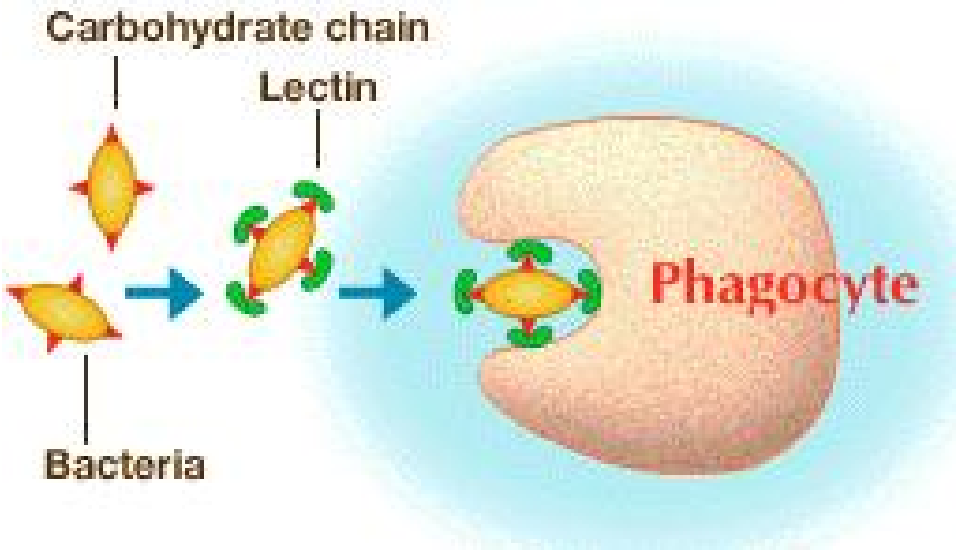
White blood cells (WBC)

- number: 4-11 thousand/ µl
- distribution:

  - granulocyte (PMN) → neutrophil (62%)
    → eosinophil (2,5%)
    → basophil (0,5%)
  - monocyte (5%) → in tissues macrophage
  - lymphocyte (30%)

Neutrophil granulocyte

- function: recognisation and phagocytation of strange factors



- the phagocytosis is stimulated, if the bacterium is marked by immunglobulines and complement factors (opsonisation)

Neutrophil granulocyte

- specific metabolism:

  • small mitochondrium ⟶ terminal oxidation is no typical of it

  ↓

  It gains energy from glycolysis

  • important the pentose-phosphate way (NADPH is required for generation of oxigene radicals)

$O_2 \longrightarrow O_2^- \longrightarrow H_2O_2 \longrightarrow OH°$

superoxid radical — hydroxil radical

Neutrophil granulocyte

- eliminational ways of phagocyted bacteria:

  - reactive oxigen radicals
    - NADPH-oxidase
    - myeloperoxidase
  - digestive enzymes
    - proteinases
  - bacteriostatic and killer proteines
    - lactoferrin
    - defensines

Killing mechanisms

Oxygen independent killing

Primer killing in lysosoms:

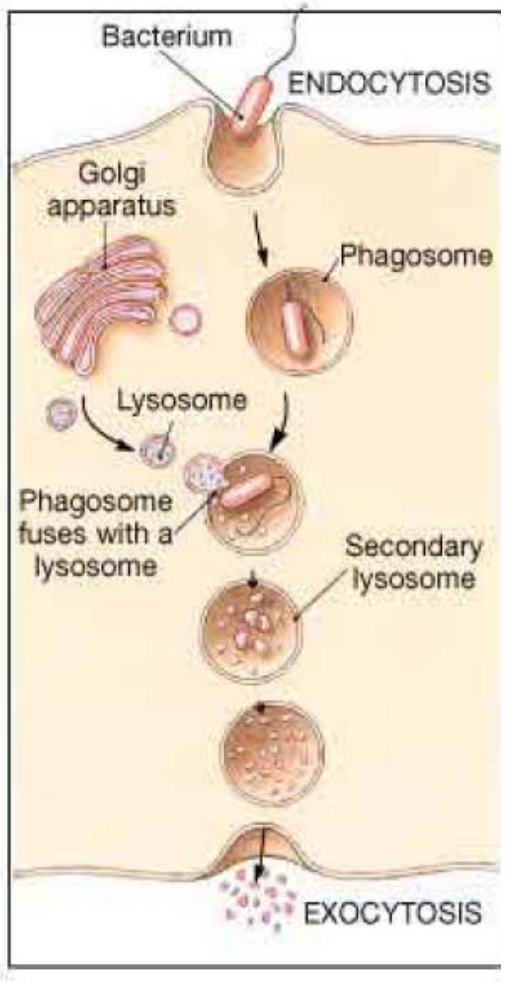
Kationic proteins

Hidrolytic enzyms (esterase, glycosidase, lipase)

Neutral esterase (kathepsin, elastase)

Kollagenase

Lizozim – lysis of bacterialcell wall



Secunder killing in lysosoms:

in 70% lisosim, kollagenase, laktoferrin- utilise of pathogen's iron

Respiratory Burst

- NADPH-oxidase: $NADPH + O_2 \longrightarrow O_2^- + H^+ + NADP^+$

  - defect : Chronic Granulomatous Disease (CGD)
    (it isn't able to kill incorporated bacteria,
    thereby cell fragments storage = granuloma)

- Function of metal ions

  - Fenton reaction: $Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + OH°$

  - Haber-Weiss reaction: $O_2^- + H_2O_2 \longrightarrow O_2 + OH^- + OH°$
    (Fe as a catalisator)

- myeloperoxidase: $H_2O_2 + Cl^- + H^+ \longrightarrow HOCl + H_2O$

Antioxidants

- functions: inactivation of releasing of oxigen radicals from neutrophils; thus they protect human cells against damaging effect

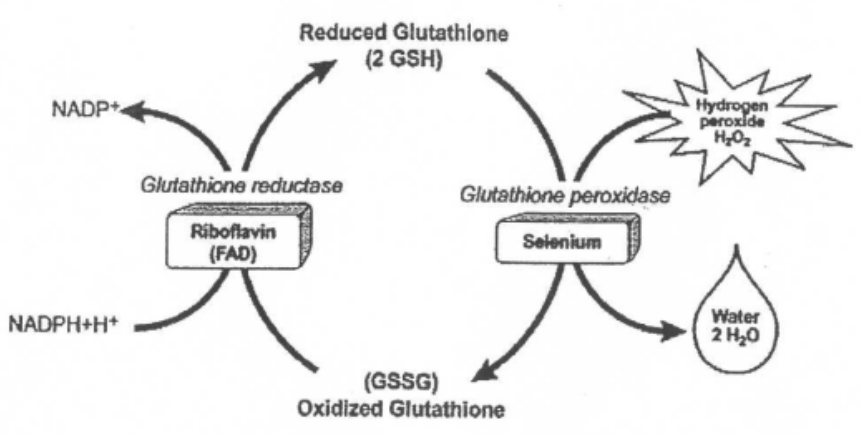
• vitamins

• enzymes

superoxid-dismutase: $O_2^- + O_2^- + 2H^+ \longrightarrow H_2O_2 + O_2$

catalase: $2H_2O_2 \longrightarrow 2H_2O + O_2$

glutatione-peroxidase



• bilirubin

• urine acid

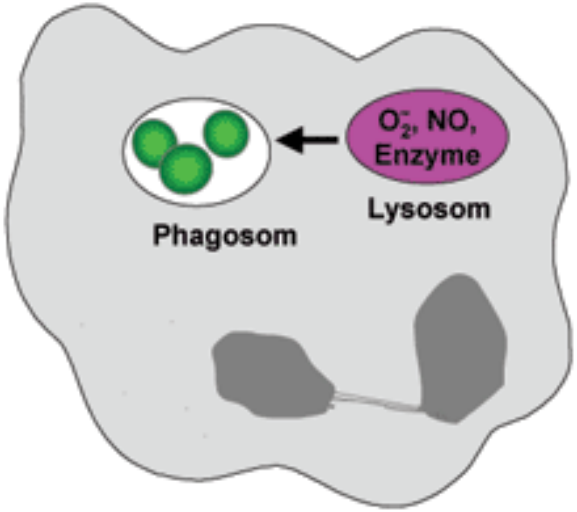
Oxidative Stress

- dislocation of oxidant-antioxidant equilibrium to oxidant direction

- results:
  - ageing
  - radiation
  - drugs
  - genetic defect (eg.: glucose-6-P-dehydrogenase)
  - iron overload
  - reperfusion (obstructed area off blood circulation get blood again)
  - chonic imflammation
  - physical exercise (if it is usual, than the organisation will be acclimatize to it, that is protect the organisation on long-distance)
- consequences:
  - lipid peroxidation
  - general cell damage (because avoidance of long-distance consequences, the DNS repair is important)

Digestive Enzymes

- they can be found as a precursor formed in azurophil granules
- the azurophil granules fuse with the phagosom and those enzymes, which are get into here, are able to reduce bacterial proteines
- types: elastase, collagenase, zselatinase, katepsin G

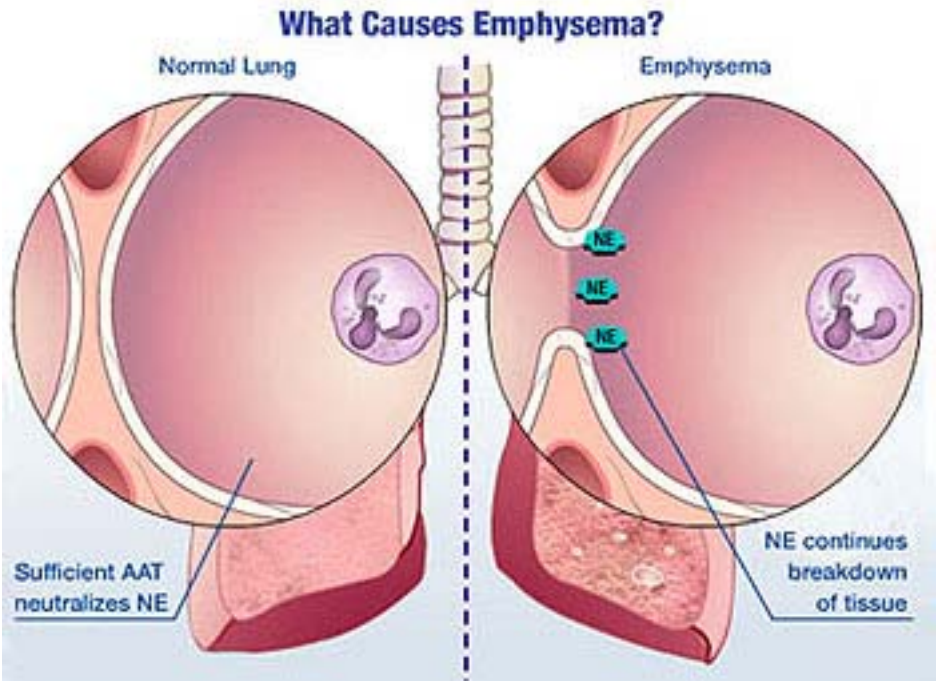


- antiproteinases (it is inactivated by releasing proteinases)
  - α1-antitripsin, α2-macroglobulin

Digestive Enzymes

- proteinase-antiproteinase equilibrium is able to dislocate; results:
  - genetic defect of α1-antitripsin
  - smoking ⟶ α1-antitripsin activity decreases

- Deficiency of α1-antitripsin ⟶ elastase activity increases



↓

it breaks down the elastin, which is found in the wall of alveoluses

↓

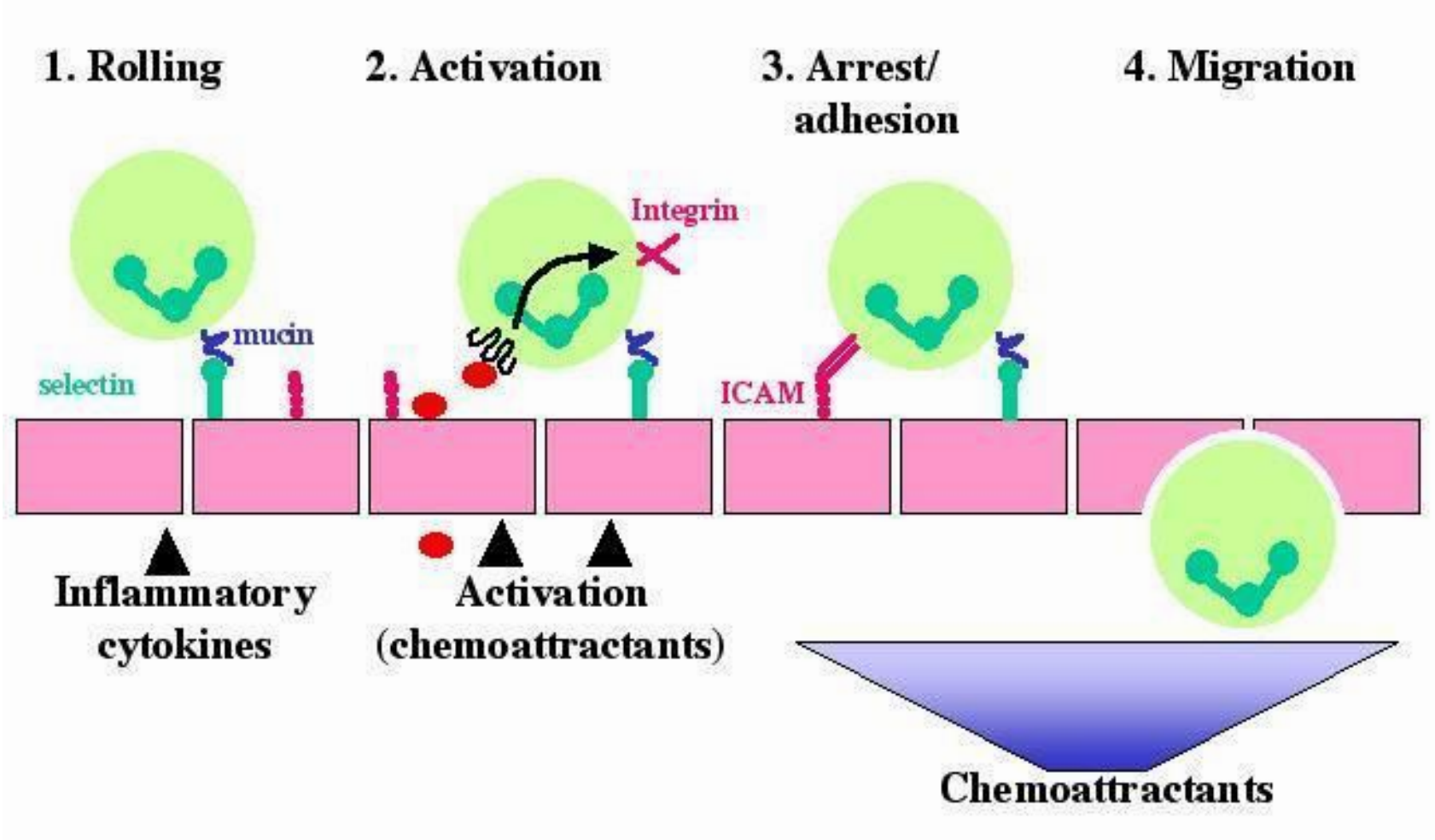
Emphysema

↙ ↘

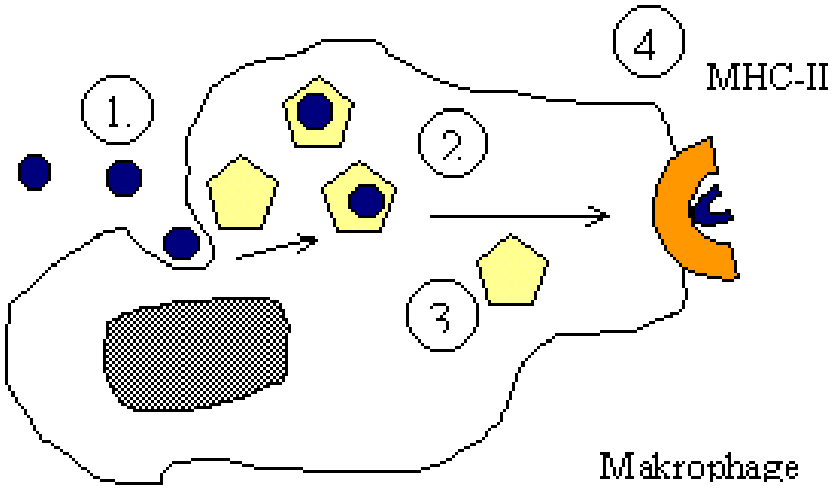
Lung dilates

Respirative area decreases

Migration of Neutrophils



Macrophages

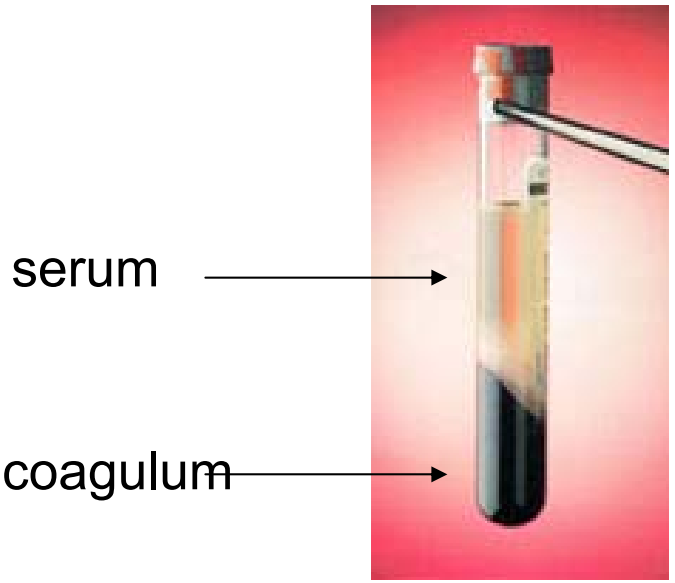


macrophage incorporates the strange matterial → macrophage demonstrates it to lymphocyte → lymphocyte is activating

Elements of Blood Plasma and Functional Significance

Blood plasma: blood without corpuscular elements (in case of blood letting : in coagulation inhibitor containing tube the corpuscular elements precipitate, and the supernatant = plasma)

Blood serum: blood plasma without coagulation factors (in case of blood letting: coagulation begins directly in the native tube, the corpuscular elements with coagulation factors are formed as a coagulum, the supernatant = serum)



Main elements of blood plasma:

- water
- ions
- gases
- nutrient derivatives
- metabolic end products

- proteins
  - plasma proteins
  - plasma enzymes (e.g.: lipoprotein lipase)
  - tissue enzymes (e.g.: ASAT, ALAT, LDH)
  - protein hormones (e.g.: insulin)
  - adhesion proteins (e.g.: fibronectin)
  - storage proteins (e.g.: ferritin)

- non-protein hormones (amino acid derivatives, steroides)

Total protein level of Plasma

Normal: 60-80 g/l

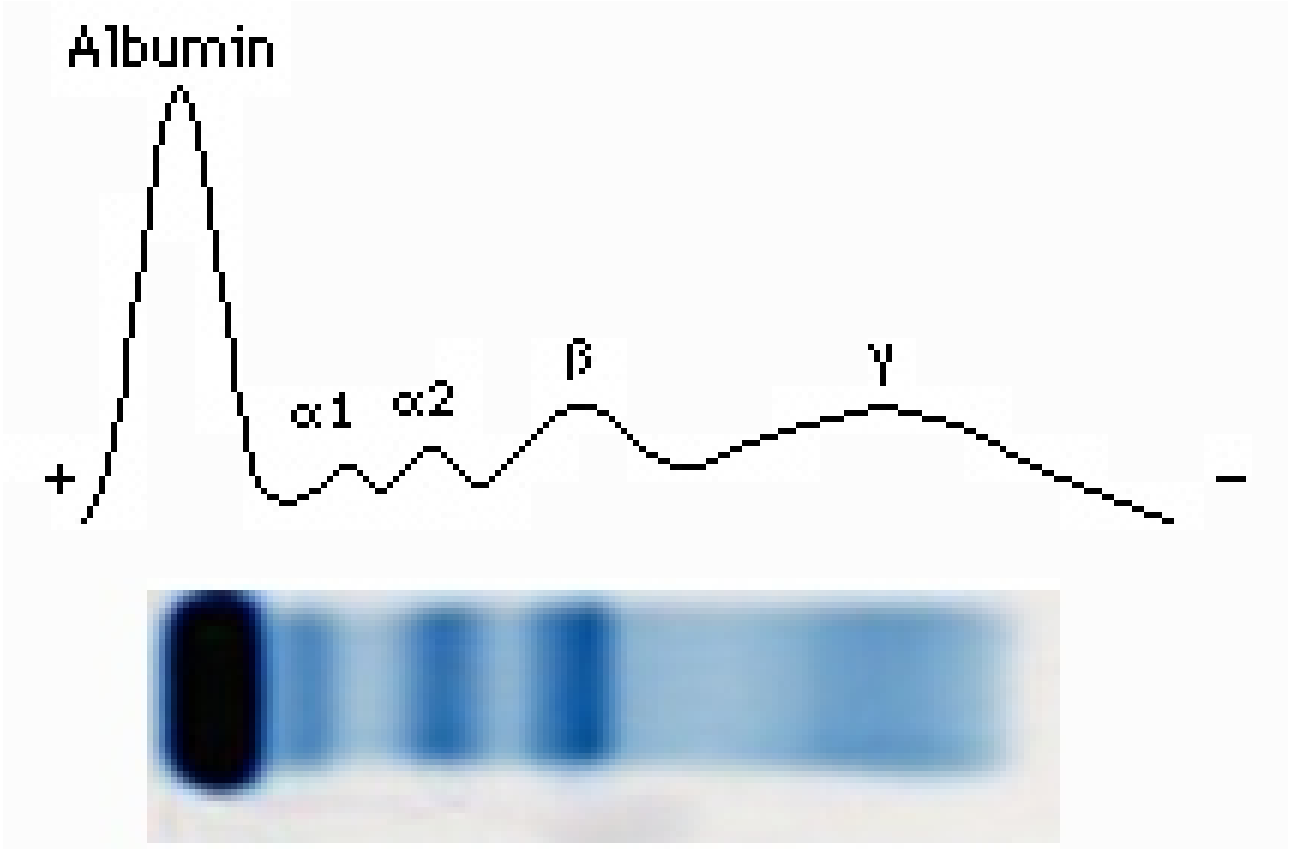
Decreasing:

- deficient feed
- disorder interferes directly with the absorption of nutrients (Malabsorptio)
- damage of the liver parenchyma (e.g.: cirrhosis)
- antibody defiency syndrome
- advanced tumors
- congenital analbuminaemia
- protein loss through gastrointestinal system
- protein loss through kidney (nephrosis syndrome)
- high burn, hemorhagic shock

Increasing:

- exsiccosis
- monoclonal gammopathies (tumor in plasma cells, if there is high amount of Ig in blood)

Plasma protein fraction (by electroforetic assays)



I. Prealbumin

- function: tiroxin binding

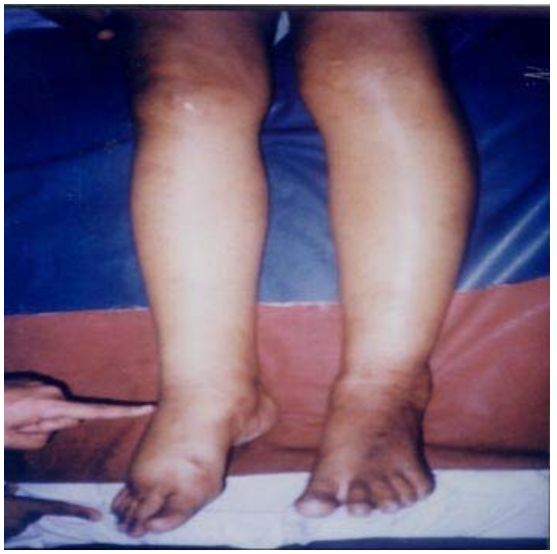
II. Albumin

- serum level: 40-60 g/l
- function:
  - maintenance of colloid osmotic pressure
  - transfer (indirect bilirubin, fatty acides, hormones, drugs)
  - protein reserve
    (if its amount decreases:

osmotic pressure decreases

↓

oedema)



lábsároedema

III. α1-globulin

1. transcortin
   - function: corticosteroid binding
2. tiroxin binding globulin
   - function: T3, T4 binding

3. α1-antitripsin

- function:
  - main protease inbibitor in blood
  - acut phase protein
- Genetic polimorfism (kb. 30 variation):
  - healthy fenotype: MM (100% activity)
  - heterozygote: MZ, MS, s (40-75% activity)
  - homozygote: ZZ (15% activity)

↳ consequence: lung: decreasing of antiprotease defense

↓

elastin fibrilles are damaged

↓

alveoluses open into one

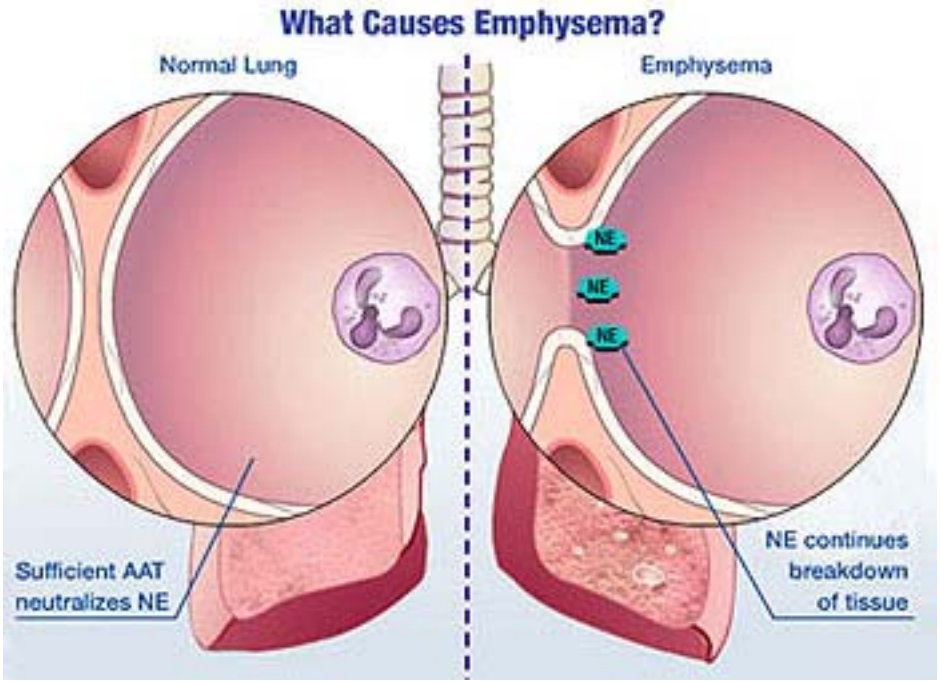
↓

emphysema

liver: a mutant protein polimerising in ER

↓

cyrrhosis



4. α1-lipoprotein (HDL)

5. α1-fetoprotein
   - Function: immunsuppression
   - Increasing of serum level:
     - malignus tumors (mainly: liver tumors)
     - gravidity
     - fetal development disorders (e.g.: vertebral column with open sacrum, open spinal column)

IV. α2-globulin

1. Ceruloplasmin
   - Function:
     - binding and transferring of Copper
     - acut phase protein
   - Decreasing of serum level :
     - liver diseases
     - Wilson's disease, Menkes's disease
     - glucocorticoides
     - In neonatal- and childhood
   - Increasing of serum level:
     - estrogen effect

2. haptoglobin
    - function: binding of free hemoglobin
    - Increasing of serum level :
        - imflammation - tumor
        - Tissue damage
    - Decreasing of serum level :
        - high hemolysis (releasing hemoglobin is binding)
        - Liver damage

3. α2-macroglobulin
    - function: panprotease inhibitor

4. protrombin (coagulation factor)

5. antitrombin III.

6. erythropoetin
    -function: stimulation of red blood cell synthesis
    - - synthesis: kidney

V.β-globulin

1. hemopexin
   - function: free hem binding

2. transferrin
   - function: Iron transport (ld.: Iron traffic)

3. ferritin
   - function: Iron storage

4. coagulation factors

5. plasminogen

6. C-reactive protein (CRP)
   - function: activates the complement system in imflammational reaction

7. fibronectin (adhesion protein)

8. sex hormone-binding globulin (SHBG)

9. β2-microglobulin

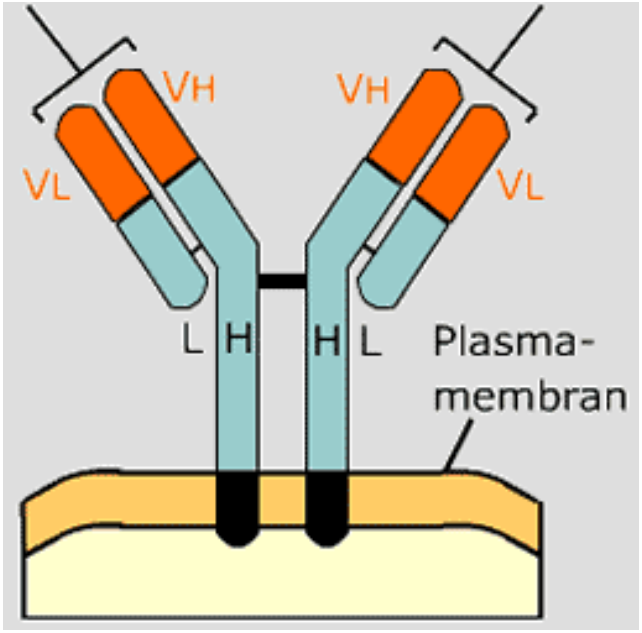
10. elements of complement system

11. β-lipoprotein (LDL)

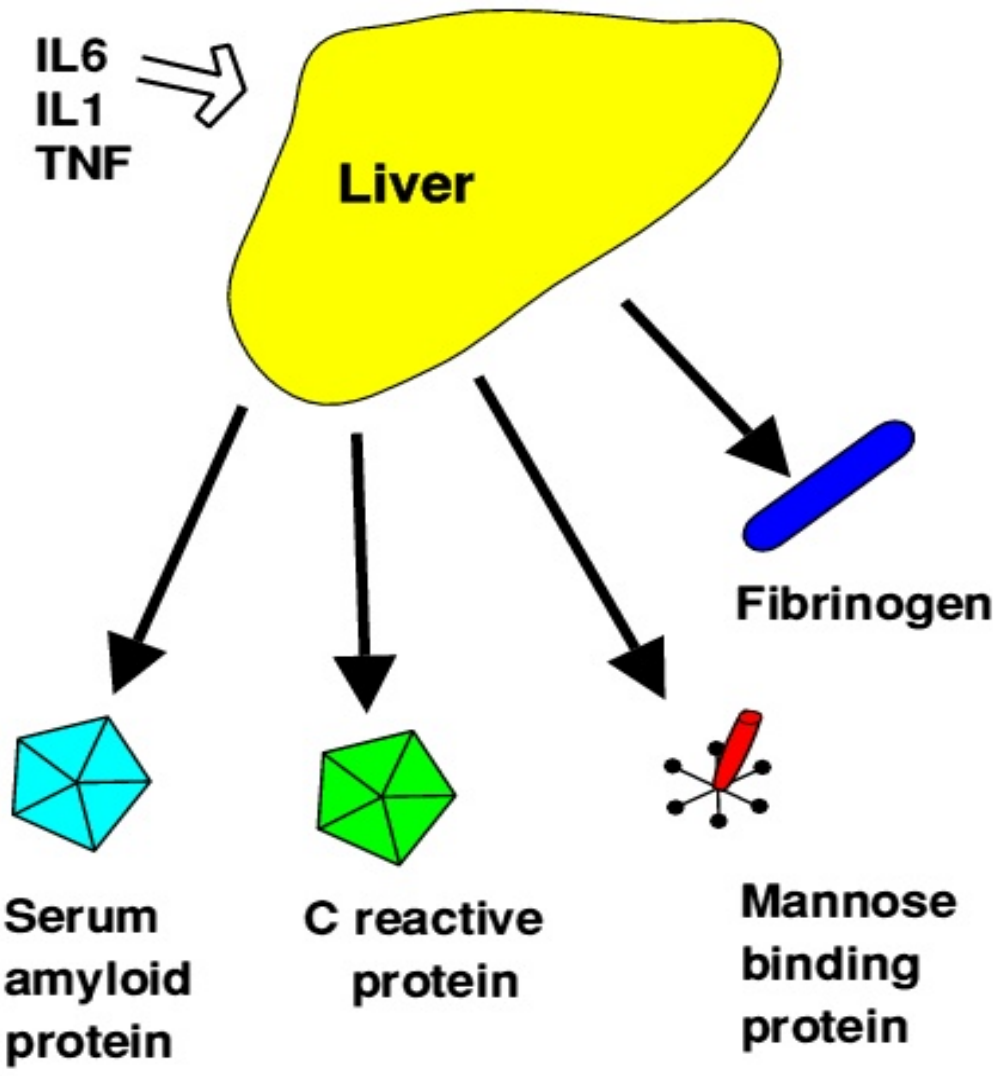
12. pre β-lipoprotein (VLDL)

VI. γ-globulin (immunglobulines)

- 4 subunits : 2 heavy chains and 2 light chains
- synthesis: B-lymphocytes



THE ACUTE PHASE RESPONSE



Akut- fázis fehérjék

protease inhibitors	a2 macroglobulin a1antitripsin
complement factors	C3, B factor, C1inhib
coagulation proteins	fibrinogen
opsonins	C3, CRP mannan binding lectin
immunmodulant proteins	C3, prot.inhib
other proteins	albumin, coeruloplazmin

Acute phase proteins

increase

C3, coeruloplazmin –1.5-2X

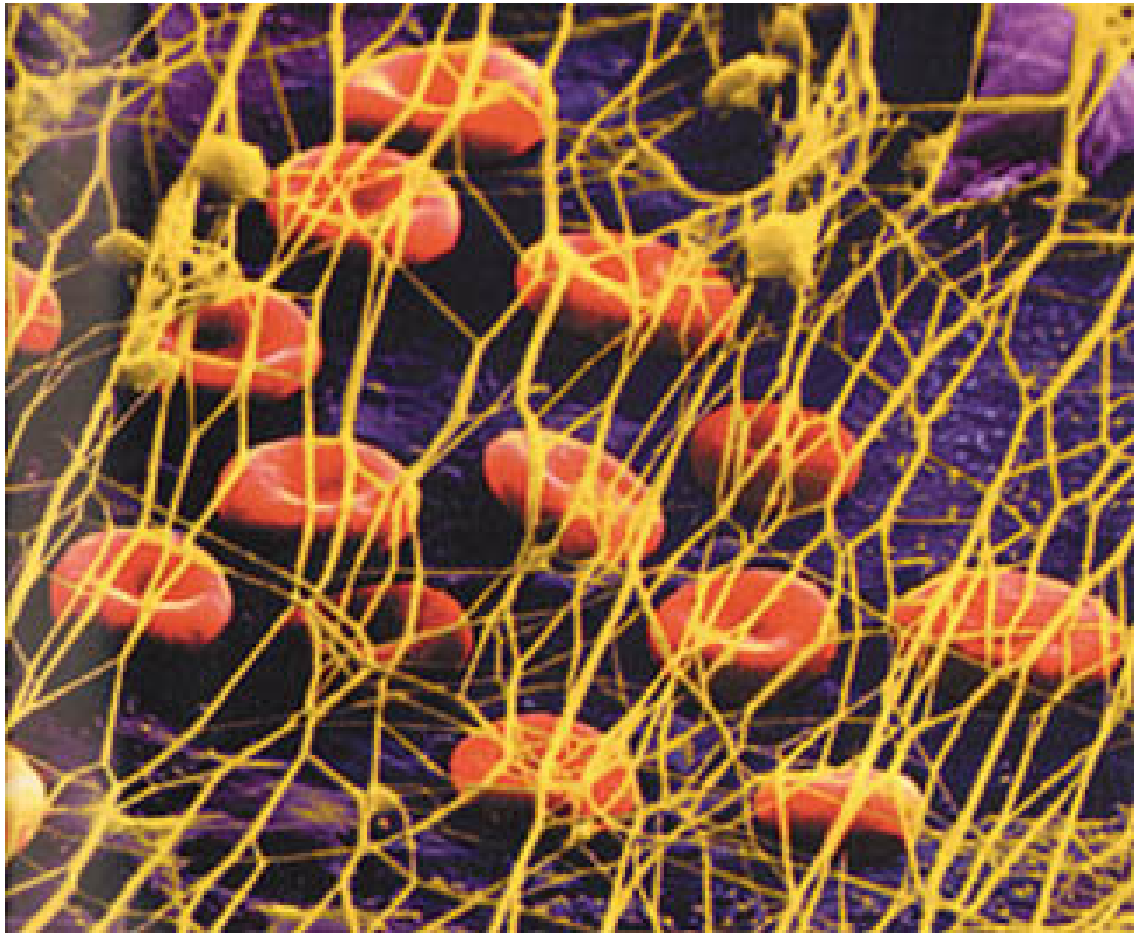
α1antitripsin,
haptoglobulin, 2-4 X
fibrinogen

C1inhibitor- 6-8X

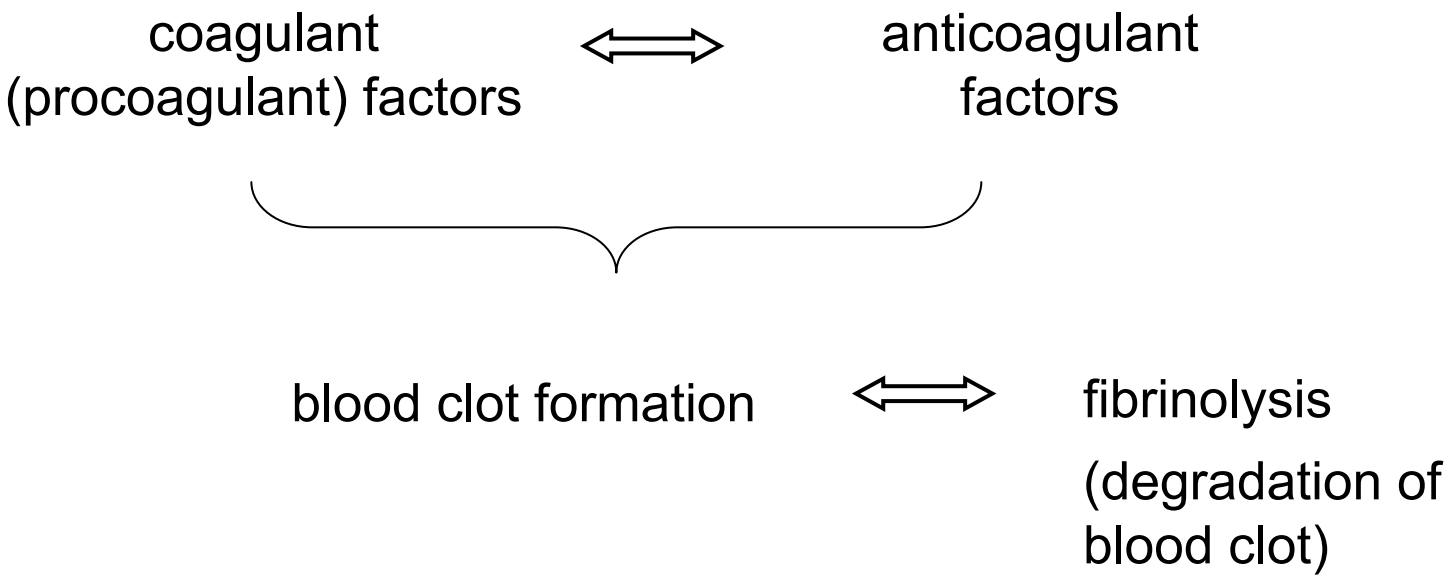
decrease

transferrin,
albumin, fibronektin
0.4- 0.6 X

Coagulation system

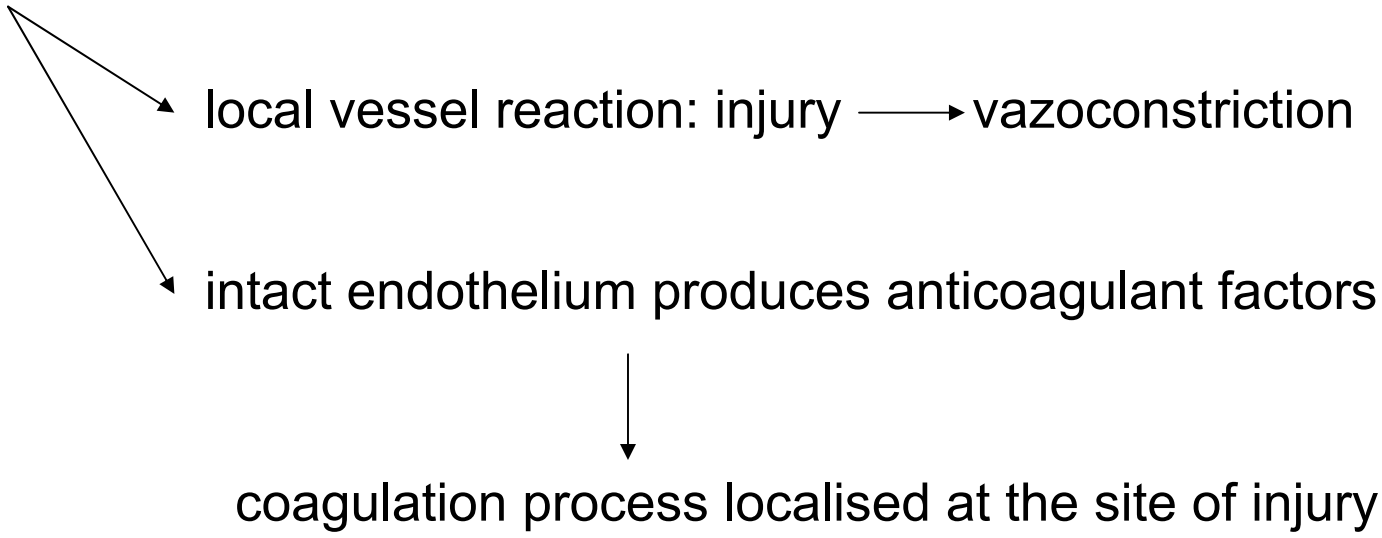


Coagulation system



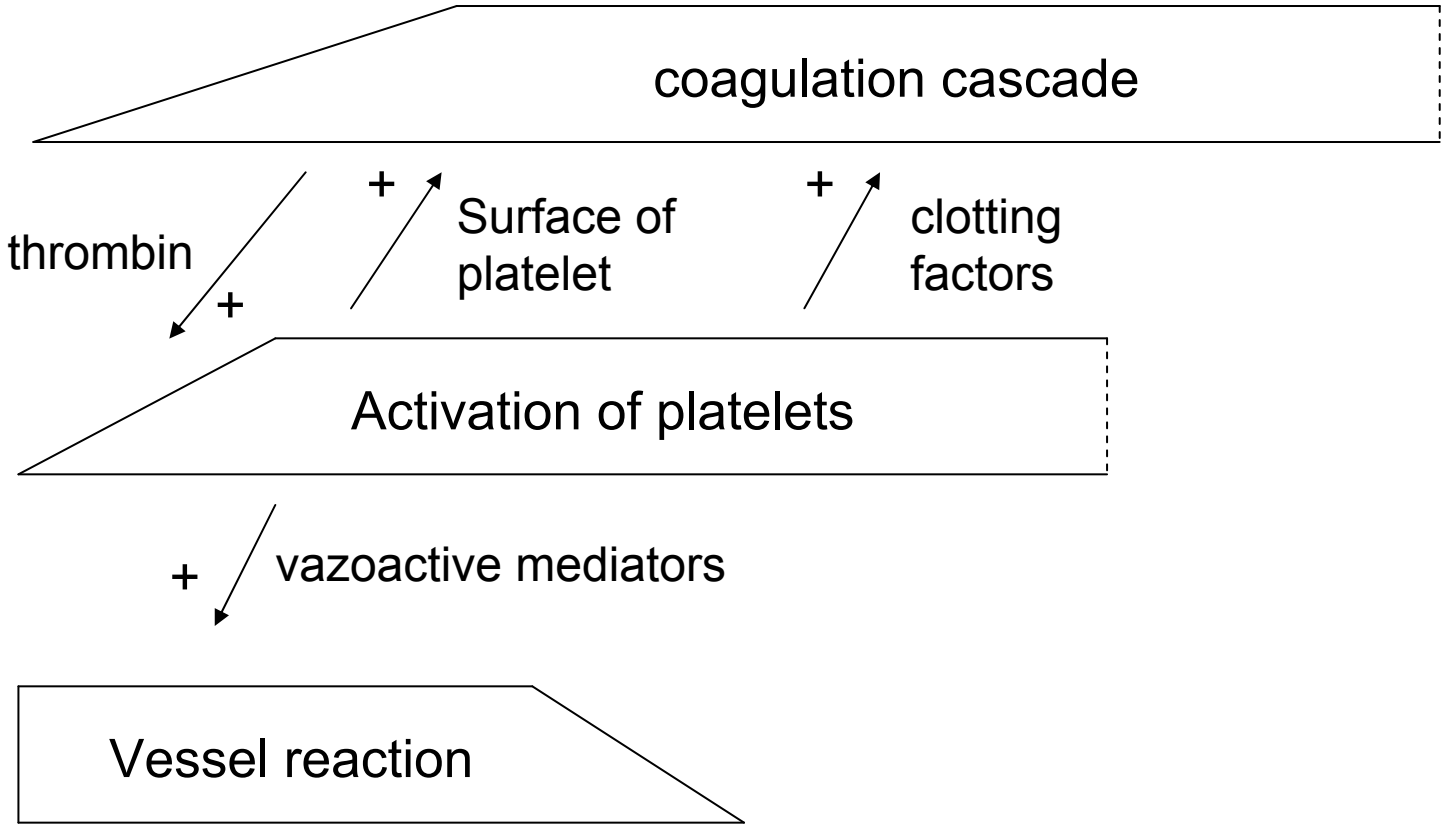
Factors involved in blood coagulation

- vessel wall (two independent effetcs)



- platelets
- blood clotting factors

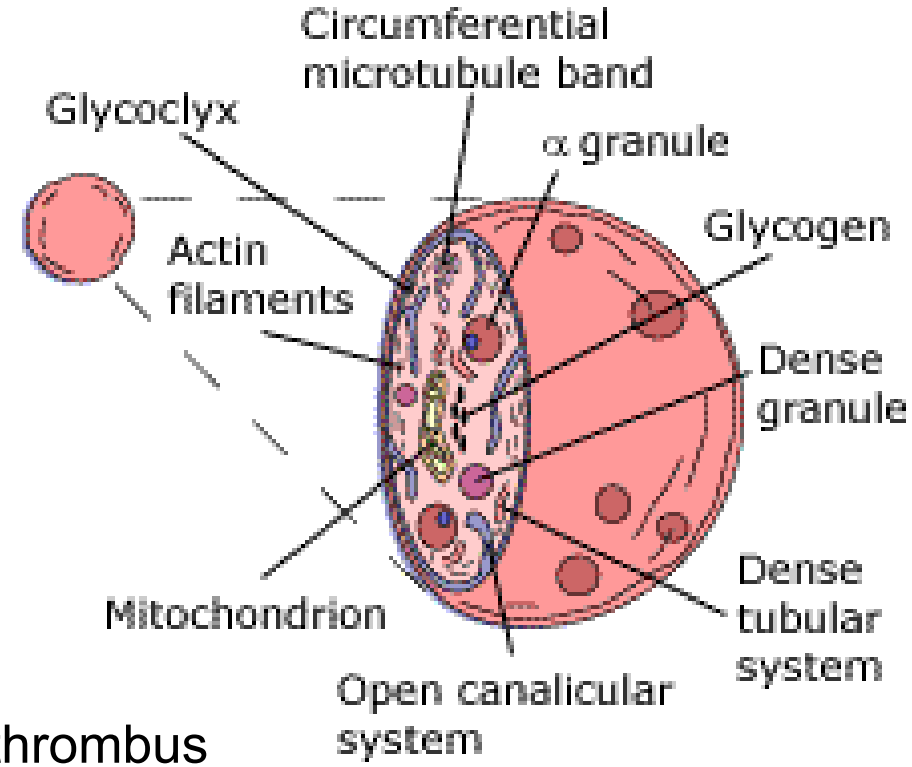
Interaction of factors involved in blood coagulation



Platelets

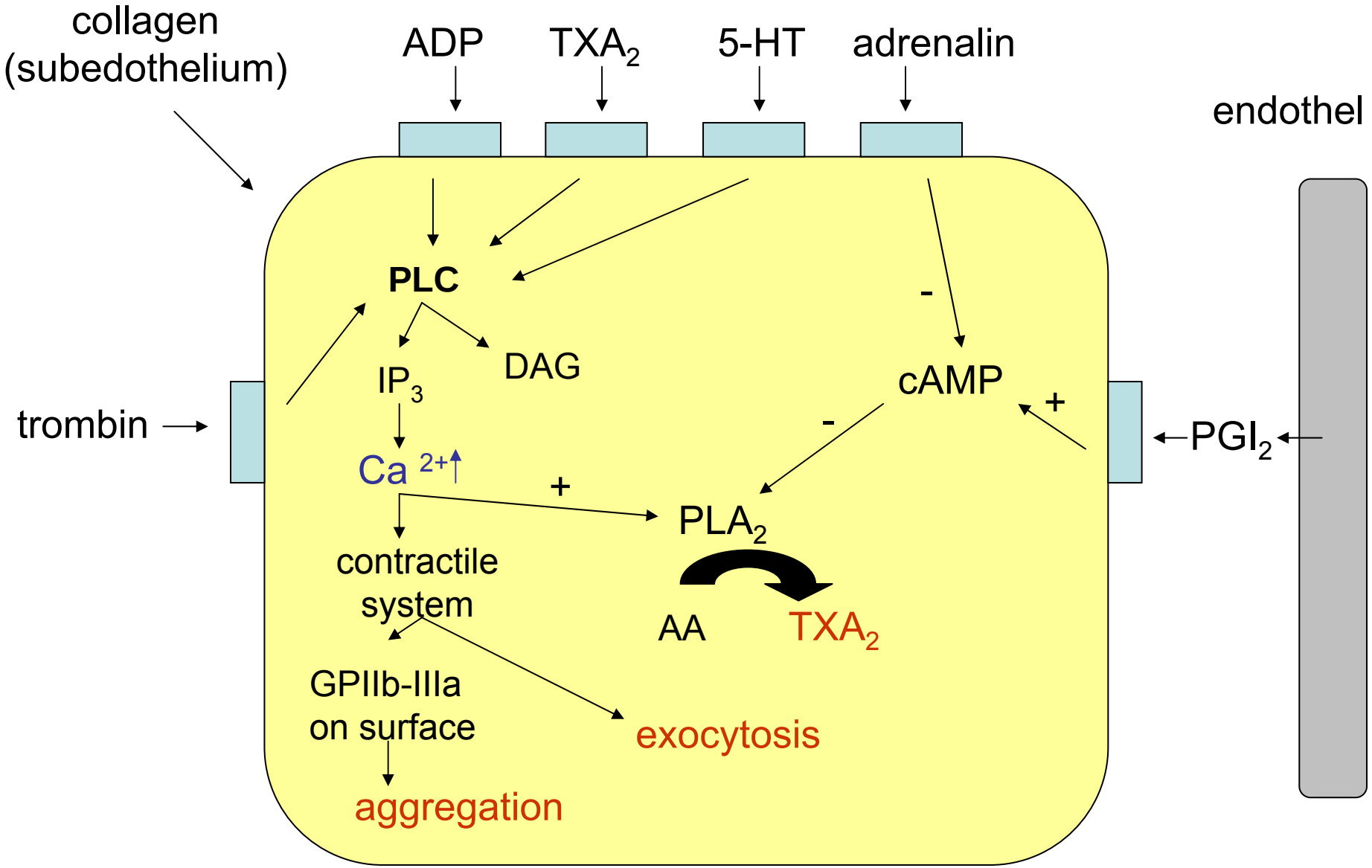
-number: 150-300.000/ µl

- structure:

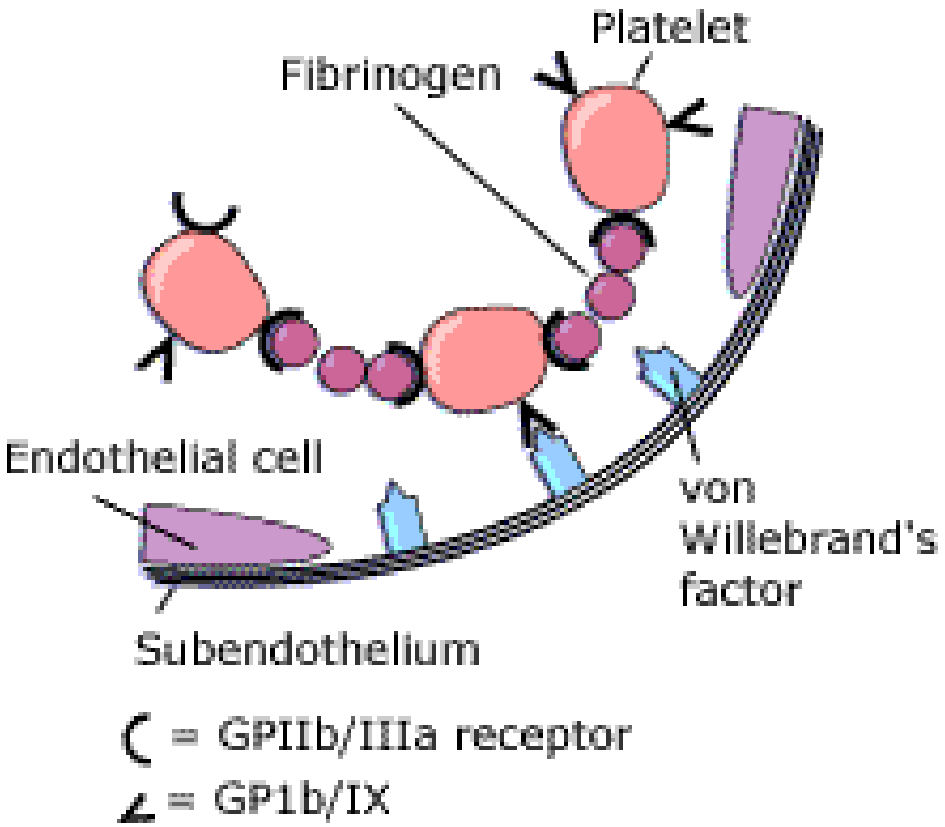


- function:
  - formation of primary thrombus (adhesion, aggregation)
  - enhanced coagulation process → activating surface for clotting factors
  - enhanced coagulation process → secretion

Platelet activation



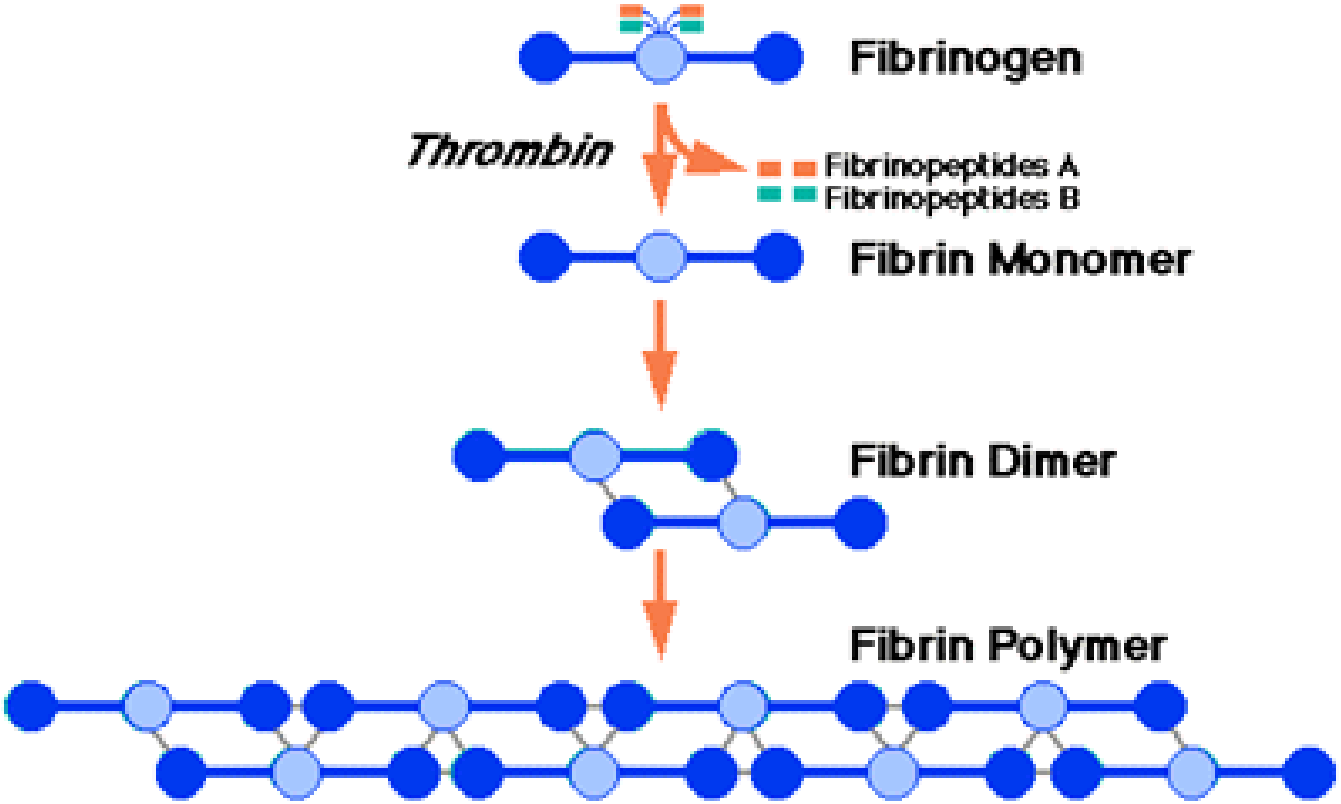
Primary thrombus



- adhesion (platelet attachement to subendothelial surface): GPIb-vWF
- aggregation (interaction of platelets): GPIIb/IIIa-n

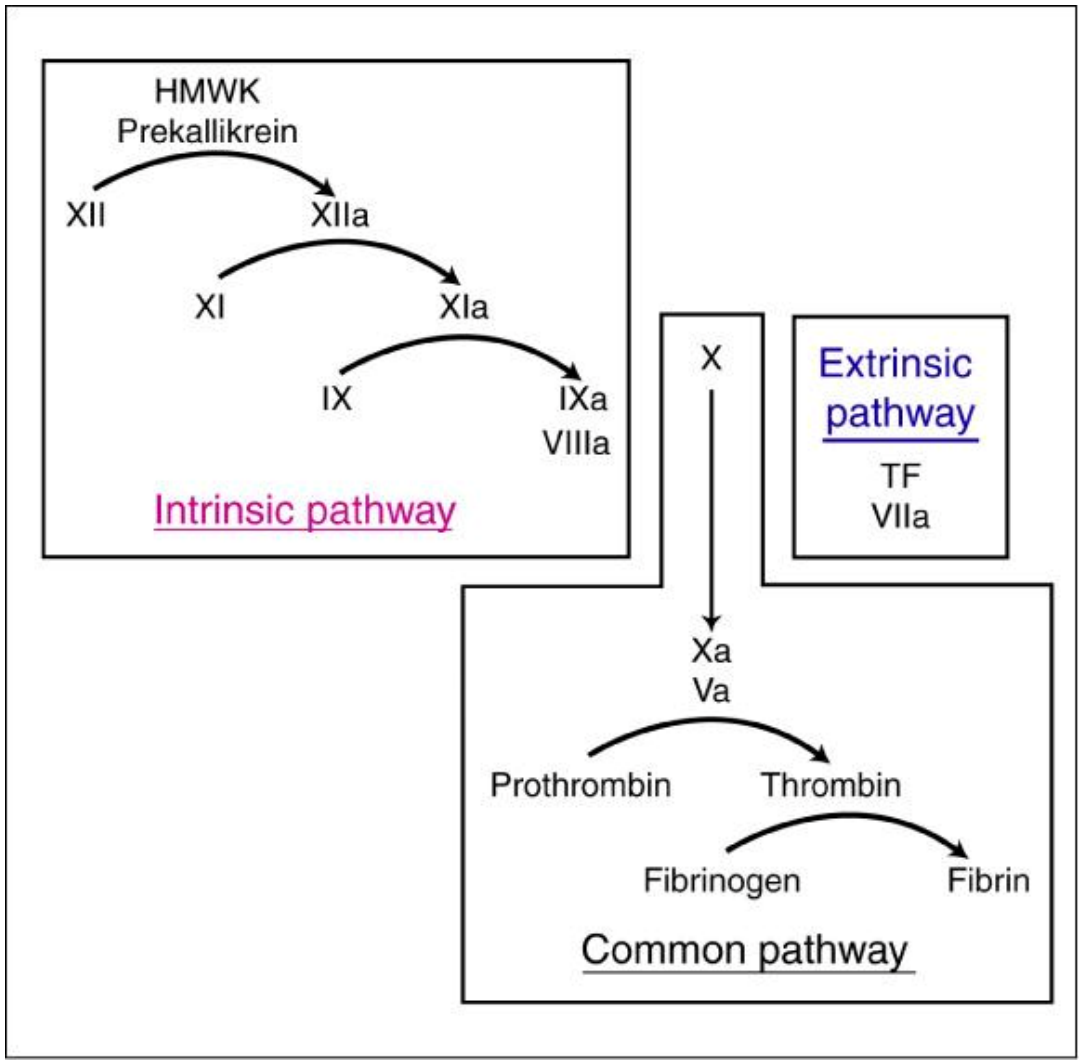
Coagulation cascade

- steps:



Coagulation cascade

- activation of trombin:



- cascade is activated by the activation of factor VII (extrinsic pathway)

- elements of intrinsic pathway (IX, XI) amplify the process

- the formed thrombin cleaves fibrinogen

Inhibitors of coagulation cascade

- protein C: - activated by trombin at the presence of trombomodulin

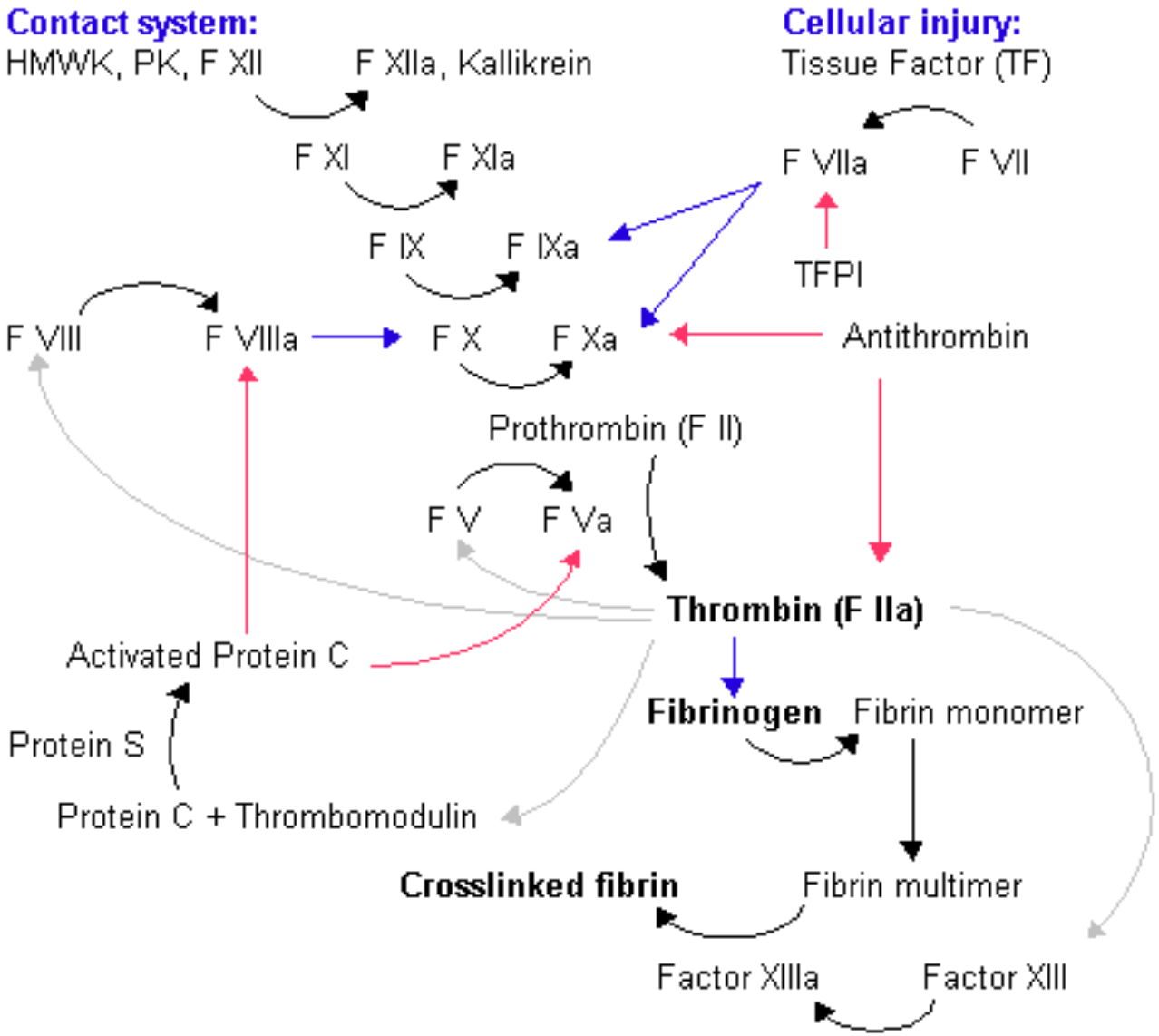
intact endothelium

- inactivation of factor V and VIII

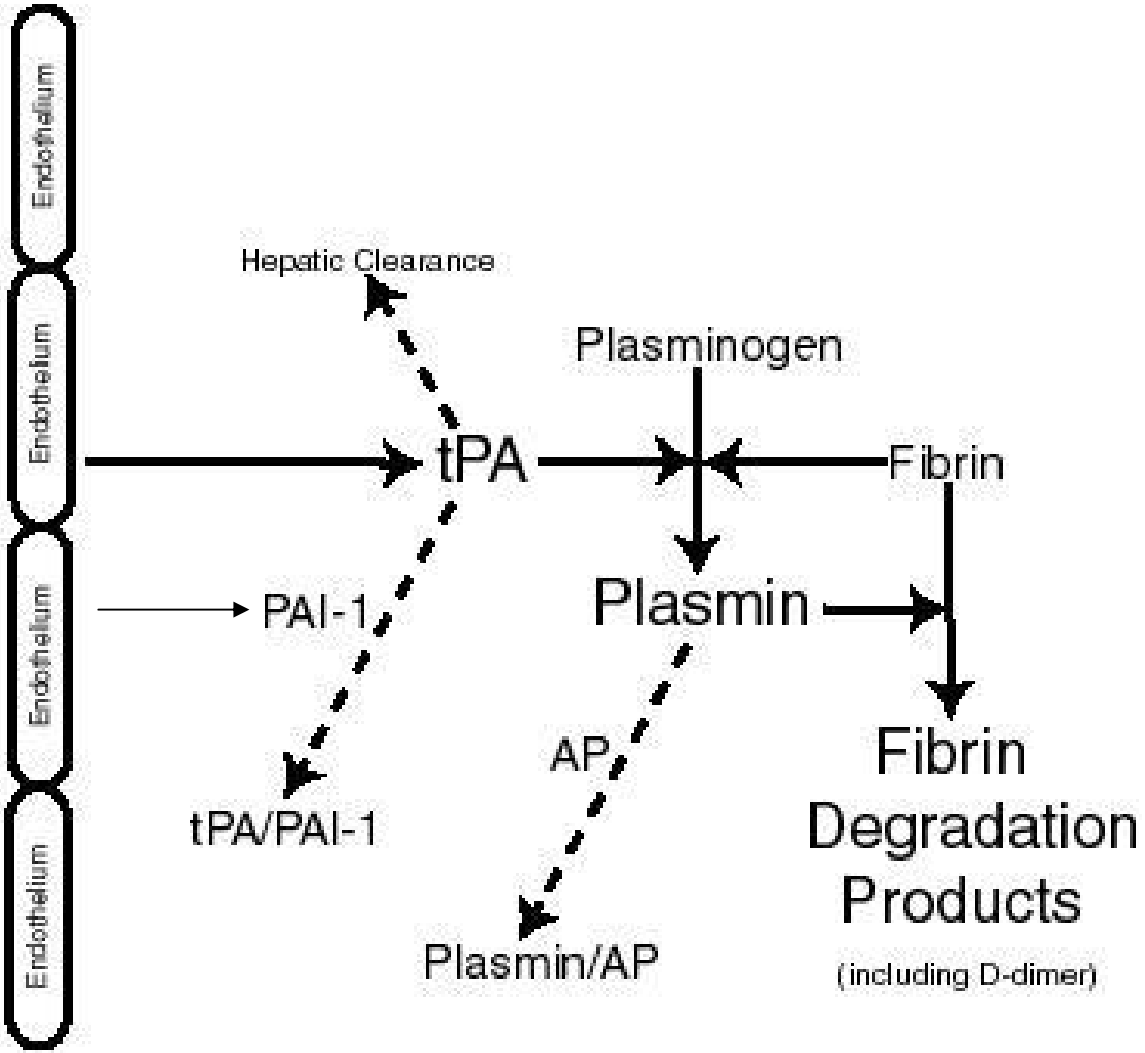
- antithrombin: - inactivates many factors (trombin, IX, X, XI, XII)

- heparine required for intensive action

Coagulation cascade



Fibrinolysis



Role of liver in coagulation

• most of the factors of coagulatin-fibrinolytic system are synthesized by the liver

↓

it can not produce enough factors in severe liver damage

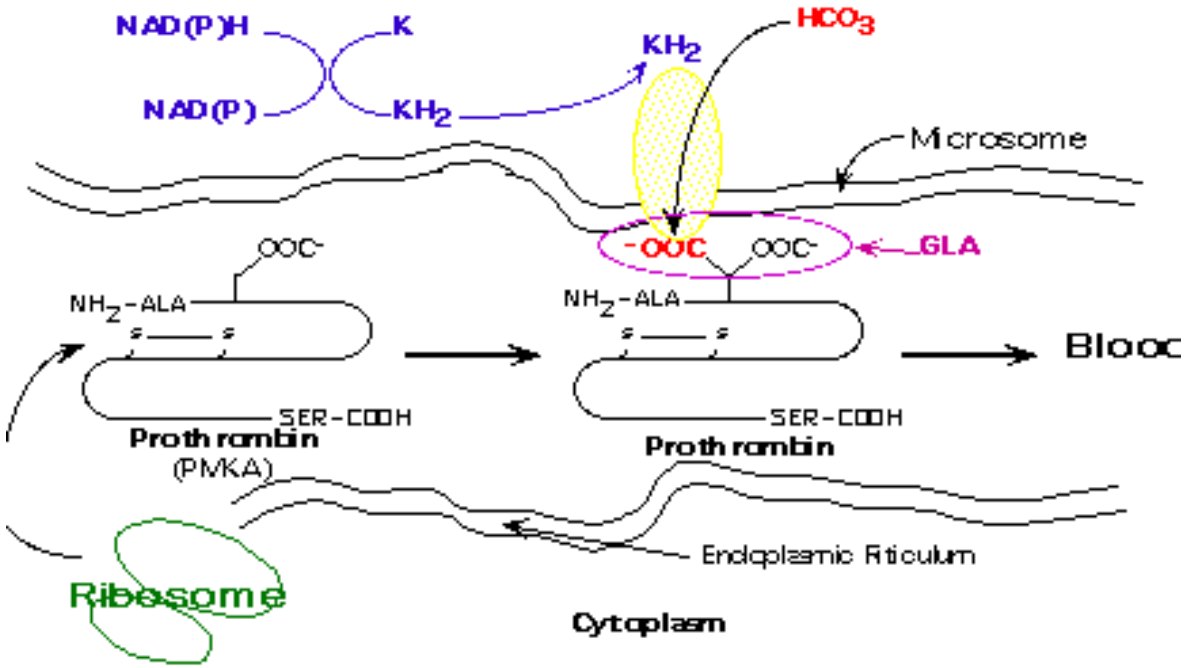
↓

haemophilia

• liver performs also posttranslational modifications (Gla-synthesis) of some factors (prothrombin, factor VII, IX, X, protein C, S)

• degredation of inactive factors

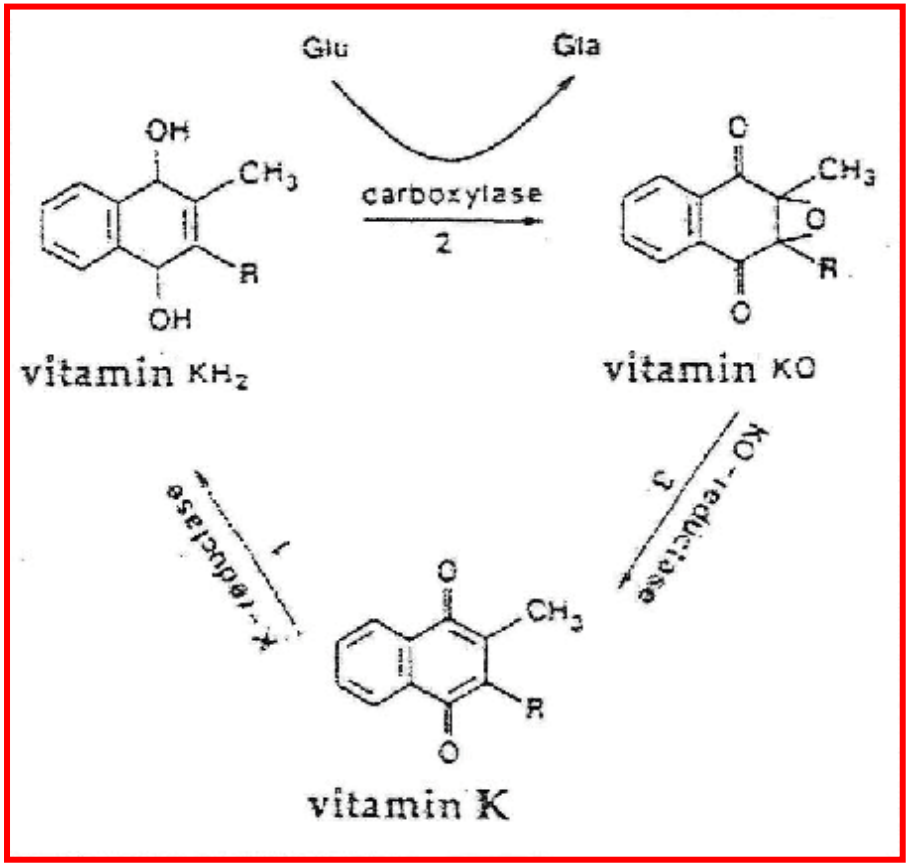
Gla-synthesis



-carboxylation of Glu

- requires vitamin K

Vitamin K cycle



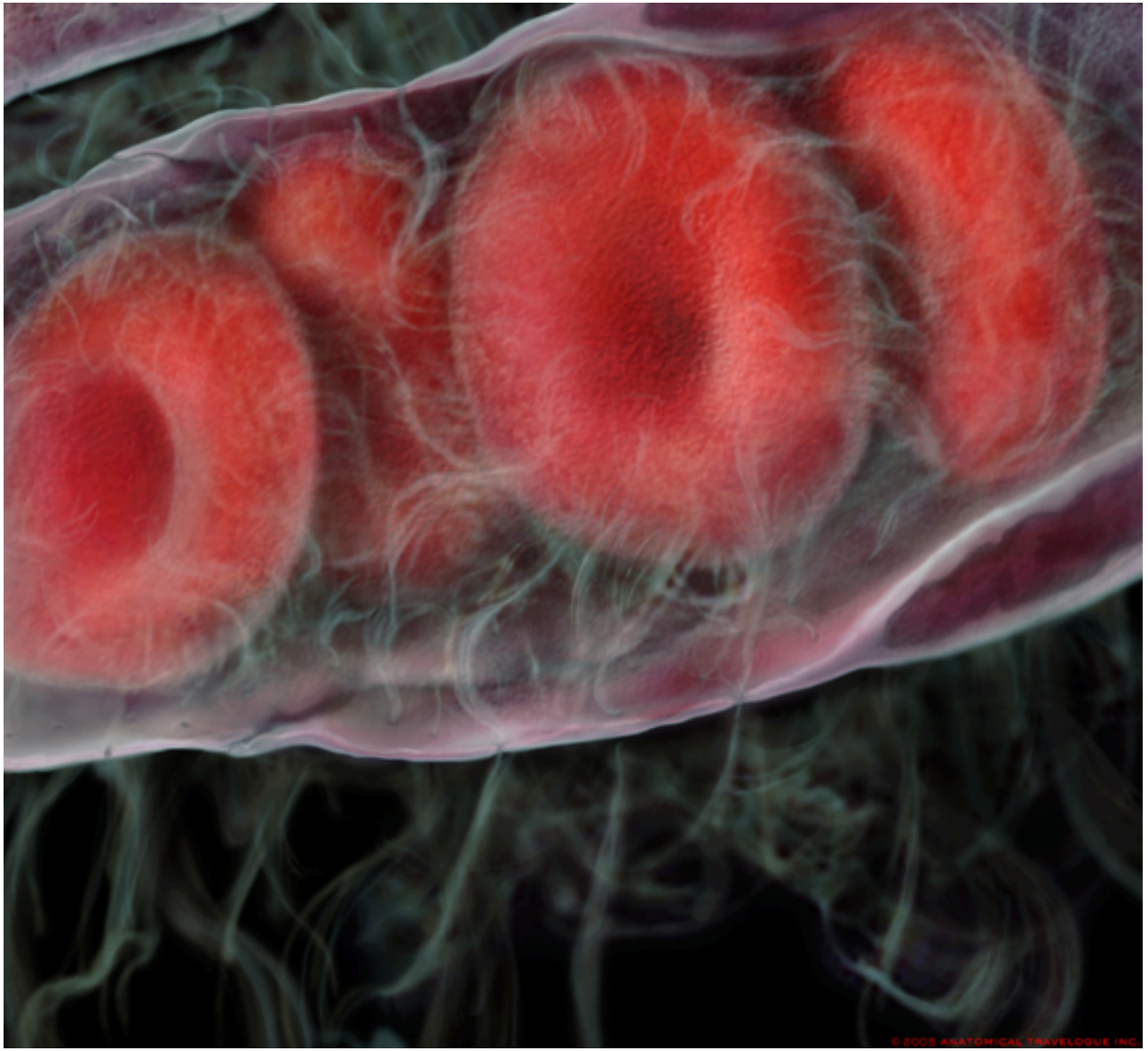
Gla-gamma karboxiglutamát

Anticoagulant factors

- aspirin: inhibition of PLA_2 → inhibition of thrombocyta activation
- heparin: enhances action of antitrombin
- kumarin derivatives (Syncumar) inhibition of vitamin K cycle

- Ca^{2+} -binding molecules (citrate, oxalate, EDTA): only in vitro

Biochemistry of Erythrocytes



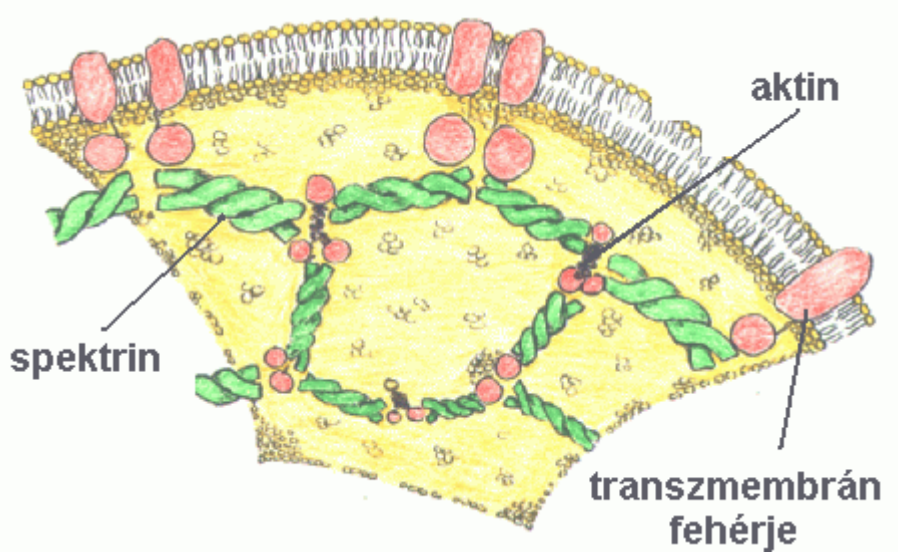
Biochemistry of Erythrocytes

- number: 4,5 – 5,5 million/ µl
- size: 7 µm
- discoid form
- spetial membran proteins

→ they easily deform

↓

they can squeeze through the smaler capillaries



- their proteins besome elder during their life time (120 days), because they don't sythetize proteins; erythrocytes loose from their flexibility

Biochemistry of Erythrocytes

Results of Specific metabolism:

- **there is no mitochondrium: it gains energy only from glycolysis**

glucose has to be there contaniously

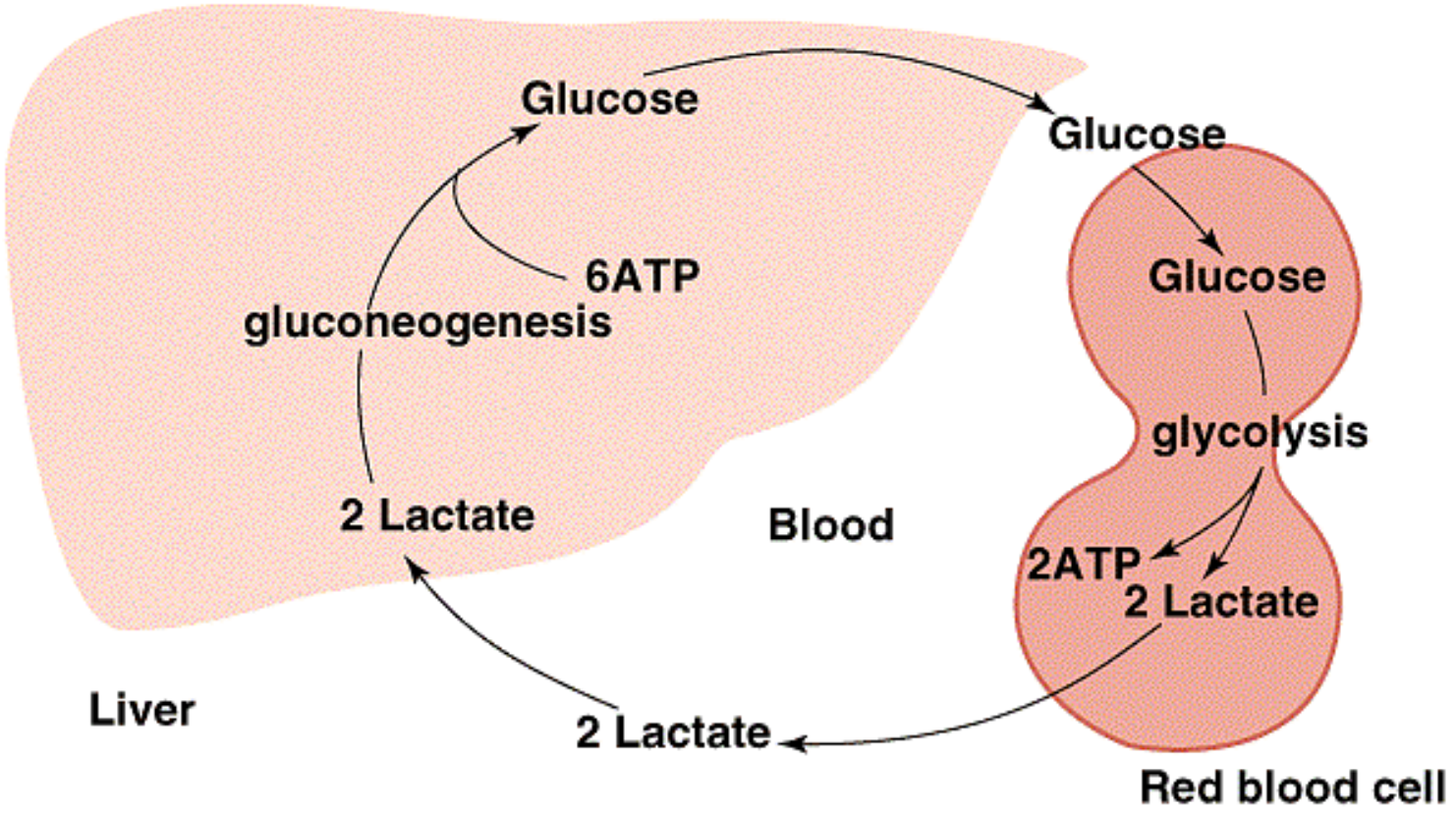
insulin independent glucose transporter (GLUT-1)

pyruvate is formed by glycolysis, it is catabolised by anaerob way

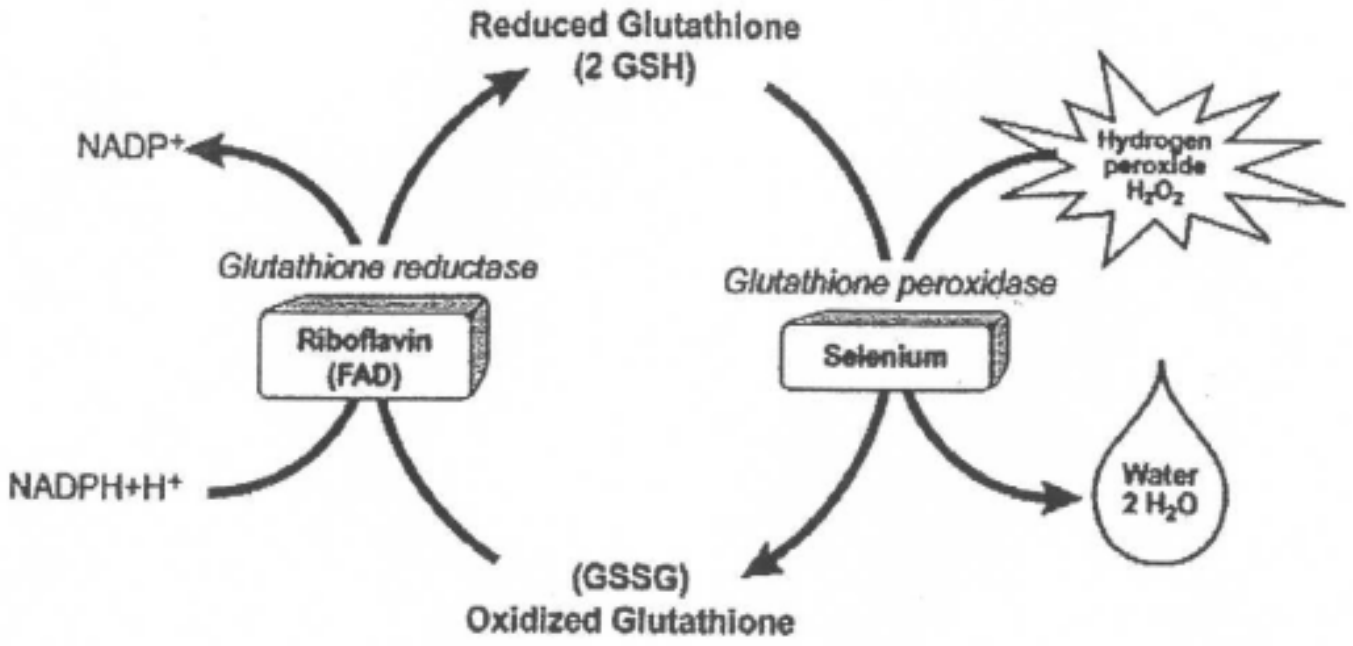
lactate is generated

Cori- cycle

Cori Cycle


Glucose
Glucose
6ATP
gluconeogenesis
Glucose
glycolysis
2 Lactate
Blood
2ATP
2 Lactate
Liver
2 Lactate
Red blood cell

- there is no nucleus ⟶ and protein synthesis
- the glutatione is the only one of the antioxidant

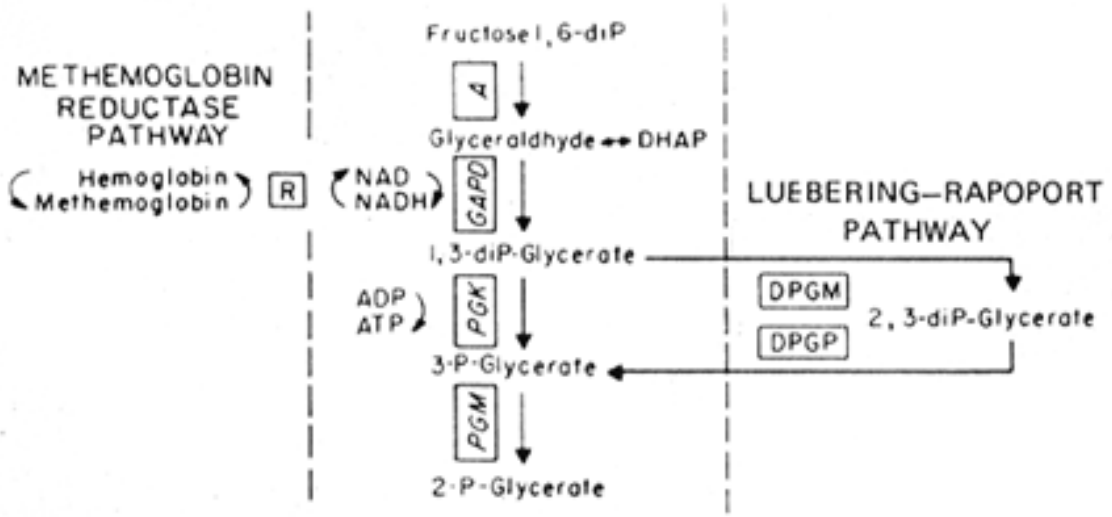


- NADPH is assured by HMP-shunt
- disorder of HMP-shunt (in case of glucose-6-P-dehydrogenase deficiency) ↓
  there is no enough NADPH
  the cell can't protect against oxidative effects ⟶ drug induced hemolytic anaemia

- **Regulation of O_2 dissociation**

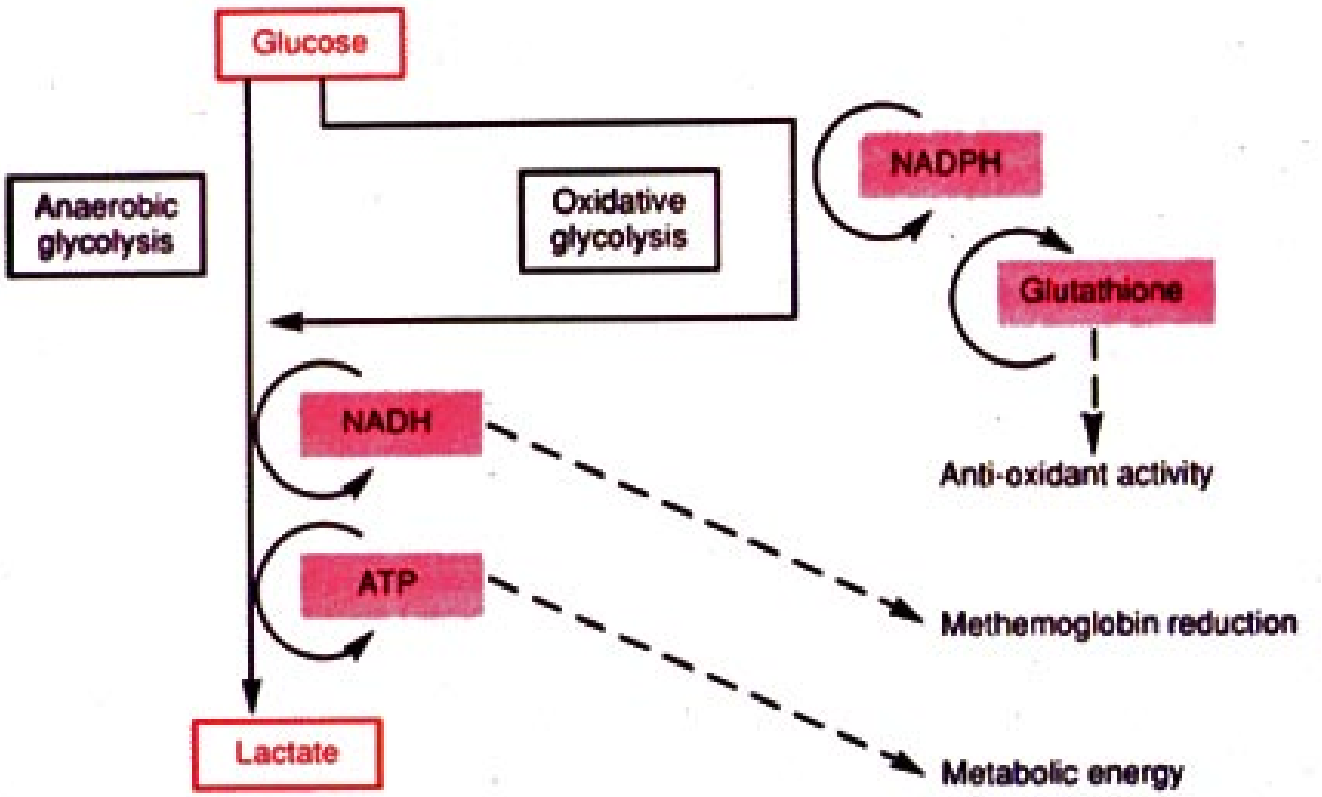
2,3 diphosphoglycerate (2,3 DPG)

Generation: from glycolysis (Rapaport-shunt)

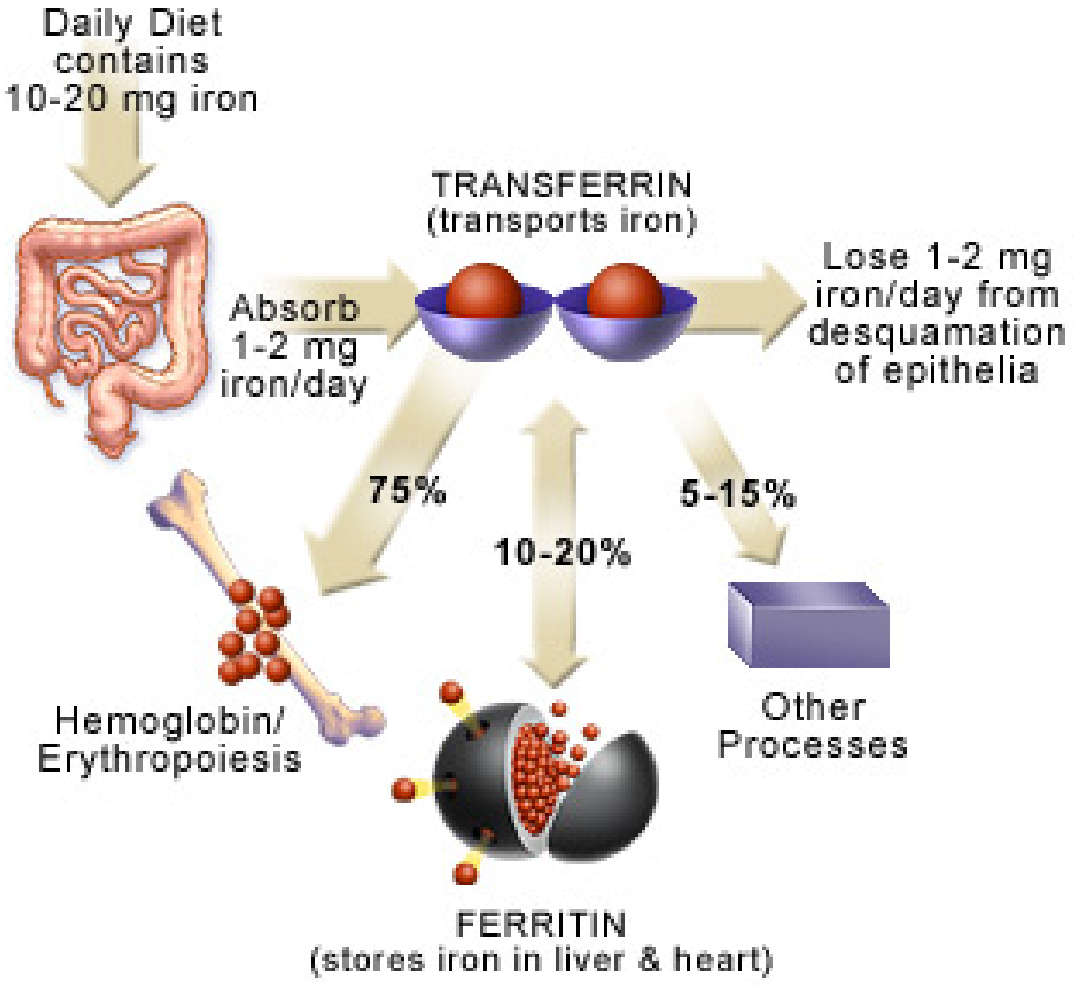


DPGM: diphosphoglycerate mutase
DPGP: diphosphoglycerate phosphatase

Utilisation of intermediates which are origined from glycolysis



Iron Metabolism of Organism



- Iron requirement: for men:1-2 mg, for whomen 2-3 mg (it is higher because of menstrual blood loss)
- for absorption need to eat 10-20 mg iron per days

Iron uptake into the cells

1. transporting transferrin is binding to receptor

↓

endocytosis

2. pH decrease in endosome

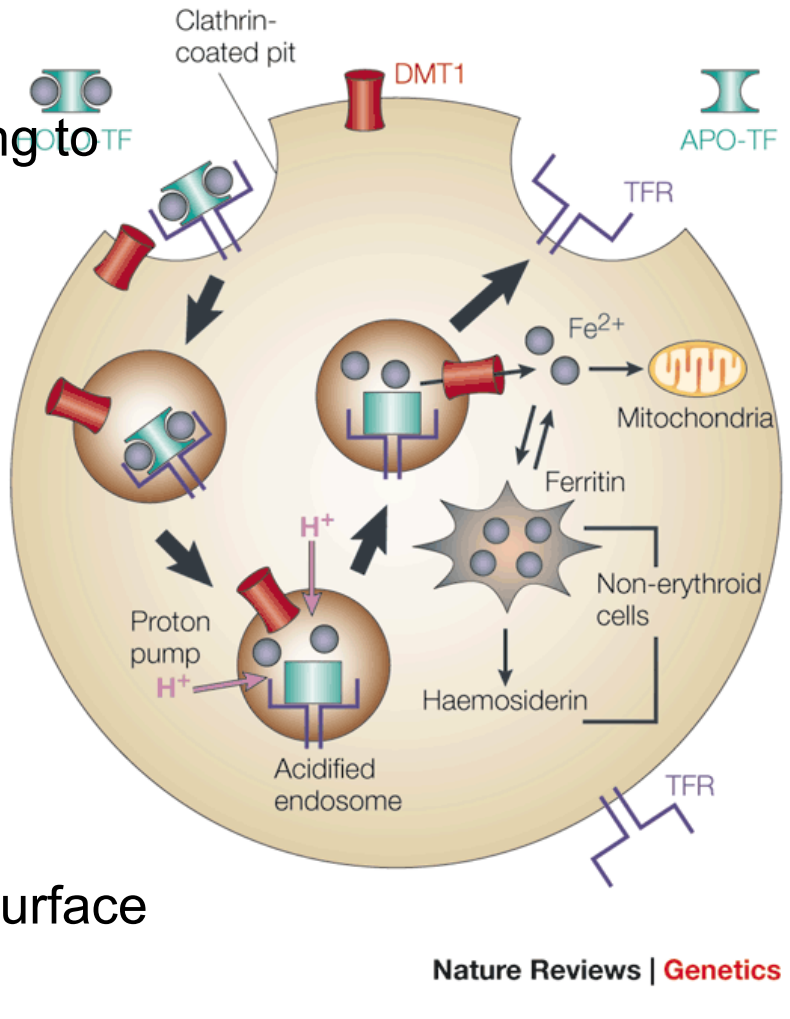
↓

transferrin gives up iron

↓

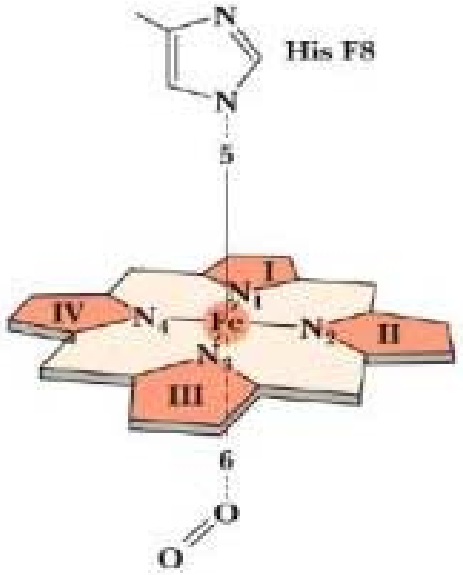
ferritin takes it up (iron storage)

3. transferrin returns onto the cell surface and dissociates from receptor



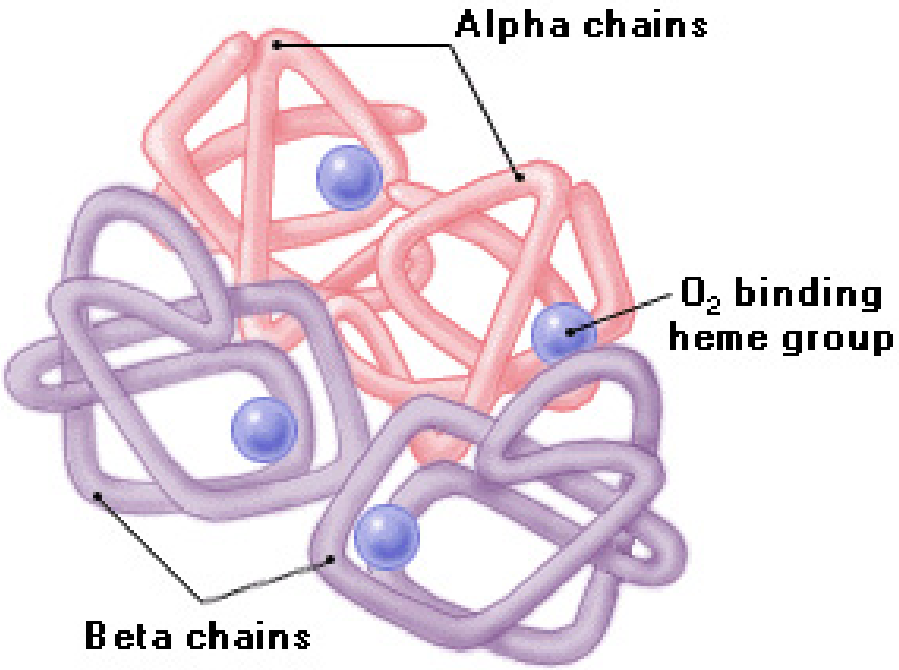
Hemoglobin

- hemoglobin
  - globin protein (4 subunits) → adult form: 2α és 2β chains
  - globin protein (4 subunits) → fetal: 2α és 2γ chains
  - hem (=protoporfirin IX + Fe^{2+}): connets to each subunits

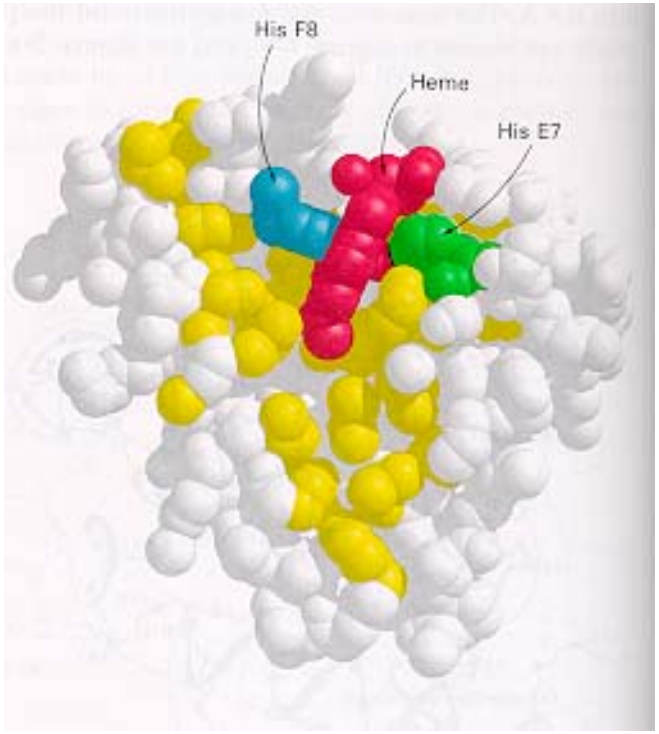


- myoglobin: 1 polipeptide + 1 hem

Structure



hemoglobin



myoglobin

Oxygen binding changes the conformation of hemoglobin

deoxygenated form → tight sructure (tight: T) (apolar and ionic chemical forces between α and β chains

oxygenated → Fe 2+ moves into the layer of porphirine ring

↓

conformation of subunits changes

↓

apolar and ionic forces are broken up

↓

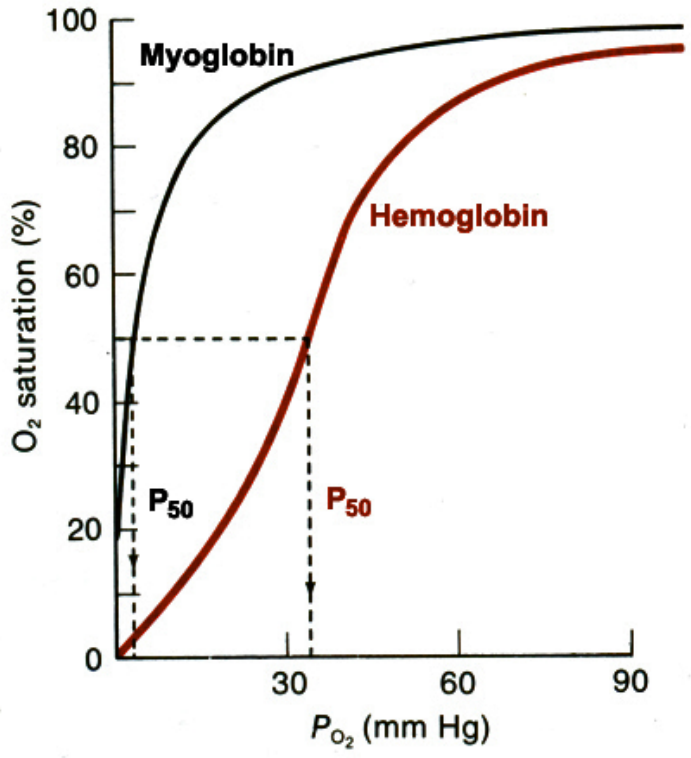
relaxed (R) conformation

Oxygen binding

- hemoglobin: cooperation among the subunits (oxygen binding caused conformational change of one chain enhances the binding capacity of neighboring chain

↓

sigmoid saturation curve



- mioglobin: 1 peptide chain (no cooperation)

↓

hyperbolic saturation curve (according to Michaelis-Menten kinetics)

Oxygen dissociation curve