

Reticuloendothelial Structure & Function of the Spleen

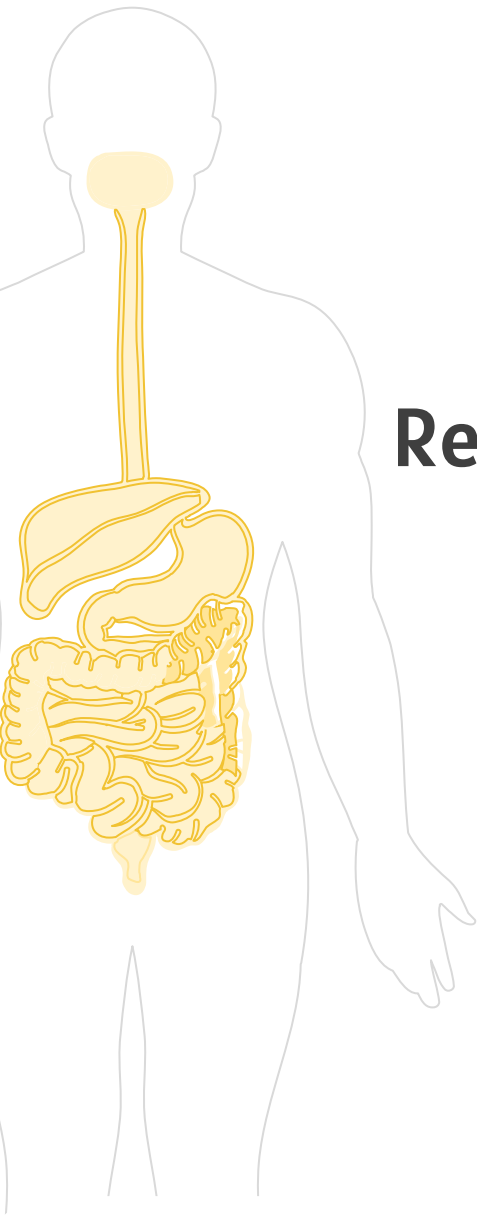
GNT Physiology

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Color Index:

- Main text
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Objectives

Describe/Define the term **Mononuclear Phagocyte system (MPS) / Reticulo-endothelial system (RES)**.

Describe the cellular components of RES.

Describe the functions of the RES.

Functions of monocytes/macrophages in different tissues

Mechanism of chemotaxis, phagocytosis and microbial killing

Explain/Define the structural functions of spleen

Describe the functions of the spleen.

Understand the basic concept of the indications and risks of splenectomy.

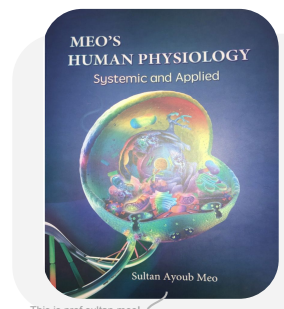
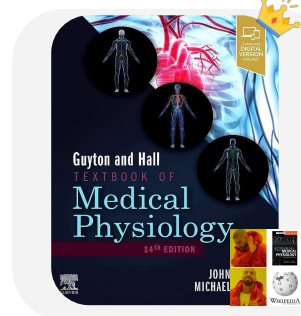
Lecture content

- Reticulo-endothelial system definition.
- Reticulo-endothelial system components.
- Functions of RES.
- Direct role in body protection.
- Indirect role in immune reaction.
- Spleen structure & Functions.
- Splenectomy indications & risks.



Resources

Only GI chapters included



This is prof sultan meo!

دَعَوَاهُمْ فِيهَا سُبْحَانَكَ اللَّهُمَّ وَتَحِيَّتُهُمْ فِيهَا سَلَامٌ يَا أٰخِرُ
دَعَوَاهُمْ اَنْ الْحَمْدُ لِلّٰهِ رَبِّ الْعٰلَمِيْنَ ﴿١٠﴾

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Overview of the immune system

Macrophages are key components of the innate immunity & activate adaptive immunity by transforming into Antigen Presenting Cells (APC).

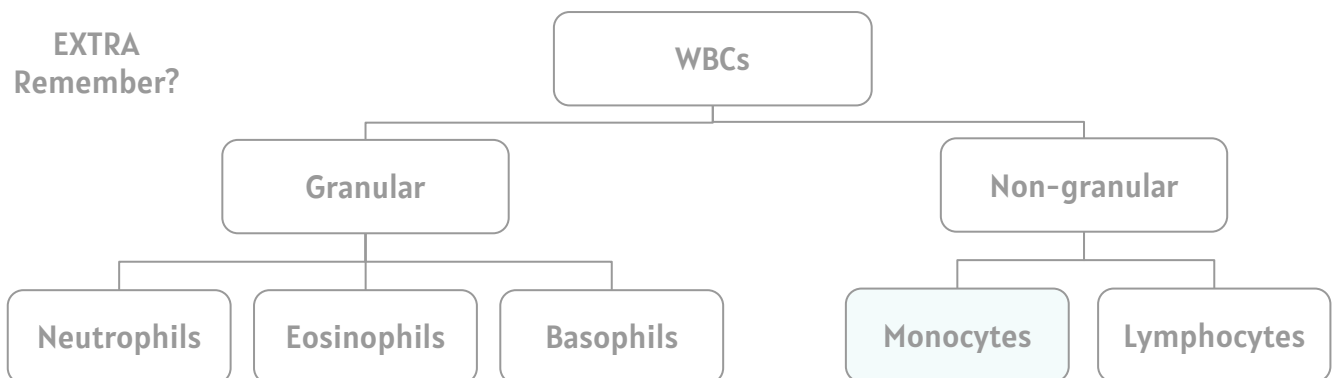
Male slides

Immunity		
	Innate immunity (Non specific)	Acquired immunity (adaptive)
Types 	<ul style="list-style-type: none"> ○ Skin is impregnated with keratin; few pathogens can penetrate if intact ○ flushing effect of sweat glands ○ mucous coat impedes attachment & entry of bacteria ○ blinking and tear production ○ stomach acid ○ nasal hair traps larger particles 	<ul style="list-style-type: none"> ◎ Passive: <ul style="list-style-type: none"> ○ Natural: From mother placental circulation to fetus ○ Artificial: Administration of antitoxin, antisera and Immunoglobulin ◎ Active: <ul style="list-style-type: none"> ○ Natural: Infection recovery from a disease ○ Artificial: Immunization by vaccination
Mediated by	<ul style="list-style-type: none"> ○ Complement ○ Cytokines ○ Phagocytes (Neut, Mono, NK) ○ Barriers ○ Blood Proteins 	<ul style="list-style-type: none"> ○ Cell Mediated: T Lymphocytes ○ Humoral: Antibody mediated (B Lymphocytes)



Reticuloendothelial system (RES)

EXTRA Remember?



Collection of cells united by the common property of phagocytosis, It is a network of connective tissue fibers (collagen type 3) inhabited by phagocytic cells such as macrophages ready to attack and ingest microbes.

Reticuloendothelial system (RES) is an older term = mononuclear phagocyte system (MNPS) new term. Reticulo refers to form a network or a reticulum (netlike structure) by cytoplasmic extensions; endothelial refers to their proximity to the vascular endothelium because of particle uptake by sinus-lining intravascular cells (Most endothelial cells are not macrophages)

Therefore, to distinguish them from polymorphonuclear leukocytes and emphasize their specialized functions RES is replaced by MPS

Monocytes transform themselves into macrophages in tissue & this system of phagocytes is called as Monocyte-Macrophage Cell System.

RES is an essential component of the immune system



M/M System Examples

Important

© Macrophage located in all tissues, differ depending on the organs in which they reside
(For a beautiful pictures, see next slide)



Skin, mucosa and Subc tissue → langerhans cell
Subcutaneous tissue → Tissue histiocytes (Fixed Macrophages)



Lymph Nodes & Spleen → Sinus histiocytes (Reticular cells) / spleen also called littoral cell



Lungs → Alveolar macrophages



Liver sinuses → Kupffer Cells



Brain → Microglia



Kidneys → Mesangial Cells



Bone → Osteoclasts



Placenta → Hofbauer cells



Granulomas → Epithelioid cells



Bone marrow → Reticular cells



Mononuclear Phagocyte System (MPS)

Male slides

Monocytes in blood circulate for 72 hours after leaving the bone marrow.

Mobile & Fixed Macrophages in Tissue (Life span of 3 months)

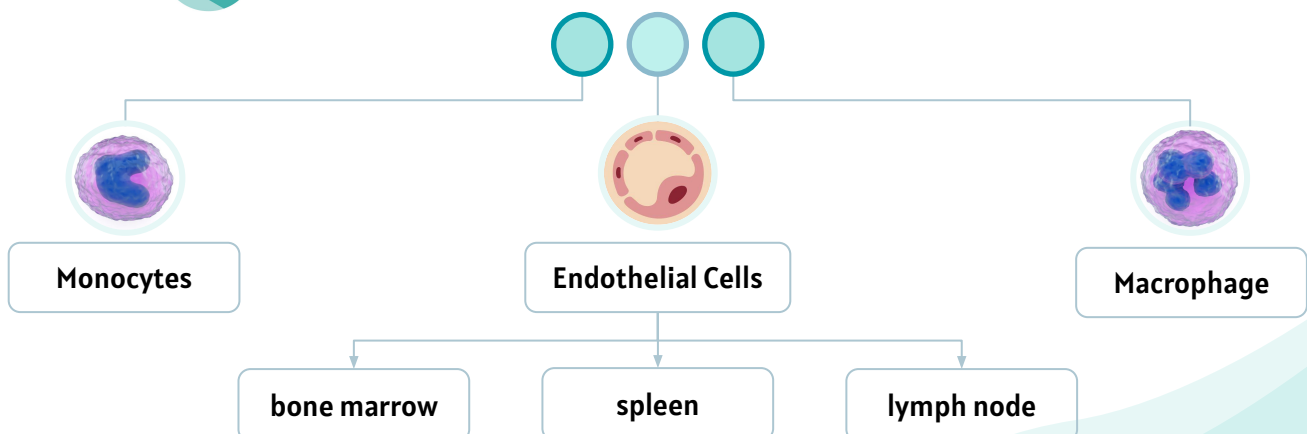
Specialized endothelial cells in bone marrow, spleen, and lymph nodes.

Some may end up as the multinucleated giant cells (Granulomas) seen in chronic inflammatory diseases such as TB



Cellular components of RES

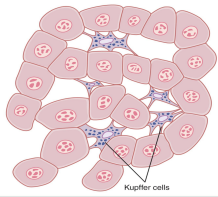
Female slides





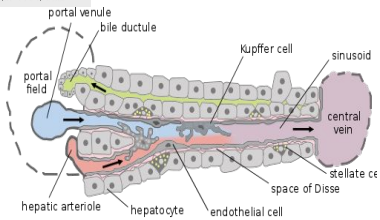
Tissue Macrophages

Liver sinuses



Kupfer cells

Figure 33-4 Kupfer cells lining the liver sinusoids, showing phagocytosis of red ink particles into the cytoplasm of the Kupfer cells.



portal venule, bile ductule, portal field, hepatic arteriole, hepatocyte, endothelial cell, Kupfer cell, sinusoid, central vein, stellate cell, space of Disse

Lymph nodes

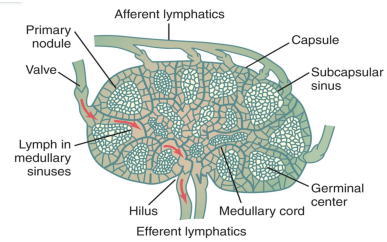


Figure 33-3 Functional diagram of a lymph node. (Redrawn from Ham AW: Histology, 6th ed. Philadelphia: JB Lippincott, 1993)

- Macrophages line nodal medullary sinuses
- Subcapsular sinus macrophages (ssms)
- Medullary sinus macrophages (msms)
- Medullary cord macrophages (mcms)

Spleen

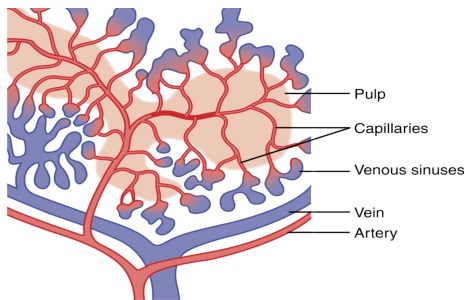
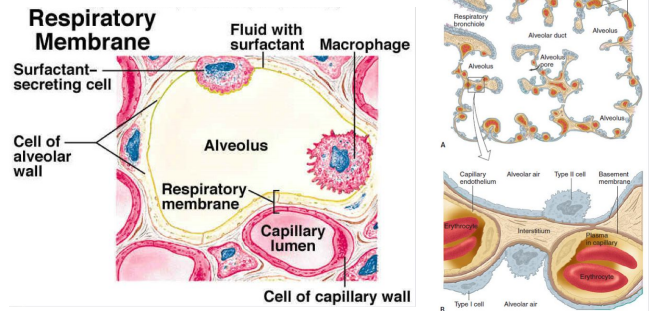


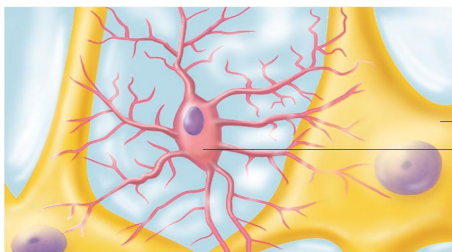
Figure 15-13 Functional structures of the spleen.

Lungs

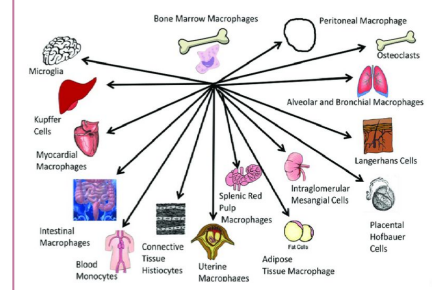


"Dust cells" because of their content of intracellular carbon particles.

CNS

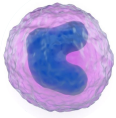


Examples of Specialized Macrophage Populations





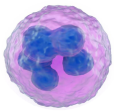
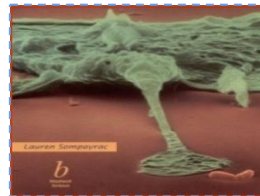
Monocyte & Macrophages



Monocyte

Male slides

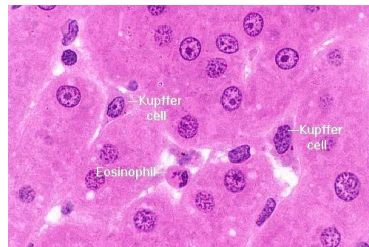
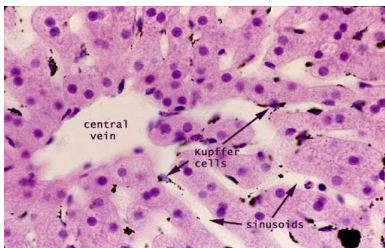
- Size: 15-20 μm (active cells 60-80 μm)
- Small granules (azurophilic) & **vacuoles** (food storage)
- More efficient Phagocytosis than Neutrophils (100 bacteria vs 3-20 by neutr larger particles like RBCs & malarial parasites)
- Life span: 10-20 hours in blood & in tissues 3m as macrophage
- Two types: mobile & fixed macrophage, because monocytes are mobile in the blood
- **Lysosomes contain lipases** (digest lipid coat of some bacteria like *mycobacterium tuberculosis*) unlike neutrophils
- Acts as antigen presenting cells
- Azurophilic granules of monocytes are **primary lysosomes** or storage granules. **Lysosomes contain acid hydrolases, MPO, HOCl, Defensins**



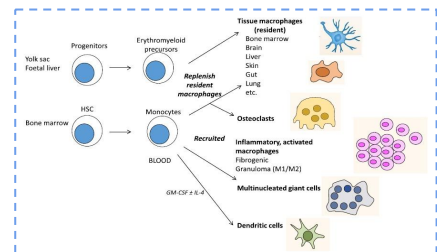
Macrophage

Female slides

- Often remain fixed to their organs.
- They filter & destroy organisms which are foreign to the body, such as bacteria, viruses.
- Some macrophages are mobile & can group together to become one big phagocytic cell in order to ingest larger foreign particles. Some may end up as the multinucleated giant cells seen in chronic inflammatory diseases such as tuberculosis.



Extra



Origin & distribution of Tissue macrophages:
 -Different tissues contain varying mixtures of embryonic and marrow-derived macrophages.



Formation of Macrophages

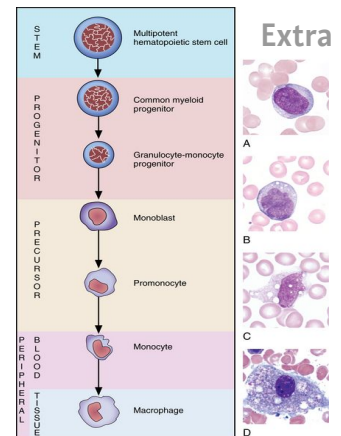
Begin by Stem cell in Bone Marrow: monoblast maturing to promonocyte then mature monocytes are released into the blood

Stay for 10-20 hours in circulation

Then it leaves the blood heading to tissues transforming into larger cells (macrophage).

Macrophage lifespan is up to few months in tissues.

Female slides



Origins and distribution of Tissue Macrophages

Male slides

- During development, erythromyeloid progenitors from yolk sac and fetal liver give rise to tissue-resident macrophages which persist during adult life as long-lived cells of widely varying morphology that turn over locally.
- At birth, bone marrow hemopoietic stem cells become the source of blood monocytes, replenishing resident populations with high turnover, such as gut, and in response to increased demand.
- Different tissues contain varying mixtures of embryonic and marrow derived macrophages.

Classically activated macrophages (M1)

- Pro-inflammatory phenotype (accelerate inflammation)
- Activated by type 2 interferon (IFN- γ) and tumor necrosis factor (α)

Vs

Alternatively activated macrophages (M2)

- Anti-inflammatory phenotype
- activated by Interlukin 4, interferon type 1 (IFN- α)



Transformation of Monocytes to Macrophage

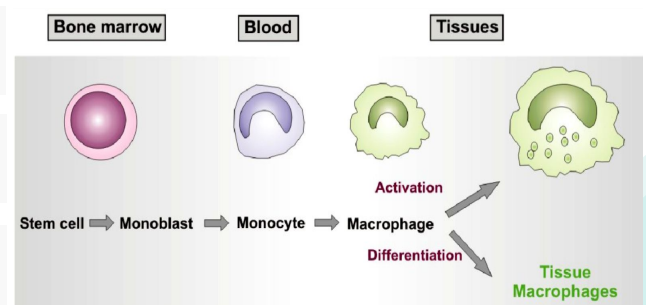
Female slides

Characterized by an increase in

1 Cell size

2 Number and complexity of intracellular organelles golgi, mitochondria, lysosomes

3 Intracellular digestive enzymes





Macrophages & Neutrophils Responses During Inflammation

Male slides

Lines of defenses:

- 1st Tissue macrophages & Physical Barriers (like hcl in stomach).
- 2nd Neutrophil invasion of the inflamed area (active inflammation)
- 3rd Monocytes-macrophage invasion of inflamed area when the inflammation becomes chronic.
- 4th Increased production of granulocytes and Monocytes by Bone marrow

MPS dysfunctions:

- Defective chemotaxis: corticosteroids, drug induced immunosuppression, AIDS, diabetes
- Defective phagocytosis: lupus erythematosus
- Microbicidal defect: chronic granulomatous disease
- Decreased cytotoxicity: Wiskott-Aldrich-Syndrome,
- Lysosomal diseases: deficiencies in the clearance of physiologic substrates



Defense properties (MACROPHAGES & NEUTROPHILS)

Male slides

- 1 **Margination:** WBC Roll, Bind and then stick along the walls of blood capillaries
- 2 **Diapedesis:** WBC squeezes itself through endothelial holes leaving blood capillaries
- 3 **Chemotaxis:** WBC move by amoeboid motion towards inflammation area following chemotactic substances (Bacterial toxins, Complement C5a, LKB4) are released from site of infection (The inflamed area will release some substance that neutrophils can detect from the BV)
- 4 **Phagocytosis:** Upon reaching the site of infection neutrophils start to engulf infecting organism

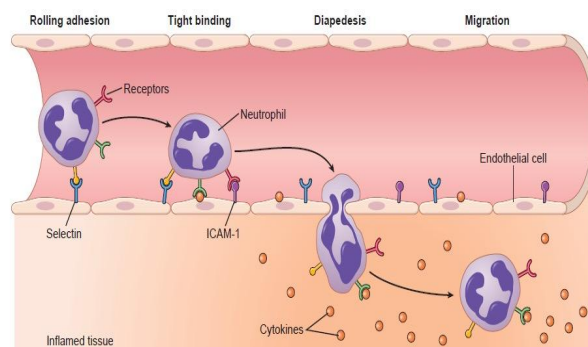


Figure 34-6. Migration of neutrophils from the blood into inflamed tissue. Cytokines and other biochemical products of the inflamed tissue cause increased expression of selectins and intercellular adhesion molecule-1 (ICAM-1) in the surface of endothelial cells. These adhesion molecules bind to complementary 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.



General functions of RES

Important

Phagocytosis

Bacteria, dead cell, foreign particles (**direct**)

Immune functions

Processing antigen and antibodies production (**indirect**) they act like Antigen Presenting Cells

Breakdown

of aging RBCs

Storage

of RBCs and circulation of iron. iron that come from the broken RBCs

Dual nature of macrophage functions, host protection versus tissue injury, is maintained in a fine balance M1 vs M2

Female slides

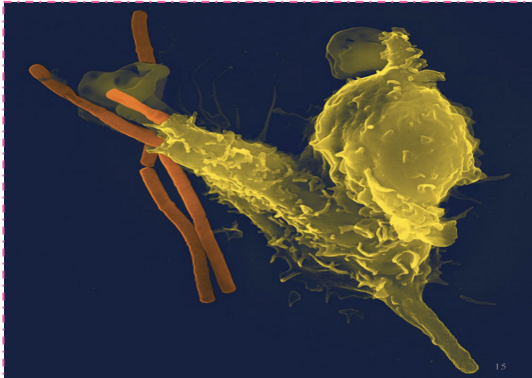
Phagocytosis: Part of the natural or innate immunity

Macrophages are a powerful phagocytic cells:

Ingest up to 100 Bacteria

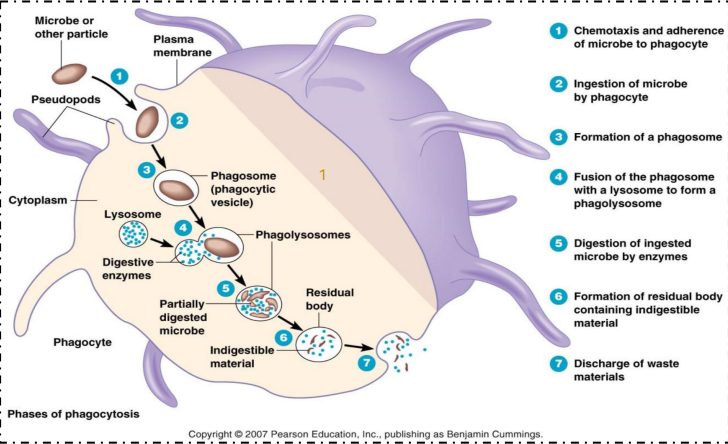
ingest larger particles such as old RBCs

get rid of waste products



A scanning electron microscope image of a single neutrophil (yellow), engulfing anthrax bacteria (orange).

Microbial Killing



Macrophages: a wandering, walking cell. "Big eater" capable of phagocytosis. Is a modified monocyte in tissues.

1) Residual bodies contain indigestible material only



Direct & Indirect functions of RES

Direct functions of RES

Male slides

Phagocytosis

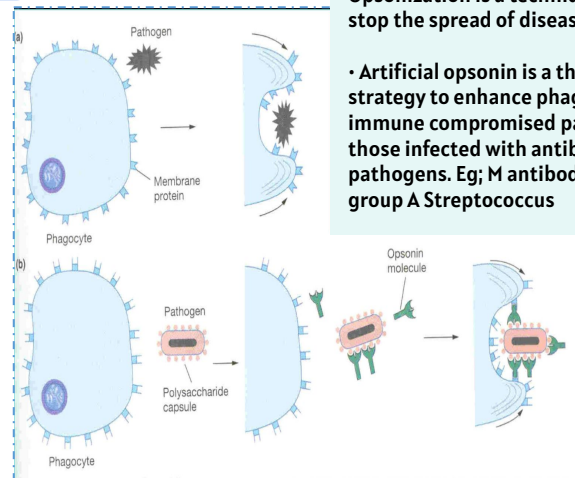
Opsonization and phagocytosis

Phagocytosis is increased by certain substance (opsonins) a process called **OPSONIZATION**.

opsonization: "to make something more tasty"

Complement 3b or antibodies like IgG make them ready for killing a process known as opsonization.

For some reason the macrophage can't eat this microbe so it enhances this substance (IgG...) to engulf and coat that microbe and make it easy to be ingested. كانت مو حلو طعمها وبعد الاضافات صارت احلى واكلها



Opsonization is a technique to kill and stop the spread of disease

Artificial opsonin is a therapeutic strategy to enhance phagocytosis in immune compromised patients and those infected with antibiotic-resistant pathogens. Eg; M antibodies for fighting group A Streptococcus

Indirect immune functions of RES

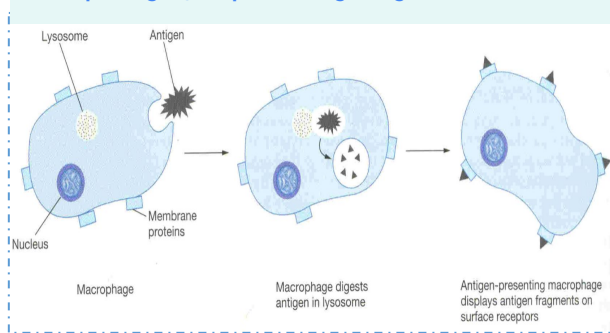
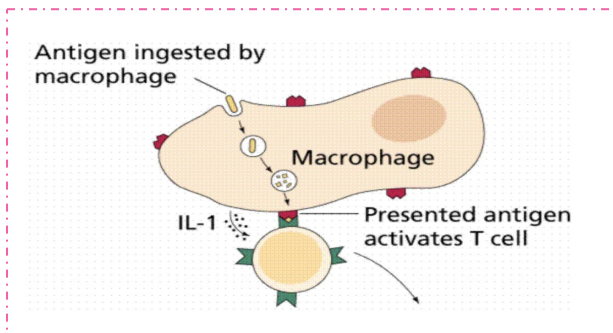
Antigen Presenting Cells

Ingesting foreign bodies

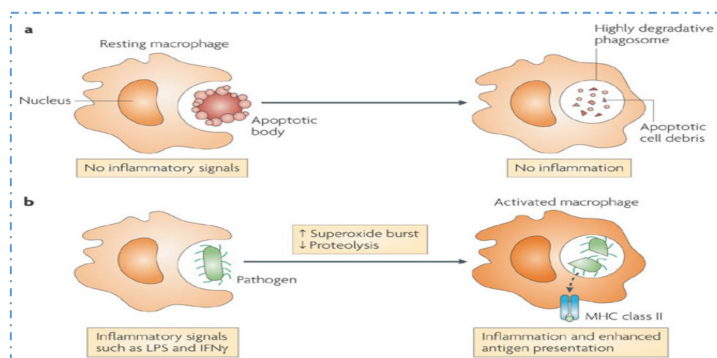
Process it

Present it to lymphocyte

After ingesting pathogen, macrophage will present the antigen of the pathogen to the corresponding helper T cell. The presentation is done by integrating it into the cell membrane and displaying it attached to an MHC class II molecule, indicating to other WBC that the macrophage is not a pathogen, despite having antigens on its surface.



Classical APCs include Macrophages, dendritic cells, Langerhans cells and B cells. Doctor Q: name 4 APCs



Lymphoid organs

Female slides

1

Thymus

High rate of growth and activity until puberty, they begins to shrink; site of **T-cell maturation**.

2

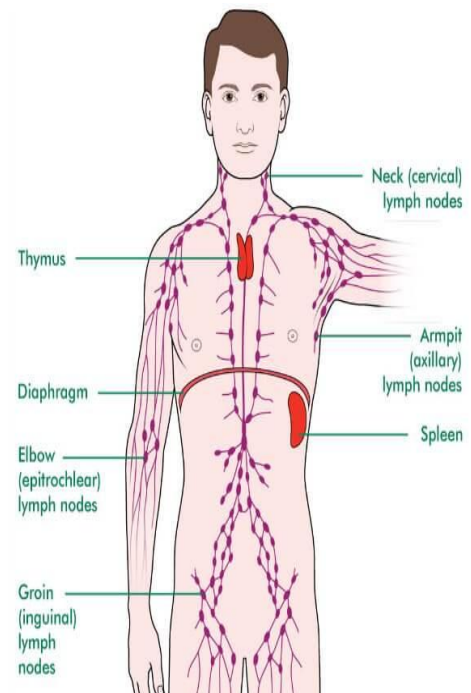
Lymph nodes

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

3

Spleen

Structurally similar to lymph nodes, it filters circulating blood to remove worn out RBCs and pathogens.



Male slides

Important

Primary Lymphatic Organs

Are where lymphocytes are **formed** and **matured**. They provide an environment for stem cells to divide and mature into B and T cells.

These include: **Red bone marrow** and **thymus gland**.

Both B and T cells are "born" in the bone marrow. However, whereas B cells also mature in the bone marrow, T cells have migrate to the thymus, which is where they mature (in the thymus)..

Secondary Lymphatic Organs

Secondary lymphoid tissues are arranged as a series of filters monitoring the contents of the extracellular fluid, i.e. lymph, tissue fluid and blood.

Secondary lymphoid tissues are also where lymphocytes are **activated**.

These include: **lymph nodes, tonsils, spleen, Peyer's patches and mucosa associated lymphoid tissue (MALT)**.

MCQ: which of the following is a Primary/Secondary lymphatic organ?

Spleen

Is a soft purple gray in color located in the left upper quadrant of the abdomen

It is a highly vascular lymphoid organ **If the spleen is damaged in trauma it has to be removed because sutures will make it bleed more**

It plays an important roles in: red blood cell integrity and has an immune functions

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 specific to splenic function.

Important

Functions of the spleen

Female slides

- 1 Hematopoiesis (hemopoiesis): during **fetal life**.
- 2 Spleen is a main site for **destruction of RBCs** specially old and abnormal e.g. spherocytosis.
- 3 **Blood is filtered** through the spleen
- 4 **Reservoir** of thrombocytes and immature erythrocytes.
- 5 Recycles **iron**

Reservoir function:

- A large number of RBCs and platelets are stored in spleen and recycles iron
- RBCs are released from spleen into circulation during the emergency conditions like hypoxia & hemorrhage

Structural functions of Spleen

White pulp

Thick sleeves of lymphoid tissue, that provides the **immune function** of the spleen.

Immunologic functions:

- trapping and processing of antigens
- initiates immunologic response (APC)
- the major site of antibody synthesis
- key role in removal of encapsulated bacteria (*Strep pneumo*) **imp** if the spleen is removed, the patient will need anti streptococcal vaccines annually.

-Macrophage activation
-Site of B cell maturation into plasma cells, which synthesize antibodies in its white pulp and initiates humoral response.

Red pulp

Surrounds white pulp, composed of **venous sinuses** filled with whole blood and splenic cords of reticular connective tissues rich in **macrophages**.

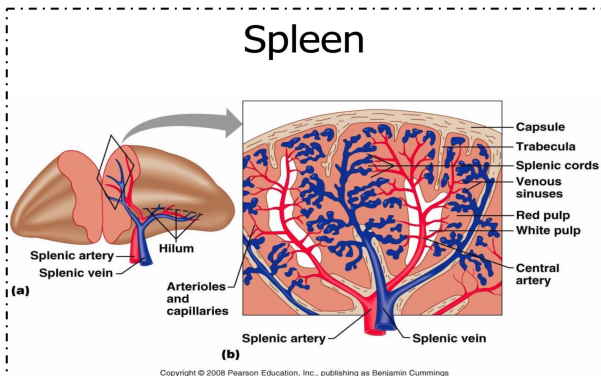
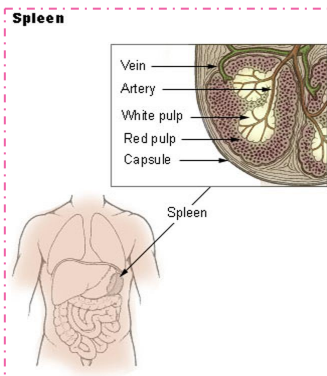
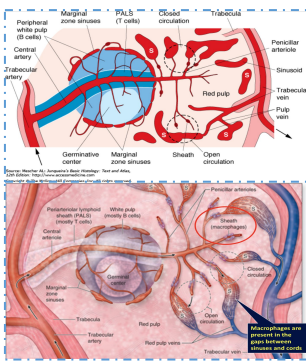
Hematological functions (filtering function):

- RBC's able to deform through sinusoidal wall and endothelium Culling (Increased in hereditary spherocytosis).
- Retrieve iron for the body

Male slides

Cytopoiesis:

- From the fourth month of **intrauterine life**, some degree of **hemopoiesis** occurs in the **fetal spleen**.
- Stimulation of the **white pulp** may occur following antigenic challenge, resulting in the **proliferation of T and B cells and macrophages**.
- This may also occur in myeloproliferative disorders, thalassaemias and chronic haemolytic anaemias. **adults with these diseases spleen begin to produce RBCs like fetal life**



IMP: Periarteriolar lymphoid sheath contains mostly T lymphocytes. T lymphocytes require thymus to be matured, so periarteriolar sheath depends on thymus.

Immune functions of the spleen

- 1 - Because the organ is directly connected to blood circulation, it responds faster than other lymph nodes to **blood-borne antigens**, filters the blood by removing the microorganisms & foreign bodies.
-Macrophages in splenic pulp phagocytose microorganisms & foreign bodies.
- 2 **Destruction and processing of antigens**, and is the major site of IgM production.
- 3 **Reservoir of lymphocytes in white pulp** (contains about 25% of T-cells and 15% of B-cells).
- 4 Site for **Phagocytosis** of bacteria and worn-out blood cells (Slow blood flow in the red pulp cords allows foreign particles to be phagocytosed)
- 5 the non-specific opsonins, properdin and tuftsin, are synthesized that bind to the receptors on the surface of macrophages and other leukocytes, stimulating their phagocytic, bactericidal, tumoricidal activity.
- 6 **Site of B cell maturation** into plasma cells, which synthesize antibodies in its white pulp and initiates humoral response.
- 7 Removes antibody-coated bacteria along with **antibody-coated blood cells**
- 8 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 promoting **tissue healing**.

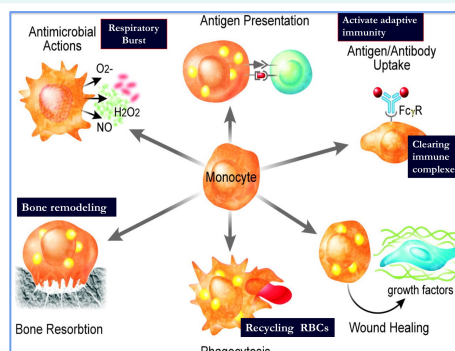
Important

Possible SAQ
(from Dr.shahid)

How Macrophages differ from neutrophils ?

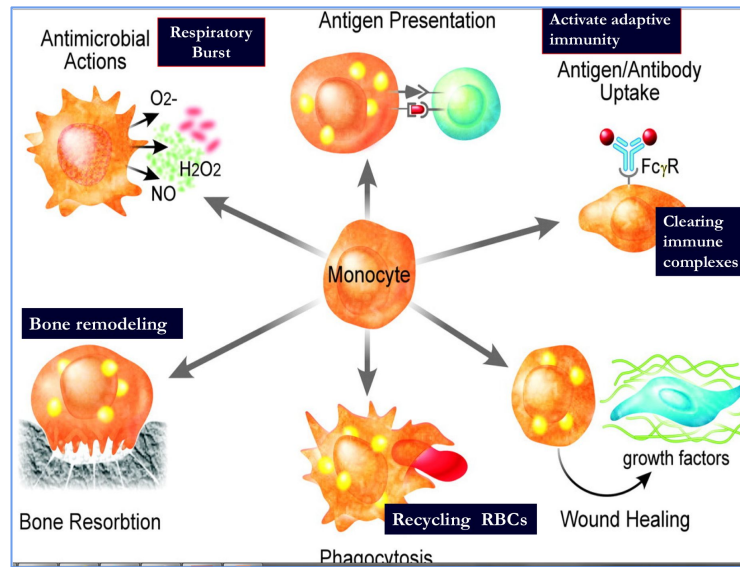
Cell	Macrophage	Neutrophil
Morphology	Large mononuclear cell with granular cytoplasm	Smaller cells with multi-lobed nucleus and neutral cytoplasmic granules.
Location	Often resident in tissues (remove routine cell debris)	Blood-requires recruitment to site of infection
Killing ability	Require activation by bacterial molecules +/- IFN γ	Activated during recruitment, then able to kill internalised bacteria automatically
After killing	Migrate to local lymph nodes	Die at site by apoptosis (then taken up by macrophages)
Antigen presentation	Can present antigen (Class II up-regulated by IFN γ)	Cannot present antigen (don't normally express Class II)

Functions of monocytes (summary from Dr.shahid)

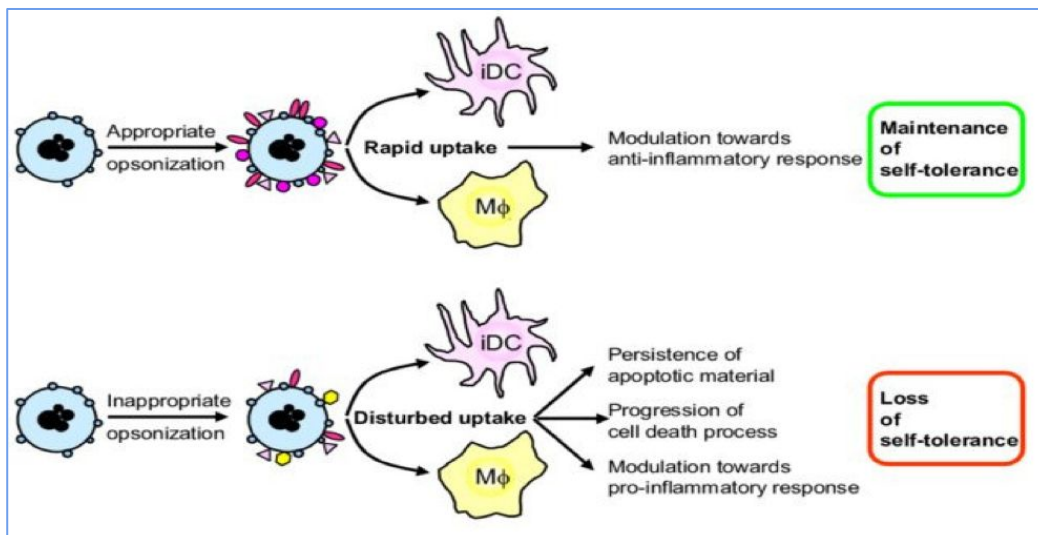
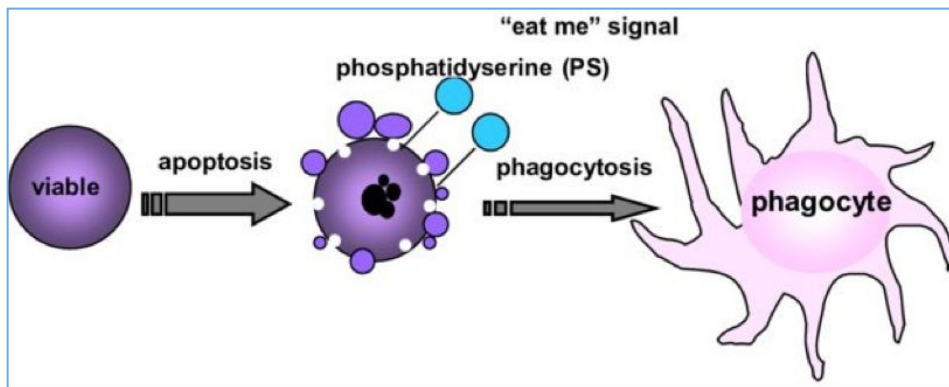


Note : This page just look at these pictures to have more general knowledge about the topic.

Functions of monocytes (summary from Dr.shahid)



The role of opsonins in the handling of apoptotic cells



TEST YOURSELF !

MCQ:

Q1) What's the function of RES?

A) Formation of thrombocytes

B) Phagocytosis and immune function

C) Destruction of Leukocyte

D) Synthesis of hemoglobin

Q2) What can we find in thymus:

A) T cells maturation

B) B cells maturation

C) RBCs

D) Destruction of pathogenic antigen

Q3) One of the general functions of RES

A) Digestion

B) Presenting Antigens

C) Breakdown of aging RBCs

D) Hematopoiesis

Q4) Autolytic enzymes of WBC is stored in?

A) Golgi apparatus

B) Ribosomes

C) Nucleus

D) Lysosomes

Answers: Q1:B | Q2:A | Q3:C | Q4:D

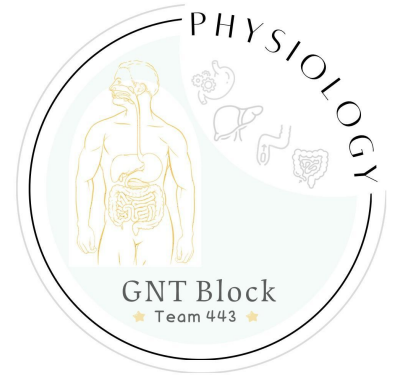
SAQ:

Q1) Enumerate the indications of splenectomy

1. Hypersplenism
2. Primary spleen cancer
3. Hemolytic anemias
4. Idiopathic thrombocytopenic purpura
5. Trauma
6. Hodgkin's disease
7. Autoimmune hemolytic disorder

Q2) what are the functions of spleen?

1. Hematopoiesis (hemopoiesis): during fetal life.
2. The main site for destruction of RBCs
3. Reservoir of thrombocytes and immature erythrocytes.
4. Filtering of the blood
5. Recycles iron



The BEST

Team Leaders

EVER..

Rafan Alhazzani

Fahad Almughaiseeb

Ghaida Aldossary

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Team Members



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