Class 2:

Haematopoiesis

(Erythropoiesis)

T

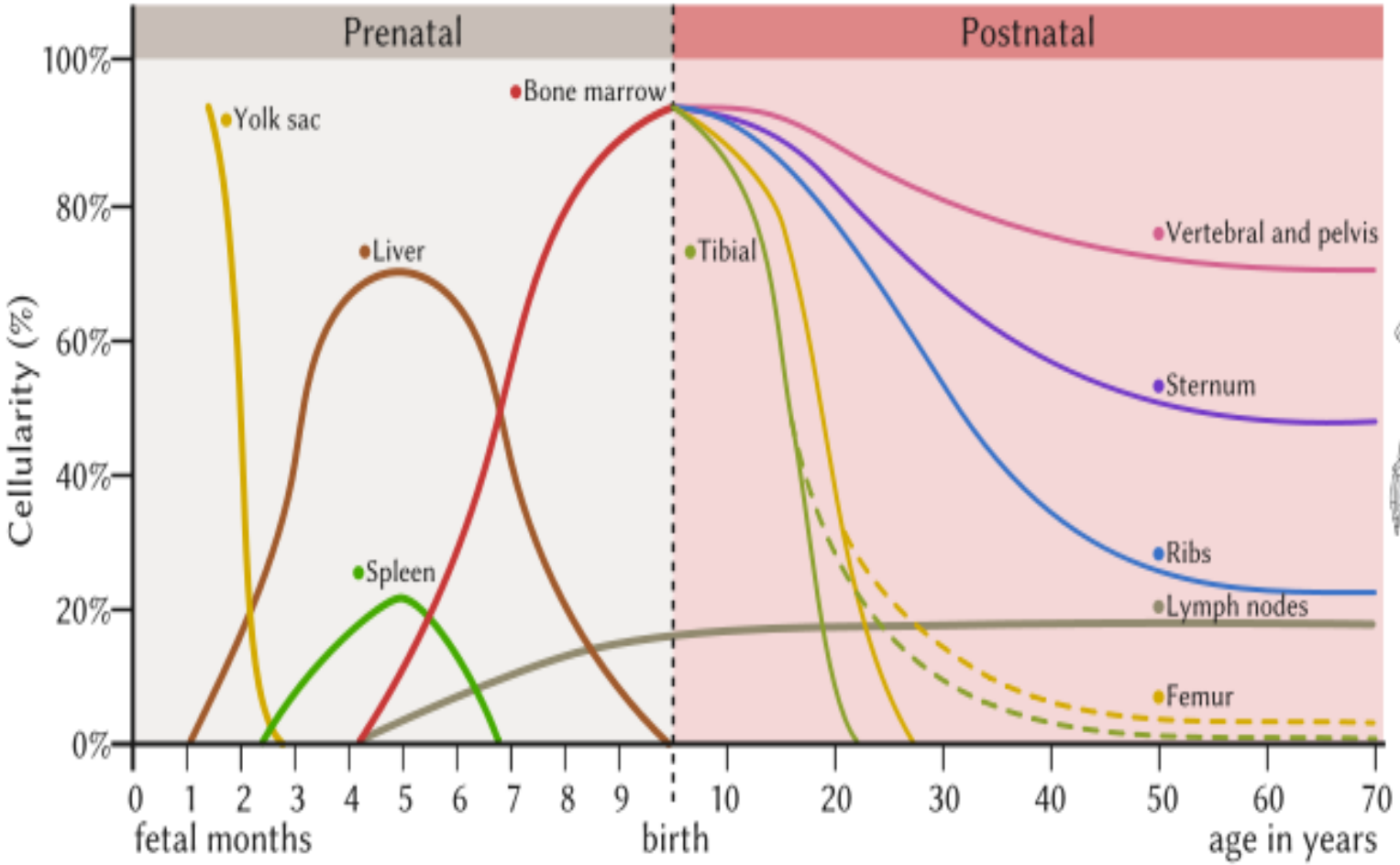
Objectives for this lecture

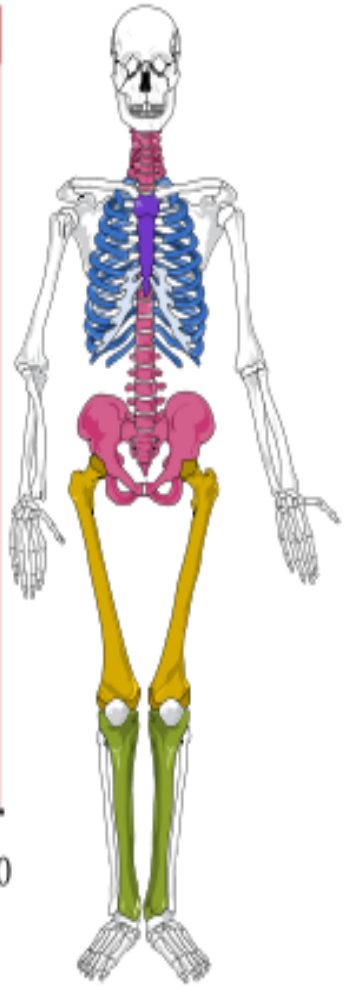
- understand the process of formation of blood cells.
- understand the normal role of each mature cell type in the blood.

Blood Cells derive from Hematopoietic Stem Cells

- ***Fetus*** - 0–2 months (yolk sac)
  - 2–7 months (liver, spleen)
  - 5–9 months (bone marrow)
- ***Infants*** - Bone marrow (practically all bones)
- ***Adults*** - Vertebrae, ribs, sternum, skull, sacrum and pelvis, proximal ends of femur

HEMATOPOIESIS





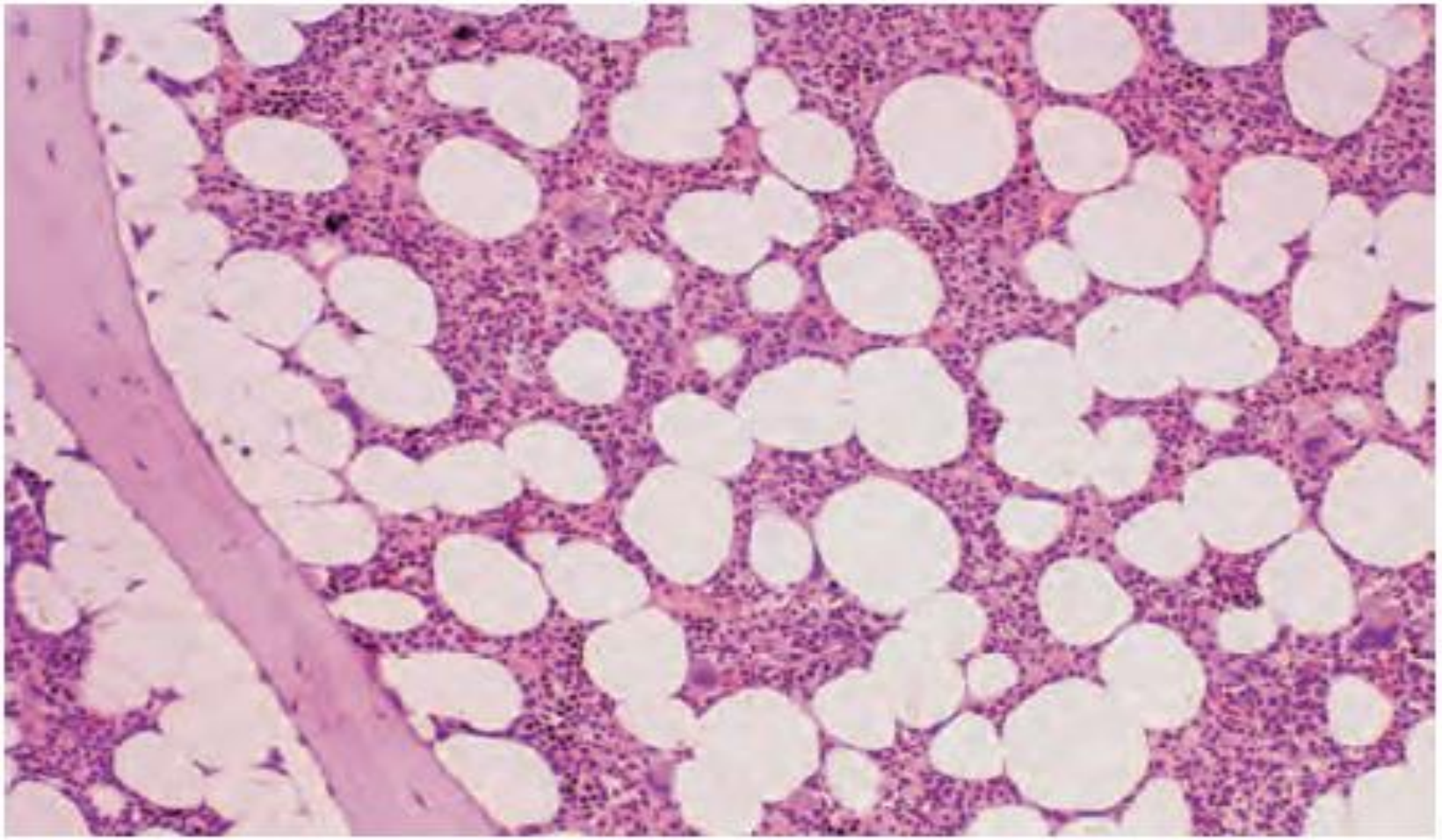


Figure 1.1 Normal bone marrow trephine biopsy (posterior iliac crest). Haematoxylin and eosin stain; approximately 50% of the intertrabecular tissue is haemopoietic tissue and 50% is fat.

- ***Stem cells may be present as:***
  - **Totipotent** : produce all the cells in an organism
  - **Pluripotent** : differentiate into cells of any of the three germ layers
  - **Multipotent** : produce only cells of a closely related family
  - **Unipotent** : produce only one type of cell

Haemopoietic stem cells (HSC)

- cells are dormant and in mice they enter cell cycle every 20 weeks.
- phenotype is unknown.
- On immunological test they have $CD34^{+}$ $CD38^{-}$.
- reside in specialized osteoblastic or vascular ‘niches’.

Bone marrow stroma

- *stromal cells matrix include :*
  - mesenchymal stem cells, adipocytes, fibroblasts, osteoblasts, endothelial cells and macrophages.
  - And secrete collagen, glycoproteins (fibronectin and thrombospondin) and glycosaminoglycans (hyaluronic acid).
  - secrete growth factors for stem cell survival.

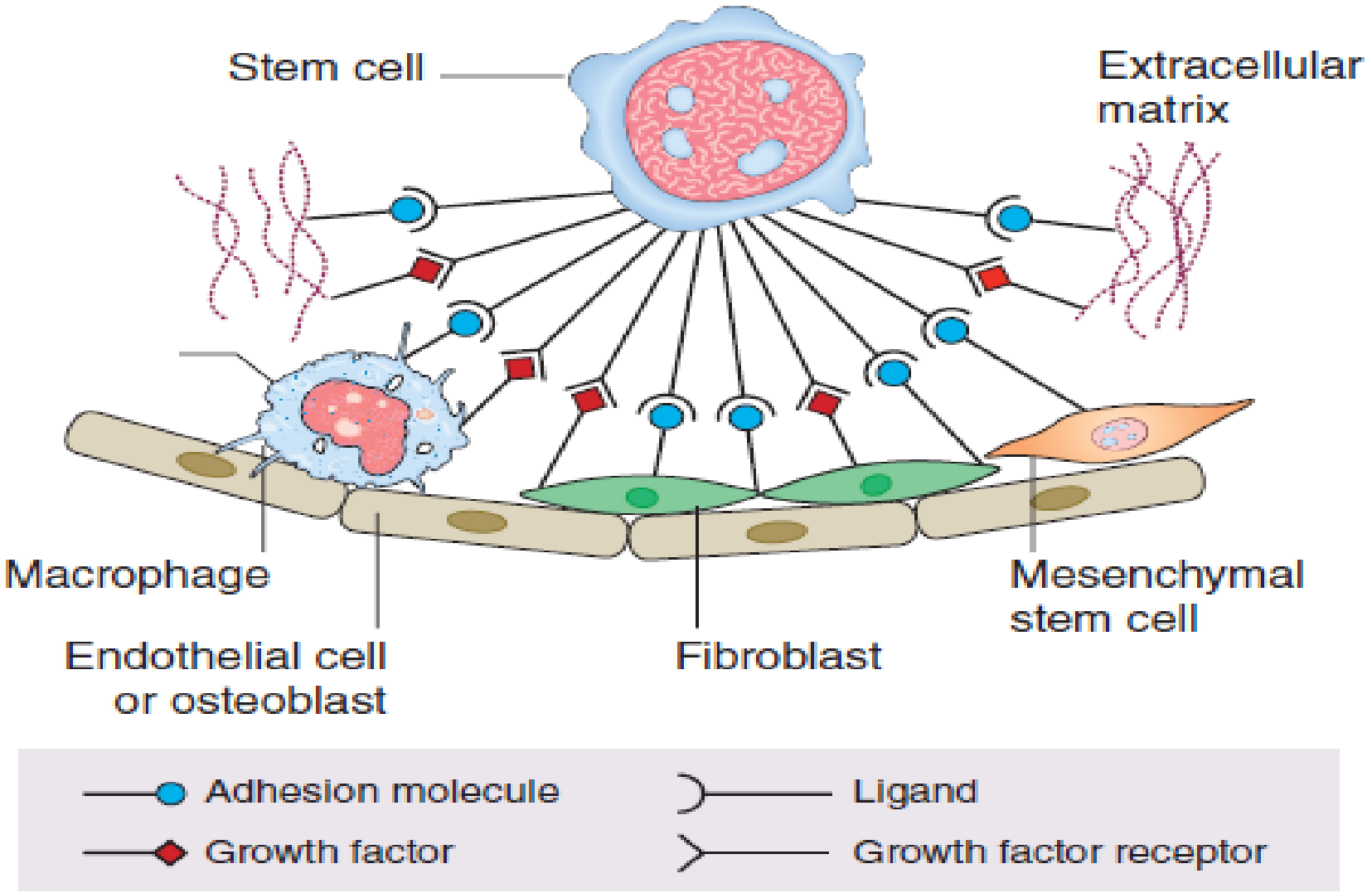
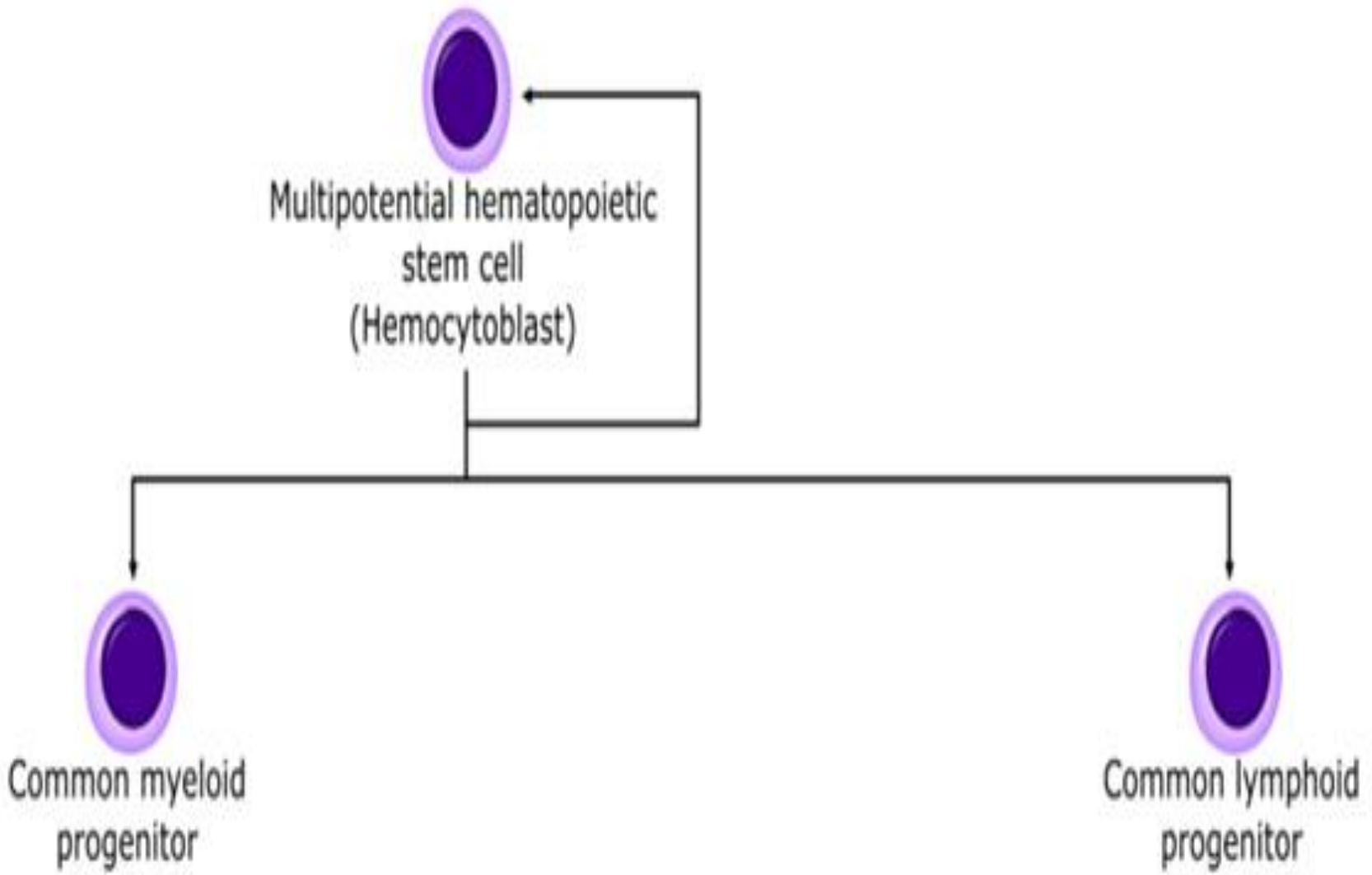


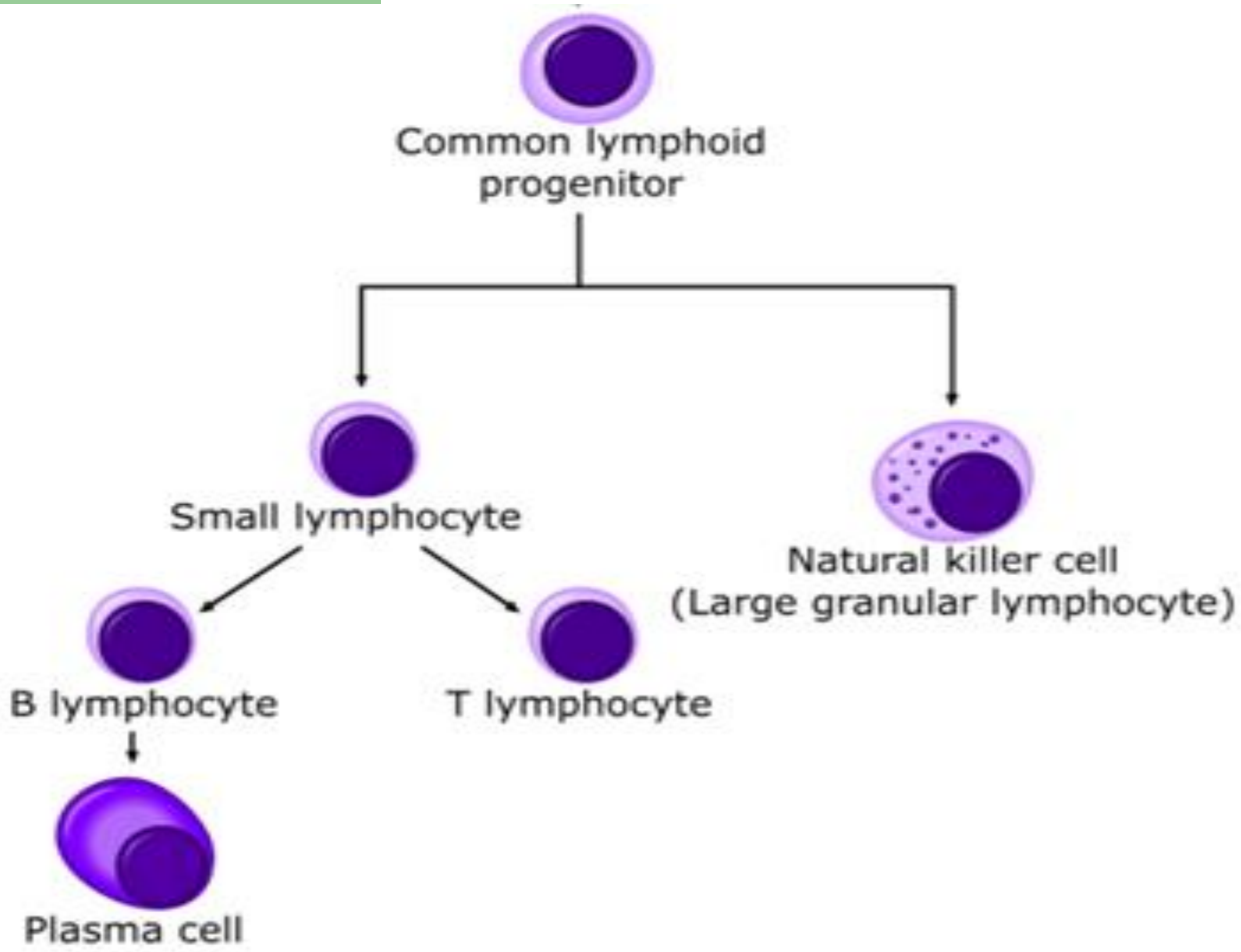
Figure 1.4 Haemopoiesis occurs in a suitable microenvironment

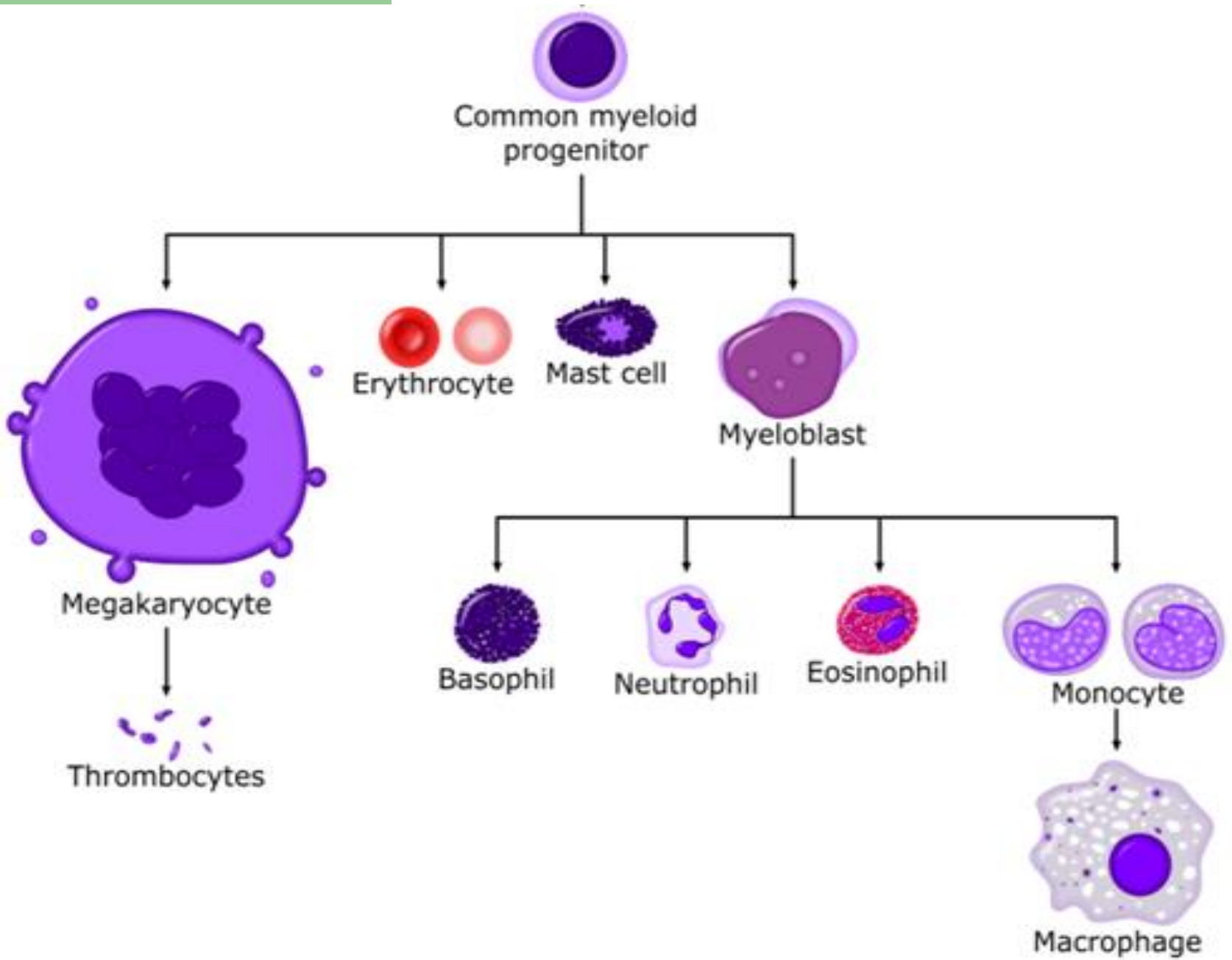
Haemopoietic stem cells

- haemopoietic stem cells (HSCs) are capable of both *self-renewal* and *differentiation* into the blood cell lineages (Multipotent).
- *giving rise to two major lineages:*

  1. *Lymphoid* lineage : B and T cells (lymphocytes)
  2. *myeloid* lineage : red cells, wight cells, granulocytes and platelets


Multipotential hematopoietic
stem cell
(Hemocytoblast)
Common myeloid
progenitor
Common lymphoid
progenitor


Common lymphoid progenitor
Small lymphocyte
Natural killer cell (Large granular lymphocyte)
B lymphocyte
T lymphocyte
Plasma cell


Common myeloid progenitor
Erythrocyte
Mast cell
Myeloblast
Megakaryocyte
Thrombocytes
Basophil
Neutrophil
Eosinophil
Monocyte
Macrophage

Lymphopoiesis

- ***Production site:***
  - ✓ *primary site:* Bone marrow.
  - ✓ *secondary site:* spleen, lymph nodes and thymus.
- Classes are:
  - *1- B cells*
  - *2- T cells*
  - *3- Natural Killer (NK) cells*
- Express CD45 and CD7 cell surface markers.

Lymphopoiesis

- Pax5 is transcription factors for B cell development.
- GATA3 factors is essential for T cell maturation.
- B cell maturation requires antigen in the lymph nodes.
- B cell recognize non-self antigens and produce immuneglobulin.

Lymphopoiesis

- T cells are formed in the thymus.
- T cells recognize a wide range of viruses and other foreign cells.
- T cells acquire both CD4 (helper) and CD8 (suppressor) cell surface markers.

Lymphopoiesis

- Cytokine cause activation of the macrophage system, granulocyte maturation and antibody synthesis by B cells.
- T suppressor (cytotoxic cells) destroy cells expressing a peptide to which their T cell receptor can bind (e.g. virally infected cells).

Lymphopoiesis

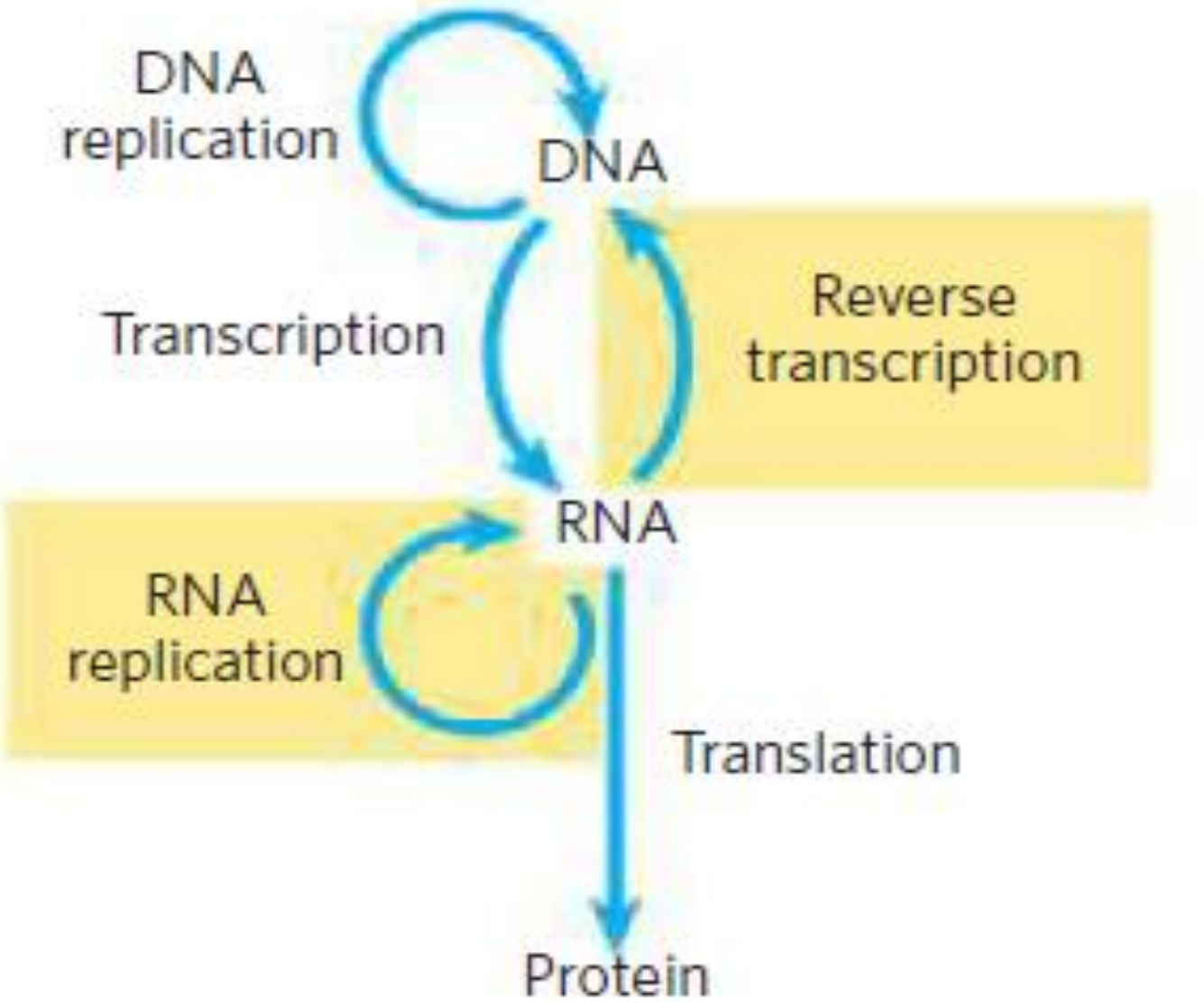
- T helper cells produce cytokines to promote an inflammatory response in presence of antigen.

Lymphopoiesis

- *Natural Killer (NK) cells* have a role in the innate immune system, through cell-mediated cytotoxicity.

Myelopoiesis regulation: *(1) transcription factors*

- Control transcription of specific genes.
- These factors help in understanding of myeloid diseases *(acute myeloid leukaemia)*


DNA replication
DNA
Transcription
Reverse transcription
RNA
RNA replication
Translation
Protein

Myelopoiesis regulation : *transcription factors….. cont.*

- *Regulate survival of stem cells:*

  transcription factors SCL, GATA-2, NOTCH-1

- *Differentiation of myeloid cell lineage:*

  CEBPα, PU.1

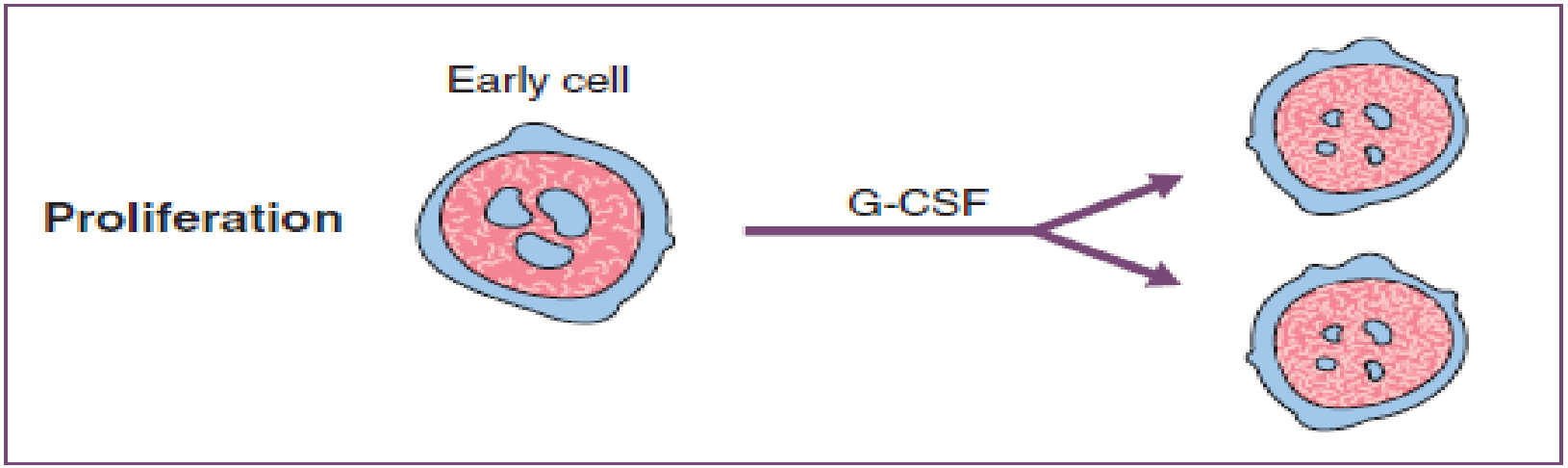
- *Differentiation of erythroid and megakaryocytic:*

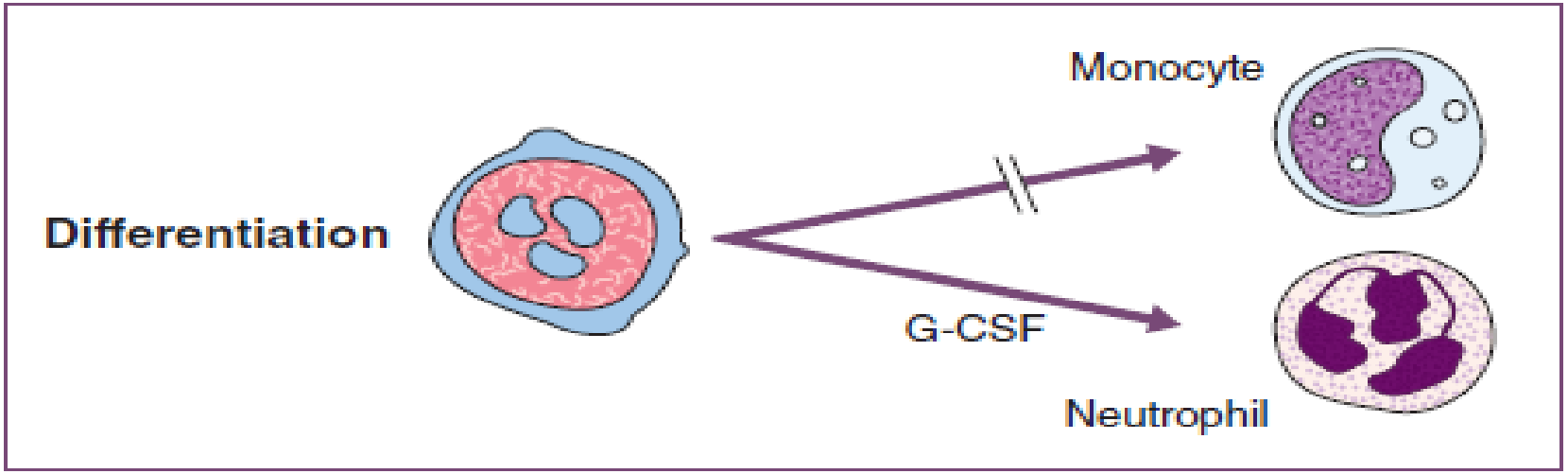
  GATA1, FOG-1 and NF-E2

Myelopoiesis regulation :
(2) myeloid growth factors

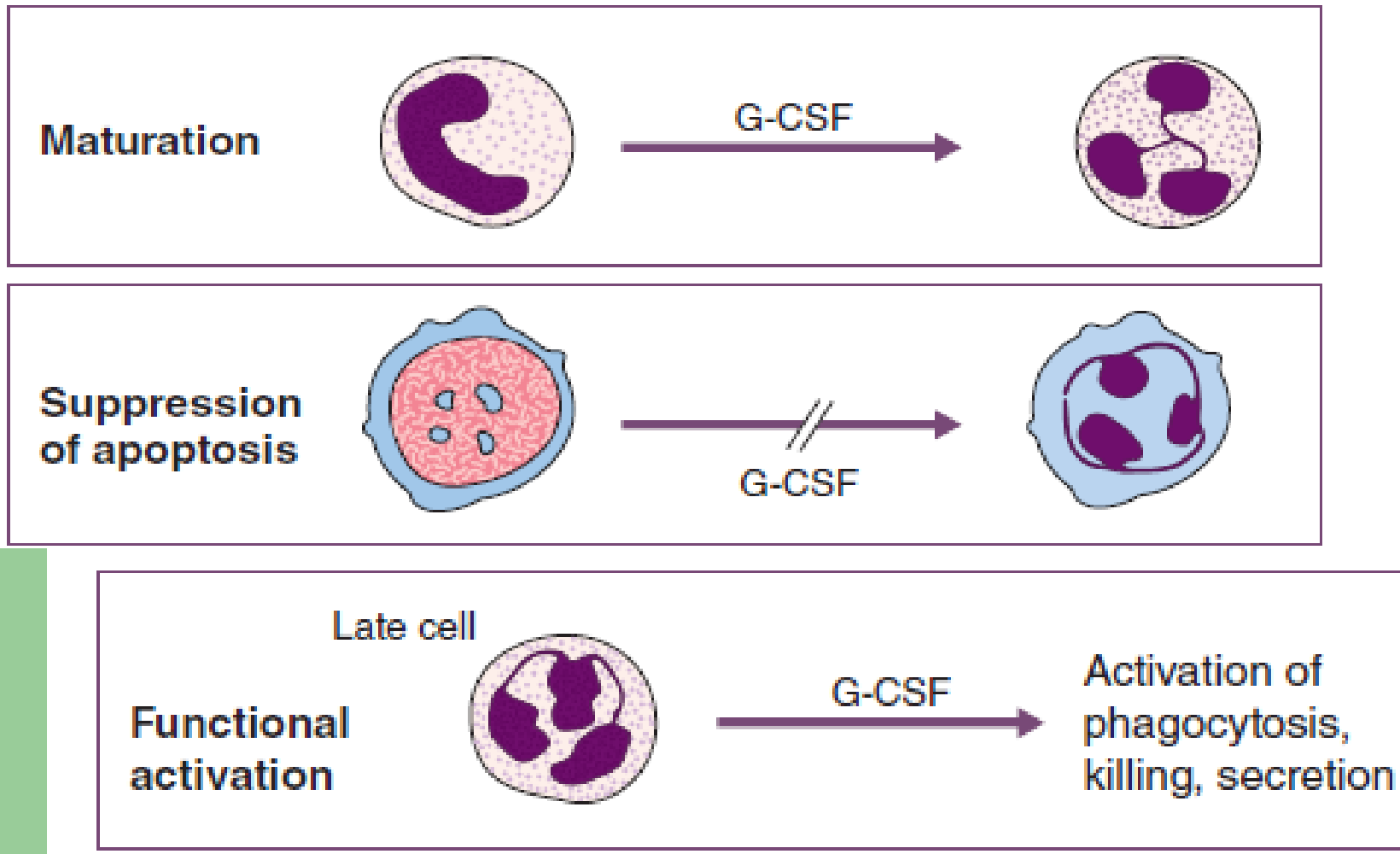
- glycoprotein hormones :
  - granulocyte colony stimulating factor (G-CSF) (stromal).
  - Thrombopoietin (kidney) and erythropoietin (kidney & liver).
- It cause: - cell proliferation
  - stimulate differentiation
  - maturation
  - prevent apoptosis

growth factors action





growth factors action



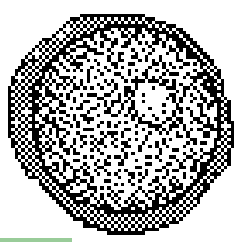
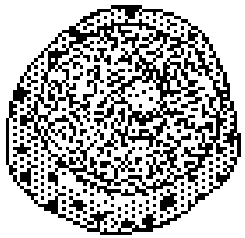
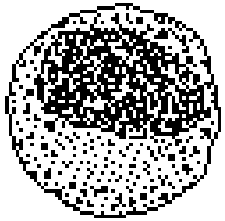
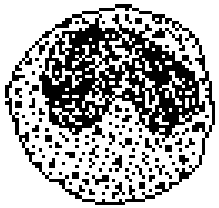
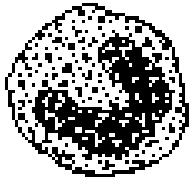
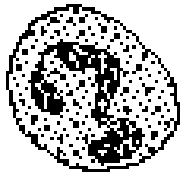
Myeloblasts

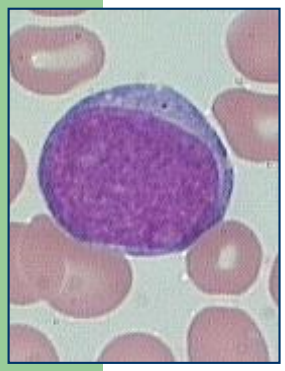
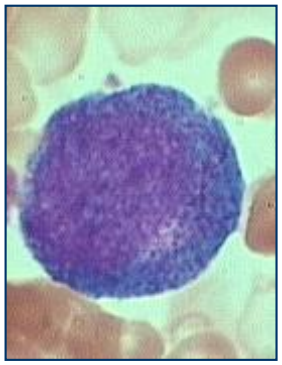
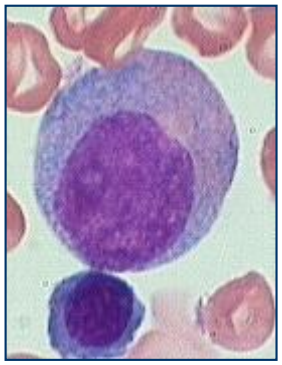
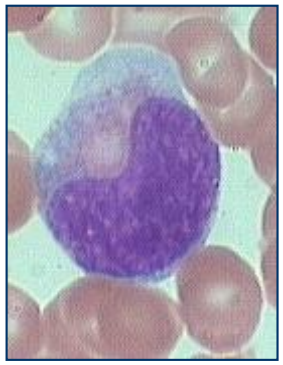
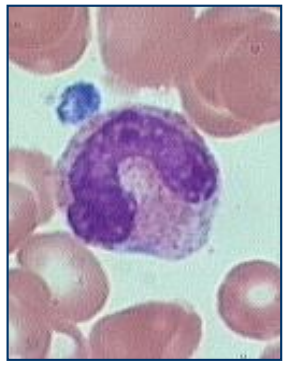
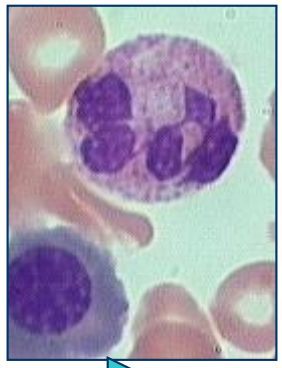
- Large cells, with open nuclear chromatin.
- Stages of neutrophil granulocytes:
  - ✓ promyelocytes
  - ✓ neutrophil myelocytes
  - ✓ neutrophil metamyelocytes
  - ✓ Neutrophil band cells

No Cell division

Myeloid maturation

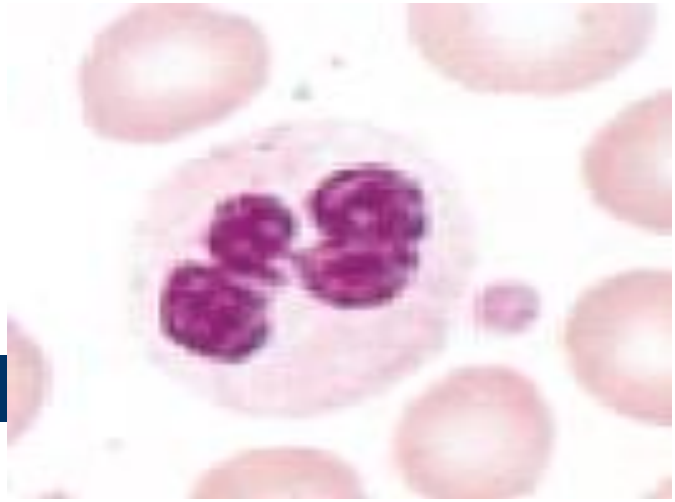
myeloblast promyelocyte myelocyte metamyelocyte band neutrophil

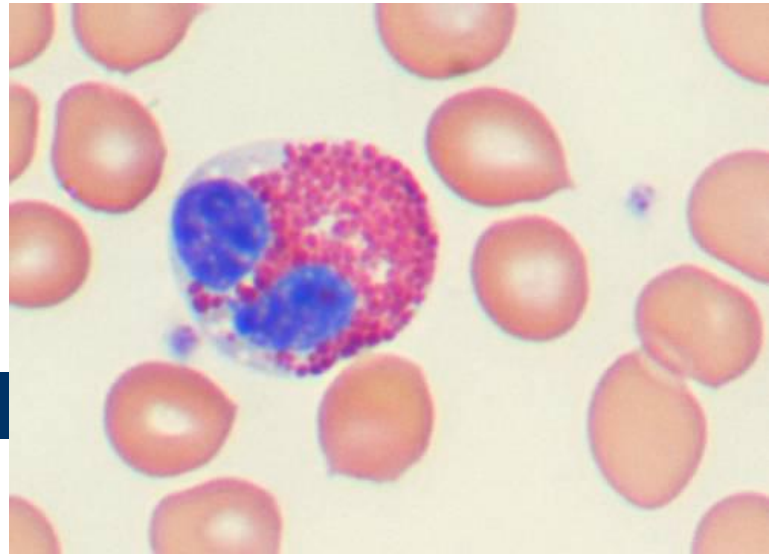
MATURATION

Mature granulocytic cells



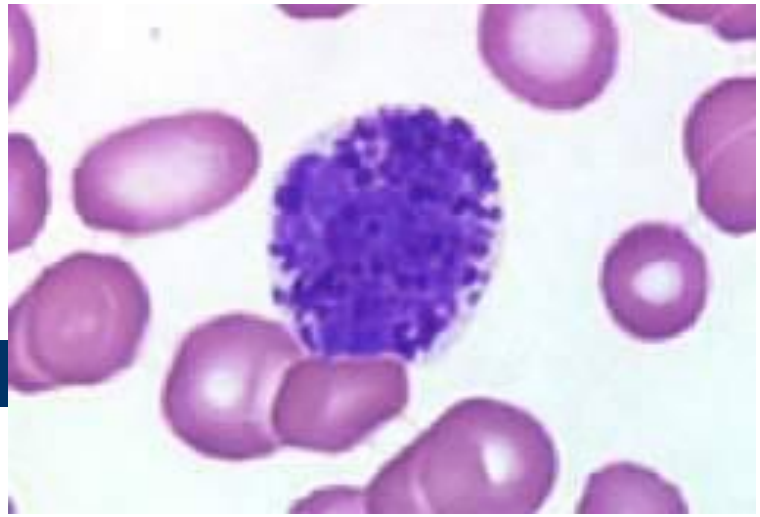
- *Neutrophils:*
  - Migrate to inflammation (chemotaxis).
  - phagocytose opsonized microbes.
  - release of reactive oxygen species
  - enzyme myeloperoxidase (MPO) generates hypochlorous acid with cytotoxic effects
  - granules contain antimicrobial agents chymotrypsin and gelatinases.

Mature granulocytic cells



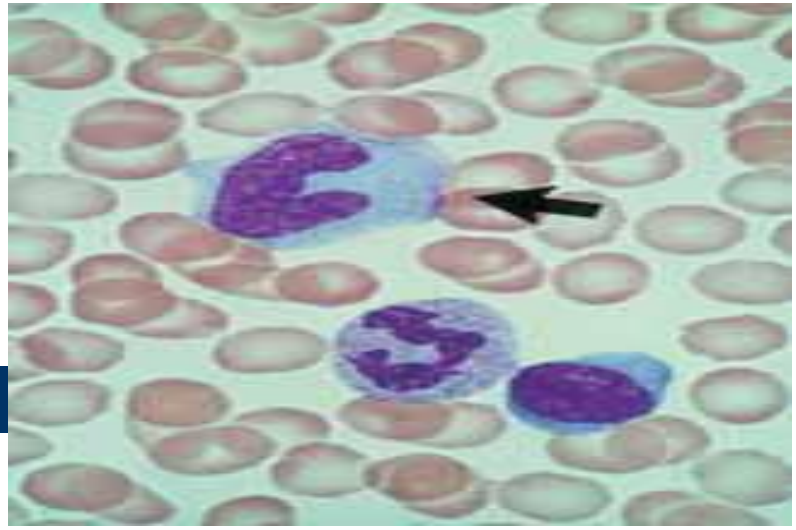
- *Eosinophils :*
  - Associated with the immune response to parasitic infection.
  - phagocytose and destroy micro-organisms.
  - found in allergy and atopy.

Mature granulocytic cells



- *Basophils :*
  - have stores of histamine and heparin as well as proteolytic enzymes. involved in immune and inflammatory responses.

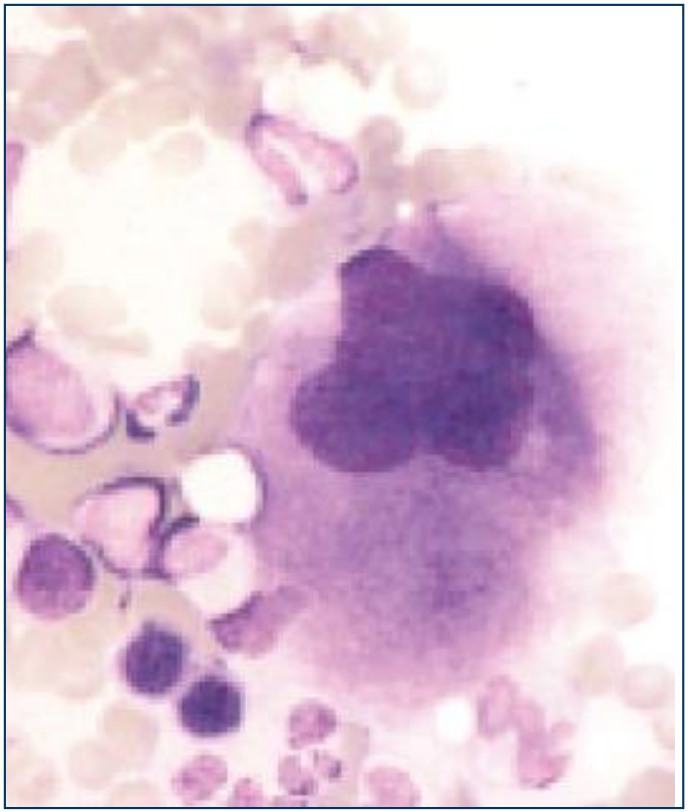
monocyte



- *Monocytopoiesis:*
  - synthesis is controlled by the GMCSF.
  - precursors of tissue macrophages.
  - roles include phagocytosis, antibody presentation to other immune cells, and a contribution to the cytokine milieu.
  - Bacteria and fungi that (not antibody coated) are phagocytosed after binding to mannose receptors on the phagocyte surface.

Megakaryocytes and platelet

- Megakaryocytes give rise to platelets.
- driven by the growth factor *thrombopoietin* (TPO).
- Platelets are formed from its cytoplasm, and rapidly discharged.
- TPO is sequestered after binding to platelet membr.



Red Blood Cells Formation *(Erythropoiesis)*

- Regulated by the hormone erythropoietin.
- *Stimulus is O2 tension* in kidney tissues:
  - Low O2 (Hypoxia) induces synthesis of hypoxia-inducible factors (HIF-1α and β).
  - Which stimulate erythropoietin production.
  - And stimulate vessel formation and transferrin receptor synthesis.
  - Increasing iron absorption

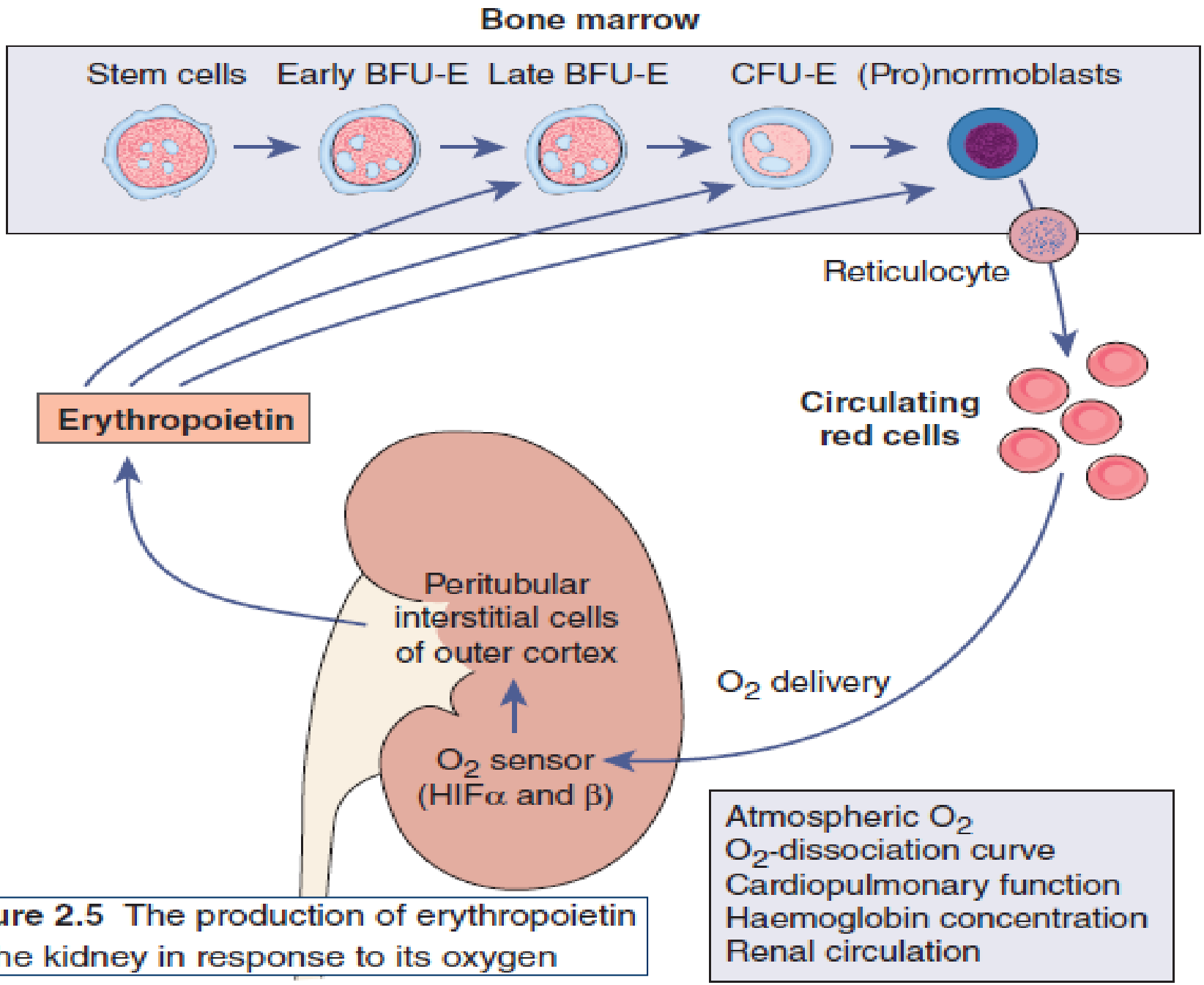
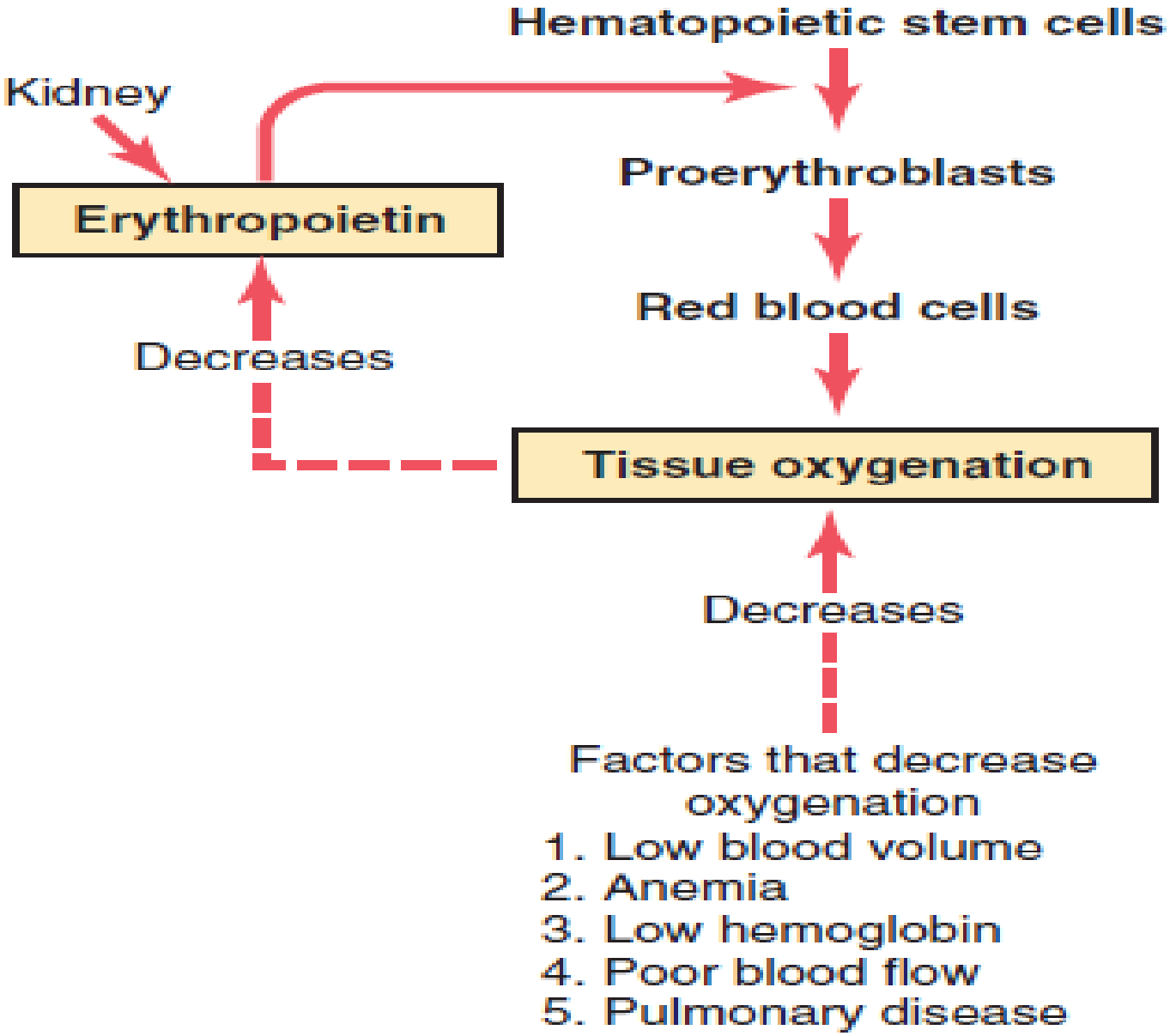


Figure 2.5 The production of erythropoietin by the kidney in response to its oxygen

- Erythropoietin receptor stimulation cause:
  - Activate transcription factors (GATA-1 and FOG-1).
  - Which cause expression of erythroid-specific genes (globin, haem, membrane proteins).

- *So, increased O2 supply to the tissues reduces the erythropoietin drive.*


Hematopoietic stem cells
Kidney
Proerythroblasts
Erythropoietin
Red blood cells
Decreases
Tissue oxygenation
Decreases
Factors that decrease oxygenation
1. Low blood volume
2. Anemia
3. Low hemoglobin
4. Poor blood flow
5. Pulmonary disease

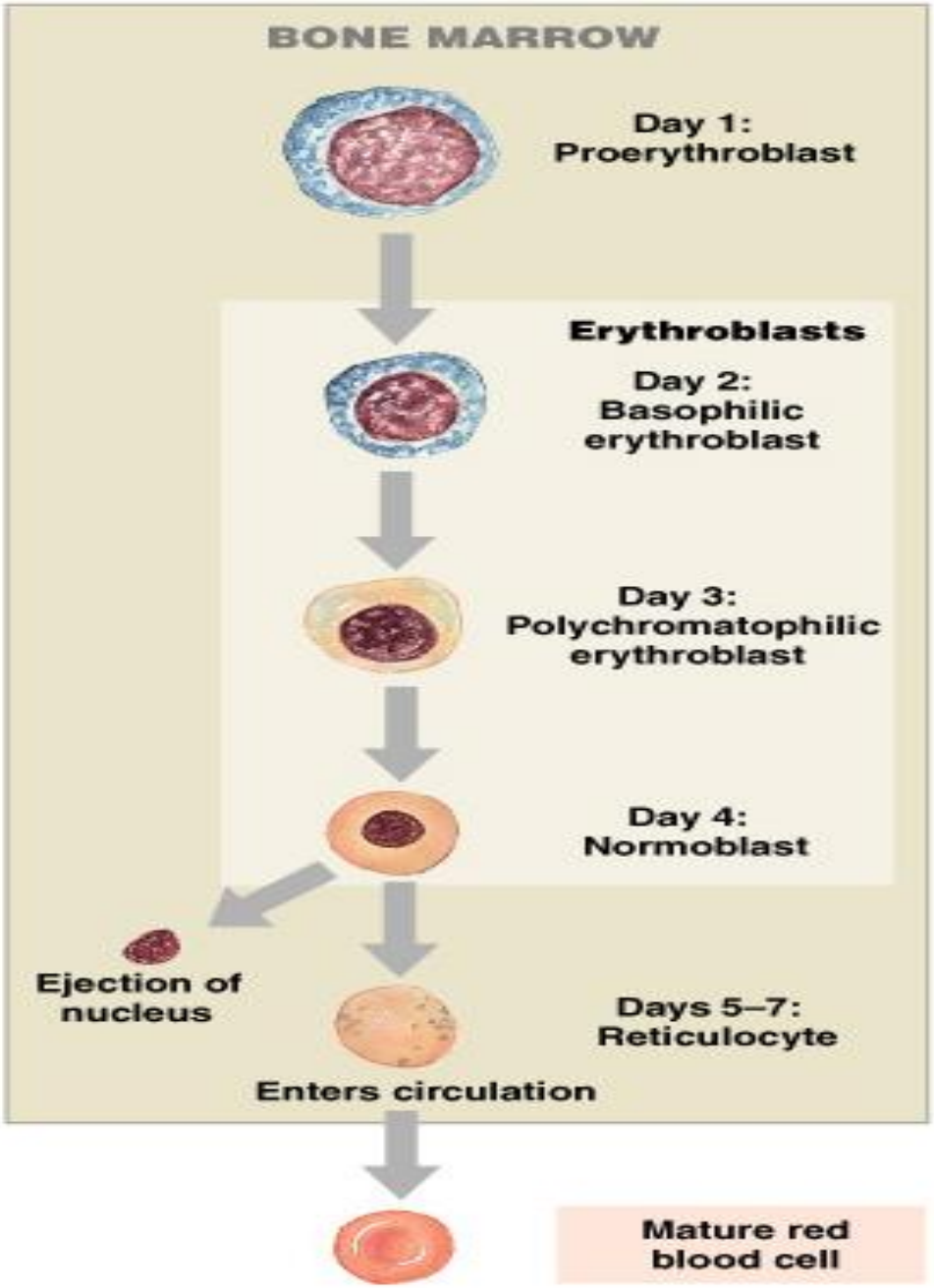
- Erythropoietin production increases in:
  - Anaemia.
  - Haemoglobin is unable to give up O2 normally.
  - Atmospheric O2 is low.
  - Defective cardiac or pulmonary function.
  - Damage to the renal circulation affects O2 delivery to the kidney.

erythropoietin therapy

- erythropoietin therapy is needed for treating anaemia.
- *For effective erythropoiesis*, marrow require:
  - ✓ Metals (iron and cobalt)
  - ✓ Vitamins (vit B12, vit B6, folate, vit C, vit E, thiamine and riboflavin)
  - ✓ Hormones (androgens and thyroxine)

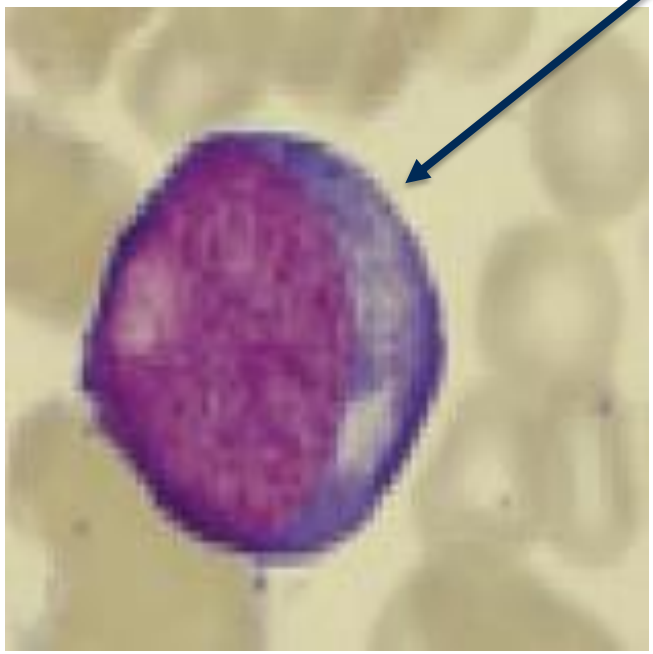
Stages of RBC Maturation

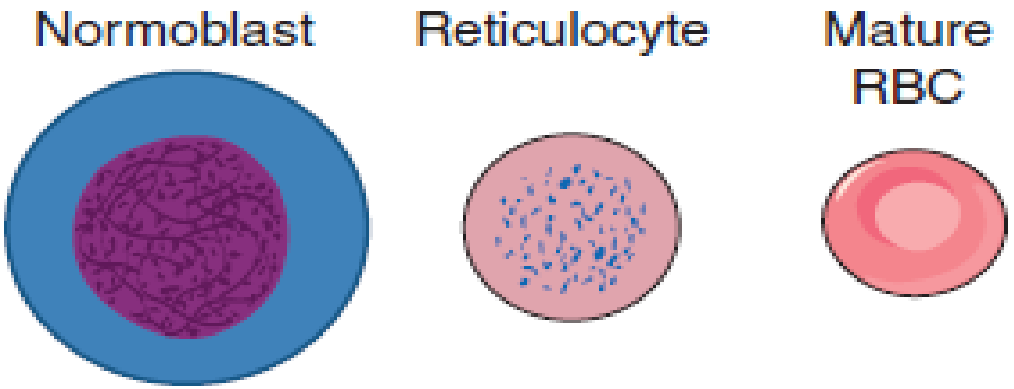
- Myeloid stem cell
- Proerythroblast
- Erythroblasts
- Reticulocyte
- Mature RBC



Erythropoiesis

- *Stages of Maturation:*
  - Myeloid stem cell
  - Proerythroblast
  - Erythroblasts
  - Reticulocyte
  - Mature RBC





Nuclear DNA	Yes	No	No
RNA in cytoplasm	Yes	Yes	No
In marrow	Yes	Yes	Yes
In blood	No	Yes	Yes

Figure 2.4 Comparison of the DNA and RNA content, and marrow and peripheral blood distribution, of the erythroblast (normoblast), reticulocyte and mature red blood cell (RBC).

Stages of RBC Maturation

- Reticulocyte is released from marrow into the peripheral blood (RNA).
- Reticulocytes have larger size.
- After one to two days in circulation, it lose ribosomes and become mature red cells.

References

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- Chris S.R. Hatton, Nevin C. Hughes-Jones, Deborah Hay, David Keeling. ***Haematology: Lecture notes***, 9th ed, 2013.
- Victor W. Rodwell, David A. Bender, Kathleen M. Botham, Peter J. Kennelly, P. Anthony Weil. Harper's Illustrated Biochemistry. McGraw-Hill Ed, 31 ed, 2018.