Hematology

HISTOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number: **2**

Subject: **WBCs and hematopoiesis**

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Price:

Last lecture we talked about Neutrophils ; their structure and their role in Inflammatory response. In this sheet we will:

- ☑ Finish neutrophils
- ☑ Talk about Eosinophils
- ☑ Talk about basophils
- ☑ Talk about monocytes
- ☑ Talk about lymphocytes
- ☑ Start hematopoiesis

Functional compartments of neutrophils

Here we are talking about neutrophils kinetic-wise (their synthesis, storage, release..) and it is REALLY important to know these things as Tight regulation of these cells is vital.

The function compartments of neutrophils present at :

1) Bone marrow : where the **synthesis** and **storage** of neutrophils occur.
2) Blood (vessels) :where the neutrophils are **released**or **marginated** (hanged at the walls of the vessels)

Now what are these compartments (figure1)
at the bone marrow:

1) Granulopoietic compartment:
   this compartment subdivide into:

   ⟶**Mitotic compartment**

   here cells undergo mitosis -they simply **divide-.**
   the steps of their divisions will be discussed in further details later, but here is the big picture
   red bone marrow contains stem cells that can differentiate into many types of cells including neutrophils
   so from stem cells we can yield neutrophils by mitosis and differentiation.

what happen in this compartment(arrows represent successive division) :
[stem cells → Myeloblast → promyelocyte →myelocyte]
these cells are considered early precursors of neutrophils>>they need to mature.

⟶Maturing compartment

what happen here is nothing but further divisions, but now into mature cells –in this compartment mature neutrophils are yielded.
[metamelyocyte → Band cells→ mature granulocyte "neutrophil"]

2) Storage compartment
this compartment act as a buffer system, capable of releasing large no. of neutrophils when needed (ex: infections)

Now compartments present at the blood vessels

3) Circulating compartment
here the neutrophils circulate throughout the blood

4) Marginating compartment
this compartment represent neutrophils that temporary do not circulate but adhere to the wall of blood vessels (particularly at the lung)

three important notes :

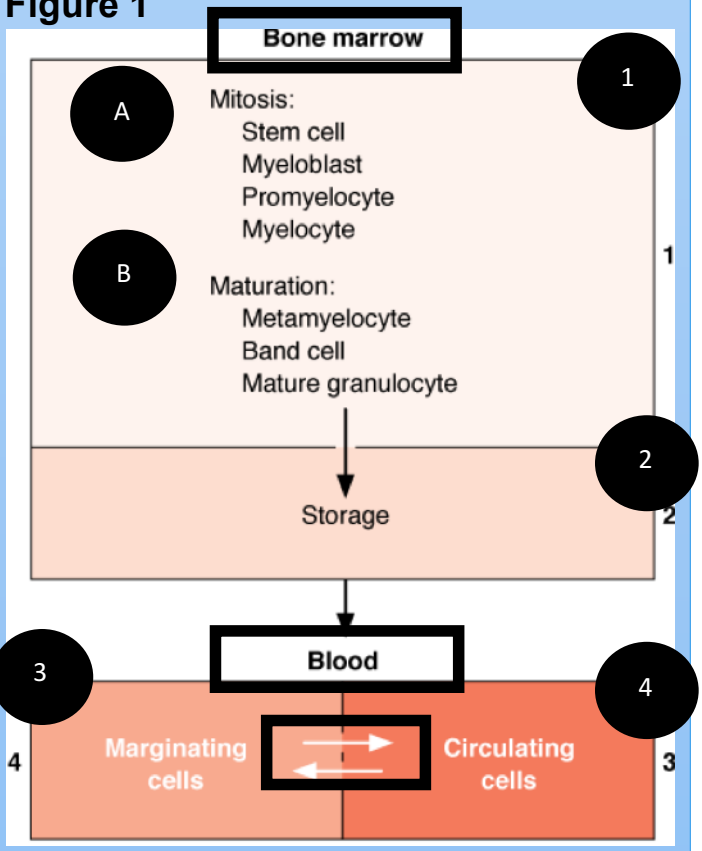
- ✓ The circulating compartment and the adherent compartment are of equal size and they frequently exchange their content of neutrophils.
- ✓ When we say "bone marrow" in this context we actually mean Red bone marrow, which is capable of producing blood cells.
  It is not present at the shaft of long bones in adults but at the sternum ,vault of the skull, ribs, hip, vertebral column (spine) and proximal end of femur. In children it's present more even in long bone shafts.
  but in adults the shafts contain yellow bone marrow which is fat.

these two clinical applications are related to the two previous notes respectively:

- ✓ **Neutrophilia**: the number of neutrophils is increased.
  now neutrophilia can be (apparent and real) these two differ in the cause, the mechanism & the duration.
  Apparent Neutrophilia: happened after intense muscular activity or injection with epinephrine.This will increase the no. of neutrophils due to a shift from marginating compartment into circulating compartment.It will last for few hours.
  Real Neutrophilia: this occur after acute infection (bacterial). Here the increase in neutrophil no. is due to an increase in the production. Lasts longer. Immature (like band cells and sometimes even metamyelocytes) cells may also appear.

- ✓ The bone marrow of shafts of long bones in adults may turn from yellow into red in case there is a high demand for blood cells, like in hypoxia, and sever bleeding.

Figure 1



1:Granulopoietic compartment , A: Mitotic compartment ,B : Maturating compartment
2: storage compartment
3:circulating compartment, 4: Marginating compartment
notice how 1 and 2 are present at the bone marrow while 3 and 4 at the blood.
also notice the dynamic equilibrium between 3 & 4.

Final notes with regard to neutrophils:

- ✓ Glucocorticoids increase the mitotic activity of neutrophils precursors this increase neutrophils count.

- ✓ Put in your mind immature neutrophils (like band cells) may normally appear in the circulating blood in bacterial infection (bronchitis and pneumonia)>> they do not always indicate leukemia.
- ✓ To diagnose leukemia :
  - Neutrophils count must be high
  -**Early** precursors of neutrophils appear in the blood film, this must be correlated with clinical history to confirm leukemia.
  -History of fever, anemia, fatigue... more details later.

  So do not hurry to leukemia in case you see immature cells at the blood film it could be just a bacterial infection (mostly severe infections).

Eosinophils

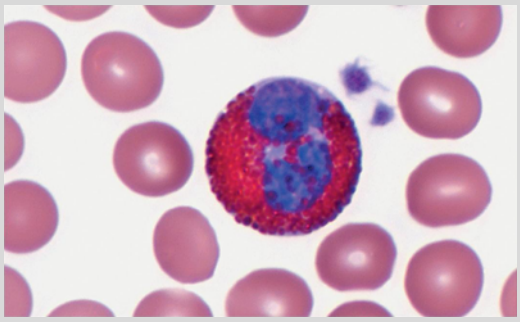
- ✓ Low in number (1-6% of leukocytes)
- ✓ Their count undergoes diurnal variation (differ from day to night) *greatest at morning least at night
- ✓ Size: their diameter is 12-17 micrometer (double size the RBCs and larger than neutrophils)
- ✓ Nucleus: bi-lobed, the presence of large granules make the nucleus hardly seen. See figure2
- ✓ Specific granules: appear bright red, these are simply lysosomes their central part is called crystalloid and it contains hydrolytic enzymes (most important histaminases 'hydrolyzes histamine')

Histamine is secreted from basophils and mast cells.
Our body need histamine but in low amount >>it dilate vessels>>delivery of blood to site of infection↑
in case of allergy
histamine is secreted in large doses >> generalized vasodilation >>hypotension>>anaphylactic shock

- ✓ Eosinophils do not have considerable bactericidal effect as the cells do not contain phagocytin nor lysozyme (which are present in neutrophils) >> limited bacteriocidal effect.
- ✓ As both neutrophils and eosinophils have peroxidases (figure 4 shows their granules)
  per cell, the amount of peroxidase in eosinophils is higher than that present in neutrophils, but since neutrophil count is higher (40-75% of leukocytes) this makes the overall content of peroxidase in neutrophils higher than eosinophils.
  [overall content= no. of cells * amount present at each cell]
  *presence of peroxidase in eosinophils gives it some bactericidal effect.
- ✓ Eosinophils have phagocytic activity. They can phagocytose antigen-antibody complex, by this they can stop histamine release, how?
  histamine is released from its granules at mast cells or basophils by a process called degranulation which occurs when an antigen binds to antibodies that are present at the surface of these cells.
  *the binding of antigen cross link two antibodies 'make a bridge'
  [antigen: AB = 1:2] figure3
  so eosinophils phagocytose this antigen-antibody complex and inhibit the degranulation of these cells and histamine release.

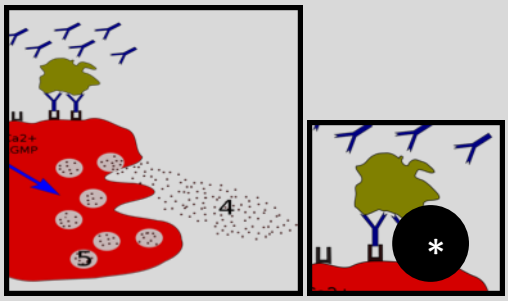
- ✓ All eosinophils have receptors for IgE >> important for destruction of parasites (this is not present at neutrophils)

Figure 2 [Eosinophil]



notice the bi-lobed nuclease and the light red granules, also notice its size (comparing to RBCs)

Figure 3



degranulation of basophil release histamine.
notice (*) how one antigen binds two Abs (bridge) this complex is phagocytosed by eosinophils.

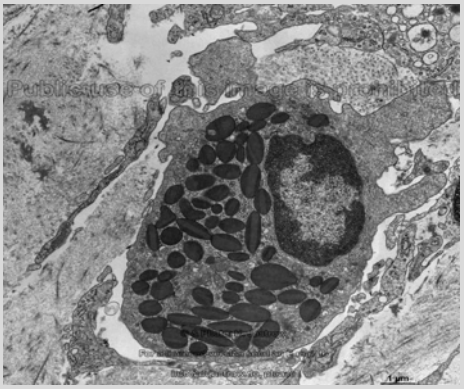
*Note: Antibodies are secreted from plasma cells and allergy is treated by antihistamines medications.

- ✓ To attract cells to the site of their action we need **chemotactic** agents. For eosinophils these are: histamine and eosinophil chemotactic factor of anaphylaxis (both are secreted from mast cells and basophils), but why these particular substance attract eosinophils?
  simply, eosinophils secret **histaminase** that can degrade excessive histamine released by basophils. And it secrets another factor called **eosinophil derived inhibitor,** this factor inhibits degranulation of mast cells thus inhibits the releasing of its content >> By this eosinophils reduce hypersensitivity.

Eosinophilia

- ✓ Increased number of eosinophils.
- ✓ Occurs in allergy and parasitic infections (ex: malarial infection)

Figure 4



EM shows eosinophils, notice the granules (these contain peroxidases)

Basophils

- ✓ Least common leukocytes (less than 1%) (figure5)
  note in differential count we might not see basophils.
- ✓ 14-16 micrometer in diameter
- ✓ Nuclease: bi-lobed
- ✓ Granules: deep blue (they are fewer but larger than those in eosinophils)
  Note: in the exam the pictures will be in black and white so you won't be able to differentiate between eosinophils and basophils depending on the color of their granules (red, blue respectively) instead we depend on the granules size (small, larger respectively) which subsequently affects the degree to which the nucleus is obscured.

  These granules are said to be metachromatic as they contain proteoglycans.
- ✓ This cell contains histamine, heparin (anticoagulant) & eosinophils chemotactic factor of anaphylaxis (ECFA)
  why is heparin needed?
- ✓ Certain types of bacteria induce some blood clotting<< heparin resolves this.

Metachromaticity from wiki : is a characteristic change in the color of staining carried out in biological tissues, exhibited by certain dyes when they bind to particular substances present in these tissues, called chromotropes.

so basophils are said to be metachromatic because we dye them with a red dye but they appear blue. (mast cells have the same characteristic)

Another characteristic that basophils share with mast cells is the presence of IgE receptors at their surfaces>> these receive IgE>> one antigen binds two IgEs (bridge) >>this stimulate degranulation and histamine release from these cells.

Basophils (along with mast cells) are responsible for allergic reactions called **Immediate hypersensitivity** this appears in:

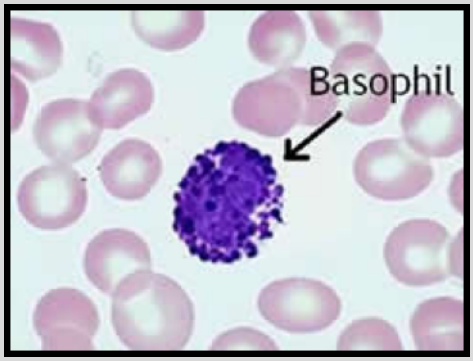
- ✓ Hay fever (allergic rhinitis : running nose all the time)
- ✓ Asthma
- ✓ urticaria (itchy skin rash)
- ✓ anaphylactic shock
- ✓ basophils account for 15% of infiltrating cells in allergic dermatitis (cutaneous basophils hypersensitivity)

.

- ✓ Smallest of leukocytes (just slightly larger than RBCs) (figure 6)
- ✓ Account for 20-25% of leukocytes (second most common after neutrophils)
- ✓ Easy to identify
- ✓ Nuclease: large round nucleus, densely stained (blue)
- ✓ Cytoplasm: relatively small, basophilic non-granular (have blue dots these are ribosomes)
- ✓ If Lymphocytosis (increase in number of lymphocytes) occurred >> the simplest guess is viral infection.
- ✓ Lymphocytes are of 2 types : B & T
- ✓ When observing a blood film most of the lymphocytes that can be identified will be small, just 3% will be large >> what is the difference between small and large lymphocytes?
  the large ones are said to **activated** and most likely these are activated B lymphocytes .
  [activated B lymphocytes= B lymphocytes become activated after interactions with specific antigens, then they become plasma cells and secret antibodies]
  in these activated cells the cytoplasm becomes visible, while in small lymphocytes the cytoplasm is hardly seen.

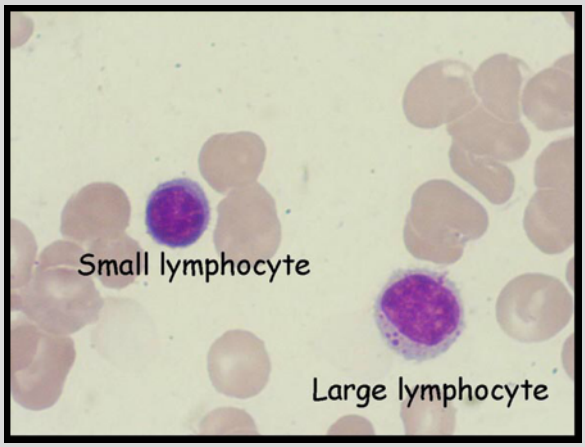
B lymphocytes induce **antibody- mediated immune** rxn (they send Abs to kill bacteria)
T lymphocytes induce **cell- mediated immune** rxn , one type of T lymphocytes is cytotoxic T lymphocyte these (by themselves) travel from lymphatic organs to the affected place and kill bac. By lympho toxins (some are called perforins بتخزق جدار الخلية)
AB-mediated immune rxn is derived against bacterial infection (mostly), when cell mediated immune rxn is derived against viral infections and tumor cells (things that change cells from inside)
Note: we can not differentiate between T & B cells by just looking at the blood film, we need special markers.

Figure 5 [basophils]



notice its basophilic large granules

Figure 6 [lymphocytes]



large nucleus& cytoplasm
notice the ratio between the nucleus size and the cytoplasm in large and small lymphocytes. Also notice that the small lymphocytes have the same size as RBCs.

Monocytes

- ✓ The largest WBCs. (20 micrometer) (figure7)
- ✓ 2-10% of leukocytes
- ✓ Nucleus: large, eccentric (at the periphery of the cell), the nucleus have deep indentation (invagination) & 2-3 nucleoli.
- ✓ Cytoplasm: stain light blue and contain pink lysosomal granules (contain peroxidase and acid phosphatase >>these can kill the Bacteria)
- ✓ Monocytes are the precursor of most macrophages.

What is the difference between monocytes and macrophages?

monocyte circulates in the blood where macrophage (most likely) is a differentiated monocyte present at tissues that preform the action of phagocytosis.

How monocytes are stimulated to differentiate into macrophages?

by certain factors that attract macrophages, which are:
-chemotaxis (invading microorganism)
-necrotaxis (presence of necrotic materials)
-Inflammation

What is the main change that occurs to monocyte to become macrophage?

increase in its content of lysosomes.

Single functional unit theory (monocyte- macrophage system) :
this describe the differention of monocyte (blood) into different types of Macrophages in different peripheral tissues.
this means that the same monocyte can give rise to:
- Kupffer cells (macrophages of the liver)
-microglial (macrophages of CNS)
-Langerhans cells (macrophages of the skin)
-osteoclast (of bones)
-antigen presenting cells of lymphoid organs. (Discussed in lec4)

Note this system does not discuss the phagocytic cells that do not originate from monocytes like those of: Vascular-Endothelial system, some reticulocytes and some fibroblasts of lymphoid organs >> all of these exhibit phagocytic activity but are not part of this system.

There are cells called multinucleated giant cells, these are nothing but a union of multiple macrophages.

Functions of Monocytes:

Manifested by the functions of macrophages into which they differentiate in tissues (they have minimal functions in blood) :

- ✓ Phagocytosis (of necrotic or inflamed tissue)
- ✓ Antigen presenting.
- ✓

Figure7 [Monocyte]

notice the large eccentric nuclease with indentation, notice its size.

Hematopoiesis

- ✓ This is the process of formation of blood cells in Human.

Prenatally, Hematopoiesis occurs in 3 phases:

1) Mesoblastic phase :
   - in the mesoderm yolk sac during (2^{nd} – 6^{th}) weeks of pregnancy
2) Hepatic phase: occurs in liver, and spleen also plays a role. (in the second trimester of pregnancy)
3) Myeloid phase (in red bone marrow) starts at the beginning of the 3^{rd} trimester

Postnatally: occurs exclusively in red bone marrow.

lets repeat this note:

in a newborne where does the red bone marrow exist ? nearly all bones
in adults where does the red bone marrow exist ? just in the sternum, ribs, pelvis, proximal end of femur and vertebrae (spine)

Clinical correlation:

a lot of tumors metastasize to spine so when they treat these with radiotherapy (or chemotherapy) there is a high chance to disturb their role in hematopoiesis specially if the dose was toxic.

what is the origin of blood cells ?
stem cells present at the red bone marrow. These stem cells are said to be multipotential , which means that they have the ability to differentiate into many progenitor cells and consequently produce all blood cell types.
there are 2 main linage of this process :

- ✓ Lymphoid >>ends by producing lymphocytes
- ✓ Myeloid>> ends by producing granulocytes, monocytes, erthryocytes and megakaryocytes (precursor of platelets).

Clinical correlation :

leukemia is classified as lymphoid or Myeloid according to the origin of the involved cells.

Final note:
synthesis of blood cells requires many cofactors, for example RBCs require erythropoietin, folic acid, vitamin B12, iron and protiens…
Note: erythropoietin is a kidney protein>>so if the patient has renal failure they will be anemic.

END OF TEXT :3