Chapter 10
Bone Marrow

Contents

General

- Specialized connective tissue of two types:
  - Red bone marrow
  - Yellow bone marrow
- Found within the spaces of bone:
  - Newborns solely have red bone marrow.
  - Adults have a 50/50 ratio between red and yellow bone marrow.
    - Red bone marrow is primarily located within the bones of the axial skeleton, corresponding to the area covered by a one-piece swimsuit.
    - Yellow bone marrow occupies the remaining spaces in the bone.
- Formed during the formation of bone (ossification).

Divided into

Two types, which may transform into each other:

- Red bone marrow
- Yellow bone marrow

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Red Bone Marrow

General

- Red color is due to:
  - Abundant blood vessels
  - High content of erythrocyte stem cells containing hemoglobin
- May transform into yellow bone marrow

Function

The site of blood cell formation (hemopoiesis)

Consists of

- Vascular space
  - Sinusoids (discontinuous capillaries)
- Hemopoietic space
  - Parenchyma
    - Hemopoietic cells in cords/islets
  - Stroma
    - Reticular connective tissue

Vascular Space

Sinusoids

General

- Special capillary with large, varying ⦸ (Chap. 17)
- Supplied by the blood vessels of the bone (Chap. 15)

Function

- Sinusoid wall forms the barrier between the hemopoietic space and vascular system.
- Newly formed blood cells reach the bloodstream by transcellular passage through temporary pores in endothelial cells.

Consist of

- Endothelium
  - Thin simple squamous epithelium without tight junctions
- Basal lamina
  - Discontinuous
- Reticular cells (adventitial cells)
  - Cover outer vessel surface partially

Hemopoietic Space

Consists of
- Parenchyma
  - Hematopoietic cells in cords/islets
- Stroma
  - Reticular connective tissue
    - Reticular cells
      - Produce reticular fibers
      - Ensheath the reticular fibers completely with their cell extensions → form an anastomosing 3D cellular meshwork
      - Can differentiate into adipocytes → yellow bone marrow
    - Extracellular matrix
      - Reticular fibers → forming an anastomosing meshwork
      - Ground substance
      - Multiadhesive glycoproteins
  - Other cells in stroma
    - Macrophages
    - Mast cells
    - Adipocytes

Hemopoiesis

General
- The formation of new blood cells.
- Main location of hemopoiesis changes during embryonic life (Table 10.1).

Table 10.1 Main site of hemopoiesis during embryonic and postnatal life

Time line	Main location	Major type of erythrocyte	
		Nucleus	Hemoglobin type
First trimester, from third week of gestation	Yolk sac	+	Fetal type
Second trimester	Liver and spleen	–	Fetal type
Third trimester	Red bone marrow	–	Fetal type
Postnatally	Red bone marrow	–	Adult type

Function

- Formation of new blood cells
  - Erythrocyte development (erythropoiesis)
  - Thrombocyte development (thrombopoiesis)
  - Leukocyte development (leukopoiesis)
- Maintain steady levels of blood cells, which all have limited life spans

EARLY STEPS IN HEMOPOIESIS

General

Development of unipotent progenitor cells from a common pluripotent progenitor cell

Formation

See Fig. 10.1.

LATE STEPS IN HEMOPOIESIS

General

- Development of mature blood cells from unipotent progenitor cells.
- Unlike the stem cells going through the earlier steps in hemopoiesis, many cells going through the later steps have a distinct morphology in the light microscope (Table 10.2).

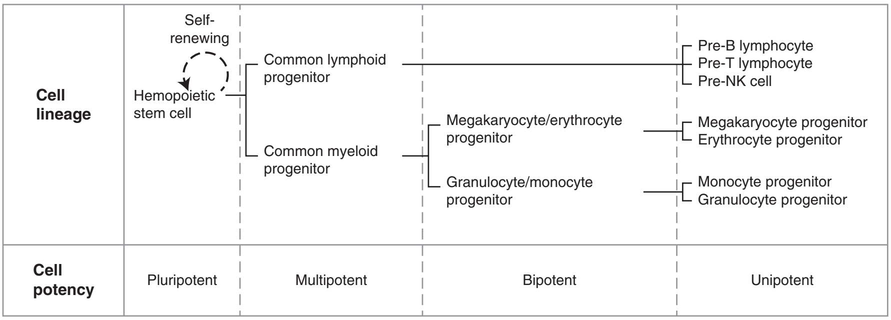


Fig. 10.1 Early steps in hemopoiesis and the cell potency of the cells

Table 10.2 Simplified later steps in hemopoiesis

Cell	⃠	Nucleus	Cytoplasm
Stem cell (–blast) ↓ Mitoses and differentiation	Large	• Large • Light (euchromatic)	• Basophilic • Without specific contents
Differentiated cell (–cyte)	Small	• Small • Dark (heterochromatic)	• Less basophilic • With specific contents

Divided into
- Erythropoiesis, erythrocyte development
- Leukopoiesis, leukocyte development:
  - Granulopoiesis, granulocyte development
  - Monopoiesis, monocyte development
  - Lymphopoiesis, lymphocyte development
- Thrombopoiesis, thrombocyte development

Erythropoiesis

General
- Duration 7 days
- Stimulated by erythropoietin

Structure
- Erythroblasts form erythroblastic islets around macrophages, which phagocytize extruded nuclei.
- Erythroblastic islets are formed in the hemopoietic space adjacent to the sinusoid wall.
- Mature erythrocytes are pushed through temporary pores in the endothelium and into the bloodstream.

Light microscopy (Table 10.3 and Fig. 10.2)
Overview of changes during erythropoiesis:
- Cell size decreases
- Nucleus
  - Decreases in size
  - Turns dark (heterochromatic)
  - Is lost at the end of development
- Cytoplasm goes from basophilic to acidophilic staining, as:
  - It fills up with the acidophilic hemoglobin.
  - Organelles are lost, including the basophilic ribosomes.

Table 10.3 Erythropoiesis

Cell	⦸	Nucleus	Cytoplasm	Free ribosomes (basophilic)	Hemoglobin (acidophilic)
Proerythroblast ↓ Mitoses	12–20 µm	• Large • Spherical	Mild basophilic due to free ribosomes	+++	–
Basophilic erythroblast ↓ Mitoses	10–16 µm	• Smaller • Darker (more hetero-chromatic)	Strongly basophilic due to many free ribosomes	++++	–
Polychro-matophilic erythroblast ↓ Mitoses	10–15 µm	• Smaller • Hetero-chromatin in checkerboard pattern	• Basophilic with acido-philic areas due to hemoglobin • Seen as distinct regions or a blend gray color	+++	+
Orthochro-matophilic erythroblast (normoblast) ↓ Nucleus extruded	8–10 µm	• Small • Dark (hetero-chromatic)	Acidophilic due to large amounts of hemoglobin, with slight basophilia due to remaining ribosomes	++	++
Reticulocyte (polychro-matophilic erythrocyte) ↓ Ribosomes lost	≈7.5 µm	No nucleus	Acidophilic with trace basophilia due to remaining ribosomes	+	+++
Mature erythrocyte	≈7.5 µm	No nucleus	Acidophilic	–	+++

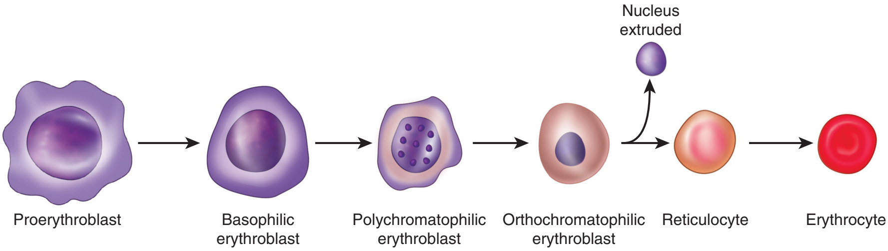


Fig. 10.2 Erythropoiesis: stages of erythrocyte development

MEMO-BOX
Use the names from erythropoiesis to remember events:
- **BASOPHILIC** erythroblast: has a strongly **BASOPHILIC** cytoplasm due to large amounts of free ribosomes, which are needed to synthesize hemoglobin.
- Polychromatophilic erythroblast: "polychrom" is Greek for multicolored, as it has acidophilic areas of hemoglobin in the basophilic cytoplasm.
- Orthochromatophilic erythroblast: "orthochrom" is Greek for correct colored, as it is now purely acidophilic similar to a mature erythrocyte, as its cytoplasm is filled up with hemoglobin.

Granulopoiesis

General
- Duration 14 days
- Stimulated by colony-stimulating factors

Structure
- Myeloblasts form clusters within the hemopoietic space some distance from the sinusoid wall.
- Mature granulocytes are motile and migrate into the lumen of sinusoids.

Light microscopy (Table 10.4 and Fig. 10.3)
Overview of changes during granulopoiesis:
- Cell size decreases slightly
- Nucleus:
  1. Decreases in size and turns dark (heterochromatic)
  2. Elongates
  3. Forms lobes at the end of development
- Cytoplasm fills with granules:
  1. Primary granules (lysosomes)
  2. Secondary (specific) granules

Monopoiesis

General
- Duration ≈ 2 days
- Stimulated by colony-stimulating factors

Light microscopy
See Table 10.5.

Table 10.4 Granulopoiesis

Cell	⦸	Nucleus	Cytoplasm	Primary granules (lysosomes)	Secondary (specific) granules
Myeloblast ↓ Mitoses	14–20 µm	• Large • Spherical • Light (euchromatic)	• Intensely basophilic • Without granules	–	–
Promyelocyte ↓ Mitoses	18–24 µm	• Large • Spherical • Light (euchromatic)	• Basophilic • Primary granules (lysosomes), which are only produced at this stage	+++	–
Myelocyte ↓ Mitoses	≈15 µm	• Smaller • Indented/elliptical • Darker (more heterochromatic)	• Weakly basophilic • Few secondary (specific) granules	++	+
Metamyelocyte ↓ Formation of nuclear lobes	≈15 µm	Elongated/kidney shaped	Many secondary (specific) granules → cells are clearly identified as • Neutrophilic • Eosinophilic • Basophilic	+	+++
Mature granulocyte	12–15 µm	Lobulated	Many secondary (specific) granules	+	+++

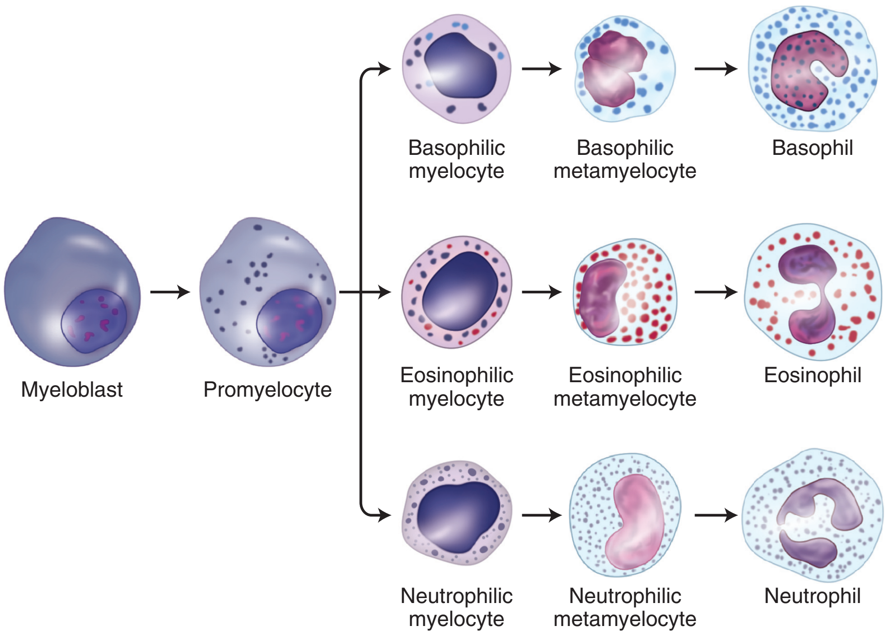


Fig. 10.3 Granulopoiesis: stages of granulocyte development

Table 10.5 Monopoiesis

Cell	⃠	Nucleus	Cytoplasm
Monoblast ↓ Mitoses	14–18 µm	• Large • Ovoid	• Basophilic • Without granules
Promonocyte ↓ Mitoses	14–18 µm	• Large • Slightly indented	• Mild basophilic • Without granules
Mature monocyte	12–18 µm	Indented/kidney shaped	• Pale basophilic • Many granules (lysosomes)

MEMO-BOX

Remember events of granulopoiesis:

- **PR**omyelocyte: **PR**imary granules in cytoplasm, which are only **PR**oduced at this stage.
- First the primary granules are formed, later the secondary granules.
- **META**myelocyte: as is “**META**morphosis” the Greek word for a change in physical form → first cell in granulopoiesis, which is clearly seen as becoming a neutrophil, eosinophil, or basophil in the light microscope, because of the many secondary granules.
- The nucleus must first be elongated, before nuclear lobes can be formed, analogous to when you need an elongated balloon to make balloon animals.

Lymphopoiesis

General

- Pre-B lymphocytes and pre-NK cells stay in bone marrow during further development (Chap. 19).
- Pre-T lymphocytes migrate to the thymus for further development (Chap. 19).

Light microscopy

See Table 10.6.

Table 10.6 Lymphopoiesis

Cell	⦸	Nucleus	Cytoplasm
Lymphoblast ↓ Mitoses	10–20 µm	• Large • Light (euchromatic)	• Sparse • Basophilic • Without granules
Mature lymphocyte	≈7 µm	• Smaller • Dark (heterochromatic)	• Thin rim • Basophilic due to many free ribosomes • Without granules

MEMO-BOX

Pre-**B** lymphocyte: stays in **B**one marrow for further development
Pre-**T** lymphocyte: migrates to **T**hymus for further development

Thrombopoiesis

General

- Duration 10 days
- Stimulated by thrombopoietin

Structure

Megakaryocytes:

- Reside in the hemopoietic space adjacent to the sinusoid wall
- Send long cell extensions through endothelial pores and into the bloodstream, where small fragments are broken off as thrombocytes

Light microscopy

See Table 10.7.

Table 10.7 Thrombopoiesis

Cell	⦸	Nucleus	Cytoplasm
Megakaryoblast ↓ Endomitoses (chromosomes replicate without nuclear- and cell division)	≈30 µm	• Large • Ovoid	Basophilic
Megakaryocyte ↓ Breaks off small fragments as thrombocytes	50–70 µm	• Multilobed • Polyploid, i.e., contains multiple sets of chromosomes	• Weakly acidophilic • Basophilic granules
Mature thrombocytes	≈3 µm	No nucleus	• Central darker-stained zone with basophilic granules • Peripheral weakly stained zone

Yellow Bone Marrow

General

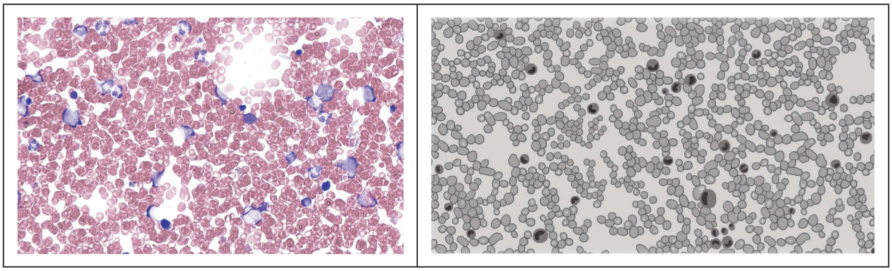
- White adipose tissue (Chap. 11) found within the spaces of bone
- Yellow color due to the abundant adipocytes
- Has no active hemopoiesis
  - Retains hemopoietic potential, i.e., can transform into red bone marrow if necessary

Function

As white adipose tissue of other locations, e.g., storage of lipids

Guide to Practical Histology: Bone Marrow

Red Bone Marrow Smear



Left: photomicrograph of red bone marrow smear. Magnification: high. Stain: Giemsa (Courtesy of professor Jørgen Tranum-Jensen, University of Copenhagen). *Right*: simplified illustration of red bone marrow smear

Characteristics

- Numerous eosinophilic erythrocytes.
  - Erythrocytes are often seen in clumps or rows.
- Numerous hemopoietic cells with nuclei.
- Large round white (empty) spaces, (lipid droplets formed from rupturing of adipocytes during aspiration of the bone marrow specimen).

Special staining

Giemsa or Wright's stain:

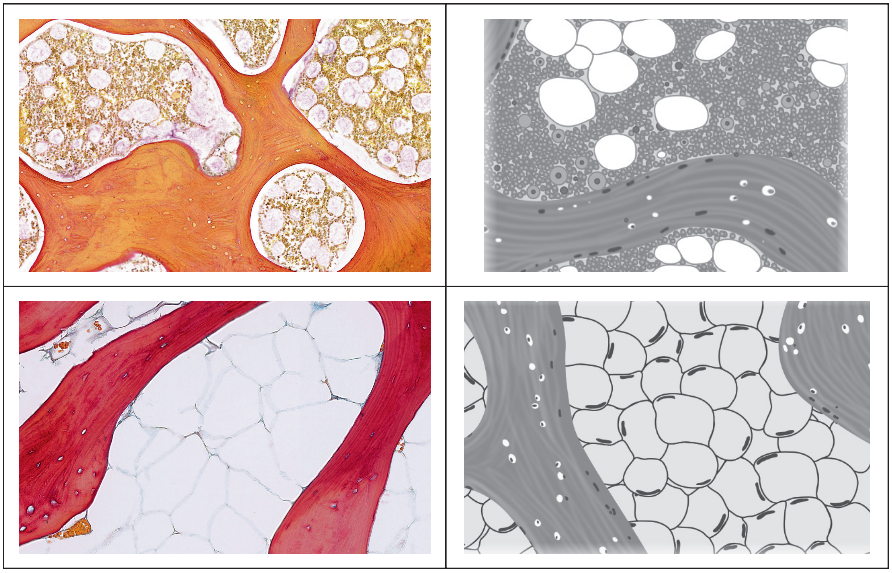
- Methylene blue (basic dye): stains basophilic
- Azure dyes (basic dyes): stain azurophilic (dark blue/purple), e.g., lysosomes
- Eosin (acidic dye): stains eosinophilic

Can be mistaken for

Blood smear:

- Contains no hemopoietic stem cells → Few cells with nuclei.
- No large round white (empty) spaces.
- At large magnification, it is easy to find fields of view lacking cells with nuclei, unlike in the red bone marrow smear.

Bone Marrow



Top left: photomicrograph of red bone marrow. Magnification: low. Stain: Van Gieson and Alcian blue (Courtesy of professor Jørgen Tranum-Jensen, University of Copenhagen). *Top right*: simplified illustration of red bone marrow. *Bottom left*: photomicrograph of white bone marrow. Magnification: low. Stain: Mallory-Azan. (Courtesy of professor Jørgen Tranum-Jensen, University of Copenhagen). *Bottom right*: simplified illustration of white bone marrow

Characteristics

- Surrounded by bone tissue
- Two types of bone marrow:
  - Red bone marrow
    - Multiple tightly packed hemopoietic stem cells
    - Multiple white spaces:
      - Sinusoids containing erythrocytes
      - Adipocytes, seen as large white (empty) polyhedral cells
  - White bone marrow
    - Multiple adipocytes
      - Large white (empty) polyhedral cells.
      - Cells form a polygonal meshwork (resembles chicken wire).

Location

- Red bone marrow
  - Primarily located within the bones of the axial skeleton, corresponding to the area covered by a one-piece swimsuit
  - For example, within the vertebrae
- White bone marrow
  - Occupies the remaining spaces in bone
  - For example, in the bones of the fingers

References

5, 25, 33, 34, 36.

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http://www.springer.com/978-3-319-41871-1

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