HEMATOPOIESIS

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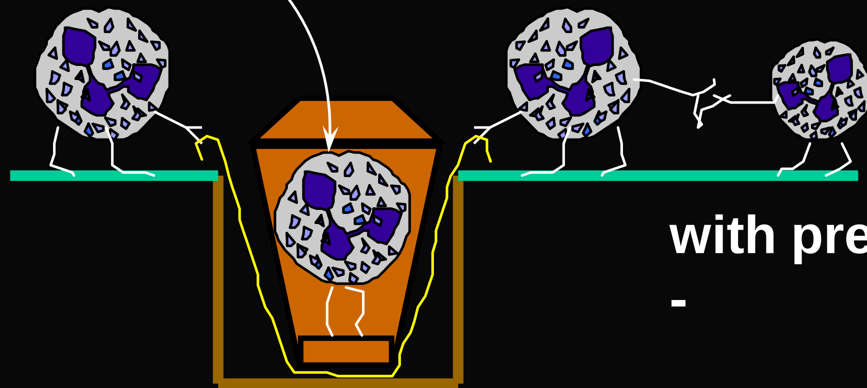
Agenda

- What is ment by haematopoiesis.
- Sites of haematopoiesis.
- Haematopoietic stem/Progenitor cells
- BM microenvironment.
- Regulation of haematopoiesis.

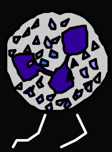
Hematopoiesis

- From Greek: hem (αἷμα) = blood, poes (ποιεῖν) = make, create
- Allows hematopoietic system to respond to stimuli such as infection, bleeding, or hypoxia by increasing production of cell line needed.
- Is the highly orchestrated process involved in the production, formation and development and replacement of all blood cells

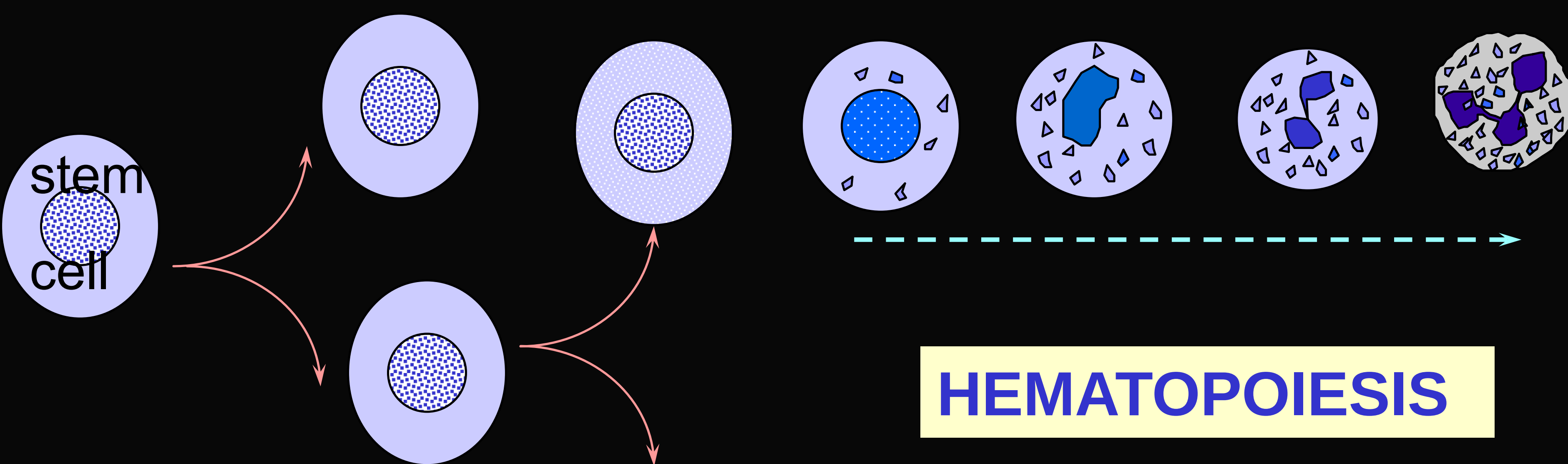
Blood cells have limited lifespans, and need to be replaced



with precisely matching numbers
-
Hematocytopoiesis



Young replacing cells come, by many *divisions* and steps of *differentiation*, from stem cells



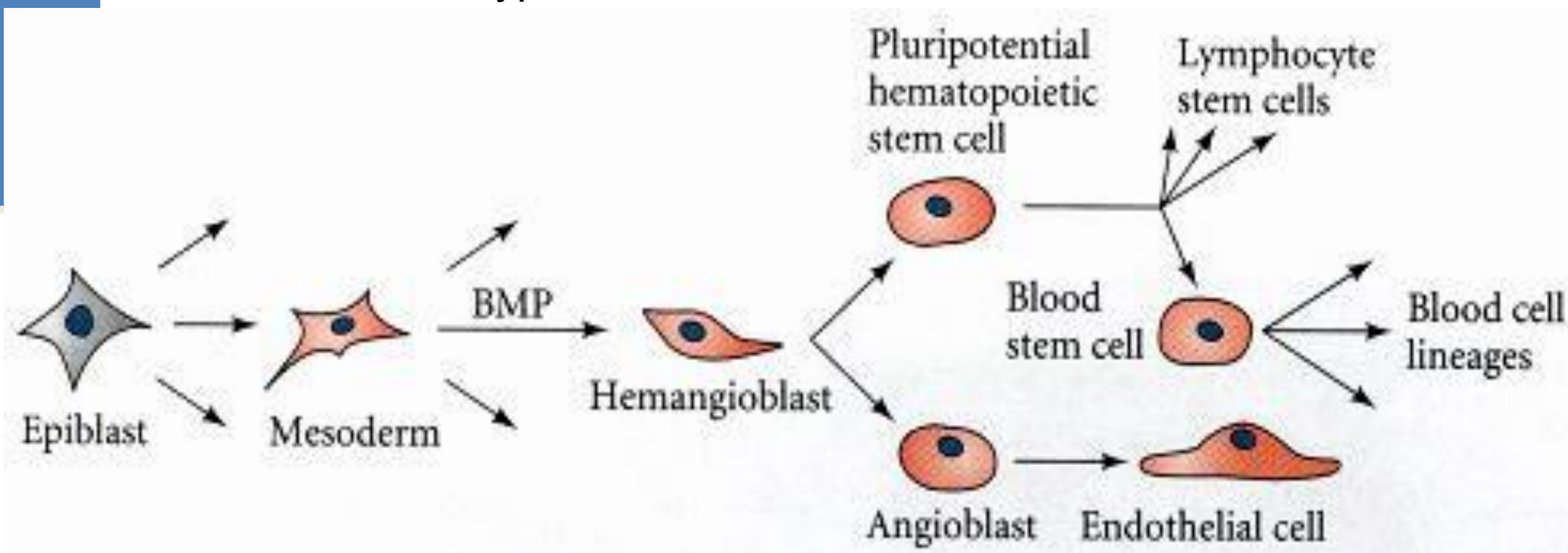
HEMATOPOIESIS

Stem Cell

- Virtually every organ has stem cells.
- These stem cells possess two major roles:
  - **Pluripotency** that gives rise to the mature cells to compose the specific organ or tissue
  - **Self-renewal** capability to supply enough cells to maintain the organ's function.
- **Totipotent** cell can give rise to a new individual given appropriate maternal support
- **Pluripotent** cell can give rise to all types of adult tissue cells plus extraembryonic tissue: cells which support embryonic development
- **Multipotent** cell can give rise to several types of mature cell

The Hemangioblast

- Studies have demonstrated that there are cells in the early embryo that have the potential to develop into both blood cells and vascular endothelial cells.
- These cells are termed **hemangioblasts** and are derived from mesodermal cells.
- **Hemangioblasts** give rise to hematopoietic stem cells that then form all the different types of blood cells

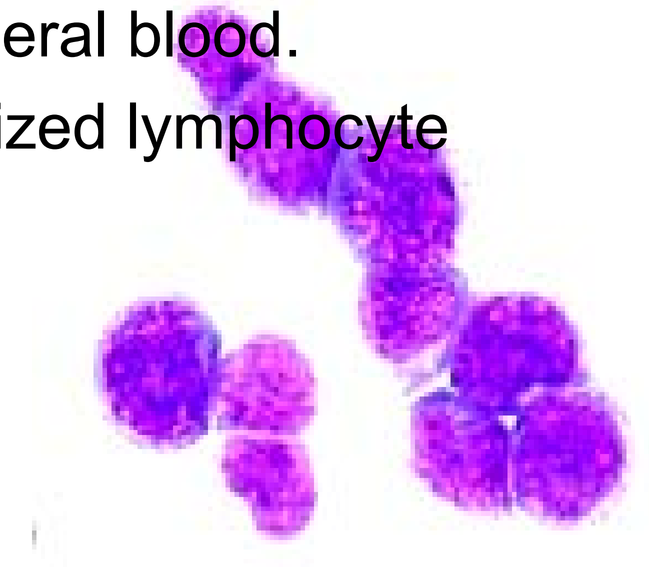


Hematopoietic Stem Cells

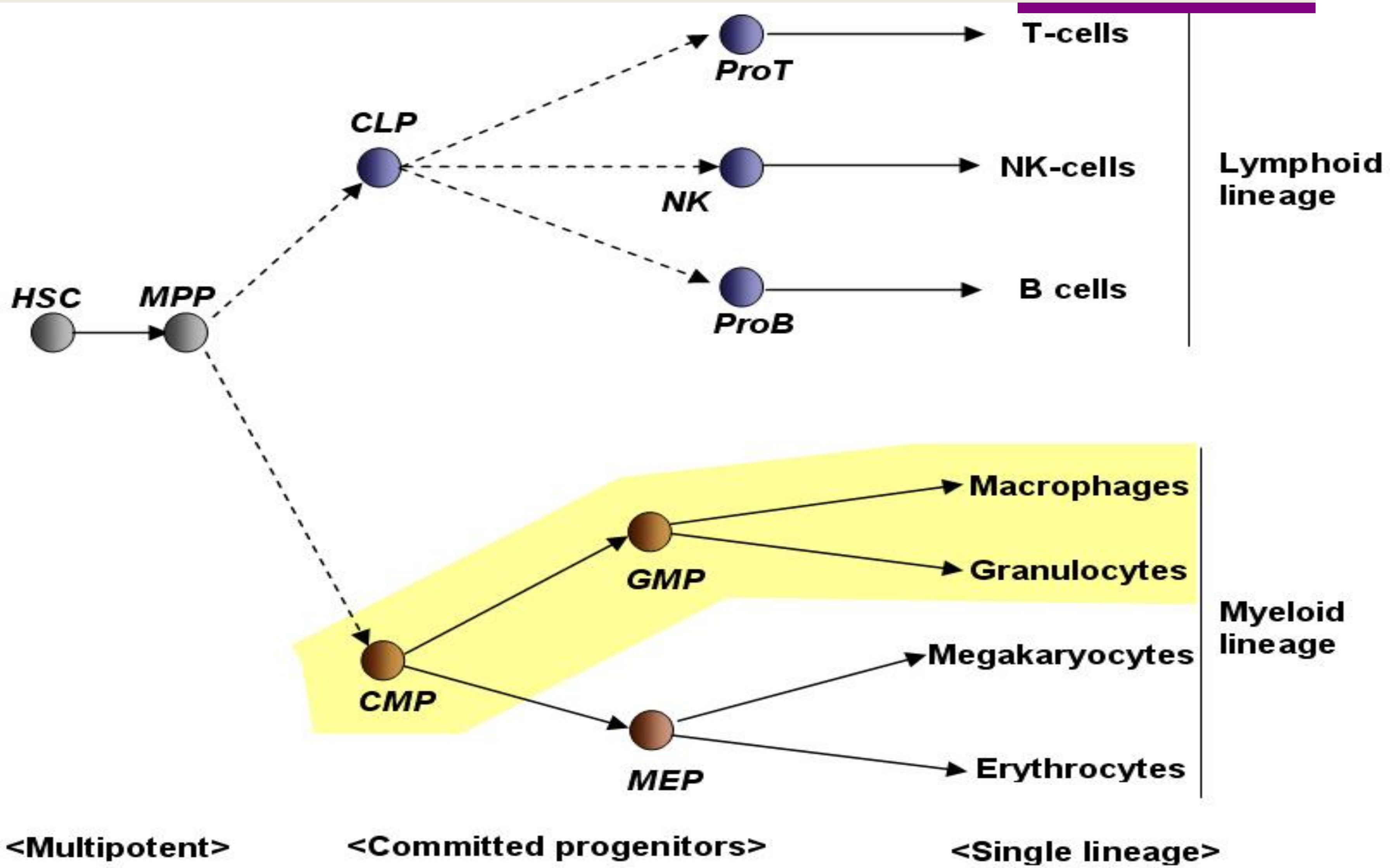
- Hematopoietic stem cells (HSC)- give rise to any blood cells
  - constant number
- Pluripotent cell capable of:
  - Self renewal: keeps the marrow cellularity (the stem cell pool) constant
- Differentiation: requires critical processes of cell-fate decision-making(result of biochemical signaling and gene regulatory networks within the cell.

Hematopoietic Stem Cells

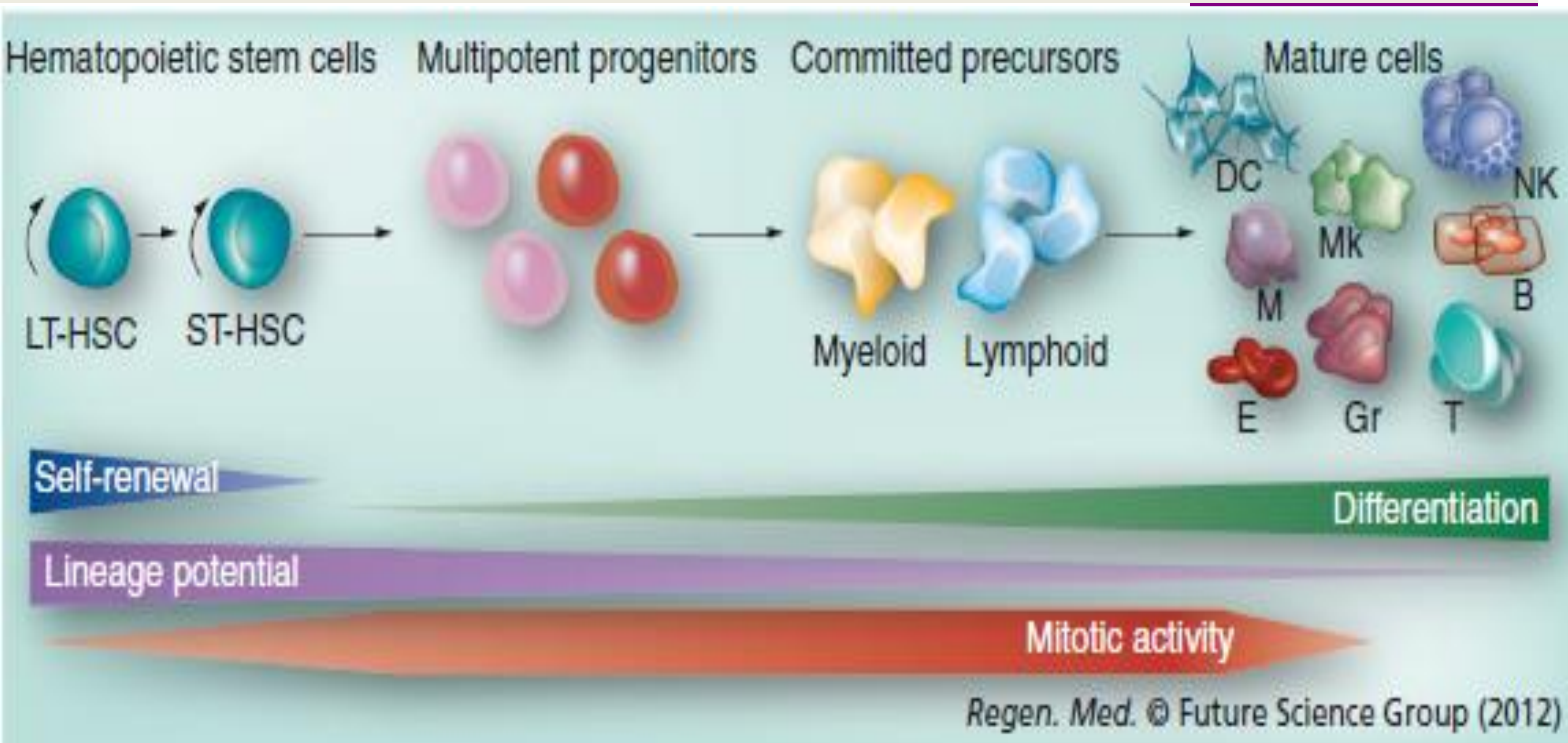
- One stem cell is capable of producing about 10^6 mature blood cells after 20 cell divisions
- HSCs represents about 1 :20 million nucleated cells of the bone marrow.
- HSCs are capable to traffic around the body and are found in low number in the peripheral blood.
- It resembles a small to medium sized lymphocyte



Scheme of Hematopoiesis

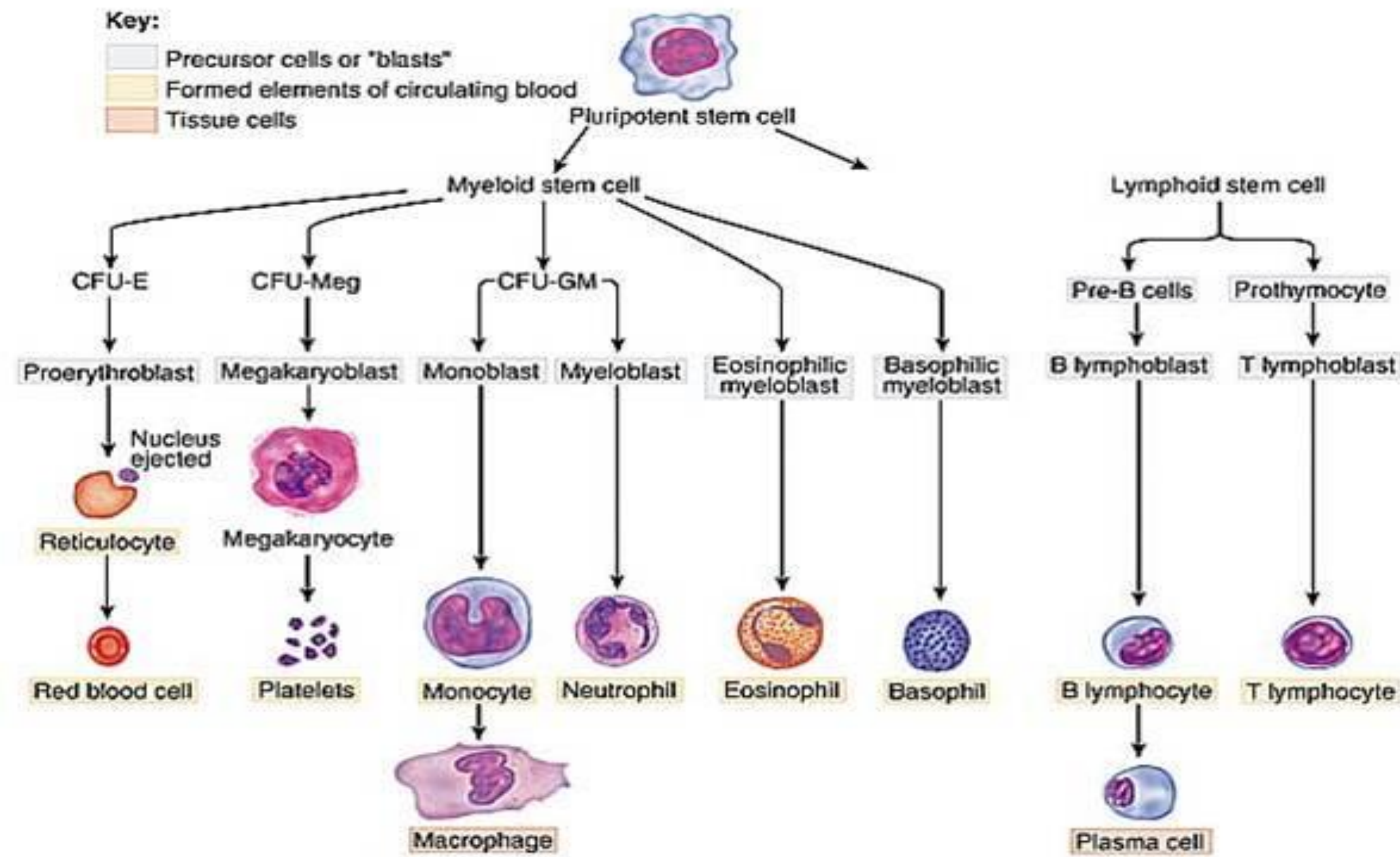


The hematopoietic system



- At the top of the hierarchy, LT and ST repopulating HSCs are capable of self-renewal and multilineage differentiation.
- They produce progenitors and precursors that massively proliferate to give rise to all types of mature hematopoietic cells (from myeloid and lymphoid lineages).

Cell hierarchy (Haemopoiesis schematic representation)



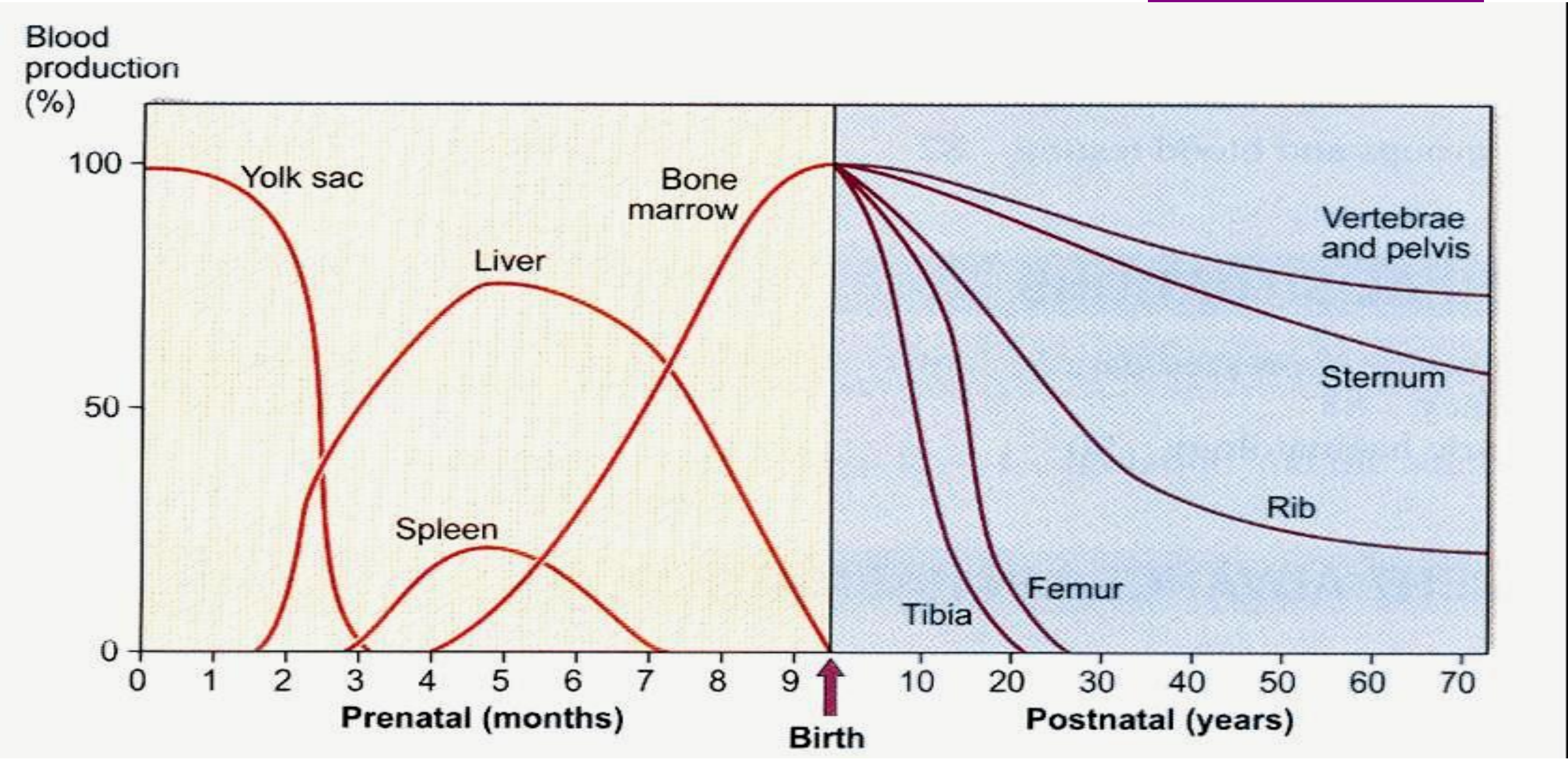
Hematopoiesis

- Medullary
  - Origin of blood cells and sequential sites of normal blood production within the bone marrow
- Extramedullary
  - Blood cell production in hematopoietic tissue other than bone marrow
    - Liver
    - Spleen
  - Compensatory mechanism to provide blood cells in times of need

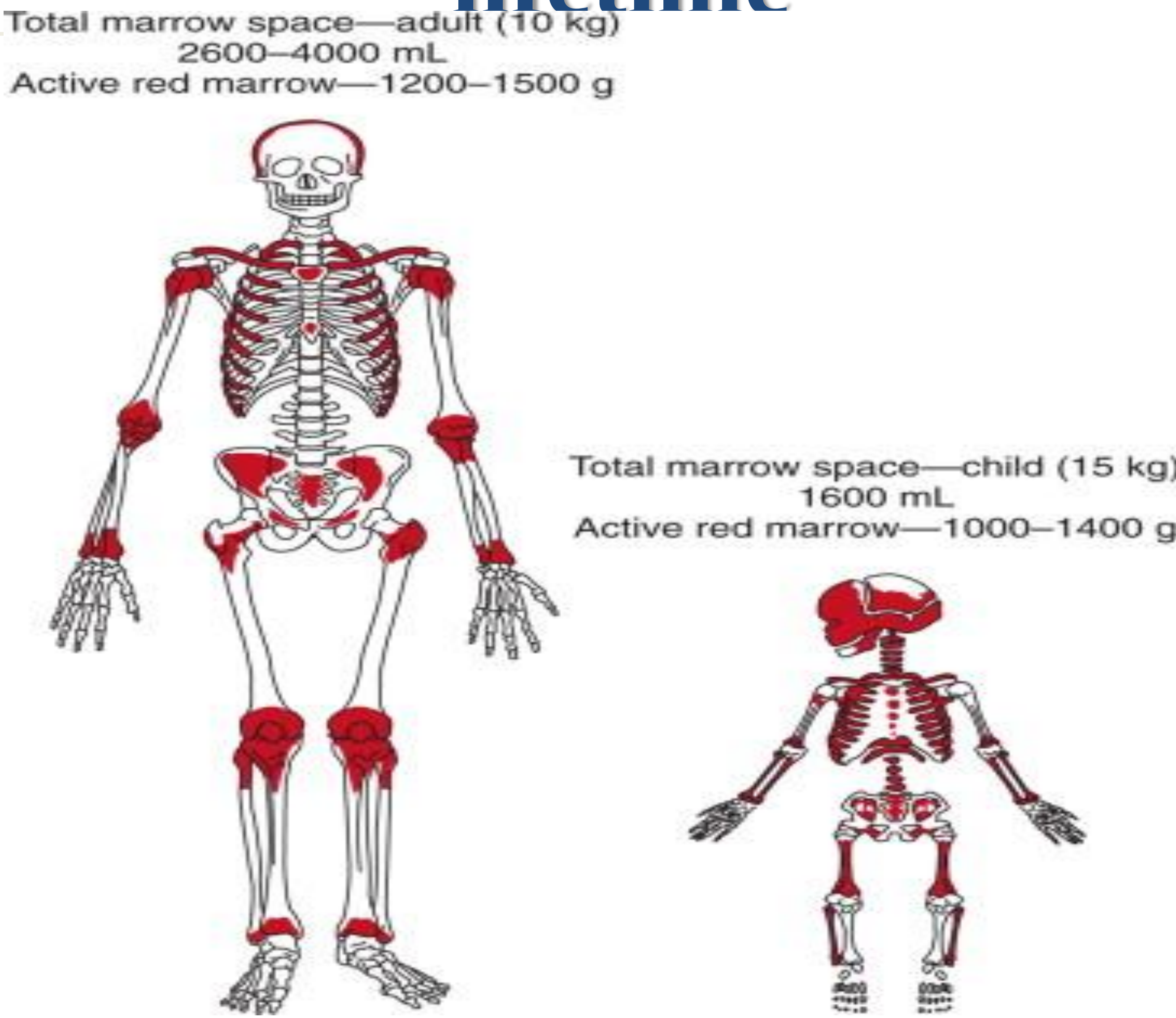
Sites of Hematopoiesis

Age	Site of hematopoiesis
Embryo	yolk sac then liver
3rd to 7th month	Spleen
4th and 5th months	marrow cavity - esp. granulocytes and platelets
7th month	marrow cavity - erythrocytes
Birth	mostly bone marrow; spleen and liver when needed
Birth to maturity	number of active sites in bone marrow decreases but retain ability for hematopoiesis
Adult	bone marrow of skull, ribs, sternum, vertebral column, pelvis, proximal ends of femurs

Hematopoietic organs



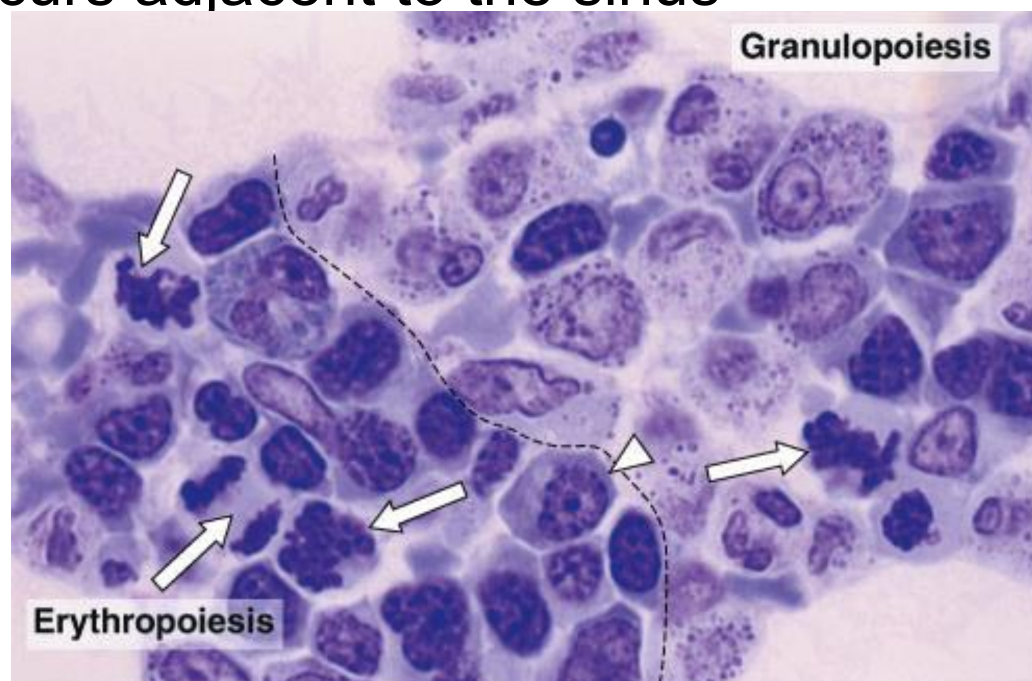
Distribution of red BM during lifetime

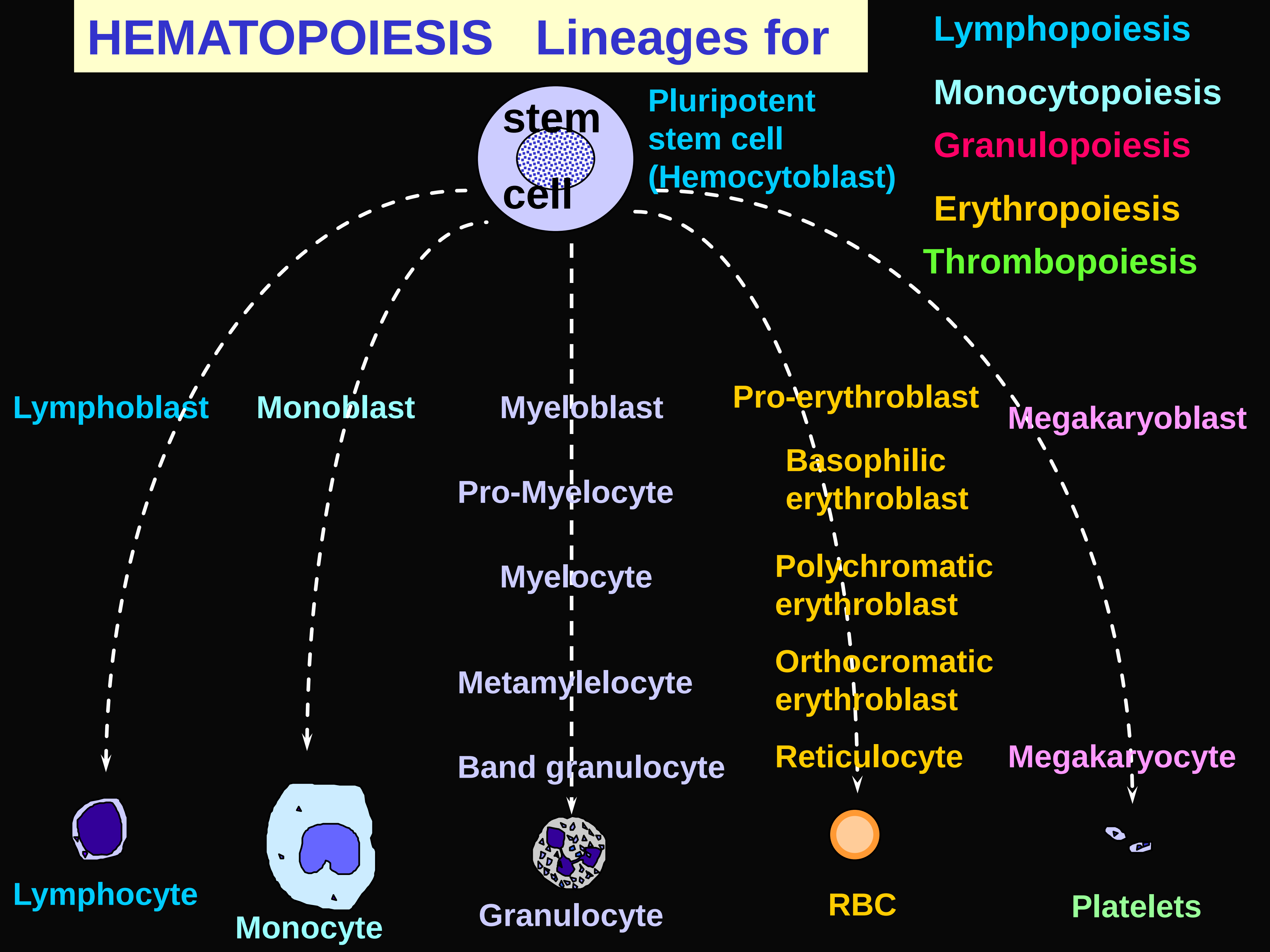


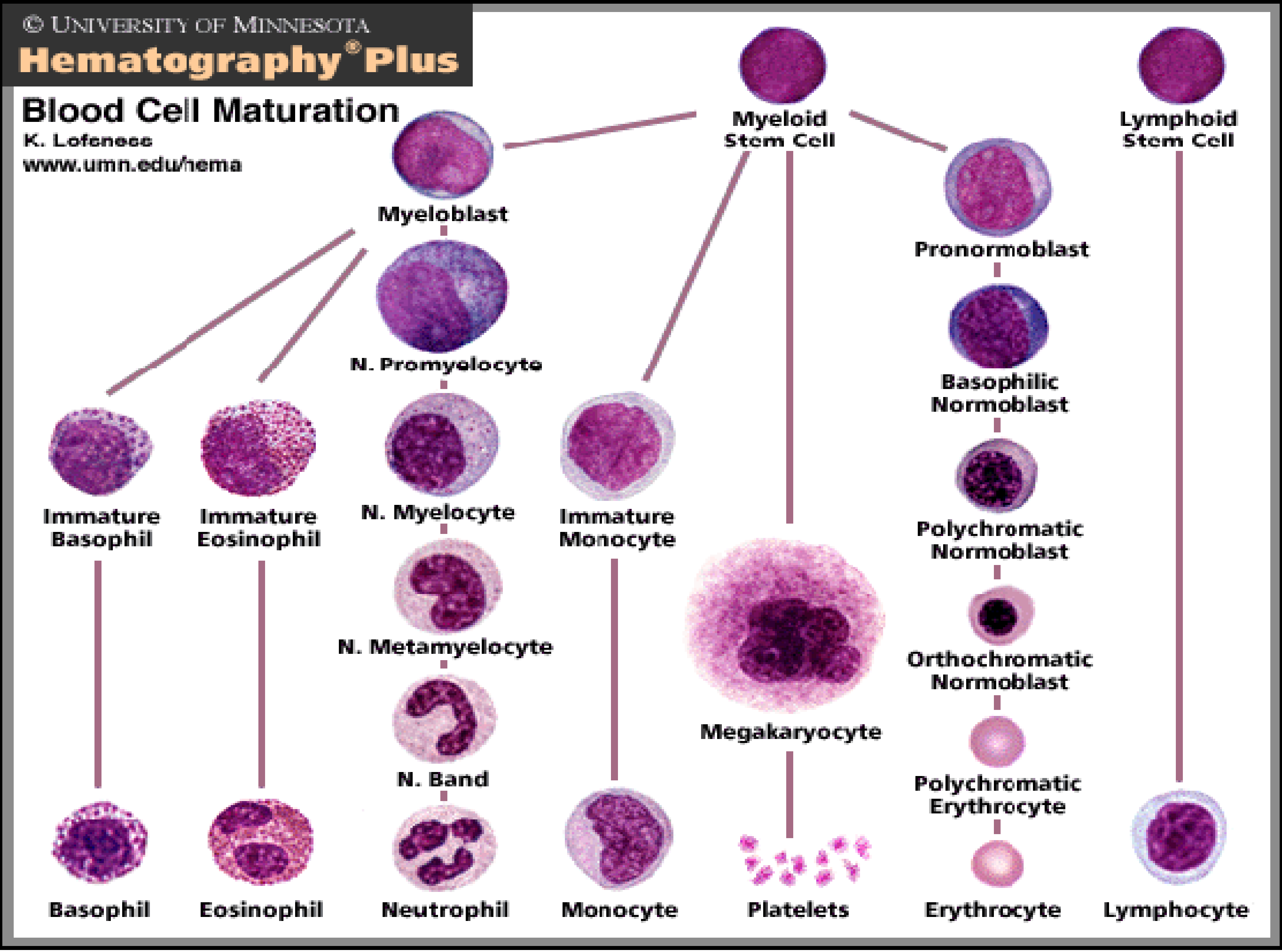
Hematopoiesis

is a compartmentalized process within the hematopoietic tissue

- **Erythropoiesis** -(erythroblastic islands)
- **Granulopoiesis** occurs in less distinct foci
- **Megakaryopoiesis** occurs adjacent to the sinus endothelium




HEMATOPOIESIS Lineages for
Lymphopoiesis
Monocytopoiesis
Granulopoiesis
Erythropoiesis
Thrombopoiesis
stem cell
Pluripotent stem cell (Hemocytoblast)
Lymphoblast
Monoblast
Myeloblast
Pro-Myelocyte
Myelocyte
Metamylelocyte
Band granulocyte
Pro-erythroblast
Basophilic erythroblast
Polychromatic erythroblast
Orthocromatic erythroblast
Reticulocyte
Megakaryoblast
Megakaryocyte
Lymphocyte
Monocyte
Granulocyte
RBC
Platelets



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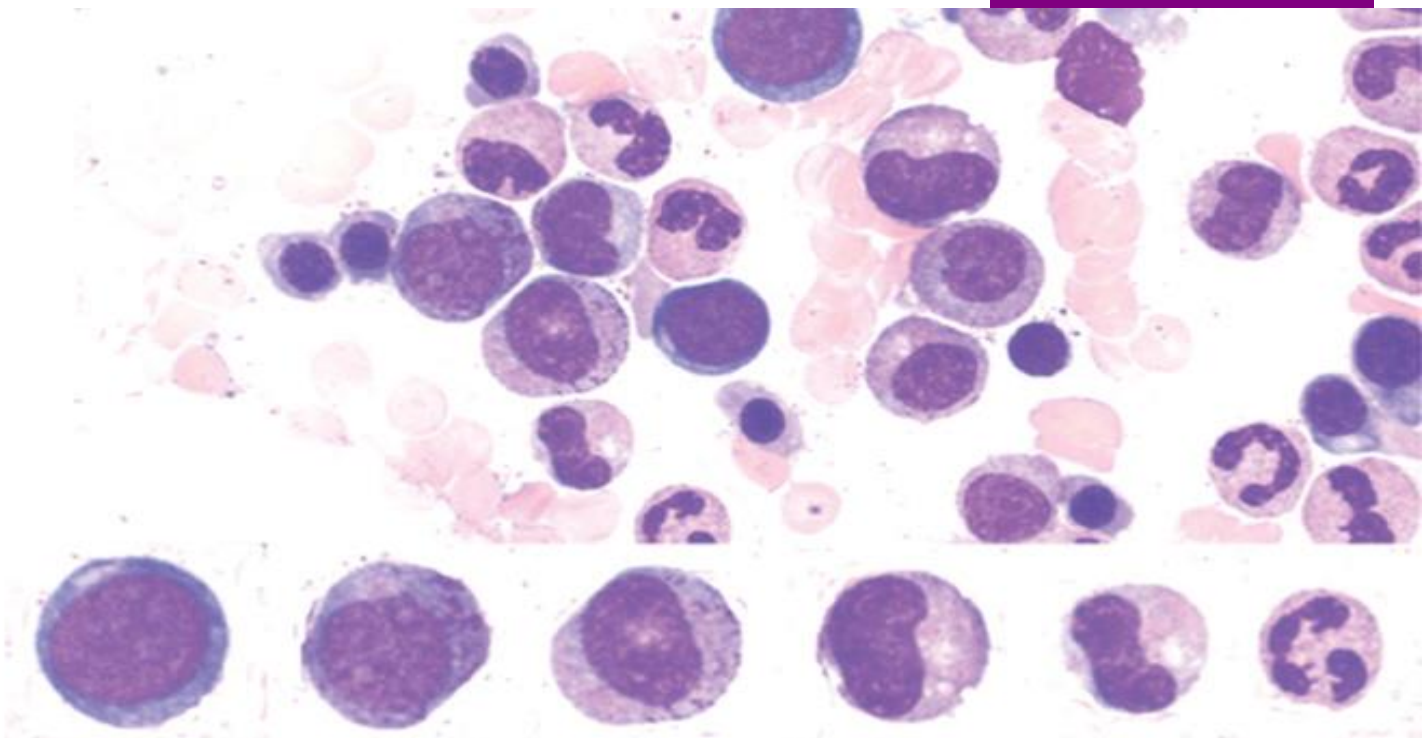
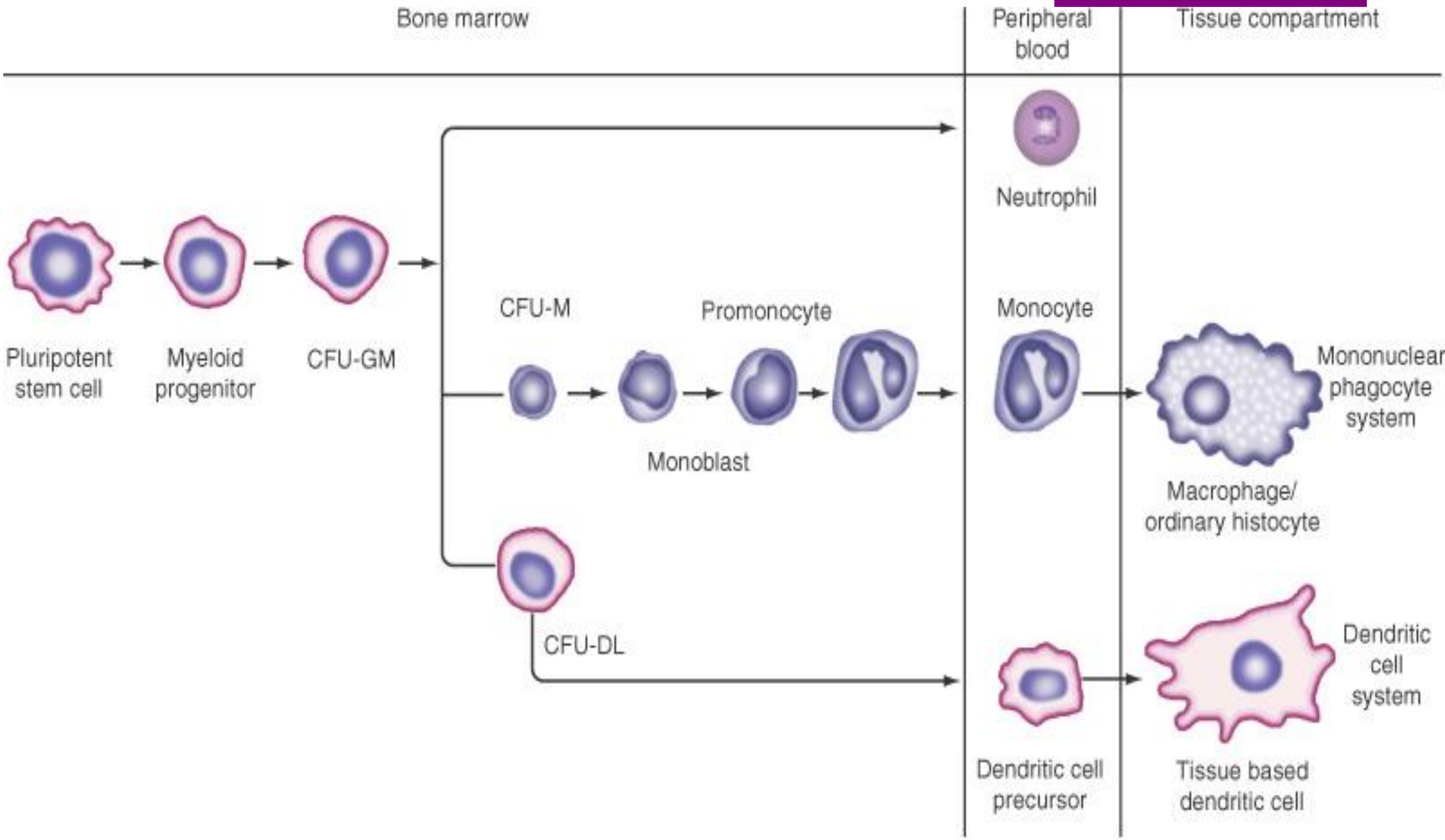
Myeloid Stem Cell
Lymphoid Stem Cell
Myeloblast
N. Promyelocyte
N. Myelocyte
N. Metamyelocyte
N. Band
Neutrophil
Immature Basophil
Basophil
Immature Eosinophil
Eosinophil
Immature Monocyte
Monocyte
Megakaryocyte
Platelets
Pronormoblast
Basophilic Normoblast
Polychromatic Normoblast
Orthochromatic Normoblast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

Granulocytopoiesis

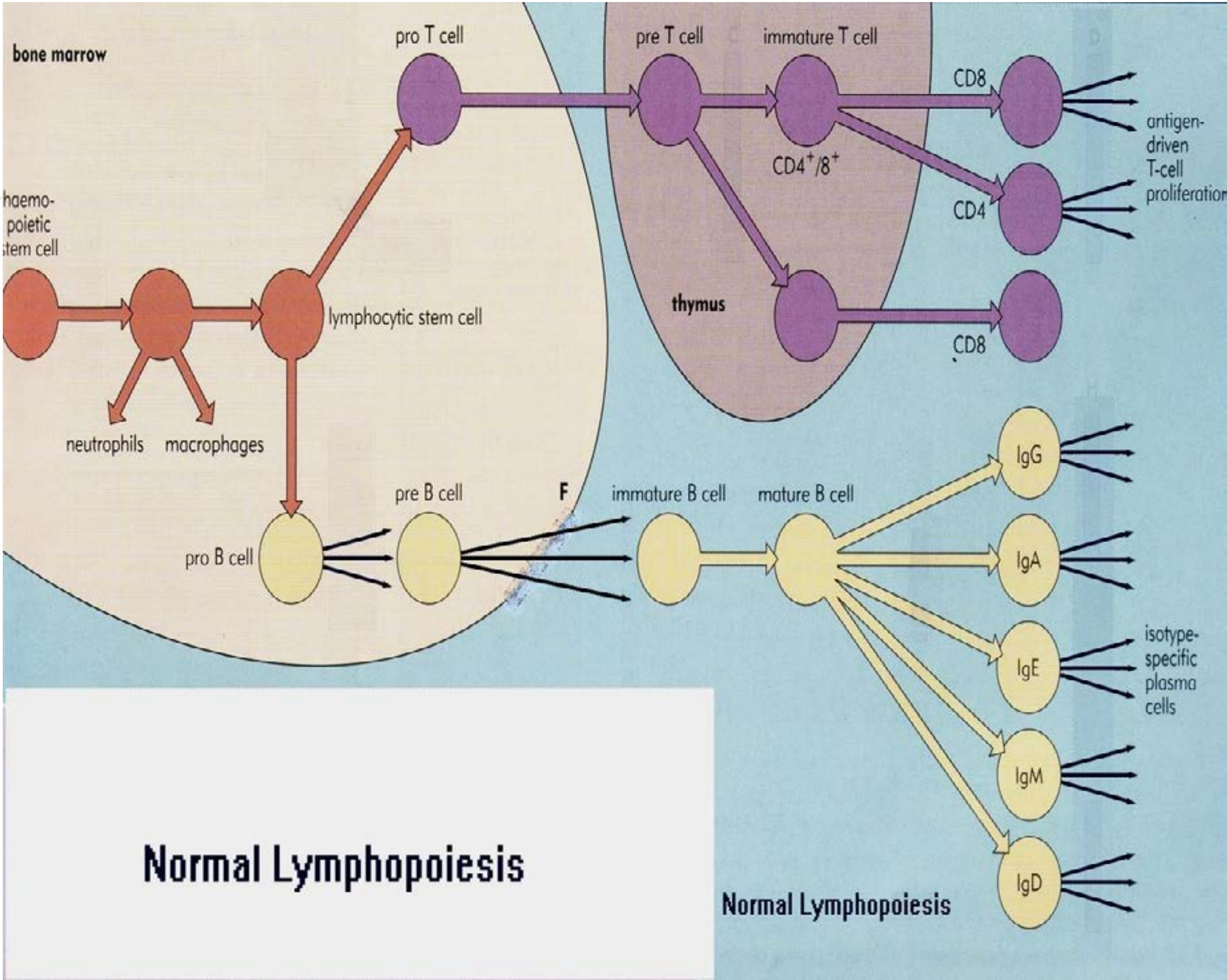


	Myeloblast	Promyelocyte	Myelocyte	Metamyelocyte	Band	Segmented neutrophil
Proliferation	++	+++	+++	+/–	—	—
Granule production						
1°		+++	+			
2°			+++	+		
3°				+++	+	

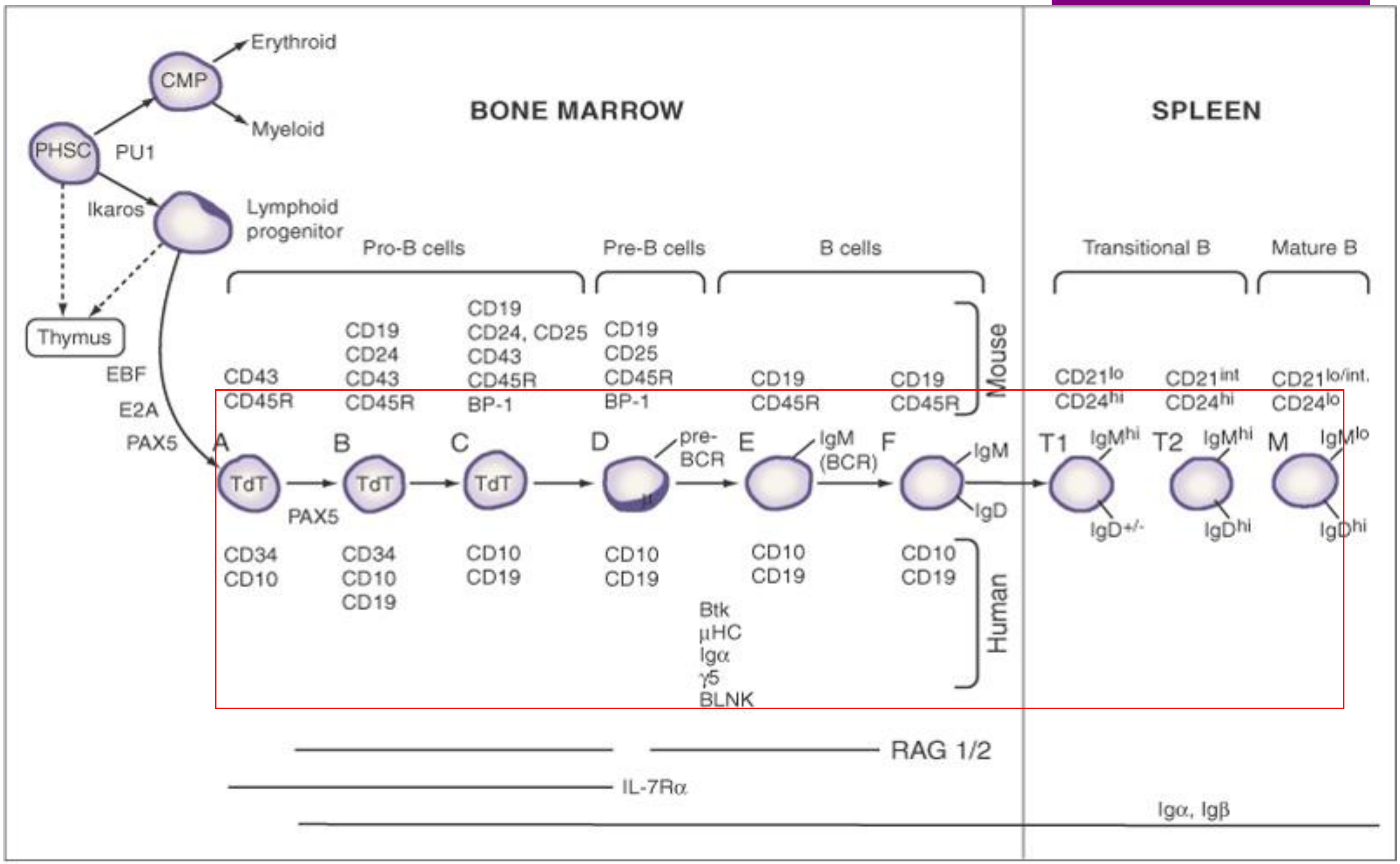
Monocytopoiesis/dendritic cells



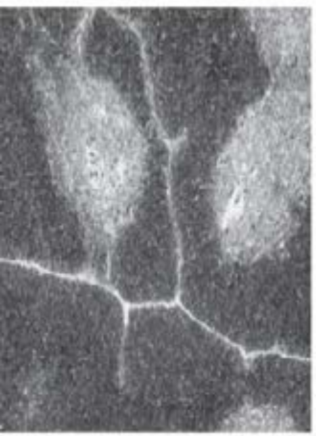
Normal Lymphopoiesis

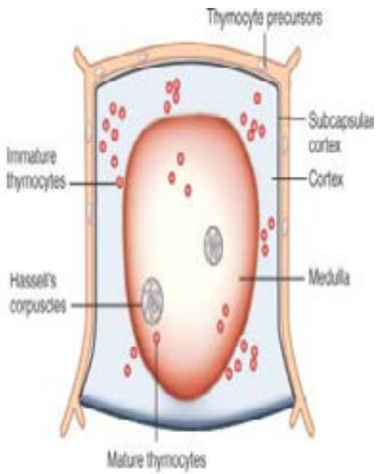


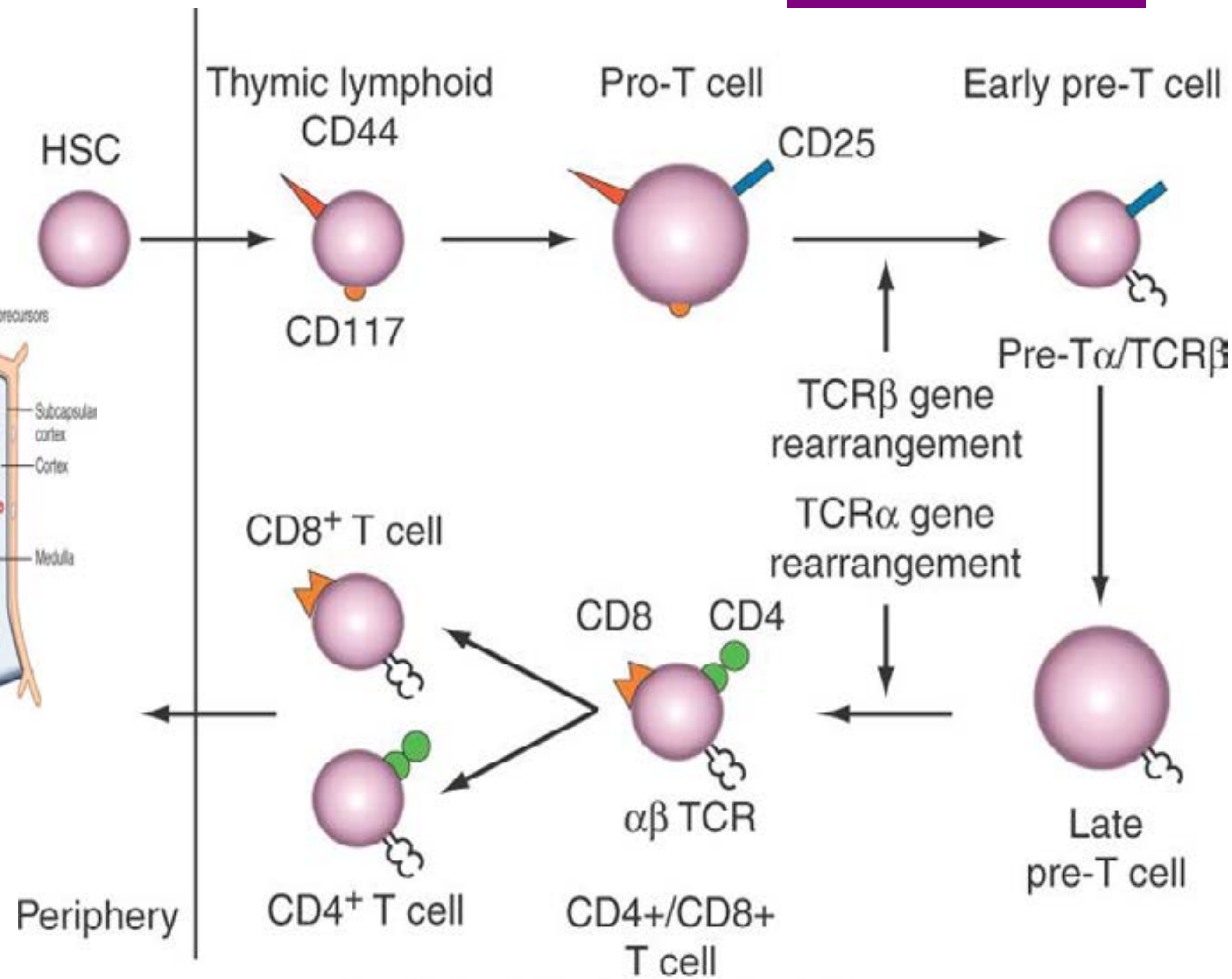
B-cell development



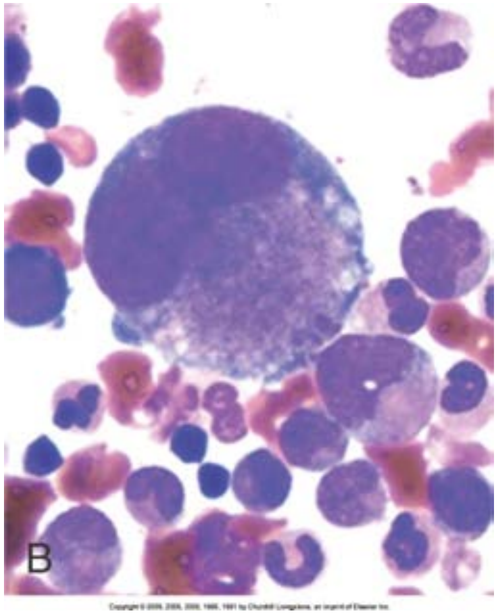
T-cell development in thymus

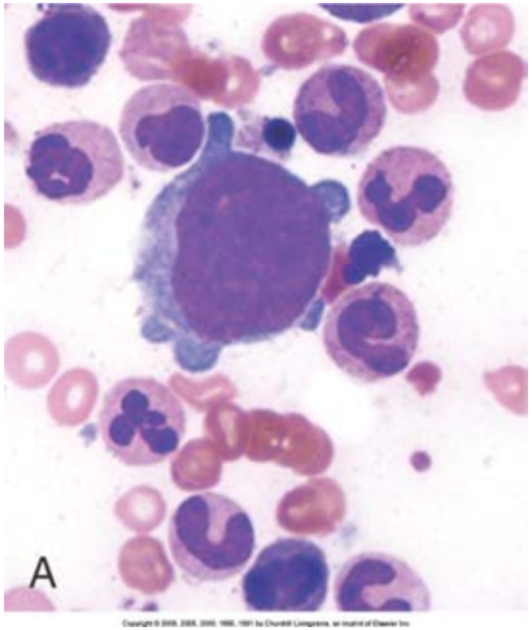


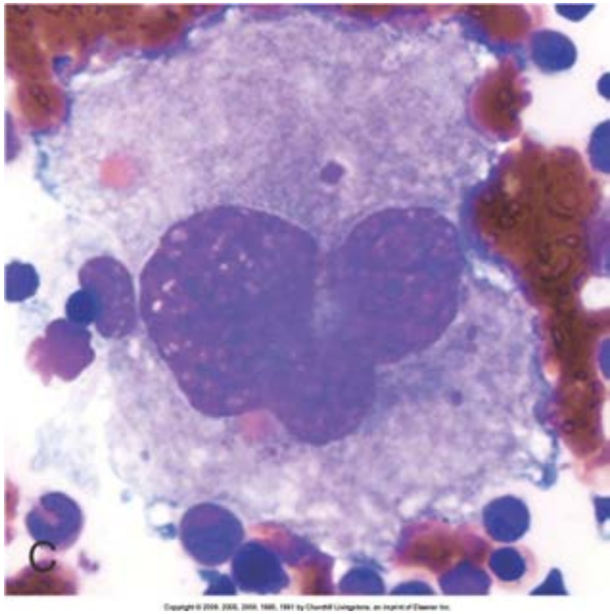




Megakaryocytopoiesis







Megakaryoblast

Promegakaryocyte

Megakaryocyte (with emperipolesis)

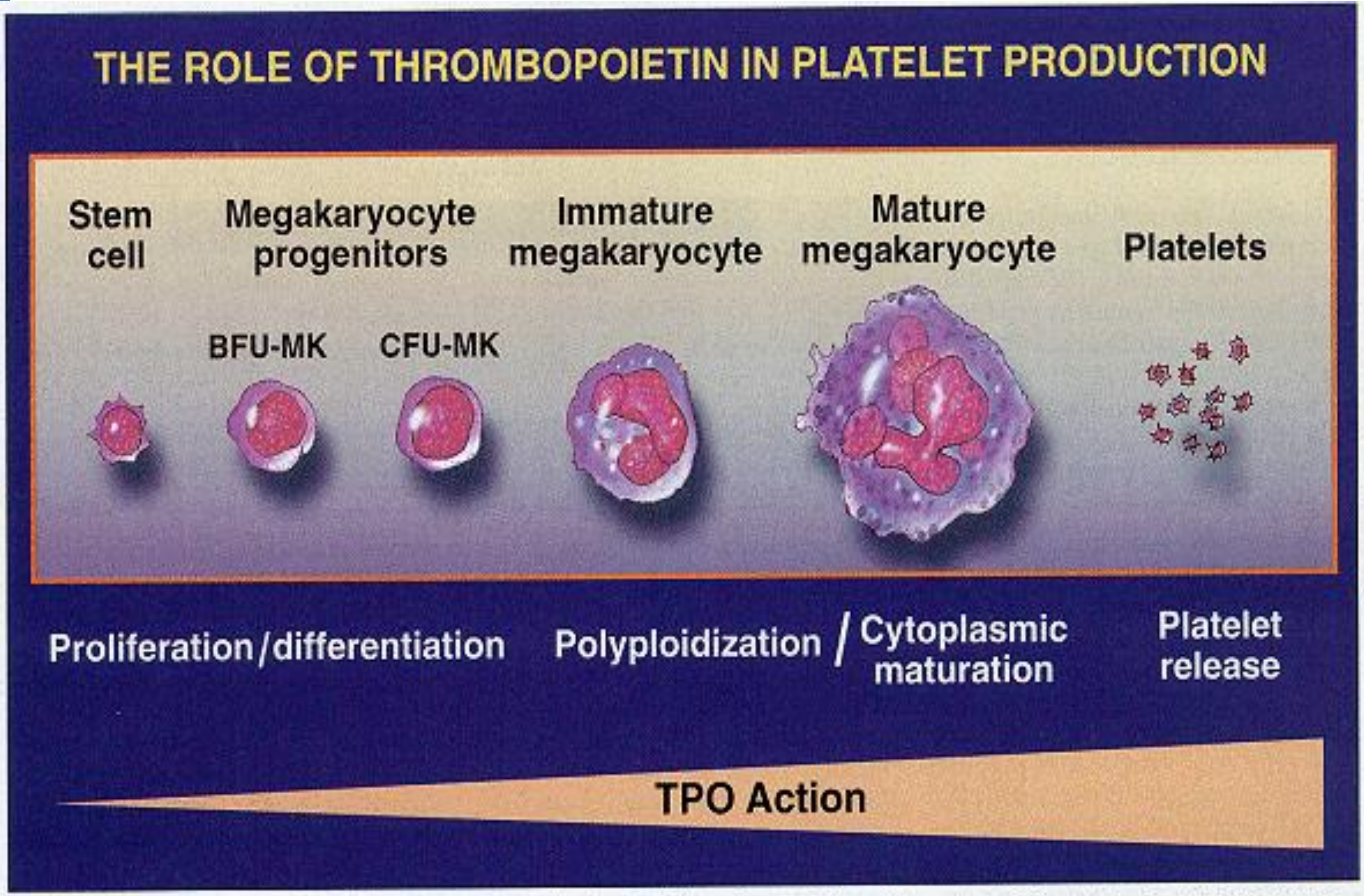
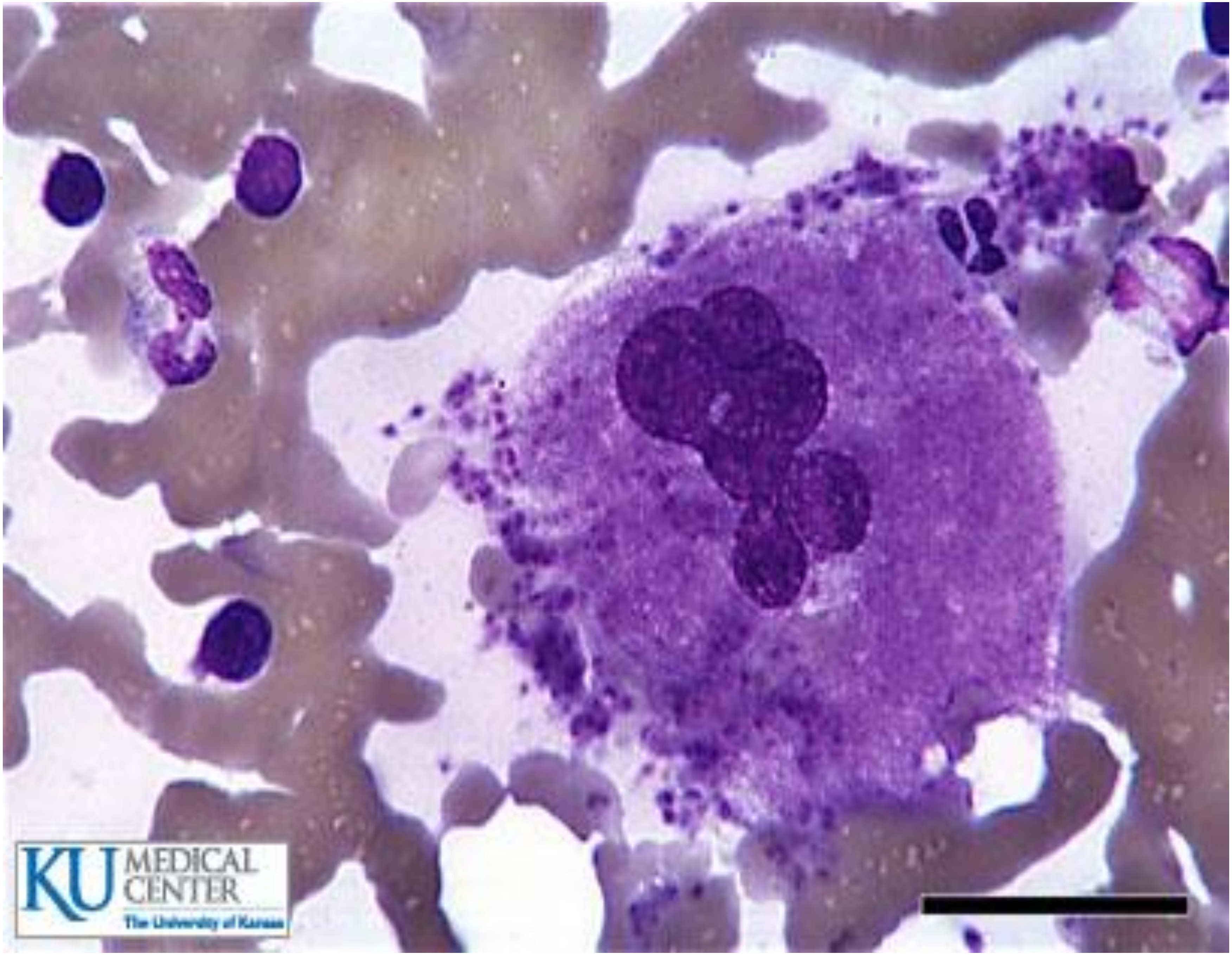


Figure 2: Regulation of Megakaryocytopoiesis by Thrombopoietin—Thrombopoietin acts at multiple levels, including proliferation and differentiation of megakaryocyte (MK) progenitors and maturation of MKs into large polyploid cells capable of producing platelets.[37,40]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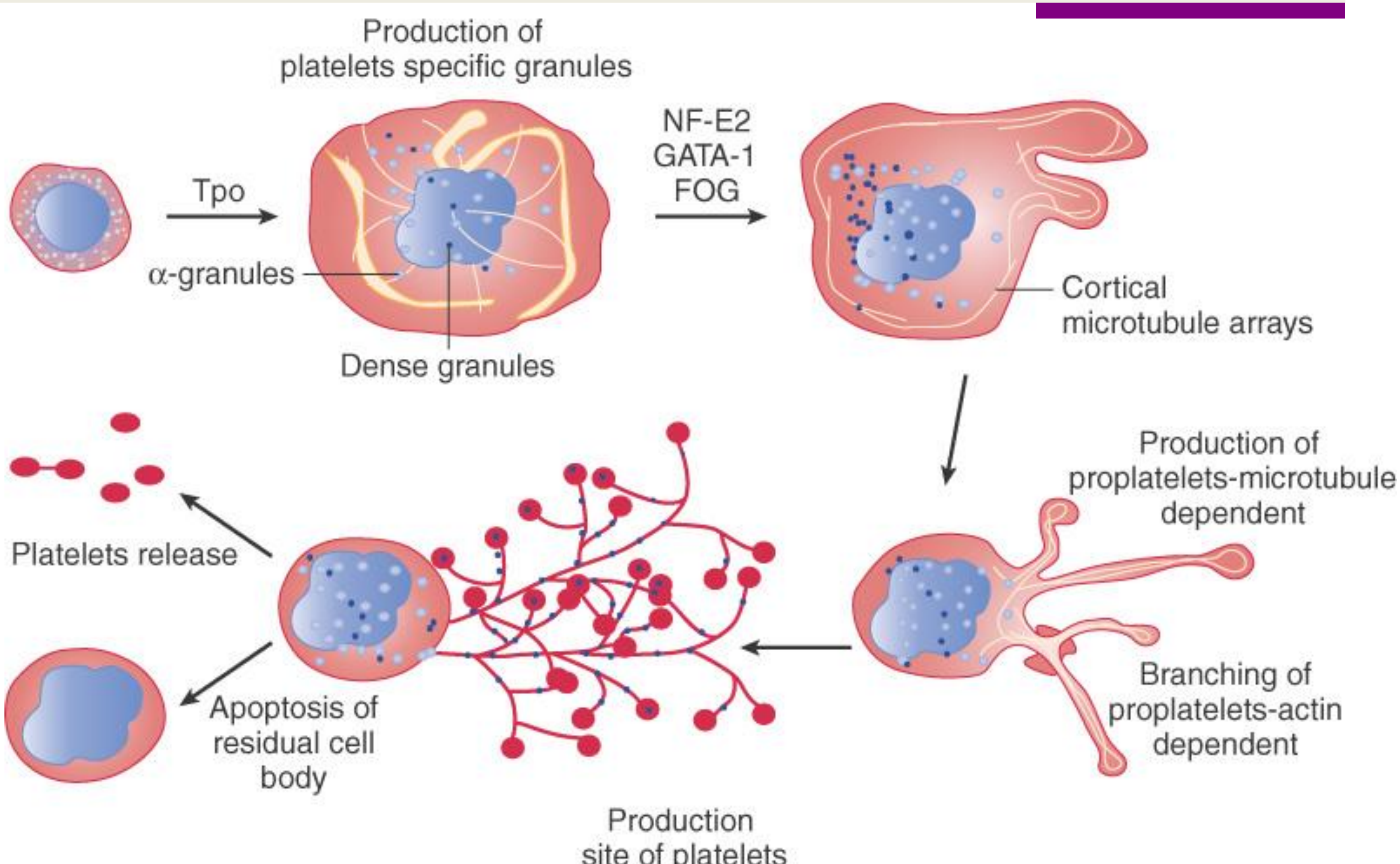
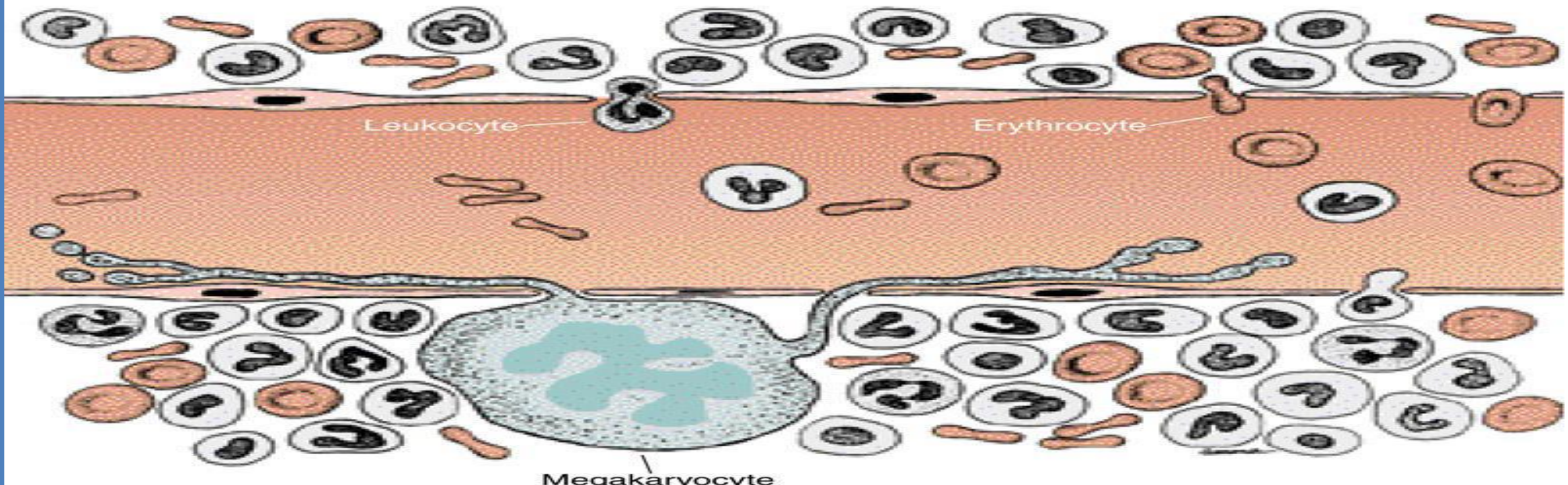
How a MGK produces platelets?

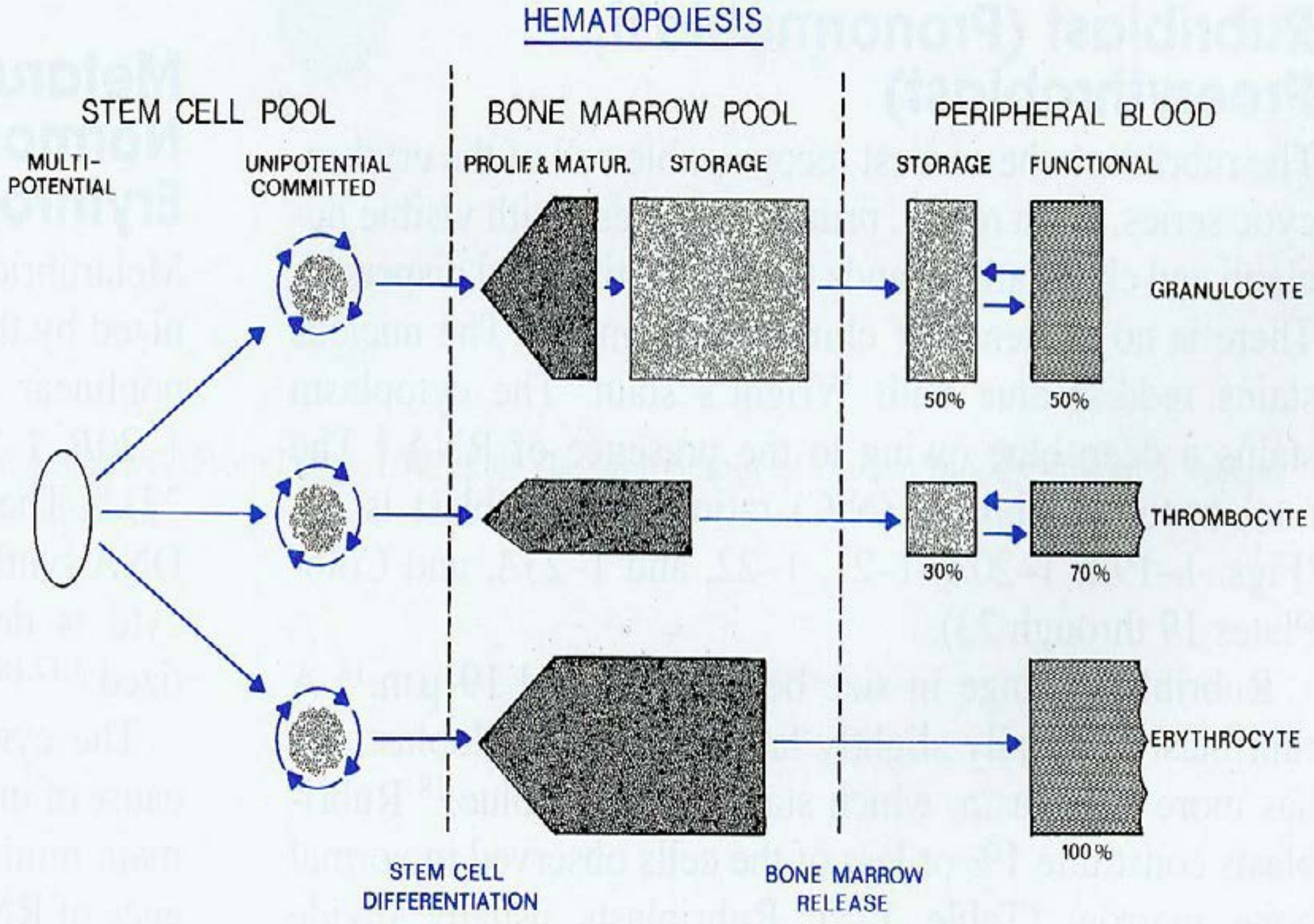


Hematopoiesis

Upon maturation, the hematopoietic cells, regulated by the reticular cells, traverse the wall of the venous sinuses to enter the bloodstream

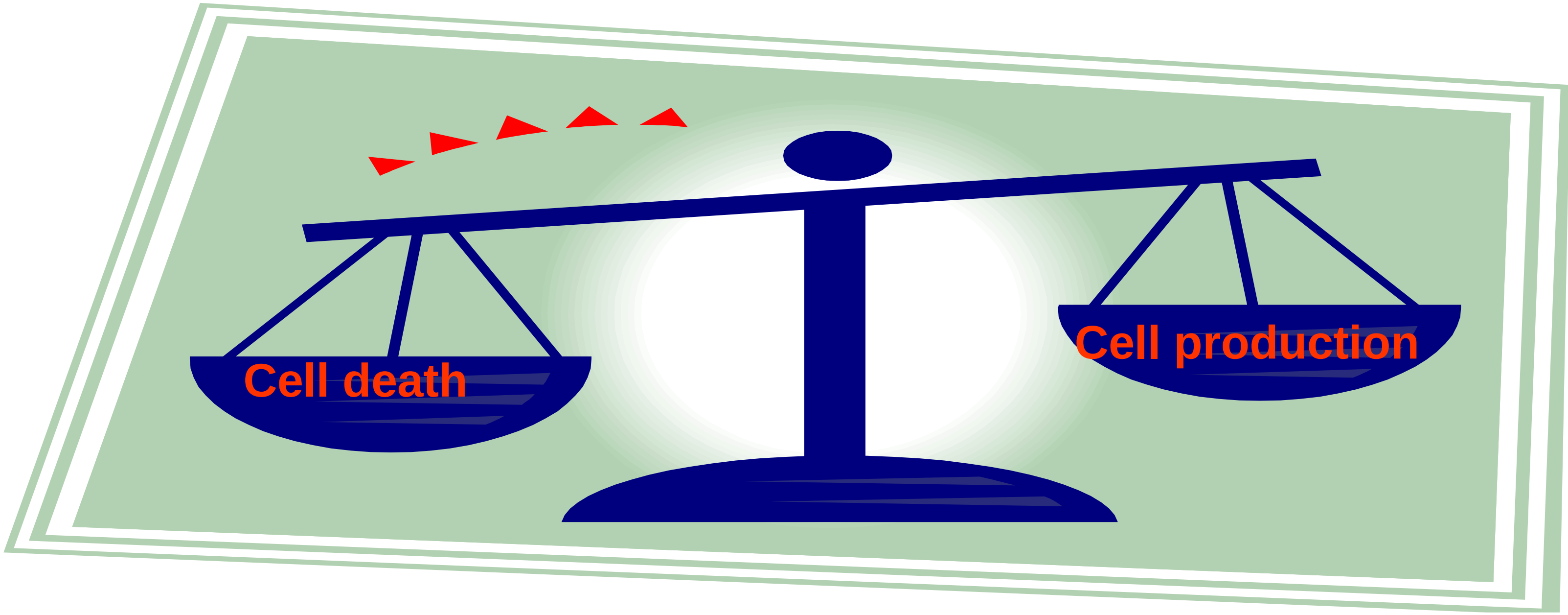


- **Leukocytes** cross the wall of the sinusoid by their **own activity.**
- **Erythrocytes** are believed to enter the sinusoid by a **pressure gradient that exists across its wall.**
- **Megakaryocytes** form thin processes (**proplatelet processes**) that cross the wall of the sinusoid and **fragment at their tips**, liberating the platelets


HEMATOPOIESIS
STEM CELL POOL
BONE MARROW POOL
PERIPHERAL BLOOD
MULTI-POTENTIAL
UNIPOTENTIAL COMMITTED
PROLIF. & MATUR.
STORAGE
STORAGE
FUNCTIONAL
GRANULOCYTE
50%
50%
THROMBOCYTE
30%
70%
ERYTHROCYTE
100%
STEM CELL DIFFERENTIATION
BONE MARROW RELEASE

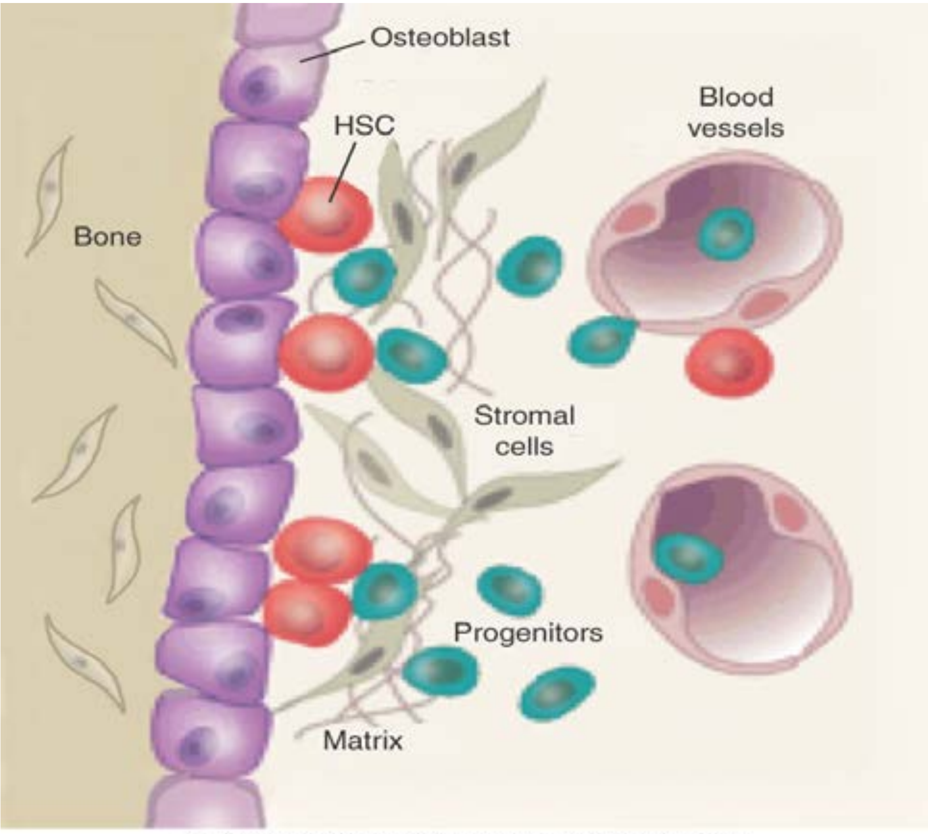
Hematopoiesis depends on

- **Microenvironmental** conditions
  - The microenvironmental conditions are furnished by cells which produce an adequate extracellular matrix
- **Growth factors**



HSC Niche

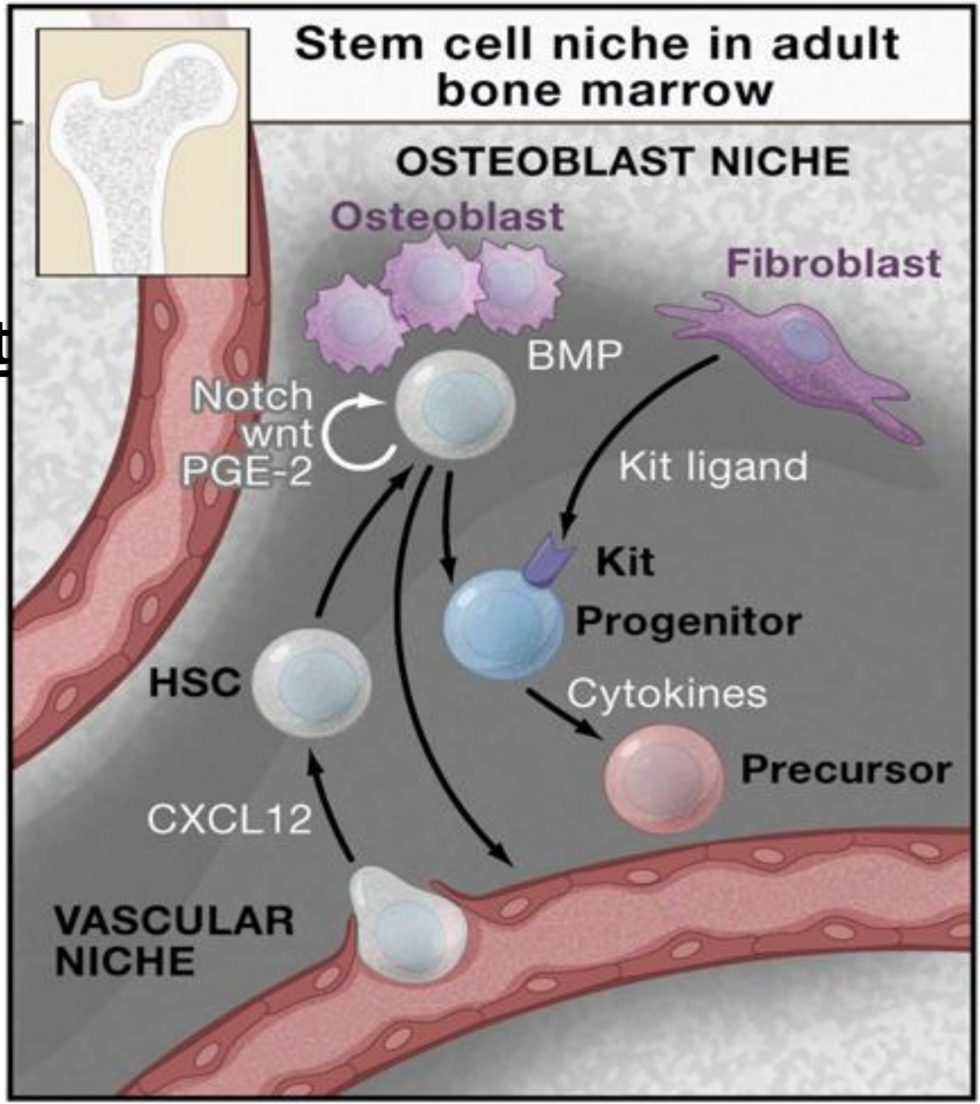
- HSCs are localized in a <u>**particular niche**</u> within the BM to maintain their self-renewal capacity.
- In contrast, the more committed progenitors accumulate in the center of the BM .



(From Moore KA, Lemischka IR: Stem cells and their niches. Science 311:1880, 2006 [modified from Fig. 3A, p. 1883].)

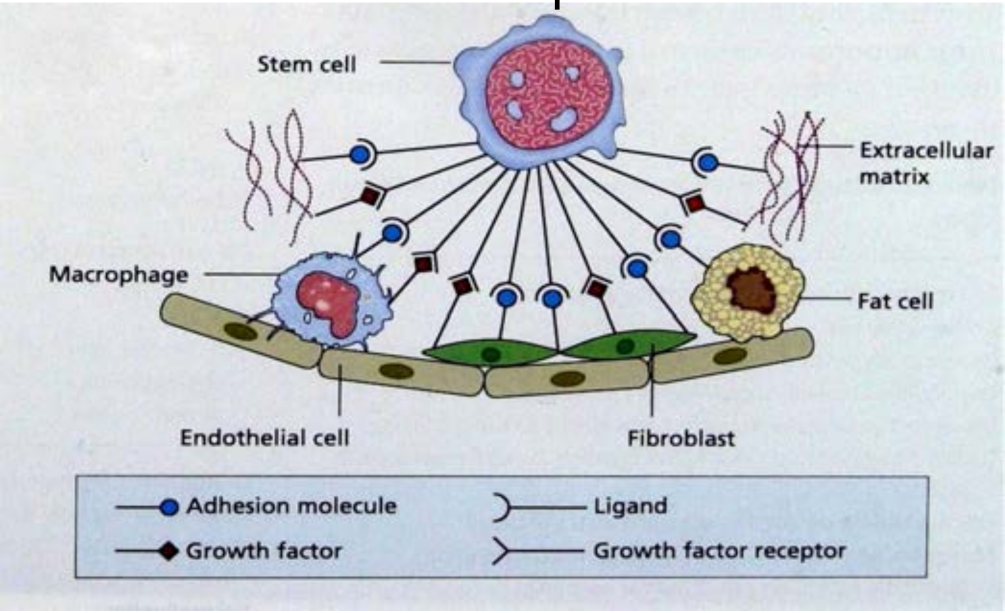
Stem Cell Niche in the Adult Bone Marrow

- **HSCs** are found adjacent to osteoblasts that are under the regulation of bone morphogenetic protein (BMP) **(Osteobast Niche).**
- HSCs are also found adjacent to blood vessels **(Vascular Niche).**
- **The chemokine CXCL12** regulates the migration of HSCs from the circulation to the bone marrow.



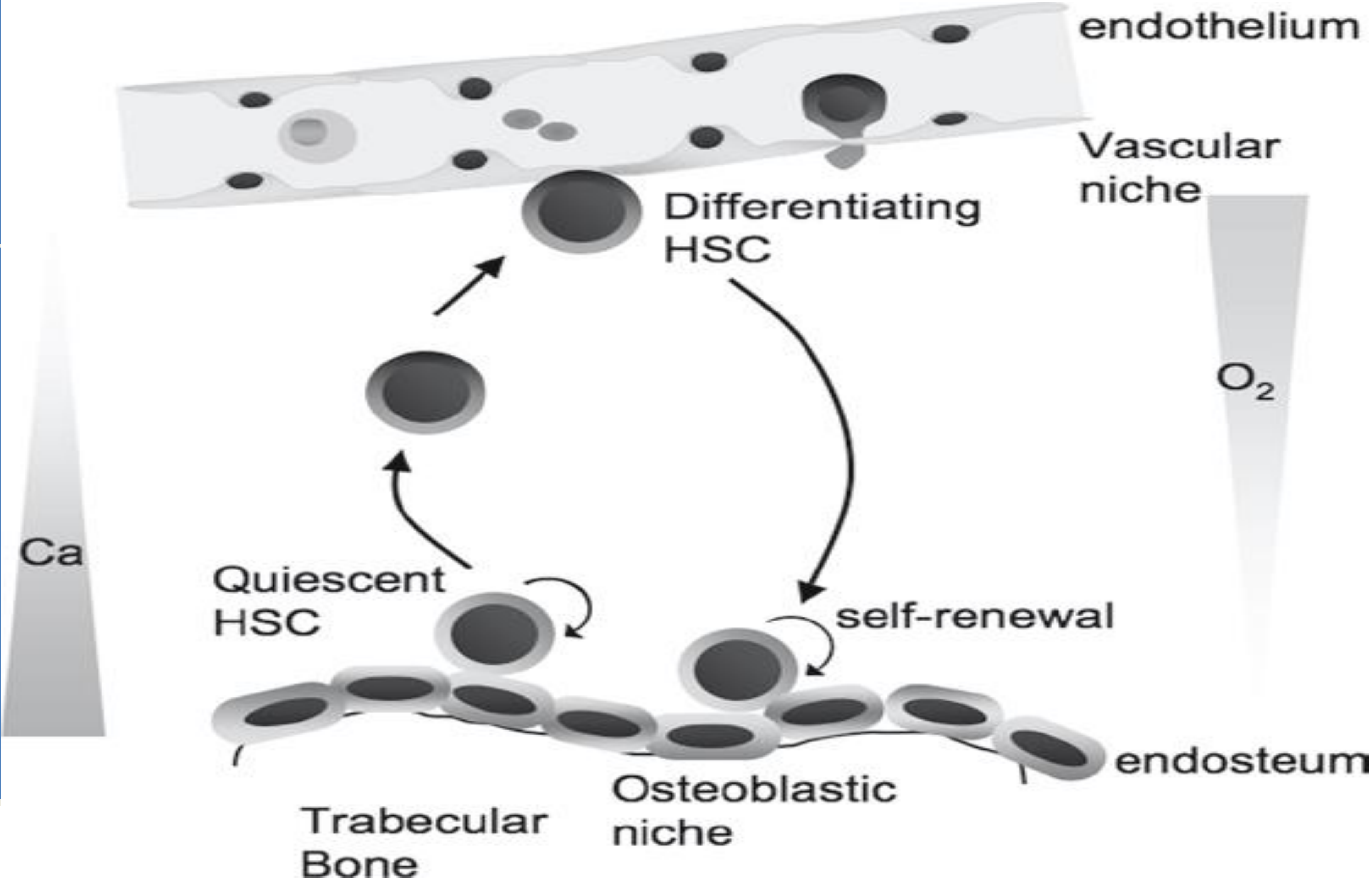
Interaction Between Hematopoietic Stem Cell and Niche

- HSC and the osteoblast bind each other via the adhesion molecules: **N-cadherin**
- Stem cell in general is in a quiescent state :G0 phase in cell cycle
- Quiescence prevents the stem cells from entering into the cell cycle and differentiation.
- This enhanced adhesion between the niche cell and the stem cell contributes to the maintenance of the quiescence of the stem cell and selfrenew.



Interaction Between Hematopoietic Stem Cell and Niche

- **<u>Osteopontin (Opn):</u>**
  - Expressed by osteoblast
  - Vontributes to the adhesion between the HSC and osteoblastic niche
  - Negatively regulates HSC proliferation: contributing to the maintenance of the stem cell quiescence.
- **<u>Thrombopoietin (Tpo)</u>** and its ligand Mpl, the regulator of megakaryopoiesis, are also critical regulators in HSC maintenance in osteoblastic niche:
  - Mpl/TPO signaling regulates cell cycle of adult quiescent HSCs to maintain the pool at the physiologically reasonable level.
- **<u>c-Myc</u> i**s another important regulator of the HSC fate:
  - c-Myc controls the balance between the HSC self-renewal and differentiation by adjusting the adhesion between HSCs and the niche



HSC stays in quiescence in osteoblastic niche and activates the cell cycle upon leaving for vascular niche, where the differentiation is initiated.
HSCs are guided by multiple factors, such as local calcium or oxygen concentration gradient between these two different kinds of niches

Haematopoietic Growth Factors

- They share a number of common properties:
  - Glycoproteins.
  - Produced by many cell types.
  - Active on stem/progenitor cells and on functional end cells.
- They may act:
  - locally at their site of production by cell to cell contact
  - or circulate in plasma.
- Multiple actions:
  - proliferation
  - differentiation
  - maturation
  - functional activation
  - and prevention of apoptosis
- Synergistic interactions

Haemopoietic Growth Factors

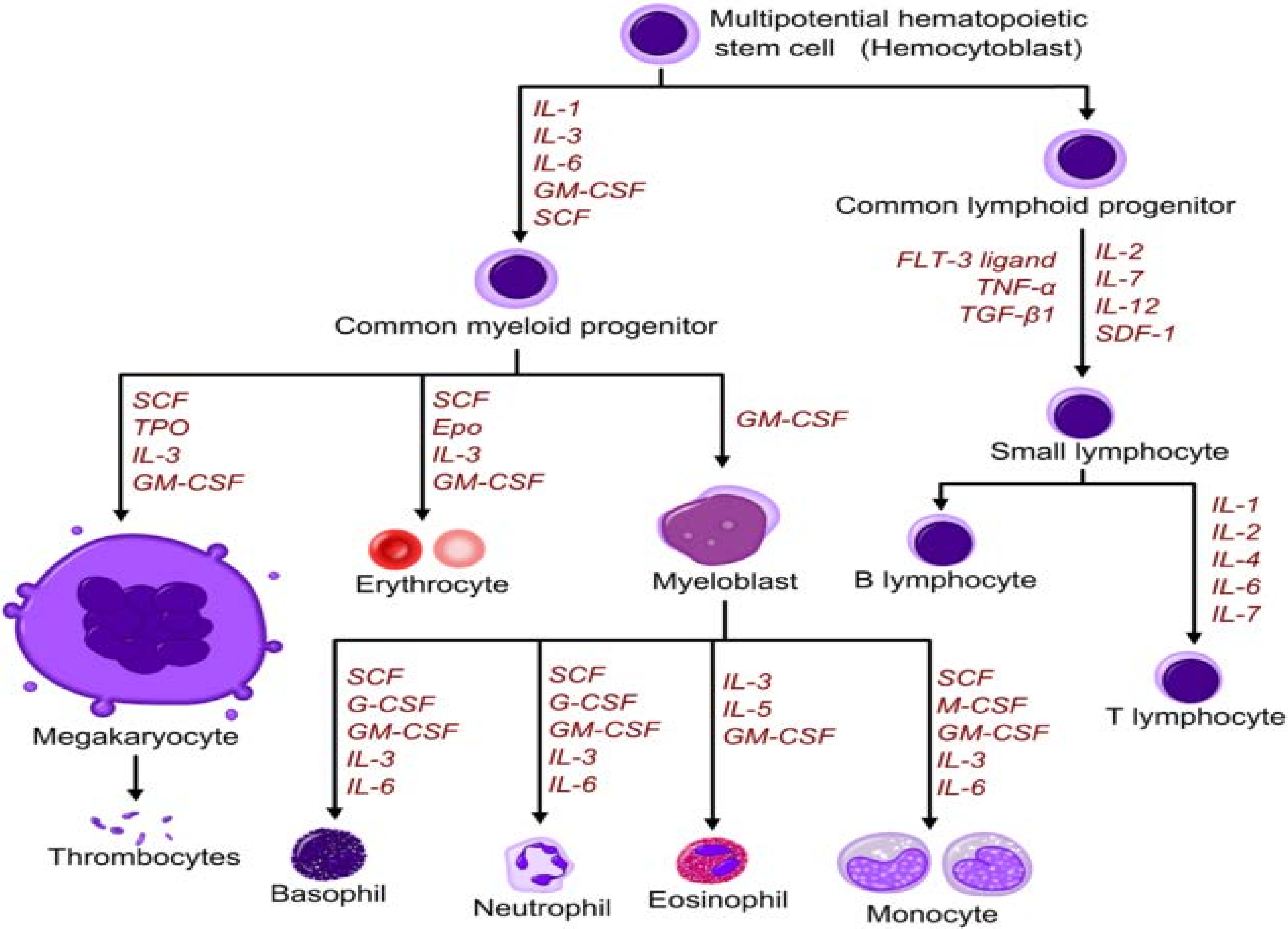
- **GM-CSF**: Granulocyte-Macrophage colony stimulating factor
  - **G-CSF**:m causes the aquisition of myeloid enzymes in granulocytes
  - **M-CSF**: Macrophage colony stimulating factor
- **Erythropoietin**: Erythropoiesis stimulating hormone
  - Induces erythroid hemoglobinization
- **Thrombopoietin**: Stimulates megakaryopoiesis
  - Thrombopoietin induces the expression of platelet-spesific proteins

Cytokines

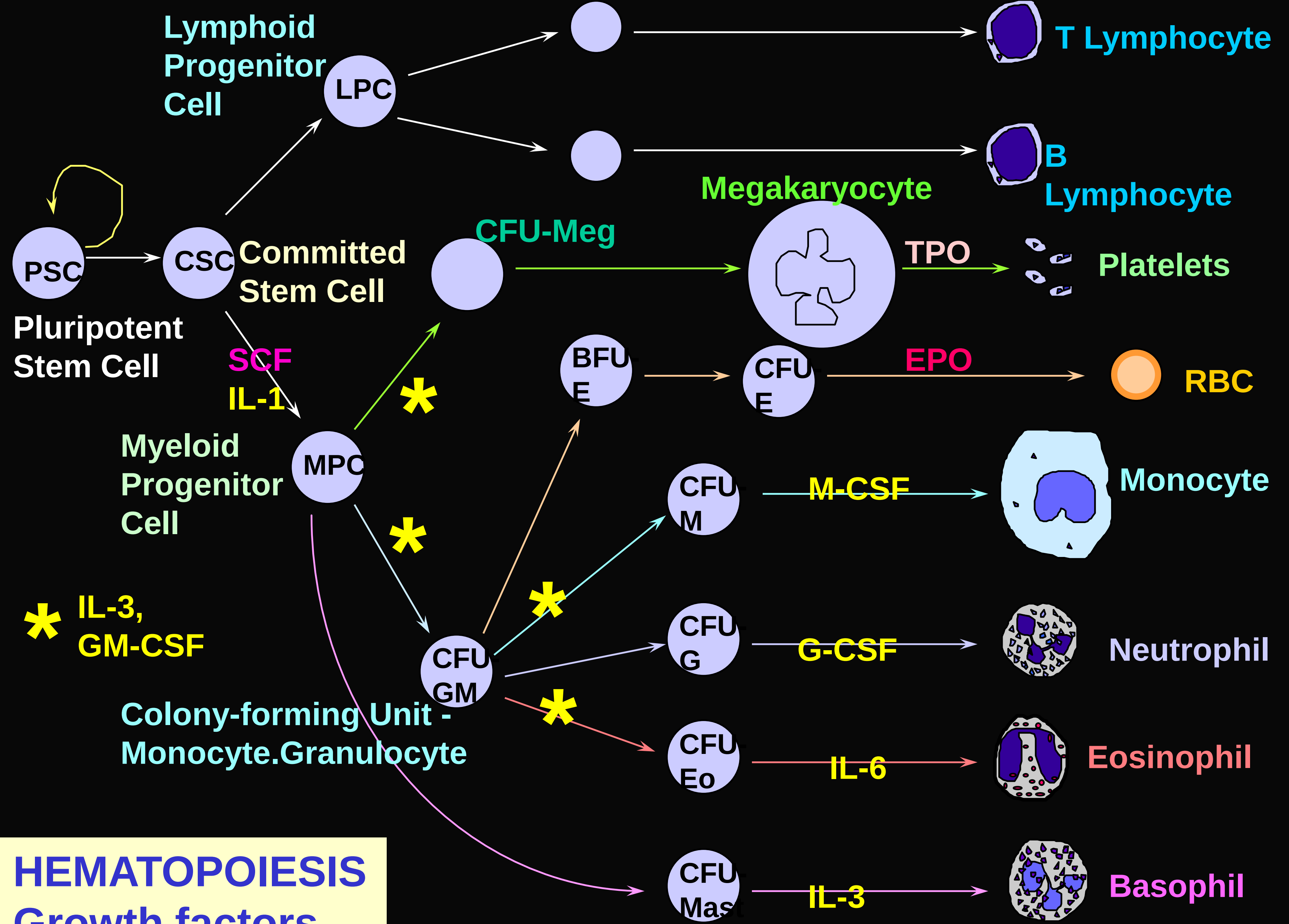
- Produced by a large variety of tissues and cell types:
  - for the purpose of cell-to-cell communication
  - Stimulate the pluripotential stem cells to proliferate and differentiate.
- Cytokines have no (e.g IL-1) or little (SCF) capacity to stimulate cell proliferation on their own, but are able to synergise with other cytokines to recruit nine cells into proliferation
- Most cells produce multiple cytokines, which can be differentially induced by various stimuli, including other cytokines, such as IL-1.
- Monocytes, T lymphocytes, endothelial cells, fibroblasts and marrow stromal cells are important sources of lymphohematopoietic cytokines.
- Erythropoietin production is an exception, because it is largely produced in the kidney in response to hypoxia

Cytokine Receptors

- Receptors are expressed in low numbers and do not exceed a few hundred per cell.
- The multipotent repopulating stem cell possesses receptors for most cytokines, but more mature cells have a more restricted distribution of receptors.
- Signaling through these receptors activates transcription factors
- Transcription factors determine cellular differentiation and specialization
- Progenitor cells differentiate toward spesific lineages:
  - GATA-1 and FOG promote erythroid and megakaryocyte differentiation
  - SCL, AML-1, and GATA-2 regulate primitive stem cell differentiation.



Various types of cytokines and growth factors are also required for hematopoiesis to occur

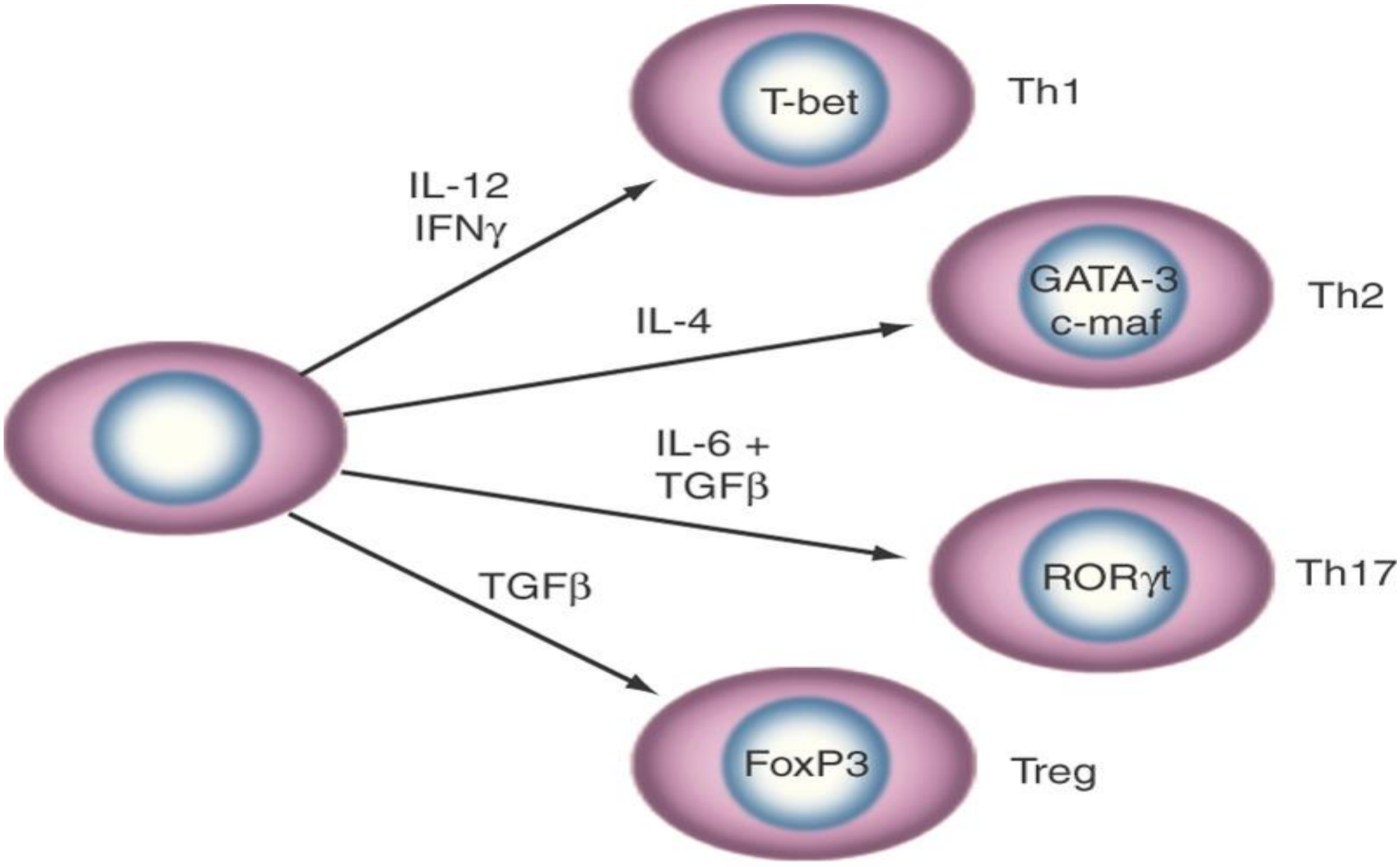


HEMATOPOIESIS
Growth factors

Myelopoiesis

- Involves the action of a variety of growth factors:
  - stem cell factor (SCF)
  - Fetal liver tyrosine kinase 3 (FLT3)
  - Granulocyte Monocyte–Colony stimulating factor (GM-CSF)
  - IL-3
  - Granulocyte–Colony stimulating factor (G-CSF)
  - Monocyte–Colony stimulating factor M-CSF
  - IL-5

T-cell subsets



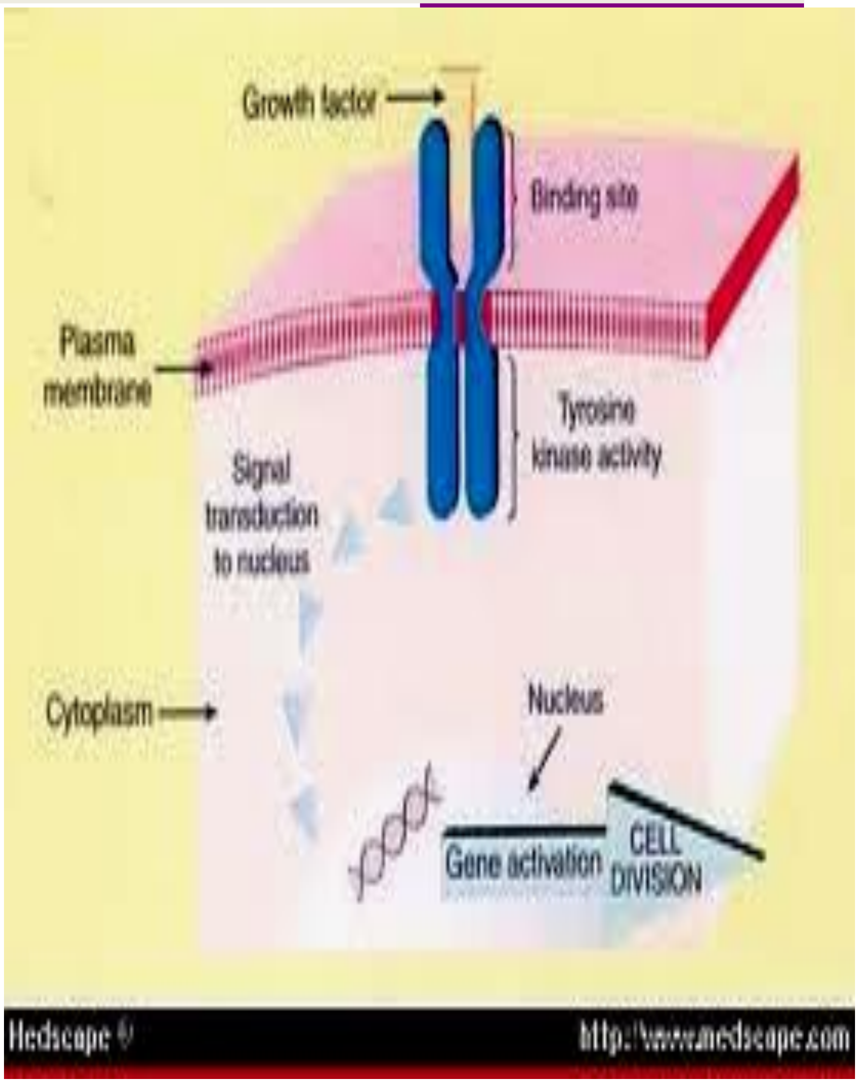
Growth factor receptors and signal transduction

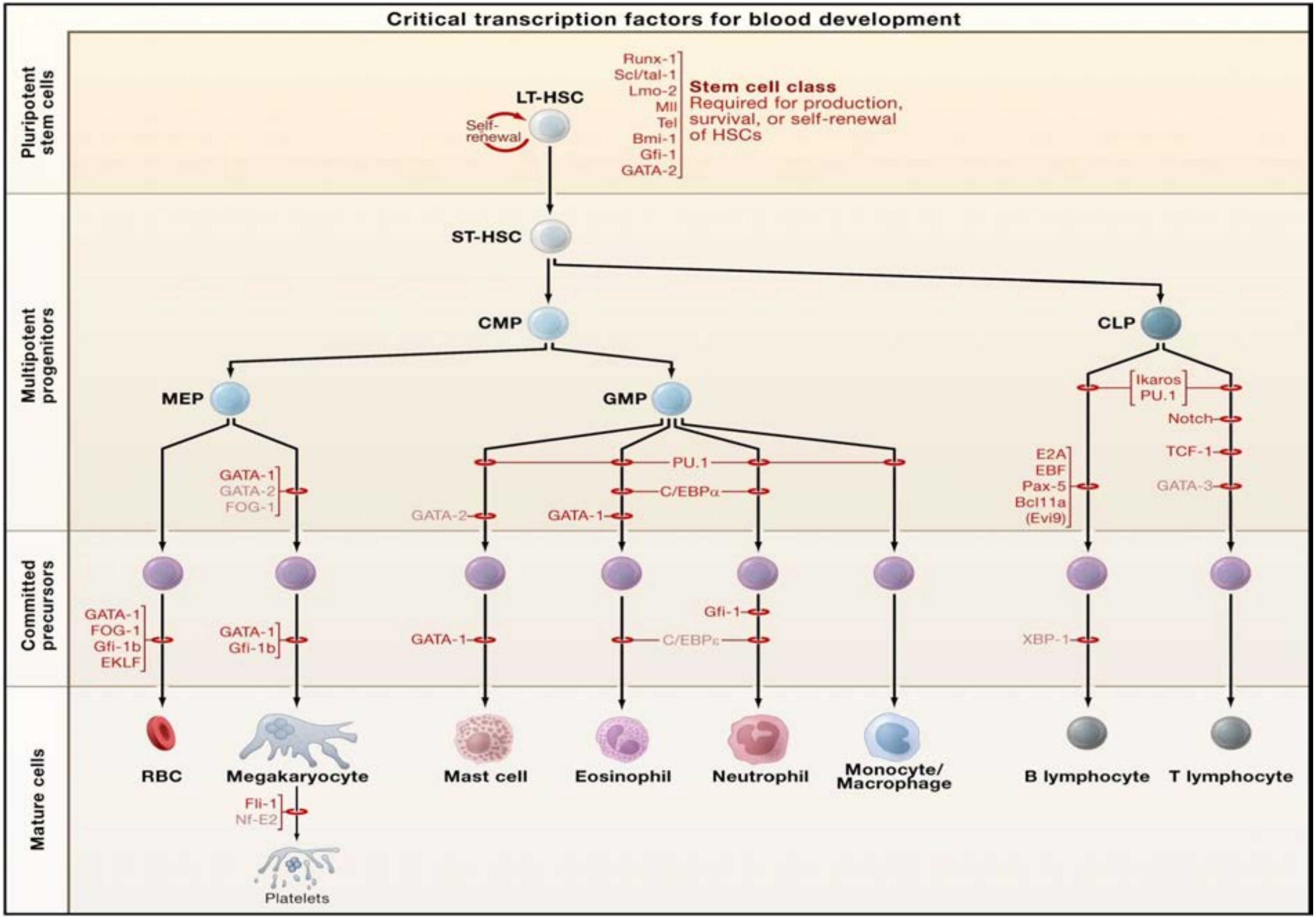
- HGFs mediate their actions through certain receptors on the target cells.
- Most of HGFs receptors belong to the haematopoietin receptor superfamily, which dimerize after binding their ligand.
- Dimerization of the receptor results in activation of a series of intracellular transcription pathways.

Growth factor receptors and signal transduction

Binding of the GF to its receptor

- **dimerization** of these receptors
- Activation of **tyrosine kinase** domain
- generation of a cascade of **biochemical events** changes in:
  - gene expression
  - cell proliferation
  - Differentiation
  - maturation
  - or prevention of apoptosis.





Many Different Transcription Factors Are Required for Hematopoiesis

Summary

- A single type of stem cells gives rise to all mature blood cells in the body.
- Pleuripotential stem cell form :
  - Lymphoid multipotential cells
  - & Myeloid multipotential cells.
- Stem cells, progenitor cells, blast cells & mature cells are different types of cells present in the bone marrow.
- The haemopoietic system is organized in a hierarchical manner
- Hematopoiesis depends on:
  - microenvironmental conditions
  - & growth factors.
- Sites of hematopoiesis varies with age.