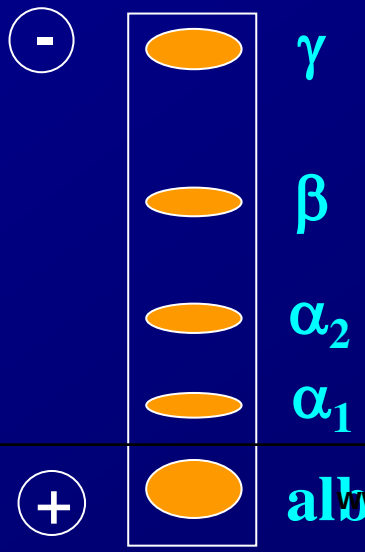
Plasma proteins

Plasma proteins

- concentration 65 –80 g/l
- simple or conjugated (glycoproteins, lipoproteins)
- separation:
  - a) salting-out methods → albumin, globulins, fibrinogen
  - b) electrophoresis → albumin, globulin α_1, α_2, β, γ fractions:

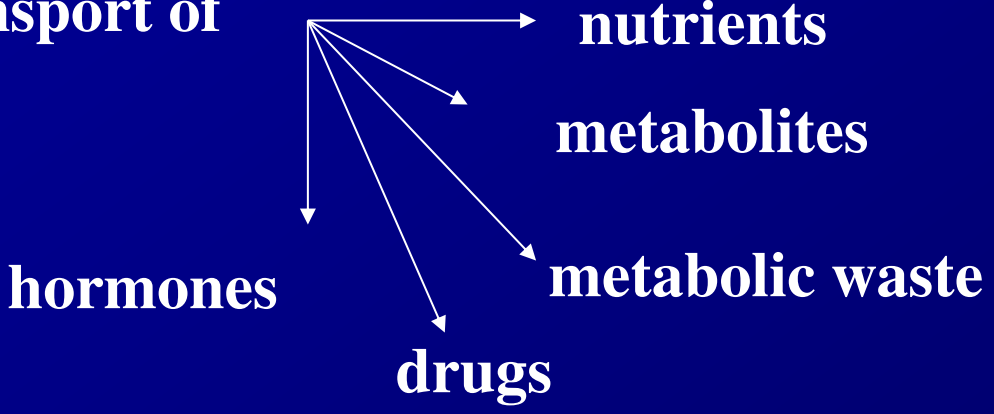


Elfo fractions of plasma proteins

Fraction	*Rel. amount (%)*	*c (g/l)*
Albumins: albumin pre-albumin (transthyretin)	52 – 58	34 – 50
α_1-globulins: thyroxin-binding globulin, transcortin, α_1-acid glycoprotein, α_1-antitrypsin, α_1-lipoprotein (HDL), α_1-fetoprotein	2,4 – 4,4	2-4
α_2-globulins: haptoglobin, macroglobulin, ceruloplasmin	6,1 – 10,1	5 – 9
β-globulins: transferrin, hemopexin, lipoprotein (LDL), fibrinogen, C-reactive protein, C3 and C4 components of the complement system	8,5 – 14,5	6 – 11
γ-globulins: IgG, IgM, IgA, IgD, IgE	10 – 21	8 – 15

Plasma proteins participate in:

1. blood coagulation
2. maintenance of homeostasis (pH, osmotic pressure)
3. defence against infection
4. transport of



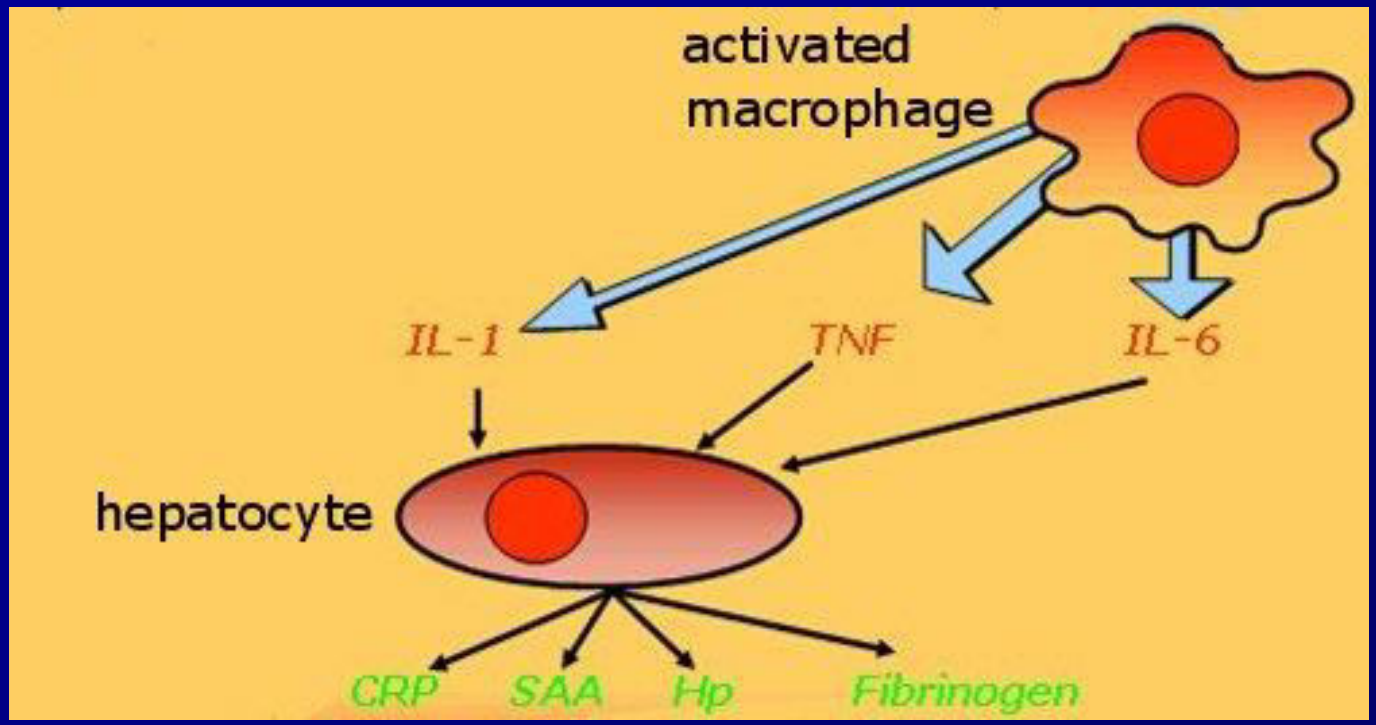
General properties of plasma proteins

- **Most are synthesized in the liver**
  Exception: γ-globulins – synthesized in plasma cells
- **Synthesized as pre-proteins on membrane-bound polyribosomes; then they are subjected to posttranslational modifications in ER and Golgi apparatus**
- **Almost all of them are glycoproteins**
  Exception: albumin
- **They have characteristic half-life in the circulation (albumin – 20 days)**
-
- **Many of them exhibit polymorphism (immunoglobulins, transferrin…)**

Acute phase reactants (APRs)

- Their levels change during acute inflammatory response
- APRs concentration changes in:
  - infection
  - surgery
  - injury
  - cancer

Acute phase reactant response



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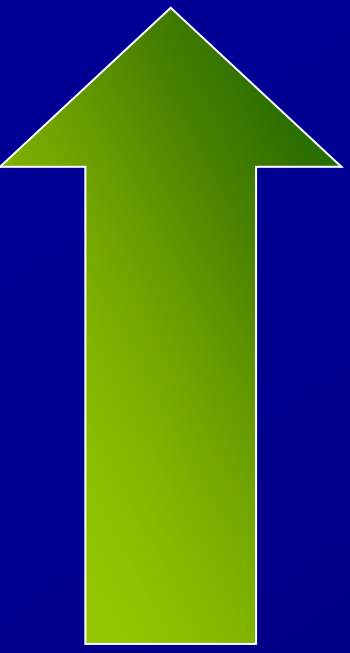
Types of APRs:



Positive

α1-antitrypsin

C-reactive protein (CRP): ~1000-fold increase!

fibrinogen

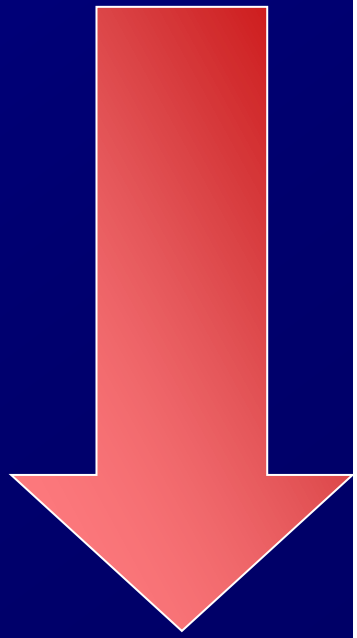
haptoglobin (HP)

C3, C4

Negative

albumin

transferrin



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ALBUMIN

- Concentration in plasma: 45 g/l
- ~ 60% of the total plasma protein

- Functions:
  - maintenance of the osmotic pressure of plasma
  - transport of:
    - steroid hormones
    - free fatty acids
    - bilirubin
    - drugs (sulfonamides, aspirin)
    - Ca^{2+}
    - Cu^{2+}

Causes of Albumin Deficiency

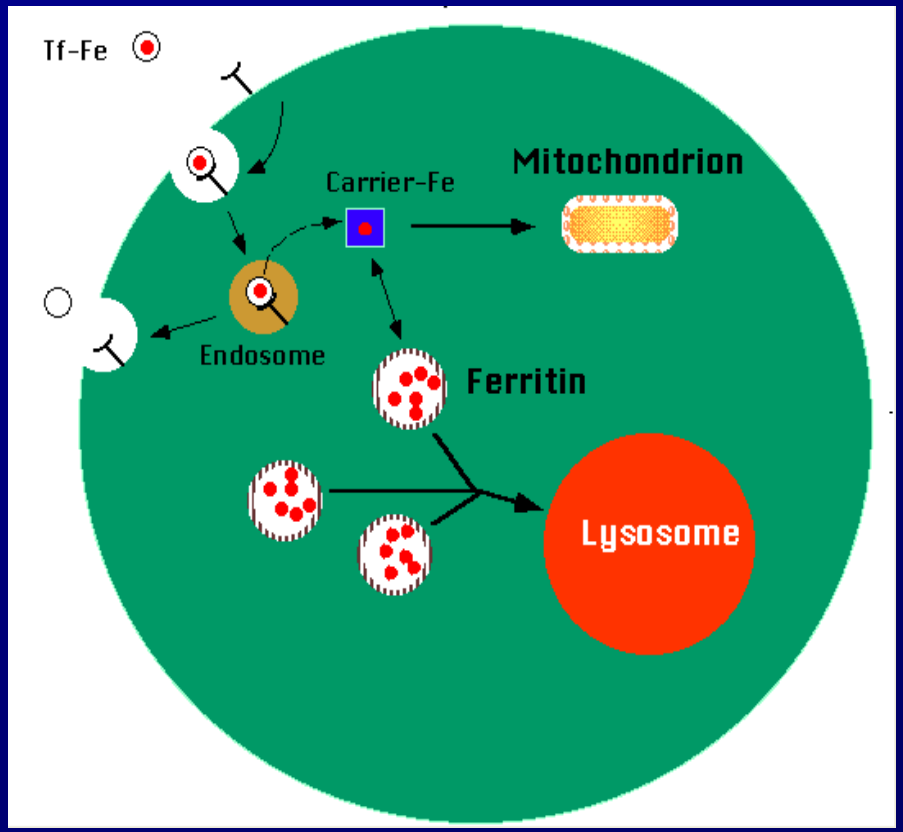
- Liver diseases (cirrhosis) – decrease in the ratio of albumin to globulins
- Protein malnutrition
- Excessive excretion by kidneys (renal disease)
- Mutation causing analbuminemia (affects splicing)

TRANSFERRIN

- Concentration in plasma: 3 g/l
- Functions:
  - transport of iron: from catabolism of heme and from food (gut) to the sites where iron is required, i.e. to the bone marrow and other organs
  - 2 moles of Fe^{3+} per 1 mol of transferrin

Receptor-mediated transferrin endocytosis

- Ferro-transferrin binds to the receptors on the cell surface → the complex is internalized into an endosome
- In endosomes, iron dissociates from trans-ferrin (enabled by low pH & $Fe^{3+} \rightarrow Fe^{2+}$ reduction) and enters cytoplasm
- Iron is delivered to intracellular sites or bound to ferritin ($Fe^{2+} \rightarrow Fe^{3+}$ oxidation and Fe^{3+} storage)
- Apotransferrin, associated with the receptor, returns to the membrane, dissociates from the receptor and re-enters plasma.



Causes of transferrin deficiency:

- Burns
- Infections
- Malignancies
- Liver and kidney diseases

Cause of relative transferrin excess:

- Iron-deficiency anaemia

FERRITIN

- Intracellular protein; only small portion in plasma
- 24 subunits surround 3000 - 4500 ions of Fe^{3+}
- Function: stores iron that can be called upon for use when needed

- Primary hemochromatosis – genetic disorder characterized by increased absorption of iron from the intestine ⇒ accumulated iron damages organs such as the liver, skin, heart, and pancreas. Concentration of ferritin is elevated.

CERULOPLASMIN

- **Conc. in plasma: 300 mg/l**

- **Functions:**
  - **carries 90% of copper in plasma (copper – cofactor for a variety of enzymes);**

    1 molecule binds 6 atoms of copper;

    binds copper more tightly than albumin that carries other 10% of copper ⇒ albumin may be more important in copper transport (donates copper to tissues more readily)

Causes of ceruloplasmin decrease:

- **Liver diseases, in particular Wilson´s disease:**
  - **genetic disease in which copper fails to be excreted into the bile and accumulates in liver, brain, kidney, and red blood cells**
  - **cause: mutations in the gene encoding for copper-binding ATPase**
  - **consequences:**
    - **accumulation of copper in liver, brain, kidneys… ⇒ liver disease, neurologic symptoms**
    - **↓ coupling of copper to apoceruloplasmin ⇒ low plasma levels of ceruloplasmin**

Causes of ceruloplasmin increase:

- **Inflammatory states**
- **Carcinomas, leukaemia**
- **Rheumatoid arthritis**

HAPTOGLOBIN

- α_2- globulin, tetrameric
- Exists in 3 polymorphic forms
- Functions:
  - binds free hemoglobin and delivers it to the reticuloendothelial cells
  - complex Hb-Hp is too large to pass through glomerulus ⇒ prevention of loss of free Hb

X

free Hb passes through glomeruli, enters tubules and precipitates therein ⇒ kidney damage

Causes of Hp increase

- Hp belongs to APRs ⇒
  - inflammation, infection
  - injury
  - malignancies

Causes of Hp decrease

- Haemolytic anaemia:
  half-life of Hp = 5 days x of complex Hp-Hb = 90 min (the complex is being rapidly removed from plasma) ⇒ Hp levels fall when Hb is constantly being released from red blood cells (as in haemolytic anaemia)

transferrin

ferritin

ceruloplasmin

haptoglobin

hemopexin (binds heme and transfers it to the liver)

- **act as antioxidants:**
  remove Fe $^{2+}$ and thus prevent the Fenton reaction:

$$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH\cdot + OH^-$$

α_1- ANTITRYPSIN (α_1-antiproteinase)

- Synthesized by hepatocytes and macrophages
- Major component (>90 %) of the α_1-fraction
- Glycoprotein, highly polymorphic
- Function: principal plasma inhibitor of serine protease (inhibits trypsin, elastase)
  - deficiency has a role in emphysema – proteolytic damage of the lung
  - methionine involved in AT binding to proteases is oxidized by smoking ⇒ AT no longer inhibits proteases ⇒ increased proteolytic damage of the lung, particularly devastating in patients with AT-deficiency