Editing file

Globular Proteins

Respiratory Block

- Main text
- Important
- Girls Slides
- Boys Slides
- Doctor Notes
- Extra

objectives

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

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

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

- To understand the diseases associated with globular proteins

Globular proteins

Proteins

Fibrous proteins

are mainly insoluble structural

globular proteins

Amino acid chains fold into shapes that resemble spheres
This type of folding increases solubility of proteins in water (why?)

Polar/ Hydrophilic groups → On the protein's surface

Nonpolar / Hydrophobic groups → In the interior

Globular proteins

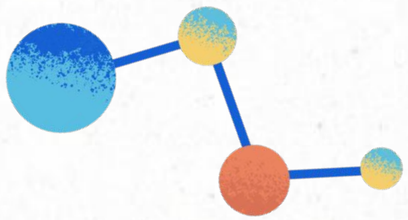
Globular proteins examples and their function:

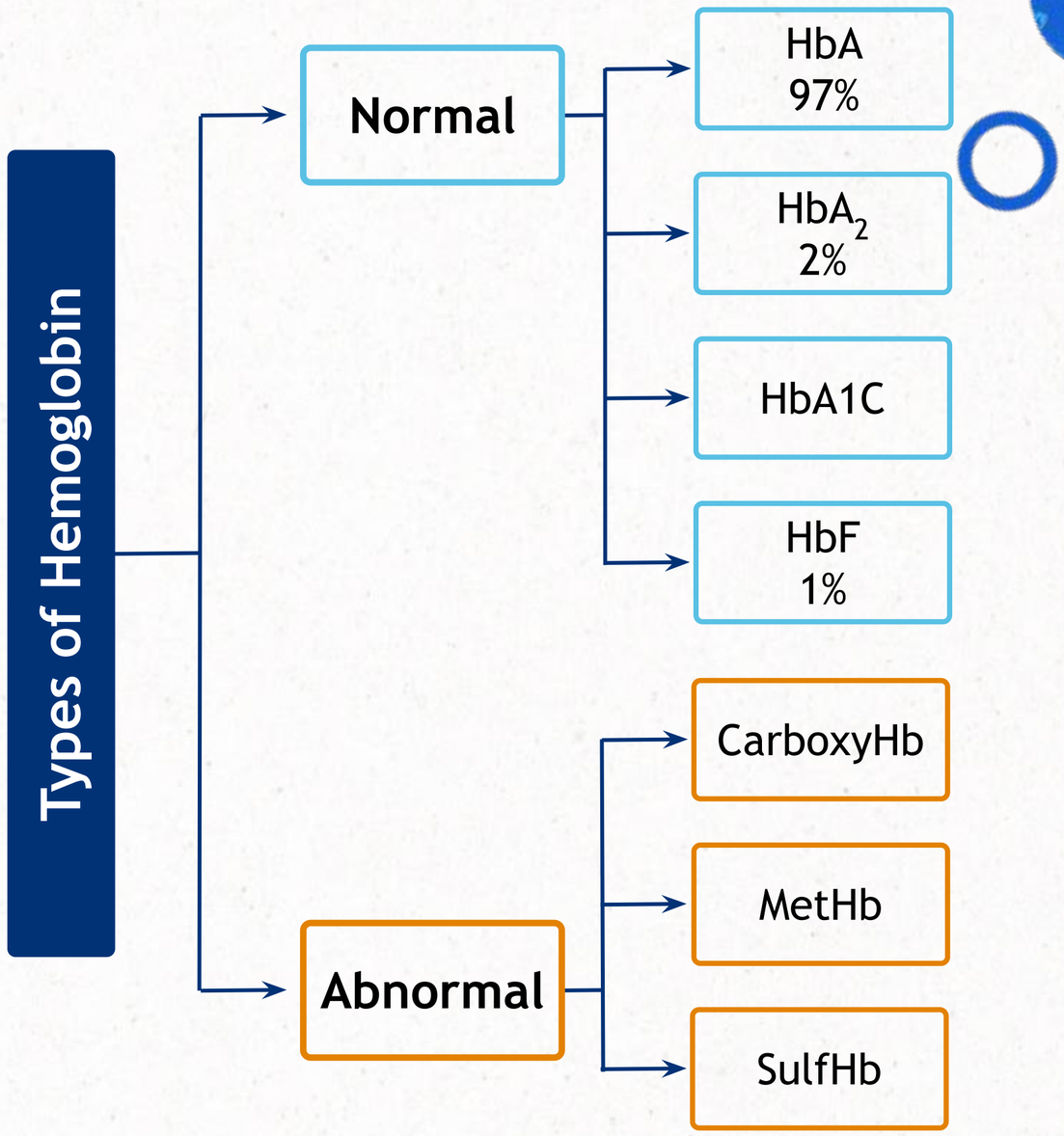
Functions		
01	Hemoglobin	oxygen transport function
02	Myoglobin	oxygen storage/supply function in heart and muscle
03	α_1, α_2 , β globulins	various functions
04	γ globulins (immunoglobulins)	Immune function
05	Enzymes	catalysis of biochemical reactions

Hemoglobin

A major globular protein in humans

- Composed of four polypeptide chains: Two α and two ß chains.
- Contains two dimers of αß subunits Held together by non-covalent interactions
- Each chain is a subunit with a heme group in the center that carries oxygen.
- Hb molecule contains 4 heme groups and carries 4 molecules of O_2.
- Normal level(g/dL):
  - Males:14-16 g/dL
  - Females:13-15 g/dL

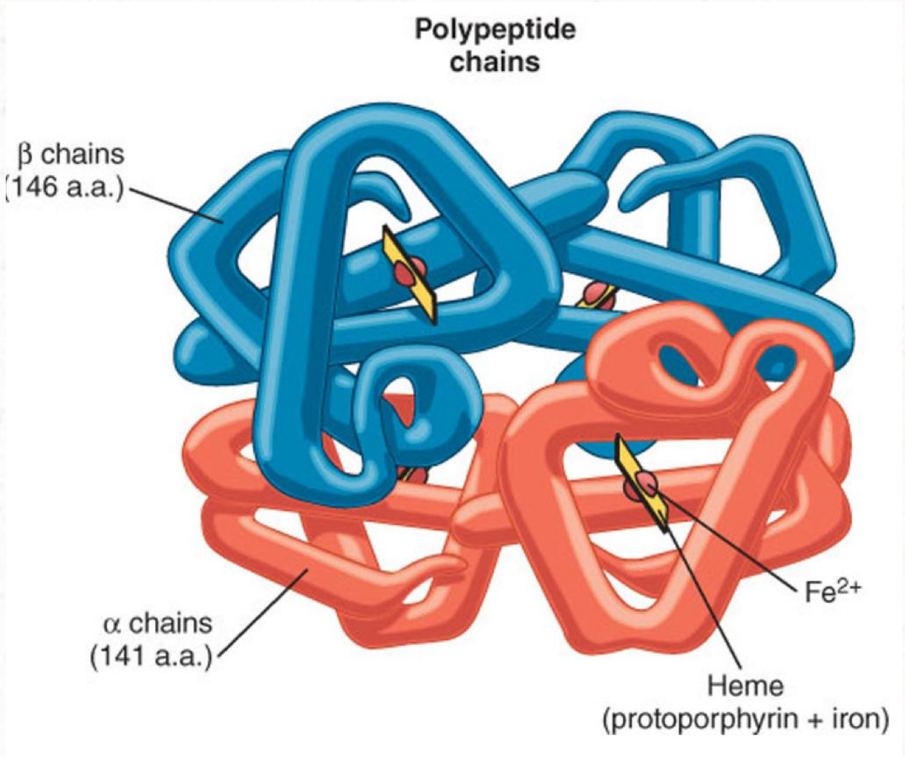




Hemoglobin

A heme consist of **protoporphyrin** and **iron** in the middle.
the The iron can be either :

1. Ferrous known as Fe^{+2} can bind to O_2 (normal)
2. Ferric known as Fe^{+3} unable to bind to O_2 (abnormal)



Hemoglobin function:

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

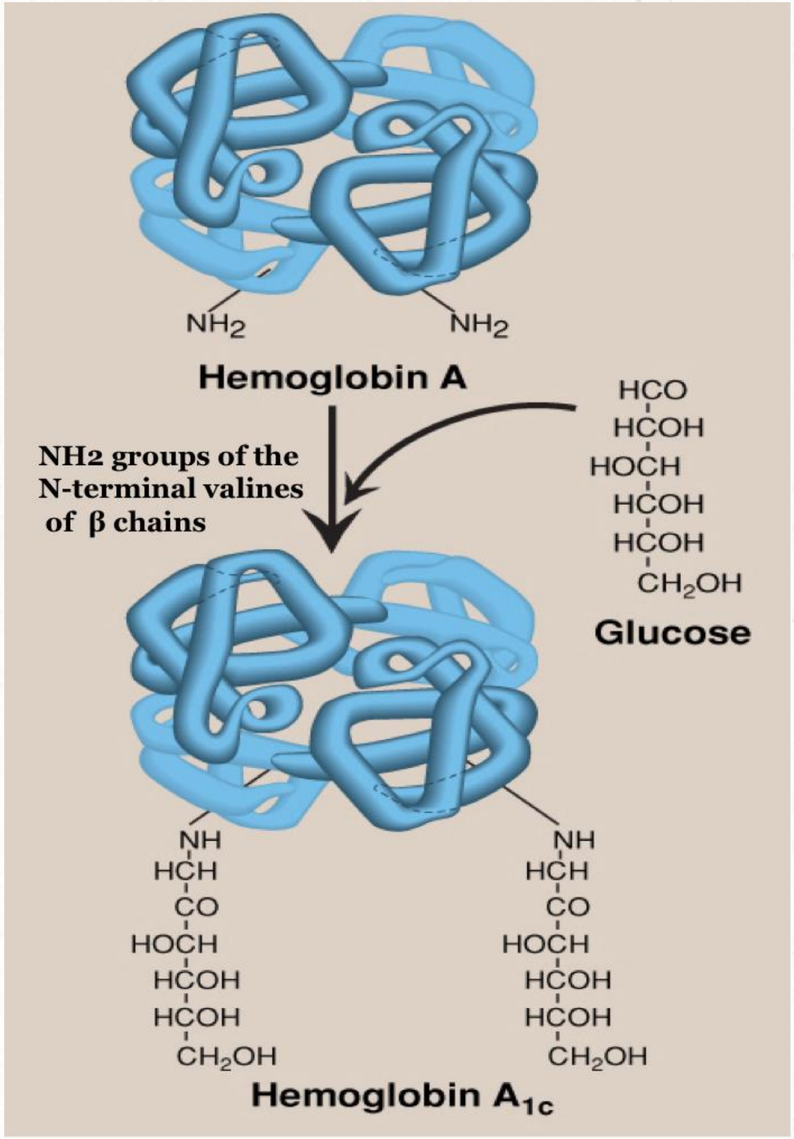
You have to know the structure and difference between each type.

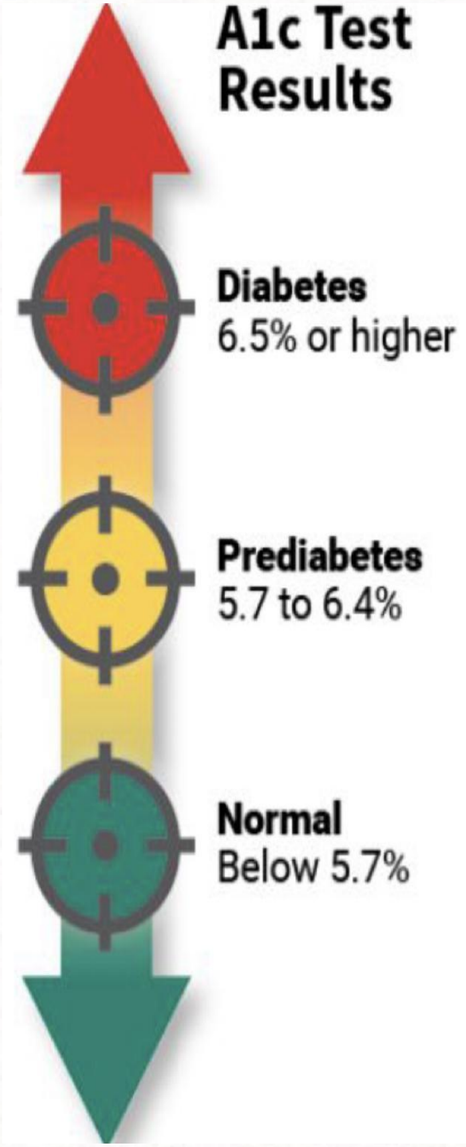
Normal Hemoglobin

Type	HbA	HbA_2	HbF (Fetal hemoglobin)	HbA1C
Structure	2α, 2β	2α, 2δ Delta	2α, 2γ Tetrameter	HbA attach to glucose
Characteristics	details in next slide	•Appears shortly before birth (in small conc). It conc increases in about the 12th week (up tp 2%) • Constitutes ~2% of total Hb physiological role is unknown	• Major hemoglobin found in the fetus and newborn • Higher affinity for O_2 than HbA Help in take O_2 from mother • Transfers O_2 from maternal to fetal circulation across placenta	• HbA undergoes non enzymatic (by itself) glycosylation, that depends on plasma glucose levels • HbA1c levels are high in patients with diabetes mellitus • NH_2 groups of the N-terminal valines of β chains
Notes	-	Marker for hepatocellular carcinoma (liver cancer), It appears slightly before or after birth and its conc increase in week 12 approximately	Little percentage is present in Adult and the function is unknown. The fetus has HbF with time it will decrease and HbA increase	It is not affected by the food

A folded polypeptide chain → Tertiary protein (Subunit)
2 x subunits (can be α, β, γ, δ..) → Dimer
2 x αβ dimer → Hemoglobin (tetramer protein)

HbA1C


NH2
NH2
Hemoglobin A
NH2 groups of the
N-terminal valines
of β chains
HCO
HCOH
HOCH
HCOH
HCOH
CH2OH
Glucose
NH
HCH
CO
HOCH
HCOH
HCOH
CH2OH
NH
HCH
CO
HOCH
HCOH
HCOH
CH2OH
Hemoglobin A1c


A1c Test Results
Diabetes
6.5% or higher
Prediabetes
5.7 to 6.4%
Normal
Below 5.7%

Hemoglobin A

HbA structure :

1. **Strong interactions** primarily **hydrophobic** (bond) between α and ß chain to form stable αß dimers.

2. **Weak ionic and hydrogen bonds** occur between αß dimer pairs in the deoxygenated state-not binding to O_2- (“T” or taut, structure of deoxyhemoglobin)

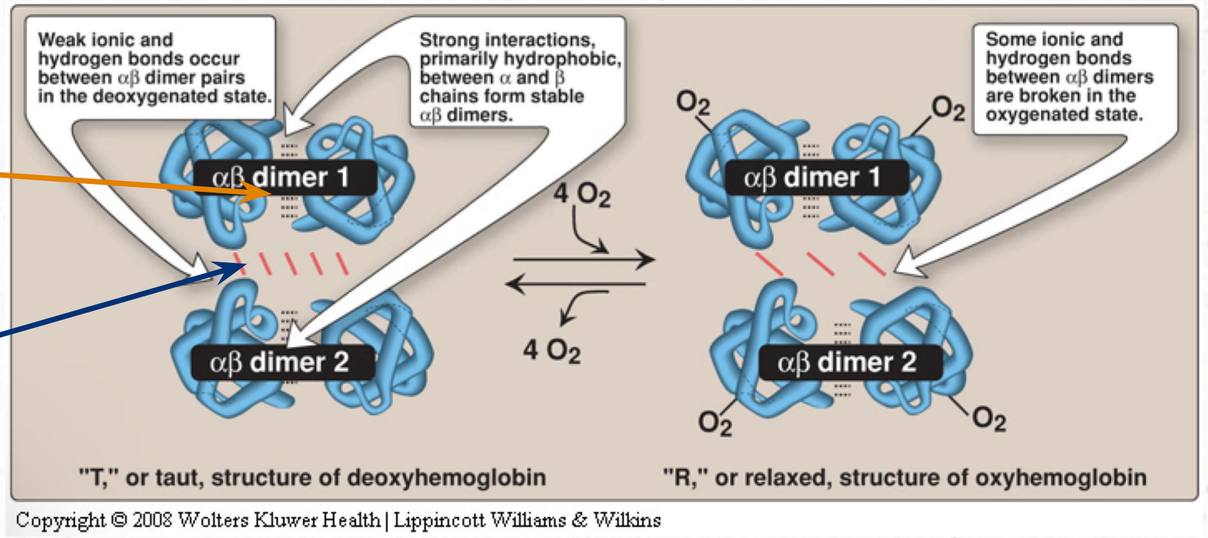
3. Some **ionic & Hydrogen bonds** between αß dimers are broken in the oxygenated state -binding to O_2- (“R” or relaxed, structure of oxyhemoglobin)

MED439: There are two types of binding in the HbA structure:
1- intra-dimer bonding: strong bonds between two subunits
2-inter-dimer bonding: weak bonds between two dimers

MED443

فيه نسبة Hydrophobic بسيطة وظيفتها -> strong interaction between a & B ولكن غالبية ال hydrophobic تكون من الداخل

Ionic and hydrogen bonds between dimers في حالة عدم وجود الأكسجين تكون deoxygenated وتعتبر روابط ضعيفة لأنها ستنكسر في حال ارتبط الأكسجين (الصورة اليمين)



Hemoglobin

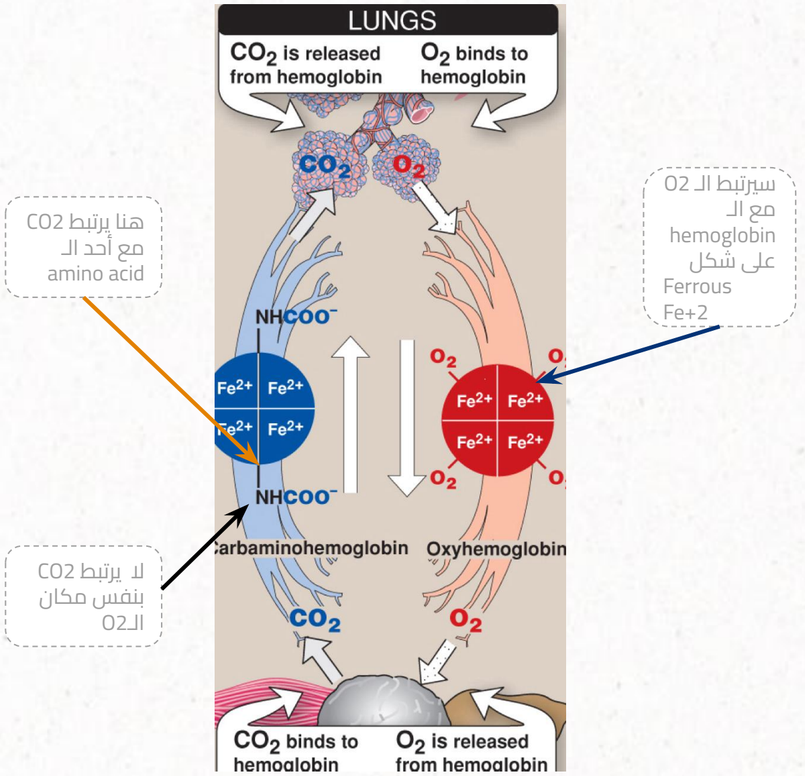
Gas Transport :

Carbaminohemoglobin and deoxyhemoglobin are different

oxyhemoglobin when the Hb is saturated with O_2

carbaminohemoglobin when the Hb is saturated with CO_2 , CO_2 binds with NH_2 of one of the amino acids

Special thanks for MED 443:



MED443:

What is the name of the bond that forms stable alpha beta dimers?

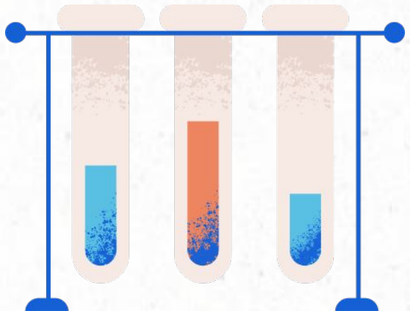
Hydrophobic bond

What is the type of bonds between alpha and beta dimers?

Hydrogen and ionic bonds

What are the bonds that break during R stage?

Ionic and hydrogen bonds



Abnormal Hemoglobin

Unable to Transport O_2 due to abnormal structure:

Type	Carboxy Hb	Met Hb	Sulf Hb
Characteristics	CO binds 200x tighter than O_2 (in smoker) and stabilizes the oxyhemoglobin	Contain oxidized Fe^{+3} (2%) that can not carry O_2	Forms due to high sulfur levels in blood (irreversible reaction)

Extra from doctor: Hemoglobin has 4 sits where O_2 can bind. if CO bind with one -or all- of these, even if the other 3 sits bind it binds to hemoglobin with O_2, then : instead of oxygen
-CO binding has very high affinity so it can't be remove easily.
-Once it is bond, it stabilize carboxy Hb structure.So the other O_2 molecules will not be giving off. even if there is a pressure difference with the tissues. (which cause hypoxia) similar thing was mentioned in foundation (cooperative binding) that: when the first unit of hemoglobin bind to O_2. it cooperate the next unit to bind to the 2nd O_2 faster than the first binding process and so on. also when one O_2 leaves it facilitated the other O_2 to leave as well. (that's how one molecules can change the hemoglobin work)

IMPORTANT!

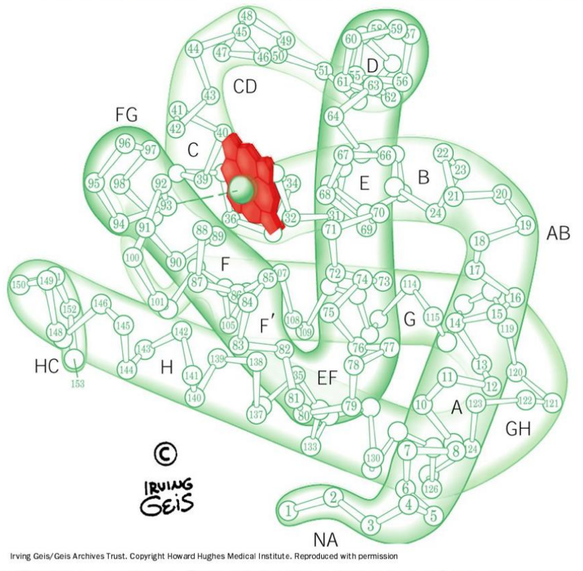
Hemoglobinopathies

Disorder of hemoglobin caused by: (Synthesis of structurally abnormal Hb or Synthesis of insufficient quantities of Normal Hb or Combination of both)

Type	Sickle cell disease	Hemoglobin c disease	Methemoglobinemia	Thalassemia
Characteristics	- Caused by a single mutation in beta globin gene - **Glutamic acid** at position **6** in HbA is replaced by **valine** - the mutant HbS contain β's chain - The shape of RBCs become sickled - causes sickle cell anemia	- caused by a single mutation in beta globin gene - **Glutamic acid** at position **6** in HbA is replaced by **Lysine** - Causes a **mild** form of hemolytic anemia	- caused by oxidation of Hb to ferric (Fe^{3+}) state - Methemoglobin can not bind oxygen - High levels of MetHb - caused by certain drugs, reactive oxygen species and NADH-Cytochrome b5 reductase deficiency - **chocolate cyanosis**: brownish blue color of the skin and blood	Defective synthesis of either **α** and **β** globin chain due to gene mutation and there is 2 type: 1. **α thalassemia:** synthesis of α globin is decreased or absent and causes **mild to moderate** hemolytic anemia 2. **β thalassemia:** synthesis of β globin is decreased or absent and causes **severe** anemia and need regular blood transfusion

Myoglobin

- A globular heme protein in heart and muscle
- Stores and supplies oxygen to the heart and muscle only
- Contain a single polypeptide chain forming a single subunit with 8 α-helix structures
- **interior** of subunit is composed of non polar amino acid
- charged amino acid located on **surface**
- heme group is present at the **center** of the molecule
- Myoglobin give red color to skeletal muscles
- supply oxygen during aerobic exercise

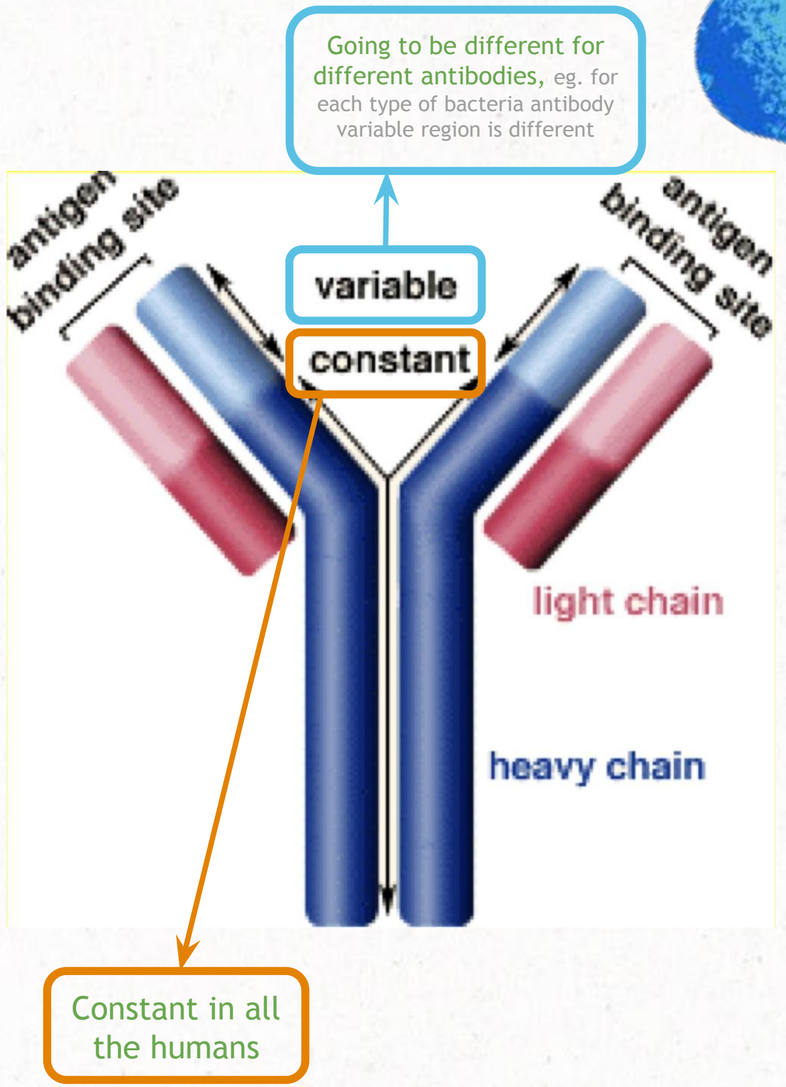


Myoglobin in disease:

- **(Myoglobinuria)**: myoglobin is excreted in **urine** due to muscle damage (Rhabdomyolysis)
- May cause acute renal failure and specific marker for muscle injury
- less specific marker for heart attack

Immunoglobulins

- Antibodies
- Defensive protein produced by the B cells of immune system
- Y shaped structure with 2 heavy and 2 light polypeptide chain
- Neutralize bacteria and viruses
- Types (IgA,IgD,IgE,IgG,IgM) MAGED



Antigen by itself are small, unrecognizable by your defense system. When the antibody is attached to it, they make it bigger in size so that it can be taken care of by the natural killer cells and your T lymphocytes

Take Home Messages

- Amino acid chains fold into shapes that resemble spheres are called globular proteins.
- Fibrous proteins are mainly insoluble, while globular proteins are soluble structural proteins
- Hb, Myoglobin, globulines and enzymes are examples of globular proteins.
- Functionally, Hb is for O2 and CO2 transport.
- HbA, HbA2 and HbF are examples of normal Hb, in which the tetrameric structure is composed of 2 a constant subunits with 2 changeable B subunits according to Hb type.
- HbA1C is HbA which undergoes non-enzymatic glycosylation, depending on plasma glucose levels.
- Carboxy-Hb, Met-Hb and Sulf-Hb are examples of abnormal Hb, in which O2 molecules are not transported due to abnormal Hb structure.
- Sickle cell (HbS) and HbC diseases are caused by a single mutation in B-globin gene.
- Disorders of Hb caused by synthesis of structurally abnormal Hb and/or insufficient quantities of normal Hb.
- Glu6 in HbS is replaced by Val, while it is replaced by Lys in HbC.
- Thalassemia is caused by a defect in synthesis of either a or ***β***-globulin chain, as a result of gene mutation.
- a-Thalassemia causes less severe eanemia than ß-Thalassemia.
- Hb is composed of 4 chains (subunits), while myoglobin is composed of a single chain.
- Myoglobin is a globular hemeprotein, which stores and supplies O2 to the heart and muscle only.
- Hb is composed of 4 chains (subunits), while myoglobin is composed of a single chain.
- Myoglobinuria is a specific marker for muscle injury and may cause acute renal failure.
- Immunoglobulins are defensive proteins produced by the B-cells.
- Immunoglobulins consist of 5 types : IgA, IgD,IgM,IgE,IgG.

References: Illustrations in Biochemistry by Lippincott 6th edition.

MCQ

Q1) What is the immuno globular protein?			
A- Gamma globulins	B- Alpha globulins	C- Beta globulins	D- Myoglobin
Q2) Hemoglobin is composed of 4 polypeptide:			
A- 2 Alpha and 2 Beta	B- 2 Alpha and 2 Gamma	C- 2 Beta and 2 Gamma	D- None of this
Q3) Hemoglobin carries :			
A- 5 O_2	B- 6 O_2	C- 2 O_2	D- 4 O_2
Q4) are High in patient with Diabetes mellitus			
A- HbF	B- HbA	C-HbA2	D-HbA1c
Q5) Form because high sulfur levels in blood			
A- Met Hb	B- Carboxy Hb	C- Sulf Hb	D- HbA1c

Answers:
1- A
2- A
3- D
4- D
5- C

SAQ

Q1) mention 2 types of Globular protein and their function

Q2) mention 2 types of abnormal hemoglobin

Q3) what is the difference between alpha thalassemia and beta thalassemia?

Answers

Q1) Hemoglobin: oxygen transport function
Myoglobin: oxygen storage and supply function in heart and muscle

Q2) Carboxy Hb + Met Hb

Q3) alpha cause mild to moderate hemolytic anemia while beta cause severe anemia

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