

# The module: Molecular, Gene and Diseases

## Session 2: Lec2

### Lecture Title: Haemoglobin and Myoglobin

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This Lecture was loaded in blackboard and you can find the material in:

**(Lippincott's Illustrated Reviews: Cell and Molecular Biology Chapters 2,3)**

For more detailed instructions, any question, or you have a case you need help in, please post to the group of session



# The Learning Objectives (LO)

1. Explain the physiological roles of myoglobin and haemoglobin.
2. Contrast the oxygen-binding properties of myoglobin and haemoglobin and explain why haemoglobin is most suited to its role as an oxygen transporter.



3. Describe the major structural differences between oxygenated and deoxygenated haemoglobin and the molecular basis of cooperativity.
4. Describe the effects of  $\text{CO}_2$ ,  $\text{H}^+$ , 2,3-bisphosphoglycerate and CO on the binding of  $\text{O}_2$  by Hb, and the physiological significance of these effects.
5. Appreciate that mutations in globin genes can give rise to diseases such as sickle cell anaemia or thalassemia.



## LO 1

### Haemoglobin:

Is an iron containing protein that transports oxygen ( $O_2$ ) in human blood from the lungs to the tissues of the body.

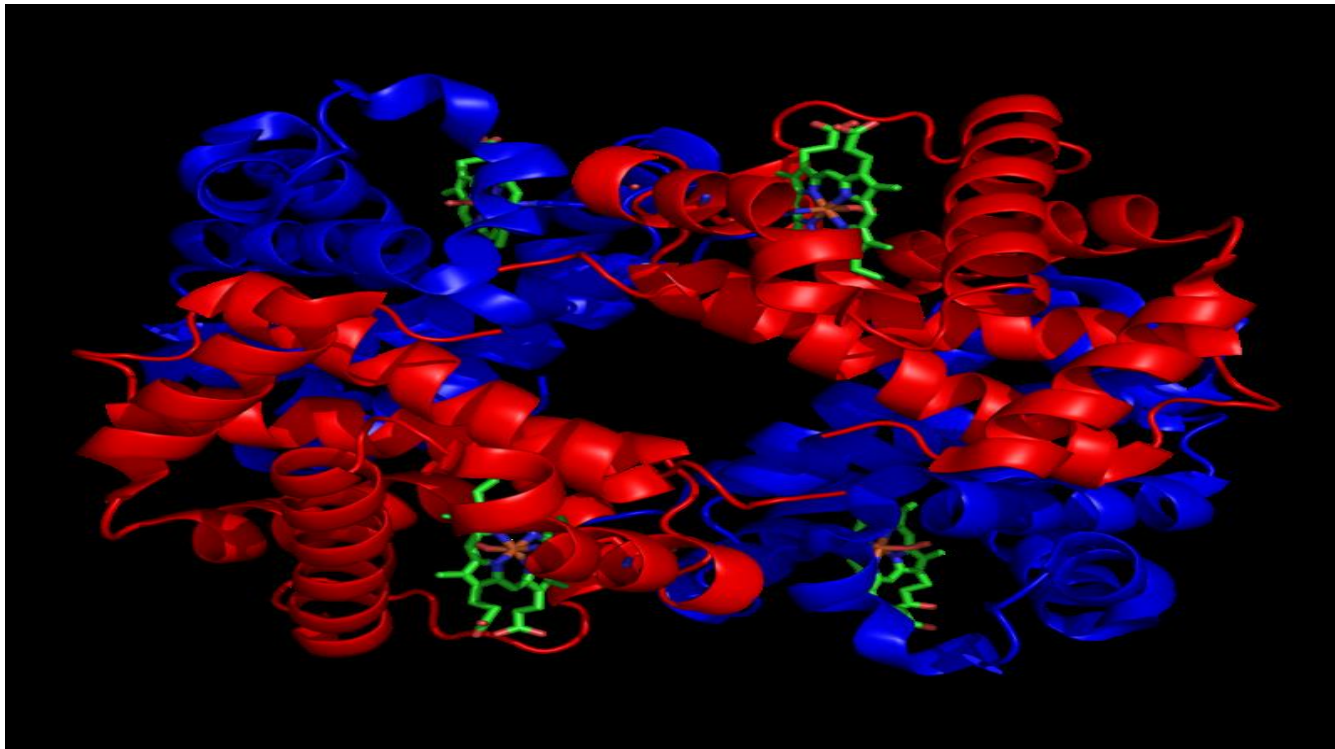
Haemoglobin = **heme** + **globin**



# Structure of haemoglobin

LO 1

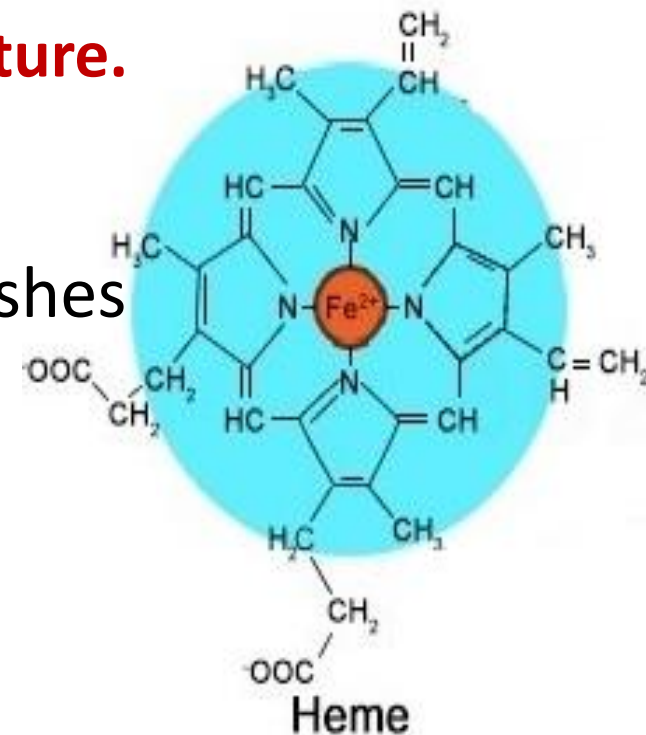
Each haemoglobin molecule is made up of four heme (iron) groups surrounding a globin (protein) group.



## LO 1

### Heme

- is an iron porphyrin compound.  
**Porphyrin is a tetrapyrrole structure.**
- Ferrous iron occupies the center of the porphyrin ring and establishes linkages with all the four nitrogens of all the pyrrole rings.



# Heme

## LO 1

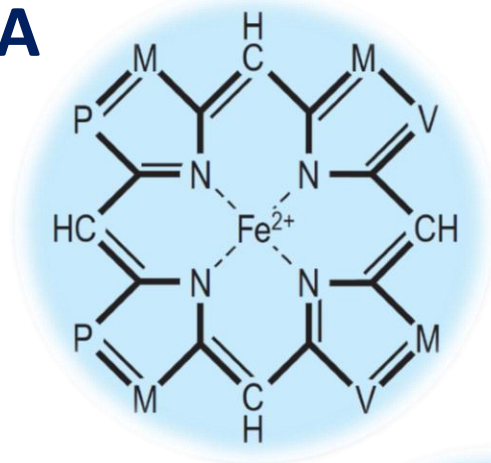
- Iron attached to six coordinated bonds
  - 4 coordinated bonds planer
  - 1 coordinated bond linked to O<sub>2</sub>
  - 1 coordinated bond linked to Histidine A.A of  $\alpha$  or  $\beta$  globin chain
- The central iron provides the reversible binding to oxygen and carbon dioxide molecules.



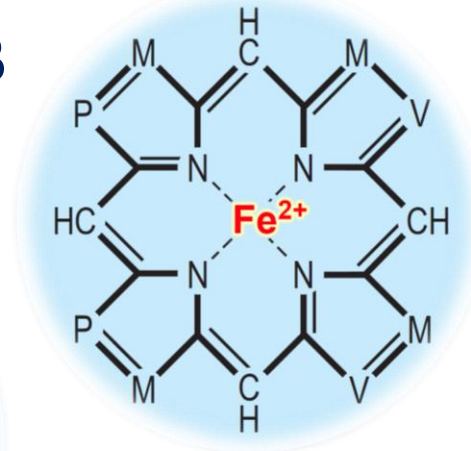


LO 1

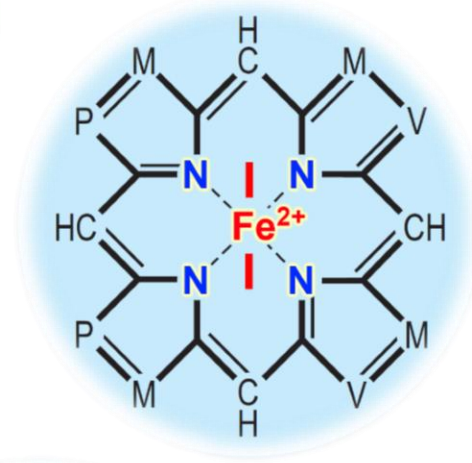
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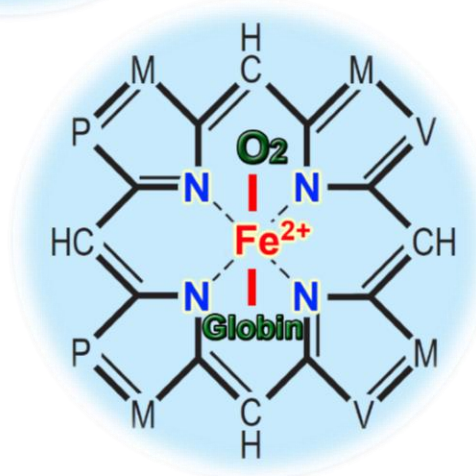
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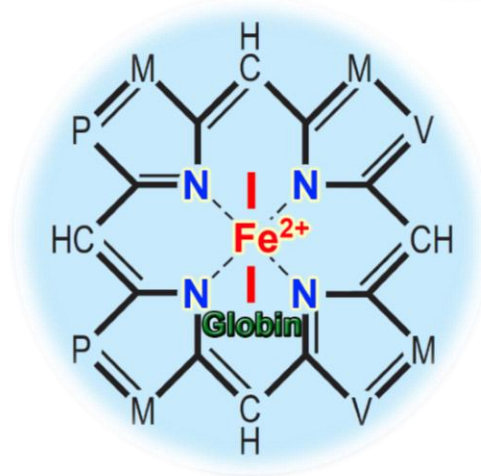
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D





## **LO 1**

# **In which compounds can we find a heme group**

**Haemoglobin (Hb).**

**Myoglobin (Mb).**

**Cytochromes.**

**Peroxidase.**



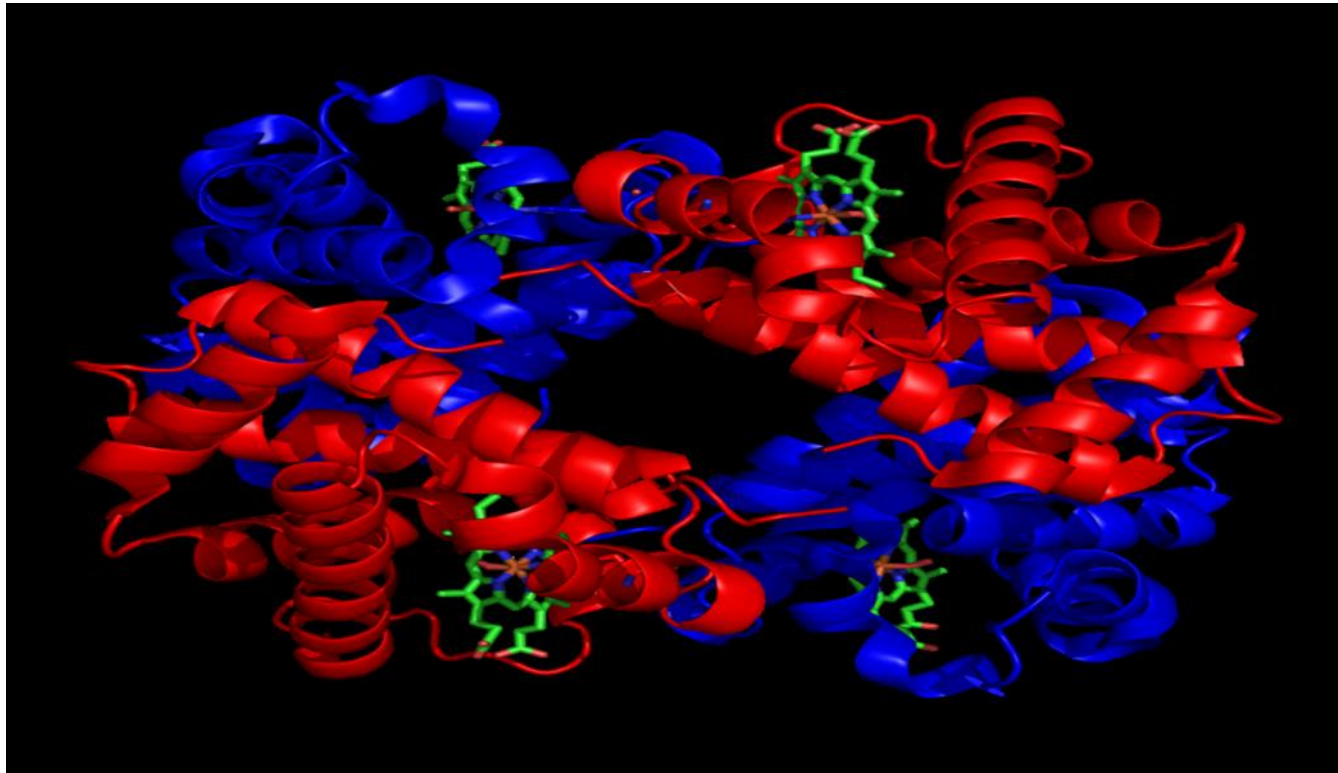
## Globin:

LO 1

- Hb comprises two pairs of globin chains that are twisted together .
- Normal adult hemoglobin contains **141 A.A** in each alpha chain and **146 A.A** in each  $\beta$  chain.



- The complete haemoglobin molecule contains **four haem groups** attached to each of **four globin chains** and may carry up to four molecules of oxygen.



## LO 1

# Normal Hb types in adults

❖ The main type of Hb is :

1. HbA<sub>1</sub> ( $\alpha_2\beta_2$ ) (97%) consisting of 2 pairs of globin chains  **$\alpha$  (141 AA residues)** and  **$\beta$  (146 AA residues)**
2. HbA<sub>2</sub> ( $\alpha_2\delta_2$ ) (2-3%) also found in adult but in small amount.



## LO 1

3. HbF (fetal hemoglobin)( $\alpha_2\gamma_2$ ): Is present primarily in embryonic life, and usually disappears from the circulation by the age of **6 months**.

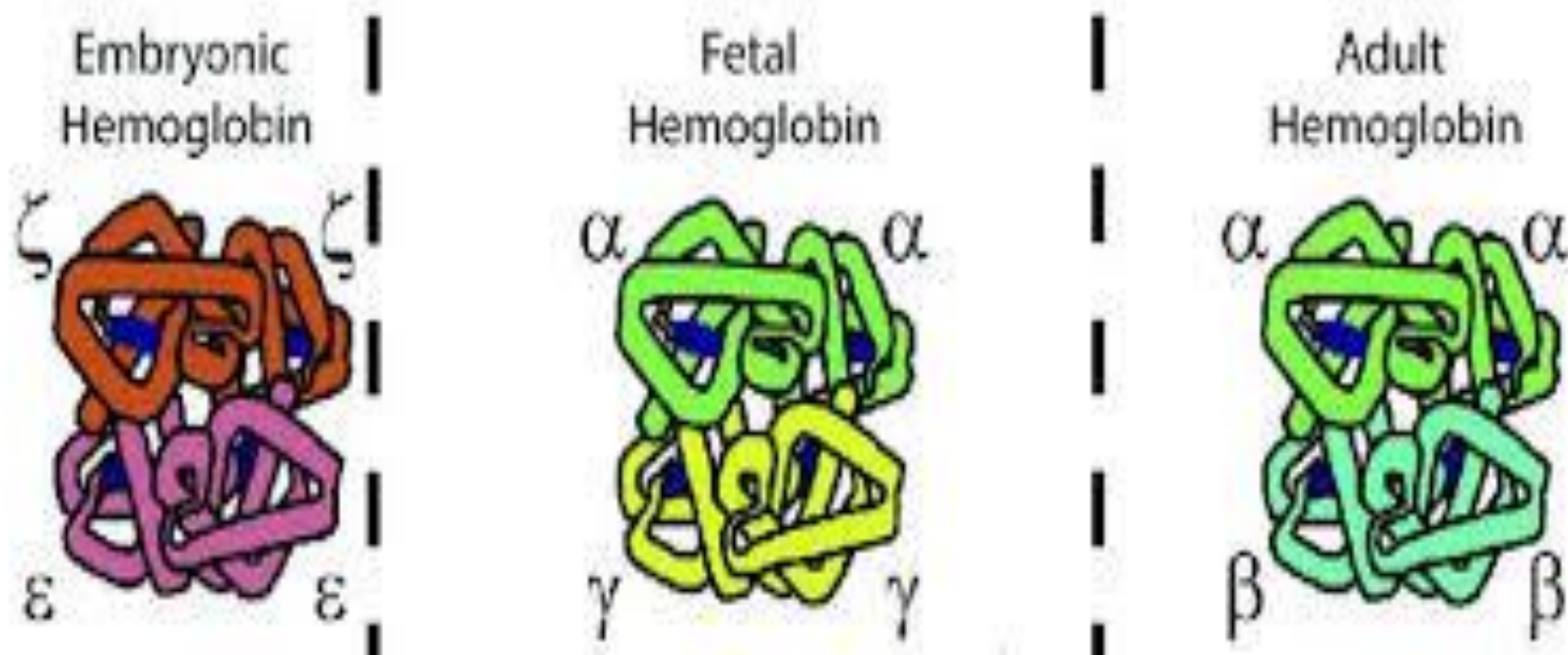
- HbF represents less than 1% of the Hb in adults.
- It having a greater affinity for oxygen than adult haemoglobin.



## LO 1

4. Gower 1 and 2: are synthesized by the embryonic yolk sac during the first month after conception.

**HbE Gower1 (  $\zeta\alpha_2\varepsilon_2$  ), HbE Gower-2 (  $\alpha_2\varepsilon_2$  )**



**LO 1**

# **NORMAL HEMOGLOBIN**

| TYPE | COMPOSITION AND SYMBOL | % OF TOTALHEMOGLOBIN |
|------|------------------------|----------------------|
| HbA1 | $\alpha 2\beta 2$      | 97%                  |
| HbA2 | $\alpha 2\delta 2$     | 2%                   |
| HbF  | $\alpha 2\gamma 2$     | <1% ( at birth 80%)  |





# Haemoglobin synthesis

LO 1

## Globin

Synthesized by  
ribosomes in the cytosol.

Embryonic haemoglobins

Gower 1- zeta(2), epsilon(2)

Gower 2- alpha(2), epsilon (2)

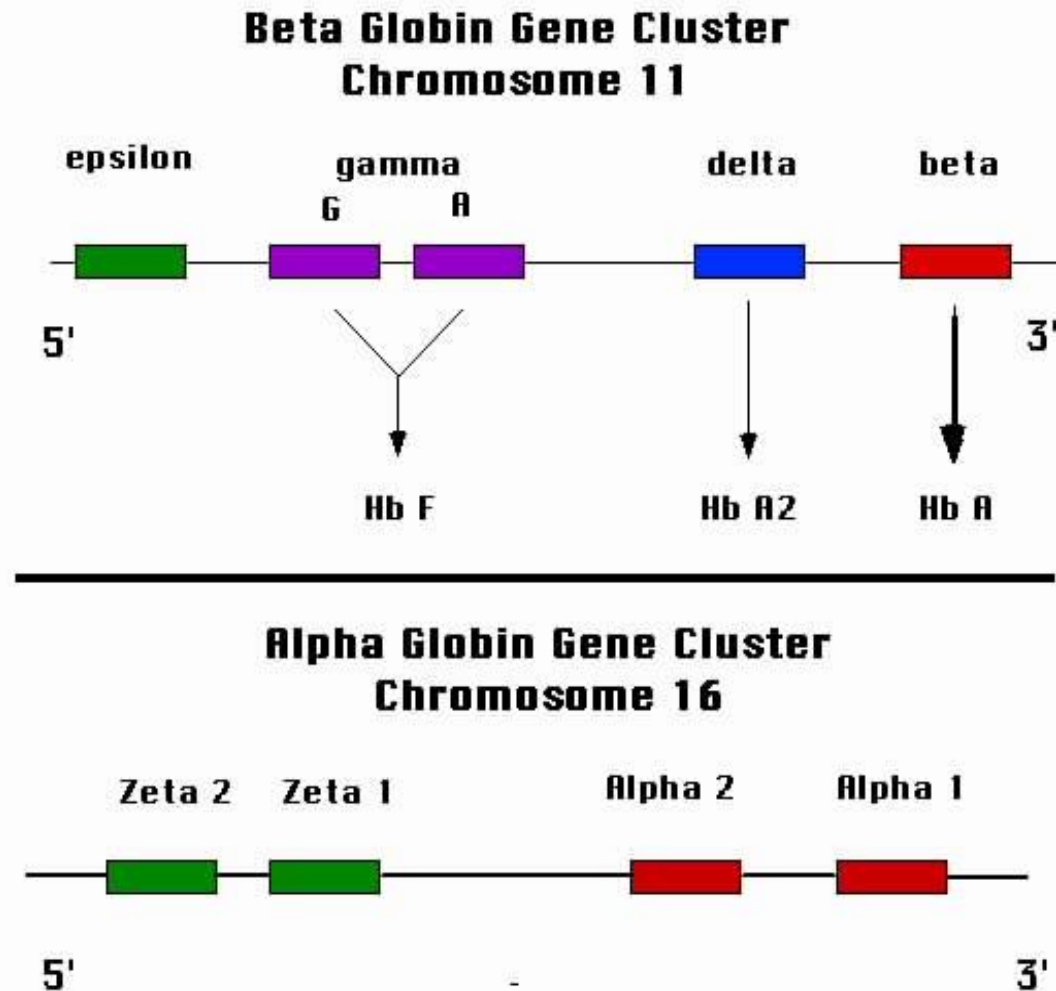
Fetal haemoglobin (HbF)

alpha(2), gamma(2)

Adult haemoglobins

HbA- alpha(2), beta(2)

HbA2- alpha(2), delta(2)



# Haemoglobin synthesis

LO 1

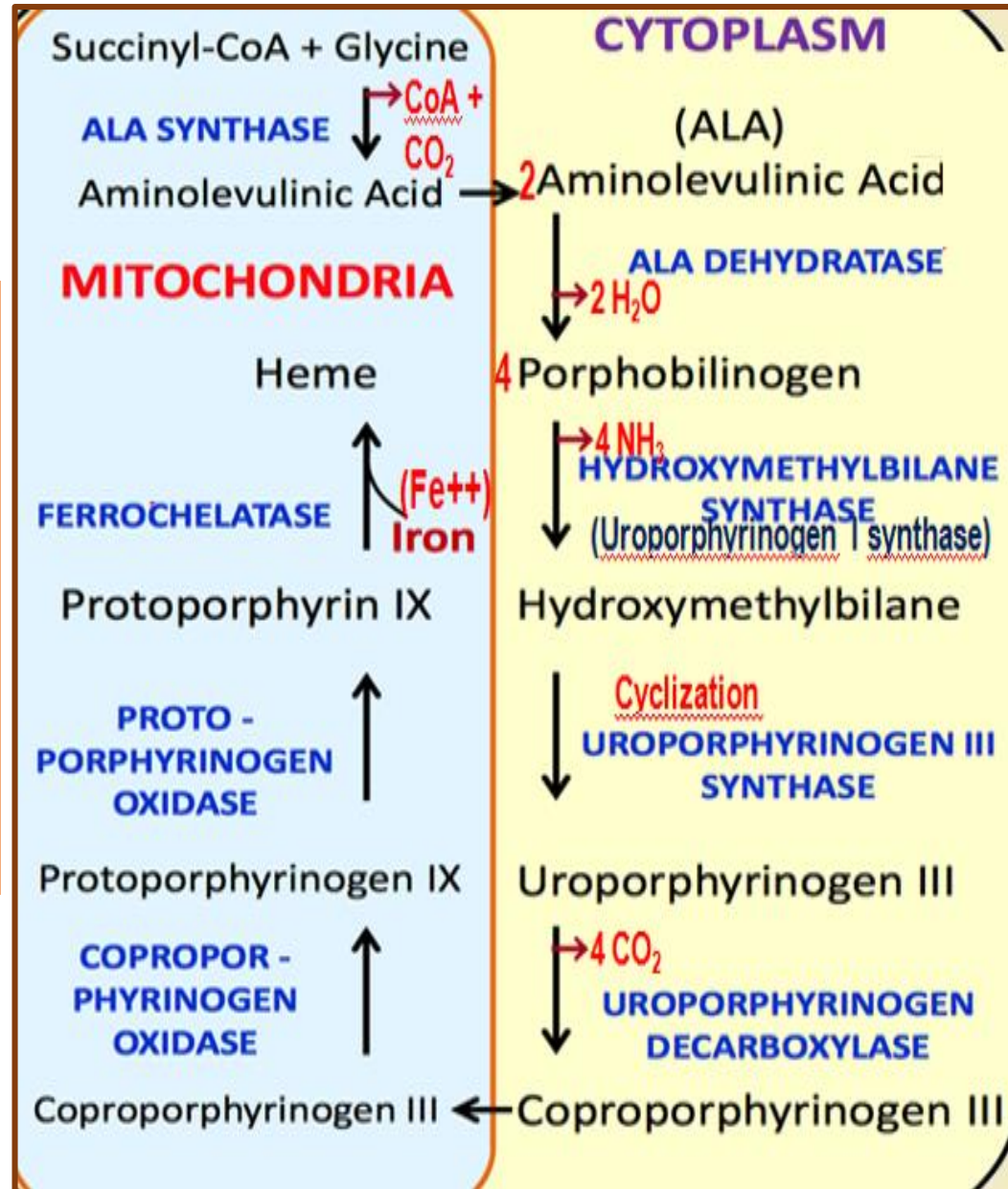
## Haem

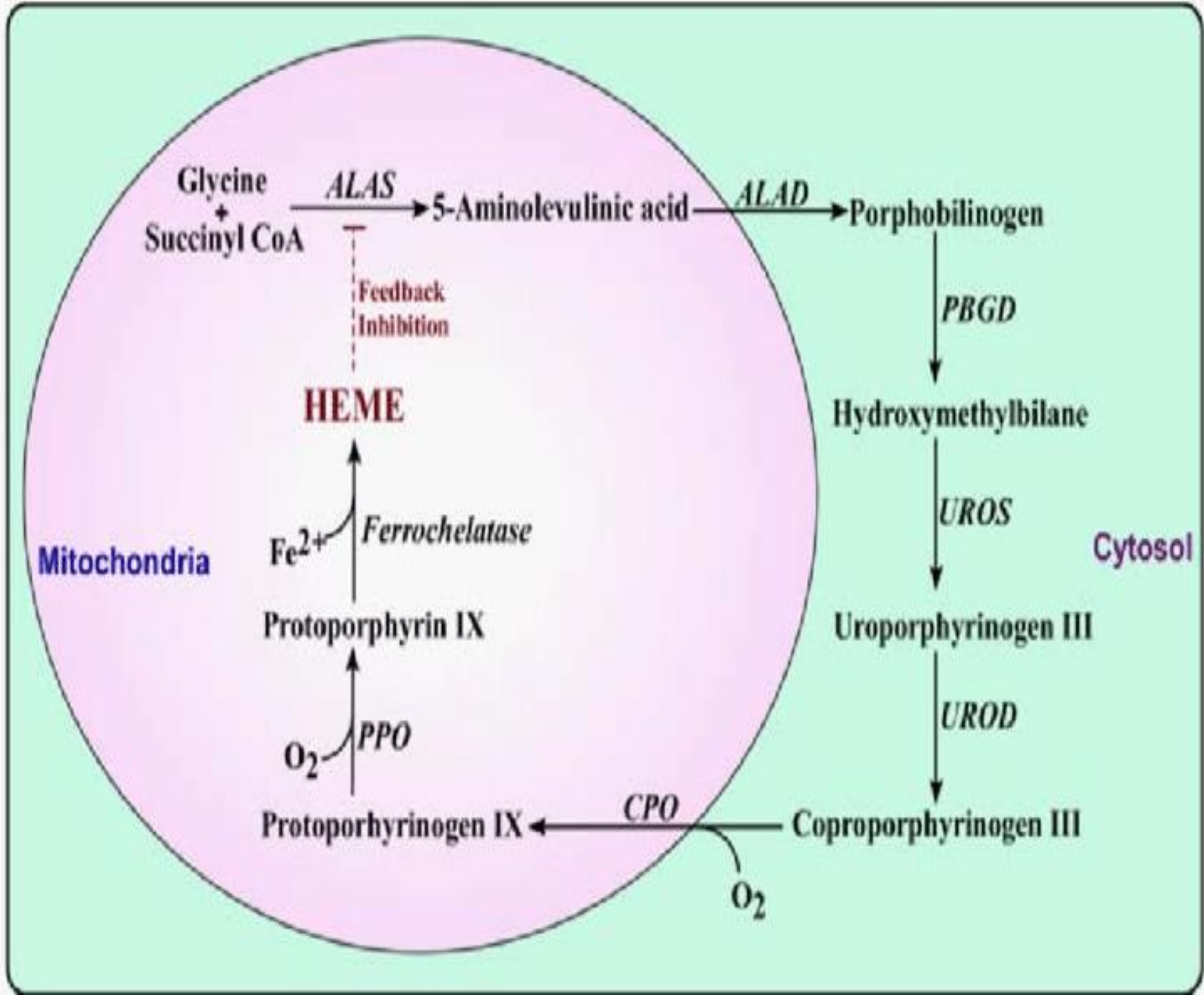
Synthesized in: bone marrow. .

The initial reaction and the last three steps in the formation of porphyrins occur in mitochondria, whereas the intermediate steps of the biosynthetic pathway occur in the cytosol.

substrates:  
Succinyl-CoA + glycine

It is an eight-step process



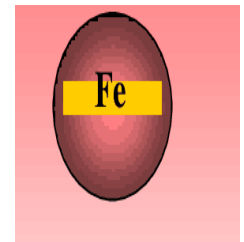


## Myoglobin:

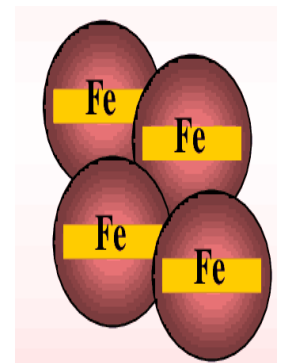
- Consists of a single polypeptide chain.
- Structurally similar to the individual globin chain of the Hb molecule.
- It can bind only to one molecule of oxygen with high affinity.
- Store oxygen inside muscle tissue to be used later on when  $P_{O_2}$  be very low.

LO 1

### Myoglobin



### Haemoglobin



# Haemoglobin vs Myoglobin:

LO 1

|                        | HAEMOGLOBIN   | MYOGLOBIN                                    |
|------------------------|---|--|
| Number of chains       | 4 polypeptide chains.   | single polypeptide chains.                   |
| Type of structure      | A tetramer.   | A monomer.                                   |
| Binds                  | Binds CO <sub>2</sub> , CO, NO, O <sub>2</sub> and H <sup>+</sup> . | Binds to O <sub>2</sub> , tightly and firmly |
| Their presence         | Systemically all over the body.                                     | In muscles cells.                            |
| Types of curve         | Sigmoid binding curve. (cooperative binding)                        | Hyperbolic curve.                            |
| Also known as          | Hb  | Mb   |
| Role                   | It is oxygen carrier  | It stores oxygen                             |
| Concentration in blood | High in RBC.  | Low.   |



## LO 2&3

### The Hb molecule exists in two forms:

#### T (tense or taut)

a) is a deoxyhaemoglobin that lacks of oxygen.

b) globin units being held tightly together by electrostatic bonds

#### R (relaxed)

a) is an oxyhemoglobin ( fully oxygenated)

b) bonds are broken when binds to oxygen

c) Hb has much higher affinity for oxygen than in T form

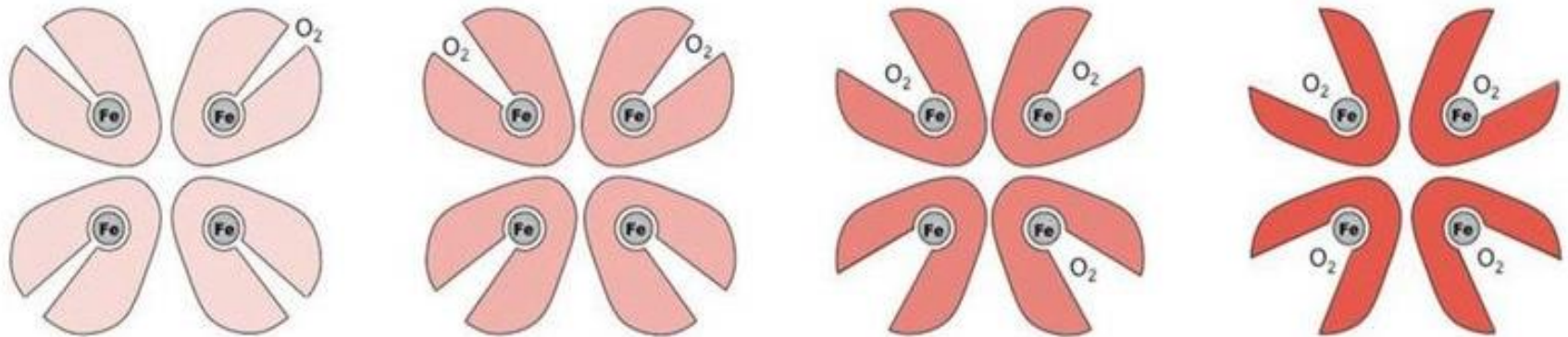




## Cooperative binding of oxygen to Hb:

LO 2

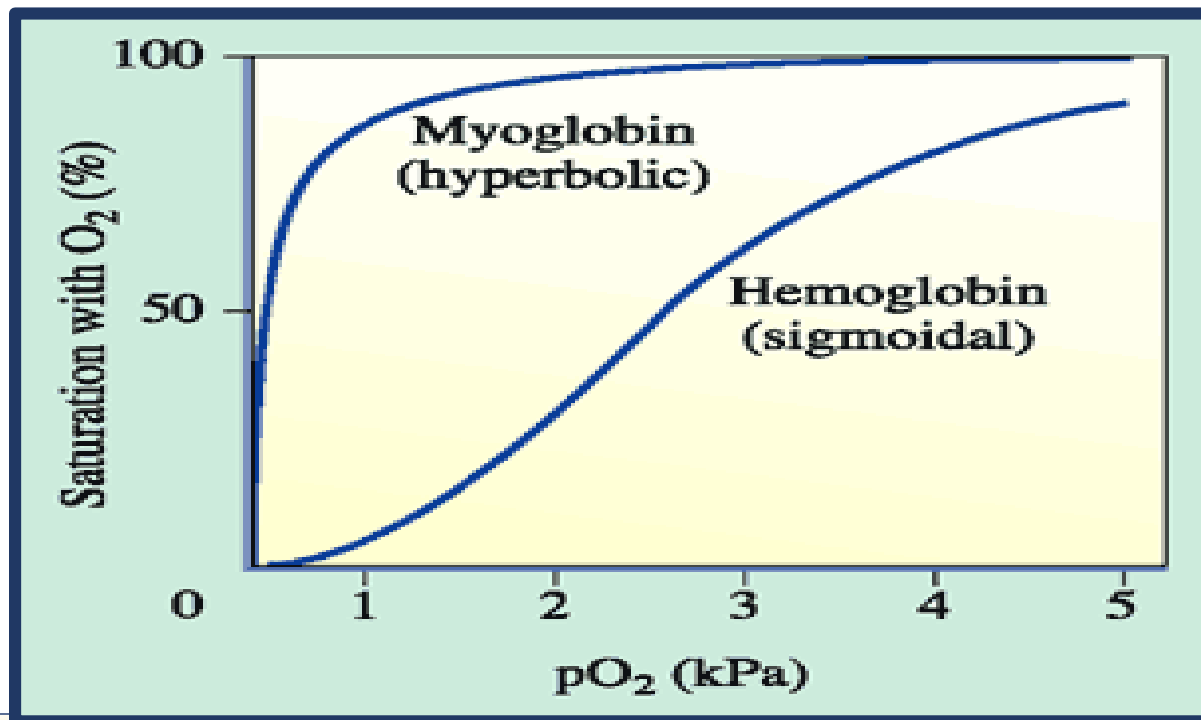
- ❖ As each  $O_2$  molecule attached, it alters the conformation of Hb, making it easier for others to be loaded with  $O_2$ .
- ❖ Conversely, as each  $O_2$  molecule is released, the change in Hb makes it easier for other molecules to be unloaded.





# Oxygen Dissociation Curve LO 2&3

Its a graphical representation of the relationship between the amount of oxygen bound to hemoglobin and the partial pressure of oxygen in the blood.



LO 4

# FACTORS THAT AFFECT OXYGEN DISSOCIATION CURVE OF HB

shift the oxygen dissociation curve to the **right** ( **low affinity of Hb to  $O_2$**  ) (Bohr effect)

- **↑ temperature**
- **↑  $PCO_2$**
- **↓ pH**
- **↑ 2,3 DPG**

shift the oxygen dissociation curve to the **left** ( **high affinity of Hb to  $O_2$**  ) (Haldane Effect)

- **↓ temperature.**
- **↓  $PCO_2$**
- **↑ pH**
- **↓ 2,3 DPG**
- **↑ CO poisoning**

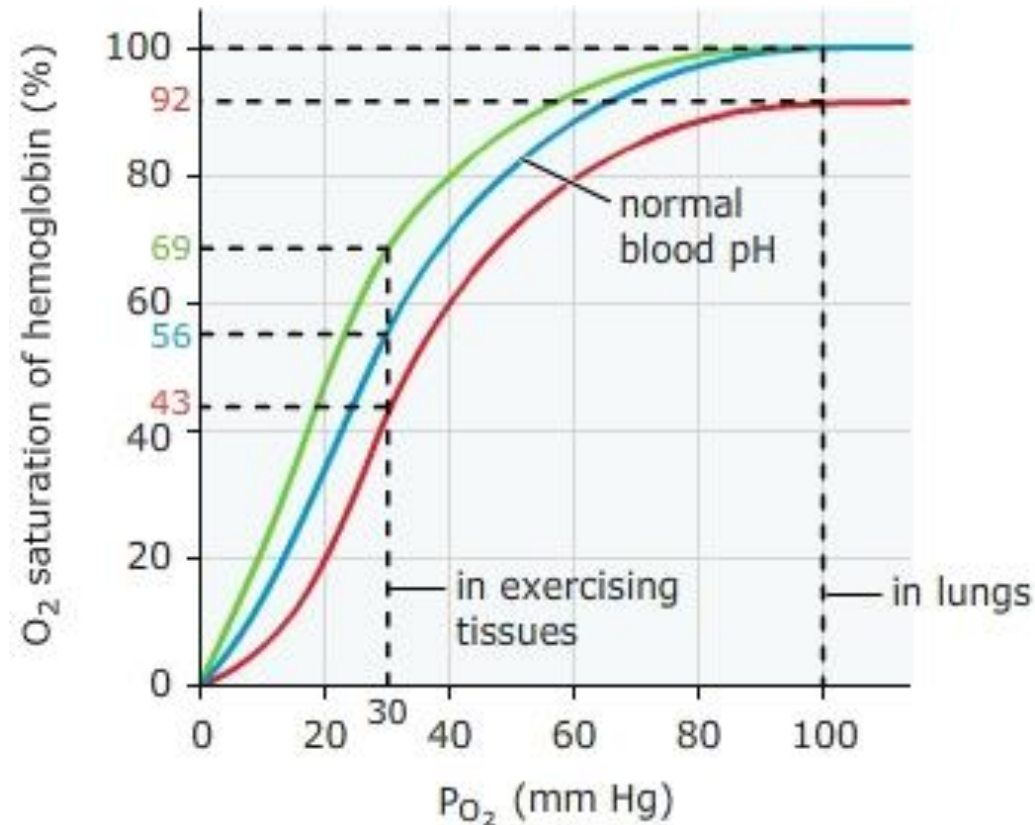


## LO 4

### (Bohr effect)

Is a decrease in the  $O_2$  affinity of a Hb in response to:

- $\uparrow$  temperature
- $\uparrow$   $PCO_2$
- $\downarrow$  pH
- $\uparrow$  2,3 DPG



**2,3 DPG:** Is a special intermediate of glycolysis in erythrocyte that plays a role in liberating  $O_2$  from Hb.

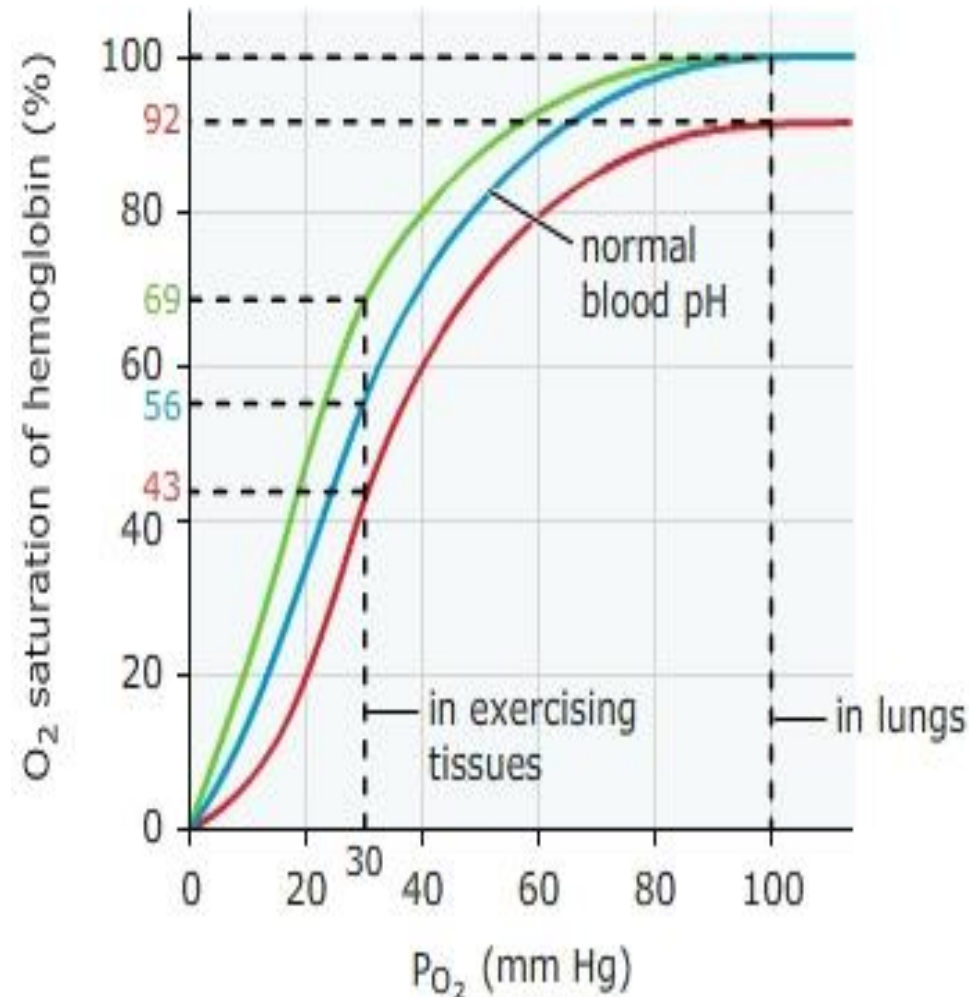


## LO 4

### (Haldane Effect)

Is an increase in the  $O_2$  affinity of Hb promotes the release of  $PCO_2$  in response to:

- ↓ temperature.
- ↓  $PCO_2$
- ↑ pH
- ↓ 2,3 DPG
- ↑ CO poisoning



## **LO 4**

**Why 2,3-BPG decreases the oxygen affinity of Hb ?**

**Explain why patient with CO**

**Poisoning has cherry red or pink  
cheek appearance.?**



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## **LO 3&4**

2,3-BPG decreases the oxygen affinity of Hb by binding to deoxyhaemoglobin but not to oxyhaemoglobin. This binding stabilizes the taut form of deoxyHb.



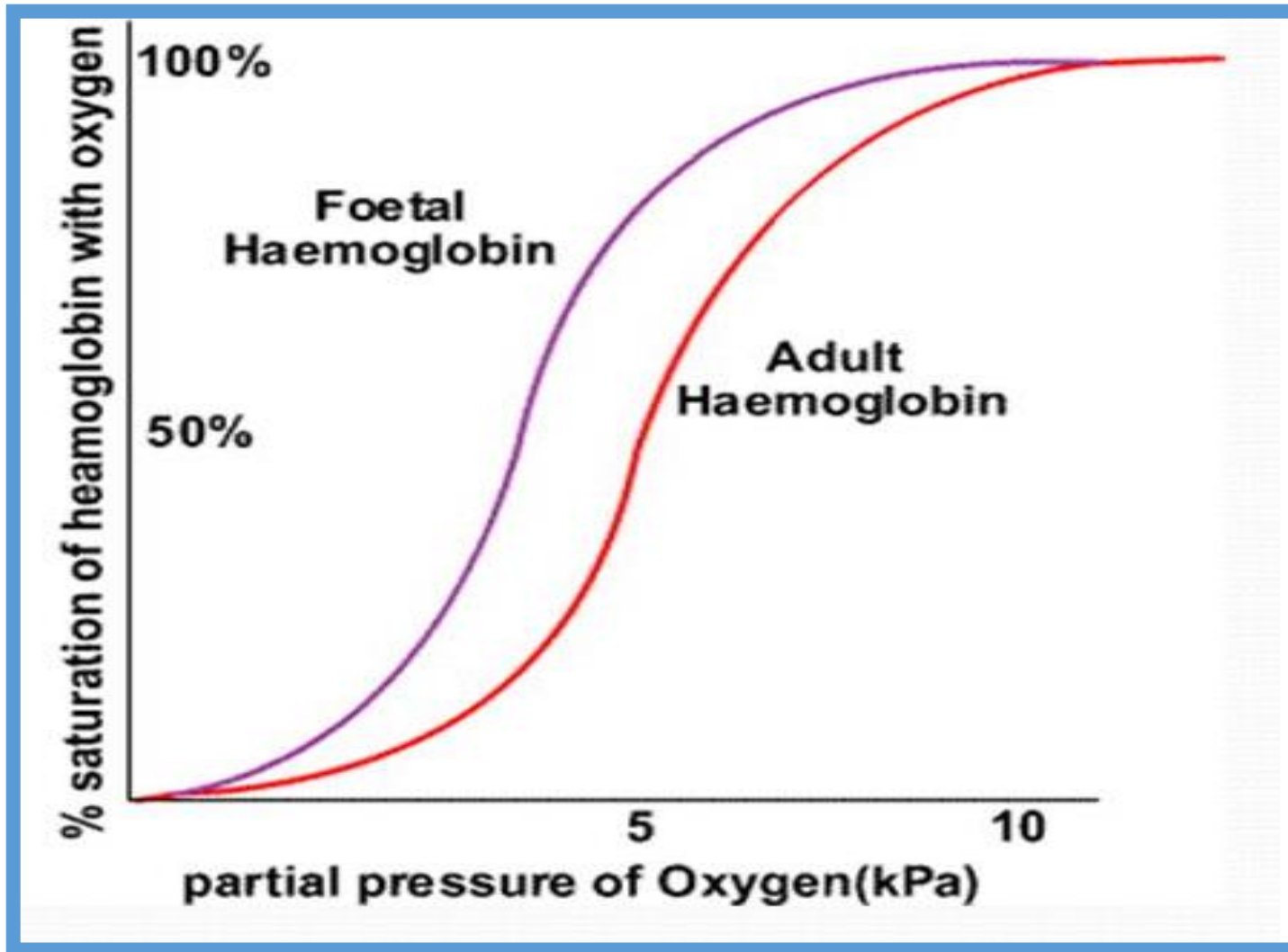
## LO 3&4

Why Hb F has high oxygen affinity than Hb A ?





## LO 3&4



## LO 3 &4

- 1) Hb F having  **$\gamma$  subunits** that allows to bind more strongly to oxygen
- 2) **2,3-BPG** interacts much more with **Hb A than Hb F.**

because the **adult  $\beta$  subunit** has more **positive charges** than the **fetal  $\gamma$  subunit**, which attract the negative charges from 2,3-BPG.

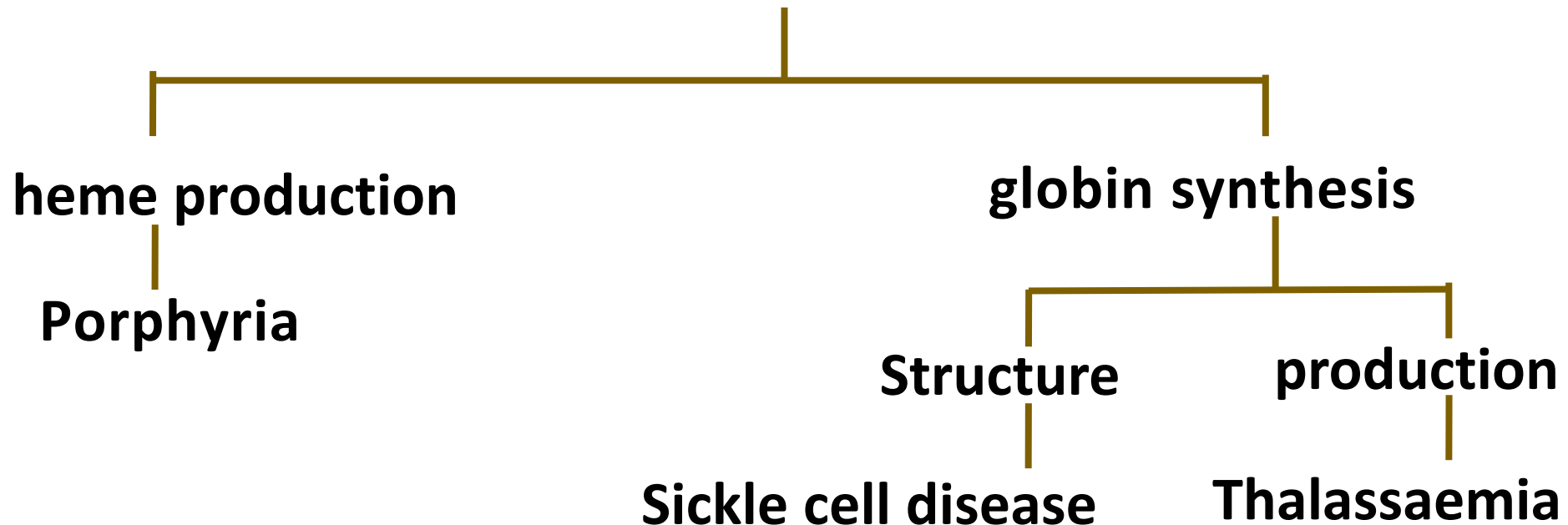
Due to the preference of 2,3-BPG for Hb A, Hb F binds to oxygen with high affinity.



**LO 5**

## Haemoglobin abnormality (haemoglobinopathy):

Is a variant form of **Hb** that is often inherited and may cause a blood disorder in



**LO 5**

# Porphyria

- Is a group of disorders caused by abnormalities in the chemical steps that lead to heme production.
- The most common types of porphyria are:

**a) Acute intermittent porphyria  
(AIP).**

**b) Porphyria Cutanea Tarda  
(PCT)**



LO 5

## Sickle Cell Anaemia.

Caused by a mutation in the  $\beta$ -globin gene that changes the sixth amino acid from **Glutamic acid (charged AA)** to **valine (nonpolar AA)**.

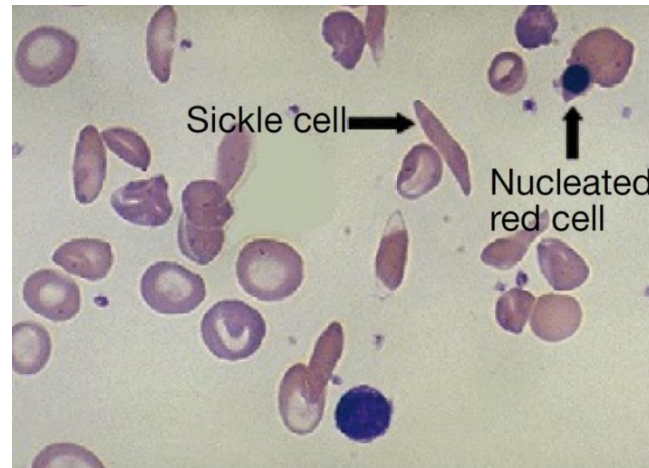
- a) **Homozygotes** only produce **abnormal  $\beta$ -chains** that make **HbS**.
- b) **Heterozygotes** produce a **mixture of normal and abnormal  $\beta$ -chains** that make normal HbA and HbS (HbAS),



LO 5

## Sickle Cell Anaemia.

When HbS is deoxygenated, the molecules of Haemoglobin polymerize to form **pseudocrystalline** structures known as '**tactoids**'. These distort the red cell membrane and produce a characteristic of **sickle-shaped cells**.



## LO 5

# Thalassaemia

There is a reduced **rate of production** in one or more of the globin chains. Which results in imbalanced globin chain synthesis.

## $\alpha$ -Thalassaemia.

defect in the synthesis of  $\alpha$  globin chain.

## $\beta$ -Thalassaemia

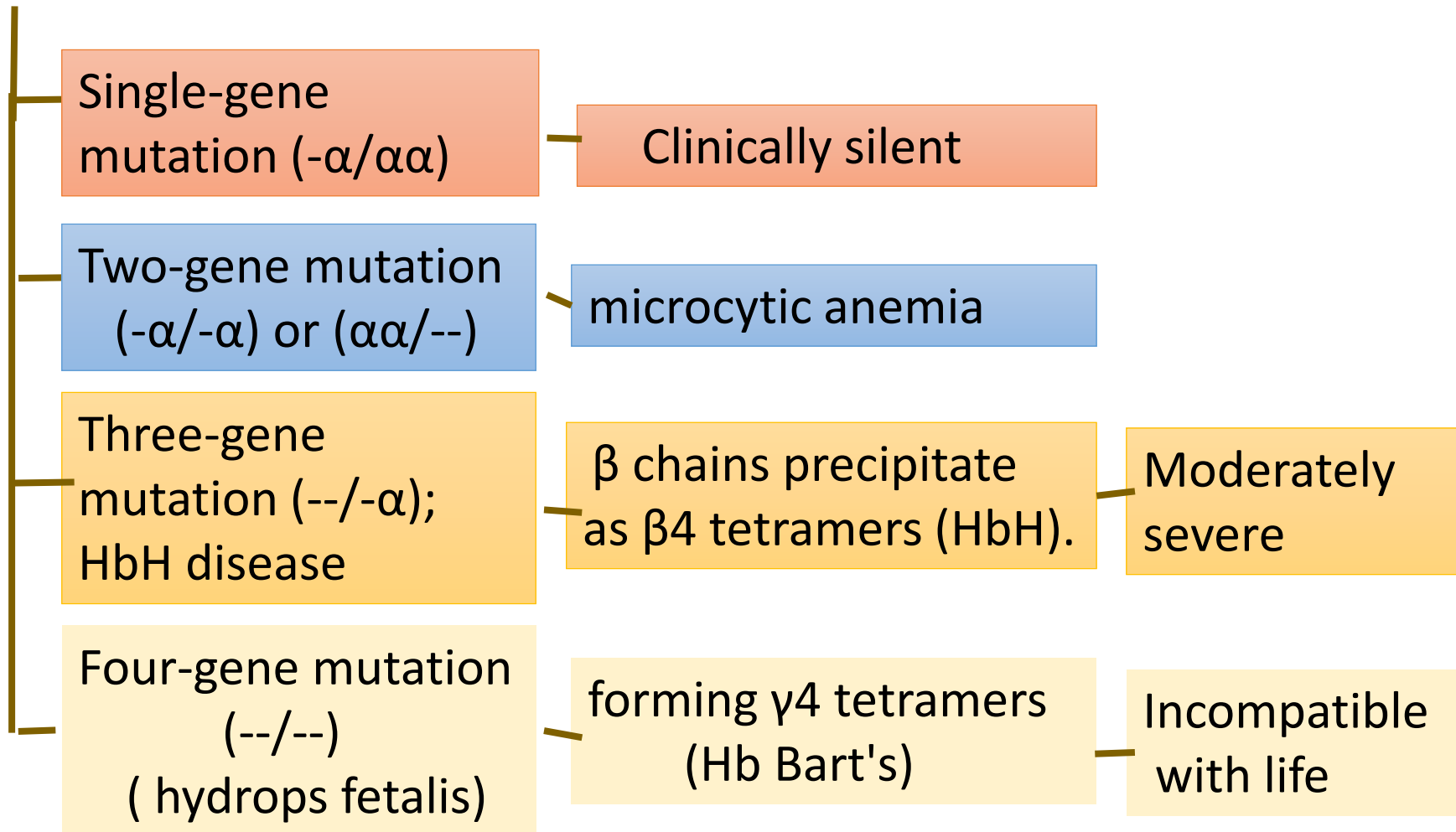
defect in the synthesis of  $\beta$  globin chain.





# $\alpha$ -Thalassaemia.

LO 5



**LO 5**

## **$\beta$ -Thalassaemia.**

**mutations in the  $\beta$ -globin gene**



**generation of a stop codon in mRNA**



**termination of globin chain synthesis**



**variable reduction in  $\beta$  globin output**



LO 5

## Types of $\beta$ -Thalassaemia.

