VIVEKANANDA COLLEGE
THAKURPUKUR
KOLKATA-700063

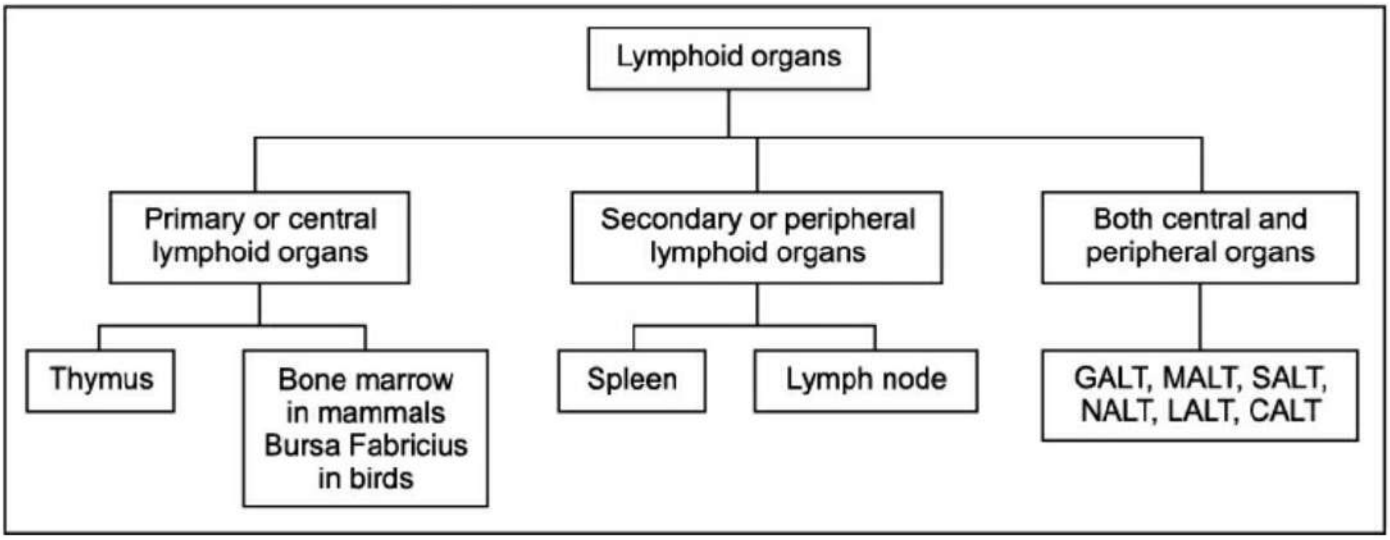
NAAC ACCREDITED 'A' GRADE

TOPIC	**: ORGANS & CELLS OF THE IMMUNE SYSTEM**
COURSE TITLE	**: IMMUNOLOGY**
PAPER	**: CC10**
UNIT	**: UNIT.1**
SEMESTER	**: 4TH SEMESTER**
NAME OF THE TEACHER	**: DR. MALABIKA BHATTACHARJEE**
NAME OF THE DEPARTMENT	**: DEPARTMENT OF ZOOLOGY [UG & PG]**

ORGANS OF THE IMMUNE SYSTEM

REFERENCE

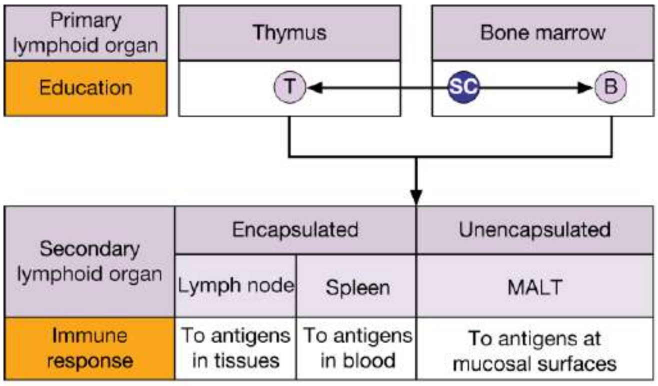
1. ROITT'S ESSENTIAL IMMUNOLOGY
2. KUBY IMMUNOLOGY
3. CELLULAR AND MOLECULAR IMMUNOLGY ABBAS
4. IMMUNOLGY MALE AND BROSTOFF
5. IMMUNOLOGY KHAN
6. CELL BRUCE ALBERTS



1. INTRODUCTION

2. A number of morphologically and functionally diverse organs and tissues have various functions in the development of immune responses.
3. These can be distinguished by function as the **PRIMARY** and **SECONDARY LYMPHOID ORGANS**. The thymus and bone marrow are the primary (or central) lymphoid organs, where maturation of lymphocytes takes place.
4. The lymph nodes, spleen, and various mucosal associated lymphoid tissues (MALT) such as gut-associated lymphoid tissue (GALT) are the secondary (or peripheral) lymphoid organs, which trap antigen and provide sites for mature lymphocytes to interact with that antigen.
5. In addition, **TERTIARY LYMPHOID TISSUES,** which normally contain fewer lymphoid cells than secondary lymphoid organs, can import lymphoid cells during an inflammatory response. Most prominent of these are cutaneous-associated lymphoid tissues.

6. Once mature lymphocytes have been generated in the primary lymphoid organs, they circulate in the blood and **<u>LYMPHATIC SYSTEM,</u>** a network of vessels that collect fluid that has escaped into the tissues from capillaries of the circulatory system and ultimately return it to the blood.



THE FUNCTIONAL ORGANIZATION OF LYMPHOID TISSUE.

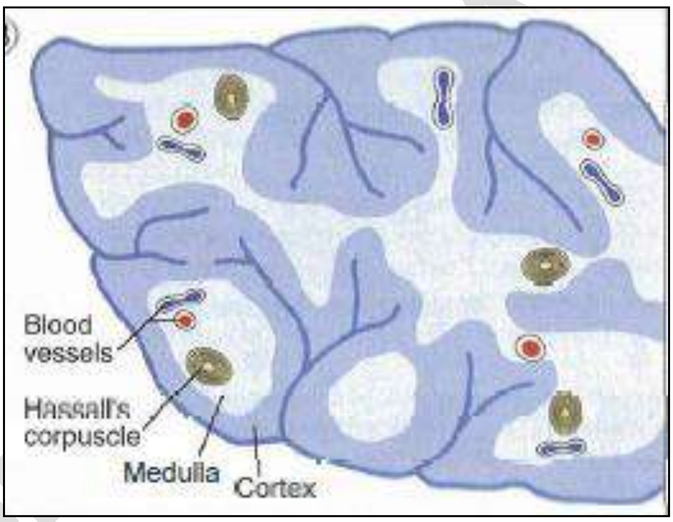
1. Hematopoietic stem cells (SC) arising in the bone marrow differentiate into immunocompetent T- and B-cells in the primary lymphoid tissues and then colonize the secondary lymphoid tissues where immune responses are organized.
2. The mucosa-associated lymphoid tissue (MALT), together with diffuse collections of cells in the lamina propria, produces antibodies for mucosal secretions.

2. PRIMARY LYMPHOID ORGANS

1. Immature lymphocytes generated in ***hematopoiesis mature and become committed to a particular antigenic specificity within the primary lymphoid organs***.
2. Only after a lymphocyte has matured within a primary lymphoid organ is the cell **immunocompetent** (capable of mounting an immune response).
3. T cells arise in the **thymus,** and in many mammals—humans and mice for example—B cells originate in **bone marrow.**

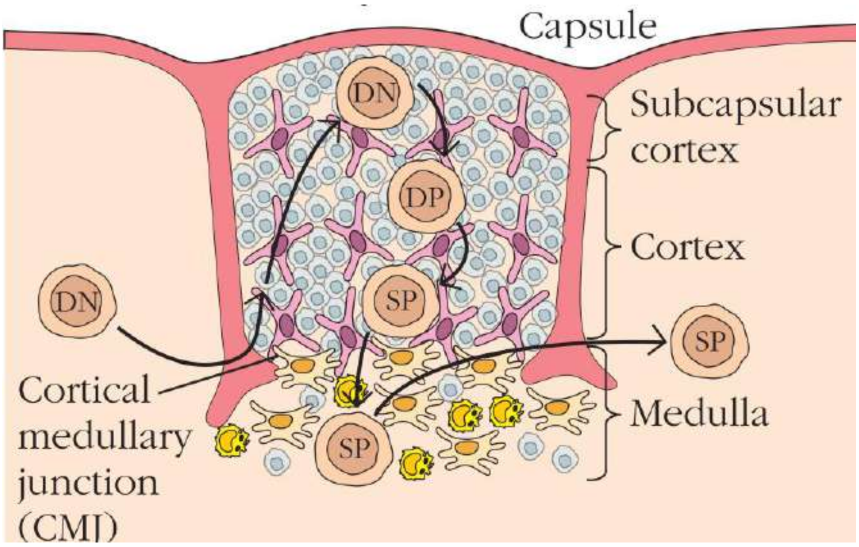
2.1.THYMUS

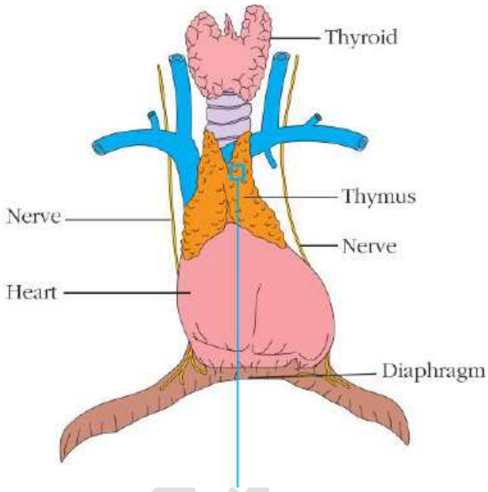
MORPHOLOGY:
The thymus is the site of T-cell development and maturation. It is a flat, bilobed organ situated above the heart.



STRUCTURE:

1. Each lobe is **<u>surrounded by a capsule</u>** and is divided into lobules, which are separated from each other by strands of connective tissue called trabeculae.
2. Each lobule is organized into two compartments: the outer compartment, or **<u>cortex,</u>** is **densely packed** with immature T cells, called **thymocytes**, whereas the inner compartment, or **<u>medulla</u>**, is **sparsely populated** with **thymocytes**.
3. Both the cortex and medulla of the thymus are crisscrossed by a **three-dimensional stromal-cell** network composed of epithelial cells, dendritic cells, and macrophages, which make up the framework of the organ and contribute to the growth and maturation of thymocytes.
4. Many of these **<u>stromal cells</u>** interact physically with the developing thymocytes. Some thymic epithelial cells in the outer cortex, called **<u>nurse cells,</u>** have long membrane extensions that surround as many as 50 thymocytes, forming large multicellular complexes.
5. Other **<u>cortical epithelial cells</u>** have long interconnecting cytoplasmic extensions that form a network and have been shown to interact with numerous thymocytes as they traverse the cortex.





FUNCTION:

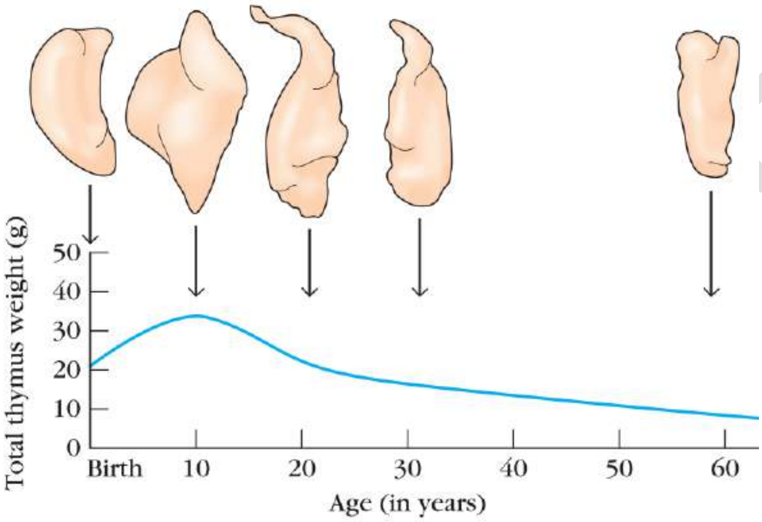
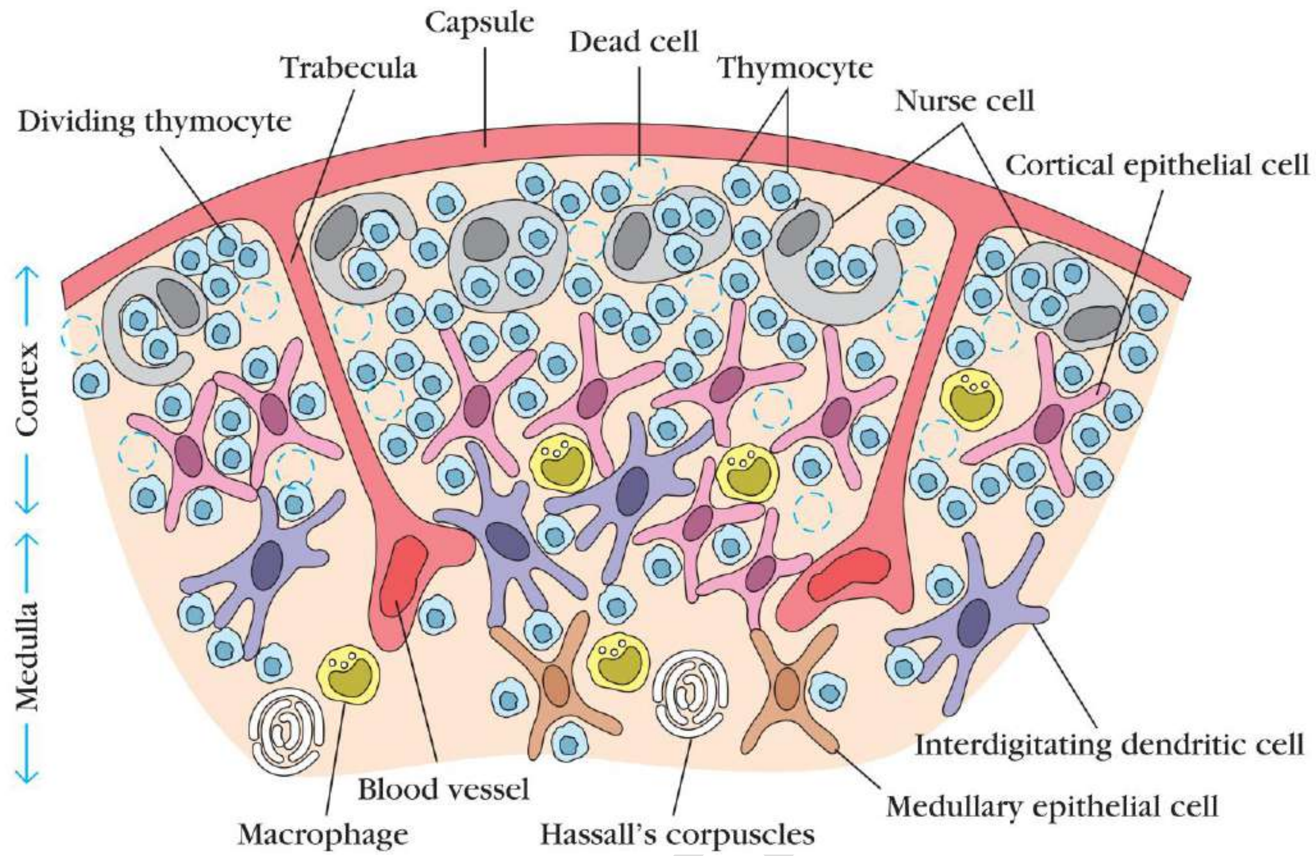


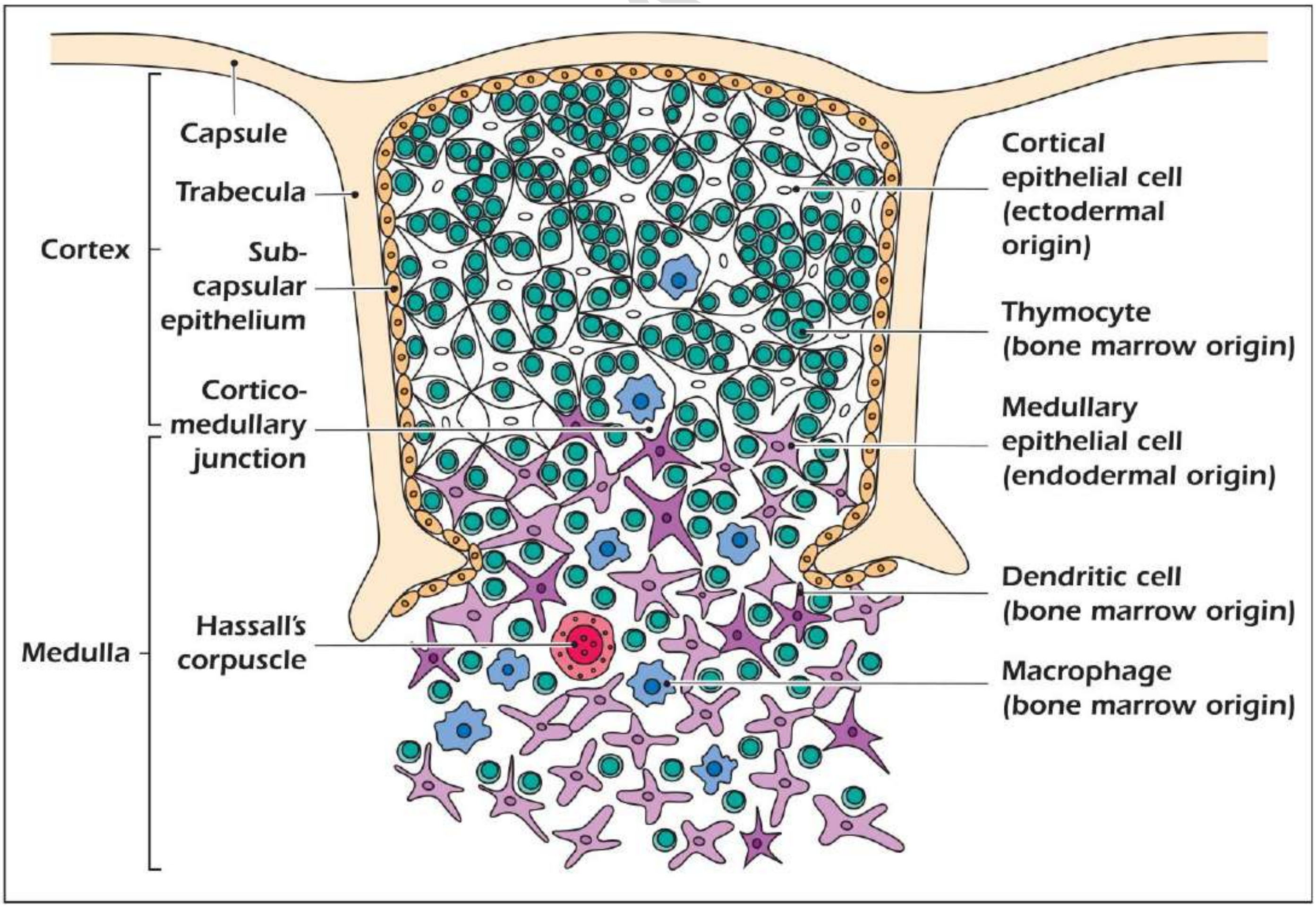
FIGURE 2-15 Changes in the thymus with age. The thymus decreases in size and cellularity after puberty.

1. The function of the thymus is **<u>to generate and select a repertoire of t cells</u>** that will protect the body from infection. As thymocytes develop, an enormous diversity of T-cell receptors is generated by a random process that produces some T cells with receptors capable of recognizing antigen-MHC complexes

2. .However, most of the T-cell receptors produced by this random process are incapable of recognizing antigen-MHC complexes and a small portion react with combinations of self antigen-MHC complexes.

3. Using specific mechanisms the thymus induces the death of those T cells that cannot recognize antigen- MHC complexes and those that react with self-antigen– MHC and pose a danger of causing autoimmune disease. More than 95% of all thymocytes die by apoptosis in the thymus without ever reaching maturity.


Capsule
Dead cell
Trabecula
Thymocyte
Nurse cell
Dividing thymocyte
Cortical epithelial cell
Cortex
Medulla
Interdigitating dendritic cell
Blood vessel
Medullary epithelial cell
Macrophage
Hassall's corpuscles

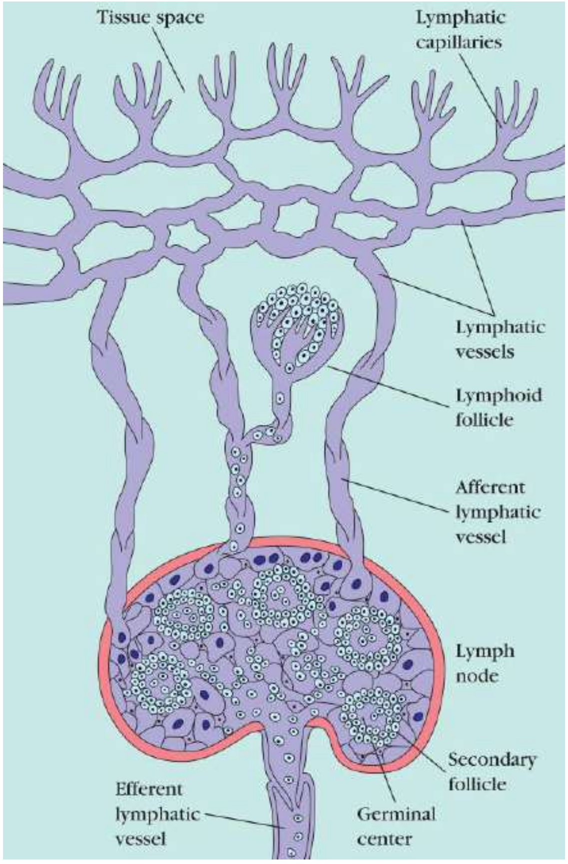

Capsule
Trabecula
Cortex
Sub-capsular epithelium
Cortico-medullary junction
Medulla
Hassall's corpuscle
Cortical epithelial cell (ectodermal origin)
Thymocyte (bone marrow origin)
Medullary epithelial cell (endodermal origin)
Dendritic cell (bone marrow origin)
Macrophage (bone marrow origin)

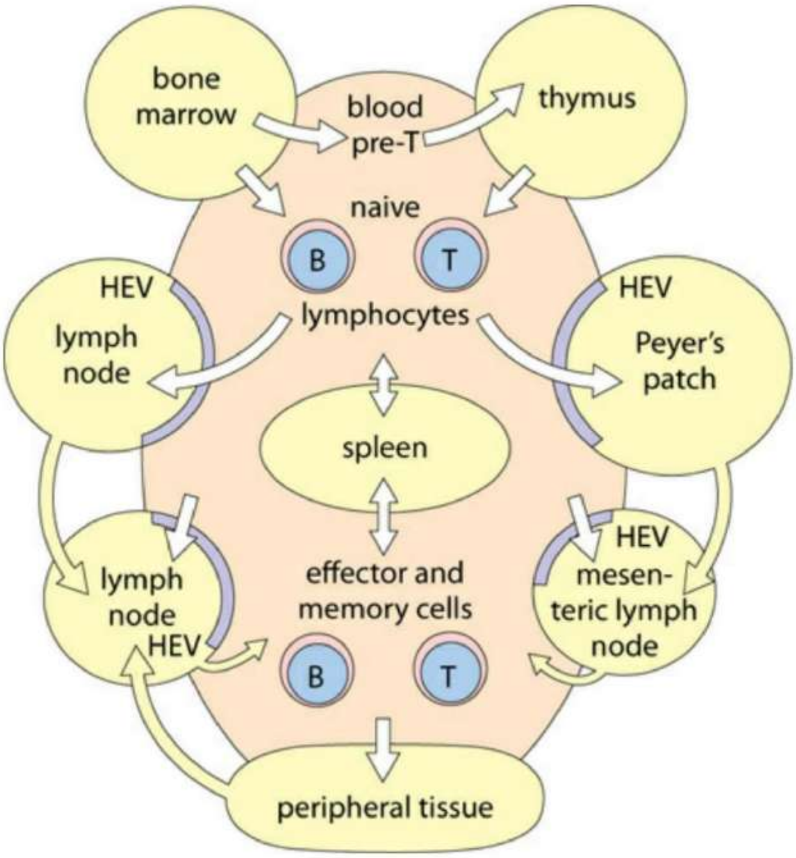
2.2 BONE MARROW

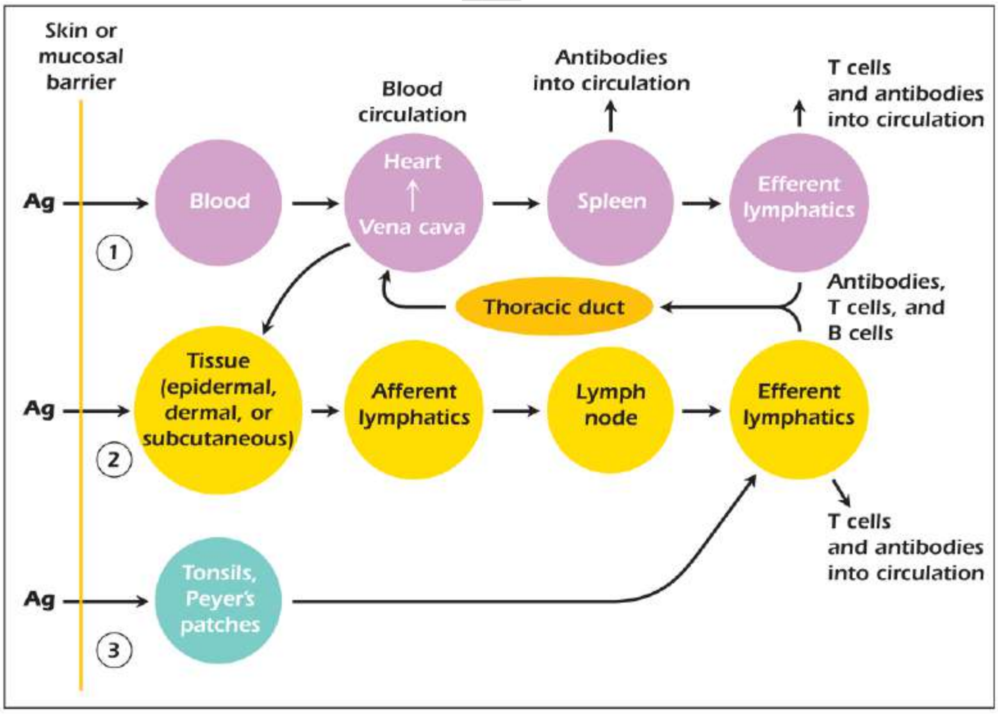
1. In humans and mice, bone marrow is the site of B-cell origin and development. Arising from lymphoid progenitors, immature B cells proliferate and differentiate within the bone marrow, and stromal cells within the bone marrow interact directly with the B cells and secrete various cytokines that are required for development.
2. Like thymic selection during T cell maturation, a selection process within the bone marrow eliminates B cells with self-reactive antibody receptors
3. Bone marrow is not the site of B-cell development in all species.
   - In birds, a ***lymphoid organ called the bursa of Fabricius, a lymphoid tissue associated with the gut, is the primary site of B-cell maturation***.
   - In mammals such as primates and rodents, there is no bursa and no single counterpart to it as a primary lymphoid organ.
   - In cattle and sheep, the primary lymphoid tissue hosting the maturation, proliferation, and diversification of B cells early in gestation is ***the fetal spleen***. Later in gestation, this function is assumed ***by a patch of tissue embedded in the wall of the intestine called the ileal Peyer's patch***, which contains a large number (1010) B cells.
   - The rabbit, too, uses g***ut-associated tissues such as the appendix as primary lymphoid tissue for important steps in the proliferation*** and diversification of B cells.

3. LYMPHATIC SYSTEM

1. As blood circulates under pressure, its fluid component **(plasma)** seeps through the thin wall of the capillaries into the surrounding tissue.
2. Much of this fluid, called **interstitial fluid,** returns to the blood through the capillary membranes. The remainder of the interstitial fluid, now called **lymph,** flows from the spaces in connective tissue into a network of tiny open lymphatic capillaries and then into a series of progressively larger collecting vessels called **lymphatic vessels**.
3. The largest lymphatic vessel, the **thoracic duct,** empties into the left subclavian vein near the heart. In this way, the lymphatic system captures fluid lost from the blood and returns it to the blood, thus ensuring steady-state levels of fluid within the circulatory system.
4. The heart does not pump the lymph through the lymphatic system; instead the ***flow of lymph is achieved as the lymph vessels are squeezed by movements of the body's muscles***. A series of ***one-way valves along the lymphatic vessels ensures that lymph flows only in one direction***.
5. When a foreign antigen gains entrance to the tissues, it is picked up by the lymphatic system (which drains all the tissues of the body) and is carried to various organized lymphoid tissues such as lymph nodes, which trap the foreign antigen.
6. As lymph passes from the tissues to lymphatic vessels, it becomes progressively enriched in lymphocytes. Thus, the lymphatic system also serves as a means of transporting lymphocytes and antigen from the connective tissues to organized lymphoid tissues where the lymphocytes may interact with the trapped antigen and undergo activation.


Tissue space
Lymphatic capillaries
Lymphatic vessels
Lymphoid follicle
Afferent lymphatic vessel
Lymph node
Secondary follicle
Germinal center
Efferent lymphatic vessel


bone marrow
blood pre-T
thymus
naive
B
T
lymphocytes
HEV
lymph node
HEV
Peyer's patch
spleen
lymph node
HEV
effector and memory cells
HEV
mesen-teric lymph node
B
T
peripheral tissue

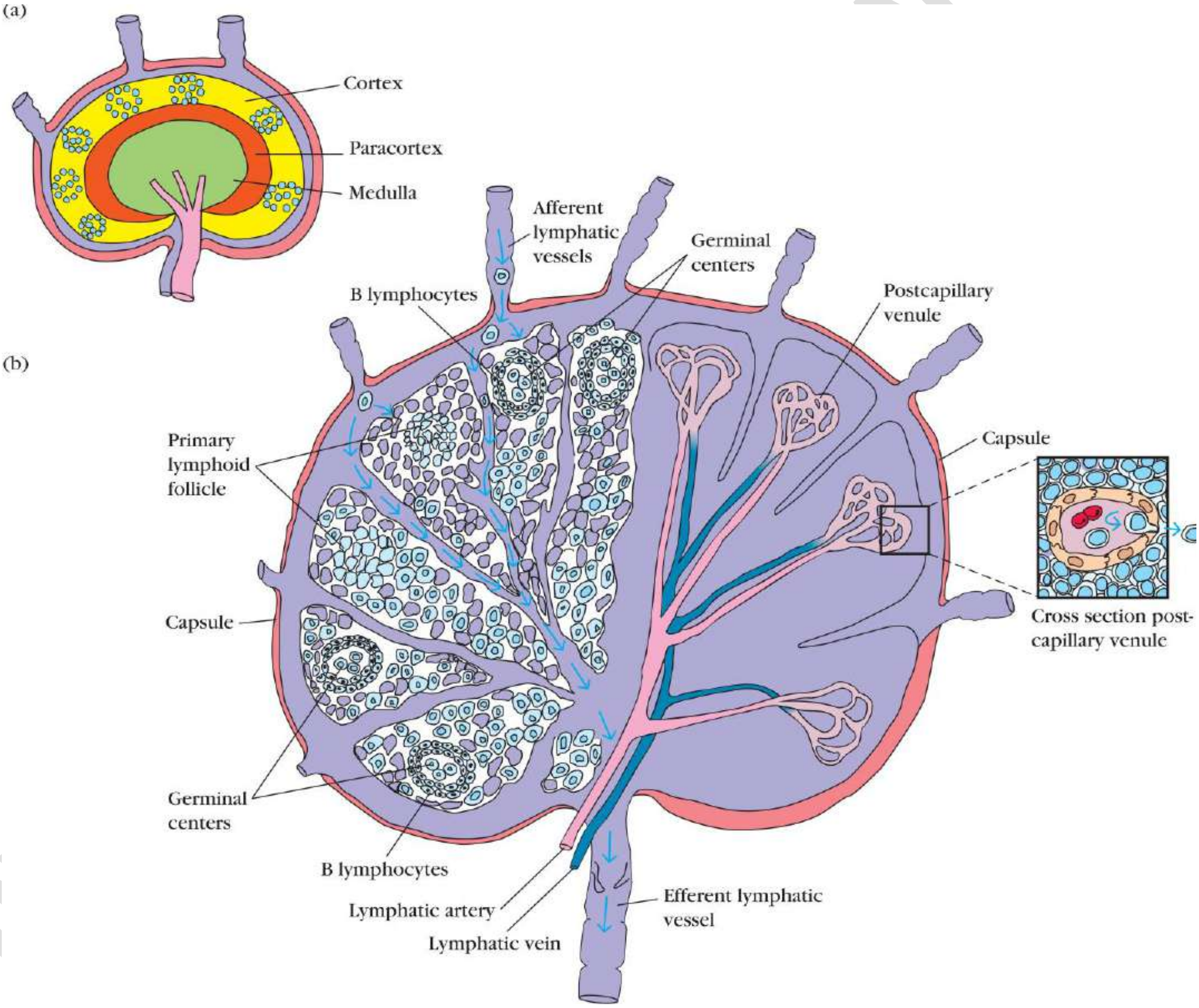

Skin or mucosal barrier
Blood circulation
Antibodies into circulation
T cells and antibodies into circulation
Ag
Blood
Heart
Vena cava
Spleen
Efferent lymphatics
1
Thoracic duct
Antibodies, T cells, and B cells
Tissue (epidermal, dermal, or subcutaneous)
Afferent lymphatics
Lymph node
Efferent lymphatics
Ag
2
T cells and antibodies into circulation
Ag
Tonsils, Peyer's patches
3

4. SECONDARY LYMPHOID ORGANS

4.1. LYMPH NODES

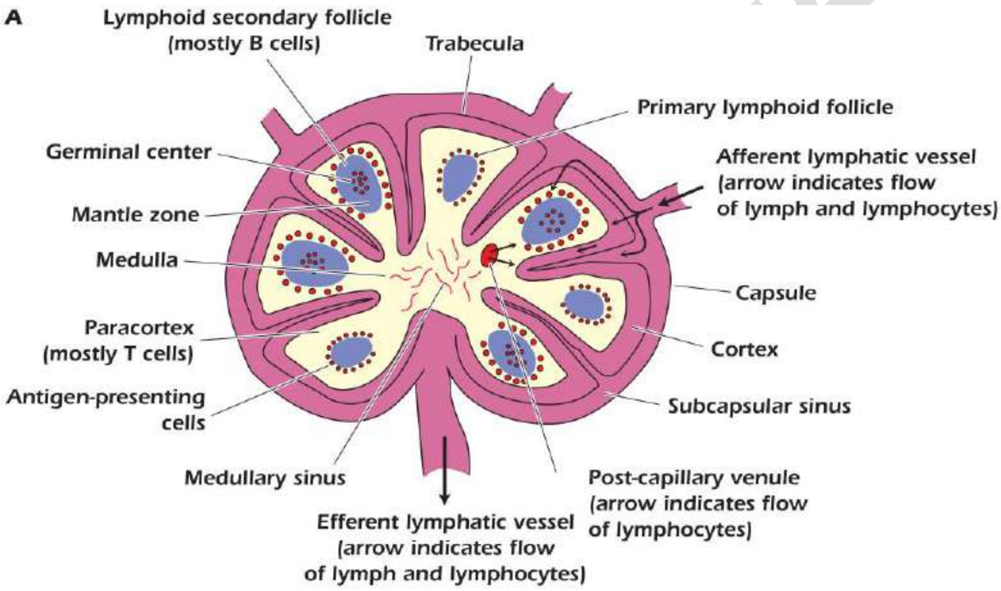
1. Lymph nodes are the ***sites where immune responses are mounted to antigens in lymph***. ***They are encapsulated bean-shaped structures containing a reticular network packed with lymphocytes, macrophages, and dendritic cells.***
2.
3. Clustered at junctions of the lymphatic vessels, lymph nodes are the first organized lymphoid structure to encounter antigens that enter the tissue spaces.
4. As lymph percolates through a node, any particulate antigen that is brought in with the lymph will be trapped by the cellular network of phagocytic cells and dendritic cells (follicular and interdigitating).
5. The overall architecture of a lymph node supports an ideal microenvironment for lymphocytes to effectively encounter and respond to trapped antigens.

MORPHOLOGICAL DIVISIONS



1. Morphologically, a lymph node can be divided into three roughly concentric regions:
   a. the cortex, **b. the paracortex, and** **c. the medulla,**
   each of which supports a distinct microenvironment (Figure 2-18).
2. The outermost layer, the **cortex,**

   a. contains ***lymphocytes (mostly B cells)***, ***macrophages***, and ***follicular dendritic cells*** arranged in primary follicles.
   b. After antigenic challenge, the primary follicles enlarge into secondary follicles, each containing a germinal center.
   c. In children with B-cell deficiencies, the cortex lacks primary follicles and germinal centers.
3. Beneath the cortex is the **paracortex,**
   a. which is populated largely by T lymphocytes and also contains interdigitating dendritic cells thought to have migrated from tissues to the node.
   b. These interdigitating dendritic cells express high levels of class II MHC molecules,which are necessary for presenting antigen to TH cells.
   c. Lymph nodes taken from neonatally thymectomized mice have unusually few cells in the paracortical region; the paracortex is therefore sometimes referred to as a **thymus-dependent area** in contrast to the cortex, which is a **thymus-independent area.**
4. The innermost layer of a lymph node,
   a. the **medulla,** is more sparsely populated with lymphoid-lineage cells; of those present, many are plasma cells actively secreting antibody molecules.

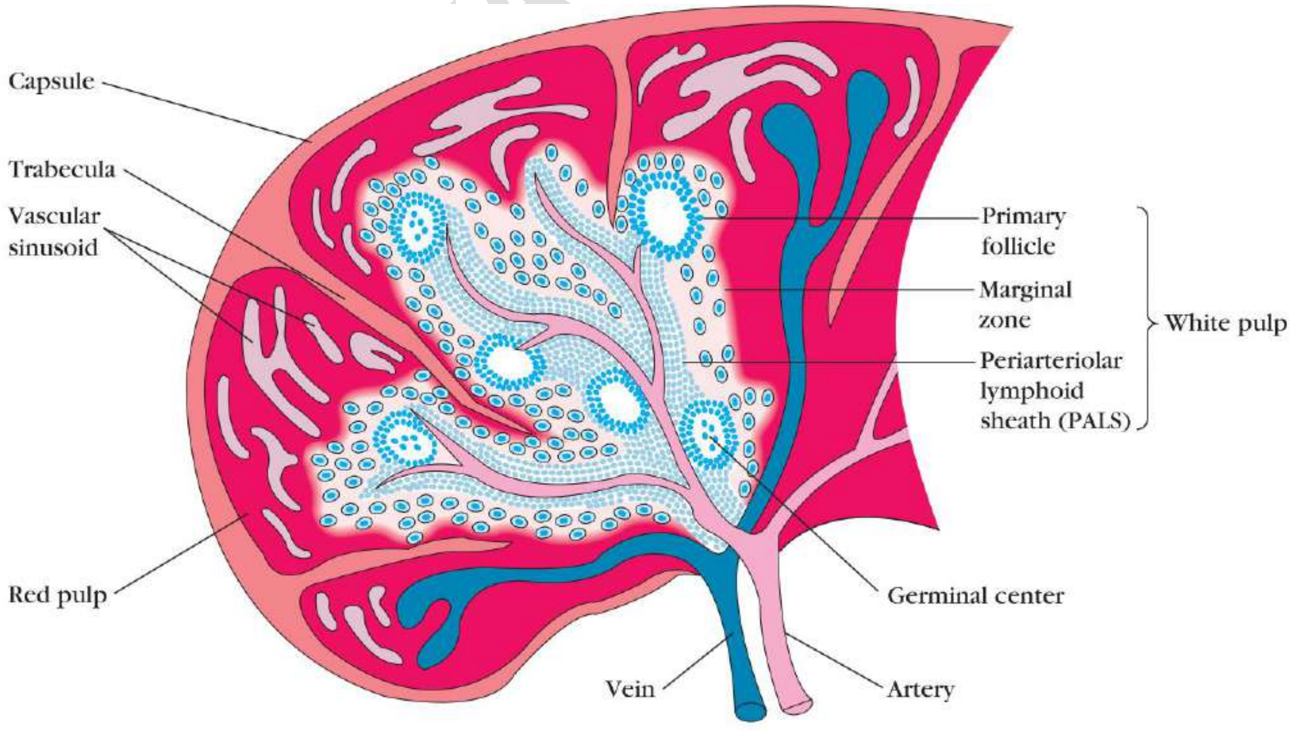


FUNCTIONS

1. As antigen is carried into a regional node by the lymph, it is *trapped, processed, and presented together with class II MHC molecules by* ***interdigitating dendritic cells*** in the paracortex, resulting in the activation of TH cells.
2. The ***initial activation of*** B cells is also thought to take place within the T-cell-rich paracortex. Once activated, ***TH and B cells form small foci consisting largely of proliferating B cells at the edges of the paracortex***.
3. Some B cells within the foci differentiate into ***plasma cells secreting IgM and IgG***. These foci reach maximum size within 4–6 days of antigen challenge. Within 4–7 days of antigen challenge, a few B cells and TH cells migrate to the primary follicles of the cortex. It is not known what causes this migration.
4. Within a primary follicle, cellular interactions between follicular dendritic cells, B cells, and TH cells take place, leading to ***development of a secondary follicle with a central germinal center***. Some of the plasma cells generated in the germinal center move to the medullary areas of the lymph node, and many migrate to bone marrow.

4.2 SPLEEN

1. The spleen plays a major role in mounting immune responses to antigens in the blood stream. It is a ***large, ovoid secondary lymphoid organ situated high in the left abdominal cavity***. While lymph nodes are specialized for trapping antigen from local tissues, the ***spleen specializes in filtering blood and trapping blood-borne antigens***; thus, it can respond to systemic infections. Unlike the lymph nodes, the ***spleen is not supplied by lymphatic vessels.***
2. Bloodborne antigens and lymphocytes are carried into the spleen through the ***splenic artery.*** Experiments with radioactively labelled lymphocytes show that more recirculating lymphocytes pass daily through the spleen than through all the lymph nodes combined.
3. The ***spleen is surrounded by a capsule*** that extends a number of projections ***(trabeculae)*** into the interior to form a compartmentalized structure. The compartments are of two types, ***the red pulp and white pulp***, which are separated by a diffuse marginal zone.
4. SPLENIC RED PULP
   a. The splenic **red pulp** consists of a network of sinusoids populated by macrophages and numerous red blood cells (erythrocytes) and few lymphocytes;
   b. It is the site where old and defective red blood cells are destroyed and removed.
   c. Many of the macrophages within the red pulp contain engulfed red blood cells or iron pigments from degraded hemoglobin.
5. SPLENIC WHITE PULP
   a. The splenic **white pulp** surrounds the branches of the splenic artery, forming a **periarteriolar lymphoid sheath (PALS)** populated mainly by T lymphocytes.
   b. Primary lymphoid follicles are attached to the PALS. These follicles are rich in B cells and some of them contain germinal centers.
   c. The **marginal zone,** located peripheral to the PALS, is populated by lymphocytes and macrophages.
6. Blood-borne antigens and lymphocytes enter the spleen through the ***splenic artery***, which empties into the ***marginal zone***. In the marginal zone, antigen is ***trapped by interdigitating dendritic cells***, which ***carry it to the PALS.***

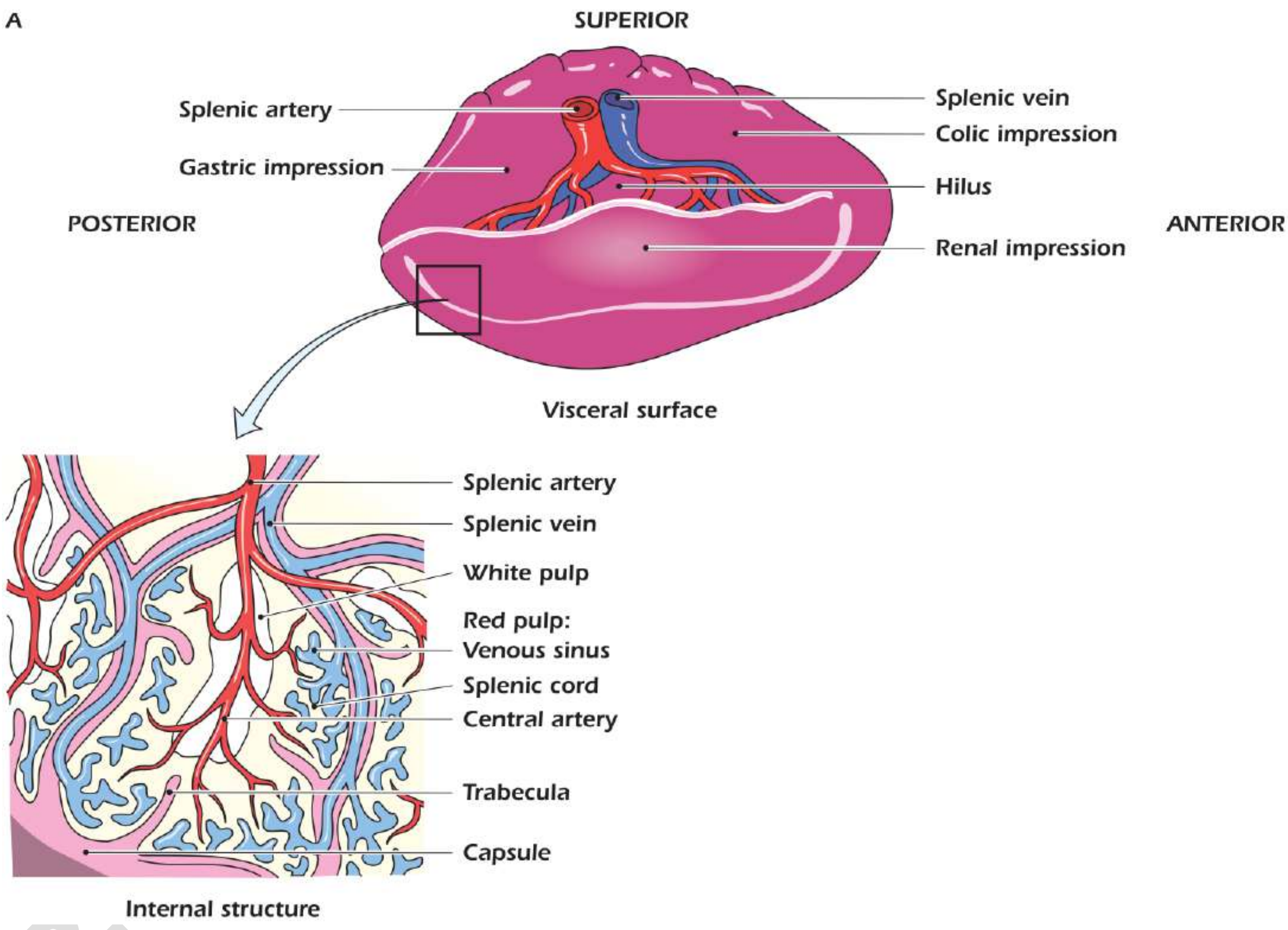


7. Lymphocytes in the blood also enter sinuses in the marginal zone and migrate to the PALS. ***The initial activation of B and T cells takes place in the T cell- rich PALS***. Here interdigitating dendritic cells capture antigen and present it combined with class II MHC molecules to T_H cells. Once activated, these T_H cells can then activate B cells. The activated B cells, together with some T_H cells, then migrate to primary follicles in the marginal zone.

8. Upon antigenic challenge, these ***primary follicles develop into characteristic secondary follicles containing germinal centers*** (like those in the lymph nodes), where rapidly dividing B cells (centroblasts) and plasma cells are surrounded by dense clusters of concentrically arranged lymphocytes.

9. The effects of splenectomy on the immune response depends on the age at which the spleen is removed. In children, splenectomy often leads to an increased incidence of bacterial sepsis caused primarily by *Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae*.

10. Splenectomy in adults has less adverse effects, although it leads to some increase in blood-borne bacterial infections **(bacteremia).**



4.3 MUCOSAL-ASSOCIATED LYMPHOID TISSUE

1. The mucous membranes lining the **digestive, respiratory, and urogenital systems** have a combined surface area of about **400 m^2** (nearly the size of a basketball court) and are the major sites of entry for most pathogens.
2. These vulnerable membrane surfaces are defended by a group of organized lymphoid tissues mentioned earlier and known collectively as **Mucosal-Associated Lymphoid Tissue (MALT)**.
   a. Structurally, these tissues range from loose, barely ***organized clusters of lymphoid cells*** in the ***lamina propria of intestinal villi to well-organized structures such as the familiar tonsils and appendix***, as well as Peyer's patches, which are found within the submucosal layer of the intestinal lining.

b. The functional importance of MALT in the body’s defense is attested to by its large ***population of antibody-producing plasma cells,*** whose number far exceeds that of plasma cells in the spleen, lymph nodes, and bone marrow combined.

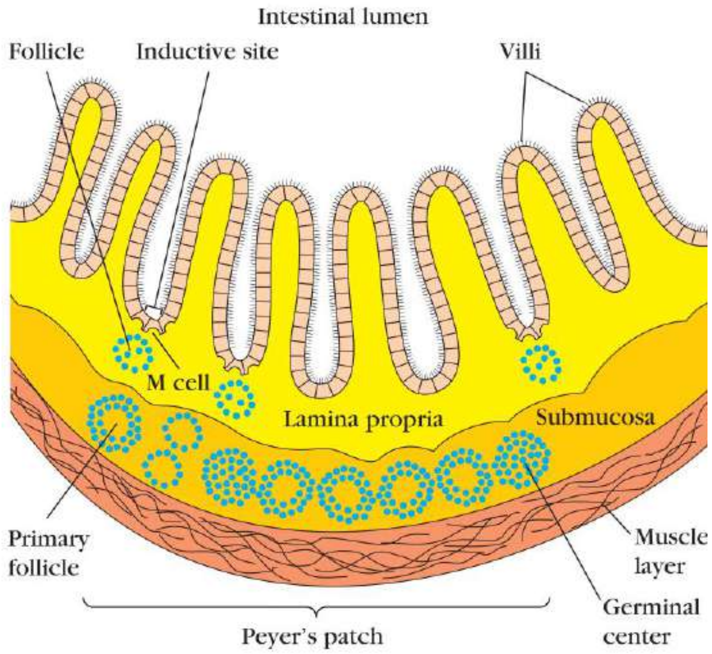


FIGURE 2-21 Cross-sectional diagram of the mucous membrane lining the intestine showing a nodule of lymphoid follicles that constitutes a Peyer’s patch in the submucosa. The intestinal lamina propria contains loose clusters of lymphoid cells and diffuse follicles.

3. The **tonsils** are found in three locations:
   - ***lingual*** at the base of the tongue;
   - ***palatine*** at the sides of the back of the mouth; and
   - ***pharyngeal (adenoids)*** in the roof of the **nasopharynx**.

a. All three tonsil groups are nodular structures consisting of a meshwork of reticular cells and fibers interspersed with lymphocytes, macrophages, granulocytes, and mast cells.

b. The B cells are organized into follicles and germinal centers; the latter are surrounded by regions showing T-cell activity.

c. The tonsils defend against antigens entering through the nasal and oral epithelial routes. The best studied of the mucous membranes is the one that lines the gastrointestinal tract. This tissue, like that of the respiratory and urogenital tracts, has the capacity to endocytose antigen from the lumen.

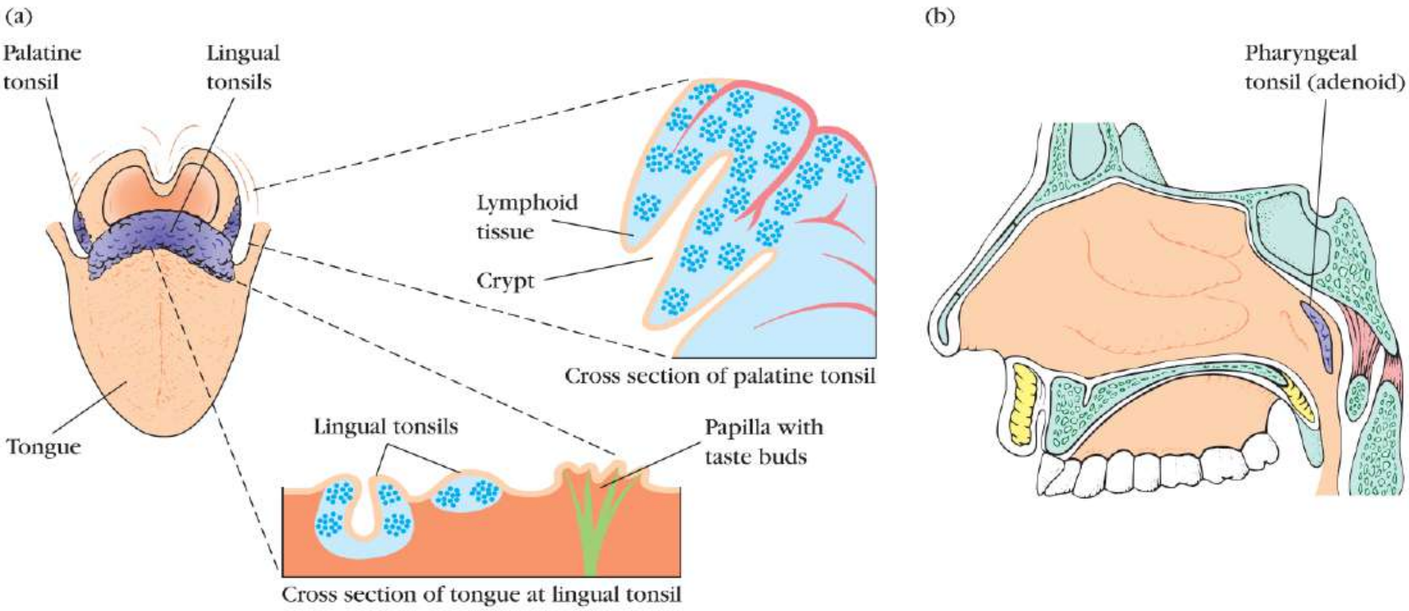


FIGURE 2-20 Three types of tonsils. (a) The position and internal features of the palatine and lingual tonsils; (b) a view of the position of the nasopharyngeal tonsils (adenoids). [*Part b adapted from J. Klein, 1982,* Immunology, The Science of Self-Nonself Discrimination, © *1982 by John Wiley and Sons, Inc.*]

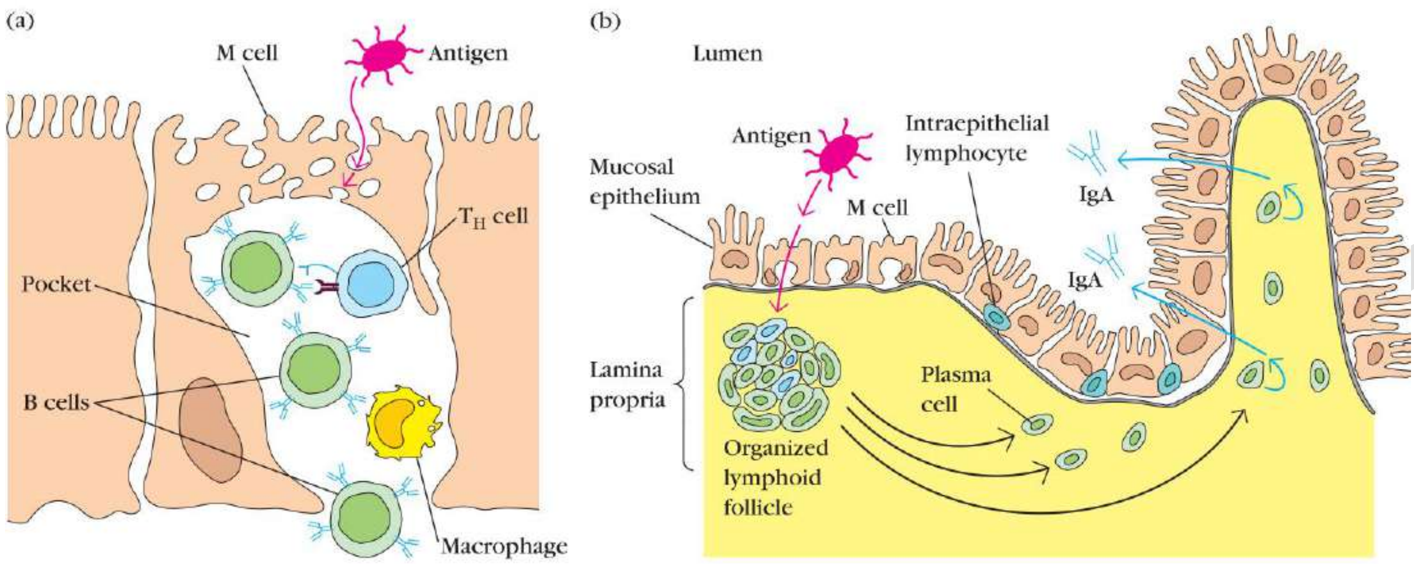


FIGURE 2-22 Structure of M cells and production of IgA at inductive sites. (a) M cells, located in mucous membranes, endocytose antigen from the lumen of the digestive, respiratory, and urogenital tracts. The antigen is transported across the cell and released into the large basolateral pocket. (b) Antigen transported across the epithelial layer by M cells at an inductive site activates B cells in the underlying lymphoid follicles. The activated B cells differentiate into IgA-producing plasma cells, which migrate along the submucosa. The outer mucosal epithelial layer contains intraepithelial lymphocytes, of which many are $CD8^+$ T cells that express γδ TCRs with limited receptor diversity for antigen.

4. Immune reactions are initiated against pathogens and antibody can be generated and exported to the lumen to combat the invading organisms. As shown in **Figures 2-21 and 2-22**, lymphoid cells are found in various regions within this tissue.
5. The outer mucosal epithelial layer contains so-called **Intraepithelial Lymphocytes (IELs).** Many of these lymphocytes are T cells that express unusual receptors (γδT-cell receptors, or γδTCRs), which exhibit limited diversity for antigen. Although this population of T cells is well situated to encounter antigens that enter through the intestinal mucous epithelium, their actual function remains largely unknown .
6. The ***lamina propria***, which lies under the epithelial layer, contains large numbers of B cells, plasma cells, activated T_H cells, and macrophages in loose clusters. Histologic sections have revealed more than 15,000 lymphoid follicles within the intestinal lamina propria of a healthy child.
   a. The ***submucosal layer beneath the lamina propria contains Peyer's patches, nodules of 30–40 lymphoid follicles***.
7. Like lymphoid follicles in other sites, those that compose ***Peyer's patches can develop into secondary follicles with germinal centers***.
   a. The epithelial cells of mucous membranes play an important role in promoting the immune response by delivering small samples of foreign antigen from the lumina of the respiratory, digestive, and urogenital tracts to the underlying mucosal-associated lymphoid tissue. This antigen transport is carried out by specialized **M cells.**
8. The structure of the M cell is striking:
   a. these are flattened epithelial cells lacking the microvilli that characterize the rest of the mucous epithelium.
   b. In addition, M cells have a deep invagination, or pocket, in the basolateral plasma membrane; this pocket is filled with a cluster of B cells, T cells, and macrophages (Figure 2-22a).
9. Luminal antigens are endocytosed into vesicles that are transported from the luminal membrane to the underlying pocket membrane. The vesicles then fuse with the pocket membrane, delivering the potentially response-activating antigens to the clusters of lymphocytes contained within the pocket.
   a. M cells are located in so-called **Inductive Sites**—small regions of a mucous membrane that lie over organized lymphoid follicles (Figure 2-22b).

10. Antigens transported across the mucous membrane by M cells can activate B cells within these lymphoid follicles. The activated B cells differentiate into plasma cells, which leave the follicles and secrete the IgA class of antibodies. These antibodies then are transported across the epithelial cells and released as **secretory IgA** into the lumen, where they can interact with antigens.
11. As described, ***mucous membranes are an effective barrier to the entrance of most pathogens***, which thereby contributes to nonspecific immunity.
    a. One reason for this is that the mucosal epithelial cells are cemented to one another by tight junctions that make it difficult for pathogens to penetrate.
    b. Interestingly, some enteric pathogens, including both bacteria and viruses, have exploited the M cell as an entry route through the mucous-membrane barrier.
    c. In some cases, the pathogen is internalized by the M cell and transported into the pocket.
    d. In other cases, the pathogen binds to the M cell and disrupts the cell, thus allowing entry of the pathogen.
    e. Among the pathogens that use M cells in these ways are several invasive ***Salmonella* species, *Vibrio cholerae***, and the polio virus.

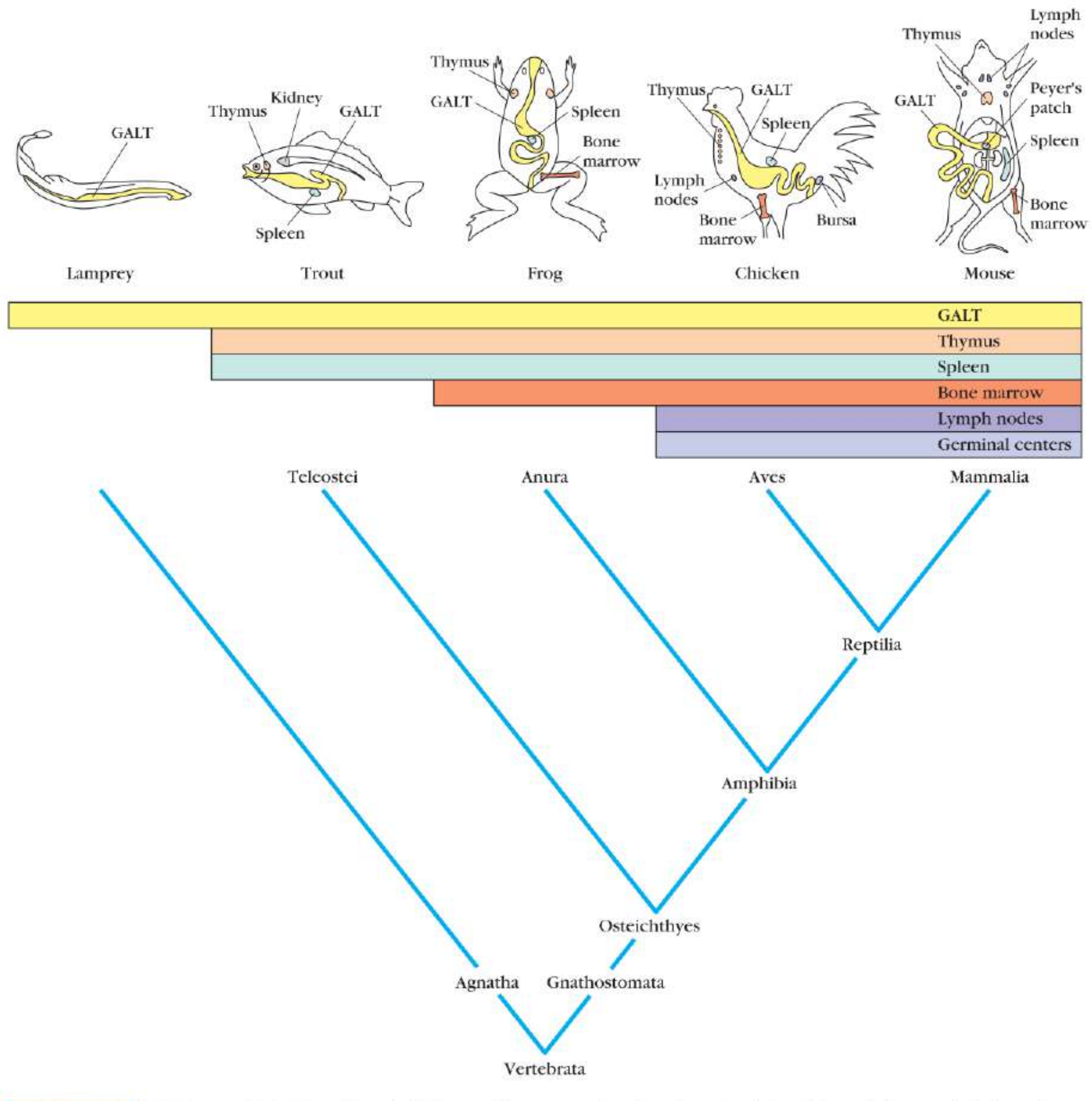


FIGURE 2-23 Evolutionary distribution of lymphoid tissues. The presence and location of lymphoid tissues in several major orders of vertebrates are shown. Although they are not shown in the diagram, cartilaginous fish such as sharks and rays have GALT, thymus, and a spleen. Reptiles also have GALT, thymus, and spleen and they also may have lymph nodes that participate in immunological reactions. Whether bone marrow is involved in the generation of lymphocytes in reptiles is under investigation. [*Adapted from Dupasquier and M. Flajnik, 1999. In* Fundamental Immunology *4th ed., W. E. Paul, ed., Lippincott-Raven, Philadelphia.*]

CELLS OF THE IMMUNE SYSTEM

1. **LYMPHOCYTES**
    1. LARGE GRANULAR LYMPHOCYTES (LGLS)
    2. γδ T CELLS
    3. INTRAEPITHELIAL LYMPHOCYTES (IEL_S) are
    4. CYTOTOXIC T (T_C)
    5. HELPER T (T_H)
    6. T_H1, T_H2, and T_H17
    7. REGULATORY T CELLS (T_{REG})
    8. B CELLS
    9. PLASMA CELLS/ANTIBODY-FORMING CELLS (AFC)
    10. B1 and B2 cells
    11. NAIVE/VIRGIN LYMPHOCYTES
2. **NK CELLS**
    1. NULL CELLS/THIRD POPULATION
    2. NK (NATURAL KILLER)
3. **ANTIGEN PRESENTING CELLS**
    1. DENDRITIC CELLS (DCS)
    2. LANGERHANS CELLS (VEILED CELLS)
    3. MACROPHAGE APCS
    4. FOLLICULAR DENDRITIC CELLS (FDCS)
    5. ICCOSOMES
    6. MARGINAL ZONE MACROPHAGES
    7. FACULTATIVE APCS
4. **PHAGOCYTES AND AUXILIARY CELLS**
    1. MONOCYTES
    2. MACROPHAGES
        i. ***Kupffer cells***
        ii. ***Mesangial phagocytes***
        iii. ***Microglial cells***
        iv. ***Synovial A***
    3. GRANULOCYTES
        i. **Neutrophils**
        ii. **Eosinophils**
        iii. **Basophils**
    4. MAST CELLS
        i. **Connective tissue mast cells (CTMCS)—**
        ii. **Mucosal mast cells (MMCS)—**

REFERENCE

1. ROITT'S ESSENTIAL IMMUNOLOGY
2. KUBY IMMUNOLOGY
3. CELLULAR AND MOLECULAR IMMUNOLGY ABBAS
4. IMMUNOLGY MALE AND BROSTOFF

1. LYMPHOCYTES

1. Lymphocytes are key cells controlling the immune response.
2. They do so by recognizing molecules produced by pathogens.
3. They can also recognize molecules on the cells of the body, although they do not normally react against the body's own tissues.
4. Molecules recognized by lymphocytes are referred to as 'antigens.'
5. Lymphocytes are of two main types: **B cells, which produce antibodies, and T cells**, which have a number of functions, including
    1. helping B cells to make antibody;
    2. recognizing and destroying cells that have become infected with intracellular pathogens;
    3. activating phagocytes to destroy pathogens that they have taken up, and
    4. regulating the level and quality of the immune response.
6. Lymphocytes recognize foreign material by specific cell-surface antigen receptors. To recognize the enormous variety of different molecules, the antigen receptors must be equally diverse. Each lymphocyte makes only one type of antigen receptor and thus can only recognize a very limited number of antigens, but as the receptors differ on each clone of cells, the lymphocyte population, as a whole, can recognize a vast range of different antigens.
7. A third, minor, population of lymphocytes **(NK cells) also contributes to antiviral defenses**.

2. PHAGOCYTES

1. Phagocytes include **blood monocytes**, **macrophages**, and **neutrophils**.
2. They can internalize (phagocytose) pathogens, antigens, and cell debris and break them down.
3. Antibodies and various other recognition molecules bound to the pathogens facilitate this process.
4. Macrophages can also process and present antigens, so that they can be recognized by T cells.

3. ACCESSORY CELLS

1. Accessory cells include eosinophil and basophil granulocytes, mast cells, platelets, and antigen-presenting cells (APCs).
2. Eosinophils have a role in protection against some parasites.
3. Basophils, mast cells, and platelets contain a variety of molecules that mediate inflammation.
4. APCs are a functionally defined group of cells; both B cells and macrophages can present antigen, but leukocyte dendritic cells are particularly important in presenting antigen to naive T cells, which have not previously encountered their specific antigen.

1. LYMPHOCYTES

Lymphocytes constitute about 20% of the total blood leukocytes. The two major populations of lymphocytes, T cells and B cells, are small lymphocytes responsible for recognizing antigens or antigen fragments.
A third population of ***large granular lymphocytes (LGLs)*** recognizes changes in host cells that may occur when they become infected.

1. **LARGE GRANULAR LYMPHOCYTES (LGLS)** are morphologically defined cells containing large amounts of cytoplasm, with azurophilic granules, which constitute 5–15% of the blood T cells.
    a. Both NK cells and γδ T cells have this morphology.
    b. T cells are lymphocytes that develop in the thymus. This organ is seeded by lymphocytic stem cells from the bone marrow during embryonic development.
    c. The cells then develop their T-cell antigen receptors (TCR) and differentiate into the two major peripheral T cell subsets; the helper T cells express CD4, and the cytotoxic T cells express CD8.
    d. T cells can also be differentiated into two populations according to whether they use an αβ (TCR2) or a γδ (TCR1) antigen receptor. The essential role of T cells is to recognize antigens associated with cells of the host.
2. **γδ T CELLS** express the γδ form of the T cell receptor.

a. They constitute <5% of the total T cells, but they are more common in particular sites, including the ***gut, skin,*** *and* ***vagina***.
b. They branch early from the main thymic developmental pathway and recognize different antigens from αβ T cells, including carbohydrates and intact proteins.

3. **INTRAEPITHELIAL LYMPHOCYTES (IEL_S)** are mixed populations of cells found in submucosal tissues. 10–40% are γδ T cells, with a dendritic appearance. The remainder are mostly **CD8+ T cells.**
4. **CYTOTOXIC T (T_C)** cells are capable of destroying virally infected or allogeneic cells. Most T_C cells express CD8 and recognize antigen associated with MHC class I molecules, which may be expressed on all nucleated cells of the body.
5. **HELPER T (T_H)** cells perform a number of functions, including helping B cells to divide, differentiate, and secrete antibody, activating macrophages to destroy pathogens that they have phagocytosed and recruiting cells to sites of inflammation.
   a. The functions are carried out by different subsets of T_H cells, which differentiate from a common precursor (T_H0) and can be distinguished by the cytokines, which they secrete.
   b. The majority of T_H cells express CD4 and recognize antigenic peptides presented on the surface of APCs by MHC class II molecules.
6. **T_H1, T_H2, and T_H17** cells are subsets of helper T cells originally identified according to the cytokines they produce. They differentiate from a common precursor (T_H0).
   i. Differentiation of T_H1 cells is promoted by **interleukin (IL)-12** and **interferon-γ (IFN-γ)**,
   ii. T_H2 cells by **IL-4**, and
   iii. T_H17 cells by **transforming growth factor-β (TGF-β)** and **IL-6**.
   a. Dendritic cells are antigen-presenting cells which are most effective at presenting antigen to naive T cells.T_H1 cells can recognize antigen presented by mononuclear phagocytes, and they interact with these cells by releasing IFN-γ, which acts as a macrophage activation factor.
   b. T_H2 cells release cytokines, such as IL-4 and IL-5, which are required for B-cell development into plasma cells. Both T_H1 and T_H2 cells can modulate the antibody response by affecting the classes of immunoglobulin produced.
   c. T_H17 cells release cytokines that promote inflammatory responses, particularly by acting on neutrophils. Some cell-surface markers are preferentially expressed on a subset of the helper T cells. For example, the chemokine receptors ***CCR5*** and ***CXCR3*** are more prevalent on T_H1 cells, whereas **CCR3** and **CCR4** are higher on T_H2 cells.
   d. All helper T cells can promote the development and activation of cytotoxic T cells and NK cells, which recognize and kill infected target cells.
7. **REGULATORY T CELLS (T_{REG})** are a population of T cells usually identified by the expression of the **transcription factor Foxp3** and/or high expression of the IL-2 receptor, CD25.
   a. They can be either CD4+ or CD8+ and are important in controlling secondary immune responses and inflammation, particularly in the gut.
   b. They also limit some autoimmune and hypersensitivity reactions, acting by direct cell–cell interactions, or by the release of anti-inflammatory cytokines including IL-10, IL-35, and TGF-β.
   c. They can also inhibit activation of other T cells by mopping up IL-2, which is required for T-cell proliferation.
8. **B CELLS** are lymphocytes that develop in the fetal liver and subsequently in bone marrow.
   a. In birds, they develop in a specialized organ, the bursa of Fabricius.
   b. Mature B cells express surface immunoglobulin, which acts as the B-cell antigen receptor (BCR).
   c. They are distributed throughout the secondary lymphoid tissues, particularly in the follicles of lymph nodes, spleen, and Peyer's patches.
   d. They respond to antigenic stimuli by dividing and differentiating into plasma cells.
9. **PLASMA CELLS/ANTIBODY-FORMING CELLS (AFC)** are terminally differentiated B cells, with expanded cytoplasm containing arrays of rough endoplasmic reticulum, devoted to the synthesis of secreted antibody.

a. Plasma cells are seen in the red pulp of spleen, the medulla of lymph nodes, the MALT, and occasionally in sites of inflammation.

10. **B1 and B2** cells are B cell subsets.
    a. In adults most B cells are of the B2 subset. They generate a wide range of antigen receptors, mature in germinal centers and respond well to T-dependent antigens and co-stimulation via CD40.
    b. The B1 subset was originally distinguished by the phenotype $CD5^+$, $CD43^+$, $CD23^-$.
    c. B1 cells develop early, have a more limited range of receptors than B2 cells, respond to a number of common microbial antigens, and sometimes produce autoantibodies. They are absent from lymph nodes, constitute 5% of splenic B cells, and are important in mucosal immunity.
11. **NAIVE/VIRGIN LYMPHOCYTES** are cells that have not encountered their specific antigen. They express high-molecular-weight variants of the leukocyte common antigen (for example, CD45RA).

CLONAL SELECTION describes the way in which lymphocytes are activated.

a. During development each lymphocyte generates an antigen receptor with a single antigen specificity.
b. If antigen is encountered, only the few clones of lymphocytes that can recognize it are stimulated to divide to provide a large pool of effector and memory cells. This is referred to as 'clonal selection.'

MEMORY CELLS are populations of long-lived T or B cells with some capacity for self-renewal that have been previously stimulated with antigen and can make an accelerated response if they encounter it again.

a. Memory B cells carry IgG or IgA as their antigen receptor, which is of higher affinity than the receptor (IgM or IgD) on naive cells.
b. Memory T cells express the CD45RO variant of leukocyte common antigen as well as increased levels of adhesion molecules LFA-3 and VLA-4.
c. Immunological memory depends on both the production of memory cells and the increase in the numbers of antigen-specific

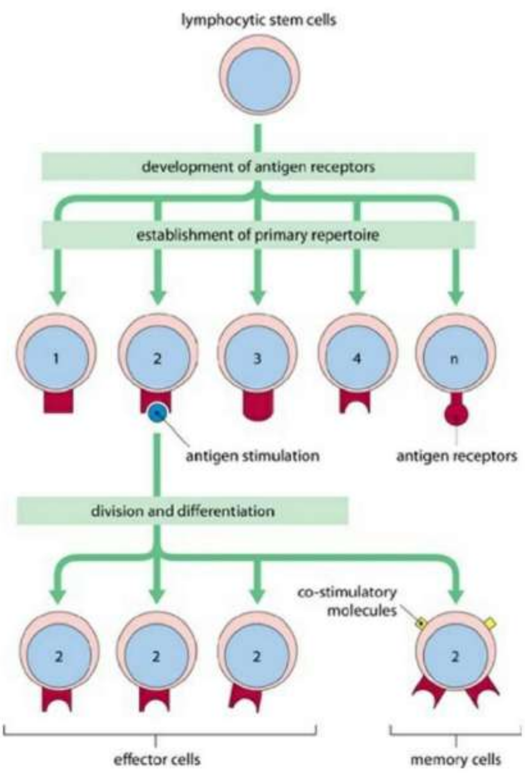


Fig. 1.3 Clonal selection and lymphocyte development.

TABLE 4.1. Antigen Recognition by B and T Cells

Characteristic	B Cells	T Cells
Antigen interaction	B-cell receptor (BCR) binds antigen (Ag)	T-cell receptor (TCR) binds antigenic peptides bound to MHC
Nature of antigens	Protein, polysaccharide, lipid	Peptide
Binding soluble antigens	Yes	No
Epitopes recognized	Accessible, sequential, or nonsequential	Internal linear peptides produced by antigen processing (proteolytic degradation)

2. NK CELLS

1. **NULL CELLS/THIRD POPULATION** cells are all descriptions of a distinct population of lymphocytes constituting 5–15% of blood mononuclear cells.
   a. They lack conventional antigen receptors (TCR, BCR), but express some markers of both T cells and mononuclear phagocytes.
   b. The great majority of these cells have the appearance of large granular lymphocytes (LGLs). Functionally they act as natural killer (NK) cells.
2. **NK (NATURAL KILLER)** cells are capable of killing a variety of virally infected or transformed target cells, particularly cells that have lost or reduced expression of MHC class I molecules, or express allogeneic MHC molecules.
   a. Thus they provide a second line of defense against viruses that attempt to evade immune recognition by downregulating the expression of MHC molecules.
   b. NK cells can use various receptors including the Fc receptor (CD16), CD2, CD69, KIRs, and lectin-like receptors to recognize target cells.
   c. NK cells kill their targets using similar mechanisms to TC cells, with the granule components perforin and granzymes being most important.

Killer immunoglobulin-like receptors (KIR) are a family of receptors that bind to MHC class I molecules and are used by NK cells to recognize their targets.

a. KIRs may have two or three extracellular immunoglobulin-like domains and they are produced in two forms, an inhibitory receptor with a long cytoplasmic tail containing ITIM motifs, and an activating receptor with a short cytoplasmic tail that can interact with ITAM-containing adaptor molecules.
b. As MHC molecules have diversified, so have the KIRs that recognize them.
c. There are several gene loci encoding KIRs (CD158).
d. The number varies between individuals and there is much polymorphism. Each NK cell expresses a subset of the available NK-cell receptors and can therefore recognize loss or change in one group of MHC molecules. T cells may also express some KIRs after activation by antigen.
e. NK cells respond to a balance of signals from the activating and inhibitory receptors in order to interact with cells of the body and respond to changes in their MHC expression.

Lectin-like receptors are a family of receptors consisting of two polypeptides, NKG2 and CD94, which are present on most NK cells and on some cytotoxic T cells.

a. They recognize leader peptides of MHC molecules, presented by a nonclassical MHC-encoded molecule, HLA-E. Loss of MHC molecules by a cell leads to a global reduction of MHC peptides presented by HLA-E.
b. Like KIRs the lectin-like receptors are produced in inhibitory and activating forms depending on their cytoplasmic tail.

MARKERS

CD system.

1. Leukocytes are differentiated by their cell-surface molecules, which are identified by monoclonal antibodies.
2. The most readily accessible marker of lymphocytes is their antigen receptor.
3. The B-cell receptor (BCR) is surface immunoglobulin, whereas T cells express the TCR. Most other markers are designated according to the CD system of nomenclature. Some of these markers are specific for individual populations of cells or particular phases of cellular differentiation.
4. Others appear only on activated or dividing cells. Many CD markers are present at varying levels on several different cell types, so that each subset of lymphocytes expresses a unique profile of surface markers.
5. More than 300 individual molecules are recognized in the CD system and some of them are found on cells other than leukocytes.

6. Particularly important are the markers used to distinguish T cells (CD2, CD3), the main T-cell subsets (CD4, CD8), activated T cells and T_{REG} cells (CD25), B cells (CD19, CD20, CD79), mononuclear phagocytes (CD64, CD68), and NK cells (CD56).

Families of proteins

1. Despite the enormous number of cell-surface molecules, most of them belong to just a few families, which share common structural features.
2. Such families include the immunoglobulin supergene family (IgSF), the 4-transmembrane (tm4) and 7-transmembrane (tm7) families, the C-type lectins, the integrins, and the complement control proteins (CCP).

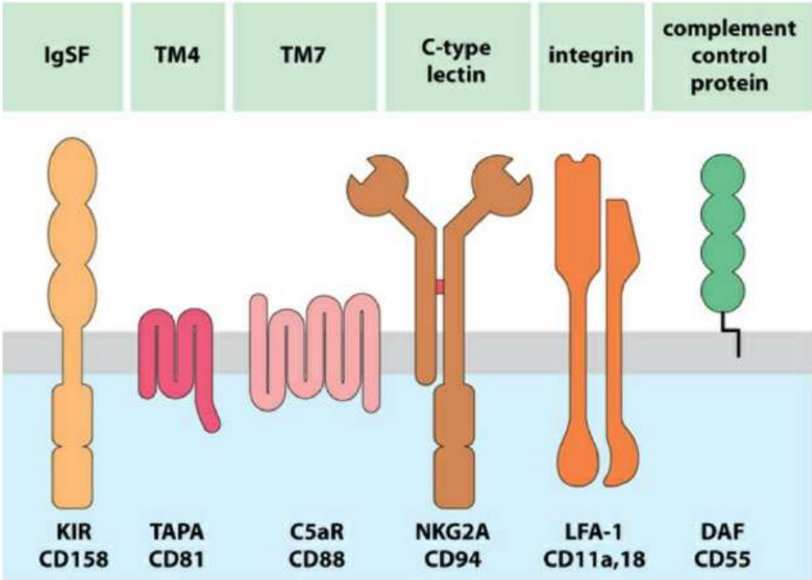


Fig. 1.4 Families of cell-surface molecules, with examples.

3.ANTIGEN-PRESENTING CELLS

Antigen-presenting cells (APC) are functionally defined cells that take up antigens and present them to lymphocytes in a form they can recognize.

a. Some antigens are taken up by APCs in the periphery and transported to the secondary lymphoid tissues, whereas other APCs are resident in these tissues and intercept antigen as it arrives.
b. B cells recognize antigen in its native form, but T_H cells recognize antigenic peptides that have become associated with MHC molecules.
c. Consequently, in order to present antigen to a T_H cell, an APC must internalize it, process it into fragments and re-express it at the cell surface in association with MHC class II molecules.
d. In addition, many APCs provide co-stimulatory signals to lymphocytes, either by direct cellular interactions or by cytokines. Dendritic cells, macrophages, B cells, and sometimes tissue cells can present antigen to T_H cells.

1. DENDRITIC CELLS (DCS) are a distinct set of APCs distributed in many tissues of the body, which differentiate from either lymphoid or myeloid precursors.

a. Dendritic cells expressing MHC class II molecules migrate to lymph nodes via the lymphoid system carrying antigen, and there they upregulate co-stimulatory molecules required for T-cell activation (CD40, CD80, CD86).
b. In lymph nodes they appear as interdigitating dendritic cells (IDCs) in the paracortex and they are very effective at presenting antigen to naive CD4+ T cells.
c. A minor population of dendritic cells enters the lymphoid tissues directly from the blood.

2. **LANGERHANS CELLS (VEILED CELLS)** are myeloid dendritic cells of the skin that pick up antigen and transport it to regional lymph nodes.
   a. They express CD207 (langerin), CD1, and high levels of MHC class II molecules and they have a characteristic racket-shaped granule, the Birbeck granule (function unknown).
   b. In ***afferent lymph they are seen as veiled cells*** and in lymph nodes they develop into dendritic cells. They are particularly important in the development of contact hypersensitivity; skin-sensitizing agents and UV radiation induce their emigration from the skin.
3. **MACROPHAGE APCS** Macrophages phagocytose antigen and some of them can also process and present it. MHC class II and co-stimulatory molecules (B7.1/B7.2, CD80/86) are induced by microbial molecules acting on Toll-like receptors, allowing the macrophages to present antigen effectively to TH1 cells.
   a. Activated macrophages also upregulate adhesion molecules (such as ICAM-1) and secrete IL-1.
   b. The recirculating macrophages of secondary lymphoid tissues are mostly seenin the medulla of lymph nodes and the red pulp of spleen.
4. **FOLLICULAR DENDRITIC CELLS (FDCS)** are present in follicles of spleen and lymph nodes, where they are tightly surrounded by lymphocytes.
   a. Complement-fixing immune complexes localize on the surface of these cells via Fc and C3 receptors, where they are presented mainly to B cells.
   b. This form of complex localization and presentation is important in the development of B-cell memory.
5. **ICCOSOMES** are beaded cytoplasmic structures present on filopodia of FDCs, which are thought to act as a long-term repository of antigens.
   a. They bud off and may be internalized by B cells.
   b. Marginal zone macrophages are present in the marginal zone of the splenic periarteriolar lymphatic sheath and along the marginal sinus of lymph nodes. T-independent antigens such as polysaccharides, tend to localize on these cells, where they are often very persistent.
6. **MARGINAL ZONE MACROPHAGES** express sialoadhesin (siglec-1, CD169), a lectin-like receptor for glycoconjugates, and they present antigens primarily to B cells.
7. **FACULTATIVE APCS** Many cells of the body can be induced to express MHC class II when stimulated by IFN-γ. Sometimes they can present antigen to CD4+ T cells, although they often fail to induce T cell division, owing to their inability to deliver co-stimulatory signals.

4. PHAGOCYTES AND AUXILIARY CELLS

Mononuclear phagocyte system is the collective term for the long-lived phagocytic cells distributed throughout the organs of the body. They are derived from bone marrow stem cells and express receptors for immunoglobulin (FcγR) and complement (CR1, CR3, and often CR4). They phagocytose antigenic particles and some have the ability to present antigen to lymphocytes. This group includes:

1. **Monocytes** are circulating cells that constitute ~5% of total blood leukocytes, which can migrate into tissues and differentiate into macrophages. They have a horseshoe-shaped nucleus, azurophilic granules, and many lysosomes.
2. **Macrophages** are large phagocytic cells found in most tissues and lining serous cavities and the lung. Resident macrophages may remain in tissues for years, while others recirculate through secondary lymphoid tissues, where they may function as APCs. The development of macrophages is promoted by macrophage colony stimulating factor (M-CSF). They differentiate into distinct subpopulations in different locations, which is influenced by signals from cells of the tissue.
   a. ***Kupffer cells*** are phagocytes that lie along the liver sinusoids. Much of the antigen entering the body through the gut is removed by these cells.
   b. ***Mesangial phagocytes*** line the glomerular endothelium where the capillaries enter the Bowman's capsule.
   c. ***Microglial cells*** are resident phagocytes of the brain, with a distinctive dendritic morphology.Colonization occurs primarily before birth and in the neonatal period.

d. ***Synovial A*** cells are phagocytes that lie on the synovial membrane of the joints, in contact with synovial fluid.

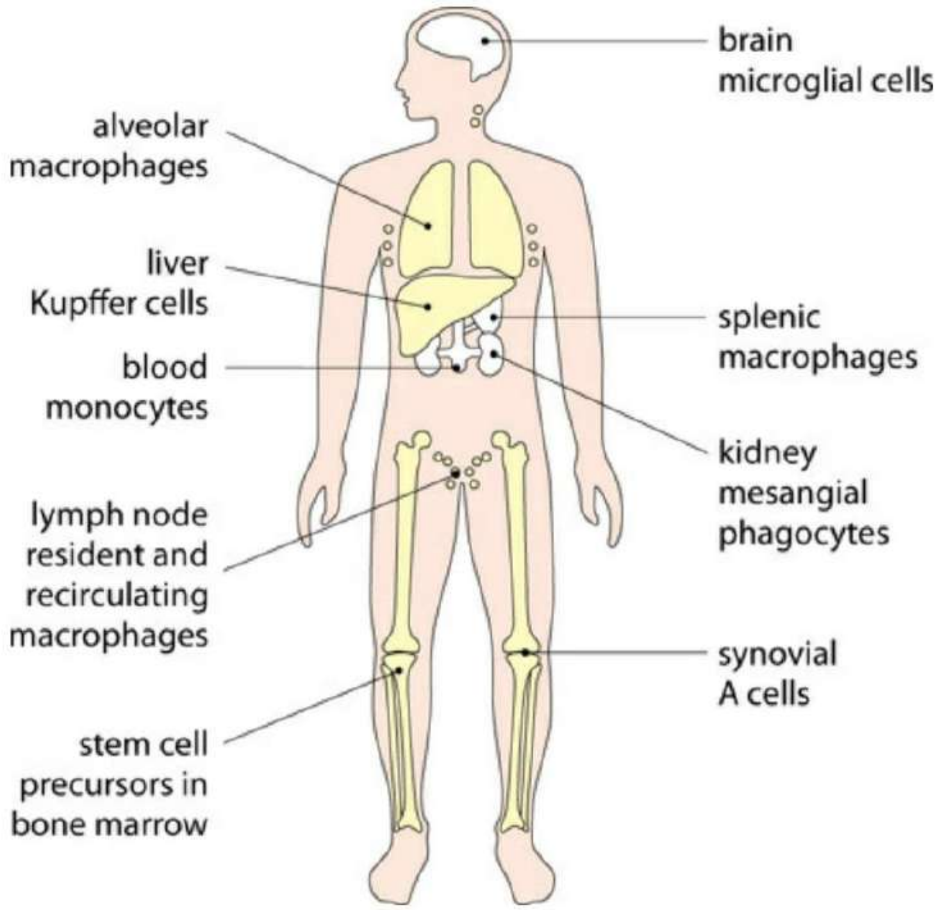
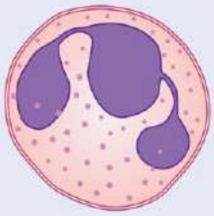
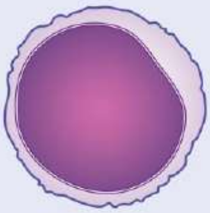
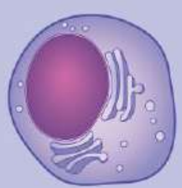
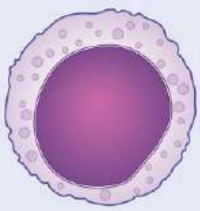
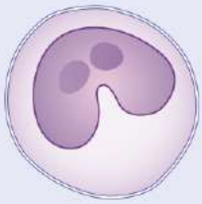
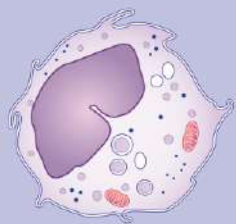
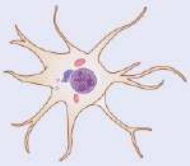
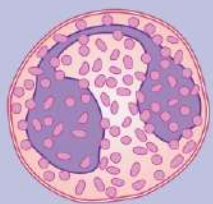
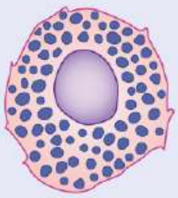
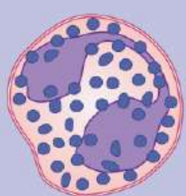
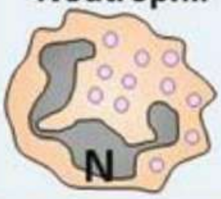
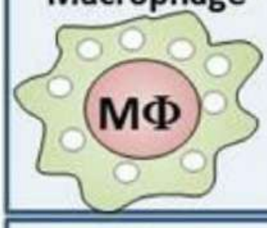
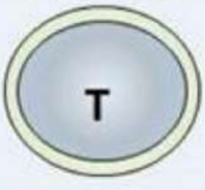


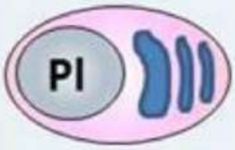
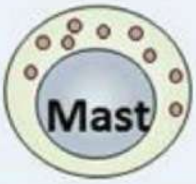
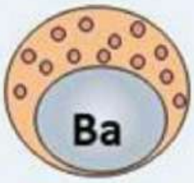
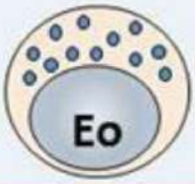
Fig. 1.7 Mononuclear phagocyte system.

3. **GRANULOCYTES (POLYMORPHS),** recognizable by their multi-lobed nuclei and numerous cytoplasmic granules, constitute the majority of blood leukocytes. They are classified by staining as:
   1. **Neutrophils**—professional phagocytes and the most abundant of the blood leukocytes (>70%). They spend less than 48 hours in the circulation before migrating into the tissues under the influence of chemotactic stimuli, where they phagocytose material and eventually die. They have receptors for antibody and complement to facilitate the uptake of opsonized particles.
   2. **Eosinophils**—comprising 2–5% of blood leukocytes. Their granules contain a crystalloid core of basic protein, which can be released by exocytosis, causing damage to a number of pathogens, particularly parasitic worms. The granules also contain histaminase and aryl sulfatase, which downregulate inflammatory reactions.
   3. **Basophils**—constituting <0.5% of blood leukocytes. Their granules contain inflammatory mediators and they are in some ways functionally similar to mast cells.
4. **Mast cells** are present in most tissues, adjoining the blood vessels. They contain numerous granules with inflammatory mediators, such as histamine and platelet-activating factor (PAF), released by triggering with C3a or C5a, or by cross-linking of surface IgE bound to their high-affinity IgE receptor (FcεRI). Stimulation causes them to produce prostaglandins and leukotrienes.
   There are two types of mast cell, thought to be derived from a common precursor.
   a. **Connective tissue mast cells (CTMCS)**—the main tissue-fixed mast cell population. They are ubiquitous, distributed around blood vessels, and contain large amounts of histamine and heparin. They are inhibited by sodium cromoglycate.
   b. **Mucosal mast cells (MMCS)**—present in the gut and lung. They are dependent on IL-3 and IL-4 for their proliferation and they are increased during parasitic infections of the gut.

Myeloid Cell	Tissue Location	Physical Description	Function
Neutrophil or polymorpho-nuclear (PMN) cell 	Most abundant circulating blood cell	Granulocyte with a segmented, lobular nuclei (3–5 lobes) and small pink cyto-plasmic granules	Phagocytic activity aimed at killing extracellular pathogens
Lymphoid Cell	**Tissue Location**	**Physical Description**	**Function**
Lymphocyte 	Bloodstream, secondary lym-phoid tissues	Large, dark-staining nucleus with a thin rim of cytoplasm Surface markers: B lymphocytes – CD19, 20, 21 T lymphocytes – CD3 Helper T cells – CD4 CTLs – CD8	No function until activated in the secondary lymphoid tissues
Plasma cell 	Bloodstream, sec-ondary lymphoid tissue and bone marrow	Small eccentric nucleus, intensely staining Golgi ap-paratus	Terminally differentiated B lymphocyte that secretes antibodies
Natural killer cell 	Bloodstream	Lymphocyte with large cytoplasmic granules Surface markers: CD16, 56	Kills virally infected cells and tumor cells

Myeloid Cell	Tissue Location	Physical Description	Function
Monocyte 	Circulating blood cell	Agranulocyte with a bean or kidney-shaped nucleus	Precursor of tissue macrophage
Macrophage 	Resident in all tissues	Agranulocyte with a ruffled cytoplasmic membrane and cytoplasmic vacuoles and vesicles	• Phagocyte • Professional antigen presenting cell • T-cell activator
Dendritic cell 	Resident in epithelial and lymphoid tissue	Agranulocyte with thin, stellate cytoplasmic projections	• Phagocyte • Professional antigen presenting cell • T-cell activator
Eosinophil 	Circulating blood cell recruited into loose connective tissue of the respiratory and GI tracts	Granulocyte with bilobed nucleus and large pink cytoplasmic granules	• Elimination of large extracellular parasites • Type I hypersensitivity
Mast cell 	Reside in most tissues adjacent to blood vessels	Granulocyte with small nucleus and large blue cytoplasmic granule	• Elimination of large extracellular parasites • Type I hypersensitivity
Basophil 	Low frequency circulating blood cell	Granulocyte with bilobed nucleus and large blue cytoplasmic granules	• Elimination of large extracellular parasites • Type I hypersensitivity

Neutrophil 	*Key functions*: Phagocytosis and killing of bacteria and fungi *CD markers*: CD66b, CD177 *Physical features*: Characteristic multi-lobed nucleus, abundant intracellular granules, 12-15 µm *Blood frequency*: 50-70 %
Monocyte 	*Key functions*: Source of most tissue macrophages, circulate in blood to be recruited to sites of inflammation, detection of PAMPs, secretion of inflammatory cytokines *CD markers*: CD14. *Major subtypes*: Inflammatory ($CD14^{lo}$ $CD16^{+}$), reparative ($CD14^{hi}$ $CD16^{-}$). *Blood frequency*: 5-10 %
Macrophage 	*Key functions*: Phagocytosis of microbes, debris and dead host cells, PAMPsdetection, secretion of cytokines and chemokines to modulate immune responses and tissue repair. *CD markers*: CD68. *Major subtypes*: M1 (pro-inflammatory), M2 (involved in tissue repair & remodelling)
Conventional DC 	*Key functions*: Capture of antigen and migration to lymph nodes, presentation of antigen to naïve T-cells, detection of PAMPs, secretion of cytokines to direct immune responses. *CD markers*: CD11c, CD123. *Physical features*: Numerous long projections of the cell membrane, motile on activation.
Plasmacytoid DC 	*Key functions*: Detection of viral PAMPs via endosomal TLRs, secretion of large quantities of type I interferon which promotes anti-viral defence, presentation of antigen to T-cells. *CD markers*: CD123, CD303, CD304. *Blood frequency*: 0.2-0.4%
T-lymphocyte 	*Key functions*: Discrimination of highly specific antigens presented on MHC, clonal expansion, assisting B-cell and macrophage activation (CD4+), or killing virally infected cells (CD8+). *CD markers*: CD3. *Major subtypes*: $CD8^{+}$ (CTLs), $CD4^{+}$ (inc T-reg, Th1, Th2, Th17). *Blood frequency*: 5-25%

B-lymphocyte 	*Key functions*: Detection of antigen using the B-cell receptor, differentiation to plasma cells to produce circulating antibody, maintenance of memory to surface antigens *CD markers*: CD19, CD20. *Major subtypes*: Follicular B-cell, marginal zone B-cell, B-1 B-cell. *Blood frequency*: 1-7%
Plasma cell 	*Key functions*: Antibody production and secretion, these are the effector cell form of B-lymphocytes *CD markers*: CD27 *Physical features*: Extended cytoplasm, extensive secretory vesicle system. Resident in bone marrow.
NK cell 	*Key functions*: Killing of host cells that are infected, damaged or dysfunctional, production of IFN-γ *CD markers*: CD16+CD56+CD3- *Physical features*: Similar to other lymphocytes *Blood frequency*: 1-6%
Mast cell 	*Key functions*: Release of pro-inflammatory and anti-microbial substances from intracellular granules when activated, particulary in response to IgE cross-linking *Physical features*: Tissue based, numerous cytoplasmic granules which bind basic dyes. Generally not found in blood
Basophil 	*Key functions*: Considered to be similar to mast cells, they release cytoplasmic granule contents on activation by IgE *CD markers*: CD203c *Physical features*: Cytoplasmic granules binding basic dyes *Blood frequency*: 0.2-0.5%
Eosinophil 	*Key functions*: Release of cytoplasmic granule contents on activation that may damage parasites, such as helminths *CD markers*: CD49d *Physical features*: Cytoplasmic granules binding acidic dyes *Blood frequency*: 1-3%