BONE MARROW AND HEMATOPOIESIS

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HEMATOPOIESIS

The process of producing blood cells i.e. RBCs, WBCs and platelets.

The cells responsible for hematopoiesis begins to appear in embryonic period in the yolksac around 3rd week of gestation. These cells are called hematopoietic stem cells.

STEM CELLS

Stem cells are special human cells that are able to develop into many different cell types. This can range from muscle cells to brain cells. In some cases, they can also fix damaged tissues.

Whenever stem cells multiply, some of the cells will develop into differentiated cells while others will maintain their own population, hence have a property of self-renewal.

HEMATOPOIETIC STEM CELLS

The hematopoietic stem cells initially appear in yolk sac but they also develop in mesoderm of aorta, mesoderm of gonads and mesoderm of mesonephron. These stem cells eventually transfer to the liver of fetus around 3rd month. Some stem cells move to spleen and lymph nodes.

STEM CELLS IN BONE MARROW

Just before birth, hematopoietic activity in liver stops. This is because somewhere around 4th month of fetal life, the stem cells start migrating from liver, spleen and lymph nodes to bone marrow. By the time baby is born, all hematopoietic activity is carried out by bone marrow.

Bone marrow is of two types:

a) **Red bone marrow** which is the active and highly vascular bone marrow. In new born baby, all born marrow is red bone marrow. Red bone marrow remains active only in membranous bones. Upto puberty, almost all bone marrow is red. After puberty, hematopoiesis stops in long and peripheral bones. Around age 18 or 20, hematopoiesis is limited to axial skeleton and proximal ends of humerus and femur.
b) **Yellow bone marrow** which is inactive due to large number of fat cells and less hematopoietic cells. After puberty, the bone marrow other than axial skeleton and proximal ends of humerus and femur is of yellow marrow type.
If there is need of excessive hematopoietic activity, yellow bone marrow has the capacity to be re-activated and converted into red bone marrow.

Bone marrow is one of the largest organs of body and its size and weight is equal to liver.

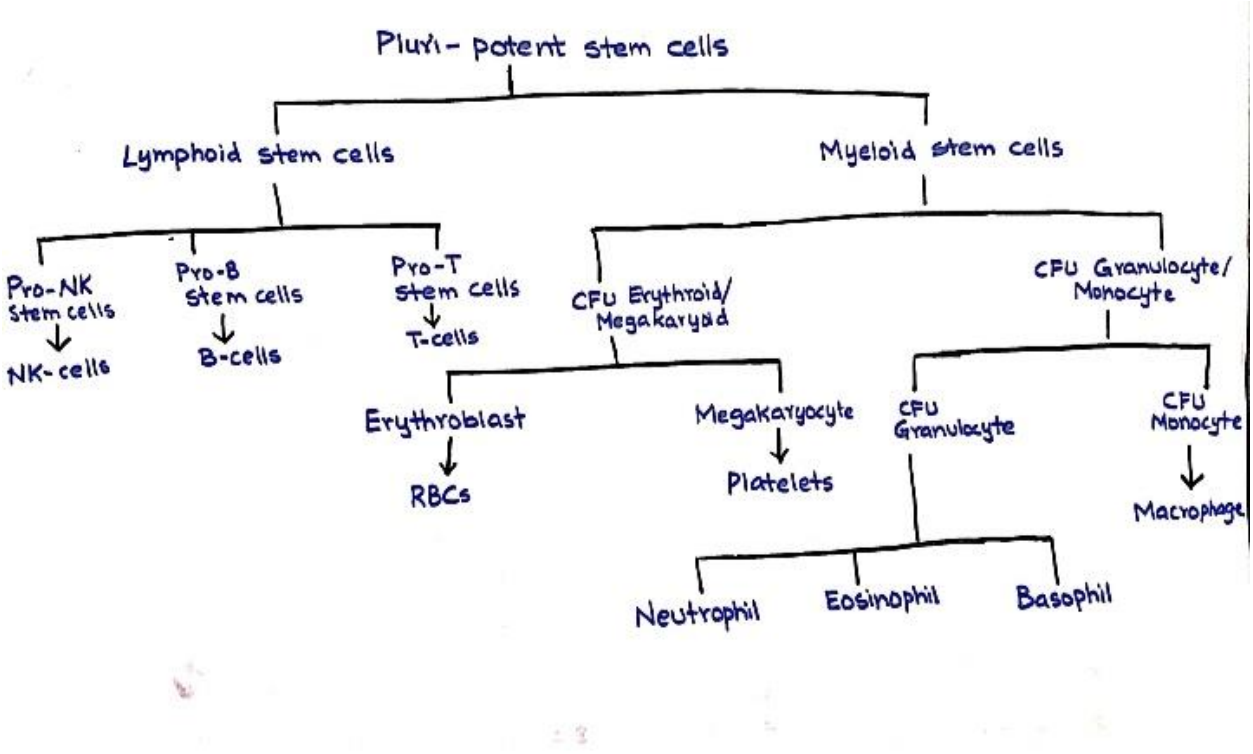
HAIR-ON-END APPEARANCE

Hair-on-end appearance of skull is a radiologic appearance of skull which is a characteristic feature of chronic hemolysis usually seen in patients with thalassemia and sickle cell anemia.

HEMATOPOIESIS

During RBC development, the Proerythroblast undergoes

1. Size maturation (size decrease progressively)
2. Nuclear maturation (from euchromatin to heterochromatin to complete loss of nucleus)
3. Cytoplasmic maturation (progressive synthesis of Hb)



PLURI-POTENT STEM CELLS

Hematopoiesis begins with **pluri-potent stem cells.**

Pluri-potent stem cells differentiate into **multipotent stem cells** which are

1. Common lymphoid stem cells
2. Common Myeloid stem cells

(All the bone marrow and blood cells other than lymphoid cells are called myeloid cells)

1. COMMON LYMPHOID STEM CELLS

The common lymphoid stem cells are further divided into three committed stem cells. These are:

1. Pro-NK stem cells
2. Pro-T stem cells
3. Pro-B stem cells

PRO-NK STEM CELLS

The pro-NK stem cells move to peripheral circulation and develops into NK cells.

PRO-T STEM CELLS

The pro-T stem cells move towards thymus for maturation and after maturity move to peripheral circulation and are called T-lymphocytes. All mature T-lymphocytes have CD3+ on surface. Along with CD3+ some T-cells may have CD4+ while others may have CD8+

T-cells are of two types:

1. Helper T-cells (having CD4+)
2. Cytotoxic T-cells (having CD8+)

Helper T-cells are further divided into two types:

1. **T-Helper 2 (T_{H2})**

T_{H2} stimulate B cells and convert B cells into plasma cells. T_{H2} release interleukin 4 and interleukin 5.

Interleukin 4 acts as B-cell growth factor.

Interleukin 5 acts as B-cell differentiation factor

2. **T-Helper 1 (T_{H1})**

T_{H1} convert monocytes into highly active macrophages. T_{H1} release interferon gamma and tumor necrotic factor.

T_{H2} helps in humoral immunity while T_{H1} assist cellular immunity.

PRO-B CELLS

Pro-B cells when acted upon by T_{H2}, convert into plasma cells to produce antibodies.

2. COMMON MYELOID STEM CELLS

Myeloid stem cells divide into three types of committed stem cells:

1. Colony forming unit (CFU) Erythroid/Megakaryoid/basophilic stem cells
2. CFU Granulocyte/ Monocyte
3. CFU Eosinophils

CFU Erythroid/Megakaryoid/basophilic stem cells

These stem cells will give rise to erythroblast, megakaryoblast and basoblast.

Erythroblast move to peripheral circulation where they convert into fresh RBCs known as Reticulocyte and eventually into mature RBCs.

The **megakaryoid cells** will produce platelets.

Basophilic stem cells gives rise to basophils. Basophils resemble mast cells. Basophils have protein receptors on their cell surface that bind IgE, an immunoglobulin involved in macroparasite defense and allergy.

Basophils are similar in both function and appearance to **mast cells**. The difference is that mast cells are released from bone marrow while basophils are derived from myeloid stem cells.

CFU GRANULOCYTE/MONOCYTE

Granulocytes are precursor cells which produce myeloblast which convert into **neutrophil**.

CFU Monocyte produce monoblast which will convert into monocytes.

Monocytes when move to tissues are called macrophages.

When monocytes move to an inflammated tissue, it is called **inflammatory macrophage.**

Some monocytes shift to CNS during early phase of development and these monocytes become permanent residents of CNS and are called **microglea.**

Macrophages of liver are called **Kupfer cells**.

Macrophages present in alveoli are called **alveolar macrophages**.

Macrophages of spleen and lymph nodes are called **Dendritic cells.**

Kidney macrophages are called **Mesengeal cell**.

Macrophages of bone are called **osteoclasts.**

CFU EOSINOPHILS

CFU eiosiniphils produce eiosinoblast which will eventually produce eosinophils.

APLASTIC ANEMIA

A condition that occurs when the pluripotent stem cells or multipotent stem cells donot multiply well (i.e. hypoproliferation) due to which body stops producing enough blood cells. The condition leaves you fatigued and more prone to infections and uncontrolled bleeding.

LEUKEMIA

Leukemia results from over-proliferation of stem cells. Leukemia is a blood cancer caused by a rise in the number of WBCs in the body.

STROMAL CELLS

Bone marrow has a lot of stromal cells which helps in concentrating soluble growth factors thereby influencing stem cells proliferation i.e. these stromal cells support the hematopoietic process. The stromal cells have cell-to-cell interactions with hematopoietic cells which direct their proliferation.

SOLUBLE GROWTH FACTORS

Certain soluble growth factors are available commercially including erythropoietin, thrombopoietin, granulocyte/monocyte colony stimulating factor.

ERYTHROPOIETIN

Erythropoietin is produced mainly by kidneys. In chronic renal failure, patient becomes severely deficient in erythropoietin. Due to this deficiency, erythropoiesis slows down and person develops anemia. In chronic renal failure, erythropoietin injections are given.

THROMBOPOIETIN

It is a soluble factor which stimulates the production and differentiation of megakaryotes, which are the bone marrow cells producing platelets.

HOMING

Homing is the process whereby bone marrow cells including stem cells, progenitor cells and differentiated cells, find their way into the bone marrow after being injected into the blood stream.

HEMANGOBLAST

Under certain cicumstances, bone marrow stem cells can be induced to produced hemangoblast. Hemangoblasts are the multipotent precursor cells that can differentiate into both hematopoietic and endothelial cells.

SINUSOID NETWORKS IN BONE MARROW

Single layer of endothelial cells lines sinusoid networks in bone marrow. These endothelial cells are coated by basement membrane. This basement membrane is discontinuous at many points.

INTERSTITIUM OF BONE

The spaces between sinusoids is called interstitium of bone marrow. The stem cells are present in the interstitium. The mature cells pass through the endothelial cells from the interstitium to the sinusoids and this movement is called trans-cellular migration.

PLATELET PRODUCTION

The large megakaryoblast present in interstitium have finger-like processes which extend into the sinusoids. When blood flows rapidly through sinusoids, the finger-like processes breaks away and converts into platelets which move to the blood.

ERYTHROPOIESIS

Erythroblast in the interstitium goes through developmental changes. Their size decrease, the nucleus condenses and eventually disappears. Total erythropoiesis process takes about 1 week under strong influence of erythropoietin.

Erythropoietin is produced in endothelial cells of peritubular capillaries of kidneys. Endothelial cells of peritubular capillaries have the capability to monitor the oxygen in blood. If partial pressure of oxygen is low, endothelial cells will start synthesizing and releasing erythropoietin which will move to bone marrow to accelerate erythropoiesis and increased production of RBCs take place thereby increasing oxygen carrying capacity of blood.

Development of Erythroblasts

Proerythroblasts → Early basophilic normoblast → Intermediate normoblast → late normoblast → Reticulocyte → mature RBCs

Proerythroblast – large cell with fine chromatin nucleus (euchromatin) with basophilic cytoplasm (blue) and prominent nucleoli. Whenever cytoplasm is rich in mRNA and ribosomes, the cytoplasm will be blue-colored.

Early basophilic normoblast – smaller than proerythroblasts with more condensed chromatin and lower nuclear-cytoplasmic ratios. The cytoplasm is deep blue and a pale perinuclear halo may be present.

Intermediate normoblast (Polychromatophilic) – nucleus condenses, chromatin lumps and Hb starts appearing. Known as polychromatophilic due to the two colored cytoplasm, blue representing basophilic cytoplasm due to polysomes and red representing Hb.

Late Normoblast (Orthochromatic) - In the late normoblast stage, the chromatin is dark, dense, and clumped, ready to be extruded. Cytoplasm is like mature red cell, reflecting a high Hb content.

Reticulocyte – The nucleus leaves the cell and the newly formed cell is called reticulocyte. Normally reticulocyte percentage in blood is 1-2%

Mature Erythrocyte – Reticulocyte moves to sinusoids network and within 1-2 days, it develops into mature RBCs.

MEGALOBLASTIC ANEMIA

For nuclear maturation and condensation of erythroblast, **B12 and folic acid** are required. The deficiency of B12 and folic acid leads to uncondensed chromatin network even though hemoglobin is produced. This normoblast keeps producing hemoglobin in abnormally large quantities. This large, abnormally developed cell is called megaloblast. Most of these cells are destroyed within bone marrow, due to which RBC production is slowed down. So total RBCs in blood is reduced and this results in megaloblastic anemia.

For cytoplasmic maturation of erythroblast, iron is required. Hb cannot be produced without iron.

GRANULOPOIESIS

Myeloblast → Promyelocyte → Myelocytes → Immature Neutrophils → mature neutrophils

Granulopoiesis produces **65%** of bone marrow cells

Erythropoiesis produce **25%** of bone marrow cells

Lymphopoiesis produce **10%** of bone marrow cells

Myeloid-Erythroid ratio → **3:1**

BONE MARROW EXAMINATION

1. Bone marrow aspirations
2. Bone marrow biopsy

Bone marrow aspiration and bone marrow biopsy are procedures to collect and examine bone marrow. Bone marrow aspiration and bone marrow biopsy can show whether your bone marrow is healthy and making normal amounts of blood cells. Doctors use these procedures to diagnose and monitor blood and marrow diseases, including some cancers, as well as fevers of unknown origin

Bone marrow has a fluid portion and a more solid portion. In bone marrow aspiration, a needle is used to withdraw a sample of the fluid portion. In bone marrow biopsy, a needle is used to withdraw a sample of the solid portion.

AVERAGE LIFE SPAN OF BLOOD CELLS

RBCs – 120 days

Platelets – 7 to 8 days

Neutrophils – 24 to 48 hours (During inflammation, life span may reduce to 6-7 hours)