METABOLISM

Doctor 2020 | MEDICINE JU

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We finished talking about the first group of plasma proteins which is Albumin, now we will talk about the second one which is Globulins.

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

*We talked about γ-globulins in the summer semester.

α1-globulins:

1- α1-antitrypsin:

- As its name implies it antagonizes the action of trypsin (trypsin works as a protease; breaks down proteins, located inside the intestine).
- When it was firstly discovered they found that it opposes the work of trypsin, after a while it was discovered that it opposes the work of a lot of proteases, accordingly they renamed it as α1-antiprotenase, α1-antiprotease. (3 synonyms for the same protein).

- α1-Antiproteinase (52 kDa)
  Even though the molecular weight of it is less than the albumin but it doesn't migrate ahead of it why? It's related to the protein you're putting in the gel electrophoresis if it's glycosylated or not, is it in the monomeric form or is it bounded as dimer or trimer… it affects its molecular weight in crossing the gel. The 52 kDa is its pure molecular weight.
- Neutralizes trypsin & trypsin-like enzymes (elastase)
- 90% of α1- globulin band (the most frequent)
- Many polymorphic forms (at least 75).
- Alleles Pi^M, Pi^S, Pi^Z, Pi^F (MM is the most common).
- Deficiency (genetic): emphysema (ZZ, SZ). MS, MZ usually not affected.
- Increased level of α1- antitrypsin (acute phase response)

Each gene has 2 alleles, each allele will make a copy of the protein, most common form (MM) it doesn't lead to any pathology (normal condition) one copy of M type is enough to function well.

An illness will occur when the body can't produce at least one M type.

α1-antitrypsin is an antiprotease, one of the proteases that it antagonizes its action is elastase. (Elastase breaks down elastic tissue (elastin) found mainly in the lungs).

Emphysema is a disease that affects the lungs, it causes degradation of the alveoli walls

Elastin is present in the alveoli walls which are present in large amounts in the lungs to increase surface area available for gas exchange and decrease the amount of air present in the lungs, so breaking these walls will decrease the surface area available for gas exchange and increase

the amount of air in the lungs, so it would be harder to breathe, less gas exchange because of the decreased surface area.

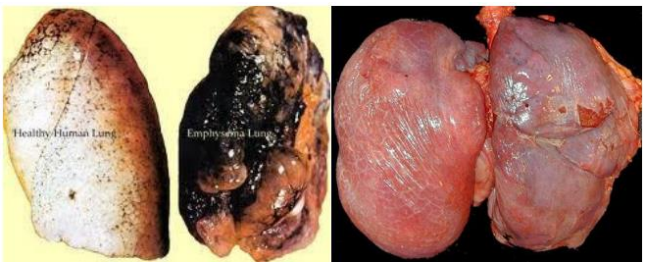
Patients of emphysema have what we call barrel chest because the amount of air increased, and the surface area of gas exchange decrease.

How does emphysema occur? When an inflammation happens, inflammatory cells will come (microphages, neutrophiles) that will release the elastase, elastase will break the elastic tissue, α1-antitrypsin will try to oppose this to protect the lungs, if the person has the MM form it will protect the lungs well, but if the person has another type which has a reduced capacity of binding to the elastase (like ZZ,SS,SZ,FF,FZ phenotypes; any phenotype that doesn't include M allele) the worst is ZZ phenotype; capacity of binding toward elastase get reduced to 10%.

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

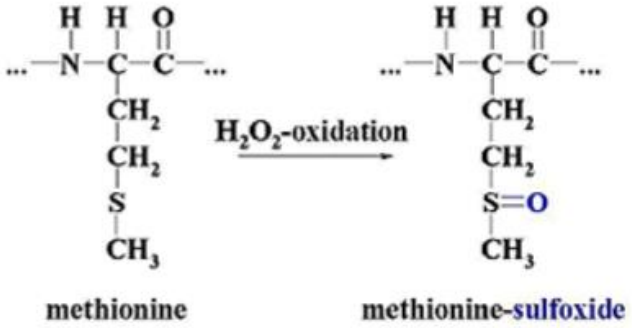
Active elastase + ↓ or no α_1–AT → Active elastase → Proteolysis of lung → Tissue damage

Smoking & antitrypsin deficiency



- Chronic inflammation.
- Oxidation of Met358.
- devastating in patients with Pi^{ZZ}

Emphysema can be a result of smoking, smoking causes chronic inflammation, which means more and more microphages and neutrophiles → more and more elastase to be produced→ more and more degradation of the alveoli walls. Also, smoking oxidizes specific methionine residue found on the surface of α1-anti-trypsin (this methionine is very important in the process of binding to the elastase).



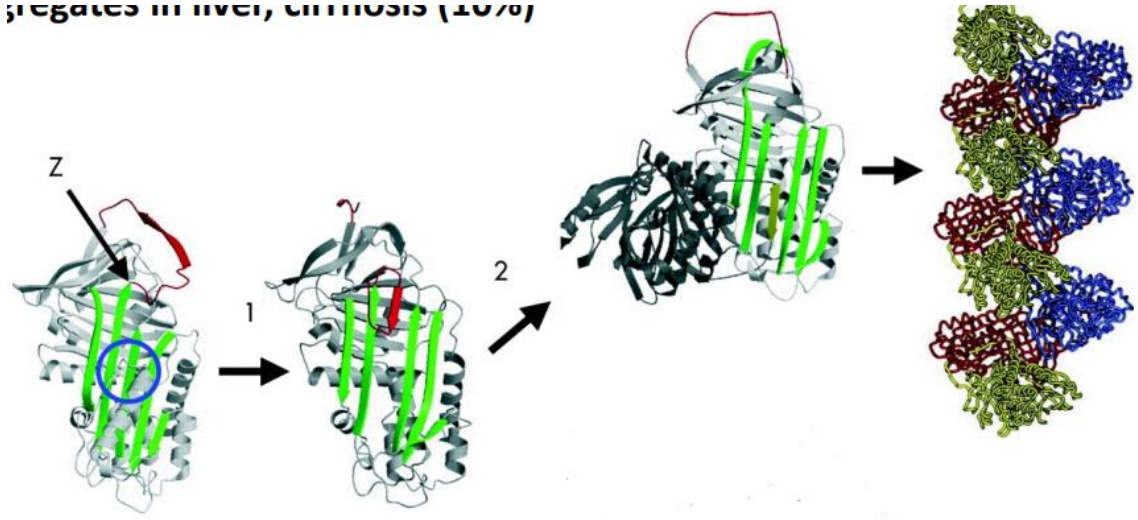
(Methionine: non-polar amino acid, it contains sulfur, but it's bounded to carbon from both sides, it won't participate in reactions, it's not usually oxidized), but it can be oxidized under harsh conditions and this what smoke does, it oxidize this methionine residue and convert it to methionine-sulfoxide → its affinity decreases and it will become unable to bind to elastase → elastase will keep on degrading the alveoli wall.

If a person has ZZ phenotype and smoke at the same time his case will be very complicated.

Liver disease and α1-anti-trypsin deficiency

Also, the ZZ phenotype affect the liver, 10% of the population who has ZZ phenotype end up with cirrhosis (تشمع الكبد).

There is a difference in the amino acids between Z and M phenotype these differences will lead to different forms. The ZZ phenotype antitrypsin has an extra loop and beta sheet. The beta sheet of an antitrypsin protein has high affinity towards the loop of another, so they will polymerize and form alpha-1 antitrypsin aggregates in the liver which can't leave and results in the killing of liver cells, and then leads to fibrosis then to cirrhosis of the liver.



2- α1-fetoprotein:

- As the name implies this protein is related to the fetus.
- Synthesized primarily by the fetal yolk sac (in high concentration) and then by liver parenchymal cells.
- Very low levels in adult (not detectable).
- 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 Normally
  - Hepatoma & acute hepatitis
  - we find it in high concentration (pathologically) in case of cancer like all other plasma proteins.

3- α1-acid glycoprotein.

4- Retinol binding protein:

Retinol: It is one of the organic compounds forming Vitamin A. (water soluble vitamins work as co-enzyme, lipid soluble vitamins none of them work as co-enzyme, chemical structure of water-soluble enzymes is clear, but in the case of lipid soluble enzymes there is no unique structure for them, it's a group of structures related to each other).

There are Different forms of Vitamin A, one of them is β-carotene that is found in all fruits and vegetables and give them the color according to its concentration. This β-carotene is a big molecule that will be broken into 2 halves to give 2 retinal molecules (aldehyde), then it will be reduced to retinol (alcohol) it's important in vision. And this protein is one of the α1-golublins that carry the retinol to the organs.

α2-golbuolins

1-Haptoglobin

- 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

There were no changes in the beta through generations (no polymorphism) that's why they are identical (2β) but there were polymorphism in alpha.

- Binds the free hemoglobin (65 kDa); prevents loss of hemoglobin & its iron into urine (we have free hemoglobin because some of the cells will break down while moving, normally) I care about hemoglobin because it contains iron.
- Haptoglobin half life is 5 days, it binds to free hemoglobin (M.W= 90+65=155 kDa) it became a very big complex; so the chance of losing iron decreased.
- Hb-Hp complex has shorter half-life (90 min) than that of Hp (5 days), so it goes to the liver and degrades to take the iron out and preserve it.
- Decreased level in hemolytic anemia

Examples of enzymes that uses metals as co-enzymes:

- **Amine oxidase**
- **Copper-dependent superoxide dismutase**
- **Cytochrome oxidase: Cytochrome is important in cellular respiration, people who die from cyanide toxicity is because it attaches to this enzyme, also the carbon mono-oxide toxicity.**
- **Tyrosinase**

2-Ceruloplasmin

Metals are important to the body because

they work as co-enzyme (copper is a metal).

It works as a storage for copper not

as a transporter.

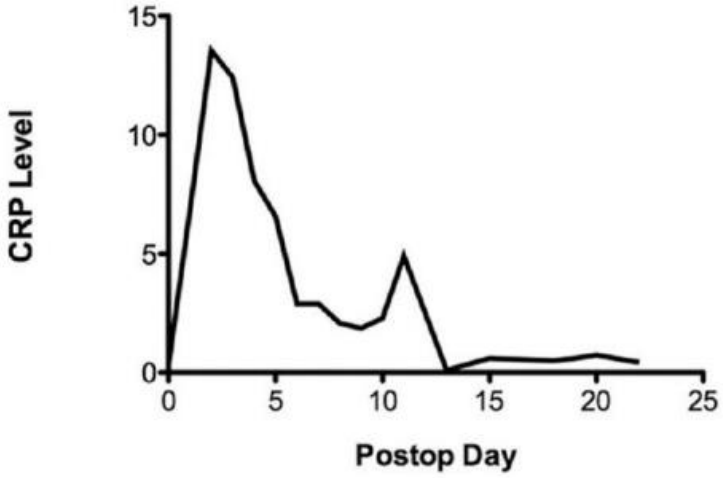
- A copper containing glycoprotein (160 kDa)
- It contains 6 atoms of copper
- Metallothioneins (regulate tissue level of Cu)
- Regulates copper level: contains 90% of serum Cu
- A ferroxidase: oxidizes ferrous to ferric (transferrin), (to transport the iron it must be in the ferric form)
- Albumin (10%) is more important in transport
- Decreased levels in liver disease (ex. Wilson's, autosomal recessive genetic disease; it is group of conditions; a mutation occurs, it affects either the function of the protein or it reduce its synthesis; at the end the concentration of the copper through the circulation will be higher (because there is no protein to bind to it; so copper will aggregate in the tissues, eyes …etc. examination of the lens of the eye is an indicator for this disease).

β – globulins

C Reactive Protein (CRP)

- When it was first discovered, it was found that it binds with the C fraction of the polysaccharide that is present in the cell wall of a type of bacteria called pneumococci, then it was discovered that it binds to a lot of things but the name sticked with it.

- It is an acute phase protein. It is undetectable in healthy individuals. But its levels increase in cases of inflammatory diseases (like acute rheumatic fever, bacterial infection, gout), trauma, cancer, and tissue damage.
- It helps in the defense against bacteria and foreign object in the body.
- Its level reaches a peak after 48 hours of the incident. Which is used as a monitoring marker. If it is found in high levels, there must be a problem that needs to be investigated.



The End

Good Luck