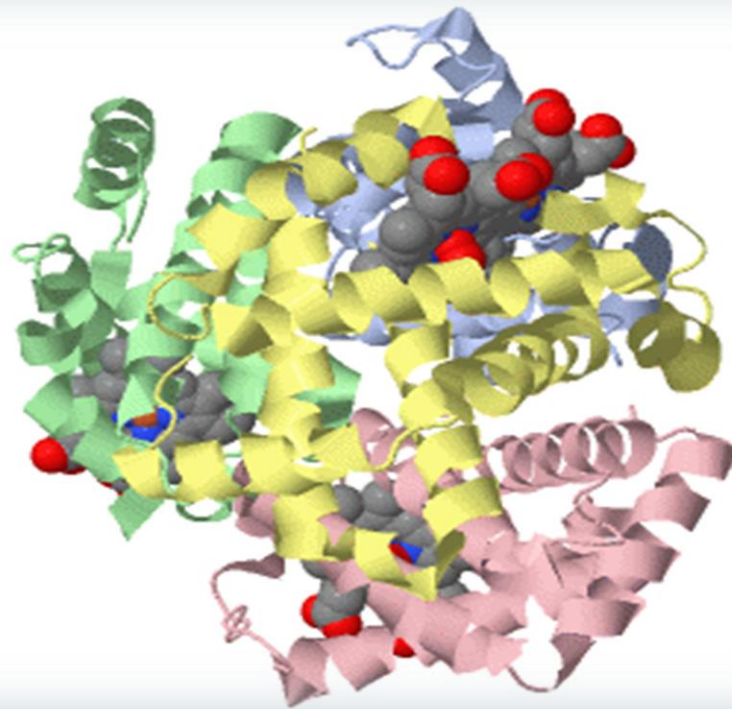


# Globular Proteins



Respiratory Block | 1 Lecture



# 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, and
  - $\gamma$ -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 proteins

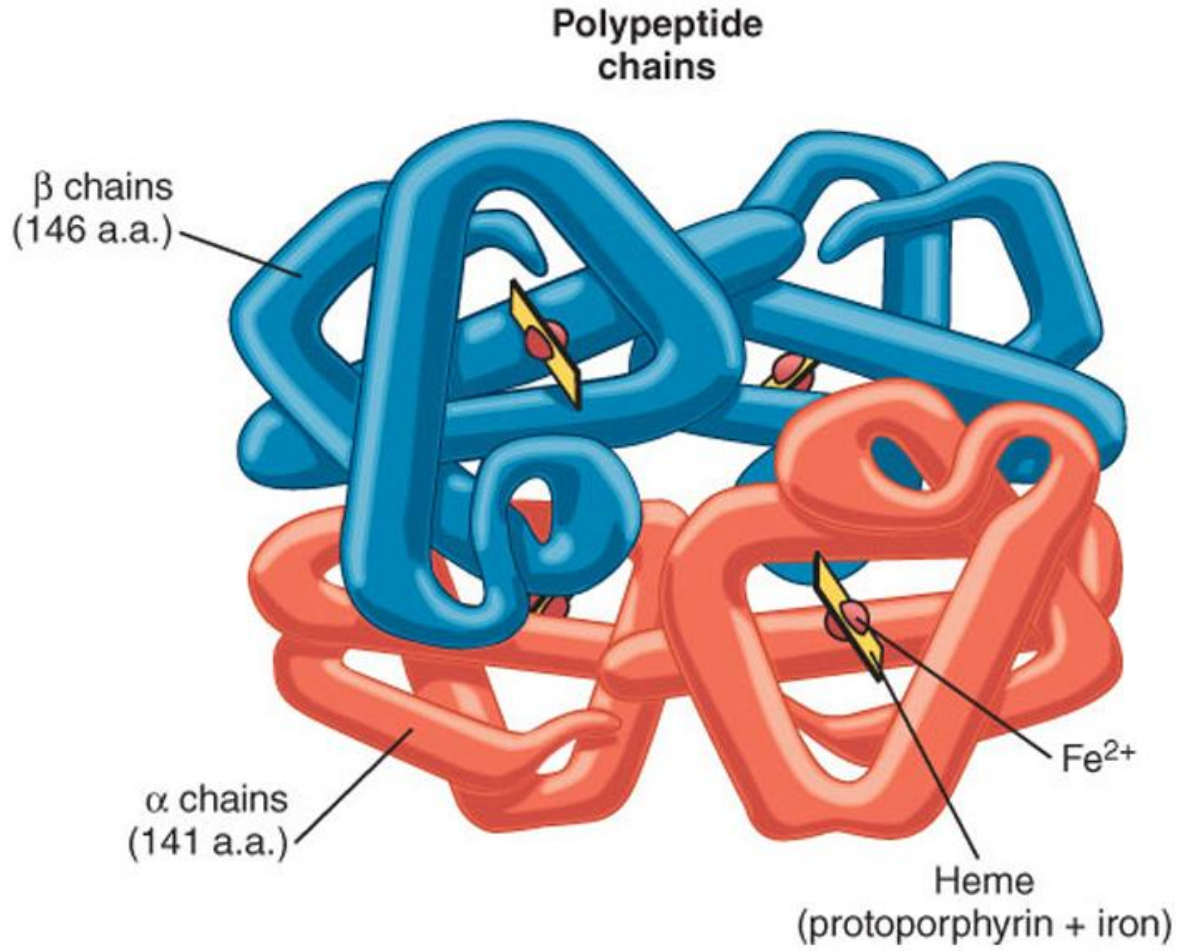
- Amino acid chains fold into shapes that resemble spheres are called globular proteins
- This type of folding increases solubility of proteins in water
  - Polar groups on the protein's surface
  - Hydrophobic groups in the interior
- Fibrous proteins are mainly insoluble structural proteins

# Globular proteins

- Hemoglobin: oxygen transport function
- Myoglobin: oxygen storage/supply function in heart and muscle
- $\alpha_1$ ,  $\alpha_2$ ,  $\beta$ -globulins: various functions
- $\gamma$ -globulins (immunoglobulins): immune function
- Enzymes: catalysis of biochemical reactions

# Hemoglobin

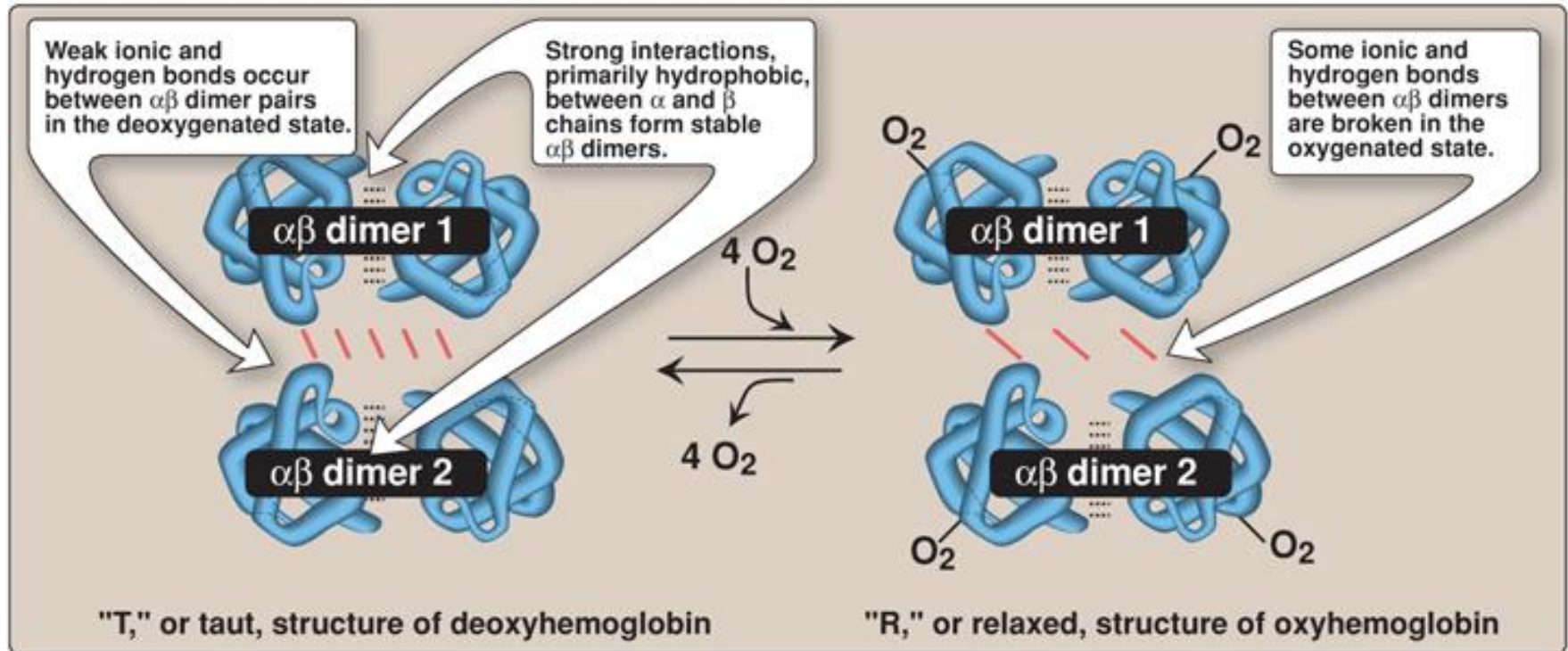
- A major globular protein in humans
- Composed of four polypeptide chains:
  - Two  $\alpha$  and two  $\beta$  chains
- Contains two dimers of  $\alpha\beta$  subunits
  - Held together by non-covalent interactions
- Each chain is a subunit with a heme group in the center that carries oxygen
- A Hb molecule contains 4 heme groups and carries 4 molecules of  $O_2$



# Types of Hb

<b>Normal:</b>	HbA (97%)
	HbA <sub>2</sub> (2%)
	HbF (1%)
	HbA <sub>1c</sub>
<b>Abnormal:</b>	Carboxy Hb
	Met Hb
	Sulf Hb

# HbA structure





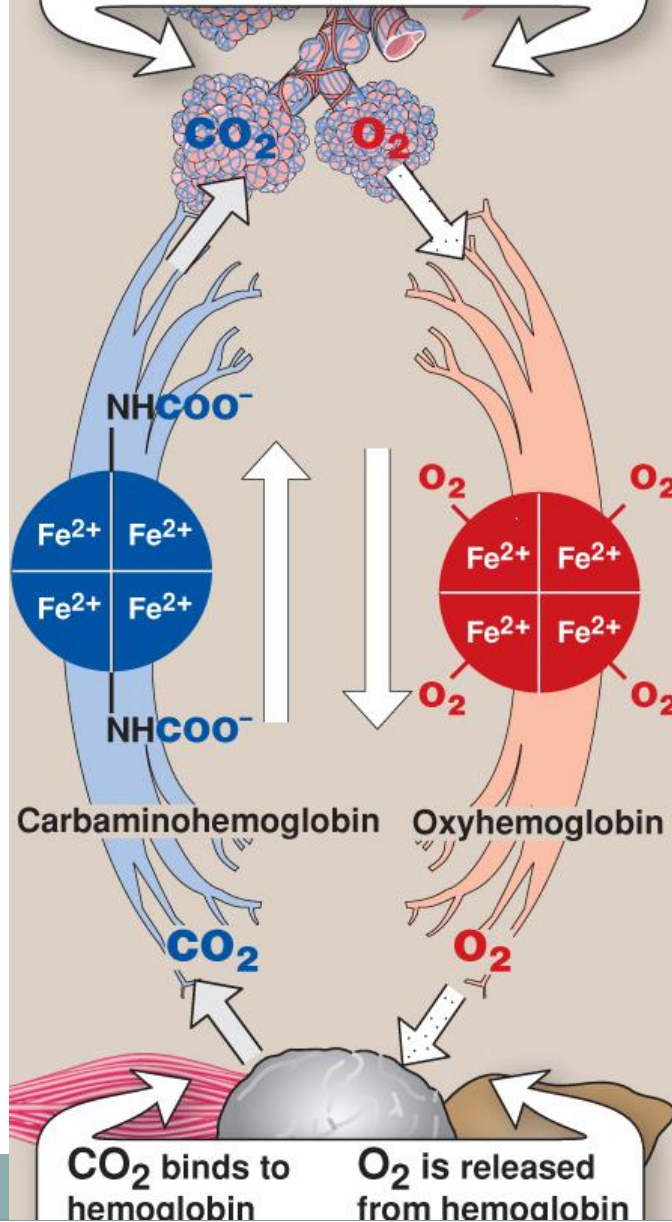
# Hemoglobin function

- Carries oxygen from the lungs to tissues
- Carries carbon dioxide from tissues back to the lungs
- Normal level (g/dL):
  - Males: 14-16
  - Females: 13-15

# LUNGS

$\text{CO}_2$  is released  
from hemoglobin

$\text{O}_2$  binds to  
hemoglobin



# Types of hemoglobin

## Fetal hemoglobin (HbF):

- Major hemoglobin found in the fetus and newborn
- Tetramer with two  $\alpha$  and two  $\gamma$  chains
- Higher affinity for  $O_2$  than HbA
- Transfers  $O_2$  from maternal to fetal circulation across placenta

# Types of hemoglobin

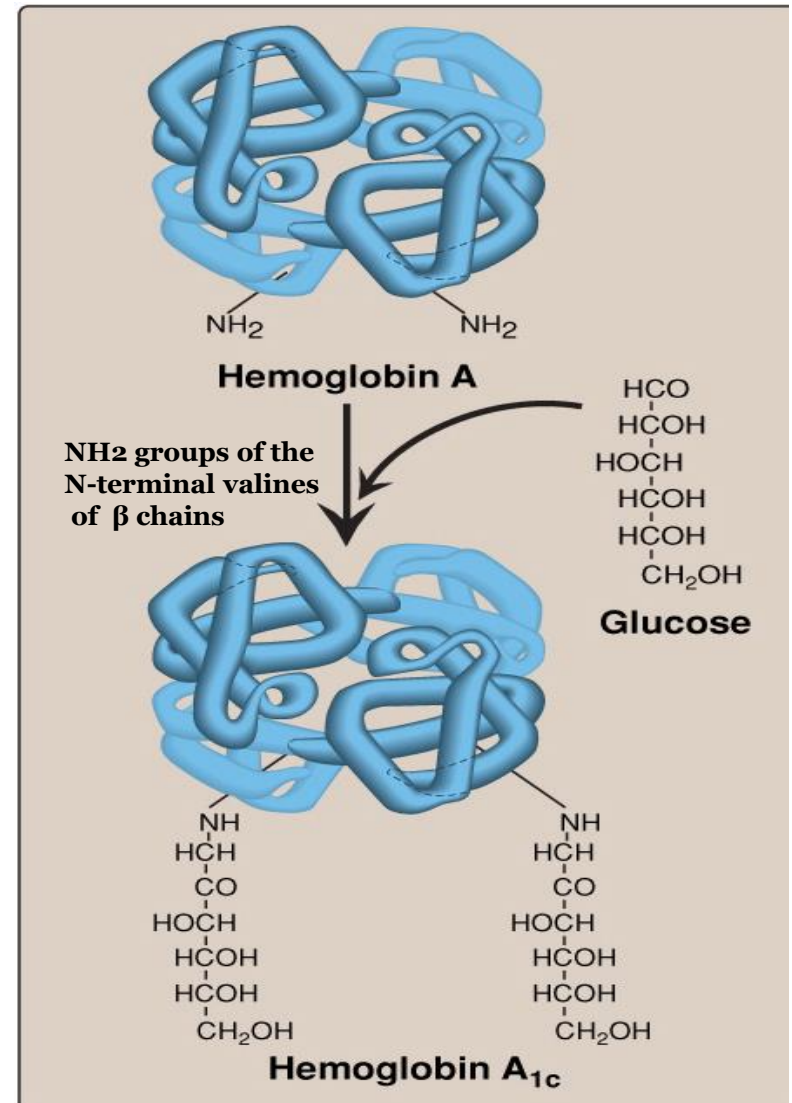
HbA<sub>2</sub>:

- Appears shortly before birth
- Constitutes ~2% of total Hb
- Composed of two  $\alpha$  and two  $\delta$  globin chains

# Types of hemoglobin

HbA<sub>1c</sub>:

- HbA undergoes non-enzymatic glycosylation
- Glycosylation depends on plasma glucose levels
- HbA<sub>1c</sub> levels are high in patients with diabetes mellitus



# Abnormal Hbs

Unable to transport O<sub>2</sub> due to abnormal structure:

- Carboxy-Hb: CO binds 200X tighter than O<sub>2</sub> (in smokers) and stabilizes the oxyhemoglobin
- Met-Hb: Contains oxidized Fe<sup>3+</sup> (~2%) that cannot carry O<sub>2</sub>
- Sulf-HB: Forms due to high sulfur levels in blood (irreversible reaction)

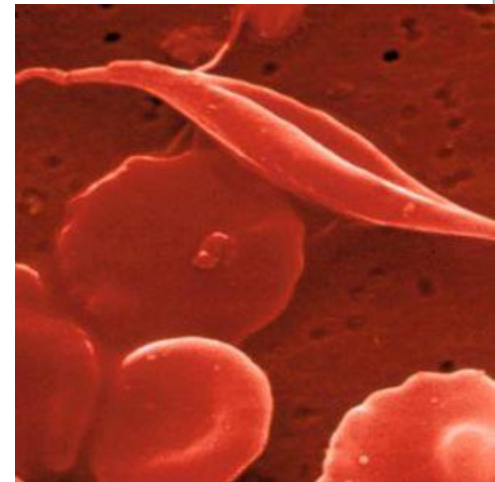
# Hemoglobinopathies

- Disorders of hemoglobin caused by:
  - Synthesis of structurally abnormal Hb
  - Synthesis of insufficient quantities of normal Hb
  - Combination of both

# Hemoglobinopathies

## Sickle cell (HbS) disease

- Caused by a single mutation in  $\beta$ -globin gene
- Glutamic acid at position 6 in HbA is replaced by valine
- The mutant HbS contains  $\beta^s$  chain
- The shape of RBCs become sickled
- Causes sickle cell anemia





# Hemoglobinopathies

## Hemoglobin C disease:

- 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

# Hemoglobinopathies

## Methemoglobinemia:

- Caused by oxidation of Hb to ferric ( $\text{Fe}^{3+}$ ) state
- Methemoglobin cannot bind oxygen
- Caused by certain drugs, reactive oxygen species and NADH-cytochrome b5 reductase deficiency
- Chocolate cyanosis: brownish-blue color of the skin and blood

# Hemoglobinopathies

## Thalassemia:

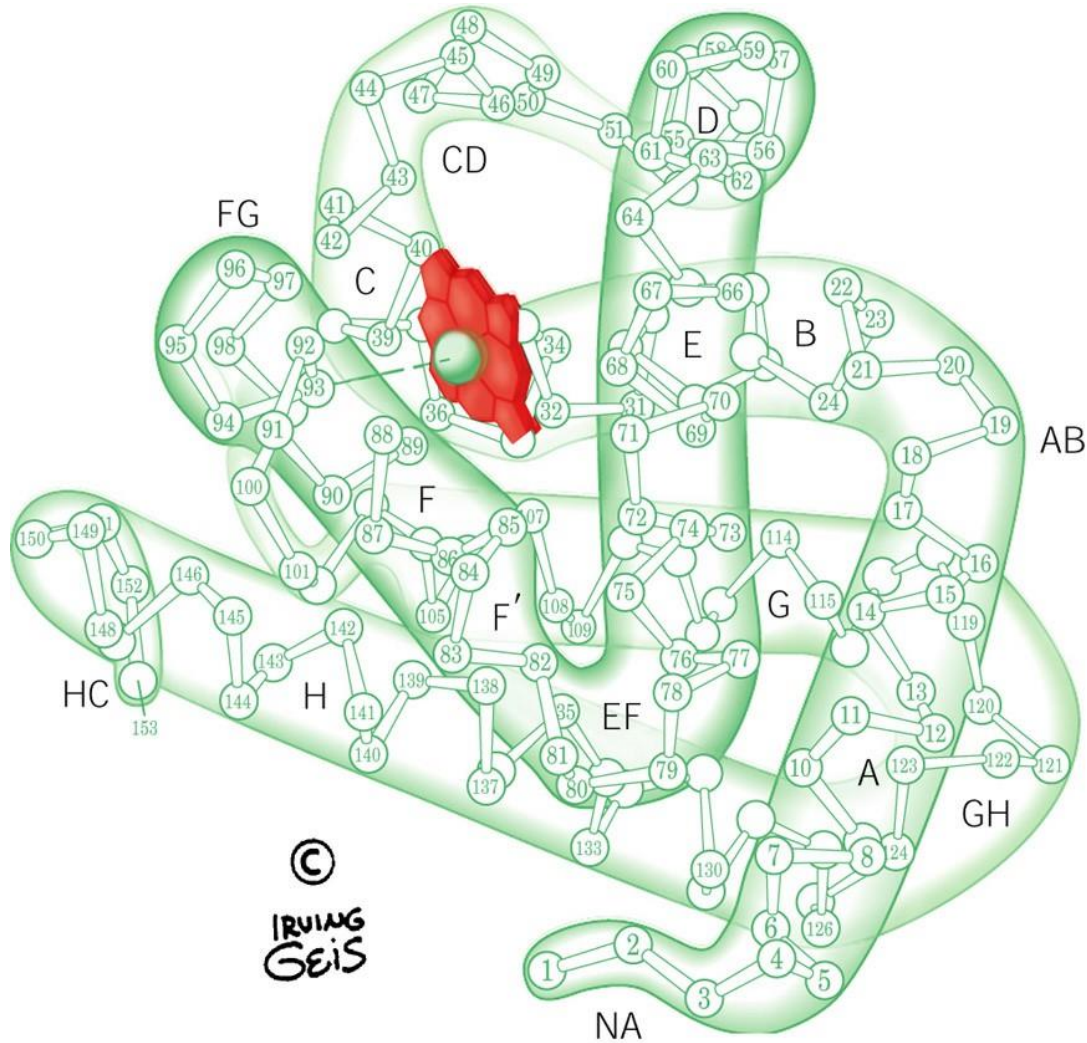
- Defective synthesis of either  $\alpha$  or  $\beta$ -globin chain due to gene mutation
- $\alpha$ -thalassemia:
  - Synthesis of  $\alpha$ -globin chain is decreased or absent
  - Causes mild to moderate hemolytic anemia
- $\beta$ -thalassemia:
  - Synthesis of  $\beta$ -globin chain is decreased or absent
  - Causes severe anemia
  - Patients need regular blood transfusions

# Myoglobin

- A globular hemeprotein in heart and muscle
- Stores and supplies oxygen to the heart and muscle only
- Contains a single polypeptide chain forming a single subunit with eight  $\alpha$ -helix structures
- The interior of the subunit is composed of nonpolar amino acids

# Myoglobin

- The charged amino acids are located on the surface
- The heme group is present at the center of the molecule
- Myoglobin gives red color to skeletal muscles
- Supplies oxygen during aerobic exercise



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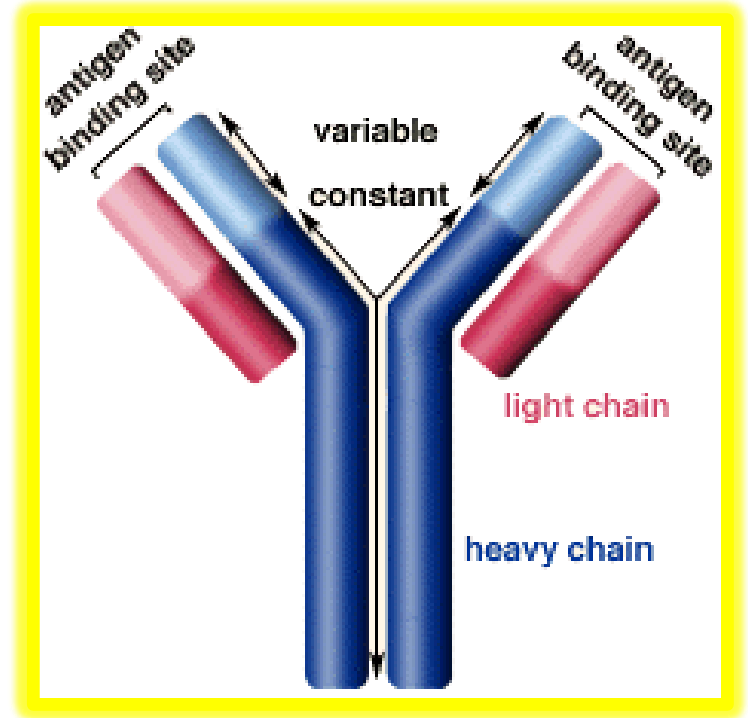
# Structure of myoglobin

# Myoglobin in disease

- Myoglobinuria: Myoglobin is excreted in urine due to muscle damage (rhabdomyolysis)
- May cause acute renal failure
- Specific marker for muscle injury
- Less specific marker for heart attack

# 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





# 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<sub>2</sub> and CO<sub>2</sub> transport.
- HbA, HbA<sub>2</sub> and HbF are examples of normal Hb, in which the tetrameric structure is composed of 2 $\alpha$  constant subunits with 2 changeable  $\beta$  subunits according to Hb type.

# Take Home Messages

- HbA<sub>1c</sub> 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<sub>2</sub> 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  $\beta$ -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<sub>2</sub> binding leading to chocolate cyanosis.
- Thalassemia is caused by a defect in synthesis of either  $\alpha$ - or  $\beta$ -globulin chain, as a result of gene mutation.
- $\alpha$ -Thalassemia causes less severe anemia than  $\beta$ -Thalassemia.
- Myoglobin is a globular hemeprotein, which stores and supplies O<sub>2</sub> to the heart and muscle only.

# Take Home Messages

- 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.

# References

- Illustrations in Biochemistry by Lippincott 6<sup>th</sup> edition.