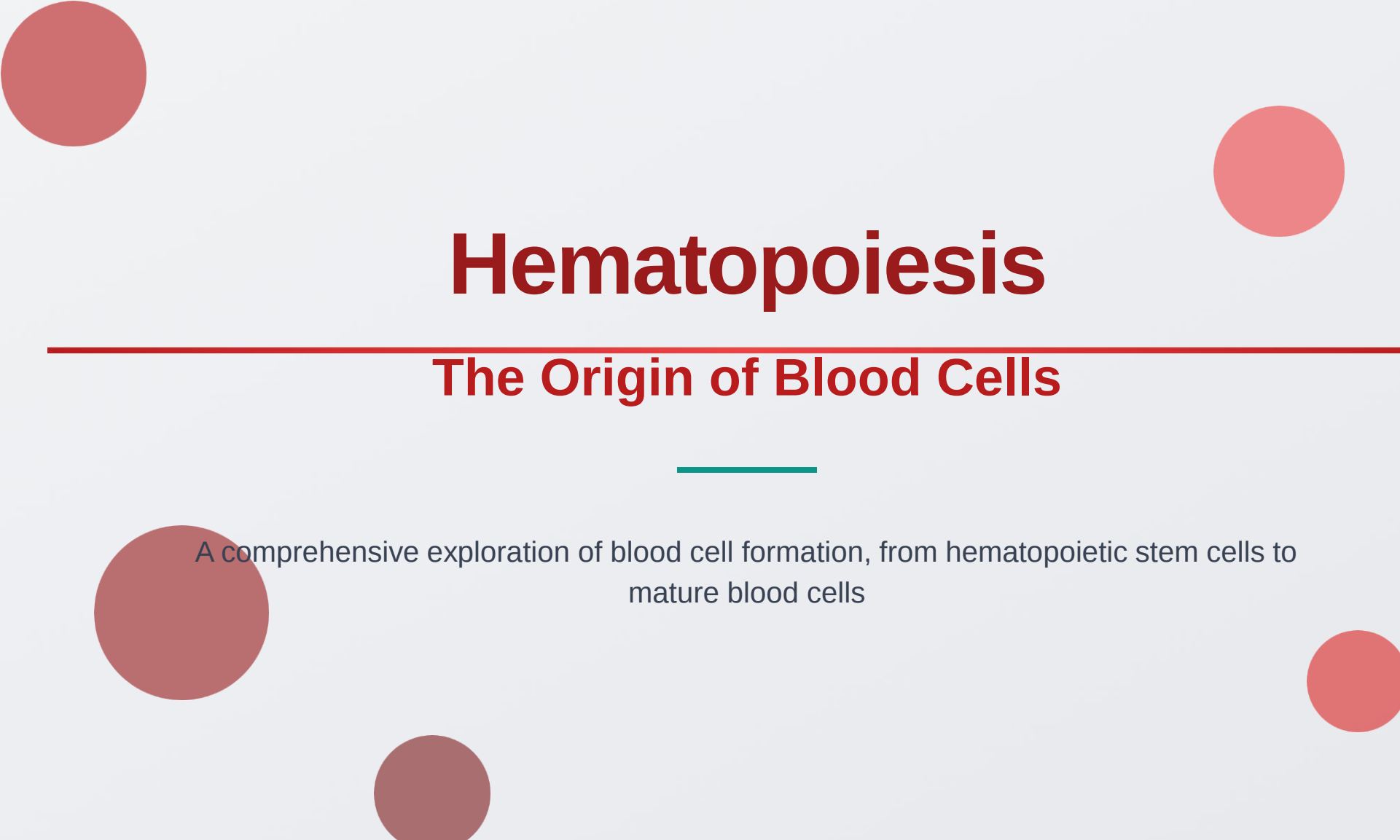




Hematopoiesis

The Origin of Blood Cells

A comprehensive exploration of blood cell formation, from hematopoietic stem cells to mature blood cells

Introduction to Hematopoiesis

Definition

Hematopoiesis is the **continuous process** of blood cell formation from hematopoietic stem cells (HSCs) primarily within the bone marrow.

Continuous Renewal

Ensures constant replenishment of erythrocytes (red blood cells), leukocytes (white blood cells), and platelets to maintain physiological demands.

Immune Challenge Response

Adapts to the body's immune challenges by adjusting blood cell production rates as needed.

Regulation

Hematopoiesis is tightly regulated by various growth factors, cytokines, and signals from the bone marrow microenvironment.



Locations of Hematopoiesis Throughout Life



Embryonic Development

- **Yolk Sac** (first 2-3 weeks): Initial site for primitive red blood cells
- **Fetal Liver** (6th week at birth): Primary site during second trimester
- **Bone Marrow** (third trimester): Gradually takes over production



Adult Period

- **Red Bone Marrow:** Predominant site in flat and short bones
- Includes pelvic bones, vertebrae, ribs, skull bones and Proximal ends of femurs and humerus



Extra-medullary hematopoiesis

- Under certain pathological conditions (such as severe anemia or myeloid diseases), hematopoiesis can reactivate in extra-medullary organs such as the liver and spleen, a phenomenon called extra-medullary hematopoiesis.

Hematopoietic Stem Cells (HSCs)

Hematopoietic stem cells (HSC) are multipotent cells located mainly in the bone marrow, capable of differentiating into all blood cells (erythrocytes, leukocytes, platelets).

Hematopoietic Stem Cells (HSCs): origin

Location: HSCs reside primarily in the adult bone marrow, but may also be present at very low levels in the peripheral blood.

Hematopoietic niche: They interact closely with their environment, called hematopoietic niche, which consists of stromal cells, cytokines, and the extracellular matrix. This environment regulates their proliferation, differentiation and migration.

Hematopoietic Stem Cells (HSCs): Characteristics



Self-renewal

The ability to divide and produce more stem cells, maintaining a constant reservoir throughout life.



Multipotency

The capacity to differentiate into various types of blood cells, crucial for bone marrow transplants.



Differentiation

The ability to develop into specific progenitor cells and then into different types of mature blood cells.



Lineage Differentiation



Myeloid Lineage

- Erythrocytes (red blood cells)
- Granulocytes (neutrophils, eosinophils, basophils)
- Monocytes/macrophages
- Megakaryocytes (platelet producers)



HSC Marker



Lymphoid Lineage

- B lymphocytes
- T lymphocytes
- NK (Natural Killer) cells

HSC Maturation Process

Hematopoietic stem cells (HSCs) undergo several stages to become mature blood cells, with each stage having distinct characteristics and potential.



Multipotent Progenitors

Differentiate into myeloid or lymphoid progenitor cells with more restricted developmental potential.



Specific Progenitors

Evolve into specialized lines, such as precursors of red blood cells or white blood cells.



Precursor Cells

Cells committed to a specific cell line with restricted differentiation pathway.



Mature Cells

Final functional blood cells (erythrocytes, leukocytes, platelets).

CD34 Marker

CD34 is the most important and commonly used surface marker for isolating and identifying HSCs in humans.

HSCs are characterized by their ability to self-renew and differentiate into all blood cell types.

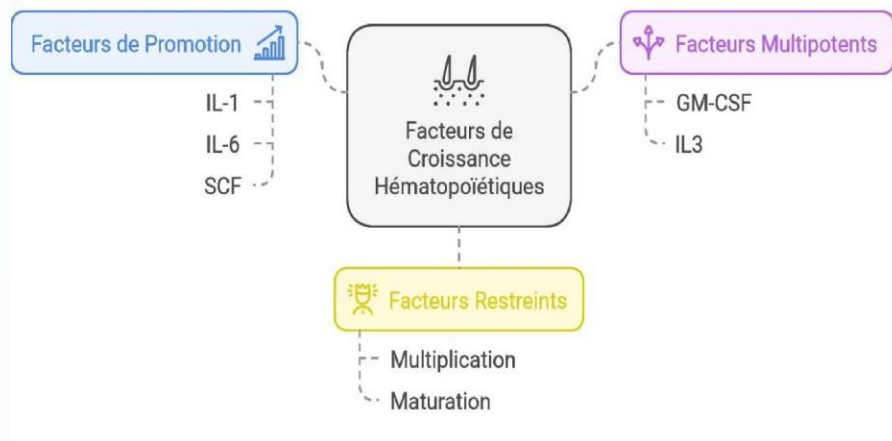


CD34+
HSCs

Regulation of Hematopoiesis

Overview

HSC proliferation and self-renewal are strictly regulated by a combination of intrinsic (cell-specific) and extrinsic (micro-environmental) signals. This regulation is multifactorial.



Relationships between different types of hematopoietic growth factors and cytokines

Promoting Factors

- IL-1, IL-6, IL-4
- SCF (stem cell factor)

Increase stem cell number in cell cycle and sensitize totipotent stem cells to other factors

Multipotent Factors

- GM-CSF (Granulocyte Macrophage-CSF)
- IL-3

Support survival and differentiation of immature stem cells after sensitization

Restricted Factors

- Act on committed stem cells (precursors)

Promote multiplication and maturation of specific cell lines

Negative Regulatory Factors

- TGF β (Transforming growth Factor β)
- TNF α (Tumor necrosis factor α)
- Interferon

Inhibit hematopoiesis, either generally or specifically

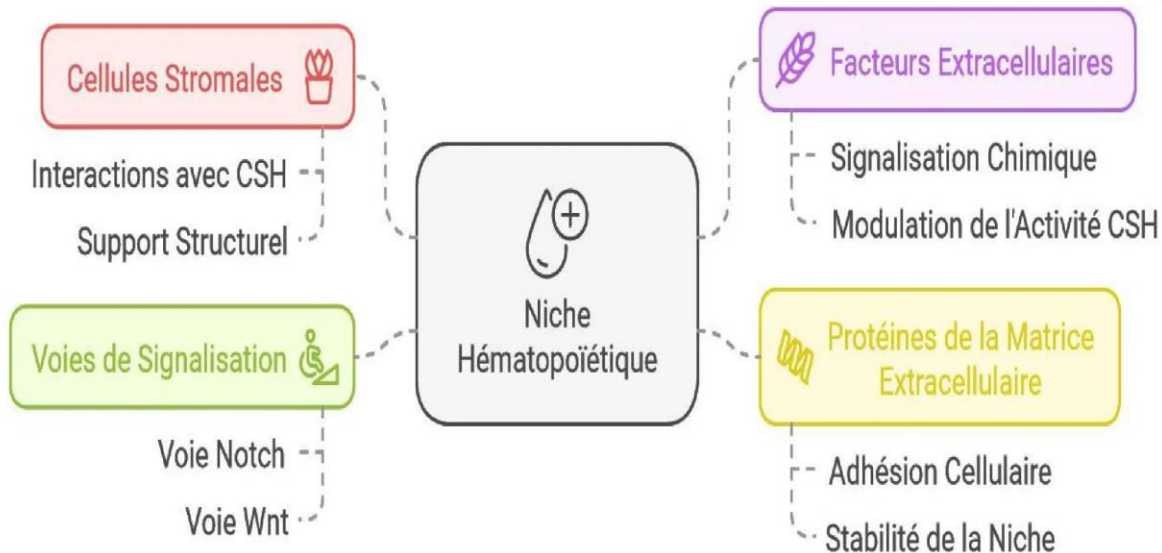
Transcription Factors

GATA-2, PU.1, and Notch are crucial for regulating signaling pathways that influence HSC commitment to different cell lines.

The Hematopoietic Niche

Definition

The hematopoietic niche is the bone marrow microenvironment critical for regulating HSC proliferation, differentiation, and migration.



Components

Stromal Cells

Provide structural support and secrete regulatory factors

Extracellular Factors

Glycoproteins and cytokines that regulate HSC behavior

Extracellular Matrix

Proteins that provide structural and biochemical support

Signaling Pathways

Notch, Wnt, and other pathways that regulate HSC fate

Key Functions

- ✓ Support HSC self-renewal and proliferation
- ✓ Regulate HSC differentiation into specific lineages
- ✓ Maintain HSC quiescence or activation based on demand
- ✓ Control HSC migration to and from the bone marrow

Lymphopoiesis: B and T Cell Development

Lymphoid Engagement

Stem cells differentiate into lymphoid precursor cells, giving rise to B cells, T cells, and NK cells.



HSCs



Lymphoid Progenitors



mature Lymphocytes

Notch Signaling

- **Notch-1 activation** promotes T-cell differentiation
- absence of Notch signaling allows B-cell development

Cytokines

- **IL-7** crucial for B and T cell development
- **IL-15** supports NK cell differentiation

B Cell Development

- Primary site: Bone marrow
- Under IL-7 and Pax5 influence
- Responsible for antibody production

T Cell Development

- Primary site: Thymus
- Under Notch signaling and IL-7 influence
- Orchestrates immune responses

NK Cell Development

- Direct differentiation from progenitors
- IL-15 influence
- Innate immune response

Myelopoiesis: Development of Myeloid Cells

Myelopoiesis is the formation of myeloid cells (include granulocytes (neutrophil, eosinophils, and basophils), monocytes (which become macrophages in tissues), megakaryocytes (which produce platelets) and erythrocytes from myeloid progenitors under the influence of specific growth factors. For example, erythropoietin (EPO) stimulates the differentiation of erythroid progenitors, while G-CSF stimulates the production of granulocytes

Granulopoiesis

Differentiation into granulocytes under G-CSF and GM-CSF influence.

 Neutrophils, Eosinophils, Basophils

Monocytopoiesis

Production of monocytes under M-CSF influence.

 Macrophages in tissues

Erythropoiesis

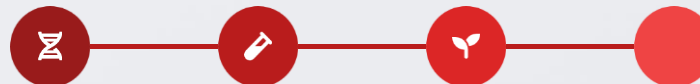
Formation of red blood cells stimulated by erythropoietin (EPO).

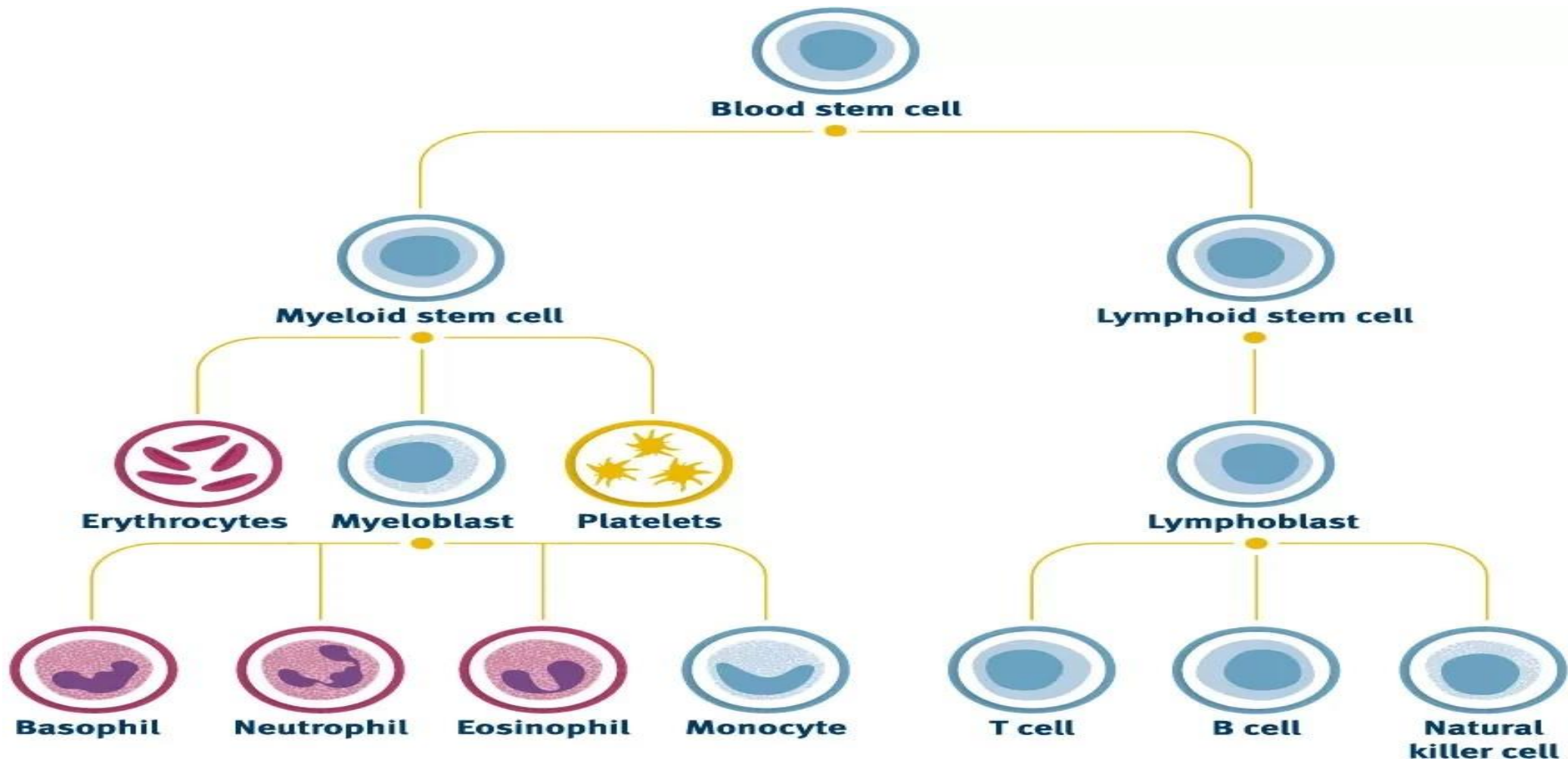
 Oxygen-carrying cells

Megakaryopoiesis

Production of megakaryocytes stimulated by thrombopoietin (TPO).

 Platelets for blood clotting





Lymphopoiesis and myelopoiesis.

Clinical Implications and Disorders



Bone Marrow Transplantation

- ✓ Uses hematopoietic stem cells to restore blood cell production
- ✓ Critical treatment for leukemia, lymphomas, and certain anemias
- ✓ Replaces damaged or diseased bone marrow with healthy stem cells



Hematological Disorders

Leukemia: Uncontrolled production of abnormal white blood cells

Lymphomas: Cancers of the lymphoid cells

Anemias: Conditions affecting red blood cell production



Clinical Relevance

Understanding hematopoiesis is crucial for developing treatments for blood disorders. Hematopoietic stem cell characteristics, including self-renewal, multipotency, and differentiation abilities, are fundamental to these clinical applications.