Hematopoiesis

1. Hemopoietic tissues

2. Stages and sites of hemopoiesis

3. Hematopoiesis:
   - erythropoiesis
   - granulopoiesis
   - megakaryocytopoiesis

4. Regulation of hematopoiesis
Hematopoiesis, Gr. *haima*, blood + *poiesis*, a making (origin and maturation of new blood cells)

- **erythopoiesis** = formation of erythrocytes
- **granulopoiesis** = formation of granulocytes
- **mono-/lymphocytopoiesis** = formation of agranulocytes
- **megakaryocytopoiesis** = formation of platelets
Hematopoietic tissues:

- blood-forming tissue, consisting of reticular fibers and similarly specialized connective tissue cells of mesenchymal origin that give rise to new blood cells

- myeloid tissue, Gr. μυέλος, *myelos*, marrow (red bone marrow) = formation of most of the blood cells: erythrocytes, granulocytes and thrombocytes (platelets)

- lymphoid tissue (thymus, spleen) = formation of T-lymphocytes, proliferation of B-lymphocytes, immune defense (lymph nodes and associated lymphoid tissue, MALT, GALT, BALT)
Periods of hematopoiesis

- prenatal hematopoiesis (intraembryonic):
  - mesoblastic (megaloblastic) phase – 14 days (2nd gestational week)
    - yolk sac mesoderm ⇒ hemocytoblasts
  - hepatolienal phase – 5th to 6th gestational week
    - liver ⇒ erythrocytes
    - spleen ⇒ Er+granulocytes, lymphocytes (after 5th month)
    - thymus ⇒ T-lymphocytes
  - medullary (myeloid) phase – since 4th month
    - bone marrow
    - liver and spleen

- postnatal hematopoiesis:
  - myeloid phase – in red bone marrow (textus myeloides)
    - red (hematogenous)
    - yellow bone marrow
**Mesoblastic phase**

- **Megaerythroblastic hematopoiesis:**
  - erythrocytopoiesis, incl. normoblast
  - absent granulo, mono- and lymphocytopoiesis
- **initial blood cell** – *hemocytoblast* = pluripotential stem cell:
  - large, spherical, basophilic
  - synthesize hemoglobin
  - form primitive erythrocytes
    - (located in groups or islets “blood islands”, retain their nuclei)
Hepatolienal phase

**NB!** from 2\textsuperscript{nd}-3\textsuperscript{rd} month until birth

- **Hematopoietic organs:**
  - liver
  - spleen
  - thymus

- Normal precursor cells and erythrocytes, no megakaryoblasts
- Erythroblasts (from lymphoid organs)
- Begin of leukopoiesis
- Lymphocyte appearance
Medullary phase

✓ begin in clavicle – 2nd month
✓ in the 5th fetal month – the major blood-forming organ is the red bone marrow
✓ all cell lines of hematopoiesis
✓ lymphoid organs – only lymphoblasts

Granulopoiesis

Erythropoiesis
Red bone marrow

Bone marrow:
- Mitosis:
  - Stem cell
  - Myeloblast
  - Promyelocyte
  - Myelocyte
- Maturation:
  - Metamyelocyte
  - Band cell
  - Mature granulocyte
- Storage
- Blood
  - Marginating cells
  - Circulating cells

Platelets, Leukocyte, Megakaryocyte, Erythrocyte

Blood flow

Prof. Dr. Nikolai Lazarov
Unitary (monophyletic) theory

✓ Alexander A. Maximow, 1901

✓ Common undifferentiated stem cell (hemocytoblast):
  - one of 1000 nuclear cells in the bone marrow
  - origin: mesenchyme of the embryonic sac (3rd week)
  - functionally distinct but morphologically indistinct
  - has the potential to give rise to any type of blood cells

Pluripotent stem cell

Progenitor cell (CFU, CFC) (uni- and bipotent)

Precursor (blast) cell

functional blood cell
Stem cells

(colony-forming units)

- CFU – erythrocyte (CFU-E)
- CFU – granulo-monocyte (CFU-GM)
- CFU – lymphocyte (CFU-L)
- CFU – megakaryocyte (CFU-Me)

Two types of pluripotent stem cells:

- **type I** – 10% in permanent mitosis
- **type II** – 90% in G₀ phase

### Table 13-1. Changes in Properties of Hemato poetic Cells during Differentiation.

<table>
<thead>
<tr>
<th>Stem Cells</th>
<th>Progenitor Cells</th>
<th>Precursor Cells (Blasts)</th>
<th>Mature Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential</td>
<td>Mitotic activity</td>
<td>Typical morphological characteristics</td>
<td>Influence of growth factors</td>
</tr>
<tr>
<td>Self-renewing capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagram:

- Lymphoid multipotential cells
  - Migrate to lymphoid organs
  - Lymphocyte-colony forming (LCFC)
  - Erythrocyte-colony forming (ECFC)
  - Megakaryocyte forming (MCFC)
  - Monocyte-colony forming (MCFC)
  - Granulocyte-colony forming (GCFC)
  - Eosinophil-colony forming (EoCFC)
  - Basophil-colony forming (BCFC)

- Myeloid multipotential cells remain in bone marrow
  - MGCFC
  - GCFC
  - MCFC
  - EoCFC
  - BCFC

- Lymphoblast
  - B and T lymphocytes
  - Erythroblast
  - Megakaryoblast
  - Megakaryocyte
  - Promonocyte
  - Monocyte
  - Neutrophilic myelocyte
  - Eosinophilic myelocyte
  - Basophilic myelocyte
  - Neutrophilic granulocyte
  - Eosinophilic granulocyte
  - Basophilic granulocyte
The Nobel Prize in Physiology or Medicine 2012

Sir John B. Gurdon, Shinya Yamanaka

The Nobel Prize in Physiology or Medicine 2012 was awarded jointly to Sir John B. Gurdon and Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent"
Българска академия на науките и Посолство на Япония в България
с подкрепата на Министерството на образованието и науката
Организират публична лекция на
Нобеловия лауреат по физиология и медицина
проф. Шиня Яманака
Директор на Център за изследване и приложението на плурипотентни стоволови клетки, Университета в Киото

„Индусирани плурипотентни стоволови клетки – нова ера в медицината”

На търговската церемония, проф. Яманака ще бъде удостоен с почетното звание „Доктор хонорис куаза” на Българската академия на науките

20 август (понеделник) 2018 г., 11:00 часа
Зала „Проф. Марин Дринов”, ул. „15 Ноември“ № 1

Host: Bulgarian Academy of Sciences
Co-host: Embassy of Japan in Bulgaria
with the support of the Ministry of Education and Science
Lecture of the Nobel Laureate in Physiology or Medicine
Prof. Shinya Yamanaka
(Director of Center for iPS Cell Research and Application, Kyoto University)

„New Era of Medicine with iPS Cells”
At official ceremony Prof. Yamanaka will be awarded honorary degree of the Bulgarian Academy of Sciences “Doctor Honoris Causa”

20 August (Monday) 2018, 11:00 a.m.
Venue: Lecture Hall “Prof. Martin Drinov”, Bulgarian Academy of Sciences,
15 November Str. № 1
Basic principles in maturation of red blood cells:

- decrease in cell size and volume
- loss of nuclear material and disappearing of cellular organelles:
  - increase of condensed chromatin
  - decrease in the number of nucleoli
  - basophilia is replaced by acidophilia
- synthesis and accumulation of hemoglobin
  - decrease in the processes of dividing
  - loss in the proliferative capabilities
  - decrease in the synthetic processes
Erythrocytopoiesis

- duration – approximately 7 days
- the division stops at normoblast level
- stimulated by erythropoietin, folic acid, iron, vitamin B₁₂

<table>
<thead>
<tr>
<th>Cell</th>
<th>Size</th>
<th>Nucleus</th>
<th>Cytoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proerythroblast</td>
<td>20-30 µm</td>
<td>large, prominent nucleolus</td>
<td>basophilic</td>
</tr>
<tr>
<td>Basophilic erythroblast</td>
<td>15-20 µm</td>
<td>condensed, no visible nucleolus</td>
<td>basophilic</td>
</tr>
<tr>
<td>Polychromatophilic erythroblast</td>
<td>12-15 µm</td>
<td>reduced under 50%</td>
<td>basophilic to acidophilic</td>
</tr>
<tr>
<td>Orthochromatophilic erythroblast (Normoblast)</td>
<td>8-10 µm</td>
<td>small, condensed</td>
<td>no basophilia is evident</td>
</tr>
<tr>
<td>Polychromatophilic erythrocyte (Reticulocyte)</td>
<td>8-10 µm</td>
<td>no nucleus</td>
<td>acidophilic</td>
</tr>
</tbody>
</table>
✓ differentiation and maturation – about 11-14 days

✓ Basic principles in granulocyte formation:
  ➢ moderate decrease in the cell volume
  ➢ increase in the nuclear density and segmentation
  ➢ accumulation of specific granules

Granulocytopoiesis
The myelocyte is the last cell to divide.

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<thead>
<tr>
<th>Cell</th>
<th>Size</th>
<th>Nucleus</th>
<th>Cytoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloblast</td>
<td>15-21 µm</td>
<td>large with finely dispersed chromatin</td>
<td>light blue, without visible granules</td>
</tr>
<tr>
<td>Promyelocyte</td>
<td>18-30 µm</td>
<td>oval with condensed chromatin</td>
<td>basophilic with azurophilic granules (blue)</td>
</tr>
<tr>
<td>Myelocyte</td>
<td>12-15 µm</td>
<td>small oval</td>
<td>specific granules (pink)</td>
</tr>
<tr>
<td>Metamyelocyte</td>
<td>12-15 µm</td>
<td>kidney-shaped</td>
<td>filled with granules</td>
</tr>
</tbody>
</table>
Lymphocytopoiesis

- in lymphoid tissue:
  - thymus
  - lymph nodes
  - spleen

- maturation principles:
  - condensation of chromatin
  - decrease in cellular volume
  - dedifferentiation ability

- no evident morphological changes in differentiation:
  - pluripotent stem cell
  - unipotent progenitor cell
  - B- and T-cell stem cell
  - lymphoblast (15-20 µm)
  - prolymphocytes
  - B- and T-lymphocytes
Monocytogenesis

✓ maturation (55 h):
  ➢ decrease in cell size
  ➢ appearance of small number of fine azurophilic granules

✓ monocytes arise from a pluripotent stem cell in the bone marrow:
  ➢ multipotent progenitor cell
  ➢ bipotent progenitor cell
    (committed for neutrophils and monocytes)
  ➢ monoblast
  ➢ promonocyte
  ➢ monocyte
**Thrombopoiesis**

- **megakaryocyte** (Gr. *megas*, big, + *karyon*, nucleus, + *kytos*, cell), giant cell (35-150 µm) in the red bone marrow
- **maturation stages:**
  - megakaryoblast
  - promegakaryocyte
  - megakaryocyte – 500-5000 platelets
<table>
<thead>
<tr>
<th>Cell</th>
<th>Size</th>
<th>Nucleus</th>
<th>Cytoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>megakaryoblast</td>
<td>15-60 µm</td>
<td>large ovoid or kidney-shaped, numerous nucleoli, peripherally dense heterochromatin</td>
<td>homogenous and intensely basophilic</td>
</tr>
<tr>
<td>promegakaryocyte</td>
<td>30-70 µm</td>
<td>large and highly lobulated</td>
<td>lightly-stained with centrally located azurophilic granules</td>
</tr>
<tr>
<td>megakaryocyte</td>
<td>35-150 µm</td>
<td>irregularly lobulated, highly polyploid (4N-64N), coarse chromatin and no visible nucleoli</td>
<td>spotted basophilic with azurophilic granules</td>
</tr>
</tbody>
</table>
Regulation of hematopoiesis

- hematopoietic growth factors
- colony-stimulating factors (CSF)
- hematopoietins (poietins)

Table 13-2. Main Characteristics of the Five Best-Known Hematopoietic Growth Factors (Colony-Forming Substances).

<table>
<thead>
<tr>
<th>Name</th>
<th>Human Gene Location and Producing Cells</th>
<th>Main Biological Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocyte (G-CSF)</td>
<td>Chromosome 17, Macrophages, Endothelium, Fibroblasts</td>
<td>Stimulates formation (in vitro and in vivo) of granulocytes.</td>
</tr>
<tr>
<td>Granulocyte + macrophage (GM-CSF)</td>
<td>Chromosome 5, T lymphocytes, Endothelium, Fibroblasts</td>
<td>Stimulates in vitro and in vivo production of granulocytes and macrophages.</td>
</tr>
<tr>
<td>Interleukin 3 (IL-3)</td>
<td>Chromosome 5, T lymphocytes</td>
<td>Stimulates in vivo and in vitro production of all myeloid cells.</td>
</tr>
<tr>
<td>Erythropoietin (EPO)</td>
<td>Chromosome 7, Renal interstitial cells (outer cortex)</td>
<td>Stimulates red blood cell formation in vivo and in vitro.</td>
</tr>
</tbody>
</table>
Thank you...