

Protein Structure

Editing File

Color Index:

- Main Text (black)
- Female Slides (Pink)
- Male Slides (Blue)
- Important (Red)
- Dr's Notes (Green)
- Extra Info (Grey)

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 Proteins?

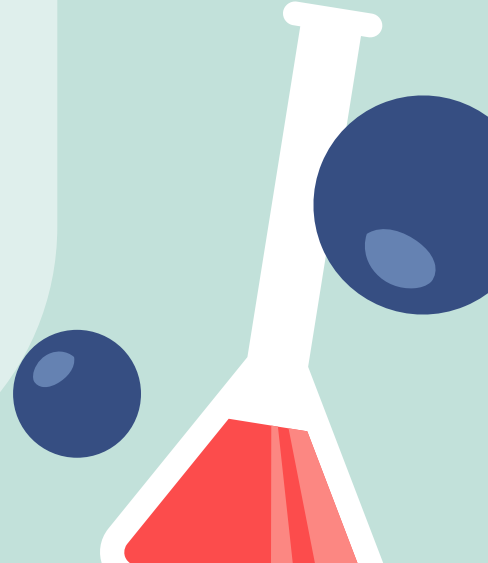
Proteins are large, complex molecules that play many critical roles in the body.

- Proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached to one another in long chains.
- There are mainly **20 different types of amino acids** that can be combined to make a protein.
- The sequence of amino acids determines:
 - Each protein's unique three dimensional (3D) structure.
 - The protein's specific function

What Are Proteins?

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

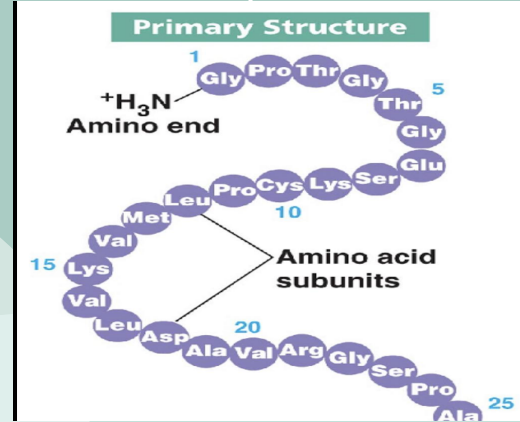
- 1- Antibody
- 2- Enzyme
- 3- Messenger
- 4- Structural component
- 5- Transport and storage





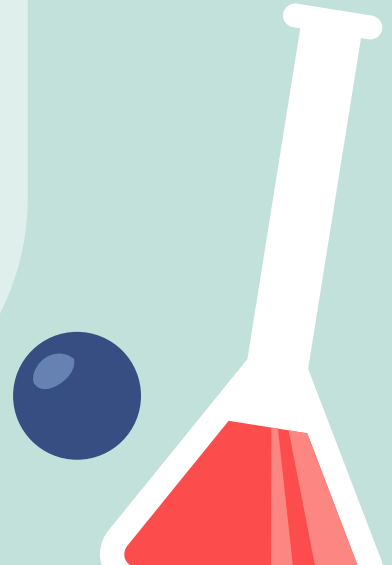
Primary structure

- It is the **linear sequence of amino acids**.
- Covalent bonds in the primary structure of protein:
 - **Peptide bond**.
 - Disulfide bond (if any) (connects 2 residues of cysteine).
- The primary structure is the simplest and first-level form of structure.
- Peptide bonds are very strong and they require enzymes to be broken.



How to determine the primary structure Sequence?

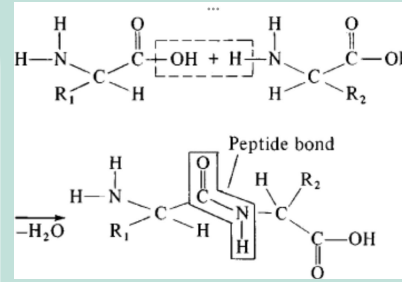
- DNA sequencing (**indirect**)
- **Direct** amino acids sequencing



Peptide Bond (Amide Bond)

- Each amino acid in a chain makes **2** peptide bonds.
- The amino acids at the **two ends of a chain make only 1 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

Residue: the molecule after remove water molecule



Peptides

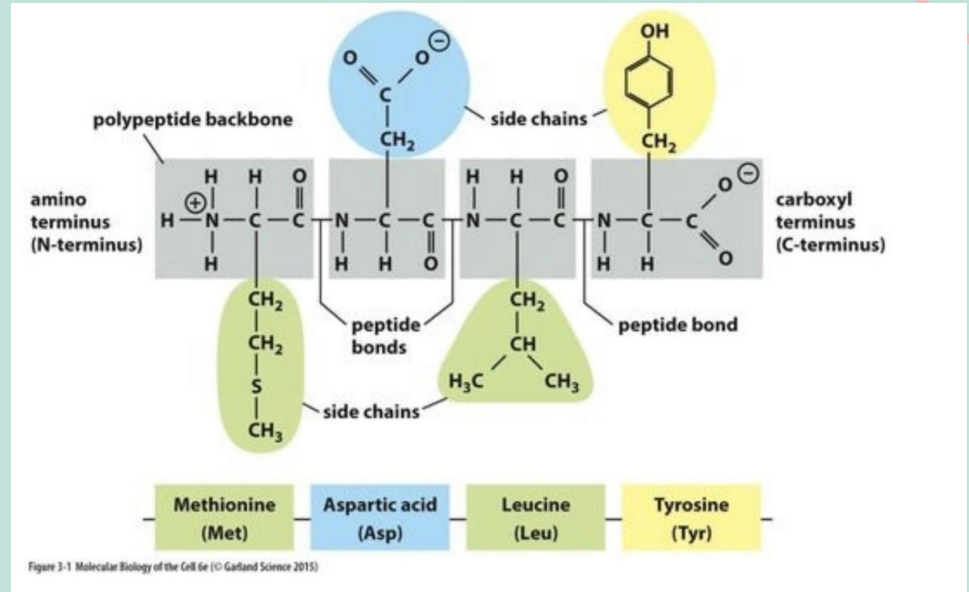
NOTE 438:

- Residue: amino acid in polypeptide chain
- We always read from N-terminus to C-terminus

Note:

- Tripeptide has 2 peptide bonds

Peptide bond=Amide bond



Peptides

Amino acids can be **polymerized** to form chains:

- Two amino acids → dipeptide → one peptide bond.
- Three amino acids → tripeptide → two peptide bonds.
- Four amino acids → tetrapeptide → three peptide bonds.
- Few (2-20 amino acids) → oligopeptide.
- More (>20 amino acids) → polypeptide.

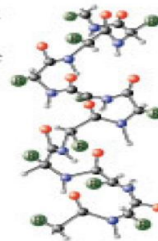
How to determine the primary structure sequence?

- DNA sequencing.
- Direct amino acids sequencing.

Secondary structure

- It is regular **arrangements** of amino acids that are located near to each other in the linear sequence.
- Excludes the conformations (3D arrangements) of its side chains.
- **α -helix**, **β -sheet** and **β -bend** are examples of secondary structures frequently found in proteins.

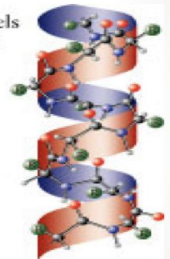
Ball-and-stick model of a portion of the α -helical secondary structure of a protein molecule



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



Secondary structure

α -helix:

- It is a right-handed spiral, in which side chains of amino acids extended outward.
- **Hydrogen bonds:** Stabilize the α -helix. form between the peptide bond carbonyl oxygen and amide hydrogen.
- Amino acids per turn: Each turn contains **3.6 amino acids**.

Secondary structure

Amino acids that disrupt an α -helix:

- **Proline** → imino group, interferes with the smooth helical structure.
- **Glutamate, aspartate, histidine, lysine** or **arginine** → form ionic bonds.
- Bulky side chain, such as **tryptophan**.
- Branched amino acids at the β -carbon, such as **valine** or **isoleucine**.

Secondary structure

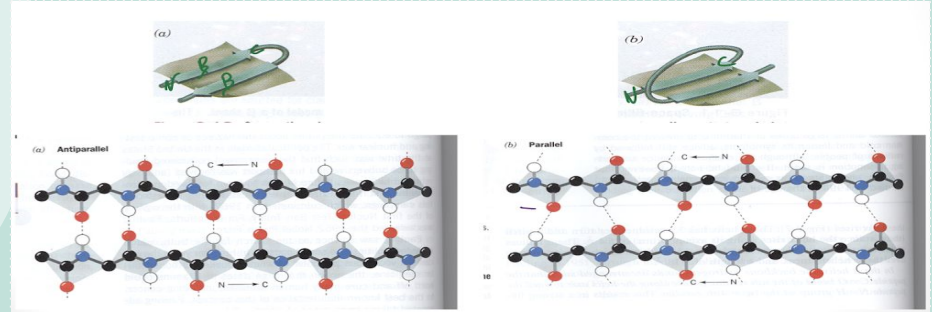
β -sheet:

Composition:

- Two or more polypeptide chains make **hydrogen bonding** with each other
- Also called **pleated sheets** because they appear as folded structures with edges

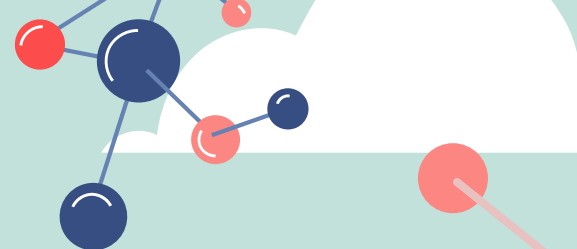
β -sheet:

- **Antiparallel**
- **Parallel**



Hydrogen bonds in parallel direction are less stable than in antiparallel direction

Other Secondary Structure Examples



1- β -bends (reverse turns)

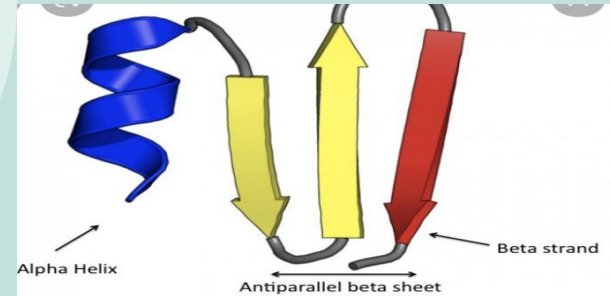
- Reverse the direction of a polypeptide chain
- Usually found on the surface of the molecule and often include charged residues
- The name comes because they often connect successive strands of antiparallel β -sheets
- β -bends are generally composed of four amino acids residues, proline or glycine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

Proline is in the β -bends frequently because it bends due to its imino group.

Glycine: is the smallest amino acids which makes it easier to bend.

2- Non-repetitive secondary

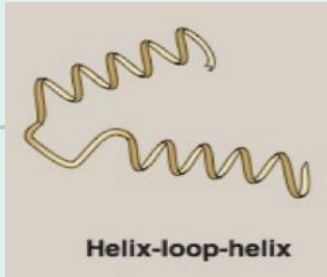
E.g. loop or coil conformation



Supersecondary Structure (Motifs)

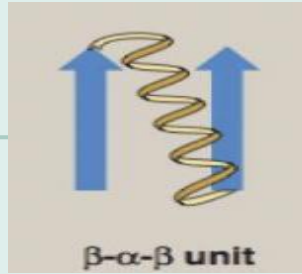
Supersecondary structure is a combination of secondary structural elements, such as:

α α motif:



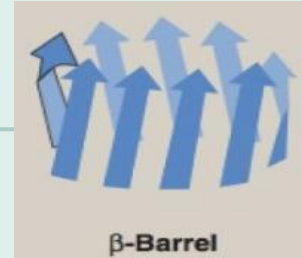
two α helices together

β α β motif:



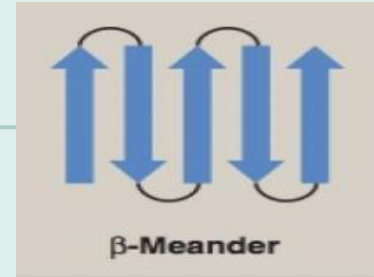
α helix connecting two β sheets

β barrels:



rolls of β sheets

β hairpin:



reverse turns connecting antiparallel β sheets

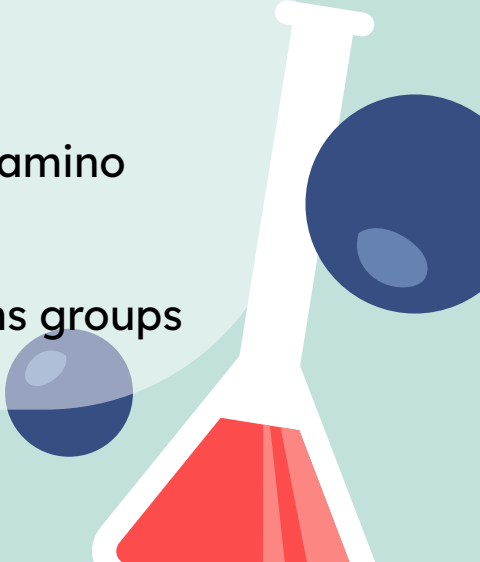
Tertiary Structure

- Tertiary structure: the three-dimensional (3D) structure of an entire polypeptide chain including side chain (**R**).
- Domains: the fundamental **functional** and 3D **structural** units.
- Polypeptide chains that have **>200** amino acids have 2 or more domains. The core of a domain: is built from combinations of supersecondary structural elements (**motifs**) and their side chain.
- Domains can combine to form tertiary structure

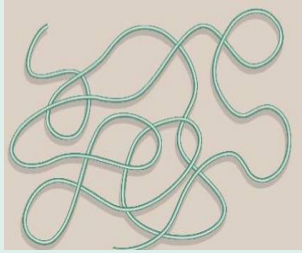


Tertiary Structure

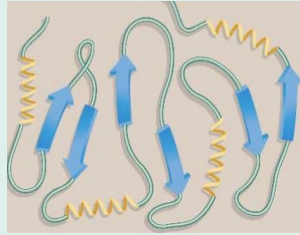
Interactions stabilizing tertiary structure:

- **Disulfide:** SS (Cysteine with Cysteine covalent bond).
 - **Hydrophobic interactions:** between nonpolar amino acids in the interior of the polypeptide (most important interaction that stabilizes the tertiary structure)
 - **Hydrogen bonds:** between polar and hydrophilic amino acids.
 - **Ionic interactions:** oppositely charged side-chains groups reactions
- 

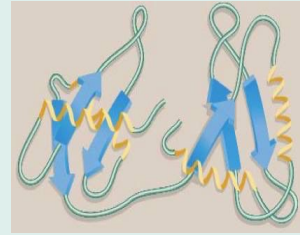
Protein Folding



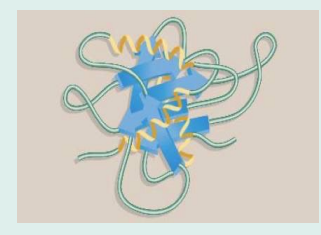
Primary structure



Secondary structure



Supersecondary Structure



Tertiary Structure

- Some proteins exist in quaternary structure (level of folding after tertiary)
- Chaperons are folded by other chaperons.

Chaperons:

- Specialized group of proteins, required for the proper folding of many species of protein
- Chaperons interact with polypeptides at various stages during the folding process

- Also known as “**heat shock**” proteins لأنه يزداد عند وجود الحرارة

- They make sure that the folding process is done right

Quaternary Structure

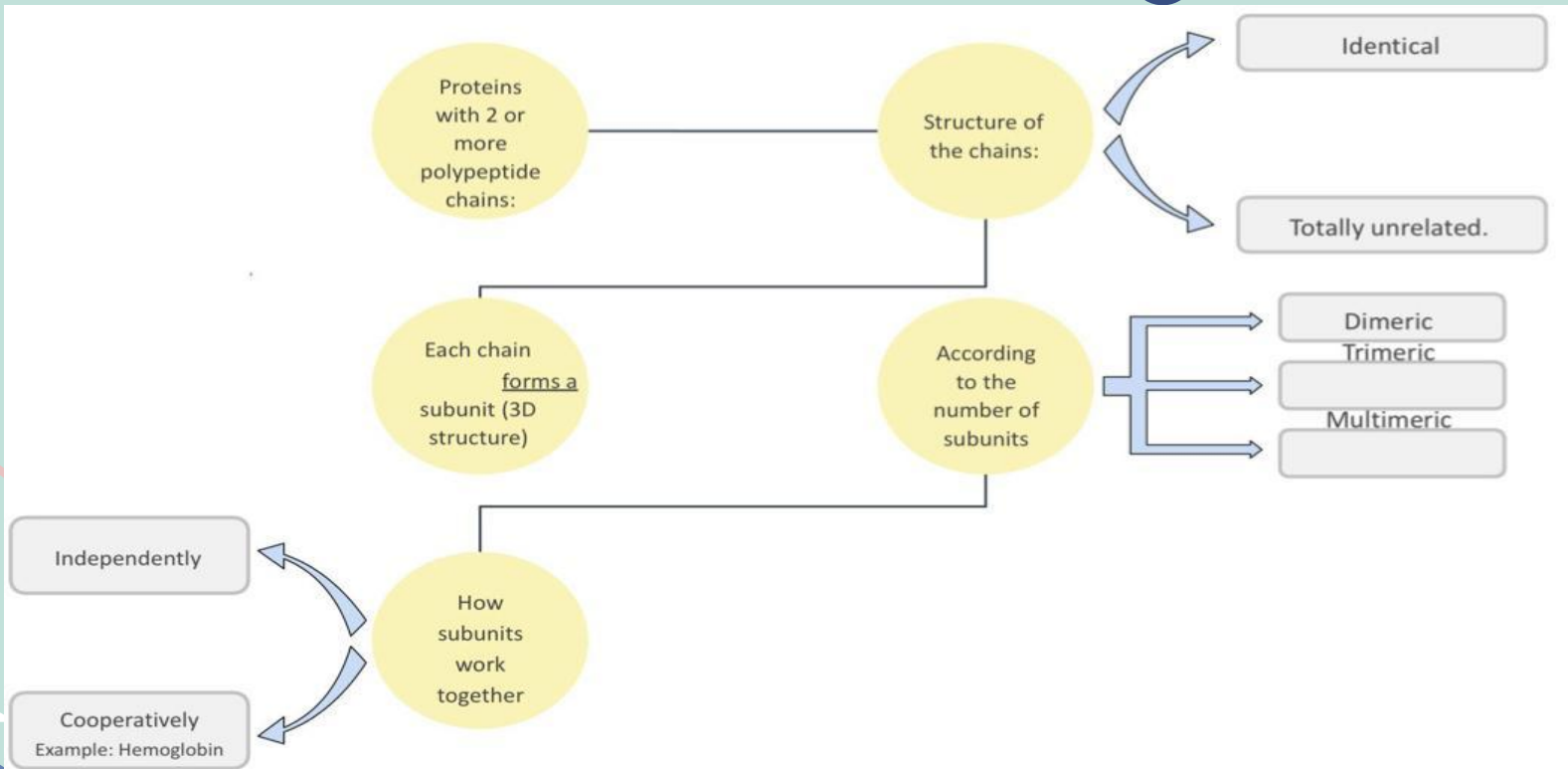
- Some proteins contain two or more polypeptide chains that may be structurally identical or totally unrelated
- Each chain forms a 3D structure called **subunit**.
- According to the number of subunits: **Dimeric**, **Trimeric**, **multimeric**
- Subunits may either function independently of each other,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

NOTE441:

- Protein has 1 polypeptide chain → the protein has 3 levels of structure only (primary, secondary, tertiary).
- Protein has >1 polypeptide chains → the protein has 4 levels of structure (primary, secondary, tertiary, quaternary).
- Nascent protein: the primary structure of a protein.
- Native protein: the mature protein that has been folded.
- The quaternary structure is the last complexity.

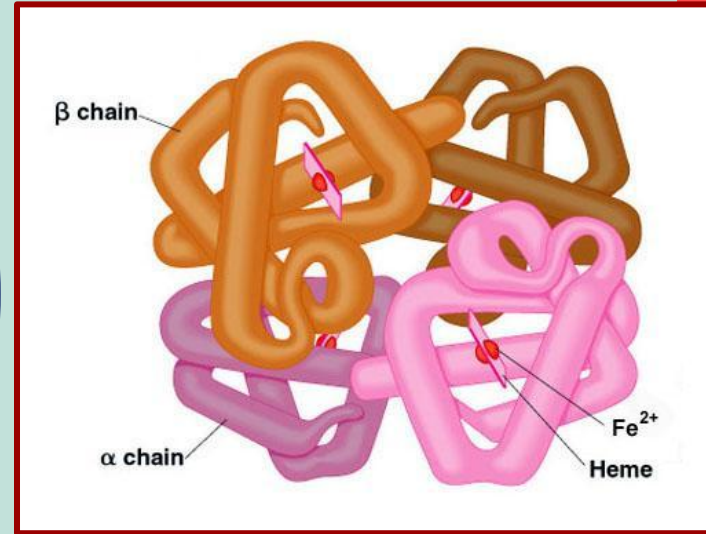
Quaternary Structure

441 Illustration




Hemoglobin

- 1- **Globular** protein (round/spherical)
- 2- α_2 and β_2 (4 subunits)
- 3- **Oligomer** (Multisubunit protein)
- 4- two identical subunits are called **proteomes**



Denaturation of Proteins

- 
- Denaturation 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 the solution

E.g the protein in the egg “albumin” once we put it in “heat” it will be denatured and become insoluble.



Denaturation agents

```
graph TD; A[Denaturation agents] --> B[Heat]; A --> C[Organic solvents]; A --> D[Mechanical mixing]; A --> E[Detergents]; A --> F[Strong acids or bases]; A --> G["Ions of heavy metals (e.g. lead and mercury)"]
```

Heat

Organic solvents

Mechanical mixing

Detergents

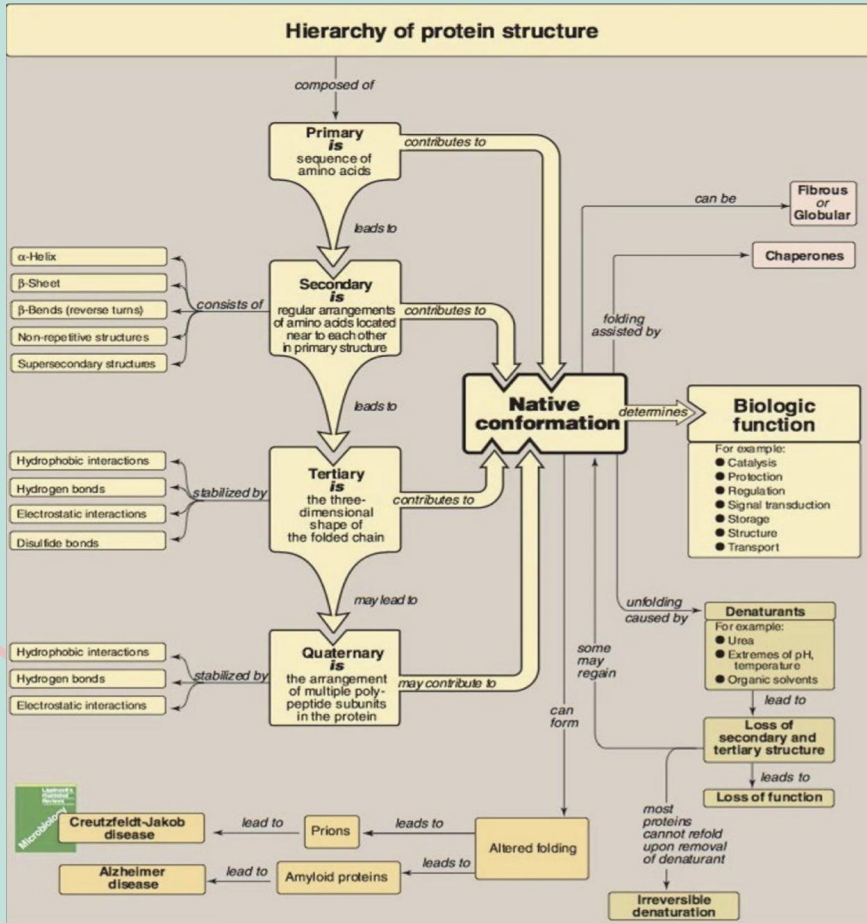
Strong acids or bases

Ions of heavy metals (e.g. lead and mercury)

Protein Misfolding

- Every protein must fold to achieve its normal conformation and function
- Abnormal folding of proteins leads to a number of diseases in human, e.g. Alzheimer's and prion diseases

Alzheimer's disease	Creutzfeldt-Jacob (prion) disease
<p>β amyloid protein is a misfolded protein. It forms fibrous deposits or plaques in the brain</p>	<p>Prion protein is present in normal brain tissues. In diseases brains, the same protein is misfolded. Therefore it forms insoluble fibrous aggregates that damage brain cells.</p>



Summary

Take Home Messages

- Native conformation of the protein: functional, fully folded structure.
- Unique 3D structure of native conformation is determined by primary structure (amino acid sequence)
- Interactions between amino acids 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 the protein's structure, which aren't accompanied by hydrolysis of peptide bonds.
- Diseases can occur when an apparently normal protein assumes a conformation that is cytotoxic, as in the case of Alzheimer's or Prion's disease.

Question 1

there are .. different types of amino acids?

A 9

C 11

B 10

D 20

Question 1

there are .. different types of amino acids?

A 9

C 11

B 10

D 20

Question 2

**Tripeptide
has ..?**

A

**2 peptide
Bonds**

B

**3 peptide
Bonds**

C

**4 peptide
Bonds**

Question 2

**Tripeptide
has ..?**

A

**2 peptide
Bonds**

B

**3 peptide
Bonds**

C

**4 peptide
Bonds**

Question 3

The amino acid with a free amino group is called carboxyl terminus?

True

False

Question 3

The amino acid with a free amino group is called carboxyl terminus?

True

False

Question 4

Two or more polypeptide chains make hydrogen bonding with each other?

True

False

Question 4

Two or more polypeptide chains make hydrogen bonding with each other?

True

False

Biochemistry Team

Yasser Almutairi

Ahmad Addas

Hossam Alhussain

Faisal Alomran

Abdullah Alzoom

Abdulrahman Almalki

Ziyad Alenazi

Ziyad Bukhari

Tariq Alshumrani

Talal Alrobaian

Mohammed Almurshid

Essam Nawaf

Abdullah Almutlaq

**Alanoud
Alnajawi**

Ghala Alyousef

Huda Bassam

Manar Alqahtani

Marwa Fal

Jenan Al-Sayari

Rahaf Aldawood

Mays Altokhais

Lura Almusaeib

Shaden Alotaibi

Aljawharah Alyahya

Norah Albahdal

Ghaida Alotaibi

Ghida Alkahtani

Lama Alhayan

Shaden Alshammari

Team Med444