بسم الله الرحمن الرحيم

Hematopoiesis

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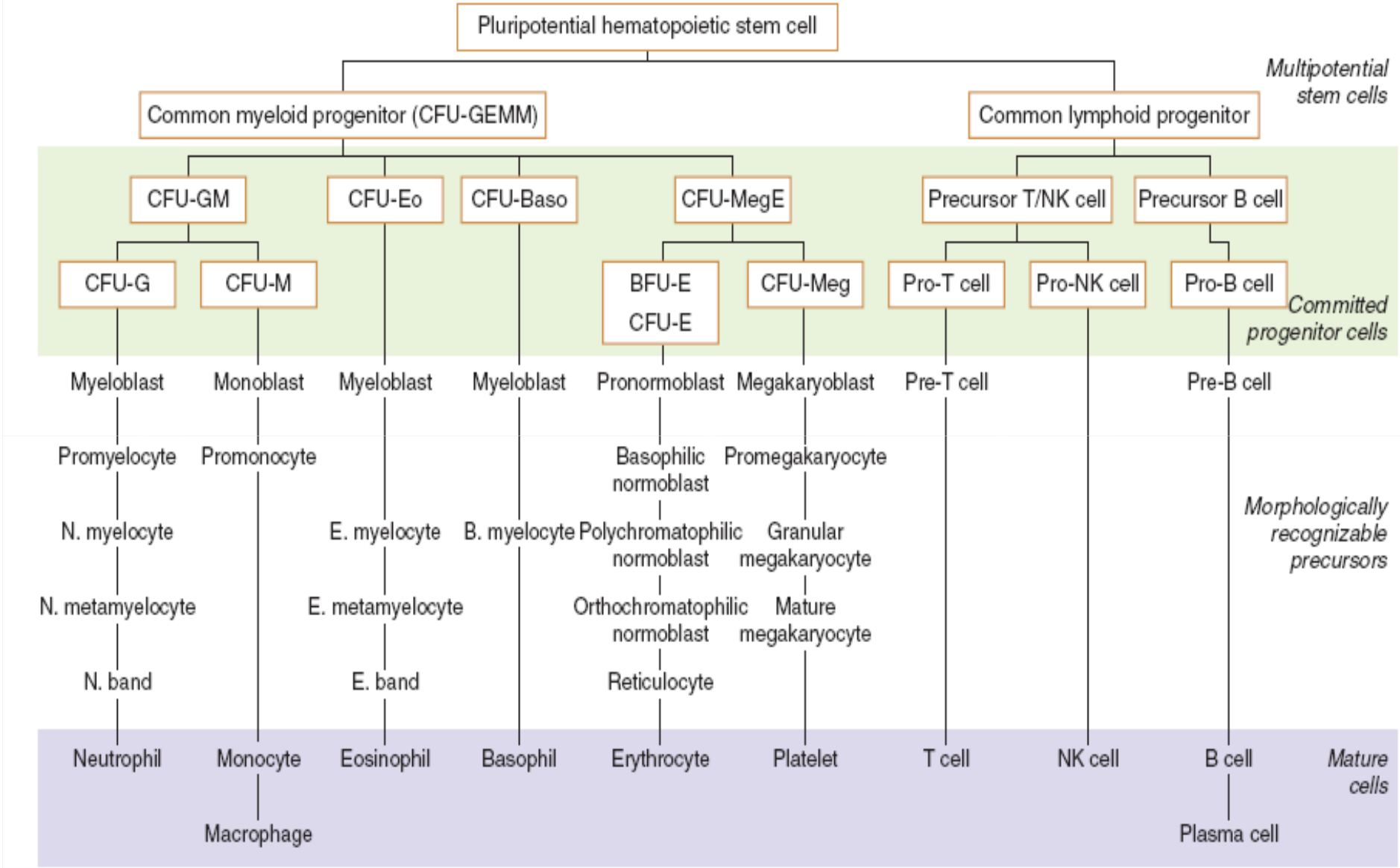
Hematopoiesis

- is the process by which immature precursor cells develop into mature blood cells.
- The currently accepted theory on how this process works is called the monophyletic theory which simply means that a single type of stem cell gives rise to all the mature blood cells in the body.
- This stem cell is called the pluripotential (pluripotent) stem cell.

pluripotential hematopoietic stem cells

- are stem cells found in the bone marrow.
- They are called pluripotential because these cells have the ability to differentiate into any of several types of blood cells.

- **Myeloid cells** is a subsummating term for all hemopoietic cells except the lymphoid ones (T-cells, B-cells, NK-cells, dendritic cells).
- The tissue of bone marrow, where they form, is called **myeloid tissue**.


Pluripotential hematopoietic stem cell
Multipotential stem cells
Common myeloid progenitor (CFU-GEMM)
Common lymphoid progenitor
CFU-GM
CFU-Eo
CFU-Baso
CFU-MegE
Precursor T/NK cell
Precursor B cell
CFU-G
CFU-M
BFU-E
CFU-E
CFU-Meg
Pro-T cell
Pro-NK cell
Pro-B cell
Committed progenitor cells
Myeloblast
Monoblast
Myeloblast
Myeloblast
Pronormoblast
Megakaryoblast
Pre-T cell
Pre-B cell
Promyelocyte
Promonocyte
Basophilic normoblast
Promegakaryocyte
N. myelocyte
E. myelocyte
B. myelocyte
Polychromatophilic normoblast
Granular megakaryocyte
Morphologically recognizable precursors
N. metamyelocyte
E. metamyelocyte
Orthochromatophilic normoblast
Mature megakaryocyte
N. band
E. band
Reticulocyte
Neutrophil
Monocyte
Eosinophil
Basophil
Erythrocyte
Platelet
T cell
NK cell
B cell
Mature cells
Macrophage
Plasma cell

Microenvironment

- Stem and progenitor cells
- Stromal cells
- Extracellular matrix
- Growth factors, cytokines
- Passenger cells

Stromal Cells

- Macrophages
- Fibroblasts
- Fat cells
- Endothelial cells

Extracellular matrix

- Fibronectin
- Collagens
- Laminin
- Elastin
- Proteoglycans

HSCs

- Human HSCs express CD34 but lack the MHC class II antigen, HIA-DR
- CD34 is a glycoprotein that is encoded on chromosome lq
- and is expressed by hematopoietic stem cells as well as early progenitor cells.
- These cells also express high levels of multi drug-resistant (MDRI) protein
- and lack lineage commitment markers such as CD38, CD33, thy-I, and CD7l.

- These earliest known precursor cells constitute less than 1% of bone marrow
- have the morphology of blasts.
- HSCs also occur in small numbers in the peripheral blood and are increased with administration of growth faerors and/or some chemotherapeutic agents, allowing the use of peripheral blood as well as bone marrow to obtain stem cells used for bone marrow transplantation

colony-forming units (CFU)

- The existence of these cells were determined by clever experiments on animals. Bone marrow cells are extracted from an animal, which is then subjected to radiation. This destroys any bone marrow cells. Once this is accomplished, the previously collected cells are then injected into the blood stream and eventually make their way into the spleen (which has a similar environment as bone marrow for hemopoiesis). The cells multiply and form colonies, which contain only certain types of blood cell or blood cell precursors. These cells are defined as colony-forming units (CFU).

Cytokines

- are small protein molecules that are the core of communication between immune system cells, and even between these cells and cells belonging to other tissue types. They are actively secreted by immune cells as well as other cell types in response to external stimuli. Cytokines that are produced by immune cells form a subset known as lymphokines
- Most cytokines are not growth factors.
- Cytokines mediate many important physiological functions including
  - growth, development, wound healing and immune response.

- Cytokines act by binding to their cell-specific receptors. These receptors are located in the cell membrane and each allows a distinct signal transduction cascade to start in the cell, that eventually will lead to biochemical and phenotypical changes in the target cell. Typically, receptors for cytokines are also tyrosine kinases.

Growth factor

- is a protein that acts as a signalling molecule between cells (like cytokines and hormones) that attaches to specific receptors on the surface of a target cell and promote differentiation and maturation of these cells.
- Several well known growth factors are :

- Stem Cell Factor (SCF)
- Erythropoietin (EPO)
- thrombopoietin (TPO)
- granulocyte-colony stimulating factor (G-CSF)
- granulocyte-macrophage colony stimulating factor (GM-CSF)
- platelet-derived growth factor (PDGF)

Stem Cell Factor (SCF)

- kit ligand or steel factor
- 4q
- Synergy with IL3, GM-CSF to stimulate erythriod-myeloid –lymphoid progenitor

Flt-3 ligand

- Synergy with SCF
- Not affected in mast cell

Erythropoietin (EPO)

- glycoprotein hormone
- Most erythropoietin is produced in the renal cortex.
- it is also produced in the liver (mainly in the fetus), the brain and uterus.
- Erythropoietin production is stimulated by low oxygen levels in interstitial cells of the peritubular capillaries in the kidneys. It is not known exactly where in the kidneys erythropoietin is formed. One likely possibility is that the renal tubular epithelial cells secrete the erythropoietin
- 7q
- BFU-E , CFU-E , pronorm , baso.norm.

- Increased erythropoietin:AA-Hypoxia-tumors(RCC-HCC-Hemangioblastoa)
- Deficiency of erythropoietin : CRF-post transfusion

- Synthetic erythropoietin is available as an expensive injectable therapeutic agent produced by recombinant DNA technology.
- extensively used as an ergogenic aid, a doping drug, in some sports

Thrombopoietin

- *thrombopoietin* (*c-mpl ligand*) is the recently discovered (1994)
- *thrombopoietin* (*c-mpl ligand*) linked to the cell surface receptor *c-mpl*.
- Thrombopoietin regulates the differentiation of megakaryocytes and platelets
- glycop hormone that regulates the production of plt.
- 3 q26

GM-CSF

- Source: T-cells, endothelial cells, fibroblasts
- Supports: CFU-GM, BFU-E and CFU-Meg
- 5q

G-CSF

- Source: T cells, fibroblasts, endothelials,MAC
- Supports terminal differentiation of neutrophils
- The gene for G-CSF is located on chromosome 17
- recombinant form of G-CSF is used to accelerate recovery from neutropenia. Chemotherapy can cause myelosuppression and unacceptably low levels of white blood cells, making patients prone to infections and sepsis.

Platelet-Derived Growth Factor (PDGF)

- **Principal Source**
  - platelets, endothelial cells, placenta
- **Primary Activity**
  - promotes proliferation of connective tissue, glial and smooth muscle cells

Interleukins

- are a group of cytokines that are expressed by white blood cells (leukocytes, hence the *-leukin*) as a means of communication (*inter-*).
- The function of the immune system depends in a large part on *interleukins*, and rare deficiencies of a number of them have been described, all featuring autoimmune diseases or immune deficiency.

Interleukin-1 (IL-1)

- is secreted by the mon-mac ,fib,lym,endo,and dendritic cells.
- It is an important part of the inflammatory response.
- 2q
- The two forms of IL-1 are ： **IL-1α ， IL-1β**
- The IL-1 receptor antagonist IL-1Ra is used in the treatment of RA .
- It also re-sets the hypothalamus thermoregulatory center, leading to an increased body temperature (fever).
- Modulator of inflammation
- Stimulate HPC prolifration
-

Interleukin-2 (IL-2)

- is an interleukin, a type of biological response modifier, a substance that can improve the body's natural response to disease.
- It binds to IL-2 receptor(CD 25).
- secreted by T cells
- 4q
- stimulates growth and differentiation of T - B - NK cell response.
- Autocrin factor
- It can be used in immunotherapy to treat cancer. It enhances the ability of the immune system to kill tumor cells

Interleukin 3

- Multipotential CSF
- Source: T cells-endo-fib-mac
- 5q
- Growth of stem cells
- Supports growth of committed precursors
- function is quite similar to GM-CSF.

Interleukin-4

- Source: T cells-mast cell

- Activate :B-T cell -mac-mast cell
  - Switching fator (igG to igE)
  - Induced G-CSF&M-CSF
  - Increased PLT (with IL11)

- Co-discovered by Dr. Ellen Vitetta and her research group in 1982.

Interleukin-5

- Activate cytotoxic T cell
- Induced ig secretion
- Stimulate eos.

Interleukin-6

- B cell diffrentiation
- Ig secretion
- Growth factor for malignant plasma cell
- Increased myeloid (with IL3)
- Increased PLT (with IL4)

Interleukin-7

- Pre B-T

Interleukin 8

- is a chemokine
- produced by mon-macrophages ,fib -T cell
- IL-8 attracts neutrophils-mon ,T cell at the site of inflammation

Interleukin 9 (IL-9)

- is a cytokine produced by T-cells and specifically by CD4+ helper cells.
- T cell groth factor
- Myeloid&erythroid prolifration

Interleukin -10

- also known as human cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine, capable of inhibiting synthesis of pro-inflammatory cytokines like IFN-gamma, IL-2, IL-3, TNFα and GM-CSF by cells such as macrophages and the Type 2 T helper cells.
- However, it is also stimulatory towards certain T cells, mast cells and B cells.
- It is mainly expressed in monocytes and Type 2 T helper cells

Interleukin -11

- Synergy wiyh IL3 &IL4 to stimulate meg.& stem cell prolifration

Hematopoiesis

- primordial (prehepatic) phase
- hepatosplenothymic phase
- medullolymphatic phase

Hematopoiesis

Primitive hematopoiesis

- "*blood islands*" of the mesenchyme of yolk sac in embryos (days 15-18)
- Prodominant Primitve erythroblast
- Primitve erythroblast are large and megaloblasticand formed intravascularly and retain their nuclei
- *RBCs are nucleated* and expressing embryonic globin chains

Definitive hematopoiesis

- liver in 6 w – 6 mon *(lesser degree spleen-LN)*
- *BM*
- *RBCs are non-nucleated* and expressing fetal or adult globins
- extravascularly
- Granulopoiesis-meg.

There are two types of marrow:
-- Yellow marrow (Inactive) composed primarily of fat.
-- Red marrow (active in hematopoiesis)

Distribution of active marrow can be determined by administering radioactive iron:

LOCATION	% of TOTALMARROW
Pelvis	40
Vertebrae	28
Cranium-mandible	13
Ribs	8
Sternum	2
Ends of long bones	8

Hematopoiesis after Birth

- Occurs in the ***red bone marrow*** and ***lymphoid tissues***
- Pleuripotential Stem Cell- ***Morphologically indistinguishable from lymphocytes***
- ***Less common in peripheral blood***
- *Only one in a million nucleated cells is a CFU*

Sites & Timing of Hematopoiesis

- Begins during fetal development
  - yolk sac 4th week
  - liver
  - spleen
  - bone marrow: 20th week on
- Although all bone marrow retain hematopoietic potential the number of active sites diminishes with age
- Adult :
  - primarily in cancellous bone and medullary canals of long bones
  - Skull, ribs, sternum, vertebral column, pelvis and the proximal ends of the femur