Cells and organs of the immune system

Primary lymphoid organs—including the bone marrow and the thymus—regulate the development of immune cells from immature precursors.

Secondary lymphoid organs—including the

1-spleen,

2-lymph nodes

3- MALT mucosal associated lymphoid tissue

specialized sites in the gut and other mucosal tissues—coordinate the encounter of antigen with antigen-specific lymphocytes and their development into effector and memory cells.

THIRD LECTURE

Cells of the Immune System

- Embryonic stem cells have the capacity to generate every specialized cell type in an organism (in other words, they are *pluripotent*).
- Adult stem cells, in contrast, have the capacity to give rise to the diverse cell types that specify a particular tissue. Multiple adult organs harbor stem cells ("adult stem cells") that can give rise to mature tissue-specific cells.
- The HSC is considered the paradigmatic adult stem cell because it can differentiate into all the types of blood cells.

Remarkably, all functionally specialized, mature blood cells (red blood cells, granulocytes, macrophages, dendritic cells, and lymphocytes) arise from a single cell type, the **hematopoietic stem cell (HSC)**.

The process by which HSCs differentiate into mature blood cells is called **hematopoiesis**. Two primary lymphoid organs are responsible for the development of stem cells into mature immune cells: the bone marrow, where HSCs reside and give rise to all cell types; and the thymus, where T cells complete their maturation.

Cells of the Myeloid Lineage Are the First Responders to Infection

- Cells that arise from a common myeloid progenitor (CMP) include red blood cells (erythroid cells) as well as various types of white blood cells (myeloid cells such as granulocytes, monocytes, macrophages, and some dendritic cells).
- Myeloid cells are the first to respond to the invasion of a pathogen .

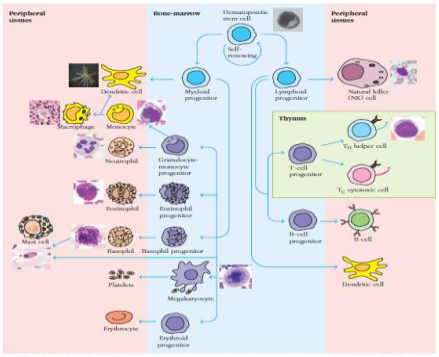

FIGURE 2-1 **Hematopoiesis.** Self-renewing hematopoietic stem cells give rise to lymphoid and myeloid progenitors. Most immune cells mature in the bone marrow and then travel to peripheral organs via the blood. Some, including mast cells and macrophages, undergo further maturation outside the bone marrow. T cells develop to maturity in the thymus.

Neutrophils

- Neutrophilic leukocytes, particularly the polymorphonuclear (PMN) type, provide an effective host defense against bacterial and fungal infections. The antimicrobial function of PMNs is essential in the innate immune response.
- Although the monocytes-macrophages and other granulocytes associated with phagocytosis and a localized inflammatory response. The formation of an inflammatory **exudate (pus),** which develops rapidly in an inflammatory response, is composed primarily of neutrophils and monocytes.

Granulocytes

Granulocytes are at the front lines of attack during an immune response and are considered part of the innate immune system.

Granulocytes are white blood cells (leukocytes) that are classified as neutrophils, basophils, mast cells, or eosinophils on the basis of differences in cellular morphology and the staining of their characteristic cytoplasmic granules.

All granulocytes have multilobed nuclei that make them visually distinctive and easily distinguishable from lymphocytes, whose nuclei are round.

The cytoplasm of all granulocytes is replete with granules that are released in response to contact with pathogens.

These granules contain a variety of proteins with distinct functions: Some damage pathogens directly; some regulate trafficking and activity of other white blood cells, including lymphocytes; and some contribute to the remodeling of tissues at the site of infection.

- Neutrophils are recruited to the site of infection in response to inflammatory molecules (e.g., chemokines) generated by innate cells (including other neutrophils) that have engaged a pathogen.
- Once in tissues, neutrophils phagocytose (engulf) bacteria very effectively, and also secrete a range of proteins that have antimicrobial effects and tissue remodeling potential.
- Neutrophils are the dominant first responders to infection and the main cellular components of pus, where they accumulate at the end of their short lives. Although once considered a simple and "disposable" effector cell, the neutrophil has recently inspired renewed interest from investigations indicating that it may also regulate the adaptive immune response.

- PMNs are also phagocytic cells, the PMN is the principal leukocyte constitute the majority (50% to 70%) of circulating leukocytes and are much more numerous than eosinophils (1%–3%), basophils (_1%), or mast cells (_1%).
- After differentiation in the bone marrow, neutrophils are released into the peripheral blood and circulate for 7 to 10 hours before migrating into the tissues, where they have a life span of only a few days.
- In response to many types of infections, the number of circulating neutrophils increases significantly and more are recruited to tissues, partially in response to cues the bone marrow receives to produce and release more myeloid cells. The resulting transient increase in the number of circulating neutrophils, called **leukocytosis**, is used medically as an indication of infection.

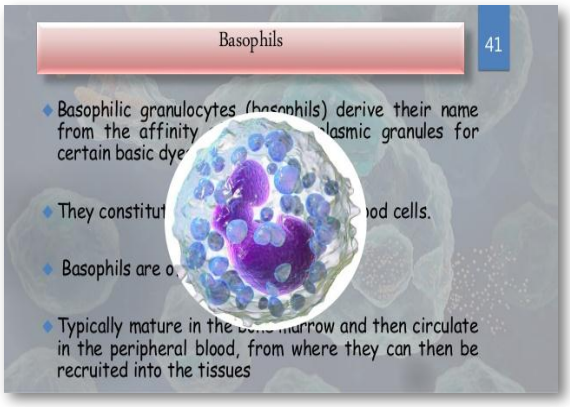

Table 3-1 Function and Types of Granules in Neutrophils

Function	Azurophilic (Primary) Granules	Specific (Secondary) Granules
Microbicidal	Myeloperoxidase	Cytochrome b558 and other respiratory burst components
	Lysozyme	Lysozyme
	Elastase	Lactoferrin
	Defensins	
	Cathepsin G	
	Proteinase-3	
	Bacterial permeability-increasing protein (BPI)	
Cell migration		Collagenase
		CD11b–CD18 (CR-3)
		N-formulated peptides (e.g., *N*-formyl-methionyl-leucylphenylalanine receptor [FMLP-R])

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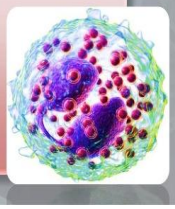
EOSINOPHIL

- The granulocytes whose granules stain with acidic dyes are called eosinophils.
- They comprise 2-5% of white blood cells and have bilobed nuclei.



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Basophils have a short life-span of several days.

Interleukin-3 (IL-3) promotes the production and survival of human basophils in vitro and can induce basophili in vivo.

Mediators stored preformed in the cytoplasmic granules of basophils include chondroitin sulphates, proteases and histamine

Chondroitin sulphates probably contribute to the storage of histamine and neutral proteases, and basophils are the source of most of the histamine found in normal human blood.

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- Eosinophils have Fc receptors for IgG and IgE antibodies and for C3b, enabling them to bind to opsonized targets.
- They then secrete their antibiotic granule contents (including major basic protein and eosinophil cationic protein) and reactive oxygen species to bring about damage to the target.

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- In contrast to the phagocytosis and intracellular digestion normally displayed by neutrophils, eosinophils secrete their granule contents for extracellular digestion of infectious pathogens which are too large to be engulfed.
- Eosinophils also produce cytokines, prostaglandins and leucotrienes, and enzymes which can inhibit the inflammatory products of mast cells

Myeloid Antigen-Presenting Cells

Myeloid progenitors also give rise to a group of phagocytic cells (monocytes, macrophages, and dendritic cells) that have **professional antigen-presenting cell (APC)** function.

- Myeloid APCs are considered cellular bridges between the innate and adaptive immune systems because they make contact with a pathogen at the site of infection and communicate this encounter to T lymphocytes in the lymph node (“antigen presentation”).
- Each APC can respond to pathogens and secrete proteins that attract and activate other immune cells.

Mast cells

- are released from the bone marrow into the blood as undifferentiated cells; they mature only after they leave the blood.
- Mast cells can be found in a wide variety of tissues, including the skin, connective tissues of various organs, and mucosal epithelial tissue of the respiratory, genitourinary, and digestive tracts. Like circulating basophils, these cells have large numbers of cytoplasmic granules that contain histamine and other pharmacologically active substances. Mast cells also play an important role in the development of allergies.

- **Monocytes** make up about 5% to 10% of white blood cells and are a heterogeneous group of cells that migrate into tissues and differentiate into a diverse array of tissue-resident phagocytic cells, including macrophages and dendritic cells.
- During hematopoiesis in the bone marrow, granulocyte-monocyte progenitor cells differentiate into pro monocytes, which leave the bone marrow and enter the blood, where they further differentiate into mature monocytes.

- Each can ingest pathogens via phagocytosis, digest pathogenic proteins into peptides, then present these peptide antigens on their membrane surfaces.
- Each can be induced to express a set of costimulatory molecules required for optimal activation of T lymphocytes.
- However, it is likely that each plays a distinct role during the immune response, depending on its locale and its ability to respond to pathogens.
- Dendritic cells, in particular, play a primary role in presenting antigen to—and activating—naïve T cells.
- Macrophages and neutrophils are especially efficient in removing both pathogen and damaged host cells, and can provide a first line of defense against pathogens.

- Some macrophages are long-term residents in tissues and play an important role in regulating their repair and regeneration.

Other macrophages participate in the innate immune response and undergo a number of key changes when they are stimulated by encounters with pathogens or tissue damage.

- These are referred to as ***inflammatory macrophages*** and play a dual role in the immune system as effective phagocytes that can contribute to the clearance of pathogens from a tissue, as well as antigen-presenting cells that can activate T lymphocytes.
- **Osteoclasts** in the bone, **microglial cells** in the central nervous system, and **alveolar macrophages** in the lung are tissue-specific examples of macrophages with these properties.

- Two broad categories of monocytes have recently been identified. 1-*Inflammatory monocytes* enter tissues quickly in response to infection.
- *2- Patrolling monocytes*, a smaller group of cells that crawl slowly along blood vessels, provide a reservoir for tissue-resident monocytes in the absence of infection.
- Monocytes that migrate into tissues in response to infection can differentiate into specific tissue **macrophages**. Like monocytes, macrophages can play several different roles.

Dendritic cell

- The dendritic cell is considered the most efficient activator of naïve T cells.
- The discovery of the **dendritic cell (DC)** by Ralph Steinman in the mid 1970s resulted in awarding of the Nobel Prize in 2011.
- Dendritic cells are critical for the initiation of the immune response and acquired their name because they are covered with long membranous extensions that resemble the dendrites of nerve cells and extend and retract dynamic increasing the surface area available for browsing lymphocytes.

- They are more diverse a population of cells than once was thought, and seem to arise from both the myeloid and lymphoid lineages of hematopoietic cells.

- Many macrophages also express receptors for certain classes of antibody. If an antigen (e.g., a bacterium) is coated with the appropriate antibody, the complex of antigen and antibody binds to antibody receptors on the macrophage membrane more readily than antigen alone and phagocytosis is enhanced.
- In one study, for example, the rate of phagocytosis of an antigen was 4000-fold higher in the presence of specific antibody to the antigen than in its absence. Thus, an antibody is an example of an **opsonin**, a molecule that binds an antigen marking it for recognition by immune cells. The modification of particulate antigens with opsonins (which come in a variety of forms) is called **opsonization** .

- It is important to note that **follicular dendritic cells** do not arise in bone marrow and have completely different functions from those described for the dendritic cells discussed above. Follicular dendritic cells do not function as antigen-presenting cells for TH-cell activation.
- These dendritic cells were named for their exclusive location in organized structures of the lymph node called lymph follicles, which are rich in B cells. The interaction of B cells with follicular dendritic cells is an important step in the maturation and diversification of B cells.

- Dendritic cells perform the distinct functions of antigen capture in one location and antigen presentation in another.
- Outside lymph nodes, immature forms of these cells monitor the body for signs of invasion by pathogens and capture intruding or foreign antigens.
- They process these antigens, then migrate to lymph nodes, where they present the antigen to naïve T cells, initiating the adaptive immune response.

When acting as sentinels in the periphery, immature dendritic cells take on their cargo of antigen in three ways. They engulf it by phagocytosis, internalize it by receptor-mediated endocytosis, or imbibe it by pinocytosis. Indeed, immature dendritic cells pinocytose fluid volumes of 1000 to 1500 _m3 per hour, a volume that rivals that of the cell itself.

- It is clear that myeloid cells are not the only cells that can present antigen efficiently. As mentioned above, lymphoid derived dendritic cells are fully capable APCs.
- In addition, activated B lymphocytes can act as professional antigen presenting cells.
- B cells can internalize antigen very efficiently via their antigen-specific receptor, and can process and present antigenic peptides at the cell surface.
- Activated B cells also express the full complement of costimulatory molecules that are required to activate T cells.
- By presenting antigen directly to T cells, B cells efficiently solicit help, in the form of cytokines, that induces their differentiation into memory cells, as well as into antibody-producing cells (plasma cells).