The immune system consists of a complex network of specialized organs and tissues through which innate and adaptive immune cells continuously circulate. This interconnected communication network provides the immune system with three essential properties:

1. **A significant capacity for information exchange**, either through intercellular membrane contacts or the release of soluble mediators. These exchanges occur between immune system components (e.g., interactions between innate and adaptive immune cells) as well as with other physiological systems (e.g., neuro-immune-endocrine interactions).
2. **An efficient effector mechanism** capable of protecting the body's integrity.
3. **A strong regulatory system**, which is crucial to maintaining immune system balance (homeostasis) at all times and ensuring an appropriate immune response.

II.1. B Cells and Lymphoid Organs

To optimize the essential cellular interactions involved in the recognition, activation, and effector stages of the immune response, most immunocompetent cells are grouped within lymphoid organs. These organs are interconnected and linked to the general bloodstream. Lymphoid organs are classified into two categories:

A) Primary (Central) Lymphoid Organs

In mammals, these include:

- **Bone marrow**: The site of lymphopoiesis and B cell maturation.
- **Thymus**: The site of T cell maturation.

B) Secondary (Peripheral) Lymphoid Organs

These include:

- **Lymph nodes**
- **Spleen**
- **Mucosa-associated lymphoid tissues (MALT)**, which are found in mucosal surfaces such as the respiratory, gastrointestinal, and urogenital tracts

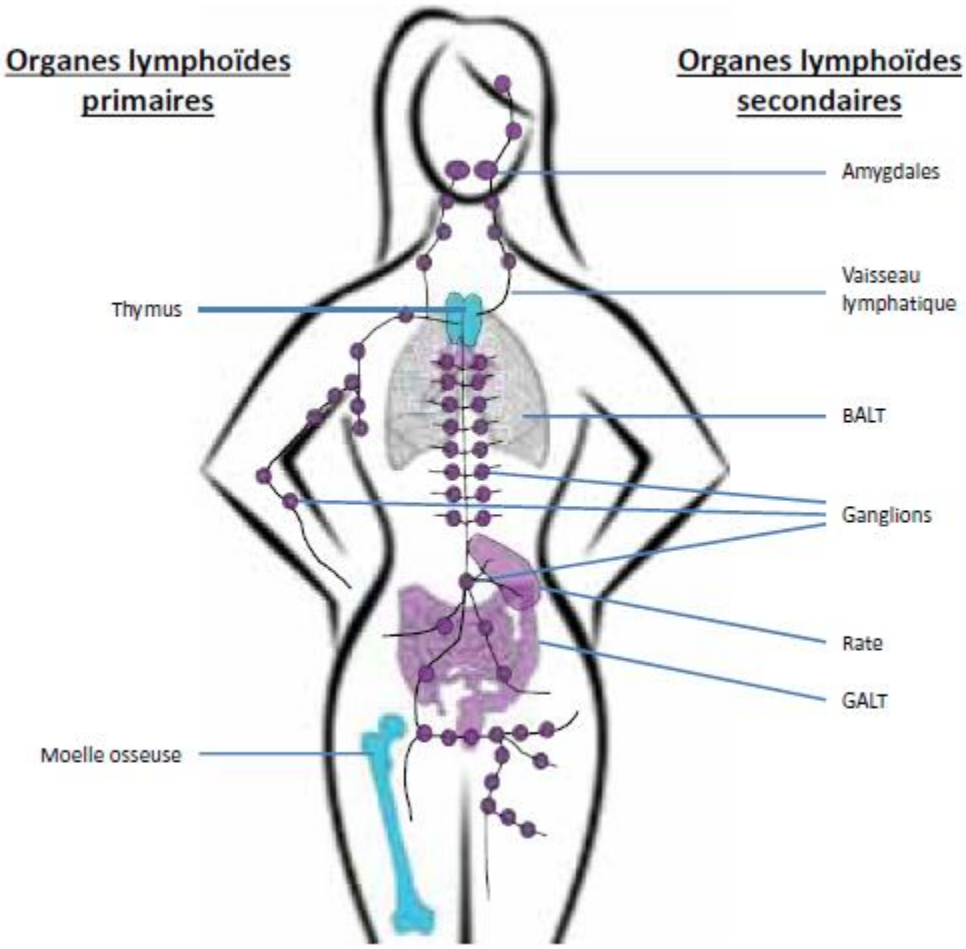

Fig 4: Localization of Primary and Secondary Lymphoid Organs.

II.1.1. Primary (Central) Lymphoid Organs

The central lymphoid organs are the sites of lymphocyte maturation and differentiation. The development of these lymphocytes occurs entirely independently of antigen presence and is regulated by the inductive activity of the epithelium-derived reticulum.

These organs exhibit intense mitotic activity, which facilitates the genetic rearrangements necessary for the creation of membrane glycoproteins that specifically recognize antigens (TCR, BCR). Only lymphocytes with functional rearrangements will migrate out of these organs, which serve as the site for the acquisition of the antigenic repertoire as well as the learning of self-tolerance.

II.1.1.1. Bone Marrow

Bone marrow is not solely a lymphoid organ, as it is also the site of **hematopoiesis** (the production of blood cells), containing all blood cell lineages. It is located at the center of bones, including the **vertebrae, ribs, pelvis, humerus, and femur**.

In addition to being the site of hematopoiesis, bone marrow is where **B lymphocytes (B cells) mature**, from the acquisition of the **B cell receptor (BCR)** to the **negative selection** of self-reactive B lymphocytes. This maturation occurs in the **bone marrow stroma**, progressing from the outer surface of the medullary cavity toward the center, where the most mature cells are concentrated. The process is facilitated by **cellular interactions and signals from stromal cells**.

In humans, bone marrow has **three main functions in lymphopoiesis**:

- It functions as a **hematopoietic organ**, maintaining a constant supply of **T and B lymphocyte precursors**.
- It serves as the **primary lymphoid organ for B cell lineage**.
- It hosts a portion of **antigen-activated B lymphocytes**, which differentiate into **plasma cells** that secrete antibodies.

II.1.1.2. Thymus

The **thymus** is the site of **maturation and education (selection process) of T lymphocytes (T cells)**. It is a **median, 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 **trabeculae**—invaginations of the surrounding capsule. Within these lobules, two distinct regions can be identified:

- The **outer cortical zone (cortex)**
- The **inner medullary zone (medulla)**

Lymphoid precursors originating from the **bone marrow** enter the thymus through **post-capillary venules** located at the **corticomedullary junction**. From there, they migrate first to the **cortex** and then toward the **medulla**. These regions have different cellular compositions, facilitating various maturation processes aimed at preserving **thymocytes** that possess a **functional T-cell receptor (TCR)** with **limited self-recognition capacity**.

- **The cortex** is densely populated with **immature thymocytes** and contains a few **macrophages**.
- **The medulla** contains **fewer thymocytes** but has a higher number of **macrophages and dendritic cells**.

In addition to **thymocytes** at various stages of development, the **thymus** also consists of:

- **Epithelial cells and fibroblasts** in the **cortex**
- **Macrophages and dendritic cells** in the **medulla**

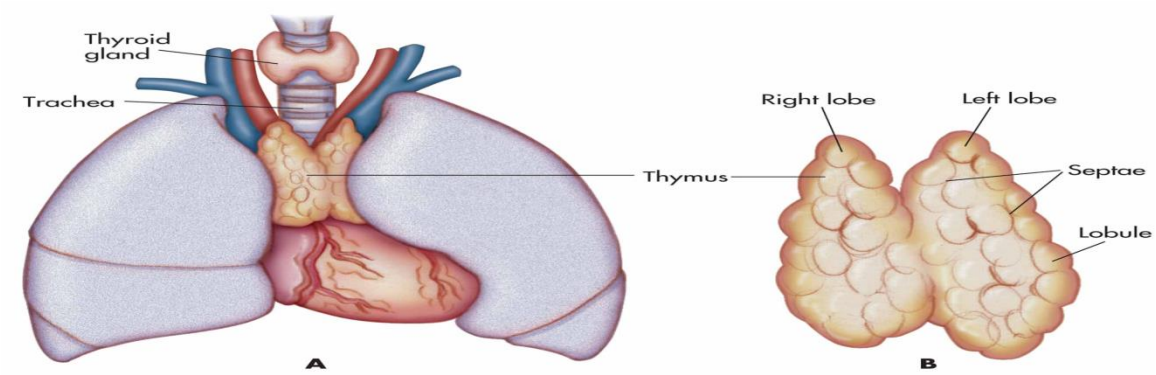

Fig 5: Thymus

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

II.1.2. Secondary Lymphoid Organs

Secondary lymphoid organs are specialized structures that receive T lymphocytes from the thymus and B lymphocytes from the bone marrow. These peripheral organs are where immune cells encounter antigens arriving through the lymphatic system, bloodstream, or mucosal epithelium.

Secondary lymphoid organs are divided into two categories:

- **A systemic compartment**, responsible for the **immune protection of the internal environment**. This includes:
    - The **spleen**
    - Most **lymph nodes**
    - Part of the **diffuse lymphoid system**
    - The predominant immunoglobulin (antibody) is **IgG and IgM**.
- **A mucosal compartment** specialized in **mucosal defense**. This includes:
    - **Diffuse lymphoid tissue** in mucosal layers
    - **Lymph nodes** draining these areas
    - **The mammary gland**
    - The predominant immunoglobulin in this compartment is **secretory IgA (sIgA)**.

II.1.2.1. The Spleen

The **spleen** is the **largest secondary lymphoid organ**, weighing approximately **150 to 200 grams**. It has an **oval shape** and is located in the **left hypochondrium** (upper left abdomen). Unlike other lymphoid organs, the **spleen is exclusively connected to the bloodstream**, which it **filters** through its **extensive vascularization**, allowing it to perform **immune surveillance of bloodborne antigens**.

During **embryonic development**, the spleen initially functions as a **hematopoietic organ**, similar to the **fetal liver**. After birth, the spleen consists of two main regions:

- **Red pulp** (**99% of its volume**), rich in **macrophages**, primarily responsible for the **breakdown of red blood cells (erythrocytes)**.
- **White pulp** (**1% of the spleen's mass**), located around **arterioles**, where **immune responses** are initiated.

The **white pulp** is mainly composed of **lymphocytes** and is divided into:

- A **central T-cell zone (T zone)**, rich in **T lymphocytes**.
- A **peripheral B-cell zone (B zone)**, rich in **B lymphocytes**.

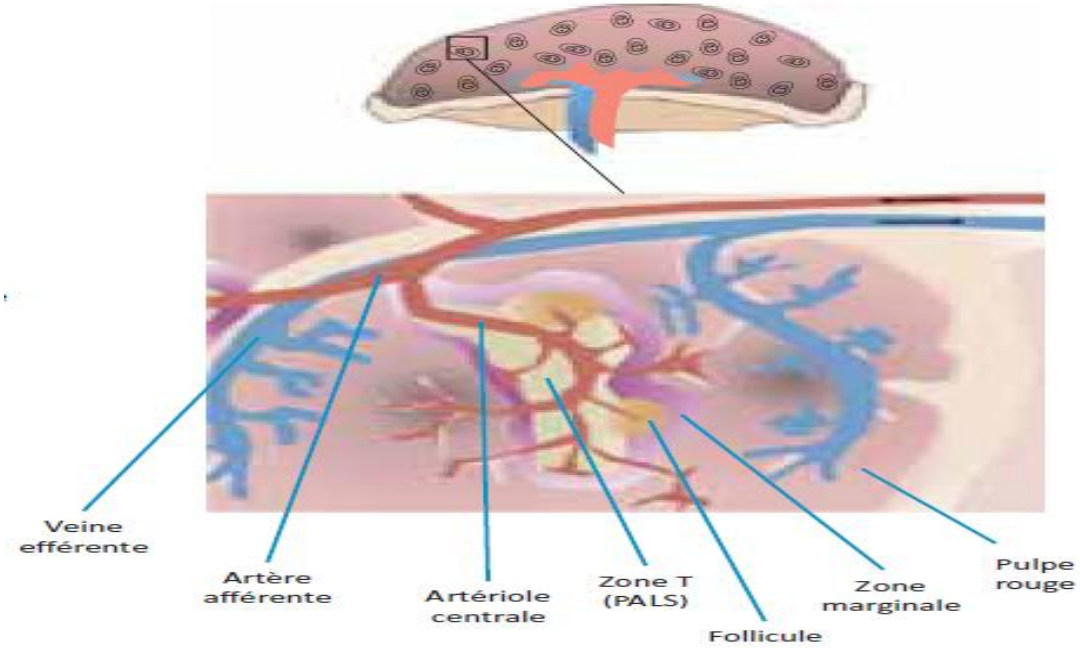

Fig 6: The spleen

II.1.2.2. Lymph Nodes

Lymph nodes are **capsulated**, round or kidney-shaped structures measuring **1 to 15 mm in diameter**, with **500 to 1,000 nodes** present in the human body. They are **distributed throughout the body** to monitor various regions, draining **lymph** from **interstitial fluid** that bathes tissues through their **afferent lymphatic vessels**.

Lymph nodes function as **filters**, concentrating **soluble antigens** or those captured by **antigen-presenting cells (APCs)**. Their **strategic position at the intersection of blood and lymphatic circulation** optimizes **antigen detection** by immune cells, facilitating the **initiation of adaptive immune responses**.

The **lymph node parenchyma** is divided into three distinct regions:

1. **The Cortex**:
    a. The **outermost** and **subcapsular** region.
    b. Contains mostly **B lymphocytes**.
2. **The Deep Cortex (Paracortex)**:
    a. The **middle region** of the lymph node.
    b. Rich in **T lymphocytes** and **dendritic cells**, which strongly express **MHC class II** to present antigens to T cells.
    c. **Primary site of T-cell immune response induction**.
3. **The Medulla**:
    a. The **deepest region**, located near the **hilum**, where lymph exits the node.
    b. Rich in **B lymphocytes**, but primarily contains **plasma cells**, which are responsible for **antibody production**.
    c. Also contains **numerous macrophages**.

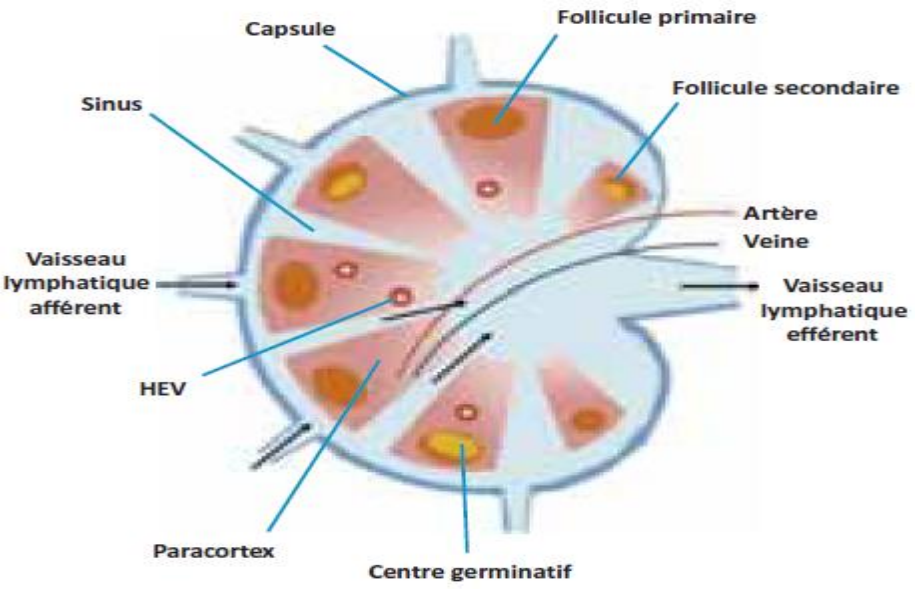

Fig 7: Lymph Nodes

I.1.2.3. Mucosa-Associated Lymphoid Organs

Mucosa-associated lymphoid organs fall under the collective term **Mucosa-Associated Lymphoid Tissue (MALT)**. This includes numerous and diverse **lymphoid structures**, representing **80% of the body's total lymphoid tissue mass**. MALT plays a **crucial role** in protecting against **antigens that enter through mucosal epithelia**, which collectively cover a surface area of over **400 m²** (including the **respiratory, digestive, and urogenital mucosa**).

MALT consists of **diffuse lymphoid tissues** as well as **organized structures**, such as:

- **Peyer's patches** in the digestive tract
- **The appendix**
- **The tonsils**

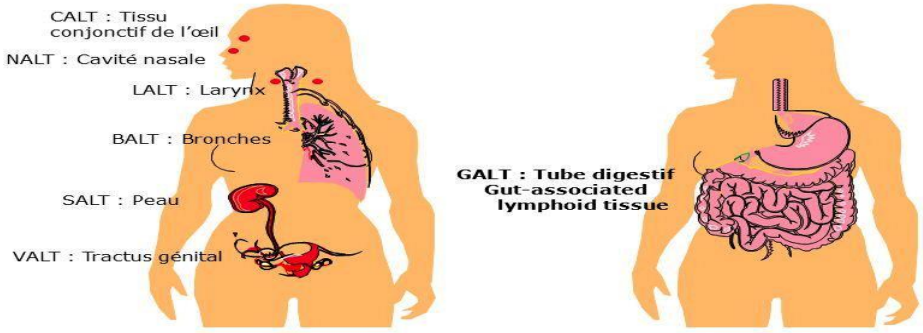

Fig 8: Mucosa-Associated Lymphoid Organs

II.1.3. B Lymphocytes

B lymphocytes (B cells) derive their name from the **"Bursa of Fabricius"**, an organ in birds where B cells mature. In humans, however, **B cells mature in the bone marrow**. They are characterized by the presence of a **B-cell receptor (BCR)**, which enables them to recognize **antigenic fragments**.

B lymphocytes play a key role in **humoral immunity**, which involves the production of **specific antibodies (immunoglobulins) against pathogens**.

Once activated, a **naïve B lymphocyte** can differentiate into:

- **Plasma cells**, which actively **produce antibodies**.
- **Memory B cells**, which provide **long-term immunity** by rapidly responding to future infections by the same pathogen.

II.1.4. B Cell Education in the Bone Marrow

B lymphocytes develop from **stem cells** that colonize the **bone marrow** around the **14th week of fetal development**. Their development is heavily dependent on **interactions with cytokines** and **stromal cells** in the bone marrow. Among the **key cytokines**, **interleukins 1, 6, and 7** play the most crucial roles. The **bone marrow remains the primary site of B cell production throughout life**.

B cell Development Occurs in 2 phases:

1. **Antigen-Independent Phase (Lymphopoiesis):**
    - Takes place in the **bone marrow**.
    - Results in the formation of **naïve B cells** with **membrane-bound antibodies** from **hematopoietic stem cells**.

Objective: Expression of **functional membrane-bound antibodies** that form the **B cell receptor (BCR)**, allowing antigen recognition.

2. **Antigen-Dependent Phase (Immunopoiesis):**
    - Occurs in **secondary lymphoid organs** (such as the **spleen and lymph nodes**).
    - Leads to the differentiation of **naïve B cells** into:
        - **Effector B cells (Plasma cells)**, which **produce antibodies**.
        - **Memory B cells**, which provide **long-term immunity**.

Objective: Differentiation of **B cells into plasma cells** that **secrete antibodies in response to a specific antigen**.

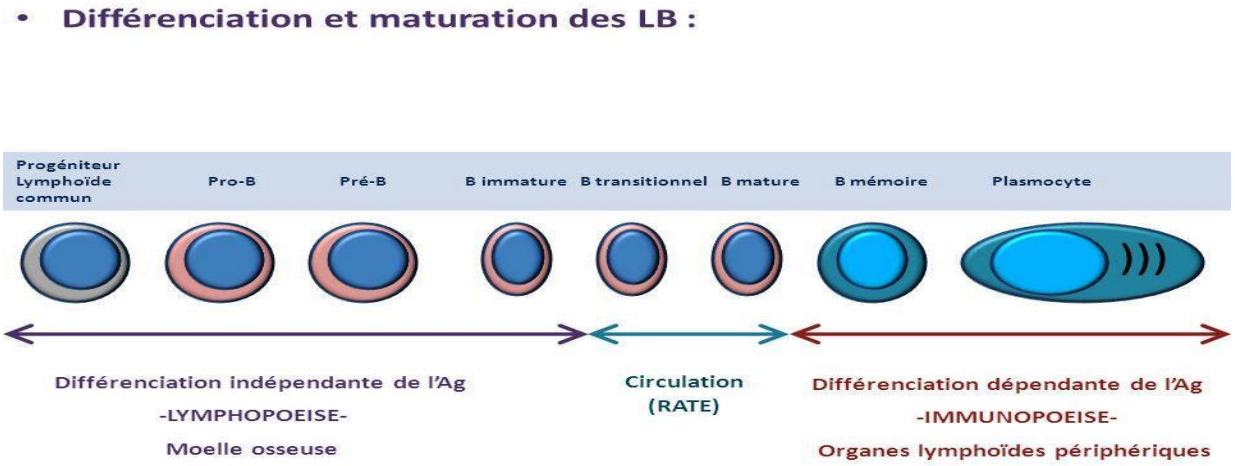

Fig 9: Lymphocytes B différenciation and maturation

II.2. T Cells and Thymic Education

T lymphocytes (T cells) play a crucial role in **adaptive immunity** as they **orchestrate, coordinate, and execute immune responses** to eliminate pathogens.

- **CD4+ T cells (T helper cells or Th cells)** act as **immune response mediators**, activating other immune cells to directly combat infections.
- **CD8+ T cells (cytotoxic T cells)** function as **killer cells**, directly destroying target cells that express specific antigens.

The majority of T cells express the **TCRαβ receptor**, but a small subset, **TCRγδ T cells (1–10% of total T cells),** is mainly found in **blood, skin, and mucosal tissues**.

T Cell Maturation in the Thymus

In the **thymus**, **immature T cells** interact with specialized **epithelial cells, dendritic cells, and macrophages**. These interactions facilitate **T cell selection and differentiation**, ensuring the development of functional immune cells.

Cytokines, such as **interleukins 1, 2, 6, and 7**, act as important **regulatory factors** in this process.

A **large majority of T cells**, especially those that could be **harmful to the body**, are **eliminated** during selection to prevent autoimmune reactions.

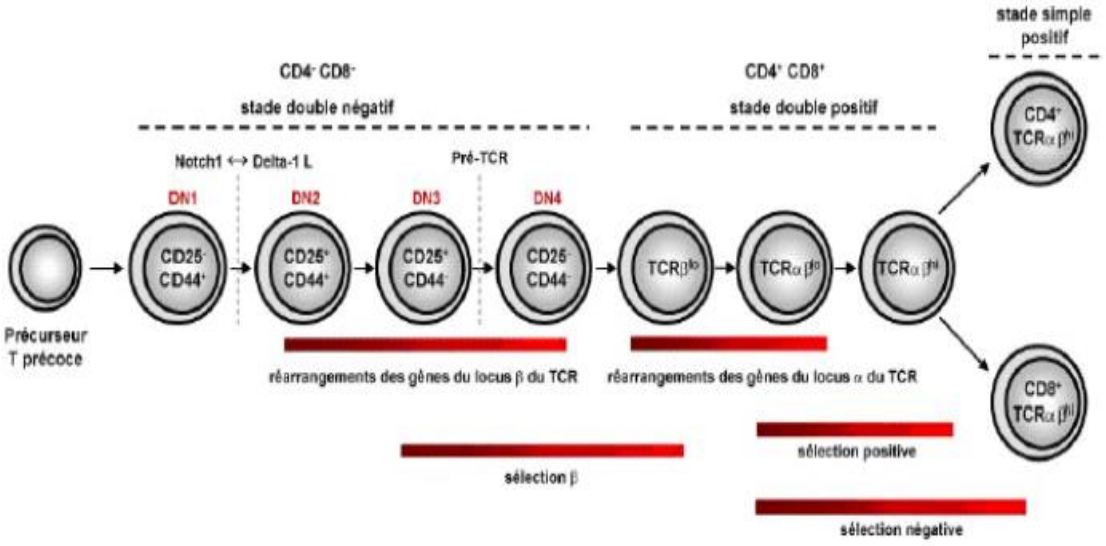

Figure 10: Lymphocytes T différenciation and maturation.

II.3. Other Cells (Myeloid Cells)

II.3.1. Phagocytic Cells

Phagocytic cells act as the **scavengers** of the body, capable of engulfing bacteria and dead cells through **phagocytosis**. These include **macrophages, dendritic cells, and granulocytes (polymorphonuclear cells).**

a) Monocytes

Monocytes are **immature blood cells** from the leukocyte family, originating from **bone marrow**. Once they migrate into tissues, they differentiate into **macrophages and dendritic cells**.

b) Macrophages

Macrophages are the **primary phagocytic cells**, derived from monocytes. They can also function as **antigen-presenting cells (APCs)**, though less efficiently than dendritic cells. They present **MHC class II molecules** and express **CD4, B7, and CCR5 receptors**, along with most **pattern recognition receptors (PRRs)**.

Each tissue contains **resident macrophages** with specialized names:

- **Kupffer cells** (liver)
- **Microglial cells** (nervous system)
- **Alveolar macrophages** (lungs)

c) Dendritic Cells

Dendritic cells are immune cells with **cytoplasmic projections (dendrites)**, found in all tissues, particularly the **epidermis and thymus**. They originate from either **myeloid (monocytes) or lymphoid precursors**.

- Function as **phagocytic cells and professional antigen-presenting cells (APCs)**
- Activate **both B and T lymphocytes** in **secondary lymphoid organs**
- Express **PRRs, CD4, B7, MHC class I and II molecules**

They play a **crucial role in initiating adaptive immune responses**.

d) Granulocytes (Polymorphonuclear Cells or PMNs)

Granulocytes originate from the **bone marrow** and are named **"polymorphonuclear"** due to their **multi-lobed nucleus** (a historical misnomer, as they are not multinucleated). They are classified into:

- **Neutrophils**: Most abundant in the blood, key players in **phagocytosis**, attracted to infection sites by **chemokines** released from macrophages and other cells.
- **Basophils**: Least abundant, play a major role in **allergic reactions**. They release **histamine** (induces inflammation) and **heparin** (prevents clotting and increases capillary permeability).
- **Eosinophils**: Specialize in **antiparasitic defense**, releasing **granules** to attack parasites, and play a **minor role in allergies**.

II.3.2. Mast Cells

Mast cells are **tissue-resident leukocytes** involved in **allergic reactions**. They are found in **connective tissues, lungs, lymph nodes, spleen, and bone marrow**.

- Function similarly to basophils, but are **tissue-resident**
- Express **Fc receptors (RFC) for IgE antibodies**, crucial in allergic responses
- **Effects**:
    - **Amplification of inflammation**
    - **Inhibition of blood clotting**
    - **Increased capillary permeability to facilitate immune cell migration (diapedesis)**

II.3.3. Natural Killer (NK) Cells

Natural Killer (NK) cells are **cytotoxic lymphocytes** found in **blood and peripheral lymphoid organs**.

- Destroy **infected, damaged, or IgG-tagged cells**
- Produce **cytokines like IFN-γ** to enhance immune responses
- Act as a **bridge between innate and adaptive immunity**

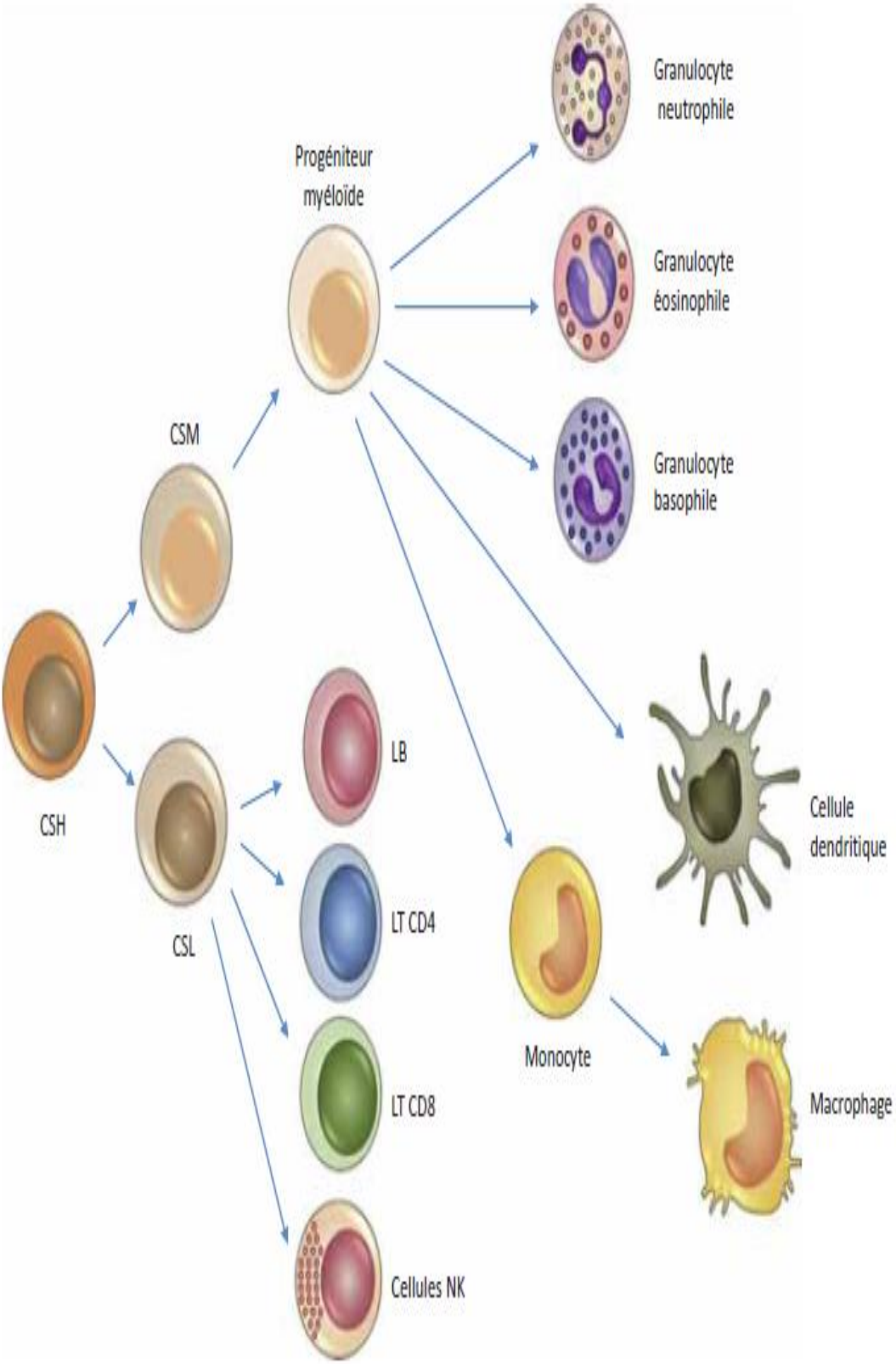

Fig 11: The cells of the immune system