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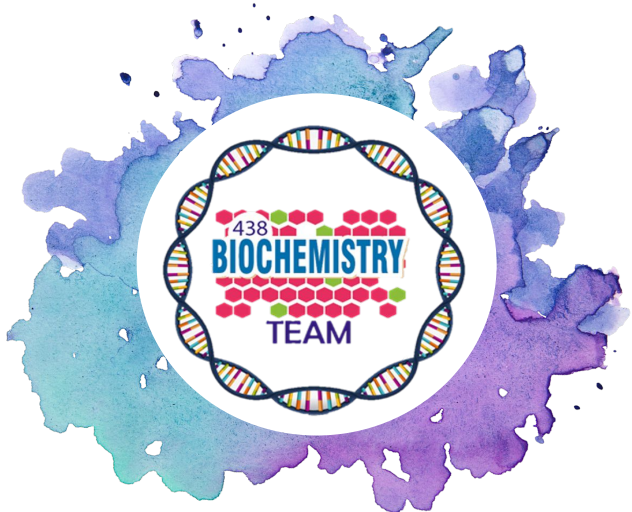
MED438

Respiratory Block

Globular proteins

Color Index:

- Original content
- Important
- Extra info, Dr's notes
- Only in girls' slides
- Only in boys' slides



Objectives:

Slide No. 3

- Describe the globular proteins using common examples
  - ➔ like: hemoglobin and myoglobin.

Slides (4,5)
Slide No. 9
Slide No. 11

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

Slides (4,6)

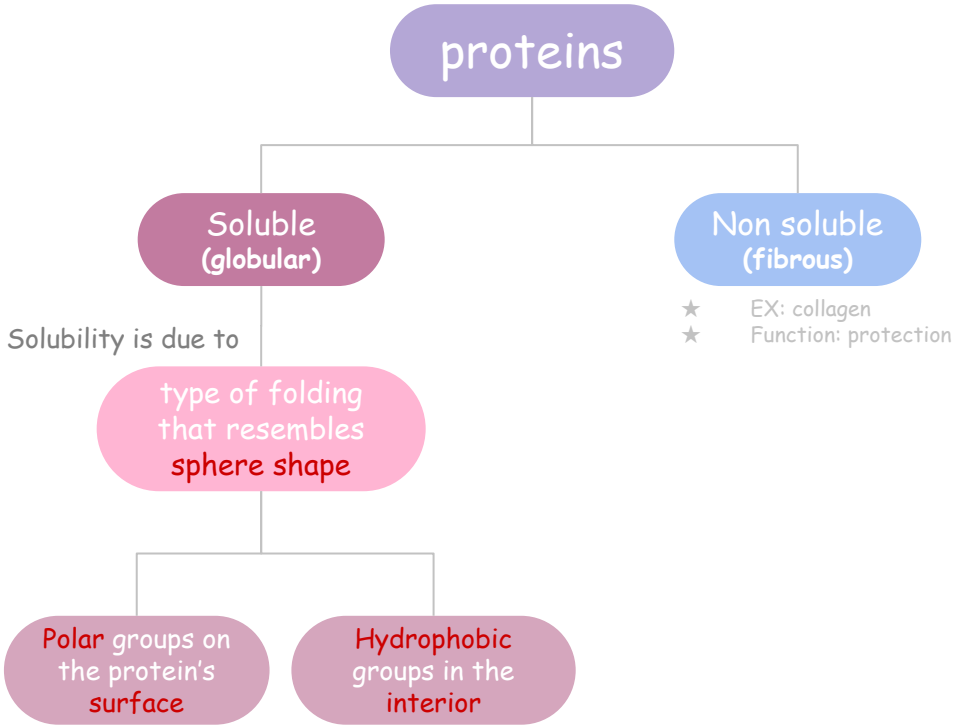
- Know the different types of hemoglobin and difference between normal and abnormal hemoglobin

Slides (8,10)

- Understand the diseases associated with globular proteins

★ **Objective:** Describe the globular proteins using common examples

Globular proteins



Types	Function
Hemoglobin	O_2 transport All over the body
Myoglobin	O_2 storage/supply only in heart and muscle
α1, α2, β-globulins	various functions
γ-globulins (immunoglobulins)	immune function
Enzymes	catalysis of biochemical reactions

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

★ **Objectives:** 1) study the structure and functions of globular proteins
2) Know the different types of hemoglobin and difference between normal and abnormal hemoglobin

Hemoglobin

Functions	Normal level (g/dL)	Types	
Carries O_2 lungs -> tissues	Males: 14-16 Females: 13-15	**Normal** "Aable to transport O_2"	HbA (97%) "most abundant"
			HbA_2 (2%)
			HbF (1%)
			HbA_{1c}
Carries CO_2 tissues -> lungs		**Abnormal** "Unable to transport O_2"	Carboxy Hb (bound to CO)
			Met Hb
			Sulf Hb

★ **Objective:** study the structure and functions of globular proteins

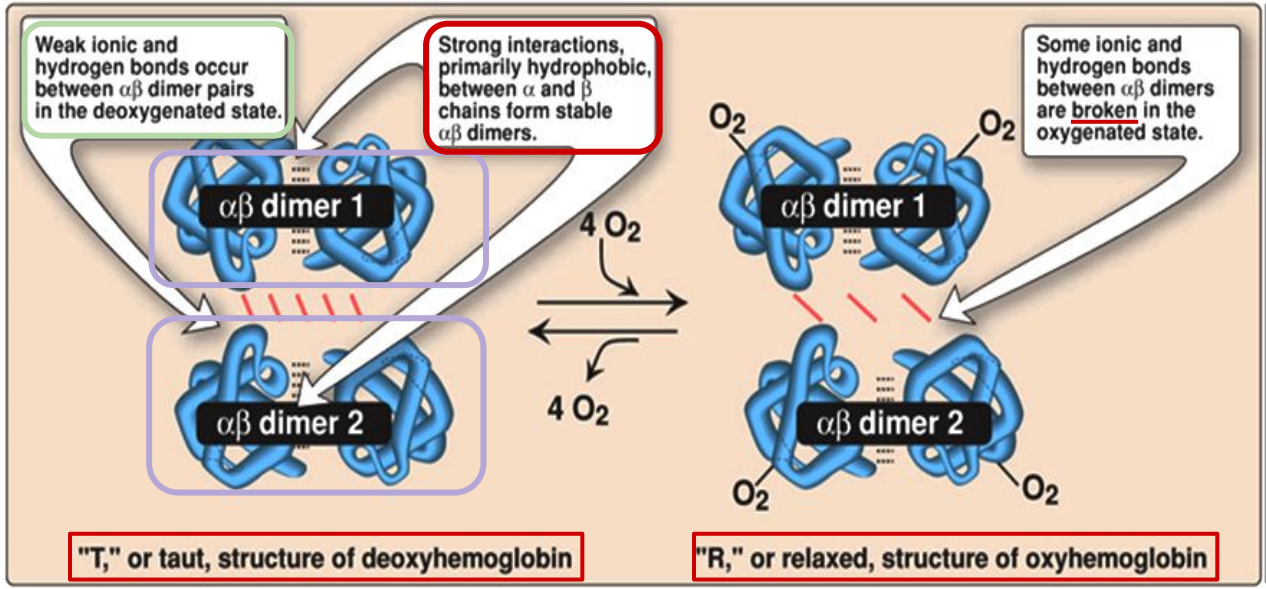
Hemoglobin (HbA) structure

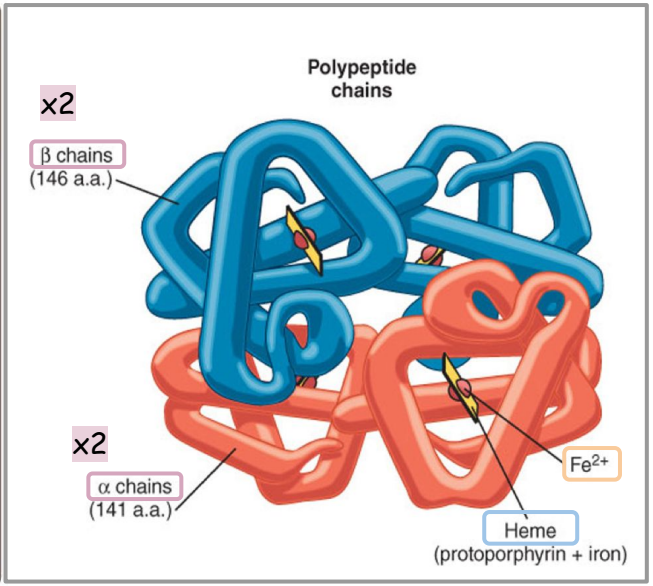
★ **4** polypeptide chains

★ **2** dimers of ab subunits

- Held together by non-covalent interactions

★ Contains **4 heme** groups and carries **4 molecules of O_2** 4x2 = 8 Oxygen atoms





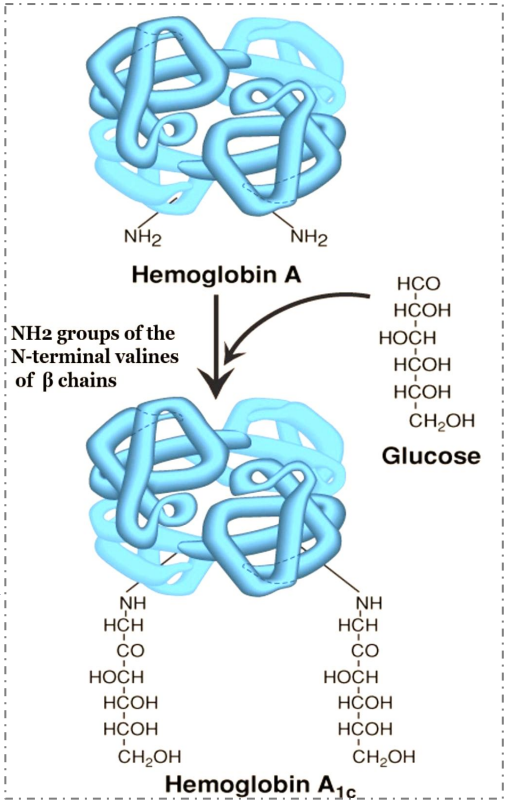
Fe^{+2} : Ferrous state (reduced form) (less stable)

Fe^{+3} : Ferric state (oxidative form) (more stable)

★ **Objective:** Know the different types of hemoglobin and difference between normal and abnormal hemoglobin

Types of Hemoglobin

	(HbF) Fetal Hemoglobin	HbA_2	HbA_{1c}
characteristics	Major hemoglobin found in the **fetus** and newborn.	Appears shortly before birth (~8th month)	HbA undergoes non enzymatic **glycosylation**.
importance	Transfers O_2 from maternal to fetal circulation across placenta. * Due to: Higher affinity for O2 than HbA	Constitutes ~2% of total Hb.	HbA_{1c} levels are high in patients with diabetes Mellitus * Due to: Glycosylation (depends on plasma glucose levels)
structure	• 2 α chains • 2 γ chains.	• 2 α chains • 2 δ chains.	



★ **Objective:** know the difference between normal and abnormal hemoglobin

Abnormal Hemoglobins

★ Unable to transport O_2 due to abnormal structure:

1 Carboxy-Hb

CO replaces O_2 and binds 200X tighter than O_2 (in smokers & heat devices)

★ Hemoglobin bound to **CO2** is called **carbamino**hemoglobin

★ Hemoglobin bound to **CO** is called **carboxy**hemoglobinn

2 Met-Hb

Contains oxidized Fe^{3+} (~2%) that cannot carry O_2

★ Ferroxidases is the enzyme responsible for oxidation of Fe^{2+}

3 Sulf-HB

Forms due to high sulfur levels in blood

(irreversible reaction)

➔ Can't be reversed by increasing O_2 levels

Hemoglobinopathies

Disorders of hemoglobin caused by:

- Synthesis of structurally **abnormal** Hb
- Synthesis of insufficient quantities of **normal** Hb
- Combination of **both**

★ **Objective:** understand the diseases associated with globular proteins

* β6 Glu = Glutamic acid at position **6** in HbA

** An enzyme convert ferric (Fe^{+3}) to ferrous (Fe^{+2}),

*** α chains are coded by 2 genes —absence→ mild anemia
β chains are coded by 1 gene → severe anemia

Hemoglobinopathies

Synthesis of structurally **abnormal** hemoglobins (hemolytic anemia-HbC)

Sickle cell disease HbS

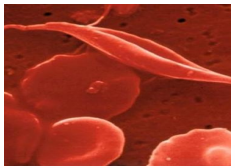
Caused by

single mutation in β-globin gene (βs chain)

Consists of

* β^6 Glu -> valine

The shape of RBCs become sickled.



HbC (mild form)

Caused by

single mutation in β-globin gene.

Consists of

* β^6 Glu -> lysine

Synthesis of insufficient quantities of **normal** hemoglobins

α-Thalassemia *** (Mild)

Caused by

gene mutation.

Decreased synthesis of α chains

β-Thalassemia (Severe)

Caused by

gene mutation.

Decreased synthesis of β chains

Needs regular blood transfusion.

Methemoglobinemia

Caused by

1) ** NADH-cytochrome b5 reductase deficiency
2) Certain drugs
3) Reactive oxygen species.

oxidation
Fe^{+2} -> Fe^{+3}

Inability to bind O_2

Chocolate cyanosis

brownish-blue color of the skin and blood.

★ **Objective:** study the structure and functions of globular proteins

Myoglobin

- A globular hemeprotein in heart and skeletal muscle

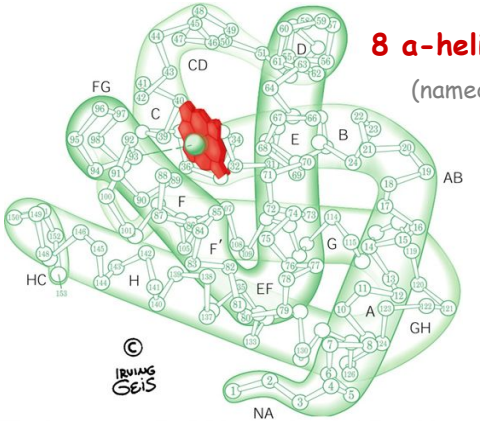
Function

- Store and supply oxygen
- gives red color to skeletal muscles.

★ Supplies oxygen during aerobic exercise.

structure

- single polypeptide chain
- single subunit
  - The heme group is present at the center of the molecule
  - Location of amino acids
    - Nonpolar -> interior
    - charged -> surface



8 a-helix structures.

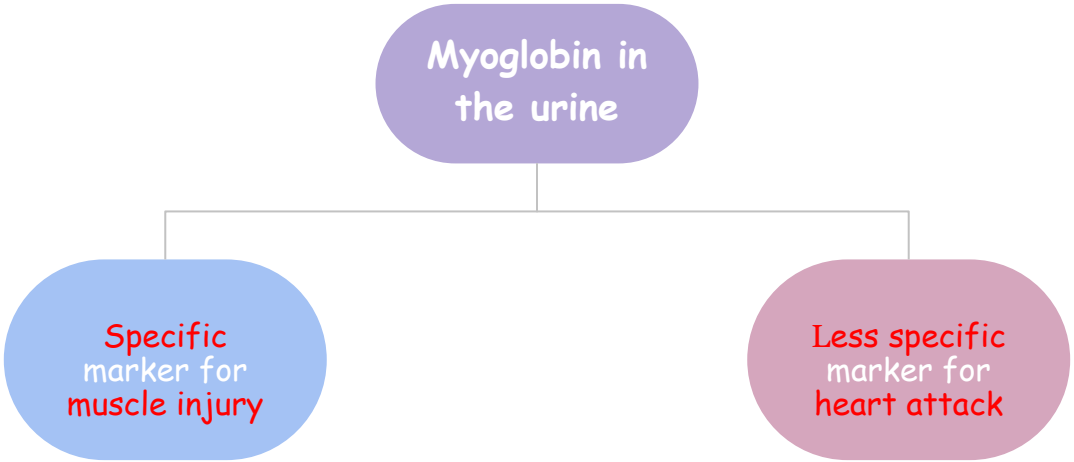
(named from A to H)

Myoglobin in disease

★ Myoglobinuria:

Myoglobin is excreted in urine due to **muscle damage (rhabdomyolysis).**

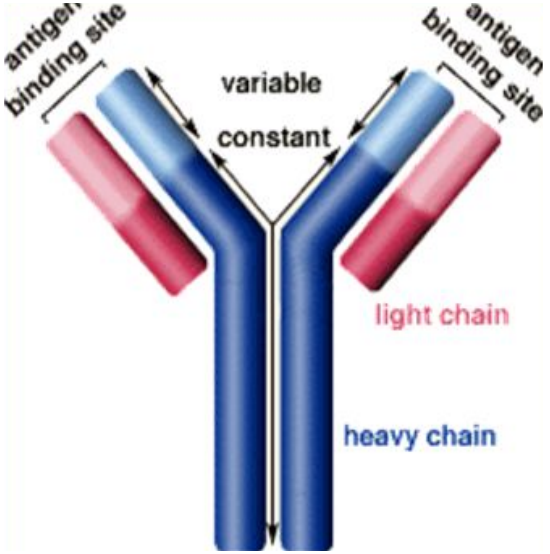
May cause **acute** renal failure



Immunoglobulins

- Defensive proteins produced by the B-cells of the immune system.

Function	structure	Types
Neutralize bacteria and viruses	Y-shaped structure with: ★ 2 heavy ★ 2 light polypeptide chains	• IgM • IgA • IgG • IgE • IgD ماجد



★ Antigens are small "can't be detected by macrophages" -> immunoglobulins neutralize them -> can be detected by macrophages

Take home message

- 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 O2 molecules 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 message

- 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 severe anemia than β-Thalassemia.
- Myoglobin is a globular heme protein, 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

Globular protein

Hemoglobin

HbA
Most abundant

structure
- 2 α chains
- 2 β chains.

importance
O_2 transport

HbA2

structure
- 2 α chains
- 2 δ chains.

HbA1c

structure
HbA + glucose

importance
Diagnosis of diabetes

HbF

structure
- 2 α chains
- 2 γ chains.

importance
O_2 transport

Mother -> fetus

Myoglobin

structure
8 α-helix

importance
- O_2 storage & supply
- red color of muscles

disease
Myoglobinuria
(presence in urine)

diseases
- Sickle cell disease HbS (β^6 Glu -> valine)
- HbC (β^6 Glu -> lysine)
- α-Thalassemia (↓ α chains)
- β-Thalassemia (↓ β chains)
- Methemoglobinemia (Fe^{+2} -> Fe^{+3})

Quiz

MCQs

Q1: The glycosylated form of HbA called:
a) HbA_2 **b)** HbC **c)** HbA_{1c} **d)** HbF

Q2: which of the following is correct concerning glutamic acid in hemoglobin C disease ...
a) Position 4 in HbA is replaced by lysine **b)** Position 6 in HbA is replaced by valine
c) Position 4 in HbA is replaced by valine **d)** Position 6 in HbA is replaced by lysine

Q3: Myoglobin Contains a single polypeptide chain forming a single subunit with?
a) 2 a-helix structures **b)** 8 a-helix structures
c) 4 a-helix structures **d)** 6 a-helix structures

Q4: Sickle cell disease is caused by?
a) A single mutation in a-globin **b)** A single mutation in β-globin
c) Double mutation in a-globin **d)** Double mutation in β-globin

Q5: Which one of the following statements concerning the hemoglobins is correct?
a) HbA is the most abundant hemoglobin in normal adults.
b) Fetal blood has lower affinity for oxygen because HbF has increased affinity for 2,3-BPG.
C) The globin chain composition of HbF is a2δ2.
D) HbA1c differs from HbA by a single, genetically determined amino acid substitution.

Q6: Which type of thalassemia needs blood transfusion?
a) alpha thalassemia **b)** gamma thalassemia **c)** beta thalassemia **d)** delta thalassemia

SAQs

Q1: The bonds between two dimers are broken in which state?

Q2: what are Immunoglobulins?

Q3: A 67-year-old man presented to the emergency department with a 1-week history of angina and shortness of breath. He complained that his face and extremities had taken on a blue color. His medical history included chronic stable angina treated with isosorbide dinitrate and nitroglycerin. Blood obtained for analysis was brown. What'is the most likely diagnosis?

★ **MCQs Answer key:**

1) C 2) D
3) B 4) B
5) A 6) C

★ **SAQs Answer key:**

1) Oxygenated state
2) Defensive proteins produced by the B-cells of the immune system...Neutralize bacteria and viruses..Y-shaped structure with 2 heavy and 2 light polypeptide chains.
3) Methemoglobinemia

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★ You must be the change you
Wish to see in the World.
كن أنت..التغيير الذي تريد أن تراه في العالم

438 BIOCHEMISTRY TEAM

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