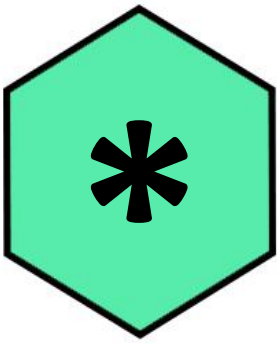


Sheet Slides

Done By

RAHAF MUWALLA

Contributed in the Scientific Correction

Ibrahim N. Dbaybo

Contributed in the Grammatical Correction

Ibrahim N. Dbaybo

Doctor

Dr. Diala

-We discussed that the **albumin** is the major constituent of plasma proteins.

Prealbumin

-Small protein.

-Short half-life(2Days). >

-Combines with:

1- T4 (Thyroxine) and T3

2- Retinol binding protein

-Decreased in case of Hepatic damage in liver + Tissue necrosis

-Sensitive marker of poor protein nutrition, why?

It has a short half-life of 2 days, which allows us to detect any change in its levels.

If there is a problem in nutrition, we can't detect it with albumin due to its long half-life(20days).

-smaller than albumin, so it travels at a rate faster than that of albumin in gel electrophoresis.

-Transthyretin is the new name of Prealbumin.

NOTE:

-Prealbumin isn't related to the process of maturation of albumin. Albumin is produced in an immature way. Albumin (before maturing) has signal peptides which direct it to ER for modification, and to excretion to blood. These signal peptides are cleaved before albumin is excreted from hepatocytes, giving us mature albumin.

Prealbumin and albumin are two different proteins.

ACUTE PHASE PROTEINS

- are proteins that increase in level during inflammatory. This increase varies between 50% and 1000 folds.

-**Examples**: C-reactive protein, α1-antitrypsin, haptoglobin.

- These proteins play a role in body's response to inflammation.

- their level increase during chronic and acute inflammatory states and Cancer.

-There are some groups of them reduce during inflammation.

1- C-Reactive Protein (CRP)

- Undetectable in healthy individuals.

- Is detected in patients with diverse inflammatory diseases:

>Acute rheumatic fever, bacterial infection, and gout

>It is also detected in Tissue damage

- So, it is a biomarker of tissues injury, infection, and inflammation.

-It is called C-Reactive Protein because it reacts with C substance (polysaccharide in Pneumococci and molecular groups on a wide variety of bacteria.

****

2- α1-Antiproteinase(α1-antitrypsin)

-Inhibits trypsin, elastase, and other proteases

-52kD Glycoprotein(394 A.A with 3 oligosaccharides chains)

-Makes up 90% of α1 fraction of human plasma(he **alpha-1 fraction** includes **alpha-1** antitrypsin, transcortin, and thyroid-binding globulin)

-Works by inhibiting serine protease

-It is produced by hepatocytes + macrophages.

- **α1-antitrypsin** has many polymorphic forms.

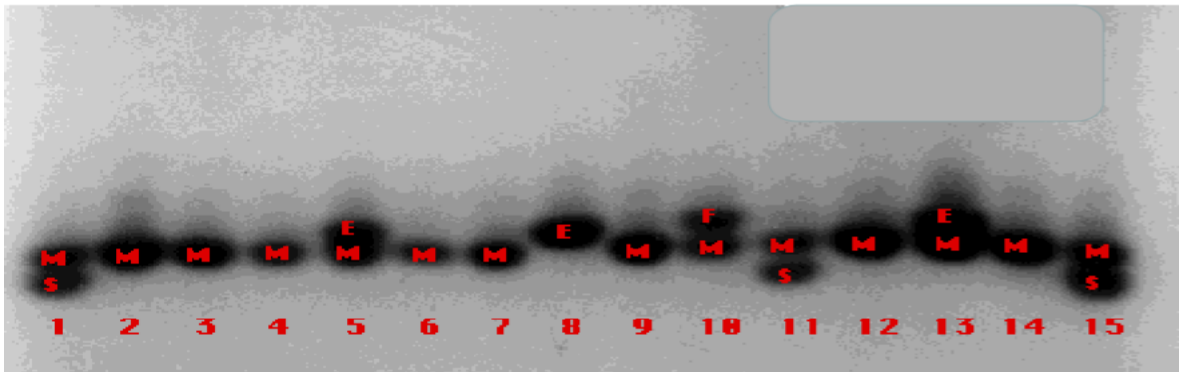
there are four alleles: Pi^M, Pi^S, Pi^Z, Pi^F

-The major genotype is MM

- Individuals with ZZ (homozygous) genotype and SZ (heterozygotes) develop defects in the protein which causes emphysema

- Individuals with MS or MZ genotypes are usually not affected

Electrophoresis of an ezyme that exhibits polymorphism



- Different polymorphisms generate bands with different sizes

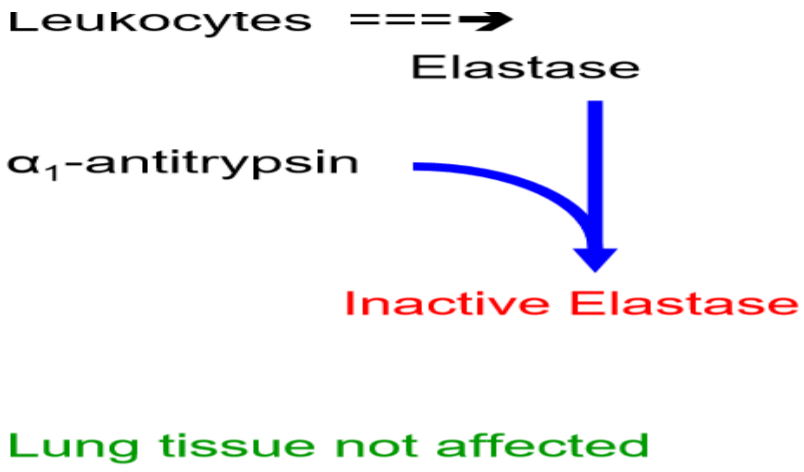
****

**How does α1-antitrypsin protect the lung?

Normally→ during inflammatory process→ activation of Leukocytes→ Leukocytes activate elastase→ elastase will start destruction.

➔ In order to stop elastase, **α1-antitrypsin** will be activated and will inhibit elastase.

➔ Lung tissue unaffected



Abnormality → low concentration of **α1-antitrypsin,** so elastase will remain active → elastase will destruct elastic fiber → as a result, **lung tissue will be destructed.**

****

-Deficiency of **α1-antitrypsin** is caused either by smoking or genetic mutation.

-Smoking and α1-antitrypsin deficiency

Smoking oxidizes methionine 358 (met358) → inactivation

Met358 is involved in binding **α1-antitrypsin** to proteinase (elastase for example)

When met358 is oxidized → no binding between **α1-antitrypsin**and elastase→ elastase remains active →destruction of lung tissue.

-Individuals with Pi^{ZZ} phenotype have the highest risk.

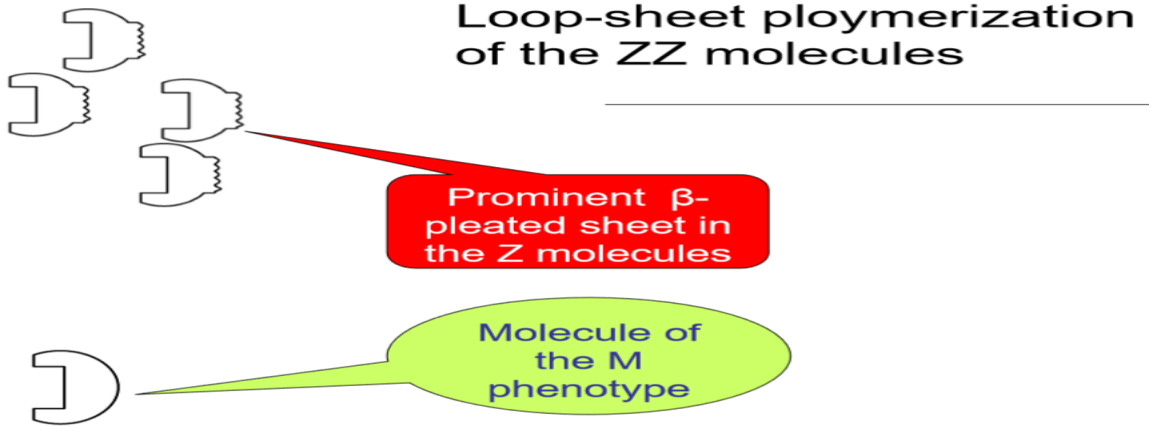
****

-α1-antitrypsin deficiency in liver disease

-Polymerization of ZZ molecules in the endoplasmic reticulum of hepatocytes.

-Aggregation is due to interaction between a loop in one molecule and a prominent β-pleated sheet in another molecule of the protein.

-As a result of aggregation, a large complex will be formed, and it won't be excreted into the blood stream



Ceruloplasmin(α2-globulin)

-α2-globulin(160kD)

- tight binding to copper

-90% of the plasma copper bind to the α2-globulin.

- α2-globulin has a high capacity to bind with copper (6 atoms/molecule).

- Albumin binds the remaining 10%

- Has oxidase activity (ferroxidase)→ oxidation specifically on iron (affects iron metabolism). -->it binds to copper but oxidizes iron!

- Low level in **Wilson disease**→ which is hepatolenticular degeneration due to the problems in copper metabolism.

****

Transferrin: Iron binding Protein

-Transferrin is responsible for the transfer of iron from one organ to another.

- RBCs need to be broken down after 120 days for renewal

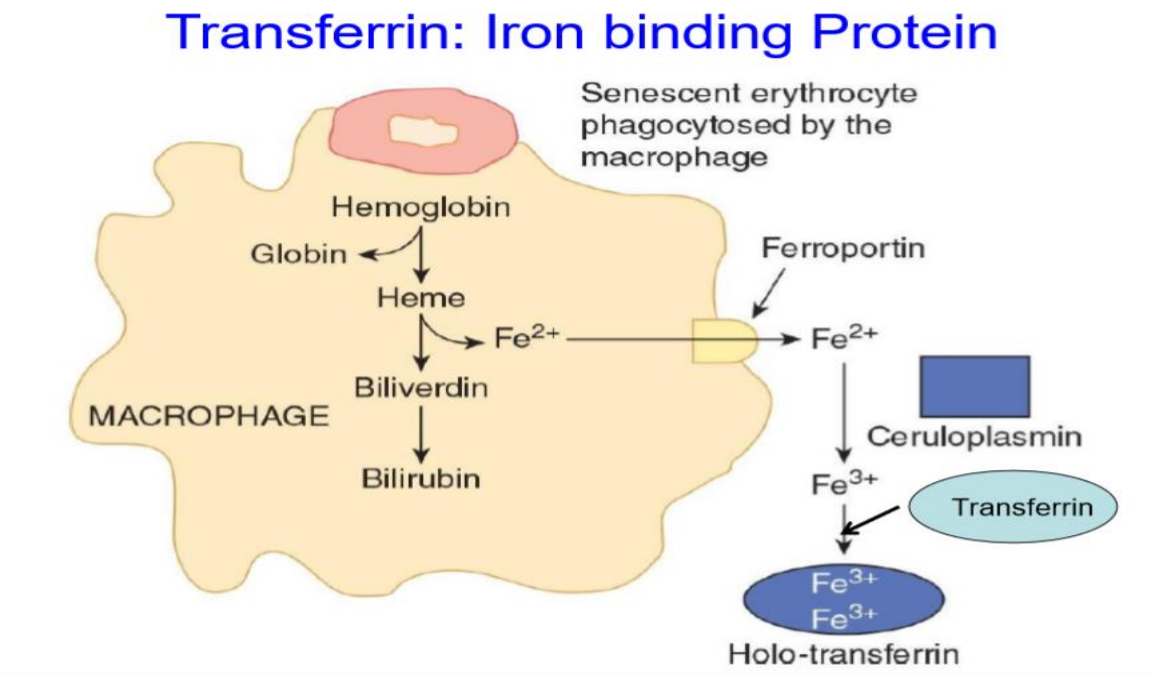
***Reticuloepithelial system** is a generalized phagocytic system located in all tissues, including the spleen, which is the major site of RBCs degradation.

-During the degradation of RBCs, hemoglobin, a major protein in RBCs, will get metabolized. Hemoglobin contains Heme group and iron(Fe^{2+})(ferrous)

- ➔ Heme group is the part of hemoglobin that binds to iron(ferrous)
- ➔ Fe^{+2} will get released by **ferroportin**, exiting the macrophage.
- ➔ Outside the phage, transferrin is always available to collect iron.
- ➔ Transferrin can bind to iron **only** if it in Fe^{+3} form, so we need **ceruloplasmin(α2-globulin)** to oxidize Fe^{+2} into Fe^{+3}(ferrous to ferric). The transfer of iron by transferrin will not take place, unless **ceruloplasmin(α2-globulin)** oxidizes the iron molecule.

****That's all what we should know about iron metabolism for the time being.**

To sum up:



Hapatoglobin(Hp)

- 90kD
- Synthesized mainly by hepatocytes.
- Two kinds of polypeptide chains: (4 polypeptide chains)
- • Two α chains. • one β chain.
- Has three polymorphic forms: Hp 1-1, Hp 2-1, Hp 2-2
- Polymorphism is associated with many inflammatory diseases.
- Is one of the acute phase proteins(its levels increase during inflammatory responses)
- Levels also increase in burns and in nephrotic syndrome
- 10% of the hemoglobin(hb) degraded each day is released into the plasma.
  - ➔ Haptoglobin, characterized by its tight binding of free hemoglobin (not covalently), will bind to the hemoglobin before being broken down by reticuloendothelial(free hemoglobin).
  - ➔ Why does haptoglobin bind to hemoglobin?
    -Because hemoglobin, as a protein, is intermediate in size(65kDa). Meaning that if the body releases it as a free protein after degradation of RBC, it is going to leak to the kidney and get excreted instead of reusing it in another

RBC. Excretion of iron will cause iron deficiencies, obliging us to increase our iron uptake through nutrition to replenish what we have lost.

-But if binding was to occur → the complex, haptoglobin(90kD) along with the hemoglobin, will be about (155kDa), making it very large to get excreted through the kidney.

Haptoglobin level

- Haptoglobin level Measured as Hb binding capacity to hemoglobin (Normally 40-180 mg of Hb binding capacity).

-Haptoglobin has a half-life of 5 days.

- **Hemolytic anemia**: kind of anemia where, large amounts of RBCs are hemolyzed, causing very large amounts of hemoglobin to be released.

*Why does haptoglobin, in the case of **Hemolytic anemia**, decrease?

The hemoglobin-haptoglobin complex (Hb-Hp complex) has a very short half-life of 90 minutes (80 times faster than haptoglobin), unlike that of a free haptoglobin (5 days). High concentrations of hemoglobin released due to hemolysis will bind to haptoglobin, forming the compound and decreasing the levels of haptoglobin dramatically, causing Haptoglobin deficiencies.

α1-fetoprotein (AFP)

-It is a fetal protein very important for development.

-First discovered in the serum of the fetus

-Its level gradually decreases postnatally

-detectable in maternal blood in pregnancy.

-very low levels in adults

-High levels could indicate liver cancer. Found in high levels during some congenital defects

- **Down's syndrome**: congenital problem associated with low level of **α1-fetoprotein (AFP).**

α2-Macroglobulin

- Large protein 720 kDa (huge protein)

- Tetramer of 4 identical chains.

- 8-10 % of the total plasma proteins.

-Synthesized by:
1-Monocytes (white blood cells) 2- Hepatocytes (liver cells) 3-Astrocytes (Neuroglia)

-Level varies with age, gender.

-Increased level in nephrotic syndrome.

-Important in transport of zinc

-works as protease inhibitor especially for pancreatic proteases (Trypsin) + pepsin, plasmin, thrombin.

- Inhibitor of: Coagulation and Fibrinolysis.

- Forms complex with the proteinase followed by clearance.

- Binding to many cytokines (signal molecules such as: TGF, PDGF, Etc) and directing them to their target cells.

Copper

- Daily intake 2-4 mg - Body contains ~ 100 mg

-An essential trace element; exist in small amounts but it is essential and important in maintaining homeostasis

- Works as a Cofactor for several enzymes (Cytochrome oxidase, amine oxidase)

- What makes it important in acting as a cofactor is its ability to alternate between two oxidative states (Cu2+ and Cu+). This is specifically important in oxidation-reduction reactions.

-Excess amounts of Copper is harmful. It can oxidize proteins and lipids, bind to nucleic acids, and enhance the production of free radicals by excessive, unwanted oxidation of lipids and proteins.

-It is also important in iron homeostasis, melanin formation, as well as cellular respiration, synthesizing different tissues, and getting rid of oxidative stress.

- Metallothioneins, a group of small proteins regulate tissue level of copper and maintain its normal level.

Good luck