Sheet ○ Slides

Subject :	Structure-function relationship 1
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Number :	4

You have taken some lectures in regard to amino acids, their structures, how they look like, their properties, and what modifications can occur on amino acids.

So give some examples about modified amino acids

1) Thyroxine : from tyrosine
2) Histamine: by decarboxylation of histidine
3) Monosodium glutamate: which is a glutamic acid derivative
4) Hyroxylysine and hydroxyproline: from lysine and proline, respectively.
5) ɣ-aminobutyric acid (GABA): by decarboxylation of glutamic acid
6) Tyrosine: from Phenylalanine
7) Serotonin: by hydroxylation then decarboxylation of tryptophan
8) Catecholamines: first hydroxylation of phenylalanine occurs to get tyrosine then another hydroxylation of tyrosine to get L-dopa then decarboxylation of L-dopa occurs to get dopamine then hydroxylation of dopamine at Cβ to get norepinephrine and finally by methylation of norepinephrine we get epinephrine.

Where does tryptophan amino acid exist in a high concentration?
In milk, so that's why babies like milk and they get relaxed because tryptophan is converted into serotonin which gives them relaxation which helps them to sleep.
Our subject today and for the coming lectures is about structure-function relationship.

structure-function relationship

Structure is always related to function. And if you change a little bit in the structure, accordingly the function will change. In structure-function relationship we will see some proteins examples and how their structures are related to their function. As we know that

there are many functions of proteins and many classifications. And we also know that whenever we want to classify anything, we will look at differences, and depending on these differences we can classify. So as you know that many different proteins have many different functions in the body and depending on these differences we can classify proteins according to their function as follows:

1) Transporters: ex, A- hemoglobin, which transports oxygen in the blood. B- glycoproteins, which transport lipids which are hydrophobic and can't move in the blood freely since blood is hydrophilic.
2) Contractile proteins
3) Defense :such as antibodies
4) Cell-cell identity
5) Enzymes

And because proteins differ in their structure, we can classify them according to structure as follows:

1) Fibrous : in the form of elongated extended fibres
2) Globular: in the form of a globe.

   As you have learnt from previous lectures that proteins can be classified into simple proteins and conjugated proteins. Simple proteins perform their function by themselves but conjugated proteins have to bind something extra (nonproteinous) to get the protein functional. We can also classify proteins according to their charges (acidic, basic, neutral) or according to their solubility (water soluble, water insoluble) and many other classifications. We will study the classification according to structure of proteins and we will see how their structure is

related to their function and how this specific structure can perform its function.

Classification of proteins according to structure:

1) Fibrous: such as collagen, elastin, and keratin.
2) Globular: such as myoglobin, hemoglobin, and immunoglobulin.

Fibrous proteins are needed in the muscles since they are rigid and strong because they are twisted or packed on each other which means we are excluding water which makes them water insoluble molecules.

→ How can I make an insoluble, fibre-like, and strong structure?
Assume you have an empty box and you want to fill it and utilize the whole existing area and not leave any extra empty space.
You need to you to fill the space with structures which are <u>regular or identical in shape</u>. The same concept is applied for proteins where if I can use only one type of a secondary structure such as a-helices <u>solely</u> then that means that I am utilizing the whole space and finally I get strong, fibrous protein. If there were more than one type of secondary structures in the protein then that means that there will be more vacuity in this protein which will be occupied by water molecules making this structure soluble .Such types of proteins are called globular proteins.

Fibrous proteins

Collagen
Elastin
Keratin

1) Collagen

50 % of the body's dry weight is proteins and $\frac{1}{4}$ of them is Collagen. In some tissues, collagen may be dispersed as a gel that gives support to

the structure, as in the extracellular matrix. In other tissues, collagen is bundled in tight, parallel fibres that provide great strength, as in tendons .Collagen is the most abundant protein in vertebrates. About 25% of mammals' proteins are collagen. → 25 different types of collagen exist.

Structure of collagen:

Collagen is a fibrous protein polymer; its monomer is tropocollagen, three polypeptides (referred to as 'a-chains') twisted or wrapped around each other in a rope-like triple helix. But what makes them wrapped in such a way? Collagen is rich in proline and glycine, both of which are important in the formation of the triple-stranded helix. Proline facilitates the formation of the helical conformation of each a-chain because its ring-structure causes "kinks" in the peptide chain. [Note: The presence of proline dictates that the helical conformation of the a-chain cannot be an a-helix. Another difference between a-helix and a-chain which exists in collagen is that the a-helix is right-handed whereas a-chain is left handed]. Glycine, the smallest amino acid, is found in every third position of the polypeptide chain. It fits into the restricted spaces where the three chains of the helix come together.The glycine residues are part of a repeating sequence, –Gly–X–Y–, where X is frequently proline and Y is often hydroxyproline (but can be hydroxylysine). Thus, most of the a chain can be regarded as a polytripeptide whose sequence can be represented as (–Gly–Pro–Hyp–)333.

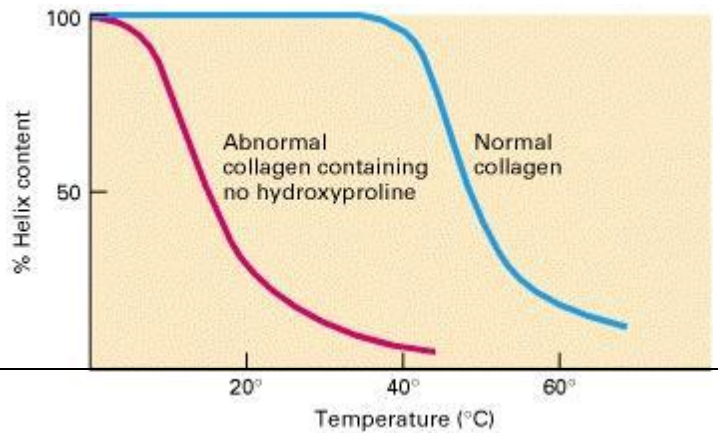
- The glycine content within collagen is 33% and the content of proline is around 13 %.

Collagen also contains hydroxyproline and hydroxylysine. These residuses result from the hydroxylation of proline and lysine residues after their incorporation into polypeptide chains. Hydroxyproline is important in stabilizing the triple-helical

structure of collagen because it maximizes interchain hydrogen bond formation. The hydroxyl group of the hydroxylysine residues of collagen may be enzymatically glycosylated (bonding with carbohydrates). Does glycosylation occur randomly or specifically?

As you know that glycoproteins are classified into O-glycoproteins and N- glycoproteins. O-glycoproteins bind to oxygen that is present in the side chain of serine, threonine, and sometimes hydroxylysine. N- glycoproteins bind to nitrogens that are present in the side chain of asparagine amino acid. This means that it is not a random process. Because of the ability of collagen to bind carbohydrates it is called a glycosylated protein. The hydroxyl group of hydroxylysine also contributes in the hydrogen bonding making the molecule stronger. Lysine and hydroxylysine can be oxidized. Oxidization of lysine and hydroxylysine makes aldehyde in the side chain and the structure becomes aldehydes called allysine and hydroxyallysine. This oxidization is done by an enzyme called lysyl oxidase. The reactive aldehydes that result (allysine and hydroxyallysine) can condense with lysyl or hydroxylysyl residues in neighbouring collagen molecules to form covalent cross-links and, thus, mature collagen. So how do tropocollagen molecules bind to each other to make up a microfibril? Covalent interactions which are known as cross-links. This bond is perpendicular to the long axis. Cross-links occur between lysine from one tropocollagen monomer and oxidized lysine from another.

So what is the importance of hydroxyproline? It maximizes <u>hydrogen bonding</u>



which maintains the helical formation. If hydroxyproline were absent, the helical shape could be broken easily especially with heat which makes hydrogen bonding longer and finally breaks it which disrupts the helical formation. If we compare collagen that contains hydroxyproline with collagen that doesn't, we find that in the collagen that contains hydroxyproline, at temperature of 40°, the helical formation is retained 100% because of the presence of hydrogen bonding. Helical formation of that which doesn't contain hydroxyproline (as a result of the absence of the enzyme that adds hydroxyl group to proteins such as in the Genetic mutation or whatever) gets disrupted at lower temperature, at about 37° there is almost no helical formation.

How can I add hydroxyl group to the proline? How can I add hydroxyl group to lysine? How does oxidization of lysine happen?
The enzyme that adds hydroxyl group to proline is called prolyl hydroxylase and the enzyme that adds hydroxyl group to lysine is called lysyl hydroxylase and the enzyme which makes oxidization on lysine is called lysyl oxidase.
Any of these enzymes may get genetic mutation, and they need vitamin C to function well. And any deficiency in this vitamin will make problems

- **Diseases related to problems with collagen:**

- **Scurvy**: if there is shortage in vitamin c, those enzymes will not work properly, and there will be no hydroxylation. Symptoms include spontaneous bleeding in the gum, loosening of teeth, and bruises under the skin.
- **Osteogenises imperfecta:** is a genetic disease which affects collagen 1 formation. Collagen 1 is found in bones and the sclera of

the eye. Patients always complain of repeated fractures because they have a problem in collagen 1. Because the defective Type I collagen is not forming correctly, sclerae are usually given a bluish colour. This is due to the sclera being thinner than normal.