

Lecture (1)

Hematopoiesis

(Basic Concepts)

Lecture Objectives:

- Definition of hematopoiesis.
- Anatomy of hematopoiesis.
- The cellular pathways of hematopoiesis.
- Specific differentiation pathways.
- Hematopoietic growth factors.
- The formation of blood cells.

Definition of Hematopoiesis:

- Production of red blood cells, white cells, and platelets (blood cell formation).

Anatomy of Hematopoiesis:

- **First Trimester:** Yolk Sac
- **Second Trimester:** Liver and Spleen
- **Third Trimester:** Central, Peripheral Skeleton
- **Adulthood:** Axial Skeleton
 - Vertebral Bodies
 - Sternum
 - Ribs
 - Pelvis
- Hematopoiesis may re-expand into fetal sites in times of severe demand, e.g. thalassemia, MF (**Extramedullary hematopoiesis**).

The cellular pathways of hematopoiesis:

- Overall Cellular Organization of Hematopoiesis:
 1. Stem Cells:
 - Totipotent.
 - Multipotent.
 2. Progenitor Cells.
 3. Precursor Cells.
 4. Effector Cells.

The cellular pathways of hematopoiesis:

I. Stem cells:

Totipotential Stem Cells : "The Godfather Cells":

1. Unlimited Self-Renewal.
2. Unlimited Differentiation: can give rise to any cellular element.
3. Present in Marrow in Small Numbers.
4. Highly Resistant to Chemotherapy.
5. Reside Primarily in Marrow. Small numbers circulate in blood.
6. Surface Antigen -CD34+ ("Cluster of Differentiation 34").
7. Look like Small Lymphocytes.
8. Dysfunction leads to aplastic anemia or certain types of leukemia.

The cellular pathways of hematopoiesis:

Multipotential Stem Cells: -i.e. Lymphoid, Myeloid Stem Cells

1. Derived from Totipotential Stem Cells.
2. Capable of Extended Self Renewal.
3. Capable of Extended Differentiation
 - Lymphoid stem cells give rise to all categories of mature lymphocytes.
 - Myeloid stem cells give rise to red cells, granulocytes, monocytes, and platelets.
4. Lymphoid stem cell can give rise to so-called "lymphoproliferative" malignancies such as acute lymphocytic leukemia
5. Myeloid Stem cell can give rise to so-called "myeloproliferative" malignancies such as acute myeloid leukemia

The cellular pathways of hematopoiesis:

II. Progenitor Cells -CFU's (Colony Forming Units):

1. Derived from Multipotential Stem Cells.
2. Capable of limited self-renewal.
3. Capable of limited differentiation.
 - CFU-GEMM (colony forming unit -granulocyte, erythrocyte, macrophage, megakaryocyte).
 - CFU-ME (colony forming unit – megakaryocyte - erythrocyte).
 - CFU-GM (colony forming unit – granulocyte - monocyte).
 - CFU-G (colony forming unit -granulocyte).
4. Responsive to Hematopoietic Growth Factors, e.g. Erythropoietin stimulates CFU-E, GM-CSF stimulates CFU-GM, G-CSF stimulates CFU-G, etc.
5. Express differentiation antigens -surface proteins such as CD19 -B-lymphocyte.

The cellular pathways of hematopoiesis:

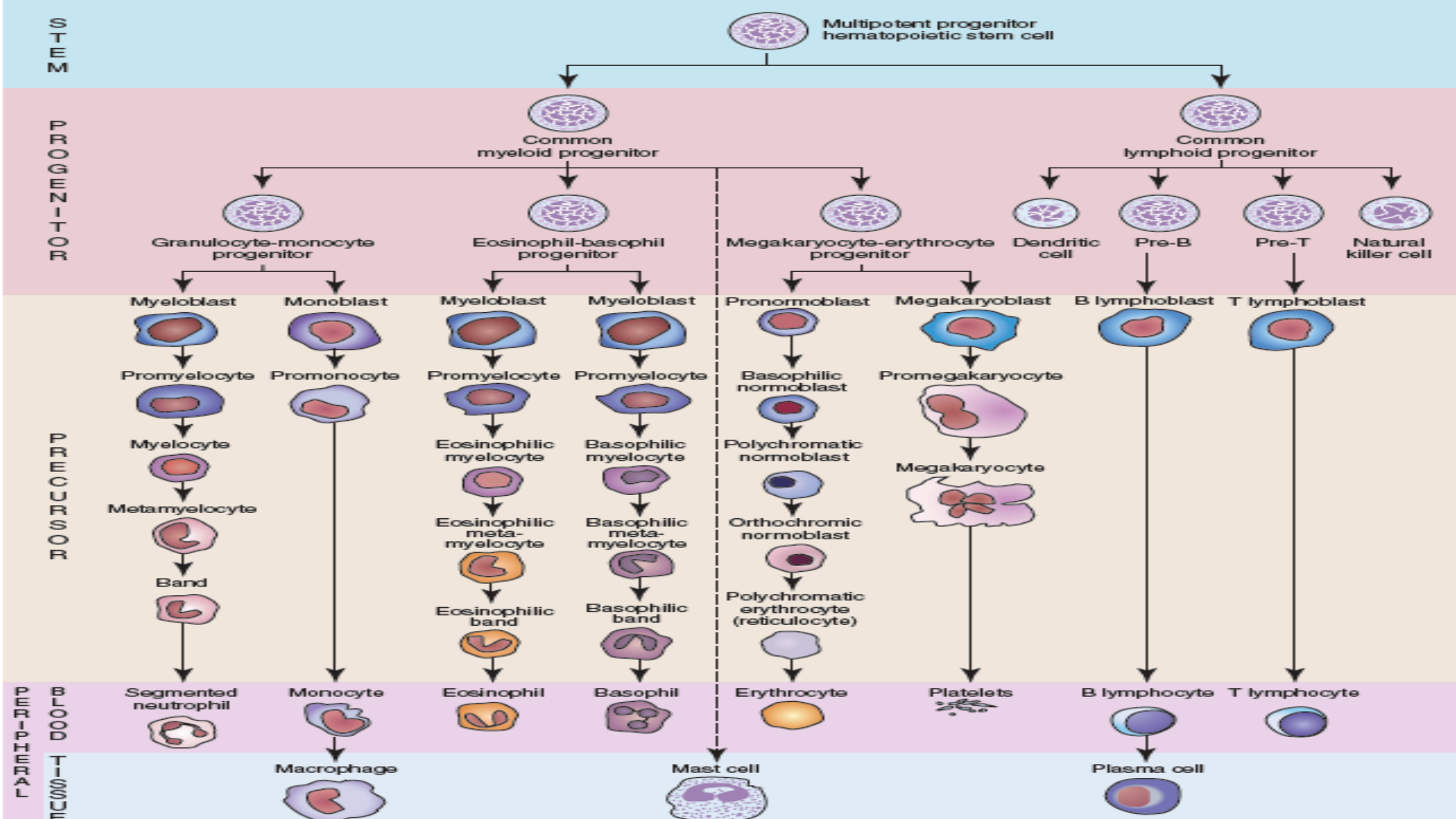
III. Precursor Cells -Blasts and their progeny:

- First morphologically identifiable cells:
 - Erythroblast -Red Cells.
 - Myeloblast -Granulocytes.
 - Monoblast –Monocytes.
 - Lymphoblast –Lymphocytes.
 - Megakaryoblast –Platelets.
- Little if any self-renewal.

The cellular pathways of hematopoiesis:

IV. Mature Effector Cells:

- Red Cells: carry oxygen, carbon dioxide; lifespan 120 days.
- Neutrophils: phagocytosis, killing.
- Monocytes: phagocytosis, killing, antigen presentation.
- Lymphocytes: identify cells as self or non-self.
- Platelets: hemostasis.



Specific differentiation pathways:

I. Neutrophils - Granulopoiesis:

1. Totipotent Stem Cell -CD 34+

2. Myeloid Stem Cell

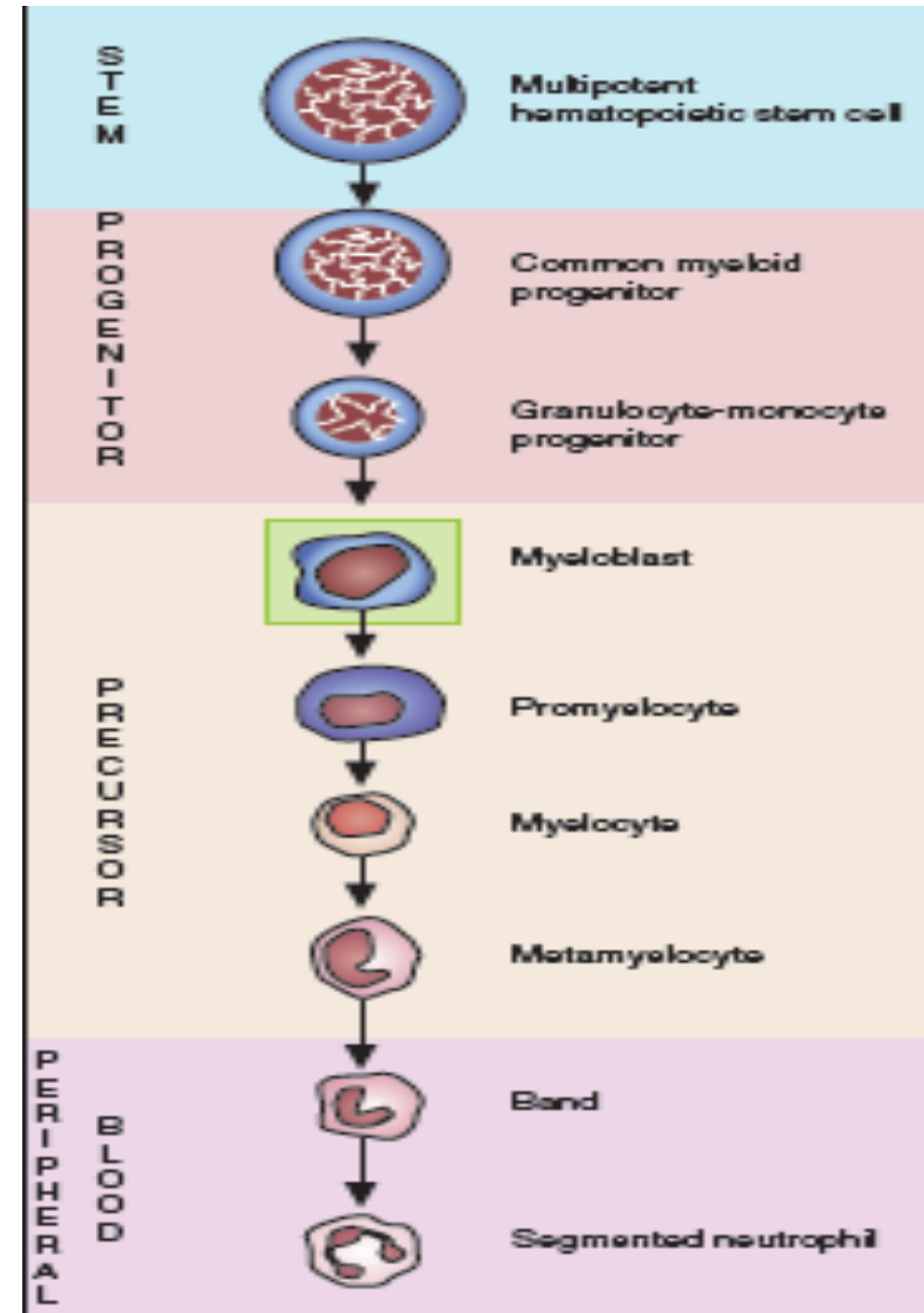
3. Progenitor -CFU-GM

4. Progenitor -CFU-G

5. Precursors

- Myeloblast
- Promyelocyte
- Myelocyte
- Metamyelocyte (Juvenile)
- Band (Staff)
- Neutrophil

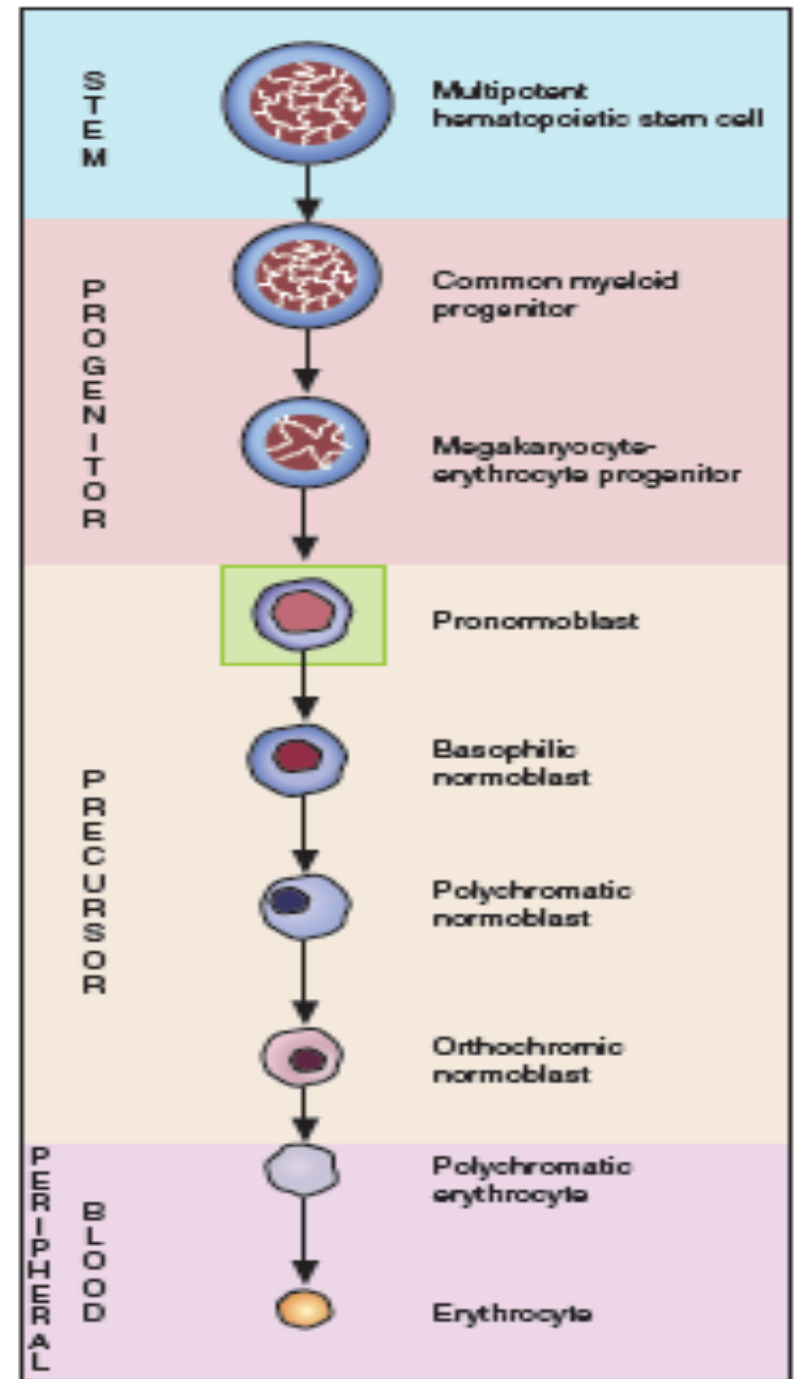
- Kinetics of Neutrophil Production -14 days from myeloblast to neutrophil corresponds to time for neutrophil recovery following chemotherapy



Specific differentiation pathways:

II. Red Cells – Erythropoiesis:

1. Totipotent Stem Cell -CD34+
 2. Myeloid Stem Cell
 3. Progenitor -BFU-ME
 4. Progenitor -CFU-ME
 5. Precursors
 - Proerythroblast
 - Basophilic erythroblast (Early)
 - Polychromatophilic erythroblast (Intermediate)
 - Orthochromatic erythroblast (Late)
 - Reticulocyte
 - Erythrocyte
- Kinetics of red cell production: 5 days from erythroblast to reticulocyte corresponds to time to response to iron therapy in iron deficiency.



Specific differentiation pathways:

III. Lymphocytes – Lymphopoiesis:

1. Antigen Independent Phase:

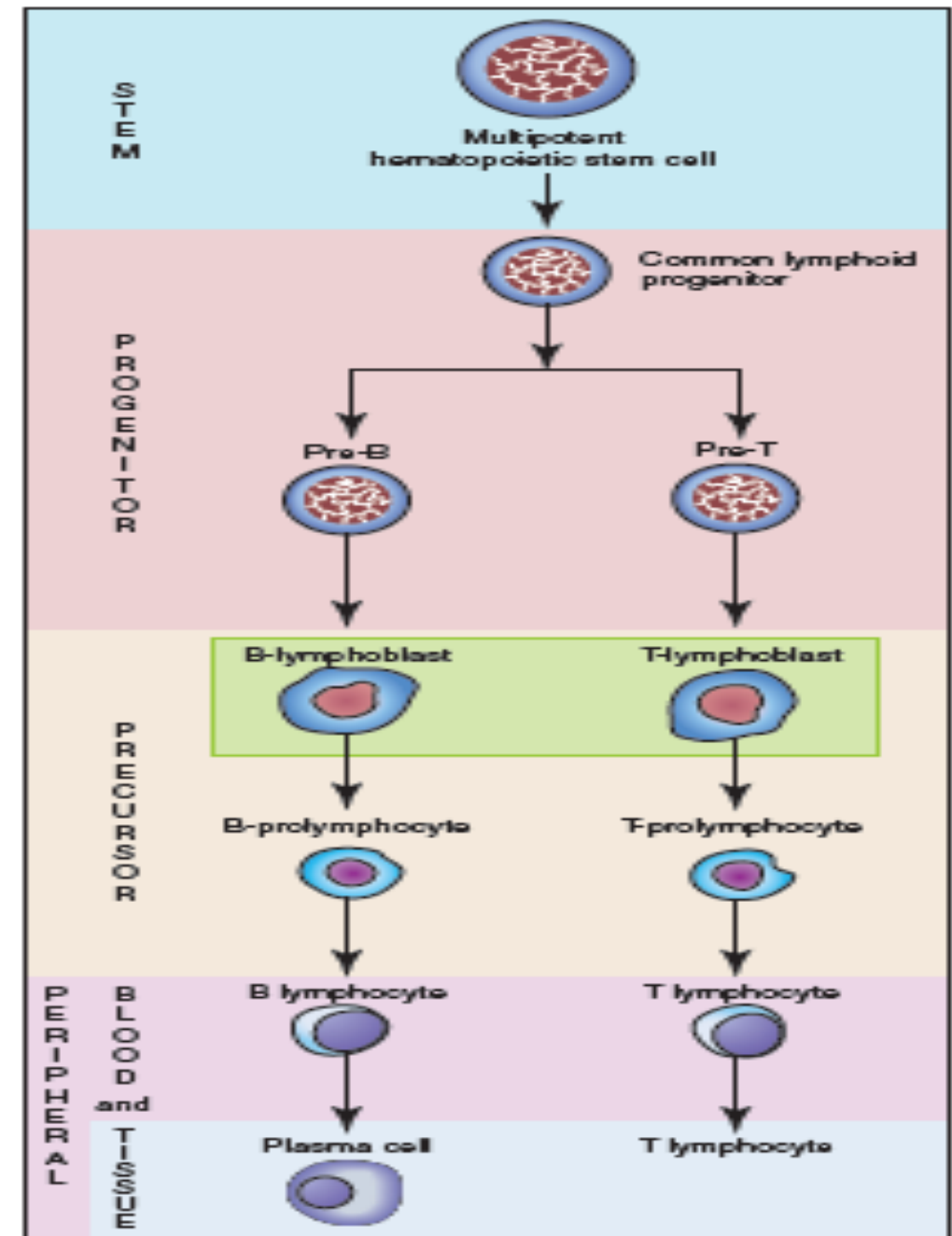
- Initial lymphopoiesis takes place in bone marrow.
- Maturation takes places in lymph nodes, thymus.

2. Antigen Dependent Phase:

- Second cycle of differentiation and proliferation in response to antigen exposure.

3. Memory Phase:

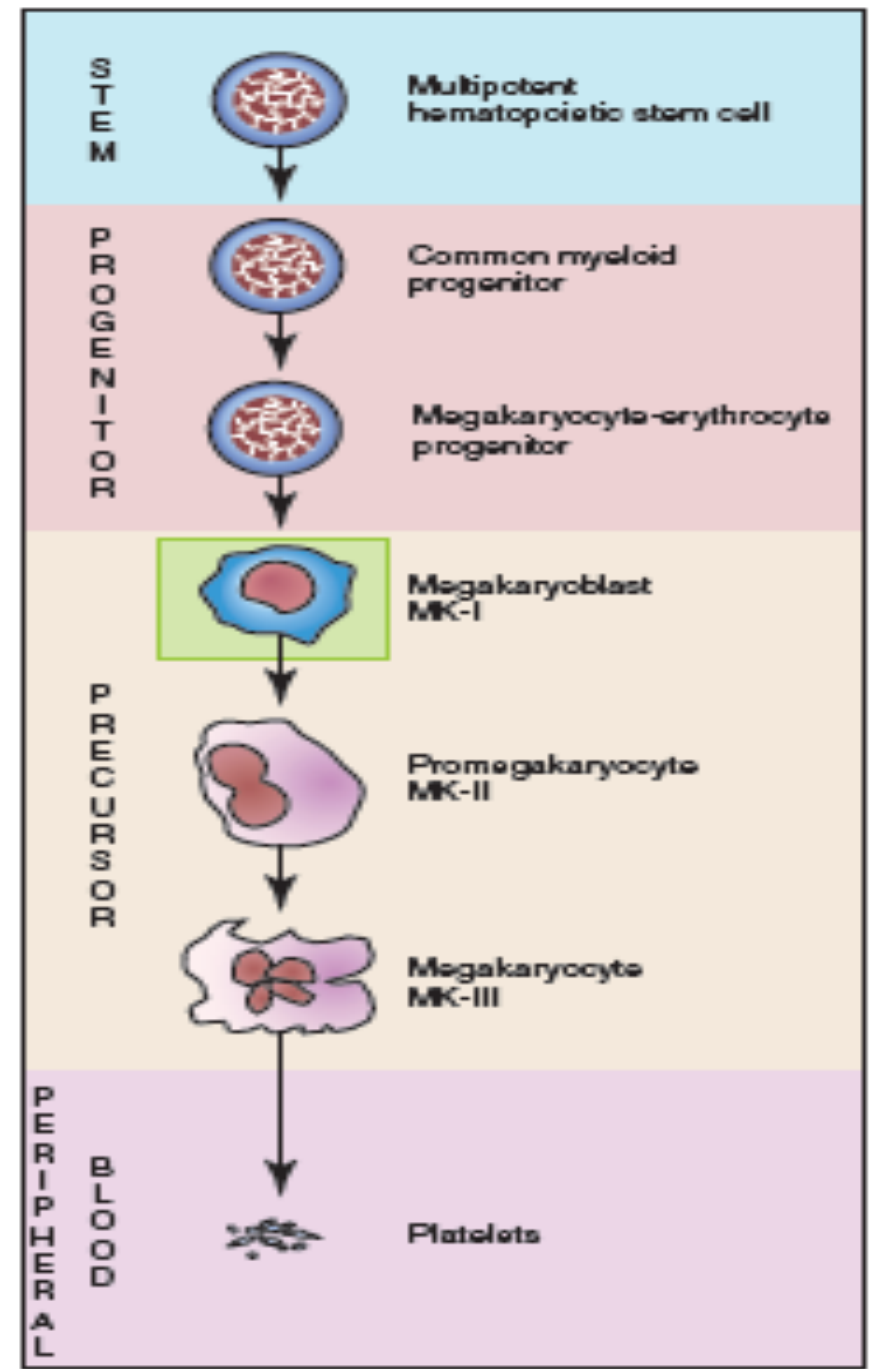
- Follows antigen exposure
- May live for years



Specific differentiation pathways:

IV. Platelets – Megakaryopoiesis:

1. Promegakaryoblast (MK-1)
2. Megakaryoblast (MK-2) -DNA replication without cell division
3. Megakaryocyte (MK-3) -polyploid nucleus
4. Platelet release via cytoplasmic fragmentation



Hematopoietic Growth Factors:

1. Erythropoietin (EPO):

- Synthesized in Kidney.
- Induces proliferation of CFU-E.
- Synthesis rises when red cell level falls.

2. Stem Cell Factor (SCF):

- Stimulates Totipotent, Pluripotent Stem Cells to enter differentiation pathway.

Hematopoietic Growth Factors:

3. Granulocyte-Monocyte Colony Stimulating Factor (GM-CSF):

- Secreted by lymphocytes, endothelial cells, stromal cells in marrow.
- Stimulates production of granulocytes, monocytes.
- Commercially available.

4. Granulocyte Colony Stimulating Factor (G-CSF):

- Secreted mainly by marrow stromal cells.
- Mainly, but not exclusively, stimulates production and function of granulocytes.
- Synthesis rises in response to infections.

Hematopoietic Growth Factors:

5. Interleukins (IL1, IL2, IL3, ... IL13):

- Mediate multiple, highly complex communications between various classes of white blood cells.
- Levels rise in response to infections.

The formation of blood cells:

- All the various types of blood cells are produced in the **bone marrow** arise from a single type of cell called a **pluripotent stem cell**.
- These stem cells:
 - are very rare (only about one in 10,000 bone marrow cells);
 - are attached (probably by adherens junctions) to osteoblasts lining the inner surface of bone cavities;
 - express a surface protein designated CD34;
 - produce, by mitosis, two kinds of progeny:
 - more stem cells.
 - Cells that begin to differentiate along the paths leading to the various kinds of blood cells.

Which path is taken is regulated by the need for more of that type of blood cell which is, in turn, controlled by appropriate cytokines and/or hormones. For example:

- **Interleukin-7(IL-7)** is the major cytokine in stimulating bone marrow stem cells to start down the path leading to the various **lymphocytes**(mostly B cells and T cells).
- **Erythropoietin(EPO)**, produced by the kidneys, enhances the production of **red blood cells(RBCs)**.
- **Thrombopoietin(TPO)**, assisted by Interleukin-11 (**IL-11**), stimulates the production of **megakaryocytes**. Their fragmentation produces **platelets**.
- **Granulocyte-monocyte colony-stimulating factor(GM-CSF)**, as its name suggests, sends cells down the path leading to both those cell types. In due course, one path or the other is taken.

- Under the influence of **granulocyte colony-stimulating factor(G-CSF)**, they differentiate into **neutrophils**.
- Further stimulated by interleukin-5 (**IL-5**) they develop into **eosinophils**.
- Interleukin-3 (**IL-3**) participates in the differentiation of most of the white blood cells but plays a particularly prominent role in the formation of **basophils**(responsible for some allergies).
- Stimulated by **macrophage colony-stimulating factor(M-CSF)** the granulocyte/macrophage progenitor cells differentiate into **monocytes**, the precursors of **macrophages**.