MUNI
MED

Physiology of blood. Blood types. Immune system.

Budínská Xenie

Final exame questions

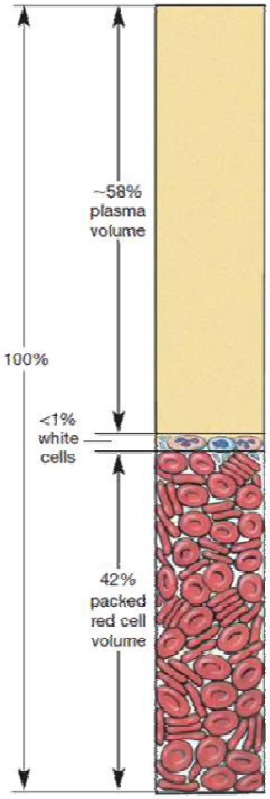
- 76. Blood composition – values
- 77. Red blood cell. Haemolysis.
- 78. Haemoglobin and its derivatives
- 79. Suspension stability of RBC (sedimentation rate)
- 80. Mechanism of innate immunity
- 81. Acquired immunity
- 82. Blood groups antigens
- 83. Function of platelets
- 84. Hemocoagulation
- 85. Anticlotting mechanism

Functions of the blood

- homeostatic function
  - buffering
  - thermoregulation (transport of heat)
- transport of substances
  - blood gases
  - nutrients
  - metabolites
  - vitamins
  - electrolytes
- humoral control of organism (hormones)
- defence of organism (immune functions)
- blood clotting

Basic characteristics

- Suspension character
- 6 - 8% total body mass
- 55% - fluid phase (plasma)
- 45% - formed phase (blood cells)



This table lists the normal ranges of values.

	MALES	FEMALES
Hematocrit		
Hematocrit is the percentage of total blood volume that is occupied by packed (centrifuged) red blood cells.	40–54%	37–47%
Hemoglobin (g Hb/dL* whole blood)		
The hemoglobin value reflects the oxygen-carrying capacity of red blood cells. (*1 deciliter (dL) = 100 mL)	14–17	12–16
Red cell count (cells/μL)		
A machine counts erythrocytes as they stream through a beam of light.	4.5–6.5 x 10^3	3.9–5.6 x 10^3
Total white count (cells/μL)		
A total white cell count includes all types of leukocytes but does not distinguish between them.	4–11 x 10^3	4–11 x 10^3
Differential white cell count		
The differential white cell count presents estimates of the relative proportions of the five types of leukocytes in a thin blood smear stained with biological dyes.		
Neutrophils	50–70%	50–70%
Eosinophils	1–4%	1–4%
Basophils	<1%	<1%
Lymphocytes	20–40%	20–40%
Monocytes	2–8%	2–8%
Platelets (per μL)		
Platelet count is suggestive of the blood's ability to clot.	150–450 x 10^3	150–450 x 10^3

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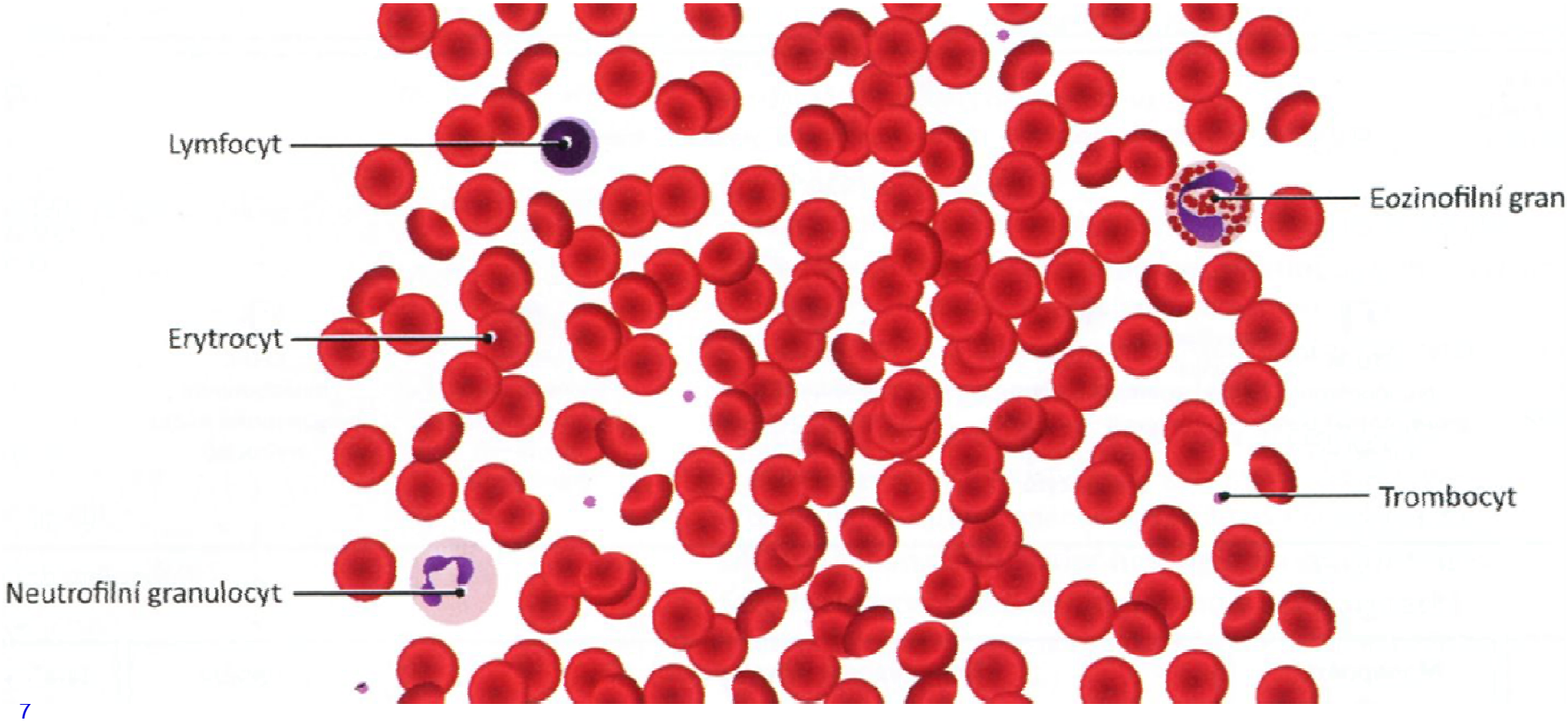
Blood plasma. Inorganic substances

- Na^+ (137-147 mmol/l): osmotic pressure, volume, pH
- Cl^- (98-106 mmol/l): osmotic pressure, volume, pH
- K^+ (3,8-5,1 mmol/l): muscle aktivity
- Ca^{2+} (2,1-2,7mmol/l): nerve excitability, muscle aktivity, blood clotting, membrane permeability, bone mineralization
- P (0,65-1,62 mmol/l): pH regulation, bone mineralisation
- Mg^{2+} (0,75-1,25 mmol/l): enzyme activity, nerve excitability
- HCO_3^- (25-34 mmol/l): CO2 transport, pH maintenance
- Fe (16-25 µmol/l): part of haemoglobin - gas transport
- I (275-630 nmol/l): thyroid hormone production

Blood plasma. Organic substances.

- Plasma proteins 60-80 g/l
  - Albumins (40-48 g/l): oncotic pressure, transport of ions, fatty acids, hormones
  - Globulins (18-30 g/l)
    - α-globulins: transport of hormones, metals, vitamins
    - β- globulins: heme binding, vit. B12, iron, cholesterol transport
    - γ- globulins: antibodies, specific immunity
  - Fibrinogen (3 g/l): blood clotting
- Lipids (4-10 g/l)
- Glucose (4-5,5 mmol/l)
- Nitrogen substances (0,2-0,4 g/l): urea, bilirubin, amino acids
- Hormones, vitamins, enzymes, drugs

Formed blood elements



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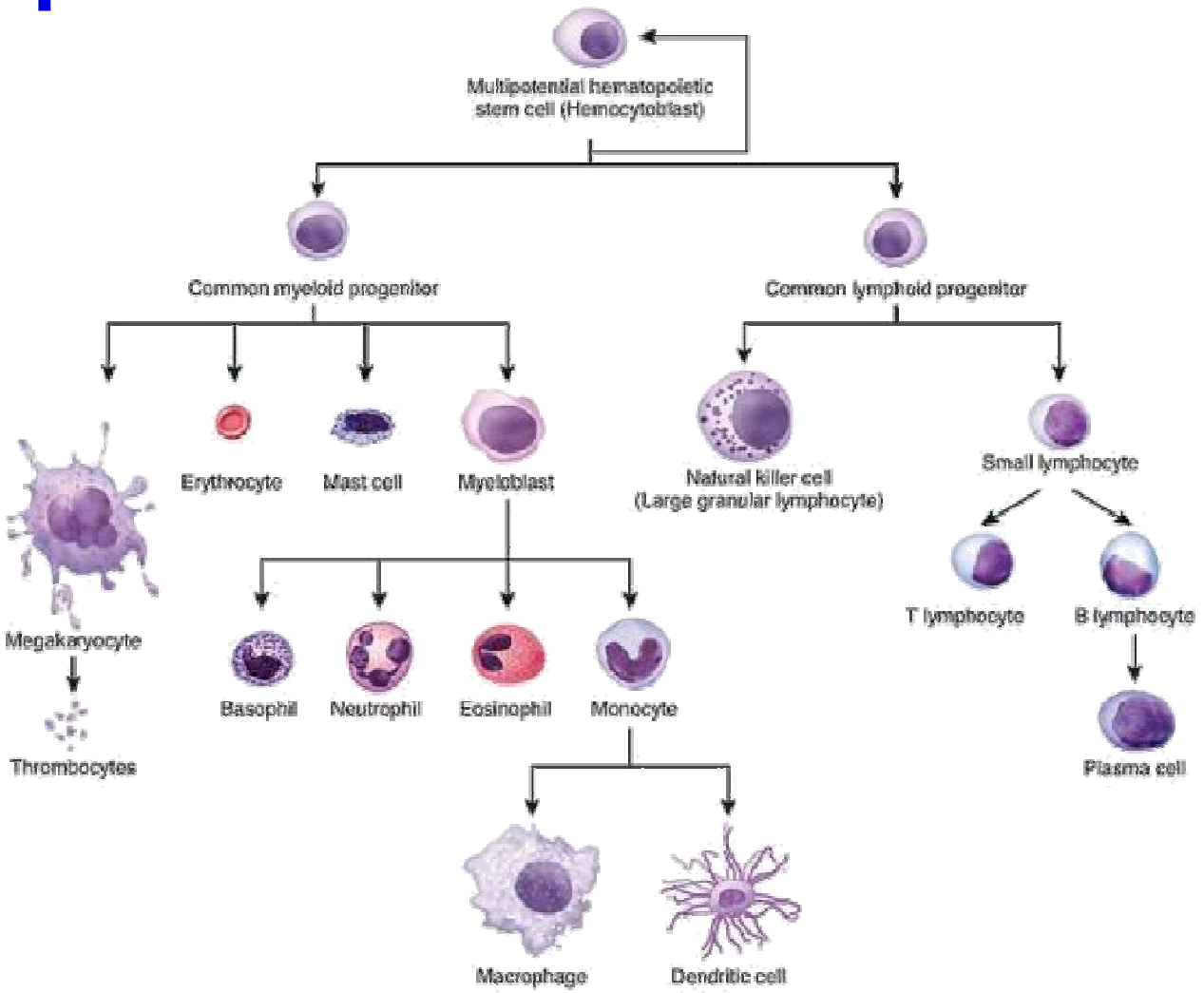
Haematopoiesis



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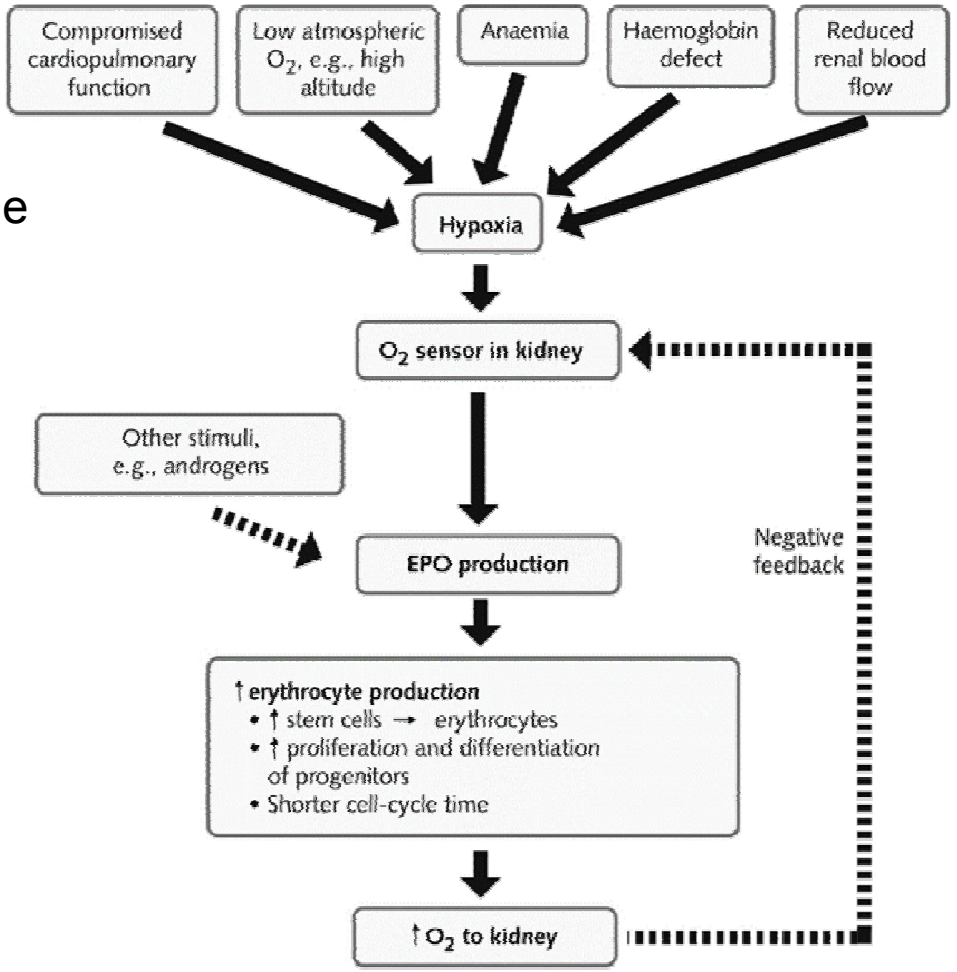
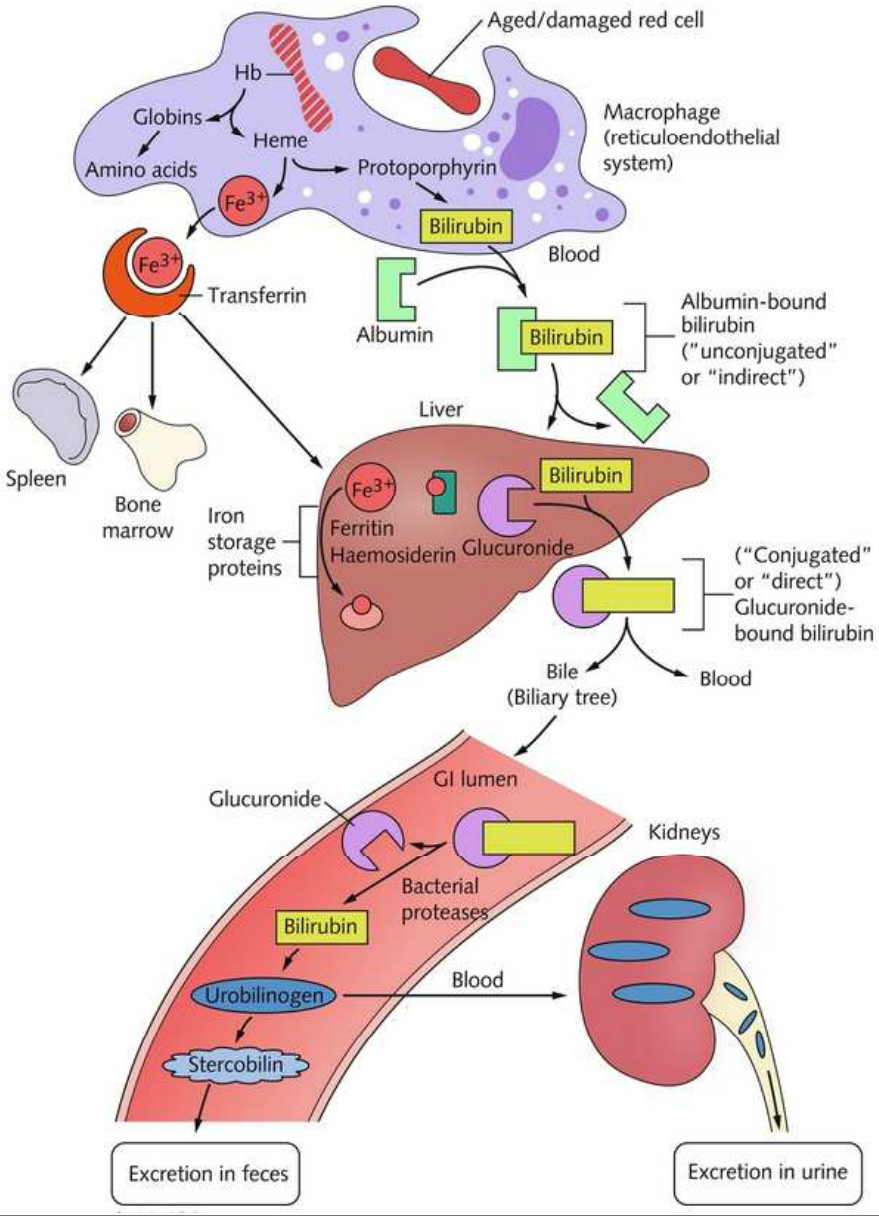
Erythropoiesis

- Erythropoietin - formation in the kidneys
  - acts on sensitive determinate progenitor cells in the bone marrow
  - stimulates nucleic acid synthesis
  - activates genes required for haemoglobin synthesis
  - increases Fe intake
- Substances needed for erythrocyte production
  - amino acids: the protein part of haemoglobin
  - iron: binding of oxygen to haemoglobin and myoglobin
  - vitamin B12: essential for DNA synthesis
  - Folic acid: essential for DNA synthesis



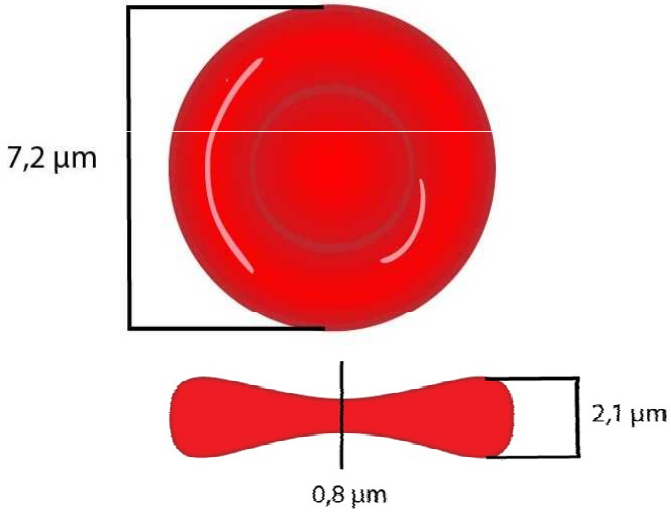
Extinction of red blood cel

- Spleen: phagocytosis of old and damaged erythrocytes
- Hemoglobin=globin+hem
- Globin – amino acids
- Hem=CO2+Fe+biliverdin
- Fe – synthesis of additional hemoglobin



Red blood cell

		Men	Women
Hematocrit (Hct) (%)		47	42
Erythrocytes (RBC) (10^6/µl)		4,5 - 6,3 x10^6	4,2–5,4x10^6
Haemoglobin (Hb) (g/l)		140 - 180	120 - 160
Mean volume of ery (MCV) (fl)	= Hct x 10 / RBC (10^6/µl)	82 - 97	82 - 97
Mean content of Hb in ery (MCH) (pg)	= Hb x 10 / RBC (10^6/µl)	27 - 33	27 - 33
Mean concentration of Hb in ery (g/100ml)	= Hb x 100 / Hct	32 - 36	32 - 36
Mean diameter of ery (MCD) (µm)		7,5	7,5



- biconcave disc - the shape increases the surface by 30%
- shape is ensured by the protein ***spectrin***
- shape plasticity important for penetration through narrow capillaries

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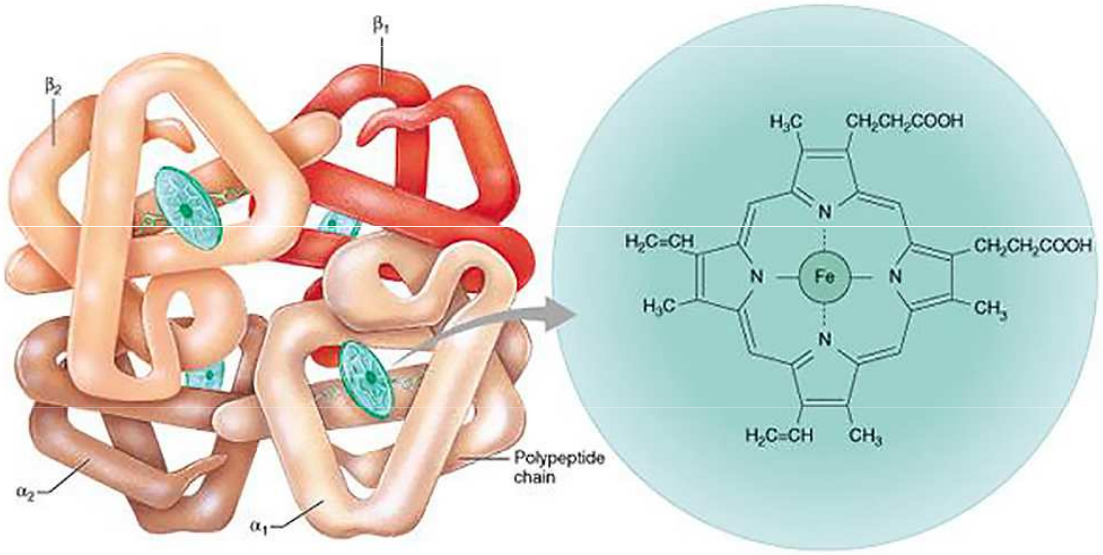
Functions of the RBC

- Transport of respiratory gases
- Buffering system
- Maintaining blood viscosity

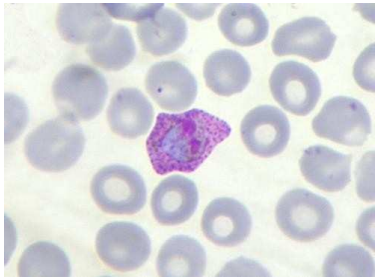
Haemoglobin

- Red pigment transporting oxygen.
- Protein, 64 450, 4 subunits.
- Hem – derivative of porphyrine containing iron, conjugated with polypeptides (globin)
- Types of hemoglobin:
  - Embryonic haemoglobin (t2e2, a2e2)
  - Fetal haemoglobin: Hb F, b2g2
  - Adult haemoglobin: Hb A, a2b2
- Hemoglobin derivative:
  - oxyhaemoglobin - O_2
  - carbaminohaemoglobin – CO_2
  - methaemoglobin – Fe^{3+} in hem
  - carboxyhaemoglobin – CO



Hemolysis

- Breakdown of RBC due to disintegration of its membrane – hemoglobin and intracellular fluid are spilt into the solution
- Physical (mechanical damage):
  - shaking, ultrasound, extreme temperature changes, UV radiation
- Osmotic (hypotonic solution)
- Chemical
  - strong acids and bases, fat solvents, surfactants (detergents)
- Toxic
  - bacterial toxins, poisons (plant, snake, insect, spider), parasites
- Immunological
  - transfusion of incompatible blood



Malaria
(Plasmodium spp.)

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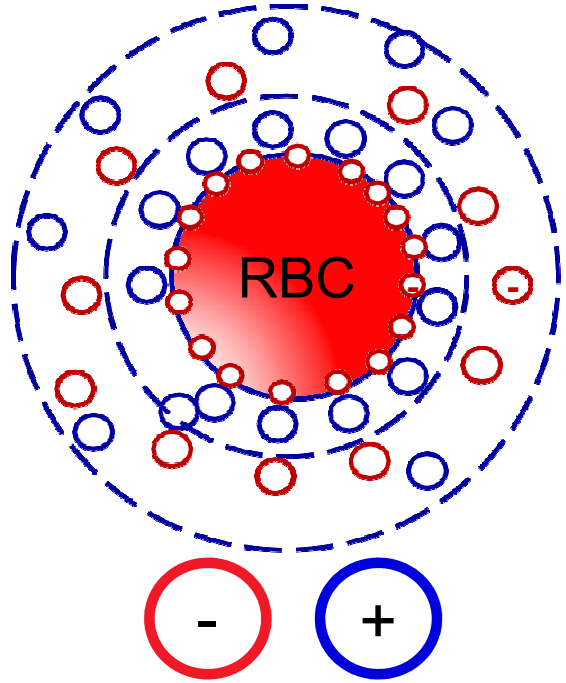
Suspension stability of blood

- Helmholtz electrical double-layer:
  - negative charge on the membrane of RBC (sialic acid)
  - 1st layer: positively charged ions (primarily Na+)
  - 2nd layer: negatively charged ions (Cl-)
- RBCs repel each other => suspension stability
- **Sedimentation rate** indirectly corresponds to suspension stability of blood
- Fahraeus-Westergren (FW) – direct method
  - A glass tube in vertical position
  - Measured after 1 hour (2 hours)
- Wintrobe
  - 100 mm long, thin glass tube in oblique position (45°)
  - Measured after 15 minutes



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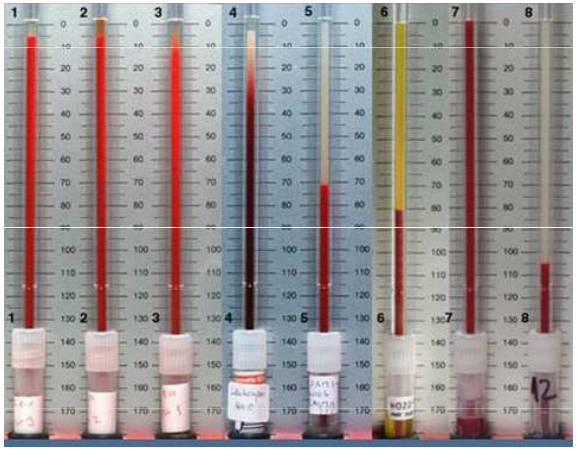
Sedimentation rate

- Men: 2-8 mm/h
- Women: 7-12 mm/h
- Newborns: 2 mm/h
- Infants: 4-8 mm/h



Effect on ESR	↑ value	↓ value
Erythrocytes		
Number of RBCs	decelerates	accelerates
Size of RBCs	accelerates	decelerates
Plasma		
Albumin	decelerates	accelerates
Imunoglobulins	accelerates	decelerates
Fibrinogen	accelerates	decelerates
Lipids	accelerates	decelerates

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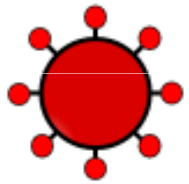
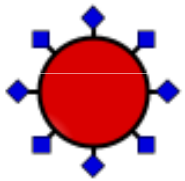
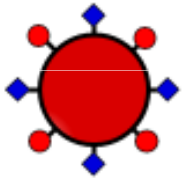
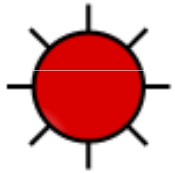
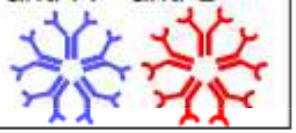
Blood groups

- is a classification of blood, based on the presence and absence of antigenic substances on the surface of red blood cells
- antigens (depending on the blood group system):
  - proteins
  - carbohydrates
  - glycoproteins
  - glycolipids
- some of these antigens are also present on the surface of other types of cells of various tissues

AB0 system

- Antigens on the surface of RBCs (agglutinogens): A, B
- Antibodies in the blood (agglutinins): anti-A, anti-B (IgM)

Blood groups	Group A	Group B	Group AB	Group 0
Prevalence in CZ	41%	18%	9%	32%
RBCs				
Antigens on RBCs	A 	B 	A a B 	none
Antibodies in the blood	anti-B 	anti-A 	none	anti-A + anti-B 

Immunization against A and B happens during the first months of life (these antigens are also in the diet) – agglutinins are then in the blood for the rest of the life

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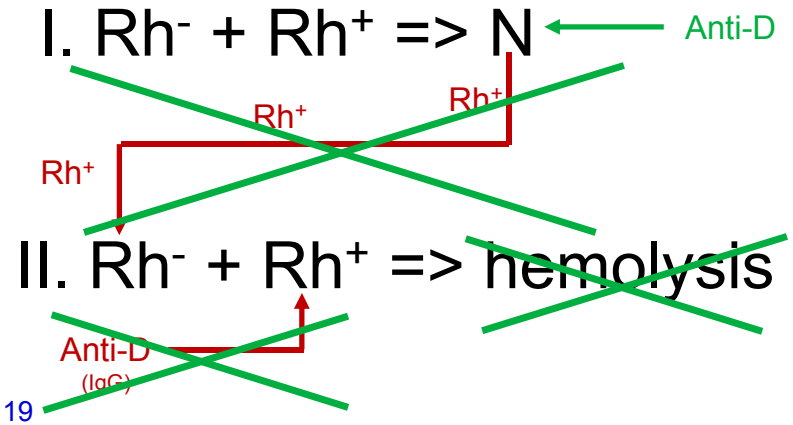
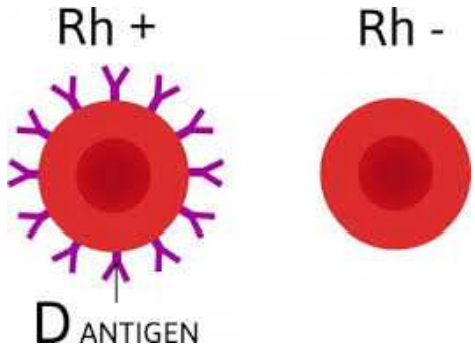
Rh factor

- Antigens D, d (also C,c, E, e, which are weaker) are only on RBCs
  - The strongest one is an antigen D – if present → Rh+ blood group
  - In recessive homozygotes (dd) → blood group Rh- (17% in Europe, <1% elsewhere)
- in Rh- blood, antibodies (anti-D, IgG) develop only after immunization
  - The first reaction is weaker, the next encounter with Rh+ blood will trigger a stronger immune response → hemolysis





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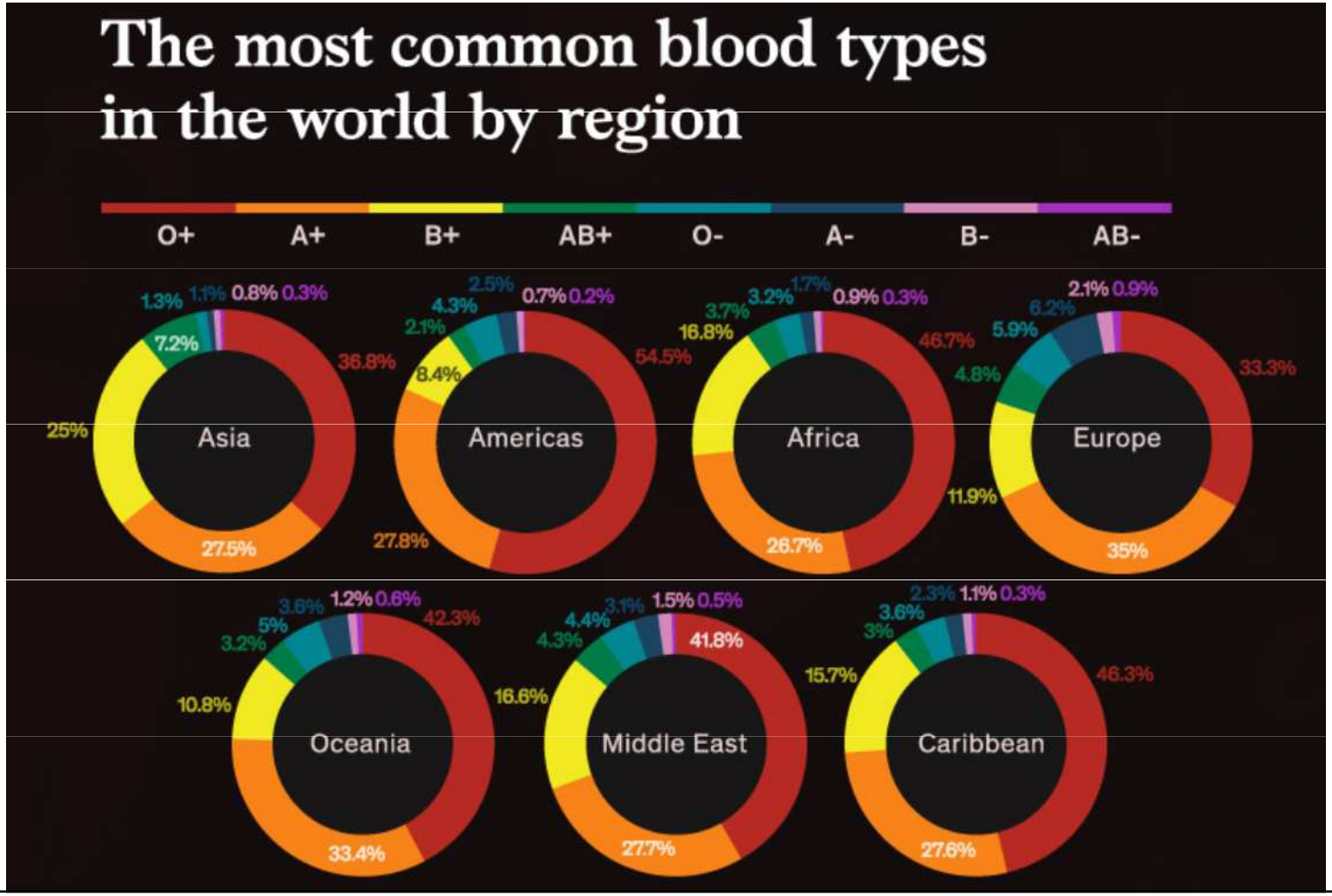
Blood groups



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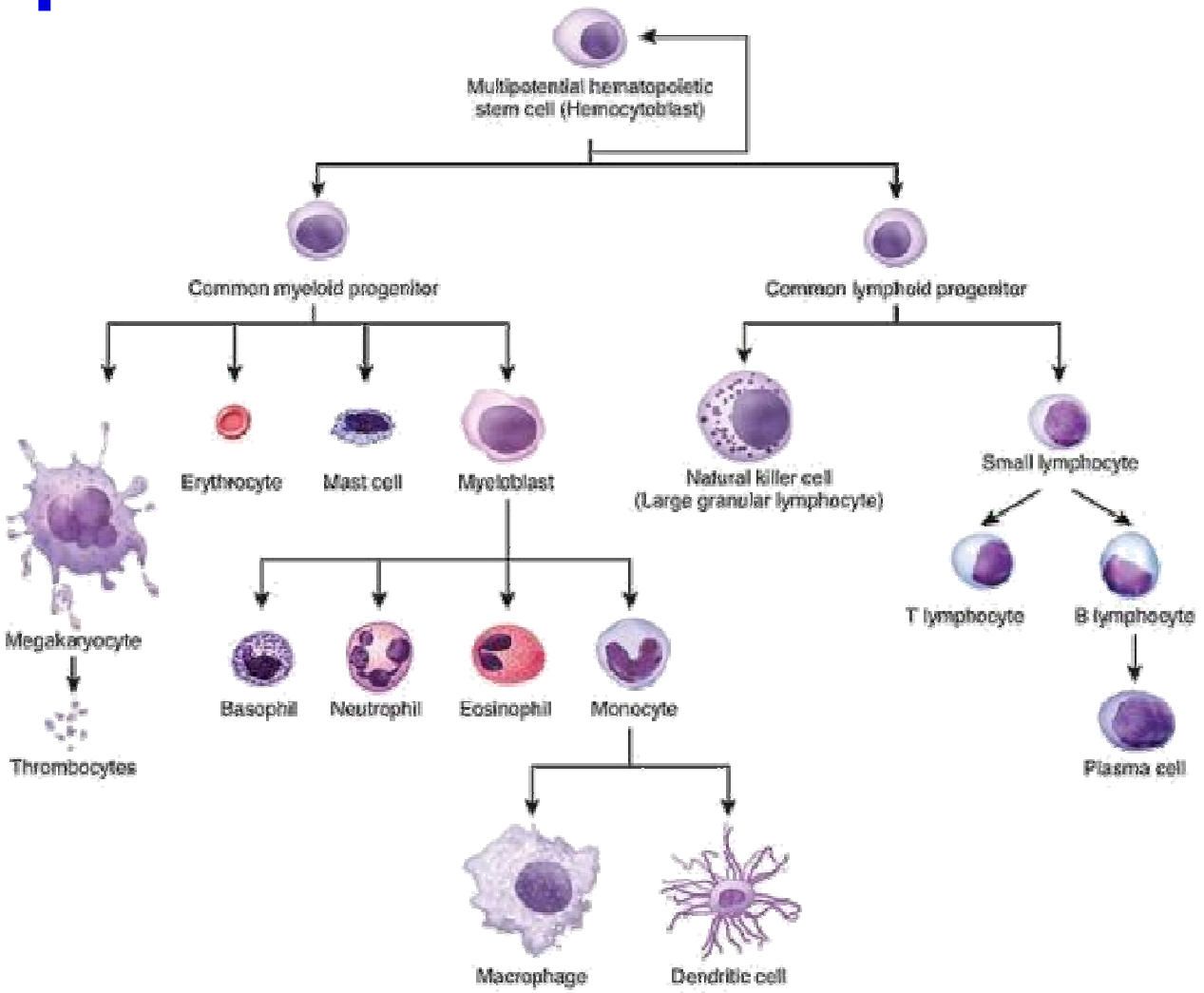
Haematopoiesis



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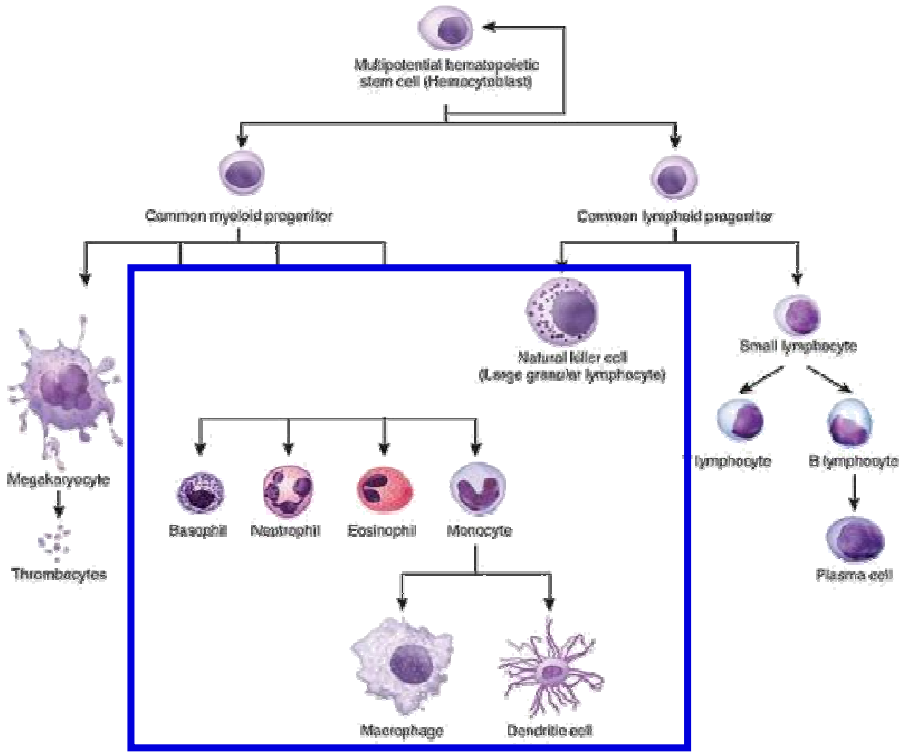
Innate immune system

- already in place
- rapid response
- non-specific pattern response
- functions:
  - physical barriers
  - leukocyte recruitment (inflammation)
  - antiviral defenses
- Parts:
  - physical/chemical barriers
  - phagocytes (neutrophils, macrophages, dendritic cells, mast cells, NKCs)
  - complement



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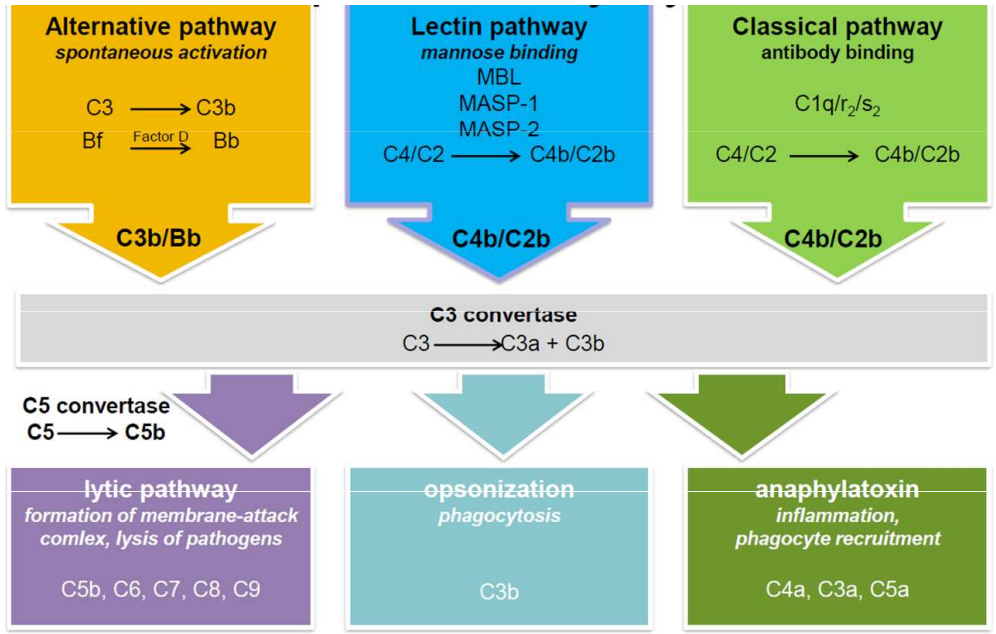
Recognizing invaders

- Pathogen-associated molecular patterns (**PAMPs**):
  - common molecular patterns typically found on pathogens (ex. Bacterial lipopolysaccharides, mannose, viral nucleic acids)
- Damage-associated molecular proteins (**DAMPs**):
  - common molecular patterns found on the surface of injured or dead host cells (ex. Heat shock proteins)
- Pattern recognition receptors:
  - receptors on cells of the immune system that recognize PAMPs and DAMPs
  - when the pattern recognition receptor binds a ligand (PAMP or DAMP) this triggers signal pathway activation → transcription factors → gene expression of inflammatory and antiviral products → recruitment/activation of immune cells

Complement cascade

- system of proteins; part of the innate immune system
- functions:
  - cell lysis (membrane attack complex – MAC)
  - opsonize
  - attract other immunological cells
- complement activation pathways:
  - classical activation pathway
  - alternative activation pathway
  - lectin activation pathway



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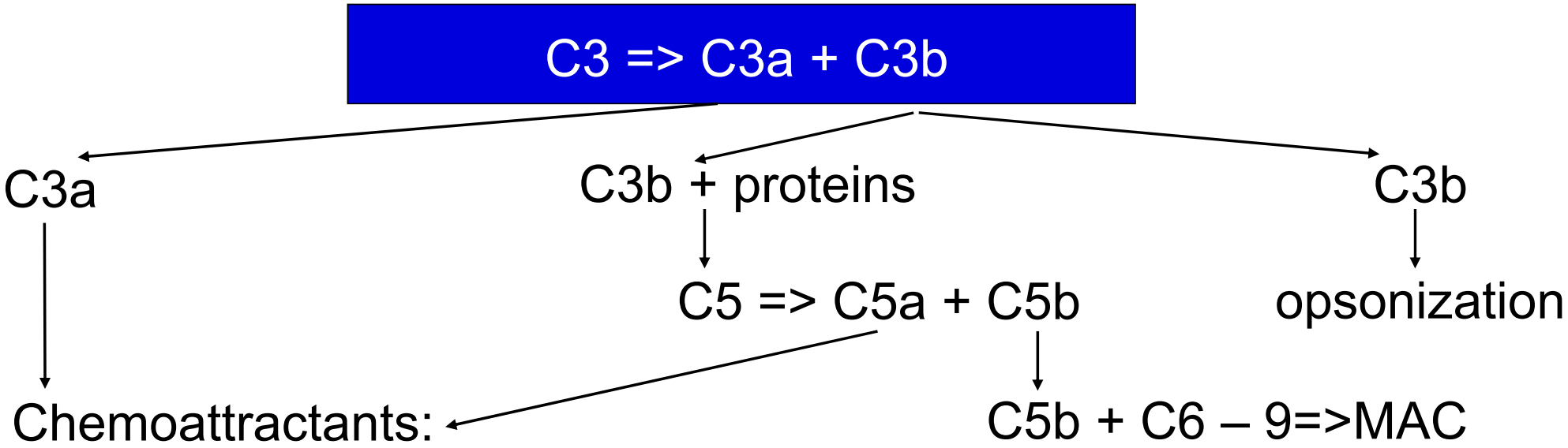
Complement activation pathways

- classical (Ab dependent) complement activation pathway:
  - IgM/IgG brings together multiple C1 complexes
  - inhibitor falls off C1
  - C1 starts cascade that cleaves C3
- alternative (Ab INdependent) complement activation pathway:
  - spontaneous cleavage of C3
- lectin complement activation pathway:
  - mannose binding lectin (MBL) binds mannose on pathogen surface
  - activates MASP
  - MASP cleaves C3

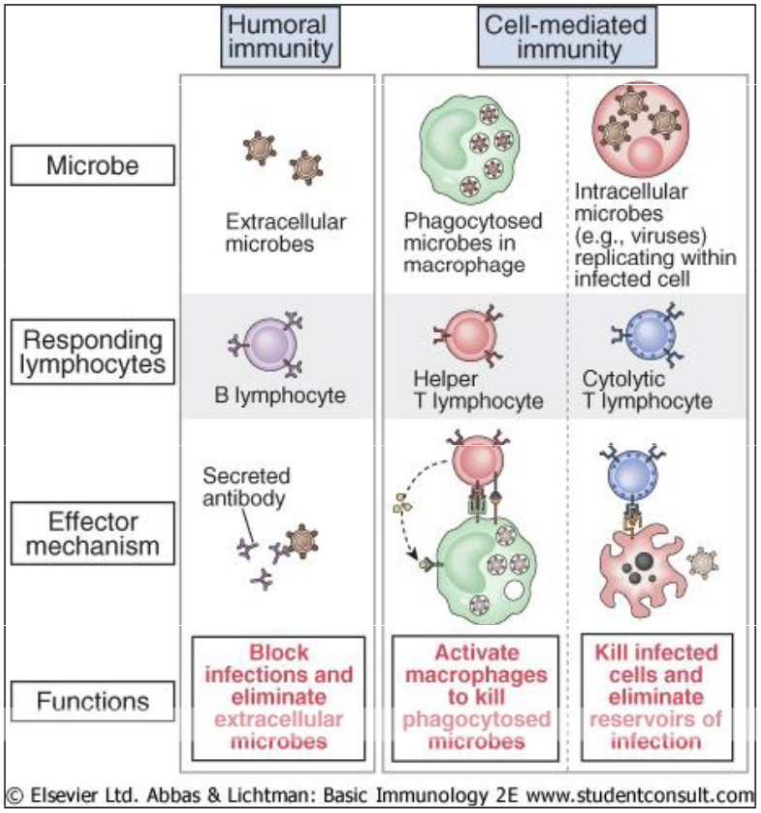
Common pathway



The membrane attack complex (**MAC**) is a complex of proteins typically formed on the surface of pathogen cell. Assembly of the MAC leads to pores that disrupt the cell membrane of target cells, leading to cell lysis and death.

Adaptive immune system

- develops in response to pathogen (antigen)
- specific (responds to Ag)
- diverse (recognizes a lot of Ags)
- immunological memory
- humoral immunity:
  - targets extracellular pathogens in blood + mucosal secretions
  - B-cells → make Ab
- cell-mediated immunity:
  - targets intracellular pathogens
  - T-cells (Cytotoxic T-cells (CD8+), Helper T-cells (CD4+)



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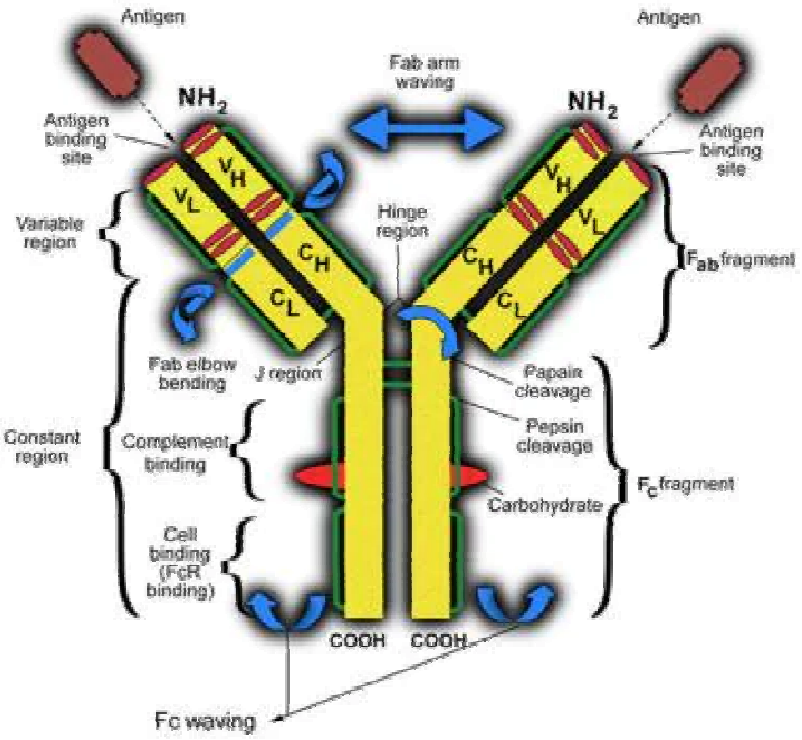
Major histocompatibility complex

- **MHC I** expressed on all nucleated cells
- what's happening inside cell (endogenous peptides)
- MHC class I recognized by CD8+ T cells
- **MHC II** expressed on APCs
- shows what's happening outside cell (exogenous peptides)
- MHC II recognized by CD4+ T cells

Immunoglobulin structure



- 2 identical heavy chains
- 2 identical light chains
- constant region (**Fc**) remains the same among all antibodies in a class
- **Fab** fragments (fragment antigen-binding region) are responsible for antigen recognition and binding; form the "arms" of the Y;
- The variable region (**Fv**) is the top part of the Fab fragment; this area varies between antibodies; contains the paratope (antigen binding site)

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- IgM:
  - is the first antibody produced by activated naive B-cells
  - first response to early infection
  - can be attached to cell surface or secreted into blood & lymph
  - can activate classical complement pathway
- IgG
  - is the most abundant ab in blood
  - can pass from parent to fetus via the placenta
  - tags antigens so phagocytes can eat them (opsonization)
  - capable of antibody-dependent cellular cytotoxicity
- IgA:
  - is responsible for mucosal immunity
  - secreted in GI, respiratory, and genitourinary tracts and found in saliva, tears, & milk
- IgE:
  - provides helminth protection
  - is responsible for mast cell degranulation
- IgD
  - co-expressed with IgM
  - least understood