



Protein structure

- Color Index:

- **Important.**
- Extra Information.
- **Doctors slides.**

436 Biochemistry team

Objectives

By the end of this lecture, the students should be able to:

- ▶ 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 proteins?

They are large, complex molecules

Play many critical roles in the body

They do most of work in the cell

they are made up of hundreds or thousands of smaller units called amino acids which are attached to one another in long chains by a peptide bond.

They are required for the structure, function and regulation of the body's tissues and organs

What are proteins?

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

The **sequence of amino acids determines** :

1- each protein's unique three-dimensional (3D) structure

2- its specific function.

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

Antibody

Enzyme

Messenger

Structural component

Transport/storage

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.

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.

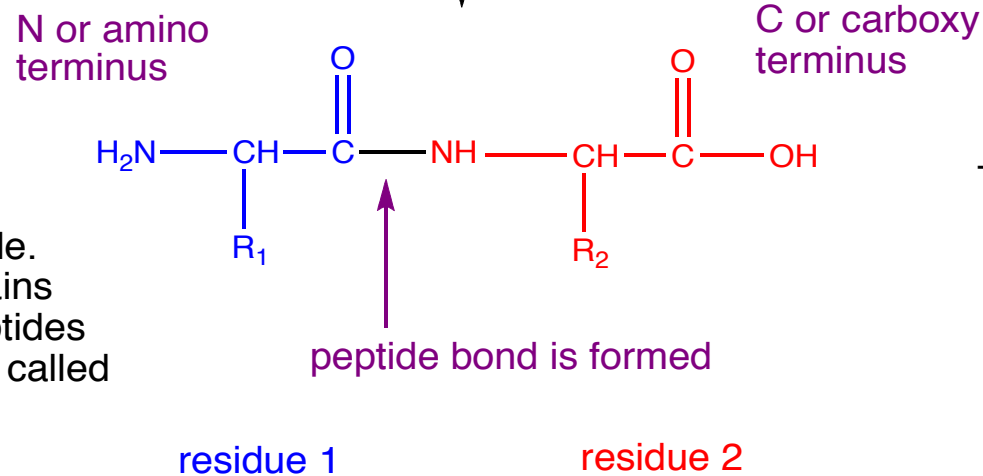
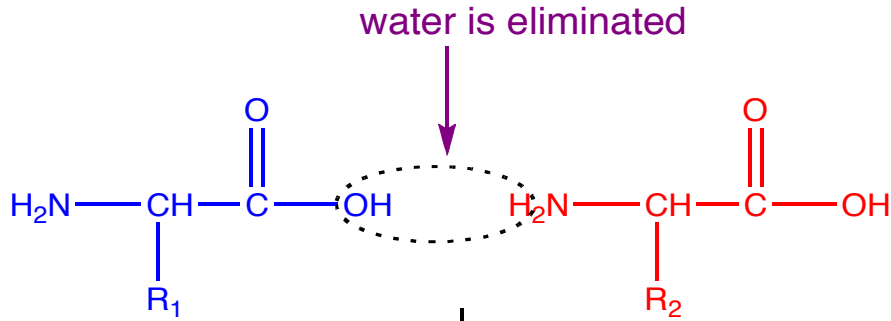
The amino acid with a free amino group is called amino terminus or NH₂-terminus.

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

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

Peptide bond (amide bond):

two amino acids condense to form...



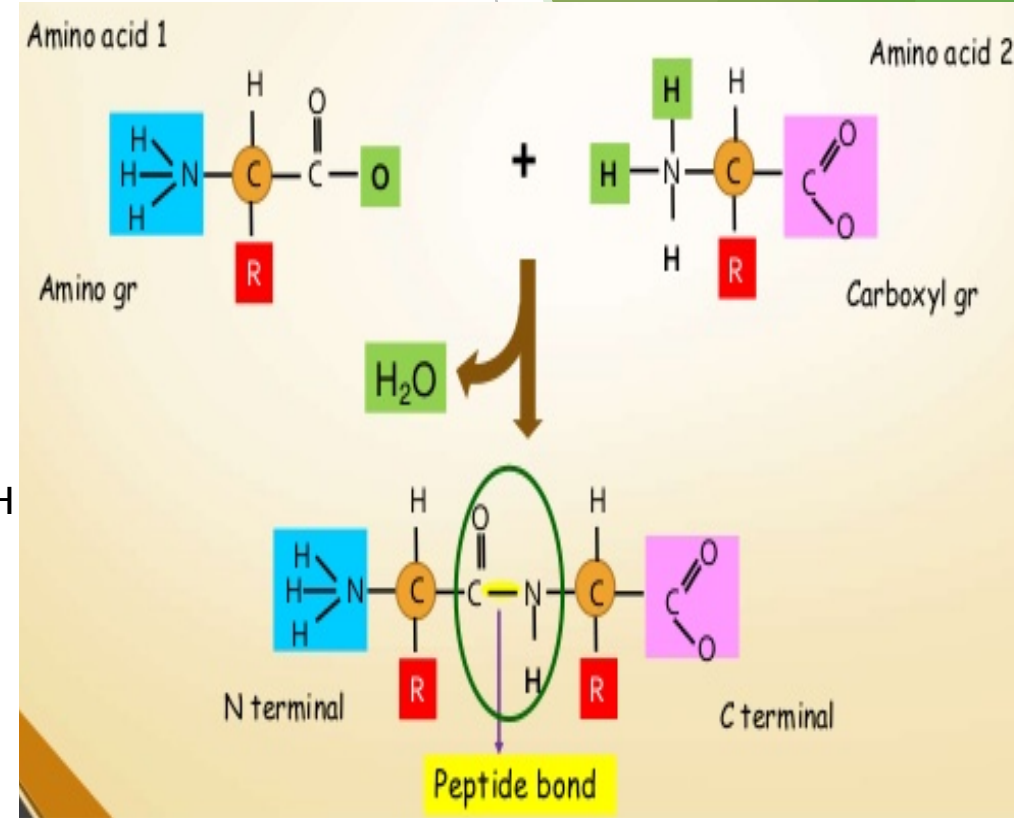
+ HOH

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

ملاحظة:

Residues : amino acid in a peptide chain

We always start from N terminus to C terminus



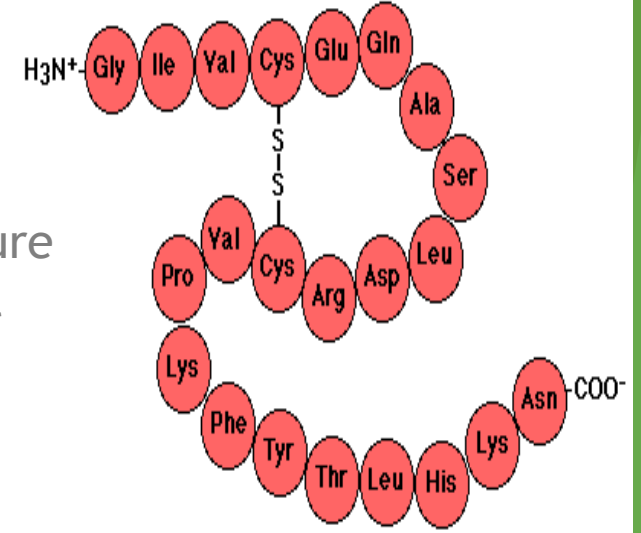
1. Primary structure

- ▶ 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.

**Primary structure proteins are not functional

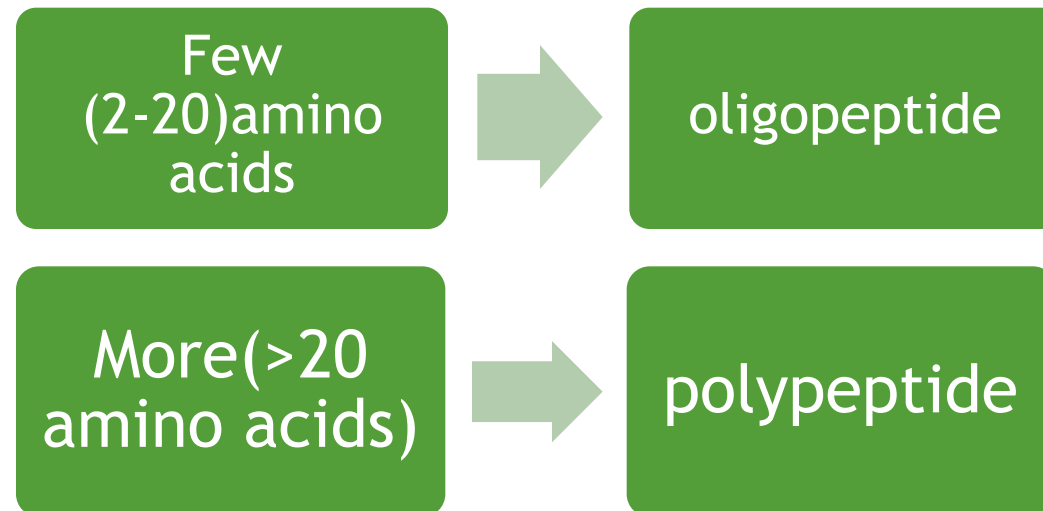
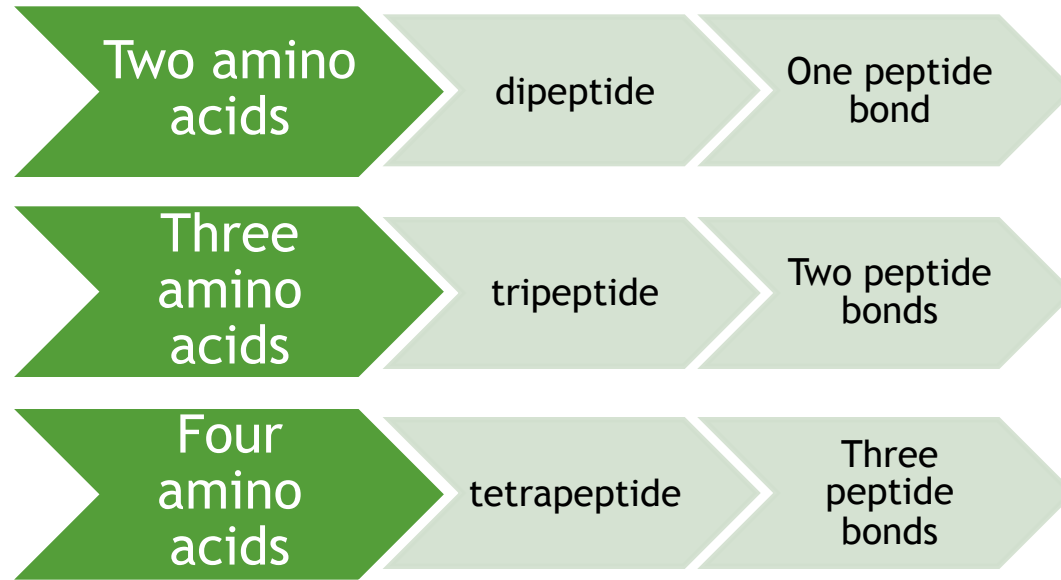


ملاحظة:

- **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.

peptides

- ▶ Amino acids can be polymerized to form chains:

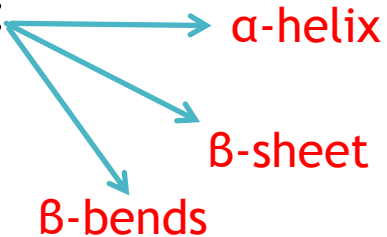


2.Secondary structure

*It is also not functional

- It is regular arrangements of amino acids that are located near to each other in the linear sequence.

- Examples of secondary structures frequently found in proteins are:



- **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

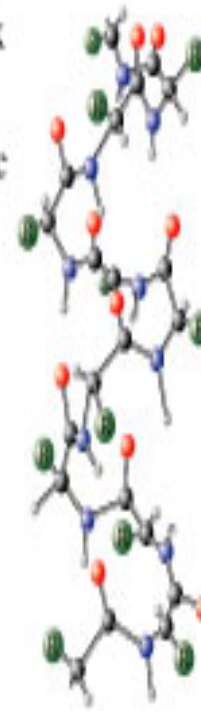
2. side chains of amino acids extended outward.

3. Hydrogen bonds are what stabilize the α -helix.
(Hydrogen bonds form between the peptide bond carbonyl oxygen and amide hydrogen)

4. Amino acids per turn: Each turn contains 3.6 amino acids.
(كل لفة فيها 3.6 حمض أميني)

(يعني اللفة الأولى بتحتوي على 3 أحماض و الرابعة بتسوي رابطة هيدروجينية مع الحمض الأول)

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



: تابع α -helix :

-Amino acids that disrupt an α -helix:

- ▶ **Proline** → imino group, interferes with the smooth helical structure.

(لأنه تركيبه على شكل حلقة فيخرب 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 فيغير الشكل)

- ▶ Branched amino acids at the β -carbon, such as → **valine or isoleucine**.


للفهم أكثر:*

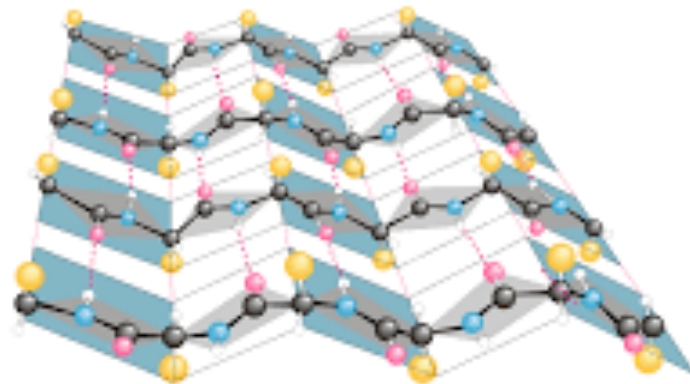
<https://www.youtube.com/watch?v=V3DgrOG1exY>

Secondary structure

❖ β -sheet (Composition of a β -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.**

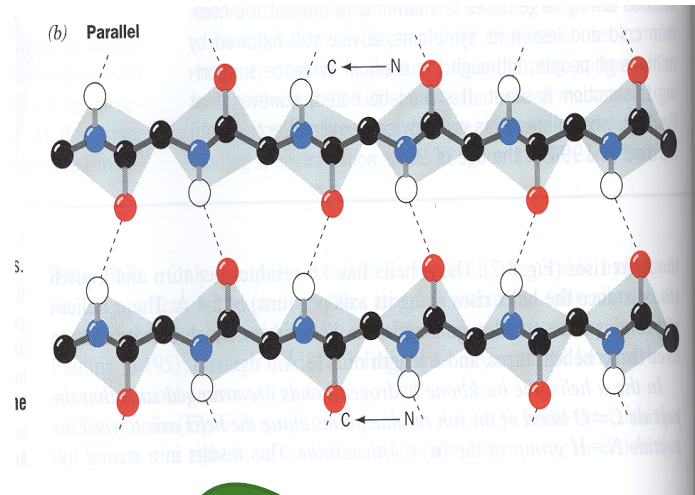
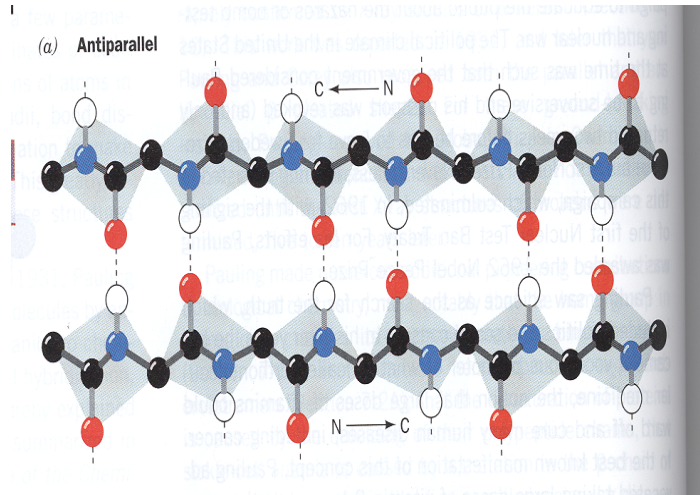
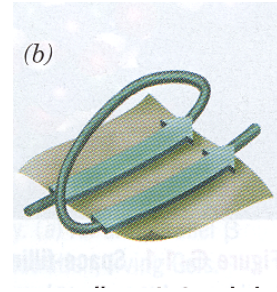
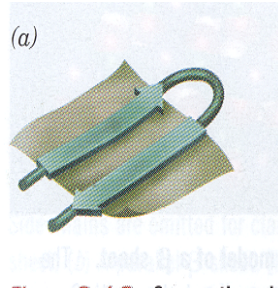


للفهم أكثر:*

<https://www.youtube.com/watch?v=koyE9Nplacc>

Secondary structure

► β -sheet (Antiparallel and parallel sheets)



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

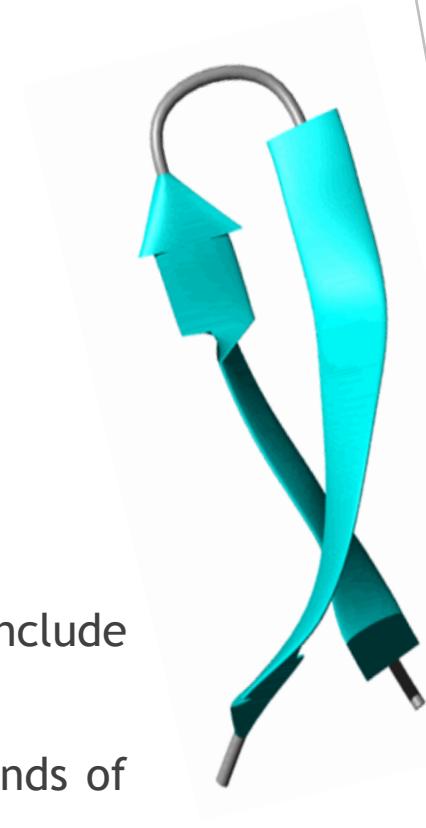
- ▶ Other secondary structure examples:

- ▶ β-bends (reverse turns):

- ▶ Reverse the direction of a polypeptide chain.
 - ▶ Usually found on the surface of the molecule and often include charged residues.
 - ▶ The name comes because they often connect successive strands of antiparallel β-sheets.
 - ▶ β-bends are generally composed of four amino acid residues, proline or glycine are frequently found in β-bends.

- ▶ Nonrepetitive secondary structure:

- e.g. loop or coil conformation.

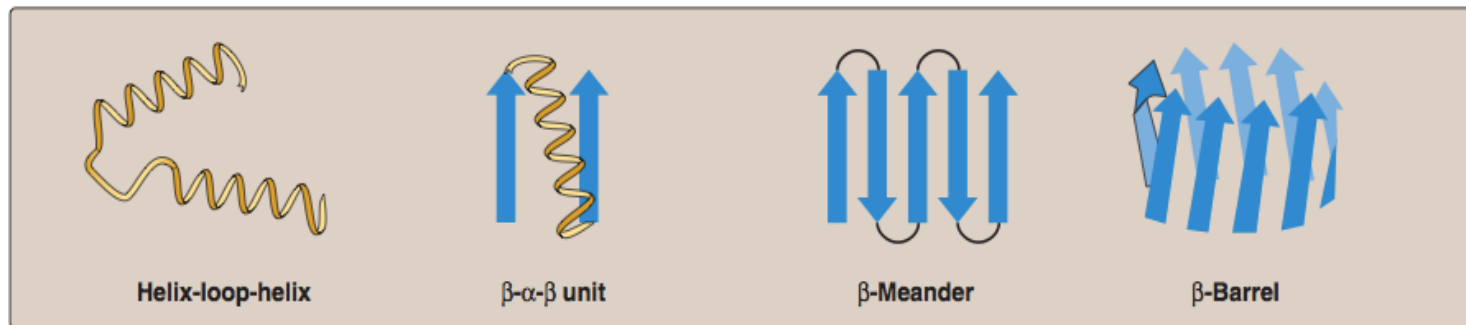


Secondary structure

Other secondary structure examples:

Supersecondary structures (motifs):

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



α α motif: two α helices together

β α β motif: a helix connects two β sheets

β hairpin: reverse turns connect antiparallel β sheets

β barrels: rolls of β sheets

Tertiary structure

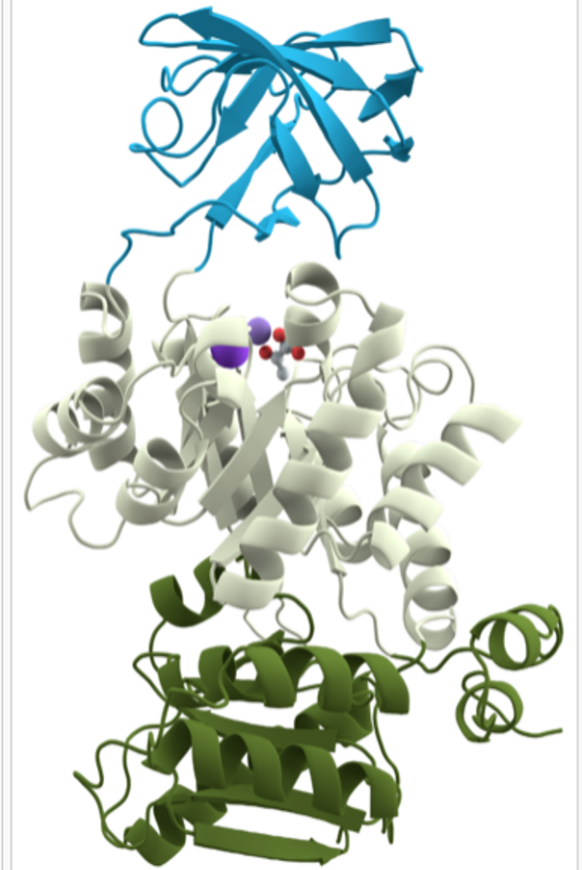
What is it?

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

Domains are

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

- 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.



a protein with three domains

supersecondary structural elements (motifs)

→ The core of a domain

→ Domains

When combined

→ tertiary structure.

Interactions stabilizing tertiary structure:

Disulfide bonds.

a covalent linkage formed from the sulfhydryl group ($-SH$) of each of two cysteine residues to produce a cystine residue

Hydrophobic interactions.

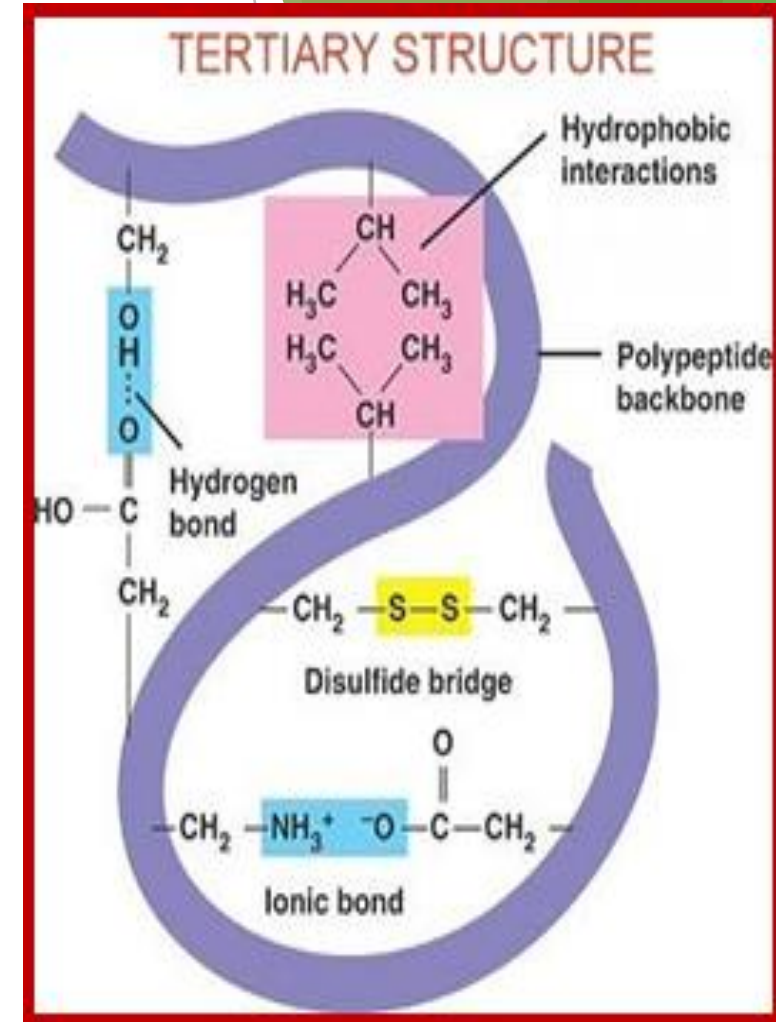
Amino acids with nonpolar side chains tend to be located in the interior of the polypeptide molecule, where they associate with other hydrophobic amino acid

Hydrogen bonds.

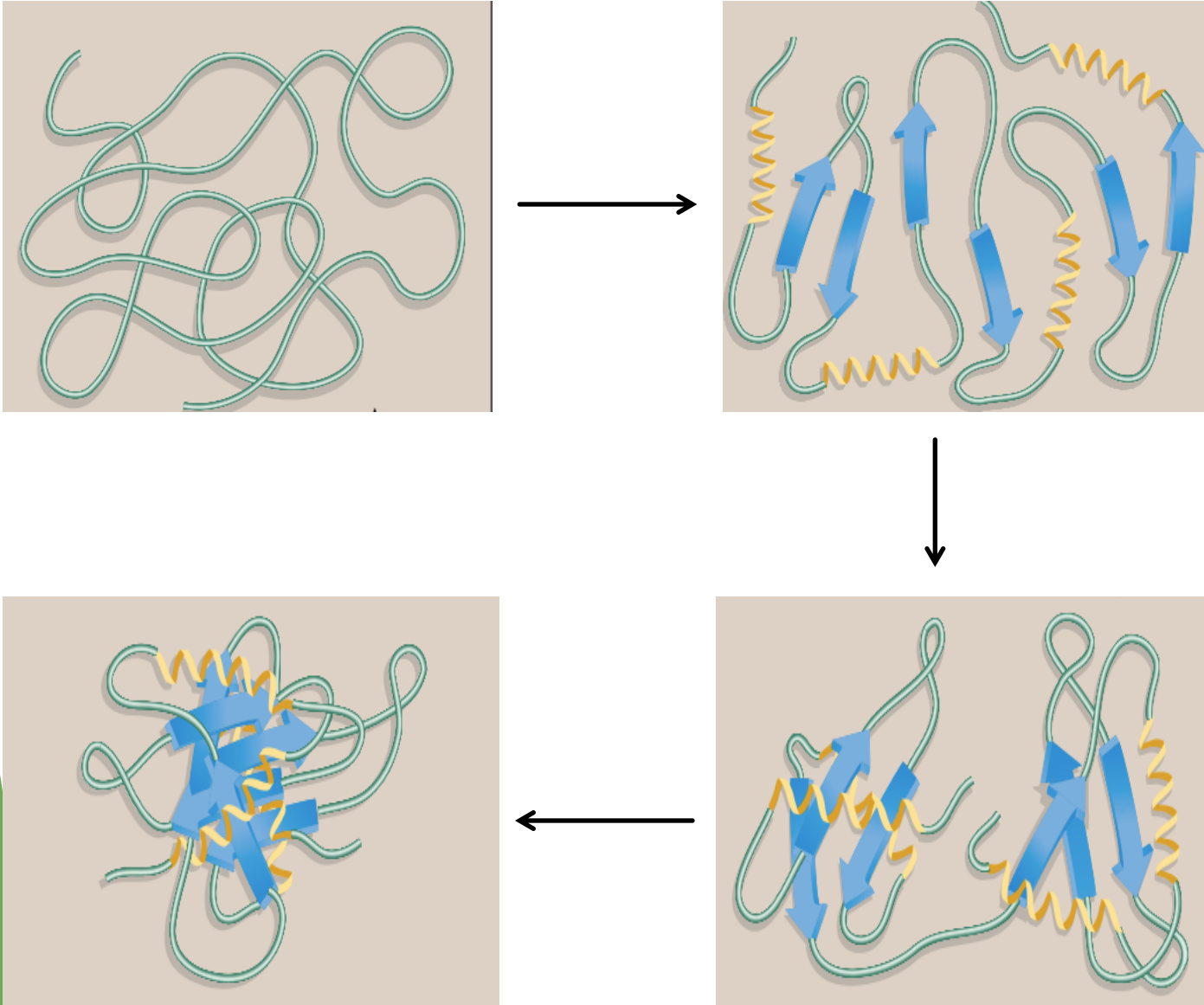
Amino acid side chains containing oxygen- or nitrogen-bound hydrogen

Ionic interactions.

Negatively charged groups can interact with positively charged groups such as : carboxylate group ($-COO^-$) in the side chain of aspartate and amino group ($-NH_3^+$)



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>

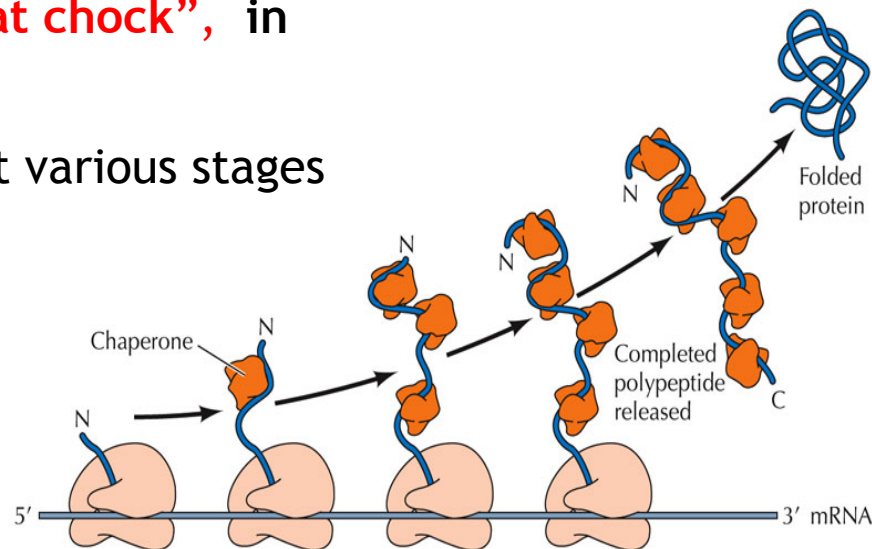
Tertiary structure

Chaperons

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

Role of chaperons, also known as “heat shock”, in protein folding:

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



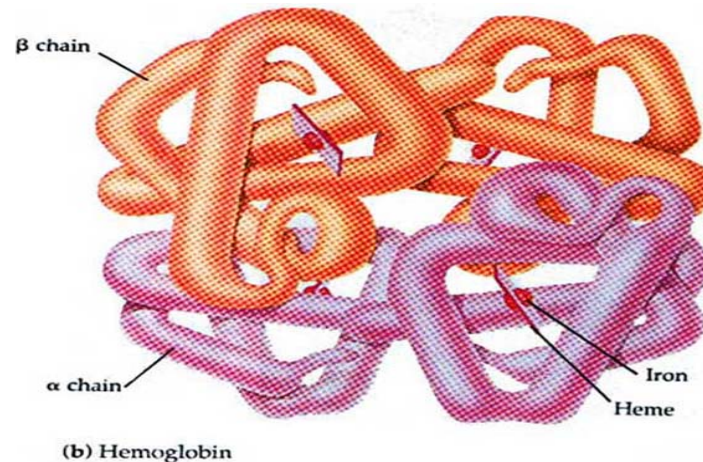
Quaternary structure

- ▶ 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.

Example:

Hemoglobin

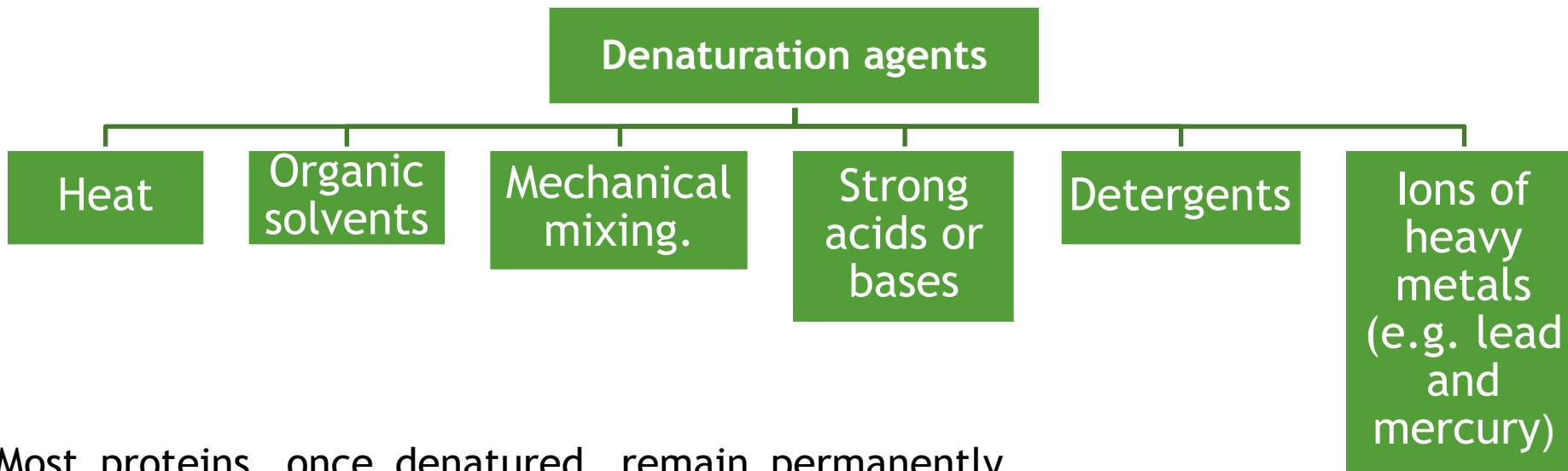
- Hemoglobin is a **globular** protein.
يعني ان لها شكل كروي spherical ("globe-like")
- A multisubunit protein is called oligomer (an oligomer usually refers to a macromolecular complex)
- Composed of **$\alpha_2 \beta_2$ subunits** (4 subunits).
- Two same subunits are called protomers.
(a protomer 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.
- Denatured proteins are often insoluble and, therefore, precipitate from solution.

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

B amyloid protein is a misfolded protein.

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

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

Creutzfeldt-Jacob or prion disease

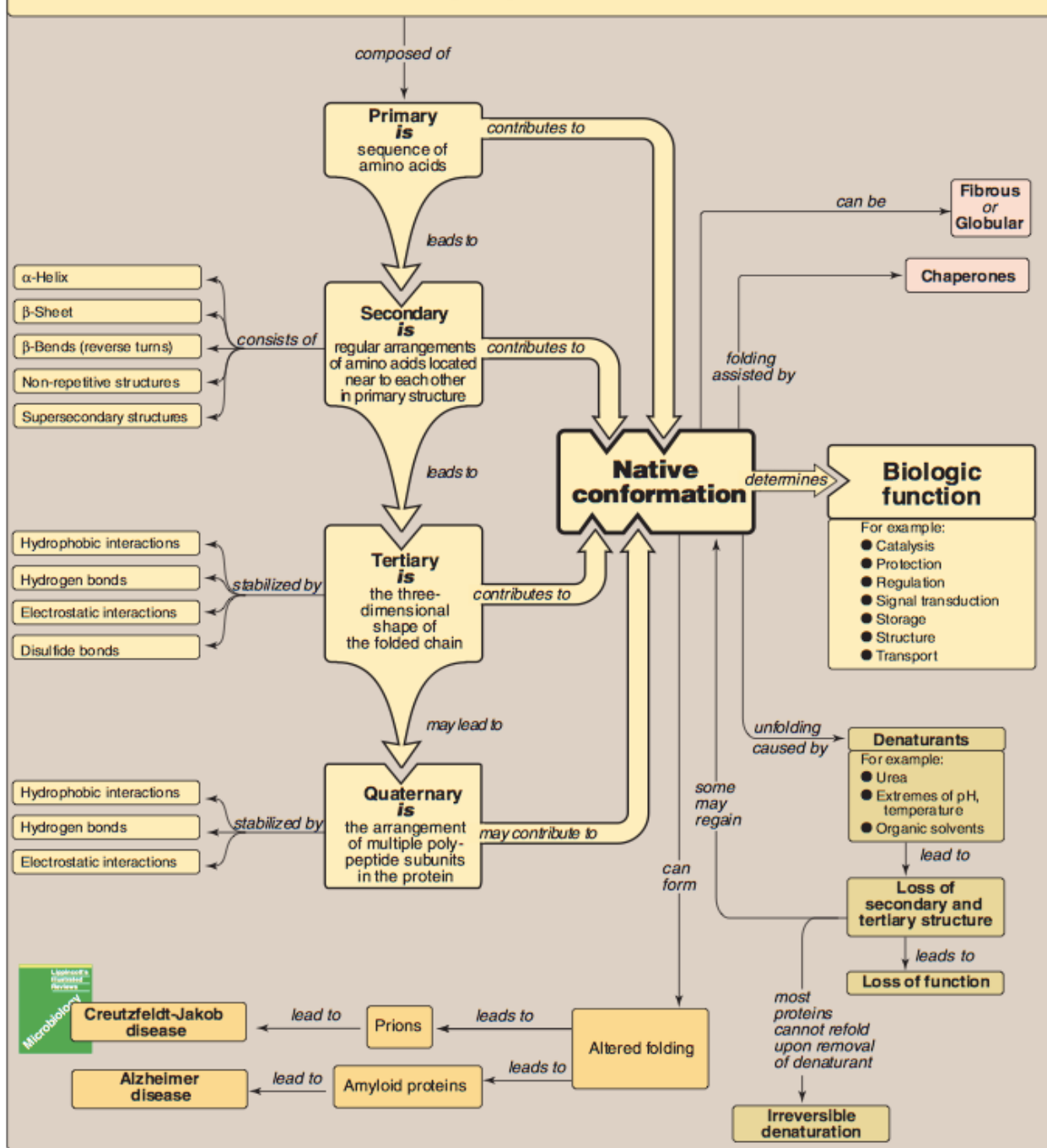
Prion protein is present in normal brain tissue , in diseased brains, the same protein is misfolded.

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

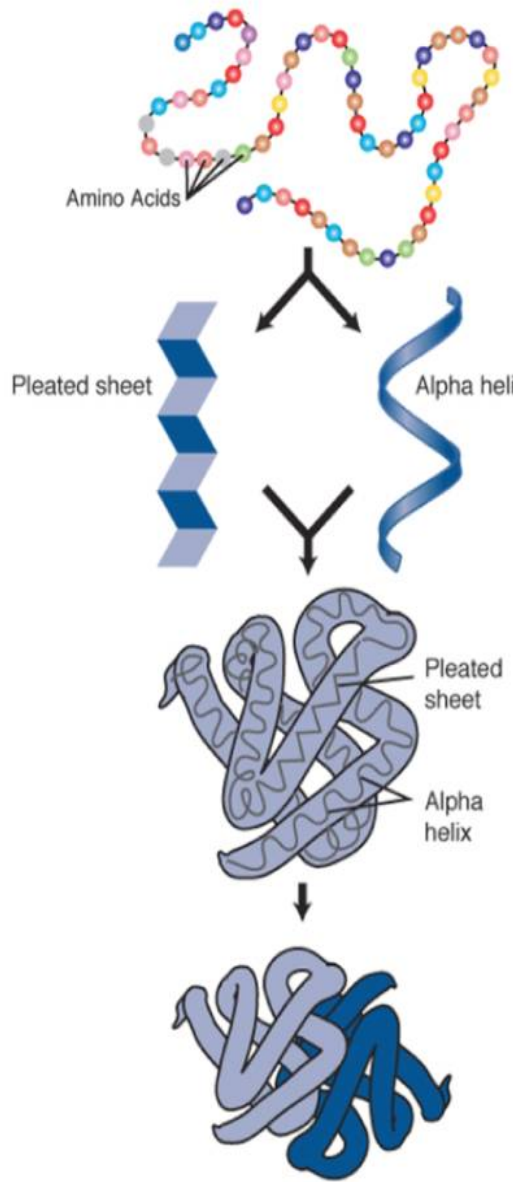
Take home messages

- ▶ 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.

Hierarchy of protein structure



Protein



Levels of protein organization

Primary protein structure is sequence of a chain of amino acids

Secondary protein structure occurs when the sequence of amino acids are linked by hydrogen bonds

Tertiary protein structure occurs when certain attractions are present between alpha helices and pleated sheets.

Quaternary protein structure is a protein consisting of more than one amino acid chain.

Review

MCQs

<https://www.onlineexambuilder.com/bio/exam-98731>

Video:

[Overview of protein](#)

[Protein structure](#)

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