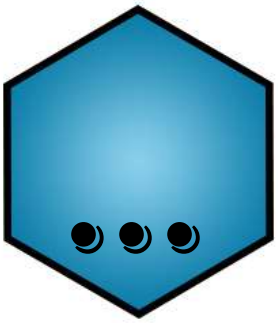

Faculty of medicine – JU2018

◉ Sheet ○ Slides

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MAMOUN AHRAM

RIVISION

COLLAGENS

- Are a family of fibrous proteins with a 25 different type in multicellular animals.

- They are the most abundant type of proteins, and they named collagen type I , collagen type II , collagen type III and so on.

- The main function of collagen is to **provide structural support to tissues**, so the primary feature of typical collagen is **stiffness**.

- Its triple stranded helical protein in which 3 collagen polypeptide chains called (alpha) chains **=>** ropelike superhelix shape.

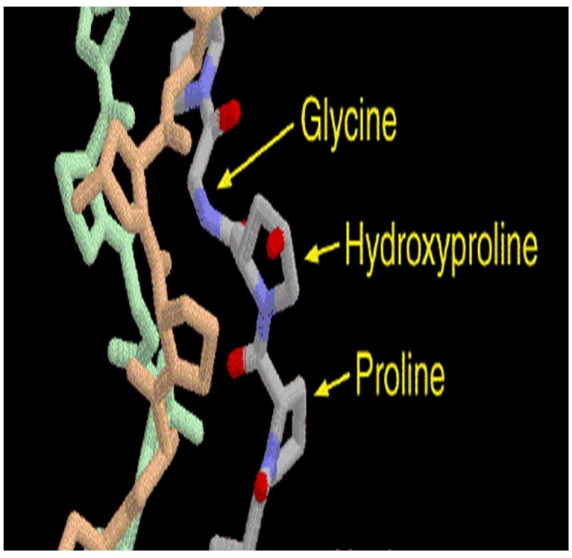
- **Composition of collagen and their function :**

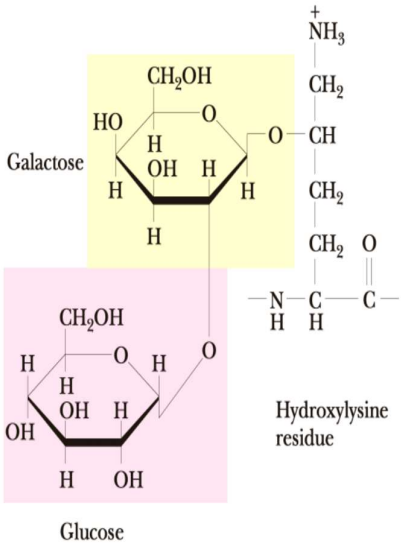
1- **Glycine :** which helps the molecule in packing so it's minimizing the repulsion between R groups forming a third of the total structure of the primary protein.

2- **Proline** : it creates the kinks and stabilize the helical structure in each chain of collagen chains , and it is rigid amino acid so it makes the molecule rigid also ,, forming about 13% of the primary structure of the protein.

3- **Hydroxyproline :** helps in the formation of more hydrogen bonds, strengthening the interaction between the 3 alpha chains in which they are given numbers alpha 1, alpha 2, alpha, etc.

4- **Hydroxylysine :** serve as attachment sites of polysaccharides making collagen a glycoprotein (Glycosylation) .





5- Lysine: helps forming covalent linkages between alpha chains and that's happened only when the lysine become oxidized .

***oxidation of lysine*:** you must convert the amino group on the lysine side chains into an aldehyde derivative known as allysine, covalent aldol cross-link form between hydroxylysine residues and lysine or another oxidized lysine (forming the tropocollagen which is the monomer of collagen) .

Hydroxyproline :

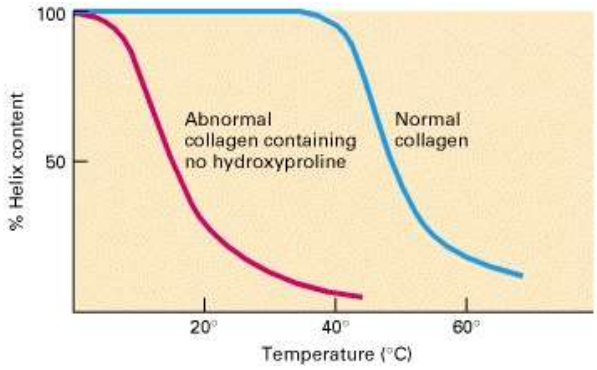
Purpose of hydroxyproline

To illustrate the importance of hydroxyl proline :

A- If there is a defect in the hydroxylation of the hydroxyproline "a defect in the enzyme **prolyl hydroxylate** which is the enzyme that adds the hydroxyl group to the proline" **makes the collagen molecule become more fragile and makes it breaks up easily VS. the normal collagen.**

The stability of collagen is compromised when proline isn't hydroxylated!!!!! HOW???

WHITHOUT hydrogen bonds between hydroxyproline residues, so the collagen helix is unstable and loses most of its helical content at temperatures above 20°C , **while the normal collagen is stable even at 40°C .**



Symptoms of scurvy:

1-hair and teeth loss

2-decrease in RBC level

3-scourbutic gums: the triangle shaped area between the teeth showing redness

4-skin can be injured easily

B- SCURVY: disease is caused by a dietary deficiency of ascorbic acid (vitamin c).

"lack of vitamin C resulting from not eating vitamin C in food for at least a month"

Vitamin C is important for the hydroxylase enzyme in "proline hydroxylation process", so the deficiency in the amount of hydroxyproline in collagen will lead to the formation of weak collagen molecules

So , anything depends on collagen becomes fragile .

Elastins

Resilience VS. flexibility

When we see a baby with nice lovely cheeks what we do mostly?

- we grab and stretch them, but they never come out in our hands, mmmm why?

- they are not being stretched because of their collagen (because its rigged), they are being stretched because of their **ELASTIN**.

COLLAGEN provides stability and rigidity, While ELASTIN provides flexibility.

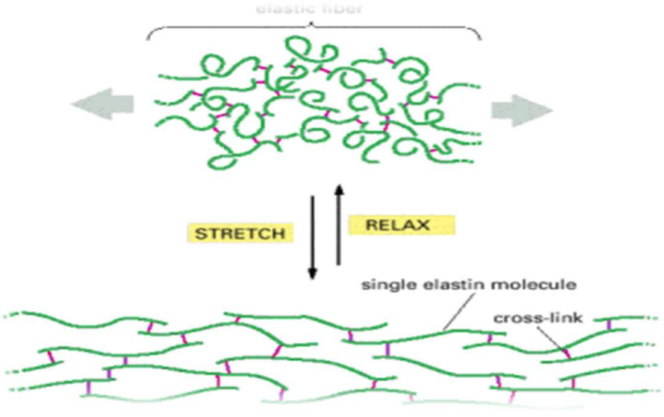
- Many tissues, such as skin, blood vessels and lungs needed to be both strong and elastic in order to function.

- A network of elastic fibers in the extracellular matrix of these tissues gives them the required **RESILIENCE** so that they are recoil after transient stretch.

- The interwoven inelastic collagen fibrils with elastic fibers limit the extent of stretching and prevent the tissue from TEARING.

EXAMPLE: in blood vessels we have a combination of collagen and elastic fibers, so we can see them stretch and expand when the blood is pumped because of its elastin fibers, but we have never seen a blood vessel raptured because of collagen .

The components of elastin:



1. Rich in proline and glycine.

2. Some hydroxyproline.

* the main component of elastic fibers is elastin which is a highly hydrophobic protein because of that its fibers can gather again together after expanding .

* It has no hydroxylysine

* It's not glycosylated so it's not a glycoprotein.

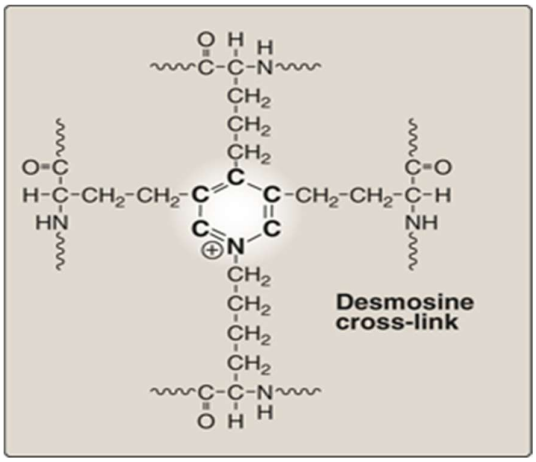
* The primary component (**tropoelastin**) is cross linked between lysines to one another.

The structure of elastin: the elastin protein is composed largely of 2 types of short segments that alternate along the polypeptide chain:

1. Hydrophobic segments, which are responsible for the elastic properties of the molecule.

2. Alanine -and lysine- rich alpha helical segments, which form cross-link between adjacent molecules

* Three allysyl side chains plus one unaltered lysyl side chain from a desmosine crosslink



KERATINS

Two important classes of proteins that have similar amino acid sequences and biological function are called α-and β-keratins , which as members of a broad group of intermediate filament proteins .

We will focus on α – keratin in this sheet.

α-keratin is the major proteins of hair and fingernails as well as animal skin.

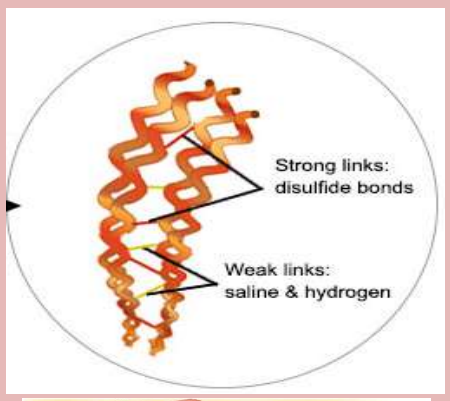
α-keratin has an unusually high content of cysteine.

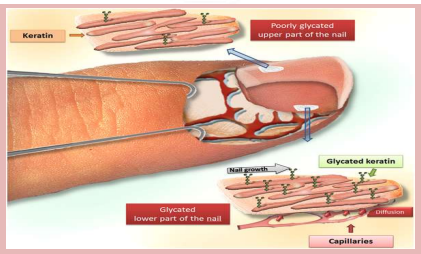
α keratin is found in

FINGERNAILS

are tough and rigid because there are a lot of disulfide linkages between cysteines

α-keratin can be hardened by the introduction of disulfide cross-links between cysteines (fingernails).

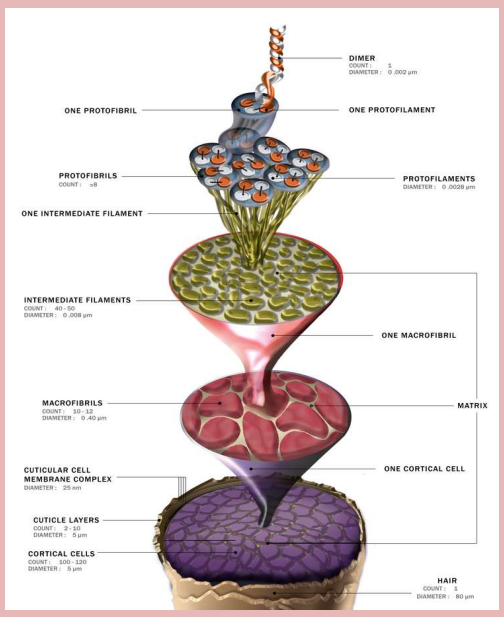




HAIR

Is flexible , there are less disulfied linkages between the cysteine, and it's also different among people according to the number of disulfide linkages between different keratine molecules

Two helical α-keratin molecules (protofilaments) interwine forming a dimer. Two dimers twist together to form a 4-molecule protofibril. Eight protofibrils combine to make one microfibril. Hundreds of microfibrils are cemented into a macrofibril



African hair: Kinky and rounded because there are a lot of disulfide linkages between different types of keratin

Smooth silky hair: The least number of disulfide linkages

Temporary Wave

When hair gets wet, water molecules disrupt some of the hydrogen bonds, which help to keep the alpha-helices aligned. When hair dries up, the hair strands are able to maintain the new curl in the hair for a short time.

Permanent wave

A reducing substance (usually ammonium thioglycolate) is added to reduce some of the disulfide cross-links. The hair is put on rollers or curlers to shift positions of alpha-helices. An oxidizing agent, usually hydrogen peroxide, is added to reform the disulfide bonds in the new positions until the hair grows out.

GLOBULAR PROTIENS

MYOGLOBIN AND HEMOGLOBIN

They both bound to a **heme** group, heme group allows to these proteins to bind to oxygen, but the purpose is different.

Myoglobin: stores **O2** in muscles and release it in the durations of oxygen deprivation (**toxic conditions**) so **oxymyoglobin** release its bound oxygen.

Myo: related to muscles.

Hemoglobin

Has 2 important functions :

1a.Transporting of O_2: **it binds with oxygen and transports it to the peripheral tissues and releases it.**

1b.Transporting of CO_2: **collects CO_2 from peripheral tissues and get rid of it by lungs in the breathing process.**

2.blood buffering: **since we have a lot of hemoglobin molecules in our blood and it has these amino acid groups and R chains that can bind and release protons which plays very important rule in blood buffering.**

HEMOPROTEINS : specialized group of proteins containing heme as a prosthetic group.

Prosthetic group: non protein-organic molecule that binds with proteins covalently.

Hollow proteins: proteins that have non-protein groups attachment.

The heme group is a prosthetic group.

Both hemoglobin and myoglobin are hemoproteins.

The protein environment dictates the function of the heme.

Myoglobin: it's a monomer formed of one polypeptide, so it has a primary, secondary and tertiary structures. ((doesn't have a quaternary structure))

Myoglobin is a monomeric protein that is mainly found in in muscle tissue.

It includes a prosthetic group, the heme group

It can be present in two forms:

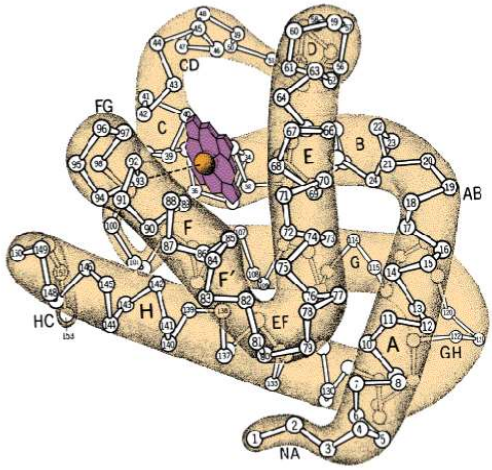
oxymyoglobin (oxygen-bound)

deoxy myoglobin (oxygen-free)

MYOGLOBIN CARACTARISTICS:

1. Full of alpitses of globular protein: looks rounded like a ball

2. It has the hydrophobic amino acids hidden in the core of the protein and we have on the outside the charged and polar amino acids. Its function is to keep the iron in the ferrous state to keep it always capable to attract with oxygen.



The tertiary structure of myoglobin 8 α-helices, designated A through H, that are connected by short non-helical regions and the heme group is right in the middle

Arrangement of amino acids:

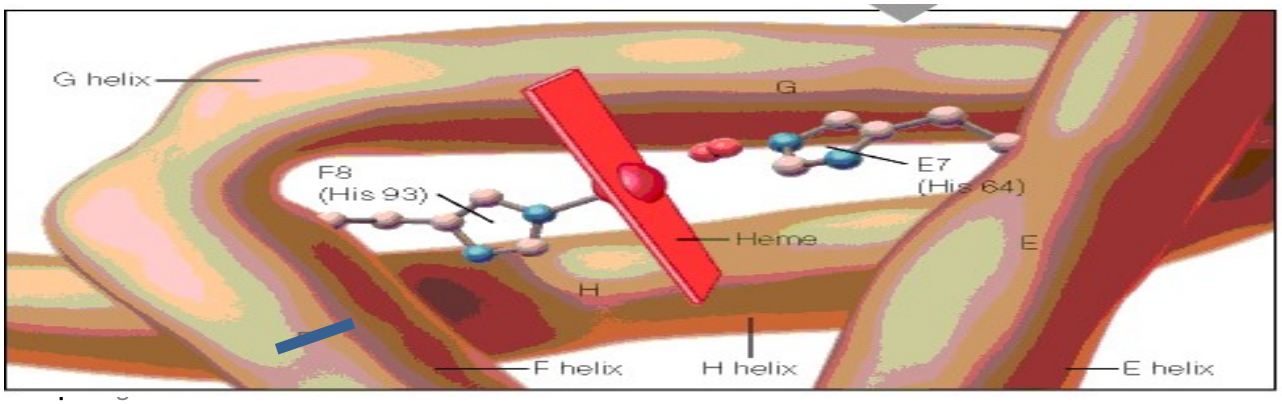
Like other globular protein, amino acid R-groups exposed on the surface of the molecule are generally hydrophilic, while those in the interior are predominantly hydrophobic.

Except for two histidine residues in helices E and F (known as E7 and F8)

F8 His is designated as **proximal His**, whereas **E7 His** is known as **distal His**

Proximal His: close to the heme and its purpose is to bind with the heme group

Distal His: relatively far away from the heme and its function is to act like a **gate** that allows the oxygen to go in and binds with iron or its closes and don't allow other molecules to get inside the myoglobin molecule.



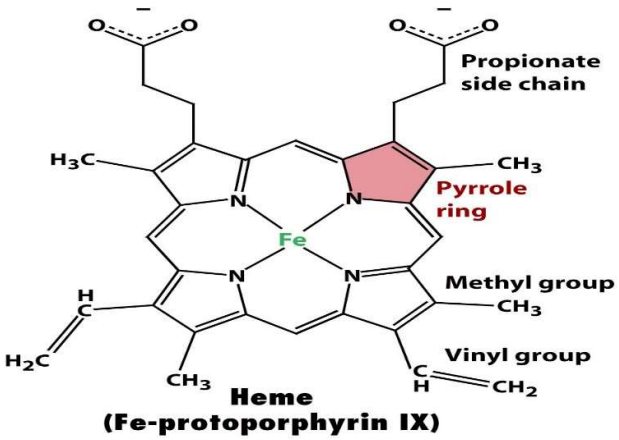
And these two histidine residues are surrounded by hydrophobic amino acids and there is a reason for why histidine residues is specifically and there is a reason for why they are surrounded by hydrophobic amino acids … and that's the beauty of Biochemistry.

Heme group:

Both proteins contain a heme group.

It is a prosthetic group (a non-protein group covalently attached to a protein).

Heme is a flat molecule that has four cyclic groups known as pyrrole rings. Each ring is connected with iron which could form 6 covenant bonds (6 coordinates).



IRON:

Iron can bind in the center of the four rings.

Fe is in the <u>ferrous</u> state (Fe^{+2}) can form 6 bonds (functional):

- 4 with the nitrogen of the rings.

- One (known as the fifth coordinate) with the nitrogen of a histidine imidazole (known as proximal His).

- One with O_2 (the sixth coordinate)

Oxidation of iron to the Fe^{+3}, <u>ferric</u> state makes the molecule incapable of normal O_2 binding (NOT functional).

Upon absorption of light, heme gives a deep red color but in ferric state gives a Blue color.

Structure – function relationship of myoglobin (summary)

The planar heme group fits into a hydrophobic pocket of the protein and the myoglobin-heme interaction is stabilized by hydrophobic attractions.

The heme group stabilizes the tertiary structure of myoglobin.

The distal histidine acts as a gate that opens and closes as O_2 enters the hydrophobic pocket to bind to the heme.

The hydrophobic interior of myoglobin (or hemoglobin) prevents the oxidation of iron because they donate electrons so electrons transfer from hydrophobic amino acids to iron, and so when O_2 is released, the iron remains in the Fe^{+2} state and can bind another O_2.

Other significances of distal histidine:

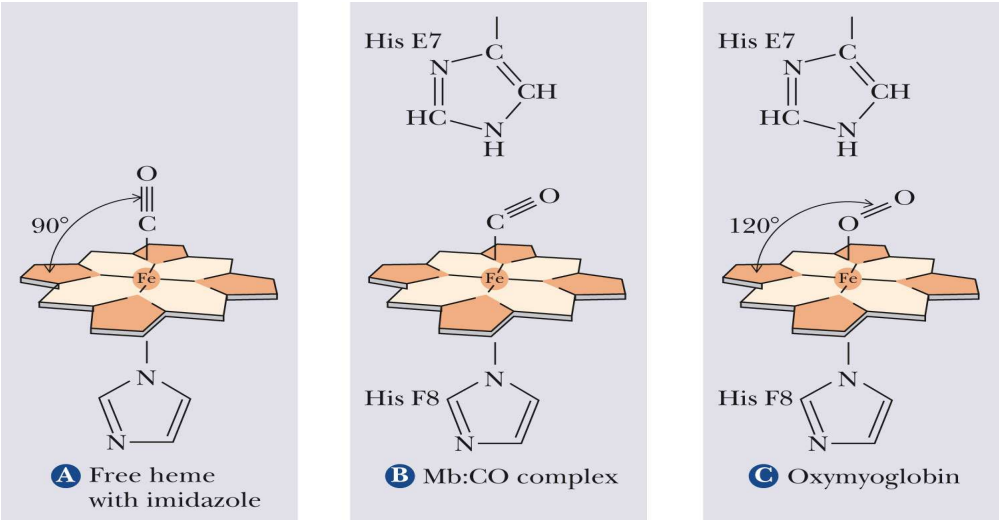
1. Because it's so close to the oxygen so it makes an angel between iron and oxygen which compromises the affinity and the interaction between O_2 and Fe so it makes it easier for oxygen to be released.

2. If we have a free heme group and we add equal amounts of carbon monoxide and oxygen, CO will bind with iron 25000 times affinity higher than O_2 so as a protection mechanism it allows the heme not to be saturated with CO (weakening the interaction between iron and CO)

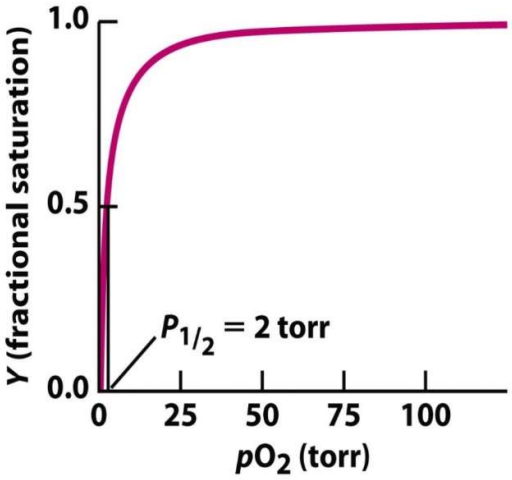
BUT why people don't die from CO since its affinity is so high?

1.the level of CO is too low in the air

2.weakening of the bond as a result of distal histidine.



Saturation curve of oxygen binding to myoglobin



The binding of O_2 to myoglobin follows a **hyperbolic** saturation curve

Myoglobin binds O_2 with high affinity.

O_2 is released only in the case of hypoxia .

In peripheral tissues the level of O_2 is about 20-30 torr

The P50 (oxygen partial pressure required for 50% of all myoglobin molecules) for myoglobin ~2.8 torrs or mm Hg.

Given that O_2 pressure in tissues is normally 20 mm Hg, it is almost fully saturated with oxygen at normal conditions

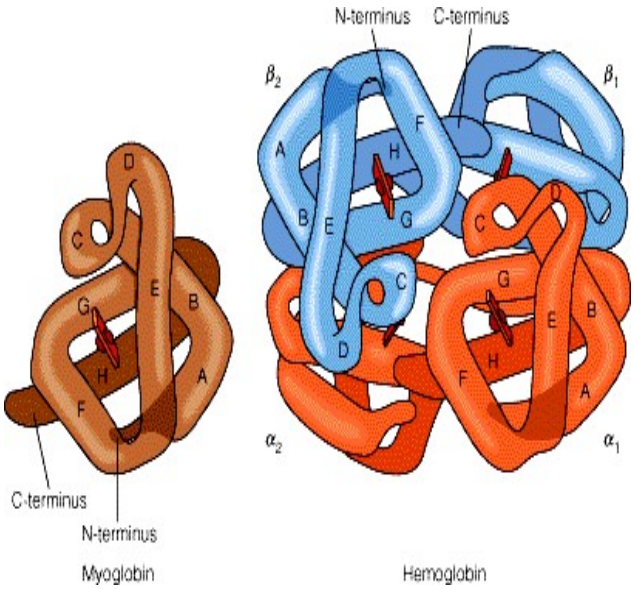
In lungs the level of O_2 is about 100 torr , again 100% of myoglobin is saturated with oxygen
With increasing the pressure or the concentration the fractional saturation increases

P50: 50% of myoglobin is saturated with oxygen

At 2 torr pressure 50%of myoglobin is bound to O_2 and

this really high affinity relative to hemoglobin

HEMOGLOBIN



Hemoglobin is tetrameric hemeprotein (FOUR protein chains known as globins with each bound to heme so we have 4 heme groups .

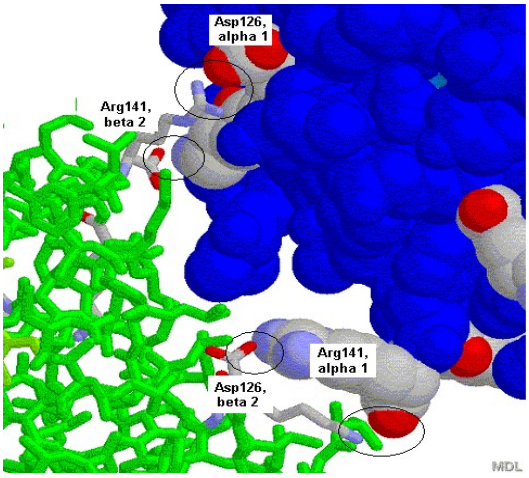
In adults, the four globin proteins are of two different types known as α and β, so a hemoglobin protein is an α2β2 globin protein.

The α and β chains contain multiple α-helices where α chains contains 7 α-helices and β chains contains 8 α-helices (similar to myoglobin).

THE QUESTION IS: HOW ARE THESES CHAINS INTERACTE WITH EACH OTHER?

1.via hydrophobic interactions, therefore hydrophobic amino acids are not only present in the interior of the protein chains, but also on the surface and that's helps the two polypeptides interact with each other.

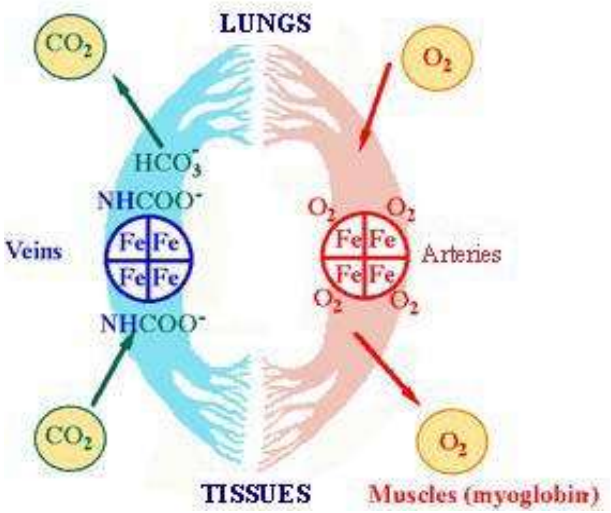
2.via electrostatic interactions (salt bridges), and hydrogen bonds is also existed between the 2 different chains.



How many types of hemoglobin according to its affinity are there in our body?

1.high affinity hemoglobin: it must bind with oxygen efficiently and become saturated at the high oxygen pressure found in lungs (approximately 100 mm Hg).

2.low affinity hemoglobin: after releasing oxygen in tissues it turns to become unsaturated in tissues where the low pressure of oxygen (about 30 mm Hg).

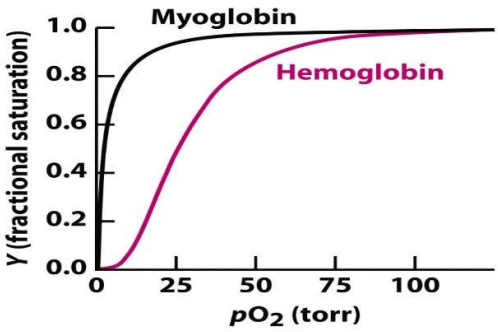


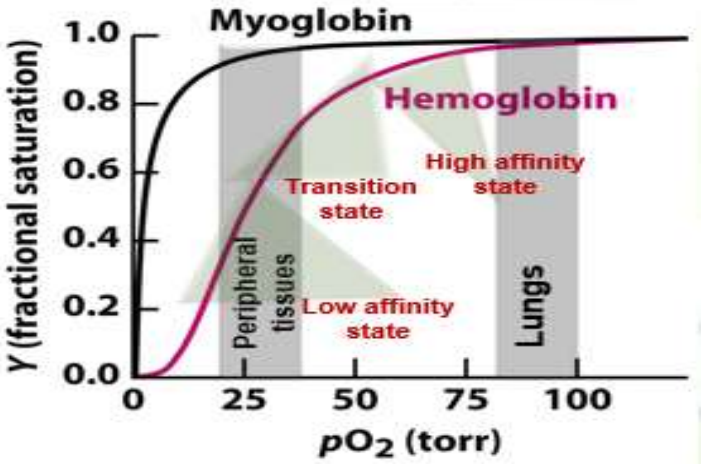
The saturation curve of hemoglobin binding to O_2 has a sigmoidal shape (S-shape) .

At 100 mm Hg, hemoglobin is 95-98% saturated (oxyhemoglobin).

As the oxygen pressure falls, oxygen is released to the cells of peripheral tissues .

In contrast to a low p50 for myoglobin, the p50 of hemoglobin is approximately 26 torr where 50% of hemoglobin is bound to oxygen .





Hemoglobin is an allosteric protein (from Greek "allos" = "other", and "stereos" = "shape").

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 exists in two forms, T-state and R-state

The T-state is also known as the "taut" or "tense" state and it has a low-binding affinity to oxygen.

The R-state is known as the "relaxed" state and it has 500 times higher affinity to oxygen than as the T conformation.

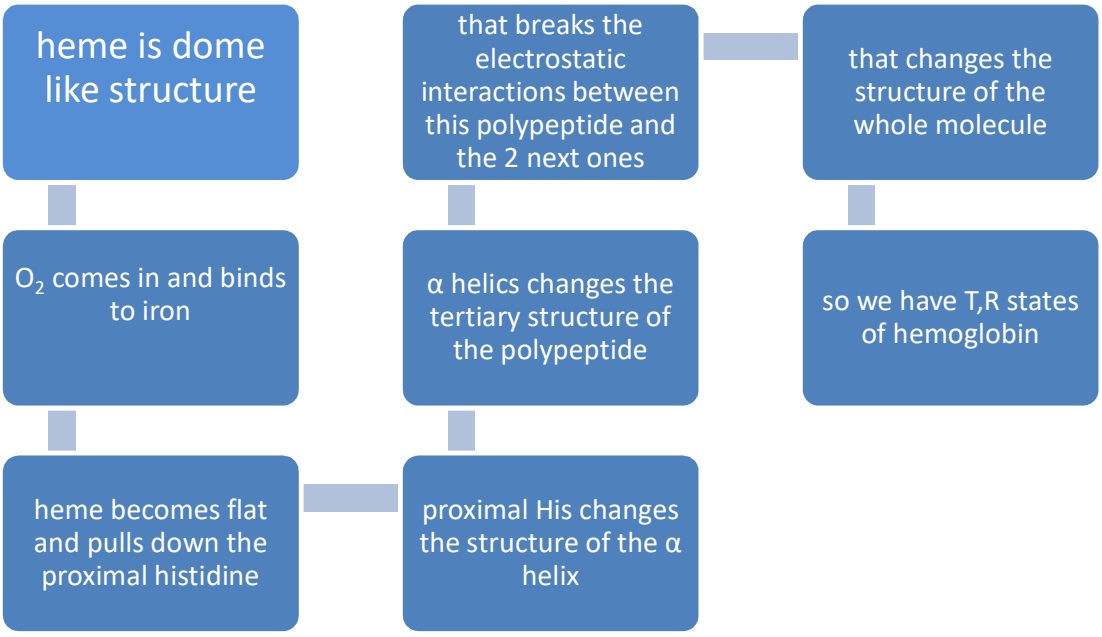
Binding of O_2 causes conformational changes in hemoglobin, converting it from the low affinity T-state to the high affinity R-state.

HOW DOES HEMOGLOBIN GO THROUGH THIS TRANSITION FROM HIGH TO LOW affinity states?

By breaking the electrostatic interactions between chains and then the molecule becomes relaxed turns from T to R.

BUT WHY AND HOW??

Because of the tiny movement of the heme group just for 1 nm .



But this doesn't happen in myoglobin because myoglobin is monomeric protein so this allosteric change in the structure only takes place in proteins that have quaternary structures and formed of multiple polypeptides.

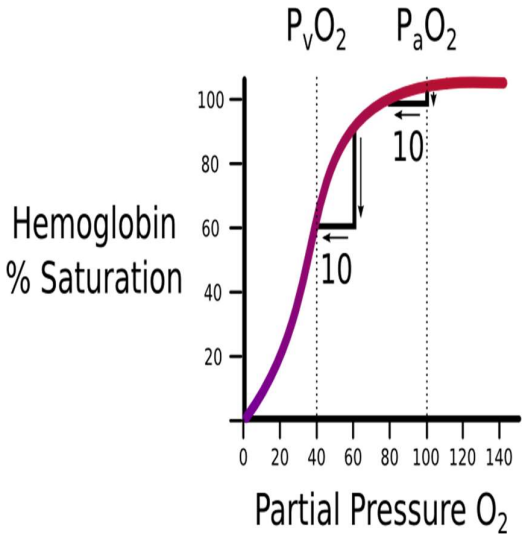
In myoglobin, movement of the helix does not affect the function of the protein.

Conformational changes lead to cooperativity among binding sites.

Binding of the first O_2 breaks some salt bridges with the other chains increasing the affinity of the binding of a second molecule.

Binding of the second O_2 molecule breaks more salt bridges increasing the affinity towards binding of a third O_2 even more, and so on.

Binding is cooperative.



A sudden drop in pulmonary capillary oxygen tension does not affect hemoglobin saturation

But when the partial pressure of O_2 get very low as a result of exercising the hemoglobin saturation decreases so more and more oxygen released in the peripheral tissues (level of O_2 is about 20 or lower)

ما خلقنا ل نيأس....

خلقنا لنقف على شرفة الحياة ولنخوضها مطمئنين واثقين به وإن طال وقوفنا فالأمل ما زال موجود

ما تنسونا من دعائكم

Good luck