Blood

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PharmDr. Zuzana Soldánová

Department of Chemical Drugs
Department of Molecular Biology and Pharmaceutical Biotechnology

Blood

- blood volume constitute 6 – 8% of body weight (adult with 70 kg has approximately 5,6 l of blood)

- **normovolemia**
  - normal amount of circulating blood

- **hypervolemia**
  - increased amount of circulating blood

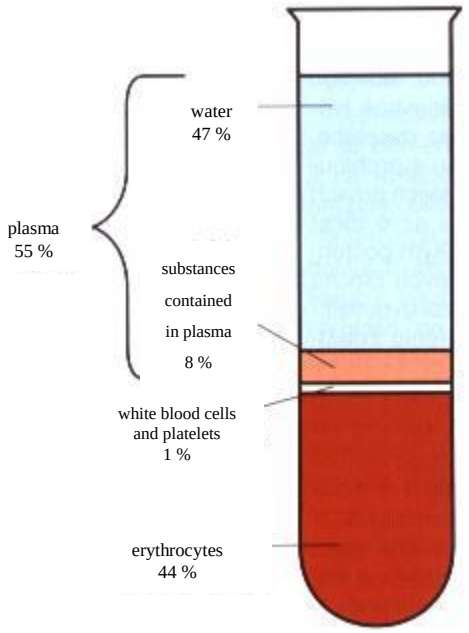
- **hypovolemia**
  - decreased amount of circulating blood

- for evaluation it is important to consider the **hematocrit value**
  - percentage amount of formed elements in the total blood volume
  - normal cell to plasma ratio
    - Simple normo-, hyper- and hypovolemia
  - elevated hematocrit values
    - polycythaemic normo-, hyper- a hypovolemia
  - decreased hematocrit values
    - oligocytemic normo-, hyper- a hypovolemia

Blood composition

- **Formed elements**
  - ≈ 45 % full blood
  - contains
    - erythrocytes (≈ 45 % full blood)
    - leukocytes
      - granulocytes
      - monocytes
      - lymphocytes
    - Platelets (thrombocytes)

- **blood plasma**
  - liquid phase of blood
  - ≈ 54 % full blood
  - contains
    - water (90 %)
    - ions
    - Low molecular weight nonelectrolytes
    - proteins



Dostupné z: http://medicina.cz/clanky/2564/34/Krev/

Hematocrit

Blood element volume/total plasma and blood element volume

0,41 – 0,46

Blood composition

- Plasma
  - it contains fibrinogen and other blood clotting factors
  - it is obtained by centrifugation after addition of anticoagulants

- Serum
  - it does not contain fibrinogen and coagulation factors
  - it is obtained after centrifugation of the clotted blood
  - it contains platelet disintegration products (higher levels of CP a K^+)

Blood function

- **1. Transport function**
  - transport O_2 from lungs and CO_2 from tissues
  - transport of nutrients from the intestine
  - transport of hormones to target tissues
  - transport of waste metabolites to the kidneys and lungs
  - transport of metal ions and vitamins
- **2. Defense function**
  - maintenance of hemostasis (haemostasis)
    - coagulation
  - defense against infection
    - antibodies
    - leukocytes
- **3. Maintenance function**
  - homeostasis
    - pH
    - osmolality
    - temperature
    - water

BLOOD PLASMA PROTEINS

Blood plasma proteins

- Plasma protein concentration is 62 – 82 g/l.

- **Plasma protein electrophoresis**
  - diagnostics
  - overview of protein spectrum
  - globulins γ, β, α_2, α_1 and albumin

- **Funtion of proteins in plasma**
  - enzymes
  - enzyme inhibitors
  - transport proteins
  - defense function
  - clotting and fibrinolysis factors
  - maintaining oncotic pressure

- **Structural types of proteins**
  - simple polypeptides
  - glycoproteins
  - lipoproteins (global)

The most important blood plasma proteins

- **Transport function**
  - albumin
  - transferrin
  - ceruloplasmin
  - haptoglobin
  - hemopexin
  - prealbumin
  - RBG (retinol binding globulin)
  - TBG (thyroid binding globulin)
  - transcortin
  - SHBG (sex hormone binding globulin)
  - transcobalamines
- **Coagulation factors**
- **Defense function**
  - immunoglobulins
  - complement proteins
  - CRP (C-reactive protein)
- **Proteins associated with inflammation**
  - CRP
  - C3, C4, C1 INA
  - α 1-antitrypsin
  - α 1-antichymotrypsin
  - α 1-acid glycoprotein
  - haptoglobin
  - ceruloplasmin
  - fibrinogen

Plasma protein electrophoresis is used for diagnostics and overview of protein spectrum. Constitution: γ globulins (16 %), β globulins (12 %), α_2 globulins (8 %), α_1 globulins (4 %) and albumin (60 % and it consists only 1 protein).

Albumin

- major plasma protein
- synthesis in the liver
- 10 – 12 g/day
- 35 – 53 g/l (serum)
- molecular weight ≈ 69 000
- 585 amino acids
- degradation
  - most likely endocytosis in capillary endothelium, bone marrow and hepatocytes
- biological half-life **20 days**
- daily production 10 – 12 g/day

- **Transport function**
  - fatty acids
  - Ca^{2+}
  - Cu^{2+}
  - steroid hormones
  - bilirubin
  - T_4, T_3
  - medicines (salicylates, sulfonamides, penicillin, barbiturates, …)

- **Importance**
  - maintaining oncotic pressure
  - buffering ability

- **Hypoalbuminemia**
  - causes
    - liver disorders
    - malnutrition
    - loss of fluid by kidney or burns, chronic inflammation
    - hyperhydration
  - consequence
    - ascites and edema
    - hypoalbuminemic alkalosis
    - hypocalcaemia

- **Hyperalbuminemia**
  - dehydratation
  - therapy of diuretics

Blood plasma proteins

Prealbumin

- synthesis in the liver
- serum concentration
  - 0,1 – 0,4 g/l
- biological half-life is **2 days**
- binds thyroxine in plasma
- forms a complex with the protein transporting vitamin A (retinol binding protein)
- the decreased value maybe a marker of malnutrition and the state of proteosynthesis

Haptoglobin

- synthesis in the liver
- serum concentration
  - 1 – 3 g/l (α_2-globulin)
- biological half-life is **5 days**
- polymorphic forms Hp1-1, Hp2-1, Hp2-2
- function
  - uptake of plasma Hb
    - Hb-Hp complex is taken up by RES (biological half-life is 90 minutes)
- importance
  - prevents free Hb to penetrate through the kidneys
- decreased levels in hemolytic anaemia and decreased proteolysis in the liver
- increased levels
  - is one of the acute phase reactants

Proteins transporting metal ions in plasma

Transferrin

- synthesis in the liver
- concentration 2,5 – 4,0 g/l (serum)
  - increased concentration in sideropenic anaemia
  - decreased concentration in chronic anaemia of another type
- β_1-glycoprotein
- importance
  - transport of Fe^{3+} into the tissues
- normally ≈ 1/9 is saturated, 4/9 has 1 binding site occupied, 4/9 are free (1/3 of total transferrin is saturated)
- people who are addicted to alcohol – carbohydrate deficient transferin CDT

Ferritin

- synthesis in liver, spleen, bone marrow,..
- apoferritin has a molecular weight of ≈ 81 000 (24 subunits)
- up to 20 types of isoferritins
- binding capacity – 4500 Fe^{3+}/apoferritin
- importance
  - a major form of iron deposition in cells of
    - liver
    - spleen
    - intestine
    - bone marrow
- only a small amount is released into the blood, the serum concentration reflects the supply of Fe

Hemosiderin

Ceruloplasmin

- synthesis in the liver
- biological half-life **4 – 10 days**
- α_2-globulin
- molecular weight ≈ 132 000
- binds 6 Cu^{2+}
- serum concentration is ≈ 0,3 – 0,6 g/l (blue color)
- binds 95 % Cu^{2+} present in the blood, the remaining 5 % is transported by albumin
- the binding of Cu is weak (albumin is primarily responsible for transport of Cu^{2+} to tissues)
- oxidizes Fe^{2+} to Fe^{3+}
- belongs to the acute phase reactants

- **importance**
  - is necessary for oxidation of Fe^{2+} to Fe^{3+} in blood (plasma soluble feroxidase)
    - is needed for redistribution of Fe between the liver and other organs
  - the ceruloplasmin analog (hepestin) acts similarly in enterocytes, oxidizing of Fe^{2+} to Fe^{3+}
  - low level in Wilson‘s disease
  - enzymes requiring Cu^{2+}
    - cytochrome C oxidase
    - superoxide dismutase
    - lysyl oxidase
    - tyrosinase
    - ascorbic acid oxidase
    - dopamine beta-hydroxylase

Metabolism of Cu

- 4 - 6 mg Cu per day in the food, about 40 % is absorbed and approximately the same amount is returned to the intestine via the bile
- Cu^{2+} is rapidly resorbed in the stomach and small intestine and enters the portal vein, binding to albumin
- liver uptake (mechanism is unknown)
- the liver is the central organ of CU homeostasis
  - Cu is deposited here, gets into the blood an the form of ceruloplasmin and is excreted in the bile
- **Wilson's disease**
  - dysfunctional P-ATPase, which transports Cu into the bile
  - accumulation of Cu in the liver and other tissues (liver damage)
  - neurological symptoms (accumulation of Cu in the basal ganglia)
  - the result is low ceruloplasmin plasma levels (Cu does not bind to apoceruloplasmin)
  - the concentration of Cu^{2+} in serum and urine is increased
- **Menkes' s disease**
  - dysfunctionalCu- P-ATPase in enterocytes and other cells (not in the liver)
  - broken resorption of Cu from the intestine
  - deficiency of Cu in serum, accumulation in cells
- α_2-macroglobulin
  - binds trypsin, elastase and other proteases
  - mechanism of action: closes protease into the pocket

Acute phase proteins

- plasma levels of some proteins increase during inflammation (or in some tumors)
  - induced by cytokines (interleukins, TNF,…), which enter the bloodstream from macrophages, epithelial cells, fibrocytes

- have specific functions
  - for example: inflammatory process regulators
  - inhibitors of proteolytic processes
  - immunomodulators…

- **Representatives**
  - α_1- acid glycoprotein (orosomucoid) – inhibits trypsin, elastase and other proteases, ↑ inflammation, tumors – development of emphysema (lungs lose elasticity)
  - α_1-antitrypsin
  - haptoglobin
  - ceruloplazmin
  - fibrinogen
  - C-reactive protein
  - procalcitonin
  - cytokines (IL-6, IL-8, TNF-α)
  - neopterin
  - elastase
  - phospholipase A_2

Acute phase proteins

C-reactive protein

- synthesis in the liver
  - is stimulated by cytokines
- molecular weight ≈ 100 - 115 000, β-fraction
- part of the molucule is homologous to the constant part of the Ig heavy chain
- activates the complement system
  - binds C-polysacharide from pneumococci
- concentration in healthy human is low
  - increase 6 – 9 hours after the onset of inflammation
  - peak after 1 – 3 days
- an increase occurs especially in bacterial infection
  - for viral infections is the increase small
  - marker of bacterial infection

Procalcitonin

- calcitonin precursor
- forms in thyroid C-cells
- in bacterial infections as well as in monocytes, macrophages and neurocrine cells
- acute phase reactant
- serum concentration increases already within 2 – 3 hours (20 times)
- biological half-life **24 hours**
- is considered to be a parameter of inflammation with a greater resolution than other acute phase reactants

Complement proteins

- a complex of proteins (20) contained in the inactive form in plasma
- factors of non-specific humoral immunity
- activation (antigen-antibody, bacterial wall polysaccharide reaction to C3b)

Vascular endothelium

Description

- ~ 1% of the total body weight
- the largest organ of the body with secretory function
- total area of endothelium ~ ? 350 m^2
- Importance
  - regulation of blood flow
  - blood vessel tone platelet activation
  - adhesion of monocytes to the vessel wall
  - thrombogenesis
  - lipid metabolism
    - modification of lipoproteins
  - vascular growth and adjacent smooth muscle
  - presence on the surface of many receptors

- **The endothelium is a large and very active endocrine organ.**

- **morphological barrier between blood plasma and interstitial space**

Damage

- membrane damage
  - release of membrane proteins
- whole cell damage
- release of cellular proteins (TM, TFPI , vWF)
- contributes to damage
  - high blood pressure
  - turbulent flow in arteries
  - infiltration of endothelium by immunocomplex
  - disorders caused by excessive accumulation of organic substances (thesaurusism)
- for example, damage could cause
  - higher levels of LDL, especially glycated LDL in diabetics
  - higher homocysteine levels
  - tobacco smoke
  - lack of oxygen in the body
  - cytostatics
  - ionizing radiation

HEMATOPOIETIC TISSUE

Hematopoietic tissue

- there is an intensive cell division
- derived from **pluripotent hematopoietic stem cells**
  - partially differentiate
  - they produce **unipotent hematopoietic stem cells**
    - give rise to a certain blood lineage
- other cells (morphologically identifiable) are present in hematopoietic organs and blood
- under normal conditions, their losses are offset by their new creation
  - erythrocytes
  - granulocytes
  - lymphocytes
  - platelets

Stem cells

- required specific humoral factors influence to proliferate and differentiate
  - growth factors
  - cytokines
    - erythropoietin
    - thrombopoietin and others

- Hematopoietic disorders
- defect at the level of plural- or unipotent stem cells
  - leukemia
  - aplastic anemia

- defect at the level of maturing or mature cells of individual blood series

RED BLOOD CELL DISORDERS

Disorders on the stem cells level

Aplastic anemia (bone marrow depression)

- reduction of cells in blood (**pancytopenia**)
  - reduction in the number of cells of all hematopoietic lineages in the bone marrow except the lymphoid lineage and replacement of the bone marrow with fat cells
  - bone marrow is unable to compensate for the loss of blood cells due to their natural destruction

- consequences
  - fatique
  - emphysema (by reducing the number of erythrocytes)
  - frequent infections (by reducing the number of leukocytes)
  - possible bleeding symptoms (decrease in platelet count)

- Etiology
  - **strain and genetic influences** (in Japan and China there are more aplastic anemias than in Europe)
  - **chemical factors** (substances with a benzene or nitrobenzene ring, some drugs such as chloramphenicol and antirheumatics)
  - **ionizing radiation**
  - **viral infections** (hepatitis A virus)
  - **i mmune reactions** (autoimmune processes, for example production of antibodies against stem cells, action of cytotoxic T lymphocytes)
  - **all effects are transient (stem cells transplatation)**

Paroxysmal nocturnal hemoglobinuria

- Paroxysmal nocturnal hemoglobinuria (PNH)
- **recurrent erythrocyte disintegration at night and urinary excretion of blood strain**
- myeloid lineage stem cells disorder
- Patogenesis
  - defect of a gene producing a protein that is bound to the cell membrane and prevents the lytic effects of complement
  - at night the tendency to develop respiratory acidosis is due to a slight decrease in pH, the complement is activated by an alternative route and therefore hemolysis easily occurs the involvement
  - damage of granulocytes and platelets does not manifest itself significantly (except for more frequent thromboses)
  - sometimes leukemia may develop

Disorders in erythrocytes lineage

- red blood cells
  - part of a cellular restoration systém consisting of stem cells, erythroid cells in the bone marrow and erythrocytes
  - The lifetime is approximately 120 days
  - Disorders of **differentiation** and **maturation** of erythroid cells in hematopoietic tissues is reflected in erythrocyte production
  - Disorders affecting erythrocytes are reflected in the function of hematopoietic tissue
- erythrocytes and the hemoglobin contained therein are part of the physiological oxygen transport mechanism
- determine the amount of oxygen that blood can bind to the lungs and thus the amount of oxygen delivered by the tissue
- the amount in the blood depends on the tissue tension of oxygen
  - the sensor is located in the kidneys and at a reduced amount the **erythropoietin** production gene is activated in the kidneys
    - glycoprotein
    - **growth factor**
    - Increase differentation of unipotent stem cells into the developmental stages of red blood cells

Structures containing Heme

Hemoglobin

- is **hemoprotein** present in the cytoplasm of erythrocytes
- transports **O_2** and **CO_2** between the lungs and various tissues
- heme belongs to cyclic tetrapyrols (porphyrins)

- Physiological concentrations of Hb in the blood:

Adults:

men 135 – 175 g/l

women 120 – 168 g/l

Myoglobin

- is a single-stranded globular protein
  (153 amino acids, 17 kDa) containing 1 heme
- stores and transports **O_2** in **skeletal and cardiac muscle**
- contained in the cytosol of cells
- marker of myocardial damage in ischemic heart disease
- **α-helix 75 % of the molecule, A-H (8 α-helices),**
- **suface is polar**
- **inside non-polar except His E7-distal, His F8-proximal , HYDROPHOBE POCKET**

Deriváty hemoglobinu

- **Oxyhemoglobin** (oxyHb) = Hb with bounded O_2
- **Deoxyhemoglobin** (deoxyHb) = Hb without bounded O_2
- **Methemoglobin** (metHb) – contains **Fe^{3+}** instead of Fe^{2+} in the heme group
- **Carbonylhemoglobin** (HbCO) – CO binds to Fe^{2+} heme in case of CO poisoning or smoking. CO has 200x higher affinity for Fe^{2+} than O_2.
- **Carbaminohemoglobin** ($HbCO_2$) - CO_2 is noncovalently bound to the globin chain of Hb. $HbCO_2$ transports CO_2 in the blood (about 23%).
- **Glycated hemoglobin** (HbA1c) **is produced by a spontaneously nonenzymatic reaction with Glc (globins).** Patients with DM have higher concentrations of HbA1c
  - (› 7%) than healthy people due to prolonged hyperglycaemia.

Hemoglobin concentration in blood

- is closely related to the number of red blood cells and depends on the ratio between the amount of extinct and newly produced erythrocytes

- **decrease of erythrocytes formation** or **increased extinction**
  - decrease in hemoglobin concentration in blood
  - causes **anemia**

- **increased erythrocytes formation** beyond their **extinction or decreasing plasma volume**
  - arises **polycythemia (polyglobulia)**
  - **blood hemoglobin concentration increases**

Anemia

- **decrease in hemoglobin concentration in blood volume unit**

- according to the size of the erythrocytes
  - **normocytic**
  - **microcytic** (smaller erythrocytes)
  - **macrocytic** (bigger erythrocytes)

- according to the hemoglobin content in the area
  - **normochromic**
  - **hypochromic** (with less amount of hemoglobin)
  - **hyperchromic** (with more amount of hemoglobin)

- the etiological point of view better describes the pathogenesis of anemia
  - **anemia from decreased erythrocyte formation**

  - **anemia due to increase erythrocyte loss**

Anemia from decreased erythrocyte formation

- **1. Anemia induced by erythropoietin deficiency**
  - **often accompanies with:**
    - chronic kidney disease, malnuttrition, anemia in immature newborns, reduction of pituitary or thyroid function

- **2. Anemia caused by a cellular disorders of hematopoietic tissue**
  - toxic damage to bone marrow cells
  - aplastic anemia
  - anemia caused by ionizing radiation

- **3. Iron deficiency anemia**
  - transferrin
  - Fe deposited as ferritin and hemosiderin
  - by reducing synthesis, by reducing the ability to respond to anemia

- **4. Folic acid and vitamin B_{12} deficiency anemia**
  - vitamin B_{12} is necessary to maintain a constant level of tetrahydrofolate
  - folic acid is essential for nucleotide synthesis

Anemia due to increased erythrocyte loss

- **1. Acute blood loss**
  - a loss of 500 to 1000 ml of blood is well tolerated
  - for larger losses → shock

- **2. Chronic blood loss**
  - most often into the gastrointestinal tract
  - associated with loss of iron
    - development of anemia (breakdown of erythrocytes in spleen and macrophages)

- **3. Haemolytic anemia**
  - A. Haemolytic anemia caused by an internal erythrocyte defect
    - A.1 Hereditary spherocytosis (hereditary disease)
    - A.2 Disorders of erythrocyte metabolism (earobic and anaerobic glycolysis – pyruvate kinase, glukose phosphoisomerase and triosephosphoisomerase)
    - A.3 Hemoglobinopathy
    - A.4 Paroxÿsmal nocturnal hemoglobinuria
  - B. Haemolytic anemia caused by erythrocyte damage by external factors
    - burns, poisoning, mechanical damage

Polycystemia

- the concentration of hemoglobin and erythrocytes in the blood volume unit may be increased
  - relatively
    - with reduced plasma volume
  - absolutely
    - with an increased erythrocytes amount in the blood
      - primary polycythaemia
      - secondary polycythaemia

WHITE BLOOD CELL DISORDERS

Disorders on the stem cells level

White blood cell disorders

- basic function of white blood lineage
  - specific immune response of the individual
  - non-specific immune response of the individual
    - disposal of corpuscular particles and bacteria
    - formation of antibodies
    - mediating of tissue immunity
- production from myeloid pluripotent hematopoietic stem cells
  - granulocytes
  - cells of the monocyte-macrophage system
  - erythrocytes
  - megakaryocytes
- are produced by proliferation and differentiation of multi- (toti-) potent hematopoietic stem cells and proliferation and differentiation of precursors in thymus and lymph nodes
  - lymphocytes
- the proliferation and differentiation of white blood cell lineage is determined by the activation of cytokines
  - GM-CSF
    - a growth factor affecting the formation of granulocytes and macrophages
  - G-CSF
  - M-CSF
  - interleukins
    - T- a B-lymphocytes
  - tissue growth factors

Function of granulocytes and monocytes

- neutrophil granulocytes
  - disposal of foreign material
  - ability to migrate to the site of infection
  - the ability of phagocytosis
  - the ability to destroy phagocytosed bacteria
- eosinophilic granulocytes
  - elimination of substances releasing at the meeting of the individual with the antigen
    - histamine
    - 5-hydroxytryptophan
    - bradykinin
- basophilic granulocytes
  - the function is not fully clarified
- monocytes
  - circulating part of mononuclear phagocytic system
  - arise in the bone marrow, transfer to the blood and migrate to tissues, where they turn into tissue **macrophages**
  - Kupffer cells in the liver
  - Langerhans cells in the epidermis
  - peritoneal (abdominal) macrophages
  - osteoclasts
  - microglia cells
  - Function
    - defense against microorganisms
    - removing of old and damage cells
    - defense against tumor formation and metastasis
    - production of biologically active substances (including cytokines)
    - produce proliferation inhibitors (prostaglandins PGE_1 a PGE_2)

Neutropenia

- causes
  - granulocytosis in newborns and young children
  - in pregnancy
  - during hard physical work and strenuous sports erformance
  - infectious disease (bacterial) or inflammation
  - diseases associated with steile inflammation or tissue necrosis
    - heart-attack
    - muscle inflammation
  - endogenous intoxication
    - diabetic coma
    - uremic coma
    - gout
    - lead poidoning
    - administration of some drugs and hormones
  - tumors
  - acute blood loss and haemolysis
  - stress

- the pathogenic stimulus causes an increased need for granulocytes in the tissues
  - transfer of cells from marginal cash
  - already formed granulocytes from the bone marrow are washed into the blood
  - young cells in the blood adhere to the vessel wall
  - replenish intravasal volume
  - at the same time, the production of CSF increases and newly formed granulocytes appear in the blood in about 6 – 8 days

- stress
  - marginal leukocytes transfer to intravasal cash
  - the amount of circulating granulocytes increases
    - granulocytosis after adrenalin washout, in the early stages of irradiation
  - the effect of ACTH and glucocorticoids on the increase in granulocyte counts is due to accelerated leaching of granulocytes from the bone marrow and slowing the movement of cells to marginal volume

Eozinophilia

- accompanied with
  - allergic reactions
  - parasitic infections
  - insufficient adrenal cortex function
  - hypo- and hyperfunction of the thyroid gland
  - neoplasmic processes

Bazophilia

- accompanied with
  - some infectious diseases
  - haematological diseases
    - chronic myeloid leukemia
    - Hodgkin's disease
    - true polycythaemia
    - chronic haemolytic anemia

Monocytosis

- in some diseases an important diagnostic indicator
  - endocarditis
  - tuberculosis
  - infectious hepatitis
  - Hodgkin's disease
  - and others

- **infectious mononucleosis**
  - viral disease
  - Ebstein-Barr virus
  - cytomegalovirus
  - cells resembling monocytes are multiplied in the blood
    - atypical lymphocytes

Neutropenia

- the number is decreasing
  - in their **reduced production**
    - bone marrow depression
    - reduction of growth factor production
    - ineffective granulopoiesis
      - cell maturation diorders
- **increased blood clearance**
  - increased cell transfer to marginal volume
  - the initial stages of infectious diseases
  - increased spleen activity
    - hyperspleenism
    - in leukemia, lymphomas and spleen enlargement (spleenomegaly)
  - formation of autoantibodies against leukocytes

Eozinopenia and basopenia

- reducing the number of **eosinophilic** granulocytes
  - marrow suppression
  - increased production of ACTH and glucocorticoids
  - after glucocorticoid therapy

- **basophilic** granulocytes
  - small amounts in the blood
    - the reduction is inaccurately determined

Leukemia

- malignant hematopoietic cell proliferation
- characterized by **maturation arrest and uncontrolled proliferation** of cells from white blood lineage
- monoclonal character
  - a pathological cell population (cell clone) is derived from one cell in which a functionally significant mutation has occurred
- leukocytes under normal conditions lose differentiation proliferative ability
- in leukemia, maturation is stopped at a certain stage of development and immature cells appear in bone marrow and blood (different types of blasts in acute forms) or in chronic forms, more or less mature cells accumulate
- the classification is based on
  - from cell morphology
  - presence of specific differentiation traits
- from clinical point of view
  - acute
  - chronic

Leukemia

- Etiology
  - genetic factors
  - congenital genetic defects accompanied by chromosomal aberrations (Down syndrome)
    - higher incidence of leukemias
  - children of parents with leukemia
    - the same as in the other population
  - most defects that increase the possibility of leukemia are acquired
  - influence of ionizing radiation
  - exporure to chemicals
    - compounds with benzene and nitrobenzene ring
  - exposure to viruses
    - animals: RNA viruses
    - humans: so far only indirect evidence

- Pathogenesis
  - leukemogenic factor (mutagen) alters the hematopoietic stem cell gene equipment, resulting in a pathological cell clone
  - with impaired differentiation, maturation and abnormal proliferation

Leukemia

- Myelodysplastic syndrome
  - preleukemic state
  - cells of the myeloid lineage are affected
  - only ineffective hematopoiesis
- Chronic myeloid leukemia
  - cells of the myeloid lineage are affected
  - associated with:
    - increased bleeding
    - hepatic function impairment
- Acute myeloblastic leukemia

Disorders of lymphocyte function

- **Production disorders**
  - Lymphocytosis (increased lymphocyte amount)
  - Lymphopenia (decreased amount and lymphocyte production or increased loss)

- **Lymphoproliferative diseases**
  - Acute lymphoblastic leukemia
    - childhood
  - Chronic lymphocytic leukemia
    - older age, proceeding slowly
  - Malignant lymphomas
    - lymph nodes
  - Hodgkin's disease (malignant lymphogranuloma)
    - a characteristic for age group of 15 – 34 years old and then up to about 50 years old
    - first the neck area, then the lymph nodes and then the bone marrow is affected
  - Non-hodgkin's lymphomas
    - B-lymphocytes

- **Monoclonal gammopathy**
  - B-lymphocytes
  - kidney failure
  - presence of monoclonal immunoglobulins

HEMOSTASIS

Hemostasis

- a process that follows a disruption of vascular integrity
- blood vessels, platelets and hemocoagulation are involved in haemostasis
- the result is a clogging (lesion overlap) in the vessel within minutes

- **Hemostasis has four phases:**

  1. constriction of blood vessels

  2. creation of a „provisional plug“ (white thrombus)

  3. fibrin network formation – self clotting (stoppet stabilization)

  4. thrombus dissolution by plasmin

- **Primary hemostasis**
  - vasoconstriction (immediately)
  - platelet adhesion (tenths to units of seconds)
  - platelet aggregation (seconds to minutes)

- **Coagulation system**
  - factor activation (seconds to minutes)
  - fibrin formation (minutes)

- **Fibrinolysis**
  - activation of fibrinolysis (minutes)
  - clot lysis (hours)

Platelets

- nuclear-free cell fragments, platelets have mitochondria
- formation of fragmentation from megakaryocytes of bone marrow (pluripotent stem cells → myeloid stem cells → megakaryocyte → thrombocyte)
- the main regulator of production is **thrombopoietin** (production in the liver, kidneys)
- discoid shape maintained by cytoskeleton (actin a myosin)
- the energy source is glycolysis
- contain granules with specific substances
  - dense granules: ADP, ATP, serotonin, Ca^{2+}
  - alpha granules: vWF, fibrinogen, PDGF, thromboxane A_2, PAF….
- average lifetime is 10 days, then breakdown in the spleen
- during adherence to the vascular wall the platelets change their shape – pseudopodia appear, release granules

- Function of platelets during hemostasis
  - Adhesion
  - Aggregation
  - Constriction
  - Thrombus formation
  - Healing
- **Platelet activation involves shape changes. increased movement, volume in granula release, aggregation and adhesion**

- under physiological condition, the platelets are not in contact with the endothelium
- vascular wall damage → exposure of collagen in the subendothelial layer → adhesion of platelets to collagen via specific membrane receptors (integrin, cell adhesion molecule, glycoprotein IV and so on) and vWF
- by binding to collagen, the platelets are activated
  - reorganization of cytoskeleton (actin polymerization),
  - change of shape
  - creating of pseudopodia
- induction of phospholipase C by collagen → release of arachidonic acid → release of TXA_2 → support of aggreagation
- **thrombin** binding to receptors on platelet surface → activation of phosphatidylinositol system
- DG activates the pleckstrin protein → aggreagation and release of secretory granules
- among released molecules is ADP → activation of other platelets, their adhesion to the platelet layer of platelets
- negatively charged phosphatidylserine (srambling) is expressed in the outer layer of the phospholipid membrane
- platelet eggregation (fibrinogen binds to and binds fibrinogen glycoproteins IIb, IIIa)
- serotoninu release, PGDF – vasoconstriction
- platelets provide a surface for activating the coagulation mechanism

Platelets

Coagulation factors

- mostly synthesized in the liver and released into the blood in the form of inactive precursors
- factor VIII (and probably IX and XII) synthesis also in the spleen
- Von Willebrand faktor – endothelial cells, platelets
- bind to negatively charged surface phospholipid membranes of platelets, erythrocytes, leukocytes and endothelial cells
- Ca^{2+} is also required for binding

Clotting factors

- many clotting factors are zymogens (inactive precursors) of serine proteases
- (XII, XI, IX, VII, X, II, thrombin)
- are activated by hydrolytic cleavage of a portion of the peptide chain
- zymogen becomes and active by protease
- amplification effect

Platelets

The role of vitamin K in blood clotting

- vitamin K is essential for the formation of coagulation factors II, VII IX and X

- acts as a cofactor in the carboxylation of N-terminal glutamyl residues to γ-carboxyglutamate (post-translation modifications)

Clot control

- blood clotting must remain confined to the local reaction
- the thrombin concentration must be controlled
- there is a balance between activation and inhibition at each stage of the cascade

- coagulation inhibitors
  - thrombin inhibiting antithrombin
  - control of clotting by thrombomoduline – protein C system
  - Tissue factor protein inhibitor (TFPI)

Blood coagulation disorders

- Increased bleeding
  - **Vitamin K deficiency**
    a problem with vitamin resorption, for example lack of bile acids, in obstruction or liver disorders
  - **Haemophilia** (most often abnormality or lack of factor VIII – type A haemophilia or factor IX) only men
  - **Thrombocytopenia** (thrombocyte deficiency)

- The most common patterned coagulopathy
- **vWf**
  - Von Wilebrand's disease

- **Clotting factor VIII**
  - Haemophilia A
  - recessively inherited, associated with X chromosome

- **Clotting factor IX**
  - Haemophilia B
  - Recessively inherited, associated with X chromosome

THANK YOU FOR YOUR ATTENTION