SHEET NO.

2

IMMUNOLOGY

DOCTOR 2019 | MEDICINE | JU

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Immunology

We will talk about the cells of the immune system.

Immune system has cells, molecules and physical barrier which do the immunity job.

•The cells of the innate and adaptive immune system are normally present as circulating cells in the blood and lymph, as anatomically defined collections in lymphoid organs, and as scattered cells in virtually all tissues.

The majority of the immune cells and the cells in the blood come from the bone marrow, so in the bone marrow we have stem cells (Hematopoietic stem cell) that give other stem cells:

1) Lymphoid stem cells: Differentiate into Natural killer cell (NK cells), T-cell and B-cell (T and B cells are in the adaptive immunity and we will talk about them in the next lecture).

2) Myeloid stem cells (MSC): which differentiate into the majority of the cells in the blood, some of these cells have a relation with the immune system and others don't have a relation with the Immune system.

A) Cells that don't have a relation with immune system:

1- Erythroblast: is differentiated into Erythrocytes that will lose its nucleus and is converted into (RBCs).

2-Megakaryoblast: is differentiated into Megakaryocytes which is converted into platelets after fragmentation.

B) Cells that have a relation with immune system:

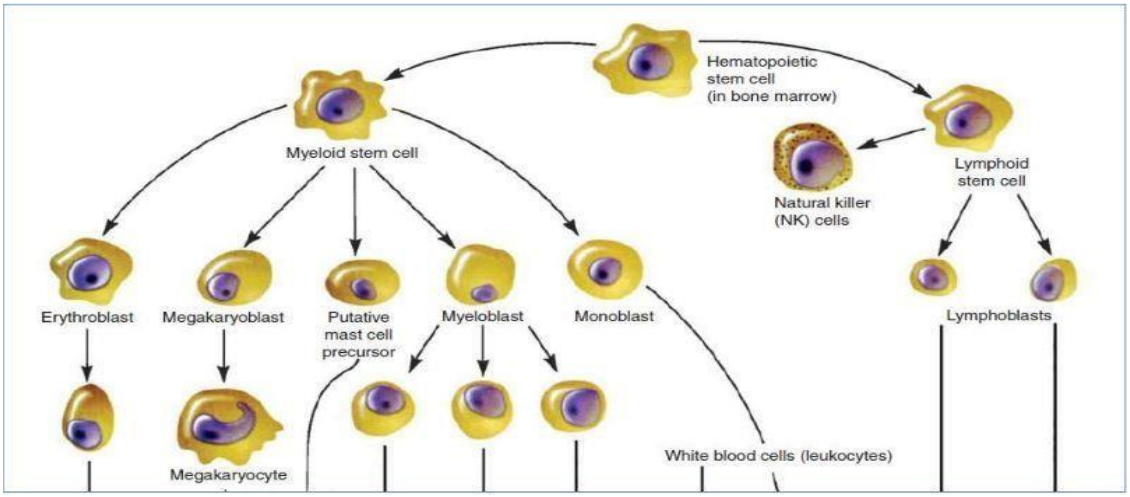
1) Putative mast cell precursor: scientists know that the mast cell has a precursor, but we don't know from where this precursor is originated and hence it is putative.

2) Myeloblast: It gives us three precursor cells that will differentiate into three cells known together as Granulocytes (because all of them have granules).

Granulocytes: Neutrophils, Basophils and Eosinophils.

NOTE: We can name the mast cell as a Granulocytes also because it has many granules.

3) Monoblast: It will differentiate into monocytes, when these monocytes arrive to the tissue, they will differentiate into either **Macrophage or Dendritic cells**.



We will talk about these cells as groups:

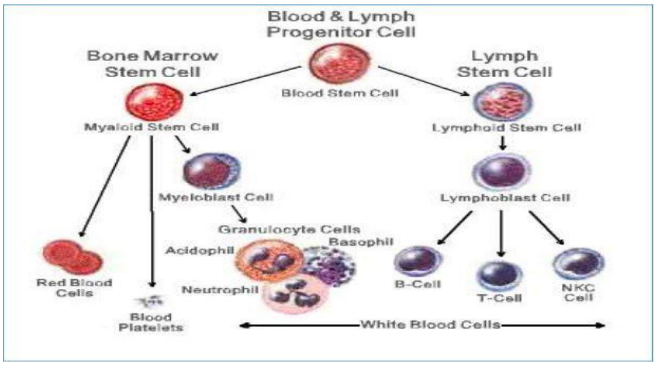
•Phagocytes.

•Mast Cells, Basophils, Eosinophils (we put them together because they have similarity in the function and shape).

•Antigen-Presenting Cells.

•Lymphocytes.

- **Granulocytes, T-cell, B-cell and NK cell together we call them leukocytes (White blood cells).**



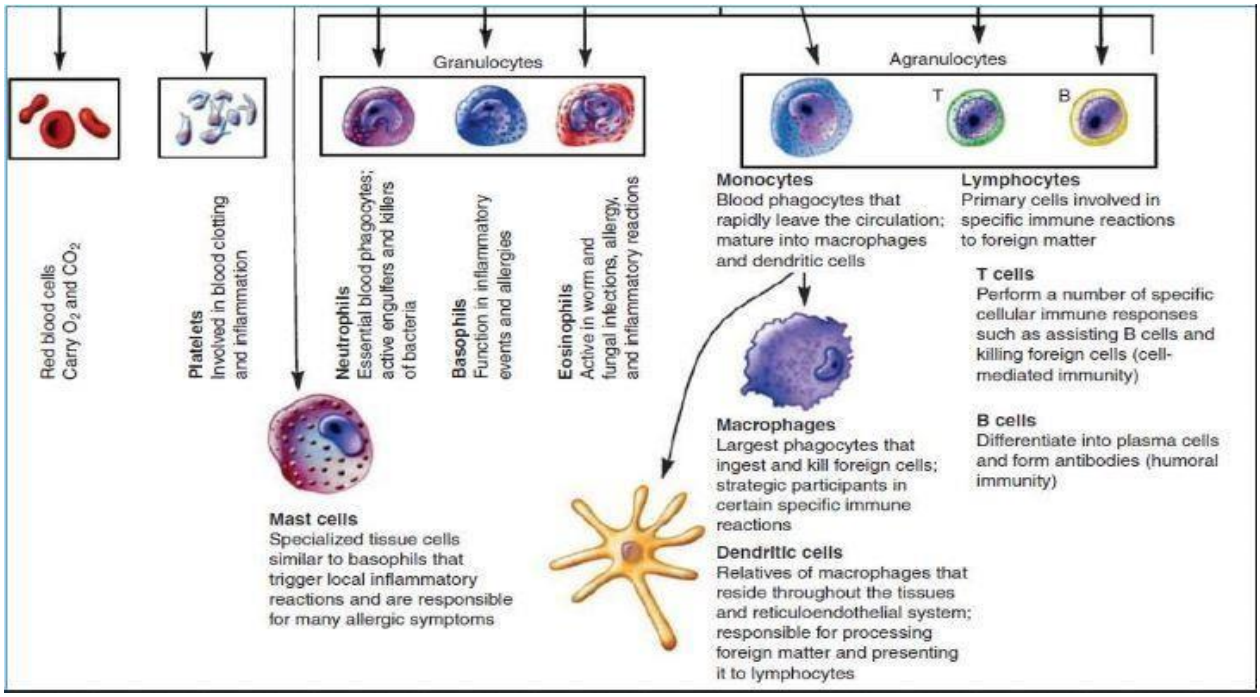
Now let's study the distribution of these white blood cells in the blood:

- Neutrophils are the most abundant leukocyte in the blood (make up 70 percent).
- It is called neutrophils because its granules don't stain and remain neutral, basophils give a blue color and the eosinophils give a reddish color.

Mast cell (that we consider it as a granulocyte) located at the side of the blood vessel.

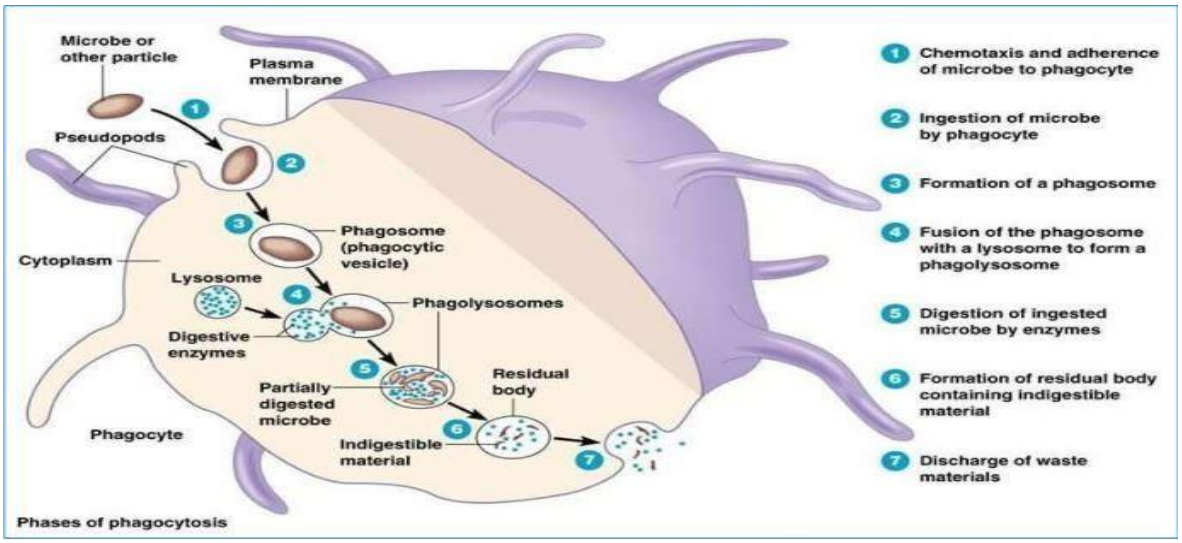
TABLE 2–1 Normal Blood Cell Counts

	Mean Number per Microliter	Normal Range
White blood cells (leukocytes)	7400	4500-11,000
Neutrophils	4400	1800-7700
Eosinophils	200	0-450
Basophils	40	0-200
Lymphocytes	2500	1000-4800
Monocytes	300	0-800



1) Phagocytes: which include Neutrophils and Macrophage.

The mechanism of phagocytosis is explained in the picture:



Notes about the picture:

- **Chemotaxis**: a process in which the phagocyte will follow a certain gradient from a molecule in the bacteria. when it arrives to the bacteria, there will be adherence between the phagocyte and the bacteria, and the bacteria will be pulled inside the phagocyte in a vesicle surrounded by a lipid membrane forming a **phagosome**.

- **Lysosomes** which contain digestive enzymes, low PH, and some antimicrobial peptides, maybe reactive oxygen species (ROS) will fuse with the phagosome formation a **phagolysosome**, then digestion of microbe takes place.
- Finally, secretion of the indigestible material and harmless by-products outside the cell or presenting an antigen in the cell surface on certain receptor if the phagocyte has the ability to do this like **macrophage,** (because not all phagocytes have the antigen presentation ability).

⇨ **Why is the antigen put on the cell surface?** Because lymphocytes will come, bind and process the antigen, and make a strong Immune response (activation of the **adaptive immune system**).

When we say that these cells are phagocytes, that doesn't mean their only role is to make phagocytosis, because the cell may have more than one role, but we can say that the main role for them is phagocytosis, and we will see in the macrophage that It makes more than one important function.

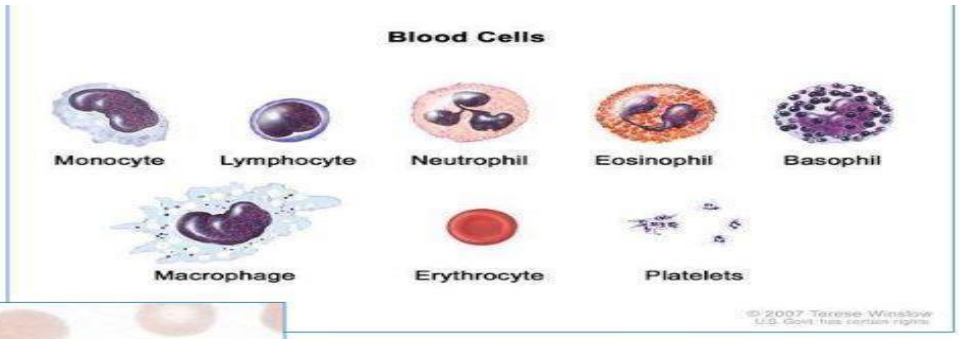
•Phagocytes also communicate with other cells in ways that promote or regulate immune responses.

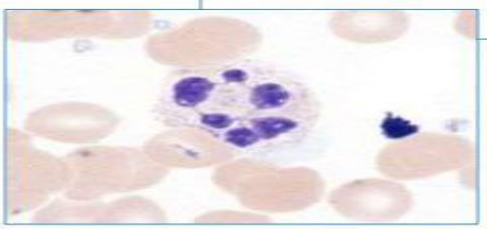
Neutrophils: **It has a special shape, the nucleus is segmented into 3-5 lobules, and that why It is also called polymorphonuclear leukocytes (Its nucleus has many shapes). other granulocytes have a similar shape to Neutrophils but with less lobules.**

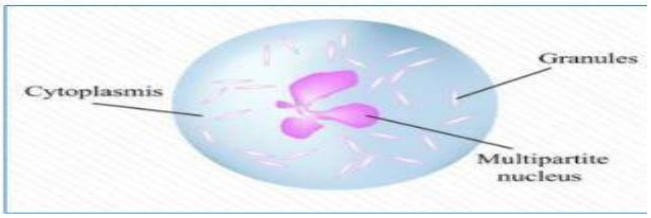
⇨ They are the most abundant population of circulating white blood cells and mediate the earliest phases of inflammatory reactions (It arrives firstly at the site of injury).

⇨ So, without any danger or injury (before they reach the tissue) they are circulating in the blood, and they have a lifespan of about 6 hours and then die by apoptosis (programmed cell death).

⇨ Production of neutrophils is stimulated by granulocyte colony-stimulating factor(G-CSF). Since the lifespan is just 6 hours and It still the abundant leukocyte in the blood, that means we produce a lot of them (about 100 billion neutrophils per day in an adult body, and this number may increase in the case of the infection).







•The cytoplasm of the Neutrophils contains granules of two types:

1) The majority, called Specific granules: they are filled with enzymes such as lysozyme (which breaks down the bond between NAM and NAG in the cell wall), collagenase which breaks the peptide bond in the collagen, and elastase which breaks down the elastic fibers, and these enzymes are important because when the neutrophils enter the tissue, they need to penetrate the ECM and reach the site of infection, so these enzymes help the cell to move easily in the tissue.

2) azurophilic granules: which are lysosomes containing enzymes and other microbicidal substances.

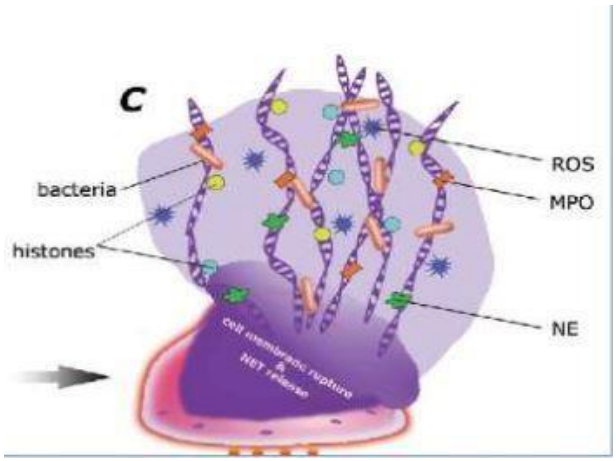
Neutrophils may migrate to sites of infection within a few hours after the entry of microbes.

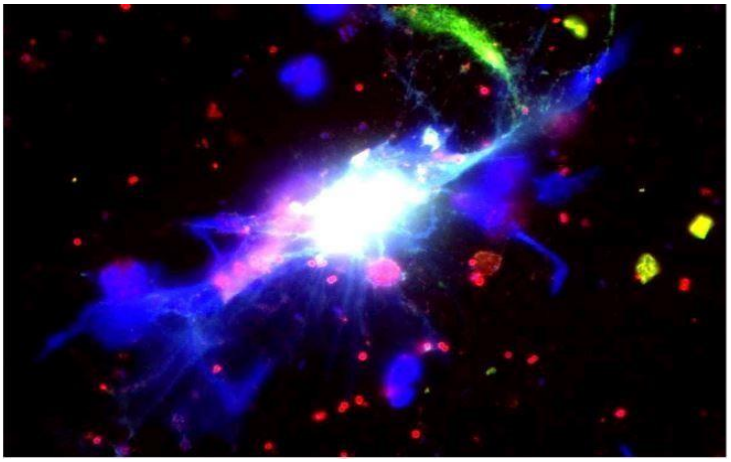
•After entering tissues, neutrophils function for a **few hours** and then die.

Also, the neutrophil has a mechanism that is discovered recently called **Neutrophil extracellular traps (NETs).**

Scientists found that some neutrophils may get their DNA (which is inside the nucleus around the histone proteins) out the cell, and when the DNA gets outside the nucleus, it will cover a large area.

So, NETs are networks of extracellular fibers, primarily composed of DNA from neutrophils, the DNA bind to the histones and maybe some molecules that are harmful for the bacteria like ROS and **Myeloperoxidase (MPO)**, and this DNA binds pathogens, and traps the bacteria.

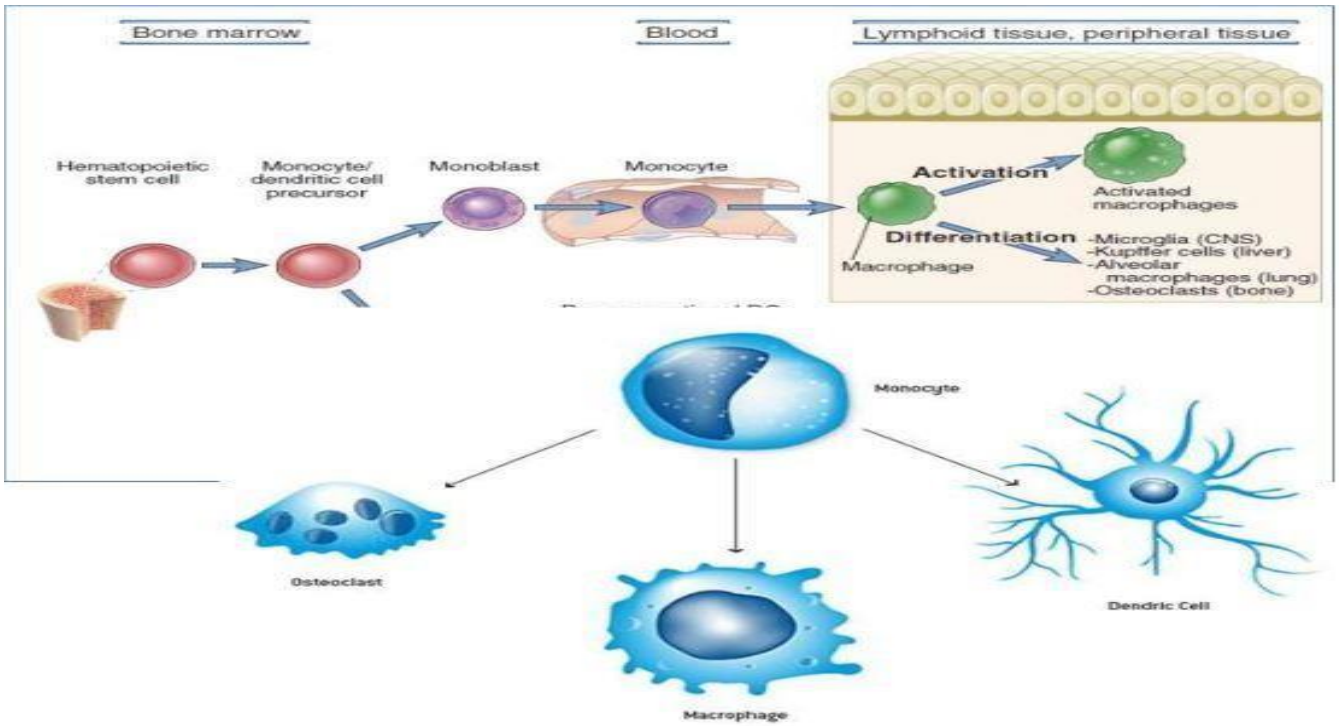




In this picture, the red substance is the bacteria, and the blue one is the neutrophil (the stain for the DNA is blue), so we note that some of neutrophils don't make anything (small blue substance) and the DNA is still inside the nucleus , but in middle of the picture, there is a big blue stain which indicate that the DNA gets out the nucleus and trapes many red stained bacteria, and this means the activation of the NETs in this cell.

Now let's talk about the second phagocyte which is the **macrophage.**

Macrophage comes from the monocyte which is circulating in the blood, and when the monocyte enters the tissue, it will differentiate into either macrophage or dendritic cell which is antigen-presenting cell.



Macrophage:

It has an important role in the hemostasis. Subtle differences in the morphology and function of macrophages develop as result of the influence of a particular microenvironment on a particular monocyte, and these differences have given rise to the use of tissue-specific names. Macrophages that develop in the liver, sinusoids, kidney, brain, connective tissues, or bone are known, respectively, as Kupffer cells, mesangial phagocytes, microglial cells, histiocytes, or osteoclasts.

•Once monocytes enter the tissues, they mature and become macrophages. Macrophages in different tissues have been given special names to designate specific locations.

Sometimes the monocyte follows the infection signal and goes there fast and becomes **Activated Macrophage**, then it makes the immune response.

⇨ **macrophages have many functions:**

•In addition to ingesting microbes, macrophages also ingest dead host cells as part of the cleaning up process after infection or sterile tissue injury.

•Activated macrophages secrete proteins, called cytokines, that bind to signaling receptors on other cells and thereby instruct those cells to respond in ways that contribute to host defense. These cytokines are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis (the formation of blood cellular components).

•Macrophages serve as APCs that display antigens to and activate T lymphocytes.

•Another important function of macrophages is to promote repair of damaged tissues by stimulating new blood vessel growth (angiogenesis) and synthesis of collagen-rich extracellular matrix (fibrosis).

- ❖ Macrophage-like cells are phylogenetically the oldest mediators of innate immunity.
- ❖ Drosophila (fruit fly) has cells that are similar to the macrophages, it has innate immunity similar to us, and these cells are called **hemocytes.**

How do the macrophages organize their functions? Sometimes they kill the bacteria and make phagocytosis, and in another time, they release cytokine and regulate an immune response!!

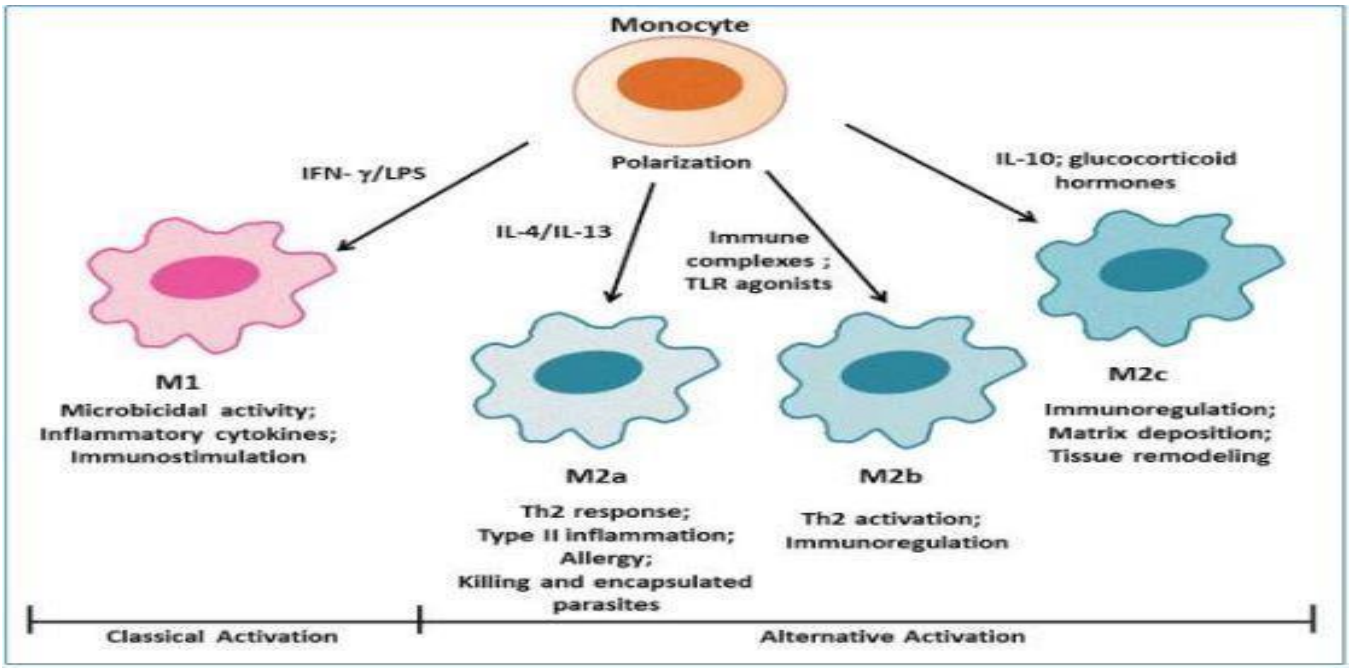
It seems that the monocyte when it reachs the tissue, depending on the environment and cytokines that it finds, it makes the suitable response.

When the monocyte reaches the tissue:

- ⇨ If it finds microbes or interferon gamma (**IFNγ**) or LPS, it will differentiate into M1 which has a microbicidal activity and secrete inflammatory cytokines to stimulate the immune response, and this is called **classical activation** of the macrophage ⟹ **Immunostimulation**.

- ⇨ If the inflammation already took place, it will differentiate to M2, and produce proteins that are responsible for **immunoregulation** rather than immunostimulation.

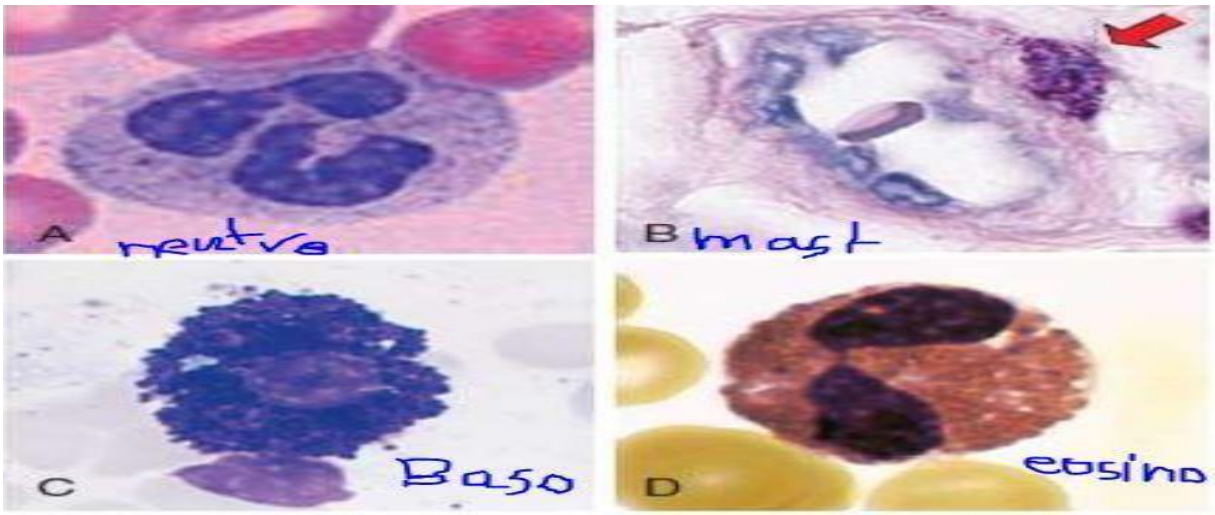
- ⇨ In some cases, the monocyte reaches the tissue after the injury, but there isn't an evidence of virus existence or **IFNγ, then the environment will polarize the monocyte to become an immune regulatory macrophage that helps in matrix deposition and tissue remodeling.** So, macrophages can acquire distinct functional capabilities, depending on the types of activating stimuli.



Now let's talk about the second group of cells:

2) Mast Cells, Basophils, Eosinophils: common feature of these cells is their involvement in immune responses that protect against helminths and immune responses that cause allergic diseases.

- ⇨ The most important one is the mast cell, basophils and eosinophils don't have important role in the immune response, and their percentage in the blood is less than 1%, and they aren't related mainly to immune diseases.



⇨

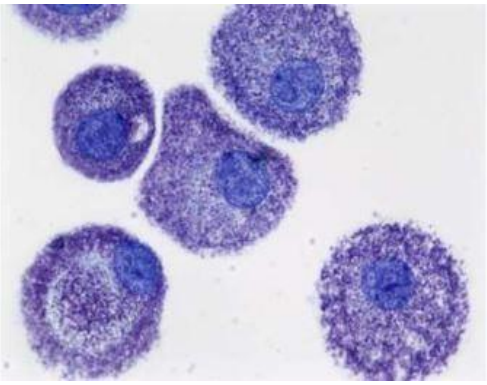
Mast cell:

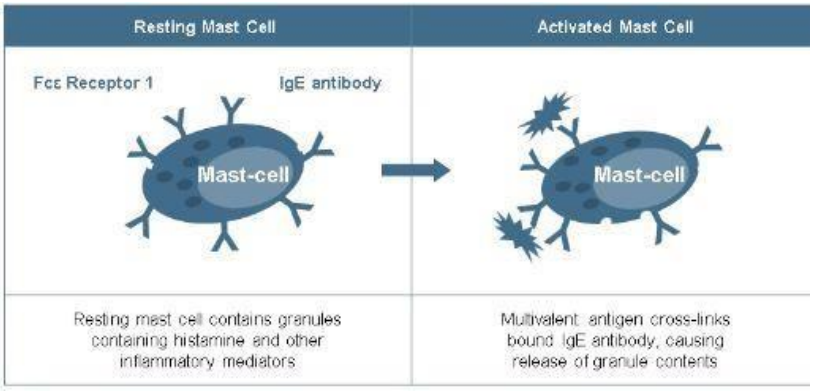
Mast cells are bone marrow–derived cells that are present in the skin and mucosal epithelium and contain abundant cytoplasmic granules filled with cytokines histamine, and other mediators.

•Mature mast cells are not found in the circulation, but they are constitutively present in healthy tissues, usually adjacent to **small blood vessels and nerves**. So, the mast cell mostly found in the tissues especially in the site of the allergy, because these cells contain granules that is filled with cytokines **histamine**.

•Mast cells express plasma membrane receptors for **IgE and IgG** antibodies and are usually coated with these antibodies.

- ⇨ **Briefly**: the antigen (**allergen**) binds to the antibodies in mast cell surface activating it, then the mast cell releases the contents of the granules like histamine, producing allergy.





•**Basophils** are blood granulocytes with many structural and functional similarities to mast cells.

•Like mast cells, basophils express IgG and IgE receptors, bind IgE, and can be triggered by antigen binding to the IgE.

•Basophils constitute less than 1% of blood leukocytes, normally not present in tissues and their importance is uncertain.

•**Eosinophils** are blood granulocytes that express cytoplasmic granules containing enzymes that are harmful to the cell walls of parasites but can also damage host tissues.
But in these days, our exposure to parasites has been reduced so that make the eosinophils less important.

•**Several lines of evidence suggest that deficiency of eosinophils is not associated with any characteristic abnormality.**

GOOD LUCK