SAWA UNIVERSITY

امراض الدم الكورس الأول

Hemopoiesis and Erythropoiesis

جامعـــــــة ســـــــــاوة الاهلية — Sawa University

كليـــــة التقنيـــات الصحيـة والطبيـة — College of health and medical techniques

قسم تقنيات المختبرات الطبية — Department of Medical Laboratories

....المرحلـــــــــــــة .....الثالثة — . ..... Third ..... Stage

الجانب النظري — محاضرة رقم 2..3.

Theoretical — Lecture No. 3…2..

تدريسي المادة : د وضاح علي حسين

CONTENTS OF THIS TEMPLATE

- Hemopoiesis
- Erythropoiesis
- RBC membrane

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Hematopoiesis and Erythropoiesis

Hematopoiesis and Erythropoiesis

Hematopoiesis is the process of formation of all blood cells i.e RBCs , WBCs platelets from the pluripotent stem cell; (The hematopoietic stem cells HSC).

Erythropoiesis : process of development and maturation of RBC

Hematopoiesis and Erythropoiesis

The fist generation stem cell called as pleuripotent stem cell

and the term pleuripotent stem cells refers that they have a potency to convert into many different type of tissues .

pleuripotent stem cells (HSC) in the BM divides into two different types of multipotent stem cells

multipotent stems cells are the cells that have the capacity to self

*

All blood cells arise from a single type of pluripotent stem cell (HSC)

HSC in the bone marrow divide and differentiate into multipotent stem cells that can give rise to all the blood cell types .

The two types of multipotent stem cells (HSC) are :

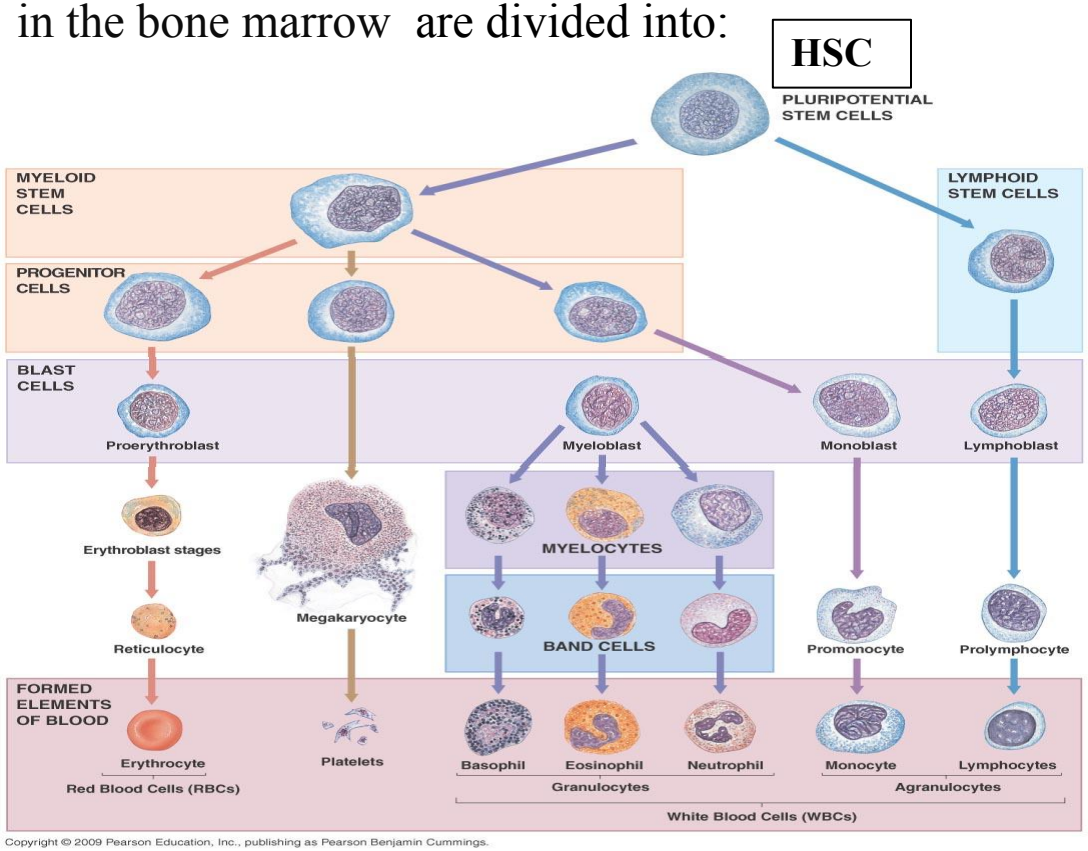
1 . Lymphoid stem cells produce lymphocyte

2 . Common myeloid stem cells produce cells related myeloid system all blood cells other than lymphoid cells WBC , Monocyte , RBC , and platelets

Lineage Cells of Hematopoiesis- HSCs

Hemopoietic Stem Cells in the bone marrow are divided into:

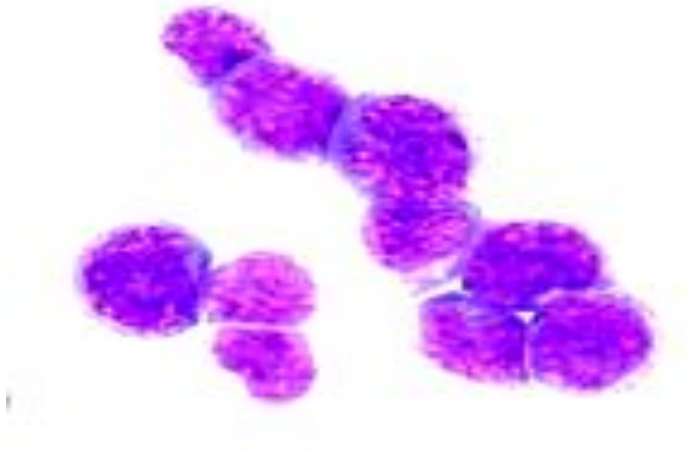
1. Myeloid stem cells
2. Lymphoid stem cells



HSCs represents about 1 :20 million nucleated cells of the bone

marrow. It resembles a small to medium sized lymphocyte.

They are capable to traffic around the body and are found in low number in the peripheral bloo



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HSC : Cells that are able to

1) Self-renew to form ‘parent pool’ (can create more stem cells indefinitely)

2) Differentiate into (become) specialized, mature cell types.

3) Mitotic activity

4) Influence by growth factors

.

5)Multipotentiality Capacity to generate cells of all the lympho haemopoietic lineages

Hematopoietic stem cells

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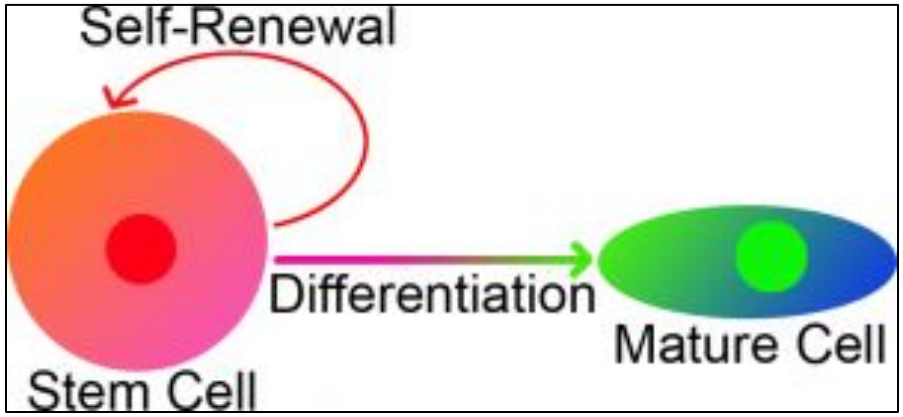
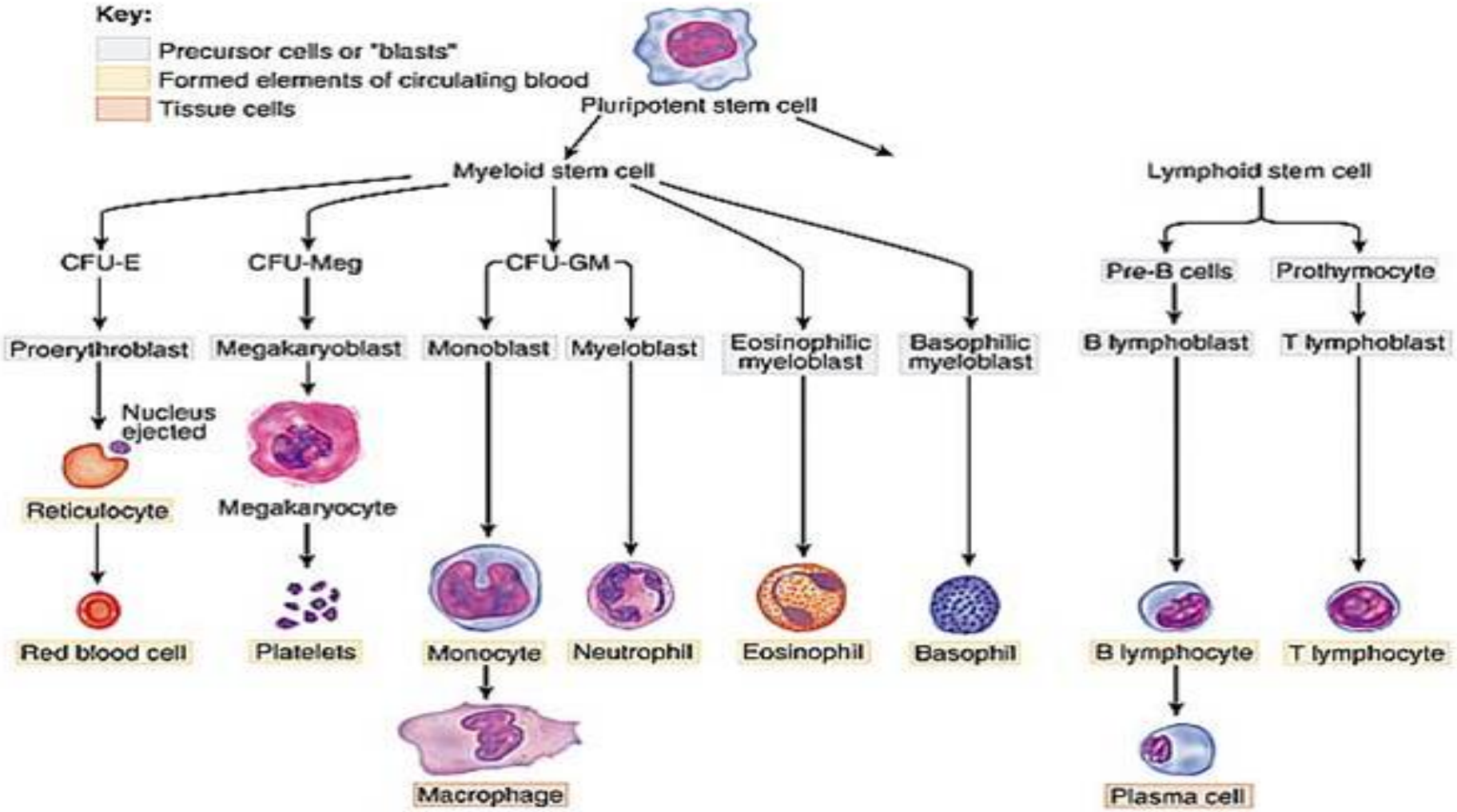


Hemopoiesis (Gr. *haima* , blood + *poiesis* , a making) **include:**

- Erythropoiesis
- Leukopoiesis
- Granulopoiesis
- Monocytopoiesis
- Thrombopoiesis
- Lymphopoiesis

Units of colony forming cells (progenitor cells for blood cells)

- A commited stem cells that form erythrocyte is called (CFU – E)
- Commited cells that form granulocyte basophil eosinophil and monocyte
  called (CFU – GM)
- Commited cells that form megakaryocytes (CFU – M)
  platelets derived from these cells
- Lymphoid lineage of CFU-lymphocytes (CFU-L).


Key:
Precursor cells or "blasts"
Formed elements of circulating blood
Tissue cells
Pluripotent stem cell
Myeloid stem cell
Lymphoid stem cell
CFU-E
CFU-Meg
CFU-GM
Pre-B cells
Prothymocyte
Proerythroblast
Megakaryoblast
Monoblast
Myeloblast
Eosinophilic myeloblast
Basophilic myeloblast
B lymphoblast
T lymphoblast
Nucleus ejected
Reticulocyte
Megakaryocyte
Red blood cell
Platelets
Monocyte
Neutrophil
Eosinophil
Basophil
B lymphocyte
T lymphocyte
Macrophage
Plasma cell

**

Stem cells require their proliferation and differentiation :
certain regulatory factors

Hemopoitic growth factors (colony stimulating factors)
Nutritional Factors
Hormonal Factors
Healthy Liver and Bone marrow
Suitable micro environment , provide by the marrow space

*

Haemopoietic growth factors

- GM-CSF
  - Granulocyte-Macrophage colony stimulating factor
- M-CSF
  - Macrophage colony stimulating factor
- Erythropoietin
  - Erythropoiesis stimulating hormone

(These factors have the capacity to stimulate the proliferation of their target progenitor cells when used as a sole source of stimulation)

- Thrombopoietin
  - Stimulates megakaryopoiesis

*

Formation of Blood Cells

- Pluripotent stem cells produce
  - Myeloid stem cells
    - Give rise to red blood cells, platelets, monocytes, neutrophils, eosinophils and basophils
  - Lymphoid stem cells give rise to
    - Lymphocytes
- Hemopoietic growth factors regulate differentiation and proliferation
  - Erythropoietin – RBCs
  - Thrombopoietin – platelets
  - Colony-stimulating factors (CSFs) and interleukins – WBCs

* Site where hematopoiesis

Cells responsible to do function of hemopoiesis are first seen in

1. Yolk sac of embryo in third week of embryonic development.
2. Bone marrow
3. liver
4. spleen

Embryonic life

The yolk sac is the main site of haematopoiesis at first few weeks

At 10 – 12 weeks gestation , the liver and spleen are the principle site of hemopoiesis till approximately 24 weeks

Bone marrow function starts from the 4^{th} – 5^{th} months of gestation and is the major site of hemopoiesis till birth

.

Hemopoiesis Initiated in Early Embryonic Development & Continue.

1. Yolk-sac phase.
2. Hepatic phase.
3. [illegible]se.

1

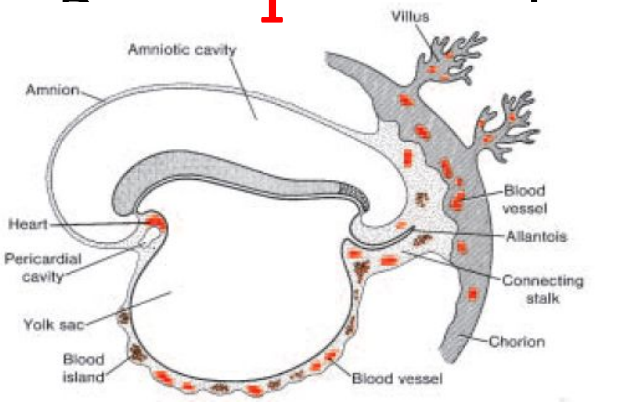
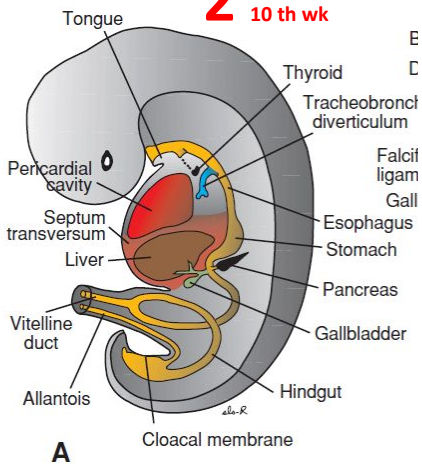


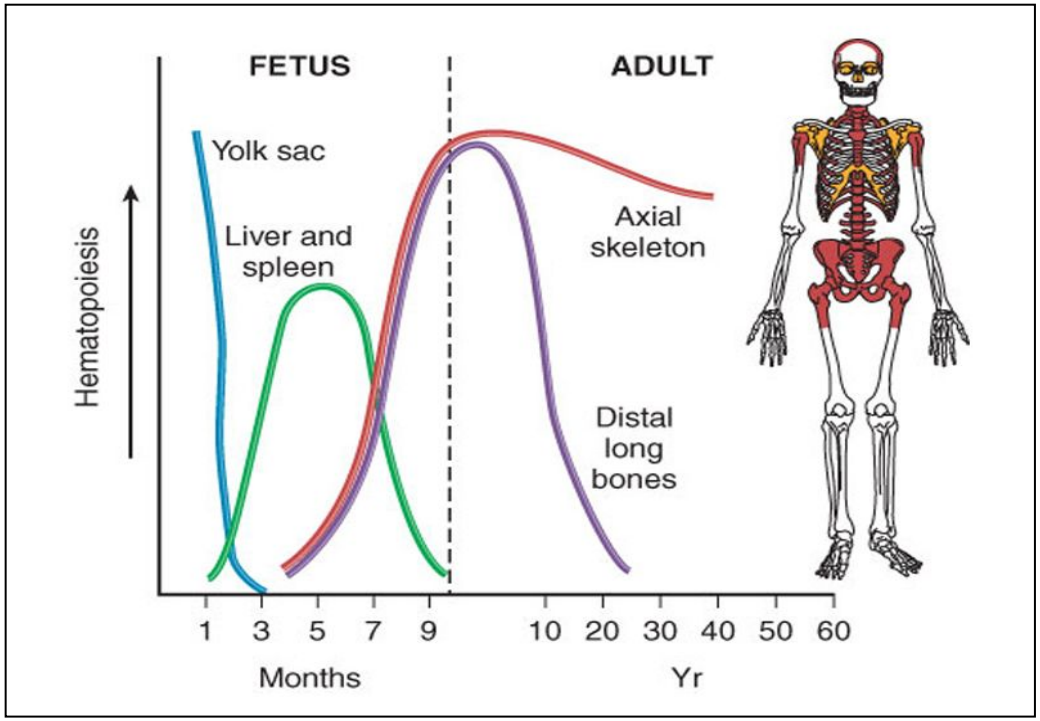
Figure 5.15 Extraembryonic blood vessel formation in the villi, chorion, connecting stalk, and wall of the yolk sac in a presomite embryo of approximately 19 days.

2 10 th wk



3 4th m.

** Hematopoiesis



During fetal life :

Yolk sack

Liver and spleen

Bone marrow

After birth :

Infant:

BM of all bones.

- Gradual replacement of active (red) marrow by inactive (fatty) tissue.

Adults:

Flat bones and proximal ends of femur

**

children, erythropoiesis can occur in the bone marrow of most bones of human skeleton but gradually recedes with time

Adult life, hematopoiesis is found mainly in flat bones

(sternum, pelvis , sacrum , vertebrae, ribs and proximal ends of long femur) .

**Factors necessary for erythropoiesis

- Erythropietin (hormone of erythropoiesis secreted by the kidney)
- Thyroxin
- Hemopoietic growth factors (interleukin 3 , 6, 11)
- Vitamins (vit c , d , e , b)
- Maturation factors vit b12 and folic acid required for DNA synthesis

*Regulation and Requirements for Erythropoiesis

.

Erythropoietin (EPO) which is synthesized mainly from kidneys. Liver and BM macrophages may be also a source of Epo.

Erythpoietin is secreted in response to anoxia caused for example by anemia or high altitude

Erythropioesis also depend on adequate supplies of iron, amino acids, and vitamins

**FACTORS NECESSARY FOR HEMOGLOBIN FORMATION

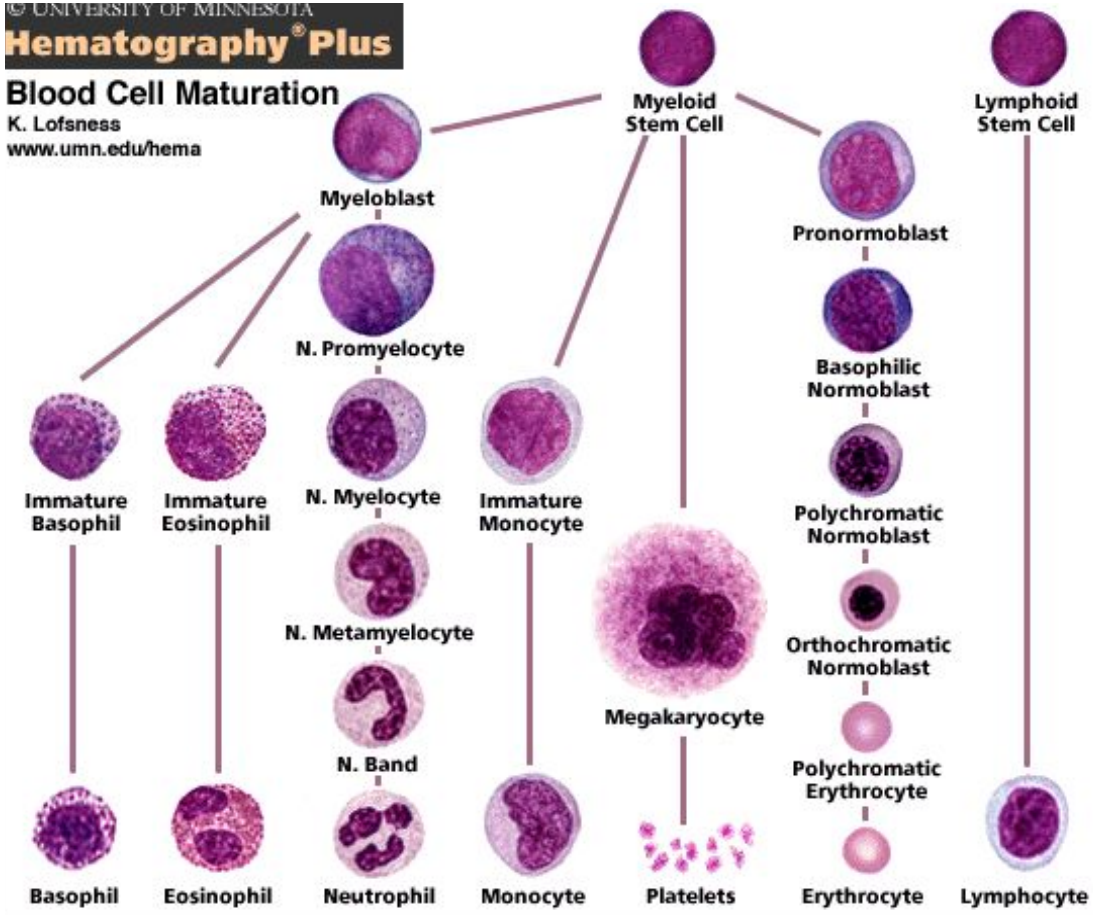
- Various materials are essential for the formation of hemoglobin in the RBCs such as:
- First class proteins and amino acids of high biological value — for the formation of globin.
- Iron — for the formation of heme part of the hemoglobin.
- Copper — for the absorption of iron from GI tract.
- Cobalt and nickel — for the utilization of iron during hemoglobin synthesis.
- Vitamins: Vitamin C, riboflavin, nicotinic acid and pyridoxine — for hemoglobin synthesis.

.

STAGES OF ERYTHROPOIESIS

The various stages between CFU-E cells and matured RBC are:

1. Proerythroblast
2. Early normoblast
3. Intermediate normoblast
4. Late normoblast
5. Reticulocyte
6. Matured erythrocyte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Hematography® Plus
Blood Cell Maturation
K. Lofsness
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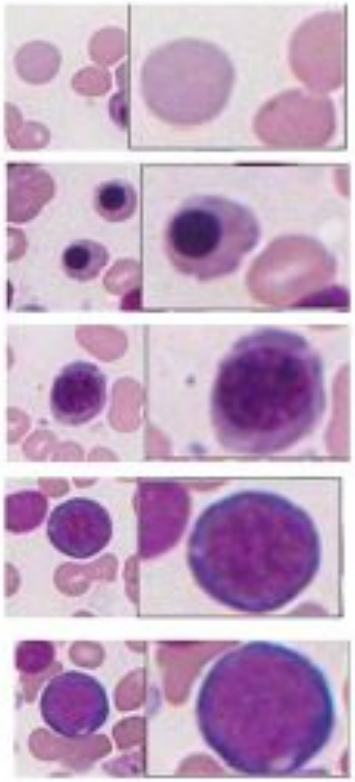
Myeloid Stem Cell
Lymphoid Stem Cell
Myeloblast
Pronormoblast
N. Promyelocyte
Basophilic Normoblast
Immature Basophil
Immature Eosinophil
N. Myelocyte
Immature Monocyte
Polychromatic Normoblast
N. Metamyelocyte
Orthochromatic Normoblast
Megakaryocyte
N. Band
Polychromatic Erythrocyte
Basophil
Eosinophil
Neutrophil
Monocyte
Platelets
Erythrocyte
Lymphocyte

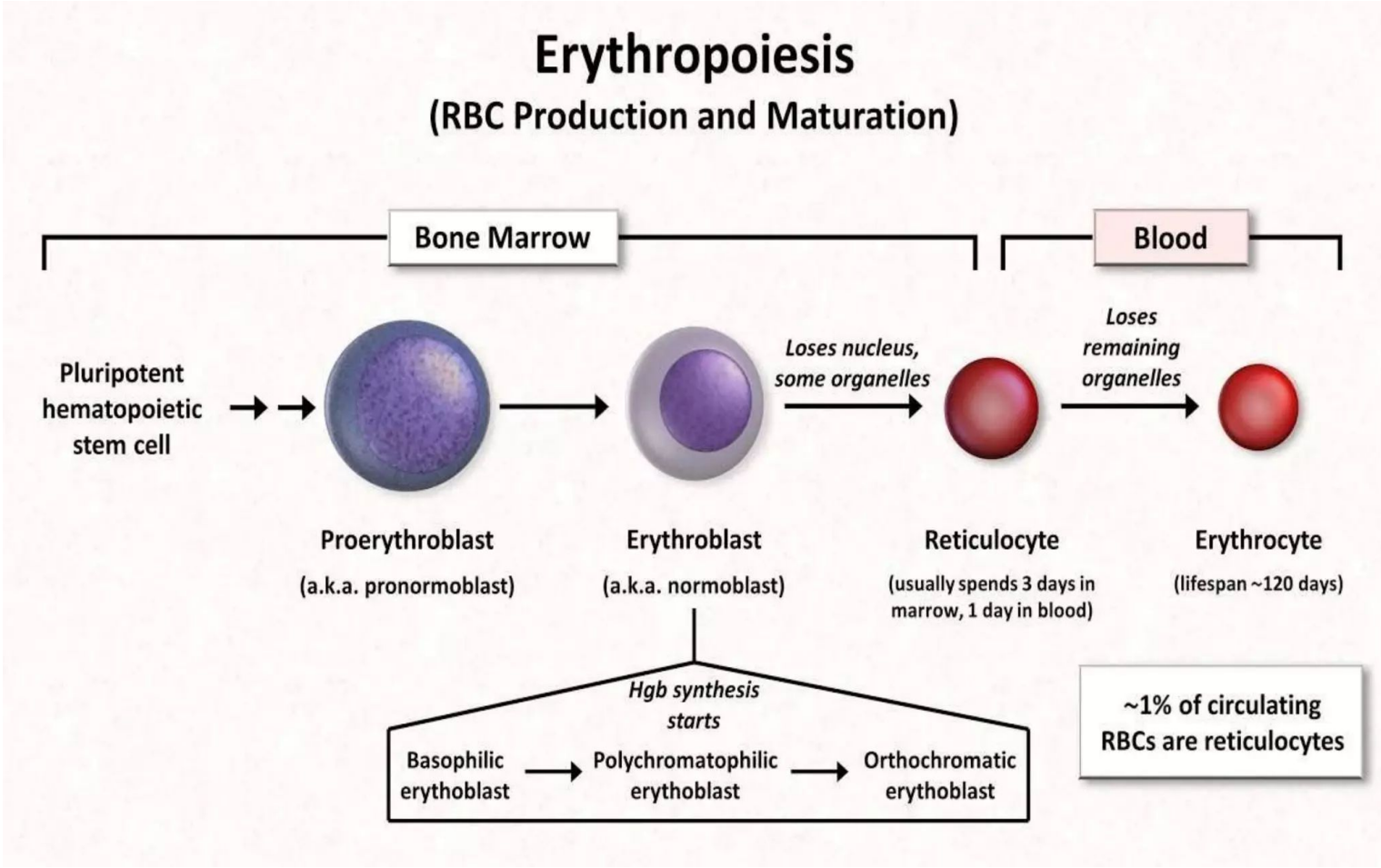
*

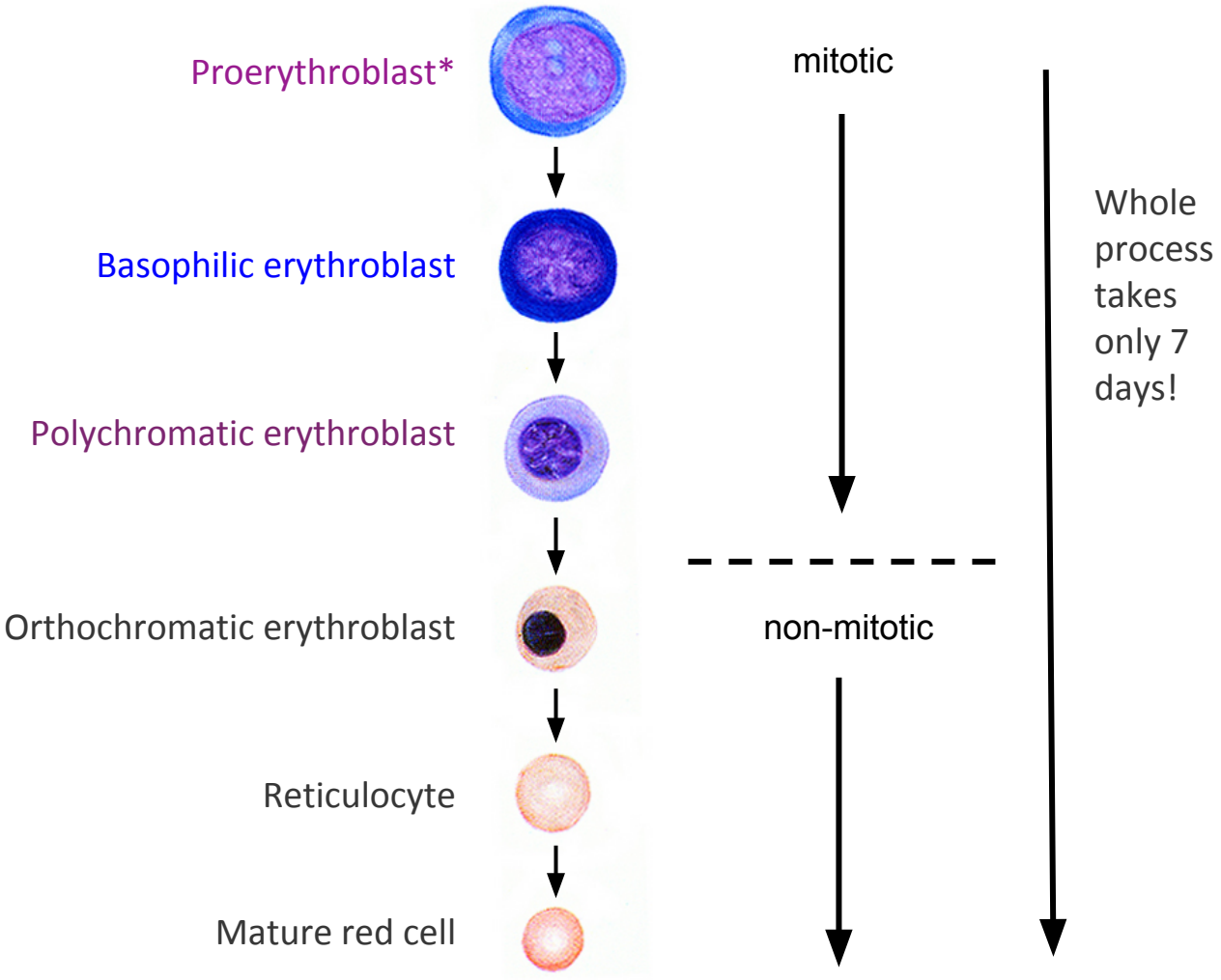
Erythropoiesis



Erythrocytes	No nucleus and red cytoplasm
Reticulocytes	No nucleus and blue - grey cytoplasm
Orthochromatophilic erythroblasts	Dark, small, spherical nucleus blue – grey cytoplasm
Polychromatophilic erythroblasts	Darkening, fractured ,spherical nucleus and mixed pools of grey and blue cytoplasm
Basophilic erythroblasts	Fractured, spherical nucleus and thin rim of dark blue cytoplasm
Proerythroblasts	Uniformly light, spherical nucleus with thin rim of medium to dark blue cytoplasm

*


Erythropoiesis
(RBC Production and Maturation)
Bone Marrow
Blood
Pluripotent hematopoietic stem cell
Loses nucleus, some organelles
Loses remaining organelles
Proerythroblast
(a.k.a. pronormoblast)
Erythroblast
(a.k.a. normoblast)
Reticulocyte
(usually spends 3 days in marrow, 1 day in blood)
Erythrocyte
(lifespan ~120 days)
Hgb synthesis starts
Basophilic erythoblast
Polychromatophilic erythoblast
Orthochromatic erythoblast
~1% of circulating RBCs are reticulocytes


Proerythroblast*
Basophilic erythroblast
Polychromatic erythroblast
Orthochromatic erythroblast
Reticulocyte
Mature red cell
mitotic
non-mitotic
Whole process takes only 7 days!

*

1. Erythropoietin promotes the following processes:

i. Production of proerythroblasts from CFU-E of the bone marrow.

ii. Development of proerythroblasts into matured RBCs through the several stages

iii. Release of matured erythrocytes into blood.

.

2. Thyroxine

Being a general metabolic hormone, thyroxine accelerates the process of erythropoiesis at many levels.

3. Hemopoietic Growth Factors or growth inducers are the interleukins – 3, 6 and 11 and stem cell factor .

Generally these factors induce the proliferation of HSCs.

4. Vitamins

The vitamins A, B, C, D and E are necessary for erythropoiesis. Deficiency of these vitamins causes anemia.

MATURATION FACTORS

Vitamin B12 (Cyanocobalamin).

Vitamin B12 is essential for synthesis of DNA, cell division and maturation in RBCs

. Vitamin B12 is stored mostly in liver and in small quantity in muscle. Its deficiency causes pernicious anemia (macrocytic anemia) in which the cells remain larger with fragile and weak cell membrane.

Folic Acid

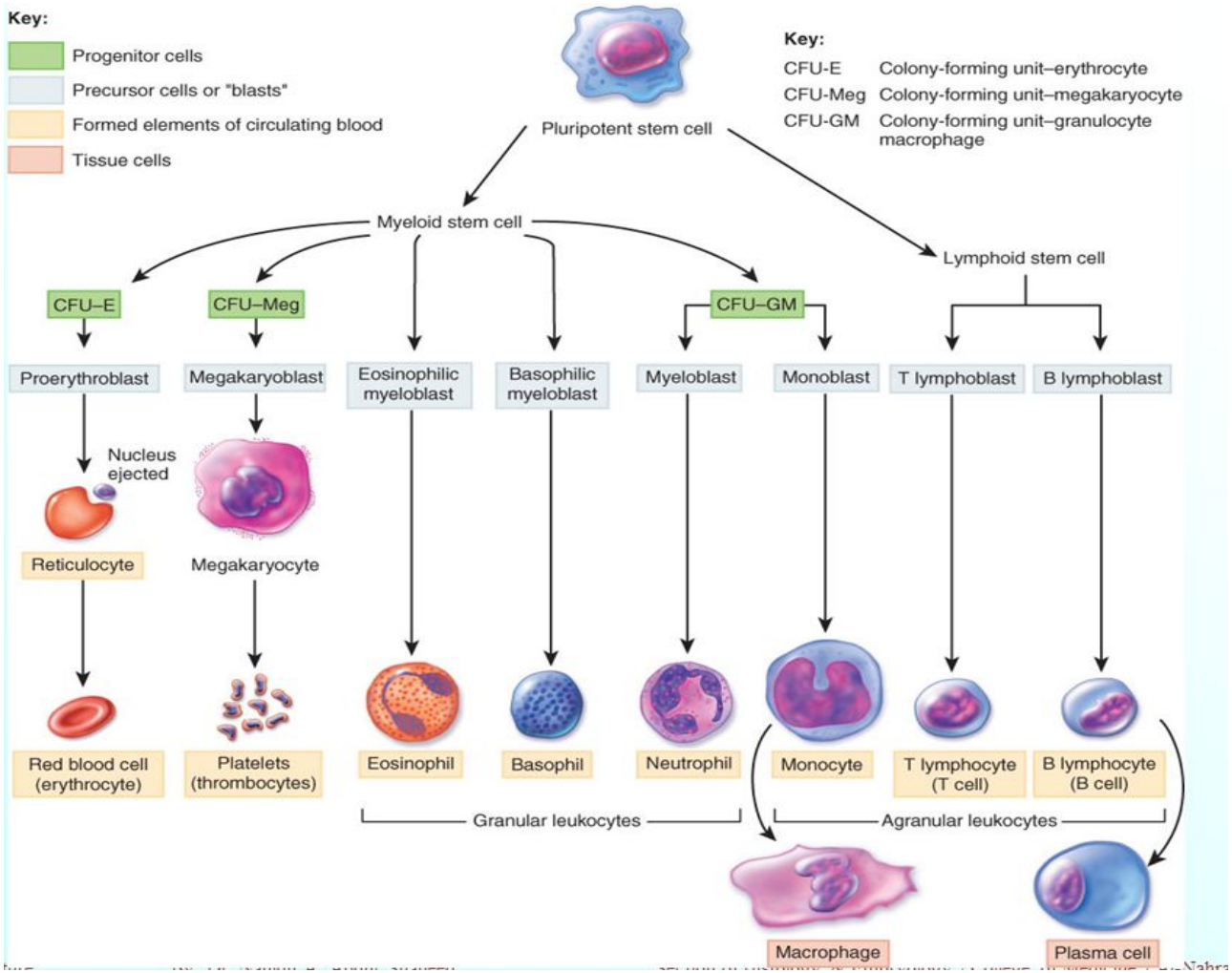
Folic acid is also essential for the synthesis of DNA.

Deficiency of folic acid decreases the DNA synthesis causing maturation failure.

Here the cells are larger which leads to megaloblastic anemia.

Myelopoiesis

Involves the action of a variety of growth factors e.g. stem cell factor (SCF), Fetal liver tyrosine kinase3(FLT3),Granulocyte Monocyte–Colony stimulating factor (GM-CSF), IL-3, Granulocyte–Colony stimulating factor (G-CSF), Monocyte–Colony stimulating factor M-CSF and IL-5.


Key:
Progenitor cells
Precursor cells or "blasts"
Formed elements of circulating blood
Tissue cells
Key:
CFU-E Colony-forming unit–erythrocyte
CFU-Meg Colony-forming unit–megakaryocyte
CFU-GM Colony-forming unit–granulocyte macrophage
Pluripotent stem cell
Myeloid stem cell
Lymphoid stem cell
CFU–E
CFU–Meg
CFU–GM
Proerythroblast
Megakaryoblast
Eosinophilic myeloblast
Basophilic myeloblast
Myeloblast
Monoblast
T lymphoblast
B lymphoblast
Nucleus ejected
Reticulocyte
Megakaryocyte
Red blood cell (erythrocyte)
Platelets (thrombocytes)
Eosinophil
Basophil
Neutrophil
Monocyte
T lymphocyte (T cell)
B lymphocyte (B cell)
Granular leukocytes
Agranular leukocytes
Macrophage
Plasma cell

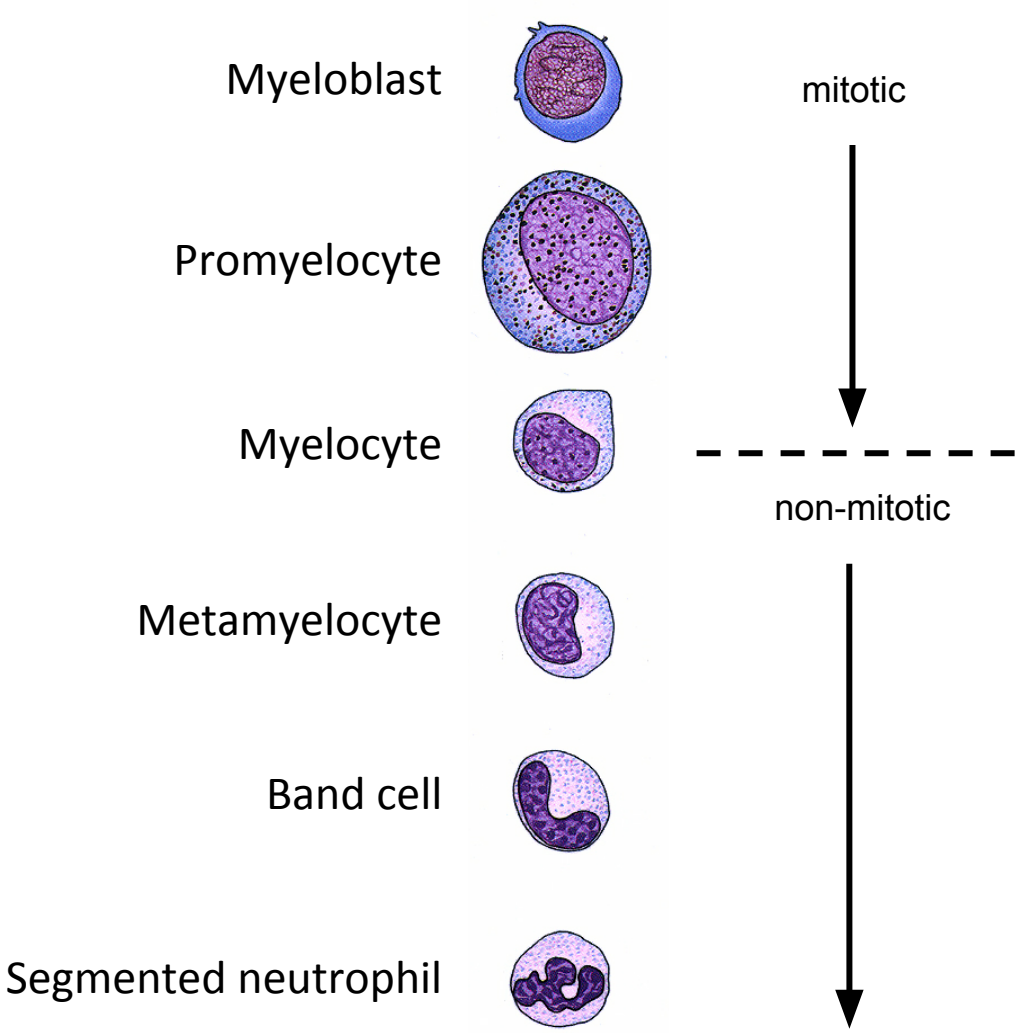
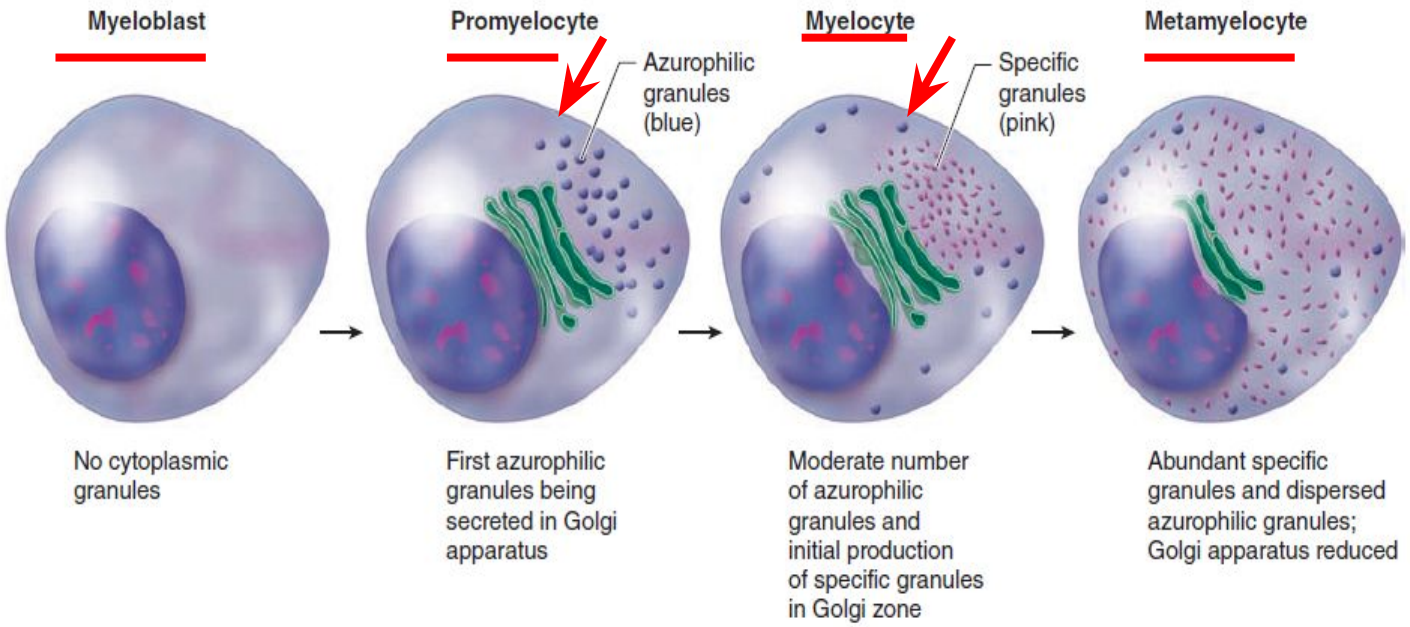
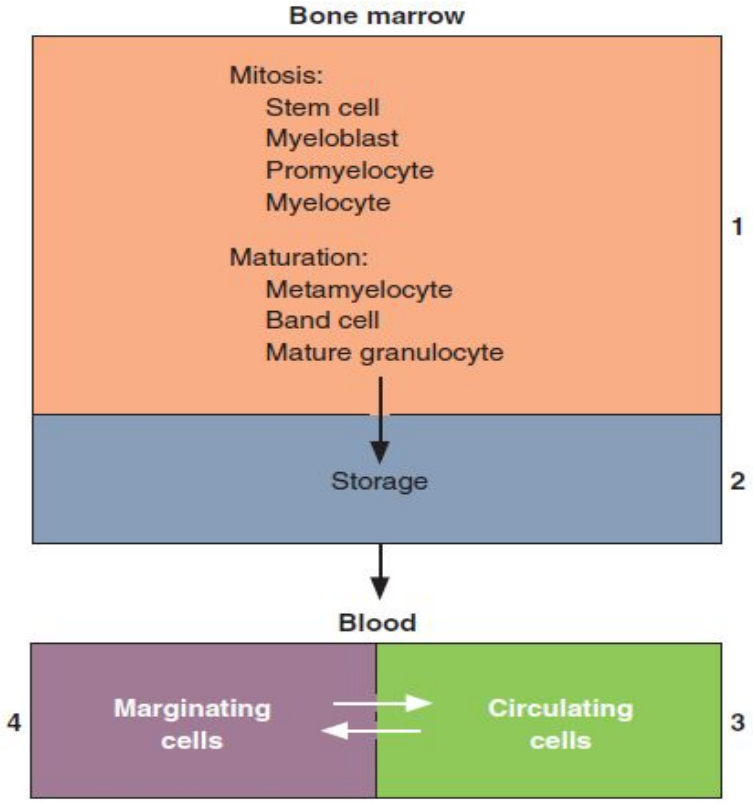

Myeloblast
Promyelocyte
Myelocyte
Metamyelocyte
Band cell
Segmented neutrophil
mitotic
non-mitotic

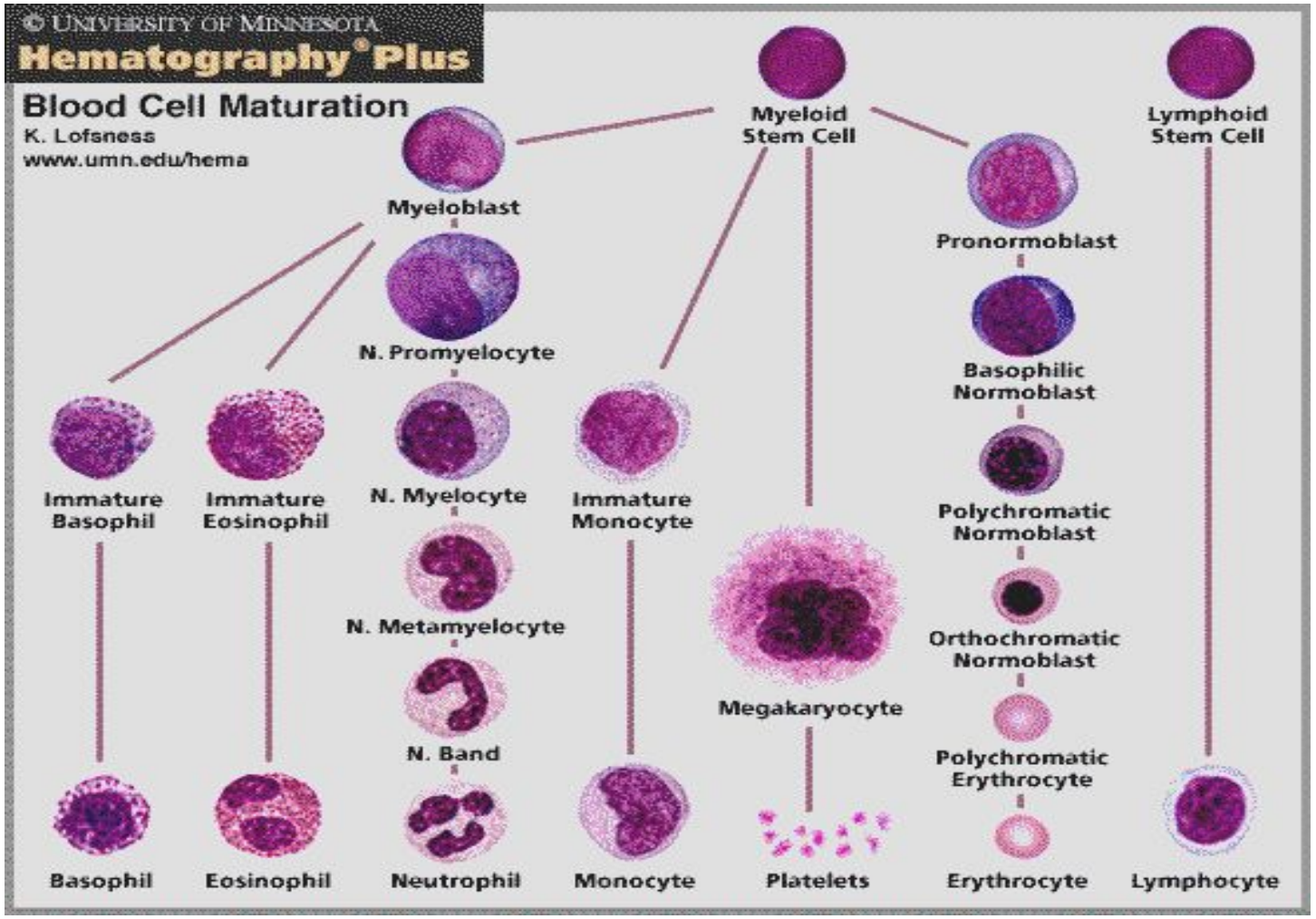
FIGURE **13–8** **Granulopoiesis: Formation of granules.**



Illustrated is the sequence of cytoplasmic events in the maturation of granulocytes from **myeloblasts**. Modified lysosomes or azurophilic granules form first at the **promyelocyte** stage and are shown in blue; the specific granules of the particular cell type form at the **myelocyte** stage and are shown in pink. All granules are fully dispersed at the **metamyelocyte** stage, when indentation of the nucleus begins.

FIGURE **13–12** **Compartments of neutrophils in the body.**

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Myeloid Stem Cell
Lymphoid Stem Cell
Myeloblast
Pronormoblast
N. Promyelocyte
Basophilic Normoblast
Immature Basophil
Immature Eosinophil
N. Myelocyte
Immature Monocyte
Polychromatic Normoblast
N. Metamyelocyte
Orthochromatic Normoblast
Megakaryocyte
N. Band
Polychromatic Erythrocyte
Basophil
Eosinophil
Neutrophil
Monocyte
Platelets
Erythrocyte
Lymphocyte

Lymphopoiesis

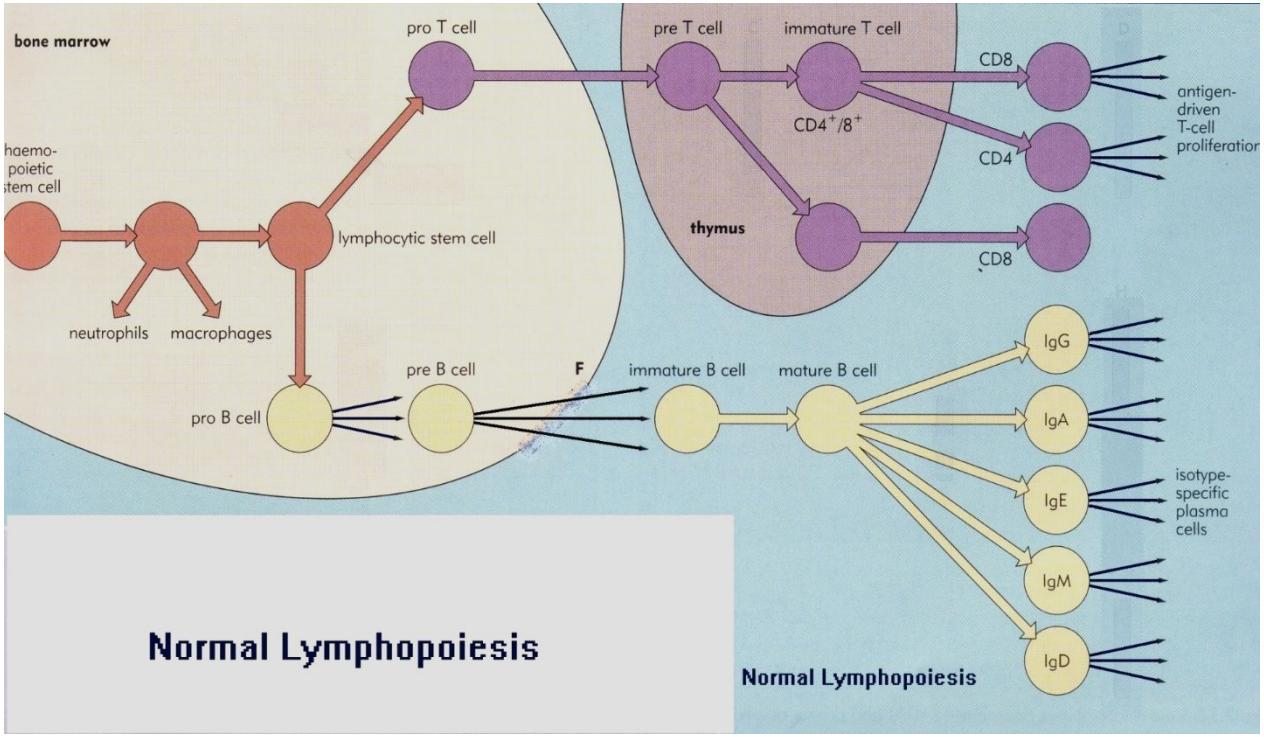
- Lymphocytes are immunologically competent cells.
- Primary lymphoid organs: Bone marrow, Thymus.
- Secondary lymphoid organs: Lymph nodes, Spleen, Lymphoid tissues.
- Lymphocytes:
    - B and T lymphocytes
    - NK killer cells

Lymphopoiesis

B lymphocytes develop in the bone marrow.

T lymphocytes develop in the thymus.

B and T cells then leave and populate secondary lymphoid organs (lymph nodes, spleen).


bone marrow
haemo-
poietic
tem cell
neutrophils
macrophages
lymphocytic stem cell
pro T cell
pro B cell
pre B cell
F
pre T cell
immature T cell
thymus
CD8
CD4+/8+
CD4
CD8
antigen-
driven
T-cell
proliferation
immature B cell
mature B cell
IgG
IgA
IgE
IgM
IgD
isotype-
specific
plasma
cells
Normal Lymphopoiesis
Normal Lymphopoiesis

Thrombopoiesis (Megakaryopoiesis)

- The earliest progenitor commited to the megakaryocytic lineage is the megakaryocytic burst forming cell (meg-BFC).
- A later progenitor megakaryocyte colony forming unit(meg-CFU) gives rise to colonies of smaller number of megakaryocytes
- It gives rise to clusters of 100 or more megakaryocytes.
- Platelets production: fragmentation of the cytoplasm of the megakaryocytes.
- Normally, 1/3 platelets are pooled in the spleen.

Thrombopoiesis

- Thrombopoiesis

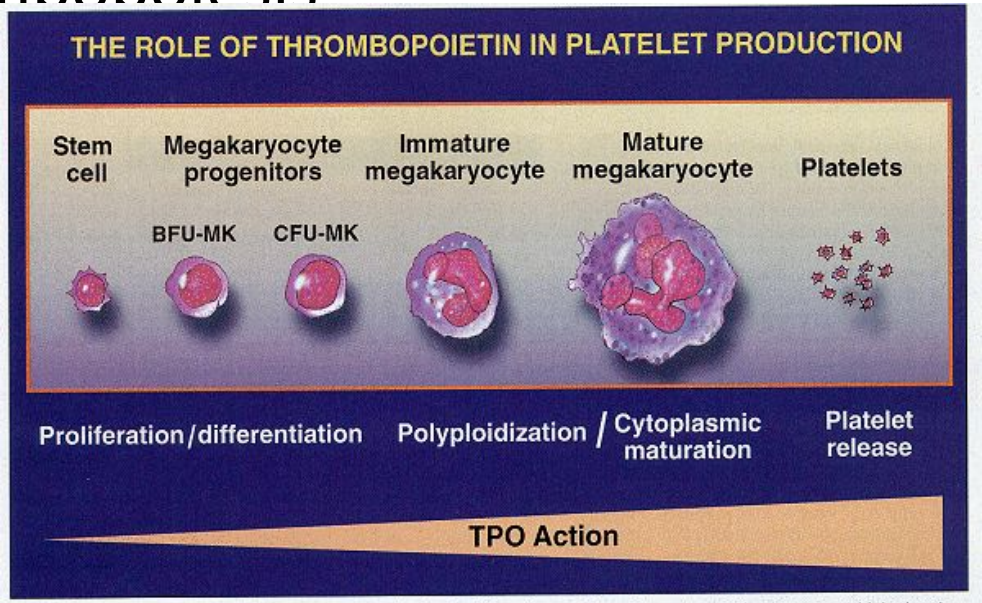
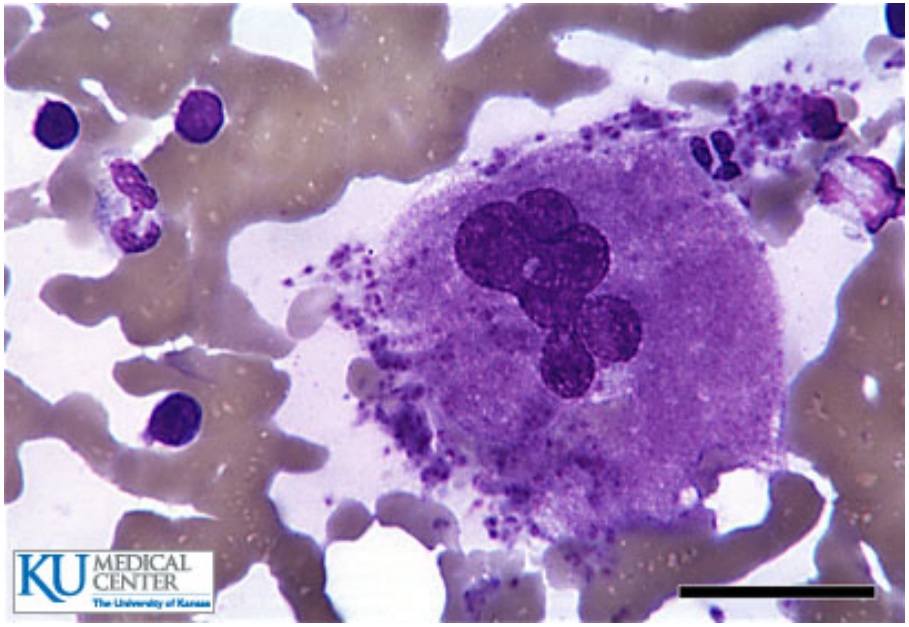


Figure 2: Regulation of Megakaryocytopoiesis by Thrombopoietin—Thrombopoietin acts at multiple levels, including proliferation and differentiation of megakaryocyte (MK) progenitors and maturation of MKs into large polyploid cells capable of producing platelets.[37,40]


KU MEDICAL CENTER
The University of Kansas

***Red blood cell membrane

*

- RBC membrane consist of
- Protein 50%
- Lipid 43%
- Carbohydrte 7%

- Carbohydrate they occur only on the on the external surface of the red blood cell
  They are composed of glycoproteins and glycolipid

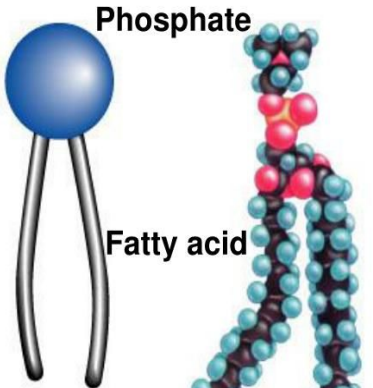
Lipid

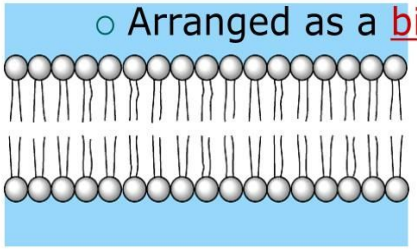
- Lipid components of the red cell membrane are
- 60% phospholipid
- 30% cholesterol
- 10% sphingolipids

*

Phospholipids

- Fatty acid tails
  - hydrophobic
- Phosphate group head
  - hydrophilic
- Arranged as a bilayer





Proteins

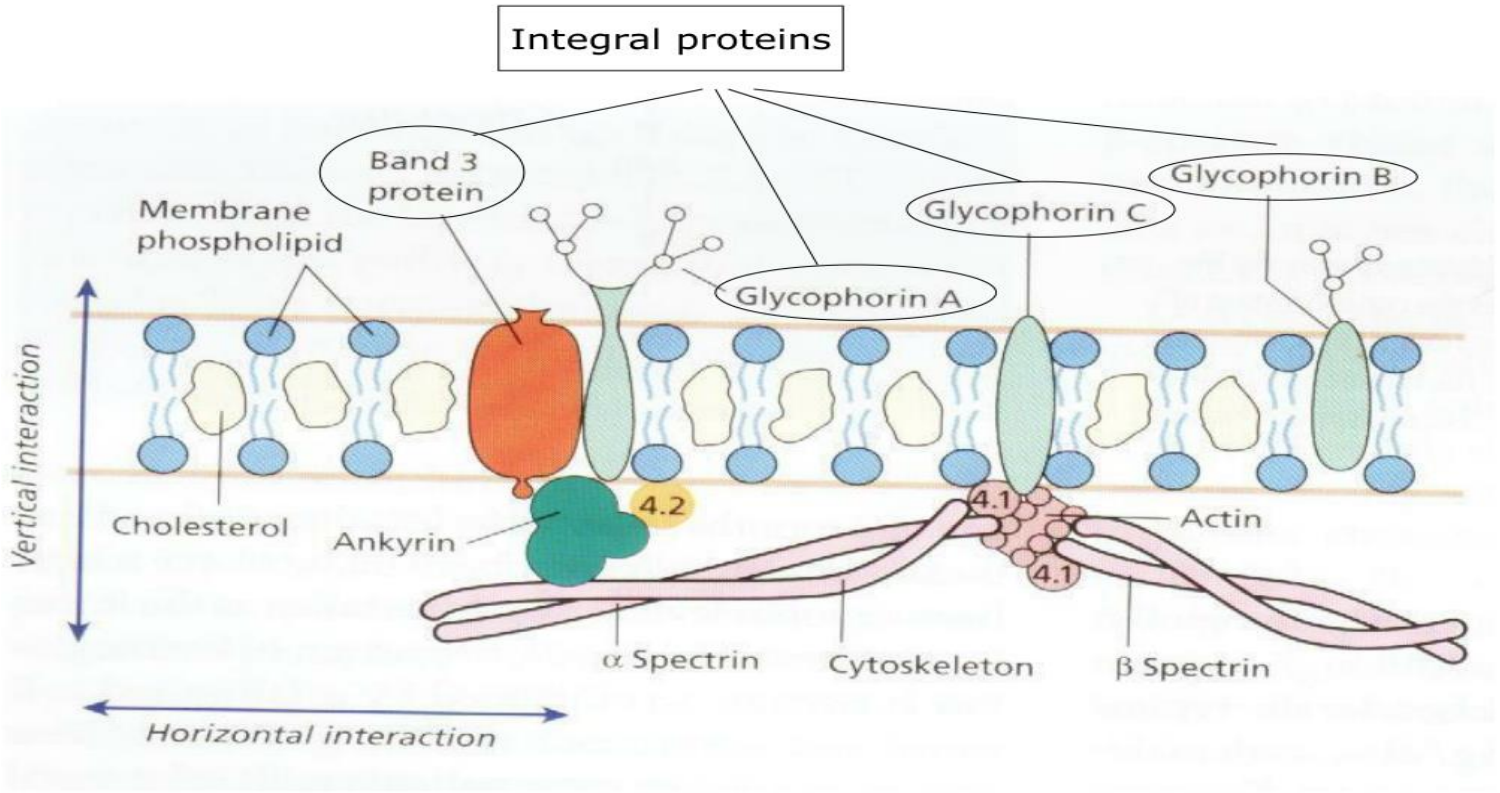
These are either peripheral protein or integral protein penetrating the lipid bilayer

The RBC peripheral protein interact to form a cytoskeleton

1. spectrin most abundant consist of alfa and beta chain if denatured RBC will take spherical shape
2. ankyrin
3. protein 4,1
4. actin

*Proteins

These are either peripheral protein or integral protein penetrating the lipid bilayer



*

Integral protein

They are penetrate the lipid bilayer

1. band 3 protein
2. glycophorin A, B & C
3. glucose transport protein
4. transferrin receptors

Blood group antigens

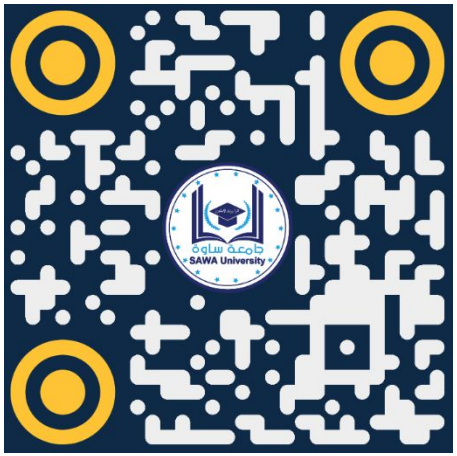
1. protein including Rh , duffy , kidd
2. carbohydrate ABO lewis and P
3. combination of protein and glycolipid M , N

- Q1 Enumerate categories and types of proteins in the red cell membrane

Q2 Enumerate types of multipotent stem cells (

HSC) in the bone marrow :

Q3 write shortly about Haemopoietic growth factors



Scan to get the lecture