

Lecture : 8 section 1 , 2 , 3

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Done By Ali Khresat

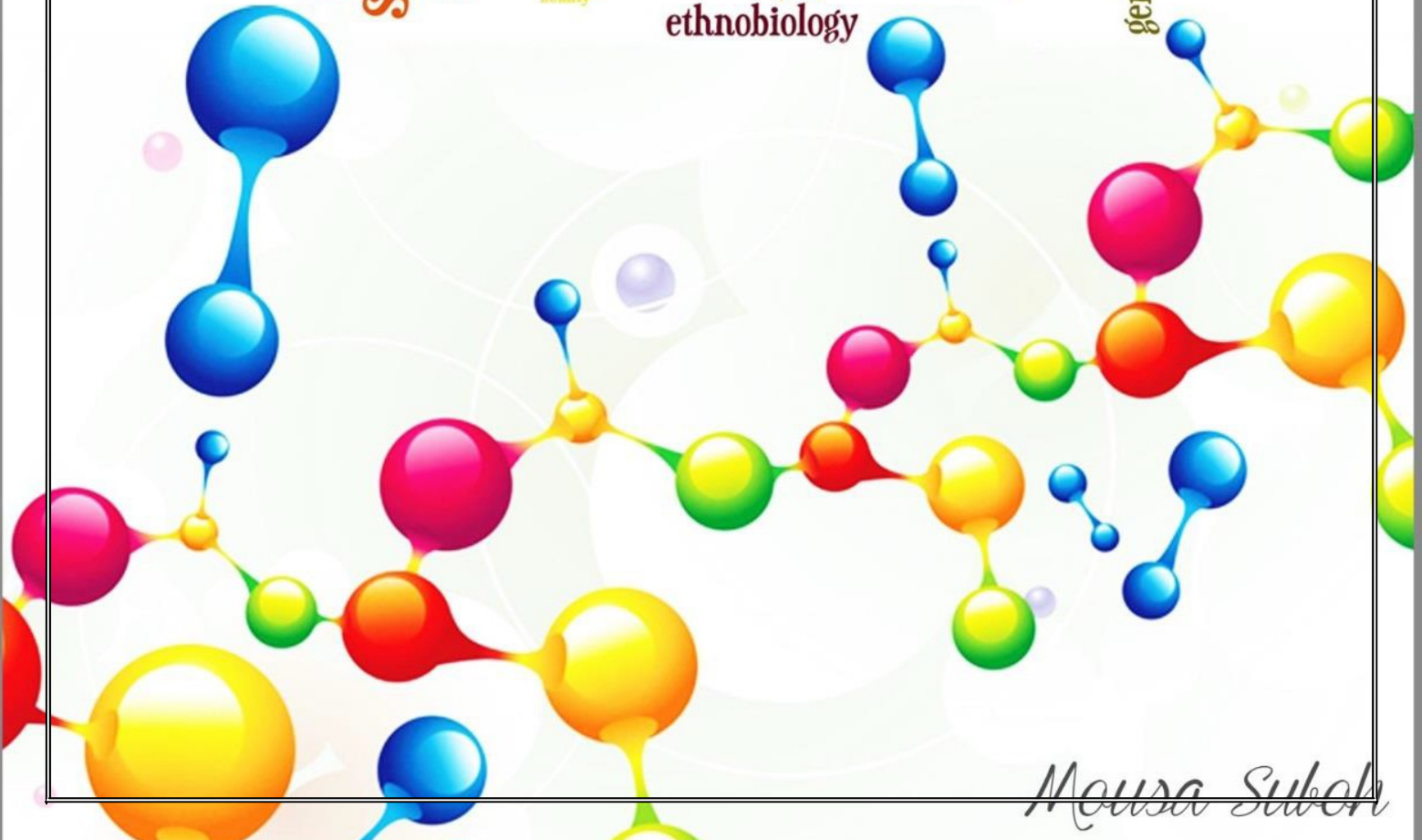
Slide  Sheet



Medical Committee  
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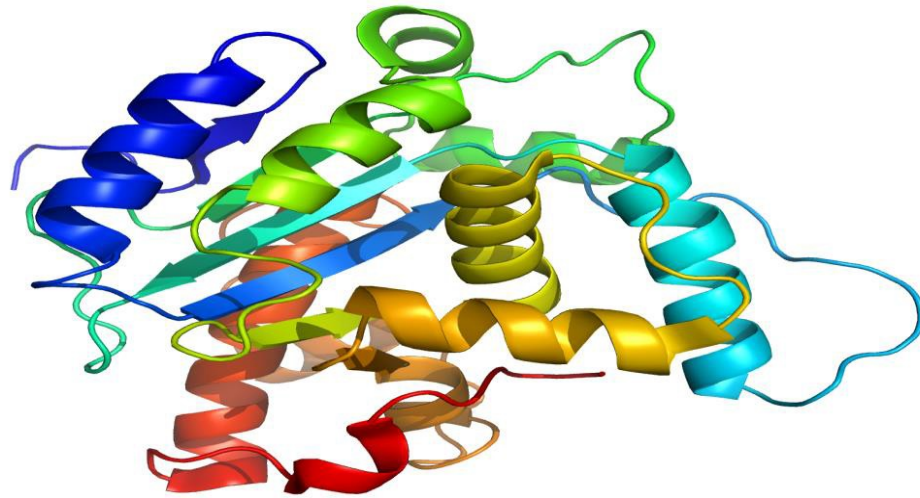
# Biochemistry

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Mousa Suboh

## Structure-function relationship of proteins



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we have talked about proteins, the structure of proteins and features of proteins now we will talk about how this structure is related to the functions .

-the structures that we are going to discuss are :

Fibrous proteins including :

1-

collagen

2- Elastin

3- Keratin

Globular proteins including : 1-

Hemoglobin

2-Myoglobin

\*proteins are divided into Fibrous and globular proteins according to their **structure**.

Done by

2

Ali Khresat

## Collagen:-

It is the most abundant protein in vertebrates it make up 25% of mammals proteins , there are 25 different types of collagen that differ based on their unique chemical composition and also collagen has a great strength that's why it's a structural protein .

### Structure-function relationship :-collagen

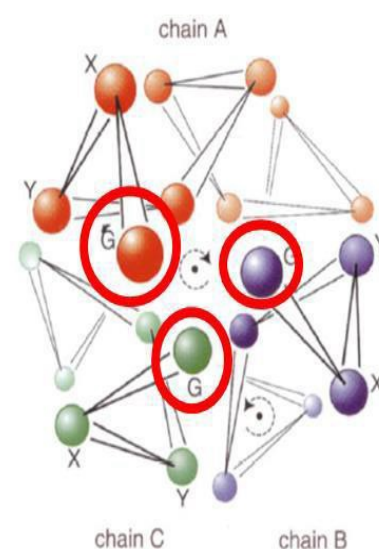
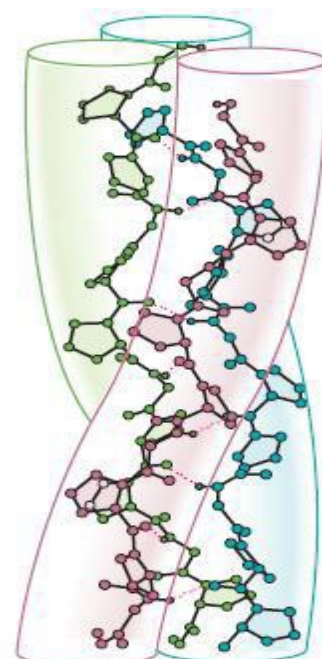
is a quaternary structure protein composed of tertiary structure proteins connected to each other , collagen is a polymer composed of tropocollagen monomers .

Tropocollagen is composed of 3 polypeptide chains twisted around each other, because it is twisted some of the amino acids will be located peripherally not within the twist while other amino acids are within the twist itself .

-collagen has an unusual amino acid composition and sequence

- Glycine is found at almost every third residue by 33%
- Proline makes up about 17% of collagen
- Hydroxyproline derived from proline
- Hydroxylysine derived from lysine

-the amino acid that is located within the twist



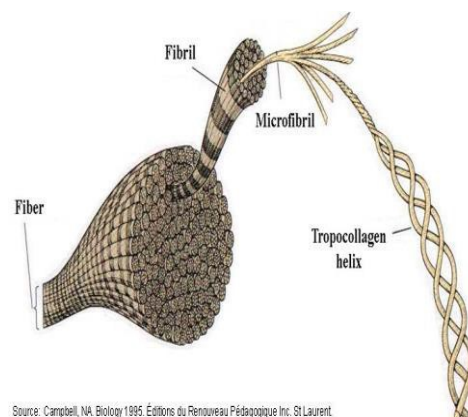
of the 3 polypeptide chains is **Glycine** because it is a small amino acid and because of that the resulting protein twist will be tight ,well-packed, strong and that what occurs in collagen if the amino acid was big like proline no such tight packing will take place .

-peripherally on the twist can be any amino acid .

-The presence of proline in the tropocollagen helps to produce Kinking in its structure and stabilize the helical conformation of collagen.

-Tropocollagen is 300 nm long and 1.5 nm in diameter held together by hydrogen bonding .

- 5 Tropocollagen molecules will make a microfibril which are connected with each other by Aldehyde links, a number of microfibrils will make a larger collagen fibril and collagen fibrils which are strengthened by covalent cross- links between lysine residue will finally make a collagen fiber



Source: Campbell, NA. Biology 1995. Éditions du Renouveau Pédagogique Inc. St-Laurent.

-the helix in tropocollagen is not an  $\alpha$ -helix keep that in your mind you can recognize that by :

1- looking at the  $\alpha$ -helix it is right handed but the strand in tropocollagen is left handed

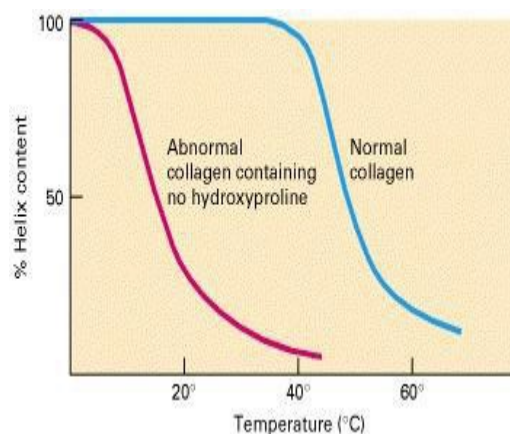
2-here is 3.6 amino acids per turn in  $\alpha$ -helix while there is 3.3 amino acids per turn in tropocollagen which means that the strand is more relaxed and extended in tropocollagen.

## Functional purposes of amino acids in tropocollagen

-Glycine :- it is needed to pack collagen well and tightly

-Proline:- Creates the kinks and stabilize the helical conformation .

-Hydroxyproline :- hydrogen bonding and cross-linking between Hydroxyprolin residues helps to preserve the helical structure of collagen , usually collagen can stand temperature up to 40 degrees and preserve 100% of it's helical conformation and that is due to the hydrogen bonding between hydroxyproline residues if we have collagen without hydroxyproline due to any genetic disease it will not stand temperature and will start to rapture(look at the figure ) .



- Hydroxylysine :-

The doctor said in the previous lecture that there are complex proteins that are associated with carbohydrates through 2 ways either through nitrogen in Asparagine or through Oxygen in the hydroxyl group of Serine , Threonine , Tyrosine

And Hydroxylysine.

-we can conclude from above that one of the functions of hydroxylysine is to **serve as an attachment site for polysaccharides** .

-Lysine residue can also be oxidized into an Allysine (Al means aldehyde) and that is followed by **covalent aldol cross-linking to strengthen collagen** .

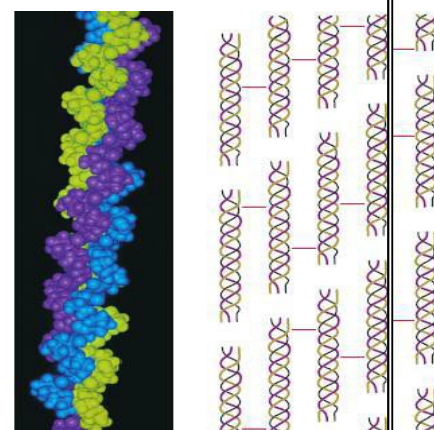
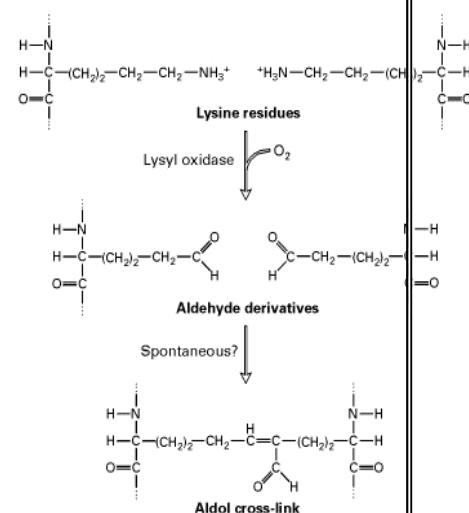
### **Collagen related diseases :-**

-Cross-linking in collagen is very vital and important it **varies according to tissue and increases with age** that's why old meat seems tuff and rigid while young meat seems soft so people tend to buy meat of young sheeps .

-**Scurvy** :-it's a disease characterized by deficiency of vitamin C which is required for the synthesis of Collagen in humans because Vitamin C it's a cofactor required for the activity of the enzymes important for hydroxylation of proline and as we said hydroxyproline is important for cross linking and strengthening collagen as a result of Scurvy there will be no cross linking and collagen will be weak .

### **Symptoms of Scurvy :-**

1-the patient will start complaining from spontaneous bleeding under the skin in



which a weak hit on the skin will cause bleeding to occur under it.

2-loss of teeth

3- the color of the skin will be pale



Osteogenesis imperfecta :- a disease affecting collagen type 1 in bones causing spontaneous fractures .

The most important Symptom in osteogenesis imperfecta that it cause discoloration in the Sclera of the eye (White part of the eye ) Causing it to appear blue because collagen is weak and it will show the venous blood behind it .

### **Elastin** :

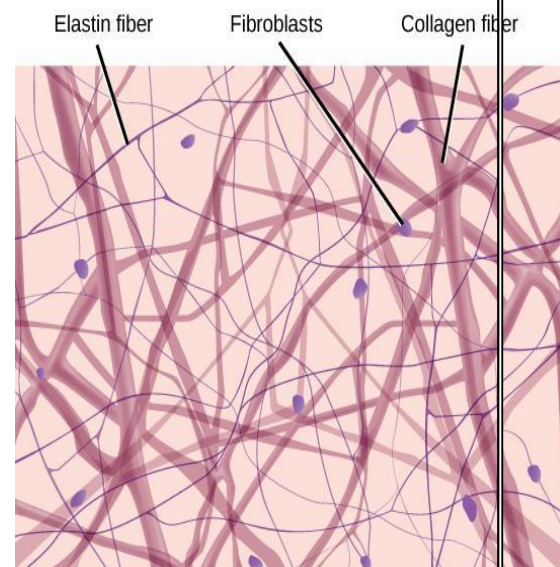
-It is a fibrous protein in the connective tissue that allows many tissues in the body to resume their original shape after stretching or contracting so it contributes for the tissue's elasticity

#### Features of elastin :-

-flexible

-it is found in the skin , lungs , blood vessels because these organ stretch and relax so there must be elastin in them .

-Elastic fibrils are interwoven by collagen fibrils in the connective tissue





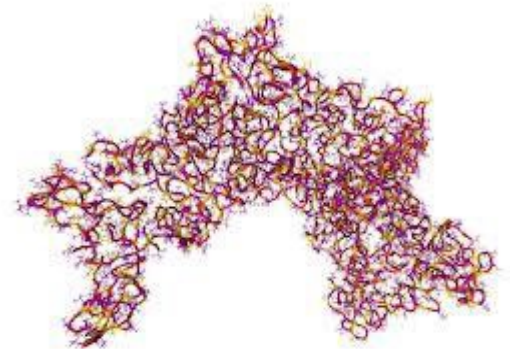
to prevent the tissue from overstretching and tearing .

-The shape of elastic fibers is compact (before stretching ) and extended after stretching like a fur ball .

-Elastin is not Glycosylated, it's not a glycoprotein which means that there is no hydroxylation of lysine in elastin (no hydroxylysine residue)and that is a unique property to distinguish it from collagen which is richly glycosylated(there are many hydroxylysine residues )

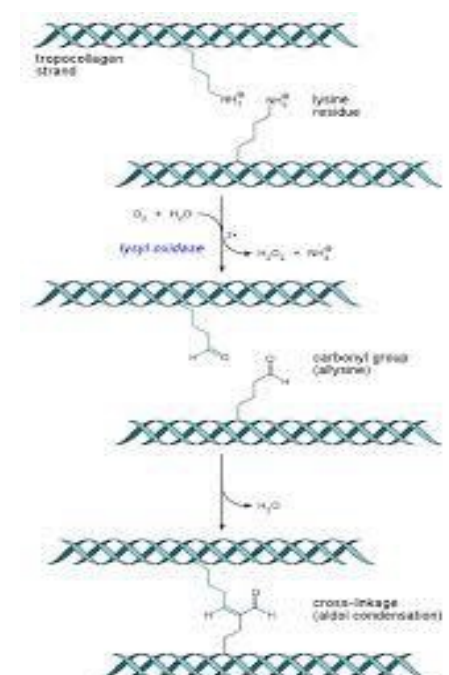
The structure of Elastin:-

-Elastin is rich in hydrophobic amino acids (Gly,Val,Pro ) that's why elastin protein seems condensed and aggregated because the only interaction that cause aggregation of proteins is Hydrophobic interactions between hydrophobic amino acids any other reaction will push the amino acids away from each other .



-Elastin is made by linking many soluble tropoelastin molecules by a reaction catalyzed by Lysyl oxidase enzyme that helps to oxidize Lysine to Allysine (aldehyde ) and produce many insoluble cross linking between tropoelastin molecules to make elastin

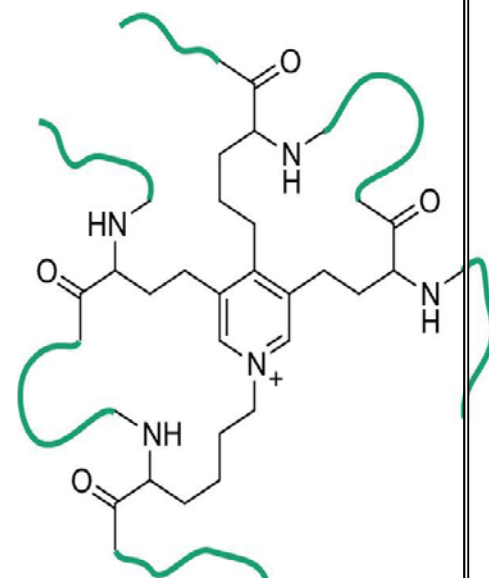
-We should always remember that Elastin don't need Lysyl Hydroxylase because Hydroxylysine is not needed for cross-linking and instead we use Lysyl oxidase



to produce Allysine for cross-linking .

-There are many types of links of tropoelastin molecules one of them is Desmosine

-Desmosine is a cross linked structure in the elastic tissue that is formed between 3 allysine side chains plus one unaltered Lysine side chain .



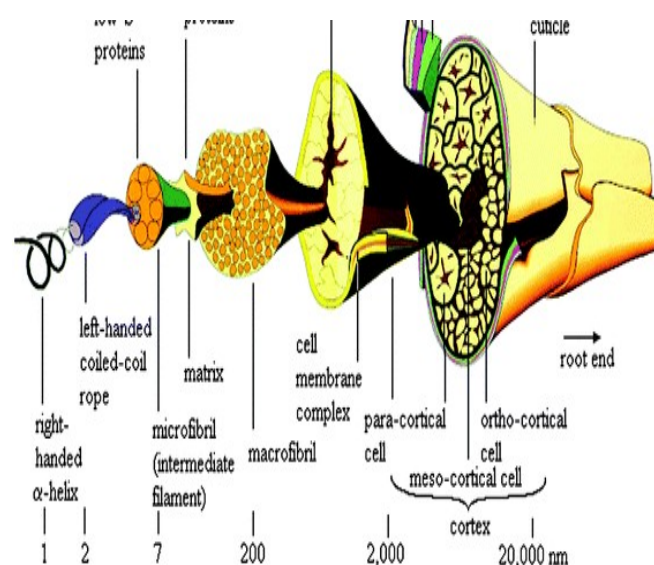
### Keratin

-it is the basic component of skin and its appendages (Hair ,nails) .

-there are 2 main types of Keratin :  $\alpha$ -Keratin in mammals and  $\beta$ -keratin in birds and reptiles .

The structure of Keratin :-

The secondary structure of keratin is  $\alpha$ -helix , 2  $\alpha$ -helices unit with each other and twist to form a structure called Coiled coil , 2 coiled coils molecules will make a structure called protofibril , 7-8 protofibrils will make a microfibril , 100 microfibrils will make a macrofibril which eventually makes Keratin fiber .



-Keratin is special than other fibrous proteins because it's cystein content is very high which means it is highly concentrated with Sulfur .

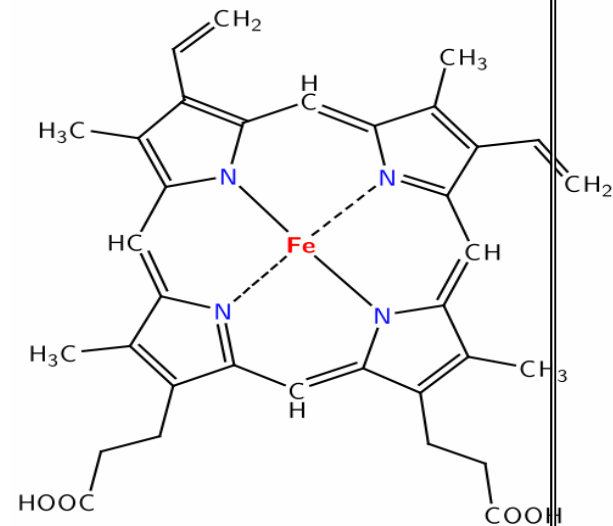
-according to Sulfur content keratin is classified into hard Keratin(high S concentration) , soft keratin (Low S concentration)

### Globular proteins:-

-Now we are going to discuss globular proteins which are Myoglobin and Hemoglobin but first let's discuss a structure that is common in both globular proteins which is heme group .

-Heme group : it's a macrocyclic ring that contain one large ring called Porphyrin ring containing Iron and four small rings containing Nitrogen called Pyrrole rings .

-If you remove the iron atom in the middle and replaced it with Mg the resulting molecule will be Chlorophyll

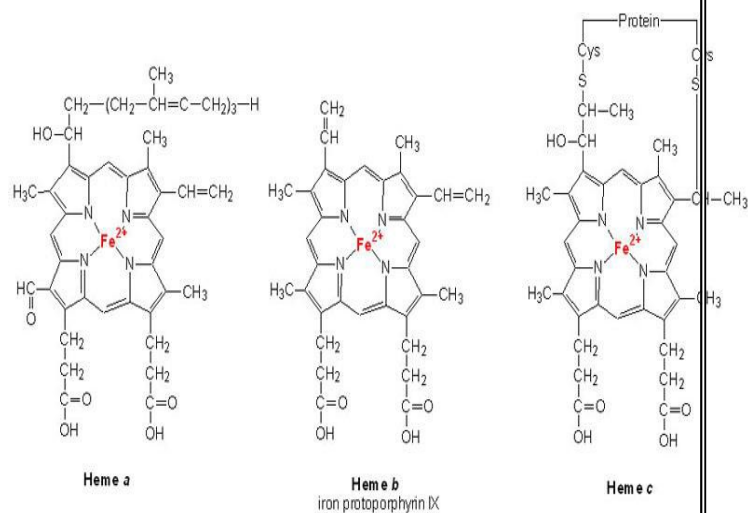


-there are many types of Heme that are located in different proteins like :

1-Heme b : found in Hemoglobin and Myoglobin

2-heme c : found in Cytochrome C in the Mitochondria

3-Heme A : found in group 4 in electron transport chain .



-Heme is a prosthetic group (a nonpolypeptide structure that is required for the activity of proteins ) that means

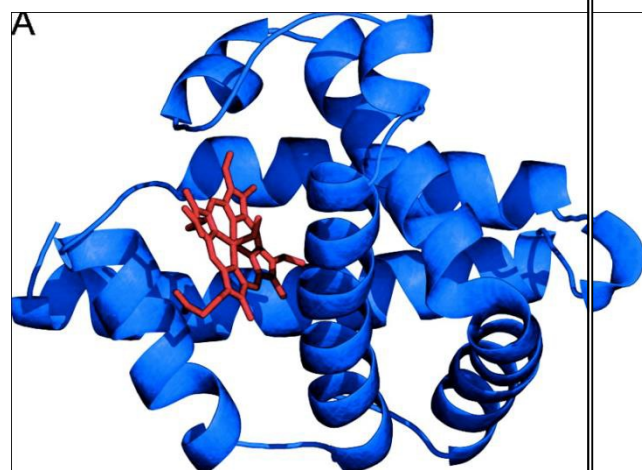
heme is required for the activity of Myoglobin and Hemoglobin .

## Myoglobin

-the first protein to be determined structurally by X-ray crystallography

-it is found in muscle tissue and function as a store of oxygen .

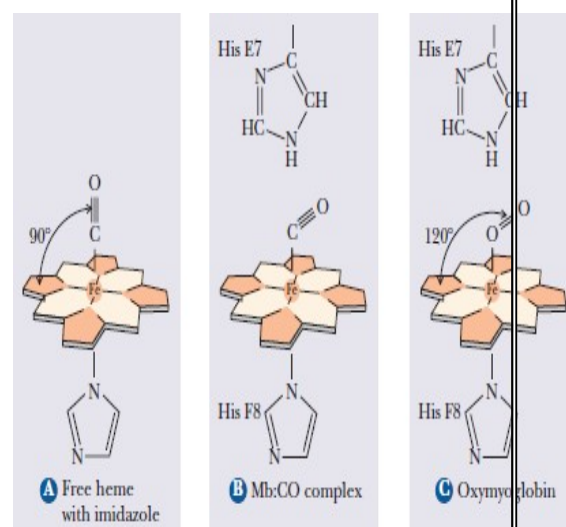
-composed of 8  $\alpha$ -helices within them there is a hydrophobic pocket which contains the Heme



-Iron atom in heme can make 6 bonds 4 of them are done with the Nitrogen atom in the Pyrrole ring leaving 2 unbounded electrons on Iron in the proximal and distal position (Up and down) .

- one of these electrons is bonded to Imidazole ring of Histidin proximally Leaving the the last electron free and unbounded on the distal position .

-on the distal position there is another histidin molecule that isn't bounded to Iron but it works as a gate for oxygen binding, it let oxygen in or out and also it prevent the perpendicular binding of Oxygen and Carbon monoxide .



-perpendicular binding is the strongest type of binding with highest affinity so if Oxygen or Carbon monoxide bind perpendicularly on Iron it's not easy for them to be released again so we don't need O<sub>2</sub> or CO to bind perpendicularly on iron and that is the function of distal

Histidin it creates a steric repulsion with O<sub>2</sub> or CO making their binding in an angled form (lower affinity ).

-in other words : we have two Histidins one is Proximal bounded to Iron it's function is to stabilize the heme in the hydrophobic pocket ,Distal Histidin not bounded to Iron and function as a gate .

-there is 2 oxidation states for iron :

1- Fe(II): Reduced state with high affinity for oxygen 2-

Fe (III): Oxidized state with low affinity for oxygen

-for iron to bind oxygen it must be all the time reduced

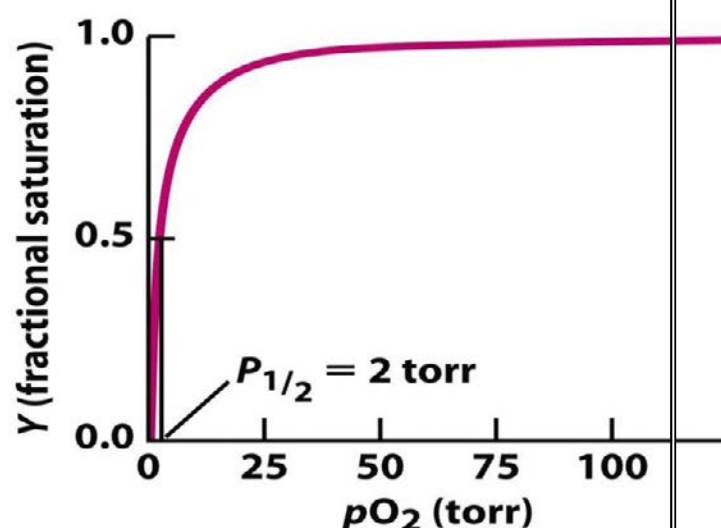
-iron is kept reduced through many ways :

1- through enzymes

2- Hydrophobic pocket helps to keep Heme reduced all the time.

### Oxygen binding to myoglobin:-

-oxygen affinity towards Myoglobin is very high this means that when Oxygen pressure is low Myoglobin might achieve saturation because whenever oxygen is presented it will bind to it (high affinity for oxygen) .



-how much Oxygen pressure is needed to achieve 50 % saturation in Myoglobin ?

We need 2 torr (mmHg) to achieve 50% saturation but in tissue Oxygen pressure is 20 torr so all Myoglobin in tissue

are fully saturated with Oxygen and that's what we need to make sure that the cells in the tissue will work properly .

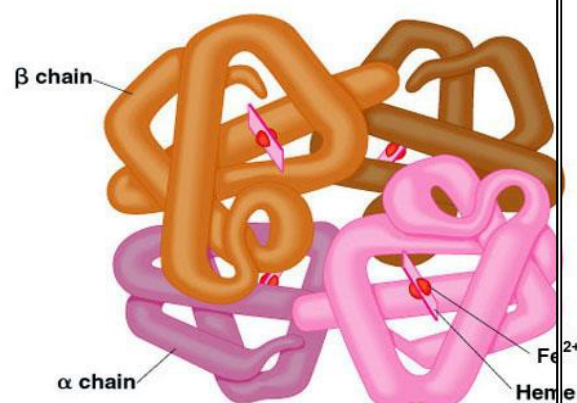
## Hemoglobin

-O<sub>2</sub> carrier protein in red blood cell that helps to transport oxygen to tissues .

-Hemoglobin is completely different than Myoglobin because hemoglobin is in RBC in blood stream and it's impossible to find it in tissues and also Myoglobin can't be found in the blood stream .

-it is composed of four polypeptide chains (2  $\alpha$ -globulin , 2  $\beta$ -globulin).

-each globulin molecule contain a heme group which contain Iron atom so each hemoglobin molecule can bind to 4 oxygen atoms .



-the function of Hemoglobin is completely different than myoglobin , Hemoglobin has to do 2 different functions first it will capture oxygen and bind it in the lungs then release oxygen in the tissue how ??

Because it has 2 functions it must work in two ways that's why we have a quaternary structure with more than one subunit(alpha and beta) when the relationship between subunits is different the function will be different , To answer that question we need to know that hemoglobin achieve 50 % saturation of oxygen at 26 torr when Hemoglobin reach the lungs where the pressure is 100 torr O<sub>2</sub> will bind with Hemoglobin and achieve 100 % saturation and when it reaches the tissue where the

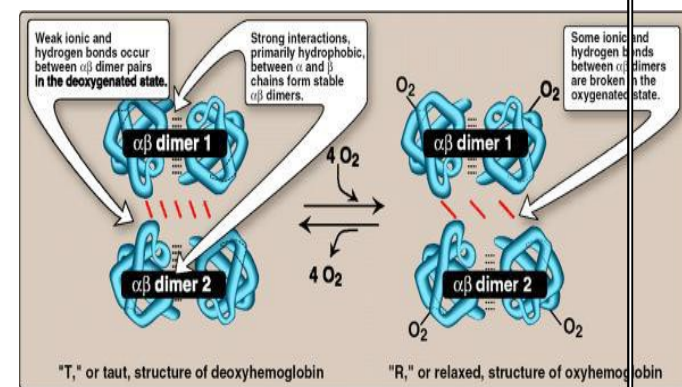
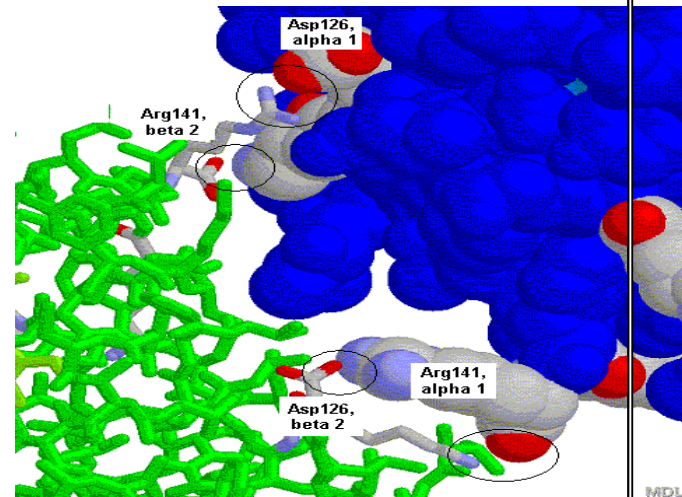
pressure is 20 torr which is lower than 26 oxygen will be released from Hemoglobin to the tissue .

**Chain interactions in Hemoglobin :-**

-Its known that nonpolar amino acids are located in the interior of the protein and also polar amino acids are located in the exterior of the protein.

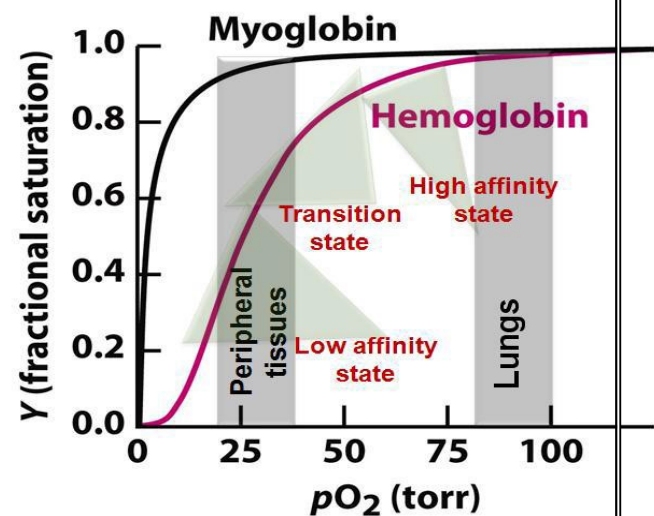
- some nonpolar amino acids can be located in the exterior of the protein to perform a specific function which is in case of Hemoglobin for Hydrophobic interactions to bind Hemoglobin subunits together .

-in addition to hydrophobic interactions , hydrogen bonding and salt bridges also present between hemoglobin subunits .



**The saturation curve of Hemoglobin :-**

-the saturation curve for hemoglobin is sigmoidal (S-shaped ) when hemoglobin reaches the lungs where oxygen pressure is high (about 100 torr) hemoglobin will be fully saturated but as hemoglobin reaches the tissue where oxygen pressure falls to 20 oxygen is released and saturation decreases .



-Hemoglobin exist in 2 states:

1-high affinity state (R-state ) : in lungs , happens when oxygen pressure is high (high affinity ) and it's also known as the relaxed state .

2-low affinity state (T-state) : in tissue , happen when oxygen pressure is low (low affinity ) and it's also known as the tense state .

### Hemoglobin as an allosteric protein :-

-An allosteric protein : a protein where binding of a molecule (ligand) to one part of the protein affects binding of a similar or a different ligand to another part of the protein .

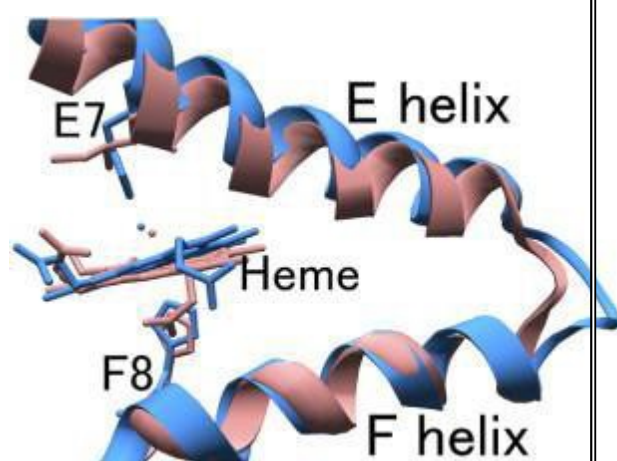
-Hemoglobin is an allosteric enzyme because when oxygen binds to the first subunit it will increase the affinity of the second subunits toward oxygen .

-Myoglobin is not an allosteric protein because its made of one polypeptide chain (one subunit ) so in order for a protein to be allosteric it must have more than one subunit

### Structural changes of Hemoglobin toward oxygen binding

- Heme is dome shaped and iron is located outside the plane when oxygen bind to Fe it will stretch the iron atom making it inside the plane which will stretch the heme making it planar

-Stretching the heme will stretch the proximal Histidin that is attached to it , proximal histidin is a part of amino acid sequence so stretching it will stretch the amino acids attached to it and that will cause a conformational change in the subunit in which oxygen is attached to





-a conformational change in one subunit due to O<sub>2</sub> binding will cause changes in the interactions (Hydrophobic, salt bridges, Hydrogen bonding) between other hemoglobin subunits and that will increase the affinity of other subunits to bind with Oxygen that's why binding of O<sub>2</sub> to one subunit affect the affinity of other subunit (Allosteric protein).

### Quiz:-

1-the most abundant amino acid in collagen is :

A-proline B-Glycine C-Valine D-Hydroxyproline

2-one of the following statements is wrong about elastin :

A-it requires the activity of Hydroxylase for cross linking

B- it is rich in hydrophobic amino acids

C-it is presented in blood vessels

D-when Lysyl oxidase enzyme is denatured elastin will be affected

3-one of the following is not one of the characteristics of Hemoglobin :

A-it contains 2 different types of subunits

B- it contains a prosthetic group

C-it is an allosteric enzyme

D- none of the above

4-one of the following segments of polypeptide chains can't form a continuous alpha-helical structure :

A-Gly-Met-Pro-Lys-Ala

B-Gly-Cys-Asp-Ser-His

C-Cys-Phe-Gly-Ser-Val-Gln D-Gly-Arg-

His-Lys-Arg

5-one of the following amino acids has two chirality centers

A-Leucine B-Isoleucine C-Tyrosine D-A+B E- B+C

6-Vitamin C prevents scurvy by :

A-it's involved in the formation of B-pleated sheet of collagen

B-it is used to hydroxylate proline in the primary structure of collagen

C-it's involved in metabolism of Heme used in hemoglobin

D-it encourage the formation of disulfide linkages in collagen

7- the structure of myoglobin consist of :

A-almost entirely of Beta-sheet

B-mixture of Alpha Helix and beta sheet

C-**almost entirely of Alpha Helix**

D-super secondary motif structure

8-hemoglobin is an allosteric enzyme because :

A- It has more than one subunit

B- Binding of O<sub>2</sub> to one subunit will increase the affinity of other subunits

C- Binding of O<sub>2</sub> to one subunits will change the hydrophobic interactions between other subunits

D-All of the above

Answers: 1-B 2-A 3- D 4-A (proline breaks the alpha helix because of it's cyclic structure )

5-**B** 6-B 7- C 8-D

Done by : Ali Khresat

-Sorry if the sheet was too long but it was a hard lecture , I hope I clarified everything .