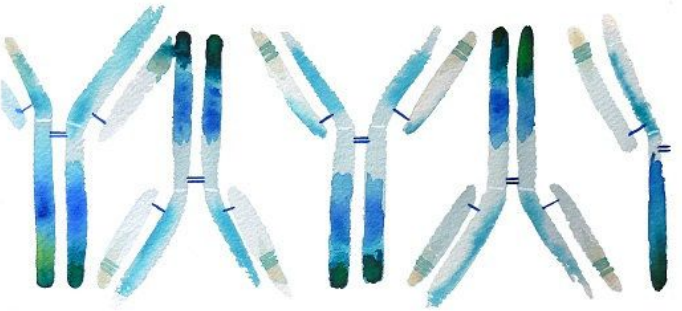
Medical Immunology



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Lecture 4

- Lymphocytes consist of distinct subsets that are **different in their functions** and protein products, but are **morphologically similar**.

- **B** (**B**ursa of Fabricius) lymphocytes originate in the **b**one marrow and **early maturation** occurs there. Also, **T** (**T**hymus) lymphocytes originate in the bone marrow, but **mature** in the **thymus**.

- Membrane proteins are used as **phenotypic markers** to **distinguish distinct populations of lymphocytes**

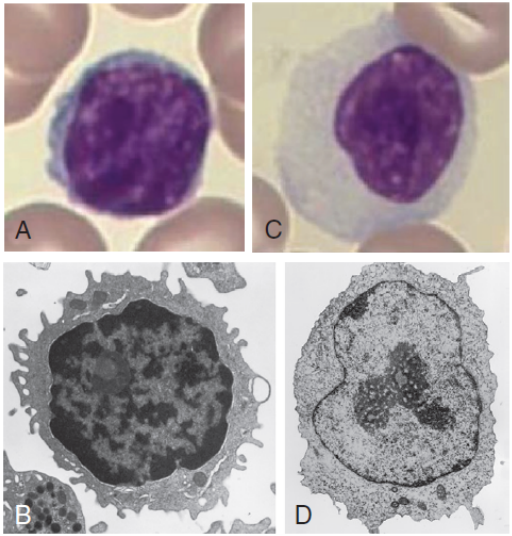
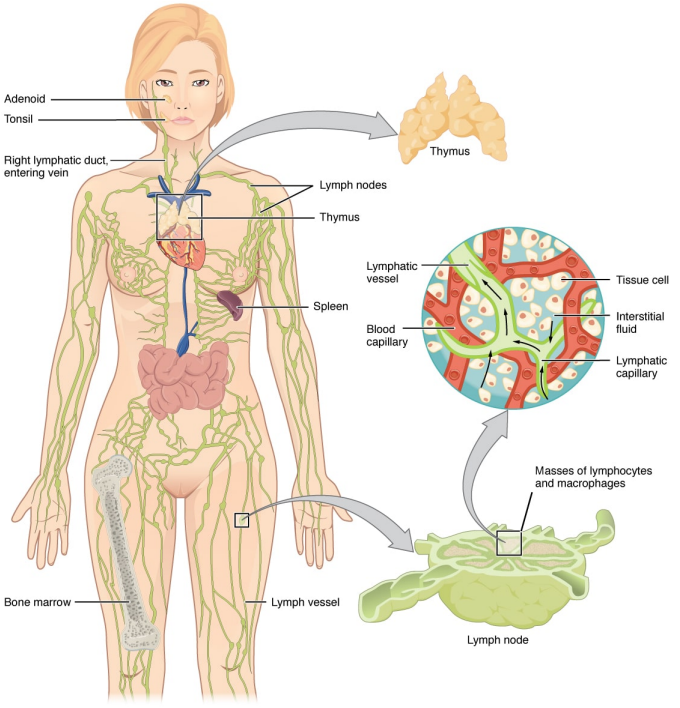


FIGURE 2–7 Morphology of lymphocytes. A, Light micrograph of a lymphocyte in a peripheral blood smear. *(Courtesy of Jean Shafer, Department of Pathology, University of California, San Diego. Copyright 1995-2008, Carden Jennings Publishing Co., Ltd.)* **B,** Electron micrograph of a small lymphocyte. *(Courtesy of Dr. Noel Weidner, Department of Pathology, University of California, San Diego.)* **C,** Light micrograph of a large lymphocyte (lymphoblast). *(Courtesy of Jean Shafer, Department of Pathology, University of California, San Diego. Copyright 1995-2008, Carden Jennings Publishing Co., Ltd.)* **D,** Electron micrograph of a large lymphocyte (lymphoblast). *(From Fawcett DW. Bloom and Fawcett: A Textbook of Histology, 12th ed. Chapman & Hall, New York, 1994. With kind permission of Springer Science and Business Media.)*

Cells of the immune system / Lymphocytes

The total number of lymphocytes in a healthy adults about 5 × 1011. Of these:

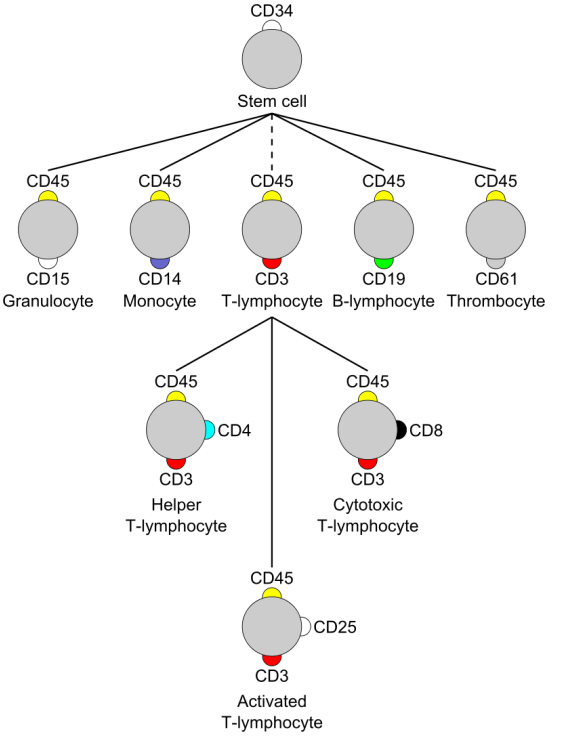
- ~2% are in the blood,
- ~10% in the bone marrow,
- ~15% in the mucosal lymphoid tissues of the gastrointestinal and respiratory tracts, and
- ~65% in lymphoid organs (mainly the lymph nodes and spleen)



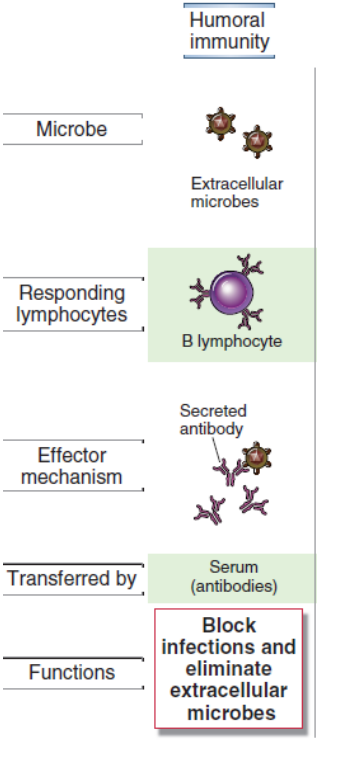
Cells of the immune system / Cluster of differentiation

- The cluster of differentiation (CD) is a protocol used for the **identification** and **investigation** of **cell surface molecules** providing targets for immunophenotyping of cells.

- In terms of physiology, CD molecules can act in numerous ways, often acting as **receptors** or **ligands** important to the cell and some function as **adhesion** molecules.

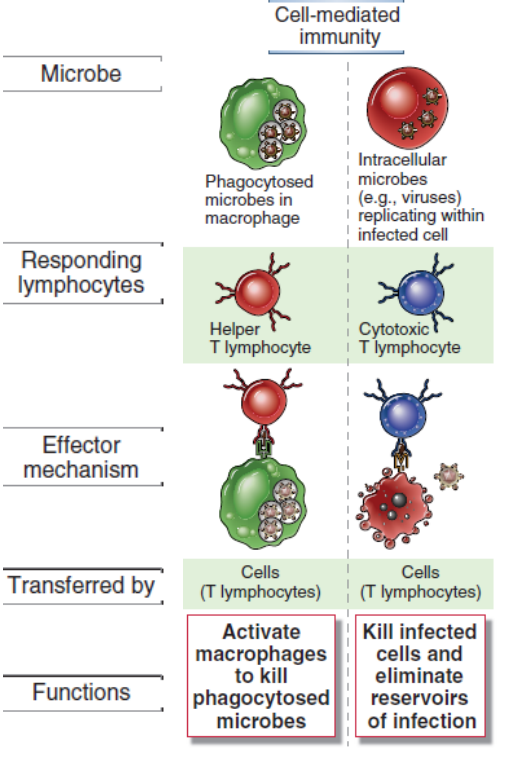


- B-lymphocytes are the **only cells capable of producing antibodies**.
- They recognize **extracellular (including cell surface) antigens** and differentiate into antibody-secreting **plasma cells**, thus functioning as the mediators of humoral immunity.



Cells of the immune system / Lymphocytes/ T-lymphocytes

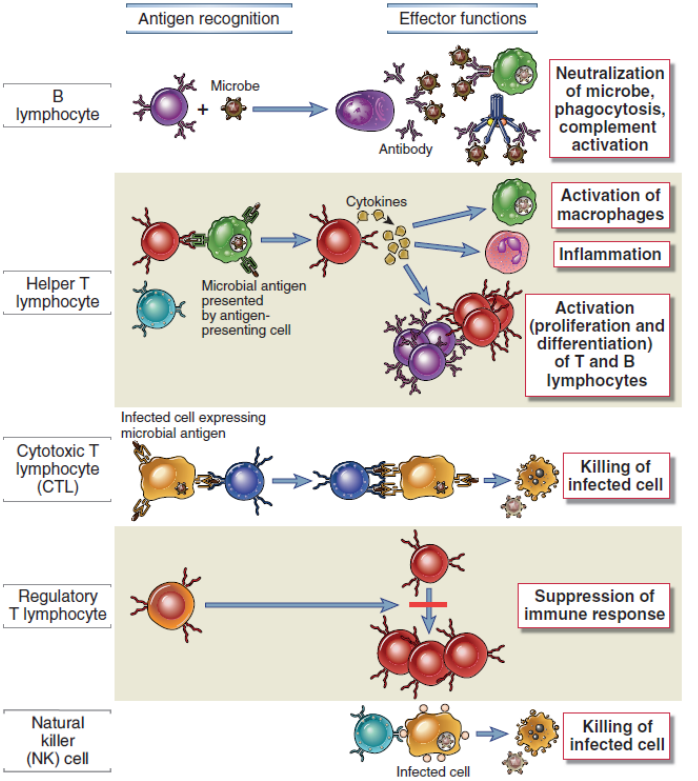
- T lymphocytes, the cells of cell-mediated immunity, **recognize the antigens of intracellular microbes** and either **help** phagocytes to **destroy these microbes** or **directly kill the infected cells**.
- **T cells do not produce antibody molecules**.
- Their antigen receptors are membrane molecules distinct from but structurally related to antibodies.



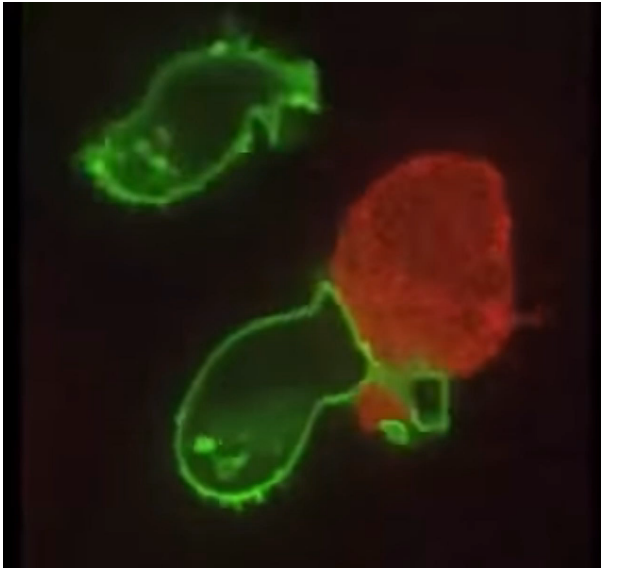
Humoral immunity is mediated by molecules in the blood and mucosal secretions, called antibodies, which are produced by cells called B lymphocytes.

Cell-mediated immunity is mediated by T lymphocytes.

viruses and some bacteria, survive and proliferate inside phagocytes and other host cells, where they are inaccessible to circulating antibodies. Defense against such infections is a function of cell mediated immunity, which promotes the destruction of microbes residing in phagocytes or the killing of infected cells to eliminate reservoirs of infection.



Through the action of **perforin**, **granzymes** enter the cytoplasm of the target cell and their serine protease function triggers the **caspase** cascade, which eventually lead to **apoptosis** (programmed cell death).



Cells of the immune system / Lymphocytes

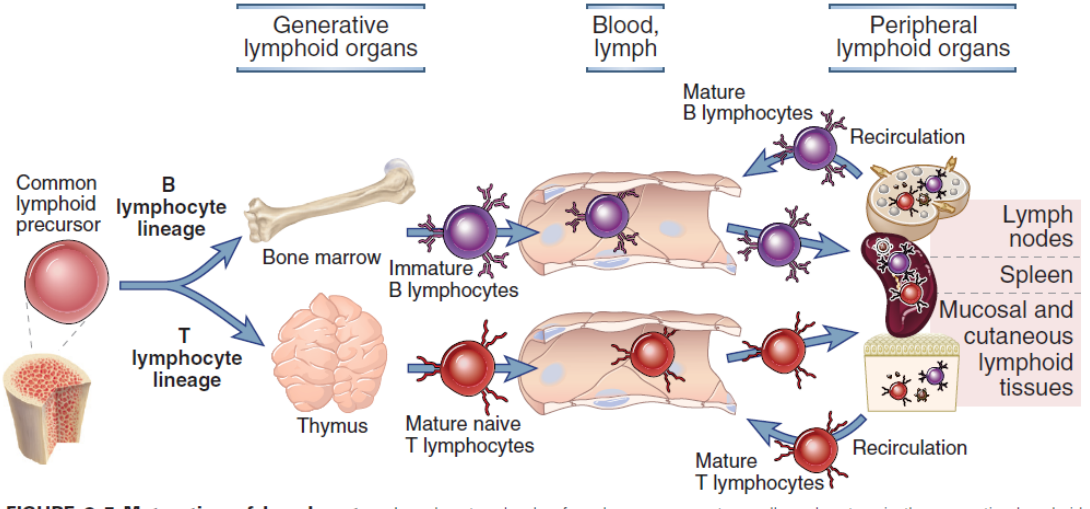


FIGURE 2–5 Maturation of lymphocytes. Lymphocytes develop from bone marrow stem cells and mature in the generative lymphoid organs (bone marrow and thymus for B and T cells, respectively) and then circulate through the blood to secondary lymphoid organs (lymph nodes, spleen, regional lymphoid tissues such as mucosa-associated lymphoid tissues). Fully mature T cells leave the thymus, but immature B cells leave the bone marrow and complete their maturation in secondary lymphoid organs. Naive lymphocytes may respond to foreign antigens in these secondary lymphoid tissues or return by lymphatic drainage to the blood and recirculate through other secondary lymphoid organs.

Cells of the immune system / Lymphocytes

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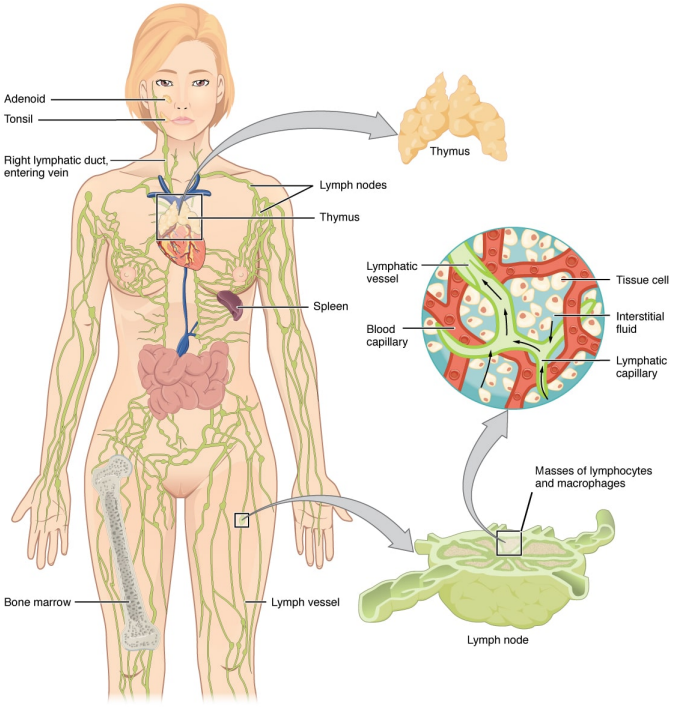
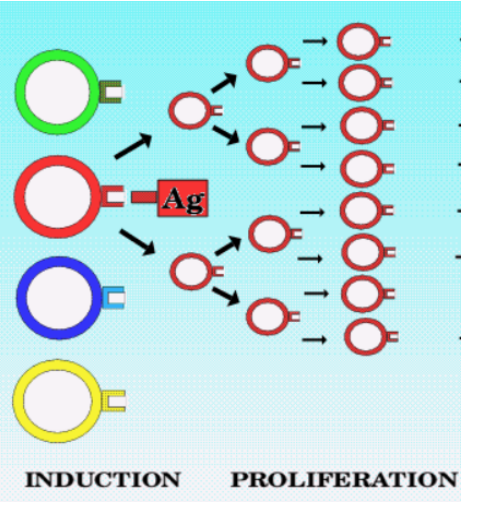


- **Lymphocytes**, the unique cells of **adaptive** immunity, are the only cells in the body that express **clonally** distributed **antigen receptors**, each with a fine **specificity** for a different antigenic determinant.

- Each **clone** of lymphocytes consists of the **progeny of one cell** and expresses antigen receptors with a **single specificity**.

- There are **millions** of **lymphocyte clones** in the body, enabling the organism to **recognize** and respond to **millions** of foreign **antigens**.



- How the enormously diverse repertoire of antigen receptors (millions), and therefore specificities, is generated from a small number of genes for these receptors in the germline*?

- Genes encoding the **antigen receptors** of lymphocytes are formed by **recombination of DNA segments during the maturation of these cells**. There is a random aspect to these somatic recombination events that results in the generation of millions of different receptor genes and a highly diverse repertoire of antigen specificities among different clones of lymphocytes.

- The **antigen receptors** are basically **antibodies** bound to the cell surface.

*Germline DNA: The DNA in germ cells (egg and sperm cells that join to form an embryo). Germline DNA is the source of DNA for all other cells in the body. Also called constitutional DNA.

- In contrast with most organs, such as the heart, which does the same job throughout life, the immune system **needs to adapt to an environment that is always changing**. This problem is solved by investing in strategies that **exploit the power of random change itself**.

- **Using randomness in this way creates waste, but preserves responsiveness.**

Tonegawa's Nobel Prize work elucidated the genetic mechanism of the adaptive immune system, which had been the central question of immunology for over 100 years. Prior to Tonegawa's discovery, one early idea to explain the adaptive immune system suggested that each gene produces one protein; however, there are under 19,000 genes in the human body which nonetheless can produce millions of antibodies.

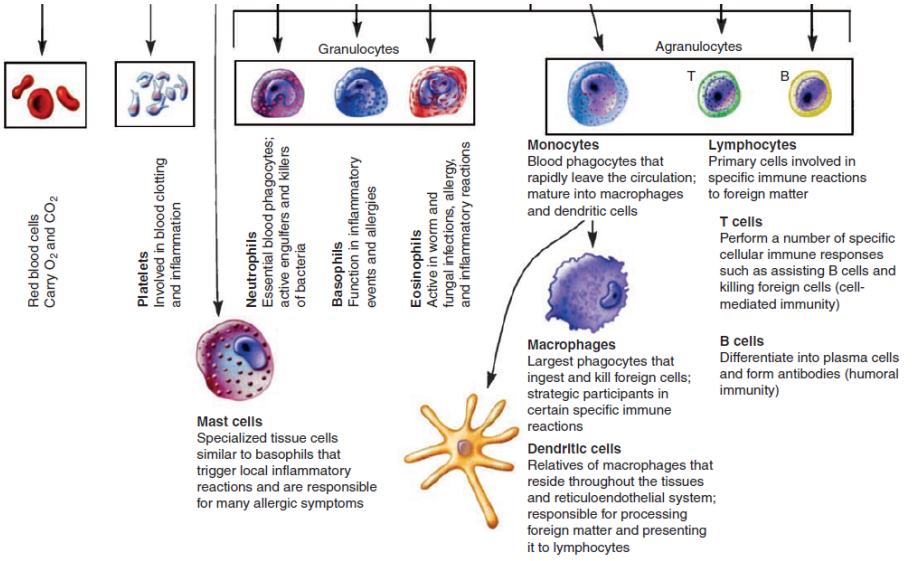
TABLE 2–2 Lymphocyte Classes

Class	Functions	Antigen Receptor and Specificity	Selected Phenotype Markers	Percentage of Total Lymphocytes (Human)		
				Blood	Lymph Node	Spleen
αβ T lymphocytes						
$CD4^+$ helper T lymphocytes	B cell differentiation (humoral immunity) Macrophage activation (cell-mediated immunity) Stimulation of inflammation	αβ heterodimers Diverse specificities for peptide–class II MHC complexes	$CD3^+$, $CD4^+$, $CD8^-$	50-60*	50-60	50-60
$CD8^+$ cytotoxic T lymphocytes	Killing of cells infected with viruses or intracellular bacteria; rejection of allografts	αβ heterodimers Diverse specificities for peptide–class I MHC complexes	$CD3^+$, $CD4^+$, $CD8^-$	20-25	15-20	10-15
Regulatory T cells	Suppress function of other T cells (regulation of immune responses, maintenance of self-tolerance)	αβ heterodimers Unresolved	$CD3^+$, $CD4^+$, $CD25^+$ (most common, but other phenotypes as well)	Rare	10	10
γδ T lymphocytes	Helper and cytotoxic functions (innate immunity)	γδ heterodimers Limited specificities for peptide and nonpeptide antigens	$CD3^+$, $CD4^+$, and CD8 variable			
B lymphocytes	Antibody production (humoral immunity)	Surface antibody Diverse specificities for all types of molecules	Fc receptors; class II MHC; CD19, CD21	10-15	20-25	40-45
Natural killer cells	Cytotoxic killing of virus-infected or damaged cells (innate immunity)	Various activating and inhibitory receptors Limited specificities for MHC or MHC-like molecules	CD16 (Fc receptor for IgG)	10	Rare	10
NKT cells	Suppress or activate innate and adaptive immune responses	αβ heterodimers Limited specificity for glycolipid-CD1 complexes	CD16 (Fc receptor for IgG); CD3	10	Rare	10

*In most cases, the ratio of $CD4^+CD8^-$ to $CD8^+CD4^-$ is about 2:1.
IgG, immunoglobulin G; MHC, major histocompatibility complex.

Cells of the immune system

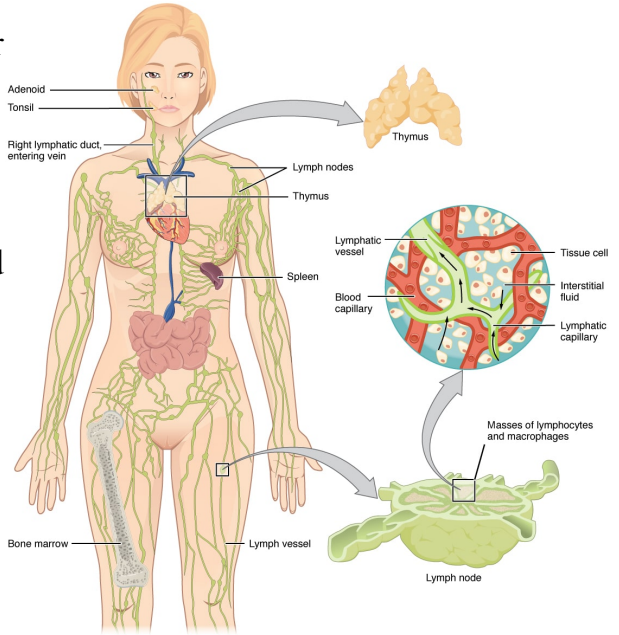
- **Phagocytes**
- **Mast Cells, Basophils, Eosinophils**
- **Antigen-Presenting Cells**
- **Lymphocytes**



Tissues of the immune system

To **optimize the cellular interactions** necessary for antigen recognition and lymphocyte activation in adaptive immune responses, **lymphocytes and APCs are localized and concentrated in anatomically defined tissues** or organs, which are also the sites where foreign antigens are transported and concentrated

Lymphoid tissues are classified as generative organs, also called **primary or central lymphoid organs**, where lymphocytes first express antigen receptors and attain phenotypic and functional maturity, and as peripheral organs, also called **secondary lymphoid organs**, where lymphocyte responses to foreign antigens are initiated and develop



Tissues of the immune system/ primary lymphoid tissue/ Bone Marrow

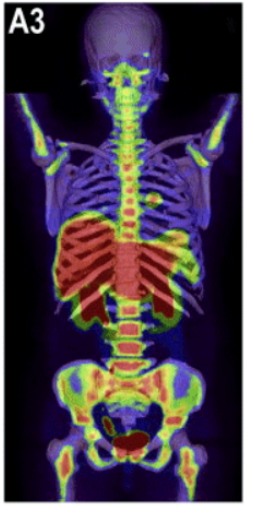
- The bone marrow is the site of generation of most mature circulating blood cells, including red cells, granulocytes, and monocytes, and the site of early events in B cell maturation.

The generation of all blood cells, called hematopoiesis occurs initially, during fetal development, in blood islands of the yolk sac and the para-aortic mesenchyme, then shifts to the liver between the third and fourth months of gestation, and gradually shifts again to the bone marrow.

- At birth, hematopoiesis takes place mainly in the bones throughout the skeleton, but it becomes restricted increasingly to the **marrow of the flat bones.**

Percentage of total bone marrow activity by bony site

Site	Mean ± SD
Skull	2.9 ± 2.1
Proximal humeri	1.9 ± 1.2
Sternum	2.9 ± 1.3
Ribs and clavicles	8.8 ± 4.7
Scapulas	3.8 ± 0.9
Cervical spine	4.3 ± 1.6
Thoracic spine	19.9 ± 2.6
Lumbar spine	16.6 ± 2.2
Sacrum	9.2 ± 2.3
Pelvis	25.3 ± 4.9
Proximal femurs	4.5 ± 2.5

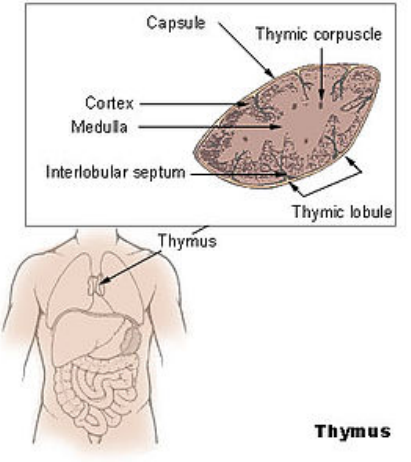


Tissues of the immune system/ primary lymphoid tissue/ Thymus غدة زعترية

- The thymus is **the site of T cell maturation**. The thymus is a bilobed organ situated in the **anterior mediastinum**. Each lobe is divided into multiple lobules by fibrous septa, and each lobule consists of an outer cortex and an inner medulla.

- A subset of these epithelial cells found only in the medulla, called **thymic medullary epithelial cells** (often abbreviated as TMEC), play a special role in **presenting self antigens to developing T cells** and causing their deletion.

- Maturation in the thymus begins in the **cortex**, and as thymocytes mature, they migrate toward the medulla, so that the medulla contains mostly mature T cells



Thymus

- By the early teens, the thymus begins to atrophy and thymic stroma is mostly replaced by adipose (fat) tissue.

Tissues of the immune system/ primary lymphoid tissue/ Thymus

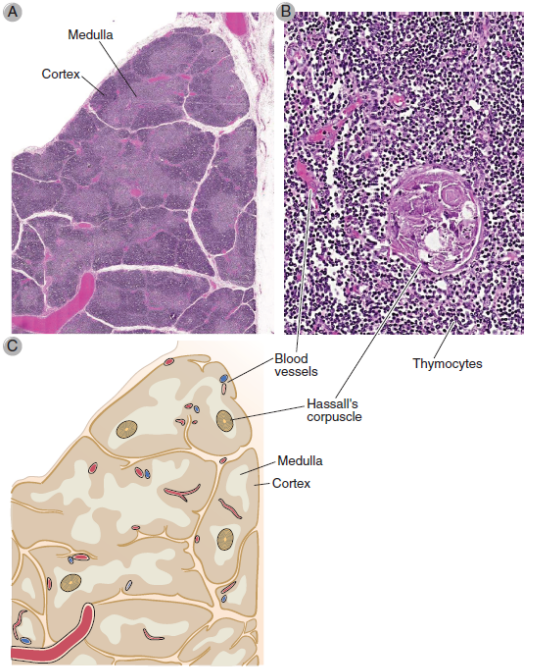
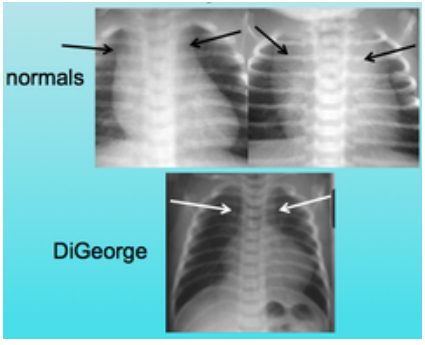


FIGURE 2–10 Morphology of the thymus. A, Low-power light micrograph of a lobe of the thymus showing the cortex and medulla. The darker blue-stained outer cortex and paler blue inner medulla are apparent. **B,** High-power light micrograph of the thymic medulla. The numerous small blue-staining cells are developing T cells called thymocytes, and the larger pink structure is Hassall's corpuscle, uniquely characteristic of the thymic medulla but whose function is poorly understood. **C,** Schematic diagram of the thymus illustrating a portion of a lobe divided into multiple lobules by fibrous trabeculae.



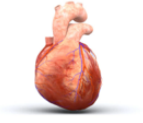
DiGeorge Syndrome

CATCH-22

Cardiac abnormalities
Abnormal facies
Thymic absence/abnormality, **T** cell abnormality
Cleft palate
Hypocalcemia
Chromosome **22**

Microdeletion in chromosome 22

Thymic hypoplasia → Hypocalcemia → Neonatal Seizure or Tetany



Congenital heart defect

Abnormal facies

Cleft palate

Humans with DiGeorge syndrome suffer from T cell deficiency because of mutations in genes required for thymus development.

- In the “nude” mouse strain, which has been widely used in immunology research, a mutation in the gene encoding a transcription factor causes a failure of differentiation of certain types of epithelial cells that are required for normal development of the thymus and hair follicles. Consequently, these mice lack T cells and hair.

Tissues of the immune system/ The lymphatic system

- The lymphatic system, which consists of specialized vessels that drain fluid from tissues into and out of lymph nodes and then into the blood, is essential for **tissue fluid homeostasis** and **immune responses**.

- The lymphatic system **collects microbial antigens** from their portals of entry and **delivers them to lymph nodes**, where they can stimulate adaptive immune responses.

- **Microbes/ antigens**, **Dendritic cells**, and **inflammatory mediators** reach **lymph nodes** from the tissue.

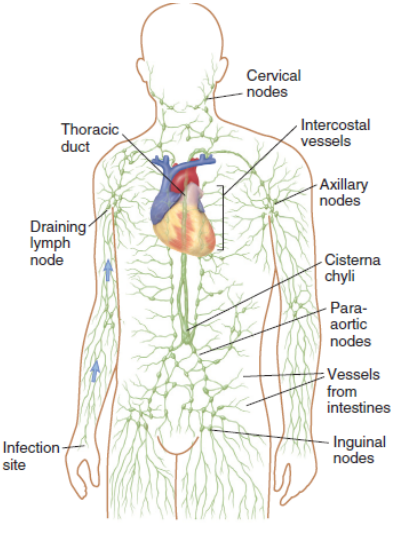


FIGURE 2–11 The lymphatic system. The major lymphatic vessels, which drain into the inferior vena cava (and superior vena cava, not shown), and collections of lymph nodes are illustrated. Antigens are captured from a site of infection and the draining lymph node to which these antigens are transported and where the immune response is initiated.

Tissues of the immune system/ Secondary lymphoid tissue/ lymph nodes

- Lymph nodes are **encapsulated, vascularized secondary lymphoid organs** with anatomic features that favor the initiation of adaptive immune responses to antigens carried from tissues by lymphatics.

- **Follicles are the B cell zones**. They are located in the lymph node cortex and are organized around FDCs, which have processes that interdigitate to form a dense reticular network. While T-cells in the parafollicular cortex.

- The anatomic segregation of B and T lymphocytes in distinct areas of the node is dependent on cytokines that are secreted by lymph node stromal cells in each area and that direct the migration of the lymphocytes

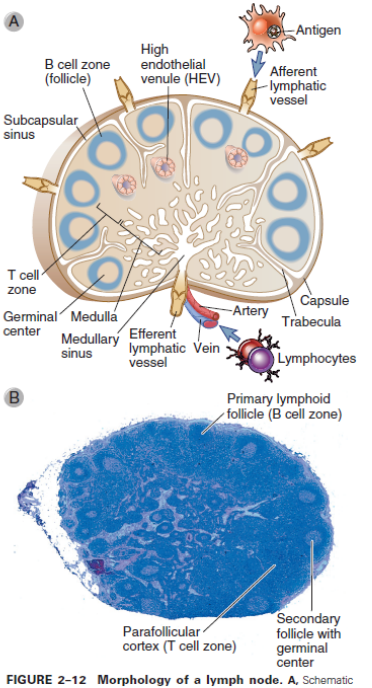
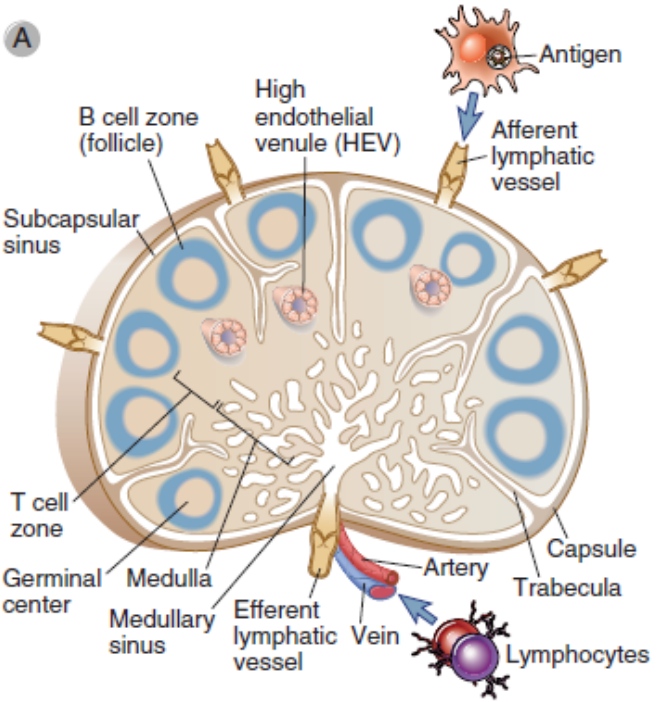


FIGURE 2–12 Morphology of a lymph node. A, Schematic diagram of a lymph node illustrating the T cell–rich and B cell–rich zones and the routes of entry of lymphocytes and antigen (shown captured by a dendritic cell). **B,** Light micrograph of a lymph node illustrating the T cell and B cell zones. *(Courtesy of Dr. James Gulizia, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)*

Tissues of the immune system/ Secondary lymphoid tissue/ lymph nodes



- The type of cytokines that determine where B and T cells reside in the node are called **chemokines** (chemoattractant cytokines), which bind to chemokine receptors on the lymphocytes.

- The anatomic segregation of T and B cells ensures that each lymphocyte population is in **close contact with the appropriate APCs**, that is, **T cells with dendritic cells and B cells with FDCs.**

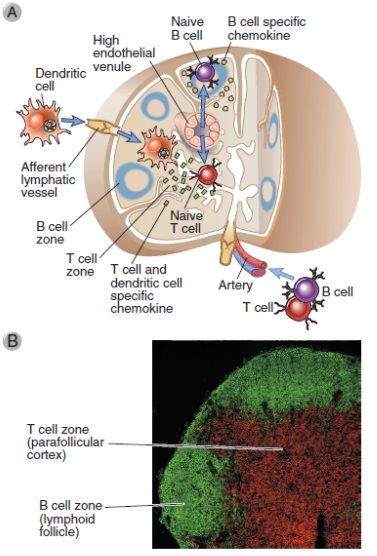
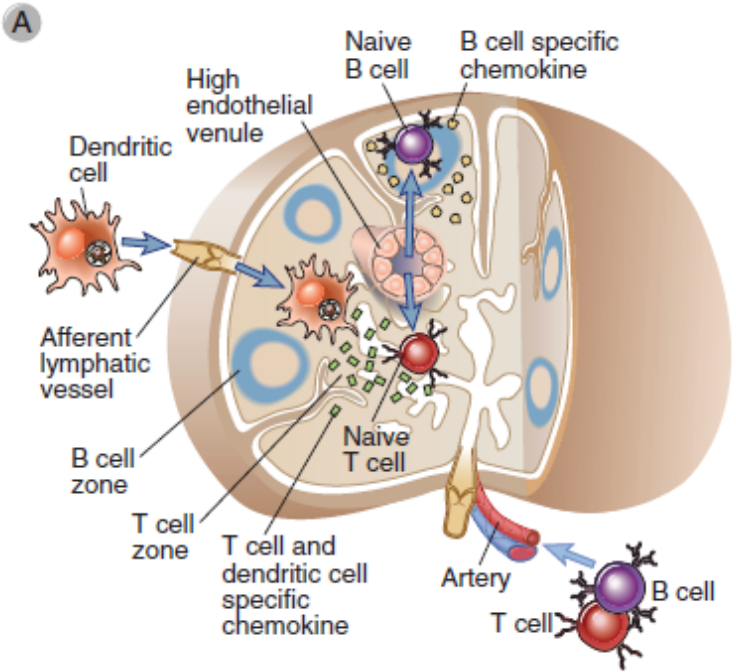


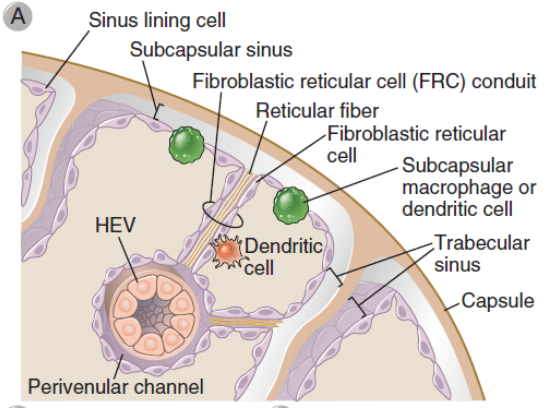
FIGURE 2–13 Segregation of B cells and T cells in a lymph node. A, The schematic diagram illustrates the path by which naive T and B lymphocytes migrate to different areas of a lymph node. The lymphocytes enter through an artery and reach a high endothelial venule, shown in cross section, from where naive lymphocytes are drawn to different areas of the node by chemokines that are produced in these areas and bind selectively to either cell type. Also shown is the migration of dendritic cells, which pick up antigens from the sites of antigen entry, enter through afferent lymphatic vessels, and migrate to the T cell–rich areas of the node. **B,** In this section of a lymph node, the B lymphocytes, located in the follicles, are stained green; the T cells, in the parafollicular cortex, are red. The method used to stain these cells is called immunofluorescence (see Appendix IV for details). *(Courtesy of Drs. Kathryn Pape and Jennifer Walter, University of Minnesota School of Medicine, Minneapolis.)* The anatomic segregation of T and B cells is also seen in the spleen (see Fig. 2-15).

Tissues of the immune system/ Secondary lymphoid tissue/ lymph nodes



- Viruses and other high molecular- weight antigens are taken up by **sinus macrophages** and **presented to cortical B lymphocytes.**

- Low-molecular-weight soluble antigens are transported to **resident dendritic cells** that extend processes and capture and pinocytose soluble antigens. The contribution of this pathway of antigen delivery may be important for **initial T cell immune responses** to some microbial antigens, but larger and sustained responses require delivery of antigens to the node by **tissue dendritic cells**



Tissues of the immune system/ Secondary lymphoid tissue/ lymph nodes

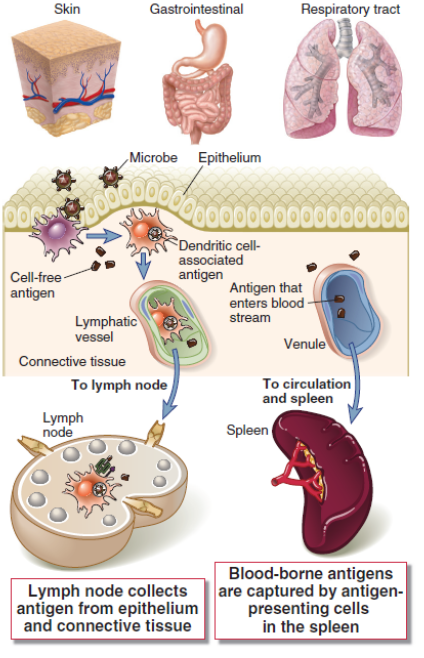


FIGURE 6–3 Routes of antigen entry. Microbial antigens commonly enter through the skin and gastrointestinal and respiratory tracts, where they are captured by dendritic cells and transported to regional lymph nodes. Antigens that enter the blood stream are captured by APCs in the spleen.

Tissues of the immune system/ Secondary lymphoid tissue/ Spleen

- The spleen is a highly vascularized organ whose major functions are to **remove aging and damaged blood cells** and **particles** (such as **immune complexes and opsonized microbes**) from the circulation and to **initiate adaptive immune responses** to **blood-borne antigens.**

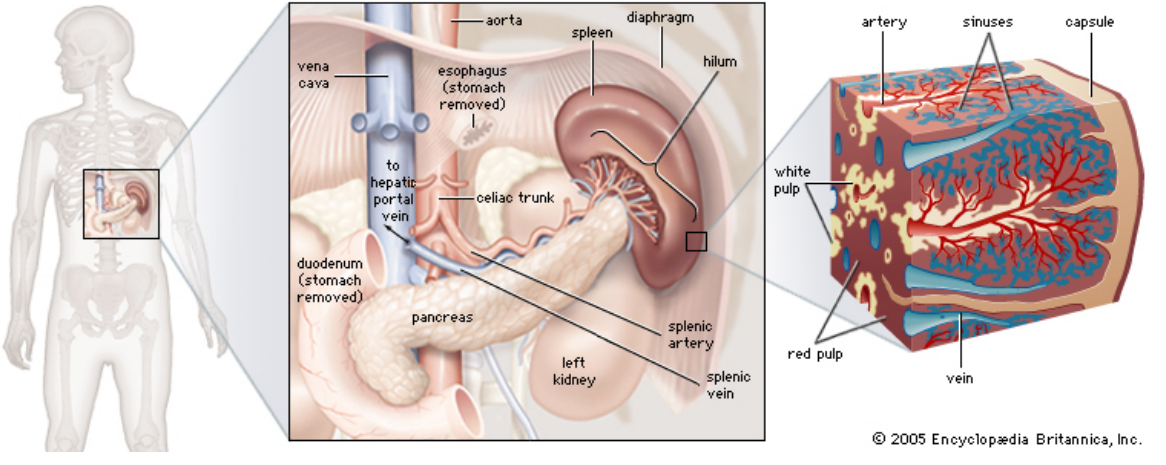
- The splenic parenchyma is anatomically and functionally divided into the **red pulp**, composed **mainly of blood-filled vascular sinusoids**, and the **lymphocyte-rich white pulp.**

- Blood enters the spleen through a single splenic artery, which pierces the capsule at the hilum and divides into progressively smaller branches that remain surrounded by protective and supporting fibrous trabeculae

- The **red pulp** macrophages serve as an important **filter for the blood**, removing microbes, damaged cells.

- Individuals lacking a spleen **are highly susceptible to infections with encapsulated**

Tissues of the immune system/ Secondary lymphoid tissue/ Spleen

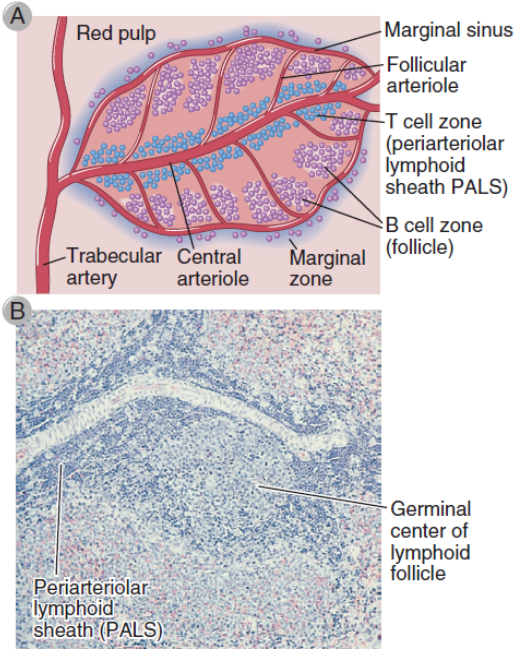


The spleen weighs about 150 g in adults and is located in the **left upper quadrant of the abdomen**.

- The function of the **white pulp** is to promote adaptive immune responses to blood-borne antigens.

- The white pulp is organized around central arteries, which are branches of the splenic artery distinct from the branches that form the vascular sinusoids. Several smaller branches of each central artery pass through the lymphocyte-rich area and drain into a marginal sinus.

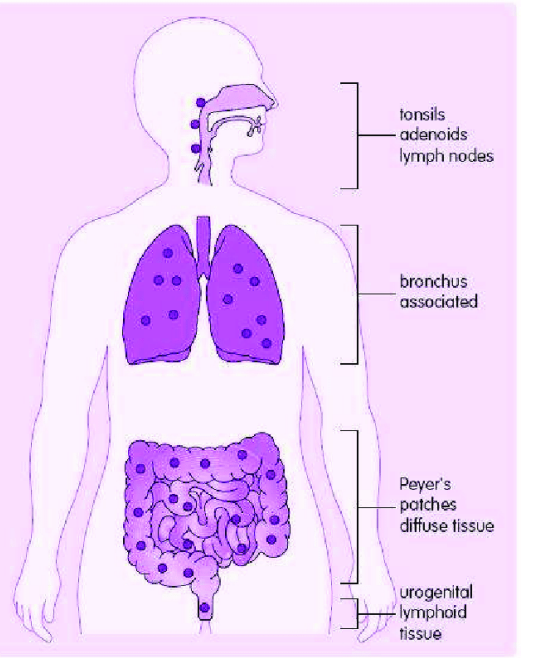
- A region of specialized cells surrounding the marginal sinus, called the marginal zone, forms the boundary between the red and white pulp.



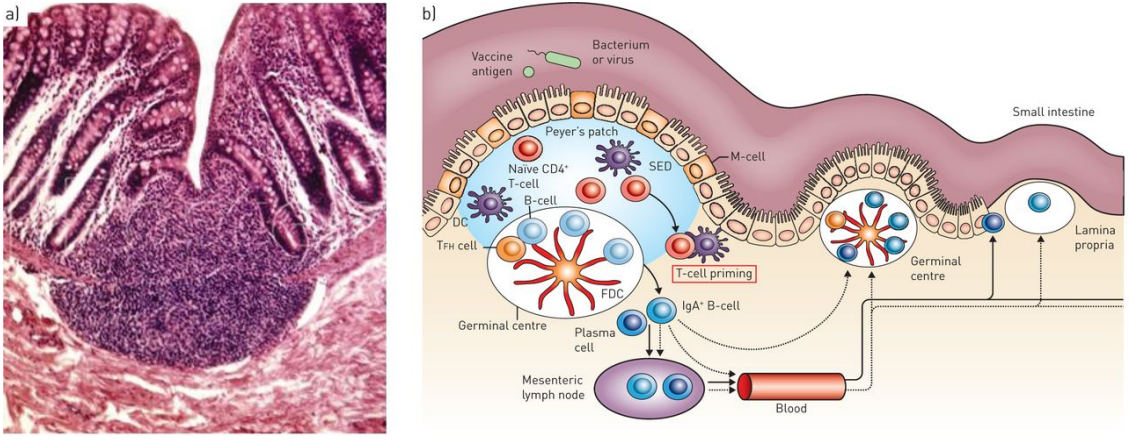
Tissues of the immune system/ Regional Immune Systems

- Each major epithelial barrier of the body, including the **skin**, **gastrointestinal mucosa**, and **bronchial mucosa**, has its own system of lymph nodes, **non encapsulated lymphoid structures**, and diffusely distributed immune cells, which work in coordinated ways to provide specialized immune responses against the pathogens that enter at those barriers.

- Mucosa-associated lymphoid tissue (MALT) is involved in immune responses to ingested and inhaled antigens and microbes.



Tissues of the immune system/ Regional Immune Systems



Normal small intestine histology with Peyer's patches. b) Initiation of the immune response in the gut: antigens are taken up by microfold (M)-cells and process to the resident dendritic cells (DCs) in Peyer's patches. T-follicular helper (TFH) cells interact with B-cells and follicular dendritic cell (FDC) thus forming a germinal centre. Antigen specific plasma cells and memory B-cells are generated and migrate through the blood and mesenteric lymph nodes

Further reading:

Cellular and Molecular Immunology. 7th Edition..
Chapter 2. Cells and tissues of the immune system

Secondary lymphoid organs: responding to genetic and environmental cues in ontogeny and the immune response. Journal of Immunology 183:2205-2212, 2009.