Biochemistry

Globular proteins

There is no elevator to success, you have to take the stairs !

- Important.
- Extra Information.
- **Doctors slides**

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436 Biochemistry team

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Objectives:

1. describe the globular proteins using common examples like hemoglobin and myoglobin.

2. To study the structure and functions of globular proteins like:
   Hemoglobin (a major globular protein)
   Myoglobin, and
   γ-globulins (immunoglobulins) .

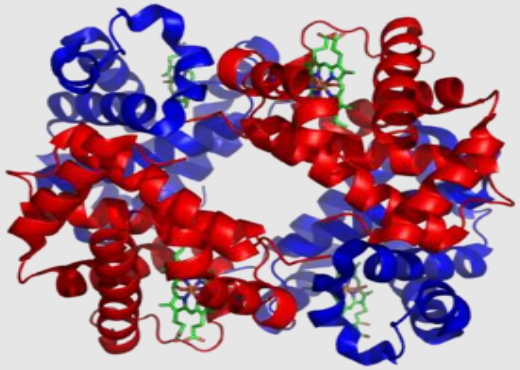
3. To know the different types of hemoglobin and difference between normal and abnormal hemoglobin .

4. To understand the diseases associated with globular proteins .

- Amino acid chains fold into shapes that resemble spheres are called globular proteins

Globular protein

- This type of folding increases solubility of proteins in water :



Polar groups on the protein's surface

They come from the side chain of amino acid

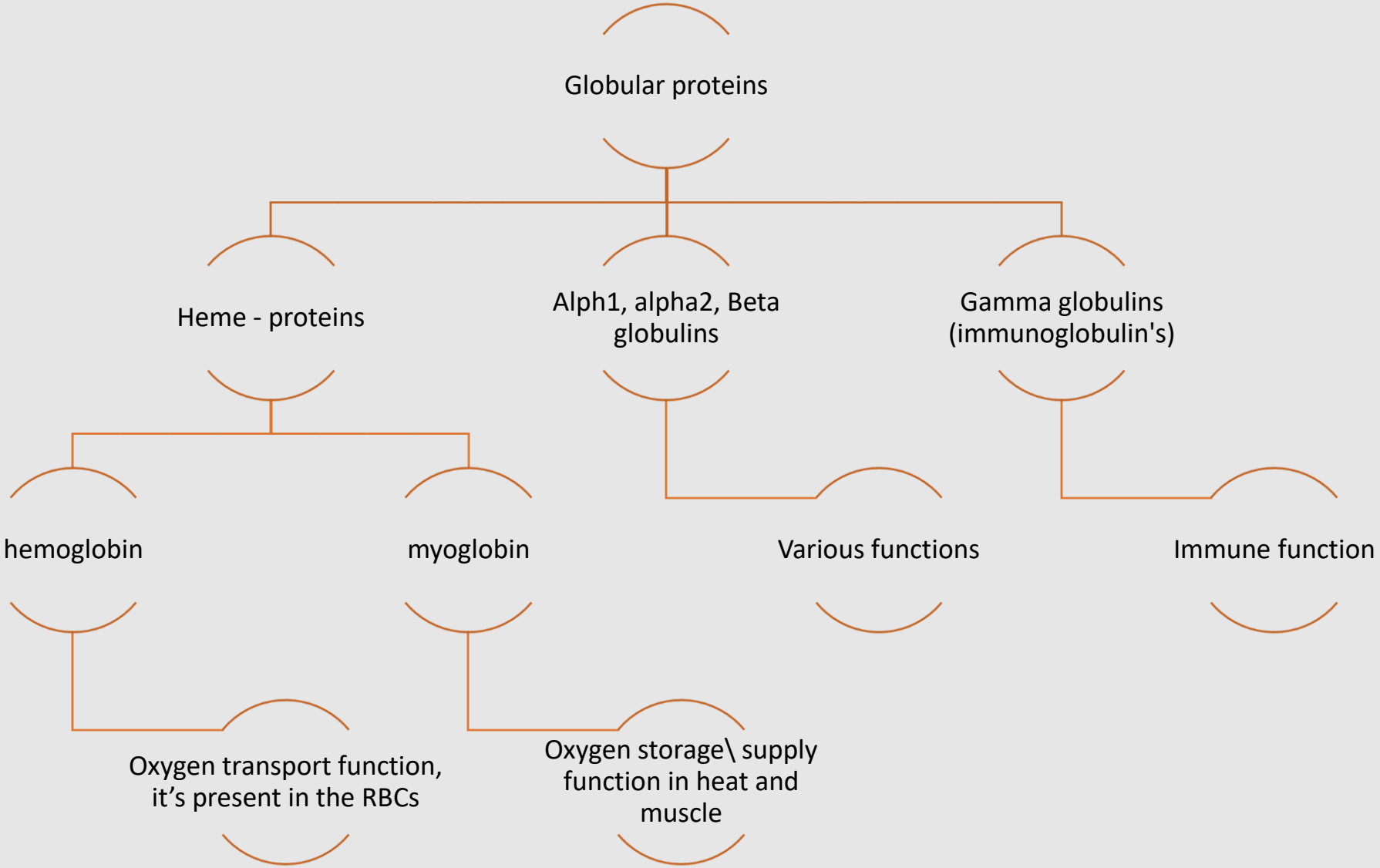
Hydrophobic groups in the interior

- Fibrous proteins are mainly insoluble structural proteins

The sequence of the protein is what determine the structure and the structure is what determine the function of it

-Globular proteins have functional properties.
ex: they can work as enzymes
-Fibrous proteins are structural only.

What makes the protein soluble is the ability to interact with water



Enzymes: catalysis of biochemical reactions.

hemoglobin and myoglobin are the two most abundant heme-proteins in humans.

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Hemoglobin

A major globular protein in humans

Composed of four polypeptide chains: (subunits)

Two α and two β chains

Contains two dimers of $\alpha\beta$ subunits

Held together by non-covalent interactions

Each chain is a subunit with a heme group in the center that carries oxygen

A Hb molecule contains 4 heme groups and carries

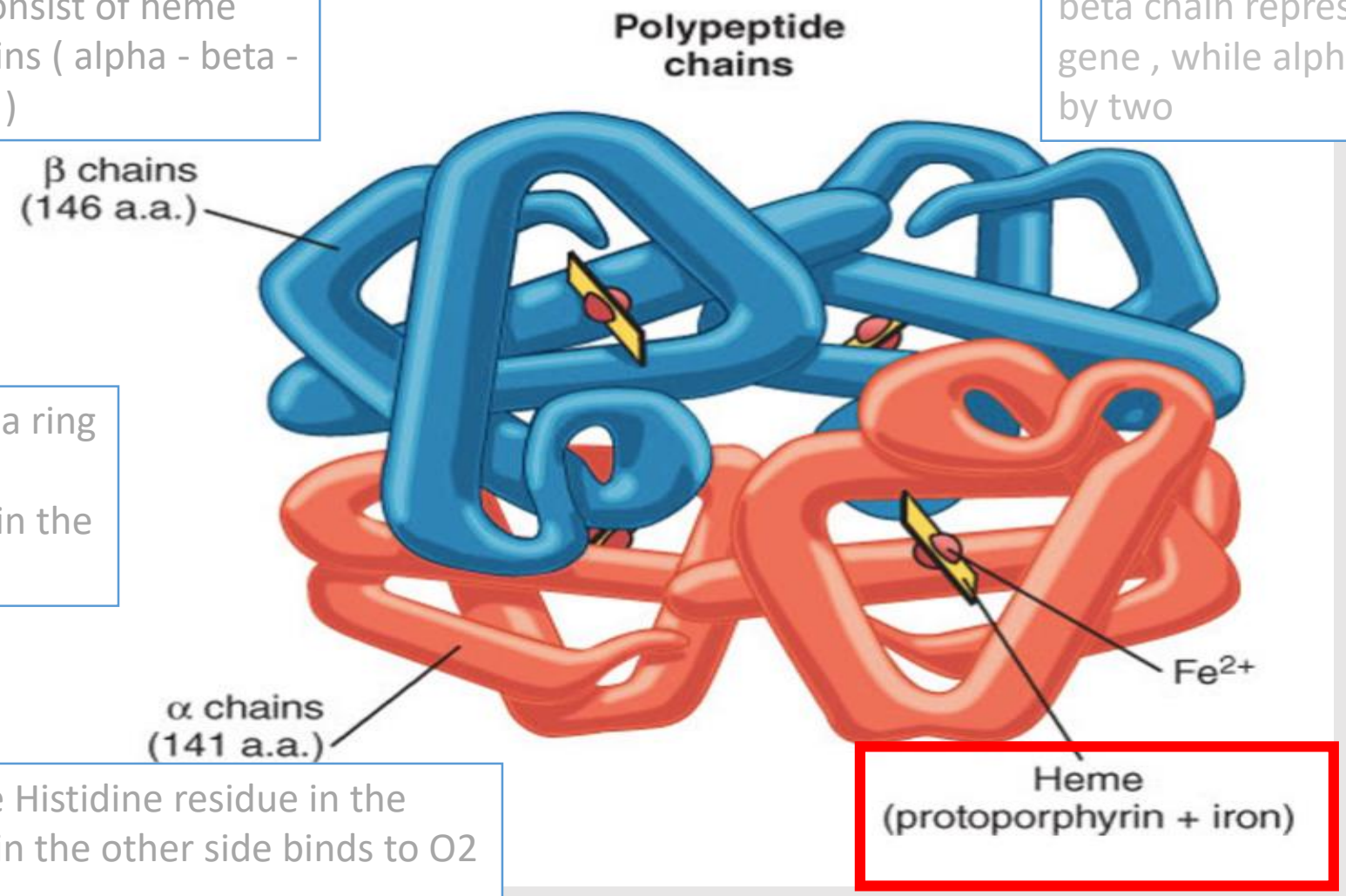
4 molecules of O_2

- the bond within the dimer itself is very strong because it has covalent and Hydrophobic bonds .while, the bond between the 2 dimers is weaker because it has ionic and van der val bond .
- 1 hemoglobin > 4 heme group > 4 oxygen molecules.

Hemoglobin Structure

Hemoglobin consist of heme group and chains (alpha - beta - gamma - delta)

beta chain represented by one gene , while alpha represented by two



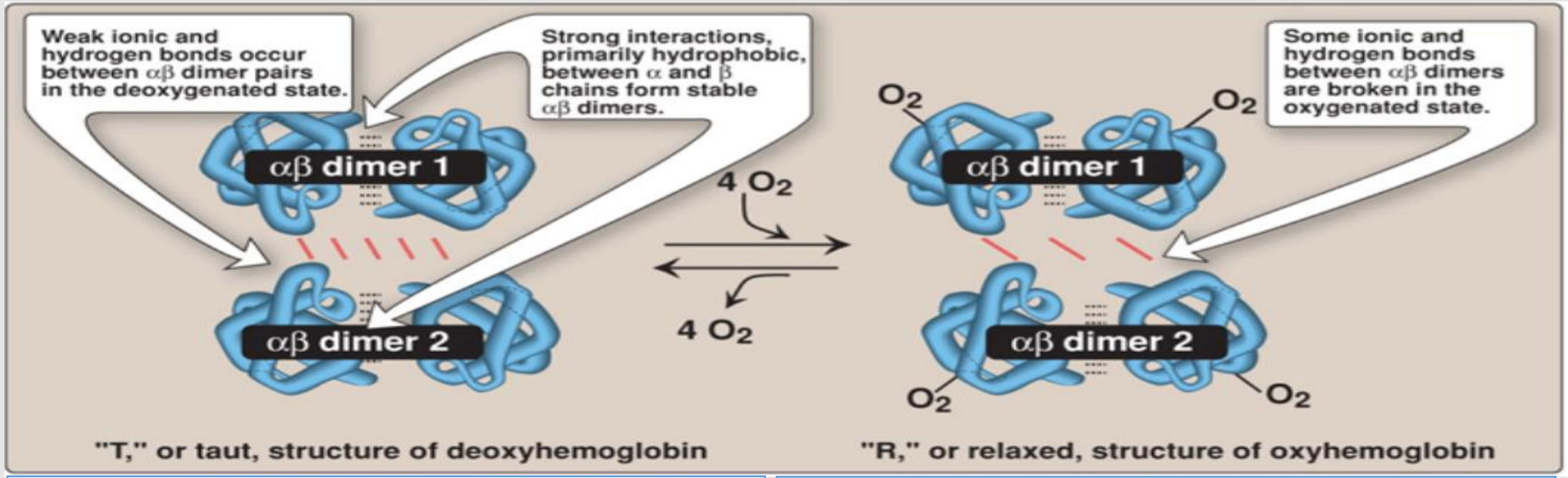
the heme is in a ring form and the ferrous iron is in the center

Iron binds with the Histidine residue in the globule chain and in the other side binds to O2

Types of hemoglobin

Normal :	**Abnormal: not able to transport O2 due to the structure of it.**
HbA (97%) It is the major hemoglobin	Carboxy – HB: (IMPORTANT NOTES) CO replaces O_2 and binds 220X tighter than O_2 (Smokers) it can produce toxic concentrations of carboxyhemoglobin in the blood for example increased levels of CO are found in the blood of tobacco smokers. CO toxicity appears to result from a combination of tissue hypoxia and direct CO- mediated damage at cellular level.
HbA_2 (2%)	Met- HB: Contains oxidized Fe^{3+} (~2%) that cannot carry O_2
HbF (1%) fetal or neonates It is increased in hepatocellular carcinoma patients	Sulfur-HB: Forms due to high sulfur levels in blood (irreversible reaction) (increased in people who have been using sulfur containing drugs for a long period of time)
HbA_{1c}	

Hemoglobin A (O_2 binding to hemoglobin)



T form: The deoxy form of hemoglobin is called the "T, or taut (tense) form. In the T form, the two alpha beta dimers interact through a network of ionic bonds and hydrogen bonds that constrain the movement of the polypeptide chains.
The T conformation is the low-oxygen-affinity form of hemoglobin.

R form: The binding of O_2 to hemoglobin causes the rupture of some of the polar bonds between the dimers, allowing movement. This leads to a structure called the "R" or relaxed form. The R conformation is the high-oxygen- affinity form of hemoglobin.

Types of normal hemoglobin

HbA_2

- Composed of two α and two δ globin chains
- Appears before birth
- Constitutes ~2% of total Hb in an adult body.

HbA_{1c}

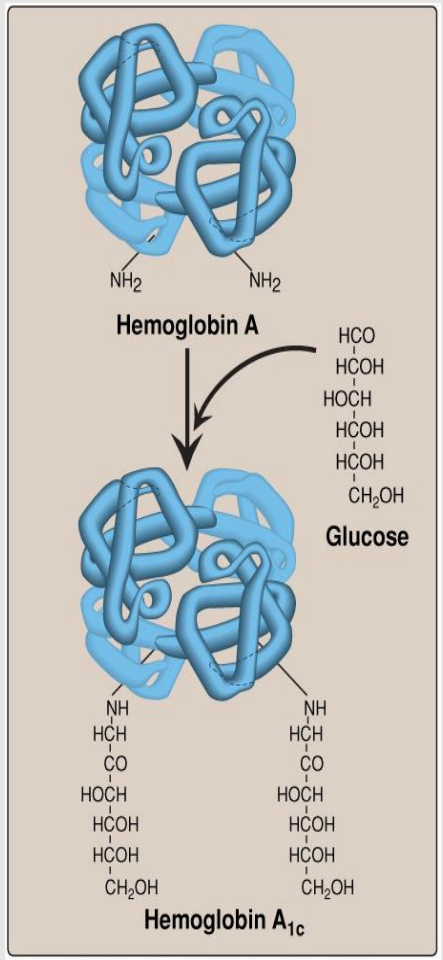
- HbA undergoes non-enzymatic glycosylation, which depends on plasma glucose levels so we can get HbA_{1c}
  - It has glucose residues attached predominantly to the NH2 groups of the N-terminal valines of the β-globin chains
- HbA_{1c} levels are high in patients with diabetes mellitus

Fetal hemoglobin (HbF)

- Composed of two α and two γ globin chains
- Has higher affinity for O_2 than HbA
  - Which facilitates the transfer of
  - O_2 from the maternal circulation across the placenta to the RBCs of the fetus.
- Major hemoglobin found in the fetus and newborn

- HbA1c is a marker for diabetes, and it is modified form of HbA2.
- The most abundant form of glycosylated hemoglobin is HbA1c
- **Hb A1c identifies how long has the patient been maintaining his/her blood glucose level for a period of 2-3 months; therefore it's a better marker for diagnosing and monitoring diabetic patients)**

HbA_{1c}



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Hemoglobin function

Hemoglobin is found exclusively in red blood cells.

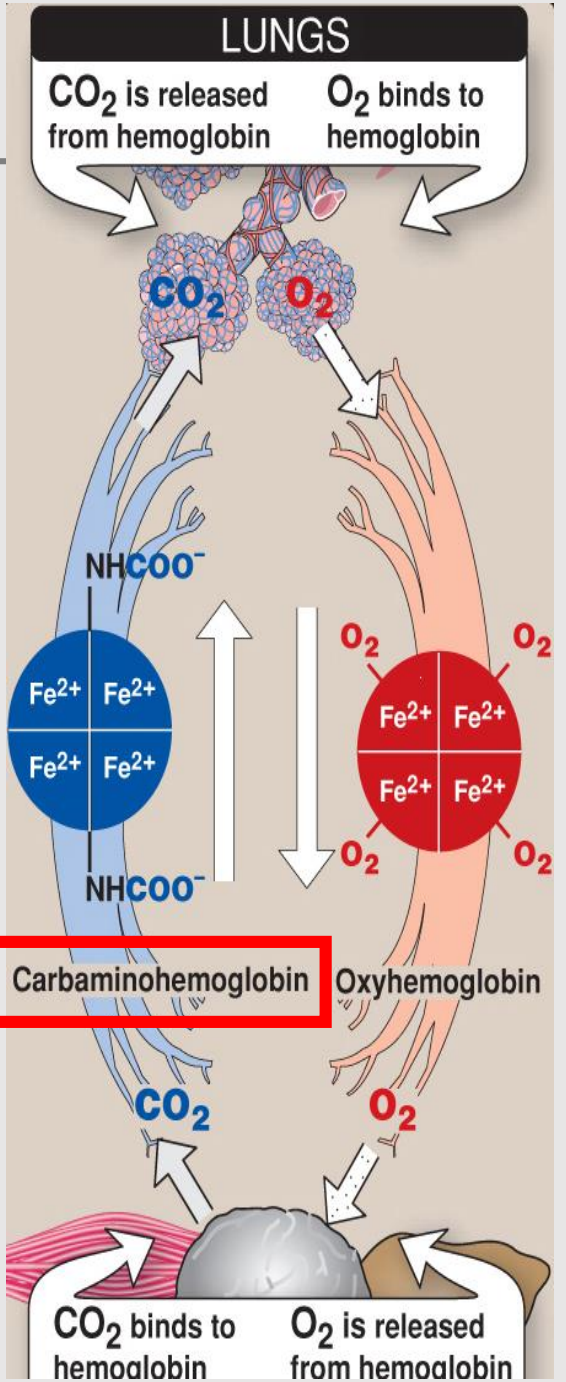
- Carrying oxygen from the lungs to tissues.
- Carries carbon dioxide from tissues back to the lungs.

Normal levels (g/dL):
Males: 14-16
Females: 13-15

oxygenated Hb called oxyhemoglobin
But Hb that has CO2 called carbaminohemoglobin

Extra information:

Hb's main function is to transport O_2 from the lungs to the capillaries of the tissues, and can carry 4 molecules of O_2.
Also Hb can transport H+ and CO_2 from the tissues to the lungs.
And most of CO2 is hydrated and bicarboniated.
And it's produced in the RBCs



Hemoglobin in diseases

All are autosomal recessive

Hemoglobinpathies are genetic disorders of hemoglobin are caused by:
*Synthesis of structurally abnormal Hb (qualitative)
*Synthesis of insufficient quantities of normal Hb (quantitive)
OR
A combination of both

Hemoglobinopathies	Description	
Sickle cell disease (HbS)	**Caused by a single mutation in B-globin genea**	Glutamic acid at position 6 in HbA is replaced by **valine** The mutant HbS contain B^s chains The shape of RBC's are sickled Cause sickle cell anemia. It is caused by single point mutation
Hemoglobin C disease (HbC)		Glutamic acid at position 6 in HbA is replaced by **lysine** Cause a mild form of hemolytic anemia (no specific therapy is required)

Hemoglobin in diseases cont.

<table>
<tr><th>Hemoglobinopathies</th><th colspan="2">Description</th></tr>
<tr><td>Methemoglobinemia</td><td colspan="2">Caused by the oxidation of Hb to ferric Fe^{3+} state
Methemoglobin cannot bind to O_2
Caused by certain drugs, reactive O_2 species, and NADH-cytochrome b5 reductase deficiency
Chocolate cyanosis: the brownish-blue color of the skin and blood (IMPORTANT)</td></tr>
<tr><td rowspan="2">Thalassemia</td><td rowspan="2">Defective synthesis of either alpha or beta global chains due to gene mutation.

Beta-thalassemia has higher risk than alpha-thalassemia
because
beta-thalassemia has only two copies of the gene while alpha-thalassemia has four copies.
That's why beta-thalassemia need regular blood transfusion and cause severe anemia</td><td>Alpha-thalassemia:
- Synthesis of alpha-globin chain is decreased or absent
- Cause mild to moderate hemolytic anemia.</td></tr>
<tr><td>Beta thalassemia:
Synthesis of beta-globin chain is decreased or absent
Cause severe anemia
Need regular blood transfusion .</td></tr>
</table>

Myoglobin

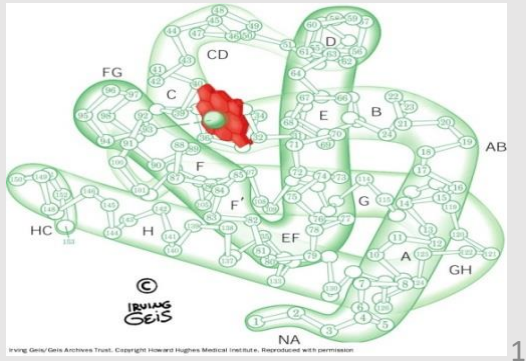
A globular hemeprotein in heart and skeletal muscle

Acts as O_2 carrier that increases the rate of transport of O_2 within muscle cell.

Function	Structure
Stores and supplies oxygen to the heart and skeletal muscle only	Contains a single polypeptide chain forming a single subunit with **eight** a-helix structures
It gives red color to skeletal muscles	The interior of the subunit is composed of nonpolar amino acids
Supplies oxygen during aerobic exercise	The charged (polar) amino acids are located on the surface (forming hydrogen bond) while The heme group is present at the center of the molecule

Single chain will bind to one Heme. So Myoglobin molecule will bind to one O_2

Explanation: Forming the structure of myoglobin is stabilized by hydrophobic interaction.

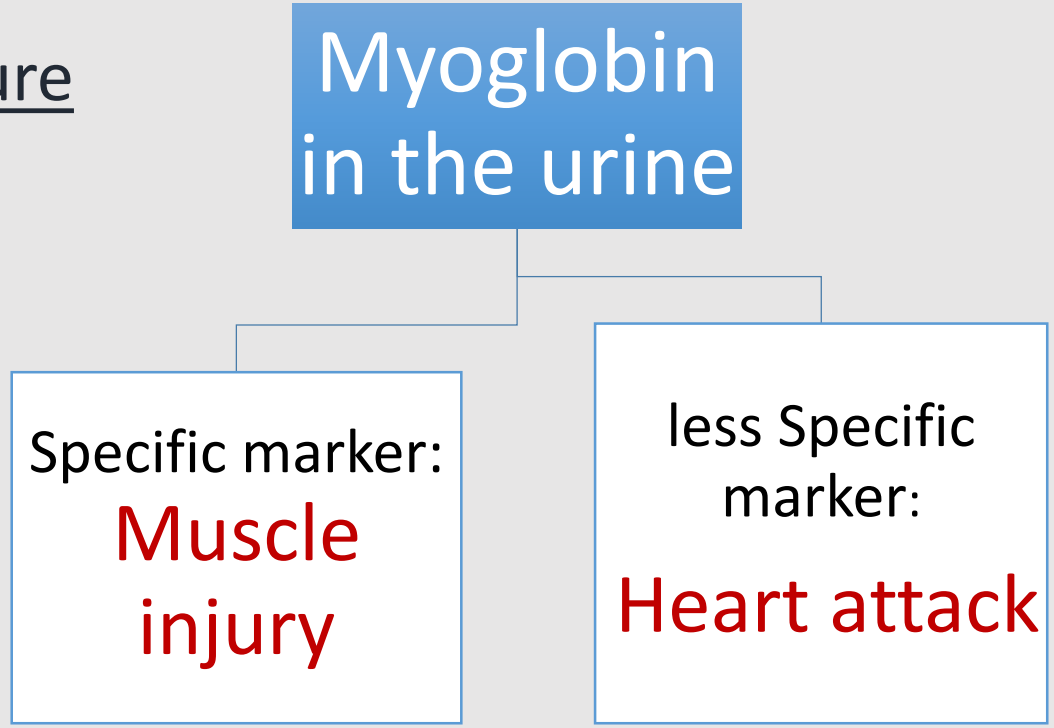


Myoglobin in diseases

- **Myoglobinuria**: Myoglobin is excreted in urine due to muscle damage (rhabdomyolysis it means the destruction of muscle cells)
- May cause acute renal failure

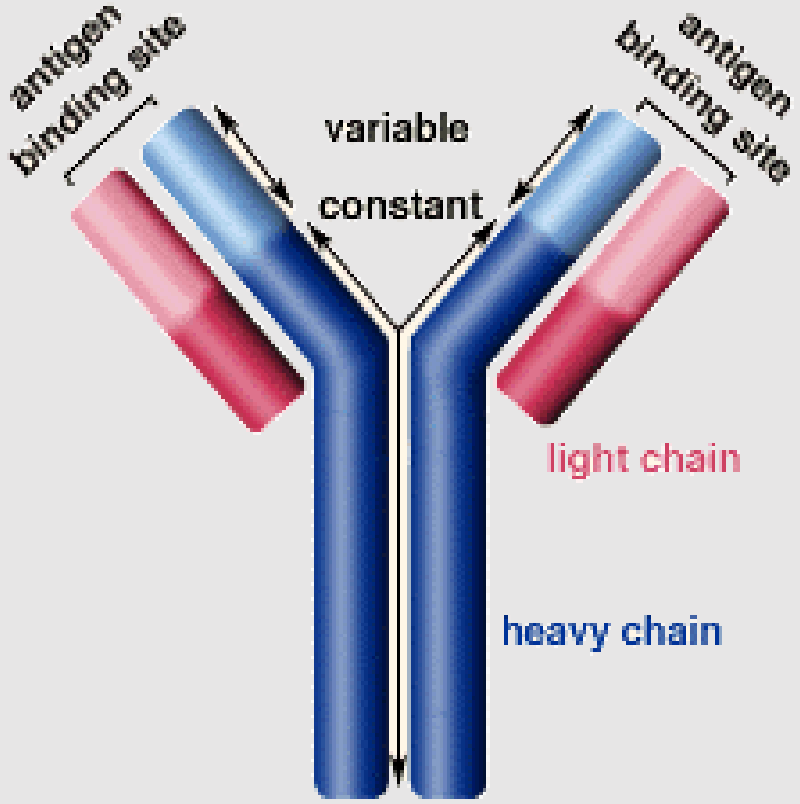
The most common causes of myoglobinuria in adults are : trauma, alcohol and drugs.

IMPORTANT NOTE:
The cause of myoglobinuria is muscle damage and myoglobinuria may cause acute renal failure



Immunoglobulins

- Defensive proteins produced by the B-cells of the immune system
- **Y-shaped** structure with 2 heavy and 2 light polypeptide chains
- Neutralize bacteria and viruses
- Types: IgA, IgD, IgE, IgG, IgM



Explanation: The antibodies bind with the antigen and makes immune complex which trigger the immune system and the macrophages start engulf this complex

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Summary

Hemoglobin:
4 Chains
Transports O2 and CO2

Normal HB: 4 Types
-HbA –HbA2 –HbF –HbA1C

Abnormal HB: 3 Types
-Carboxy Hb –Met Hb –Sulf Hb

Hemoglobinopathies: 4 types
1- Sickle cell disease (HbS)
2- Hemoglobin C disease (HbC)
3- Methemoglobinemia
4- Thalassemia (alpha or beta)

Myoglobin:
1 Chain
Stores O2
Gives red color to skeletal muscles

Myoglobin disease:
Myoglobinuria

Immunoglobulins:
4 Chains
Neutralizes Bacteria

5 Types: Ig G, A, M, E, D

Quiz

SAQ

https://www.onlineexambuilder.com/globular-proteins-saq/exam-127554

MCQ's

https://www.onlineexambuilder.com/globular-proteins/exam-127546

https://www.onlineexambuilder.com/globular-proteins/exam-128219

Helpful video

Hemoglobin Video: https://www.youtube.com/watch?v=89feCoBXRGE

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THANK YOU

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

- Review the notes

- https://www.youtube.com/watch?v=89feCoBXRGE

- Lippincott's Illustrated Reviews: Biochemistry, 6th E

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