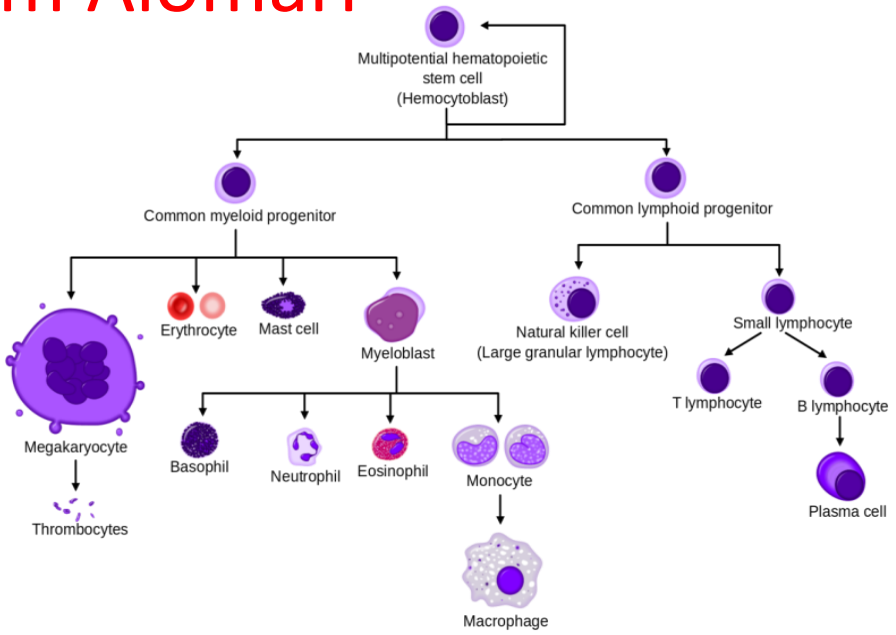
Hematopoiesis

Dr.Mariam Alomari

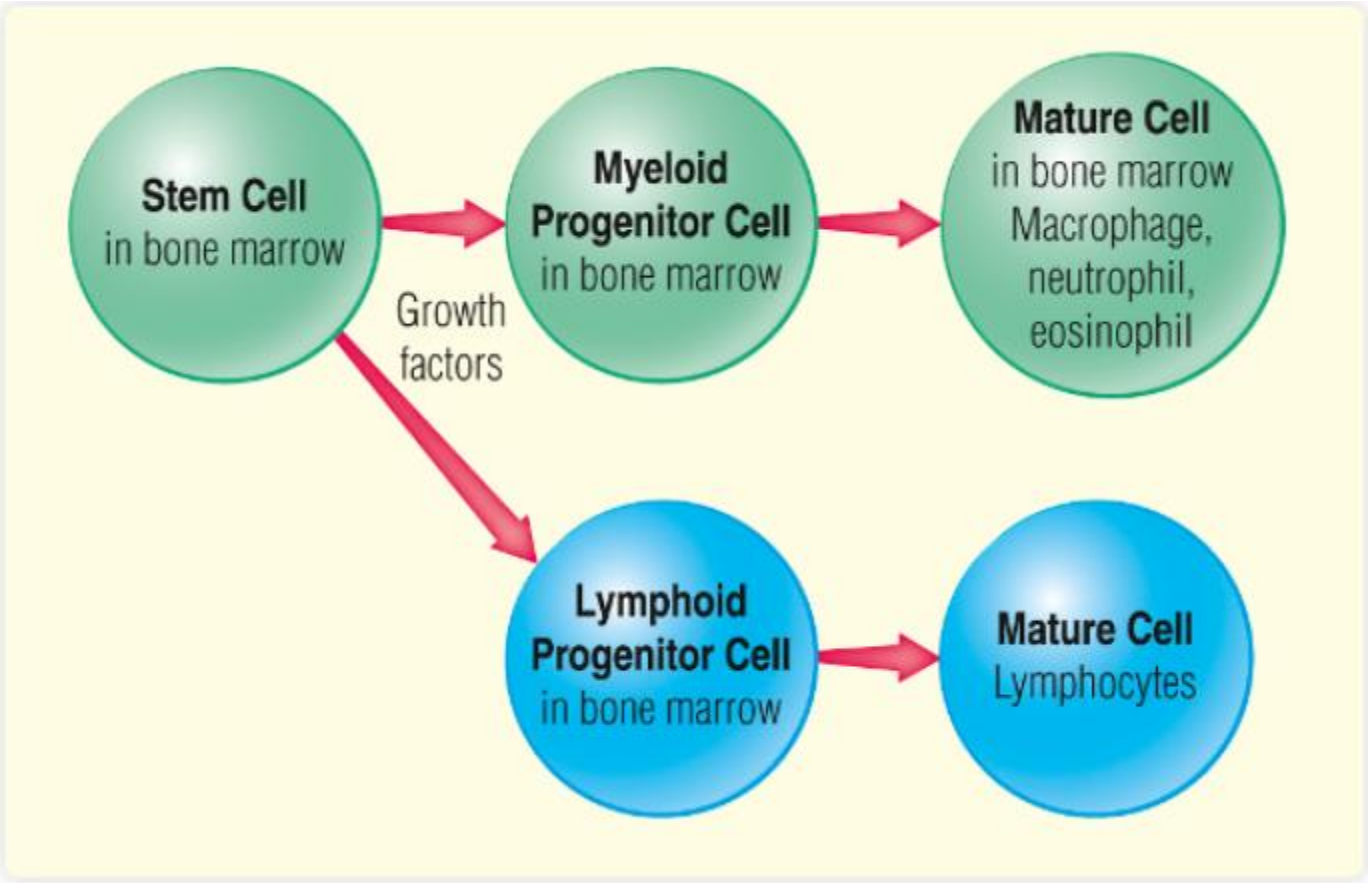


Medical immunology M215
Lecture 10

Hematopoiesis

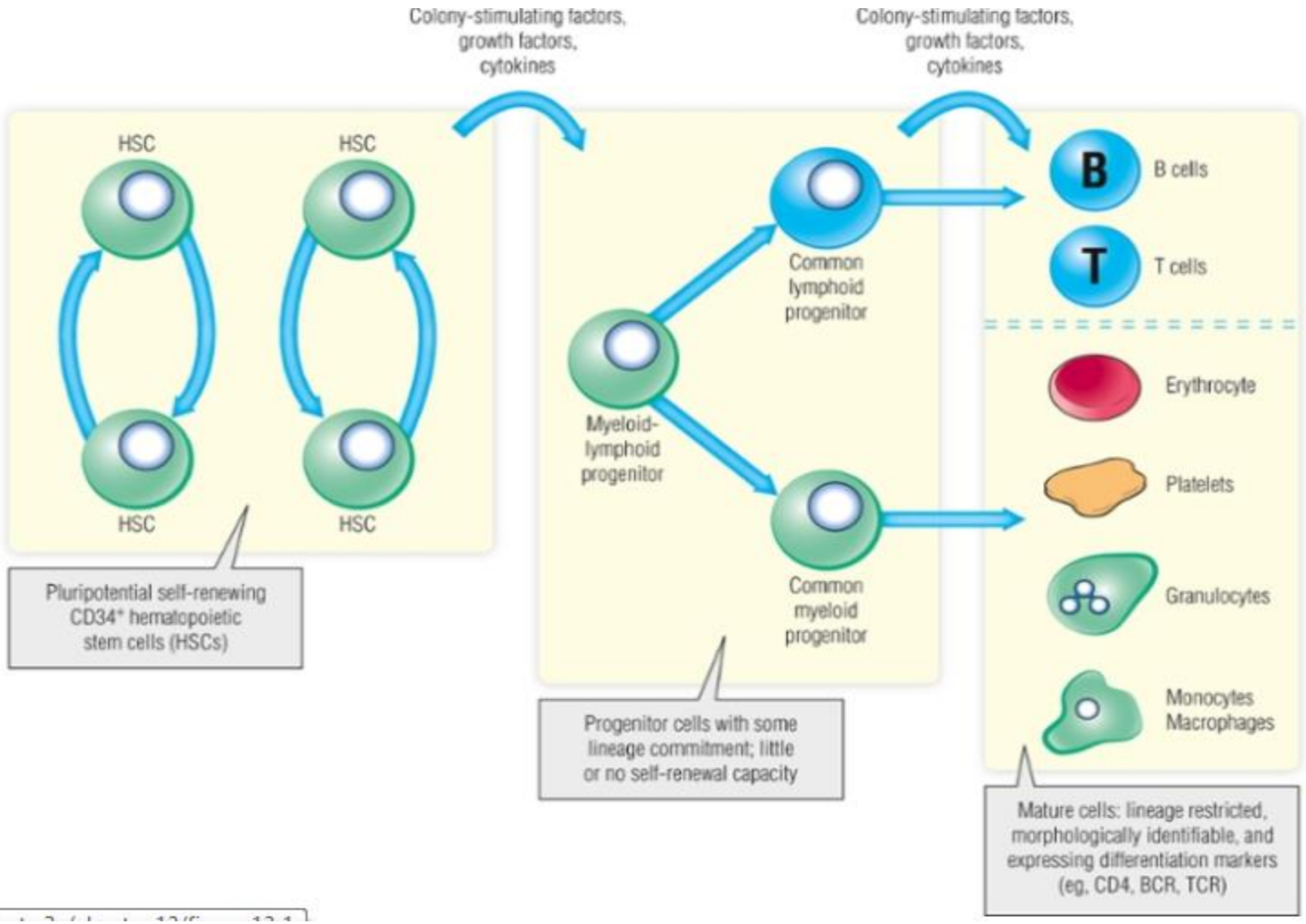
Hematopoiesis is the process whereby all blood cells are formed

In humans, the bone marrow is the major site for hematopoiesis



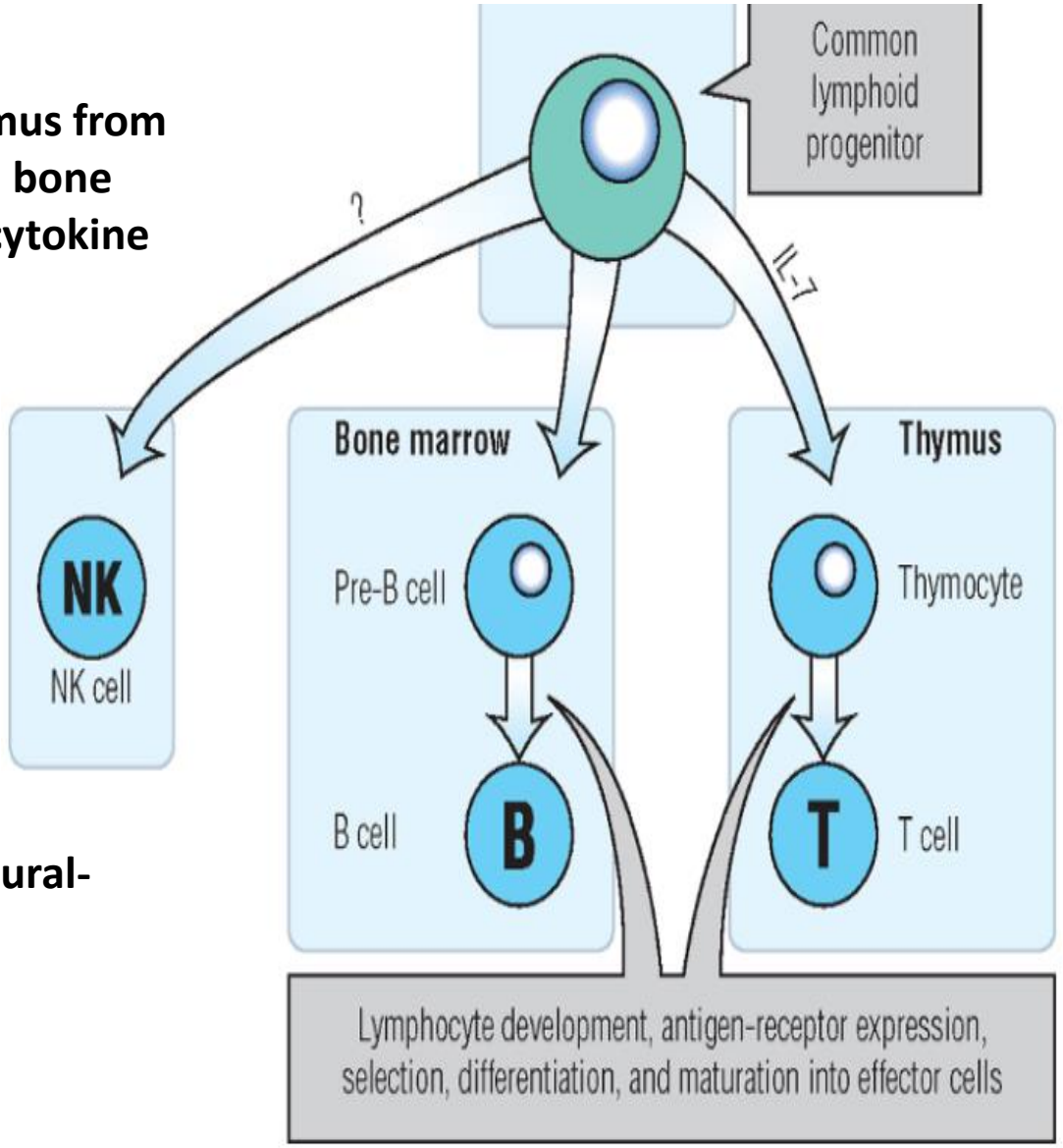
Hematopoietic stem cells (HSCs)

- **pluripotential, and self-renewing.**
- **They give rise to all the blood cell types (lineages)**
- **express a protein designated as CD34**
- **There they are induced to differentiate further by the large number of growth factors found in these tissues (e.g colony-stimulating-factors (CSFs))**



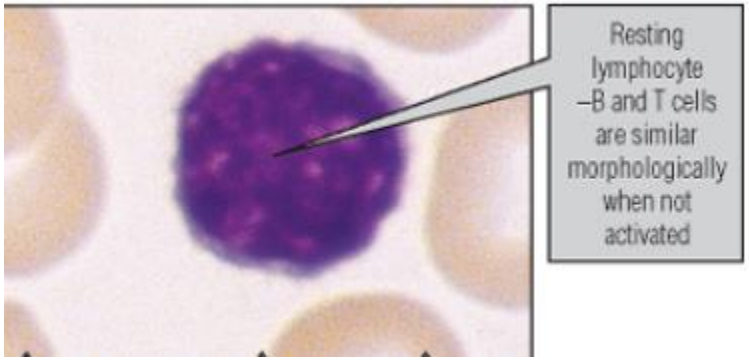
Development of the lymphoid cell

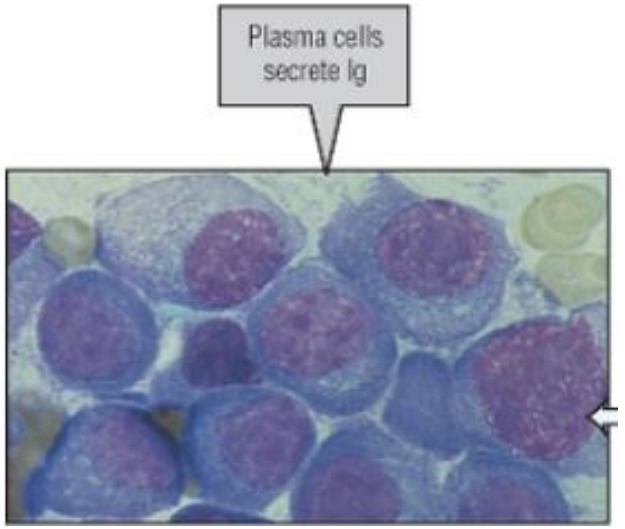
- **T lymphocytes develop in the thymus from thymocyte precursors derived in the bone marrow under the influence of the cytokine interleukin-7 (IL-7).**
- **IL-7released from nonlymphoid stromal cells in the bone marrow**
- **The developmental pathway for natural-killer (NK) cells is not yet well defined**



B Cell

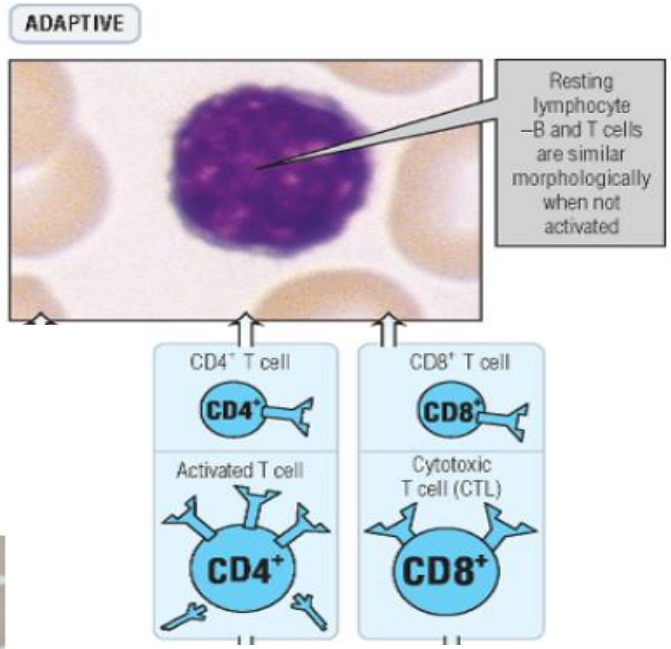
- **Cells that produce antibody**
- **Express immunoglobulin as an antigen-specific receptor along with several other important molecules, such as major histocompatibility complex (MHC) class II molecules and the co-receptor molecule CD19**
- **Have a large nucleus surrounded by a small rim of cytoplasm (rest state)**
- **Stimulated by antigen to form a larger blast cell with more cytoplasm, extensive endoplasmic reticulum, and secretory capacity for antibody**





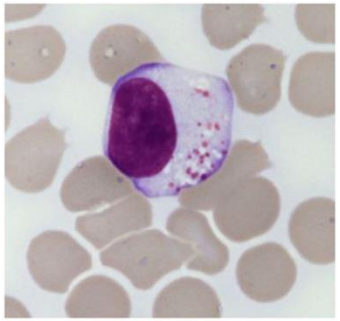
T cells

- Morphologically, T cells resemble unstimulated B cells
- T cells consist of two major subsets: $CD4^+$ helper cells and $CD8^+$ cytotoxic cells
- Major source of antigen-specific protection against viral infection and other intracellular infections



Natural Killer Cells (NK)

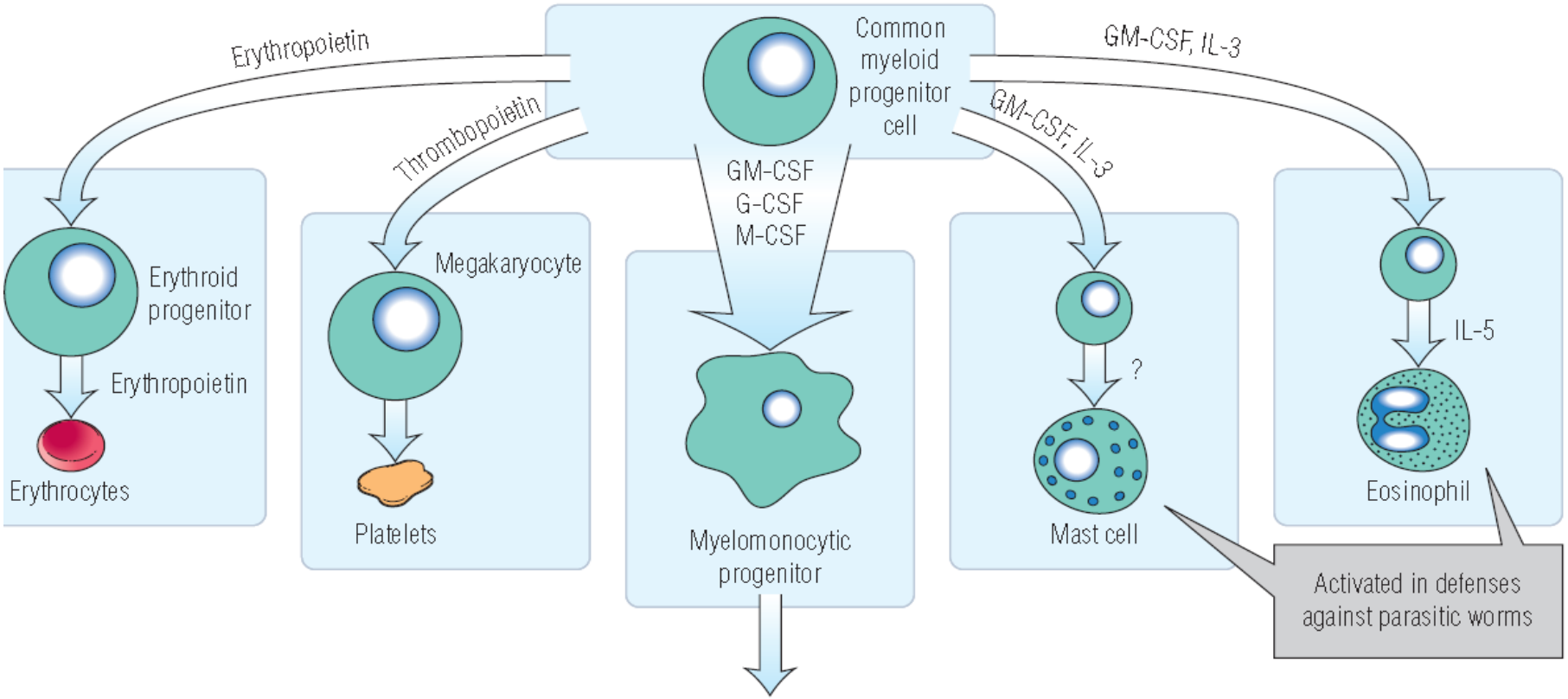
- lymphocytes that do not have clonally distributed antigen-specific receptors
- Part of the innate immune system and lyse certain virally infected cells and some tumor cells
- Carry receptors (KIR) that are specific for molecules expressed on infected cells



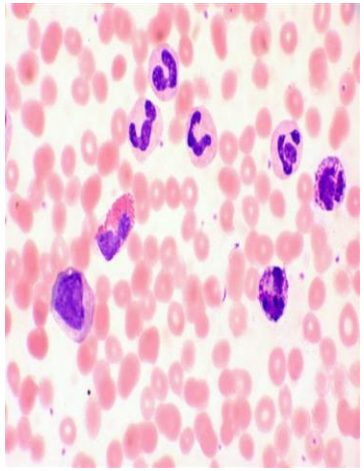
Myeloid Cells

The various differentiation pathways are stimulated by the actions of different growth factor combinations—

❑erythropoietin stimulates development of erythrocytes,



Myeloid Cell Types



1. Neutrophils

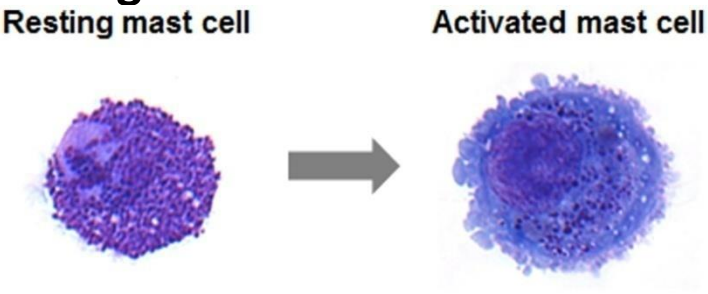
- **Exhibit phagocytic and cytotoxic activities**
- **Migrate to sites of inflammation and infection in response to chemotactic factors**
- **Short-lived with a half-life of about 6 hours**
- **Have nuclei with two to five lobes**
- **Development under the influence of G-CSF**
- **They contain both primary granules, loaded with lysosomal enzymes including myeloperoxidase and elastase, and secondary granules containing lysozyme**

2. Mast Cells

- **Have large granules that can be stained purple with dyes**

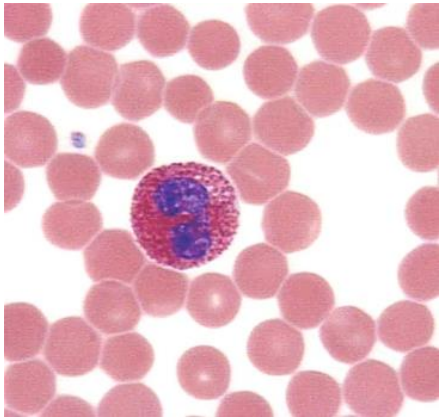
These granules contain heparin and histamine but do not contain hydrolytic enzymes

- **Express specific receptors on their surface for the Fc region of certain immunoglobulins, i.e., FcR_{γ} and FcR_{ε}**
- **Have important roles in allergic responses**



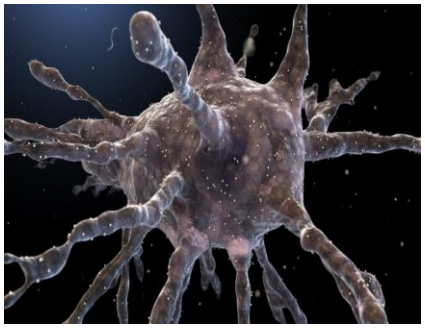
3. Eosinophils

- characterized by a nucleus with two or three lobes.
- Have large, specific granules, which contain heparin, as well as peroxidase and other hydrolytic enzymes.
- have phagocytic and cytotoxic activity and express Fc receptors, specifically FcR_{γ} and FcR_{ε}.
- These cells also function to combat certain parasitic infections—particularly worms



4. Monocytes/Macrophage

- The largest blood cells, contain many granules and have a lobular-shaped nucleus.
- Have bacteriocidal activity, and can carry out antibody-dependent cell-mediated cytotoxicity .
- Migrate out of the blood into the tissues and become tissue macrophages, e.g., the Kupffer cells of the liver.
- Express the monocyte/macrophage marker protein designated CD14.
- Macrophages have a central role at the dividing line between the innate and specific immune response because of their role in antigen processing and presentation



5. Dendritic Cells

- **Irregularly shaped cells with many branchlike processes.**
- **Motile and found in the blood and lymph and in most organs.**
- **Critical in antigen-capture and uptake in peripheral tissues.**
- **In the presence of infection, and under the influence of cytokines, they mature and migrate to lymphoid organs where they present antigen, activate T cells, and help develop a protective adaptive immune response**
- **Two main types of DCs are conventional DCs (cDCs) and plasmacytoid DCs (pDCs)**
- **The cDCs secrete IL-12, which activates the TH1 subset of T cells, and pDCs secrete the antiviral cytokine interferon-alfa.**

Colony-Stimulating Factors and Cytokines Important for Hematopoiesis

FIG. 12.5 Colony-Stimulating Factors and Cytokines Important for Hematopoiesis

Molecule	Major Cellular Sources	Major Biological Activity
Colony-stimulating factors		
Granulocyte	Monocytes, macrophages, fibroblasts, endothelial cells	Stimulates neutrophil formation
Granulocyte-macrophage	T cells, monocytes, macrophages, fibroblasts, endothelial cells	Stimulates proliferation and differentiation of myeloid progenitors
Monocyte/macrophage	Monocytes, macrophages, fibroblasts, endothelial cells	Stimulates proliferation and differentiation of monocytes and macrophages
Interleukins		
3	T cells	Stimulates multiple hematopoietic cells
4	T cells, activated mast cells	Stimulates B cells (to produce IgE), T_H2 cell differentiation and mast cells
5	T cells	Stimulates differentiation and activation of eosinophils, activates B cells for immunoglobulin production
7	Stromal cells in the bone marrow	Stimulates T-cell progenitor proliferation and differentiation, and is an essential growth factor for mature T cells

Box 12.3

Administration of Granulocyte Colony–Stimulating Factor for Neutropenia

Because of its important role in hematopoiesis, granulocyte colony-stimulating factor (G-CSF) has become a well-characterized protein. The G-CSF gene has been cloned, and a recombinant form of G-CSF has been produced for use in treatment because it causes an increase in neutrophil production in the bone marrow. Apart from its role in autologous stem cell transplantation, in vivo administration of G-CSF has been approved for the treatment of neutropenias caused by several conditions, including cancer chemotherapy and acute leukemia. The enhanced neutrophil levels produced by G-CSF treatment have been shown to protect these otherwise neutropenic patients from life-threatening bacterial infections (see Box 21.1).

The Organs and Tissues of the Immune System

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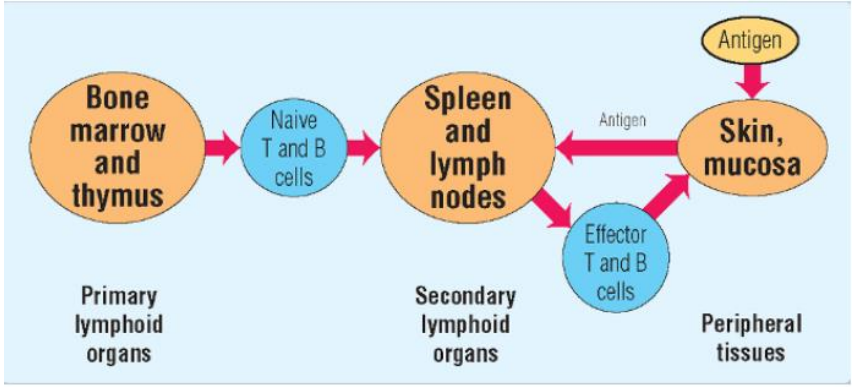
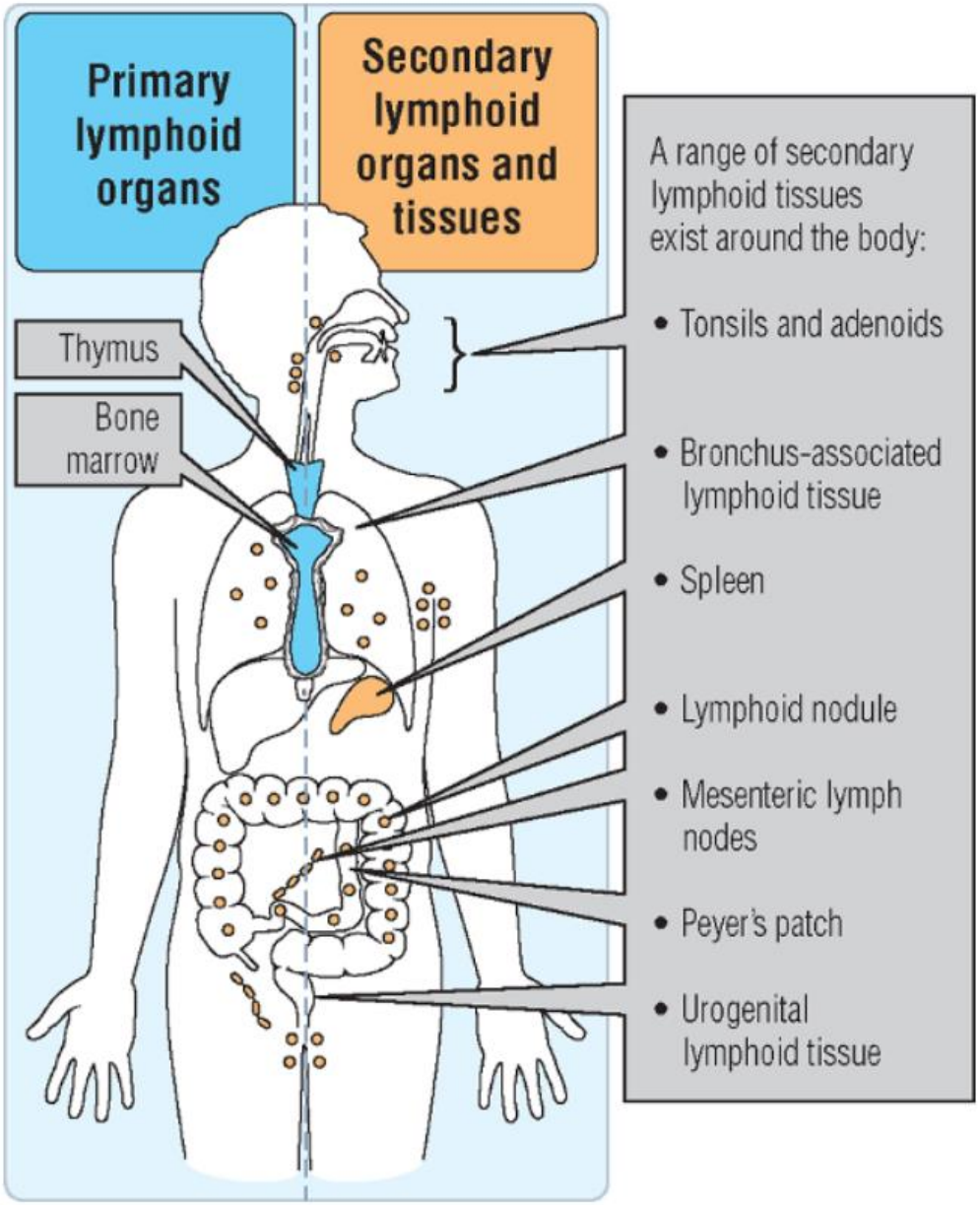


Medical immunology M215
Lecture11

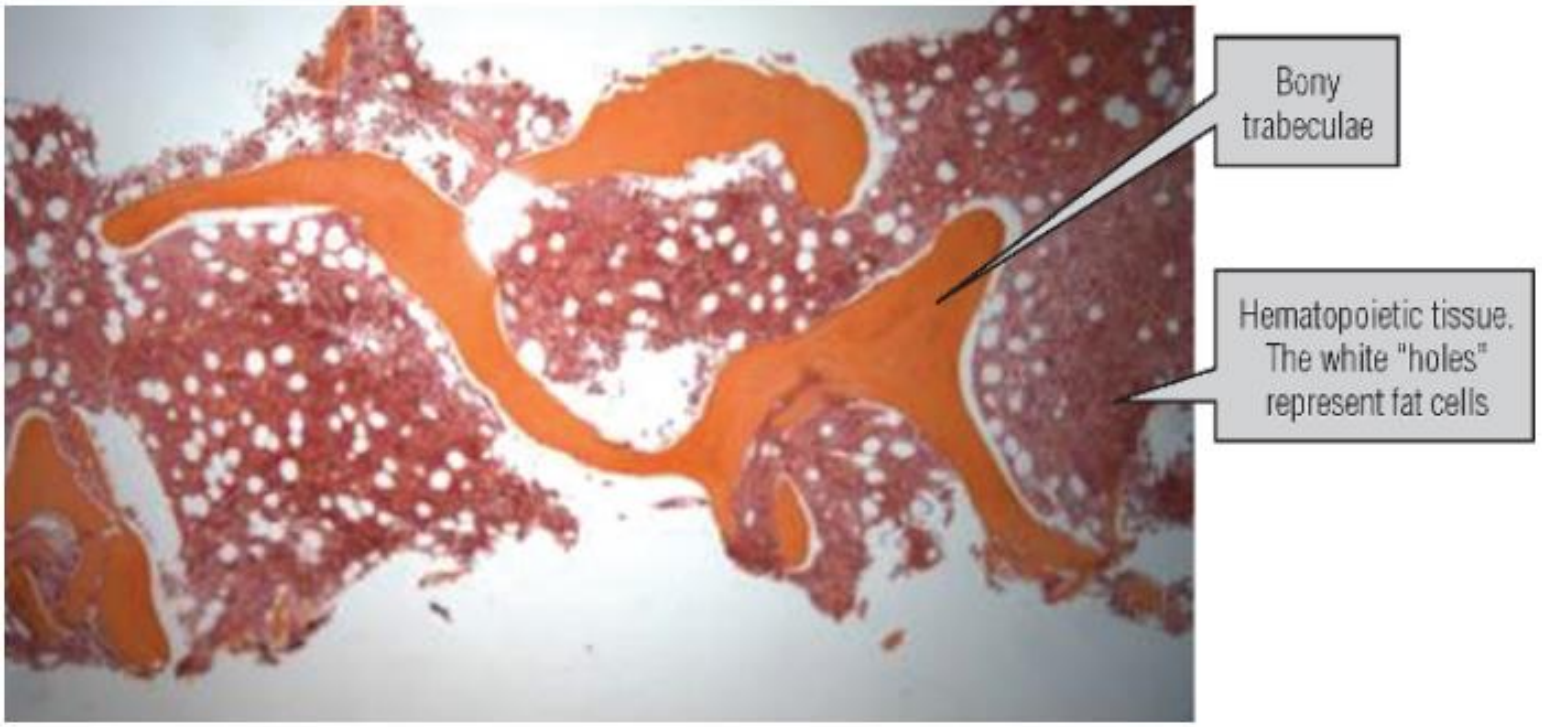
Major lymphoid organs in the adult human



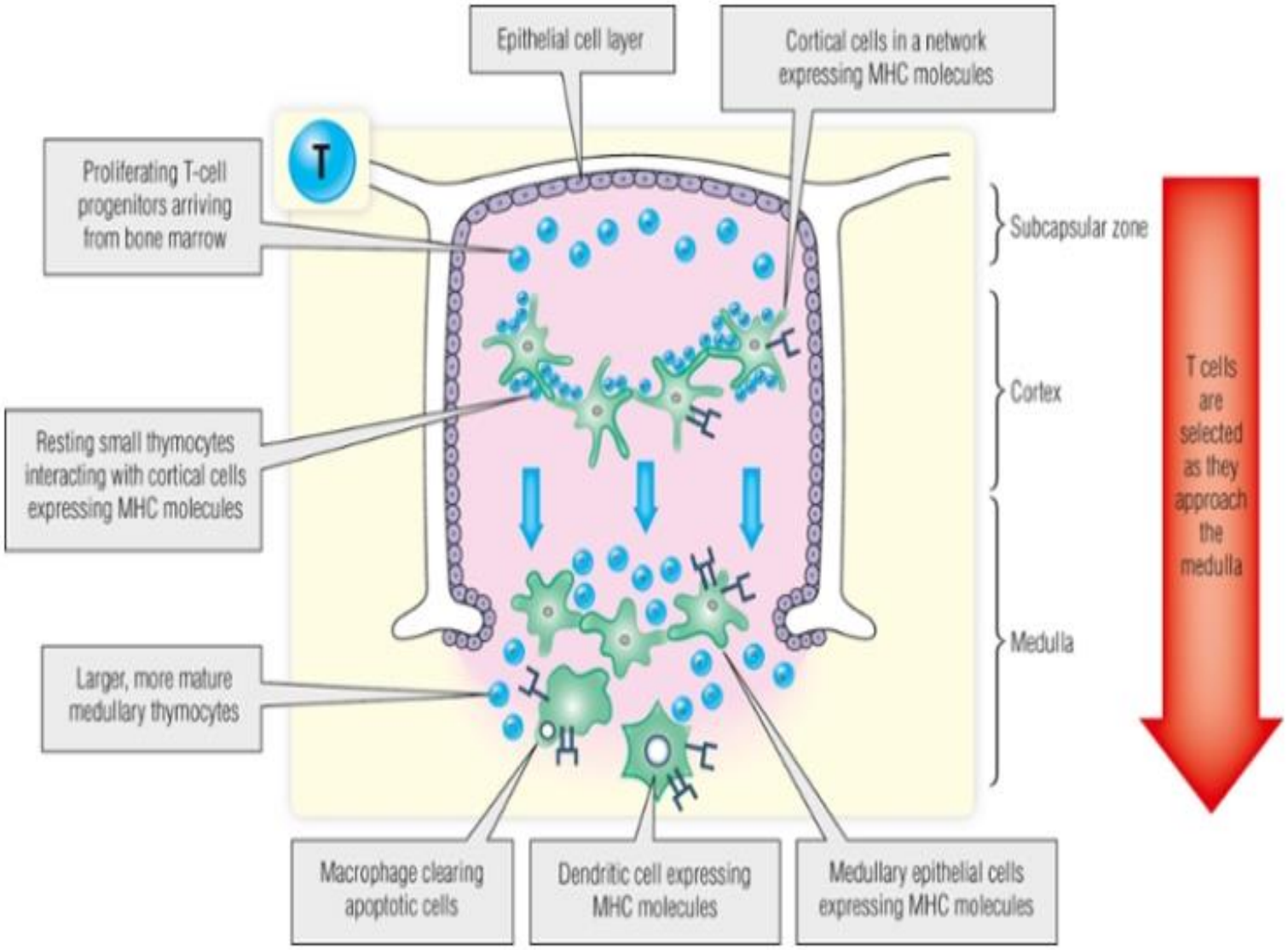
Bone Marrow

All of the blood cell types except mature T lymphocytes are generated in the extensive cavities in the bone marrow.

B-cell generation takes place in these internal cavities; development from B-cell progenitors to immature B cells occurs in a radial direction toward the center of the bone



Thymus


Epithelial cell layer
Cortical cells in a network expressing MHC molecules
T
Proliferating T-cell progenitors arriving from bone marrow
Subcapsular zone
Cortex
Medulla
T cells are selected as they approach the medulla
Resting small thymocytes interacting with cortical cells expressing MHC molecules
Larger, more mature medullary thymocytes
Macrophage clearing apoptotic cells
Dendritic cell expressing MHC molecules
Medullary epithelial cells expressing MHC molecules

Thymus

The thymus is a bilobed organ, found in the anterior mediastinum

The thymus forms from two types of epithelial cell (endoderm and ectoderm) derived from the third pharyngeal pouch

Each of the lobes of the thymus is divided further into lobules by connective tissue septae called trabeculae

- **The subcapsular zone containing the earliest progenitor cells**
- **The cortex, which is densely packed with developing T cells that are undergoing selection**
- **The medulla containing fewer, but more mature, T lymphocytes; these have survived the selection processes and are about to be released to the periphery**

Spleen

❖ **It is a major "filter" for the blood, removing opsonized microbes and dead red blood cells**

❖**It is also the main site for responses to blood-borne antigens**

❖ **spleen has two main areas:**

1. red pulp, containing chiefly macrophages and red blood cells in the process of disposal

2. white pulp, containing dense lymphoid tissue.

The white pulp is segregated into B- and T-lymphocyte areas

A. Periarteriolar lymphoid sheaths (PALS): T cells area

B. Lymphoid follicles (some with germinal center) : B cells

Box 13.1
Risks of Splenectomy

A 28-year-old man presents to the emergency department in shock with low blood pressure and high fever. He underwent an emergency splenectomy 2 years prior but has not been on antibiotics since then. A diagnosis of postsplenectomy invasive sepsis is made. He is resuscitated and started on penicillin and makes a prompt recovery. A day later, pneumococcus is cultured from blood taken in the emergency department, confirming the diagnosis.

The spleen is a soft, spongy organ that bleeds easily following trauma. In certain situations, such as seat-belt–mediated trauma sustained to the midsection in a car accident, the spleen can be ruptured and must be surgically removed.

Several thousand people have undergone splenectomy in the United States. Splenectomized patients are more susceptible to infection by encapsulated bacteria such as pneumococci. This is true for two reasons. First, the spleen contains many of the T-independent B cells that make antibody against the polysaccharide capsule of these bacteria. Second, the spleen contains a large number of macrophages, which phagocytose opsonized bacteria in the blood. Splenectomized patients are significantly at risk for infectious disease and are therefore maintained on lifelong prophylactic antibiotics. They also receive vaccines against some of the pathogens for which they are at risk.

lymph node

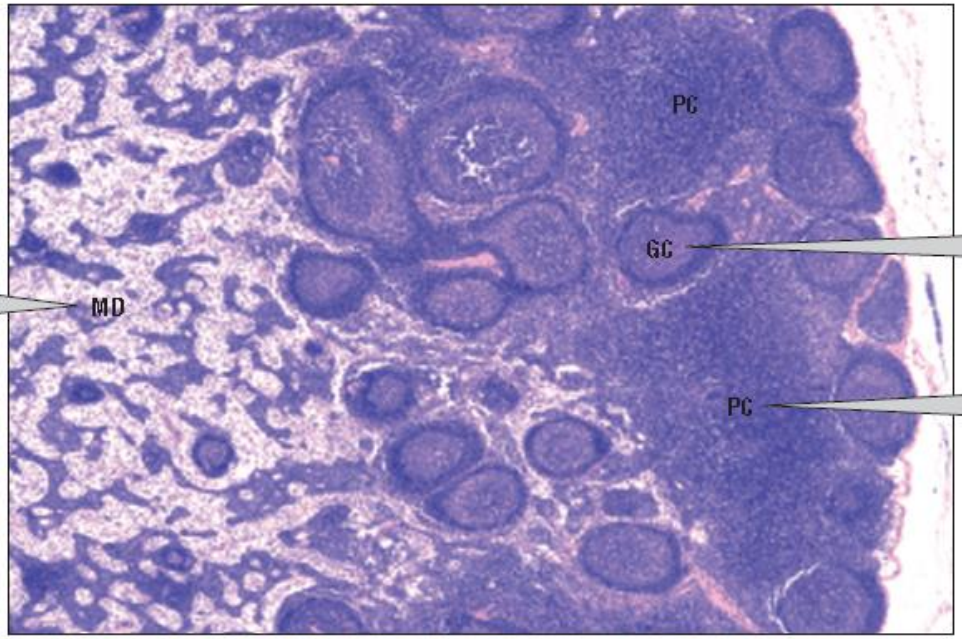
- A lymph node is a bean-shaped structure
- found clustered in groups at sites where numerous blood and lymph vessels converge
- Lymph nodes function to concentrate lymph-borne antigens for presentation to T cells

- A lymph node is organized into several areas

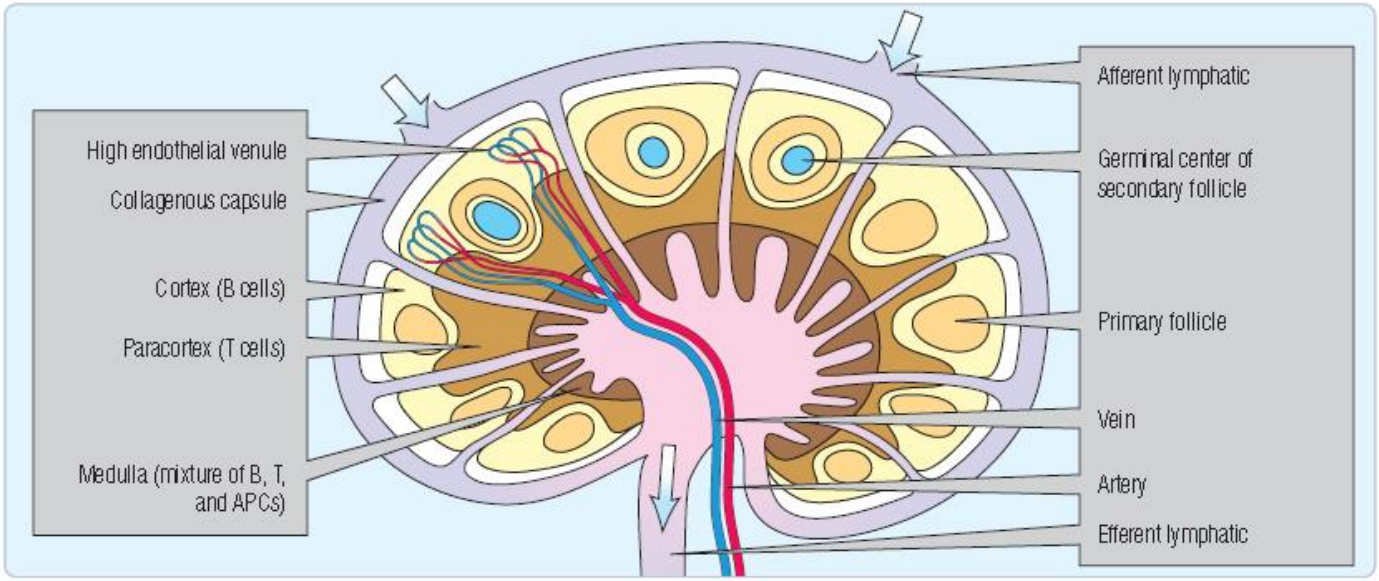
a. cortex is predominantly the site of B cells
b. Paracortex is predominantly a $CD4^+$ T-cell area
c. Medulla contains a mixture of B cells, T cells, and macrophages.

During a infection, B and T cells in the node are activated Fluid and cells are accumulated in the node leading to lymph-node enlargement (the "swollen gland" typical of response to infection)

(a)


PC
GC
MD
PC
Medulla region (MD) containing a mixture of B cells, T cells and APCs
Secondary follicle with a germinal center (GC) rich in B cells
Paracortex (PC) rich in T cells

(b)


High endothelial venule
Collagenous capsule
Cortex (B cells)
Paracortex (T cells)
Medulla (mixture of B, T, and APCs)
Afferent lymphatic
Germinal center of secondary follicle
Primary follicle
Vein
Artery
Efferent lymphatic

Box 13.2
Lymphadenopathy

A 26-year-old man attends your clinic complaining of lumps in his throat. On further questioning, he has had a sore throat for about 4 days and is very anxious because his father was recently diagnosed with laryngeal cancer. On examination, your patient has some redness of the fauces and tonsils, which are slightly enlarged with two small (approximately 1-cm diameter) lymph nodes in the right anterior triangle. You explain that the patient's symptoms are most consistent with an acute viral infection of the upper respiratory tract and that treatment is not necessary. To be safe, you take a throat swab to rule out bacterial pathogens.

Lymphadenopathy is usually the consequence of acute infection. Localized lymphadenopathy occurs as a consequence of localized infection, as is the case here, and is usually associated with a localizing sign; in this case, the throat was inflamed. Lymphadenopathy that persists for more than a few days or affects many different sites may indicate other disease processes, such as chronic infection (eg, tuberculosis or HIV) or malignancy.

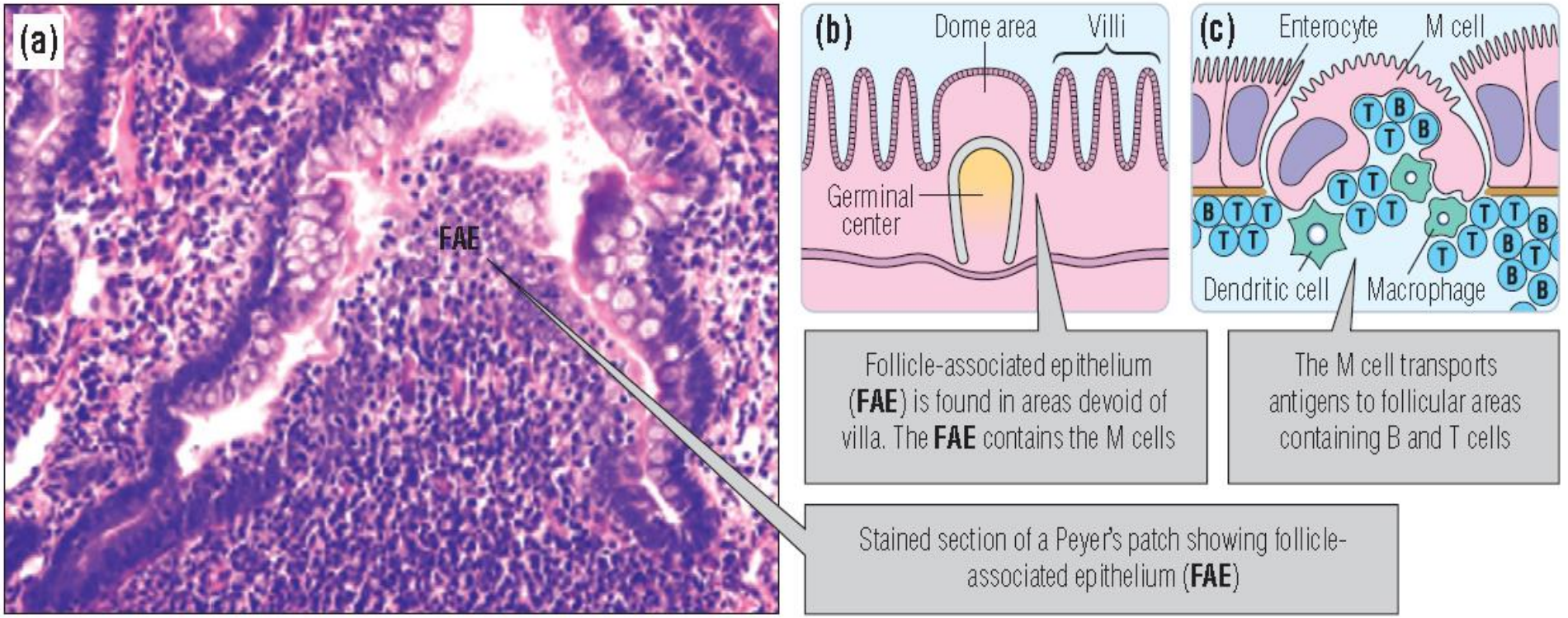
Mucosa-Associated Lymphoid Tissue(MALT)

❖**The mucosal immune system handles antigen at a contact point between the host and the environment**

❖**The mucosal immune system is principally composed, in humans, of lymphoid tissue**

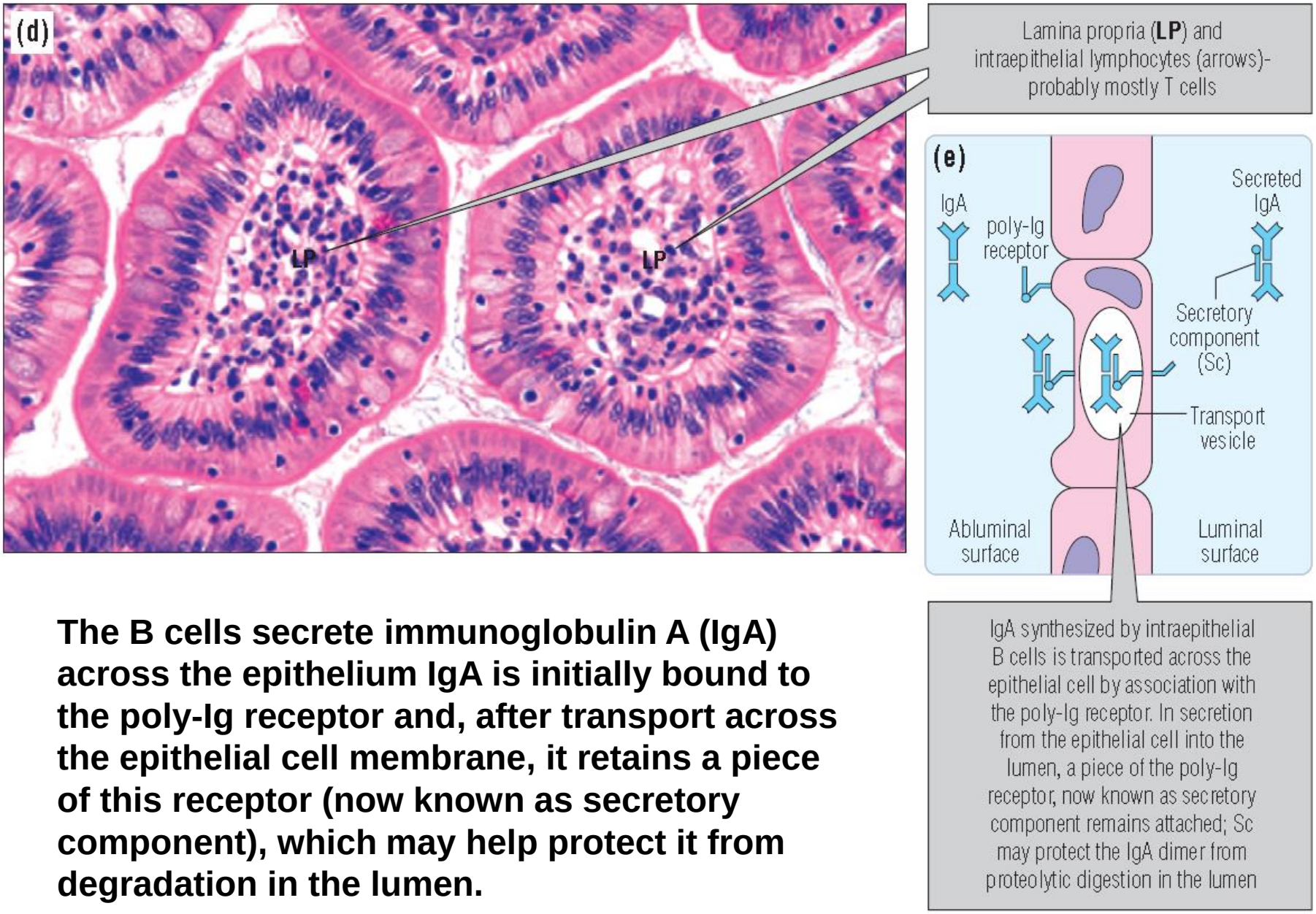
a. **In respiratory gastrointestinal tracts : known as nasopharyngeal-associated lymphoid tissue (NALT) e.g tonsils and adenoids**
b. **In gastrointestinal tracts :known as gut-associated lymphoid tissue (GALT; e.g., Peyer's patches)**

Mucosa-Associated Lymphoid Tissue(MALT)



- MALT contain a specialized epithelial cell type (M cells) that takes up antigens that are inhaled or ingested by the process of **pinocytosis** ⟹ The M cells transport antigens by a transcellular transport process called transcytosis into the subepithelial tissues where they encounter lymphocytes.

Transport of immunoglobulin A across epithelium



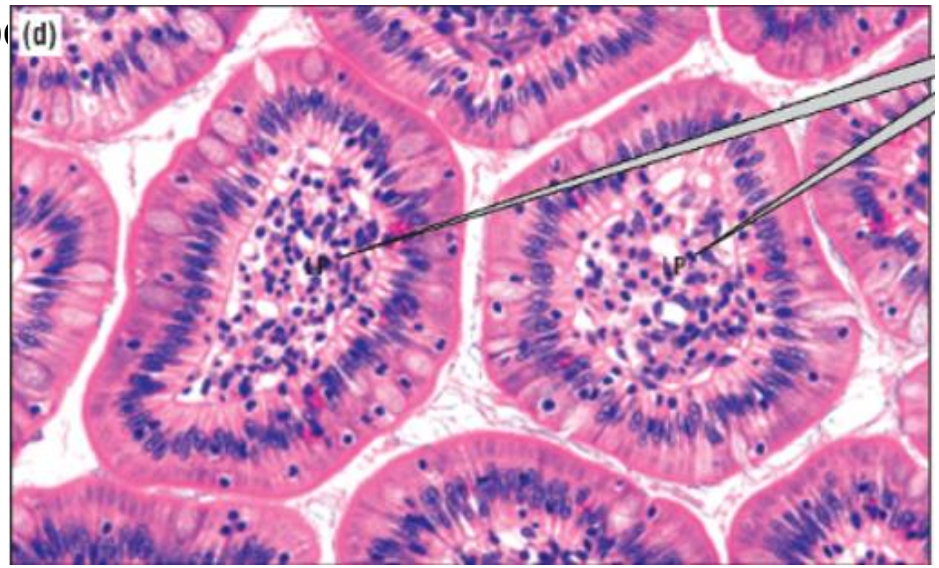
The B cells secrete immunoglobulin A (IgA) across the epithelium IgA is initially bound to the poly-Ig receptor and, after transport across the epithelial cell membrane, it retains a piece of this receptor (now known as secretory component), which may help protect it from degradation in the lumen.

Intraepithelial Lymphocytes

❖**The mucosal epithelium of the gastrointestinal, respiratory, and reproductive tracts contains large numbers of lymphocytes. These lymphocytes are mostly T cells (~90%)**

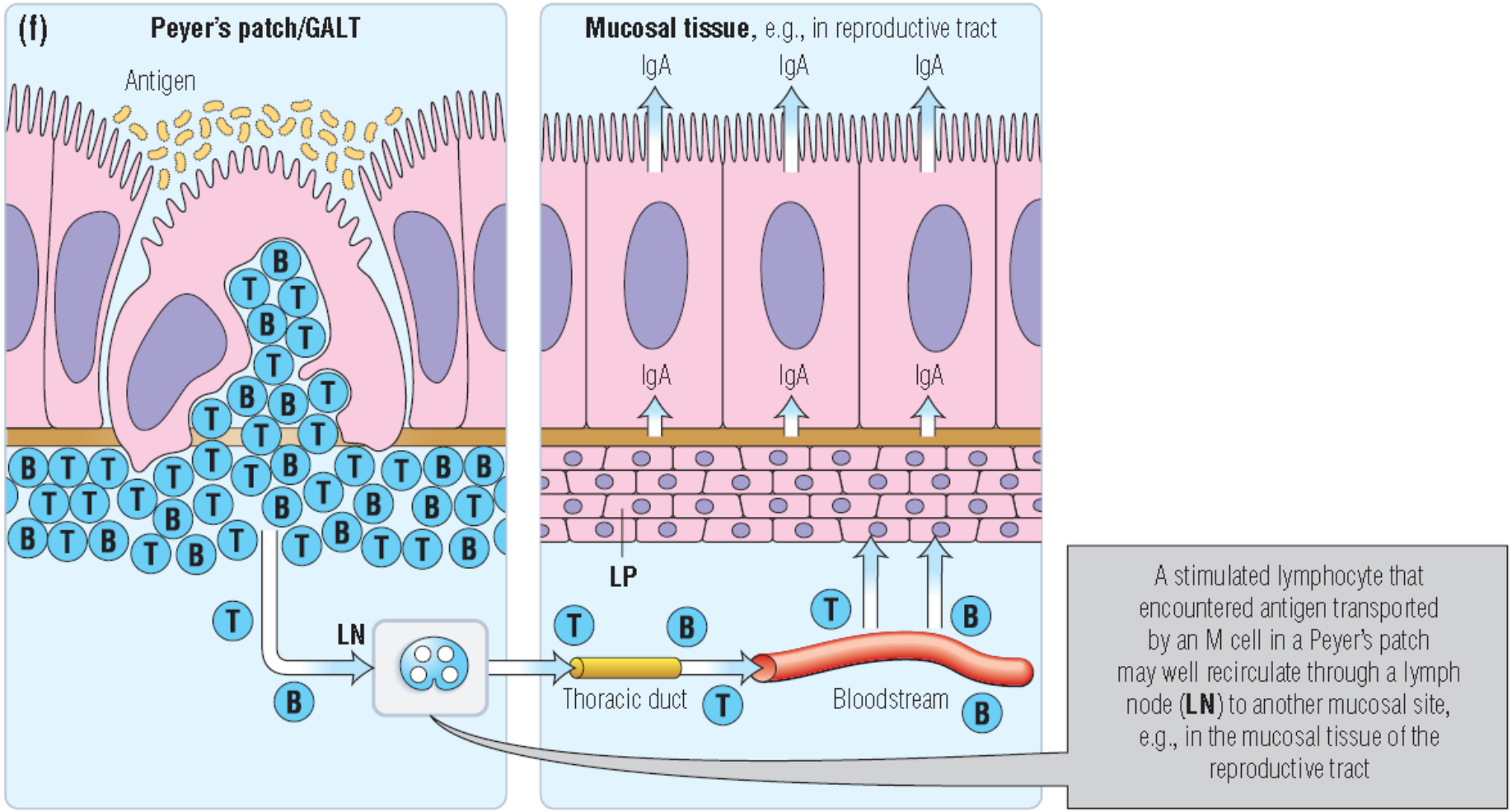
❖**Intraepithelial lymphocytes act to protect the host against viral and bacterial pathogens encountered in the gut. In addition to their role as effector T cells,**

❖**The intraepithelial T cells secrete cytokines that have a role in regulating immune responses in the mucosa. This regulatory role may, for example, prevent excessive resp**

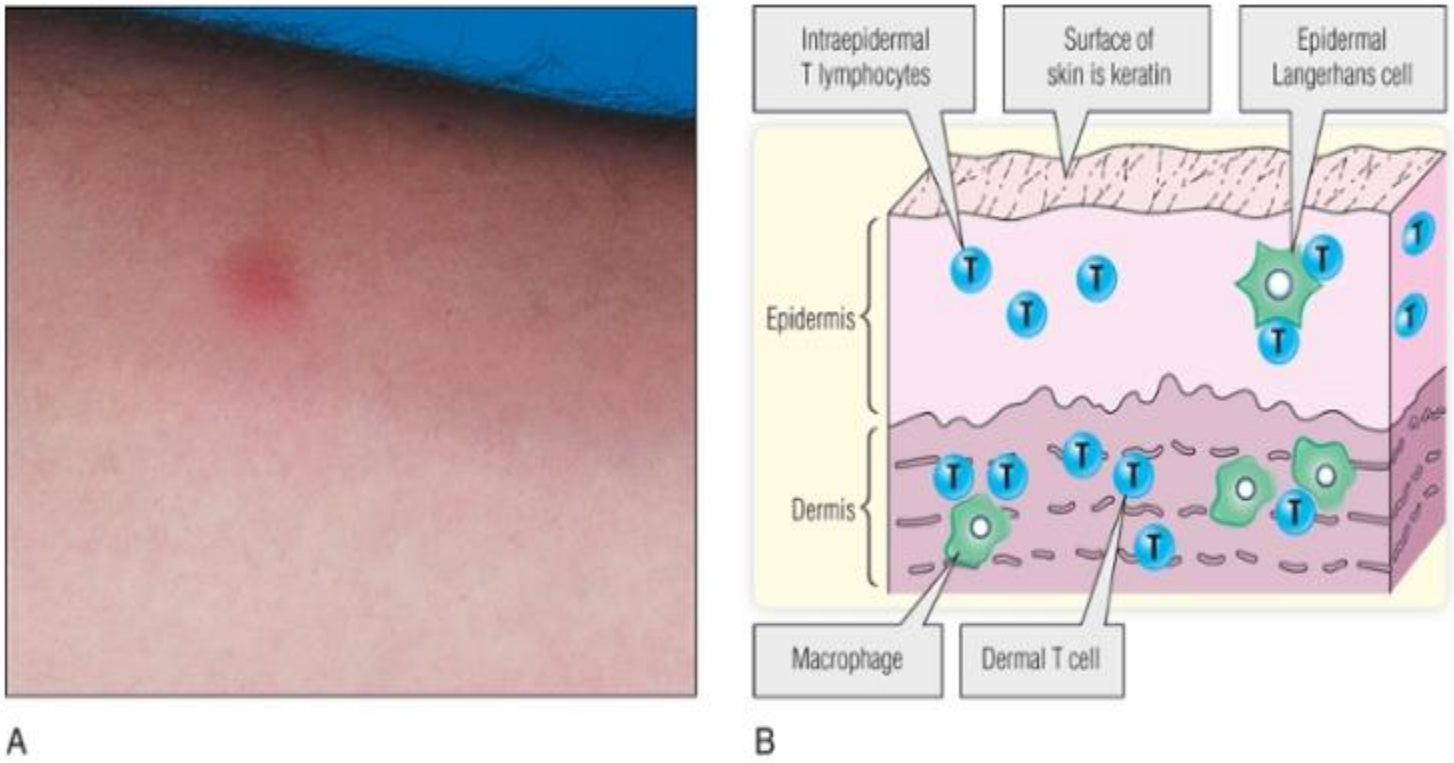


Recirculation

After exposure to antigen in the MALT, lymphocytes may leave and home to other mucosal tissues. (recirculation or trafficking) from Peyer's patches in the gut to other mucosal surfaces



Skin: The Cutaneous Immune System



The epidermal layer of the skin has numerous dendritic cells called *Langerhans cells*

The T cells found in the epidermal layer, the *intraepidermal T cells*, are chiefly $CD8^+$ T cells that carry γδ T-cell receptors

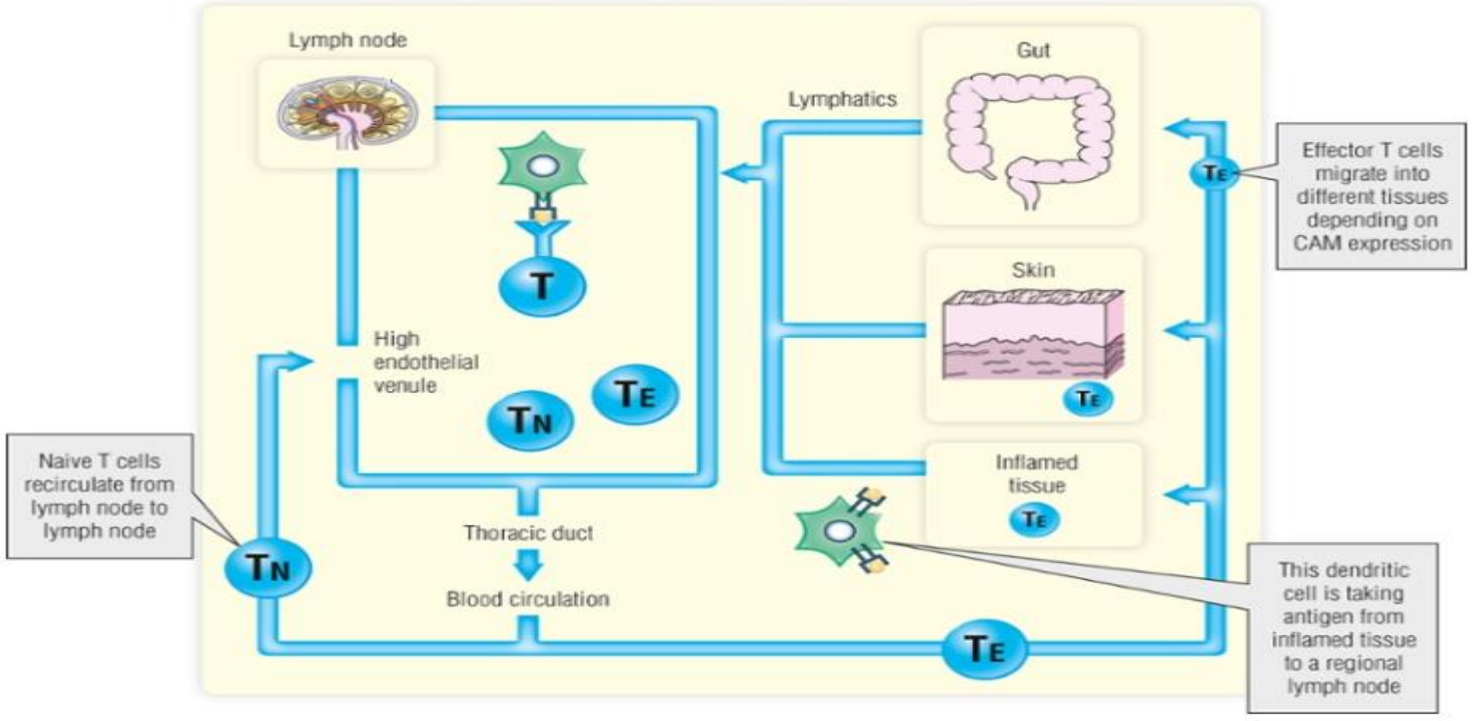
LYMPHOCYTE RECIRCULATION TRAFFICKING AND HOMING

a lymphocyte makes acircuit of the human body, from the blood, to the tissues, to the lymphatic system, and returns to the blood, once or twice a day.

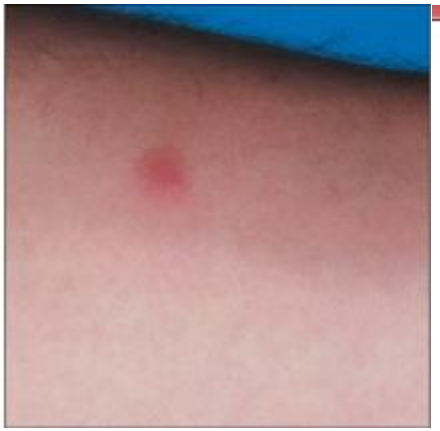
Most of the circulating lymphocytes are T lymphocytes.

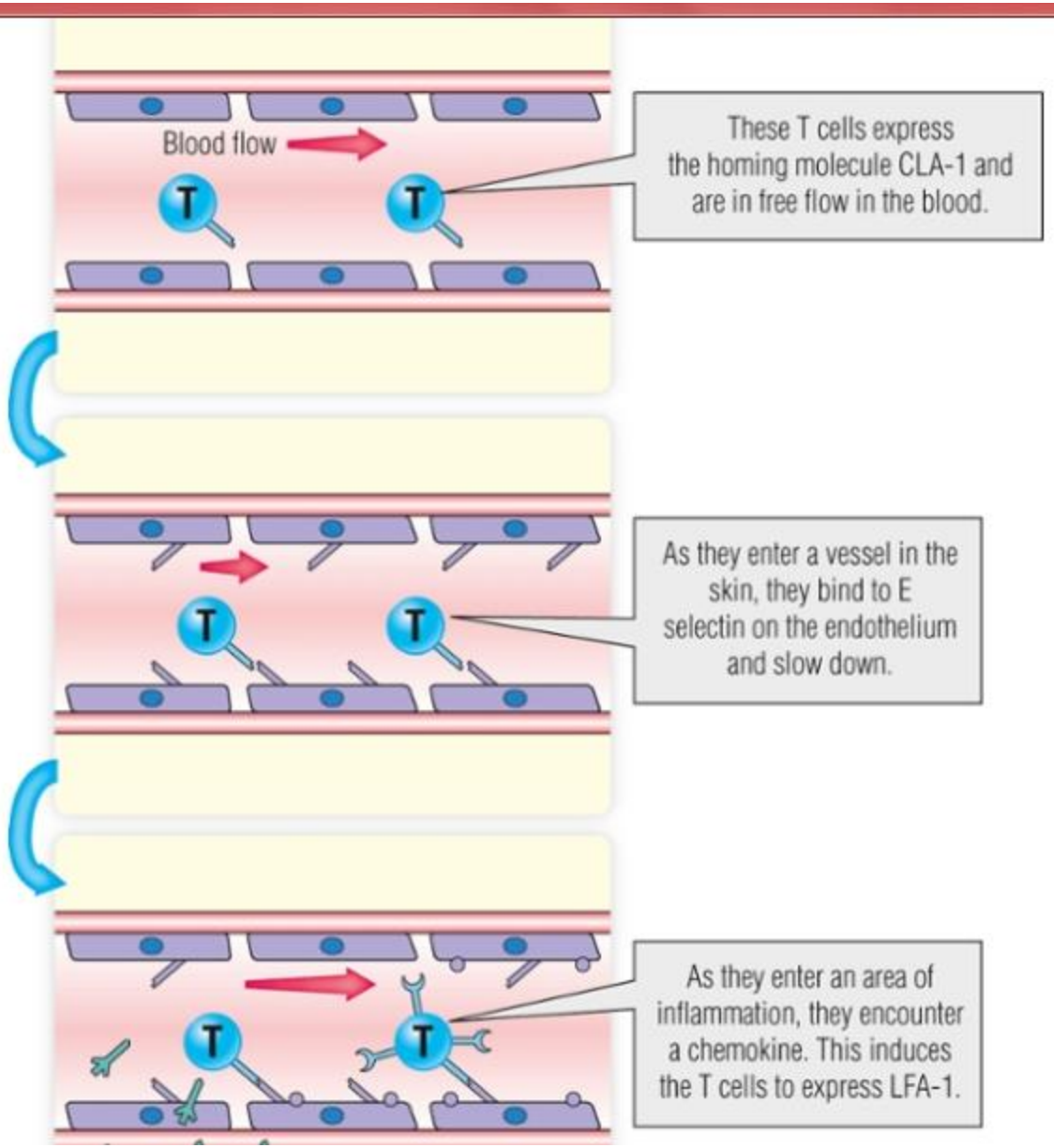
lymphocyte homing

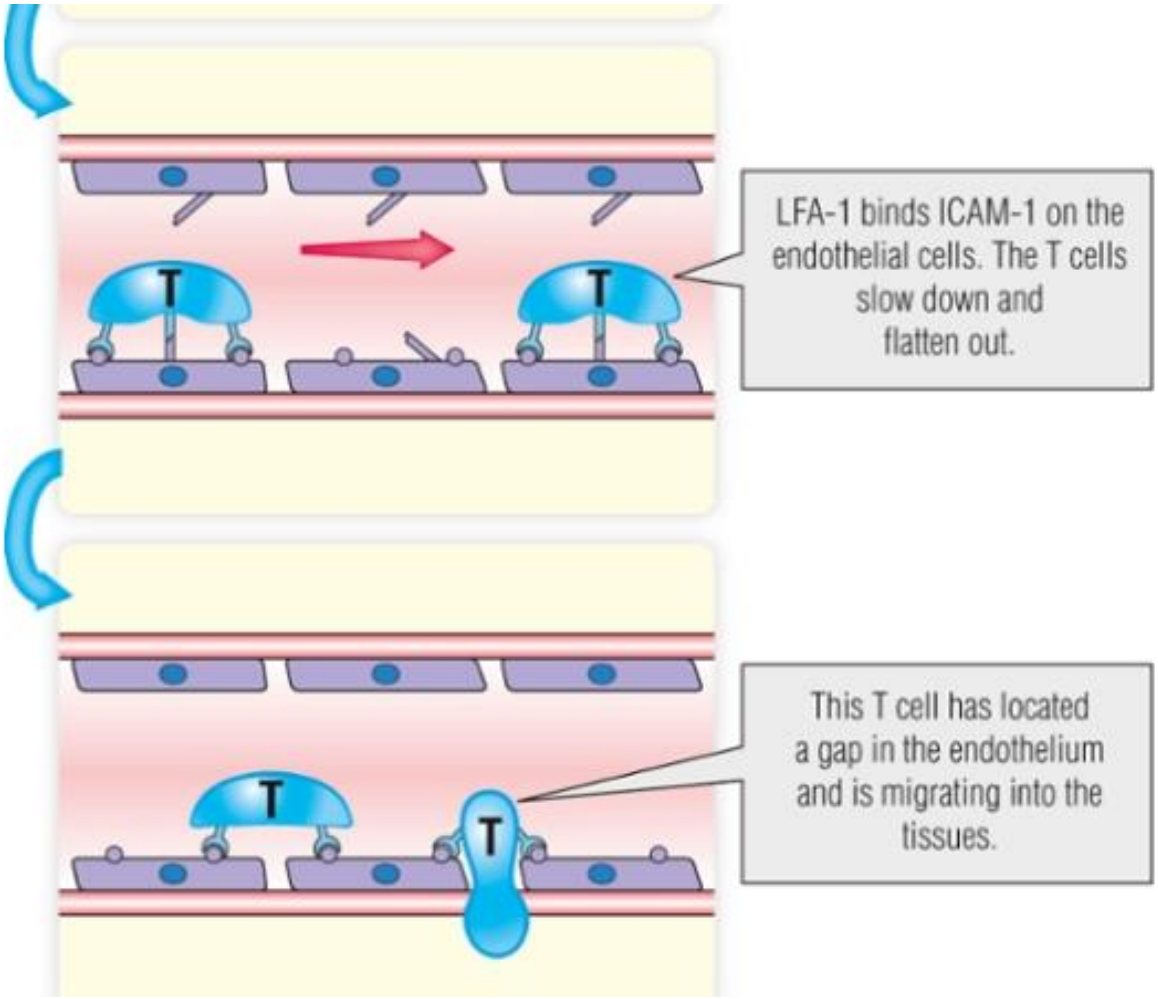
T lymphocytes migrate to and lodge in selected tissue sites, where they



How skin-specific T cell respond to local inflammation






T
T
LFA-1 binds ICAM-1 on the endothelial cells. The T cells slow down and flatten out.
T
T
This T cell has located a gap in the endothelium and is migrating into the tissues.

Lymphocyte recirculation and homing is regulated by receptor-ligand interactions between members of the different families of cell adhesion molecules (selectins, addressins, integrins)

TABLE 13.1 Ligands and Cell Adhesion Molecules

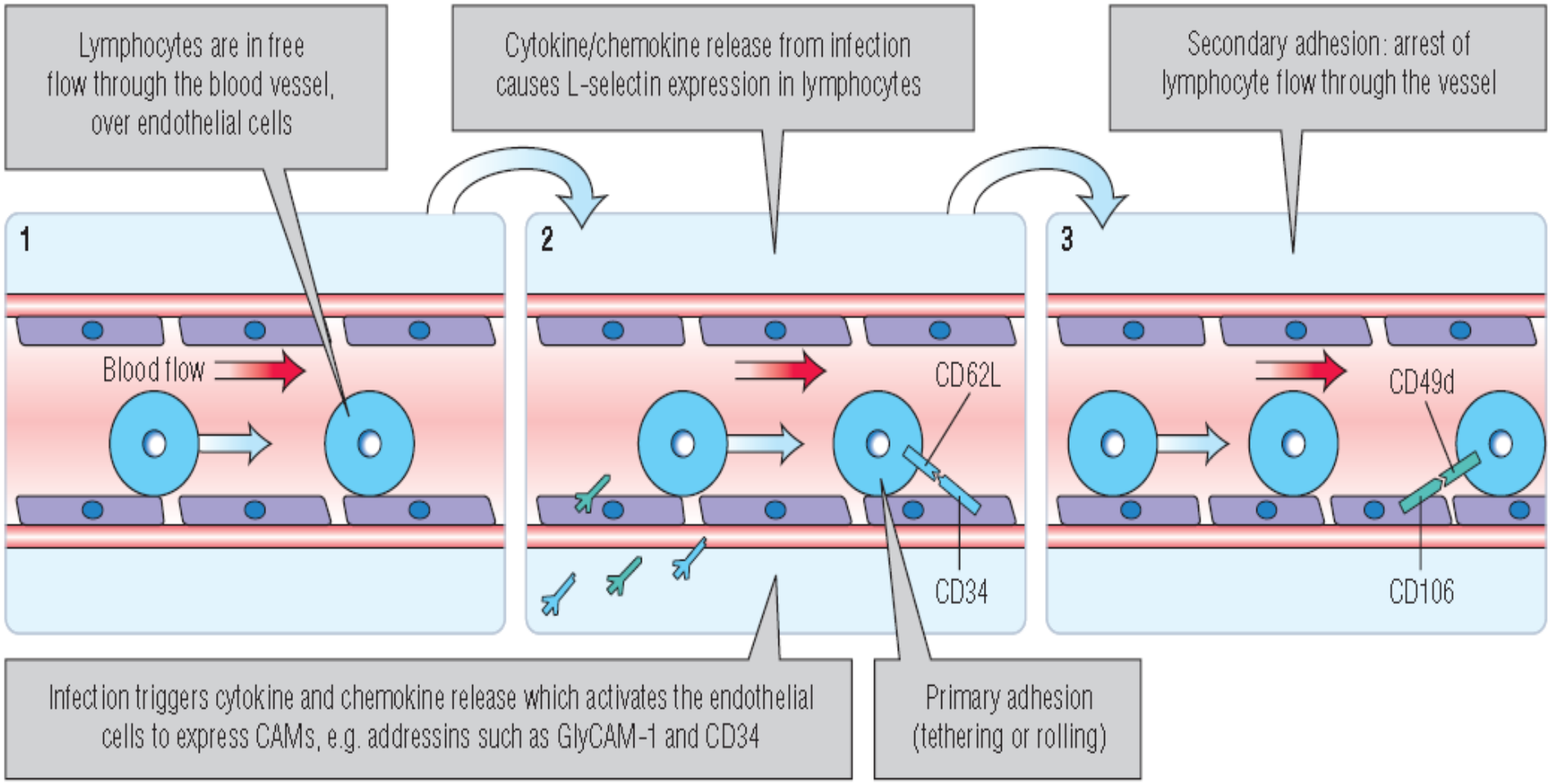
Function of Ligand Pair	CAM on Lymphocyte	CAM on Local Tissue
Recirculation of naive T cells to lymph nodes	L selectin on naive T cells	GLYCAM1 on high endothelial blood vessels
Homing of effector T cells into the gut	Integrin α4/β6 on effector lymphocytes	MADCAM1 on mucosal endothelium
Homing of effector T cells into the skin	CLA-1 on effector lymphocytes	E-selectin on skin endothelium
Homing of lymphocytes into inflamed tissue	LFA-1 on T cells activated by chemokines	ICAM1 on inflamed endothelium
Stabilization of immune synapse	LFA-1 on T cells activated by antigen recognition	ICAM1 on antigen-presenting cell

CAM, cell adhesion molecule; *CLA,* cutaneous lymphocyte antigen; *GLYCAM,* glycosylation-dependent cell adhesion molecule; *ICAM,* intercellular adhesion molecule; *LFA;* leukocyte function–associated antigen; *MADCAM,* mucosal vascular addressin cell adhesion molecule.

Lymphocyte Extravasation

steps in lymphocyte extravasation.

1. Primary adhesion to endothelium 2. Lymphocyte activation



Lymphocyte Extravasation