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Subject :	THE STRUCTURE OF PROTEINS
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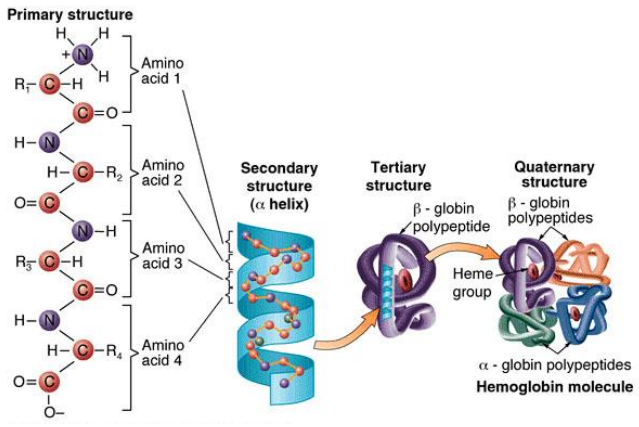
Number :	2

THE STRUCTURE OF PROTEINS

Proteins are polymers of amino acids linked by peptide bonds.
There are many different conformations for each molecule but only one or few are **native conformations** (the three-dimensional structure that is properly folded, functional and stable)

There are 4 Levels of protein structure
A-Primary structure: the linear sequence of amino acid residues in which N-terminal amino acid is listed first ,linked by covalent peptide bond
B-Secondary structure: the localized organization of **parts** of a polypeptide chain due to H-bonds.
C-Tertiary structure: the three-dimensional structure includes the arrangement of all the amino acids backbone+ side chains of a polypeptide chain in addition to other prosthetic groups (extra groups may be added to the protein which are nonaminoacids group such as metal ions, heme group,carbohydrates,lipids)
*some proteins are made of multiple polypeptides cross-linked (connected) with each other. These are known as multimeric proteins. **D-Quaternary structure** describes the number and relative positions of the subunits in a multimeric protein.

Note that if the protein structure unfolds it will go back to its native structure because it's stable, but not all of them will do it.



1-The primary structure

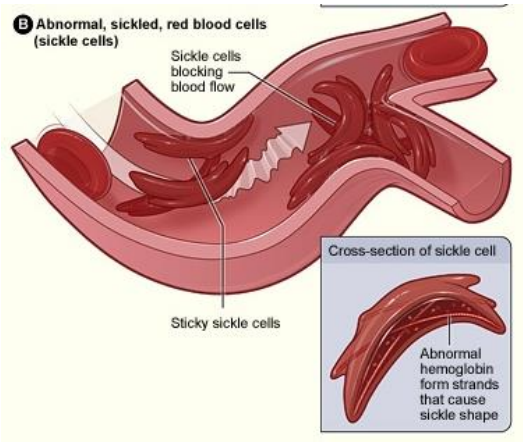
it's the order in which amino acids are covalently linked together and it determines the overall structure which determines the proteins properties
Example: Leu—Gly—Thr—Val—Arg—Asp—His

An example of the importance of primary structure is the **sickle-cell anemia** in this genetic disease, red blood cells cannot bind oxygen efficiently. The red blood cells also assume a characteristic sickle shape, giving the disease its name.

It is caused by a change of only one amino acid in the 6th position of β globin (Glu to Val).

The mutation results in: 1) arrays of aggregates of hemoglobin molecules, 2) deformation of the red blood cell, and 3) clotting in blood vessels and tissues.

Note that: The amino acid replacement changes the hemoglobin shape which changes the red blood cell shape



2-The secondary structure:

are localized and organized structures within a protein and it's the H-bonded arrangement of the backbone of the protein, the poly peptide chain. We have to say that the nature of the bonds in the peptide backbone plays an important role here .Within each amino acid residue are two bonds with **reasonably** free rotation: (1) the bond between the alpha carbon and the amino nitrogen of that residue (known as phiφ) and (2) the bond between the alpha carbon and the carboxyl carbon of that residue (known as psiψ) ,then the conformation of a protein backbone can be described by specifying the values of the mentioned angles which can be repeated (the values) at regular intervals along the amino acid chain.

-Remember: that the double bond of the carbonyl group has a resonance structure resulting in a planar amide (planar polypeptide group)

-so at every alpha carbon two planers rotate freely around it at the opposite corner of each.

note: **only the backbone is considered in the secondary and the primary

structures

Common secondary structures

There are common secondary structures that are present in proteins **but not all proteins have all of these secondary structures**, it depends on the primary sequence which determines the secondary and tertiary and quaternary structure.

Secondary structures are:

1-Alpha helix

2- Beta-pleated sheet

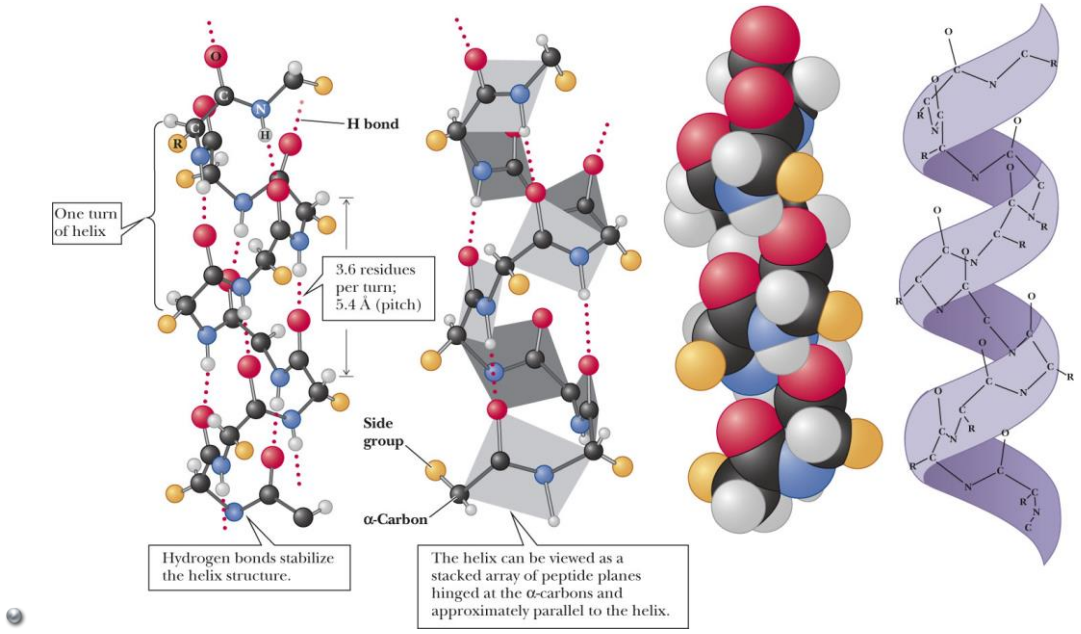
3-Turns

4-Loops

1-alpha helix: there are many of helices; the most common one is alpha helix. Each full turn of alpha helix has an average of 3.6 amino acids in it, and The pitch of the helix *(the linear distance between corresponding points on successive turns or it's the distance between amino acid and the one right below/above it*) is 5.4 Å…1 Å = 10^{-10} m

-the H-bonds are parallel to the helix axis

This compontment is very stable and its what characterises secondary structures that they are stablized by H-bonds and these bonds exisits between groups that make the peptide bond (backbone not the R group)



There are amino acids NOT found in a-helix like

- 1-**glycine** because it's **too small** amino acid, with only one H in R group. Due to this, it is capable of taking a lot of shapes so it can destabilize the alpha helix by breaking the helical pattern.

2-Proline is another example because it's too rigid (cannot turn) and there is no rotation around phi bond so it makes a bend on the helix .In addition to that it's not H-bond donor (the alpha amino group cannot form H-bond).

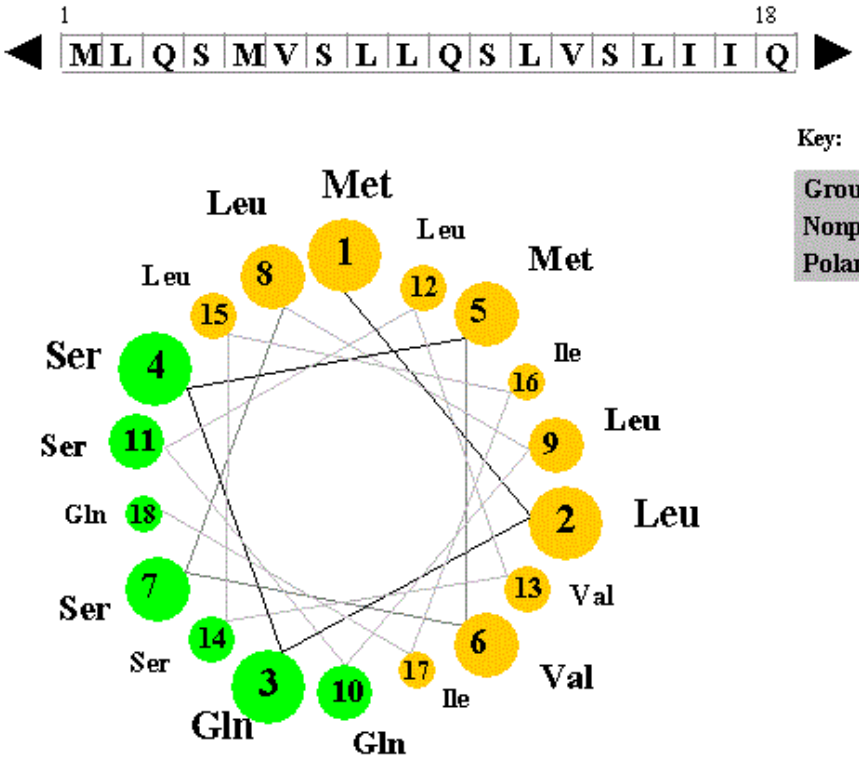
3-Also we have **Amino acids with branches at the β-carbon atom (valine, threonine, and isoleucine)** (have large side chains).

4-Close proximity of a pair of charged amino acids with similar charges causing electrostatic repulsion destabilize the alpha helix.
Eq. lys and Arg, Glu and Asn.

5- Amino acids with bulky side chains (steric hindrance)

There is always an exception, like proline which usually exists at the END of the alpha helix…Why? Because the alpha helix has smooth turn and proline breaks this smoothnesstobreak the alpha helix to start another structure.

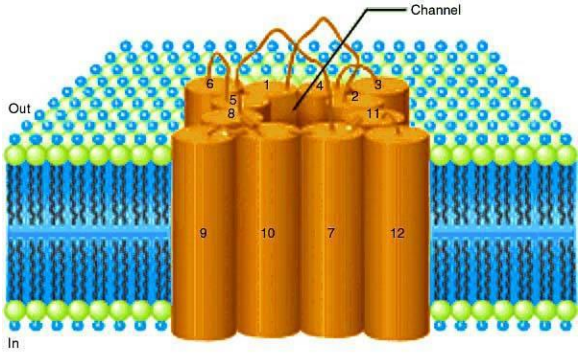
**Amphipathic alpha helices:



Is an alpha helix that has hydrophobic amino acids and on The other side a hydrophilic (polar) amino acids , play a crucial role in mediating the interaction of peptides and proteins with membranes

… but who this work?

For each alpha helix in an ion channel > the side chains whether polar or non-polar are pointed to the outward of the helix so If we looked at the ion channel from the top we will see that the R groups of the hydrophilic amino acids are pointing inward the channel (towards the core) in which the charged ions will move freely . On the other side of each helix (the non-polar pointing side chains) is the hydrophobic region (the phospholipid bilayer) which will facilitate the hydrophobic interactions and stabilization.



2-β pleated sheet

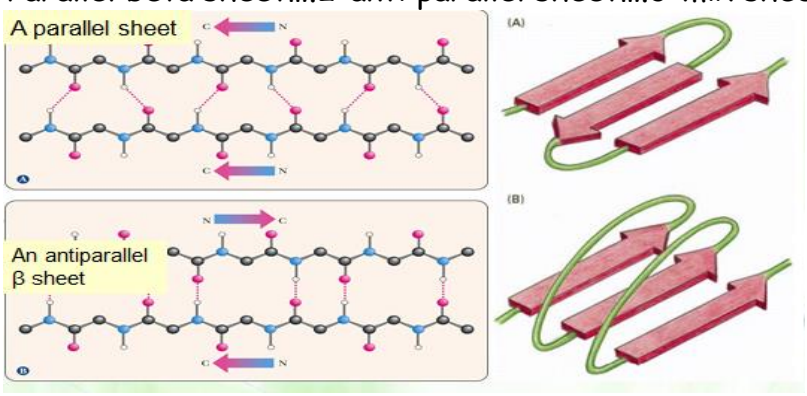
In beta sheets the peptide backbone is almost completely extended,

Made up of multiple beta **strands** (beta strand has a zigzag structure due to the H-bond with R groups extending outwards),on top of each other.

Note that the hydrogen bonds are perpendicular to the direction of the protein chain, not parallel to it as in the a-helix.

There are 3 types of beta sheets depending on the direction and orientation of beta strands.

1-Parallel beta sheet….2-anti parallel sheet….3-mix sheet



Parallel beta sheet: same direction beta strands … Each amino acid can form two hydrogen bonds with two different amino acids that are separated by another amino acid.

Anti-parallel: opposite direction beta strands … each amino acid can form two hydrogen bonds with the ONLY ONE other amino acid (more stable).
**Mix have both of them

*β sheets can form between many strands, typically 4 or 5 but as many as 10 or more such β sheets can be purely antiparallel, purely parallel, or mixed.

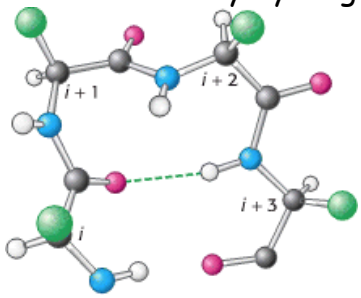
*amino acids can disrupt beta strands particularly proline.

*Valine, threonine and Isoleucine tend to be present in β-sheets (the opposite of alpha helices) because these bulky side chains can be oriented above or below the sheet so it will reduce the steric hindrance.

Irregularities in regular structures are not required to know.

3-Turns (β turn or hairpin bend)
U-shaped
*It exist to connect different secondary structures
proline and glycine are common in turns.
* Composed of only four amino acids → two of them are proline and glycine → proline creates a kink and glycine fits in a small position in the turn and this amino acid doesn't make steric hindrance.

* Turns are stabilized by hydrogen bonding between amino acid no.1 and no.4 the rest are not involved in any hydrogen bonding.



Loops also a secondary structure component which are longer than turns and much more irregular .(contribute to the function)

****super secondary structure: it's the combination of more than one of secondary structures coming together**

1- Motifs: repetitive secondary structure (alpha helix then a turn and so one), a small portion of a protein (20aminacids), they may not tell us about a certain function but they may tell us about a certain structure for a protein. They have to be repetitive, not separated by any other structure.

Types of motifs:

A-Helix-loop-helix is found in many proteins that bind DNA. It is characterized by two a-helices connected by a loop.(N –shaped)

B-Helix-turn-helix is a structural motif capable of binding DNA. It is composed of two a helices joined by a short strand of amino acids. Another more complex motif is the (U-shaped) 3-**immunoglobulin fold**, such as antibodies and the folds are found in their antigen binding sites.

2- Domains

Tertiary structure

The overall conformation of a polypeptide chain/the three-dimensional arrangement of all the amino acids residues/the spatial arrangement of amino acid residues that are far apart in the sequence

Zooming into the tertiary structure you would find localized arrangement of specific structures (e.g. helical structure) which is part of the 3D structure of the protein (secondary structures).

Ways to look at tertiary structures: (slide 31)

-ball and stick (commonly used): balls represent the atoms and the sticks represent the bonds

-trace structure (less common)

-ribbon structure represent the alpha helices (ribbon) and the beta strands (Arrows)

-cylinder structures (less commonly used) represent the alpha helices (cylinder) and the beta Strands (arrows)

- Space filling structure (commonly used): atoms are represented by spheres of different colors whose radii are proportional to the radii of the atoms.

-protein surface map shows the external structure of the protein, it dosen't give any details about the internal of the protein.

What determines the tertiary structure of a protein?

Non-covalent interactions between the R-chains (H-bonds, hydrophobic interactions, Van Der Waals interactions and the electrostatic interactions)

***H-bonds**: between polar R-groups (remember that the secondary structure is stabilized by H-bonds within the backbone). They can occur between amino acids and the surrounding environment.

***Charged-charged interactions** (**electrostatic interactions** or **salt bridges**): e.g. between lysine (positively charged) and glutamic acid (negatively charged).

***Charged-dipole** interactions: between the charged group and surrounding environment (water)

***Van der Waals**: the weakest and the most dynamic interactions are due to the temporary clustering of electrons in one side →having so many of them in a protein form a very strong force in the protein.

***Hydrophobic interactions (the most important force)**: A system is more thermodynamically (energetically) stable when hydrophobic groups are clustered together rather than extended into the aqueous surroundings.

Notes: *Polar amino acids can be found in the interior of proteins (channel proteins)

*In this case, they form hydrogen bonds to other amino acids or to the polypeptide backbone

*They play important roles in the function of the protein

What stabilize the 3-d structure of protein?

(**1-Disulfide bonds……2-Mental ion)**these two factor only stabilize the structure, that means they don't determine the structure so if we break a sulfide bond the protein will not go to its native structure.

Disulfide bonds (the only covalent bonds contribute to the tert.structure)

*the side chain of cysteine contains a reactive sulfhydryl group (—SH), which can oxidize to form a disulfide bond (—S—S—)to a second cysteine.

*The crosslinking of two cysteines to form a new amino acid, called cystine.

Example of the way that disulfide bonds contribute to the structure of a protein is the insulin hermone structure which is composed of two polypeptide chains referred to A chain and B chain ,links them together the interchain disulfide bridges, And there is intrachain disulfide bridges only on the A chain connects two cystien residues

Metal ions

several proteins can be *complexed to a* single metal ion that can stabilize protein structure by forming:

1-Covalent interaction (myoglobin)
2-Salt bridges (carbonic anhydrase)

- **Note: simple protein : a protein that is only composed of amino acids without any prosthetic groups added to it.**
- **Conjugated protein: contains a prosthetic group (ex. hemoglobin)**

Domain

Domains are supersecondary structure (made of multiple secondary structures)
domain is a compactly folded region of polypeptide found in proteins with similar function and/or structure.

*Domains with similar conformations are associated with the particular function.

- **Ex.the kinase domain**

What are the main differences between domains and motifs?

1) Motifs can tell us about folding or structure of a protein, but not necessarily the function. On the other hand, domains can indicate a certain function for a certain protein.
2) Domains are larger than motifs. A domain may consist of 100-200 residues in

various combinations of α helices, β sheets, turns & random coils.

Note:
*They fold independently of the rest of the protein.

*Domains may also be defined in functional terms

1-Enzymatic activity

2-Binding ability (e.g., a DNA-binding domain)

THE END :D

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