Structure-function Relationship

The functions of proteins are maintained because of their ability to recognize and interact with a variety of molecules. The three-dimensional structural conformation provides and maintains the functional characteristics. In the three-dimensional structure of proteins, the hydrophilic polar charged residues are seen on the outer surface and then non-polar hydrophobic residues inside, out of contact with water. The three-dimensional structure, in turn, is dependent on the primary structure. So, any difference in the primary structure may produce a protein which cannot serve its function. To illustrate the structure-function relationship, the following three proteins are considered; each belongs to a different class in the functional classification

Enzymes

The first step in enzymatic catalysis is the binding of them enzyme to the substrate. This, in turn, depends on them structural conformation of the active site of the enzyme, which is precisely oriented for substrate binding .

Transport Proteins

Hemoglobin, the transporter of oxygen is a tetrameric protein (alpha 2, beta 2), with each monomer having a heme unit. Binding of oxygen to one heme facilitates oxygen binding by other subunits. Binding of H^+ and CO_2 promotes release of O_2 from hemoglobin. This allosteric interaction is physiologically important, and is termed as Bohr effect. Even a single amino acid substitution alters the structure and thereby the function, e.g. in sickle cell anemia (HbS), the 6th amino acid in the beta chain is altered, leading to profound clinical manifestations.

Structural Proteins

Collagen is the most abundant protein in mammals and is the main fibrous component of skin, bone, tendon, cartilage and teeth. Collagen forms a superhelical cable where the 3 polypeptide chains are wound around itself. In collagen, every 3rd residue is a glycine. The only amino acid that can fit into the triple stranded helix is glycine. Replacement of the central glycine by mutations can lead to brittle bone disease. The triple helix of collagen is stabilized by the steric repulsion of the rings of hydroxyproline and also by the hydrogen bonds between them. In vitamin C deficiency, failure of hydroxylation of proline leads to reduced hydrogen bonding and consequent weakness of collagen. The quarter staggered triple helical structure of collagen is responsible for its tensile strength.

PHYSICAL PROPERTIES OF PROTEINS

1. Protein solutions exhibit colloidal properties and therefore scatter light and exert **osmotic pressure**. Osmotic pressure of plasma proteins is clinically important

2. **Molecular weights** of some of the proteins are: Insulin (5,700); Hemoglobin (68,000); Albumin (69,000); Immunoglobulins (1,50,000).

3. **Shape** of the proteins also vary. Thus, Insulin is globular, Albumin is oval in shape, while Fibrinogen molecule is elongated. Bigger and elongated molecules will increase the viscosity of the solution.

4. **Isoelectric pH** of amino acids has been described previously. Since proteins are made of amino acids, the pI of all the constituent amino acids will influence the pI of the protein.

CLASSIFICATION OF PROTEINS

Classification Based on Functions

1. Catalytic proteins, e.g. enzymes
2. Structural proteins, e.g. collagen, elastin
3. Contractile proteins, e.g. myosin, actin.
4. Transport proteins, e.g. hemoglobin, myoglobin, albumin, transferrin
5. Regulatory proteins or hormones, e.g. ACTH, insulin, growth hormone
6. Genetic proteins, e.g. histones
7. Protective proteins, e.g. immunoglobulins, interferons, clotting factors.

Classification based on Composition and Solubility

According to this classification, proteins are divided into three main groups as simple, conjugated and derived proteins.

I- Simple proteins:

On hydrolysis gives only amino acids, Examples:

1- Albumin and globulins: present in egg, milk and blood. They are proteins of high biological value i.e. contain all essential amino acids and easily digested.

Albumin is a protein made by the liver. It makes up about 60% of the total protein in the blood and plays many roles. Albumin keeps fluid from leaking out of blood vesselsand transports hormones, vitamins, drugs, and substances like calcium throughout the body. Levels of albumin may decrease, to a greater or lesser degree, when conditions interfere with its production by the liver, increase protein breakdown, increase protein loss via the kidneys, and/or expand plasma volume (diluting the blood).

Two important causes of low blood albumin include:

- Severe liver disease—since albumin is produced by the liver, its level can decrease with loss of liver function; however, this typically occurs only when the liver has been severely affected.
- Kidney disease—one of the many functions of the kidneys is to conserve plasma proteins such as albumin so that they are not released along with waste products when urine is produced. Albumin is present in high concentrations in the blood, and when the kidneys are functioning properly, virtually no albumin is lost in the urine. However, if a person's kidneys become damaged or diseased, they begin to lose their ability to conserve albumin and other proteins.This is frequently seen in chronic diseases, such as diabetes and hypertension. In nephrotic syndrome, very high amounts of albumin are lost through the kidneys.

Types of globulins:

α1 globulin: e.g. antitrypsin

α2 globulin: e.g. hepatoglobin: protein that binds hemoglobin to prevent its excretion by the kidney

β-globulin: e.g. transferrin: protein that transport iron

γ-globulins = **Immunoglobulins** (antibodies) : responsible for immunity.

2- Globins (Histones): They are basic proteins rich in histidine amino acid.

They are present in:

a - combined with DNA

b - combined with heme to form hemoglobin of RBCs.

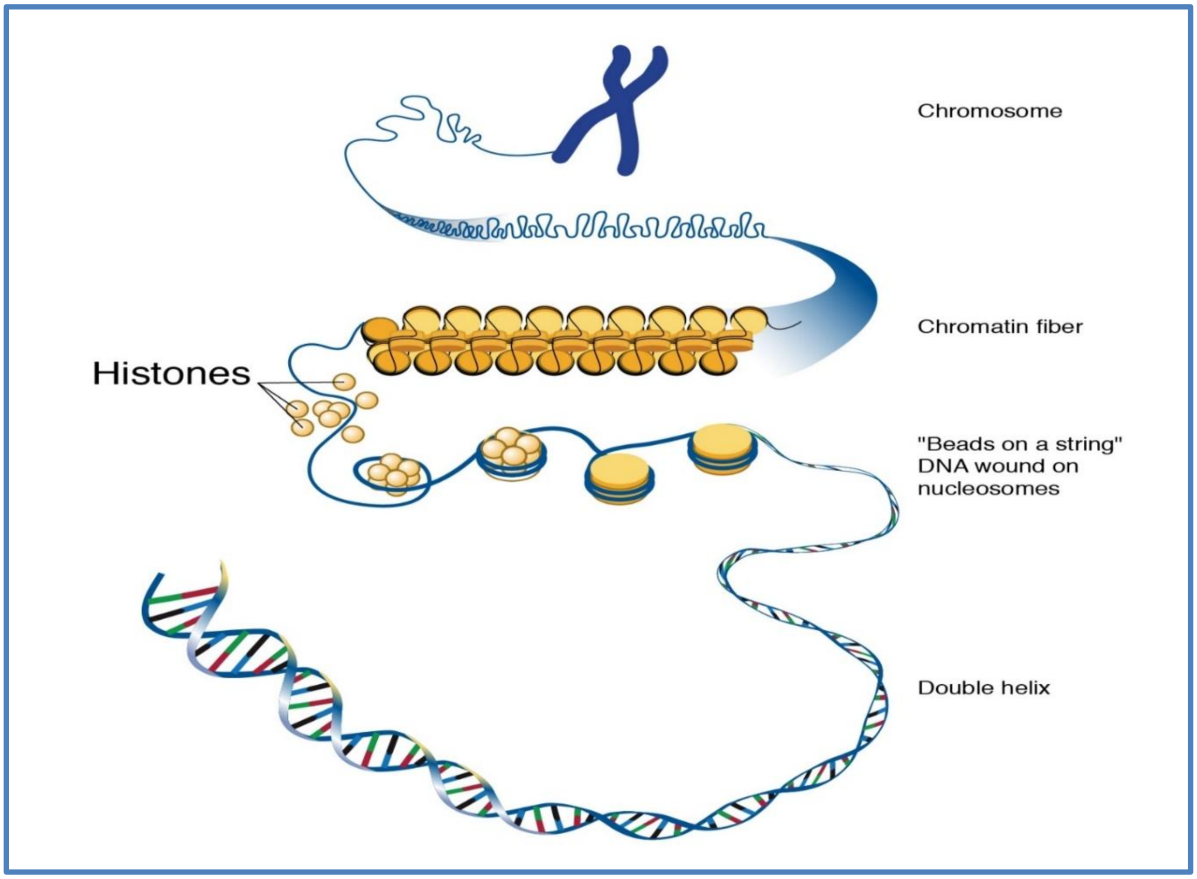

Figure: Histone

3- Gliadines They are **plant proteins** e.g., glutenin of wheat

4- Scleroproteins: They are structural proteins, not digested. include: keratin, collagen and elastin.

a- α-keratin: protein found in hair, nails, enamel of teeth and outer layer of skin. It is rich in cysteine and hydrophobic (non-polar) amino acids so it is water insoluble.

b- collagens: protein of connective tissues found in bone, teeth, cartilage, tendons, skin and blood vessels. Collagen may be present as gel e.g. in extracellular .matrix or in vitreous humor of the eye. Collagens are the most important protein in mammals. They form about 30% of total body proteins. There are more than 20 types of collagens, the most common type is **collagen I** which constitutes about 90% of cell collagens.

C- Elastin: present in walls of large blood vessels (such as aorta). It is very important in lungs, elastic ligaments, skin, cartilage, .It is elastic fiber that can be stretched to several times as its normal length.

Conjugated proteins

They are combinations of protein with a non-protein part, called **prosthetic group**
Conjugated proteins may be classified as follows

1-Glycoproteins: These are proteins combined with carbohydrates. Hydroxyl groups of serine or threonine and amide groups of asparagine and glutamine form linkages with carbohydrate residues. **Blood group antigens** and many serum proteins are glycoproteins. When the carbohydrate content is more than 10% of the molecule, the viscosity is correspondingly increased; they are sometimes known as **mucoproteins** or proteoglycans.

2- **Lipoproteins:** These are proteins loosely combined with lipid components. They occur in blood and on cell membranes.

3- **Nucleoproteins:** These are proteins attached to nucleic acids, e.g. Histones. The DNA carries negative charges, which combines with positively charged proteins.

4- **Chromoproteins:** These are proteins with coloured prosthetic groups. Hemoglobin (Heme, red); Flavoproteins (Riboflavin, yellow), Visual purple (Vitamin A, purple) are some examples of chromoproteins.

5- **Phosphoproteins:** These contain phosphorus. **Casein** of milk and **vitellin** of egg yolk are examples. The phosphoric acid is esterified to the hydroxyl groups of serine and threonine residues of proteins.

6- **Metalloproteins:** They contain metal ions. Examples are Hemoglobin (Iron), Cytochrome (Iron), Tyrosinase (Copper) and Carbonic anhydrase (Zinc).

Classification Depending on the Shape

1- Fibrous

1) polypeptides arranged in long strands or sheets
2) water insoluble (lots of hydrophobic AA's)
3) strong but flexible
4) Structural (keratin, collagen)

2- Globular

1) polypeptide chains folded into spherical or globular form
2) water soluble
3) contain several types of secondary structure
4) diverse functions (enzymes, regulatory proteins)

Classification Based on Nutritional Value

Nutritionally Rich Proteins

They are also called as **complete proteins or first class proteins**. They contain all the essential amino acids in the required proportion. On supplying these proteins in the diet, children will grow satisfactorily. A good example is **casein** of milk.

Incomplete Proteins

They **lack one essential amino acid.** They cannot promote body growth in children; but may be able to sustain the body weight in adults. Proteins from **pulses are deficient in methionine**, while proteins of **cereals lack in lysine**. If both of them are combined in the diet, adequate growth may be obtained.

Poor Proteins

They **lack in many essential amino acids** and a diet based on these proteins will not even sustain the original body weight. Zein from corn lacks tryptophan and lysine.

Diseases caused by changes in protein structure

- Sickle Cell Anemia – single amino acid change in hemoglobin related to disease.
- Osteoarthritis – single amino acid change in collagen protein causes joint damage
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