Hematopoiesis

It is from Greek meaning to make new blood, it refers to the formation of blood cellular components. All blood cellular components are highly specialized and can not divide.

Which organs are responsible for hematopoiesis?

It´s depend on the period of development, during fetal life (prenatal period):

1-Yolk sac (first trimester).

2-Liver and spleen (second trimester).

3-Bone marrow (third trimester).

After birth (postnatal period) blood cells forming by two main organs:

1- Myeloid tissues (bone marrow) (vertebra, sternum, skull, femur and ribs).
2- Lymphoid tissues (liver, spleen, lymph nodes, thymus and tonsils).

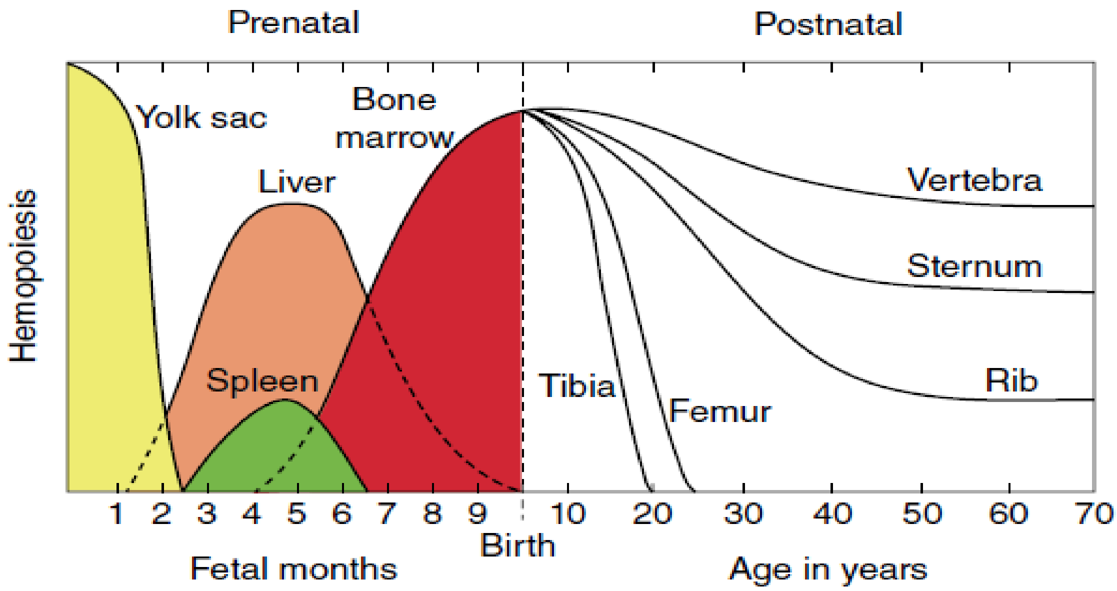


Figure 1 ***locations of hemopoiesis during development and aging***

During first seven years of human life bone marrow has red color because rich in erythroblast (cell forming RBC), in all bone cavities, after these years red bone marrow converted to yellow bone marrow in peripheral skeletons (contain fats and proteins). But in ribs, femur, skull and vertebra still red bone marrow, also when body lose blood and required more than erythrocytes, yellow marrow converted to red marrow for purpose.

In adults, the red bone marrow is located in flat bones (skull, ribs, sternum, pelvis, vertebrae) and ends of long bones, yellow bone marrow characteristic for adult long bones does not form blood but it stores fat.

Hemopoietic Stem Cells:

All blood cells are derived from a **pluripotential hemopoietic stem cell** in the bone marrow, these pluripotent stem cells are rare, proliferate slowly and give rise to two major lineages of progenitor cells, one for **lymphoid cells** (lymphocytes) and another for **myeloid cells,** that develop in bone marrow (figure 2).

Myeloid cells include granulocytes, monocytes, erythrocytes, and megakaryocytes, the lymphoid progenitor cells migrate from the bone marrow to the thymus or the lymph nodes, spleen, and other lymphoid structures, where they proliferate and differentiate.

Erythrocytes that formed by process called **erythropoiesis,** granulocytes formed by **granulopoiesis**, monocytes formed during **monocytopoiesis,** platelets continue to form from **thrombocytopoiesis** and lymphocytes produces by process called **lymphopoiesis**.

All these process regulation by several factors (figure 3).

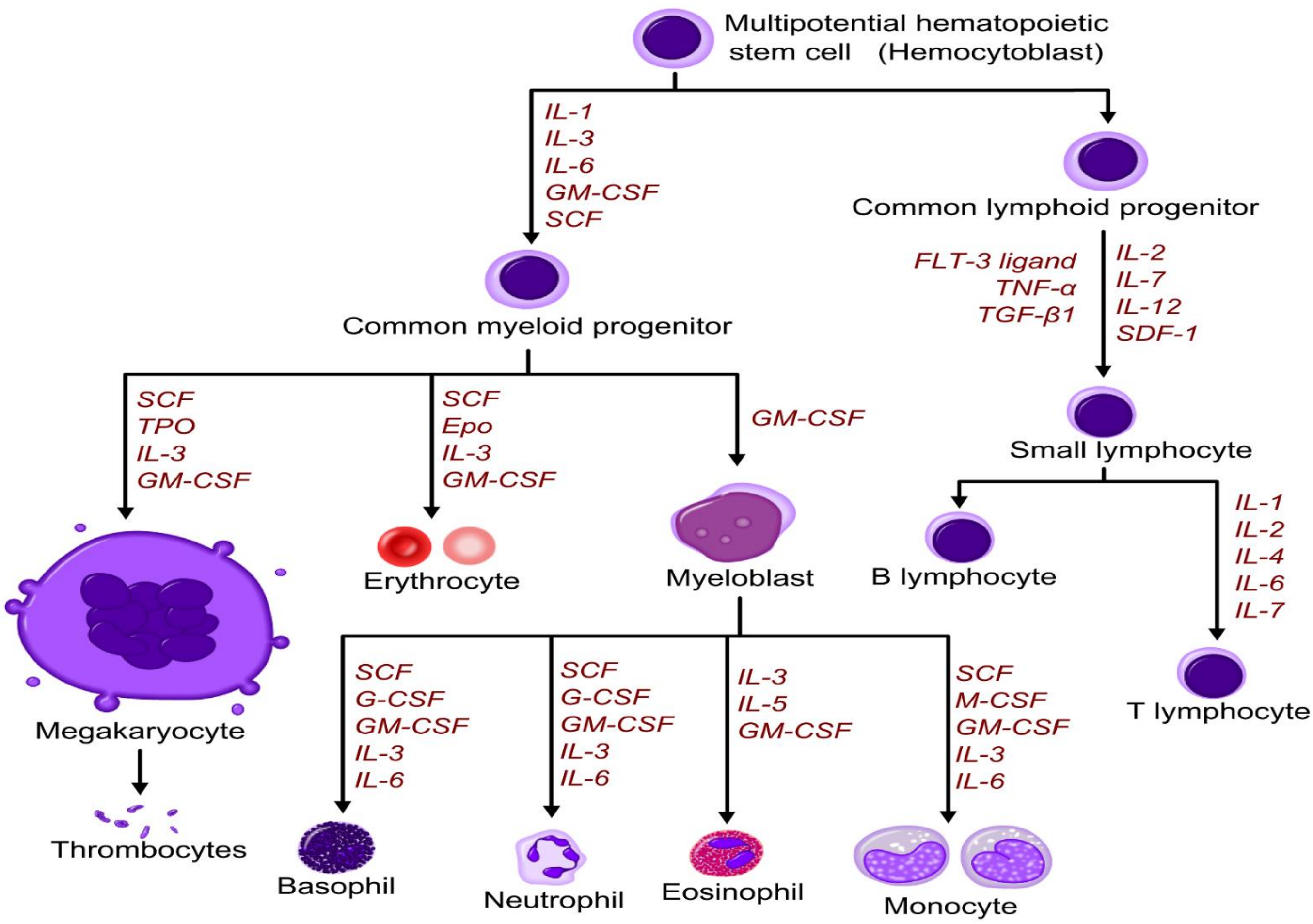


Figure2 ***Origin and differentiation stages of blood cells.***

Cytokine	Major Activities and Target Cells[a]	Important Sources
Stem cell factor (SCF)	Mitogen for all hemopoietic progenitor cells	Stromal cells of bone marrow
Erythropoietin (EPO)	Mitogen for all erythroid progenitor and precursor cells, also promoting their differentiation	Peritubular endothelial cells of the kidney; hepatocytes
Thrombopoietin (TPO)	Mitogen for megakaryoblasts and their progenitor cells	Kidney and liver
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Mitogen for all myeloid progenitor cells	Endothelial cells of bone marrow and T lymphocytes
Granulocyte colony-stimulating factor (G-CSF or filgrastim)	Mitogen for neutrophil precursor cells	Endothelial cells of bone marrow and macrophages
Monocyte colony-stimulating factor (M-CSF)	Mitogen for monocyte precursor cells	Endothelial cells of marrow and macrophages
Interleukin-1 (IL-1)	Regulates activities and cytokine secretion of many leukocytes and other cells	Macrophages and T helper cells
Interleukin-2 (IL-2)	Mitogen for activated T and B cells; promotes differentiation of NK cells	T helper cells
Interleukin-3 (IL-3)	Mitogen for all granulocyte and megakaryocyte progenitor cells	T helper cells
Interleukin-4 (IL-4)	Promotes development of basophils and mast cells and B-lymphocyte activation	T helper cells
Interleukin-5 (IL-5) or eosinophil differentiation factor (EDF)	Promotes development and activation of eosinophils	T helper cells
Interleukin-6 (IL-6)	Mitogen for many leukocytes; promotes activation of B cells and regulatory T cells	Macrophages, neutrophils, local endothelial cells
Interleukin-7 (IL-7)	Major mitogen for all lymphoid stem cells	Stromal cells of bone marrow

table 1 ***important factors regulated hematopoiesis***

Stromal cell-derived factor-1 (SDF-1), made by bone marrow (BM) stromal cells and is present in many other tissues. SDF-1 was initially identified as a potent chemoattractant for lymphocytes, monocytes, and as an enhancer of B cell proliferation.

Fms-related tyrosine kinase 3 ligand (**FLT-3**) is a protein structurally like stem cell factor (SCF), stimulates the proliferation and differentiation of various blood cell progenitors, and it was produced by bone marrow.

Transforming growth factor-beta (TG-F) can modulate and regulate bone marrow and thymic-derived cells throughout their functional life span.

Erythrocytes Red Blood Cell (RBC)

Vital component of blood that is made in the bone marrow and found in the blood, it contains a protein called hemoglobin, which carries oxygen from the lungs to all parts of the body. Checking the number of erythrocytes in the blood is usually part of a complete blood cell (CBC) test. It may be used to look for conditions such as anemia, dehydration, malnutrition, and leukemia. Also called RBC and red blood cell, that manufactured by **erythropoiesis** process.

Stages of erythrocyte formation:

The important stage of erythropoiesis is **Enucleation**, process by which the nucleus is extruded by budding off from the erythroblast, is unique to mammals. It has critical physiological and evolutionary significance in that it allows an elevation of hemoglobin levels in the blood and also gives red cells their flexible biconcave shape.

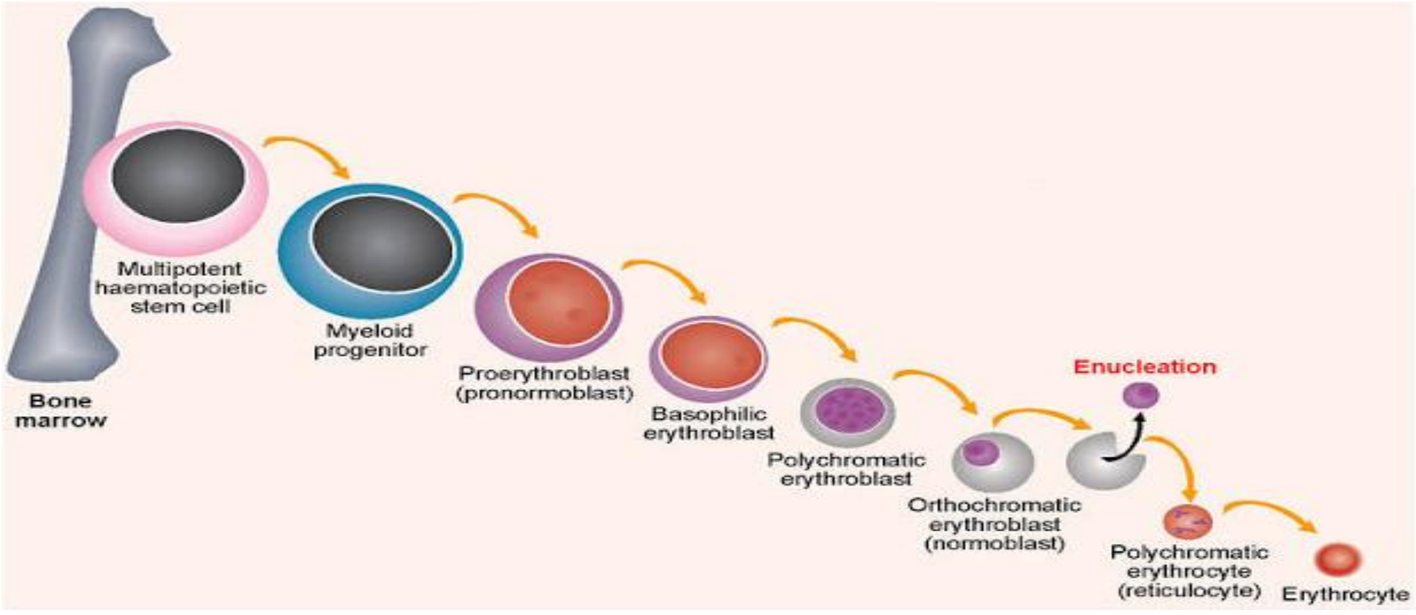


Figure 3 ***erythrocyte formation stages***

Erythrocyte features:

1- **Color:** when examined under microscope, it has **pale greenish yellow** without hemoglobin, but with hemoglobin that take **red** color.

2-Morphology: it has **biconcave** shape, **7.5 um** in diameter, thickness **2um** at the periphery and **1um** at the center, and **87um^3** in volume.

3-Elastcity: it has permeable membrane, allowed exchange of molecules such as K, Na, glucose and gases.

Advantages of Biconcave Shape of RBCs:

1-increase surface area for exchange of gases.

2-Flexibiltyof RBC during movement in blood vessels.

Notes/ RBC doesn't have ability to movement but it depends on plasma which transport RBC in blood vessels.

3-Minimal tension when the volume of cell alters.

Normal lifespan of RBC is **120 days**.

Normal RBC count:

Male: 5 – 5.5 million cells / mm^3

Female: 4.5 – 5 million cells / mm^3

Infants: 6 – 7 million cells / mm^3.

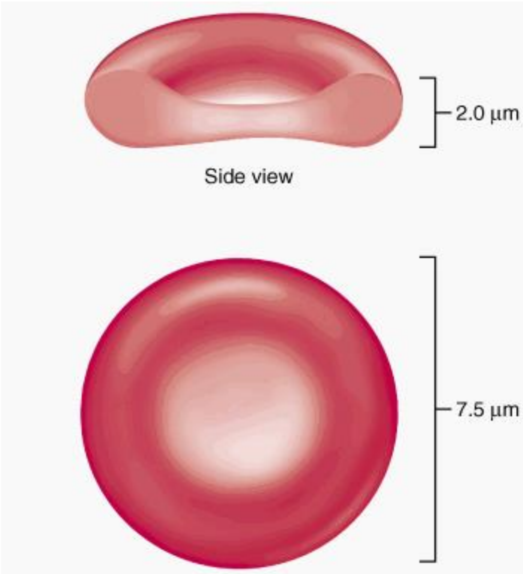


figure 4 *RBC dimension*

In several different disease causes changes in shape and number of RBC, such as sickle cell anemia and thalassemia (we will discus that later).

Erythrocyte membrane

Membrane compounds	function
A-Lipid bilayer	
1-Phospholipid	Important in selectively permeable
2-cholesterol	maintain the integrity and fluidity of cell membranes
3-glycolipid	on surface of RBC membrane to **form the ABO antigens**, and play a criti in blood transfusions.
B-Proteins integral proteins	
1-glycophorin	Imparts negative charge of rbc, and decrease interaction with other cells
2-band 3 protein	Exchanges bicarbonate for chloride (chlorine shift).
Peripheral proteins	
trophomyosin	Stabilize actin filaments
spectrin	Responsible for biconcave shape of RBC
actin	Protein-protein interactions
ankyrin	Join bind 3 protein and spectrin, to linkage cytoskeleton with bilayer
Protein 4.1	Stabilizes actin-spectrin interaction
Protein 4.2	Regulate attachment of band 3 protein with ankyrin
C-Cytoskeleton (Network of Microtubules)	**1**-modulating the shape of the cell, **2-**providing mechanical strength and integrity, **3**-enabling the movement of cells and facilitating transport of molecules.

Table 2 ***cell wall components of erythrocytes***

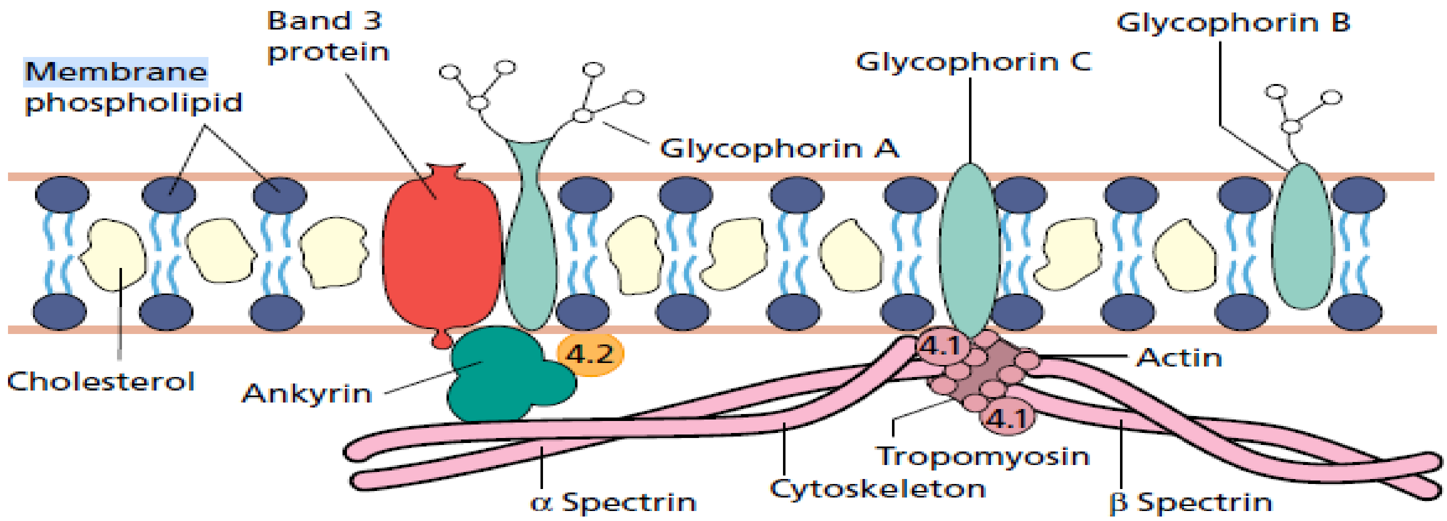


Figure 5 *components of RBC membrane*

Erythrocyte metabolism

A-Major pathway (Embden-Meyerhof pathway):

Because RBC lack mitochondria (lack Kreps cycle to produce energy), that depend on the anaerobic conversion of glucose by the **Embden-Meyerhof pathway** for the generation and storage of high-energy phosphates. Anaerobic glycolysis, one molecule of glucose yields **2 molecules of ATP**, in addition **2 molecules of lactate** are produced.

Moreover, erythrocytes have other unique glycolytic pathway for the production of **2,3-bisphosphoglycerate** (**2,3-DPG** -- storage energy compound of RBC), that called **Rapoport-Luebering shunt,** is a metabolic pathway in mature erythrocytes involving the formation of 2,3-bisphosphoglycerate (2,3-DPG), which regulates oxygen release from hemoglobin and delivery to tissues.

2-Minor pathway (Pentose Phosphate Pathway) PPP:

Minor alternative pathway for glucose oxidation called **pentose phosphate pathway,** that supplies NADPH in RBC, NADPH important in keeping reduced glutathione which have vital role for RBC survival (prevent membrane oxidation).

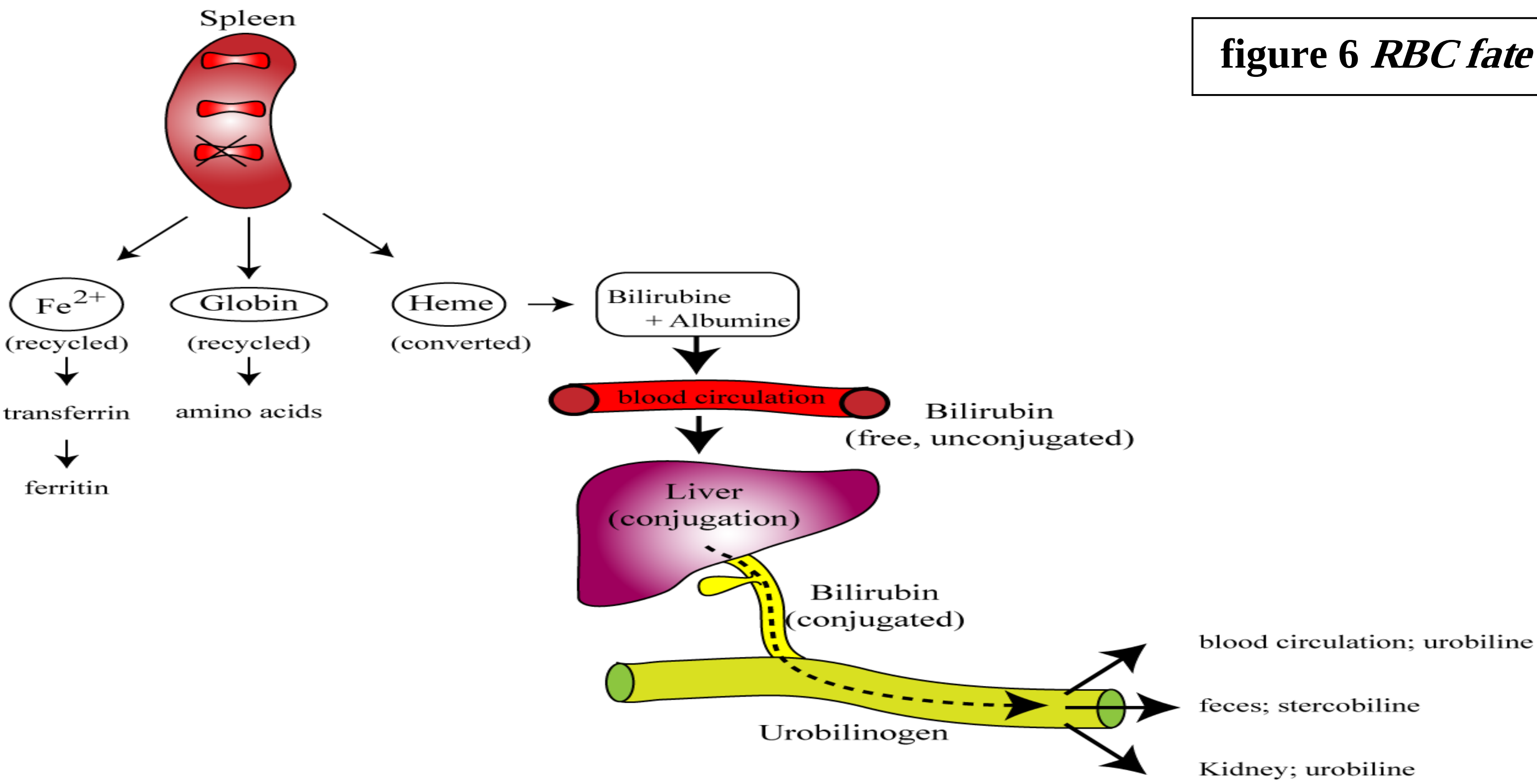
Erythrocyte fate:

After 3 months of RBC life in circulatory system, red blood cells become very old and destroyed in **blood vessels during circulation**, about 1% of RBC destruction in each minute (1 billion). When RBC damaging, the residues which engulfed by **Reticuloendothelial system** (that found in spleen, liver and bone marrow), hemoglobin ingestion to **heme** and **globin,** heme digestion to **iron** (Fe_{++}) that storage in bone marrow, and **porphyrin** which converted to **bilivirdin** that converted to **bilirubin** that attached with **albumin** (in plasma) and transport it to liver to convert it to **cholibilirubin**.

Then by bile duct **cholibilirubin** transport from liver to large intestine to convert it to **urobilinogen**, which divided to three part: 1-excretion with stool, 2- re-enter to blood and excretion by kidney 3-re-enter to liver and discharge from bile duct (recycle).

Globin chains are destroyed to **amino acid** and reabsorption to generate new proteins.

figure 6 *RBC fate*



	Pluripotent Stem Cells	Multipotent Stem Cells
DEFINITION	Pluripotent stem cells are the cells that have the potential to differentiate into any cell type of the three germ layers.	Multipotent stem cells are the cells that have the ability to differentiate into specific cell types.
LOCATION	Blastocyst	Many tissues
DIFFERENTIATION	Into any cell type of the three germ layers.	Into discrete cell types
RELATIVE POTENCY	Relative potency is high compared to multipotent stem cells.	Relative potency is low compared to pluripotent stem cells.
EXAMPLES	Embryonic stem cells and induced pluripotent stem cells.	Blood stem cells and adult stem cells.

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