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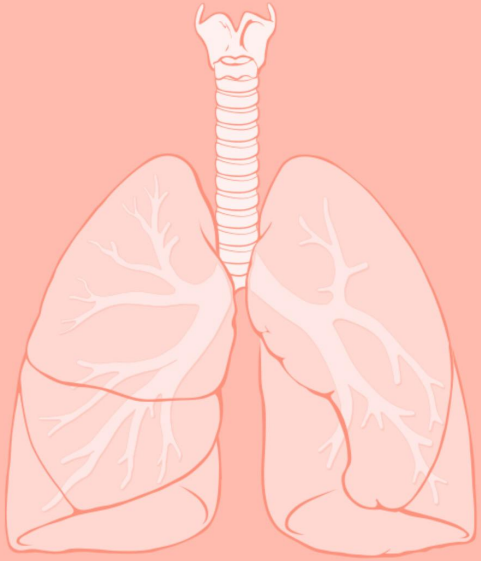
# Globular Proteins



Color index :

Main text

IMPORTANT

Extra Info

Drs Notes

Respiratory Block - Biochemistry Team

# 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
  - $\gamma$-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 protein

fibrous proteins are mainly **insoluble** structural proteins

## Globular protein

The types of folding increase the solubility in water:
1-Polar groups on the protein's surface (for interaction with $H_2O$)
2-hydrophobic groups in the interior (inner layer)

Amino acid chains folding into shapes resembles the spheres
(بروتينات كروية)

Examples of globular proteins and their functions

| Examples | Function |
|---|---|
| Hemoglobins | $O_2$ transport |
| Myoglobin | $O_2$ storage and supply in **heart and** skeletal **muscle** only |
| $\alpha_1,\alpha_2,\beta$-globulins | Various functions |
| **$\gamma$-globulins ( immunoglobulins)** | Immune function |
| Enzymes (made from globular proteins) | Catalysis of biochemical reactions |

Globin : proteins with functions related to oxygen ( transport/storage..etc)
Globulin: proteins with functions not related to oxygen. #Med438

α = alpha
β = Beta
γ = Gamma
δ = Delta

Fe+2 : Ferrous state (reduced form) (less stable)
Fe+3 : Ferric state (oxidative form) (more stable)

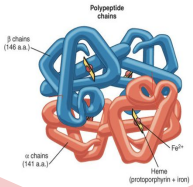
Dimer : two subunits together ( Either α or β )

# Hemoglobin

Composed of 4 polypeptide chains ( 4 subunits ) : Two α chains + Two β chains

-Contains two dimers of αβ subunits
-Held together by: **non-covalent interaction**
(Dimmer =2 United subunits)

A major globular protein in humans




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

Heme in ferrous state ( normal hemoglobin in ) makes 6 bonds ( 4 of the $N_2$ of protoporphyrin, one with the histidine group of the globulin chain & other one with $O_2$ group

A Hb molecule contains 4 heme groups and carries 4 molecules of $O_2$ ( 8 atoms )

## Types of hemoglobins ( Hb )

- Normal
- Abnormal
  - Carboxy Hb
  - Met Hb
  - Sulf Hb

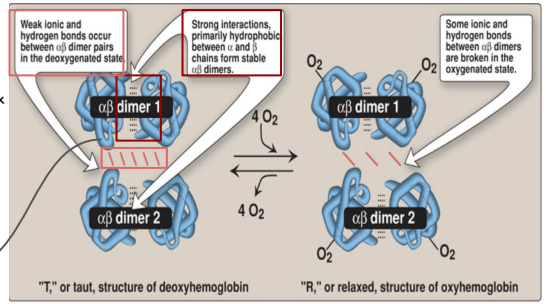
| Form | Percentage in adult |
|---|---|
| HbA | 97% 2α & 2β |
| $HbA_2$ | 2% 2α & 2δ |
| $HbA_{1c}$ | 3% - 9% |
| HbF | 1% 2α & 2γ |

# Structure of HbA

1-strong interactions primarily hydrophobic ( bond ) between α & β subunits to form stable dimmer αβ
2- week ionic and hydrogen bonds occur between αβ dimer pairs in the deoxygenated state ("T" taut deoxyhemoglobin)

3- when $O_2$ bind to the HbA will break some ionic & H bonds in αβ-dimmer in oxygenated state ("R"relaxed oxyhemoglobin )

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




# Hb Function

Carries oxygen from the lungs to tissues

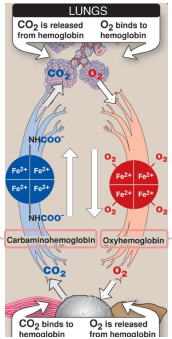
Carries carbon dioxide from tissues back to the lung

Normal level (g/dL)
14-16(g/dL)
13-15(g/dL)

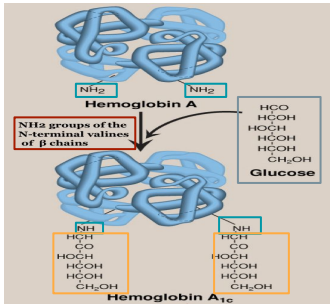
# Gas transportation

Hb Bind with 4 of O2 molecules ( **oxyhemoglobin** ) in lungs and release it in the tissue and bind with 2 of CO2 ( **carbaminohemoglobin** ) and release it in the lungs

Hb When it binds with CO2 ( carbaminohemoglobin ) you should know it doesn't bind to the site of $O_2$ , it binds to the amino acids




Hb When it binds with $O_2$ ( Oxyhemoglobin )




$HbA_{1c}$ is a marker for diabetes. When someones is diabetic. $HbA_{1c}$ levels will be high. Why is it a good marker?
Because $HbA_{1c}$ in blood hits glucose and attaches to it and since RBCs lifetime is 120 days. It measures the level of glucose in the past 3 months
More glucose = more $HbA_{1c}$ will be bounden to glucose
More $HbA_{1c}$ = more likely to be diabetic

# Types of hemoglobins

## HbA

Explained previously

## $HbA_{1c}$

- HbA undergoes non-enzymatic glycosylation
- Glycosylation depends on plasma glucose levels of β chains ( not occurring randomly )
- Glucose bind with NH2 of the N-terminal valines of β chains
- $HbA_{1c}$ levels are high in patients with diabetes mellitus ( indicates glucose levels in the blood and diagnosis of DM )

## $HbA_2$:

- Appears weeks before birth ( replace the HbF gradually )
- Constitutes ~2% of total Hb
- Composed of two α and two δ globin chains
- Increased in β-thalassemia patients

## Fetal hemoglobin (HbF):

- Major hemoglobin found in the fetus and newborn
- Tetramer with two α and two $\gamma$ chains
- Higher affinity for $O_2$ than HbA

  ( $\gamma$ chains don't bind to proteins that reduce $O_2$ affinity ) Dimer
- Transfers O2 from maternal to fetal circulation across placenta

# Abnormal Hbs: Unable to transport $O_2$ due to abnormal structure

**1** **Carboxy-Hb:** CO replaces $O_2$ and binds ×200 tighter than $O_2$ **(in smokers)** and stabilizes the oxyhemoglobin

( Note that CO isn't $CO_2$ )

**2** **Met- Hb:** Contains oxidized $Fe^{+3}$ (~2%) that cannot carry $O_2$

**3** **Sulf-Hb:** Forms due to high sulfur levels in blood **(irreversible reaction).**

Heme in ferric state (abnormal hemoglobin) it has only has 5 bonds, that's why it can't transfer the oxygen

## Hemoglobinopathies

### Disorders of Hb are caused by

- Synthesis of **structurally abnormal** Hb
- Synthesis of **insufficient quantities** of normal Hb
- Combination of **both.**( Combination of the 2 previous causes )

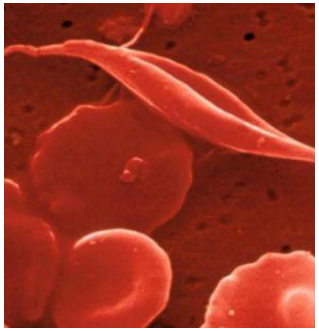
Met-Hb is standing of (Methemoglobin). It is a hemoglobin in which the iron is in Ferric form ($Fe^{+3}$) while the normal Hemoglobin contains Ferrous form ($Fe^{+2}$).
Remember that Ferric has a C in the end which is the 3rd letter in the alphabet so it will be the +3 (abnormal)

# Hemoglobinopathies

## 1 Sickle cell (HbS) disease

1-Caused by a single mutation in β -globin gene Glutamic acid ( polar - ) at position 6 in HbA is replaced by **valine** ( non polar )

2-The mutant HbS contains $\beta^S$ chain
3-The shape of RBCs become sickled
4-Causes sickle cell anemia
5- Autosomal recessive



The shape of Hb is changed to sickle cell shape

## 2 Hemoglobin C disease

1-Caused by a single mutation in β-globin gene
2- Glutamic acid ( polar - ) at position 6 in HbA is replaced by **lysine** ( polar + )
3- Causes a mild form of hemolytic anemia

Glutamic acid is an acidic polar amino acid.
Lysine is a base while Valine is a non polar.
As a result,there will be differences in properties , so Lysine & Valine can't replace Glutamic acid normally.

# Cont. Hemoglobinopathies

## 3 Methemoglobinemia

NADH- cytochrome b5 reductase enzyme is responsible for converting ferric to ferrous ( met Hb to HbA )

1- Caused by oxidation of Hb to ferric ( Fe3+ ) state
2- Methemoglobin cannot bind oxygen
3- Caused by certain drugs, reactive oxygen species and NADH-cytochrome b5 reductase deficiency
4- Chocolate cyanosis: brownish-blue color of the skin and blood ( as a result )

## 4 Thalassemia

Defective synthesis of either α or β-globin chain due to gene mutation ( 2 types ):

α-thalassemia:
- 1- Synthesis of α-globin chain is decreased or absent
- 2- Causes mild to moderate hemolytic anemia

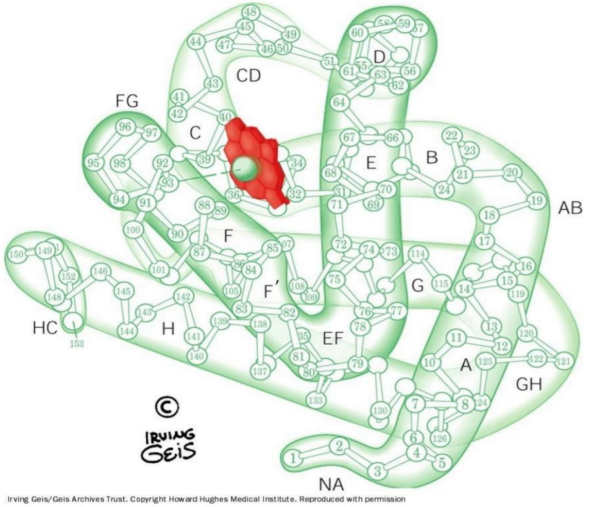
β-thalassemia:
- 1- Synthesis of β-globin chain is decreased or absent
- 2- Causes severe -fatal- anemia
- 3- Patients need regular blood transfusions ( to prevent progression )

# To summarize :

| Disease | Mutation | Causes |
|---|---|---|
| Sickle cell (HbS) disease | 1-single mutation in β -globin gene<br>2- Glutamic acid ( polar - ) at position 6 in HbA is replaced by **valine** ( non polar ) | Sickle cell anemia |
| Hemoglobin C disease | a single mutation in β-globin gene<br>2- Glutamic acid ( polar - ) at position 6 in HbA is replaced by **lysine** ( polar + ) | mild form of hemolytic anemia |
| Methemoglobinemia | oxidation of Hb to ferric ( Fe3+ ) state | Chocolate cyanosis |
| α- Thalassemia | Synthesis of α-globin chain is decreased or absent | mild to moderate hemolytic anemia |
| β - Thalassemia | Synthesis of β-globin chain is decreased or absent | Severe anemia |

# Myoglobin

1. A globular hemeprotein in Heart & Muscle
2. Stores & supplies Oxygen to the heart & skeletal muscles only
3. Contains a single polypeptide chain forming a single subunit with 8 a-helix
4. The interior of the subunit is composed of nonpolar amino acids
5. The charged amino acids are located on the surface
6. The heme group is present at the center of the molecule
7. Myoglobin gives red color to skeletal muscle
8. supplies Oxygen during aerobic exercise






Structure of myoglobin

Myoglobin has 1 subunit & bind to one $O_2$ molecule

# Myoglobin in disease:

## Myoglobinuria

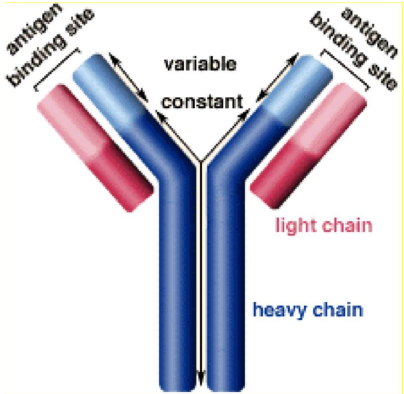
Myoglobin is excreted in urine due to muscle damage ( Rhabdomyolysis )

Rhabdomyolysis is a serious syndrome due to destruction of skeletal muscles and cardiac muscles to a lesser extent

- May cause acute renal failure
- Specific marker for muscle injury
- Less specific marker for heart attack ( the heart has its own specific marks )

# Immunoglobulins:

**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

Hi I am MAGED 👨‍⚕️

# Comparison between Hemoglobin & Myoglobin

To summarize :

| | Hemoglobin | Myoglobin |
|---|---|---|
| **Structure** | 4 Subunits<br>Carries 4 molecules of $O_2$ ( 8 atoms ) | 1 Subunit<br>Carries 1 molecule of $O_2$ ( 2 atoms ) |
| **Location** | Blood | Cardiac & Skeletal muscle |
| **Function** | Gas transportation ($O_2$ & $CO_2$) | Storage & Supplying of $O_2$ |
| Heme molecules | Four | One |
| Affinity for $O_2$ | Lower | Higher |

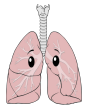
# Take Home Messages

- 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 $O_2$ and $CO_2$ transport.
- HbA, HbA2 and HbF are examples of normal Hb, in which the tetrameric structure is composed of 2α constant subunits with 2 changeable β subunits according to Hb type.
- HbA1C is a 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 $O_2$ are not transported due to abnormal Hb structure.**
- Disorders of Hb caused by synthesis of structurally abnormal Hb and/or insufficient quantities of normal Hb
- Sickle cell (HbS) and HbC diseases are caused by a single mutation in β-globin gene.

# Take Home Messages

- Glu6 in HbS is replaced by Val, while it is replaced by Lys in HbC.
- Methemoglobinemia is caused by oxidation of Hb, inhibiting $O_2$ binding leading to chocolate cyanosis.
- Thalassemia is caused by a defect in synthesis of either α- or β-globulin chain, as a result of gene mutation.
- α-Thalassemia causes less sever anemia than β-Thalassemia.
- Myoglobin is a globular hemeprotein, which stores and supplies $O_2$ 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, IgE, IgG and IgM

# Summary



## Globular proteins

- **Hemoglobin**
  - Normal Hb
    - HbA
    - $HbA_2$
    - $HbA_{1c}$
    - HbF
  - Abnormal Hb
    - Carboxy Hb
    - Met Hb
    - Sulf Hb
  - Hemoglobinopathies
    - Sickle cell (HbS) disease
    - Hemoglobin C disease
    - Methemoglobinemia
    - Thalassemia
- **Myoglobin**
  - Structure :
    - -Single polypeptide chain -single subunit
  - Function
    - Store & supply O2
  - Myoglobin in disease:
    - Myoglobinuria
- **γ-globulins Immunoglobulins**
  - Structure :
    - Y-shaped structure with: 2 heavy 2 lights
  - Function
    - Neutralize bacteria and viruses
  - Types :
    - IgA, IgD, IgE, IgG, IgM
- **$\alpha_1$,$\alpha_2$,β-globulins**
- **Enzymes**

Read more about abnormal Hbs here

# Quiz

| | | | |
|---|---|---|---|
| Q1 : a major globular protein in humans? | | | |
| A ) Hemoglobins | B ) Myoglobins | C ) Immunoglbins | D )Enzymes |
| Q2 : what is the globular protein that have only one polypeptide chain ? | | | |
| A ) Hemoglobins | B ) Myoglobins | C ) Hbs | D ) SulfHb |
| Q3 : abnormal Hb have Fe in a Ferric can't carry O2 ? | | | |
| A ) metHb | B )SulfHb | C ) HbA | D )myoglobin |
| Q4 : which bond is broken in HbA in oxyhemoglobin ? | | | |
| A ) strong hydrophobic bond | B ) weak ionic bond | C ) weak H bond | D ) both B,C |

## SAQs :

Q1: what are the normal & abnormal Hbs?

Q2: list the types of immunoglobulins

★ MCQs Answer key:

1) A 2) B 3) A 4) D

★ SAQs Answer key:

1) Normal : HbA,HbA1C,HbF. Abnormal : carboxy Hb, metHb , sulf HB

2) Remember MAGED ( IgM , IgA , IgG , IgE , IgD )

# Quiz

| Q5: A bond considered relatively strong in Hb structure | | | |
|---|---|---|---|
| A ) Ionic bonds | B ) Hydrogen bonds | C ) Hydrophobic bonds | D ) A&B |
| **Q6 : A hemoglobinopathy caused by replacement of Glutamic acid gene by Valine gene at certain position?** | | | |
| A ) Sickle cell disease | B ) Hemoglobin C disease | C ) Methemoglobinemia | D ) Thalassemia |
| **Q7: How many subunit(s) does Myoglobin have?** | | | |
| A ) 1 | B ) 2 | C ) 4 | D ) 8 |
| **Q8: Which of the following is a type of Immunoglobulin?** | | | |
| A ) IgE | B ) IgG | C ) IgM | D ) All of them |
| **Q9 : A hemoglobinopathy caused by oxidation of Hb to Ferric state?** | | | |
| A ) sickle cell disease | B ) Hemoglobin C disease | C ) Methemoglobinemia | D ) Thalassemia |

## SAQs :

Q3: what is the gene that got mutated in HBs?

Q4: what are the difference between hemoglobin & myoglobin

★ MCQs Answer key:

5) C  6) A  7) A  8) D  9) C

★ SAQs Answer key:

3) β-globin

4) (slide #13# )

## Girls team:

- Rania Almutiri
- Alia Zawawi
- Norah Alshathry
- Reem Alamri
- Renad Alhomaidi
- Norah Alasheikh
- Fatimah Alhelal
- Manal Altwaim

## Boys team:

- Abdullaziz Alrabiah
- Hamad Almousa
- Omar Alsuliman
- Bassam Alasmari
- Homoud Algadheb
- Abdullah Alanzan
- Abdullah Almazro
- Ahmad Alkhayatt
- Abdullaziz Alomar
- Mishal Alhamed

Your hardest times often lead to the greatest moments of your life , keep the faith. It will all be worth it in the end

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