MEDICINE 438's

GIT PHYSIOLOGY

LECTURE X: Reticuloendothelial System and Function of the Spleen

EDITING FILE

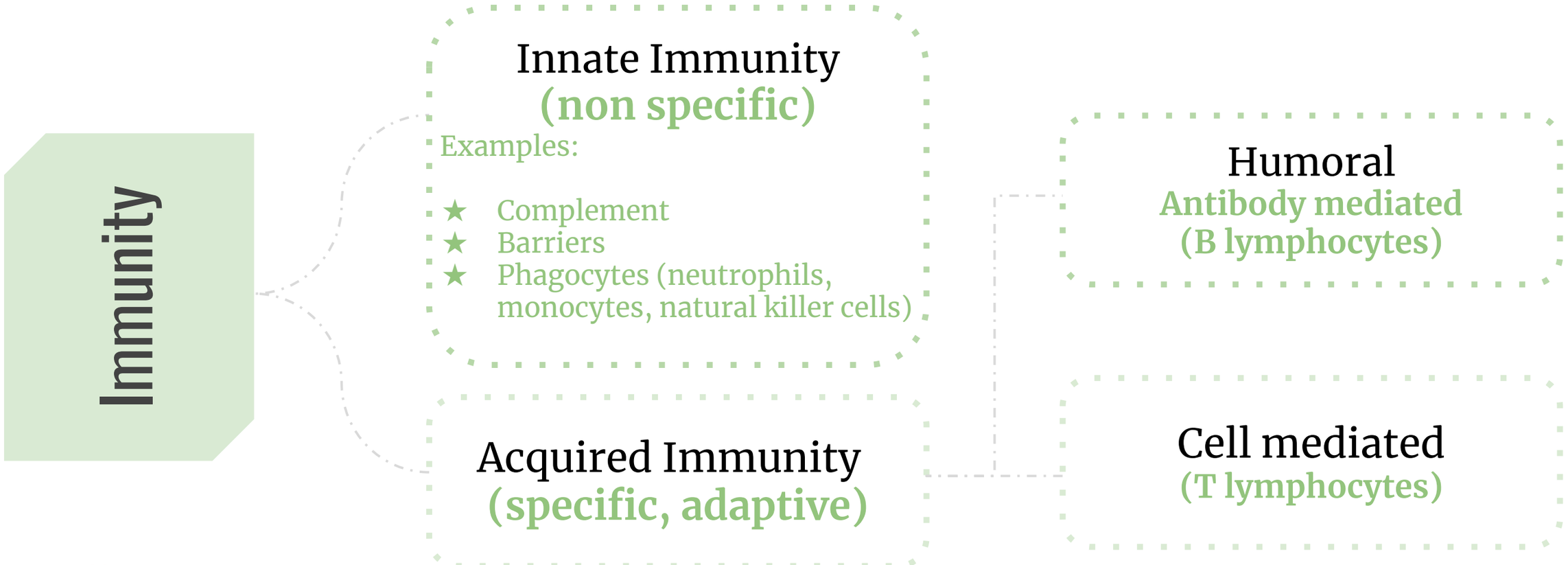
IMPORTANT | MALE SLIDES | EXTRA | FEMALE SLIDES | LECTURER'S NOTES

1 RETICULOENDOTHELIAL SYSTEM AND FUNCTION OF THE SPLEEN

Lecture Ten

OBJECTIVES

- Define the term Reticulo-endothelial system (RES).
- Describe Monocytes macrophage system (RES).
- Describe the cellular components of RES..
- Describe the functions of the RES.
- Function of monocytes/macrophages in different tissues.
- Mechanism of chemotaxis, phagocytosis and microbial killing.
- Define the structural function of the spleen.
- Describe the functions of the spleen.
- Understand the basic concept of the indication and risks of spleenectomy.



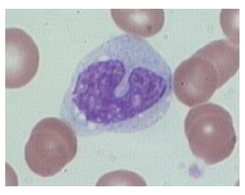
Note: Macrophages are key components of the innate immunity & activate adaptive immunity by transforming into Antigen Presenting Cells.[1]

RETICULOENDOTHELIAL SYSTEM (RES)

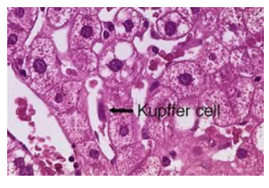
- Reticuloendothelial system is an older term for the mononuclear phagocyte system. The term is not specific, Why? Because Most endothelial cells are not macrophages (not phagocytic).
- It is a network of connective tissue fibers inhabited (occupied) by phagocytic cells such as macrophages ready to attack and ingest microbes.
- Monocytes transform themselves into macrophages (in tissues) & this system of phagocytes is called as Monocyte- Macrophage Cell System.

Cellular Componant Of RES

01 **Monocytes** In blood



02 **Macrophage**
Located in all tissues such as skin (histiocytes), liver (kupffer), spleen, bone marrow, lymph nodes, lung.



03 **Endothelial cells:** specialized in bone marrow, spleen and lymph nodes.

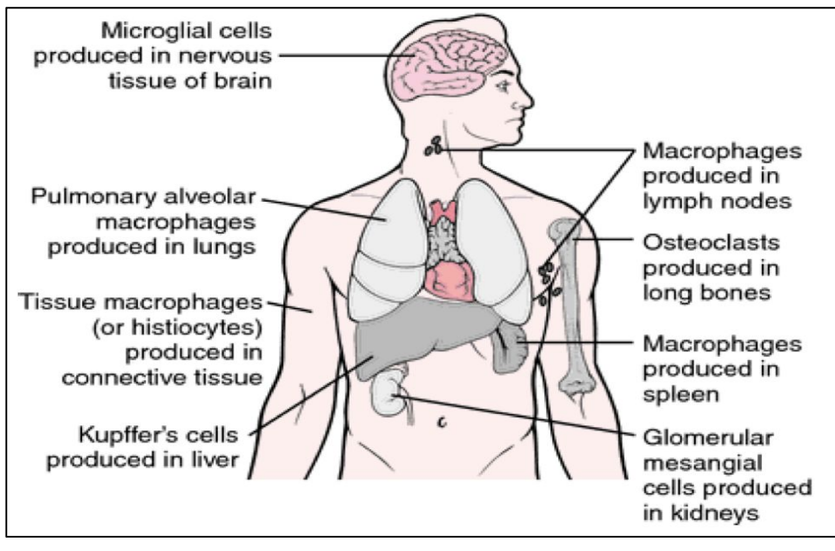


Figure 10-1

FOOTNOTES

1. **How the immune system reacts to antigens: (1)** Foreign antigen bypasses physical barriers (skin or epithelia) → **(2)** Antigen is faced with tissue-resident **macrophages** or **dendritic cells** (as in lamina propria of epidermis if antigen is able to penetrate it) → **(3)** Antigen recognized by these cells through ***pattern recognition receptors (PRRs)***, which have binding sites for antigens that humans face constantly → **(4)** Successful phagocytosis leads to antigen presentation to **lymphocytes** (they can not detect antigens on their own, they must be digested and presented as peptides to lymphocytes, **APCs** present the antigen on a plate called ***MHC-II***, which presents peptides to ***T-cell receptors***) → **(5)** Activation of adaptive immunity. If an antigen escapes tissue resident macrophages then it will most likely be drained into lymphatics to reach lymph nodes to be faced with yet another barrier of immune cells, if it escapes lymph nodes then it becomes bloodborne and can be recognized by the spleen.

General Functions of RES

Phagocytosis
Bacterial, dead cells, foreign particles (direct).

Immune function
Processing antigen and antibodies production (indirect).[1]

Breakdown of aging RBC

Storage and circulation of iron

Monocytes/Macrophages

- Size: 15-20 µm (active cells 60-80 µm).
- Small granules (azurophilic) and vacuoles.
- Azurophilic granules of monocytes are primary lysosomes or storage granules. Lysosomes contain acid hydrolases, MPO, HOCl, Defensins.
- More efficient phagocytosis than neutrophils (100 bacteria vs 3-20 by neutr, larger particles like RBCs and malarial parasites)
- Life span: 10-20 hours in blood and months or years in tissues.
- Two types: mobile and fixed.
- Often remain fixed to their organs (tissue-resident). They filter and destroy objects which are foreign to the body, such as bacteria, viruses.
- Some macrophages are mobile, and they can group together to become one big multinucleated giant cells in order to ingest larger foreign particles. This is sometimes seen in chronic inflammatory diseases like TB.
- Lysosomes of macrophages contain lipases unlike neutrophils.
- Acts as antigen presenting cells.

Types of macrophages:

Liver	Kupffer cells
Brain	Microglia
Lymph nodes, bone marrow, spleen	Reticular
Subcutaneous tissues, skin, mucosa	Tissue histiocytes (fixed macrophages).
Lungs	Alveolar cells (dust cells, due to their intracellular carbon particles)
Kidneys	Mesangial cells
Granuloma	Epithelioid cells
Placenta	Hofbauer cells
Bones	Osteoclasts

Formation Of Macrophages

Begin by Stem cell in Bone Marrow → monoblast maturing to promonocyte and mature monocytes released into blood → Stay for 10-20 hours in circulation → Then leave blood to tissues transforming into larger cells macrophage → Macrophage lifespan is longer up to few months in tissues.

Transformation of monocytes to macrophages:

★ Characterized by an increase in:

1. Cell size
2. Number and complexity of intracellular organelles golgi, mitochondria, lysosomes.
3. Intracellular digestive enzymes.

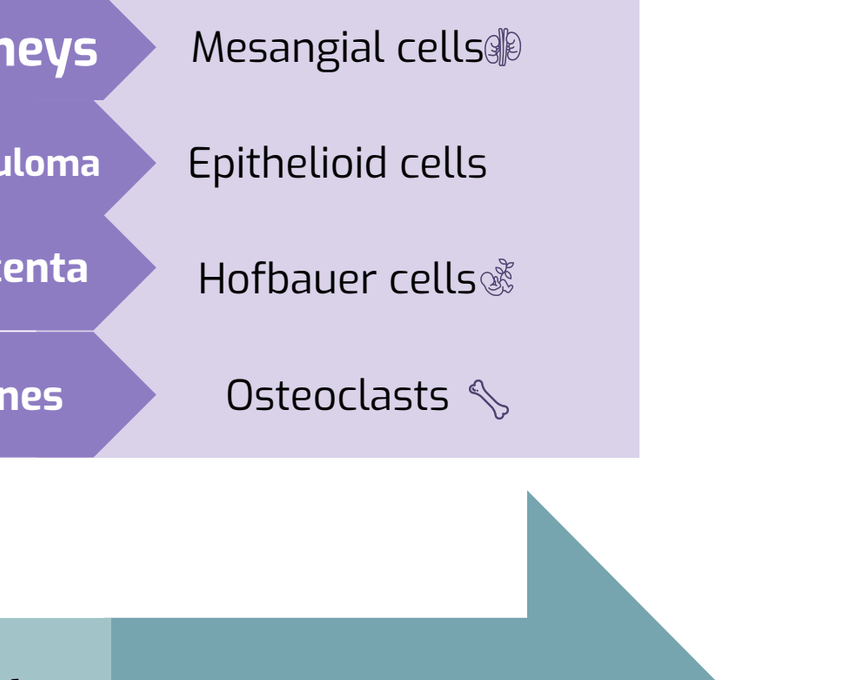


Figure 10-2

FOOTNOTES

1. Antigen presentation to T-cells by macrophages or dendritic cells → Activation of T-cells → T-cells activate B-cells → Plasma cells and antibody production

Responses During Inflammation (Macrophage And Neutrophils)

1st line

Tissue macrophages and physical barriers.

- Immediate recognition of antigen by macrophages → release inflammatory cytokines, mostly IL-1, IL-6 and TNF-alpha

2nd line

Neutrophils invasion of the inflamed area

- IL-1, IL-6 and TNF-alpha act on endothelial cells of capillaries to produce chemokines → Chemotaxis of neutrophils, also these inflammatory mediators can trigger breakdown of arachidonic acid with the production of prostaglandins → act on the hypothalamus (thermostat of the body) → Fever

3rd line

· Monocytes-macrophages invasion of inflamed area

- Further production of cytokines.

4th line

Increased production of granulocytes and monocytes by bone marrow

Defensive Properties Of Macrophages And Neutrophils

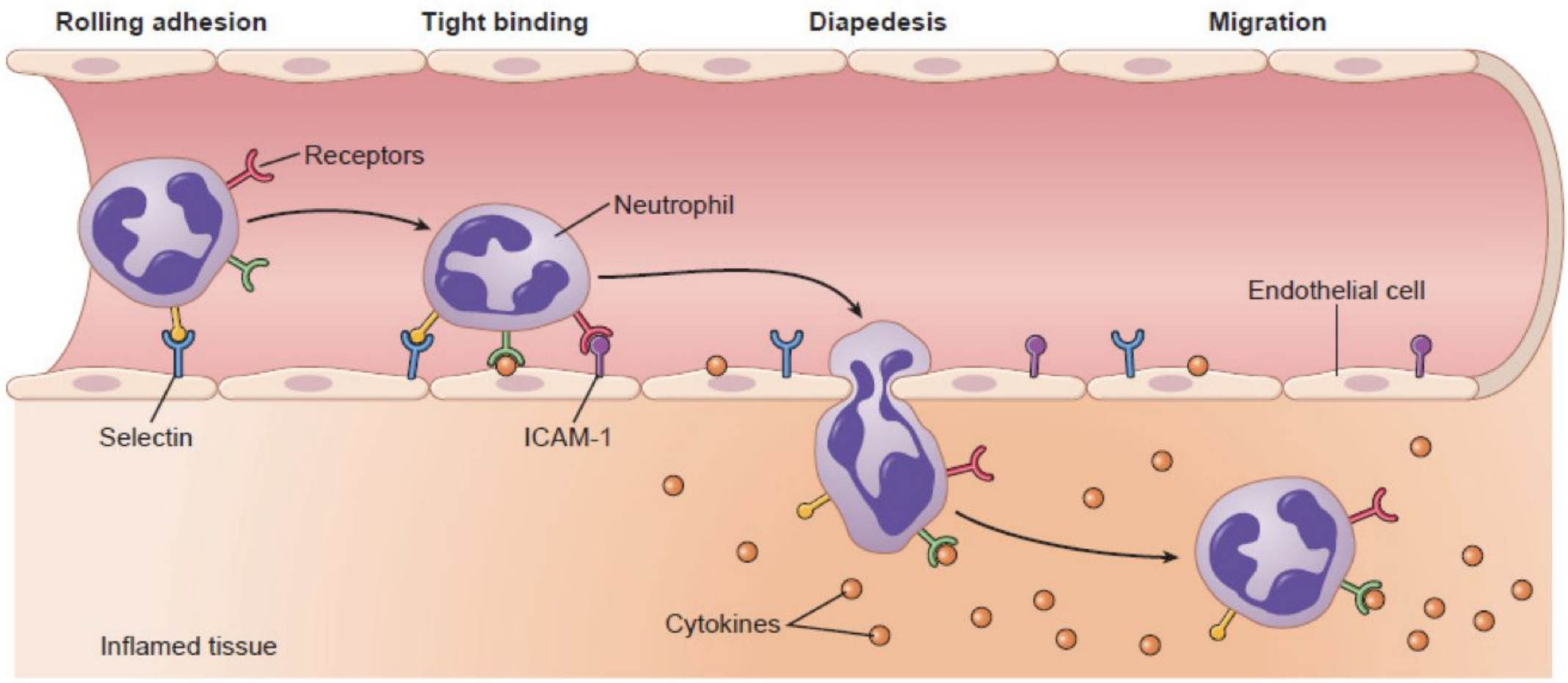


Figure 34-6. Migration of neutrophils from the blood into inflamed tissue. Cytokines and other biochemical products of the inflamed tissue cause increased expression of selectins and intercellular adhesion molecule-1 *(ICAM-1)* in the surface of endothelial cells. These adhesion molecules bind to complementary molecules/receptors on the neutrophil, causing it to adhere to the wall of the capillary or venule. The neutrophil then migrates through the vessel wall by diapedesis toward the site of tissue injury.

Figure 10-3

Margination

WBC roll, bind and then stick along the walls of blood capillaries

Diapedesis

WBC squeezes itself through endothelial holes leaving blood capillaries

Chemotaxis

WBC move by amoeboid motion towards inflammation area following chemotactic substances (bacterial toxins, complement [C5a], [LKB4] are released from site of infection

Phagocytosis

Upon reaching the site of infection neutrophils start to engulf infecting organism

01 02 03 04

4 RETICULOENDOTHELIAL SYSTEM AND FUNCTION OF THE SPLEEN

Lecture Ten

Phagocytosis

Phagocytosis — A part of the natural or innate immune process.

Macrophages — Powerful phagocytic cells:

- Ingest up to 100 bacteria.
- Ingest larger particles such as old RBC.
- Get rid of waste products.

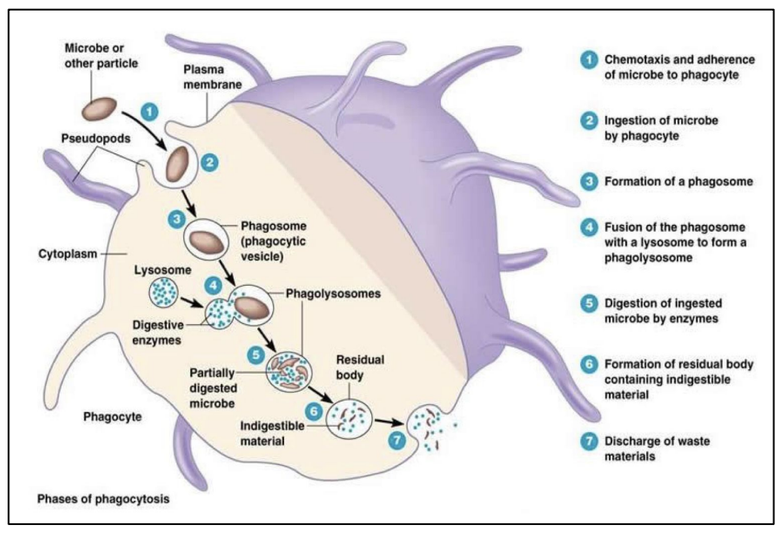


Figure 10-4 Microbial killing.

Phagocytosis is increased by certain substance a process called "opsonization" complement 3b or antibodies like IgG making antigen ready for killing.

Indirect Immune Function of RES

Ingest foreign body, process it and present it to lymphocytes.

- **Antigen Presenting Cells:** Display antigens in association with MHC-II.
- Classical APCs: B-cells, dendritic cells, langerhans cells, macrophages.

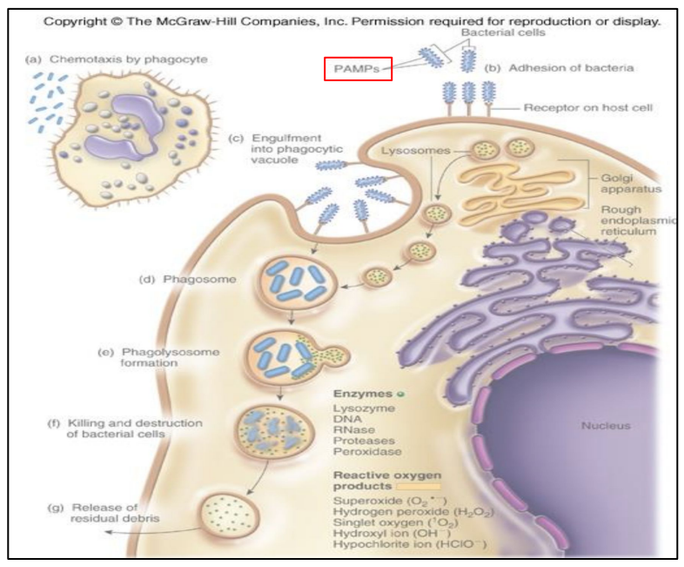


Figure 10-5 PAMPs or pattern associated molecular patterns, these are collections of molecules frequently expressed by human pathogens, such as LPS of bacterial endotoxins that are recognized immediately by macrophages and dendritic cells by receptors called pattern recognition receptors (PRRs), discussed in footnote no.1, first page.

Lymphoid Organs

1 Thymus

high rate of growth and activity until puberty, then begins to shrink; site of T-cell maturation.

2 Lymph nodes

small, encapsulated, bean-shaped organs stationed along lymphatic channels and large blood vessels of the thoracic and abdominal cavities.

3 Spleen

structurally similar to lymph node, it filters circulating blood to remove worn out RBCs and pathogens.

Primary Lymphoid Organs	Secondary Lymphoid Organs
Primary lymphatic organs are where lymphocytes are formed and mature. - They provide an environment for stem cells to divide and mature into B- and T- cells	Secondary lymphoid tissues are arranged as a series of filters monitoring the contents of the extracellular fluids, i.e. lymph, tissue fluid and blood.
Include: red bone marrow and thymus	Include: lymph nodes, tonsils, spleen, Peyer's patches and mucosa associated lymphoid tissue (MALT).
Both T-cell and B-cells are 'born' in the bone marrow. - However, whereas B cells also mature in the bone marrow, T-cells have to migrate to the thymus, which is where they mature in the thymus.	Secondary lymphoid tissues are also where lymphocytes are activated.

Spleen

- Is soft **purple gray** in color located in the left upper quadrant of the abdomen.
- It is a **highly vascular** lymphoid organ.
- It plays an important roles in RBC integrity and has **immune function**.
- It holds a reserve of blood in case of **hemorrhagic shock.**
- It is one of the centers of activity of the RES and its absence leads to a predisposition toward certain infections.
- Despite its importance, there are no tests[1] specific to splenic function.

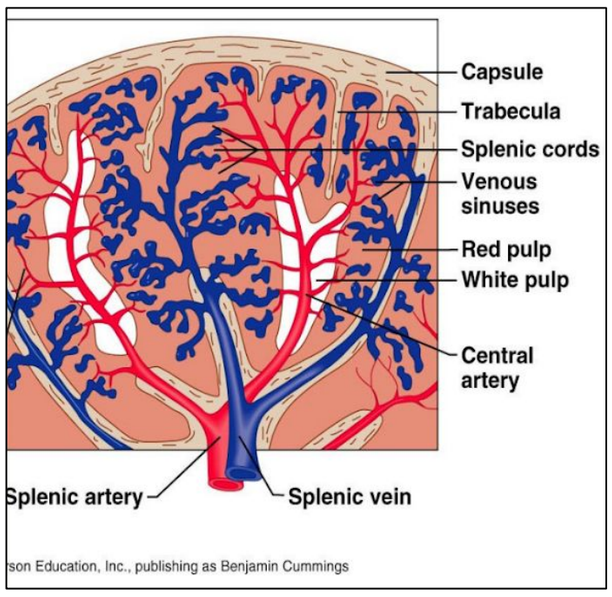


Figure 10-6

Structural Function of Spleen[1]

➔ White pulp (immunologic functions): Thick sleeves of lymphoid tissue, that provides the immune function of the spleen.

➔ Red pulp (Hematological/filtering function): Surrounds white pulp, composed of Venous sinuses filled with whole blood and Splenic cords of reticular connective tissue rich in macrophages. The blood squeezes through the trabecular cords meshwork of red pulp.

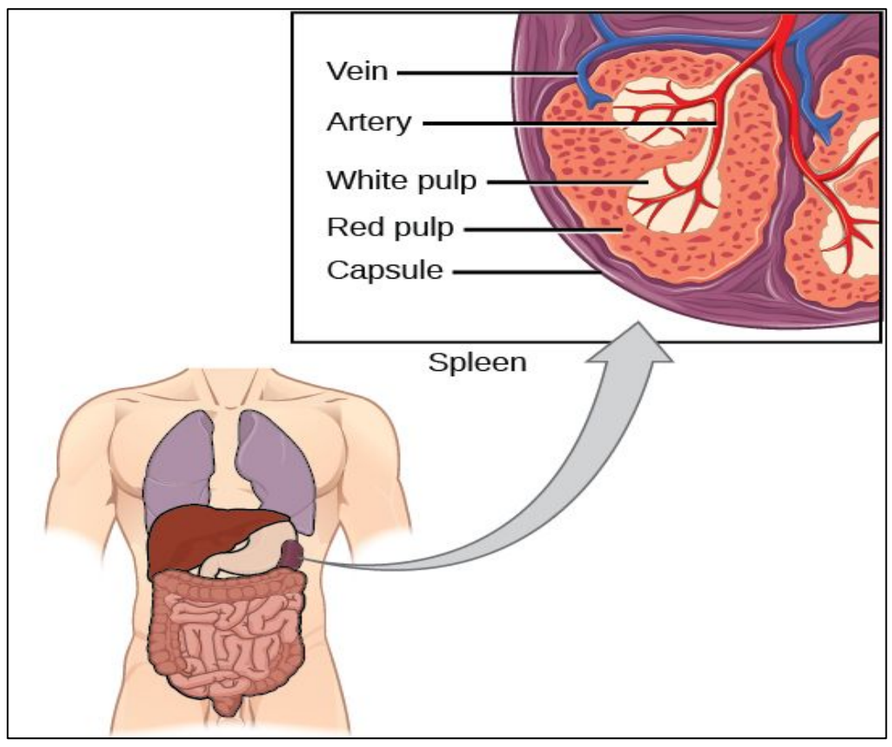


Figure 10-7

Functions of Spleen

01 Haematopoiesis (Hemopoiesis): fetal life.

02 Spleen is a main site for destruction of RBCs specially old and abnormal e.g. spherocytosis.[2]

03 Blood is filtered through the spleen.

04 Reservoir of thrombocytes (platelets) and immature erythrocytes.
(RBCs are released form spleen into circulation during the emergency conditions like hypoxia & hemorrhage.)

05 Recycles iron in red pulp.

FOOTNOTES

1. Histology: The spleen lacks afferent lymphatics, therefore it filters bloodborne antigens in the following manner: Splenic artery → Splenic arterioles (follicular arterioles in white pulp → Capillary beds in red pulp → Filtration of blood into splenic cords (here RBCs and antigens are filtered) → Drainage into venous sinosuids then into portal circulation throygh splenic vein.
2. Spherocytes are spherical RBCs that are usually mistaken by the spleen as abnormal RBCs and constantly breaks them down, resulting in autohemolysis.

Immune Functions of Spleen

Reservoir of lymphocytes in white pulp.
(contains about 25% of T cells & 15% B Cells)

Site for Phagocytosis of bacteria and worn-out blood cells (Slow blood flow in the red pulp cords allows foreign particles to be phagocytosed)

Site of B cell maturation into plasma cells, which synthesize antibodies in its white pulp and initiates humoral response. Major site of specific IgM production.

Destruction and processing of antigens.

Removes antibody-coated bacteria along with antibody-coated blood cells.

Because the organ is directly connected to blood circulation, it responds faster than other lymph nodes to blood-borne antigens.

It contains (in its blood reserve) half of the body monocytes within the red pulp, upon moving to injured tissue (such as the heart), turn into dendritic cells and macrophages that promote tissue healing.

The non-specific opsonins, properdin and tuftsin,[3] are synthesized that bind to the specific receptors on the surface of macrophages and other leukocytes, stimulating their phagocytic,bactericidal and tumoricidal activity.

Splenectomy Indications

Hypersplenism[1]: enlargement of the spleen (splenomegaly) with defects in the blood cells count.

Primary spleen cancers.

Haemolytic anaemias[2]: Sickle cell anaemia, Thalassemia,hereditary spherocytosis (HS) and elliptocytosis.

Idiopathic thrombocytopenic purpura (ITP).

Trauma (very common)

Hodgkin's disease.

Autoimmune hemolytic disorders.

FOOTNOTES

1. The reason being that with enlargement blood will tend to stay longer in the spleen, with increased number of macrophages resulting in excessive hemolysis of blood elements.
2. Spleen eats abnormal RBCs, so we're like punshining the spleen when it works efficiently, but the real problem is in the RBCs themselves
3. Properdin is a protein that regulates the complement immune system, tuftsin is important of immunoglobulin-mediated opsonization.

Risks & Complications of Splenectomy

Inflammation of the pancreas and collapse of the lungs.

Patient prone to malaria.

Excessive post-operative bleeding (surgical).

Overwhelming bacterial infection / post splenectomy sepsis.

Post-operative thrombocytosis and thus thrombosis.

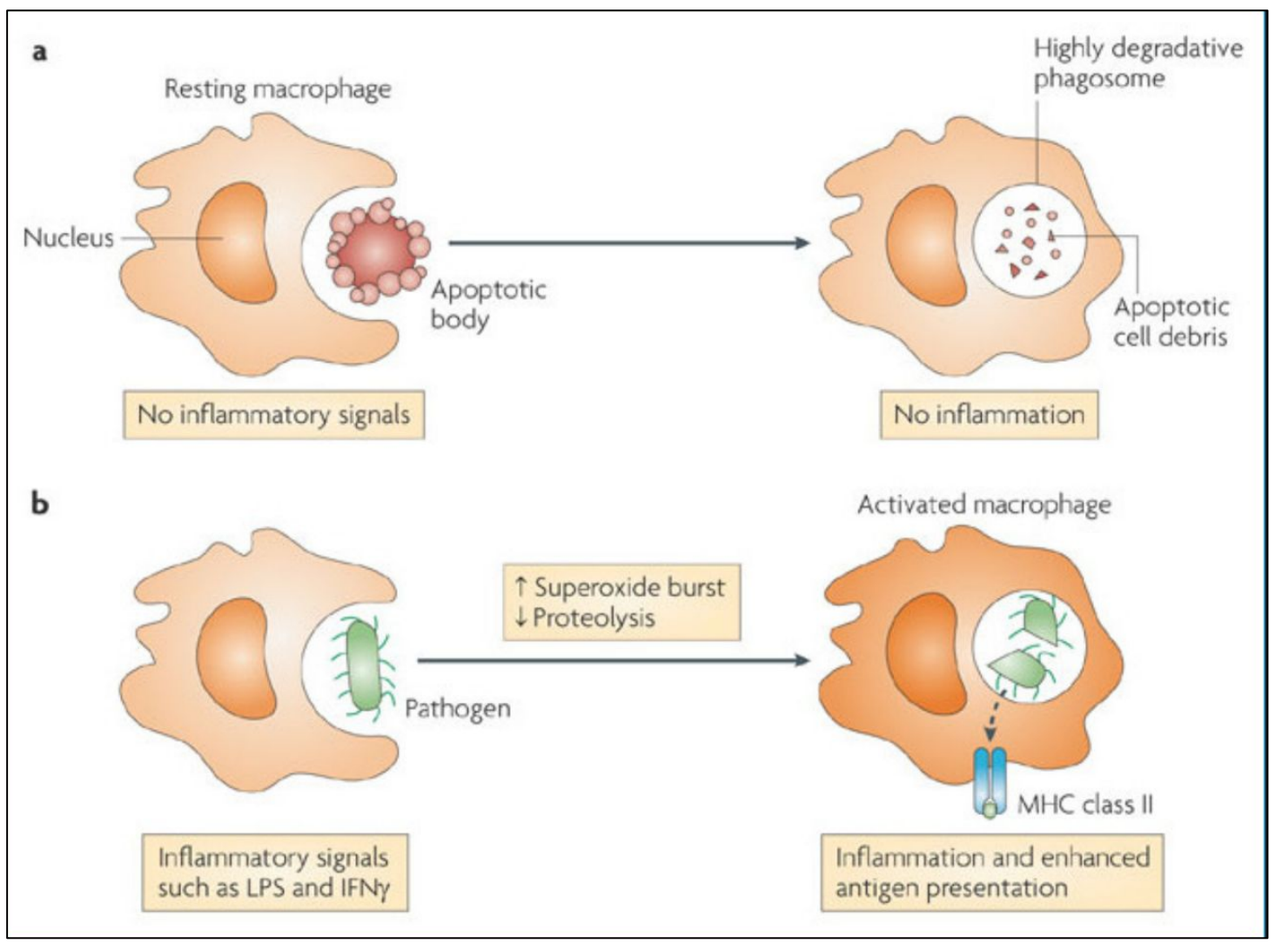


Figure 10-8

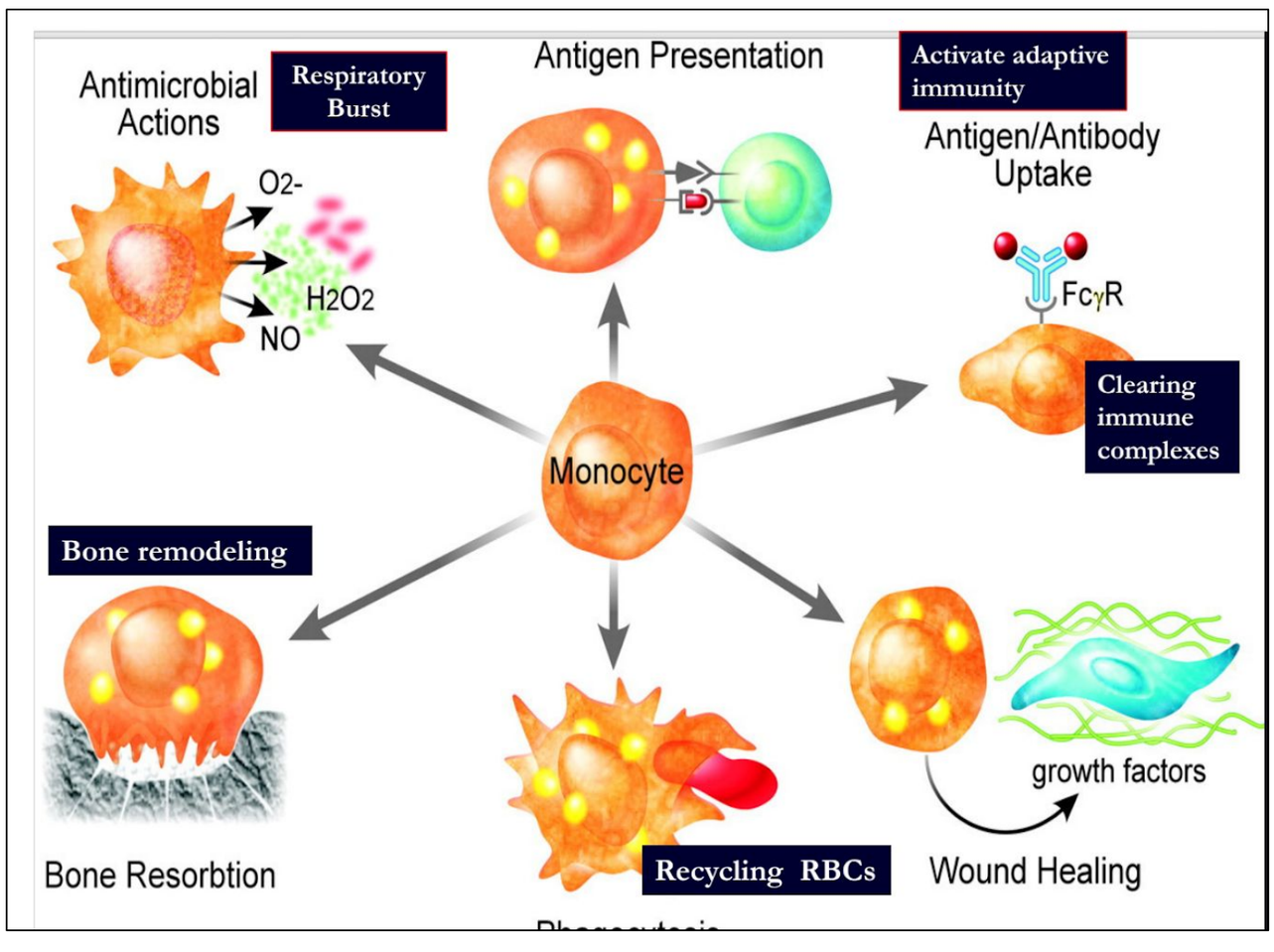


Figure 10-9

QUIZ

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1. Key components of the innate immunity & activate adaptive immunity by transforming into APCs:
A) Natural Killer cells
B) Macrophages
C) Eosinophils
D) Neutrophils

2. Reticular cells are located in:
A) Liver
B) Subcutaneous tissues
C) Bone marrow
D) Brain

3. The monocytes lifespan in circulation is:
A) 6 hours
B) Half a day
C) 3 days
D) Few months

4. In thymus:
A) T cell maturation
B) B cell maturation
C) RBCs storage
D) Destruction of pathogenic antigen

5. What does the white pulp of the spleen contain?
A) Venous sinuses
B) Splenic cord
C) Lymphoid tissue
D) Reticular connective tissue

SHORT ANSWER QUESTIONS

1. What are the cellular components of RES?
2. Write 3 types of macrophages and their location
3. Write 4 indications for splenectomy

1. Monocytes, Endothelial cells, Macrophages
2. kupffer cells → Liver
Microglia cells → Brain
Reticular cells → lymph nodes, bone marrow, spleen
Tissue histiocytes (fixed) → subcutaneous tissues Alveolar cells → Lungs
3. Hypersplenism, Primary spleen cancer, Haemolytic anemia, Trauma

ANSWER KEY: B, C, B, A, C

THIS LECTURE WAS DONE BY

Naif Alsolais, Mohannad Alqarni

FEMALE PHYSIOLOGY CO-LEADERS

Maha Alnahdi, Taif Alshammari

MALE PHYSIOLOGY CO-LEADERS

Nayef Alsaber, Hameed M. Humaid

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REFERENCES

- Guyton and Hall Textbook of Medical Physiology
- Ganong's Review of Medical Physiology