Medical Committee
The University of Jordan

SLIDE SHEET

LECTURE#: 3

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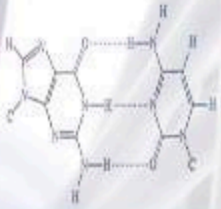
Biochemistry



Majida Al-Foqaraa'

لا تـقلْ قـد ذهبتْ أربابُهُ * * * كلُّ من سارَ على الدَّربِ وصلْ
فـي ازديادِ العلمِ إرغامُ العِدى * * * وجمالُ العلمِ إصلاحُ العملْ

Globulins

There are 4 groups of globulins: α1, α2, β, and γ.

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

α1-globulins:

1) *α1- antitrypsin* (α1- anti- protease, α1- anti-proteinase)

α1- antitrypsin is a plasma protein that antagonizes the action of trypsin and other trypsin-like enzymes (elastase)

Trypsin is a serine protease that hydrolyses proteins . It is found mainly in the digestive system (intestines).

Elastase is also a serine protease that breaks elastin in elastic tissues that are found in the lungs. Immune-cells (mainly macrophages) synthesize and release Elastase.

When there is an inflammation or any pathological condition the macrophages will secrete elastase to break the elastic tissue in the pathogens and they will degrade some damaged elastic tissues from the human body to be rebuild. But elastase's function doesn't consist of breaking normal human tissues. Therefore when elastase concentration increases, **α1- antitrypsin** will bind with it and inactivates its action.

α1- antitrypsin like any other plasma protein has at least 75 polymorphic forms. Every person has his\her own copy. These copies come from 2 genes or alleles producing 2 protein copies. These alleles are named: M, Z, S and F (Pi^M, Pi^S, Pi^Z, and Pi^F).

In ABO blood groups, O blood group is the most common. In **α1- antitrypsin** the M phenotype is the most common. The best situation (and most common) is when the two copies are of the M phenotype.

As we all know, Polymorphism is originally a mutation in the protein. The mutated protein could be a defective protein with low efficiency or a normal protein with a good efficiency.

If any change was made on the "M" phenotype, the protein might not work properly. However, having only one "M" allele in the phenotype will make the protein work efficiently (That is, at least one of the copies is of the M type). So we don't necessarily need an "MM" phenotype, but "MX" is enough for a correct function.

If there is no "M" allele in the phenotype then **α1- antitrypsin** will be weaker and will not antagonize the action of elastase. Therefore elastase

will start breaking the elastic tissues of the body especially in the lungs. The lungs have alveoli which do increase the surface area for gas exchange. When elastic tissues are broken, the alveoli's walls will break leaving more space for air but less surface area for gas exchange. This will cause **emphysema**. The chest will enlarge and become like a barrel (barrel chest).

α1- antitrypsin is an acute phase protein. So when there is an inflammation or cancer, the concentration of α1- antitrypsin will increase.

Smoking with respect to α1- antitrypsin is very harmful.

Smoking is irritant, it attracts the immune-cells (chronic inflammatory process) So Macrophages will secrete elastase all the time and this will cause emphysema. Even for a normal condition, were antitrypsin is working efficiently, it will not continuously be preventing **Elastase.** It is a chronic condition.

Also, Smoking Can oxidize certain amino acids on the surface of α1- antitrypsin .The oxidation occurs on **methionine 358**. Methionine 358 is important for the bond between α1- antitrypsin and elastase. So α1- antitrypsin will not work properly and the case will become more severe.

Smokers who have a "ZZ" or "SZ" phenotype will have a devastating case (smoke doesn't allow α1- antitrypsin to work efficiently and also the "ZZ" phenotype doesn't allow the protein to work properly).

"ZZ" phenotype also has some other cons. "ZZ" phenotype has an extra loop and a β sheet. These have affinity for each other so when 2 molecules come together they will bind together and when the 3rd molecule comes, it will also bind with them and they will aggregate. So when they aggregate in the liver (where they are synthesized), liver cells will die and cirrhosis will be the result (10% of the "ZZ" phenotypers).

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

2) α1- fetoprotein

α1- fetoprotein is another type of plasma proteins. It is found in high concentrations in the fetus. It is secreted from the yolk sac until the liver parenchymal cells are mature enough to secrete it.

Functions of α1- fetoprotein:

- Protects the fetus from immunolytic attacks
- Modulates the growth of the fetus
- Transport compounds e.g. steroids

When the level of **α1-** fetoprotein is low, Down syndrome risk will increase.

However, if the concentration of **α1-** fetoprotein is high for an adult (where it shouldn't be), then we can detect that the patient has Hepatocellular carcinoma (Hepatoma, cancer in the liver), acute hepatitis or the patient is pregnant.

Q. All plasma proteins concentrations increase due to pathologic conditions except: **α1-** fetoprotein (In pregnant women, normal, not pathologic condition)

α2- globulins

Haptoglobin (HP)

HP is a type of **α2-** globulins. It is an acute phase protein. It has a molecule weight of 90KDa. It consists of 4 subunits (tetramer) 2 identical α subunits and 2 identical β subunits.

HP is a Polymorphic and has different phenotypes. In all of its phenotypes the 2 β don't change, only the 2 α subunits differ.

Normally Hemoglobin is in RBCs, however, it can be found as free hemoglobin in the plasma. HP binds free hemoglobin that is found in the plasma.

Our body does care a lot about Iron (in hemoglobin) because it can't be synthesized like globin and heme in the body. The body doesn't want to lose the iron through the urine (kidney) so HP binds to the free hemoglobin in the plasma.

The molecular weight of hemoglobin is 65KDa and the molecular weight of the protein HP is 90 KDa. When the two of them bind together, their molecular weight will become 150 kDa. 150 KDa is a huge number and this won't allow the complex to exit out of the kidney and so the hemoglobin is preserved within the blood.

The Half- life oh HP is 5 days, and the half-life of the whole complex is 90 min. This will allow fast degradation of the complex in the liver and the liver will capture the Iron.

** Note:
When the half-life is long, there would be more chance for the element to be lost.

Hemolytic anemia causes the concentration of HP to decrease, because of the high levels of free hemoglobin that binds it.

**Did you know! :

Hemolytic anemia is a condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over.

Hemolytic anemia is caused by high rates of red blood cell destruction. Many diseases, conditions, and factors can cause the body to destroy its red blood cells

Ceruloplasmin

Ceruloplasmin is another type of **α2-** globulins. It is a Cupper containing protein.

Cupper is important in many enzymes in the body like:

- Amine oxidase
- Cupper- dependent superoxide dismutase
- Cytochrome oxidase
- Tyrosinase
- electron transport chain of oxidative phosphorylation

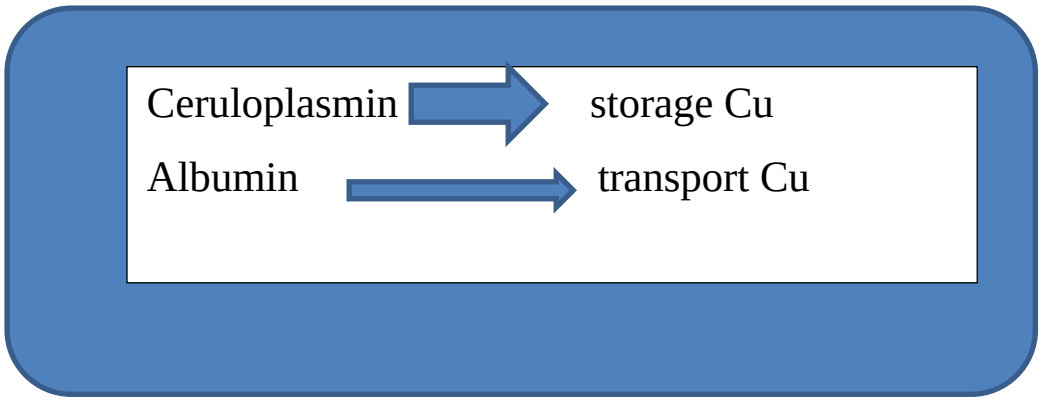
It is important to store and transfer Cu from one place to another.

When the protein has high affinity for its ligand, it can't work in transporting. But when it has a lower affinity it can work in transporting since it can bind and release the element easier.

Ceruloplasmin is a storage protein (has high affinity). It is bounded to 6 Cu atoms.

When there is a low Cu concentration in the blood, Ceruloplasmin will release Cu.

90% of the plasma Cu is bounded to Ceruloplasmin, and 10% of the Cu is bounded to albumin (lower affinity so it can be used in transporting Cu from one tissue to anther)



Ceruloplasmin regulates the Cu level within plasma only, and Metallothioneins regulate Cu level within tissues.

When we have a low concentration of Ceruloplasmin then Wilson's autosomal recessive genetic disease will be detected. Wilson's disease makes Cu precipitate on the tissues (esp. eyes and skin) and makes them yellow and glow.

** Note:

Pathological condition → normal or low concentration.

Acute phase condition → high or normal

Immunoglobulins

Immunoglobulins are from the **γ-globulins.** Immunoglobulins, antibodies are part of the immune-system.

The immune system is divided into:

1) Innate (Non-specific) immune system.
2) Acquired (Specific) immune system.

1) **Innate (Non-specific) immune system :**
   It is the same in all human beings. It comes with you when you are born (native, natural) and it uses the same mechanisms for defense all the time. So every time the body faces the pathogen, the body will behave in the same manner. It doesn't memorize what it has fought before and it doesn't recognize antigens within its system. It only recognizes microbial agents and it is non-adaptive.

   The Innate system is also divided into two main fighting lines:
   First line of defense: it consists of physical and chemical barriers.
   - the physical barriers : skin, hair and mucous membranes (lining the cavities)
   - The chemical barriers: sweat, tears, saliva, stomach acid and urine.

Second line of defense consists of: Phagocytic WBCs, Antimicrobial proteins and inflammatory response.

2) **Acquired (Specific) immune system**

It is different in every human being depending on the previous disease experiences .It has a specific immune response for each pathogen.

It utilizes antibodies, which are a product of the plasma cell, which is a product of the B lymphocytes.

And also utilizes the T lymphocytes, that fight antigens through themselves (not with antibodies)

It's response to the same pathogens increases in its magnitude.

When a person takes vaccination against a certain disease, the body will produce a weak response. But the second time the body is invaded with the same pathogens; its response will be much, much higher. So the response can increase in magnitude and it is highly adaptive and specific.

Moreover, it has memory cells that recognize microbial and non-microbial agents and self-antigens (auto immune diseases e.g. Rheumatic)

It consists of the Third line of defense.

The third line of defense consists of:

- T Lymphocytes
- Antibodies (from plasma cells that are made from B cells)

Both innate and acquired immune systems can have two forms:

1) Cellular immunity : defense through cells
2) Humoral immunity : defense through chemicals

طالت بهم أرواحهم إلى مراقي الصعود... مطالع السعود... ومراتب الخلود

ومن أراد المعالي هان عليه كل هم.. لأنه لولا المشقة ساد الناس كلهم..

فسارع ولا تلبث بناديك...

وسابق ولا تمكث بواديك..

Toi, Toi, Toi

Done by: Raneem Bader