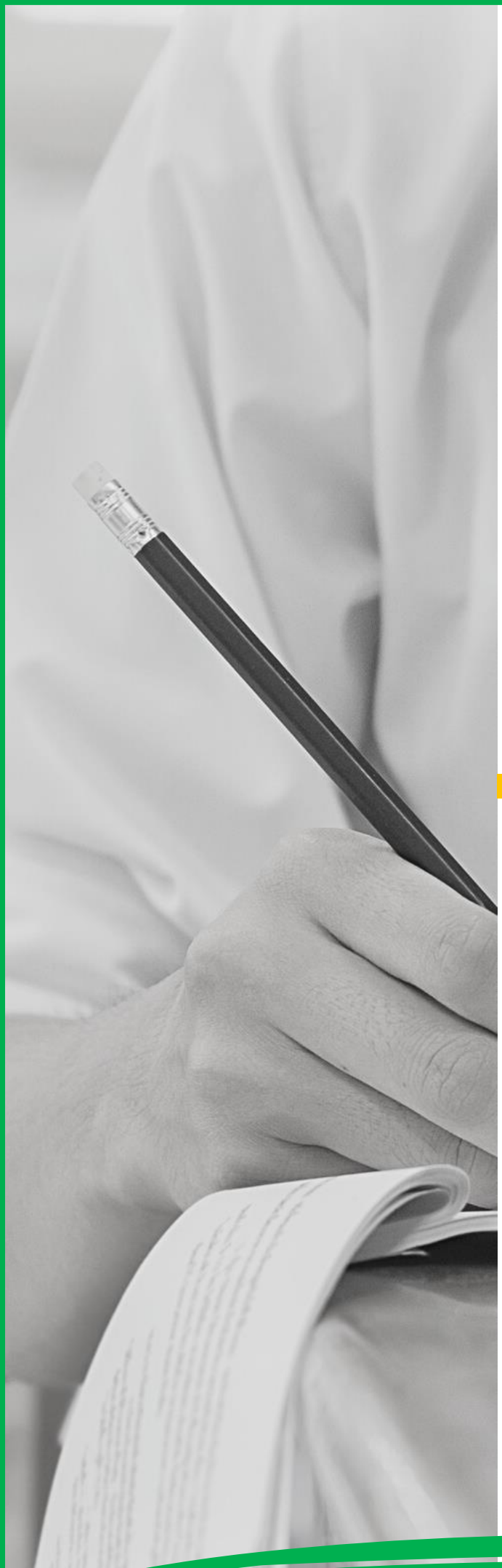

Tikrit University
College of Veterinary Medicine

Lecture 3: The Cellular Elements of Innate Immunity

Subject name: Immunology (Theoretical)
Subject year: Third Stage / 3rd Year
Lecturer name:
Assist.Prof.Dr. Agharid Ali Hussein
Prof.Dr.Bashar Sadeq Noomi
Academic Email:
agharidalrasheed@tu.edu.iq
vetbashae@tu.edu.iq

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Lecturers link

The Cellular Elements of Innate Immunity

By Assist.Prof.Agahrid Ali Hussein,PhD

Introduction

The immune system is a highly integrated defense network composed of specialized cells, tissues, and organs that work together to protect the body from infection, cancer, and foreign substances. Its components communicate through chemical signals and cell-to-cell contact, forming a dynamic equilibrium that maintains homeostasis. Understanding immune cells and their primary organs provides the foundation for studying all subsequent immune mechanisms — from antigen recognition to adaptive memory formation.

Key Terms

Hematopoietic stem cell (HSC); hematopoiesis; myeloid lineage; lymphoid lineage; granulocytes; antigen-presenting cell (APC); cytokines; chemokines.

1) Hematopoiesis: From HSCs to Immune Cells

Hematopoiesis is the continuous, life-long generation of blood cells from multipotent, self-renewing HSCs in the red bone marrow.

HSCs balance **quiescence** (to preserve the stem cell pool) with **proliferation** (to meet systemic demand). Local stromal cells and soluble factors (e.g.,**Granulocyte-Colony Stimulating Factor (G-CSF)**, **Granulocyte-Macrophage Colony-Stimulating Factor(GM-CSF)**, IL-3(myeloid cells), IL-7(lymphoid cells) tune lineage obligation and output, especially during infection or physiological stress.

Two principal branches emerge from progenitors:

- **Myeloid lineage: neutrophils, eosinophils, basophils, monocytes → macrophages, and dendritic cells, along with erythrocytes and megakaryocytes (platelets).**
- **Lymphoid lineage: B cells, T cells, NK cells, and innate lymphoid cells (ILCs).**

Granulocytes (neutrophils, eosinophils, basophils) contain cytoplasmic granules with potent antimicrobial mediators. **Agranulocytes** include lymphocytes and monocytes.

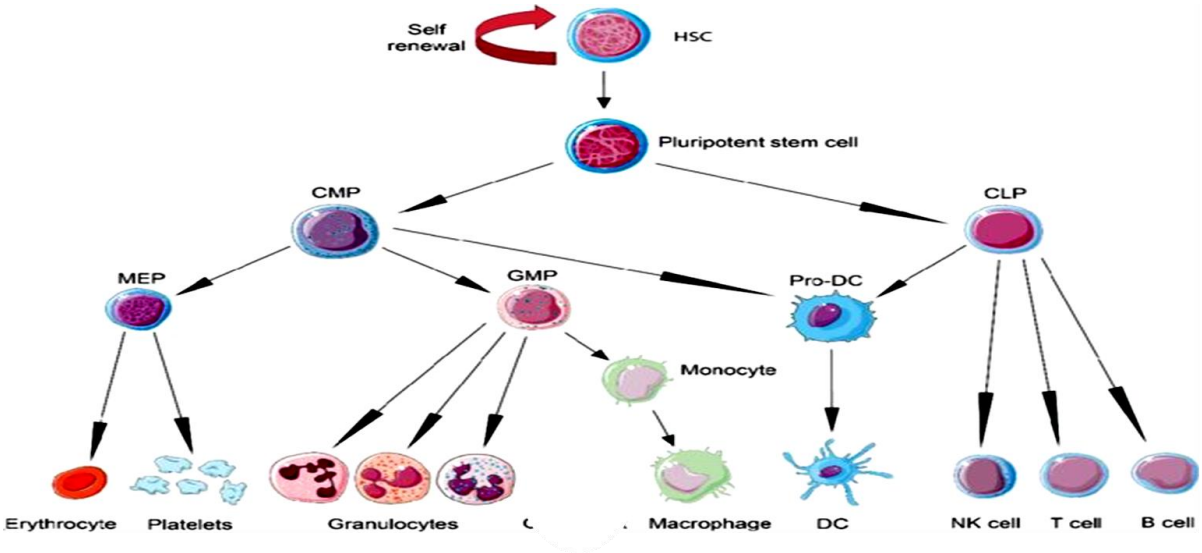


Figure 1. Hematopoiesis. HSC: Hematopoietic stem cell; CMP: Common Myeloid Progenitor; CLP: Common Lymphoid Progenitor; MEP: Megakaryoc yte/Erythroc yte Progenitor; GMP: Granuloc yte/Macrophage Progenitor; DC: Dendritic Cell.

Neutrophils

- **Neutrophils are the most abundant leukocytes, comprising 55–70% of circulating white blood cells. They represent the first line of cellular defense in the innate immune system and play a pivotal role in the early phase of inflammation. Defects in their number or function lead to severe bacterial infections, often fatal if untreated.**
- **Mature neutrophils are 12–15 µm in diameter, with a multilobed nucleus (3–5 lobes), hence termed *polymorphonuclear leukocytes (PMNs)*. They are produced in the bone marrow—about 100 billion per day—and have a short lifespan of only a few hours to days in circulation. Their cytoplasm contains three granule types, each specialized for microbial killing and tissue infiltration:**
- **Primary (Azurophilic) granules: contain *myeloperoxidase*, *defensins*, and proteases; essential for pathogen digestion and ROS generation.**
- **Secondary (Specific) granules: contain *lactoferrin* and *lysozyme*; contribute to bacterial degradation and immune modulation.**
- **Tertiary (Gelatinase) granules: contain *matrix metalloproteinases* aiding neutrophil migration through tissue.**
- **Key Functions:**
  1. **Phagocytosis – Engulfment and destruction of microbes via enzyme- and ROS-mediated killing.**
  2. **Degranulation – Release of antimicrobial enzymes within phagosomes or extracellularly.**
  3. **NET formation – Production of *neutrophil extracellular traps* (NETs) composed of DNA and antimicrobial proteins to immobilize pathogens.**
  4. **Inflammatory signaling – Secretion of cytokines and chemokines to recruit and activate other immune cells.**

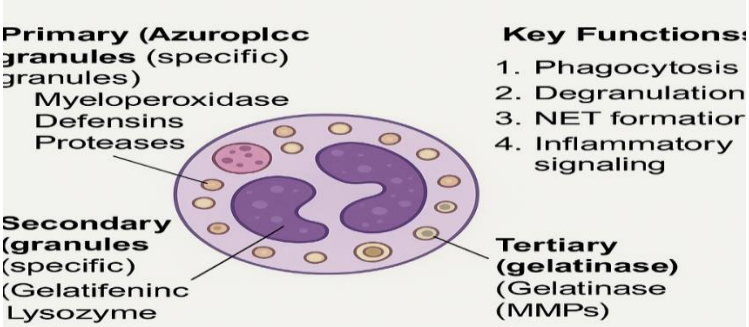


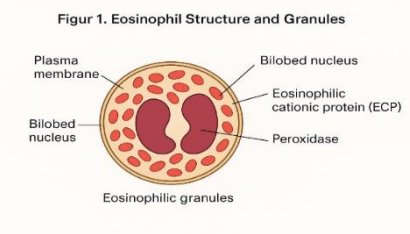
Figure. Neutrophil Granules and Functions

Eosinophils:

a) **Eosinophils are granulocytic leukocytes that contain cytoplasmic granules rich in enzymes and cationic proteins capable of damaging the cell walls of parasites and, in excess, host tissues.** Their granules stain intensely with acidic dyes such as **eosin**, owing to the presence of **basic proteins** like major basic protein (MBP) and eosinophil cationic protein (ECP).

b) Like neutrophils and basophils, eosinophils are **bone marrow–derived**. Their development from myeloid precursors is stimulated by **GM-CSF**, **IL-3**, and particularly **IL-5**, which promotes maturation and activation.

c) **Eosinophils are normally found in low numbers in the blood**, but are more abundant in **mucosal tissues** of the **respiratory, gastrointestinal, and genitourinary tracts**. **Their numbers increase during parasitic infections, allergic reactions, and inflammatory responses,** as they are recruited from circulation to affected tissues under cytokine and chemokine influence.



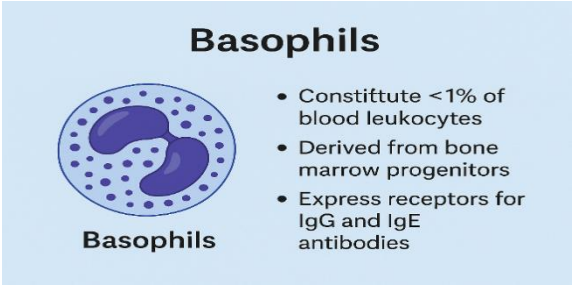
Basophils

a) **Basophils are rare granulocytic leukocytes that share many structural and functional similarities with mast cells. They constitute less than 1% of circulating white blood cells and are derived from bone marrow progenitors distinct from the mast cell lineage.**

b) **Basophils contain large cytoplasmic granules that stain strongly with basic dyes due to the presence of heparin, histamine, and other cationic mediators. These granules are responsible for many of the vascular and inflammatory effects seen in allergic and hypersensitivity reactions.**

c) **Like mast cells, basophils express high-affinity receptors for immunoglobulin E (IgE) and also bind IgG. When antigens cross-link surface-bound IgE, basophils undergo degranulation, releasing histamine, leukotrienes, and cytokines that contribute to vasodilation, increased vascular permeability, and smooth muscle contraction.**

d) **Although basophils are present in very low numbers in tissues, they play supportive roles in allergic inflammation, parasitic defense, and modulation of the Th2 immune response, although their overall contribution to host defense remains less defined compared with mast cells.**

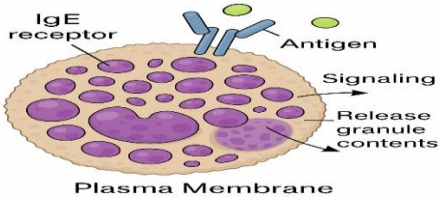


Mast Cells

a) **Mast cells are tissue-resident granulocytic immune cells that play key roles in both host defense and allergic inflammation. They express high-affinity Fc receptors for IgE and lower-affinity receptors for IgG, and are typically coated with these antibodies.**

b) **Upon antigen binding and cross-linking of surface-bound IgE, mast cells undergo degranulation, releasing a variety of preformed mediators such as histamine, heparin, and proteases, as well as newly synthesized cytokines and lipid mediators. These substances increase vascular permeability, vasodilation, and smooth muscle contraction, leading to the characteristic features of inflammation and allergic reactions.**

c) **While mast cells are essential for defense against helminth (parasitic worm) infections, they are also central to the pathogenesis of allergic disorders, including asthma, rhinitis, and anaphylaxis**



Mononuclear Phagocytes – Monocytes

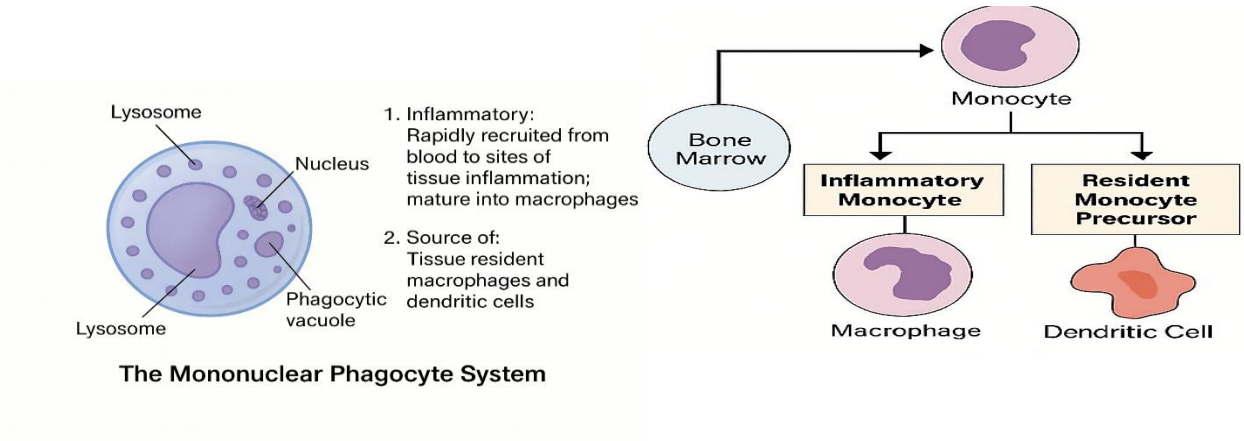
a) **The mononuclear phagocyte system comprises cells specialized in phagocytosis and immune regulation, serving key roles in both innate and adaptive immunity. The circulating precursor within this system is the monocyte, which originates in the bone marrow and enters the bloodstream in an incompletely differentiated state.**

b) **Morphology:**
Monocytes are large leukocytes measuring 10–15 µm in diameter, with a bean-shaped nucleus and finely granular cytoplasm rich in lysosomes, phagocytic vacuoles, and cytoskeletal filaments, all supporting their motility and engulfment functions

c) **Functional Subsets:**
Monocytes are heterogeneous, consisting of at least two major subsets based on surface markers and migration behavior:

d) **Inflammatory Monocytes: Rapidly recruited from the blood to sites of infection or tissue injury, where they differentiate into macrophages and contribute to inflammatory defense.**

e) **Resident Monocyte Precursors: Give rise to tissue-resident macrophages and some dendritic cells, maintaining tissue homeostasis and immune surveillance**



The Mononuclear Phagocyte System

Macrophages

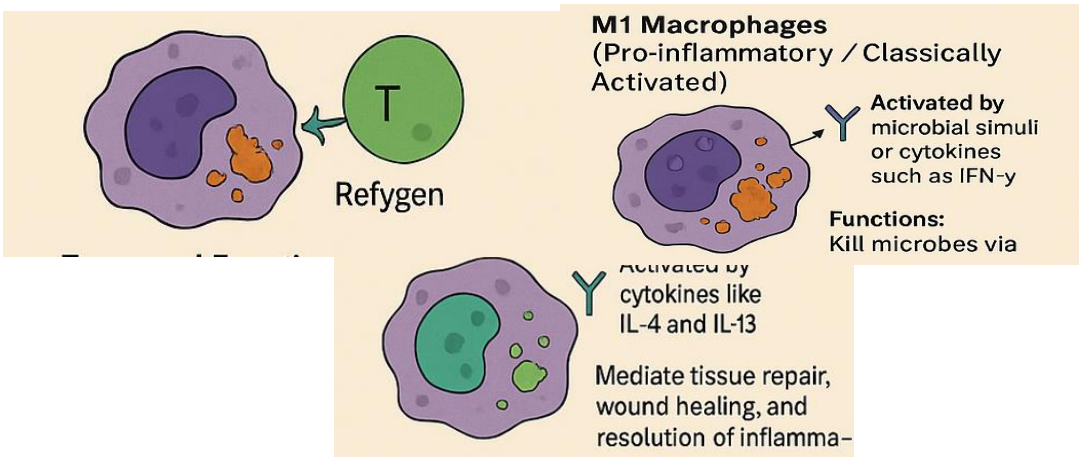
Macrophages are large, highly adaptable immune cells derived from monocytes. Their morphology and function vary by tissue and activation state. Depending on their location, they are given specific names — microglial cells (CNS), Kupffer cells (liver), alveolar macrophages (lungs), and osteoclasts (bone).

Their primary roles include phagocytosis of pathogens and debris, antigen presentation (APC) to activate T lymphocytes, and regulation of inflammatory and repair processes.

Types and Functions

1. **M1 Macrophages (Pro-inflammatory / Classically Activated):**
   Activated by microbial stimuli or cytokines such as IFN-γ.
   - **Functions: Kill microbes via reactive oxygen and nitrogen species, secrete(cytokines) TNF-α, IL-1, and IL-12, promoting Th1 T cell responses.**
   - **They also clear dead cells and enhance B cell activation.**
   - **Key Role: Defense and inflammation.**
2. **M2 Macrophages (Anti-inflammatory / Alternatively Activated):**
   Activated by cytokines like IL-4 and IL-13.
   - **Functions: Mediate tissue repair, wound healing, and resolution of inflammation.**
   - **Secrete IL-10, TGF-β, VEGF, and PGE2, supporting fibrosis, angiogenesis, and immune regulation.**
   - **Key Role: Recovery and regeneration.**

Antigens Presenting cells

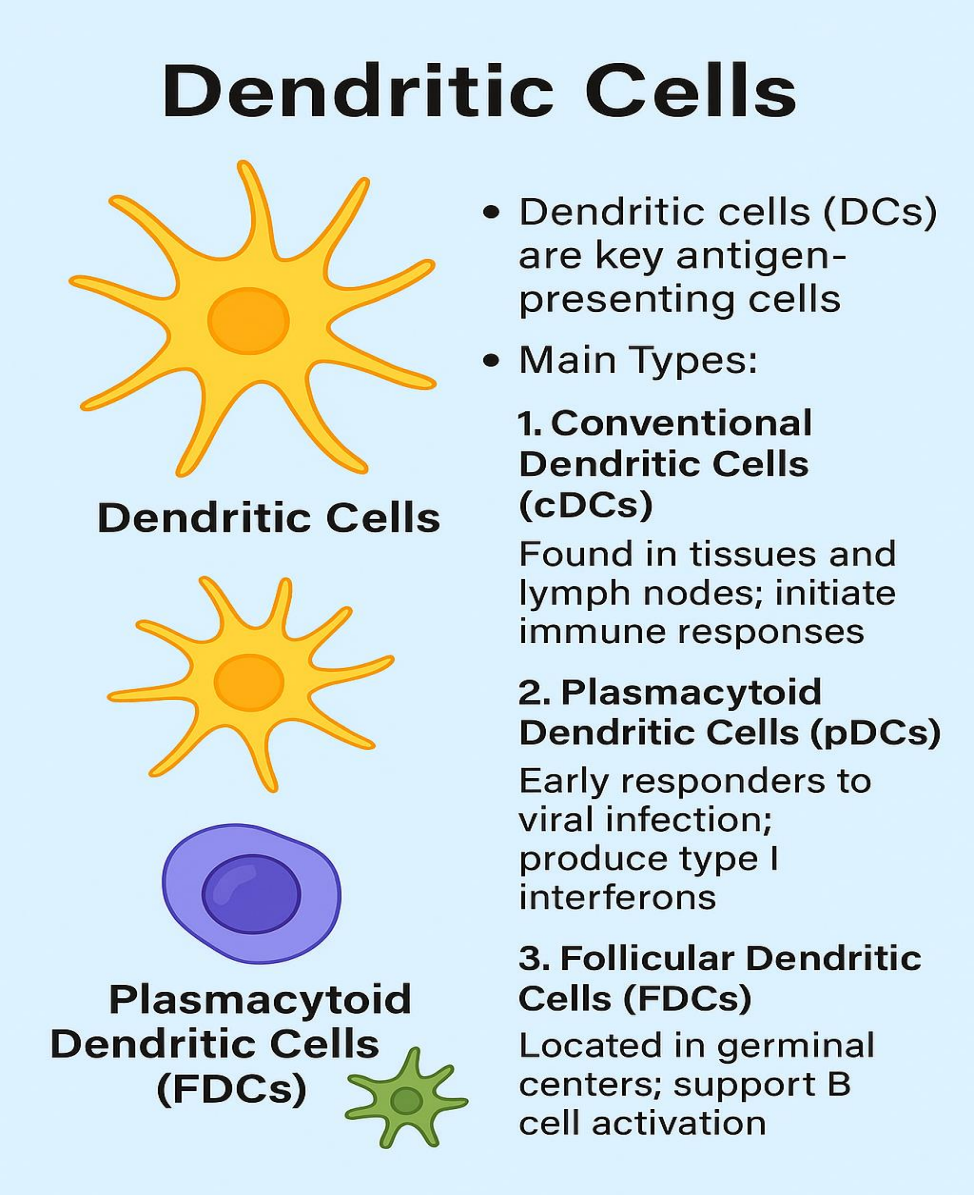


Dendritic cells

a) **Dendritic cells (DCs) are professional antigen-presenting cells (APCs) that form a critical bridge between the innate and adaptive immune systems. Their primary role is to capture, process, and present antigens to naive T lymphocytes, thereby initiating adaptive immune responses.**
b) **Morphologically, DCs are characterized by long membranous projections that increase surface area for antigen sampling. They possess phagocytic and endocytic activity and are widely distributed in lymphoid tissues, mucosal surfaces, and parenchymal organs.**
c) **DCs originate from the myeloid lineage of hematopoietic cells, sharing precursors with monocytes but not granulocytes. Once activated by pathogens, they migrate to lymphoid organs where they mature and present processed antigens to T cells.**

- **Conventional Dendritic Cells (cDCs):**
  Found in tissues and lymph nodes; specialize in presenting antigens to T cells to initiate immune responses.
- **Plasmacytoid Dendritic Cells (pDCs):**
  Early responders to viral infection; produce large amounts of type I interferons (IFN-α, IFN-β) for antiviral defense.

- **Follicular Dendritic Cells (FDCs):**
  Located in germinal centers; trap antigen–antibody complexes and support B cell activation and antibody maturation.



Innate Lymphoid Cells (ILCs)

Innate lymphoid cells (ILCs) are a recently discovered family of innate immune cells that play critical roles in host defense and tissue regulation, particularly at barrier surfaces such as the mucosal linings of the respiratory and gastrointestinal tracts.
They originate from ***common lymphoid progenitors (CLPs)*** in the bone marrow but **lack antigen-specific receptors**, which allows them to respond **rapidly** to infection, though without the **specificity** of adaptive immune cells.

Core Functions

- **Defense against pathogens:** ILCs respond rapidly to infections and tissue injury by releasing cytokines.
- **Regulation of adaptive immunity:** They modulate T and B cell activity, shaping the adaptive response.

- **Tissue homeostasis:** ILCs contribute to tissue repair, remodeling, and maintaining epithelial integrity.

Major Groups

1. **Group 1 ILCs** – Produce **interferon-gamma (IFN-γ)**; **defend against intracellular pathogens and viruses, similar to NK cells.**
2. **Group 2 ILCs** – Produce **IL-4, IL-5, and IL-13**; essential for defense against helminths and involved in allergic inflammation.
3. **Group 3 ILCs** – Produce **IL-17 and IL-22**; maintain **mucosal immunity** and promote interaction with gut microbiota.