LYMPHOID ORGANS

Lymphoid tissue

Lymphoid tissue associated with the lymphatic system is concerned with immune functions in defending the body against the infections and spread of tumors. It consists of connective tissue with various types of white blood cells enmeshed in it, most numerous being the lymphocytes.

The lymphoid tissue may be primary, secondary, or tertiary depending upon the stage of lymphocyte development and maturation it is involved in. (The tertiary lymphoid tissue typically contains far fewer lymphocytes, and assumes an immune role only when challenged with antigens that result in inflammation. It achieves this by importing the lymphocytes from blood and lymph.

Primary lymphoid organs

The **central** or **primary lymphoid organs** generate lymphocytes from immature progenitor cells. The thymus and the bone marrow constitute the primary lymphoid tissues involved in the production and early selection of lymphocytes.tissues

Secondary lymphoid organs

Secondary or **peripheral lymphoid organs** maintain mature naive lymphocytes and initiate an adaptive immune response. The peripheral lymphoid organs are the sites of lymphocyte activation by antigen. Activation leads to clonal expansion and affinity maturation. Mature lymphocytes recirculate between the blood and the peripheral lymphoid organs until they encounter their specific antigen.

Secondary lymphoid tissue provides the environment for the foreign or altered native molecules (antigens) to interact with the lymphocytes. It is exemplified by the lymph nodes, and the lymphoid follicles in tonsils, Peyer's patches, spleen, adenoids, skin, etc. that are associated with the mucosa-associated lymphoid tissue (MALT).

Development of lymphatic tissue

Lymphatic tissues begin to develop by the end of the fifth week of embryonic development. Lymphatic vessels develop from lymph sacs that arise from developing veins, which are derived from mesoderm.

The first lymph sacs to appear are the paired jugular lymph sacs at the junction of the internal jugular and subclavian veins.

The next lymph sac to appear is the unpaired retroperitoneal lymph sac at the root of the mesentery of the intestine.

The last of the lymph sacs, the paired posterior lymph sacs, develop from the iliac veins.

All lymph sacs become invaded by mesenchymal cells and are converted into lymph nodes.

The spleen develops from mesenchymal cells between layers of the dorsal mesentery of the stomach.

The thymus arises as an outgrowth of the third pharyngeal pouch.

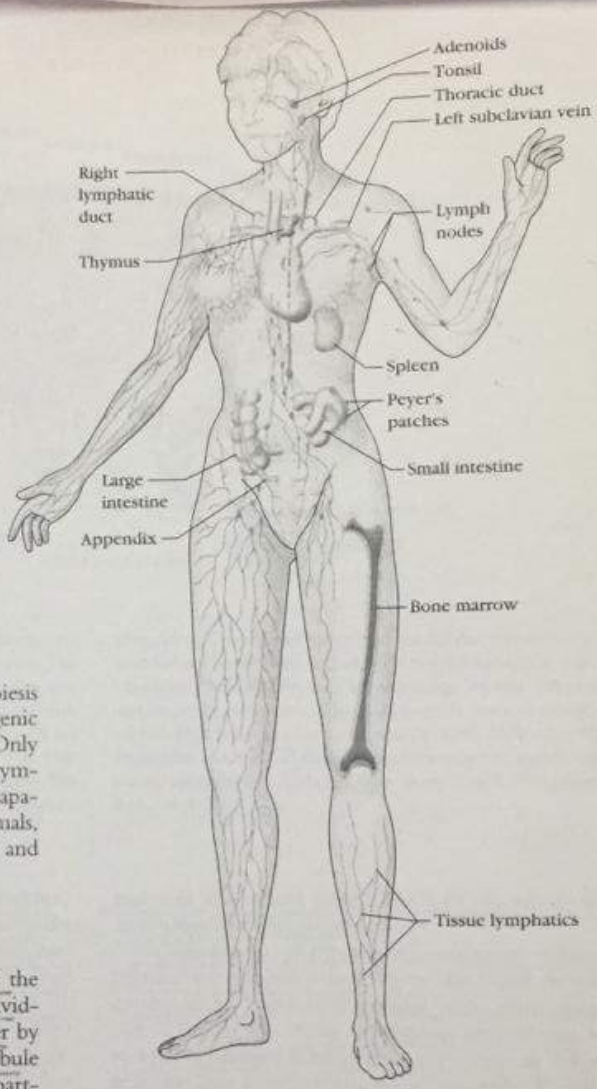
Diseases of the lymphatic system

1. Lymphedema is the swelling caused by the accumulation of lymph fluid, which may occur if the lymphatic system is damaged or has malformations. It usually affects limbs, though face, neck and abdomen may also be affected. In an extreme state the edema progresses. Skin becomes thicker with an appearance similar to elephant limbs. Is called elephantiasis. Causes are unknown in most cases, but sometimes the patient in question has a previous history of severe infection, most commonly caused by a parasitic disease, like the lymphatic filariasis for example.

2. Some common causes of swollen lymph nodes include infections, infectious mononucleosis, and cancer, e.g. Hodgkin's and non-Hodgkin lymphoma, and metastasis of cancerous cells via the lymphatic system.
3. Hodgkin's lymphoma is a type of cancer usually resulting from the white blood cells in the body becoming diseased or damaged. Presently, this kind of cancer is easily controlled.
4. Lymphangiomatosis is a disease involving multiple cysts or lesions formed from lymphatic vessels.
5. Lymphangiosarcoma is a malignant soft tissue tumor, whereas lymphangioma is a benign tumor occurring frequently in association with Turner syndrome. Lymphangioleiomyomatosis is a benign tumor of the smooth muscles of the lymphatics that occurs in the lungs.
6. Lymphoid leukemias and lymphomas are now considered to be tumors of the same type of cell lineage. They are called "leukemia" when in the blood or marrow and "lymphoma" when in lymphatic tissue. They are grouped together under the name "lymphoid malignancy".

FIGURE 3-16

The human lymphoid system. The primary organs (bone marrow and thymus) are shown in red; secondary organs and tissues, in blue. These structurally and functionally diverse lymphoid organs and tissues are interconnected by the blood vessels (not shown) and lymphatic vessels (purple) through which lymphocytes circulate. Only one bone is shown, but all major bones contain marrow and thus are part of the lymphoid system. [Adapted from Harvey Lodish et al., 1995, *Molecular Cell Biology*, 3rd ed., Scientific American Books.]



Primary Lymphoid Organs

Immature lymphocytes generated during hematopoiesis mature and become committed to a particular antigenic specificity within the primary lymphoid organs. Only after a lymphocyte has matured within a primary lymphoid organ is the cell **immunocompetent** (i.e., capable of mounting an immune response). In mammals, B-cell maturation occurs in the **bone marrow** and T-cell maturation occurs in the **thymus**.

Thymus

The thymus is a flat, bilobed organ situated above the heart. Each lobe is surrounded by a capsule and is divided into lobules, which are separated from each other by strands of connective tissue called trabeculae. Each lobule is organized into two compartments: the outer compartment, or **cortex**, is densely packed with immature T cells, called thymocytes, whereas the inner compartment, or **medulla**, is sparsely populated with thymocytes.

The actual sequence of T-cell maturation within the thymus is not completely understood. After progenitor T cells formed during hematopoiesis enter the thymus, they are thought to multiply rapidly within the cortex; this rapid proliferation of thymocytes is coupled to an enormous rate of cell death. A small subset of more mature thymocytes are then thought to migrate from the cortex to the medulla where they continue to mature and finally leave the thymus via postcapillary venules. There appear to be exceptions to this sequence, with some studies showing that a small subpopulation of cortical thymocytes can mature and leave the thymus without ever entering the medulla.

Both the cortex and medulla of the thymus are crisscrossed by a three-dimensional stromal-cell network composed of epithelial cells, interdigitating dendritic cells, and macrophages, which make up the framework

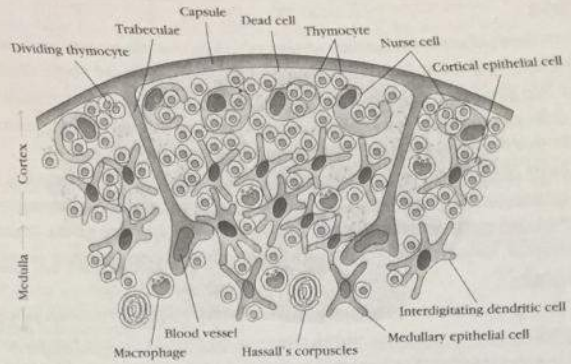


FIGURE 3-17

Diagrammatic cross-section of a portion of the thymus, showing several lobules separated by connective tissue strands (trabeculae). The densely populated outer cortex is thought to contain many immature thymocytes (blue), which undergo rapid proliferation coupled with an enormous rate of cell death. Also present in the outer cortex are thymic nurse cells (gray), which are specialized epithelial cells with long membrane processes that surround up to 50 thymocytes. The medulla is sparsely populated and is thought to contain more mature thymocytes. During their stay within the thymus, thymocytes interact with various stromal cells including cortical epithelial cells (light red), medullary epithelial cells (tan), interdigitating dendritic cells (purple), and macrophages (yellow). These cells produce thymic hormones and express high levels of class I and class II MHC molecules. Hassall's corpuscles found in the medulla contain concentric layers of degenerating epithelial cells. [Adapted from W. van Ewijk, 1991, *Annu. Rev. Immunol.* **9**:591.]

of the organ and contribute to thymocyte maturation. Many of these stromal cells physically interact with the developing thymocytes (Figure 3-17). Some thymic epithelial cells in the outer cortex, called **nurse cells**, have long membrane processes that surround as many as 50 thymocytes, forming large multicellular complexes. Other cortical epithelial cells have long interconnecting cytoplasmic processes that form a network and have been shown to interact with numerous thymocytes as they traverse the cortex. Interdigitating dendritic cells, which are located at the junction of the cortex and medulla, also have long processes that interact with developing thymocytes.

Maturation and Selection of T Cells Thymic epithelial cells secrete several hormonal factors necessary for the differentiation and maturation of thymocytes into the various types of mature T cells. Four such hormonal factors that have been characterized are α_1-thymosin, β_4-thymosin, thymopoietin, and thymulin. When bone marrow cells are cultured with these factors, membrane molecules characteristic of the T-cell lineage have been shown to appear, although the role of each of these factors in T-cell maturation remains unknown. Thymic stromal cells also secrete interleukin 7 (IL-7), which stimulates growth of thymocytes.

In the course of thymocyte maturation within the thymus, the antigenic diversity of the T-cell receptor is generated by a series of random gene rearrangements (see Chapter 11). After developing thymocytes begin to express antigen-binding receptors, they are subjected to a two-step selection process, so that only T cells recognizing antigenic peptides in the context of self-MHC molecules are released from the thymus. Thymic stromal cells, which express high levels of class I and class II MHC molecules, play a role in this selection process. During this selection process any developing thymocytes that are unable to recognize self-MHC molecules or that have a high affinity for self-antigen plus self-MHC (or self-MHC alone) are eliminated by programmed cell death. Thus only those cells whose receptor recognizes a self-MHC molecule plus foreign antigen are allowed to mature. A detailed discussion of thymic selection is presented in Chapter 12.

An estimated 95%–99% of all thymocyte progeny undergo programmed cell death within the thymus without ever maturing. This high death rate probably results primarily from the elimination of thymocytes that cannot

recognize foreign antigenic peptides displayed by self-MHC molecules and of thymocytes that recognize self-peptides displayed by self-MHC molecules. It is not known whether some sort of external signal (e.g., the presence or absence of a factor) initiates programmed cell death in those thymocytes. Some have suggested that the death of most nonselected thymocytes may be induced by endogenous glucocorticoids. It has been known for some time that cortical thymocytes, especially in rodents, are extremely sensitive to glucocorticoids, whereas mature T cells are not. For instance, when mouse thymocytes are incubated with high physiologic levels of glucocorticoids, the cells begin to die within 1–2 h by apoptosis. Injection of glucocorticoids into rats and other experimental animals leads to marked atrophy of the thymus (Figure 3-18).

Relation Between Thymic and Immune Function The first evidence implicating the thymus in immune function came from experiments involving neonatal thymectomy in which the thymus was surgically removed from newborn mice. These thymectomized mice showed a dramatic decrease in circulating lymphocytes of the T-cell lineage and an absence of cell-mediated immunity. A congenital birth defect in humans (**DiGeorge's syndrome**) and in certain mice (**nude mice**) that involves failure of the thymus to develop provides further evidence. In both cases there is an absence of circulating T cells and of cell-mediated immunity and an increase in infectious disease.

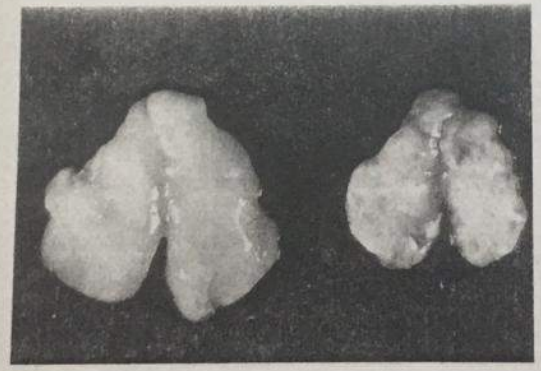
The decline in immune functions that accompanies aging, leading to an increase in infections, autoimmunity, and cancer, probably results primarily from changes in the T-cell component of the immune system. The thymus reaches its maximal size at puberty and then atrophies, with a significant decrease in both cortical and medullary cells and an increase in the total fat content of the organ. Whereas the average weight of the thymus is 70 g in infants, its average weight is only 3 g in the elderly. This thymic involution, with the associated decrease in cortical size, medullary size, and hormonal production, precedes the decrease in immune function that is seen with aging.

A number of experiments have been designed to look at the effect of age on the immune function of the thymus. In one experiment the thymus from a 1-day-old or 33-month-old mouse was grafted into thymectomized adult littermates. Mice receiving the newborn thymus graft showed a significantly larger improvement in immune function than mice receiving the 33-month-old thymus.

Bone Marrow

In birds a lymphoid organ called the bursa of Fabricius is the primary site of B-cell maturation. There is no bursa in mammals and no single counterpart to it as a primary lymphoid organ. Instead, regions of the bone marrow and possibly of other lymphoid tissues serve as the "bursal equivalent" where B-cell maturation occurs.

Immature B cells proliferate and differentiate within the microenvironment of the bone marrow. Stromal cells within the bone marrow interact directly with the B cells and secrete various cytokines that are required for the B-cell developmental process. Similar to thymic selection during T-cell maturation, a selection process



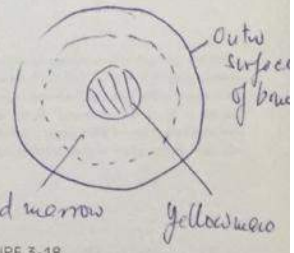


FIGURE 3-18

Effects of glucocorticosteroids on the rat thymus gland. A normal thymus *(left)* compared with the thymus of a rat 48 h following injection of a corticosteroid (5 mg/kg body weight). [From M. M. Compton and J. A. Cidlowski, 1992, *Trends Endocrinol. Metabol.* **3**:17.]

within the bone marrow eliminates B cells with self-reactive antibody receptors. This process is covered in more detail in Chapter 8.

Lymphatic System

As blood circulates under pressure, the fluid component of the blood (**plasma**) seeps through the thin wall of the capillaries into the surrounding tissue. 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 connective tissue spaces into a network of tiny open lymphatic capillaries and then into a series of progressively larger collecting vessels called **lymphatic vessels** (Figure 3-19).

The largest lymphatic vessel, the **thoracic duct**, empties into the left subclavian vein near the heart (see Figure 3-16). In this way the lymphatic system functions to capture fluid lost from the blood and return it to the blood, thus ensuring steady-state levels of fluid within the circulatory system. 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 ensure that lymph flows only in one direction.

When a foreign antigen gains entrance into 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, which trap the foreign antigen. 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.

Secondary Lymphoid Organs

Secondary Lymphoid Organs

Various types of organized lymphoid tissues are located along the vessels of the lymphatic system. Some lymphoid tissue in the lung and lamina propria of the intestinal wall consists of diffuse collections of lymphocytes and macrophages. Other lymphoid tissue is organized into structures called lymphoid follicles, which consist of aggregates of various cells surrounded by a network of draining lymphatic capillaries. In the absence of antigen activation, a lymphoid follicle—called a **primary follicle**—comprises a network of follicular dendritic cells and small resting B cells. Following an antigenic challenge, a primary follicle becomes a larger **secondary follicle**—a ring of concentrically packed B lymphocytes surrounding a center (the **germinal center**) in which proliferat-

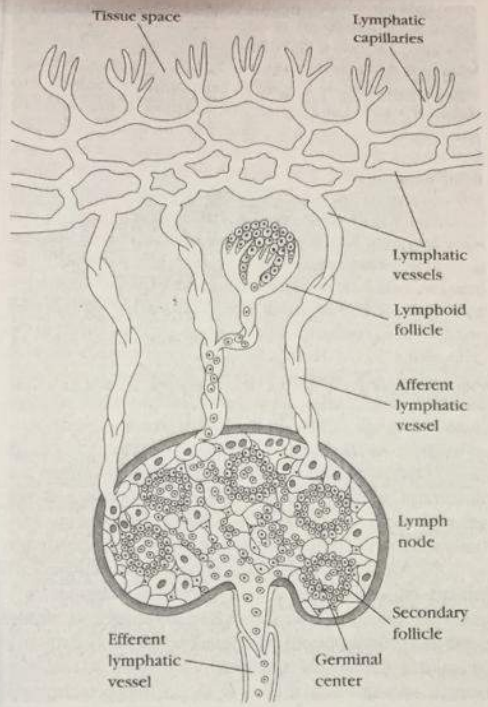


FIGURE 3-19

Lymphatic vessels. Small lymphatic capillaries opening into the tissue spaces pick up interstitial tissue fluid and carry it into progressively larger lymphatic vessels, which carry the fluid, now called lymph, into regional lymph nodes. As lymph leaves the nodes, it is carried through larger efferent lymphatic vessels, which eventually drain into the circulatory system at the thoracic duct or right lymph duct (see Figure 3-16).

ing B lymphocytes, memory B cells, and plasma cells are interspersed with macrophages and follicular dendritic cells (Figure 3-20).

The germinal center is a site of intense B-cell activation and contains large numbers of blast cells, called **centroblasts**. B cells that interact with antigen displayed on the membrane of follicular dendritic cells are induced to proliferate and differentiate into plasma and memory cells. In the absence of antigen activation, the B cells appear to undergo programmed cell death within the germinal center. The process of B-cell activation, prolifer-

1. Overview

Lymph nodes are kidney-shaped structures found at regular intervals in the lymphatic system. a few millimeters to about 1–2 cm long They are located all over the body, excluding the CNS. and range in size from 1mm to 25mm. Each lymph node is surrounded by a capsule made from a dense layer of connective tissue.

They are a secondary lymphoid organs and their role is to filter lymph and assist in the immune response. Lymphatic vessels pick up antigenic material, inflammatory mediators and antigen presenting cells (APCs) and deliver them to lymph nodes. APCs can interact with naive lymphocytes and activate an immune response.

2. Lymph Node Structure

The lymph node is divided into 3 areas. The outermost part is the **cortex**, the innermost is the**medulla** and the **paracortex** is in the middle of the two. These are shown in figure 1. B and T cells are located in separate parts of the lymph node. This allows separate areas for the cells to interact with APCs and undergo clonal expansion.

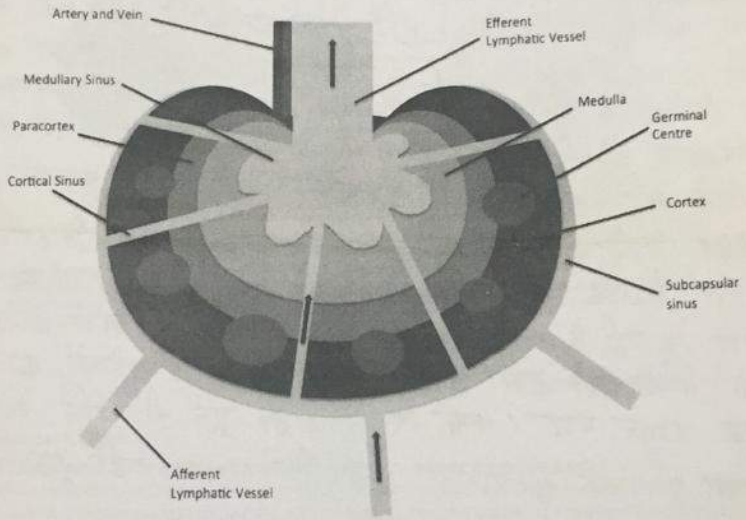


Figure 1: An overview of the lymph node structure. It shows the main areas of the lymph node (cortex, paracortex and medulla) as well as arrows indicating the direction of lymph flow through the lymph node.

a. Cortex

The cortex is a **B Cell area** containing aggregations of B cells within follicles. In an unstimulated lymph node these follicles are known as **primary follicles**. Upon stimulation by antigens, they

become **secondary follicles**. Secondary follicles have **germinal centers** in which activated B cells undergo proliferation and differentiation into plasma cells and memory B cells.

When antigen enters a lymph node it can filter through follicles in the cortex. Here the antigen can be captured and presented to B cells. If the B cell recognizes the antigen, they can take up the antigen and process it. Antigenic peptides are then presented on their class II MHC. B cells can also be partially activated by the antigen and lead to B cell migration to the cortex-paracortex border in the node. Here they encounter CD4 T cells (T helper cells) that have also migrated to the border. Activated B cells express class II MHC on their surface in order to present antigen to the CD4 T cells via their T cell receptor (TCR). If recognition occurs, the CD4 T cells are stimulated to produce cytokines that bind to the B cells. There also needs to be an additional signal of the **CD154** ligand on the T cell binding to the **CD40** ligand on the B cell. These signals stimulate the B cells to proliferate and form a cluster at the cortex-paracortex border. This interaction is shown in figure 2.

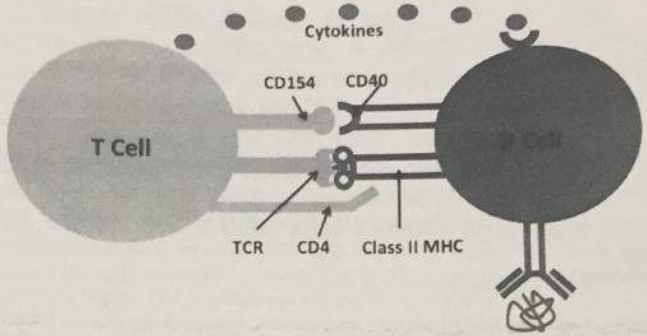


Figure 2: Interaction between CD4 T cells and B cells. An antigen can bind to a B cell antibody, and if it is recognised the antigenic peptide is taken up and processed to be presented on the Class II MHC. If this MHC-antigen complex is recognised by the T cell receptor, the T cell releases cytokines that bind to B cells. Interaction between CD154 on the T cell and CD40 on the B cell must also occur.

b. Germinal Centers

After 4-7 days some of the activated B cells and CD4 T cells migrate to primary follicles, where germinal centers will form. Primary follicles contain follicular dendritic cells (FDCs), a type of APC. FDCs have long processes that are used to contact B cells. They are specialized to capture antigen in the form of immune complexes as well as complexes of antigens, complement and antibodies. The migration of the cells is due to the chemokine **B lymphocyte chemoattractant,** released by FDCs and other cells in the B cell area, binding to the **CXCR5** receptor expressed on B and CD4 T cells.

Within the germinal center, the B cells undergo affinity maturation in which they down regulate their antibody and undergo extensive proliferation. This occurs in the **dark zone** of the germinal center. The B cells are now known as **centroblasts**. During proliferation, the cells also undergo **somatic mutation** in the hypervariable regions of H and L chain genes of the antibody. This alters the hypervariable region of the antibody, which can increase, decrease or have no effect on the antibody's affinity for the antigen.

The centroblasts then stop proliferating and re-express their membrane antibody. They are now know as **centrocytes** and are located in the **basal light zone** of the germinal center. The centrocytes must recognize the antigens on the surface of the FDCs with a strong affinity to receive a survival signal from the FDCs. If they do not, they will die by apoptosis and subsequently be engulfed by macrophages. There is competition between B cells for the antigen on the FDCs so only those cells that bind with high affinity will survive. B cells also undergo a process known as **class switching**during the centroblast/centrocyte stage. This is a stage in which the heavy chain constant regions can switch. This does not alter the antigen specificity. CD4 T cells and cytokines control this process.

The last stage of B cell differentiation occurs in the **apical light zone** of the germinal center. Here, they differentiate into either **plasma cells**, which produce large amounts of antibody, or **B memory cells**. Plasma cells can either remain in the secondary lymphoid organs or migrate to the bone marrow. B memory cells continue to recirculate through the lymphatic system.

c. Paracortex

The paracortex is mainly a **T Cell area.** The lymphocytes migrating from the blood into the lymph nodes also enter here via high endothelial venules.

Activated **dendritic cells** (DCs) travel to the paracortex of the lymph node from tissue via lymphatic vessels in response to antigen stimulation. This migration is due to the chemokine **Epstein Barr virus-induced receptor ligand** (ELC) binding to the chemokine receptor, **CCR7**, which is upregulated in a stimulated DC. During this migration, DCs process the antigen and express antigen fragments on**class II MHC** for the CD4 T cells to recognise. Antigens can also enter the lymph node on their own and are then picked up by DCs in the paracortex and presented on class II MHC molecules in the same way as above. The dendritic cell is therefore an APC.

When the DCs migrate to the T-cell areas of the node, they start to secrete ELC, which binds to**CCR7** receptors on T-cells, therefore attracting T-cells to DCs in a non-antigen specific manner. CD4 T cells have the integrin **LFA-1** on their cell surface that transiently binds to **ICAM-1** on DCs. If the T cell does not recognize the antigen it will dissociate from the DC and continue to travel through the lymph node and bind to further DCs. If the TCR recognises the class II MHC-antigen complex, signaling through the TCR causes a conformational change in the LFA-1 so that it binds with a **higher affinity** to the ICAM-1 and therefore stabilizes the association between the cells.

There also needs to be a secondary stimulus from the APC, called a **co-stimulus**, in order to activate the resting CD4 T Cell. The most important co-stimulus on a T cell is called **CD28**, which binds to either **CD80** or **CD86** molecules on APC cells (Figure 3). On recognition of both these stimuli, the T cell is now activated and can proliferate and differentiate. They are signaled to proliferate extensively by the cytokine **interleukin 2** (IL-2). CD4 T cells both release IL-2 and express the IL-2 receptor so can work in an autocrine or paracrine (on antigen stimulated neighboring cells) manner. There is also a third signal in the form of different cytokines being released from APCs which can stimulate T helper cells to differentiate into different subtypes.

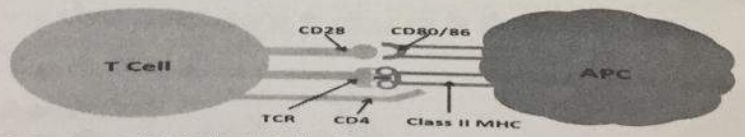


Figure 3. The activation of CD4 T cells via APCs. These T cells recognise the antigen-Class II MHC complex on the APC. A co-stimulus is also required to activate the T cell. This is provided by the the CD80/86 on the APC binding to the CD28 molecule on the T cell

d. Medulla

The medulla is less densely packed with cells. It mainly consists of lymph draining sinuses, which are separated by medullary cords. These medullary cords contain many antibody-producing plasma cells (mature B cells) as well as some memory T cells and macrophages. The plasma cells that remain in the medulla tend to be short lived and only secrete antibody, such as IgA or IgG, for a few weeks. This is in comparison to those plasma cells that are long lived as they migrate to the bone marrow and receive survival signals.

e. High Endothelial Venules

Lymphocytes are able to enter lymph nodes directly from the blood via specialised blood vessels called high endothelial venules (HEVs). These venules are called 'high' as they are made of cuboidal endothelial cells. HEVs are located in the **paracortex** of the lymph node, enabling the lymphocytes to enter the node in the T-cell area. B-cells then migrate to the cortex. This migration of B cells to the B cell area is due to the chemokine, **B-Lymphocyte chemo-attractant** (BLC). Follicular dendritic cells and stromal cells found in the B-cell area produce BLC. It binds to the **CXCR5** chemokine receptor on B cells.

In order for lymphocytes to migrate out of the HEVs, the blood flow must be slow enough for the cells to be able to attach to the walls of the vessels. The slowing of the blood is due to vasodilation of vessels. Vasodilation occurs because the high endothelial venules that are the site of migration from blood to lymph nodes are located where small diameter capillaries become larger diameter venules. This diameter change slows the blood in the same way that vasodilation as a result of inflammation occurs. The slowing of the blood allows the lymphocytes to **roll** along the vessel wall. **Cell adhesion molecules** then govern the **extravasation** of lymphocytes into the lymph node via the same mechanism as the inflammatory **response.**

f. Reticular Meshwork

The whole lymph node is filled with a reticular meshwork. It is composed of **fibroblastic reticular cells** (FRCs), **reticular fibres** and fibrous extracellular matrix. This meshwork formed by the FRCs provides the **structural framework** for the node whilst also making spaces for motile immune cells to move through. It also may function as a physical barrier, keeping immune cells in their designated compartments, as well as preventing excessive growth or disordered interactions of cells.

3. How are Lymph Nodes connected with the Lymphatic System?

Afferent lymphatic vessels bring the lymph fluid (fluid drained from tissues) into the lymph nodes at the side opposite the hilum. They empty their contents into the **subcapsular space.** The subcapsular space contains a mesh of reticular fibres, macrophages and dendritic cells. The lymph then flows through the cortex of the node. From the cortex, the lymph travels through sinuses to the paracortex and then to the medulla. It then travels through medullary cords to the efferent lymphatic vessel.

Lymph fluid leaves the lymph node via the **efferent lymphatic vessel** at the **hilum** of the node. The hilum is also the point for the entry and exit point of blood vessels and nerves. The lymph vessels from different nodes then join to eventually become 2 major lymphatic ducts, the **thoracic duct** and the **right lymphatic duct**. These then drain into venous circulation. In this manner, lymphocytes are continually being recirculated around the body. Lymphatic vessels contain valves to prevent the back flow of lymph, in the same fashion as venous circulation.

resulting in visible swelling of the nodes. Factors released in lymph nodes during antigen stimulation are thought to facilitate this increased lymphocyte migration.

Spleen

The spleen is a large, ovoid secondary lymphoid organ situated high in the left abdominal cavity. Unlike lymph nodes, which are specialized to trap localized antigen from regional tissue spaces, the spleen is adapted to filtering blood and trapping blood-borne antigens, and thus can respond to systemic infections. The spleen is surrounded by a capsule that sends 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 (Figure 3-22). The splenic **red pulp** consists of a network of sinusoids populated with

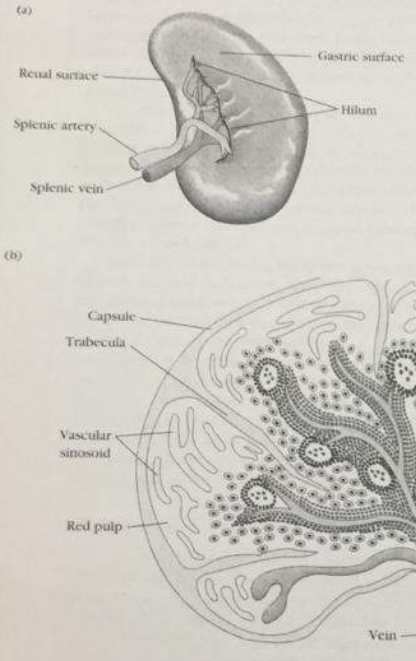


FIGURE 3-22

Structure of the spleen. (a) The spleen, which is about 5 inches long in adults, is the largest secondary lymphoid organ. It is specialized for trapping blood-borne antigens. (b) Diagrammatic cross section of the spleen. The arteriole blood supply pierces the capsule and divides into progressively smaller arterioles, ending in vascular sinusoids that drain back into the splenic vein. The erythrocyte-filled red pulp surrounds the sinusoids. The white pulp forms a sleeve, the periarteriolar lymphoid sheath (PALS) around the arterioles; this sheath contains numerous T cells. Closely associated with the PALS is the marginal zone, a B-cell–rich area containing lymphoid follicles that can develop into germinal centers.

macrophages and numerous red blood cells (erythrocytes); it is the site where old and defective red blood cells are destroyed and removed. Many of the macrophages within the red pulp contain engulfed red blood cells or iron pigments from degraded hemoglobin. The splenic **white pulp** surrounds the arteries, forming a **periarteriolar lymphoid sheath** (PALS) populated mainly by T lymphocytes. The **marginal zone**, located peripheral to the PALS, is rich in B cells organized into primary lymphoid follicles.

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 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. 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.

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

Unlike the lymph nodes, the spleen is not supplied by afferent lymphatics draining the tissue spaces. Instead, blood-borne antigens are carried into the spleen through the splenic artery, which empties into the marginal zone. As antigen enters the marginal zone, it is trapped by interdigitating dendritic cells, which carry the antigen to the periarteriolar lymphoid sheath. Lymphocytes in the blood also enter sinuses in the marginal zone and migrate to the periarteriolar lymphoid sheath. Experiments with radioactively labeled lymphocytes show that more recirculating lymphocytes pass daily through the spleen than through all the lymph nodes combined.

Save

PRIMARY LYMPHOID ORGANS VERSUS SECONDARY LYMPHOID ORGANS

PRIMARY LYMPHOID ORGANS	SECONDARY LYMPHOID ORGANS
Organs of the immune system where lymphocytes are formed and mature	Organs of the immune system which maintain mature naive lymphocytes and initiate an adaptive immune response
Allow lymphoid stem cells to proliferate, differentiate, and mature	Allow lymphoid cells to become functional
Contain either T cells or B cells	Contain both T cells and B cells
Have no contact with antigens	Have contact with antigens
Undergo atrophy with age	Increase size with age

With Age

Primary lymphoid organs undergo atrophy with age while secondary lymphoid organs increase size with age. This is another difference between primary and secondary lymphoid organs.

Conclusion

Primary lymphoid organs are a type of organs in the immune system, allowing lymphoid stem cells to proliferate, differentiate, and mature. Some examples of them in the human body are the thymus and bone marrow. On the other hand, secondary lymphoid organs are another type of organs in the immune system, which allow lymphoid cells to become specialized cells by making contact with antigens. Therefore, the main difference between primary and secondary lymphoid organs is their function in the immune cell maturation.

References:

Cutaneeous associated Lymphoid Tissue

Skin besides providing innate defence (discussed already) also produces number of cytokines which sets in inflamatory response. More so karyocites (Fig.) can also be induced to express class II MHC molecules and function as antigen presenting cell. Epidermal langerghans cells are modified dendritic cells which internelize antigen and migrate from epidermis to regional lymph nodes and after reaching there differentiate into interdigitating dendritic cells

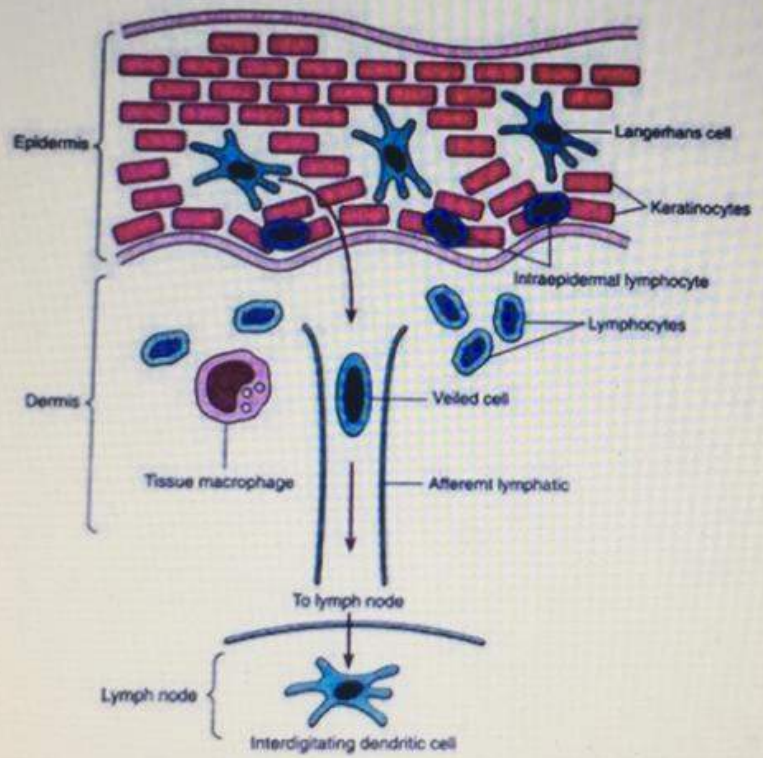
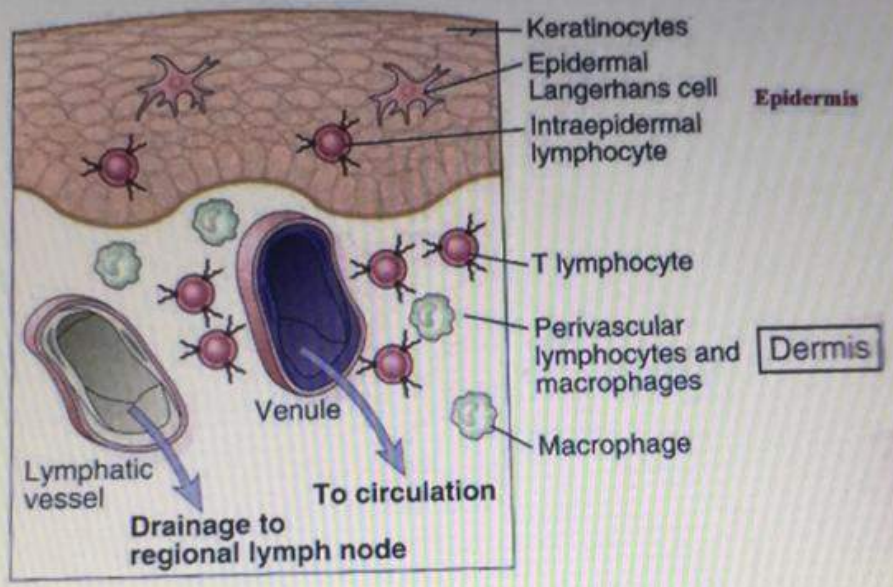


Fig. 6.31 : Cutaneous-associated lymphoid tissues : Keratinocytes, the major cells of the epidermis, secrete cytokines that may induce an inflammatory response. Langerhans cells in the skin internalise antigen and move in the lymph (as veiled cells) to lymph nodes, where it differentiates into interdigitating dendritic cells; these function as potent antigen-presenting cells. Intraepidermal lymphocytes are predominantly T cells that express the γδ T-cell



These cells use to express very high level of Class II MHC and function as APC which intern activates T helper cells.

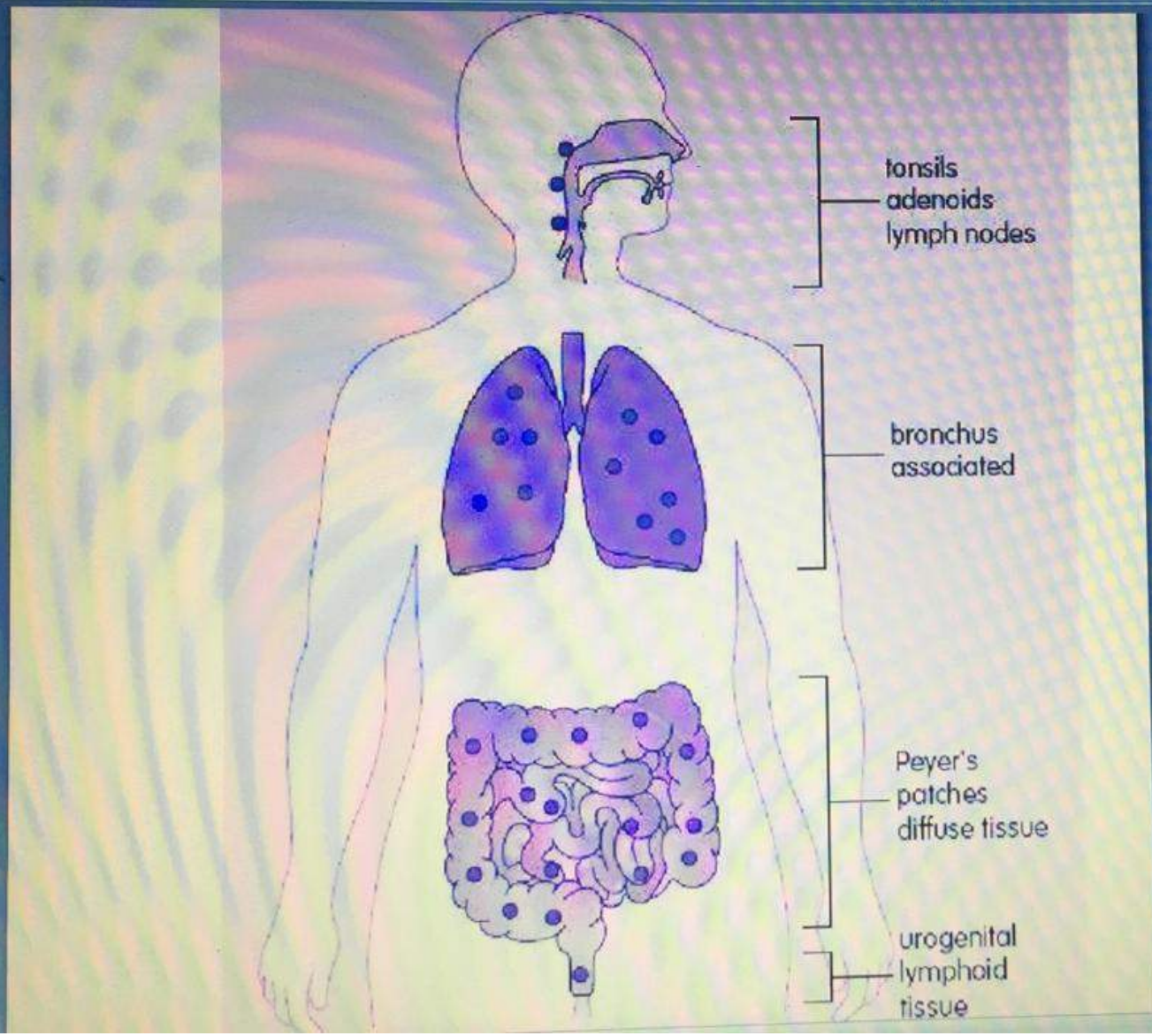
Besides this, epidermis do contains intraepidermal lymphocytwe. They are modified T cells having CD 8. It is believed that they are appropreatly located to interact with antigem which enters through skin.

However in dermis too scattered lymphocytes are found having both CD4 and CD 8 along with macrophages. Some workers believe that these are second line odf defence in the cutaneous tissue. But some scholl believe that these are preactivated T cell lines or memory cells.

Mucous associated Lymphoid Tissue

The **mucosa-associated lymphoid tissue** (**MALT**), constitute about 50% of the lymphoid tissue in human body is a diffuse system of small concentrations of lymphoid tissue found in various sub mucosal membrane sites of the body-

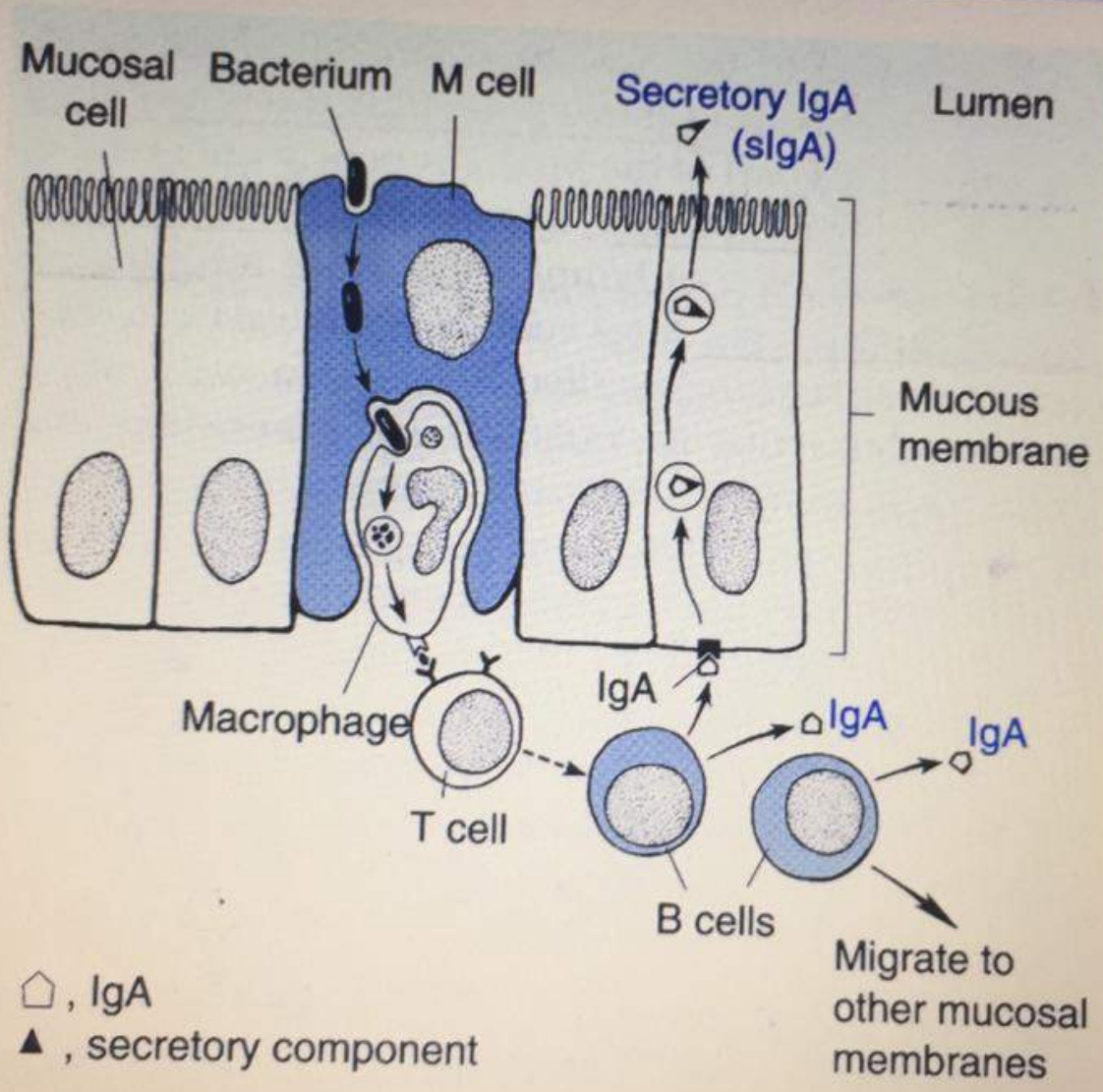
1. gastrointestinal tract,
2. nasopharynx,
3. thyroid,
4. breast,
5. lung,
6. salivary glands,
7. eye, and
8. skin.


tonsils
adenoids
lymph nodes
bronchus
associated
Peyer's
patches
diffuse tissue
urogenital
lymphoid
tissue

MALT wherever present is populated by lymphocytes such as

1. T cells
2. B cells,
3. plasma cells and
4. macrophages,

Each of these cell is situated at various sites in such a way to encounter antigens passing through the mucosal epithelium very comfortably. However, in the case of intestinal MALT, M cells are also present, which sample antigen from the lumen and deliver it to the underlying lymphoid tissue.


Mucosal cell
Bacterium
M cell
Secretory IgA (sIgA)
Lumen
Mucous membrane
Macrophage
IgA
IgA
IgA
T cell
B cells
Migrate to other mucosal membranes
, IgA
, secretory component

The components of MALT are sometimes subdivided into the following:

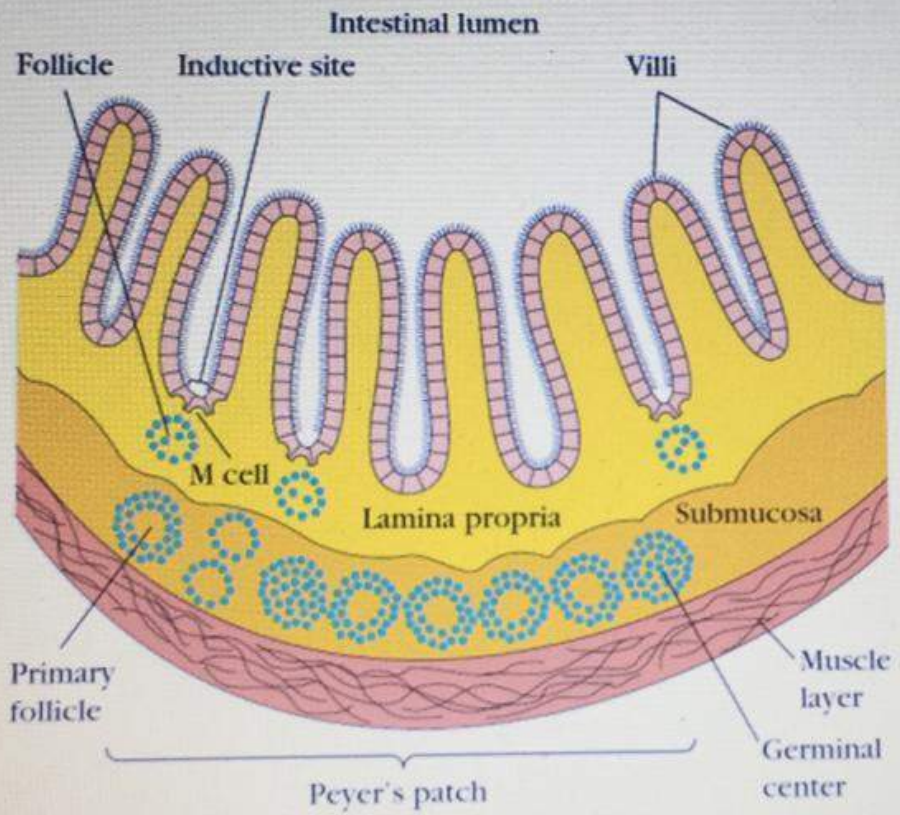
1. **GALT** (gut-associated lymphoid tissue. Peyer's patches are a component of GALT found in the lining of the small intestines.)
2. **BALT** (bronchus-associated lymphoid tissue)
3. **NALT** (nasal-associated lymphoid tissue)
4. **CALT** (conjunctival-associated lymphoid tissue)
5. **LALT** (larynx-associated lymphoid tissue)
6. **SALT** (skin-associated lymphoid tissue)
7. **VALT** (vulvo-vaginal-associated lymphoid tissue)
8. **TALT** (testis-associated lymphoid tissue)

It can be also distinguished by level of organization of the tissue:

A. **O-MALT** (organized mucosa-associated lymphatic tissue); specifically, the tonsils of Waldeyer's tonsillar ring are O-MALT.
B. **D-MALT** (diffuse mucosa-associated lymphatic tissue); MALT that is not organized as a separately macroscopically anatomically identifiable mass, tissue or organ (such as the aforementioned O-MALT) is diffuse MALT.

Wherever they are, what ever is their span, their size – they play important role in promoting immune response by delivering small samples of foreign antigen from the site fof entry to underlying lymphoid tissue.

However M cells are little different. They are flattend epithelial cells having no microvilli (Which is one of the regular feature of mucous epithelial lining). The have inveginative pockets. These pockets are filled with Lymphocytes and macrophages. Endocytosed antigens are delivered to these contained cells in associatiob with CLASS II MHC which M cells are capable of producing. This delivery takes place with in the pocket.


Intestinal lumen
Follicle
Inductive site
Villi
M cell
Lamina propria
Submucosa
Primary follicle
Muscle layer
Germinal center
Peyer's patch

MALT plays a role in regulating mucosal immunity. It may be the site of lymphomas, usually a non-Hodgkin lymphoma. A specific entity is the marginal zone B-cell lymphoma (a subtype of which is termed MALT lymphoma). Certain subtypes of marginal zone B cell lymphomas such as those occurring in the stomach are commonly caused by *Helicobacter pylori* infection.