Haemopoiesis L2C1

Haemopoiesis (Hematopoiesis)

It is a process of the development of blood cells; this term is derived from Greek words (haima), meaning blood and (poiesis), meaning creating, in which pluripotent hematopoietic stem cells proliferate and differentiate. After several steps, HSCs finally give rise to mature blood cells.

Hematopoiesis includes;-

- Erythropoiesis is the formation of RBC
- Leucopoiesis (myelopoiesis) is the formation of WBC
- Thrombopoiesis is the formation of platelets.

Site of haemopoiesis (Hematopoiesis)

The blood formed by:-

- Medullary haematopoiesis refers to blood cell production in the bone marrow.
- Extramedullary haematopoiesis refers to blood cell production outside the bone marrow, like lymphoid organs, liver, spleen & thymus.

Site of haemopoiesis

1- In the first few weeks of gestation mesenchymal cell of the yolk sac is the main site of haemopoiesis.
2- Definitive haemopoiesis derives from a population of stem cells first observed in the AGM (aorta-gonads-mesonephros) region.
3- From 6 weeks until 6–7 months of fetal life, the liver and spleen are the major haemopoietic organs and continue to produce blood cells until about 2 weeks after birth.
4- The placenta also contributes to fetal haemopoiesis.
5- The bone marrow is essential from 6–7 months of fetal life. The marrow is the only source of new blood cells during normal childhood and adulthood. In adult life, hematopoietic marrow is limited to the vertebrae, ribs, sternum, skull, sacrum, pelvis and proximal ends of the femur.
6- The developing cells are situated outside the bone marrow sinuses;

7- Mature cells are released into the sinus spaces, the marrow microcirculation, and the general circulation.

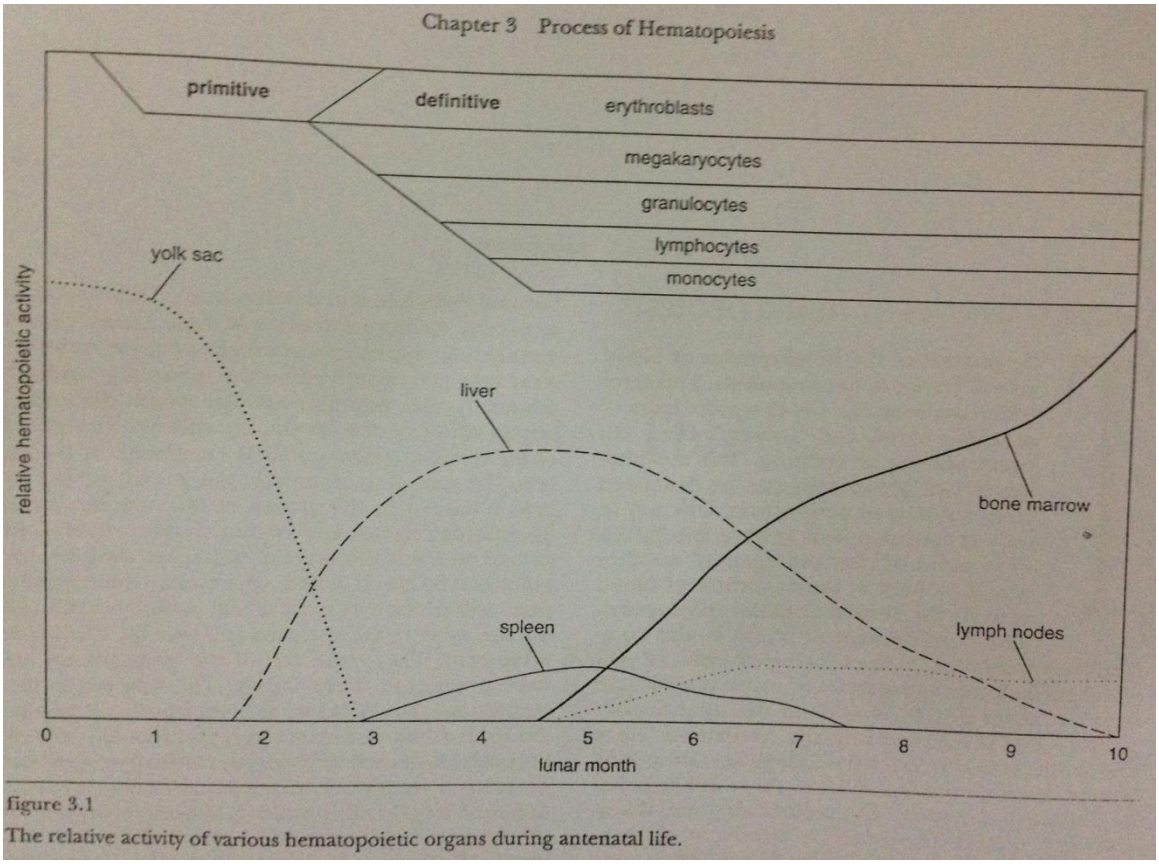


figure 3.1
The relative activity of various hematopoietic organs during antenatal life.

Table 1.1 Sites of haemopoiesis.	
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

- In **infancy,** all the bone marrow is haemopoietic
- but during **childhood,** there is the progressive fatty replacement of marrow throughout the long bones
- so that in adult life, haemopoietic marrow is confined to the central skeleton and proximal ends of the femurs and hummer

Progenitor Cells

- Upon commitment to development, the HSCs enter the next compartment, the progenitor cell compartment. This compartment consists of mainly 2 types of cells.

1- Multipotent progenitor cells (lineage-specific)

2- (Unipotent) Committed progenitor cells

- Both multipotent and unipotent cells in the bone marrow can give rise to clones (groups) composed of specific kinds of mature cells when grown in culture and are called colony-forming units (CFU).

- ***Pluripotent*** Ability to generate all mature hematopoietic cells
- **Multipotent** Ability to produce a limited range of differentiated cell lineages appropriate to their location
- ***Unipotent*** Restricted ability to differentiate and generate one specific cell type.
- ***Self-renewal***: HSCs are capable of cell division to give rise to more stem cells.
- ***Differentiation***: HSCs can differentiate and give rise to two kinds of lineage-specific multipotent progenitor cells, the common myeloid and the common lymphoid progenitors.

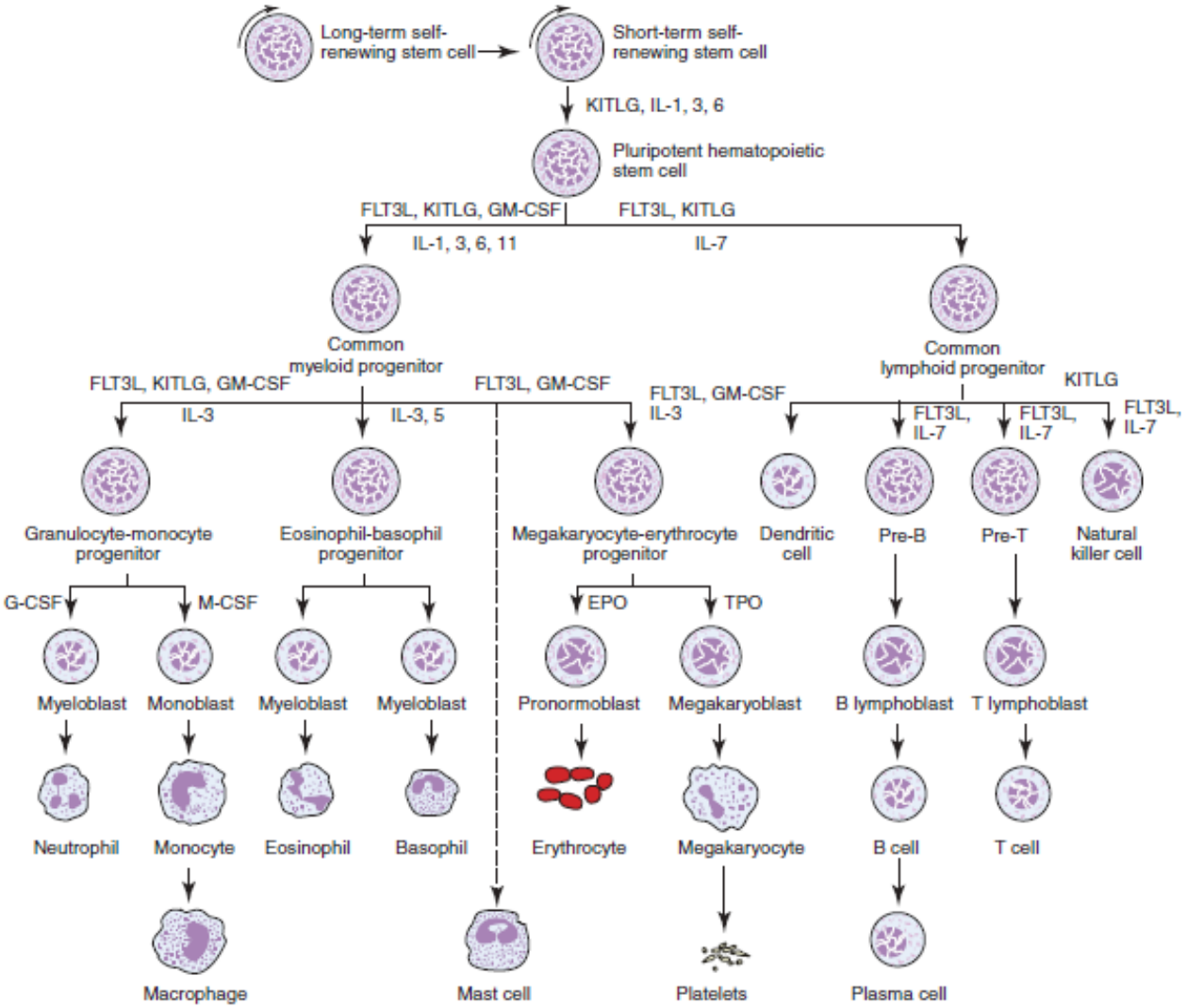


Figure 7-15 Diagram of derivation of hematopoietic cells, illustrating sites of action of cytokines. *EPO,* Erythropoietin; *FLT3L,* FLT3 ligand; *G-CSF,* granulocyte colony-stimulating factor; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *IL-1,* interleukin-1; *IL-3,* interleukin-3; *IL-5,* interleukin-5; *IL-6,* interleukin-6; *IL-7,* interleukin-7; *IL-11,* interleukin-11; *KITLG,* KIT ligand; *M-CSF,* macrophage colony-stimulating factor; *TPO,* thrombopoietin.

Bone marrow stroma

- The bone marrow forms a suitable environment for stem cell survival, self-renewal and formation of differentiated progenitor cells.
- It is composed of stromal cells and a micro-vascular network.

The **stromal cells**

- include mesenchymal stem cells, adipocytes, fibroblasts, osteoblasts, endothelial cells and macrophages
- They secrete several growth factors necessary for stem cell survival.

Mesenchymal stem cells are critical in stromal cell formation.

- Together with osteoblasts or endothelial cells, they form niches and provide the growth factors, adhesion molecules and cytokines which support stem cells,

The regulation of haemopoiesis

- Haemopoiesis starts with stem cell division, in which one cell replaces the stem cell (*self-renewal*), and the other is *committed to differentiation*.
- Several transcription factors regulate the survival and differentiation of stem cells
- Transcription factors regulate gene expression by controlling the transcription of specific genes or gene families.

Haemopoietic growth factors

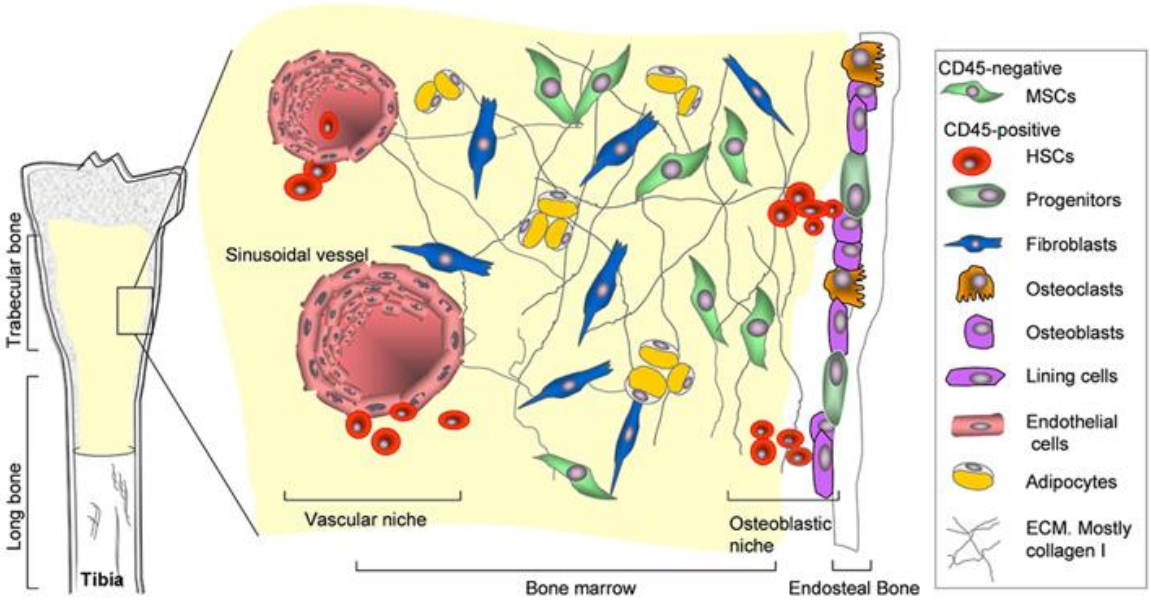
The haemopoietic growth factors are glycoprotein hormones that

(i) regulate proliferation, differentiation, and maturation of haematopoietic progenitor cells,
(ii) influence the commitment of progenitors to specific lineages, and
(iii) Affect the function and survival of mature blood cells.

Stromal cells are the major source of growth factors except for **erythropoietin**. Erythropoietin is a glycoprotein produced in the kidneys (90%) and the liver (10%).

- **Erythropoietin** stimulates progenitor cells committed to the erythroid lineage
- **Thrombopoietin** is made mainly in the liver.
- **Interleukin-3 (IL-3)** and granulocyte-macrophage colony-stimulating factor (GMCSF).
- **G-CSF** and **thrombopoietin** enhance the effects of other factors on the survival and differentiation of the early haemopoietic cells.
- Infection or inflammation can stimulate granulocyte and monocyte formation through the release of IL-1 and tumor necrosis factor (TNF), which then stimulate stromal cells to produce growth factors in an interacting network

- In contrast, **cytokines**, such as transforming growth factor-β (TGF-β) and γ-interferon (IFN-γ), can exert a negative effect on haemopoiesis and may have a role in the development of aplastic anemia.



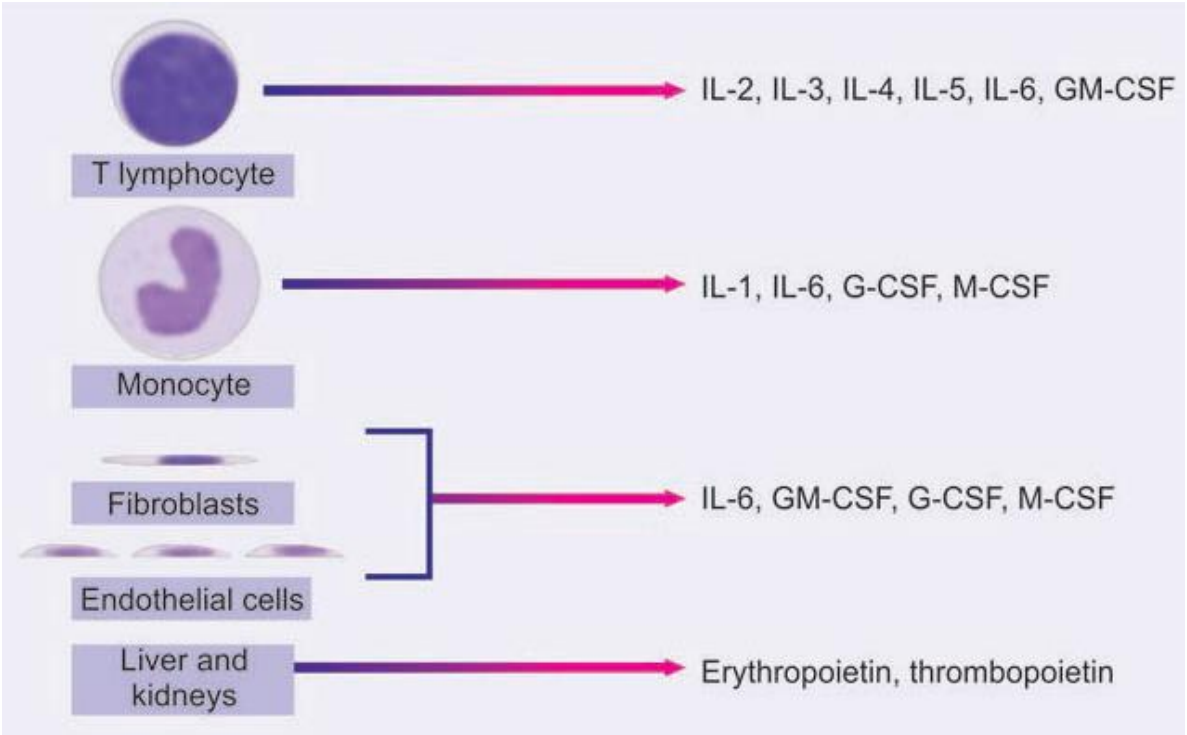


Table 1.3 Haemopoietic growth factors.
Act on stromal cells
IL-1
TNF
Act on pluripotential stem cells
SCF
FLT3-L
VEGF
Act on multipotential progenitor cells
IL-3
GM-CSF
IL-6
G-CSF
Thrombopoietin
Act on committed progenitor cells
G-CSF*
M-CSF
IL-5 (eosinophil-CSF)
Erythropoietin
Thrombopoietin*

CSF, colony-stimulating factor; FLT3-L, FLT3 ligand; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; M-CSF, macrophage colony-stimulating factor; SCF, stem cell factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.
* These also act synergistically with early acting factors on pluripotential progenitors.

Table 1.1: Selected growth facto

Growth factor	Source
1. Interleukin-1 (IL-1)	Activated macrophages
2. Interleukin-2 (IL-2)	T lymphocyte
3. Interleukin-3 (IL-3)	T lymphocyte
4. Interleukin-6 (IL-6)	T lymphocytes, monocytes/ macrophages, fibroblasts
5. C-kit ligand (stem cell factor)	
6. GM-CSF	T cells, fibroblasts, endothelial cells
7. G-CSF	Monocytes/macrophages, fibroblasts
8. M-CSF	Monocytes/macrophages, fibroblasts, endothelial cells
9. Erythropoietin	Kidneys and liver
10. Thrombopoietin	Kidneys and liver