فريق طوفان الأقصى

METABOLISM

Modifide N.

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اللهم إنا نستودعك غزه وأهلها، أمنها وأمانها،
ليلها ونهارها، أرضها وسماءها، رجالها ونساءها،
شبابها وأطفالها، يا من لا تضيع عنده الودائع.

Synthesis of the plasma proteins

- Mostly liver (albumin, globulins), y-globulins (plasma cells; lymph nodes, bone marrow, spleen)
- Most plasma proteins are synthesized as preproproteins (signal peptide)
- Various post-translational modifications (proteolysis, glycosylation, phosphorylation, etc.)
- Transit times (30 min to several hours)
- Most plasma proteins are Glycoproteins (N- or O- linked). Albumin is the major exception

Synthesis of the plasma proteins

- Some of proteins synthesized to stay in mitochondria , cell membrane , or to be secreted out of the cell.
- The secretory proteins they are synthesized in a pre-pro form (it means they are synthesized as precursors) then they will be modified at the result they will be complete protein.
- Preproprotein was cleaved maybe one or two times and modified by different mechanisms in different groups in order to make a mature protein and that mature protein taking this quaternary structure and the quaternary structure make it functional protein. The preproprotein is not functional.

Functions of plasma proteins

General functions

- A nutritive role , important for nutrition aspects.
- Maintenance of blood pH (amphoteric property) , so they are good buffers , why? Because they contain histidine amino acid which pKa is near to physiological PH , also proteins have weak acid groups (carboxylic groups) & their salts and that will help resist the changes in PH.
- Contributes to blood viscosity ; because of high concentration of albumin
- Maintenance of blood osmotic pressure ; because of high concentration of albumin

Specific functions

- Enzymes (e.g. rennin, coagulation factors, lipases –degrade triacylglycerol-)
- Humoral immunity (immunoglobulins)
- Blood coagulation factors
- Hormonal (Erythropoietin); important for the synthesis of RBCs.
- Transport proteins (Transferrin –transport Fe-, Thyroxin binding globulin –transport thyroid hormone-, Apolipoprotein -lipid moiety is removed-)

Acute-phase proteins

- (positive acute phase proteins) Levels –of plasma proteins- increase (0.5-1000 folds) in some conditions as : acute inflammation, tissue damage, chronic inflammation & cancer. Examples : C-reactive protein (CRP), α1 -antitrypsin, haptoglobin, & fibrinogen

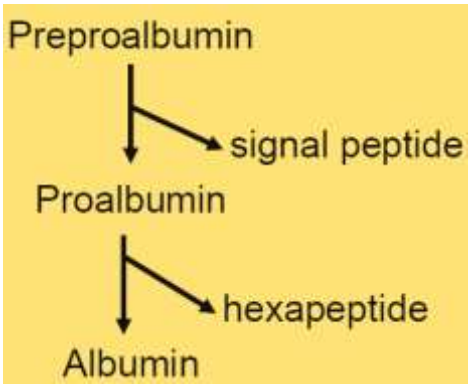
Example : If CRP concentration in physiological conditions is 20 mg/dl , under inflammation, tissue damage or cancer it'll be hundreds mg/dl.

#CRP is the mostly used marker in case of inflammation and infection , because determination of other protein except CRP quantitively is difficult.

- Negative acute phase proteins: prealbumin, albumin, transferrin ; these proteins concentrations will decrease in case of inflammation, tissue damage or cancer , because the liver would be busy in synthesizing the positive acute phase proteins

Albumin

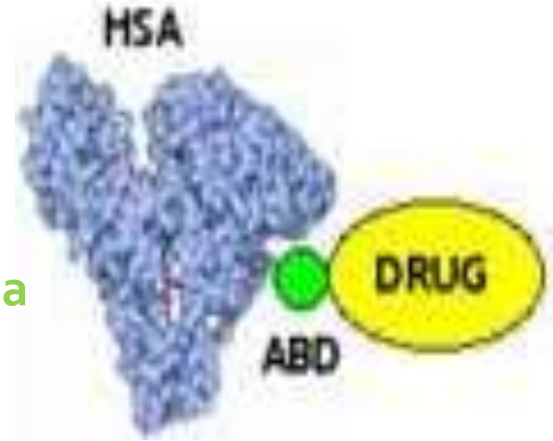
- The Major Protein in Human Plasma, 69 kDa, half-life (20 days).
- The main contributor to the osmotic pressure (75-80%)
- It plays a predominant role in maintaining blood volume and body fluid distribution.
- Liver: 12 g/day (25% of total protein synthesis) (liver function test) , if there is a problem with liver this rate will decrease.
- Synthesized as a preproprotein
- One polypeptide chain, 585 amino acids, 17 disulfide bonds (cys-cys , to support its tertiary structure)
- Proteases subdivide albumin into 3 domains; structural and functional unit within a protein's three-dimensional structure , it has specific function.
- Ellipsoidal shape (viscosity) vs. fibrinogen
- Anionic at pH 7.4 with 20 negative charges



2 proteolytic cleaveges , after 1st one preproalbumin turn onto proalbumin (cleaved first 20-30 amino acids from the N-terminal region),
the second cleavage remove hexapeptide and convert proalbumin to albumin.
These proteolytic cleaveges are important , and they give albumin its proper tertiary structure so it'll be functional, any problem in this pathway would result in non-functional albumin.

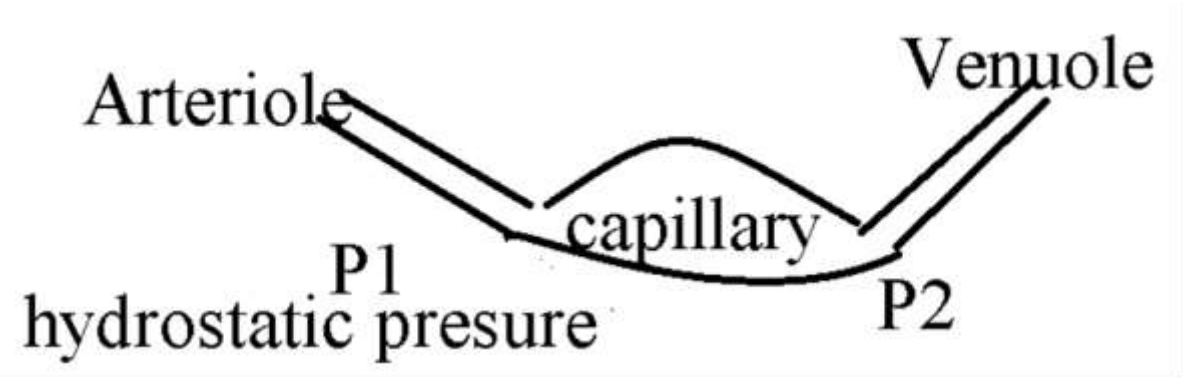
Albumin binding capacity

- **binds various ligands:**
  - ✓ **Free fatty acids (FFA)** ; lipids are stored as triglycerides in adipose tissue , lipases will degrade triglycerides when body needs energy , then after degradation fatty acids will be transferred to liver in a non-esterified form.
  - ✓ **Certain steroid hormones**
  - ✓ **Bilirubin** ; related to bile acid , product of heme degradation that comes from hemoglobin , metabolize in liver and convert it to bilirubin (yellow color).
  - ✓ **Plasma tryptophan**; give a protein a property to absorb light at 2.80 nanometer, helps to quantitate.
  - ✓ **Metals: Calcium, copper and heavy metals**
  - ✓ **Drugs: sulfonamides, penicillin G, dicumarol, aspirin (drug-drug interaction)**



CONGESTIVE HEART FAILURE

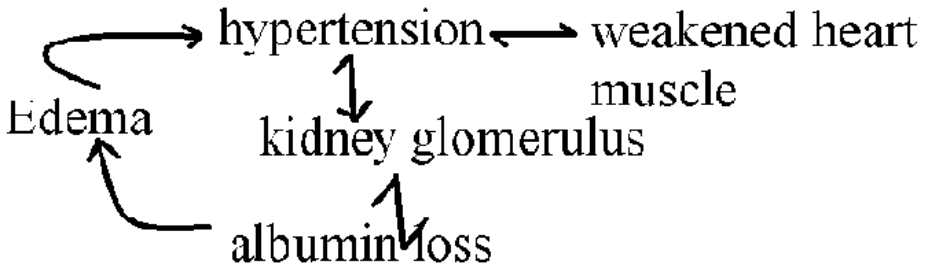
- P1>P2
- Water and salts diffuse out the capillary
- Albumin creates an osmotic force which results in reabsorption of water and electrolytes.



Because P1 is greater than P2 so water and electrolytes will diffuse outside because of the high osmatic pressure. And because of albumin there will be reabsorption of this water and salts.

CONGESTIVE HEART FAILURE

- Congestive heart failure is cycle of hypertension, weakening of cardiac muscle, kidney damage an edema.
- Hypertension can lead to loss of albumin from the kidney
- Less plasma albumin
- Less osmotic force at capillaries gives edema
- Edema increases hypertension
- Hypertension increases weakening cardiac muscle which reciprocally increases hypertension

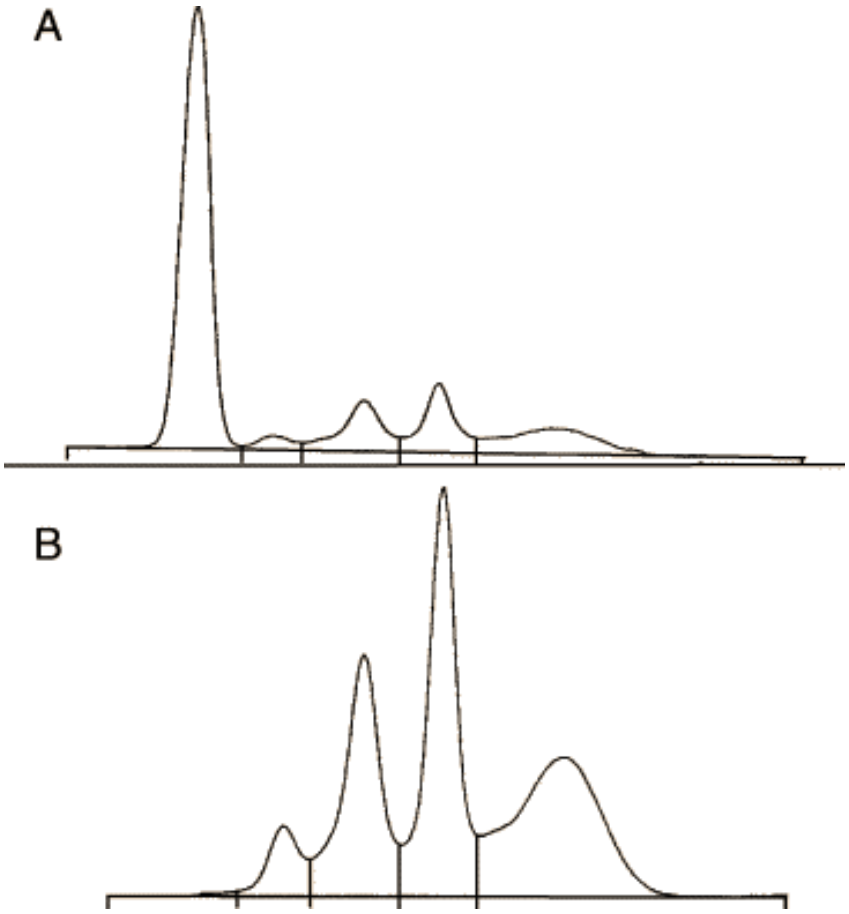


This is to show you the importance of albumin and how that (loss of albumin) can cause congestive heart failure.

In the presence of hypertension it will lead to kidney problems and the albumin in the blood will start to be lost because of the kidney disfunction
and because of the loss of the albumin there will be an Edema formation and Edema will increase the hypertension.
Hypertension will weak the heart muscle

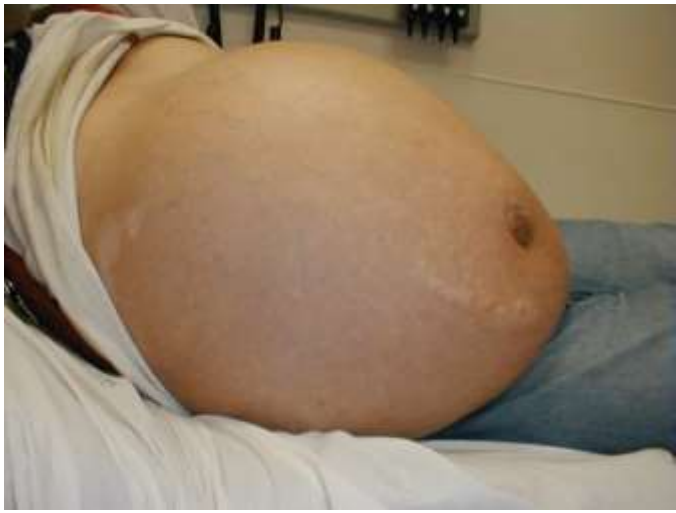
Analbuminemia

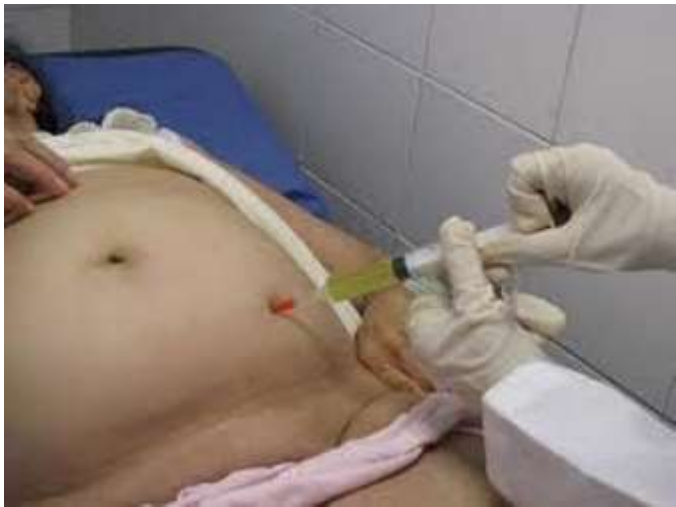
- There are human cases of analbuminemia (rare) , albumin genetically isn't synthesized.
- Autosomal recessive inheritance
- One of the causes: a mutation that affects splicing of the mRna of the gene of albumin.
- Patients show moderate edema!!!



Other clinical disorders

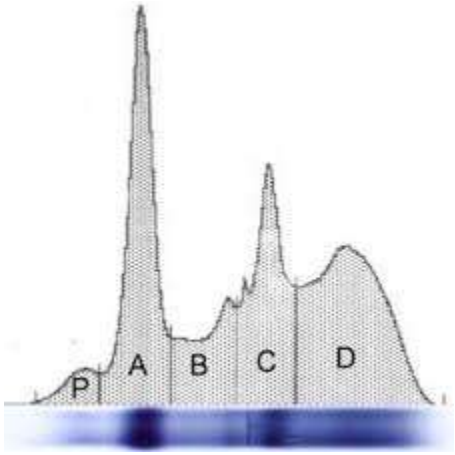
- **Hypoalbiminemia: edema seen in conditions where albumin level in blood is less than 2 g/dl**
  - ✓ **Malnutrition (generalised edema)**
  - ✓ **Nephrotic syndrome**
  - ✓ **Cirrhosis (mainly ascites)**
  - ✓ **Gastrointestinal loss of proteins**
- **Hyperalbuminemia: dehydration (relative increase)**



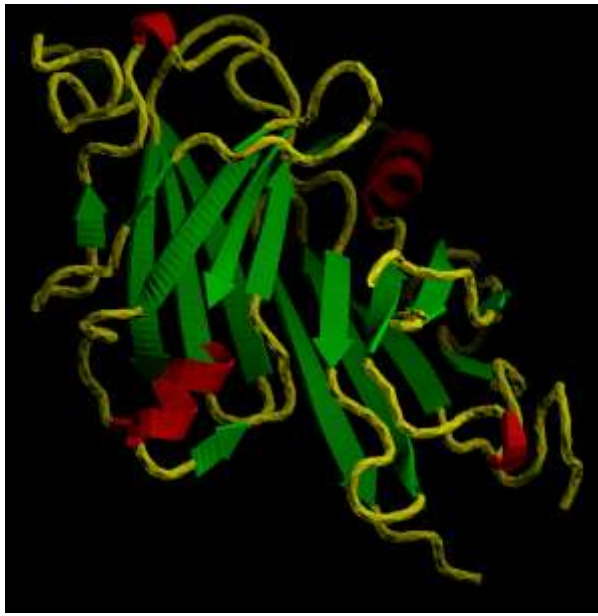


Prealbumin (transthyretin)

- Very minor plasma protein
  Migrates ahead of albumin, 62 kDa



- It is a small glycoprotein (rich in tryptophan, 0.5% carbohydrates)
- Blood level is low (0.25 g/L)



- It has short half-life (≈2 days): sensitive indicator of disease or poor protein nutrition
- Main function:
  - ✓ T_4 (Thyroxine) and T_3 carrier

Globulins

α1-globulins	α2- globulins	β- globulins	γ-globulins
▪α1-antitrypsin ▪α1-fetoprotein ▪α1- acid glycoprotein ▪Retinol binding protein	▪Ceruloplasmin ▪Haptoglobin ▪α2-macroglobulin	▪CRP ▪Transferrin ▪Hemopexin ▪β2-microglobulin	▪IGG ▪IGA ▪IGM ▪IGD ▪IGE

Just know that they are globulins and if they have a clinical significance (Don't memorize all of them).

α1-Antitrypsin

- α1-Antiproteinase (52 kDa)
- Neutralizes trypsin & trypsin-like enzymes (elastase< which found on lungs tissues) {it controls the activity of proteases}
- 90% of α1- globulin band
- Many polymorphic forms {has multiple forms} (at least 75).
- Alleles *PiM*, *PiS*, *PiZ*, *PiF* (MM is the most common)
- Deficiency (genetic): emphysema (ZZ, SZ). MS, MZ{homo or heterozygous} usually not affected

people with ZZ will affect more than people with MM

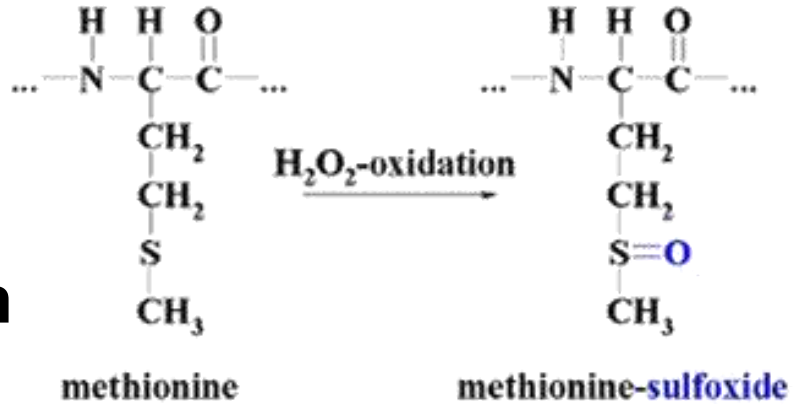
- Increased level of α1- antitrypsin (acute phase response)
- α1- antitrypsin may be affect by smoking

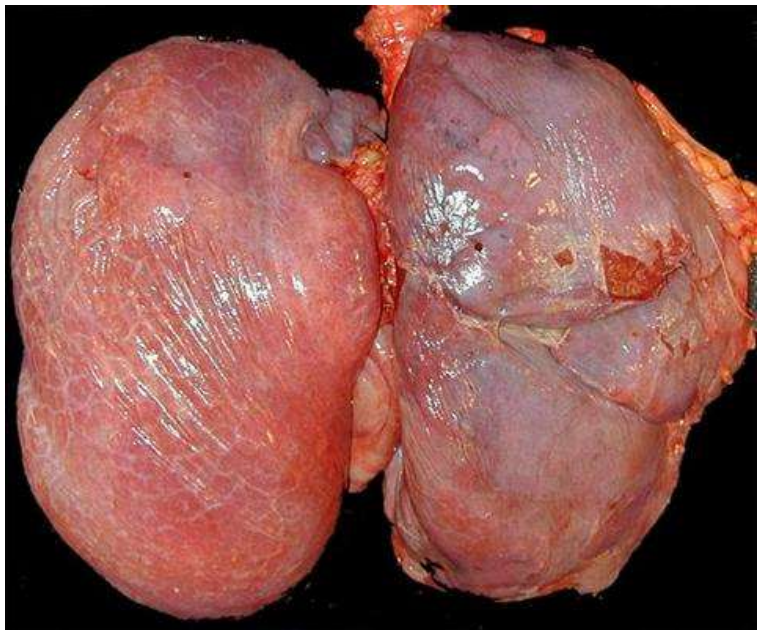
Active elastase + α_1–AT → Inactive elastase: α_1–AT complex → No proteolysis of lung → No tissue damage

Active elastase + ↓ or no α_1–AT → Active elastase → Proteolysis of lung → Tissue damage

Smoking & α1- antitrypsin deficiency

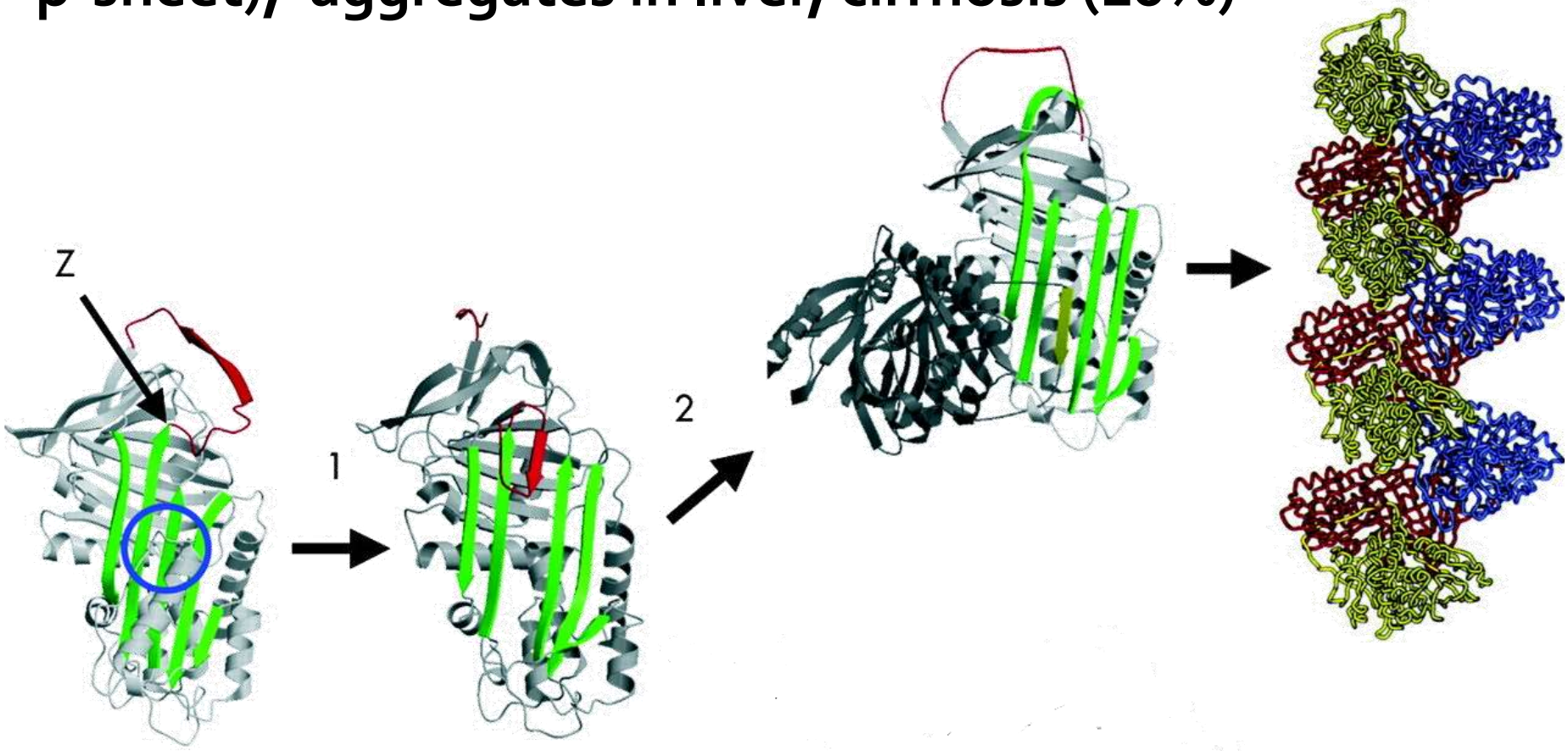
- **Chronic inflammation** (neutrophil elastase)
- **Oxidation of Met^{358}**
- **devastating in patients with *Pi^{ZZ}***





Liver disease & α1- antitrypsin deficiency

- **Liver disease: ZZ phenotype polymerization (loop with β-sheet), aggregates in liver, cirrhosis (10%)**



α1- fetoprotein

- Synthesized primarily by the fetal yolk sac and then by liver parenchymal cells
- Very low levels in adult
- Functions of α1-fetoprotein:
  - ✓ Protect the fetus from immunolytic attacks
  - ✓ Modulates the growth of the fetus
  - ✓ Transport compounds e.g. steroids
  - ✓ Low level: increased risk of Down's syndrome
- Level of α1-fetoprotein increases in:
  - ✓ Fetus and pregnant women <u>Normally</u>
  - ✓ Hepatoma & acute hepatitis

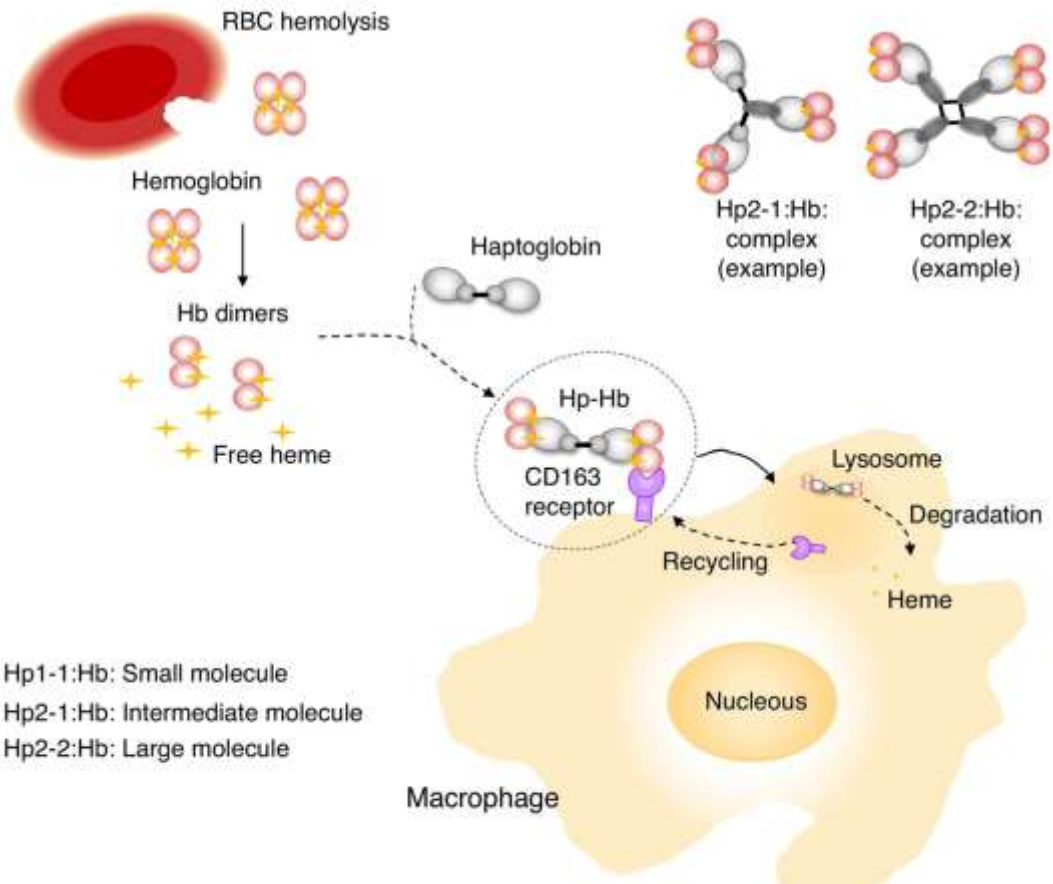
Orosomucoid/ alpha-1-acid glycoprotein

- Concentration in plasma– 0.6 to 1.4 G/dl
- Carbohydrate content 41%
- Marker of acute inflammation
- Acts as a transporter of progesterone
- Transports carbohydrates to the site of tissue injury
- Concentration increases in inflammatory diseases, cirrhosis of liver and in malignant conditions
- Concentration decreases in liver diseases, malnutrition and in nephrotic syndrome

Haptoglobin (HP)

- It is an acute phase reactant protein
- α2 glycoprotein (90kDa)
- A tetramer (2α, 2β)
- 3 phenotypes:
  - ✓ Hp 1-1⟶ α1, α1 + 2β
  - ✓ Hp 2-1⟶ α1, α2 + 2β
  - ✓ Hp 2-2 ⟶ α2, α2 + 2β

- Binds the free hemoglobin (65 kDa); prevents loss of hemoglobin & its iron into urine
- Hb-Hp complex has shorter half-life (90 min) than that of Hp (5 days)
- Decreased level in hemolytic anemia



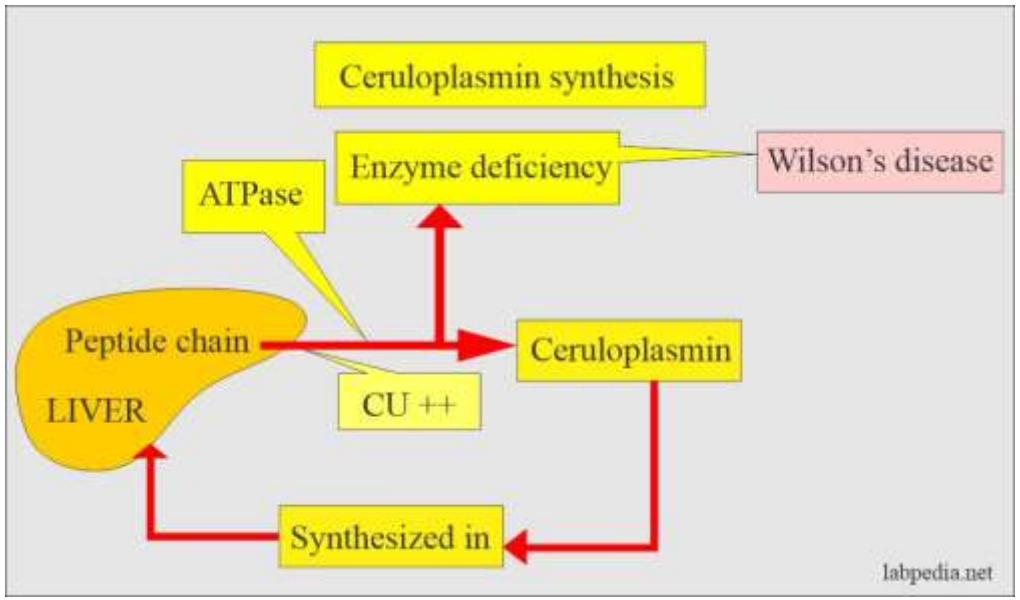
HP will bind to free hemoglobin to prevent the loosing of iron.
HP is considered as antibodies of hemoglobin.

Ceruloplasmin

Cu-containing enzymes

- Amine oxidase
- Copper-dependent superoxide dismutase
- Cytochrome oxidase
- Tyrosinase

- A copper containing glycoprotein (160 kDa)
- It contains 6 atoms of copper
- Metallothioneins (regulate tissue level of Cu)
- Regulates copper level: contains 90% of serum Cu



- A ferroxidase: oxidizes ferrous to ferric (transferrin)
- Albumin (10%) is more important in transport
- Decreased levels in liver disease (ex. Wilson's, autosomal recessive genetic disease)

Alpha- 2 Macroglobulin

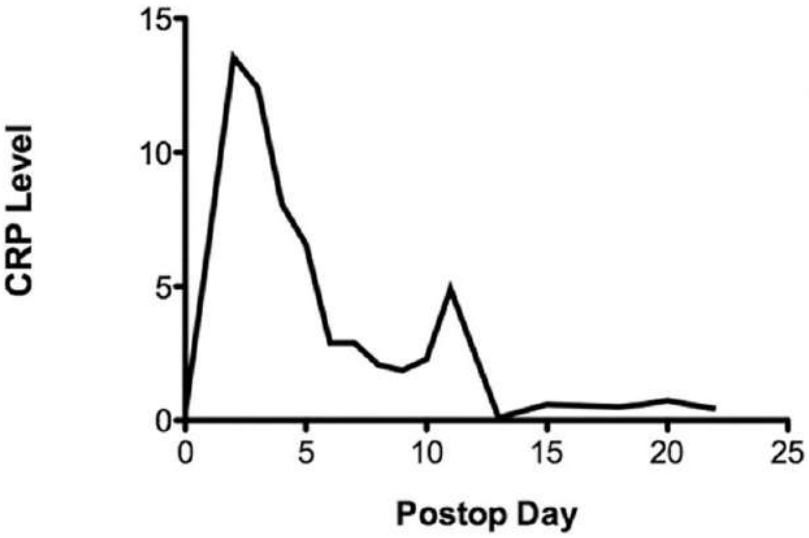
- Comprises 8-10% of the total plasma protein in humans.
- Synthesized by hepatocytes and macrophages
- Inactivates all the proteases and thus is an important in vivo anticoagulant.
- Carrier of many growth factors
- Normal serum level-130-300 mg/dl
- Concentration is markedly increased in nephrotic syndrome, since other proteins are lost through urine in this condition.

Haemopexin(β-globulin)

- Normal level in adults-0.5 to 1.0 gm/L
- Low level at birth, reaches adult value within first year of life
- Synthesized in liver
- Function is to bind haem formed from breakdown of Hb and other haemoproteins
- Low level- found in hemolytic disorders, at birth and drug induced
- High level- pregnancy, diabetes mellitus, malignancies and Duchenne muscular dystrophy

C- reactive protein (CRP)

- Able to bind to a polysaccharide (fraction C) in the cell wall of pneumococci
- Help in the defense against bacteria and foreign substances



- Undetectable in healthy individuals, detectable in many inflammatory diseases (Acute rheumatic fever, bacterial infection, gout, etc.) & Tissue damage

- Its level reaches a peak after 48 hours of incident (monitoring marker)

Complement C1 q (β-globulin)

- First complement factor to bind antibody
- Binding triggers the classical complement pathway
- Thermo labile, destroyed by heating
- Normal level – 0.15 gm/L
- Decreased level is used as an indicator of circulating Ag – Ab complex.
- High levels are found in chronic infections

γ-Gamma-globulin

- They are immunoglobulins with antibody activity
- They occupy the gamma region on electrophoresis
- Immunoglobulins play a key role in the defense mechanisms of the body
- There are five types of immunoglobulins IgG, IgA, IgM, IgD, and IgE.

Different classes of immunoglobulins

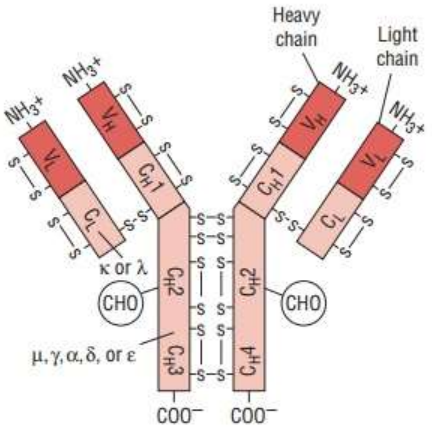
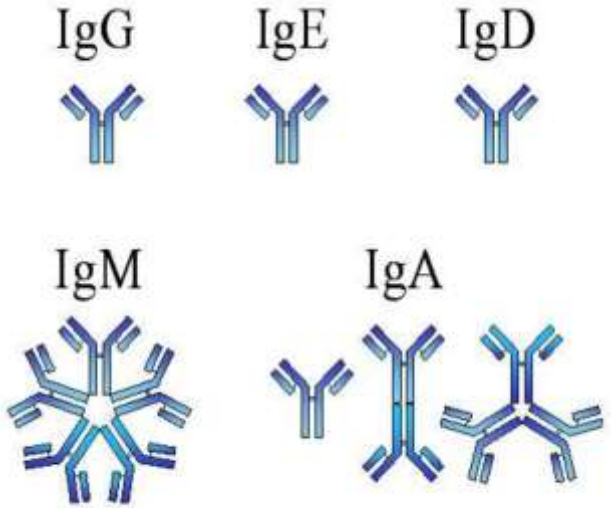


FIG. 13-1. Schematic diagram of monomer of the immunoglobulin.



Immunoglobulin Major Functions

Immunoglobulin	Major Functions
IgG `	Main antibody in the secondary response. Opsonizes bacteria, Fixes complement, neutralizes bacterial toxins and viruses and crosses the placenta.
IgA	Secretory IgA prevents attachment of bacteria and viruses to mucous membranes. Does not fix complement.
IgM Does	Produced in the primary response to an antigen. Fixes complement. not cross the placenta. Antigen receptor on the surface of B cells.
IgD	Uncertain. Found on the surface of many B cells as well as in serum.
IgE	Mediates immediate hypersensitivity Defends against worm infections.

Fibrinogen

- Also called clotting factor1
- Constitutes 4-6% of total protein
- Highly elongated with axial ratio of 20:1
- Imparts maximum viscosity to blood
- Synthesized in liver
- Made up of 6 polypeptide chains
- Chains are linked together by S-S linkages
- Amino terminal end is highly negative due to the presence of glutamic acid
- Negative charge contributes to its solubility in plasma and prevents aggregation due to electrostatic repulsions between the fibrinogen molecules.

Transport proteins

Name	Compounds transported
Albumin heavy	Fatty acids, bilirubin, hormones, calcium, metals, drugs etc.
Prealbumin-(Transthyretin)	Steroid hormones thyroxin, Retinol
Retinol binding protein	Retinol (Vitamin A)
Thyroxin binding protein(TBG)	Thyroxin
Transcortin(Cortisol binding protein)	Cortisol and corticosteroids
Haptoglobin	Hemoglobin
Hemopexin	Free haem
Transferrin	Iron
HDL(High density lipoprotein)	Cholesterol (Tissues to liver)
LDL(Low density lipoprotein)	Cholesterol(Liver to tissues)

Acute Phase Proteins

The levels of certain proteins may increase in blood in response inflammatory and neoplastic conditions, these are called Acute

phase proteins.

Examples-

- C- reactive proteins
- Ceruloplasmin
- Alpha -1 antitrypsin
- Alpha 2 macroglobulins
- Alpha-1 acid glycoprotein

Negative Acute Phase Proteins

The levels of certain proteins are decreased in blood in response to certain inflammatory processes.

Examples–

- Albumin
- Transthyretin
- Retinol binding protein
- Transferrin

Clinical significance of plasma proteins

Hyperproteinemia- Levels higher than 8.0gm/dl

Causes-

- Hemoconcentration- due to dehydration, albumin and globulin both are increased Albumin to Globulin ratio remains same.
- Causes- Excessive vomiting
- Diarrhea
- Diabetes Insipidus
- Diuresis
- Intestinal obstruction

Hypoproteinemia

Decrease in total protein concentration

- Hemodilution- Both Albumin and globulins are decreased, A:G ratio remains same, as in water intoxication
- Hypoalbuminemia- low level of Albumin in plasma

Causes-

- Nephrotic syndrome
- Protein losing enteropathy
- Severe liver diseases
- Mal nutrition or malabsorption
- Extensive skin burns
- Pregnancy
- Malignancy

Hypogammaglobulinemia

- Losses from body- same as albumin- through urine, GIT or skin
- Decreased synthesis
- Primary genetic deficiency
- Secondary – drug induced (Corticosteroid therapy), uremia, hematological disorders
- AIDS(Acquired Immuno deficiency syndrome)

Hypergammaglobulinemia

1)Polyclonal–

- Chronic infections
- Chronic liver diseases
- Sarcoidosis
- Auto immune diseases

2) Monoclonal

- Multiple myeloma
- Macroglobulinaemia
- Lymphosarcoma
- Leukemia
- Hodgkin’s disease