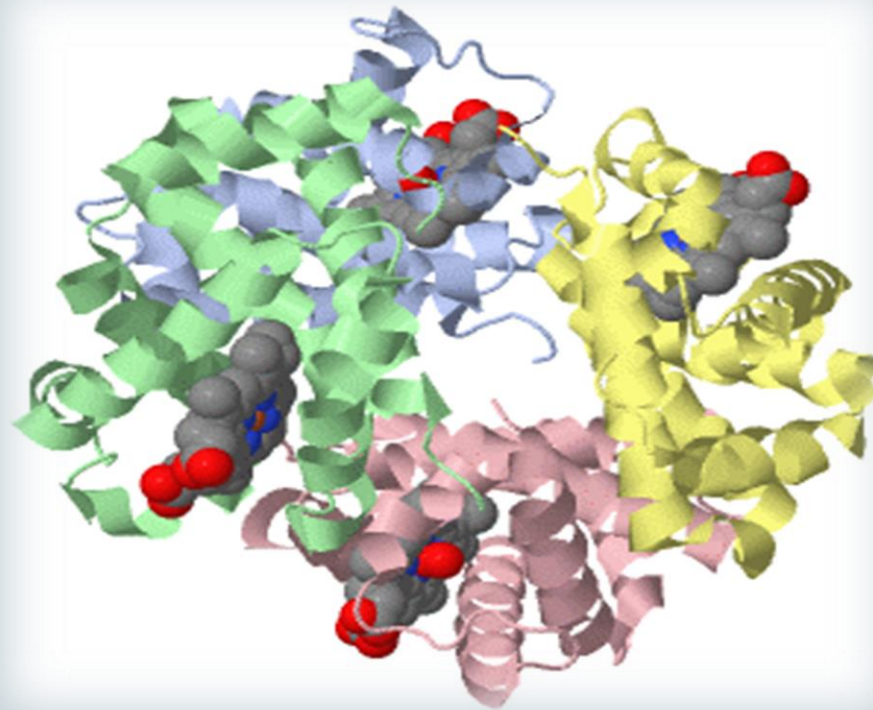


Globular Proteins



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
 - 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

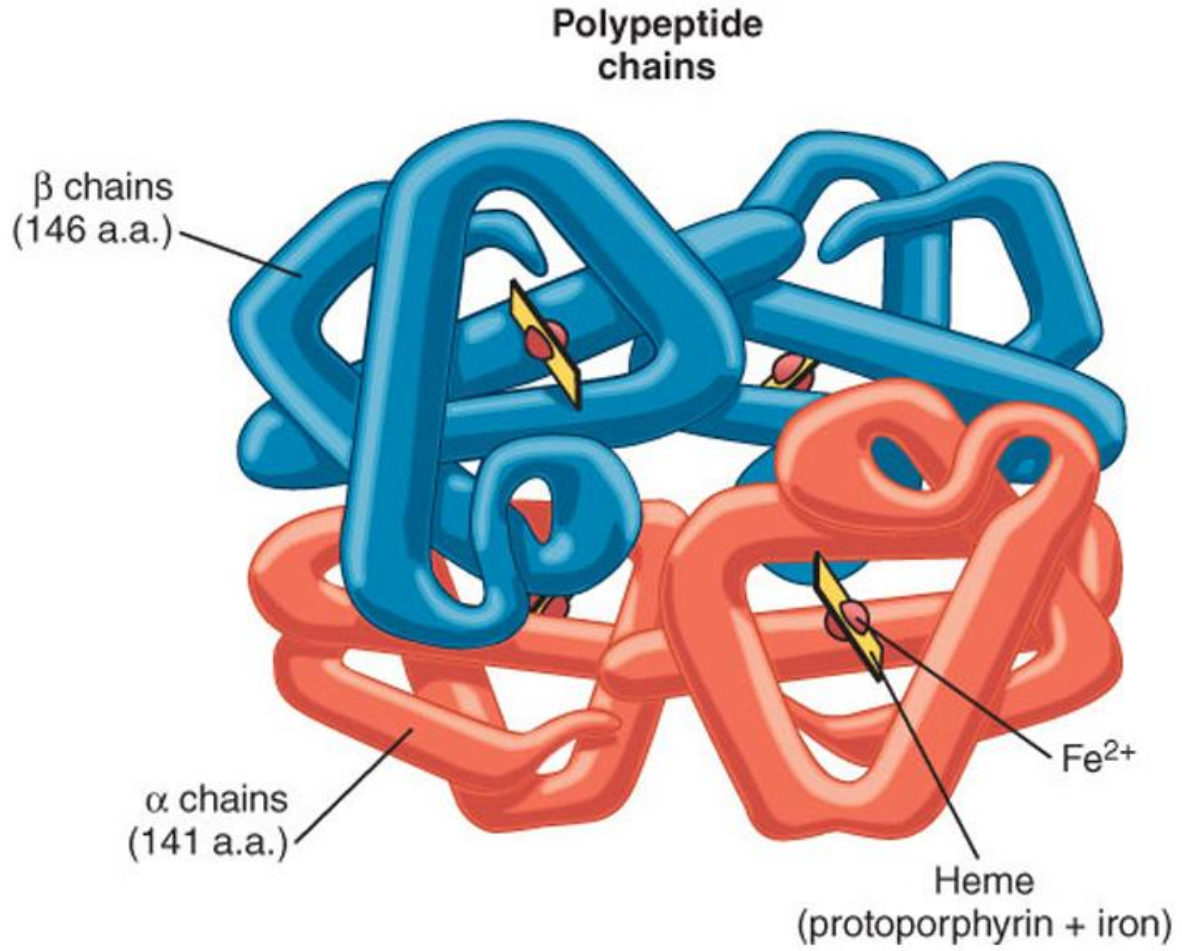
- Amino acid chains fold into shapes that resemble spheres are called globular proteins
- This type of folding increases solubility of proteins in water
 - Polar groups on the protein's surface
 - Hydrophobic groups in the interior
- Fibrous proteins are mainly insoluble structural proteins

Globular proteins

- Hemoglobin: oxygen transport function
- Myoglobin: oxygen storage/supply function in heart and muscle
- α_1 , α_2 , β -globulins: various functions
- γ -globulins (immunoglobulins): immune function
- Enzymes: catalysis of biochemical reactions

Hemoglobin

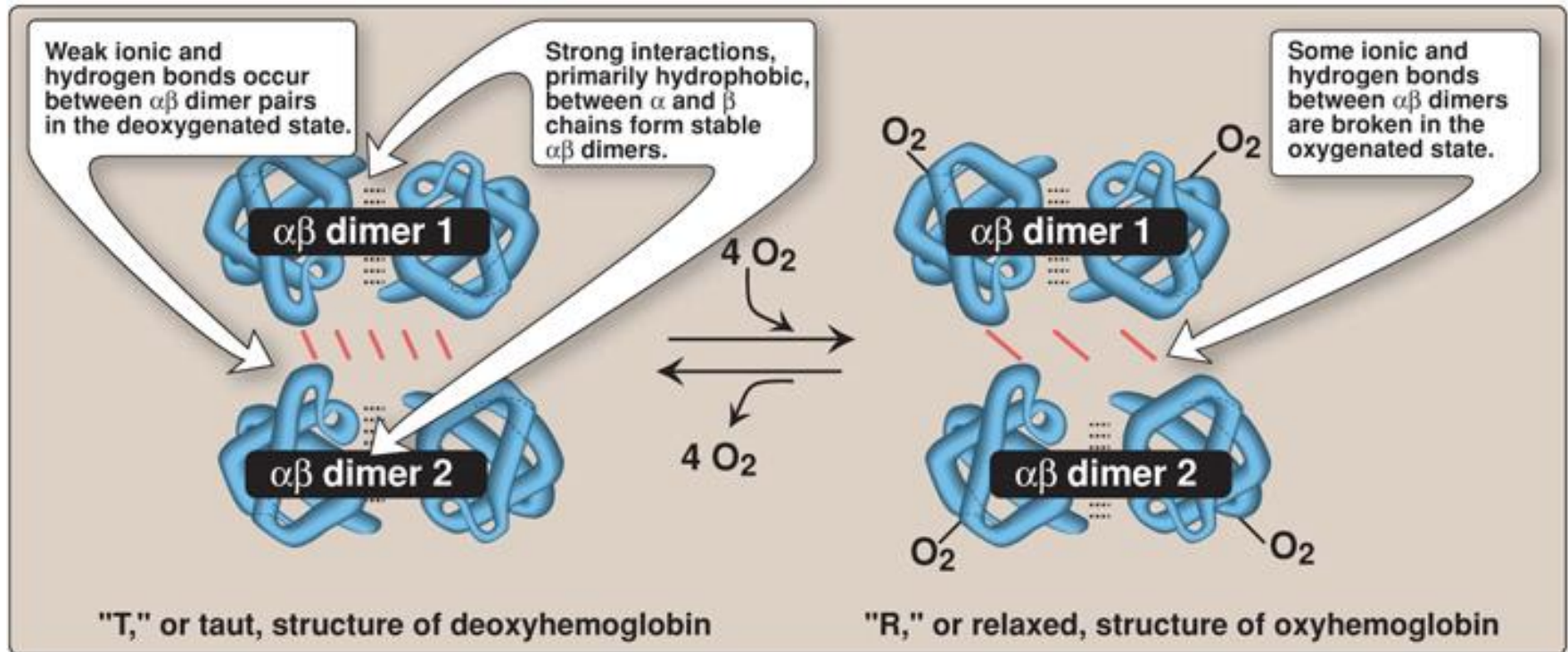
- A major globular protein in humans
- Composed of four polypeptide chains:
 - Two α and two β chains
- Contains two dimers of $\alpha\beta$ subunits
Held together by non-covalent interactions
- Each chain is a subunit with a heme group in the center that carries oxygen
- A Hb molecule contains 4 heme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



Types of Hb

Normal:	HbA (97%)
	HbA ₂ (2%)
	HbF (1%)
	HbA _{1c}
Abnormal:	Carboxy Hb
	Met Hb
	Sulf Hb

HbA structure



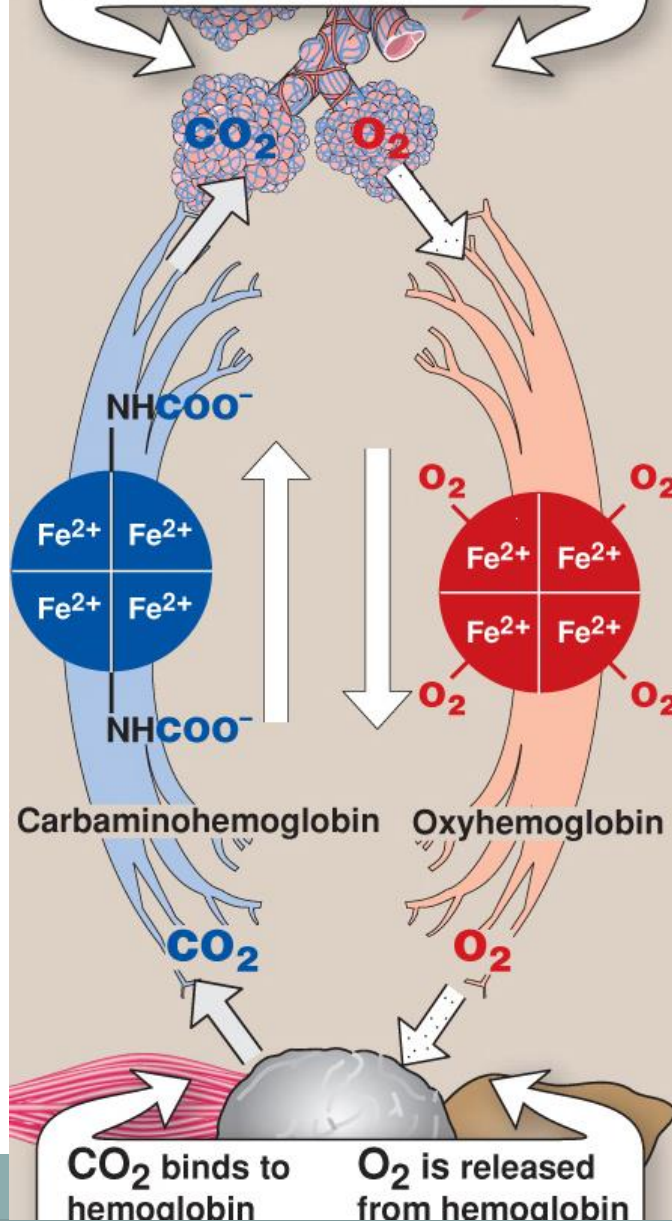
Hemoglobin function

- 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

CO_2 is released
from hemoglobin

O_2 binds to
hemoglobin



Types of hemoglobin

Fetal hemoglobin (HbF):

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

Types of hemoglobin

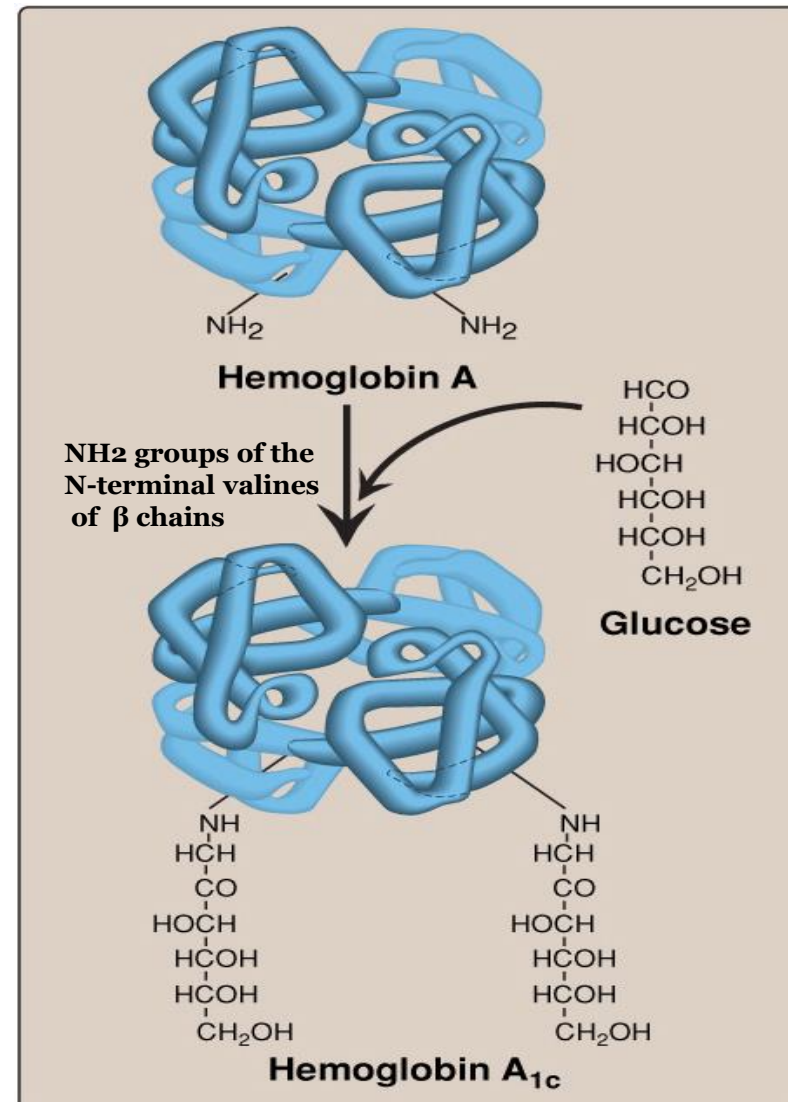
HbA₂:

- Appears ~12 weeks after birth
- Constitutes ~2% of total Hb
- Composed of two α and two δ globin chains

Types of hemoglobin

HbA_{1c}:

- HbA undergoes non-enzymatic glycosylation
- Glycosylation depends on plasma glucose levels
- HbA_{1c} levels are high in patients with diabetes mellitus



Abnormal Hbs

Unable to transport O₂ due to abnormal structure:

- Carboxy-Hb: CO replaces O₂ and binds 200X tighter than O₂ (in smokers)
- Met-Hb: Contains oxidized Fe³⁺ (~2%) that cannot carry O₂
- Sulf-HB: Forms due to high sulfur levels in blood (irreversible reaction)

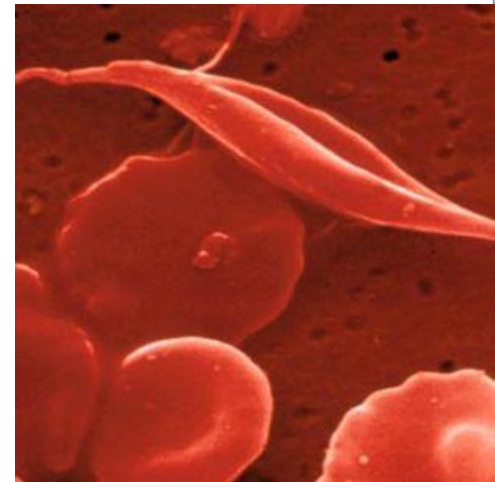
Hemoglobinopathies

- 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 β -globin gene
- Glutamic acid at position 6 in HbA is replaced by valine
- The mutant HbS contains β^s chain
- The shape of RBCs become sickled
- Causes sickle cell anemia



Hemoglobinopathies

Hemoglobin C disease:

- Caused by a single mutation in β -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 (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:

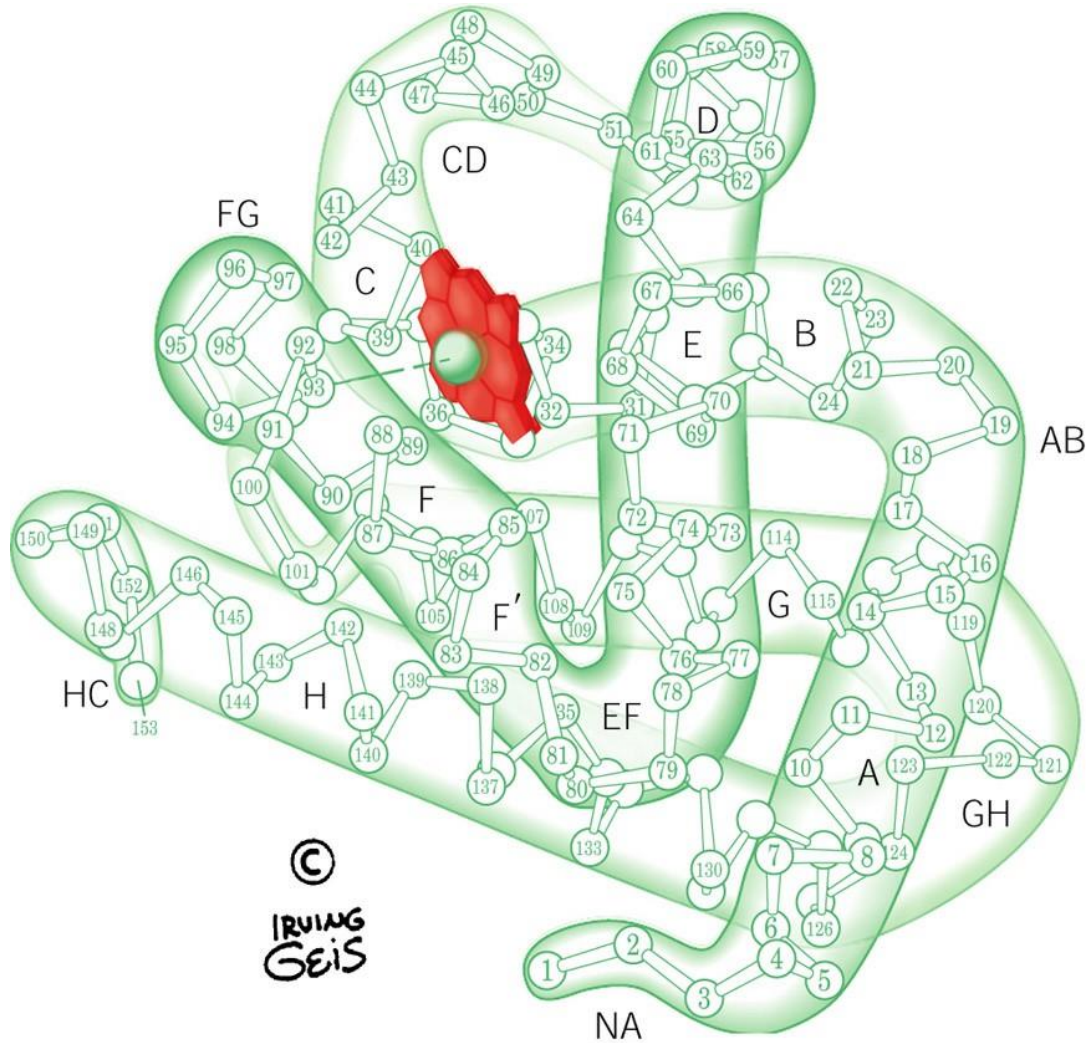
- Defective synthesis of either α or β -globin chain due to gene mutation
- α -thalassemia:
 - Synthesis of α -globin chain is decreased or absent
 - Causes mild to moderate hemolytic anemia
- β -thalassemia:
 - Synthesis of β -globin chain is decreased or absent
 - Causes severe anemia
 - Patients need 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 α -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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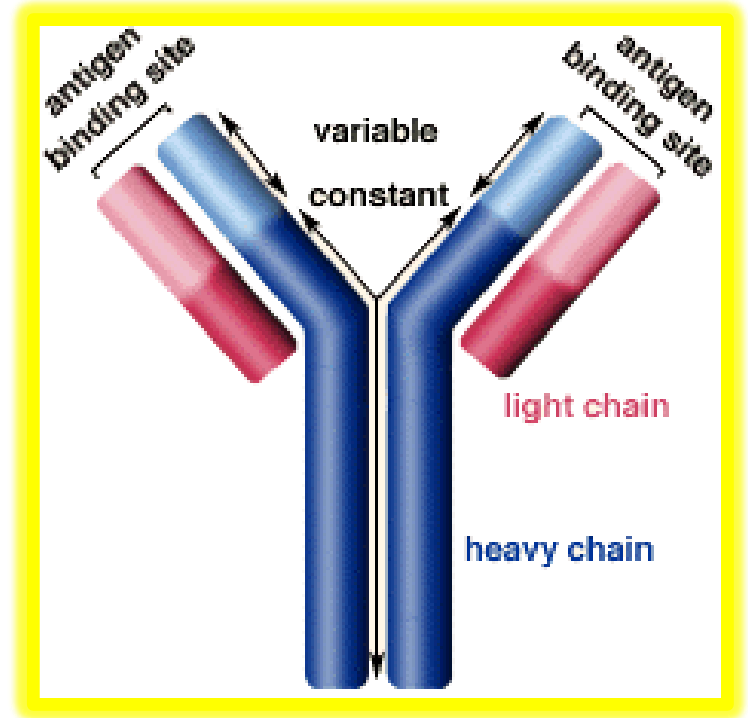
Structure of myoglobin

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 O₂ and CO₂ transport.
- HbA, HbA₂ and HbF are examples of normal Hb, in which the tetrameric structure is composed of 2 α constant subunits with 2 changeable β subunits according to Hb type.

Take Home Messages

- HbA_{1c} 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 Messages

- Glu6 in HbS is replaced by Val, while it is replaced by Lys in HbC.
- Methemoglobinemia is caused by oxidation of Hb, inhibiting O₂ 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 hemeprotein, which stores and supplies O₂ 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 6th edition.