Cells of the Immune System

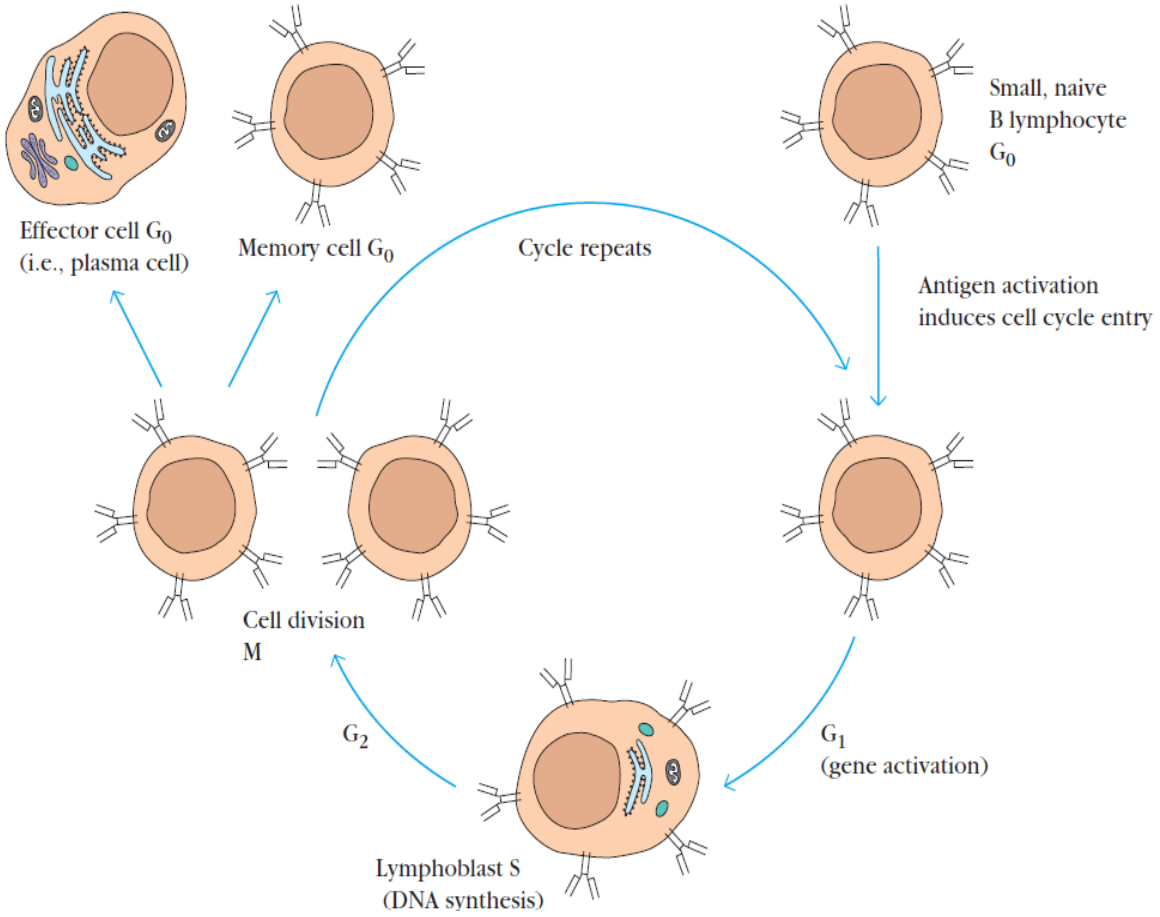
- **Lymphocytes are the central cells of the immune system, responsible for adaptive immunity in terms of:**
  - ✓ **diversity,**
  - ✓ **specificity,**
  - ✓ **memory, and**
  - ✓ **self/nonself recognition.**
- **The other types of white blood cells play important important roles in**
  - ✓ **Engulfing and destroying microorganisms**
  - ✓ **Presenting antigens,**
  - ✓ **Secreting cytokines**

TABLE 2-4 Normal adult blood-cell counts

Cell type	Cells/mm^3	%
Red blood cells	5.0×10^6	
Platelets	2.5×10^5	
Leukocytes	7.3×10^3	
Neutrophil		50–70
Lymphocyte		20–40
Monocyte		1–6
Eosinophil		1–3
Basophil		<1

Lymphoid Cells

- Lymphocytes constitute 20%–40% of the body's white blood cells and 99% of the cells in the lymph.
- There are approximately 10^{11} lymphocytes in the human body.
- These lymphocytes continually circulate in the blood and lymph and are capable of migrating into the tissue spaces and lymphoid organs, thereby integrating the immune system to a high degree.
- The lymphocytes can be broadly subdivided into three populations—B cells, T cells, and natural killer cells—on the basis of function and cell-membrane components.
- **Natural killer cells (NK cells)** are large, granular lymphocytes that do not express the set of surface markers typical of B or T cells.
- Resting B and T lymphocytes are small, motile, nonphagocytic cells, which cannot be distinguished morphologically.
- B and T lymphocytes that have not interacted with antigen— referred to as **naive,** or unprimed—are resting cells in the G0 phase of the cell cycle. Known as small lymphocytes, these cells are only about 6 m in diameter; their cytoplasm forms a barely discernible rim around the nucleus.
- Small lymphocytes have densely packed chromatin, few mitochondria, and a poorly developed endoplasmic reticulum and Golgi apparatus.
- The naive lymphocyte is generally thought to have a short life span.
- Interaction of small lymphocytes with antigen, in the presence of certain cytokines, induces these cells to enter the cell cycle by progressing from G0 into G1 and subsequently into S, G2, and M.
- As they progress through the cell cycle, lymphocytes enlarge into 15 µm-diameter blast cells, called **lymphoblasts;** these cells have a higher cytoplasm: nucleus ratio and more organellar complexity than small lymphocytes.
- Lymphoblasts proliferate and eventually differentiate into **effector cells** or into **memory cells.**



B-Lymphocytes

- The B lymphocyte derived its letter designation from its site of maturation, in the *b*ursa of Fabricius in birds or *b*one for mammalian species.
- Mature B cells are definitively distinguished from other lymphocytes by their synthesis and display of membrane-bound antibody which serve as receptors for antigen.
- Each of the approximately 1.5×10^5 molecules of antibody on the membrane of a single B cell has an identical binding site for antigen.
- Interaction between antigen and the membrane-bound antibody on a mature naive B cell, as well as interactions with T cells and macrophages, selectively induces the activation and differentiation of B-cell clones of corresponding specificity.
- In this process, the B cell divides repeatedly and differentiates over a 4 to 5 day period, generating a population of plasma cells and memory cells.
- Plasma cells, which have lower levels of membrane-bound antibody than B cells, synthesize and secrete antibody.
- All clonal progeny from a given B cell secrete antibody molecules with the same antigen-binding specificity.
- Plasma cells are terminally differentiated cells, and many die in 1 or 2 weeks.

T Lymphocytes

- T lymphocytes derive their name from their site of maturation in the *t*hymus. Like B lymphocytes, these cells have membrane receptors for antigen.
- T-cell receptor is structurally distinct/different from immunoglobulin.
- TCR recognizes only antigen that is bound to MHC.
- Cells with CD4 recognize antigen bound to class II MHC molecules, whereas T cells expressing CD8, recognize antigen bound to class I MHC molecules.
- TH cells secrete various cytokines, which play a central role in the activation of B cells, T cells, and other cells that participate in the immune response.
- Changes in the pattern of cytokines produced by TH cells can change the type of immune response that develops among other leukocytes.
- **TH1 response** produces a cytokine profile that supports inflammation and activates mainly certain T cells and macrophages.
- **TH2 response** activates mainly B cells and immune responses that depend upon antibodies.
- TC cells are activated when they interact with an antigen–class I MHC complex on the surface of an altered self-cell (e.g., a virus-infected cell or a tumor cell) in the presence of appropriate cytokines.
- This activation, which results in proliferation, causes the TC cell to differentiate into an effector cell called a **cytotoxic T lymphocyte (CTL).**
- In contrast to TH cells, most CTLs secrete few cytokines.
- Instead, CTLs acquire the ability to recognize and eliminate altered self-cells.

NATURAL KILLER CELLS

- Natural killer cell was first described in 1976,when it was shown that the body contains a small population of large, granular lymphocytes that display cytotoxic activity against a wide range of tumor cells in the absence of any previous immunization with the tumor.
- NK cells were subsequently shown to play an important role in host defense both against tumor cells and against cells infected with some, though not all, viruses.
- These cells, which constitute 5%–10% of lymphocytes in human peripheral blood, do not express the membrane molecules and receptors that distinguish T- and B-cell lineages.
- NK cells do not have T-cell receptors or immunoglobulin incorporated in their plasma membranes.
- NK cell employs NK cell receptors to distinguish abnormalities, for example, surface antigens displayed by some tumor cells and cells infected by some viruses.
- Some tumor cells and virus-infected cells display antigens against which the immune system has made an antibody response, so that antitumor or antiviral antibodies are bound to their surfaces. Because NK cells express CD16, a membrane receptor for the carboxyl-terminal end of the IgG molecule, called the Fc region, they can attach to these antibodies and subsequently destroy the targeted cells. This is an example of a process known as **antibody-dependent cell mediated cytotoxicity (ADCC).**
- Natural killer (NK) cells target and kill aberrant cells, such as virally infected and tumorigenic cells. Killing is mediated by cytotoxic molecules which are stored within secretory lysosomes, a specialized exocytic organelle found in NK cells.

Mononuclear Phagocytes

- The mononuclear phagocytic system consists of **monocytes** circulating in the blood and **macrophages** in the tissues.
- During hematopoiesis in the bone marrow, granulocyte-monocyte progenitor cells differentiate into promonocytes, which leave the bone marrow and enter the blood, where they further differentiate into mature monocytes.
- Monocytes circulate in the bloodstream for about 8 h, during which they enlarge; they then migrate into the tissues and differentiate into specific tissue macrophages or, into dendritic cells.
- Differentiation of a monocyte into a tissue macrophage involves a number of changes:
  - ✓ cell enlarges five- to tenfold
  - ✓ intracellular organelles increase in both number and complexity
  - ✓ acquires increased phagocytic ability
  - ✓ produces higher levels of hydrolytic enzymes, and
  - ✓ begins to secrete a variety of soluble factors.
- Macrophages are dispersed throughout the body. Some take up residence in particular tissues, becoming fixed macrophages, whereas others remain motile and are called free, or wandering, macrophages.
- Free macrophages travel by amoeboid movement throughout the tissues.

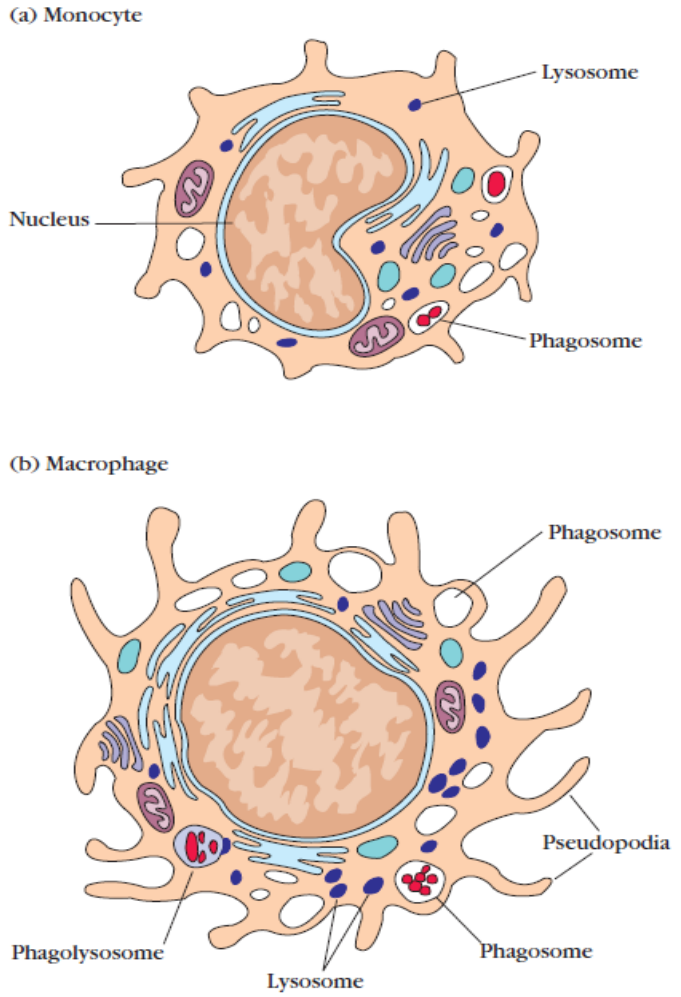


FIGURE 2-8 Typical morphology of a monocyte and a macrophage. Macrophages are five- to tenfold larger than monocytes and contain more organelles, especially lysosomes.

- Macrophage serve different functions in different tissues and are named according to their tissue location:
  - ✓ **Alveolar macrophages** in the lung
  - ✓ **Histiocytes** in connective tissues
  - ✓ **Kupffer cells** in the liver
  - ✓ **Mesangial cells** in the kidney
  - ✓ **Microglial cells** in the brain
  - ✓ **Osteoclasts** in bone
- Although normally in a resting state, macrophages are activated by a variety of stimuli in the course of an immune response.
  - ✓ Phagocytosis of particulate antigens serves as an initial activating stimulus.
  - ✓ Macrophage activity can be further enhanced by *cytokines secreted by activated TH cells*, by *mediators of the inflammatory response,* and by *components of bacterial cell walls.*
  - ✓ One of the most potent activators of macrophages is interferon gamma (IFN-ϒ) secreted by activated TH cells.

- Activated macrophages are more effective than resting ones in eliminating potential pathogens, because they exhibit:
  - ✓ greater phagocytic activity,
  - ✓ increased ability to kill ingested microbes,
  - ✓ increased secretion of inflammatory mediators,
  - ✓ increased ability to activate T cells
- Activated macrophages, but not resting ones, secrete various cytotoxic proteins that help them eliminate a broad range of pathogens, including virus-infected cells, tumor cells, and intracellular bacteria.
- Activated macrophages also express higher levels of class II MHC molecules, allowing them to function more effectively as antigen-presenting cells.
- Macrophages and TH cells facilitate each other's activation during the immune response.

TABLE 2-7 Some factors secreted by activated macrophages

Factor	Function
Interleukin 1 (IL-1)	Promotes inflammatory responses and fever
Interleukin 6 (IL-6), TNF-α	Promote innate immunity and elimination of pathogens
Complement proteins	Promote inflammatory response and elimination of pathogens
Hydrolytic enzymes	Promote inflammatory response
Interferon alpha (IFN-α)	Activates cellular genes, resulting in the production of proteins that confer an antiviral state on the cell
Tumor necrosis factor (TNF-α)	Kills tumor cells
GM-CSF, G-CSF, M-CSF	Promote inducible hematopoiesis

NEUTROPHILS

- Neutrophils are produced by hematopoiesis in the bone marrow.
- They are released into the peripheral blood and circulate for 7–10 h before migrating into the tissues, where they have a life span of only a few days.
- In response to many types of infections, the bone marrow releases more than the usual number of neutrophils and these cells generally are the first to arrive at a site of inflammation.
- The resulting transient increase in the number of circulating neutrophils, called **leukocytosis,** is used medically as an indication of infection.
- Movement of circulating neutrophils into tissues, called **extravasation,** takes several steps:
    - ✓ the cell first adheres to the vascular endothelium,
    - ✓ then penetrates the gap between adjacent endothelial cells lining the vessel wall, and
    - ✓ Finally penetrates the vascular basement membrane, moving out into the tissue spaces.
- A number of substances generated in an inflammatory reaction serve as **chemotactic factors** that promote
- accumulation of neutrophils at an inflammatory site.
- Among these chemotactic factors are some of the complement components, components of the blood-clotting system, and several cytokines secreted by activated TH cells and macrophages.

- Like macrophages, neutrophils are active phagocytic cells. Phagocytosis by neutrophils is similar to that described for macrophages, except that the lytic enzymes and bactericidal substances in neutrophils are contained within primary and secondary granules.
    - ✓ The larger, denser primary granules are a type of lysosome containing peroxidase, lysozyme, and various hydrolytic enzymes.
    - ✓ The smaller secondary granules contain collagenase, lactoferrin, and lysozyme.
- Both primary and secondary granules fuse with phagosomes, whose contents are then digested and eliminated much as they are in macrophages.
- Neutrophils also employ both oxygen-dependent and oxygen-independent pathways to generate antimicrobial substances.
- Neutrophils are in fact much more likely than macrophages to kill ingested microorganisms.
- Neutrophils exhibit a larger respiratory burst than macrophages and consequently are able to generate more reactive oxygen intermediates and reactive nitrogen intermediates (see Table 2-6).
- In addition, neutrophils express higher levels of defensins than macrophages do.

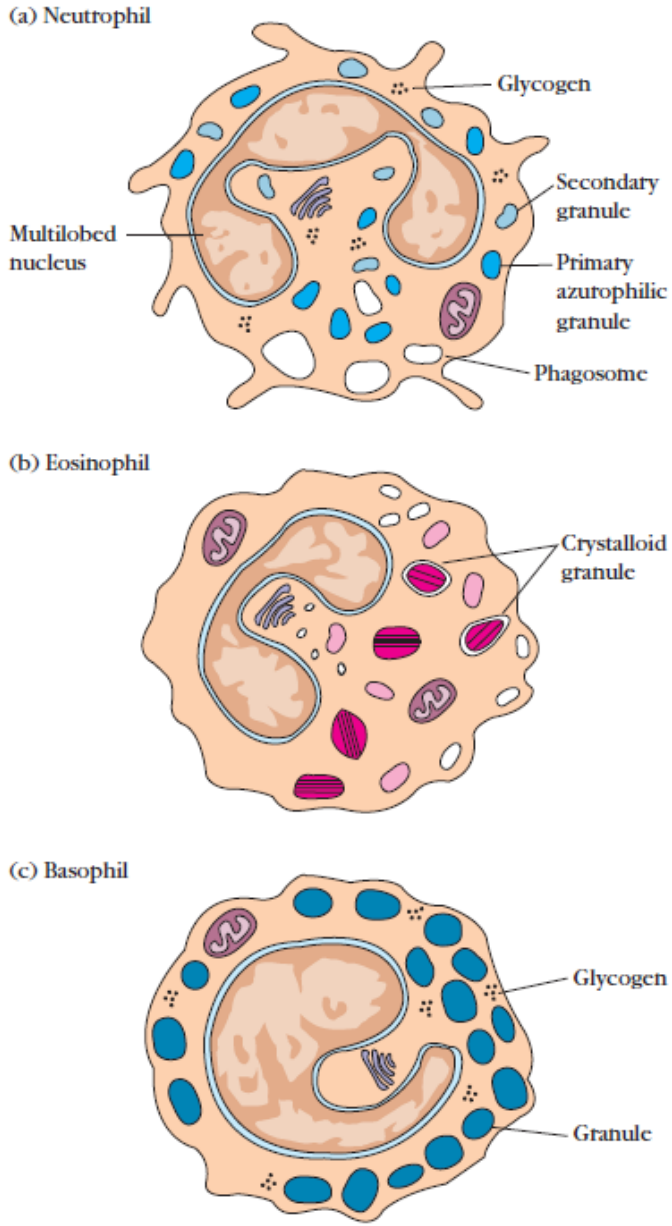


FIGURE 2-10 Drawings showing typical morphology of granulocytes. Note differences in the shape of the nucleus and in the number and shape of cytoplasmic granules.

EOSINOPHILS

- Eosinophils, like neutrophils, are motile phagocytic cells that can migrate from the blood into the tissue spaces.
- Their phagocytic role is significantly less important than that of neutrophils, and it is thought that they play a role in the defense against parasitic organisms.
- The secreted contents of eosinophilic granules may damage the parasite membrane.

BASOPHILS

- Basophils are nonphagocytic granulocytes that function by releasing pharmacologically active substances from their cytoplasmic granules.
- These substances play a major role in certain allergic responses.
- During allergic reactions, basophils release two enzymes: histamine and heparin.
- Histamine enlarges your blood vessels to improve blood flow and heal the affected area.
- Histamine opens pathways for other cells in your immune system to quickly target and respond to the allergen.

MAST CELLS

- Mast-cell precursors, which are formed in the bone marrow by hematopoiesis, are released into the blood as undifferentiated cells; they do not differentiate until they leave the blood and enter the tissues.
- 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, together with blood basophils, play an important role in the development of allergies..

DENDRITIC CELLS

- The **dendritic cell (DC)** acquired its name because it is covered with long membrane extensions that resemble the dendrites of nerve cells.
- There are many types of dendritic cells, although most mature dendritic cells have the same major function, the presentation of antigen to TH cells.
- Four types of dendritic cells are known:
- Langerhans cells, interstitial dendritic cells, myeloid cells, and lymphoid dendritic cells.
- Each arises from hematopoietic stem cells via different pathways and in different locations.
- Despite their differences, they all constitutively express high levels of both class II MHC molecules and members of the co-stimulatory B7 family.
- For this reason, they are more potent antigen-presenting cells than macrophages and B cells, both of which need to be activated before they can function as antigen-presenting cells (APCs).
- Immature or precursor forms of each of these types of dendritic cells acquire antigen by phagocytosis or endocytosis; the antigen is processed, and mature dendritic cells present it to TH cells.
- Following microbial invasion or during inflammation, mature and immature forms of Langerhans cells and interstitial dendritic cells migrate into draining lymph nodes, where they make the critical presentation of antigen to TH cells that is required for the initiation of responses by those key cells.

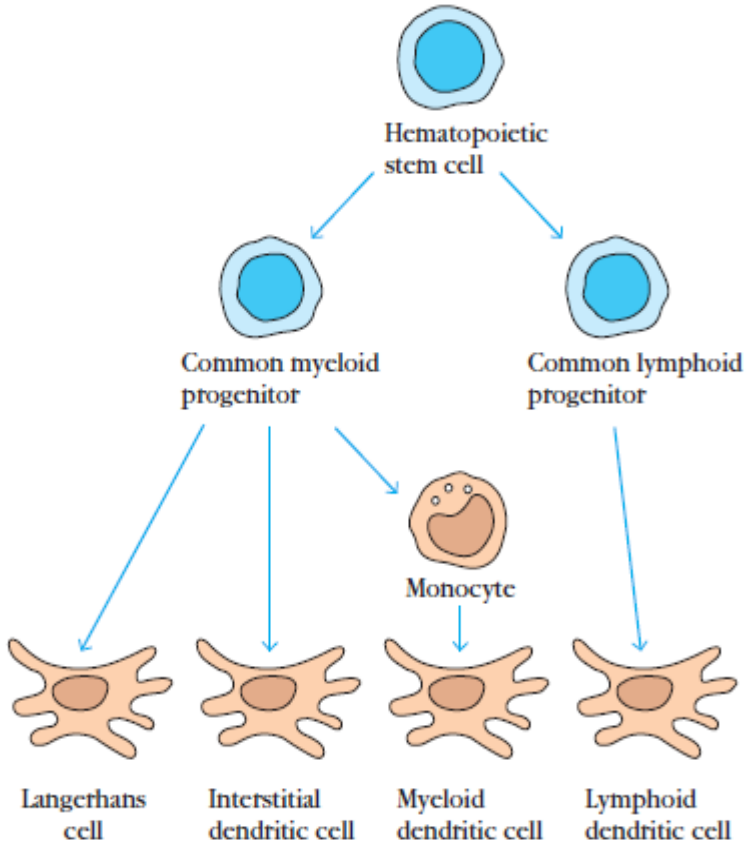


FIGURE 2-11 Dendritic cells arise from both the myeloid and lymphoid lineages. The myeloid pathway that gives rise to the monocyte/macrophage cell type also gives rise to dendritic cells. Some dendritic cells also arise from the lymphoid lineage. These considerations do not apply to follicular dendritic cells, which are not derived from bone marrow.