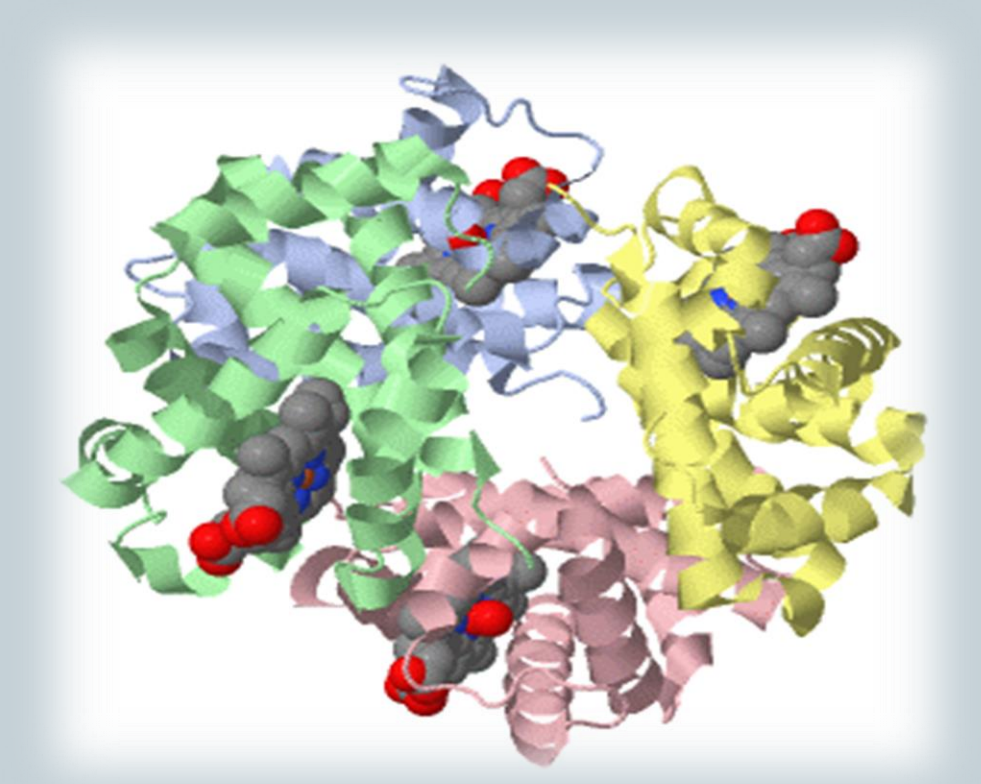
Globular Proteins

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

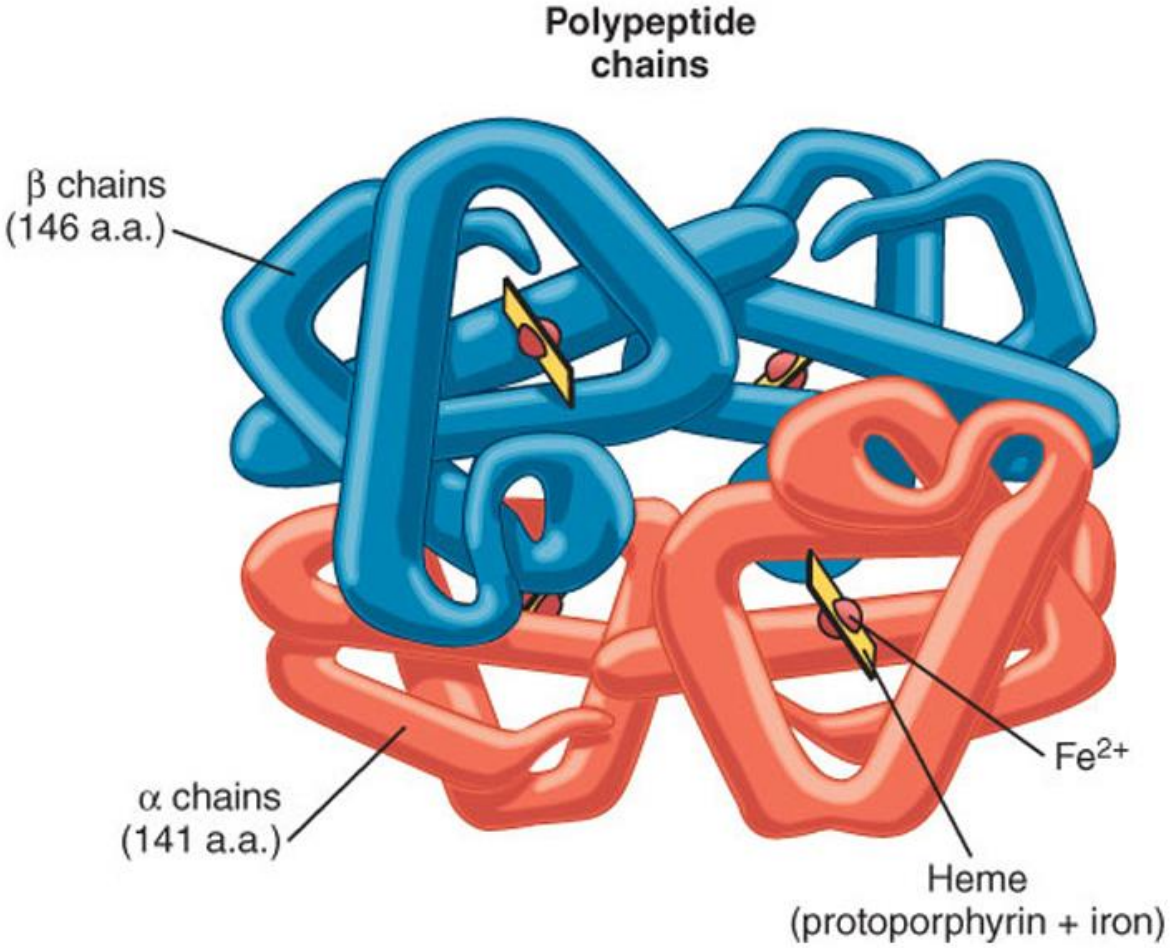
Globular proteins

- 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 αβ subunits

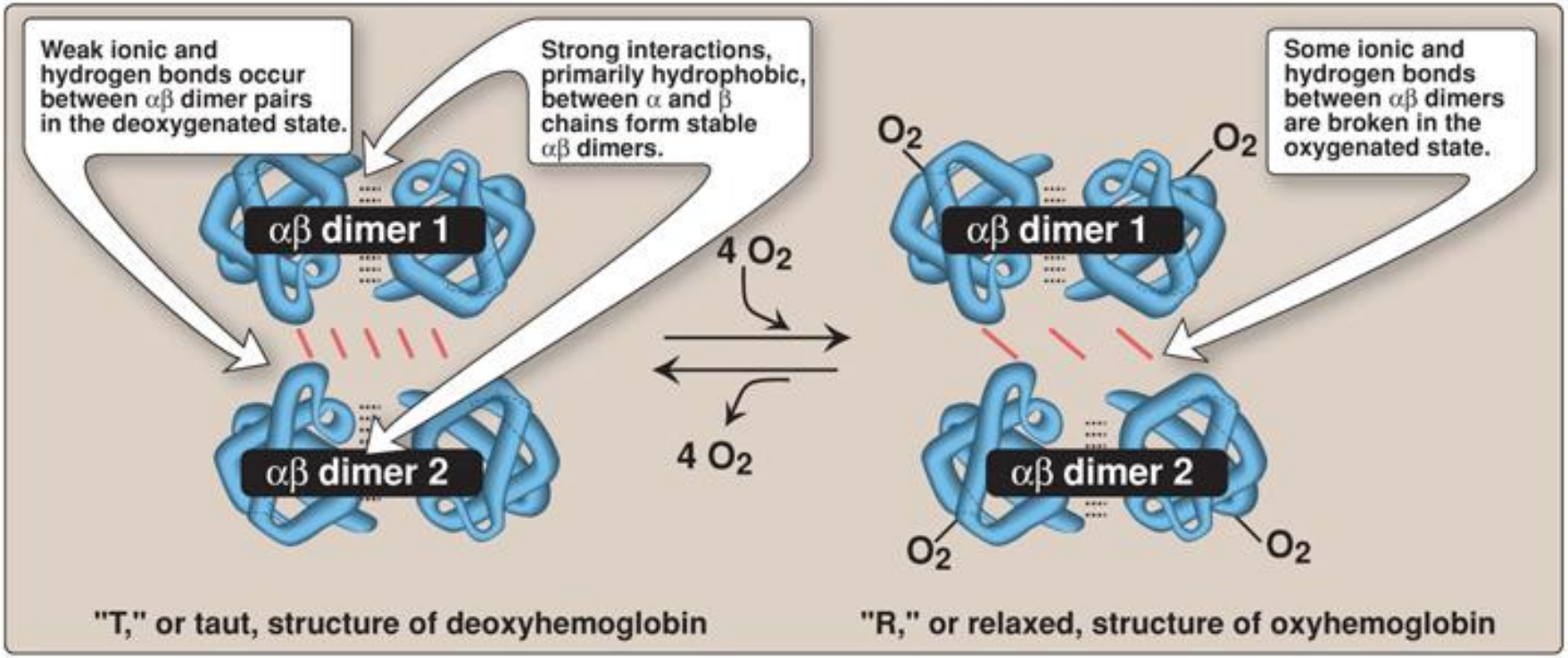
  Held together by non-covalent interactions
- Each chain is a subunit with a heme group in the center that carries oxygen
- A Hb molecule contains 4 heme groups and carries 4 molecules of O_2



Types of Hb

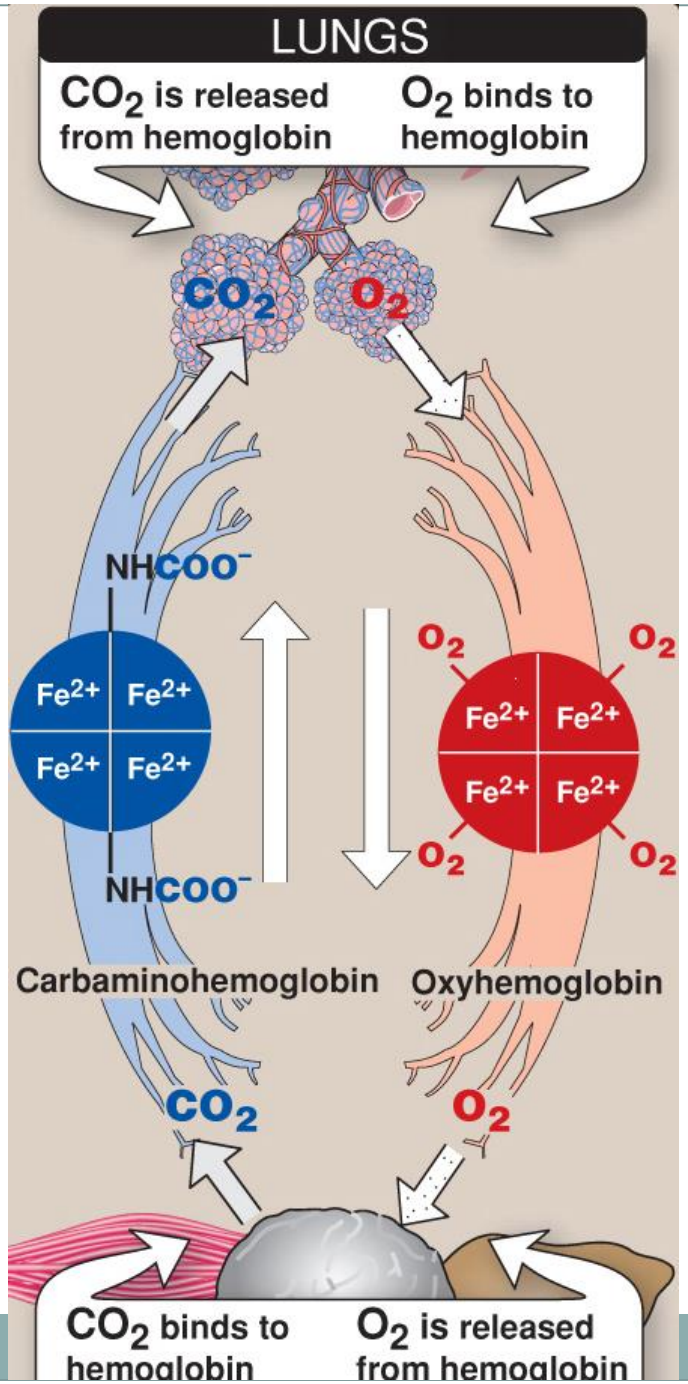
Normal:	HbA (97%)
	HbA_2 (2%)
	HbF (1%)
	HbA_{1c}
Abnormal:	Carboxy Hb
	Met Hb
	Sulf Hb

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
CO_2
O_2
$NHCOO^-$
Fe^{2+} Fe^{2+}
Fe^{2+} Fe^{2+}
$NHCOO^-$
O_2 O_2
Fe^{2+} Fe^{2+}
Fe^{2+} Fe^{2+}
O_2 O_2
Carbaminohemoglobin
Oxyhemoglobin
CO_2
O_2
CO_2 binds to hemoglobin
O_2 is released from 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

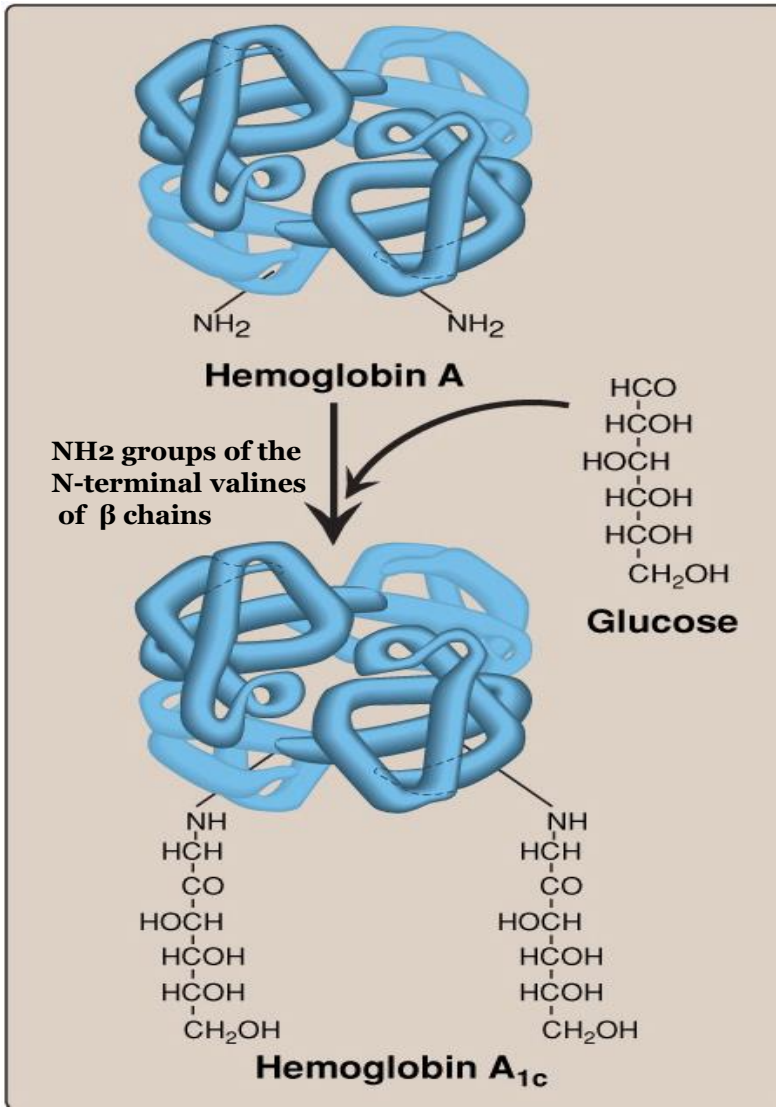
HbA_2:

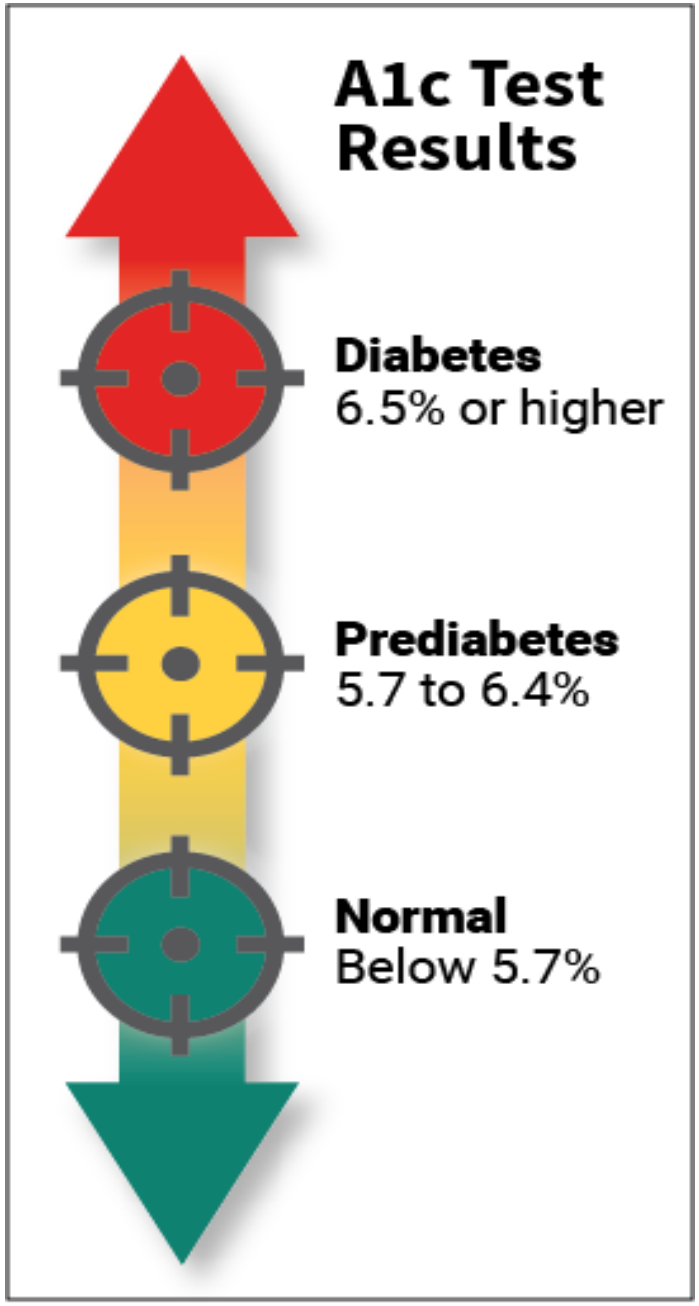
- Appears ~12 weeks after birth
- Constitutes ~2% of total Hb
- Composed of two α and two δ globin chains

Types of hemoglobin

HbA_{1c}:

- HbA undergoes non-enzymatic glycosylation
- Glycosylation depends on plasma glucose levels
- HbA1c levels are high in patients with diabetes mellitus




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

Abnormal Hbs

Unable to transport O_2 due to abnormal structure:

- Carboxy-Hb: CO replaces O_2 and binds 200X tighter than O_2 (in smokers)
- Met-Hb: Contains oxidized Fe^{3+} (~2%) that cannot carry O_2
- Sulf-HB: Forms due to high sulfur levels in blood (irreversible reaction)

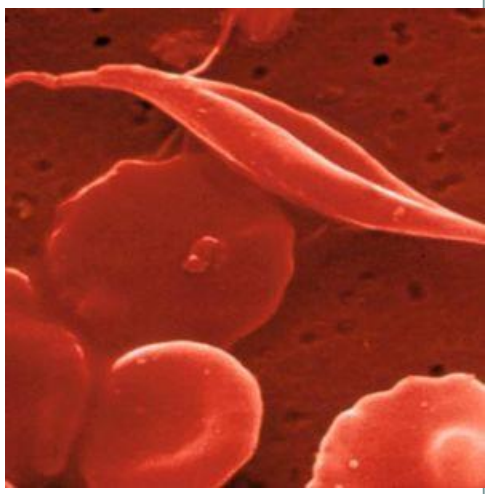
Hemoglobinopathies

- 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:

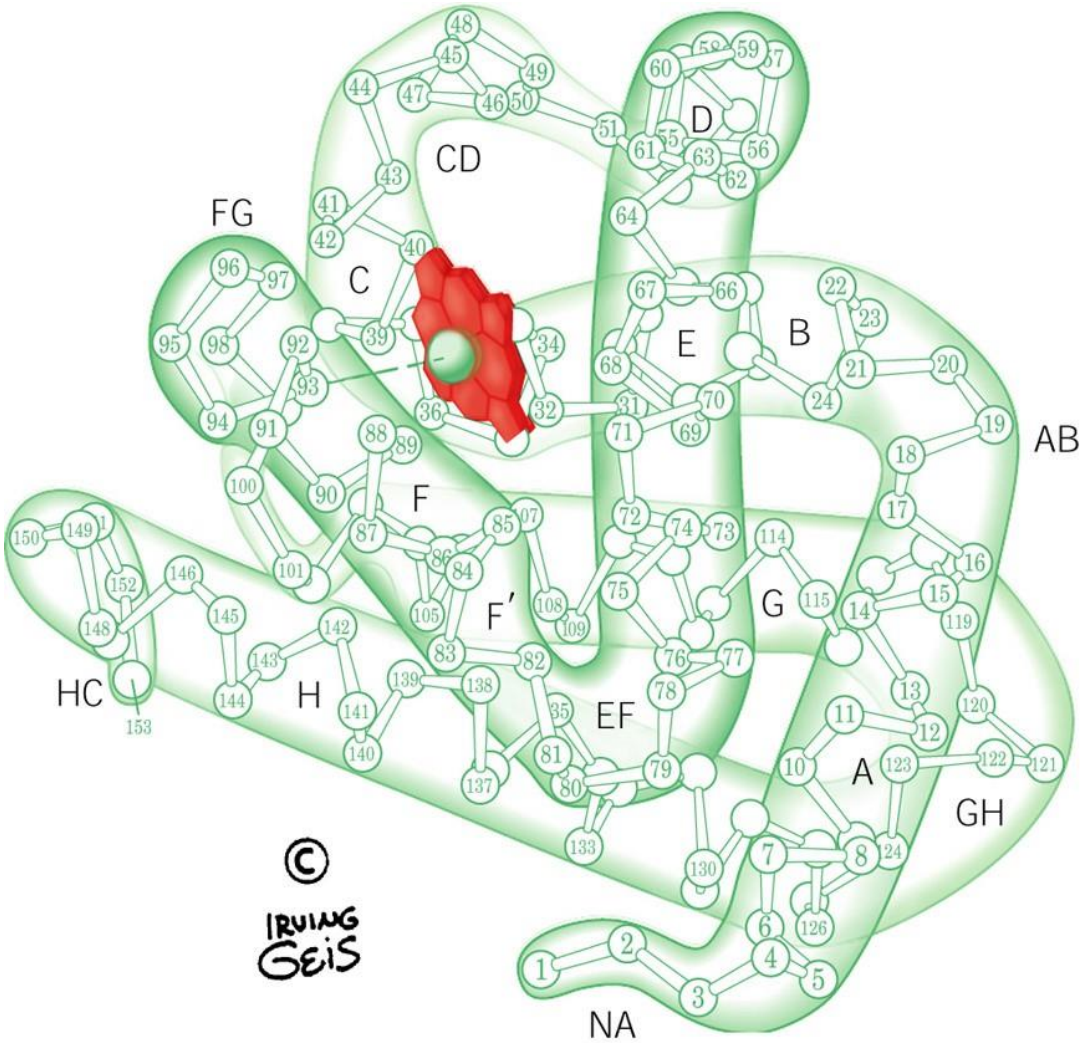
- Defective synthesis of either α or β-globin chain due to gene mutation
- α-thalassemia:
  - Synthesis of α-globin chain is decreased or absent
  - Causes mild to moderate hemolytic anemia
- β-thalassemia:
  - Synthesis of β-globin chain is decreased or absent
  - Causes severe anemia
  - Patients need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



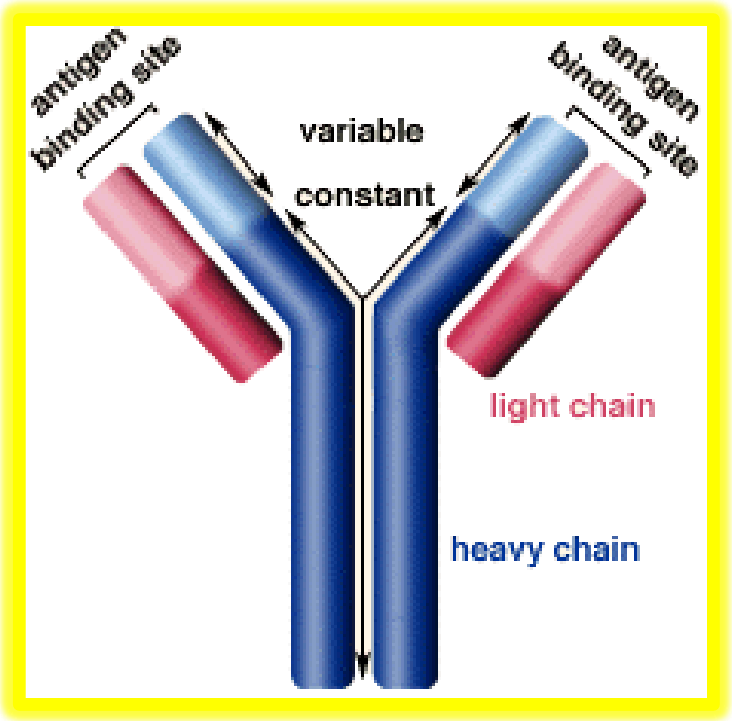
Structure of myoglobin

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_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.

Take Home Messages

- 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 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 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.

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.