Biochemistry

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TERTIARY STRUCTURE OF GLOBULAR PROTEINS

The primary structure of a polypeptide chain determines its **tertiary structure.** [Note: "Tertiary" refers both to the folding of domains and the final arrangement of domains in the polypeptide.]. **Hydrophobic side chains** are buried in the **interior,** whereas **hydrophilic groups** are generally found on the **surface** of the molecule. All hydrophilic groups located in the interior of the polypeptide are involved in hydrogen bonds or electrostatic interactions. [Note: The α-helix and β-sheet structures provide maximal hydrogen bonding for peptide bond components within the interior of polypeptides. This eliminates the possibility that water molecules may become bound to these hydrophilic groups and, thus, disrupt the integrity of the protein.]

Interactions stabilizing tertiary structure

The unique three-dimensional structure of each polypeptide is determined by its amino acid sequence. Interactions between the amino acid side chains guide the folding of the polypeptide to form a compact structure. Four types of interactions cooperate in stabilizing the tertiary structures of globular proteins.

1-Disulfide bonds: A disulfide bond is a covalent linkage formed from the sulfhydryl group (-SH) of each of **two cysteine residues ,**to produce a **cystine** residue. The two cysteines may be separated from each other by many amino acids in the primary sequence of a polypeptide, or may even be located on two different polypeptide chains; the folding of the polypeptide chain (s) brings the cysteine

residues into proximity, and permits covalent bonding of their side chains. A disulfide bond contributes to the stability of the three-dimensional shape of the protein molecule . For example, many disulfide bonds are found in proteins such as immunoglobulins that are secreted by cells. [Note: These strong, covalent bonds help stabilize the structure of proteins, and prevent them from becoming denatured in the extracellular environment.]

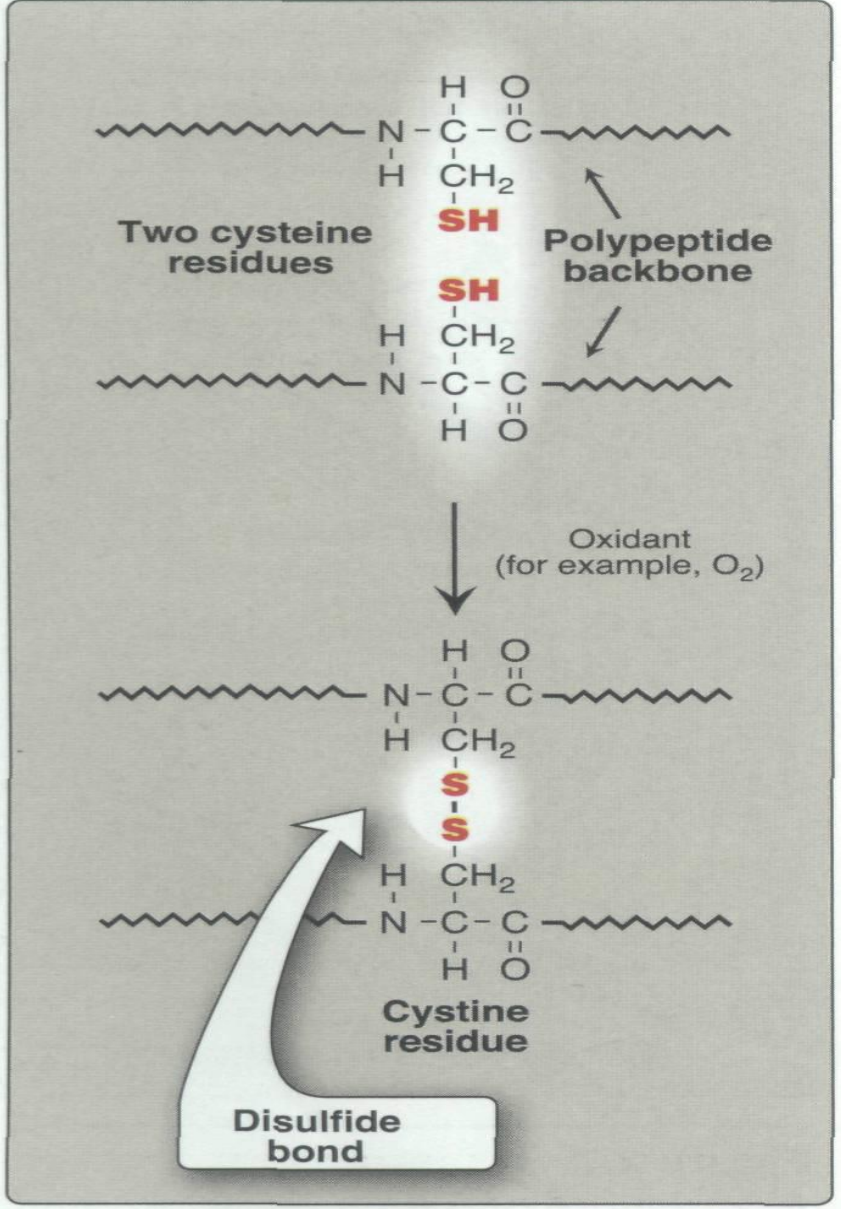


Figure 2.9
Formation of a disulfide bond by the oxidation of two cysteine residues, producing one cystine residue.

2-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 acids .In contrast, amino acids with polar or charged side chains tend to be located on the surface of the molecule in contact with the polar solvent. [Note: Proteins located in nonpolar (lipid) environments, such as a membrane, exhibit the reverse arrangement that is, hydrophilic amino acid side chains are located in the interior of the polypeptide, whereas hydrophobic amino acids are located on the surface of the molecule in contact with the nonpolar environment .] .In each case, the segregation of R-groups occurs that is energetically most favorable.

3. Hydrogen bonds: Amino acid side chains containing oxygen- or nitrogen-bound hydrogen, such as in the alcohol groups of serine and threonine, can form hydrogen bonds with electron-rich atoms, such as the oxygen of a carboxyl group or carbonyl group of a peptide bond . Formation of hydrogen bonds between polar groups on the surface of proteins and the aqueous solvent enhances the solubility of the protein.

4. Ionic interactions: Negatively charged groups, such as the carboxyl group (-COO-) in the side chain of aspartate or glutamate, can interact with positively charged groups, such as the amino group (NH3+) in the side chain of lysine.

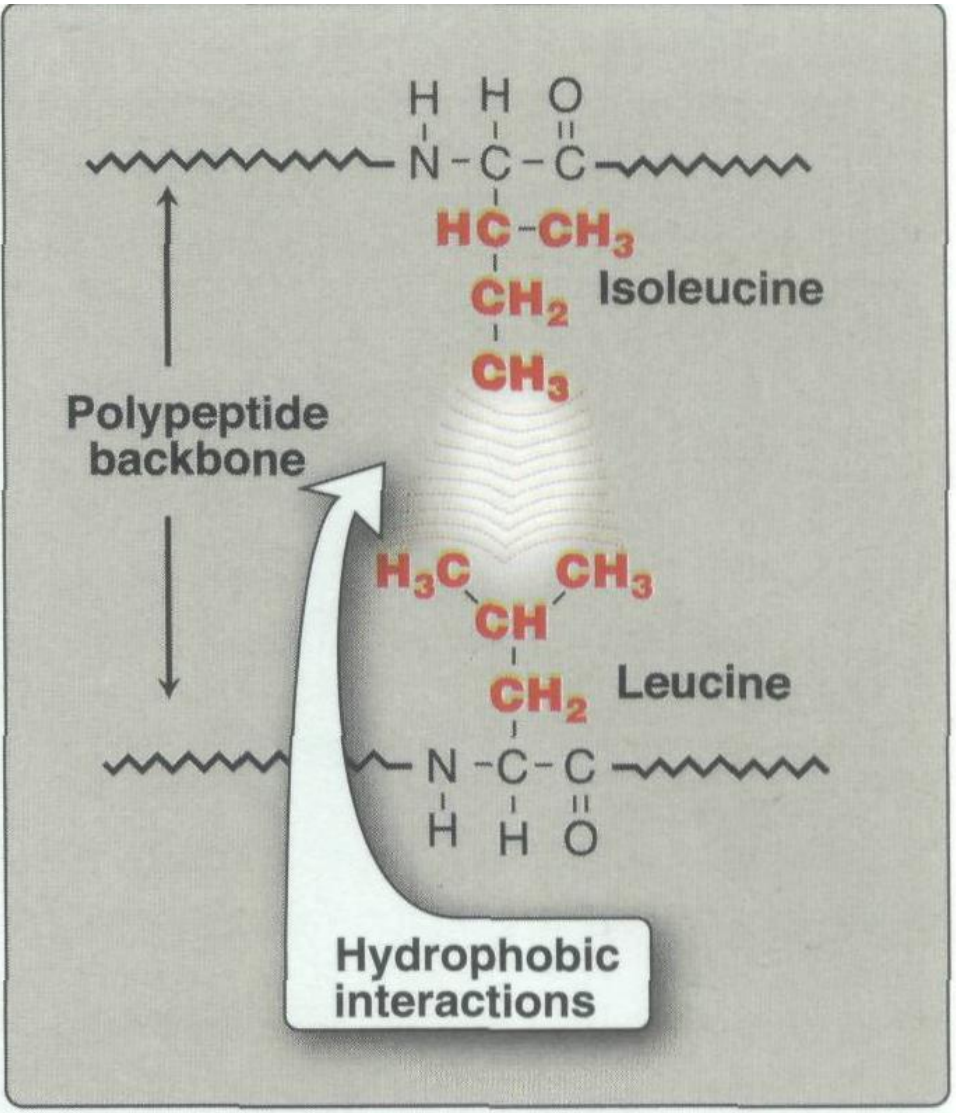


Figure 2.10
Hydrophobic interactions between amino acids with nonpolar side chains.

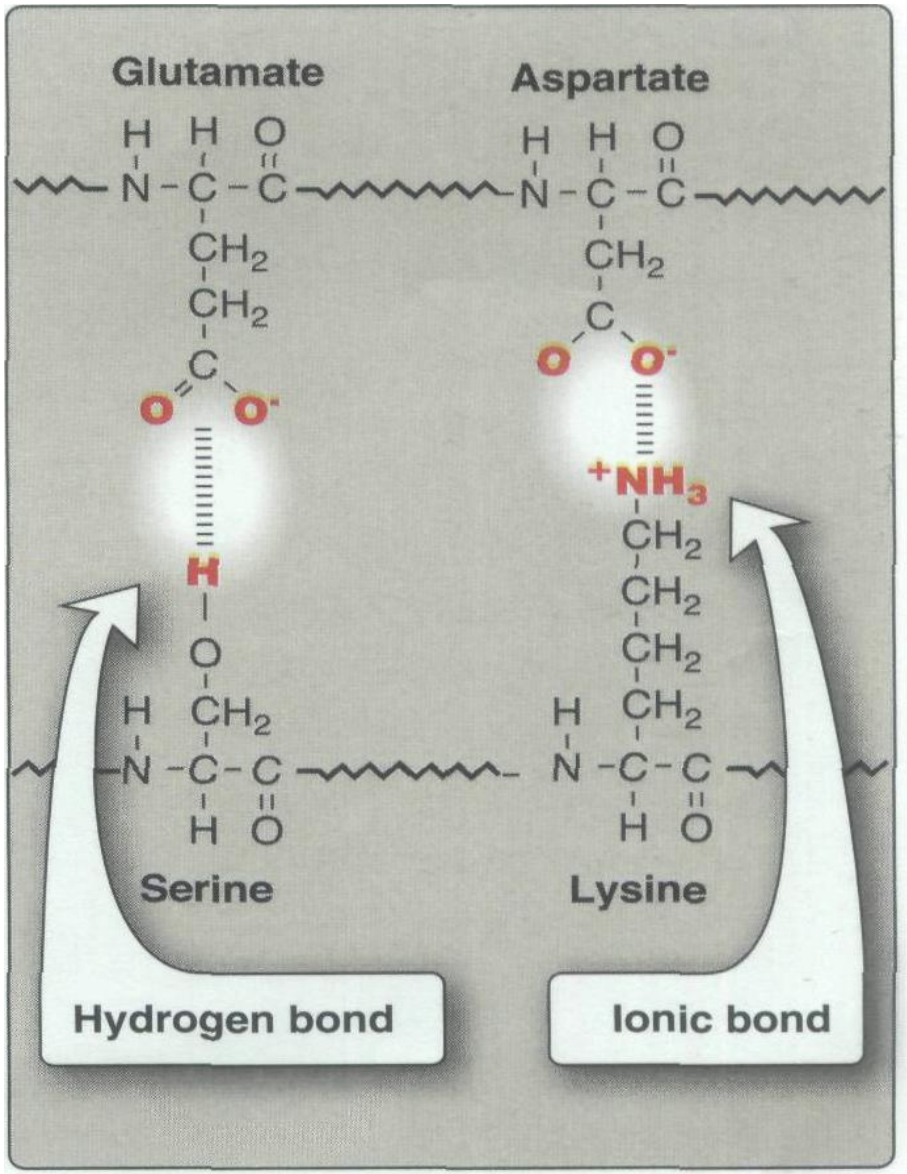
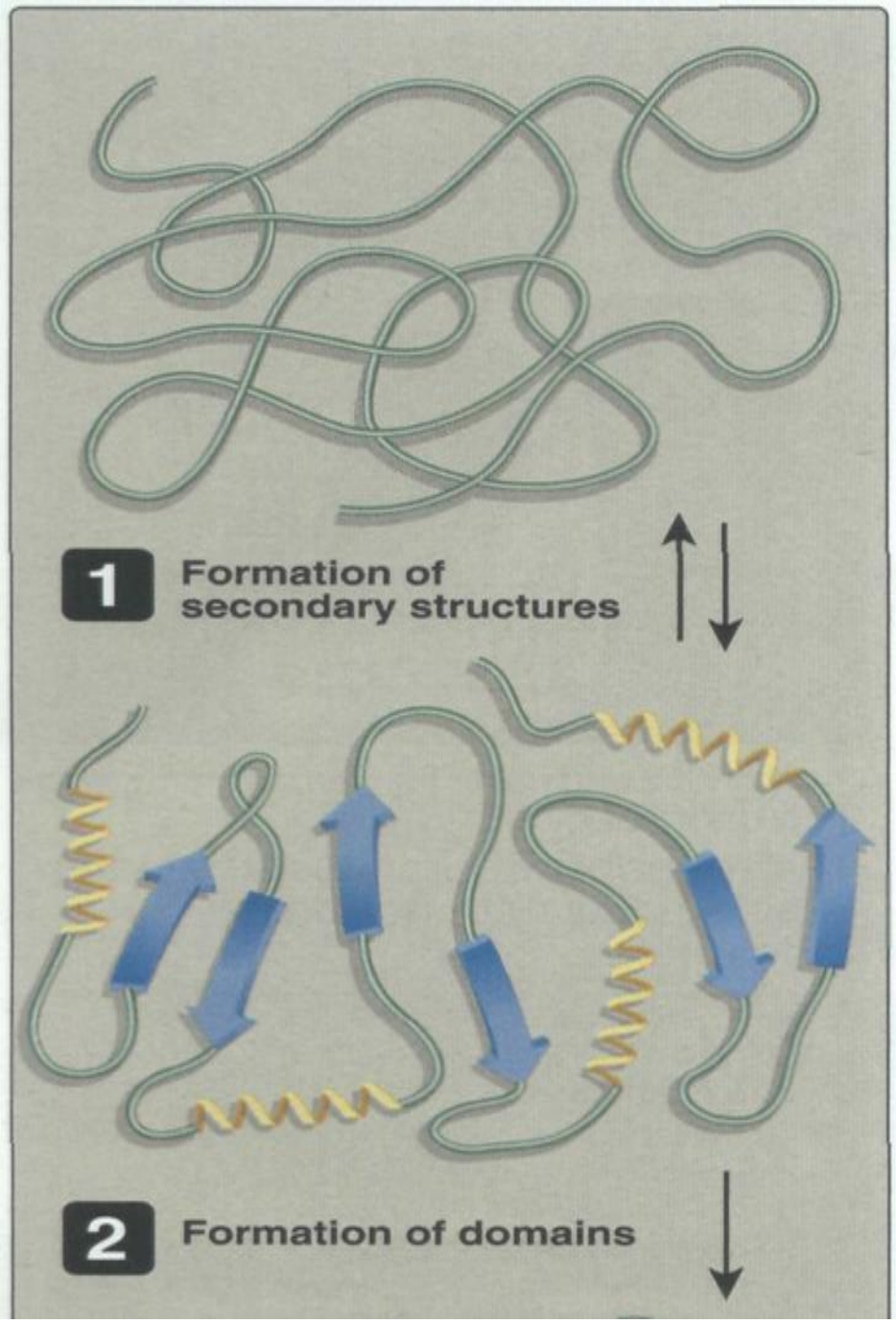


Figure 2.11
Interactions of side chains of amino acids through hydrogen bonds and ionic bonds.

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. Protein folding, which occurs within the cell in seconds to minutes, employs a shortcut through the maze of all folding possibilities. As a peptide folds, its amino acid side chains are attracted and repulsed according to their chemical properties. For example, positively and negatively charged side chains attract each other. Conversely, similarly charged side chains repel each other. In addition, interactions involving hydrogen bonds, hydrophobic interactions, and disulfide bonds all seek to exert an influence on the folding process.



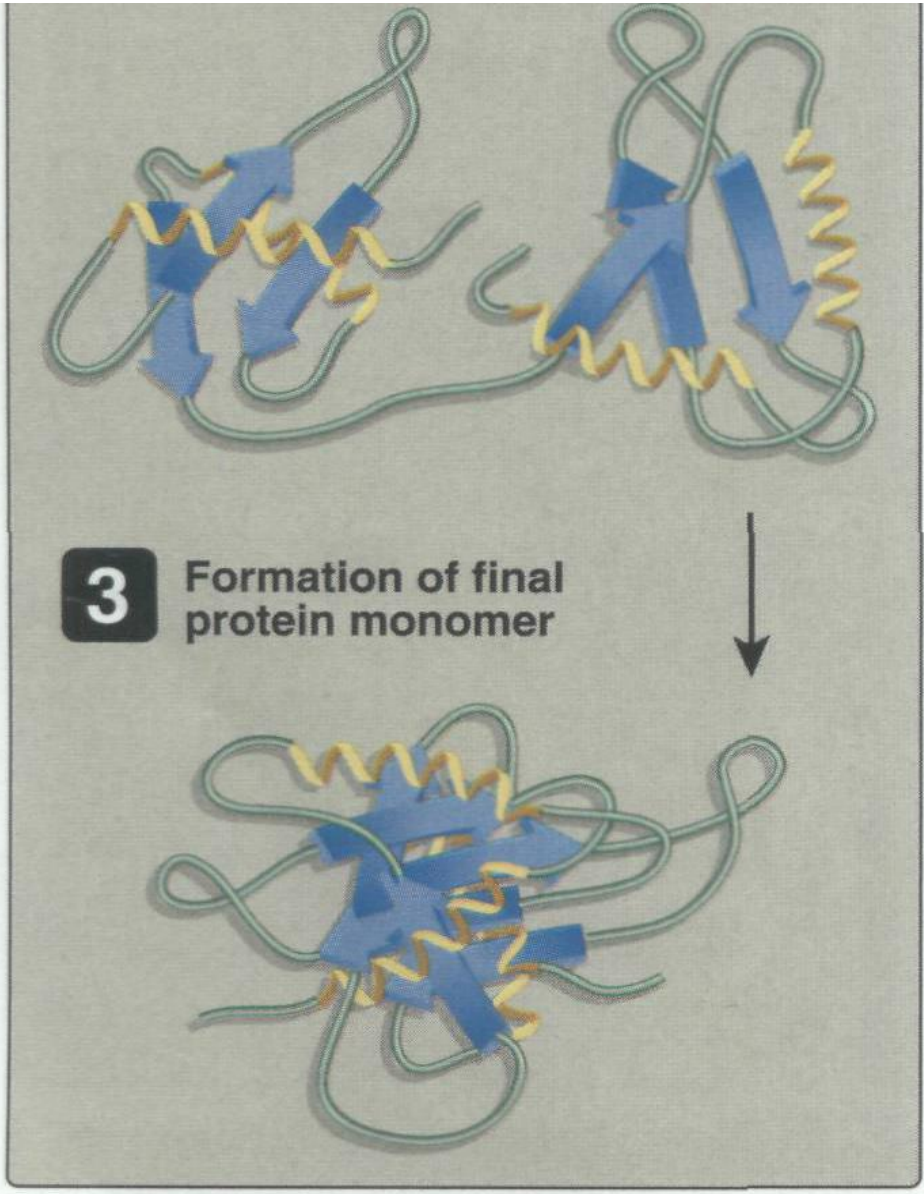


Figure 2.12
Steps in protein folding.

Role of chaperones in protein folding

It is generally accepted that the information needed for correct protein folding is contained in the primary structure of the polypeptide. Given that premise, it is difficult to explain why most proteins when denatured do not resume their native conformations under favorable environmental conditions. One answer to this problem is that a protein begins to fold in stages during its synthesis, rather than waiting for synthesis of the entire chain to be totally completed. This limits competing folding configurations made available by longer stretches of nascent peptide. In addition, a specialized group of proteins, named "chaperones," are required for the proper folding of many species of proteins.

The chaperones also known as "heat shock protein " interact with the polypeptide at various stages during the folding process. Some chaperones are important in keeping the protein unfolded until its synthesis is finished, or act as catalysts by increasing the rates of the final stages in the folding process. Others protect proteins as they fold so that their vulnerable, exposed regions do not become tangled in unproductive encounters.

QUATERNARY STRUCTURE OF PROTEINS

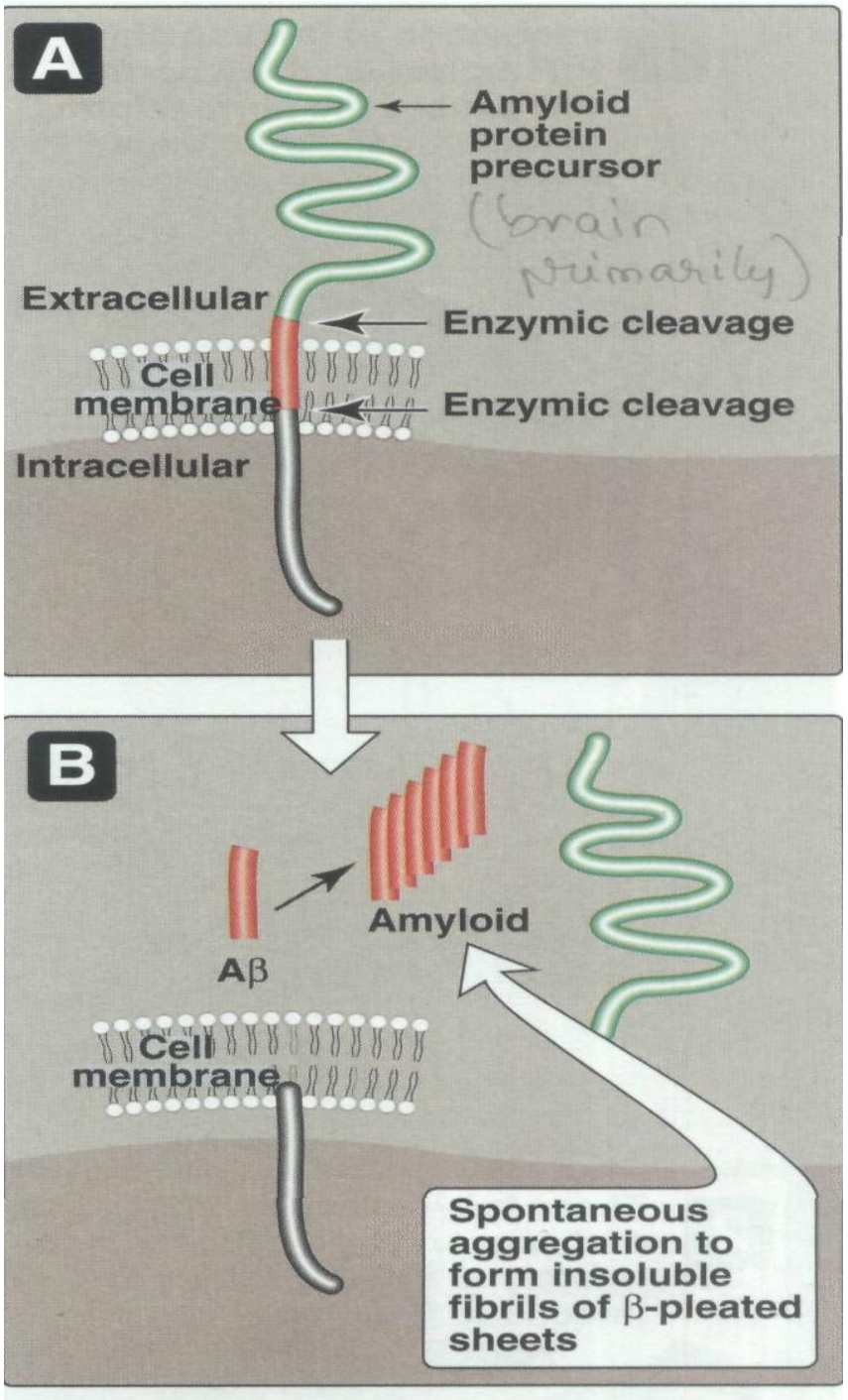
Many proteins consist of a single polypeptide chain, and are defined as monomeric proteins.. The arrangement of these polypeptide subunits is called the quaternary structure of the protein. [Note: If there are two subunits, the protein is called dimeric if three trimeric subunits and, if several subunits, multimeric Subunits that may be structurally identical or totally unrelated are held together by noncovalent interactions (for example, hydrogen bonds, ionic bonds, and hydrophobic interactions). Subunits may either function independently of each other, or may work cooperatively, as in hemoglobin, in which the binding of oxygen to one subunit of the tetramer increases the affinity of the other subunits for oxygen

Denaturation of proteins

Protein denaturation results in the unfolding and disorganization of the protein's secondary and tertiary structures, which are not accompanied by hydrolysis of peptide bonds. Denaturing agents include heat, organic solvents, mechanical mixing, strong acids or bases, detergents, and ions of heavy metals such as lead and mercury. Denaturation may, under ideal conditions, be reversible, in which case the protein refolds into its original native structure when the denaturing agent is removed. However, most proteins, once denatured, remain permanently disordered. Denatured proteins are often insoluble and, therefore, precipitate from solution.

Amyloidoses

Misfolding of proteins may occur spontaneously, or be caused by a mutation in a particular gene, which then produces an altered protein. In addition some apparently normal proteins can, after abnormal proteolytic cleavage, take on a unique conformational state that leads to the formation of long, fibrillar protein assemblies consisting of β-pleated sheets. Accumulation of these spontaneously aggregating proteins, called amyloids, has been implicated in many degenerating disease particularly in the neurodegenerative disorder, Alzheimer disease.



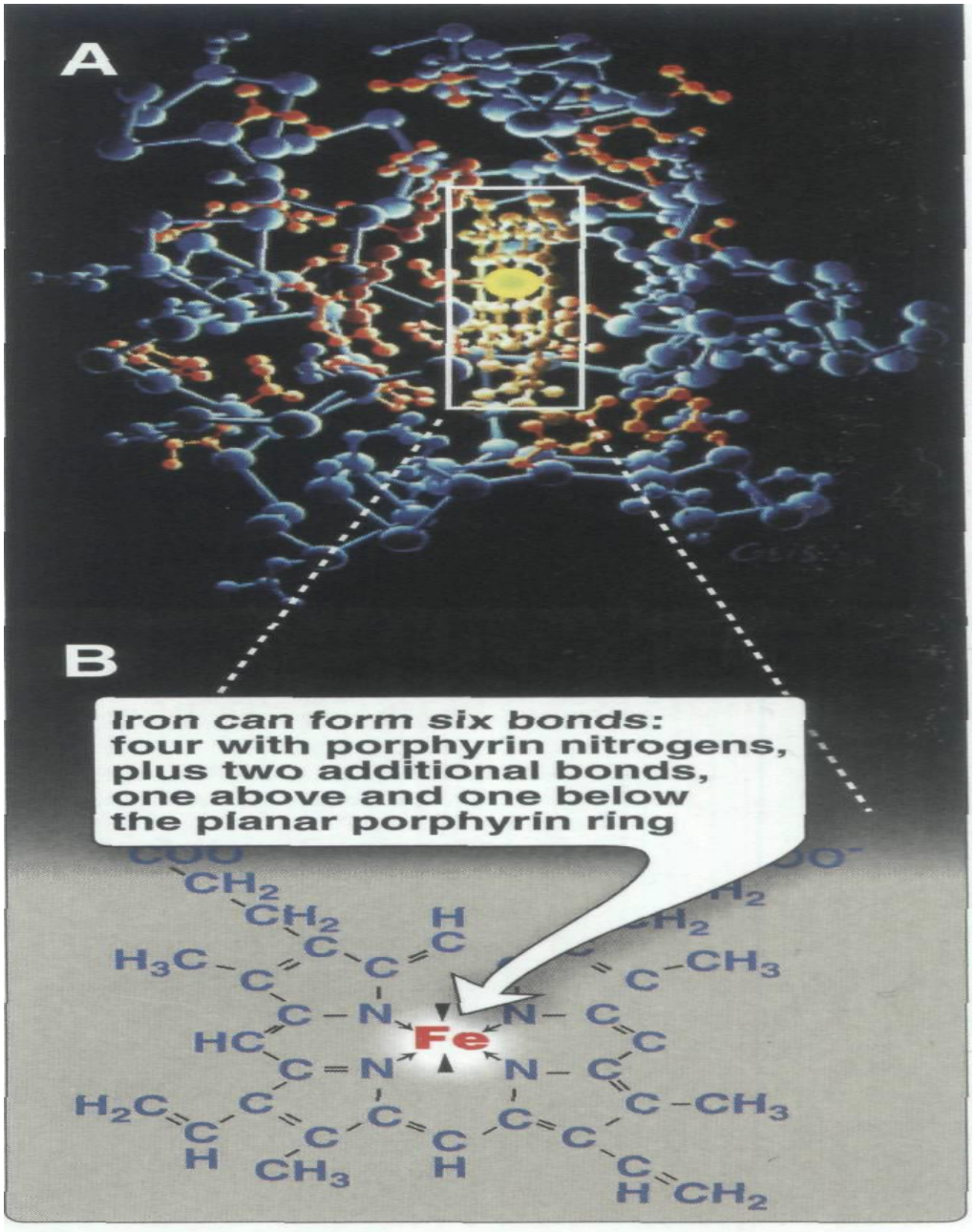


Figure 3.1
A. Hemeprotein (cytochrome c).
B. Structure of heme.

Globular Proteins

Hemoproteins are a group of specialized proteins that contain heme as a tightly bound prosthetic group. The role of the heme group is dictated by the environment created by the three-dimensional structure of the protein. For example, the heme group of a cytochrome functions as an electron carrier that is alternately oxidized and reduced . In contrast, the heme group of the enzyme catalase is part of the active site of the enzyme that catalyzes the breakdown of hydrogen peroxide. In hemoglobin and myoglobin, the two most abundant heme-proteins in humans, the heme group serves to reversibly bind oxygen.

Structure of heme

Heme is a complex of **protoporphyrin IX** and **ferrous iron Fe2+**. The iron is held in the center of the heme molecule by bonds to the four nitrogens of the porphyrin ring. The heme **Fe2+** can form two additional bonds, one on each side of the planar porphyrin ring. For example, in myoglobin and hemoglobin, one of these positions is coordinated to the side chain of a histidine residue of the globin molecule, whereas the other position is available to bind oxygen .

Fibrous Proteins

Collagen and elastin are examples of common, well-characterized fibrous proteins that serve structural functions in the body. For example, collagen and elastin are found as components of skin, connective tissue, blood vessel walls, and sclera and cornea of the eye. Each fibrous protein exhibits special mechanical properties, resulting from its unique structure, which are obtained by combining specific amino acids into regular, secondary structural elements. This is in contrast to globular proteins, whose shapes are the result of complex interactions between secondary, tertiary, and, sometimes, quaternary structural elements.

COLLAGEN

Collagen is the most abundant protein in the human body. A typical collagen molecule is a long, rigid structure in which three polypeptides (referred to as "α-chains") are wound around one another in a rope-like triple-helix . Although these molecules are found throughout the body, their types and organization are dictated by the structural role collagen plays in a particular organ.

ELASTIN

In contrast to collagen, which forms fibers that are tough and have high tensile strength, elastin is a connective tissue protein with rubber-like properties. Elastic fibers composed of elastin and glycoprotein microfibrils are found in the lungs, the walls of large arteries, and elastic ligaments. They can be stretched to several times their normal length, but recoil to their original shape when the stretching force is relaxed.