Peptides

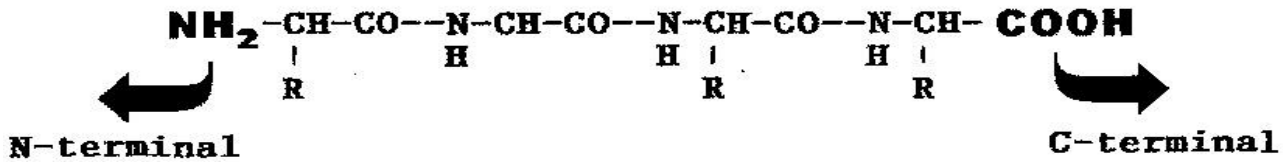
- **Definition:** Peptides are compounds, formed of less than 50 amino acids linked together by peptide bonds.
  1. Dipeptide (2 amino acids and 1 peptide bond).
  2. Tripeptide (3 amino acids and 2 p.b).
  3. Oligopeptide (3-10 amino acids).
  4. Polypeptide (10-50 amino acids).

Peptide bond:

- Definition: It is a covalent bond formed between the carboxyl group of one amino acid and the amino group of another.
- Mechanism: - it is formed by removal of water.
  - Peptide formation needs energy getting from hydrolysis of ATP
- Characters: - Peptide bond is semi-rigid bond i.e. no free rotation can occur around bond axis.

Primary structure of peptides:

- It's the arrangement of amino acids in a polypeptide chain.
- In a polypeptide chain the N-terminal amino acid (i.e. the only amino acid that contains free amino group) is always to the left side.
- The C-terminal amino acid (i.e. the only amino acid that contains free carboxyl group) is always to the right.



Separation of peptides

A. By electrophoresis
B. By exchange chromatography technique.

Biologically active peptide

Peptides include many active compounds as:

A. Glutathione:

- Definition: it is a Tripeptide formed of three amino acids: glutamate cysteine and glycine. It is also called "glutamyl-cysteinyl-glycine".

Glutathione is commonly abbreviated as G-SH where -SH indicates the sulfhydryl group of cysteine and it is the most active part of the molecule.

- Functions of glutathione:

1- Defense mechanism against certain toxic compounds (Detoxification).
2-Absorption of amino acid: glutathione has a role in transport of amino acids across intestinal cell membrane..
3- Protect against cell damage and hemolysis of RBCs: Glutathione breakdown the hydrogen peroxide (H_2O_2) which causes cell damage and hemolysis.
4- Activation of some enzymes.
5- Inactivation of insulin hormone.

B. Hormones

1. Insulin and glucagon from Pancreas.
2. Vasopressin and oxytocin from posterior pituitary gland.
3. ACTH from anterior pituitary gland.

C. β-Lipotropin is:

- Polypeptide produced by anterior pituitary.

- The precursor of β-endorphin.
- β-endorphin acts as neurotransmitter and neuromodulator.
- It has analgesic effect powerful 18-30 times than morphine.

D. Bradykinin:

1. It is released from specific plasma proteins by specific proteolytic enzyme.
2. It acts as a potent smooth muscle relaxant and produces vasodilatation and hypotension.

E. Antibiotics: e.g. valinomycin.

F. Antitumor agent: e.g. bleomycin.

G. Aspartame:

- It is a dipeptide (aspartic acid and phenylalanine) that serves as sweetening agent. It is used in replacement of cane sugar.

H. Atrial natriuretic peptide:

1. It is a peptide produced by specialized cells in the heart and nervous tissue.
2. It stimulates the production of dilute urine (opposite to vasopressin).

Proteins

Nature of proteins:

A. Composition:

1. Proteins are macromolecules formed of amino acids united together by peptide bonds.
2. Amino acids are commonly found in proteins in different proportions.
3. Some proteins are formed of 2 or more polypeptide chains.

B. Size of proteins.

1. Proteins having a very high molecular weight, ranging from 5,000 to several millions.
2. The term protein is applied to describe molecules greater than (50 a.a.).
3. Molecules contain less than 50 amino acids are termed peptides.

Functions of proteins:

1. **Enzymes:** Enzymes are protein
2. **Transport:** Of small molecules and ions e.g.
   a. Hemoglobin is a carrier for oxygen.
   b. Lipids are transported as lipoproteins.
3. **Structural elements: e.g.**
   a. Cell membrane contains proteins in the form of glycoproteins.
   b. Skin and bone: e.g. contains proteins in the form of collagen.
4. **Hormonal regulation:**
   a. Some hormones are protein in nature e.g. growth hormone.
   b. Cellular receptors that recognize hormones are proteins
5. **Defense mechanism:**
   a. Antibodies: (immunoglobulin's) are protein in nature.
   b. Keratin found in skin and other tissues is protein that protect against mechanical and chemical injury.
6. **Blood clotting:** Coagulation factors are proteins.
7. **Storage:** as ferritin which is a storage form of iron.

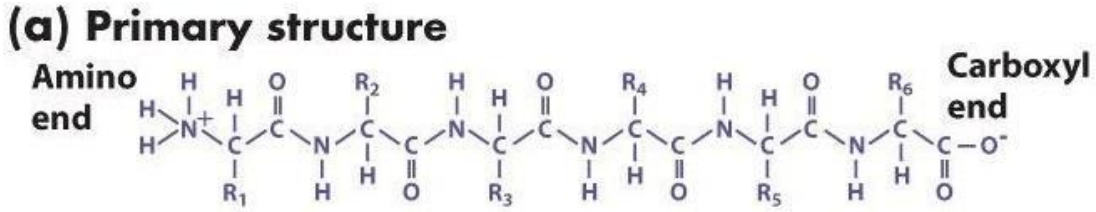
8. Control of genetic expression: many regulators of genes are protein in nature.

Conformation of proteins = (protein structure):

A. Primary structure:

- **Definition:** It is the arrangement of amino acids in the polypeptide chain.
- **Bonds responsible for the primary structure:** The peptide bonds "covalent".
- **Mechanism:**

1. Each polypeptide chain starts on the left side by free amino group of the first amino acid, It is termed N-terminal (or N-terminus) amino acid.
2. Each .polypeptide chain ends on the right side by free carboxyl group last amino acid, It is termed C-Terminal (or C-terminus) amino acid.
3. The remaining amino acids in the chains are termed: amino acid residues
4. The types and arrangement of amino acid in each protein is determined by the genetic information present in DNA.



B. Secondary structure:

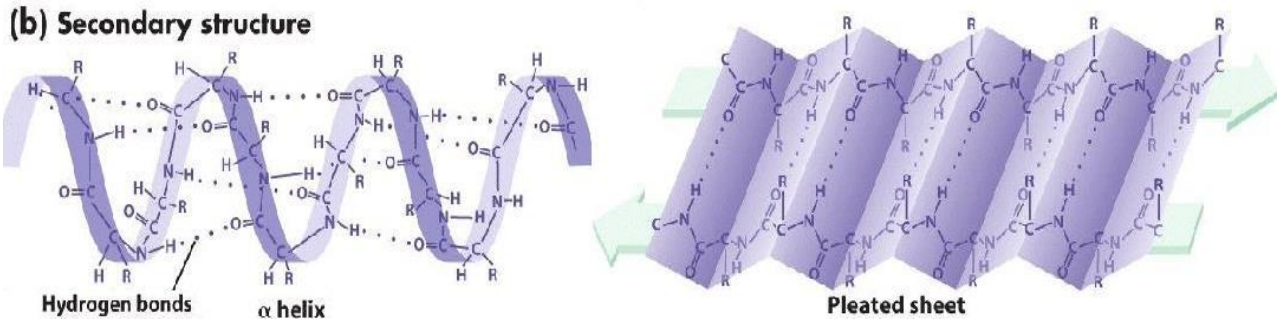
- **Definition:** It is the spatial relationship of adjacent amino acid residues.
- **Bonds responsible:** Hydrogen bond.

It is the bond between the hydrogen of -NH group of one amino acid residues and the carbonyl oxygen (C=O) of the fourth one

- **Mechanism:**

1. Secondary structure results from interaction of adjacent amino acid residues (first and fourth).
3. There are 2 main forms of secondary structure α-helix and β-pleated sheets:

The α-helix	β-pleated sheets
- Shape & formation: It is a rod like structure with the peptide bonds coiled tightly inside and the side chains of the residues (R) extending outward from the chain. - Characteristics: 1) Each (C=O) of one amino acid is hydrogen bonded to the (-NH) of the next fourth amino acid in the chain (1→4) 2) The complete turn distance equals 54 nm. 3) Each turn contains 3.6 amino acids residues.	- Shape & formation: a) This structure is formed between two or more separate polypeptide chains. It may also be formed between segments of the same polypeptide chain. b) Hydrogen bond is also responsible for its formation. It occurs between (-NH) group of one chain (or segment) and (C=O) of group of adjacent chain (or segment). - Two types of β-sheets are present: 1) Parallel β-sheets: in which the two polypeptide chains run in the same direction. 2) Antiparallel β-sheets: In which the two polypeptide chains run in opposite direction.



C. Tertiary structure:

- **Definition:** This is the final arrangement of a single polypeptide chain resulting from spatial relationship of more distant amino acid residues.
- **There are two forms of tertiary structures:**

a) Fibrous: which is an extended form e.g. keratin, collagen and elastin.

b) Globular: which is a compact form and results from folding of polypeptide chain e.g. myoglobin.

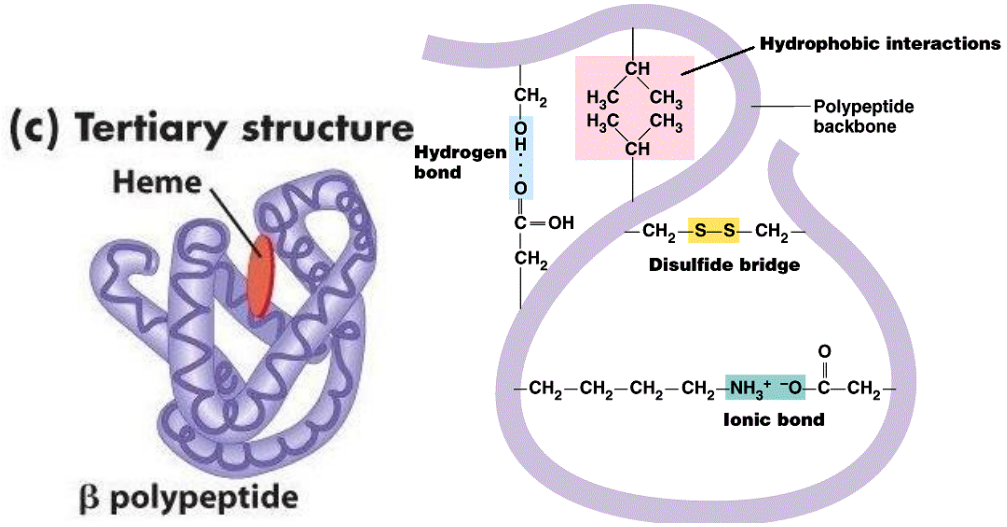
- **Bonds responsible for tertiary structure are:**

a) Hydrogen bonds: within the chain or between chains

b) Hydrophobic bonds: between the nonpolar side chains (R) of neutral amino acids.

c) Electrostatic bonds: (salt bonds): between oppositely charged groups in the side chains of amino acids e.g. amino group of lysine and carboxyl group of Aspartate.

d) Disulfide bonds: between residues within the chain.

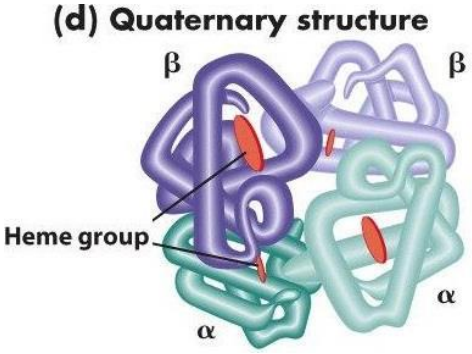


D. Quaternary structure

- Many proteins are composed of several polypeptide chains. Each poly peptide chain is called: subunits. Each subunit has its own primary, secondary and tertiary structure,
- **Bonds responsible for quaternary structure:**

a) Hydrogen bond.

b) Hydrophobic bond.



c) Electrostatic bond

- Examples of proteins having quaternary structure:

a) Insulin: 2 subunits.

b) Lactate dehydrogenase enzyme: 4 subunits.

c) Globin of hemoglobin: 4 subunits.

Denaturation

A. Definition: unfolding and loss of secondary tertiary and quaternary structure.

- Does not affect primary structure i.e. not accompanied by hydrolysis of peptide bond.
- Denaturation may be reversible (in rare cases)

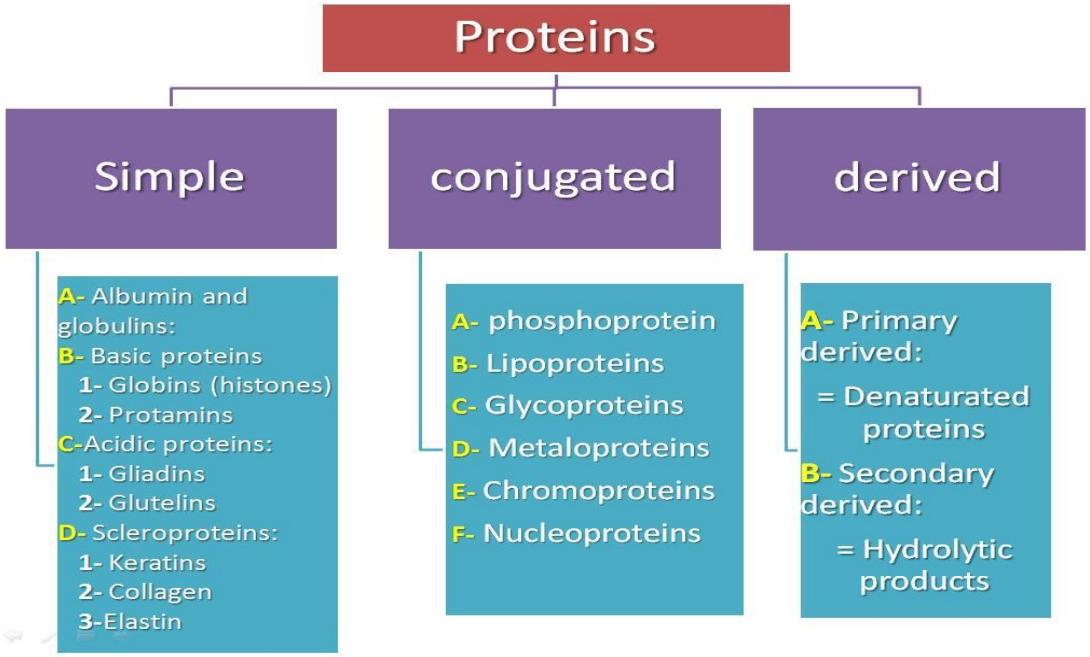
B. Effect of protein denaturation:

1. Loss of biological activity: e.g. insulin loses its activity after denaturation.
2. Denaturated protein is often insoluble.
3. Denaturated protein is easily precipitated.

C. Denaturating factors include:

1. Heat: causes coagulation and precipitation of certain proteins like albumin.
2. Organic solvents: They interfere with hydrophobic bonds of proteins.
3. Detergents: They contain both hydrophobic and hydrophilic groups i.e. amphipathic. They interfere with hydrophobic bonds of proteins.
4. Strong acids or bases: They lead to change in pH which affects the charges on polypeptide chains. As a result, hydrogen and electrostatic bonds will be disrupted.
5. Heavy metals: as lead and mercury salts:
   a) They form ionic bonds with negatively charged ions in polypeptide chains. This leads to disruption of electrostatic bonds.
   b) They unite with -SH (sulfhydryl) groups of proteins causing its denaturation (-S-Hg).
6. Enzymes: e.g. Digestive enzymes.
7. Urea, ammonium sulphate and sodium chloride: cause precipitation of proteins.
8. Repeated freezing and thawing: cause disruption of hydrogen and other bonds.

Classification of proteins



❖ *Simple proteins,*

A. Albumin and globulins:

	Albumin	globulins
Coagulated by heat	coagulable	same
Biological value	high	same
Solubility	Soluble in water	Soluble in salt solution
Molecular weight	68.000	150,000
Precipitation	By full saturated ammonium sulphate	By half saturated ammonium Sulphate
Sources: 1)Blood 2)Milk 3)Egg	Serum albumin Lactalbumin Egg albumin	Serum globulins Lactglobulin Egg globulin

B. basic proteins: Globins (=histones) and protamines: both are basic proteins i.e. rich in basic amino acids.

	Globins (=histones)	Protamins
Type of basic amino acid	Histidine	Lysine and Arginine
Solubility	In salt solution	1. In salt solution 2. In 70% ethanol
Sources: 1. Combined with DNA 2. Combined with Heme	1. In plants & animals 2. To form hemoglobin	In fish

C. Gliadins and Glutelins:

1. Both are acidic proteins i.e. rich in acidic amino acids: glutamic acid.
2. Both are present in cereals
3. Both are soluble in diluted acids and alkalies. Gliadins also soluble in 70% ethanol.

D. Scleroproteins:

They include: keratin, collagen, elastin and reticulin.

1. Keratins:

a) Location: They are found in hair, nail, enamel of teeth, and outer layer of skin.

b) Structure: They are α-helical polypeptide chains. They are rich in cysteine (which provides disulfide bonds between adjacent polypeptide chains).

c) Solubility: It is insoluble due to their high content of hydrophobic a.a

2. Collagen

a) Types of collagens:

- There are more than 12 types of collagen. Type I is the most common in human body (90%) of cell collagens.
- Collagens form about 30% of total body proteins.

b) Functions and Location:

- It is the protein of connective tissue present in skin, bones, tendons and blood vessels.
- Bones and teeth are made by adding mineral crystals to the collagen.

- Collagen may be present as a gel e.g. in extracellular matrix or in vitreous humour of the eye.

c) Structure:

1) Collagen molecules are simple protein; consist of 3 polypeptide chains called α-chains. They are twisted around each other forming triple helix molecule.

i- The 3 polypeptide chains are held together by hydrogen bonds

ii- each chains about 300 nm length and 1 .5 nm in diameter.

iii- Each chain is formed of 1050 amino acids.

2) Amino acids composition acid sequence:

i- Amino acids composition: Collagen contains 33% glycine (the smallest amino acid), 10% proline, 10% hydroxy proline and 1% hydroxylysine.

ii- Amino acids sequence: Every third amino acid in the α-chain is glycine. The repeating sequence is glycine-X-Y, where X is frequently proline and Y is often hydroxy-proline or hydroxylysine.

4) Glycosylation: Collagens are present in the form of glycoprotein. Glucose and galactose are commonly attached to collagen

5) Collagen molecule has very firm structure due to:

i- Each helical turn contains only 3 amino acids. For other proteins, each turn contains 3.6 amino acids.

ii- Glycine (the smallest amino acid) forms 33% of total molecule. This makes the polypeptide chains compact.

iii- The high content of hydroxyproline and hydroxylysine increase the number of hydrogen bonds.

d) Collagen synthesis:

1. Collagens are formed by connective tissue cells called fibroblasts.
2. Intracellular location: The polypeptide chains of preprocollagen are synthesized on the rough endoplasmic reticulum, where preprocollagen is cleaved → Procollagen + Signal (pre) sequence.
3. Proline and lysine residues are hydroxylated by a reaction that requires O_2 and vitamin C
4. Glycosylation by glucose and galactose that added to hydroxylysine residues.
5. The Procollagen (in the form of triple helix) is secreted from the cell and cleaved → Collagen
6. Cross links are produced.

e) Solubility and denaturation:

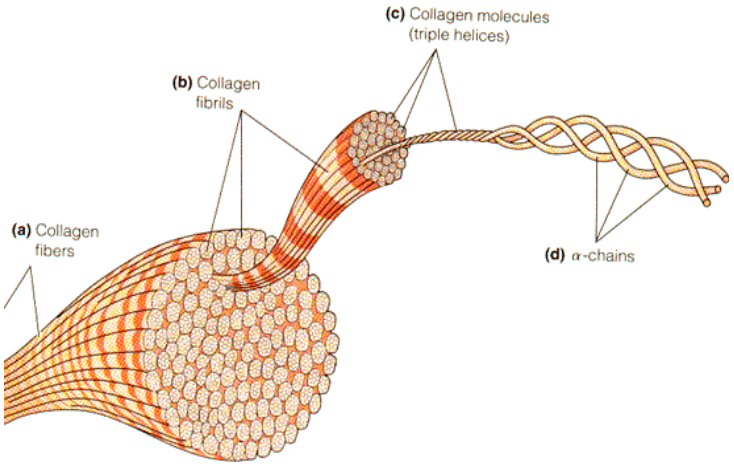
1) Solubility: Collagen is insoluble in all solvents. It is protein of low biological value and not digestible.

2) Denaturation:

- When collagen is heated, it loses all of its structure. The triple helix unwinds and the chains are separated. Then when this Denaturated mass cools down, it soaks up all of the surrounding water like sponge, forming Gelatin.

- Gelatin is soluble in water and digestible.

- Gelatin is given for patients during convalescence (in the form of jelly).



f) Collagen diseases: (Scurvy):

i- It is due to a deficiency in ascorbic acid (vitamin C). See vitamins.

3. Elastin:

a) Characters:

- It is connective tissue protein. It is rubber like i.e. it can be stretched to several times as their normal length, but recoil to their original shape when the stretching force is relaxed

b) Location:

It is present in lungs, the walls of large blood vessels and elastic ligaments.

C) Structure:

1) Elastin is formed of 4 polypeptide chain.

2) Elastin is similar to collagen, being rich in glycine (1/3 of its a.a) and proline. It is poor in hydroxyproline hydroxylysine.

3) The 4 polypeptide chains are interconnected through their lysine residues. the 4 lysine residues are linked together form a cyclic structure termed: desmosine.

Elastin is capable of undergoing 2 way stretch, due to its content of desmosine.

➢ Role of α1-antitrypsin (α1-AT) in : elastin degradation:

1) α1-antitrypsin is an enzyme produced mainly by liver. It is also produced by blood cells monocytes and macrophages.

2) It is present in blood and other body fluids.

3) It inhibits a number of enzymes and destroys proteins.

4) Role of α1-AT in the lungs: In the normal lung, the alveoli are exposed to low levels elastase enzyme released from neutrophils. Their proteolytic activity can destroy the elastin in alveolar walls: This elastase enzyme activity is inhibited by α1-antitrypsin.

5) Deficiency of α1-AT: Leads to destruction of connective tissue of alveolar walls by neutrophils elastase. This leads to lung disease called: emphysema.

	Collagen	Elastin
Number of chains	3	4
Amino acids	1/3 glycine , rich in proline , more hydroxyproline	1/3 glycine, rich in proline less hydroxyproline and , free from hydroxylysine
Structure	Fibrous	*Fibrous in extended form *Globular in relaxed form
Direction of stretch	One direction	2 Directions due to Presence of desmosine

❖ ***Conjugated proteins:*** On hydrolysis, they give protein (prosthetic group).They include: part (Apoproteins) and non-protein part

A. Phosphoprotein:

1. These are proteins conjugated with phosphate group.
2. Phosphate is attached to -OH group of serine (phospho-serine) or threonine (phospho-threonine) present in protein part.

3. Examples:

1) Casein: A milk proteins **2) Vitellin:** Present in egg yolk.

3) Phosphoenzyme: Phosphorylation (addition of phosphate to an enzyme) may activate or inactivate enzyme according to its type.

B. lipoproteins

C. Glycoproteins and proteoglycans

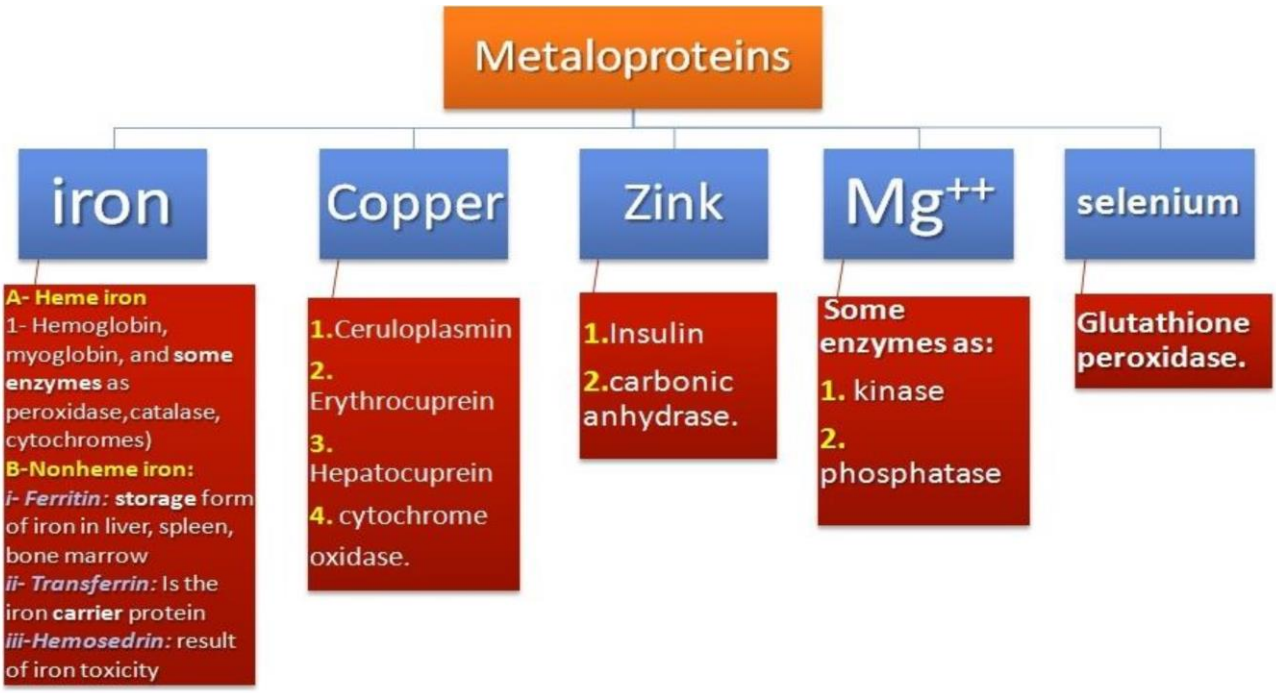
D. Nucleoproteins

E. Chromoproteins:

1. They are proteins conjugated with colored elements.

Metalochromoproteins (contain colored metal)	Non-metalochromoproteins (contain colored pigment)
1- All iron containing proteins (red) 2-All copper containing proteins (greenish blue).	1- Flavoproteins (yellow) contain Flavin pigment e.g. FAD. 2- Carotenoids: they give vitamin A. 3- Metaloproteins: (brown to black) e.g. melanin pigments of hair and iris.

F. Metaloproteins: These are proteins conjugated with metals



G. Hemoproteins

- Definition: Hemoproteins are conjugated protein formed of protein part (globin) and nonprotein prosthetic part (Heme).

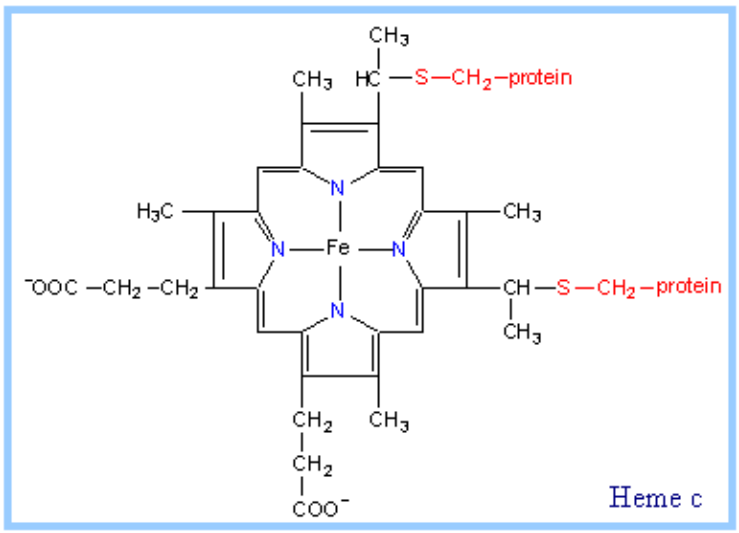
1. Hems containing iron (red in color). Thus hemoproteins are considered Metaloproteins.
2. Hemoproteins include many biologically active compounds as:

a) Hemoglobin: This carries oxygen.

b) Myoglobin: This stores oxygen in muscles.
c) Respiratory enzymes: These use oxygen.

- Structure of Heme:

1. Four Payrol rings are united together to form protoporphyrin III.
2. Iron in ferrous state (Fe^{++}) is incorporated in protoporphyrin III to form heme.



Hemoglobin:

1. It is a Metaloproteins formed of heme and globin.

- Globin is a globular protein rich in histidine amino acids. It forms about of 95% of haemoglobin molecule.
- Globin is a protein having a quaternary structure. It is formed of 2 α chain (each 141 amino acids) and 2 β chains (each 146 amino acids).

➢ Functions of hemoglobin:

1. Carries O2 to tissues and removes CO2 from them to the lungs.
2. Acts as blood buffer.
3. Synthesis of heme.

Myoglobin

1. It is found only in the cytosol of red skeletal muscle and cardiac muscle. It gives these tissues their characteristic red color.
2. It is formed of one heme molecule attached to one polypeptide Globin.
3. Myoglobin has much higher affinity for oxygen than hemoglobin. It is unable to release it except under very low oxygen tension.
4. Myoglobin concentration is increased in blood in myocardial infarction.

- Clinical aspects:

1. Myoglobinuria

a) It is the release of myoglobin from muscles after massive crush injury.
b) Myoglobin is excreted in urine, colors it dark. It may cause renal tubular Obstruction and renal failure.

2. Plasma myoglobin is increased following myocardial infarction, but measurement of serum myocardial enzymes provides a more sensitive index of myocardial infarction.

3. Sickle cell anemia:

a) The blood cells of these patients contain abnormal hemoglobin called hemoglobin S (HbS).

b) A molecule of HbS contains 2 normal α-chains and 2 mutants - chains in which glutamate at position six has been replaced by valine.

4. Thalassemias: Are anemias characterized by reduced synthesis of either alpha chain (α-Thalassemias) or beta chain (β-Thalassemias) of hemoglobin.