2nd lecture

Protein structure

Color Index:

Important

Doctor slides

Additional notes

Objectives

- Understand the peptide bonding between amino acids.
- Explain the different levels of protein structure and the forces stabilizing these structures and what happens when the protein is denatured.
- Define the α-helix and β-sheet as the most commonly encountered secondary structures in a protein molecule.
- Correlate the protein structure with function with hemoglobin as an example.
- Understand how the misfolding of proteins may lead to diseases like Alzheimer’s or prion disease.

What are the proteins ?

They are a large complex of molecules

Play many critical roles in the body تلعب دور حساس في جسم الانسان

They do most of the work in the cell

They are made up of hundreds of or thousands of smaller unit, called amino acids, which are attached to one another in a long peptide bond

- They are required for the structure, function and regulation of the body's tissue and organs.

What are the proteins ?

There are mainly 20 different types of amino acids that can be combined to make a protein.

We choose 20 Amino acids because of what's found in the DNA.

The sequence of amino acids determines :
1- each protein's unique three-dimensional (3D) structure
2- its specific function.

The sequence of Amino Acid in the DNA strand determines the 3D structure of the protein

Proteins can be described according to their large range of functions in the body:

- Antibody
- Enzyme
- Messenger
- Structural component
- Transport/storage

1.Primary structure

- It is the linear sequence of amino acids in a protein
- Covalent bonds in the primary structure of protein:
  1.Peptide bond
  2.Disulfide bond (if any) (it is not always present)

  Which is the "SS bond" , It links two residues of cysteine **NEAR TO EACH OTHER** as shown in the picture.

  - The number of disulfide bonds depends on the number of cystiene amino acid.

  ملاحظة:

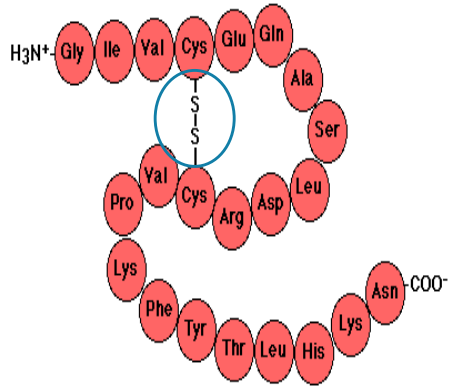
  - Peptide bond are not broken by conditions that denature proteins, such as heat
  - They can break by prolonged exposure to a strong acid or base at elevated temperatures to hydrolyze (break) these bond or by using enzymes

- **How to determine the primary structure sequence?**

1. DNA sequencing.

2.Direct amino acids sequencing.

**Primary structure proteins are not functional



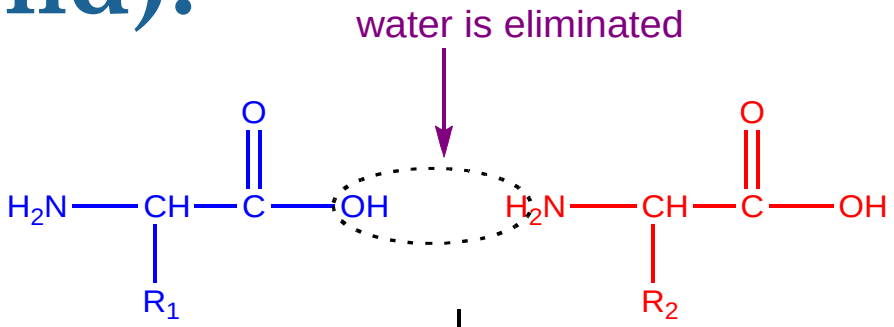
DNA sequencing or indirect sequencing means the sequence taken from the gene and translated

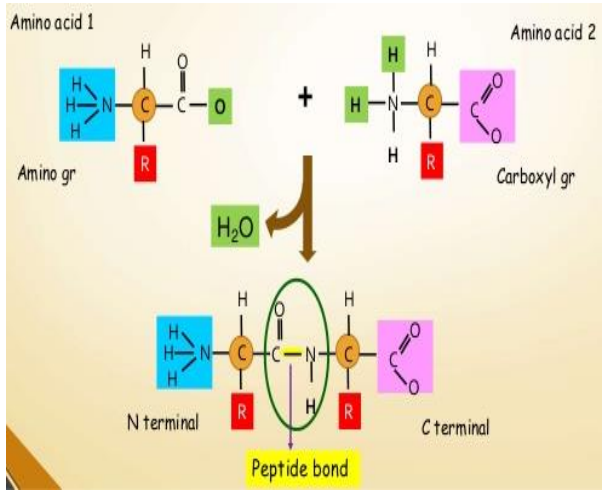
Direct amino acid sequencing means breaking down the protein by standard known methods, then we get to the primary structure

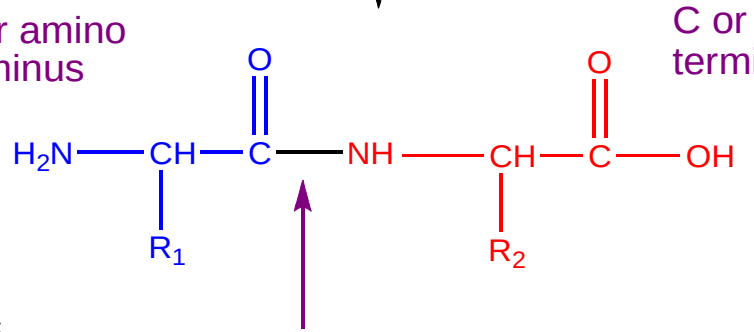
Peptide bond (amide bond):

two amino acids condense to form...

Condense
بمعنى تتكثف







+ HOH

...a dipeptide. If there are more it becomes a polypeptide. Short polypeptide chains are usually called peptides while longer ones are called proteins.

residue 1 residue 2

The 2 sides of the polypeptide does not form amide bond

ملاحظة:

Residues : amino acid in a peptide chain

We always start from N terminus to C terminus

■Peptide Bond (amide bond) :

Amide linkage that is formed between α-carboxyl group of an amino acid and α-amino group of the other amino acid.

Covalent bond formed by:
Removal of water :
1-OH from COOH
2-H from NH3 Group.
By : (dehydration)

Each amino acid (in) a chain makes two peptide bonds.

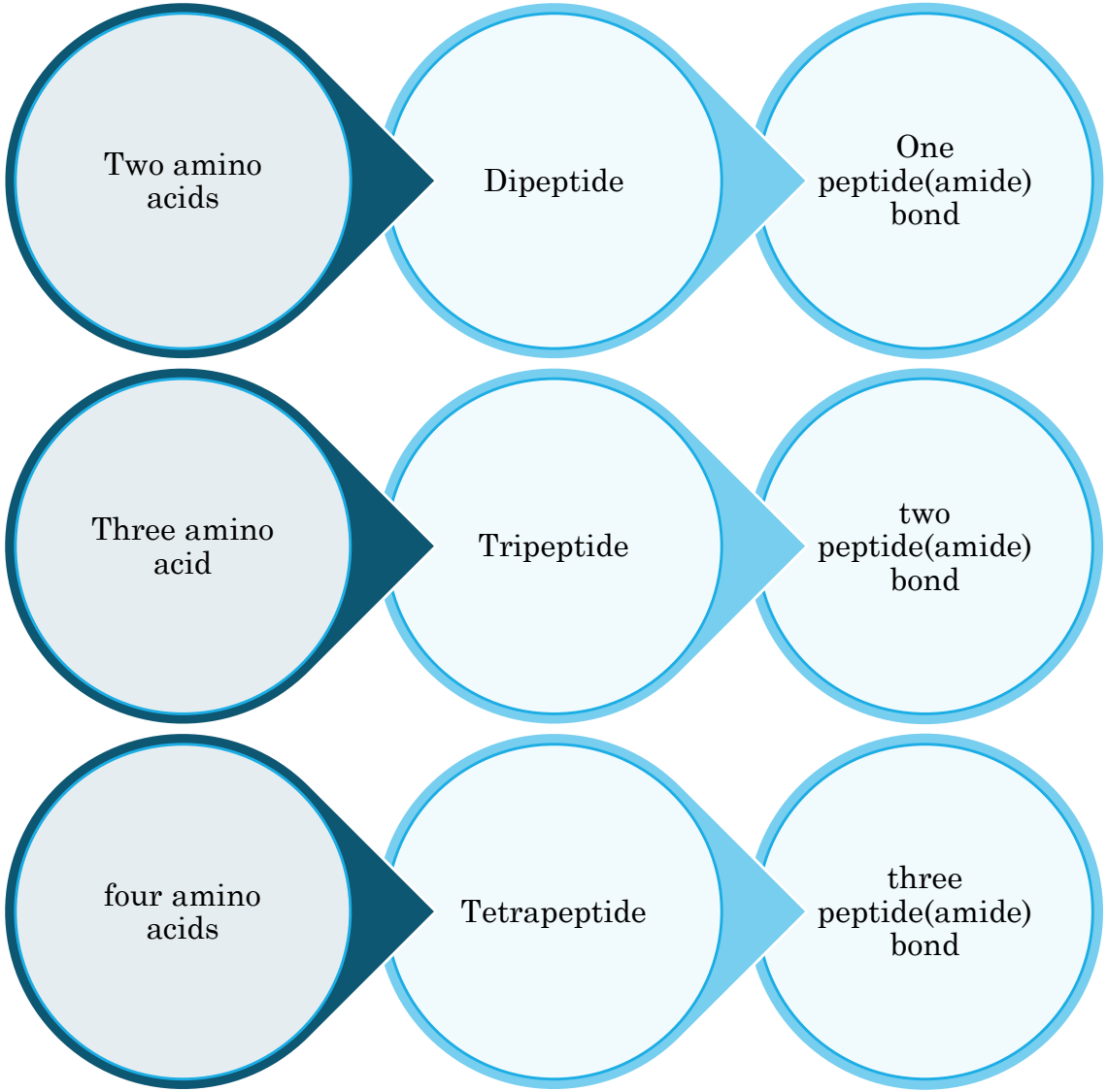
The amino acids (at the two ends) of a chain make only one peptide bond.

The amino acid with a free amino group is called amino terminus or NH2-terminus.

The amino acid with a free carboxylic group is called carboxyl terminus or COOH-terminus.

peptides

Amino acids can be polymerized to form chains:



Oligo peptide
- 2-20 amino acids

Poly peptide
- More than 20 amino acids

Oligo means a few

Poly means many

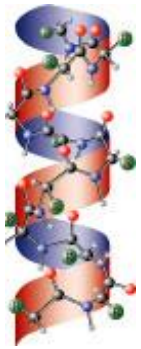
Number of peptide bonds = number of amino acid-1

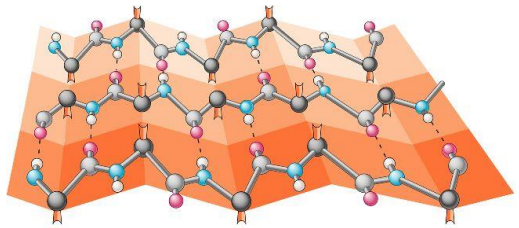
2.Secondary structure

- It is regular arrangements of amino acids that are located near to each other in the linear sequence. *It is also not functional

- Examples of secondary structures frequently found in proteins are:

α-helix	β-bends	β-sheet





- Excluding the conformations (3D arrangements) of its side chains.

*Bonds that are found in it: Hydrogen bonds

ملاحظة:

for the secondary structure , we do not look at the R side chains nor do we look at the hydrophobic interactions that give it its 3D structure so we exclude that.. We only look at the hydrogen bonds

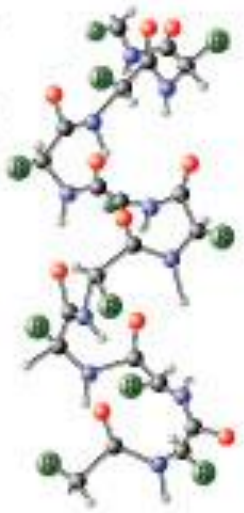
Secondary structure

α-helix

1. It is a right-handed spiral (Anti-clockwise)

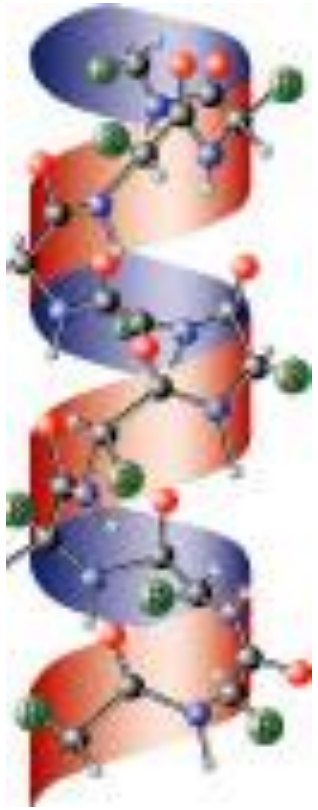
   - side chains of amino acids extended outward.
   - Hydrogen bonds are what Stabilize the α-helix. (Hydrogen bonds form between the peptide bond carbonyl oxygen and amide hydrogen)
   - Amino acids per turn: Each turn contains 3.6 amino acids.
     (يعني اللفة الأولى بتحتوي على 3 أحماض و الرابعة بتسوي رابطة هيدروجينية مع الحمض الأول)(كل لفة فيها 3.6 حمض أميني)

Ball-and-stick model of a portion of the α-helical secondary structure of a protein molecule



This ribbon model shows the general arrangement of atoms in a portion of the α-helical secondary structure of a protein molecule.

The two models superimposed



α-Helix

α-helix تابع :

-Amino acids that disrupt an α-helix:

- Proline ➔ imino group, interferes with the smooth helical structure.

  (لأنه تركيبه على شكل حلقة فبيخرب الشكل الحلزوني)

- Glutamate, aspartate, histidine, lysine or arginine ➔ form ionic bonds.

  (these are all polar CHARGED amino acids so they would form ionic bonds thus it would change the shape)

- Bulky side chain → such as tryptophan.

  (حجمه كبير فبغير الشكل)

- Branched amino acids at the ß-carbon, such as → valine or isoleucine.

Any huge R-group (side chain) will disturb the α-helix

للفهم أكثر:*

https://www.youtube.com/watch?v=V3DgrOG1exY

Secondary structure

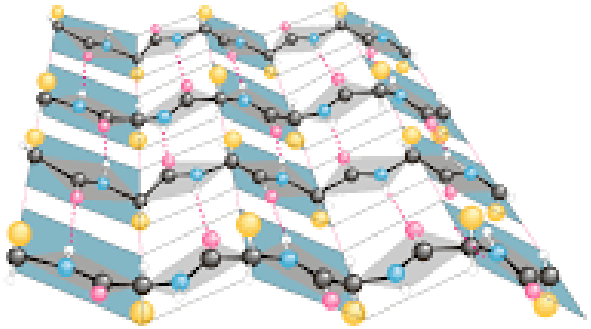
❖ **β-sheet** (Composition of a ß-sheet)

- Two or more polypeptide chains make hydrogen bonding with each other. (beta sheet could be a long polypeptide) (the helix is just one polypeptide chain)

- Also called pleated sheets:

  because they appear as folded structures with edges

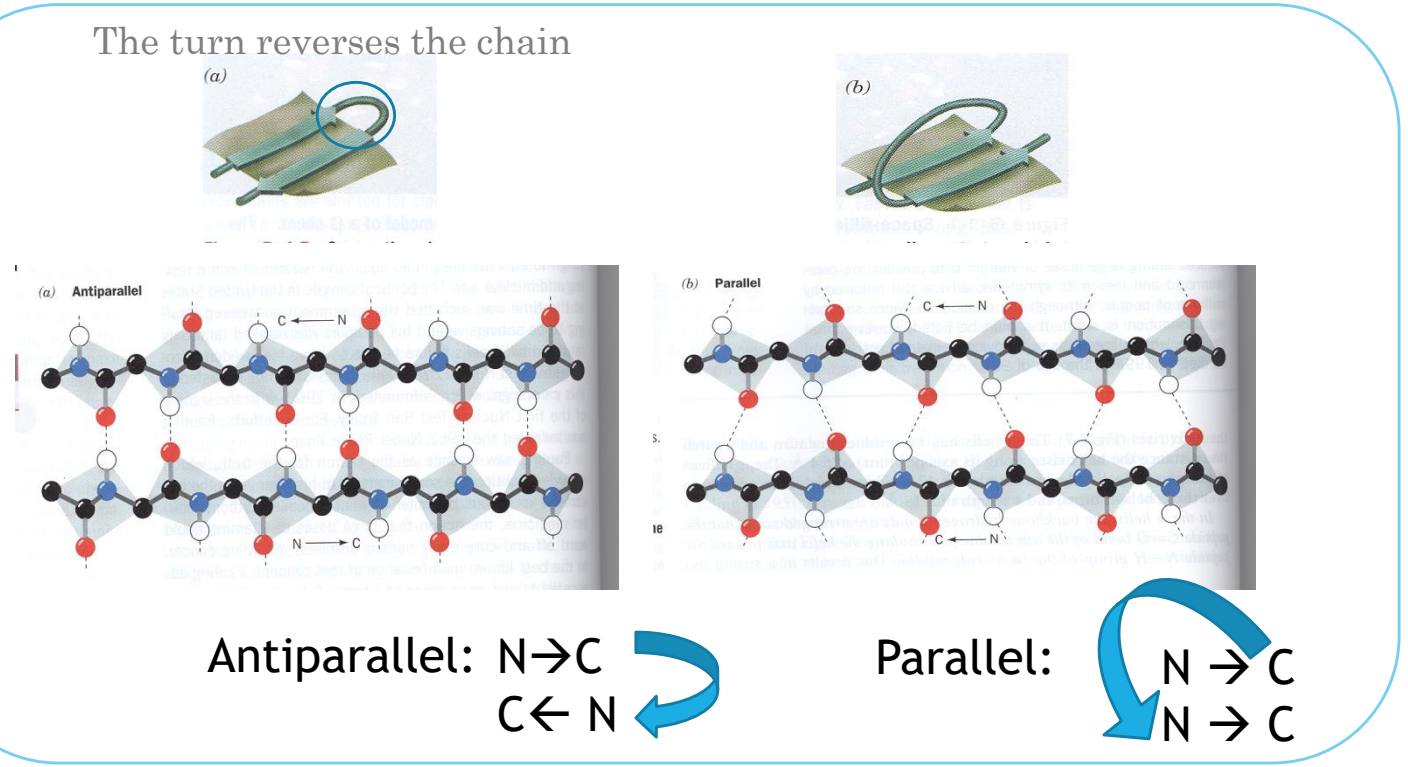
- Hydrogen bonds: Stabilize the **β-sheet**.



للفهم أكثر:*
https://www.youtube.com/watch?v=koyE9Nplacc

Secondary structure

- **β-sheet (Antiparallel and parallel sheets)**



There is some difficulty facing the ß- parallel sheet, the oxygen and hydrogen the angel between them is not vertical (90°), which makes it less stable than the ß anti parallel sheet

Hydrogen bonds in the parallel direction are less stable than in the antiparallel (notice the dotted lines in the picture..in the antiparallel the lines are straight but in the parallel , they aren't)

Secondary structure

- B-bends

B-bends

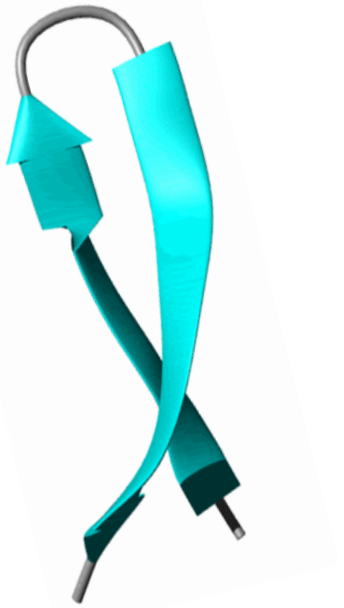
Reverse the direction of the polypeptide chain

#found in the surface

#often include residus

The name comes because they often connect successive (متتالية)strands Of antiparallel ß-sheets.

Composed of 4 amino acid, proline and glycine are frequently found in the b- bends

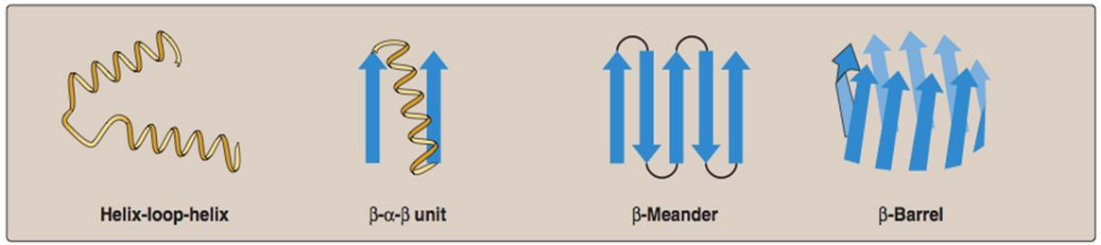


Other secondary structure

Nonrepetitive (loop,coil)

Supersecondary (motifs)

A combination of secondary structural elements (that is, α-helices, ß-sheets, and coils) . These form primarily the core (interior) region of the molecule. They are connected by loop regions .



ملاحظة *
مجموعة منها تساعد في التركيب الثلاثي

Tertiary structure

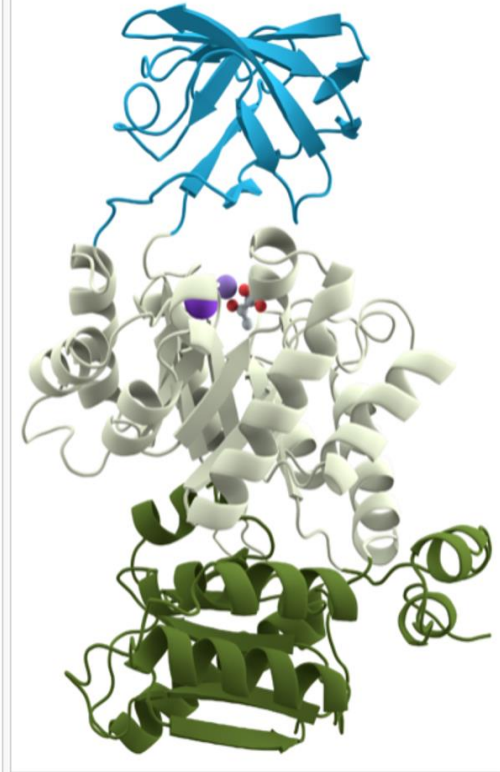
What is it?

It is the three-dimensional (3D) structure of an entire polypeptide chain including side chains.

Domains are

- The fundamental functional and 3D structural units of a polypeptide, >200 amino acids fold into two or more clusters.
- The core of a domain is built from combinations of supersecondary structural elements (motifs) and their side chains.
- Domains can be combined to form tertiary structure.

- The tertiary structure of a proteins is the functional protein.



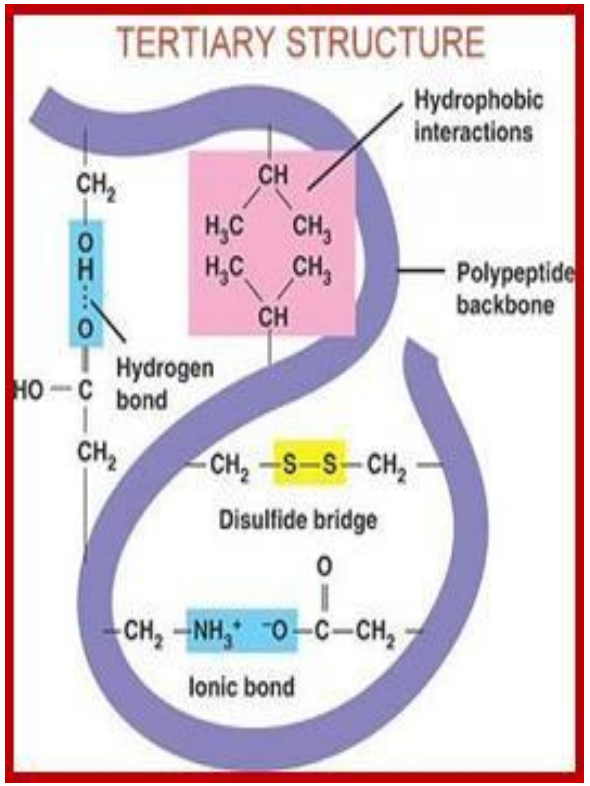
a protein with three domains

supersecondary structural elements (motifs) → The core of a domain → Domains → tertiary structure.

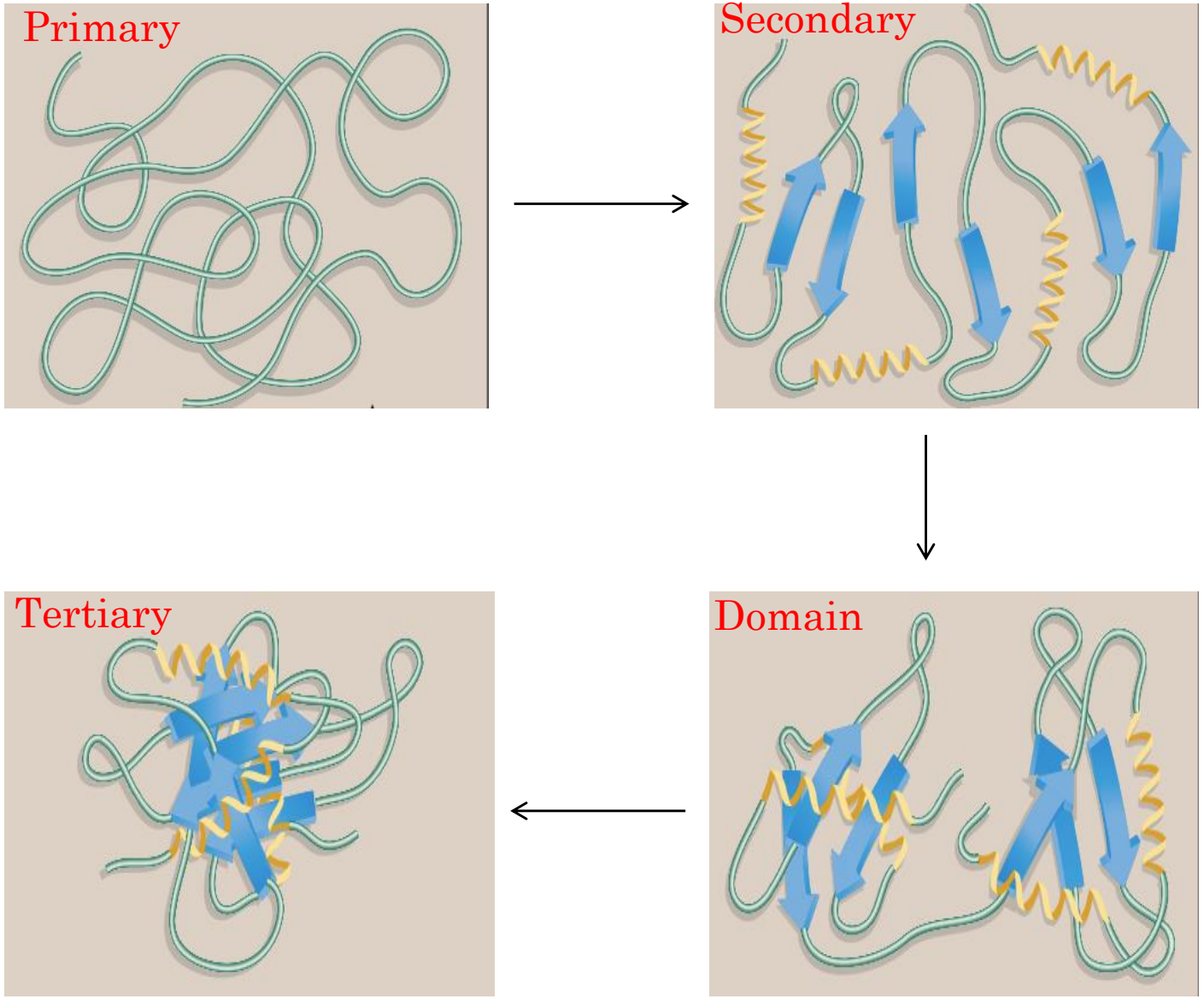
Sometimes the tertiary structure is the end product of some proteins.

Interactions stabilizing tertiary structure:

- **Disulfide bonds.**
  - Extra: a covalent linkage formed from the sulfhydryl group (–SH) of each of two cysteine residues to produce a cystine residue
- **Hydrophobic interactions.**
  - Extra:Amino acids with nonpolar side chains tend to be located in the interior of the polypeptide molecule, where they associate with other hydrophobic amino acid
- **Hydrogen bonds.**
  - Extra:Amino acid side chains containing oxygen- or nitrogen-bound hydrogen
- **Ionic interactions.**
  - Extra: Negatively charged groups can interact with positively charged groups such as : carboxylate group (– COO–) in the side chain of aspartate and amino group (– NH3+)



Tertiary structure



Protein folding:

Interactions between the side chains of amino acids determine how a long polypeptide chain folds into the intricate three-dimensional shape of the functional protein.

للفهم أكثر:
https://www.youtube.com/watch?v=QSyCPD2qlPs

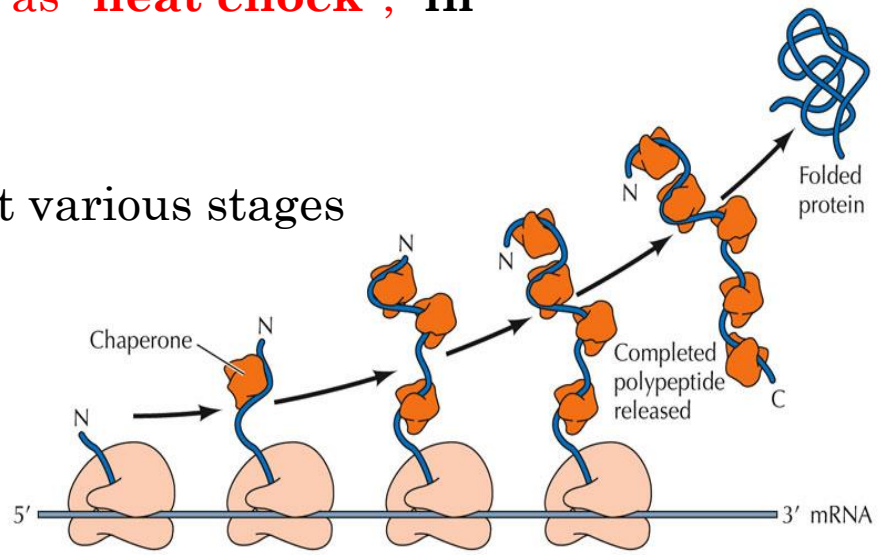
Tertiary structure

Chaperons

are a specialized group of proteins, required for the proper folding of many species of proteins.

Role of chaperons, also known as "**heat chock**", **in protein folding:**

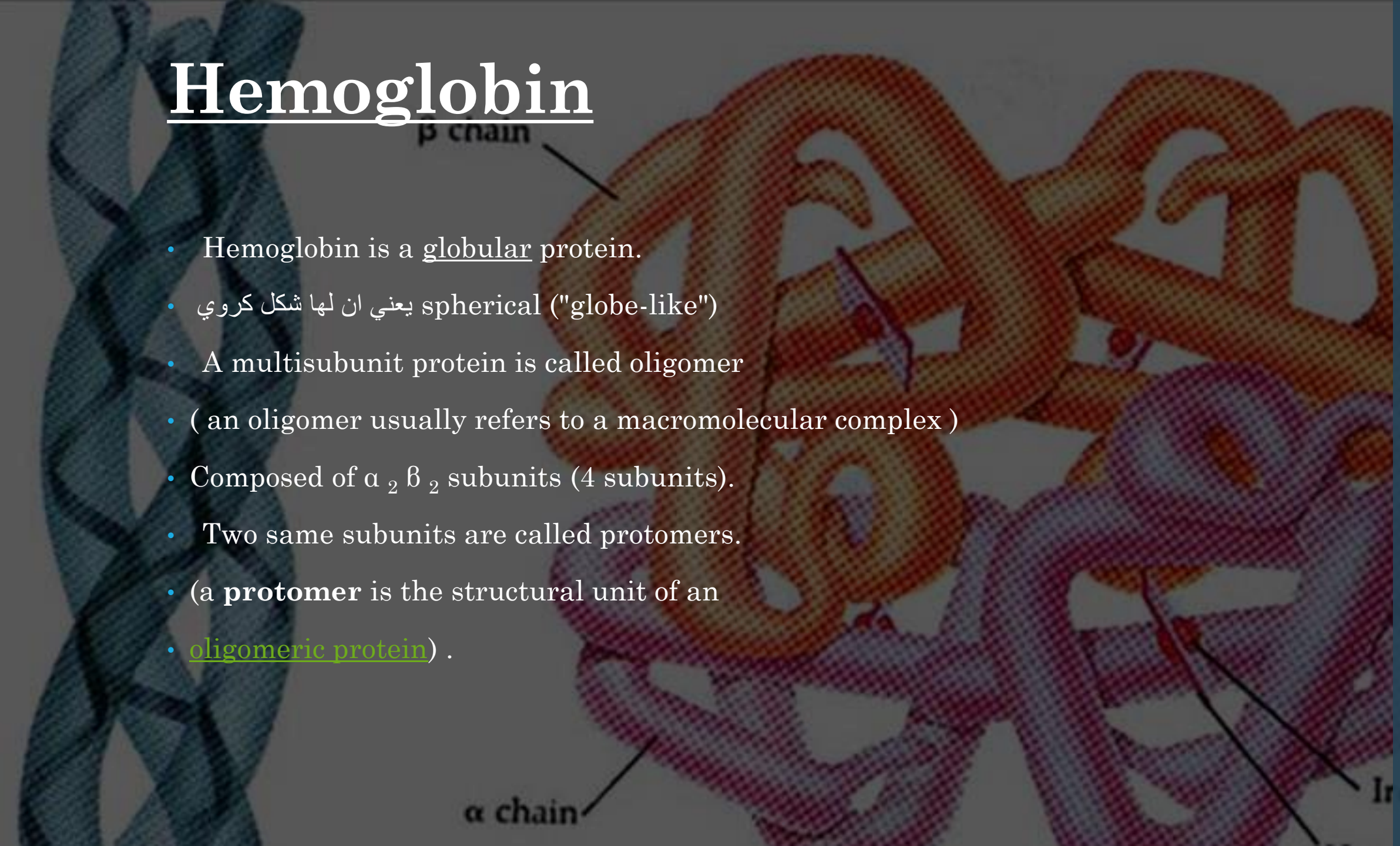
They interact with polypeptide at various stages during the folding process.
Examples of chaperons:
Hsp60 and Hsp70.



Quaternary structure

- Some proteins contain two or polypeptide chains that may be more structurally **identical** or totally **unrelated**.
- Each chain forms a 3D structure called subunit.
- According to the number of subunits: dimeric, trimeric, … or multimeric.
- Subunits may either function independently of each other, or work cooperatively, e.g. **hemoglobin**.

Hemoglobin

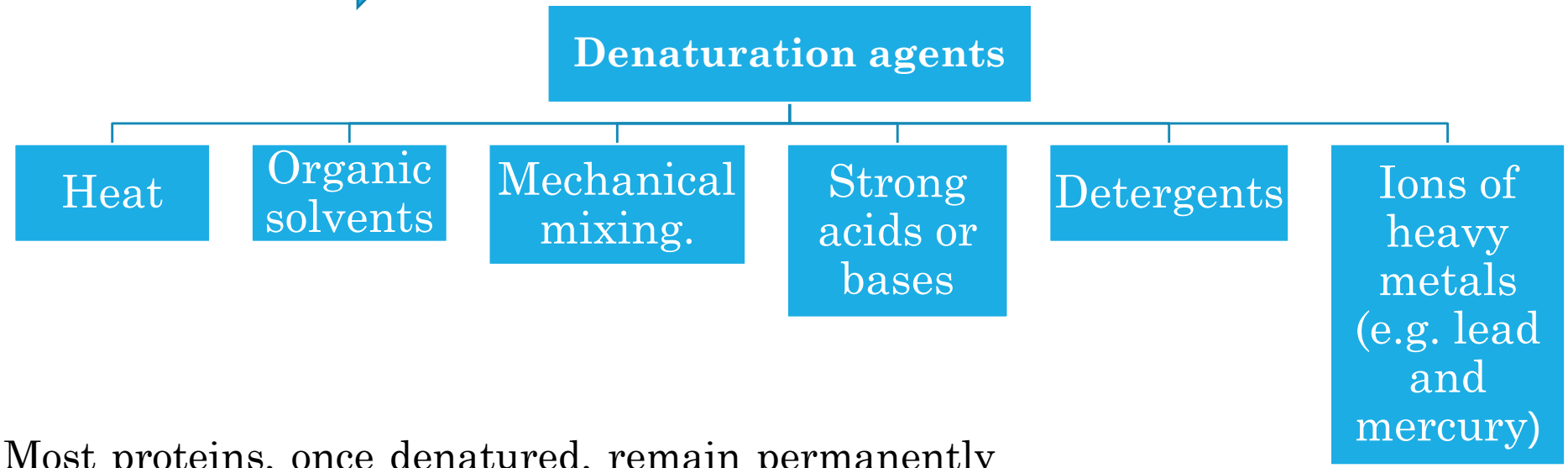


- Hemoglobin is a globular protein.
- يعني ان لها شكل كروي spherical ("globe-like")
- A multisubunit protein is called oligomer
- (an oligomer usually refers to a macromolecular complex)
- Composed of $\alpha_2 \beta_2$ subunits (4 subunits).
- Two same subunits are called protomers.
- (a **protomer** is the structural unit of an
- oligomeric protein) .

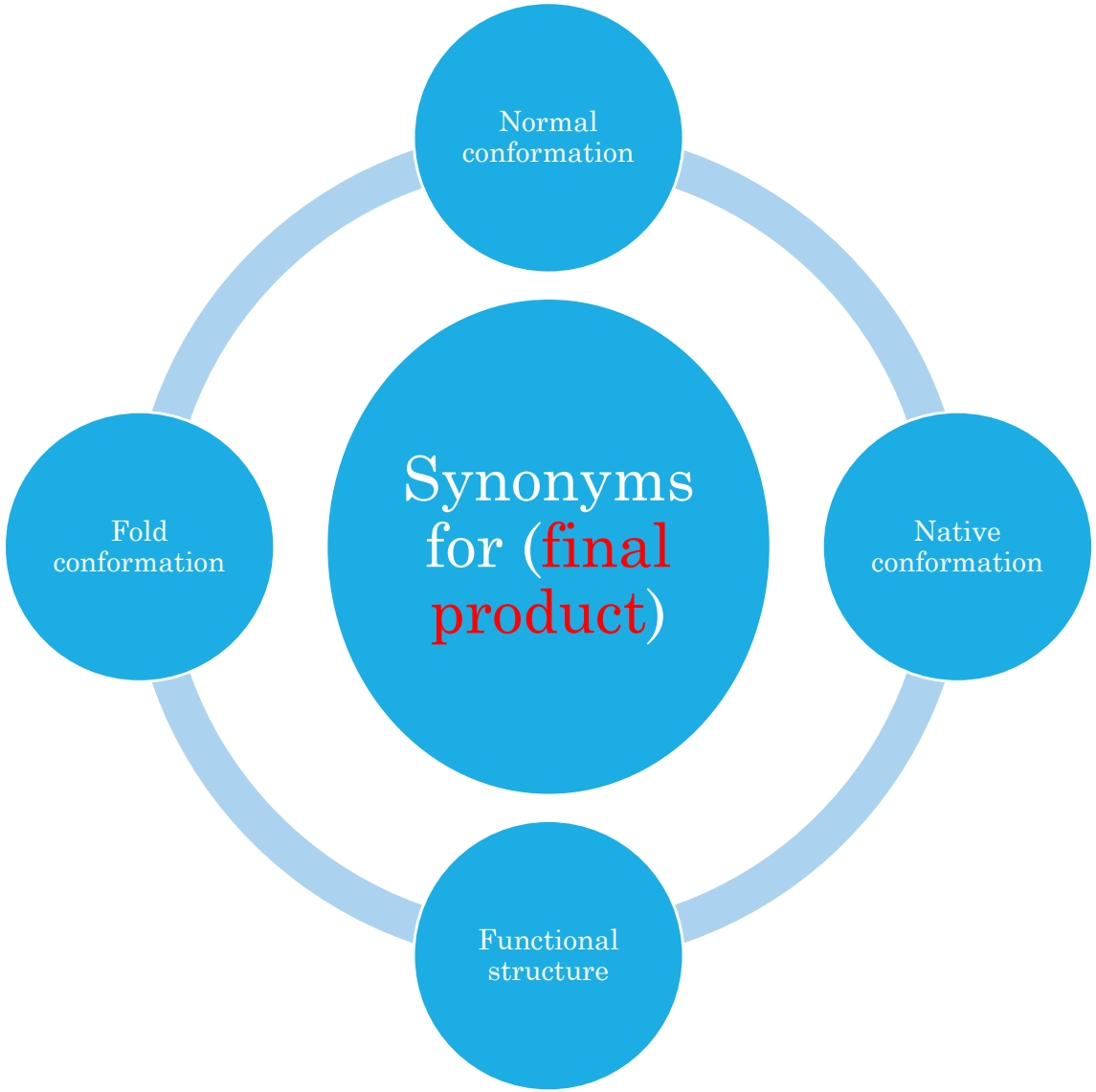
Denaturation of proteins

when a protein is denatured, it results in the

unfolding and disorganization of the protein's secondary and tertiary structures.



- Most proteins, once denatured, remain permanently disordered. (because the chaperons are ruined)
- Denatured proteins are often insoluble and, therefore, precipitate from solution. تترسب


Normal conformation
Native conformation
Functional structure
Fold conformation
Synonyms for (final product)

Protein misfolding

- Every protein must fold to achieve its normal conformation and function.

عند حدوث خلل في شكل البروتين تختل وظيفته لذلك ينتج عنه امراض للإنسان

Abnormal folding of proteins leads to a number of diseases in humans.

Alzheimer's disease

ß amyloid protein is a misfolded protein.

Amyloid is aggregates of misfolded proteins outside neurons, it interfere with neurons' ability of sending massages.

It forms fibrous deposits or plaques in the brains of Alzheimer's patients.

Creutzfeldt-Jacob or prion disease

Prion protein is present in normal brain tissue , in diseased brains, the same protein is misfolded.

It, therefore, forms insoluble fibrous aggregates that damage brain cells.

Misfolding of protein leads to change of code of the amino acid, that will produce another amino acid, sometimes that makes it toxic to the cell.

Prion protein is highly expressed in brain tissue

Another example: Sickle cell anemia

Take home messages

- Native conformation of the protein is the functional, fully folded protein structure
- The unique 3D structure of the native conformation is determined by its primary structure, i.e. the amino acid sequence
- Interactions of between the amino acid side chains guide the folding of the polypeptide chain to form secondary, tertiary and sometimes quaternary structures that cooperate in stabilizing the native conformation of the protein.
- Protein denaturation results in unfolding and disorganization of of the protein's structure, which are not accompanied by hydrolysis of peptide bonds.
- Disease can occur when an apparently normal protein assumes a conformation that is cytotoxic, as in the case of Alzheimer disease and Prion disease.

Videos:

1- Protein structure

2- Alpha helix: ·
http://www.youtube.com/watch?v=eUS6CEn4GSA&list=
U UgsuuOOUDgZPKLALDSWd7BA

3- · Denaturation of proteins ·
http://www.youtube.com/watch?v=SUCgAxI8rhg

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