Pre_ and postnatal hematopoiesis

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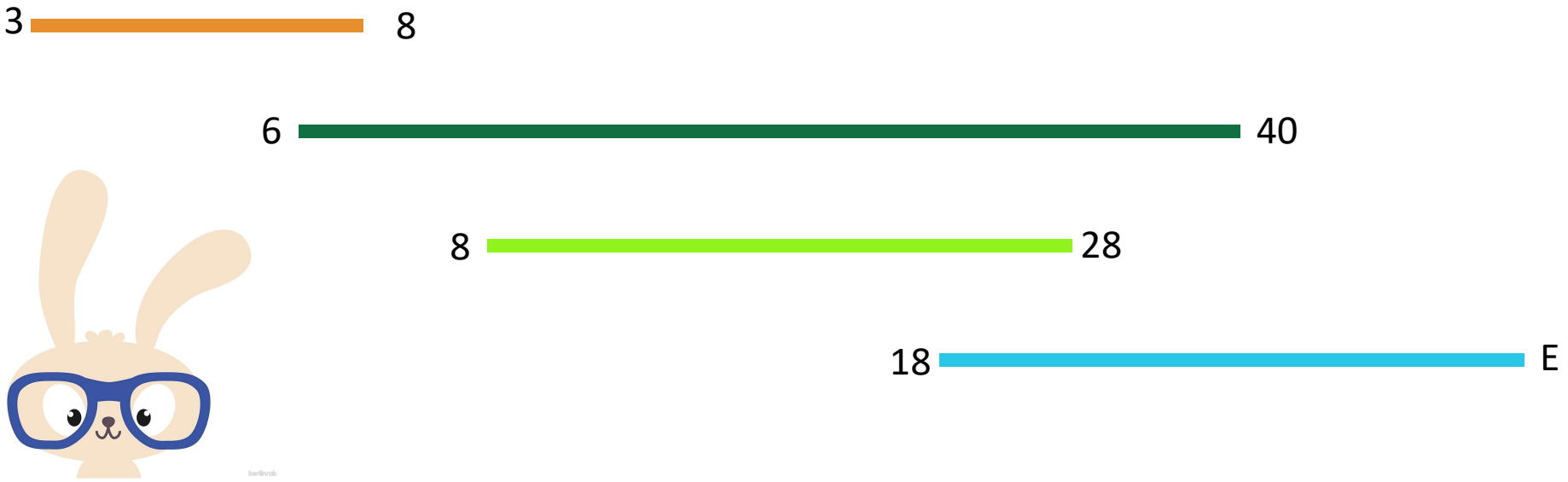
You Love a Smart Bunny

Yolk sac	Liver	Spleen	Bone marrow
3-8 weeks	6 w → birth	8 w → 28 w	18 w → adult



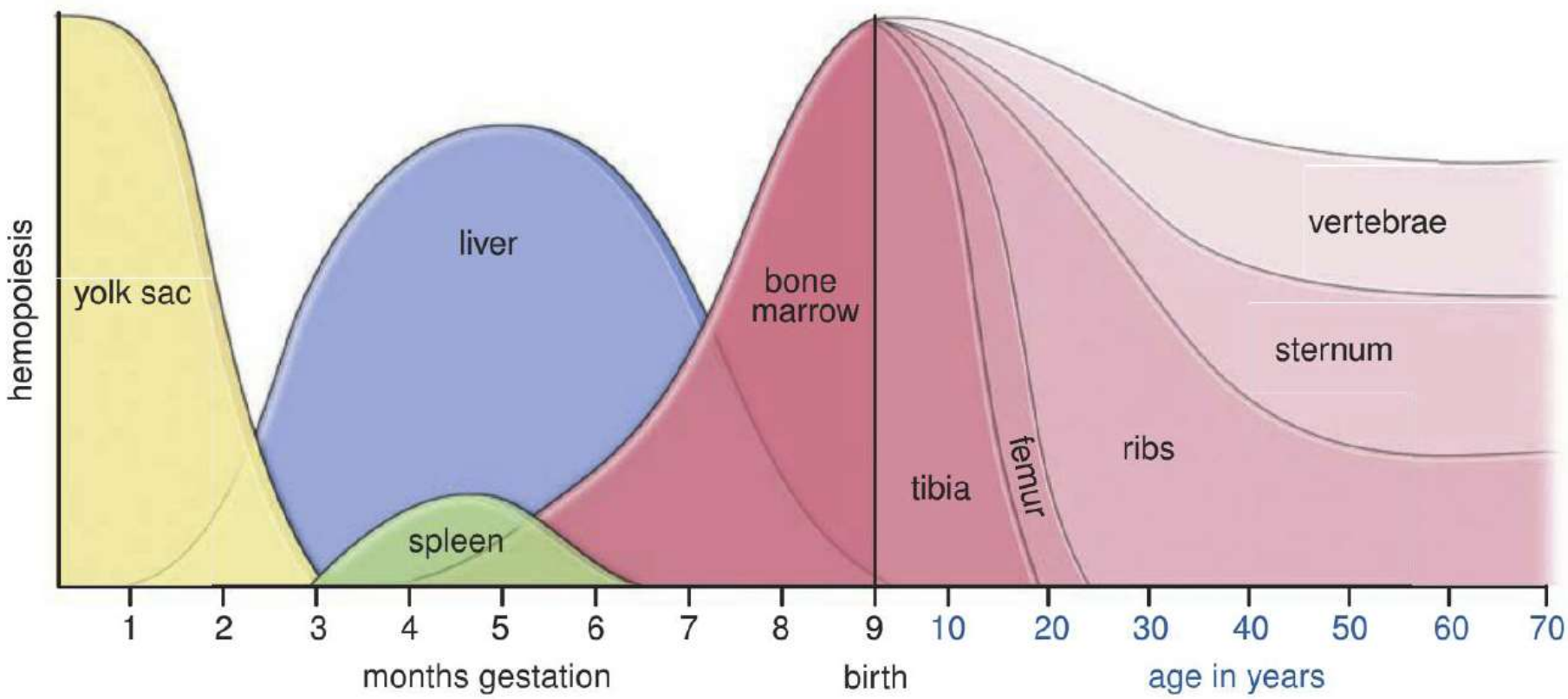
Hemopoiesis (Hematopoiesis)

- It is carried out in hematopoietic organs.

- Erythropoiesis
- Leukopoiesis
- Thrombopoiesis

■Erythrocytes, platelets and granulocytes (neutrophils, eosinophils, basophil leukocytes) of blood cells are produced in myeloreticular tissue (red bone marrow).

■Agranulocytes (lymphocytes and monocytes); they are made both in the red bone marrow and in the lymphoreticular tissues (lymphoid organs).


hemopoiesis
yolk sac
liver
spleen
bone marrow
tibia
femur
ribs
sternum
vertebrae
1
2
3
4
5
6
7
8
9
10
20
30
40
50
60
70
months gestation
birth
age in years

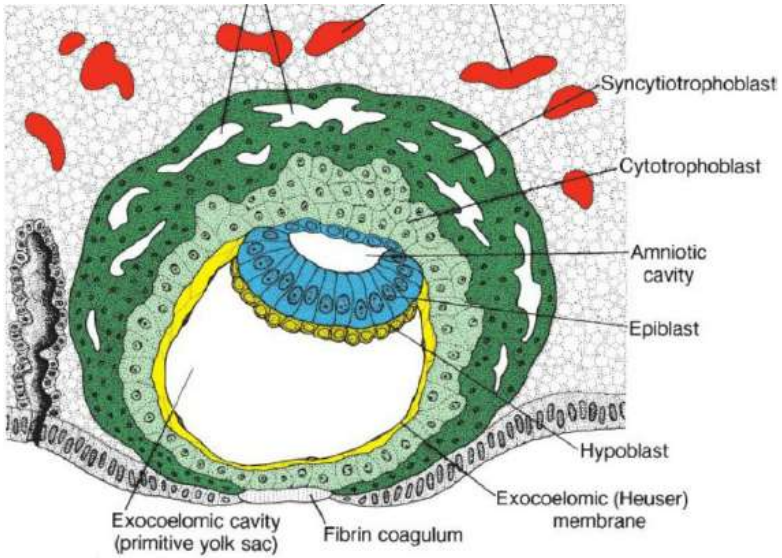
Ensuring continuity

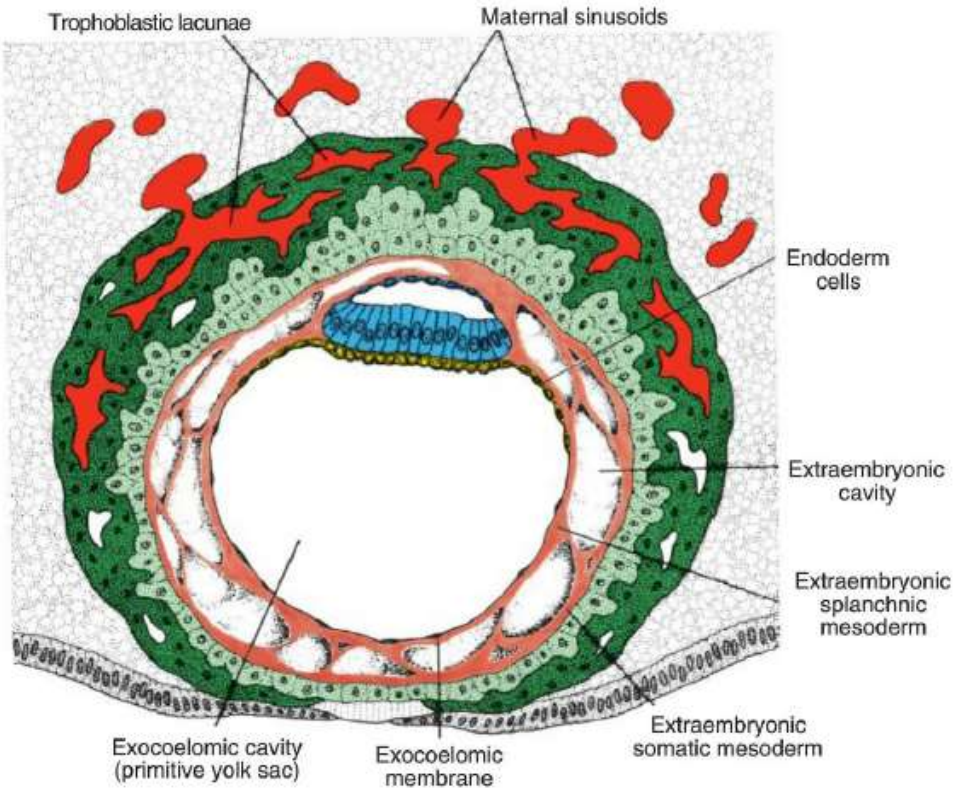
- The circulating blood cells have certain lifetimes. The cells are constantly destroyed and renewed. Therefore, a continuous production dynamics is needed.

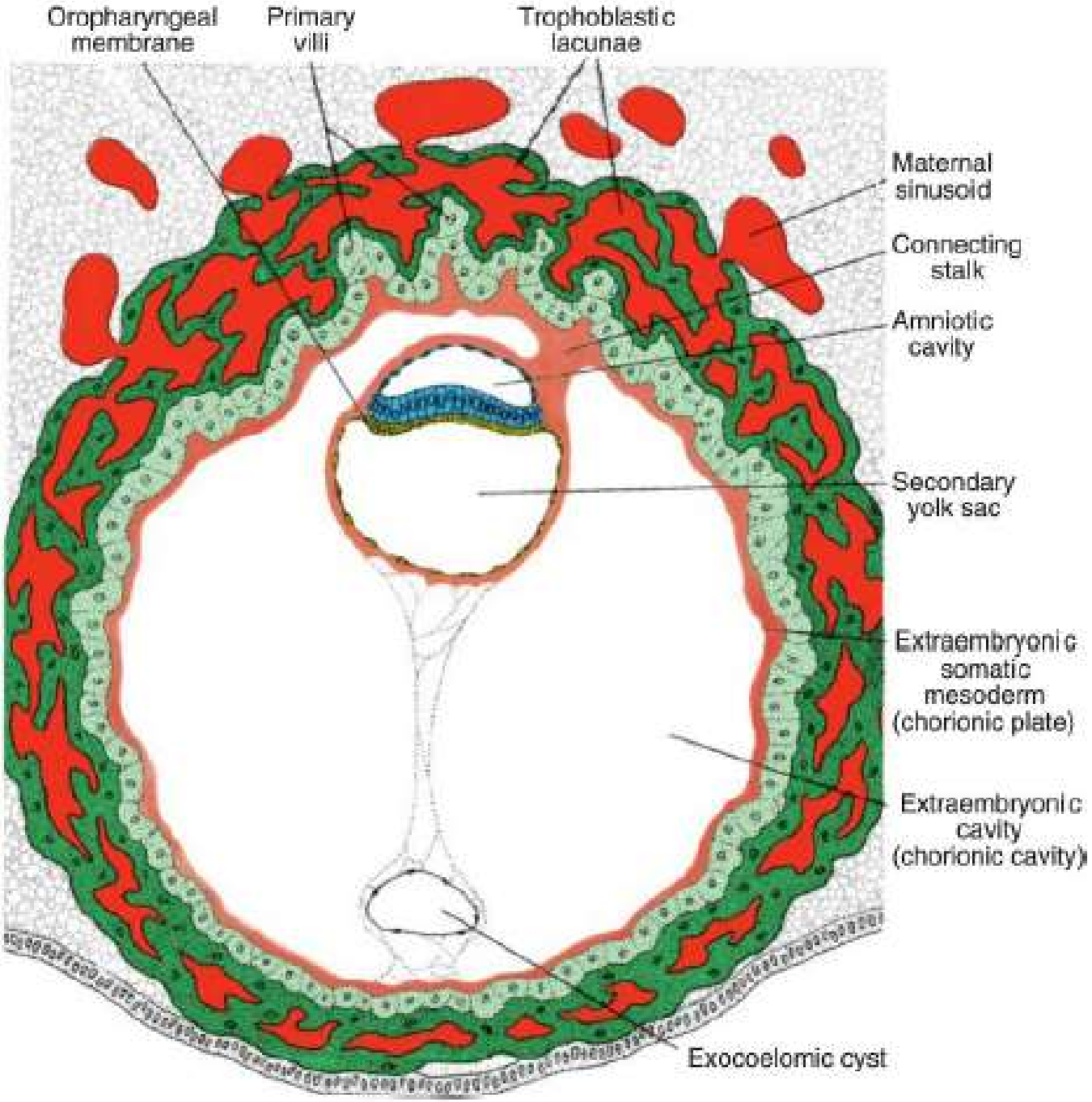
Blood product	Life span
Red blood cells	120 days
Fetal red blood cells	90 days
Platelets	7-12 days
Transfused platelets	36 hours
Neutrophils	8-12 hours in circulation 4-5 days in tissue

Prenatal hematopoiesis

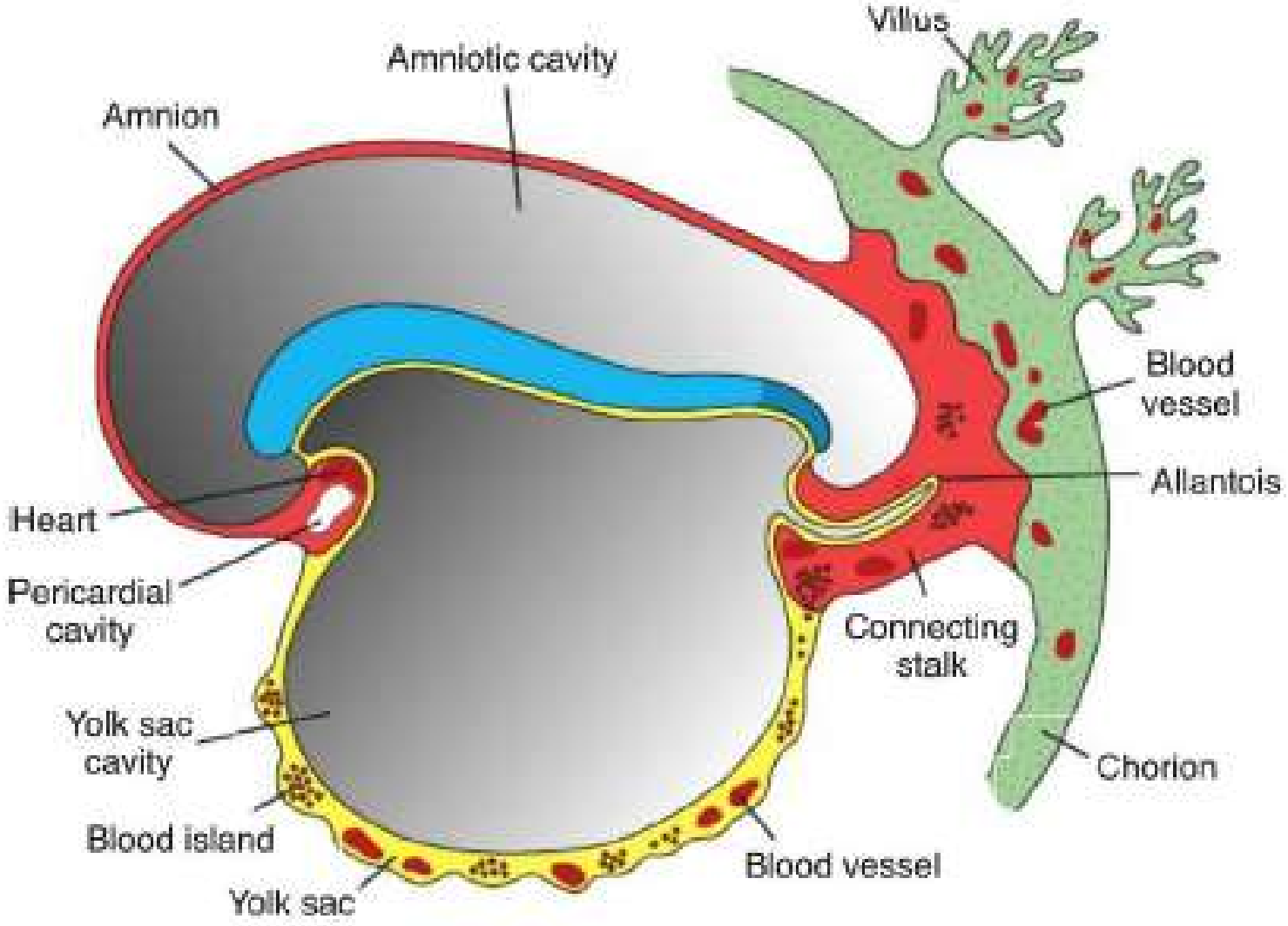
- Yolk sac Stage






Oropharyngeal membrane
Primary villi
Trophoblastic lacunae
Maternal sinusoid
Connecting stalk
Amniotic cavity
Secondary yolk sac
Extraembryonic somatic mesoderm (chorionic plate)
Extraembryonic cavity (chorionic cavity)
Exocoelomic cyst

3rd Week → Hemangioblast formation



Prenatal Hemopoez

- Mesoblastic phase

(2nd week-mesoderm of the yolk sac)

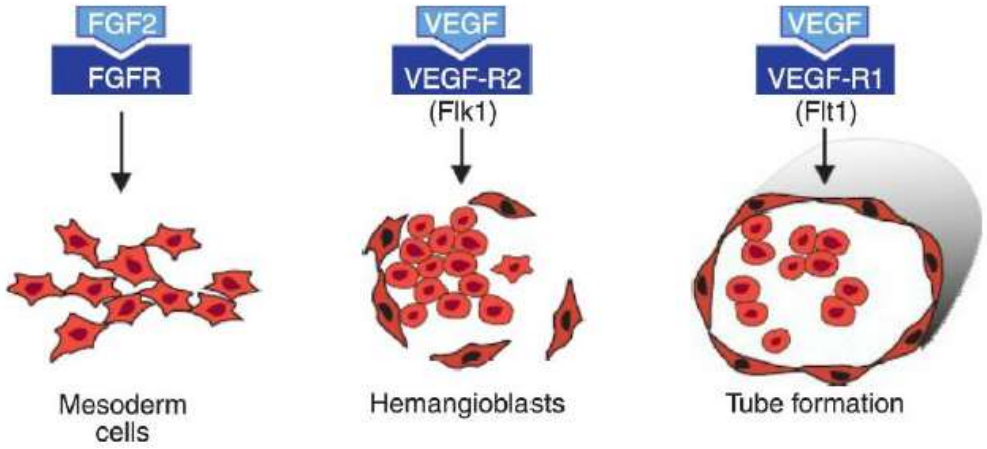
- Hepatosplenothymic phase
  - ✓ Liver (6th week)
  - ✓ Spleen (8th week)
  - ✓ Thymus (8th week)
- Medullalymphatic phase (3-5th month)

Temporary blood islets of the yolk sac

- In the 3rd week of embryological development, mesodermal cells in the yolk sac wall are differentiated into hemangioblast cells.
- These cells are the precursors of both blood cells and endothelial cells that will form the vascular system.
- Blood precursors formed in this region are temporary.
- The main hematopoietic stem cells develop from the mesoderm surrounding the aorta, called the **aorta-gonad-mesonephros region (AGM)**, next to the developing mesonephric kidney.
- These cells colonize the liver and form the main fetal hematopoietic organ (2-7th month of pregnancy)
- Cells in the liver then settle into the bone marrow, and from the 7th month of pregnancy, the bone marrow becomes the final production center

1. Mesoblastic phase

- In the 3rd week of pregnancy, when the first blood cells begin to develop from the mesoderm of the yolk sac and blood islets are formed.
- Peripheral cells in the islets make up the vascular wall, others with nucleated erythrocytes (hemocytoblast).

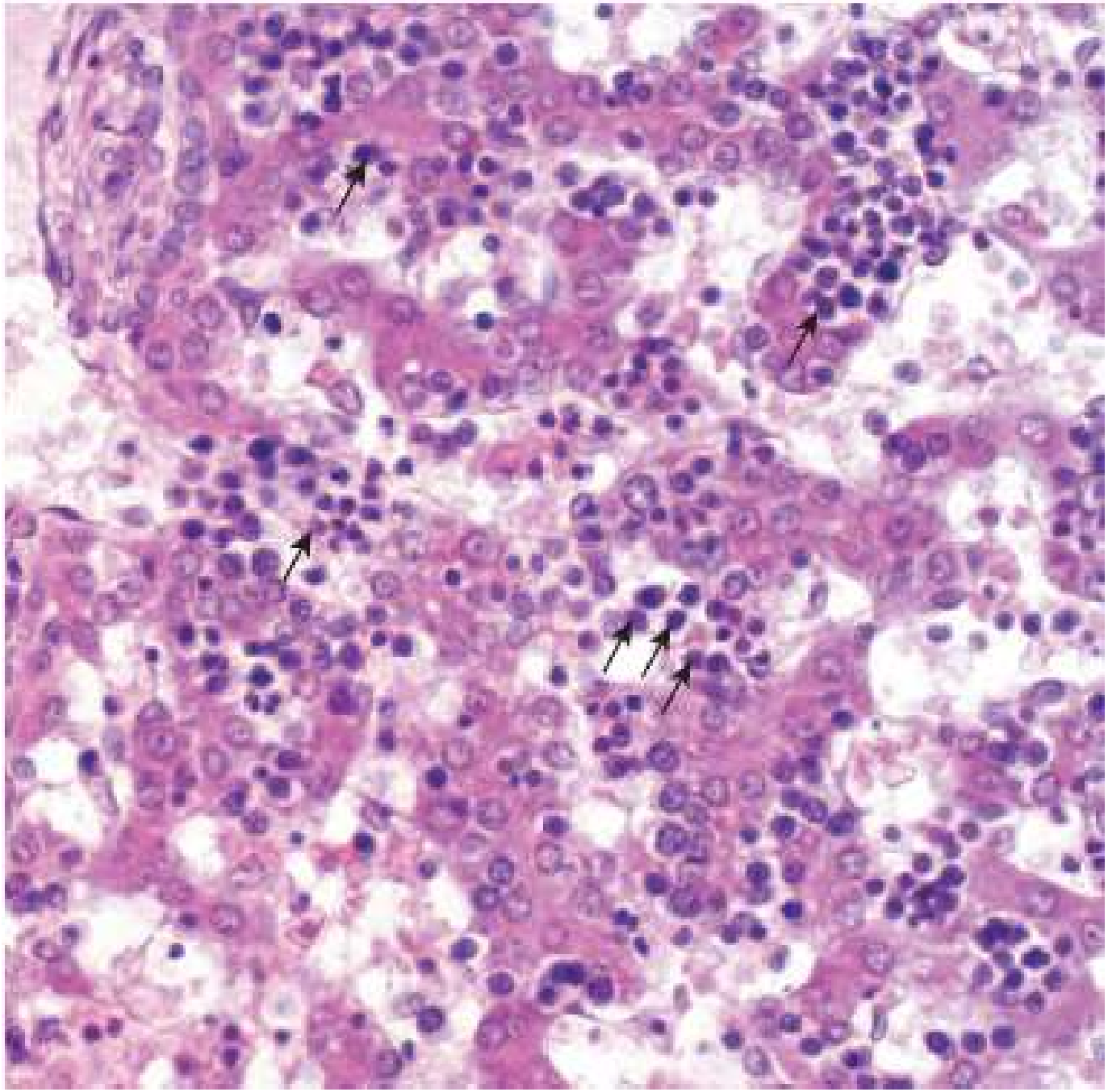


- The vascular system develops when the vessels from the blood islets connect with each other.
- From hemocytoblast; erythrocyte serial cells develop.
- Erythrocytes remain nucleated.
- The hemoglobin of erythrocytes from the yolk sac is different from that of other blood-forming organs (spleen, liver, bone marrow).
- These erythrocytes are larger than the erythrocytes made later. Therefore, named as megaloblastic erythropoiesis.
- **At this stage, only erythrocytes are made, there are no granulocytes and platelets.**

Further reading: *The hemangioblast: from concept to authentication.*
Cao N1, Yao ZX.Anat Rec (Hoboken). 2011 Apr;294(4):580-8. PMID: 21370498

2. Hepatic phase

- It replaces the mesoblastic phase at the 6th week of pregnancy. During the 2nd trimester, liver is the major blood-making organ.
- Erythrocytes are still with nucleus.
- Leukocytes appear at 8th week.



❖Hepatosplenothymic phase

- The liver is the second hematopoetic organ during development, begins blood production in about 6th week. The most active place of hemopoiesis until the middle of fetal life is the liver.
- Then its activity decreases gradually, normally the activity close to birth disappears completely.
- Although there are small erythroblast foci in the newborn, these foci are deleted in a short time.
- The adult liver is not a hematopoetic organ

3. Splenic phase

- Starts during second trimester
- Splenic ve Hepatic phase continue until the end of the pregnancy

4. Myeloid phase

- The phase when the hemopoiesis starts in bone marrow at the end of second trimester (5th month)

• Medullo-lymphatic stage

- The first hemopoetic activity in the bone marrow appears in the clavicula during 2nd and 3rd months.
- Bone marrow activity gained importance in the 4th month.
- Firstly erythrocytes, granulocytes and megakaryocytes develop. Lymphocytes and monocytes are made.
- It is the bone marrow that produces the major blood elements in the last 3 months of the fetal phase and throughout the post-natal phase.
- Bone marrow is a continuous and most important hemopoietic organ.
- The lymph nodes are activated around birth

Postnatal Hemopoiesis

- Bone marrow
- Lymphoid organs

- If necessary…

Extramedullary Hemopoiesis

(Liver + Spleen + Lymph nodes)

(In some pathological events, in adults, the shift in formation of blood cells to the spleen, liver and lymph nodes is called extra-medullary hemopoiesis.)

Postnatal Hemopoiesis

- Stem cell
  ↓
- Progenitor cells
  ↓
- Precursor cells (_blasts)
  ↓
- Mature cells

From stem cells…

- Erythropoiesis → Erythrocytes
- Granulopoiesis → Granular leukocytes
- Monocytopoiesis → Monocytes
- Megakaryocytopoiesis → Platelets
- Lymphopoiesis → Lymphocytes

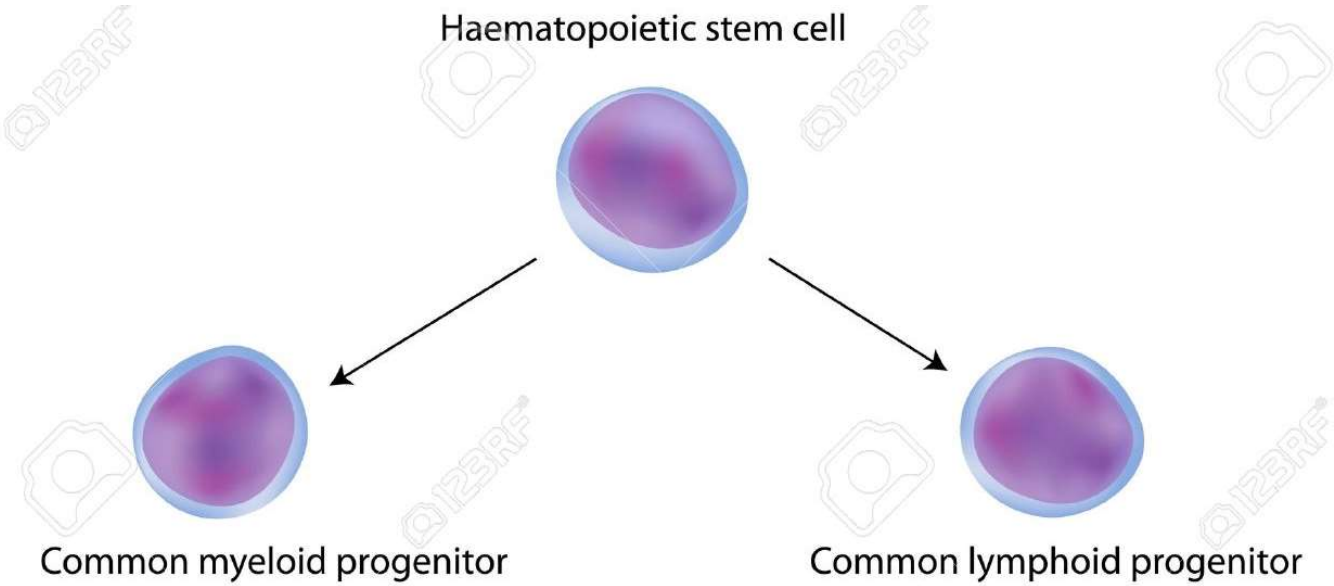
Monophyletic Theory of Hemopoiesis

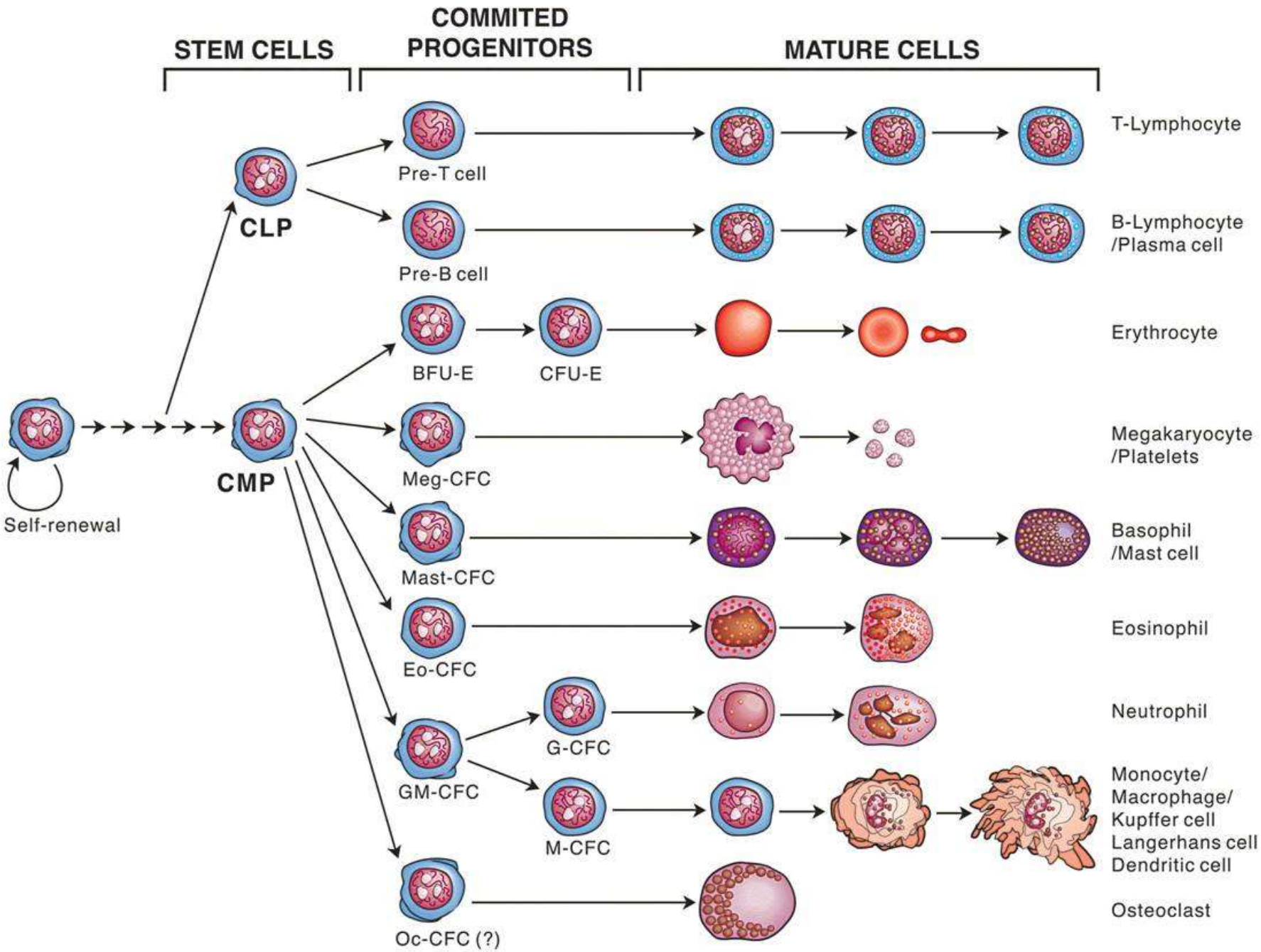
- It is the theory that all blood cells are derived from a common hemopoietic stem cell.
- The hemopoietic stem cell, also known as *pluripotential stem cell* (PPSC), is capable not only of differentiating into all the blood cell lineages but also of self-renewal.
- Recent studies indicate that HSCs also have the potential to differentiate into multiple non-blood cell lineages and contribute to the cellular regeneration of various tissues and multiple organs.
- Molecular surface markers are used to identify hematopoietic stem cells immunocytochemically

CD34+ AND CD90+ AND Lin- (lineage) AND CD38-

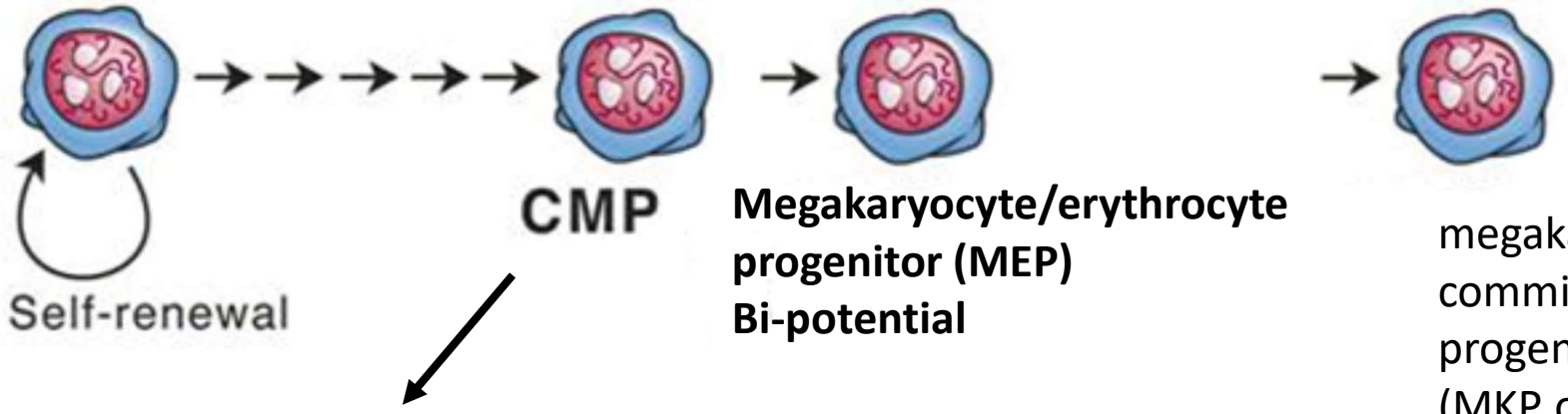
Progenitor stem cell

- Hemopoietic stem cell creates many progenitor stem cell colonies
- In the bone marrow, HSC is differentiated into two major progenitor cell colony serials
  - **Common myeloid progenitor cell**
  - **Common lymphoid progenitor cell**




STEM CELLS
COMMITED PROGENITORS
MATURE CELLS
Self-renewal
CMP
CLP
Pre-T cell
Pre-B cell
BFU-E
CFU-E
Meg-CFC
Mast-CFC
Eo-CFC
G-CFC
GM-CFC
M-CFC
Oc-CFC (?)
T-Lymphocyte
B-Lymphocyte /Plasma cell
Erythrocyte
Megakaryocyte /Platelets
Basophil /Mast cell
Eosinophil
Neutrophil
Monocyte/ Macrophage/ Kupffer cell Langerhans cell Dendritic cell
Osteoclast

Common Myeloid Progenitor Cell



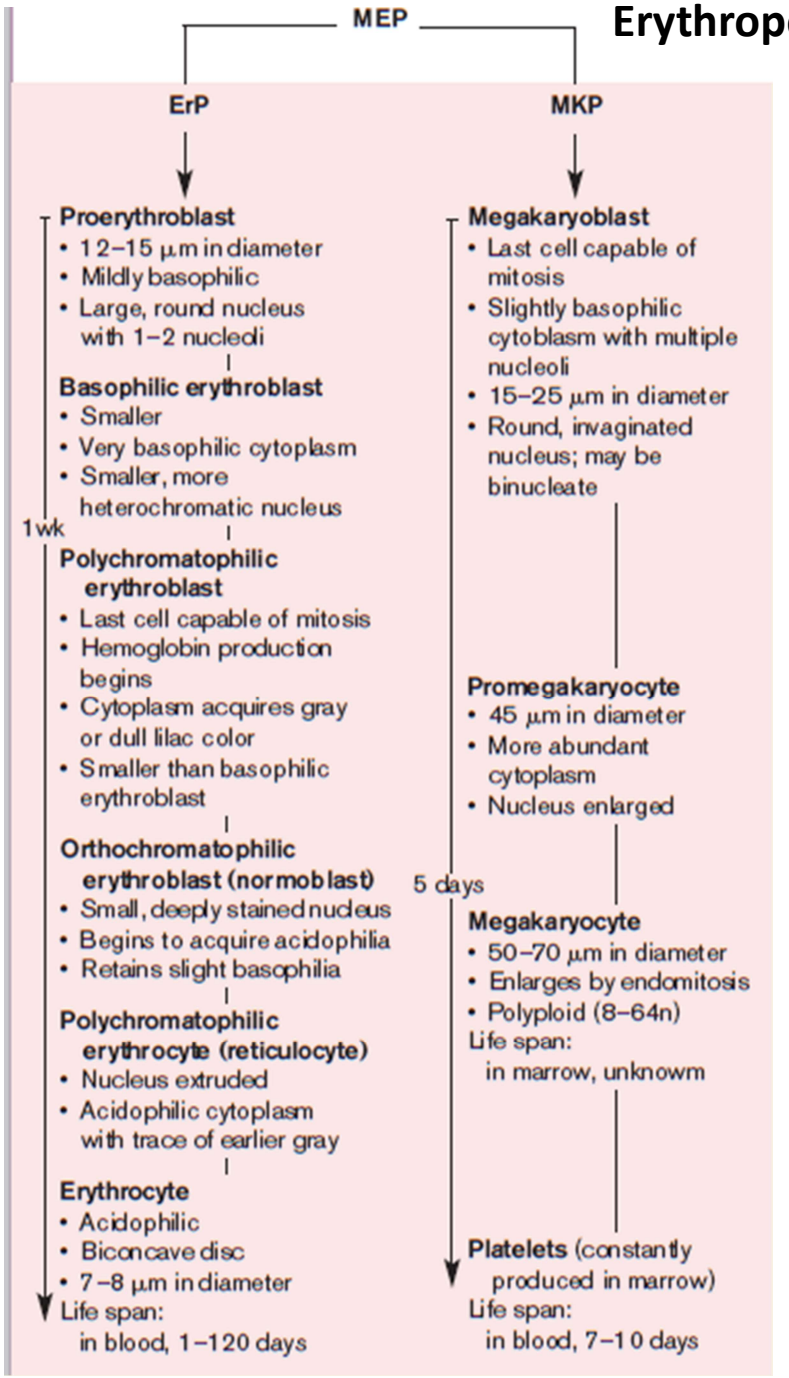
Formerly named:
colony-forming units–granulocyte, erythrocyte, monocyte, megakaryocyte
(CFU-GEMM)

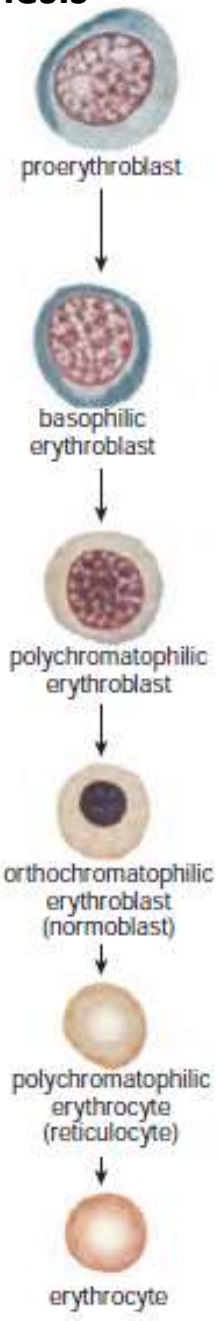
Megakaryocyte/erythrocyte progenitor (MEP)
Bi-potential

erythrocyte - committed progenitor cells (ErP *or* CFU-E)
Mono potential

megakaryocyte - committed progenitor cells (MKP or CFU-Meg)
Mono potential

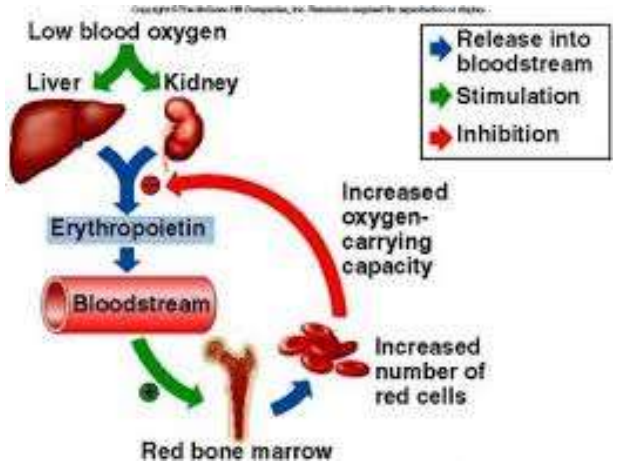
Erythropoiesis





- It starts from CMP cells that, under the influence of **erythropoietin, IL-3, and IL-4**, differentiate to MEP cells.
- Under GATA-1 influence, MEP cells transform into erythropoietin –sensitive erythrocyte -committed progenitors (ErPs or CFU-E) that give rise to the **Proerythroblast**.
- Proerythroblast, which undergoes mitosis, forms the **Basophilic Erythroblast**. Basophilic apperance is due to the dense ribosomes required for Hb production
- As Hb synthesis increases, the cell enters the **Polychromatophilic Erythroblast** stage, where it is monitored as both eosinophilic and basophilic.
- In the next stage, **Orthochromatophilic erythroblast (normoblast)** appears as a completely eosinophilic stained cell that no longer undergoes mitosis.
- Then the nucleus is removed and the cytoplasm contains web-like basophilic areas due to ribosomes that continue to Hb synthesis => **Polychromatophilic erythrocyte (reticulocyte)**

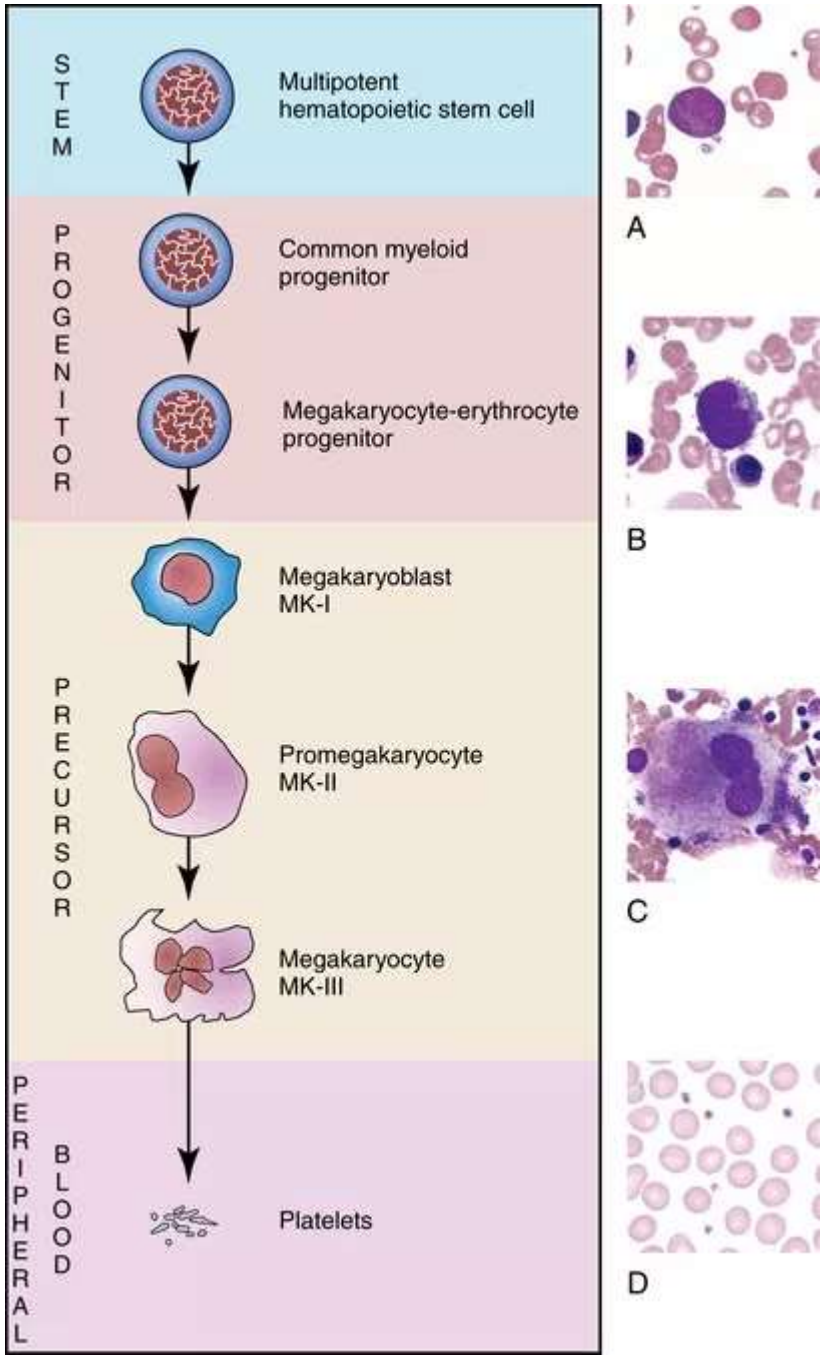
Erythropoietin



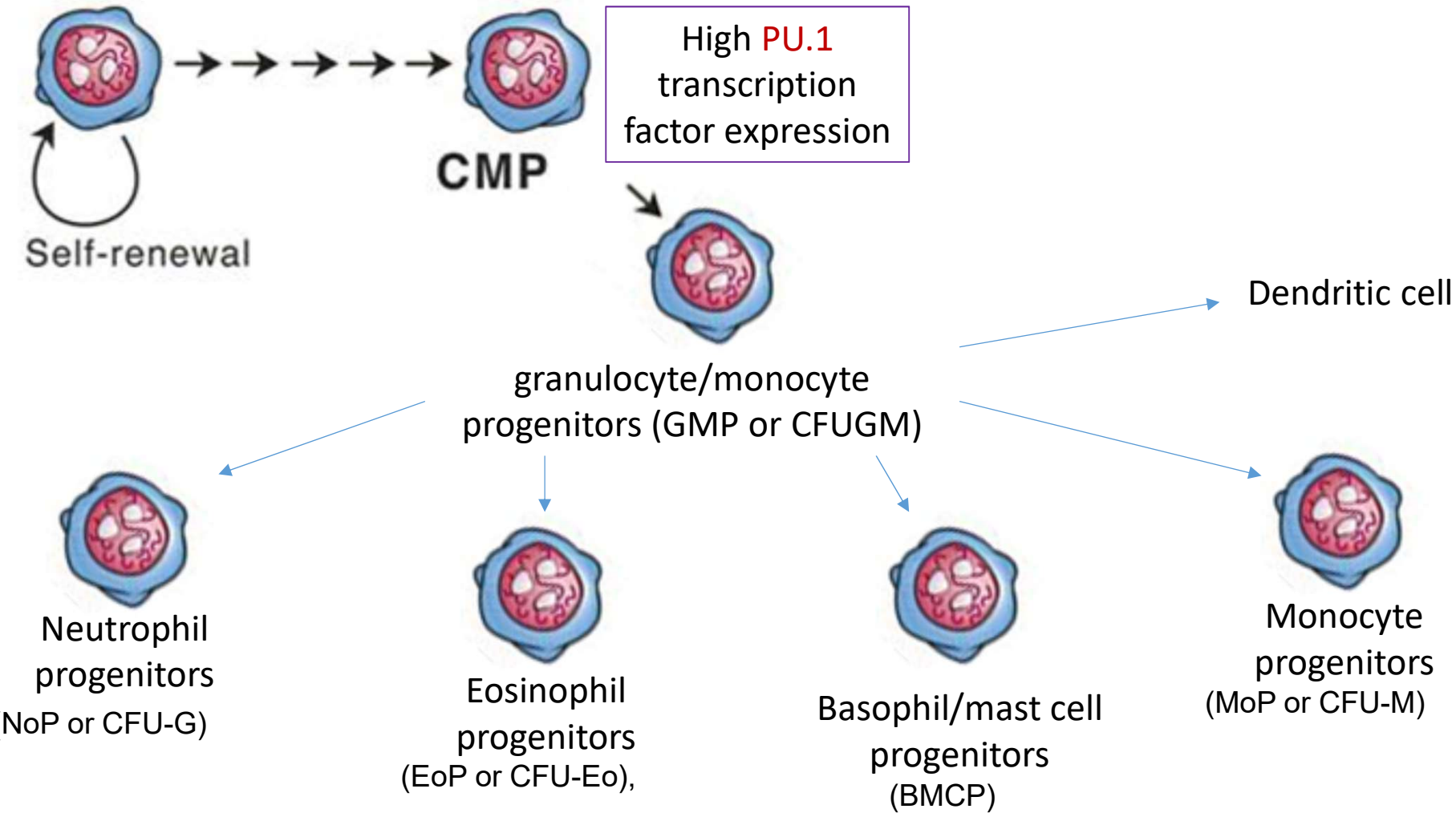
- Erythrocyte production and circulation is under the control of ERYTHROPOIETIN.
- It is a glycoprotein hormone released from KIDNEY followed by reduced blood oxygen concentration.
- The produced red blood cells are released into the blood stream immediately, not stored in the bone marrow.
- They is destroyed in the spleen after 120 days. Hemoglobin breaks down. Globin is broken down into amino acids and reused. Iron in hem is stored as hemosiderin and ferritin
- The rest of Hem is destroyed as bilirubin, which is attached to the album, carried, conjugated in liver and excreted in bile.

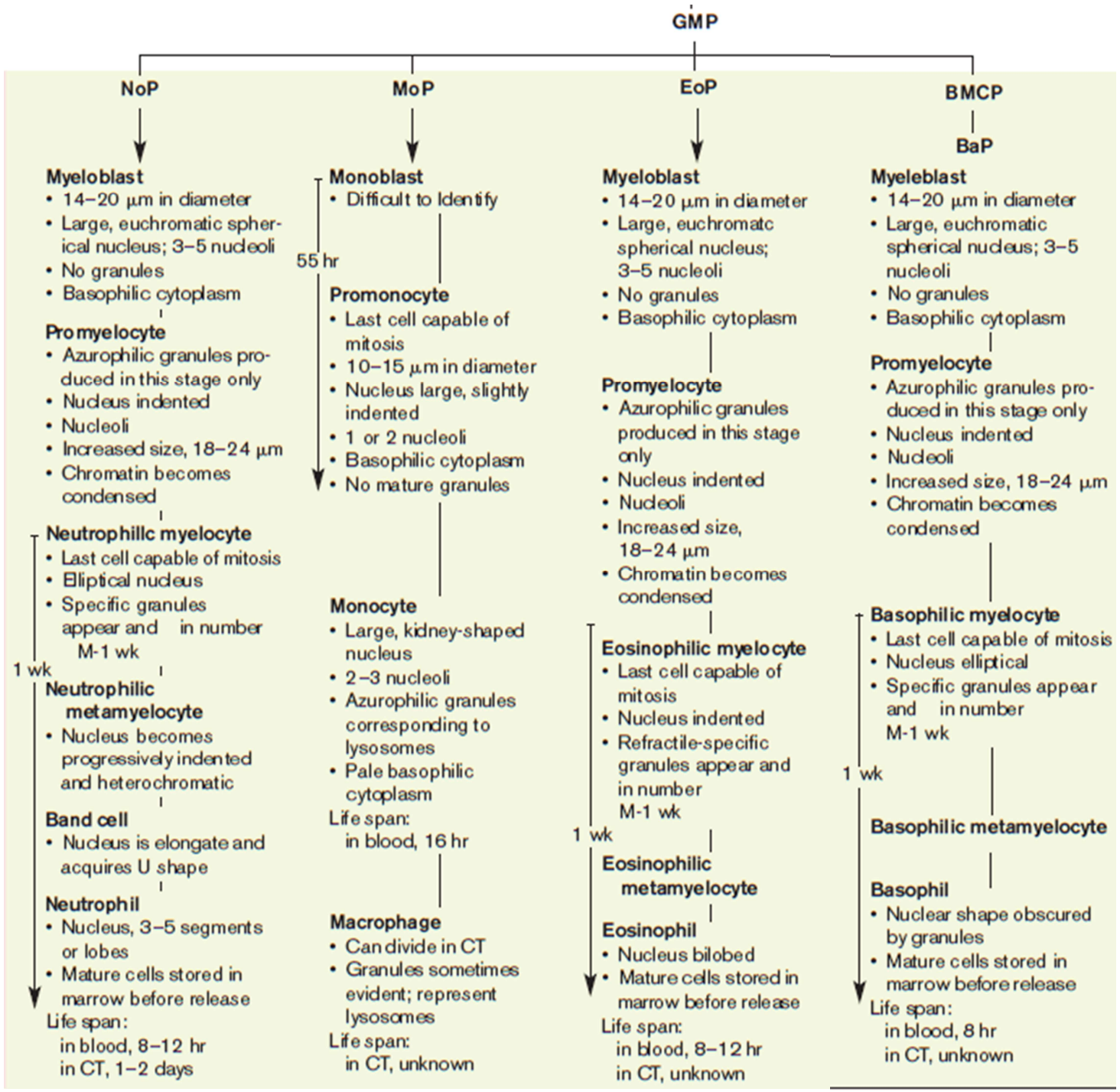
Thrombopoiesis

- Each day, bone marrow of a healthy adult produces about 1 X 10^{11} platelets,
- **MEP cell → megakaryocyte-committed progenitor (MKP) cell → megakaryoblast.**
- With the effect of **granulocyte-monocyte colony growth factor (GM-CSF)** and **IL-3**, the common myeloid progenitor cell is first differentiated to MEP and then to megakaryocyte progenitor cell (MKP).
- After the formation of **megakaryoblast**, under the effect of thrombopoetin (produced in liver and kidney), the number of nuclei increases and **megakaryocyte** is formed.

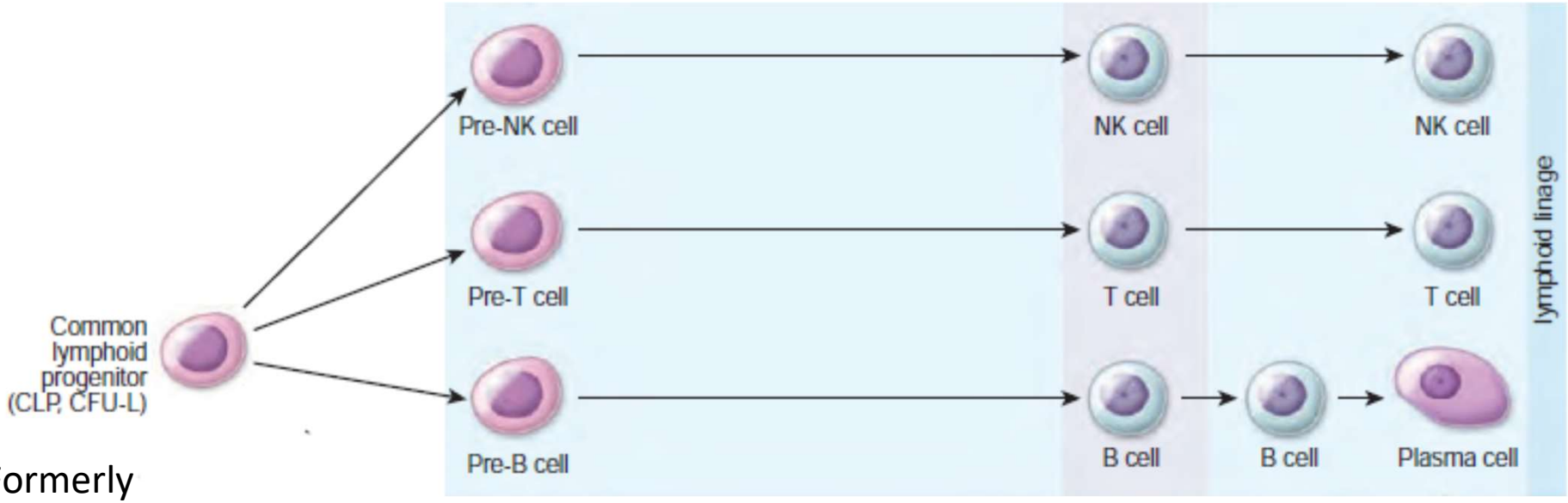


Common Myeloid Progenitor Cell




GMP
NoP
MoP
EoP
BMCP
BaP
Myeloblast
• 14–20 μm in diameter
• Large, euchromatic spherical nucleus; 3–5 nucleoli
• No granules
• Basophilic cytoplasm
Promyelocyte
• Azurophilic granules produced in this stage only
• Nucleus indented
• Nucleoli
• Increased size, 18–24 μm
• Chromatin becomes condensed
Neutrophillc myelocyte
• Last cell capable of mitosis
• Elliptical nucleus
• Specific granules appear and in number
M-1 wk
1 wk
Neutrophilic metamyelocyte
• Nucleus becomes progressively indented and heterochromatic
Band cell
• Nucleus is elongate and acquires U shape
Neutrophil
• Nucleus, 3–5 segments or lobes
• Mature cells stored in marrow before release
Life span:
in blood, 8–12 hr
in CT, 1–2 days
Monoblast
• Difficult to Identify
55 hr
Promonocyte
• Last cell capable of mitosis
• 10–15 μm in diameter
• Nucleus large, slightly indented
• 1 or 2 nucleoli
• Basophilic cytoplasm
• No mature granules
Monocyte
• Large, kidney-shaped nucleus
• 2–3 nucleoli
• Azurophilic granules corresponding to lysosomes
• Pale basophilic cytoplasm
Life span:
in blood, 16 hr
Macrophage
• Can divide in CT
• Granules sometimes evident; represent lysosomes
Life span:
in CT, unknown
Myeloblast
• 14–20 μm in diameter
• Large, euchromatc spherical nucleus; 3–5 nucleoli
• No granules
• Basophilic cytoplasm
Promyelocyte
• Azurophilic granules produced in this stage only
• Nucleus indented
• Nucleoli
• Increased size, 18–24 μm
• Chromatin becomes condensed
Eosinophilic myelocyte
• Last cell capable of mitosis
• Nucleus indented
• Refractile-specific granules appear and in number
M-1 wk
1 wk
Eosinophilic metamyelocyte
Eosinophil
• Nucleus bilobed
• Mature cells stored in marrow before release
Life span:
in blood, 8–12 hr
in CT, unknown
Myeleblast
• 14–20 μm in diameter
• Large, euchromatic spherical nucleus; 3–5 nucleoli
• No granules
• Basophilic cytoplasm
Promyelocyte
• Azurophilic granules produced in this stage only
• Nucleus indented
• Nucleoli
• Increased size, 18–24 μm
• Chromatin becomes condensed
Basophilic myelocyte
• Last cell capable of mitosis
• Nucleus elliptical
• Specific granules appear and in number
M-1 wk
1 wk
Basophilic metamyelocyte
Basophil
• Nuclear shape obscured by granules
• Mature cells stored in marrow before release
Life span:
in blood, 8 hr
in CT, unknown

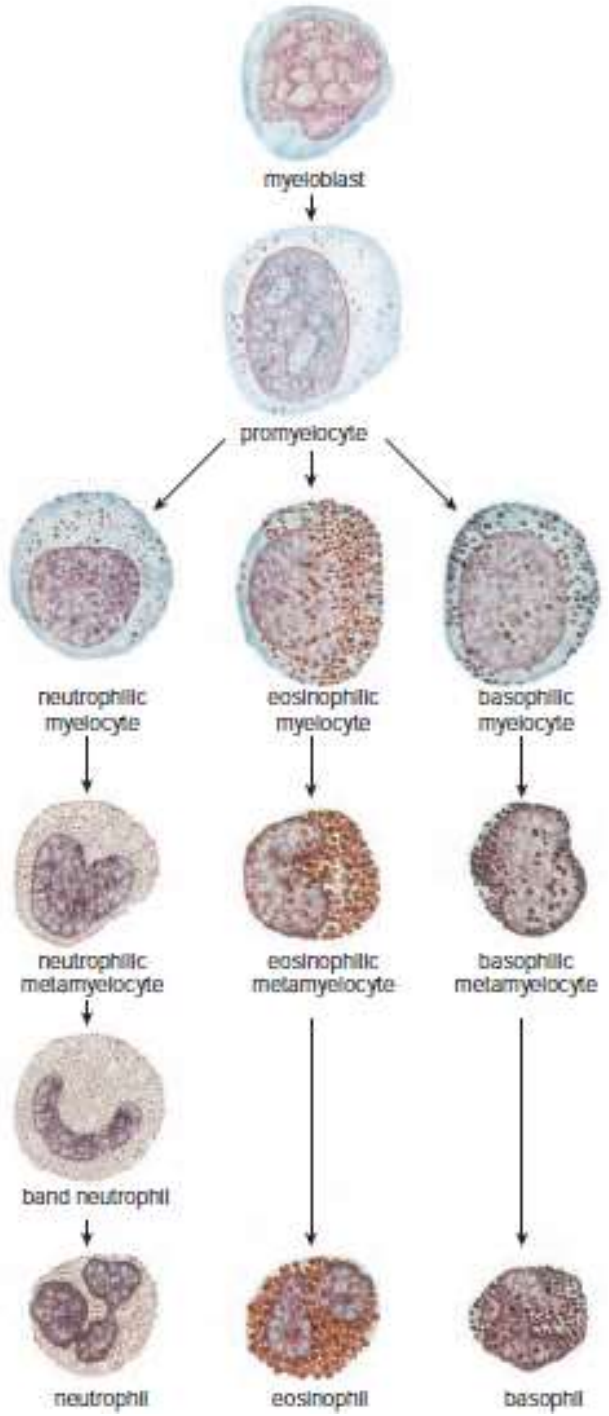
Common Lymphoid Progenitor Cell



Formerly named: *colony-forming units–lymphoid* **(CFU-L)**

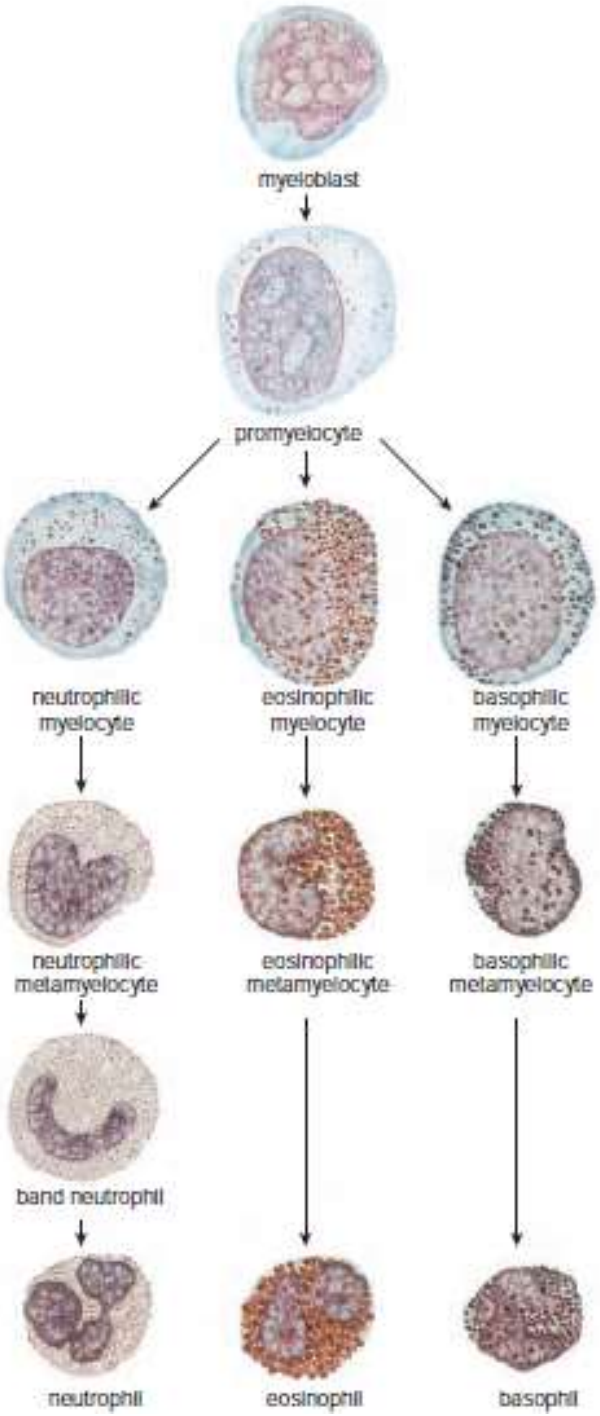
Granulopoiesis - 1

- The common myeloid progenitor cell transforms into a Granulocyte-Monocyte Progenitor cell with the effect of **GM-CSF, granulocyte colony stimulating factor (G-CSF) and IL-3**.
- **GM-CSF** is secreted by endothelial cells, T-cells, macrophages, mast cells and fibroblasts.
- It stimulates common myeloid cells to make granulocyte series and monocytes.
- **Myeloblast, promyelocyte, myelocyte, metamyelocyte, band cell, and mature neutrophil**, respectively



Granulopoiesis - 2

- The common myeloid progenitor cell turns into **Eosinophilic Progenitor cell under the action of GM-CSF, IL-3 and IL-5.**
- If there is **no IL-5** in the medium, the common myeloid serial cell turns into a **Basophil Progenitor**
- Azurophilic granules are created only at the **promyelocyte stage**, there is no production in the following mitoses
- Granule differences between granulocytes are not apparent up to the myelocytic stage. Specific granules begin to be produced in the **myelocytic stage**
- In the **metamyelocyte stage**, granular series cells can be distinguished from each other.
- The mitotic stage lasts until late myelocyte, which takes 1 week. Then the maturing period also takes about 1 week.
- For neutrophils, there is a reserve population in BM and in circulating

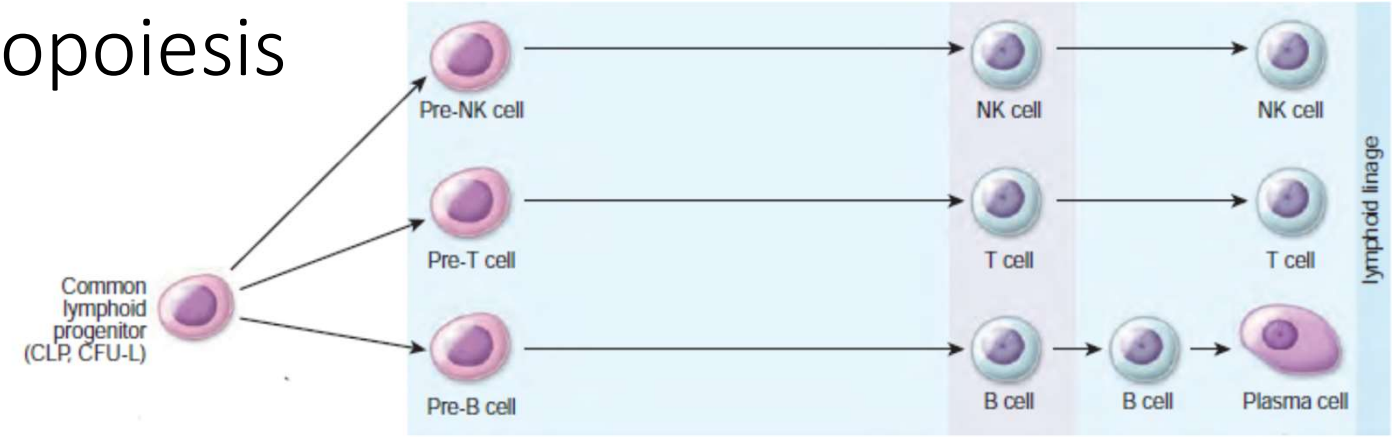


Cytokine[a]	Symbol	Source	Target
Granulocyte-macrophage colony-stimulating factor	GM-CSF	T cells, endothelial cells, fibroblasts	CMP, ErP, GMP, EoP, BaP, MKP, all granulocytes, erythrocytes
Granulocyte colony-stimulating factor	G-CSF	Endothelial cells, monocytes	ErP, GMP, EoP, BaP, MKP
Monocyte colony-stimulating factor	M-CSF	Monocytes, macrophages, endothelial and adventitial cells	GMP, MoP, monocytes, macrophages, osteoclasts
Erythropoietin	EPO	Kidney, liver	CMP, MEP, ErP
Thrombopoietin	TPO	Bone marrow	MKP, megakaryocytes
Interferon-γ	IFN-γ	$CD4^+$ T cells, NK cells	B cells, T cells, NK cells, neutrophils, monocytes
Interleukin 1	IL-1	Neutrophils, monocytes, macrophages, endothelial cells	$CD4^+$ T cells, B cells
Interleukin 2	IL-2	$CD4^+$ T cells	T cells, B cells, NK cells
Interleukin 3	IL-3	$CD4^+$ T cells	CMP, ErP, GMP, EoP, BaP, MKP, all granulocytes, erythroid cells
Interleukin 4	IL-4	$CD4^+$ T cells, mast cells	B cells, T cells, mast cells
Interleukin 5	IL-5	$CD4^+$ T cells	EoP, eosinophils, B cells
Interleukin 6	IL-6	Endothelial cells, neutrophils, macrophages, T cells	CMP, ErP, GMP, B cells, T cells, macrophages, hepatocytes
Interleukin 7	IL-7	Adventitial cells of bone marrow	Early pre-B, pre-T cells
Interleukin 8	IL-8	Macrophages, endothelial cells	T cells, neutrophils
Interleukin 9	IL-9	$CD4^+$ T cells	$CD4^+$ T cells, CMP, ErP
Interleukin 10	IL-10	Macrophages, T cells	T cells, B cells, NK cells
Interleukin 11	IL-11	Macrophages	CMP, ErP, GMP, T cells, B cells, macrophages, megakaryocytes

Monocytes

- Monocyte progenitor cell is detected in **IL-3** control from common myeloid progenitor
- Continuity of PU.1 and Egr-1 transcription factor is needed
- **IL-3 and GM-CSF** are also required for production
- Production takes about 55 hours

Lymphopoiesis



- Although lymphopoiesis occurs first and mainly in the bone marrow, the lymphoid organs then take over this task.
- Ikaros family transcription factors play a role in the differentiation of hemapoetic stem cell into common lymphoid progenitor cell.
- Cells expressing GATA-3 transcription factor develop in the T-lymphocyte direction
- These cells leave BM as pre-T-lymphocytes and develop in the thymus
- With the expression of Pax5 transcription factor, CLP cell develops in the B-lymphocyte direction.
- It completes its further development in BM, intestinal lymphoid tissue and spleen
- NK cells develop under the action of IL-2 and IL-15