

# Blood II

## Agranulocytes

- lymphocytes
- monocytes

## Hematopoiesis

- mesoblastic
- hepatosplenic
- medullary

Stages of h.

# Formed elements of the blood



- erythrocytes (RBC = red blood cells)
- thrombocytes (platelets)
- leukocytes (WBC = white blood cells)
  - granulocytes: specific granules and segmented nuclei (polymorphonuclears)
    - neutrophilic
    - eosinophilic
    - basophilic
  - agranulocytes: without specific granules, spherical to kidney-shaped nucleus (mononuclears)
    - lymphocytes
    - monocytes

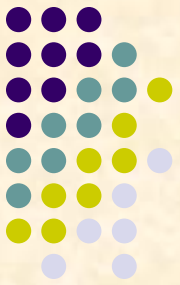
# Lymphocytes

- small: 6-8  $\mu\text{m}$  (90%)
- medium: 8-12  $\mu\text{m}$
- large < 18  $\mu\text{m}$ , lymphoblasts in lymphoid organs
  
- round-shaped nucleus, dense chromatine
  
- 20-45 % of peripheral blood leukocytes
  
- solid lymphoid organs
- MALT = mucosa associated lymphoid tissue (BALM, GALT)
- 2% circulating
  
- adaptive immunity
- differentiate into effector immune cells, T- and B-memory cells

# Lymphocytes



- CD markers
  - *cluster of differentiation*
  - immunphenotype
  - receptors, ligands, parts of signalling pathways, adhesion molecules
- B-lymphocytes
- T-lymphocytes
  - T<sub>H</sub> helpers
  - T<sub>C</sub>T cytotoxic
  - Treg regulatory, supressors
- NK-cells, natural killers



- B-lymphocytes
  - approx. 15% of circulation lymphocytes
  - bursa Fabricii, B-dependent lymphocytes
  - differentiation
    - plasma cells → Immunoglobulins; effector cells of humoral immunity
    - memory cells

# Immunoglobulins = antibodies



- circulating soluble antibodies
- chains
  - heavy:  $\mu$ ,  $\gamma$ ,  $\alpha$ ,  $\epsilon$ ,  $\delta$
  - light:  $\kappa$ ,  $\lambda$
- domains
  - constant
  - variable
- classes = isotypes
  - IgM: membrane-bound (B-cells) or soluble pentamers; early response
  - IgG: the major Ig in serum; majority of antibody-based immunity; capable of crossing the placenta
  - IgA: found in mucosae, saliva, breast milk; stabilized by secretory glycoproteins to form dimers
  - IgE: binds to mast cells and basophils (type I allergic reaction) and eosinophils (anti-parasitic reactions)
  - IgD: on B-cells; the role in serum is uncertain
- agglutination, opsonization → enhanced phagocytosis and killing
- activating the complement proteins

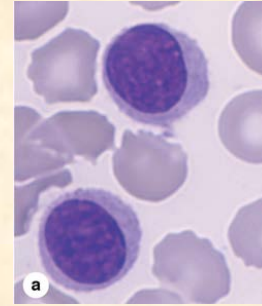
- T-lymphocytes

- T<sub>H</sub> helpers

- CD4+
- naive Th activated by APC → cytokines
- regulating lymphocytes and macrophages
  - TH1-cells → activating NK, macrophages, Tc-lymphocytes, response on intracellular pathogens
  - TH2-cells → stimulating B-lymphocytes → IgG, IgA a IgE, activating eosinophils, against i extracellular antigens
  - regulatory T-lymphocytes supressing the immuno response = Treg =Ts (supressors), autotolerance

- T<sub>C</sub>T cytotoxic

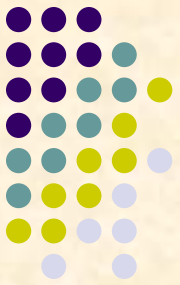
- CD8
- activate by contacting the antigenes + class I MHC → cytolytic granules
  - perforins → permeabilizing the plasmalemma
  - granzymes → apoptosis induced
  - activating Fas receptors → cell death of the target cells
  - activating macrophages





- NK-cells, natural killers
  - approx. 10 % of circulating lymphocytes
  - perforins and granzyme → destroying cells without proper class I MHC, thus targeting:
    - tumor cells
    - virus-transformed cells





# Monocytes

- 12-20  $\mu\text{m}$
  - oval or kidney-shaped nucleus
  - less dense chromatin than in lymphocytes
  - small azurophilic granules (lysosomes)
- 
- 2-12 % of peripheral blood WBC
  - circulating 1-3 days
  - diapedesis  $\rightarrow$  macrophages
- 
- phagocytosis – both innate and acquired immunity

# Mononuclear phagocyte system

(formerly: reticuloendothelial)



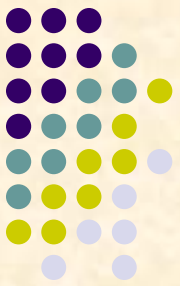
- professional macrophages
  - tissue macrophages
  - Kupffer's cells
  - dendritic cells
  - osteoclasts
  - microglia
- phagocytosis
  - phago-lysosome
  - cytokines released → chemotaxis of neutrophils et al.
  - antigen presentation for lymphocytes
  - producing growth factors

# Immunity



- innate = natural
  - neutrophils, macrophages
  - eosinophils
  - NK
- acquired = adaptive
  - humoral = antibody-mediated
    - B-lymphocytes → plasma cells → antibodies
  - cell-mediated
    - T-cells
    - APC
      - dendritic cells
      - macrophages

# The discovery of acquired immunological tolerance (P. B. Medawar, NP, 1960)



- extracted cells from mouse embryos
- injected into another mouse embryos of different strains
- when the recipient mouse developed into adult, skin grafting from the original strain was performed
- there was **no tissue rejection**
- thus, **the acquired immuno toelarnce was discovered**
- → foundation of **transplantation immunology**

# Hematopoiesis



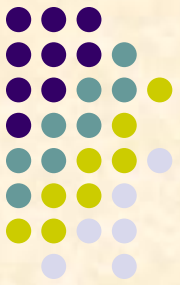
- ontogeny
  - mesoblastic period
    - extraembryonic mesenchyme of the yolk sac
    - intraembryonic mesenchyme
    - blood islands
    - week 3 – month 3
    - angioblasts → endothelium, proerythroblasts, myeloblasts
  - hepatosplenic period
    - month 2-8
    - mesenchyme of liver and spleen
    - extramedullary hematopoiesis in adults (pathology)
  - medullary period
    - since month 5
    - red bone marrow

# Bone marrow



- red
  - newborn/children: most of the skeleton
  - adults: sternum, bodies of vertebrae, ribs, shoulder blade, pelvis, flat bones of the skull, proximal epiphyses of humerus/femur
  - loose reticular connective tissue
  - fenestrated blood sinusoids
  - basal lamina discontinuous or absent
  - adipocytes
  - macrophages (nuclei of normoblasts etc.)
  - cytology: bone marrow aspiration → smears
  - trephine needle biopsy (trepanobiopsy) including the trabecular bone
- yellow
  - progressive fatty replacement → adipose tissue

# Hematopoietic cells



1. **pluripotent hemopoietic stem cells**
  - asymmetric division & self-renewal
  - → myeloid and lymphoid stem cell
2. differentiate into **progenitor cells = CFU** (colony-forming units)
  - CFU-E: erythroid lineage
  - CFU-Meg: thrombocytic lineage
  - CFU-GM: granulocyte-monocyte lineage
  - CFU-L: lymphoid lineage
3. CFU produce **precursor cells** („-blasts“)
  - mitotic division
  - no self-renewal
4. differentiate into **mature cells**
  - typical morphological characteristics
  - differentiated functional activity

# Hematopoiesis



- microenvironment of bone marrow, niche
- paracrine and endocrine differentiating and growth factors = **colony-stimulating factors (CSF) = hematopoietins**
  - erythropoetin: kidney & liver, stimulated by hypoxia
  - thrombopoetin: liver
  - cobalamin – B12 vitamin (+intrinsic factor), folic acid – B9 vitamin, Fe,...
- daily per kg of body weight
  - $2.5 \times 10^9$  erythroocytes
  - $1 \times 10^9$  granulocytes
  - $2.5 \times 10^9$  platelets



# Lineages



- lymphoid lineage, **lymphopoiesis**
  - progenitors migrating into lymphoid organs
  - central lymphoid organs (bone marrow and thymus)
  - pluripotent stem cell → CFU-L → lymphoid stem cell → B- and T-lymphoblast → B- and T-lymphocyte
- myeloid lineages
  - **erythropoiesis:** pluripotent stem cell → CFU-E → proerythroblast → basophilic erythroblast → polychromatophilic → orthochromatophilic (eosinophilic) → normoblast (nucleus ejected) → reticulocyte → erythrocyte
  - **thrombopoiesis:** pluripotent stem cell → CFU-Meg → megakaryoblast → megakaryocyte → thrombocyte
  - **granulopoiesis:** pluripotent stem cell → CFU-GM → myeloblast → promyelocyte → myelocyte (Ne, Eo, Ba) → metamyelocyte (Ne, Eo, Ba) → granulocyte (Ne, Eo, Ba)
  - **monopoiesis:** pluripotent stem cell → CFU-GM → monoblast → promonocyte → monocyte → macrophage