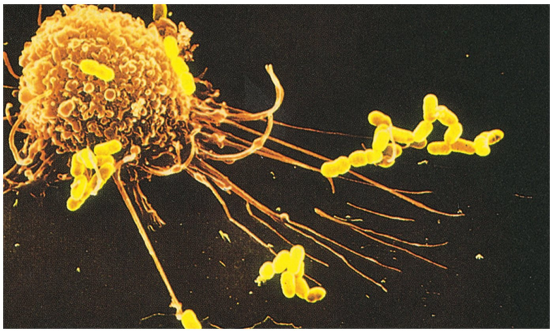
Chapter 2. Cells and Organs of the Immune System



Hematopoiesis

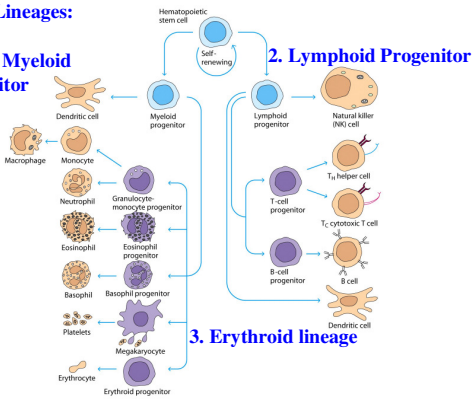
- Hematopoiesis- formation and development of WBC and RBC → bone marrow.
- Hematopoietic stem cell- give rise to any blood cells (constant number, self renewing)
- Yolk sac (2 months) → liver & spleen (3-7 months) → Bone marrow (birth)

3 Lineages:

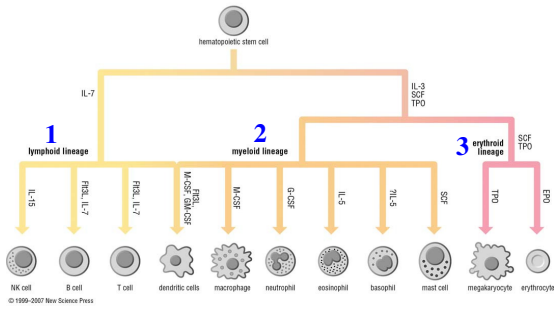
1. Myeloid Progenitor

2. Lymphoid Progenitor

3. Erythroid lineage



From **Immunity: The Immune Response in Infectious and Inflammatory Disease** by DeFranco, Locksley and Robertson



Hematopoiesis

- Progenitor commitment depends on the influence of growth factors and cytokines
- In bone marrow stromal cells support the growth and differentiation of hematopoietic cells → direct contact or growth factors.
- Stromal cells – meshwork of fat cells, endothelial cells, fibroblasts & MΦs.
- Hematopoiesis – regulated at the genetic level through several transcription factors (GATA-2, Icaros, BM11, etc)

Hematopoiesis

- Hematopoiesis maintains steady levels of blood cells
- **Regulation:**
  - Cytokines produced be bone marrow stromal cells
  - Cytokines produced by non-hematopoietic cells (T cells, MΦs)
  - Regulation of receptors for hematopoietically active cytokines
  - Removal of cells by programmed cell death

Apoptosis

- Programmed cell death
- **Changes:** shrinking, rearrangement of cytoskeleton, alteration of cell membrane permeability, chromatin condensation, cytoplasm fragmentation
- Difference between apoptosis and necrosis?

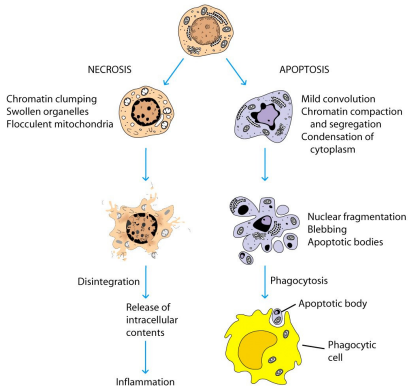
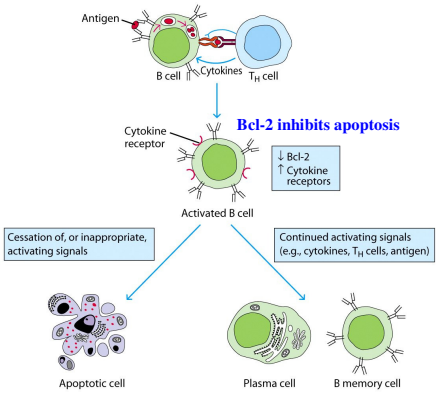


TABLE 2-2 Genes that regulate apoptosis

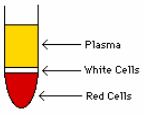
Gene	Function	Role in apoptosis
bcl-2	Prevents apoptosis	Inhibits
bax	Opposes *bcl-2*	Promotes
bcl-X_L (bcl-Long)	Prevents apoptosis	Inhibits
bcl-X_S (bcl-Short)	Opposes *bcl-X_L*	Promotes
caspase (several different ones)	Protease	Promotes
fas	Induces apoptosis	Initiates

bcl - B cell lymphoma



Cells of the Immune System

Separation of blood constituents



If heparinized blood is centrifuged, three layers are obtained:

- **Top layer - yellow liquid - plasma**
- **Middle layer - white cells (leukocytes)**
- **Lowest layer - red cells (erythrocytes)**

If the blood is allowed to clot first, the yellow supernatant is depleted of clotting factors and is referred to as serum.

TABLE 2-4 Normal adult blood-cell counts

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

Lymphocytes

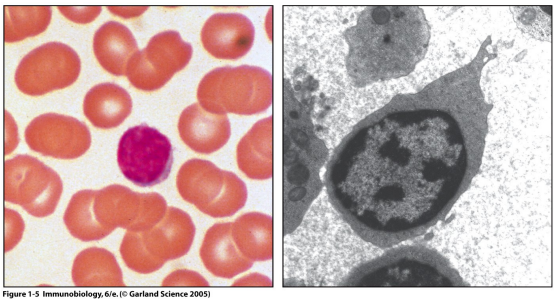
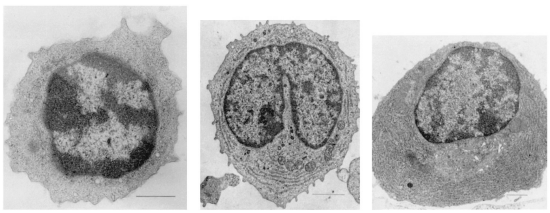


Figure 1-5 Immunobiology, 6/e. (© Garland Science 2005)

Lymphocytes

- **Three populations:**
  - B cells
  - T cells
  - NK cells
- Naïve lymphocyte →Ag exposure → Lymphoblast → Effector cells & Memory cells
  - **Effector cells**: Plasma cells, T helper (Th) or T cytotoxic (Tc)



Small lymphocyte (T or B)
6 µm diameter

Blast cell (T or B)
15 µm diameter

Plasma cell (B)
15 µm diameter

B Lymphocytes

- **CD** - cluster of differentiation (unique lymphocyte surface molecules)
- **Surface markers:**
  - Surface Ig (free Ag)
  - MHC-II molecules
  - CD35 (CR1) and CD21 (CR2)
  - CD32 (FcγRII), CD40
  - CD80 (B7-1) and CD86 (B7-2)

T lymphocytes

- **T cell receptor (TCR)** – recognizes Ag after processing and presented by major histocompatibility complex (MHC) molecules
- **Surface markers:**
  - TCR (processed Ag + MHC)
  - CD3
  - CD4 or CD8
  - CD28 (interacts with B7 molecules)

T cells

- There are two types of MHC molecule - class I MHC and class II MHC.
- There are two types of T cells: Helper (CD4+) T cells and Cytotoxic (CD8+) T cells.
- CD4+ (Helper) T cells recognize antigen presented on class II MHC. Role: Cytokine secretion
- CD8+ (Cytotoxic) T cells recognize antigen presented on class I MHC. Role: Cell killing
- Normal ratio: 2:1 (CD4 to CD8)

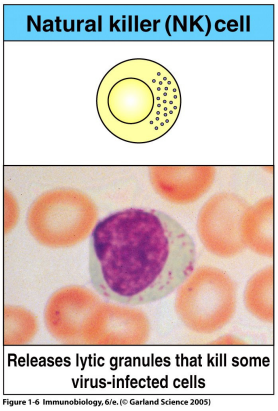
T cells

- CD4+ (Helper) T cells: Two types based on cytokine production
  - **Th1:** cytokines that support inflammation and activation of T cells and MΦs.
  - **Th2:** cytokines that activate B cells and Ab production.
- CD8+ (Cytotoxic) after activation → Cytotoxic T lymphocyte (CTL).

NK cells

- Lack TCR of T cells or sIg of B cells
- Unique surface markers: CD16 (FcγRIII) and CD56
- Action similar to Tc (CD8+) cells
- Role: destroys tumor cells and virus-infected cells
- Recognition due to altered expression of MHC-I and ADCC (Ab-dependent cell cytotoxicity)
- **NK1-T cell:** T cell and NK cell. Expresses TCR, TCR interacts with CD1 (similar to MHC), express CD16, and cell killing.

• Role: destroys tumor cells and virus-infected cells

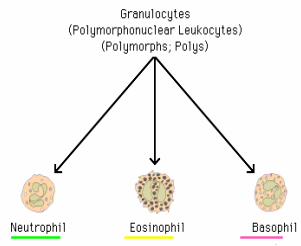


Leukocytes
(white blood cells)

a) Polymorphonuclear leukocytes (Polymorphs; Polys; Granulocytes)

B) Mononuclear leukocytes

Granulocytes



Granulocytes consist of:

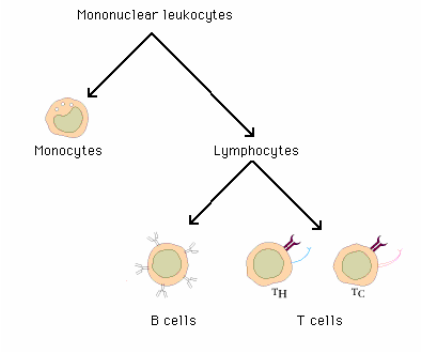
Basophils - stained by basic dyes

Eosinophils - stained by acidic dyes

Neutrophils - stained by both

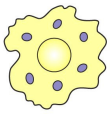
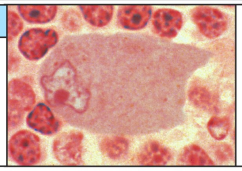
The ability to bind basic vs. acidic dyes reflects the charge of the cell, which reflects the molecules present in the cell, which determines the function of the cell. In addition to binding different dyes, these three cell types are functionally different.

The mononuclear leukocytes consist of:



Macrophage

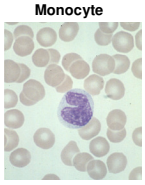
- Two main functions

Cell	Activated function
Macrophage  	Phagocytosis and activation of bactericidal mechanisms Antigen presentation

Macrophage (MΦ)

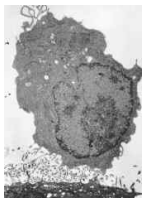
- **Monocytes develop in the bone marrow and circulate in blood, becoming macrophages upon entering the tissues – forming the mononuclear phagocyte system.**
- **Macrophages are long-lived cells.**
- **Free vs Fixed macrophages**

Monocyte



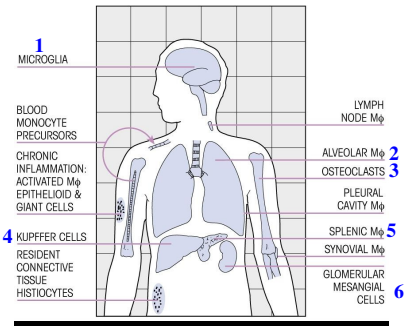
http://biomed.brown.edu/Courses/BIO189/Lab5/monocyte.htm

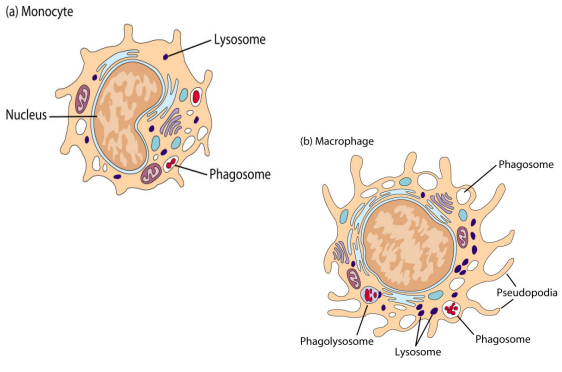
Macrophage



http://www.popcouncil.org/images/macrophage.jpg

The mononuclear phagocyte system





Phagocytosis

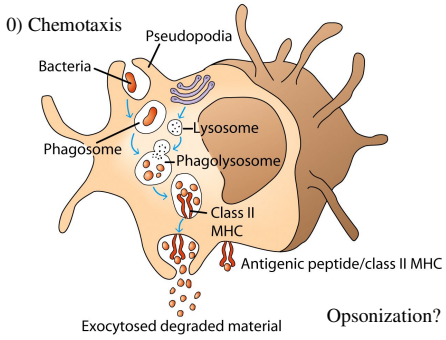


TABLE 2-6 Mediators of antimicrobial and cytotoxic activity of macrophages and neutrophils

Oxygen-dependent killing	Oxygen-independent killing
Reactive oxygen intermediates	Defensins
$O^{\bullet}_2{}^-$ (superoxide anion)	Tumor necrosis factor α
$OH^{\bullet}$ (hydroxyl radicals)	(macrophage only)
H_2O_2 (hydrogen peroxide)	Lysozyme
ClO^- (hypochlorite anion)	Hydrolytic enzymes >40
Reactive nitrogen intermediates	
NO (nitric oxide)	
NO_2 (nitrogen dioxide)	
HNO_2 (nitrous acid)	
Others	
NH_2CL (monochloramine)	

The Respiratory Burst (Oxidative Burst)

- Occurs in activated Macrophages
- Phagocytosis also activates an NADPH oxidase enzyme (cytochrome b_{558}).
- This enzyme is found on the plasma membrane as well as on the membrane of the phagolysosome.
- The NADPH oxidase mediates the following chemical reaction:

$$NADPH + 2O_2 \xrightarrow{\text{(NADPH oxidase)}} 2O_2^- + NADP^+ + H^+$$

The enzyme superoxide dismutase then catalyzes the formation of hydrogen peroxide from the superoxide:

$$2H2O + O_2^- \xrightarrow{\text{(superoxide dismutase)}} 2H_2O_2$$

The Respiratory Burst (Oxidative Burst)

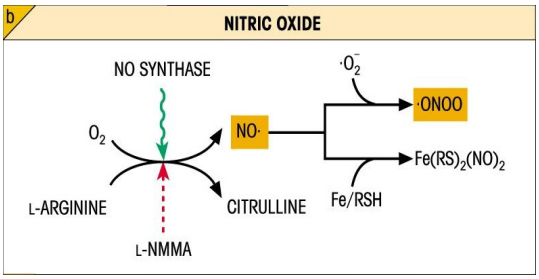
$$2H2O + O_2^- \xrightarrow{\text{(superoxide dismutase)}} 2H_2O_2$$

The **hydrogen peroxide** can then be used to generate other bactericidal compounds (hypohalides) via a peroxidase. e.g. generation of hypochlorite:

$$H_2O_2 + Cl^- \xrightarrow{\text{(myeloperoxidase)}} OCl^- + H_2O$$

Hypochlorite can kill bacteria by oxidizing proteins and lipids.

Macrophages and neutrophils also produce nitrogen compounds that can kill microorganisms. The enzyme iNOS (inducible nitric oxide synthase) generates **nitric oxide** (NO) which can subsequently be converted into peroxynitrite (ONOO).



Oxygen-Independent Mechanisms:

Antimicrobial molecules are present within cytoplasmic granules. After fusion of granules with the phagosome, these compounds come into contact with phagocytosed microorganisms and assist in killing and degradation of the phagocytosed material.

c OXYGEN-INDEPENDENT MECHANISMS

Cathepsin G Low mol. wt defensins High mol. wt cationic proteins Bactericidal permeability increasing protein (BPI)	Damage to microbial membranes
Lysozyme	Splits mucopeptide in bacterial cell wall
Lactoferrin	Complex with iron
Proteolytic enzymes Variety of other hydrolytic enzymes	Digestion of killed organisms

Figure 1.10c

Note:

All of these antimicrobial mechanisms can also act on microorganisms that have not been phagocytosed.

NADPH oxidase is also present on the plasma membrane and results in superoxide generation in the vicinity of the activated neutrophil or macrophage.

Macrophages and neutrophils can "degranulate" – release the contents of their cytoplasmic granules into the extracellular environment.

When released in this manner, destruction of healthy host cells also occurs.

Innate Immunity is sometimes Nonspecific.

Only Activated MΦ

TABLE 2-7 Some factors secreted by activated macrophages

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

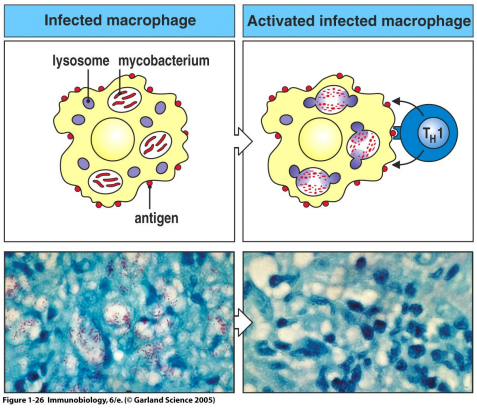


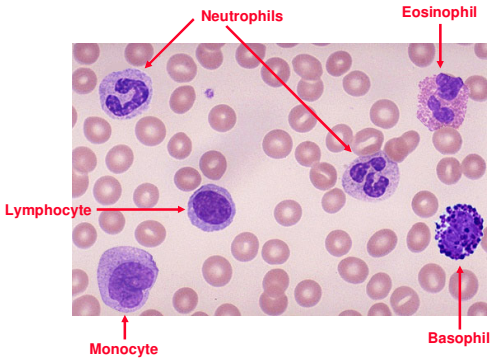
Figure 1-26 Immunobiology, 6/e. (© Garland Science 2005)

TABLE 2-5 Common CD markers used to distinguish functional lymphocyte subpopulations

CD designation*	Function	B cell	T CELL T_H	T CELL T_C	NK cell
CD2	Adhesion molecule; signal transduction	–	+	+	+
CD3	Signal-transduction element of T-cell receptor	–	+	+	–
CD4	Adhesion molecule that binds to class II MHC molecules; signal transduction	–	+ (usually)	– (usually)	–
CD5	Unknown	+	+ (subset)	+	–
CD8	Adhesion molecule that binds to class I MHC molecules; signal transduction	–	– (usually)	+ (usually)	+ (variable)
CD16 (FcγRIII)	Low-affinity receptor for Fc region of IgG	–	–	–	+
CD21 (CR2)	Receptor for complement (C3d) and Epstein-Barr virus	+	–	–	–
CD28	Receptor for co-stimulatory B7 molecule on antigen-presenting cells	–	+	+	–
CD32 (FcγRII)	Receptor for Fc region of IgG	+	–	–	–
CD35 (CR1)	Receptor for complement (C3b)	+	–	–	–
CD40	Signal transduction	+	–	–	–
CD45	Signal transduction	+	+	+	+
CD56	Adhesion molecule	–	–	–	+

*Synonyms are shown in parentheses.

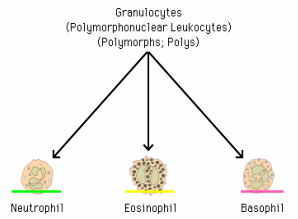
Blood Cells



- from http://medstat.med.utah.edu/WebPath/HEMEHTML/HEME100.html

Polymorphonuclear leukocytes are also called Granulocytes

They are characterized by having a multilobed nucleus and numerous cytoplasmic granules.

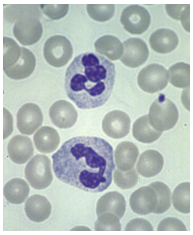


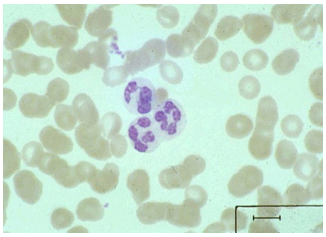
Granulocytes consist of:

Basophils - stained by basic dyes
Eosinophils - stained by acidic dyes
Neutrophils - stained by both

The ability to bind basic vs. acidic dyes reflects the charge of the cell, which reflects the molecules present in the cell, which determines the function of the cell. In addition to binding different dyes, these three cell types are functionally different.

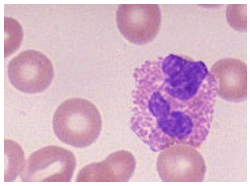
Neutrophils:
- about 50-70% of blood leukocytes are neutrophils
- have a multilobed nucleus and cytoplasmic granules
- granules are bactericidal
- main phagocytic (acute) cell. Better than MΦs
- ↑ in neutrophils – leukocytosis and infection
- recruited to site of infection/inflammation

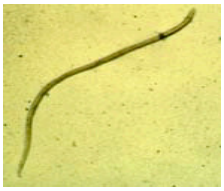




Eosinophils:

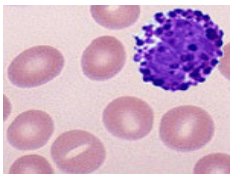
- Somewhat phagocytic; Comprise 1 - 3% of leukocytes
- Thought to be important in defense against invading parasites and worms (helminths)
- Worm infections are often accompanied by eosinophilia.
- Release eosinophilic granules that damage parasites





Basophils:

- Comprise <1% of leukocytes
- Non-phagocytic
- Release of pharmacologically active chemicals from granules → allergic reactions



MAST CELLS:

- Present mostly in tissues

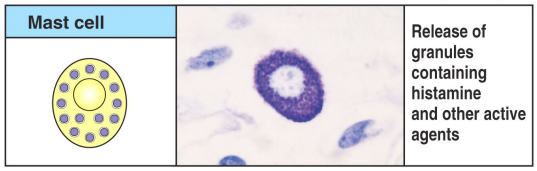
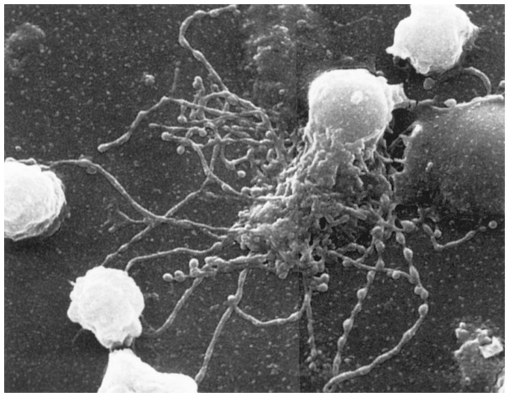
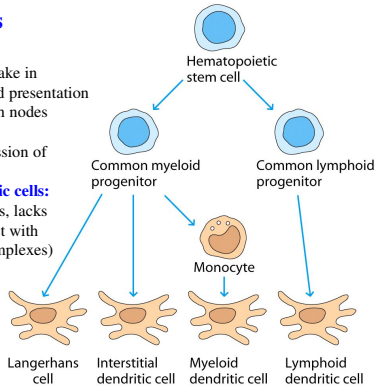


Figure 1-4 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)



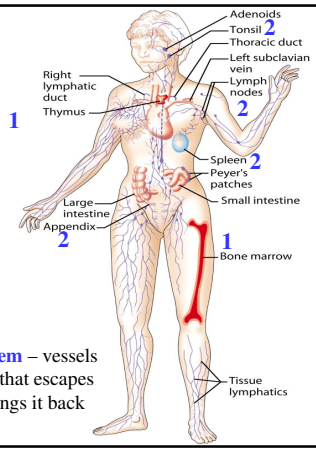
Dendritic Cells

- 4 Types
- Major role: Ag uptake in peripheral sites, and presentation to Th cells in lymph nodes
- Best APC
- Constitutive expression of MHC-II and B7
- **Follicular dendritic cells:** Unique type of cells, lacks MHC-II but interact with B cells (Ag-Ab complexes)



Organs of the Immune System

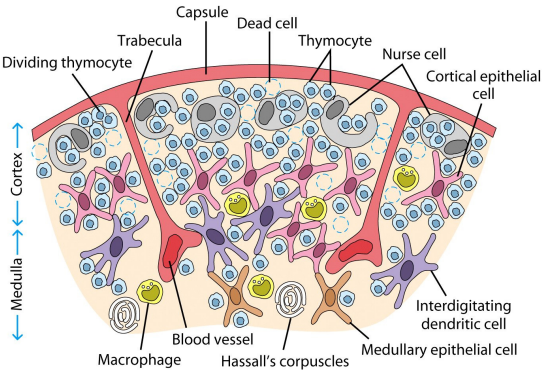
- **Primary Lymphoid Organs**
  - Bone marrow and Thymus
  - Origen and maturation of lymphocytes
- **Secondary Lymphoid Organs**
  - Lymph nodes, Spleen, Mucosal-associated lymphopid tissues (MALT)
  - Trap antigen for interaction with antigen



Lymphatic System – vessels that collect fluid that escapes the blood and brings it back to the blood

THYMUS

- Site of T cell development and maturation
- Two compartments: CORTEX and MEDULLA
  - CORTEX: Packed with immature T cells (Thymocytes)
  - MEDULLA: Sparsely populated with mature T cells
- Function: Generate populations of T cells with "correct" TCRs
- Only 5% of incoming thymocytes exit the thymus
- DiGeorge's syndrome (H) and nude mice

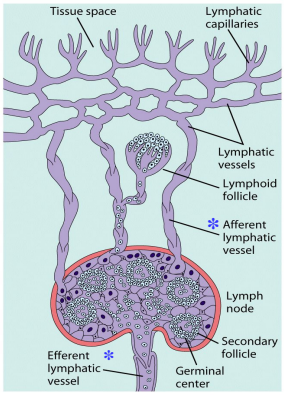


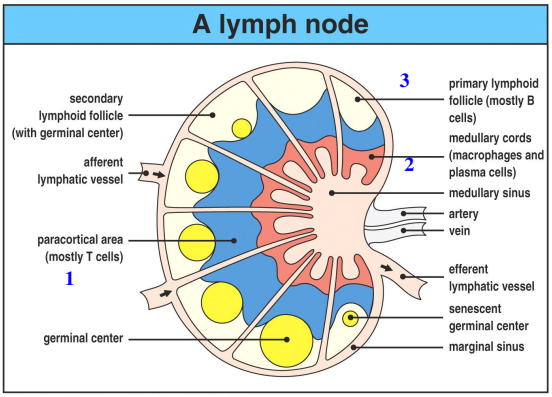
LYMPH NODES

-Site for immune responses for antigens in lymph
- Perfect design to encounter antigens

-Three regions: CORTEX, PARACORTEX and MEDULLA

-CORTEX – Primary follicles containing B cells, MΦ and DC
-PARACORTEX- T cell area
-MEDULLA- MΦ and Plasma cells



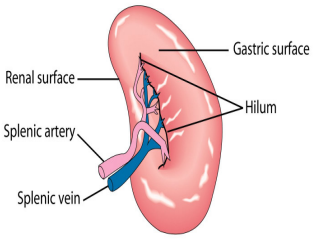


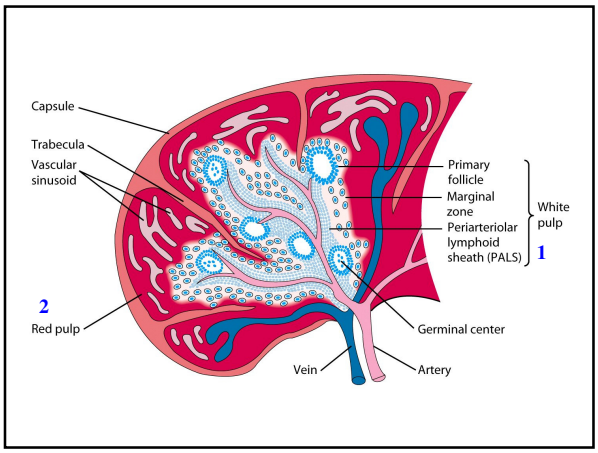
SPLEEN

- Encounters antigens in blood through the splenic artery. Removes old RBCs

-Two regions: RED and WHITE PULP

-RED PULP: MΦ and RBC
-WHITE PULP: surrounds the splenic artery to form the periarteriolar lymphoid sheath (PALS). Populated by T cells and DC
-MARGINAL ZONE: MΦ





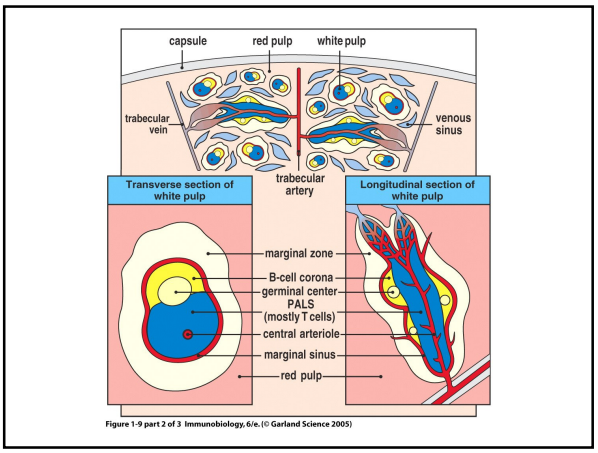


Figure 1-9 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

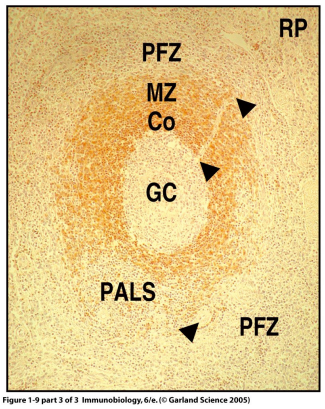
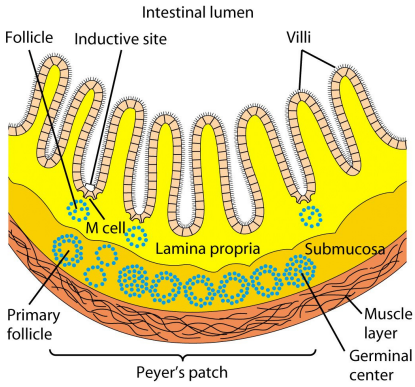


Figure 1-9 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

GUT ASSOCIATED LYMPHOID TISSUE- GALT



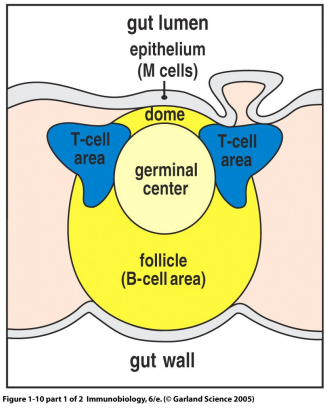
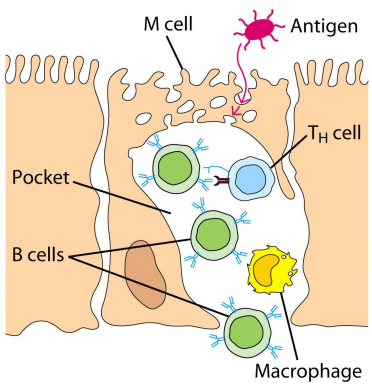
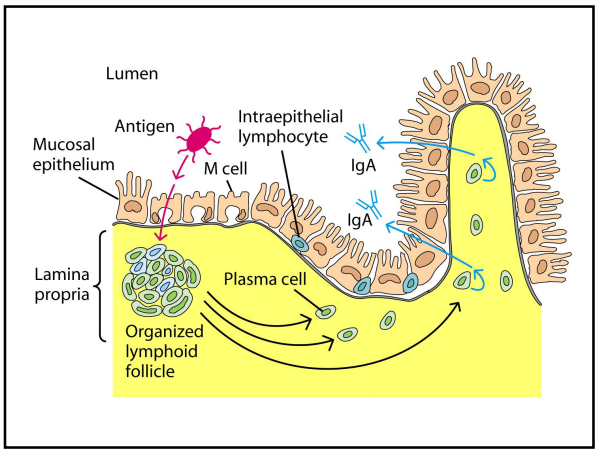


Figure 1-10 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)




Lumen
Antigen
Intraepithelial lymphocyte
Mucosal epithelium
M cell
IgA
IgA
Lamina propria
Plasma cell
Organized lymphoid follicle