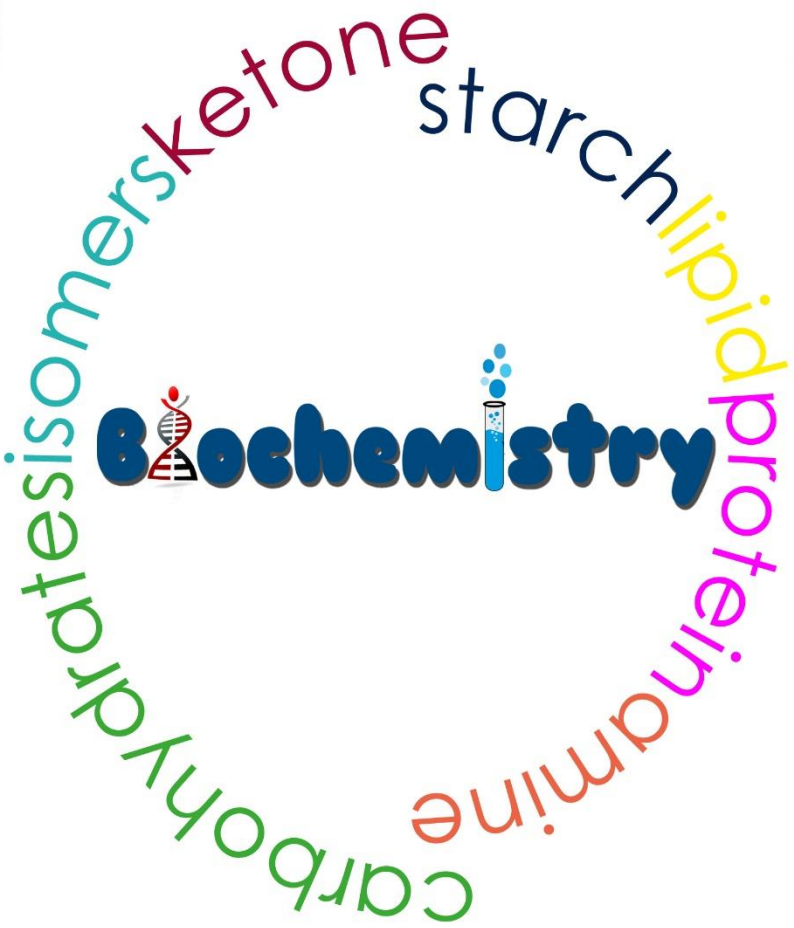

◉Sheet ○Slides

Subject :	Properties of proteins
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Number :	3

Properties of proteins:

1 -denaturation

*It is basically the unfolding of a protein shape….proteins three-dimensional structure is disrupted and the protein becomes a polypeptide with no a specific structure , function , and properties of protien .

* It involves breaking of non-covalent interactions (not covalent interactions)that determine the protein structure , so we are breaking the hydrophobic, electrostatic and Van deer Waals interactions , and in tertiary structure by reduction of disulfide bonds .

* If we remove the denaturing factor , some proteins (not all of them) can refold to its original structure and then can become functional structure .

***Denaturing factors:**

A- Heat: heat increases the kinetic energy of electrons so electrons move quicker and that disrupts Van deer Waals interactions (that shows you how Van deer Waals interactions are important eventhough they are weak).

B- Extremes of ph: it changes the charge (deprotonation and protonation depending on the group) . If we decrease the ph , acidic amino acids will become protonated and their charge will become higher, and if we increase the ph, basic amino acids will become deprotonated and the positive charge will be gone. This disrupts the electrostatic and hydrogen bonds.

C- Detergents: they are hydrophobic...So the hydrophobic amino acids will get out of their hideout and the protein would be denatured as a result of that.

>>There are different types of detergents:

1- non-ionic detergents (triton X-100): they are totally hydrophobic .

2- Sodium dodecyl sulfate (SDS): anionic (negatively charged) and it has hydrophobic tail and hydrophilic head . what will happen is that their hydrophobic tail will react with hydrophobic amino acids so the protein would be denatured , coated and negatively charged (negative charges coming from the SDS)

D- Urea and guanidine hydrochloride disrupt hydrogen bonding and hydrophobic interactions.

***Note : We can get complete denaturation of the protein if we break disulfide bonds through using a reducing agent (reduce the thiol groups) . If we remove the reducing/denaturing factor, the protein can be renatured and refold into its native conformation . But this not necessarily true for all the proteins . It is necessarily true for smaller proteins .**

2-How can a protein have a certain structure?

>>The determining factor is the amino acid sequence (primary structure). It decides the most stable structure (most energetically favorable structure and least amount of energy that body has to consume to keep it stable)

>>It depends overall on the proper angel between the amino acids (the non-covalent interactions) , in particular the hydrophobic interactions .

>>Non-protein molecules can help as well

3-Refolding of a protein (Renaturation):

*Small proteins can refold by placing the S-S bonds in the right orientation (adjacent to each other prior to formation), then the correct S-S bonds are reformed. But larger proteins need help and help is provided by other proteins known as chaperones. These proteins bind to polypeptide chains and help them fold with the most energetically favorable folding pathway (accompany other proteins that need help in folding).

*Some of these proteins are so complex that the protein itself cannot fold properly, so the hydrophobic regions will cluster together .

*Chaperones take the protein inside them (they look like a barrel) and the chaperones give the correct place for each amino acid (it mainly works with hydrophobic interactions) . Once the protein is correctly folded , it's released .

*Not proper folding of the protein will end up with the exposure of the hydrophobic regions of the different protein which in turn will interact with each other forming an aggregate of polypeptides (proteins) . That will eventually become insoluble because they are large and these aggregates can be toxic to the cells .

***Diseases result of defects in protein folding (misfolding of protein):**

1) **Prion disease**:

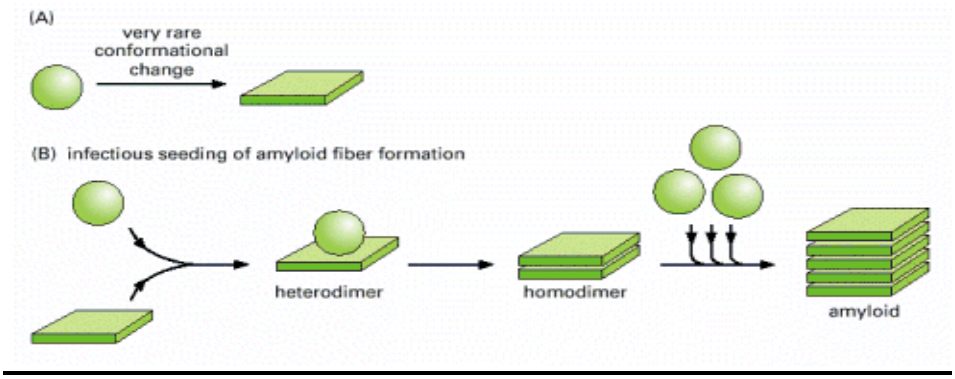
>>This disease made a revolution long time ago because it is a transmissible disease (can be transmitted from one living organism to the other) . By this disease , scientists noticed that proteins can be infectious.

>>The Prion disease has several names in living organisms . It is called Creutzfeldt-Jacob disease (in humans), and mad cow disease (in cows), and Scrapie (in sheep).

>>The Prion disease is common in Africa because they eat raw meat. Also Prion disease may affect the brain and Africans eat raw brains of animals.

*The disease is caused by a protein known as the Prion protein that is misfolded. The secondary structure of normal form of this protein is full of α-helix but the abnormal form has a lot of β strands.

*The abnormal form of prion protein will bind with another prion protein changing its structure from the normal conformation to the abnormal conformation and they will interact with other normal prion proteins forming an aggregate of abnormal prion proteins .The aggregate is known as Amyloid , which is toxic to the tissue and cells .



>>The disease is caused by a transmissible agent (abnormal protein) that can be acquired by :-

1-Infection .

2-Inheritance : which means there is a mutation in the prion gene that causes the protein to have an abnormal structure .

3-Spontaneously : which means that it may randomly happen .

2) Alzheimer's Disease:

***Important to know** : It is really common in the west and will become very common in our community in 40-50 years, because the Western community is old meanwhile and our community is old.

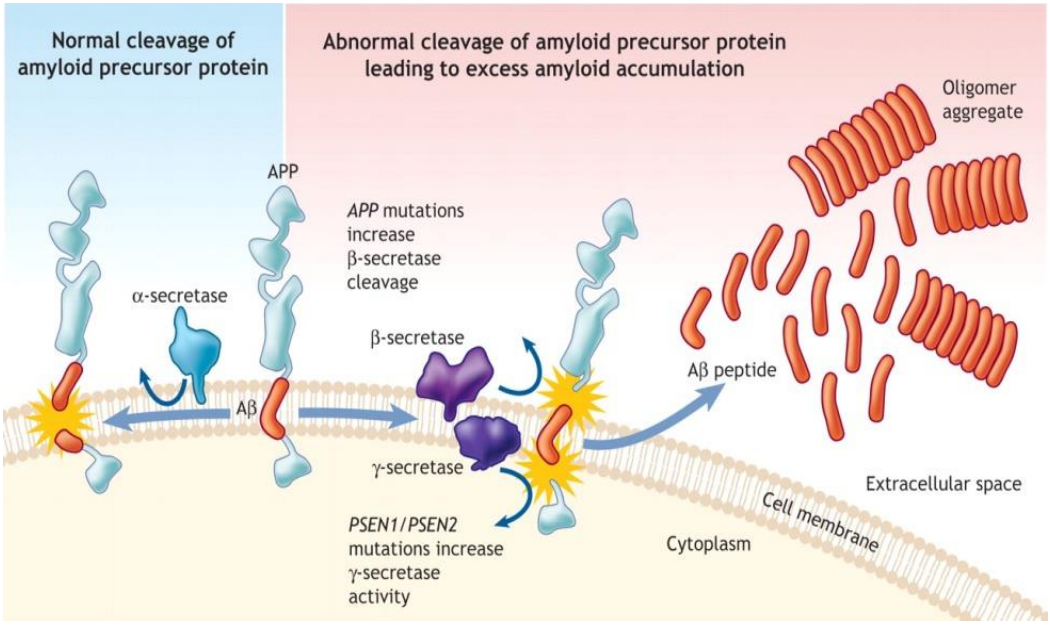
>>Not transmissible between individuals .

>>Characterized by the left-handed, triple-stranded, helical protein presence of plaques in the central nervous system. These plaques exist outside of the neurons and these plaques are mainly aggregates of proteins know as Tau and another known as Amyloid peptides (Aβ)

>>The Amyloid protein is an extracellular protein so it's present on the cell surface and exposed to the outside (it is connected to the cell surface by hydrophobic region). This protein is normally cleaved off by a process known as shedding (removing the outside cover –like snake -) , and when cells do shedding, they remove the proteins exposed on the cell surface and renew them.

>>If the Amyloid protein is not cleaved properly (from the hydrophobic portion that is integrated in the plasma membrane), having a plenty of this hydrophobic peptide will tend to aggregate forming an Amyloid plaque, which can be toxic to cells and tissues.

*Formation of plaques:



*Quaternary structure:

>>It's basically the highest level of a protein structure.

>> When you have a protein that is made of multiple polypeptides, we call each polypeptide a subunit.

>>If a protein is made of one subunit we call it monomeric and this protein doesn't have a quaternary structure.

>>If a protein is made of two subunits we say it is a dimer, three subunits is a trimer..etc

>>If we have two subunits and they are identical , then we call it homodimer , with three identical subunits we call it homotrimer , and so on …

>>In general , if the subunits are identical the protein is a homooligomer and if they are different the protein is heterooligomer, e.g. insulin is heterodimer.

>>Connection between subunits depends on the protein itself, e.g. the subunits of antibodies are connected to each other via disulfide bond , so they are connected covalently.

>>The subunits of some proteins like hemoglobin (a heterotetramer) are connected to each other non-covalently using electrostatic interactions , but mainly hydrophobic interactions(having hydrophobic amino acids).

*Complex protein structures:

>>Some proteins have more complex structure meaning that they have a non protein component like metals, sugars and lipids …etc

>>If a protein contains a non-protein component, it is called a holoprotein , and if it doesn't contain a non-protein component (it is **removed**), it is called an apoprotein - e.g. an apolipprotein is a protein that is normally modified by lipid but it doesn't have the lipid component.

>>lipoprotein is a protein with some lipids .

>> Glycoprotein is a protein with some sugars, e.g. antibodies.

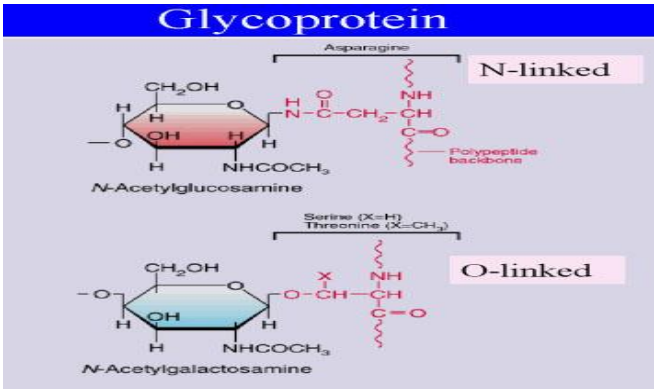
>>Proteoglycan is a sugar with some protein.

>> Other proteins are phosphorylated and these are known as phosphoproteins.

***Classes of glycoproteins:**

1) **N-linked** sugars : are sugars that are attached to the amide nitrogen of the R-group of asparagines.

2) **O-linked** sugars : are sugars that are attached to hydroxyl group of either serine or threonine and hydroxylysine (in collagen).



***Proteins can be classified to two types according to their structure:**

1) Globular proteins : look like a globe and these are diverse, e.g. myoglobin, hemoglobin and immunoglobulin.

2) Fibrous proteins : look like fibers and they mainly have a structural role they mainly function in supporting a structure, e.g. Elastins, Keratins, collagens .

*Note : There is an association between the structure and the function of the protein (they related to each other).

***The extracellular matrix:**

In our tissues we have cells that can be connected to each other. They are scattered in the extracellular environment and this extracellular environment is composed of what we call extracellular matrix (a network of proteins). These proteins connect cells with each other and connect cells with the matrix itself and our tissues, they support the tissues and they have another functions as well.

***Collagen:**

>>Collagen is not a single protein , rather it is a family of proteins (we have 28 different collagen)

>>Collagens are the most abundant proteins in mammals 25% of all proteins in our system is collagen (25% of our mass is collagen)

>>Collagen is found everywhere it is found in bones, skin, muscles, blood muscles.

>>Collagen molecules are named as type I collagen, type II collagen, type III collagen, and so on.

>>Their main function is to provide structural support so collagen provides stiffness to the tissues; hence the molecule itself should be stiff .

>>The basic unit of collagen is tropocollagen

>>Tropocollagen is a left-handed, helical protein **(not α-helix)**, triple-stranded (three chains each one is known as the α-chain that have helical conformation wound around one another in a ropelike superhelix)

>>There are different alpha genes you can have alpha I, alpha II, alpha III, alpha IV

>>Different combination of alpha chains gives different types of collagens; therefore we have 28 type of collagen.

>>More extended having 3.3 amino acid residues per turn (3.6 in α-helix)

>>The amino acid composition is **mainly** Glycine (33%) and (13%) Proline we also have hydroxyproline (9%) and some hydroxylysine each one of them has a certain function.

>>Every third amino acid is **glycine** with the preceding amino acid being **proline** or **hydroxyproline.**

***Proline** creates the kinks and stabilizes the helical conformation in each a chain and provides rigidity stiffness to the protein (give the chemical conformation of the protein).

***Glycine** is the smallest amino acid and doesn't have a charge , so the chains will be closer to each other, and so it packs the three chains forming a rigid molecule.

***Hydroxylysine** serves as attachment sites of sugars to collagen, so collagen is a *glycoprotein.*

***lysine** in primary structure of collagen gets oxidized so the amino group converts to an aldehyde, and when we have oxidized lysine with another oxidized lysine , they will form a cross link , and so again the chains are rugged . Also not oxidized lysine can form cross links with oxidized lysine.

*Cross-linking occurs not only within the tropocollagen but also between different tropcollagen giving larger structure that is stable.

***Why do we eat younger animals?**

Mainly because the cross linking is less than in an older animal so in an older animal the meat is not chewed easily (cross linking increases with age).

*If cross linking is inhibited , then the strength of the collagen fiber is reduced and as a result that will cause certain types of injuries, e.g. bones will break and blood vessels tend to tear.

***Tropocollagen** connect with each other(5 of tropocollagene) polymerize and forming microfibrils , and microfibrils connect with each other forming collagen fibrils which connect and strengthen by the formation of covalent cross-links with each other between lysine residues, forming collagen fibers(which can be easily seen under the microscope when we are looking at muscles).

***Hydroxyproline** provides further interaction by hydrogen bonds because of the presence of the hydroxyl group in the R group of proline…The evidence behind it is that if we have normal collagen , it is hardly denatured with heat . But if we have defective collagen with no hydroxyproline , it is easily denatured with heat.

*Scurvy:

A disease that is associated with defective hydroxyproline . It is common among sailors because they have deficiency vitamin C , which is important for the enzyme that hydroxylates proline. If vitamin C is not there , the enzyme is not there and proline is not hydroxylated . As a result , the interaction between α chains would be reduced , and furthermore , these individuals would have fragile blood vessels and their teeth would fall off from their gum(loose in their sockets).