Topics of this lecture: RBC

- Structural characteristics
- Hemoglobin
- Erythropoiesis
- Erythrocytes destruction
Structural characteristics

- Its small size and biconcave shape provides more surface area than other spherical cells. Why is this important?
- Major function of RBC is to transport hemoglobin.
- Erythrocytes contain mainly hemoglobin. This is why RBC could be called “bags” of hemoglobin.

Why hemoglobin has to be inside RBC and not free in plasma?
Erythrocytes / Red blood cells

- Biconcave discs, mean diameter ~7.8 µm and thickness of 2.5 / 1 µm
- Typical concentration is 4.7+/- 0.3 million per cubic mm (µl) in females and 5.2+/- 0.3 million per cubic mm (µl) in males
- Average volume (MCV) 90 – 95 µm³
- Lack a nucleus (average lifespan = about 120 days)
- Transport hemoglobin (each RBC has about 280 million hemoglobin molecules)
- Contain carbonic anhydrase (critical for transport of carbon dioxide)
Extra information about RBCs

• Each of us has 25 to 30 trillion RBCs streaming through our vessels.
• They are replaced at the average rate of 2 to 3 million cells per second.
• Without DNA and RNA the RBCs cannot synthesize proteins for repair, growth and renewal of enzymes.
• During its life each RBC travels about 700 miles as it circulates through the vasculature.
Structural Characteristics of RBC **

- No nucleus (anucleate) or organelles (no mitochondria, no endoplasmic reticulum)
- In the RBC cytosol there are different proteins such as:
  - Hemoglobin – made before loss of nucleus
    - Not only carries oxygen but also acts as protein buffer
  - Spectrin – promote changes in RBC shape
  - Enzymes: for
    1. Forming ATP from glucose metabolism
    2. Maintaining flexibility (elasticity) of the cell membrane
    3. Transport ions across the cell membrane
    4. Keeping iron in ferrous state
    5. Acting as antioxidants

Note: when these enzymes become less active in old RBCs, the cells become more fragile and RBCs rupture during their passing through tight capillaries (specially in spleen).

***Splenectomy leads to increased no. of abnormal shaped RBCs in circulation.
Where are Erythrocytes produced?

- In early weeks of pregnancy, a primitive nucleated RBC are formed in yolk sac
- Middle trimester of fetal life- Liver (mainly), spleen, lymph nodes.
- Last month of pregnancy and after birth- exclusively from Bone marrow

Sites of RBC formation in different ages

0-5 Y …..all bones of the body

5-20 Y…. The shaft of long bones become fatty and its contribution to form RBC reduced gradually and stops completely after 20 y. Heads of long bones continue to form RBC

After 20 Y….. Almost in membranous bones
Hemoglobin

• It’s the protein that makes RBC red.
• Binds easily and reversibly to oxygen
• Oxygen moves in the blood bound to hemoglobin
• Average normal values of hemoglobin
  – 16 g/100ml of blood in adult males
  – 14 g/100ml of blood in adult females
Erythropoiesis

• means erythrocytes production

• Although the various formed elements have different functions, they all arise from the same stem cell.
  – Pluripotent hematopoietic stem cell (PHSC)
    • Derived from mesenchyme – once committed it follows path
  – PHSC gives to
    1. Committed stem cells that produce RBC, granulocytes, monocytes, platelets
    2. Committed stem cells that give lymphocytes
    3. PHSC that keep supply of committed stem cells

*** note: growth inducers like interleukin-3 makes PHSC to give different committed stem cells
***Note: differentiation of different colony into different blood cells is done by different inducers

Committed stem cell that form RBC, Granulocytes, monocytes, platelets

Committed stem cell that form lymphocytes
Erythropoiesis*

- Erythropoiesis begins when a stem cell is transformed into a proerythroblast.

Proerythroblast is the first cell belonging to red blood series. At early stages of erythroblast, little of Hb starts to accumulate and in the late stages of erythroblast formation Hb concentration is increased until it forms almost 34% of volume of the cell. Very few Hb is formed by reticulocytes.
Stages of RBC Maturation*

- Committed stem cell
- Proerythroblast
- Erythroblast
- Reticulocyte
- Mature RBC

The last stage of development is called reticulocytes which do not contain nucleus and the cytoplasmic organelles are disappearing and only remnants of these remained. Reticulocytes leave bone marrow and stay in blood for 1-2 days and finally they form mature RBC.

Normal reticulocytes no. in circulation is about 1% of total RBC no.

Time needed for committed stem cells to develop to mature erythrocytes is about 5-7 days.
Erythropoiesis

• Erythropoiesis needs to be controlled so there is a balance between RBC production and destruction.

• New cells are made at a rate of more than 2 million per second in healthy people.

• This process is controlled hormonally and depends on adequate supplies of iron, amino acids, Vit. B12 and folic acid.
Erythropoiesis Control

- Erythropoietin – glycoprotein with MW of 34000.
  - There is always a small amount of this hormone in the blood keeping a basal rate of production of RBC.
  - Produced mainly by the kidneys (90%) but the liver produces some (10%).
  - A drop in normal oxygen levels (hypoxia) triggers erythropoietin formation.
    - Hypoxia is most potent stimulus for erythropoietin production.
    - Another factors increases erythropoietin production:
      1. Androgen
      2. alkalosis
      3. Catacholamines
  - Too many erythrocytes depresses erythropoietin production.
Kidney (and liver to a smaller extent) releases erythropoietin. Erythropoietin stimulates red bone marrow.

Enhanced erythropoiesis increases RBC count.

Homeostasis: Normal blood oxygen levels

1. **Stimulus:** Hypoxia (low blood $O_2$- carrying ability) due to
   - Decreased RBC count
   - Decreased amount of hemoglobin
   - Decreased availability of $O_2$

2. Kidney (and liver to a smaller extent) releases erythropoietin.

3. Erythropoietin stimulates red bone marrow.

4. Enhanced erythropoiesis increases RBC count.

5. $O_2$- carrying ability of blood increases.
Erythropoietin production and effects

***Produced by the tubular epithelial cells in kidney and hepatocytes in the liver

***EFFECTS

– Increases number of proerythroblasts
– Stimulates red bone marrow to increase rate of cells division.
Regulation of RBC production

**Erythropoietin**
- Decreases
- Kidney

Hematopoietic stem cells
- Proerythroblasts
- Red blood cells

Tissue oxygenation
- Decrease

Factors that decrease oxygenation
1. Low blood volume
2. Anemia
3. Low hemoglobin
4. Poor blood flow
5. Pulmonary disease

**Figure 32-4**

Function of the erythropoietin mechanism to increase production of red blood cells when various factors decrease tissue oxygenation.
Destruction of Erythrocytes

• The anucleate condition of erythrocytes carries with it some important limitations.
  – Red blood cells are unable to synthesize new proteins, to grow, or to divide.
  – Erythrocytes become “old” as they lose their flexibility and become increasingly rigid and fragile, and their contained hemoglobin begins to degenerate.

Aged RBCs have:
• ↓ Metabolic activity
• ↓ Enzyme activity
• ↓ ATP
• ↓ Membrane Lipids

Fragile Membrane

Cells Rupture as they pass through narrow spaces in spleen
Destruction of Erythrocytes

- Red blood cells have a useful life span of 100 to 120 days, after which they become trapped and fragment in smaller circulatory channels, particularly in those of the spleen.
  - In the red pulp of the spleen, RBC rupture when they try to squeeze through because of their fragile old membrane.
  - For this reason, the spleen is sometimes called the “red blood cell graveyard”.
Erythrocyte Destruction

• Macrophages in spleen, liver and red bone marrow phagocytize dying RBC.
  – Globin – breaks into amino acids, which can be reused to produce other proteins
  – Heme – iron and porphyrin
    • Fe – removed and recycled in spleen
    • Porphyrin – converted to bilirubin (bile pigment)
      – Yellow pigment secreted by liver into bile, which is excreted in urine and feces
Anemia

• Any decrease in blood’s oxygen-carrying capacity is known as anemia.

• Causes:
  – Insufficient number of RBC
  – Low hemoglobin content
  – Abnormal hemoglobin

• One of the major effects of anemia is the greatly increased work load on the heart.
ANEMIA

1- Blood loss: Microcytic, hypochromic an. No enough iron to form Hb
2- Aplastic An BM DIS
3- Megaloplastic, Large RBC Dec Vit B12, folic acid and Intrinsic factor
4- Pernicious anemia caused by atrophy of stomach mucosa or gastrectomy can lead to megaloplastic anemia
4-Hemolytic anemia
  a-Hereditary, Spherocytosis
  b-Sickle cell (HbS HB)
  c-Erythroblastosis fetalis Rh+
      fetus with AB from mother Rh-
  d-Thalassaemia : Inherited
      impairment of Hb production
      (Minor & major)
Effect of anemia on cardiovascular system**

- Decreased viscosity
- Decreased resistance to blood flow
- Dilatation of blood vessels
- More blood returns to the heart
- More cardiac output
Polycythemia

Primary polycythemia (polycythemia vera)
Due to increased activity of hemocytoblastic cell of bone marrow

Secondary polycythemia
Due to hypoxia

polycythemia
(Means increased RBCs no.)
Effects of polycythemia on CVS

Polycythemia Leads to

- Increased hematocrit
- Increased blood volume
- Increased venous return
- Increased blood pressure
- Decreased blood flow
- Decreased cardiac output
- Decreased venous return to the heart

More O2 is extracted from Hb and thus deoxygenated blood is increased leading to bluish discoloration of the skin (cyanosis)