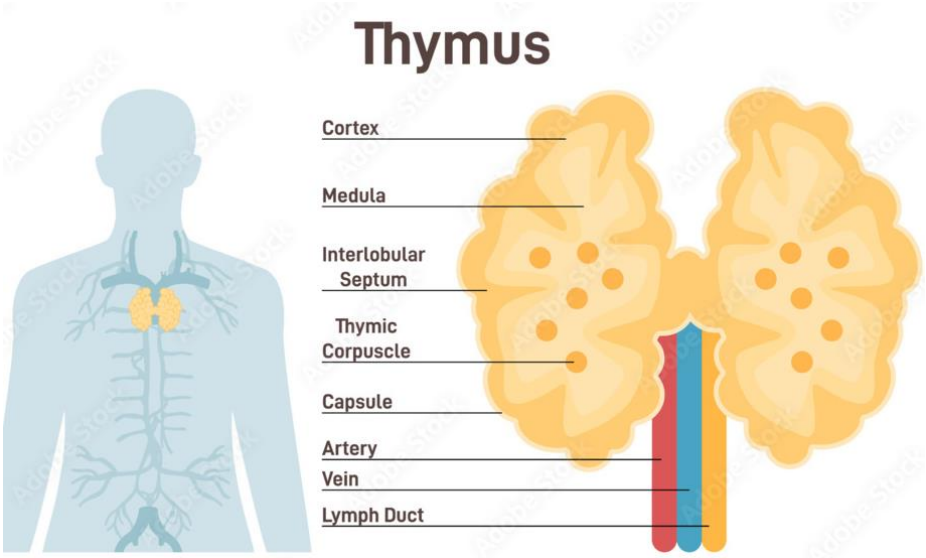

Figure 3.a: Thymus Position and overall Structure

Lymphoid precursors originating from the bone marrow enter the thymus through post-capillary venules located at the **cortico-medullary junction**. They then migrate towards the cortex before moving into the medulla. These different regions contain distinct cell populations, allowing various maturation processes to take place. The objective of this maturation is to retain thymocytes with a functional T-cell receptor (TCR) that can recognize self-antigens with limited affinity.

In addition to thymocytes at different developmental stages, the thymus is composed of **epithelial cells** in both the cortex and the medulla. The medulla also contains **macrophages** and **dendritic cells (Figure 3.b)**.

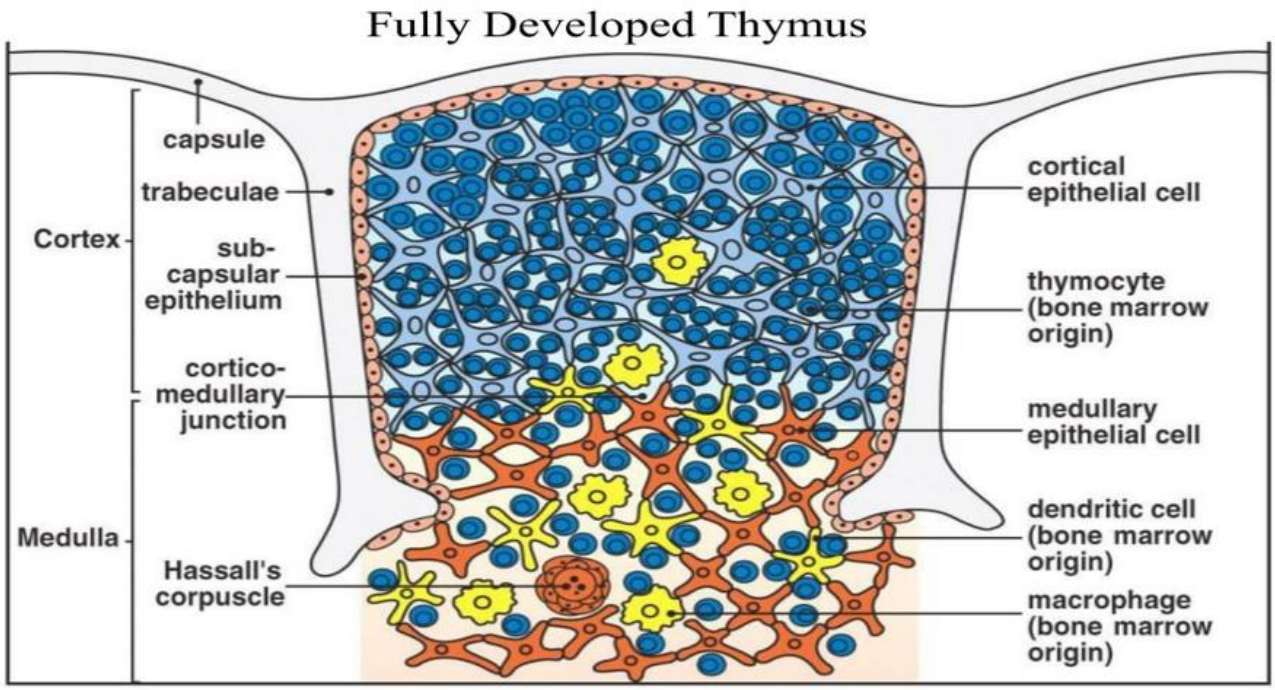

Figure 3.b: Detailed structure of Thymus gland

After completing their initial maturation stage, B and T lymphocytes leave the primary lymphoid organs as **naïve B and T lymphocytes**. They continuously circulate through the **bloodstream and lymphatic system**, passing through secondary lymphoid organs throughout the body. It is in these secondary lymphoid organs that they will encounter their specific antigen, become activated, and differentiate into effector cells.

I-1-2 Secondary (or Peripheral) Lymphoid Organs

Secondary lymphoid organs serve as sites for the **drainage and concentration of antigens** present in tissues, lymph (lymph nodes), blood (spleen), or mucosal surfaces (mucosa-associated lymphoid tissue, MALT). These organs are also highly vascularized, ensuring the **continuous circulation of naïve lymphocytes (Figure 4)**.

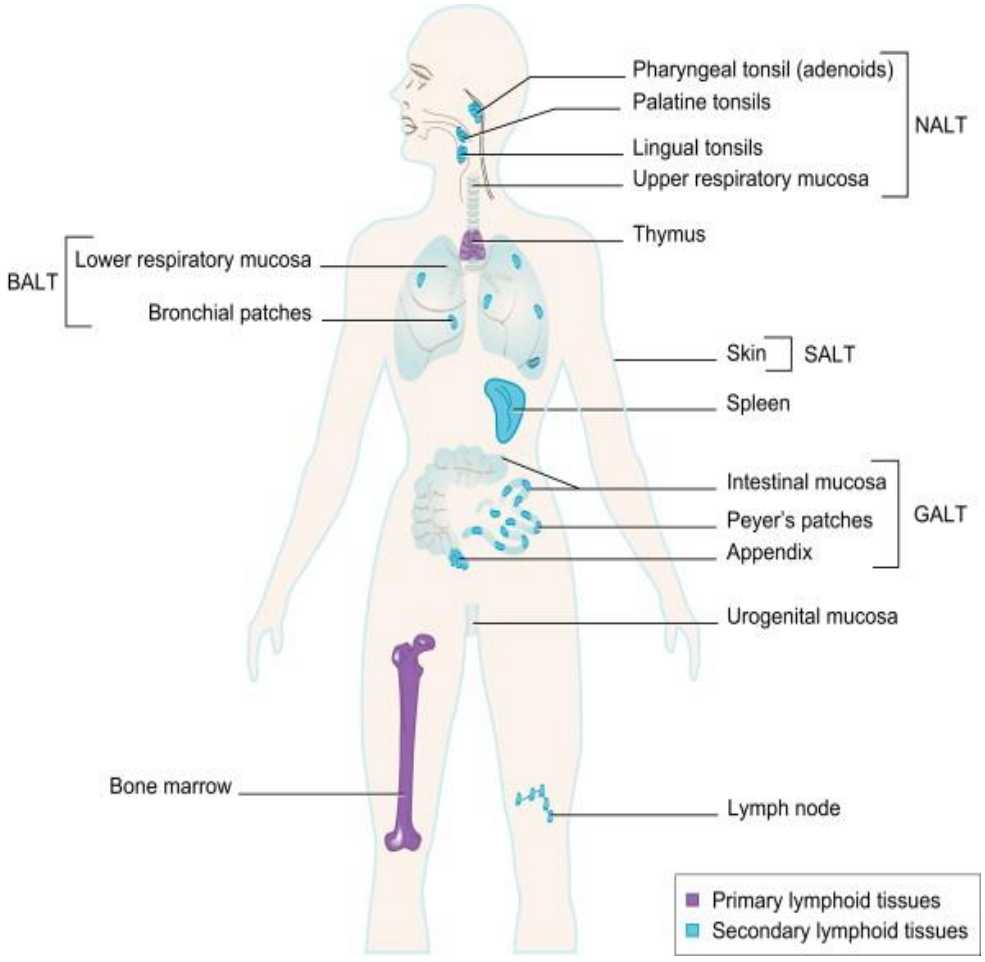

Figure 4: Secondary lymphoid organs

Thus, secondary lymphoid organs are the primary sites where antigens encounter immune cells that participate in the adaptive immune response.

A- Lymph Nodes

➔ **Structure and Organization:** Lymph nodes are encapsulated, bean-shaped structures measuring between **1 and 15 mm in diameter**, with approximately **500 to 1,000 nodes** present in the human body. They are interconnected by **lymphatic vessels**, forming chains of lymph nodes. Each lymph node has an extensive network of **afferent lymphatic vessels** and a **single efferent lymphatic vessel**.

➔ **Function:** Lymph nodes are **distributed throughout the body** to monitor different anatomical regions. They **filter lymph** originating from interstitial fluid that bathes all tissues, allowing the **concentration of soluble antigens or those captured by antigen-presenting cells (APCs)**. Their strategic position at the interface between the **blood and lymphatic circulation** optimizes antigen detection by immune cells, facilitating the activation of adaptive immune responses.

➔ **Histological Organization:** Lymph nodes are divided into **three main regions (Figure 5)**:

- The **cortical zone (B zone)** contains **lymphoid follicles rich in B lymphocytes**.
- The **paracortical zone (T zone)** consists primarily of **T lymphocytes interacting with dendritic cells**, which present antigens to them.
- The **medullary sinuses and cords**, located in the center, are **rich in macrophages** and serve as sites for **capturing particulate antigens** carried by the lymph.

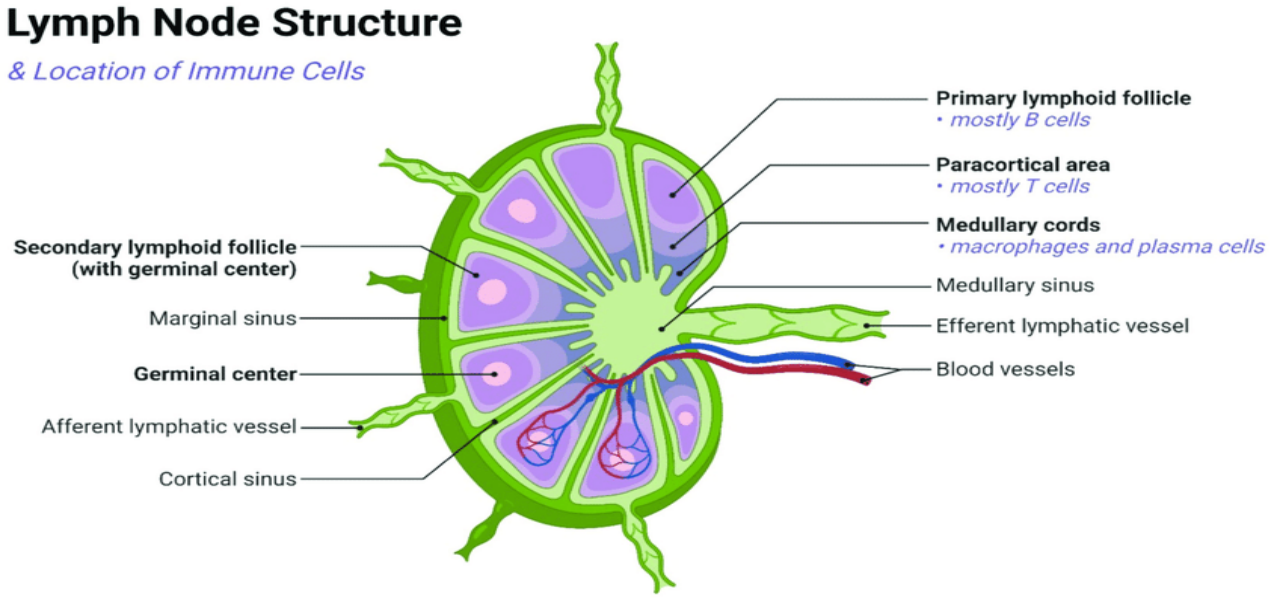

Figure 5: Lymph node structure

➔ **Lymphatic Drainage:** The lymph, along with the immune cells it carries, exits the lymph nodes through an **efferent lymphatic vessel**. The entire **lymphatic network eventually drains into the thoracic duct, which empties into the subclavian vein**, allowing immune cells to re-enter circulation.

B- The Spleen

- The spleen is the **largest secondary lymphoid organ**, weighing approximately **150 to 200 g**. It has an **oval shape** and is located in the **left hypochondrium** (upper left abdomen). Unlike lymph nodes, the spleen is connected **only to the bloodstream**, which it **filters** through an extensive vascular network, allowing it to perform **immune surveillance of blood-borne antigens**.
- During **embryonic development**, the spleen initially has a **hematopoietic function**, similar to the fetal liver. After birth, it consists of:

- **Red pulp** (99% of its volume), which is rich in **macrophages** and mainly involved in **the degradation of old or damaged red blood cells**.
- **White pulp** (1% of splenic mass), which is arranged around arterioles and serves as the **site for immune responses**.

- The **white pulp** is composed of **periarteriolar lymphoid sheaths (PALS)**, which primarily contain **lymphocytes**. It has two main zones:
  - A **central T-cell zone** (T zone), rich in **T lymphocytes**.
  - A **peripheral B-cell zone** (B zone), which includes:
    - **Primary and secondary lymphoid follicles**, where B-cell activation and differentiation occur.
    - The **marginal zone**, which plays a key role in capturing and processing blood-borne antigens.

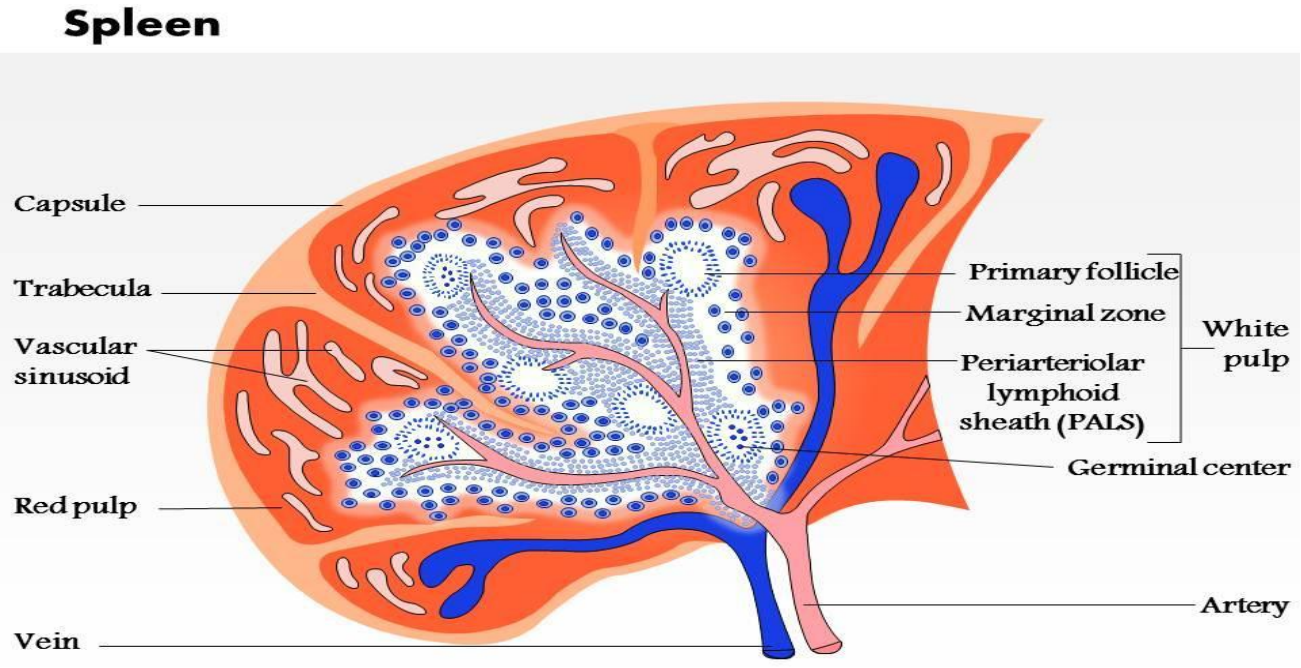

Figure 6: Spleen Anatomy

C- Mucosa-Associated Lymphoid Organs

- These organs collectively form the **Mucosa-Associated Lymphoid Tissue (MALT)**, which consists of **numerous and diverse structures**. MALT represents **80% of the body's total lymphoid tissue**, highlighting its crucial role in **protecting against antigens that enter through mucosal surfaces**. These mucosal surfaces, including the **respiratory, digestive, and urogenital tracts**, collectively cover an area of more than **400 m²**.

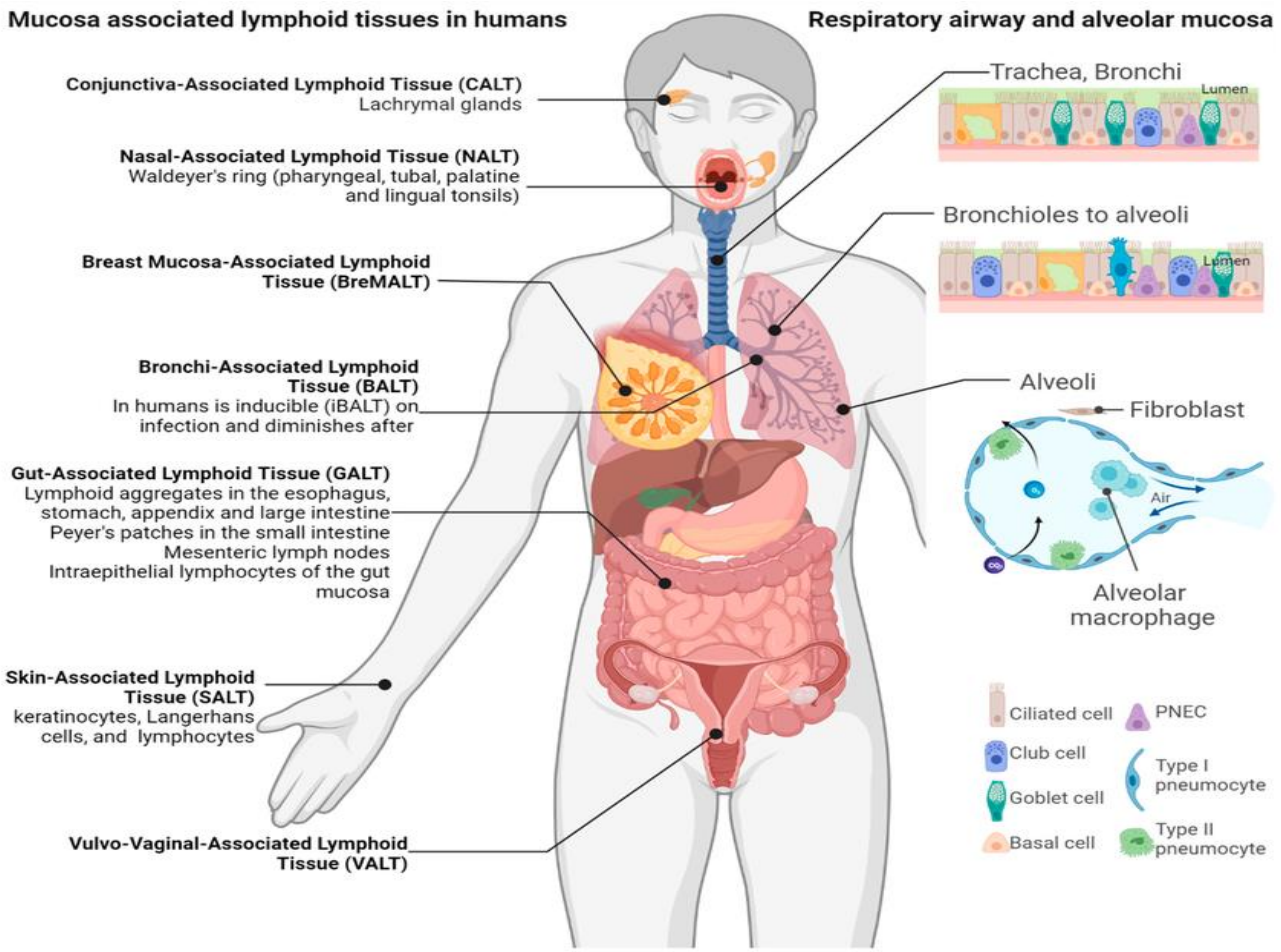

Figure 7: Mucosa-Associated Lymphoid Organs

- MALT can exist as **diffuse lymphoid tissue** or as **organized structures**, such as:
    - **Peyer's patches** in the digestive tract,
    - The **appendix**,
    - The **tonsils**.

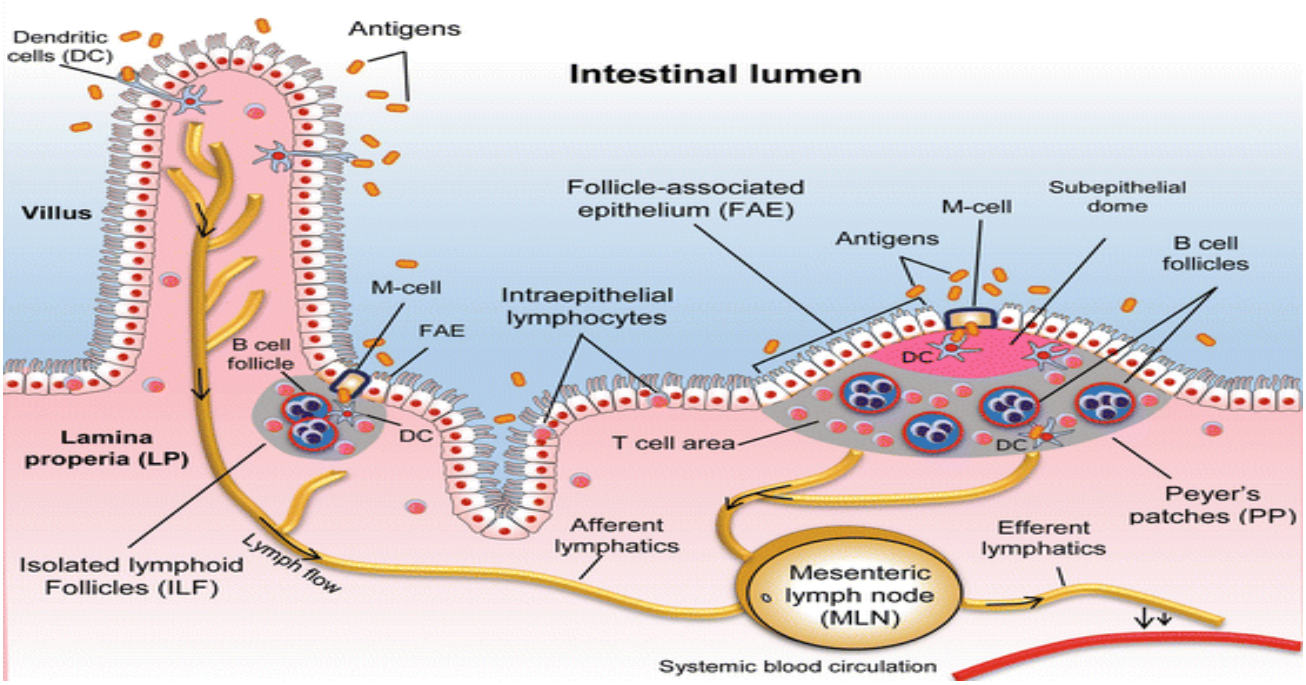

Figure 8: Peyer's patches in the digestive tract

- **Cutaneous and mucosal lymphoid systems** are found beneath the **epithelial layers of the skin and mucosal tracts (gastrointestinal, respiratory, etc.)**. At any given time, **more than half of the body's total lymphocytes** are located within mucosal tissues, reflecting their **vital role in immune defense**. Many of these lymphocytes are **memory cells**.
- Both **cutaneous and mucosal lymphoid tissues** serve as **sites for immune responses against antigens that penetrate epithelial barriers**, ensuring **rapid and effective immune protection**.

I-2 Immune System Cells

Immune cells are generally classified into **innate immunity cells** and **adaptive immunity cells**.

- **Innate immunity cells** can **rapidly activate** in response to pathogens but **do not generate immunological memory**.
- **Adaptive immunity cells** take longer to activate because they require **specific antigen recognition**, but they can establish a **memory response**, allowing for faster and stronger reactions upon future exposures.

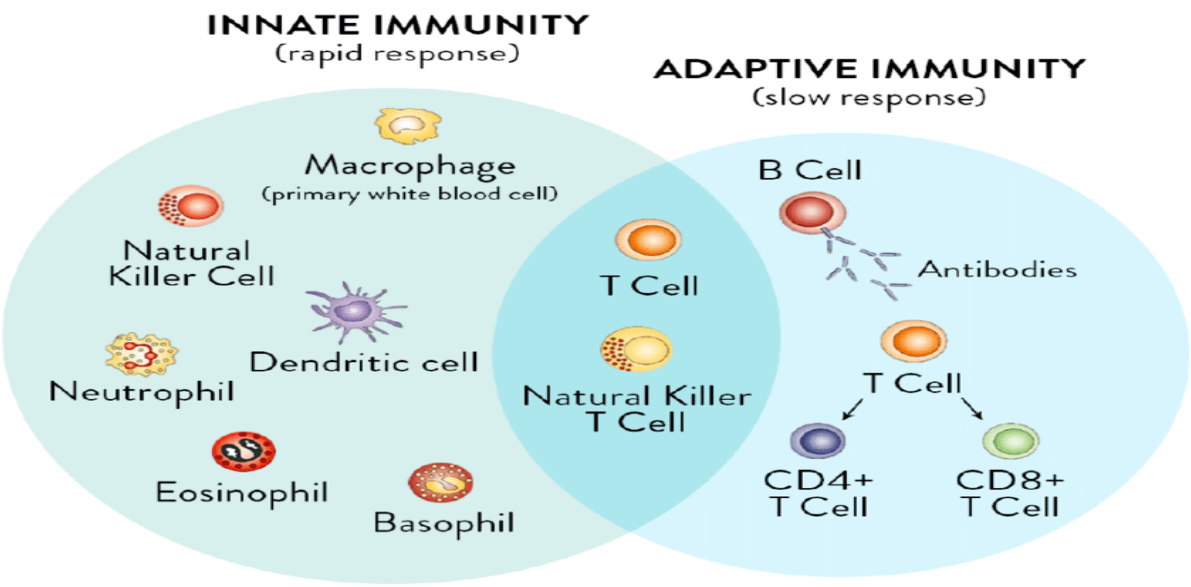

Figure 9: Immun Cells

A. Innate Immunity Cells

Among the **innate immune cells**, **neutrophils, monocytes/macrophages, and dendritic cells** play a crucial role in **phagocytosing and destroying** foreign elements. They recognize **pathogen-associated molecular patterns (PAMPs)**, which are characteristic microbial molecules, as well as **danger-associated molecular patterns (DAMPs)**, which indicate cellular stress. This recognition occurs through **pattern recognition receptors (PRRs)**.

Additionally, **natural killer (NK) cells** are part of the innate immune system and function by **eliminating virus-infected cells and tumor cells**.

1. Granulocytes

Granulocytes are divided into **three distinct types**: **neutrophils, eosinophils, and basophils**.

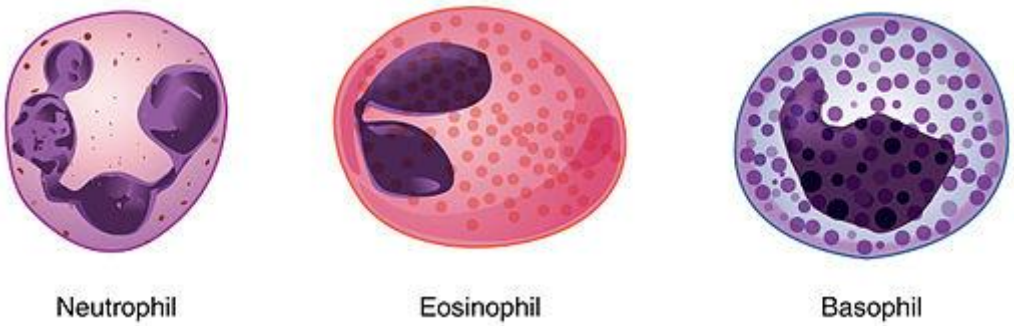

Figure 10: Granulocytes

➢ **Neutrophils**

- The most abundant granulocytes in the bloodstream, characterized by their **multilobed nucleus**.
- Play a **key role in antimicrobial defense** and **acute inflammation** through **phagocytosis** and the release of **cytoplasmic granules** (containing over 100 different enzymes).
- **First immune cells recruited** to infected tissues in response to **bacterial infections**, guided by **chemotactic factors**.
- Have a **very short lifespan** once they reach the tissues.

➢ **Eosinophils**

- Recognizable by their **bilobed nucleus** and **reddish-orange granules**, which are **cytotoxic** and **pro-inflammatory** due to their basic nature.
- Mainly found in tissues.
- Play a **critical role in anti-parasitic defense** and contribute to **certain hypersensitivity reactions**.

➢ **Basophils**

- Contain a **bilobed nucleus**, which is often difficult to see due to the abundance of **metachromatic granules**. These granules contain **histamine** and other **acidic, cytotoxic, and pro-inflammatory molecules**.
- Their **tissue equivalent is the mast cell**, which is abundant in **mucosal tissues** and contributes to **anti-infectious responses**.
- Both **basophils and mast cells** are **key players in immediate hypersensitivity reactions** (e.g., allergic responses).

2. Monocytes/Macrophages

Monocytes are **circulating immune cells** that contain **granular cytoplasm rich in enzymes**. Although **less abundant** than granulocytes, they travel in the bloodstream and **adhere to vascular walls** before migrating into tissues in response to **chemotactic factors**. Once inside the tissues, they **differentiate into macrophages**.

Macrophages have been given **specific names depending on their tissue location**:

- **Küpffer cells** in the liver
- **Microglia** in the brain
- **Mesangial cells** in the kidney
- **Osteoclasts** in bone

These are **highly phagocytic cells**, capable of engulfing a wide range of elements, including **particulate antigens, macromolecules, microbes, cells, or cellular debris**. After **destroying** these elements, they **present antigens to adaptive immune cells**, bridging **innate and adaptive immunity**.

Macrophages also **produce cytokines**, which regulate various stages of the immune response, including **tissue repair** after an immune reaction.

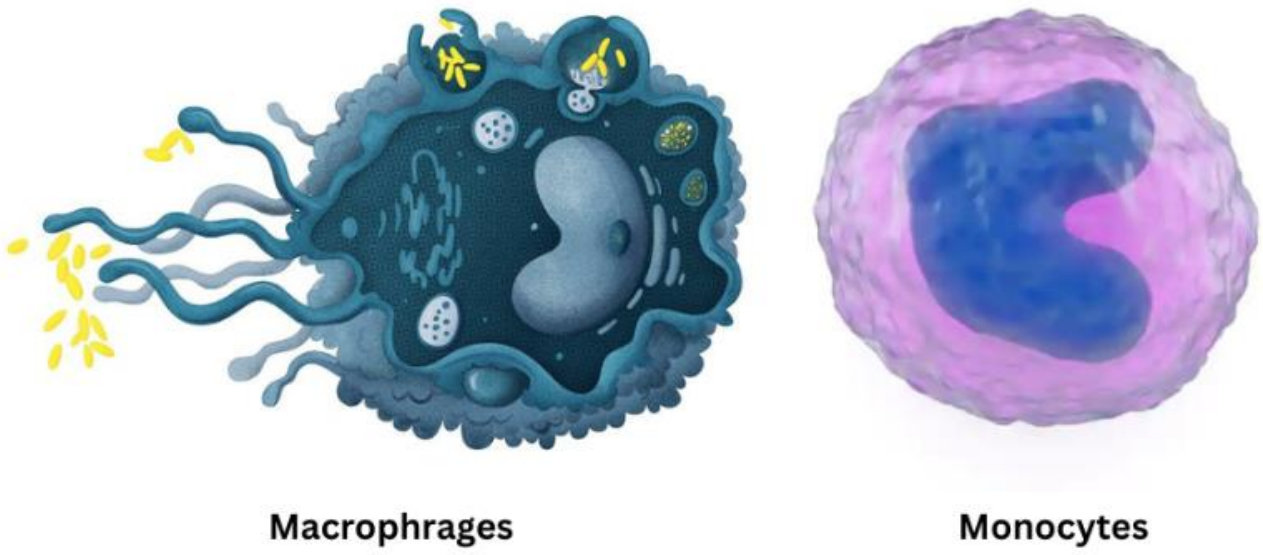

Figure 11: Macrophages and Monocytes

3. Dendritic Cells

Dendritic cells are found in **many tissues and organs** in an **immature state**, where they specialize in **antigen capture**. However, when they **leave the tissues and migrate to lymphoid organs**, they **undergo maturation**, losing their antigen capture ability but gaining the ability to **present antigens to T lymphocytes**.

Dendritic cells are the **most important antigen-presenting cells (APCs)** because they are capable of **activating naïve T lymphocytes**, making them **key initiators of the adaptive immune response**.

There are **several types of dendritic cells**, each with distinct functions, but they all play a major role in coordinating the immune response.

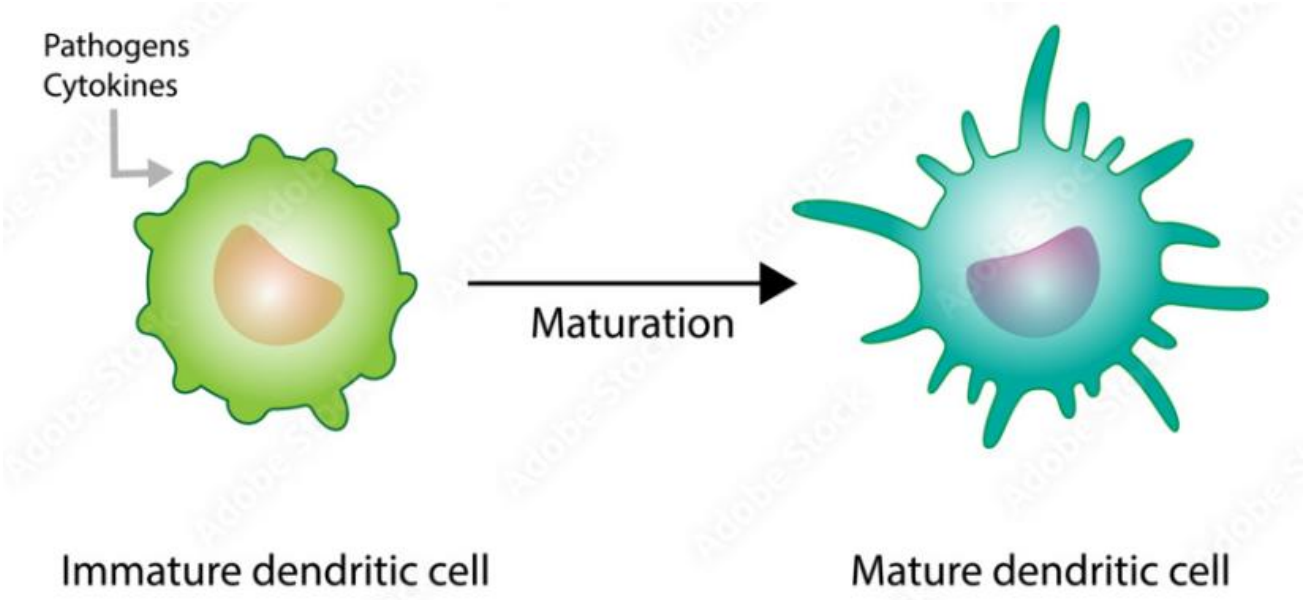

Figure 12: Dendritic Cells

4. Natural Killer (NK) Cells

Natural Killer (**NK**) cells are **cytotoxic lymphocytes** found in the **bloodstream and peripheral lymphoid organs**. They play a **crucial role** in innate immunity by recognizing and destroying **infected, damaged, or antibody-tagged (IgG-coated) cells**.

Unlike T and B lymphocytes, NK cells do not require **prior antigen sensitization**. Instead, they rely on a balance of **activating and inhibitory receptors** to distinguish between **healthy and abnormal cells**. In addition to their cytotoxic activity, NK cells are **potent cytokine producers**, especially **interferon-gamma (IFN-γ)**, which helps modulate immune responses and enhance macrophage activity.

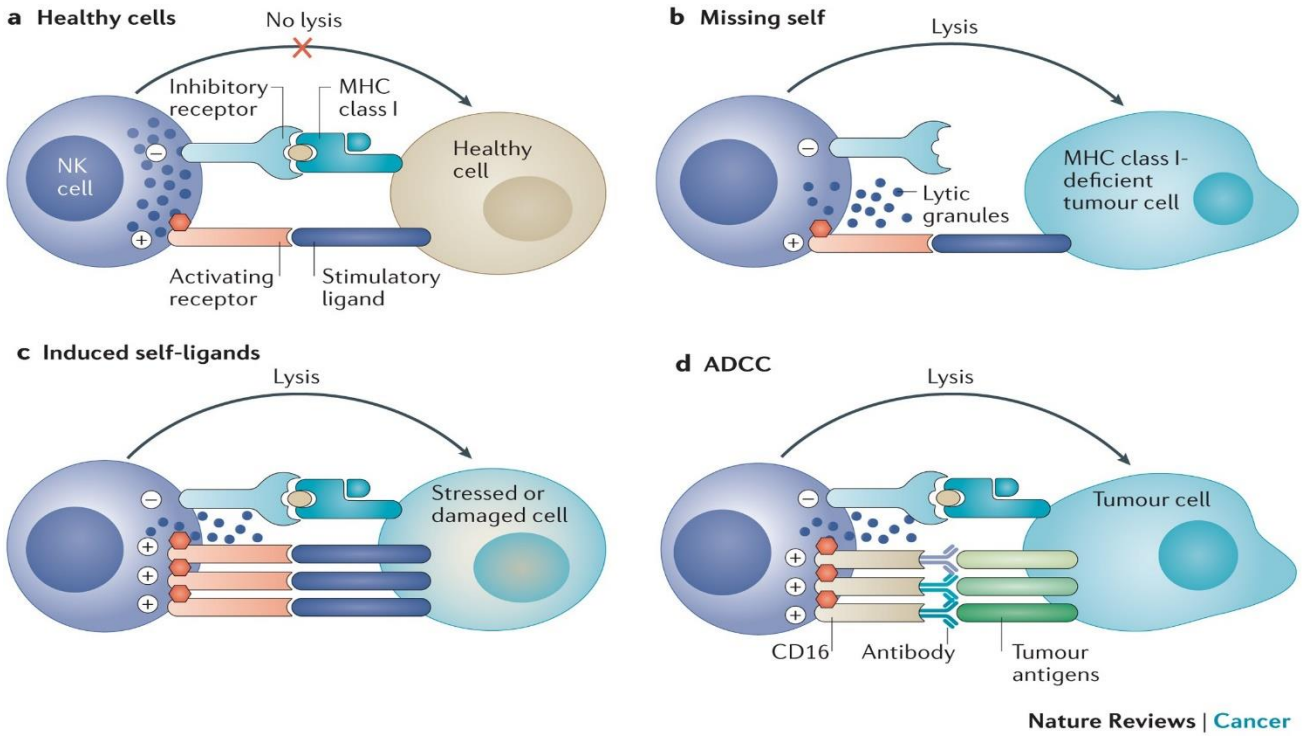

Figure 13: Mechanisms of actions of natural killer cells

B. Cells of Adaptive Immunity

- The primary cells of adaptive immunity are **B and T lymphocytes**. B lymphocytes are responsible for the **humoral immune response** (antibody production), while T lymphocytes mediate **cellular responses** (helper, cytotoxic, or regulatory). Both B and T lymphocytes have a similar morphology, with a **high nucleus-to-cytoplasm ratio** and no granulation. They are capable of specifically recognizing antigens via their **immunoreceptors**: the **BCR** (B-cell receptor) and **TCR** (T-cell receptor). The **BCR** binds to the **native antigen**, while the **TCR** binds to antigens that are **processed and presented** as peptides associated with **MHC (Major Histocompatibility Complex)** molecules.
- There are **functional subpopulations** of T and B lymphocytes, distinguished by their **phenotype**, which refers to a set of **molecular characteristics** on their membranes, and their distinct **functional properties**.

For example, among T lymphocytes, there are **two major subpopulations**:

  - **Helper T cells (Th)**, which secrete **cytokines** and are responsible for organizing both **innate and adaptive immune responses**.

- **Cytotoxic T cells**, which induce the **death of cells presenting foreign antigens** (such as those infected by viruses or intracellular pathogens) or abnormal self-antigens (such as tumor cells).
  Additionally, there are **regulatory T cells**, which play a role in **regulating and inhibiting immune responses**.

- Beyond their role as precursors to **plasma cells** (which are primarily found in the bone marrow and are responsible for producing large quantities of antibodies over a long period), B lymphocytes also act as **antigen-presenting cells (APCs)** to **T lymphocytes**. This property is key for the **cellular cooperation** between T and B lymphocytes, allowing regulation of their activation and, in turn, **antibody production**. During immune responses, both B and T lymphocytes give rise to **long-lived memory cells**, which are essential for responding more effectively to **subsequent exposure** to the same antigen (the **secondary response**).

I-3 Soluble Mediators

Numerous circulating mediators derived from immune and surrounding tissue cells participate in the initiation, maintenance, and regulation of immune responses. The main ones are as follows:

I-3-1 Cytokines

A. Generalities and Definitions:

- The development and functioning of all biological systems require intercellular communication, which relies on either direct and specific contacts between different cell types or the action of soluble mediators.

- **Cytokines** are small soluble mediators, essential for immune and inflammatory responses, as well as hematopoiesis.

- Cytokines are produced during the induction and effector phases of both **innate** and **adaptive immunity** and are involved in mediating and regulating immune and inflammatory responses. Some also play a significant role as growth factors.

- These cytokines are generally **protein-based**, often glycosylated, and have a low molecular weight (8 to 50 kDa). Their synthesis is inducible, and they act on target cells by interacting with specific **cell surface receptors**.

- Cytokines are **nonspecific mediators** that can have one or multiple cellular sources and one or multiple cellular targets.

Essential properties of cytokines:

- **Redundancy**: Different cytokines can have identical actions.
- **Pleiotropism**: A given cytokine can act on several different cell types and elicit different effects on a single cell type.

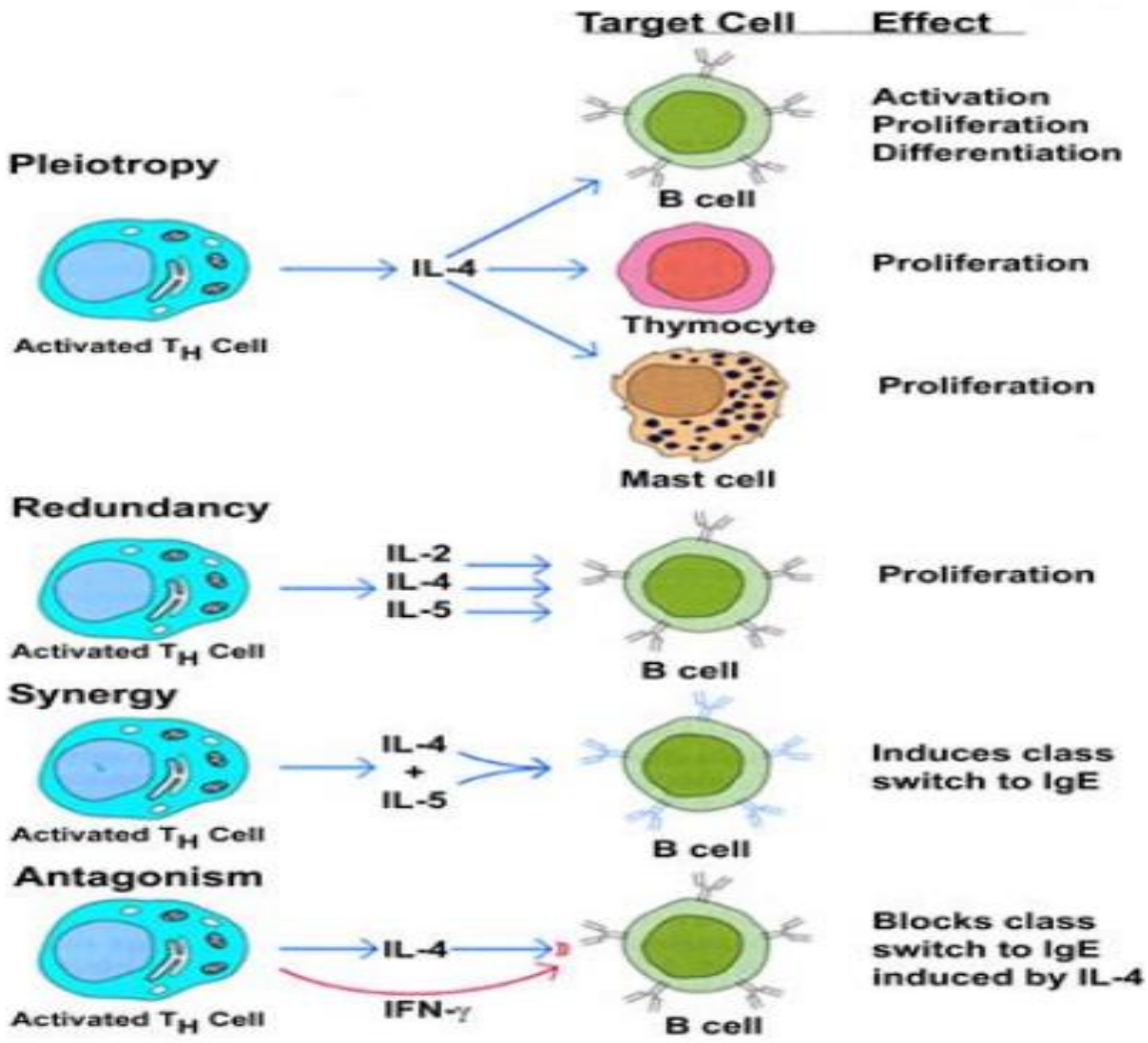

Figure 14: Essential properties of cytokines

Modes of Action:

- **Autocrine**: The cytokine acts on the producer cell itself.
- **Juxtacrine**: The cytokine acts locally on adjacent cells.
- **Paracrine**: The cytokine acts locally within the vicinity of the producer cell.
- **Endocrine**: The cytokine acts on target cells at a distance after being transported through the bloodstream.

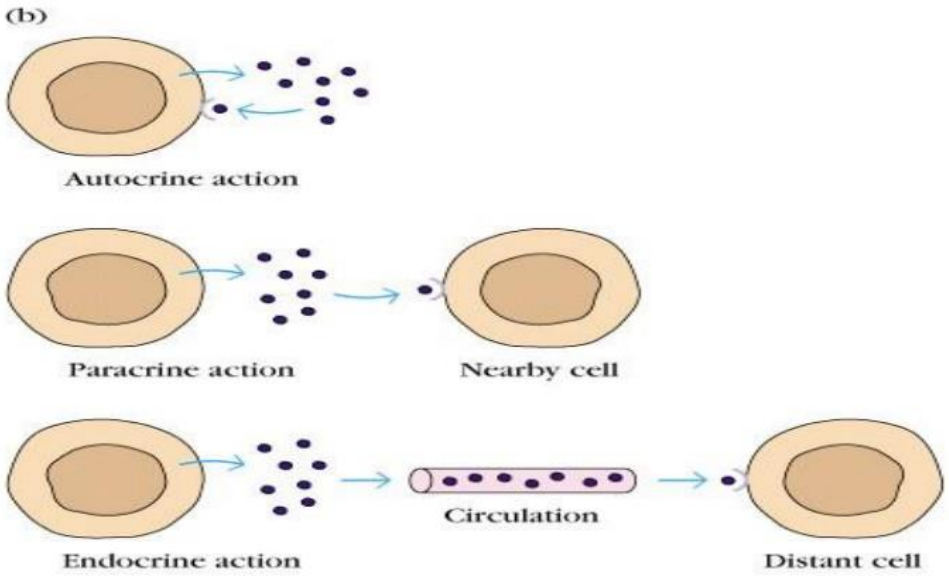

Figure 15: Mode of actions of cytokines

B. Cytokine-Receptor Binding Effects (Signal Transduction):

- The signal transmission occurs through intracellular molecules (such as **JAK** and **STAT**), activating transcription factors to induce the transcription of target genes.
- When a cytokine binds to its receptor, it leads to the transcription of specific genes and the synthesis of proteins responsible for the cytokine's biological activities.
- The signal transfer from the receptor at the membrane to the nucleus involves a cascade of phosphorylation events, leading to activation of transcription factors.
- The various signal transduction pathways provide flexibility, allowing diverse biological effects within the same cell type, including signals for **proliferation**, **inhibition**, **differentiation**, **activation**, **protein synthesis**, **mobility**, and **apoptosis**.

C. Functional Classification of Cytokines: Different classifications of cytokines exist. We adopt a classification based on the type of immune response involved, distinguishing:

- **Cytokines of immune responses**, which include almost all **interleukins**, as well as **IFN-γ** and both forms of **TNF** (α and β).
- **Antiviral cytokines**, including type 1 **interferons (IFN-α and IFN-β)**, type 2 **IFN-γ**, and **IL-16**.
- **Inflammatory cytokines**, including pro-inflammatory cytokines (**IL-1**, **TNF**, **IL-6**) and anti-inflammatory cytokines (**IL-1Ra**, **IL-10**, **TGF-β**).

- **Hematopoietic cytokines**, which include various growth factors (such as **CSF**), as well as **IL-3**, **IL-5**, and **IL-7**.
- **Chemokines**, involved in the recruitment of cells to the site of interest.

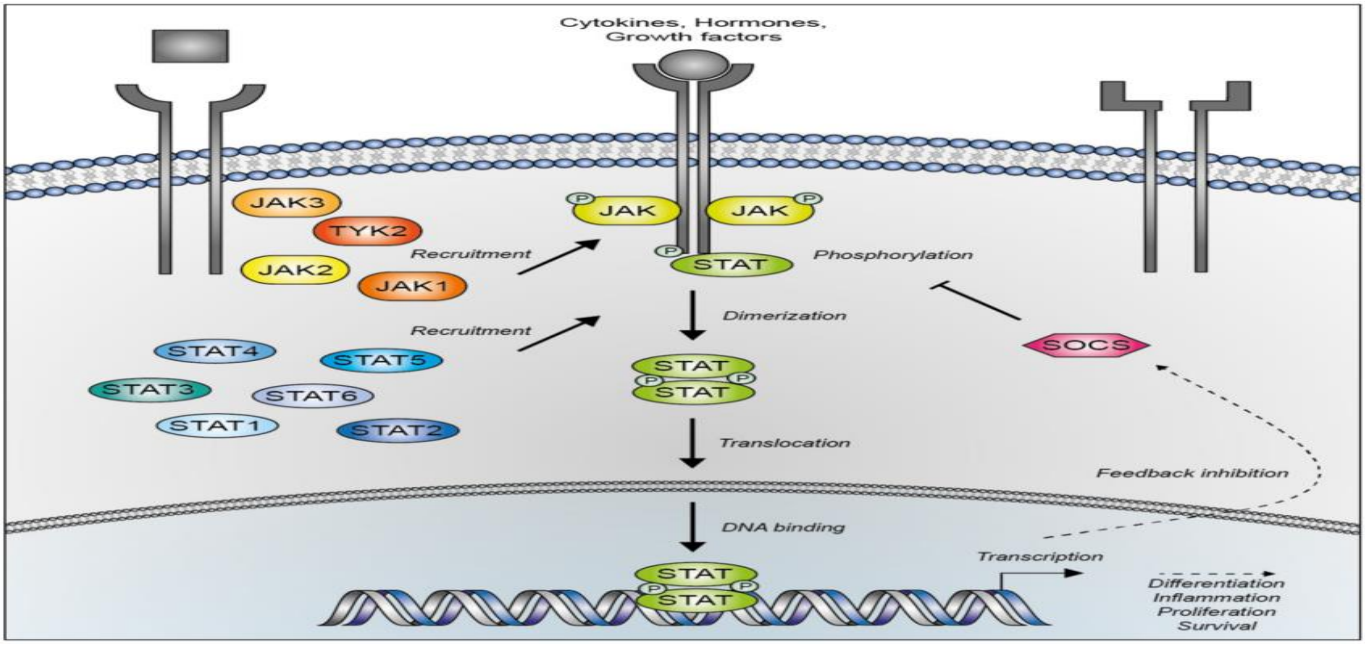

Figure 16: Cytokines signal Transduction

I-3-2 The Complement System

The complement system consists of an array of **mostly circulating proteins**, making up about 5% of the total plasma proteins. The system can be activated via three complementary activation pathways, ultimately converging on the formation of a **membrane attack complex** that causes the lysis of infectious microorganisms. Additionally, many cleavage products of complement proteins are involved in innate immunity, including the opsonin **C3b** and the anaphylatoxins **C3a** and **C5a**. Further details on the complement system are provided in **Chapter 2**.