HEMATOPOIESIS

Cell renewal, proliferation, differentiation, and maturation

Hematopoietic inductive microenvironment *(niche)* in the bone marrow = regulate hematopoietic stem cell maintenance, self-r-enewal, and differentiation; where hematopoietic stem/progenitor cells (HSCs/HPCs) grow and develop

Site of Hematopoiesis

Adults	bone marrow
Fetal development	yolk sac > aorta-gonad mesonephros (AGM) region (mesoblastic phase) > fetal liver (hepatic phase) > bone marrow (medullary phase)

ADULT HEMATOPOIETIC TISSUE

Located in the **bone marrow, lymph nodes, spleen, liver,** and **thymus**

Lymphoid development occurs in primary and secondary lymphoid tissue.

Primary lymphoid tissue

> bone marrow and thymus = (T&B lymphocytes)

Secondary lymphoid tissue (lymphoid cells that respond to foreign antigens)

> spleen, lymph nodes, and mucosa-associated lymphoid tissue

Medullary (Myeloid) Phase

5th month of development = hematopoiesis begins in the **Bone Marrow (Chief Site)**

"Medullary" = occurs in the medulla or inner part of the bone

Myeloid-to-erythroid ratio = **3:1**

Production of adult hemoglobins (**HbA1 and HbA2**)

Bone Marrow

Location = within the cavities of the cortical bones

Contains **hematopoietic cells, stromal cells, and blood vessels**

Red marrow = hematopoietically active; developing blood cells and their progenitors

Bone Marrow (cont)

Yellow marrow =hematopoietically inactive marrow; composed primarily of adipocytes (fat cells)

Retrogression = replacing the active marrow by adipocytes

> **Infancy and early childhood** = primarily red (active) marrow
> **5 and 7 years of age** = adipocytes become more abundant

Yellow marrow is capable of reverting back to active marrow in cases of increased demand on the bone marrow, such as in excessive blood loss or hemolysis

Stromal cells

Stromal cells play a critical role in the **regulation of hematopoietic stem** and **progenitor cell survival and differentiation**

Types of Stromal Cells

1. Endothelial cells

> form a single layer along inner surface of the arteries, veins, and vascular sinuses; regulate what enters or leaves the vascular sinuses

2. Adipocytes

> large cells with a single fat vacuole; regulating volume of the marrow in which active hematopoiesis occur

3. Macrophages

> phagocytosis; secrete various cytokines

4. Osteoblasts

> bone-forming cells

5. Osteoclasts

> bone-resorbing cells

Originate from **mesenchymal cells**
Secrete a **semifluid extracellular matrix** to promote cell adhesion = matrix contains fibronectin, collagen, laminin, thrombospondin, tenascin, and proteoglycans

Spleen Pathophysiology

Blood route entering the spleen:

1. **Slow-transit pathway**

> RBCs > cords > sinuses > RBC have hard time entering sinus thus, slow passage > but RBC metabolism is continuous > creates acidic, hypoglycemic, and hypoxic environment > environment stress in spleen > possible hemolysis

2. **Rapid-transit pathway**

> RBC > sinuses > venous system > exit spleen

Spleen

Largest lymphoid organ in the body

Storage site for platelets (30% total plt are kept in spleen)

2 methods to remove senescent or abnormal RBCs from the circulation:

> 1. **Culling** = cells are phagocytized
> 2. **Pitting** = splenic macrophages remove inclusions or damaged surface membrane from the circulating RBCs.

Blood enters the spleen through the **central splenic artery**

senescence = loss of a cell's power of division and growth

Thymus

Densely populated with progenitor lymphoid cells that migrated from the bone marrow and will soon give rise to T cells.

T cells from bone marrow > go to thymus > No surface markers yet (CD4 CD8) > go to corticomedullary junction > once influenced by chemokines, cytokines, and receptors > T cells go to cortex > express CD4 CD8 marker > go to medulla > T cell matures > leave thymus > go to T cell dependent areas (spleen, lymph nodes, and other lymphoid tissues)

Medulla holds mature T cells until they are needed by the peripheral lymphoid tissues

Lymph Nodes

Lymph

> fluid portion of blood escapes into the connective tissue

Lymph > Enter in Afferent vessels > lymph nodes filter lymph > Exit in Efferent vessels

Three main functions:

> 1. Site of lymphocyte proliferation from the germinal centers
> 2. Initiation of the specific immune response to foreign antigens
> 3. Filter particulate matter, debris, and bacteria entering the lymph node

Cytokines and Growth Factors

Cytokines - group of specific glyco**proteins**

> -Such as interleukins (ILs), lymphokines, monokines, interferons, chemokines, and colonystimulating factors (CSFs) have an effect on other cells.
> -**Regulate the proliferation, differentiation, and maturation of hematopoietic precursor cells**

Cytokines promote growth and survival to hematopoietic progenitor cells

Cytokines prevent hematopoietic precursor cell death by **inhibiting apoptosis**

Apoptosis - programmed cell death; eliminates unwanted, abnormal, or harmful cells.

Note: Cytokine and Growth Factor are often used synonymously

Cytokine Influence

Cytokines negative influence on hemato-poiesis	transforming growth factor-b, tumor necrosis factor-a, and the interferons
Cytokines positive influence on hemato-poiesis	stimulate production and differentiation of precursor cell

TGFβ - inhibit the growth of many types of cells; antagonize many immune responses

CFU

TABLE 7-1 Culture-Derived Colony-Forming Units (CFUs)

Abbreviation	Cell Line
CFU-GEMM	Granulocyte, erythrocyte, megakaryocyte, monocyte
CFU-E	Erythrocyte
CFU-Meg	Megakaryocyte
CFU-M	Monocyte
CFU-GM	Granulocyte, monocyte
CFU-BASO	Myeloid to basophil
CFU-EO	Myeloid to eosinophil
CFU-G	Myeloid to neutrophil
CFU-pre-T	T lymphocyte
CFU-pre-B	B lymphocyte

Early-Acting Multilineage GF

KIT ligand (stem cell factor) - early-acting growth factor

> receptor-type tyrosine-protein kinase

KIT ligand > bind to KIT receptor > signals from transduction pathways to the HSC nucleus > stimulate the cell to proliferate

FLT3

> receptor-type tyrosine-protein kinase

KIT ligand + FLT3 ligand

> Work synergistically with IL-3, GM-CSF, and other cytokines to promote early HSC proliferation and differentiation.

IL-3

> control granulocytes and macrophages production, differentiation, and function to regulate blood cell production

Activation of the KIT receptor by KIT ligand is essential in the early stages of hematopoiesis.

GM-CSF stimulate HSC differentiation to common myeloid progenitor

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) are **capable of self-renewal**

They are **pluripotent** and can differentiate into all the different types of blood cells.

Mesoblastic Phase

Begins during **nineteenth day of embryonic development**

1. Cells from the mesoderm migrate to the yolk sac> form primitive erythroblasts> produce hemoglobin (**Gower-1, Gower-2, and Portland**) for delivery of oxygen

2. Cells from the mesoderm migrate to the AGM>give rise to HSC

Occurs intravascularly

Hepatic Phase

5 to 7 gestational weeks

Liver = remaining the **major site of hematopoiesis during the second trimester** of fetal development

Liver Hematopoiesis = peak by the third month, declines after the sixth month

Thymus = site of T cell production

Kidney and spleen = site of B cell production

Production of **megakaryocytes** begins

Lymphoid cells begin to appear

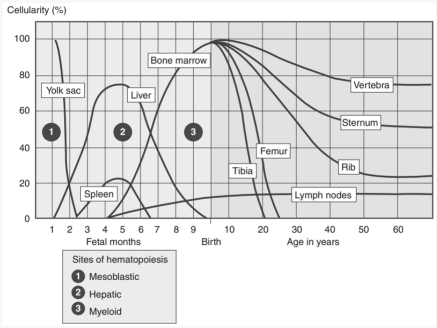
Fetal hemoglobin (**Hb F**) is the predominant hemoglobin

Spleen, kidney, thymus, and lymph nodes contribute to the hematopoietic process during this phase.

Occurs extravascularly

Thymus - the first fully developed organ in the fetus

Site of Hematopoiesis



Red Marrow

Composed of extramedullary cords that contain all developing cells (stem and progenitor cells, adventitial cells, and macrophages)

Bone foramina

where nutrient and periosteal arteries enters to provide nutrient and oxygen to the marrow; also where the blood exits from BM

Liver

Second trimester of fetal development

Major site of hematopoiesis

Hepatocytes functions:

Protein synthesis and degradation, coagulation factor synthesis, carbohydrate and lipid metabolism, drug and toxin clearance, iron recycling and storage, and hemoglobin degradation (bilirubin is conjugated and transported to the small intestine for excretion)

Kupffer cells (macrophages)

Remove senescent cells and foreign debris from the blood in the liver; secrete mediators that regulate protein synthesis in the hepatocytes

Liver Pathophysiology

Porphyrias

Defects in the enzymes involved in heme biosynthesis = accumulation of intermediary porphyrins = damage hepatocytes, erythrocyte precursors, and other tissues

Severe hemolytic anemia

Liver > increases the conjugation of bilirubin and storage of iron

Liver removes membrane-damaged RBCs from circulation

If BM is damaged (myelofibrosis)

Liver can extramedullary hematopoiesis - keep hematopoietic stem&progenitor cells to produce various blood cells

Spleen Pathophysiology

Splenomegaly

Spleen becomes enlarged and is palpable
Caused by: chronic leukemias, inherited membrane or enzyme defects in RBCs, hemoglobinopathies, Hodgkin disease, thalassemia, malaria, and the myeloproliferative disorders

Splenectomy

Excessive destruction of RBCs due to *autoimmune hemolytic anemia* (corticosteroids does not effectively suppress hemolysis) or *severe hereditary spherocytosis*

After splenectomy = **platelet and leukocyte counts increase**

Autosplenectomy

Sickle cell anemia = sickled RBCs trapped in the small-vessel circulation of the spleen = tissue damage/necrosis

Hypersplenism

Enlargement of the spleen (pancytopenia)
Most common causes **1. congestive splenomegaly 2. cirrhosis of the liver 3. portal hypertension**

Lymph Node Pathophysiology

Antigenic stimulation > cortical region develop cluster of activated B cell called germinal centers

Paracortex region = contains T cells and macrophage
Medullary cord region = contains plasma cells and B cells

Too much microorganism enter lymph node > macrophage are overwhelmed > result to adenitis (infection of the lymph node)

Worst case: malignant cells from tumors enter lymph node > spread to nearby lymph nodes

Follicles with germinal centers are called **secondary follicles**, while those without are called **primary follicles**
Germinal centers = Site of lymphocyte proliferation

Stem Cell Theory

Monophyletic theory

> Suggests that all blood cells are derived from a single progenitor stem cell called a pluripotent hematopoietic stem cell; **widely accepted theory**

Polyphyletic theory

> Suggests that each of the blood cell lineages is derived from its own unique stem cell

Common **lymphoid** progenitor

> T, B, and natural killer lymphocyte and dendritic lineages

Common **myeloid** progenitor

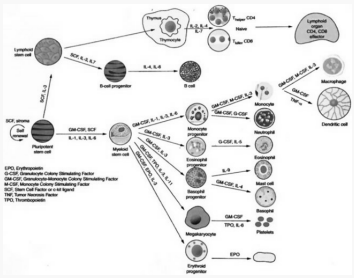
> granulocytic, erythrocytic, monocytic, and megakaryocytic lineages

SC Phenotypic & Functional Characterization

Origin of HSCs can be determined by immunophenotypic analysis using flow cytometry

General characteristics of maturation include **decrease in nuclear and cell diameter**, **loss of nucleoli**, **condensation of nuclear chromatin**, and **decreased basophilia in cytoplasm**.

Colony-Stimulating Factors



Interleukins

Proteins/group of cytokines that regulates autoimmune, inflammatory reactions, and hematopoiesis

Synergize with other cytokines

Effective at very low concentrations

LINEAGE: Erythropoiesis

The **CFU-GEMM** gives rise to the earliest identifiable colony of RBCs, called the burst-forming unit–erythroid (BFU-E)

BFU-Es under the influence of IL-3, GM-CSF, TPO, and KIT ligand develop into colony-forming unit–erythroid (CFU-E) colonies

CFU-E has many EPO receptors and has an absolute requirement for EPO

Small amount of EPO is produced by the liver

Oxygen availability in the **kidney is the stimulus that activates production and secretion of EPO**

LINEAGE: Megakaryopoiesis

The liver is the main site of production of TPO

BLOOD CELL LINEAGE