PROTEIN FOLDING

PRINCIPLE OF PROTEIN FOLDING

- Protein folding is a process in which a polypeptide folds into a specific, stable, functional, three-dimensional structure. It is the process by which a protein structure assumes its functional shape or conformation.
- Proteins are comprised of amino acids with various types of side chains, which may be hydrophobic, hydrophilic or electrically charged. It is now well known that under physiological conditions, proteins normally spontaneously fold into their native conformations but there are some exterior factors which help polypeptide chain finding its natural shape.
- Different levels of folding a protein after amino acid sequence or primary structure consist of secondary, tertiary and quaternary structures. Protein folding pathway or mechanism is the typical sequence of structural changes; in which protein find its native structure.
- 3D structure of proteins is studied by scientists using different methods and there are many types of software to survey this. Many factors control protein folding, interior and exterior factors. Creation of natural folded proteins by these factors and protein translation are simultaneous.
- Protein folding is a very sensitive process that is influenced by several external factors including electric and magnetic fields, temperature, pH, chemicals, space limitation and molecular crowding. These factors influence the ability of proteins to fold into their correct functional forms.
- Misfolded proteins denature easily and lose their structure and function. Incorrect protein folding can lead to many human diseases. Alzheimer's disease is an example of a neurodegenerative condition caused by protein misfolding.
- One approach to studying the protein folding process is the application of statistical mechanics techniques and molecular dynamics simulations to the study of protein folding.
- Some cells contain heat shock proteins or chaperones that protect proteins in the cell against heat denaturation. Chaperones help proteins to fold and remain folded under extreme temperatures. They also assist misfolded proteins in unfolding and re-folding correctly.

The Role of Chaperones in Protein Folding

- Chaperones are a group of proteins that have functional similarity and assist in protein folding. Chaperones play a very important role within the cytoplasm preventing aggregation and promoting various important functions such as translocation, degradation, and suitable protein folding.
- There are several families of chaperones and each possesses different functions. Example of chaperon proteins are the "heat shock proteins" (Hsps).
- The name Hsp was given after these proteins were discovered in bacterium. These bacteria produced more of these proteins in stressful conditions, such as higher temperatures, pH variation and hypoxic conditions. Two examples of Hsps are Hsp70 and Hsp60.

- As seen in Hsp70, Hsp60 also has two different forms. The first state is the binding form, in which ATP is bound and the unfolded proteins can enter the hole between the two rings. Hydrolysis of ATP then initiates the formation of an enclosed state, called the folding-active state. This conformational change prevents the protein from leaving and encourages folding of the proteins. This enclosed state last for around 15 seconds before the conformation changes back and the properly folded protein is released into the cytoplasm.

Hsp70

- The Hsp70 chaperone proteins are folding catalysts that assist in many kinds of folding processes such as refolding or misfolding of aggregated proteins, and folding and assembling of new proteins. These proteins are monomeric and contain two different domains called the N and C terminals. The N terminal contains ATPase whilst the C terminal binds to the substrate. ATP hydrolysis within the N terminal allows the C terminal to open and bind to the substrate.
- Hsp70 recognizes a region of the unfolded polypeptide chain termed the "extended region". This extended region contains many hydrophobic residues. Binding of Hsp70 prevents the aggregation of these proteins.

MECHANISM OF Hsp 70

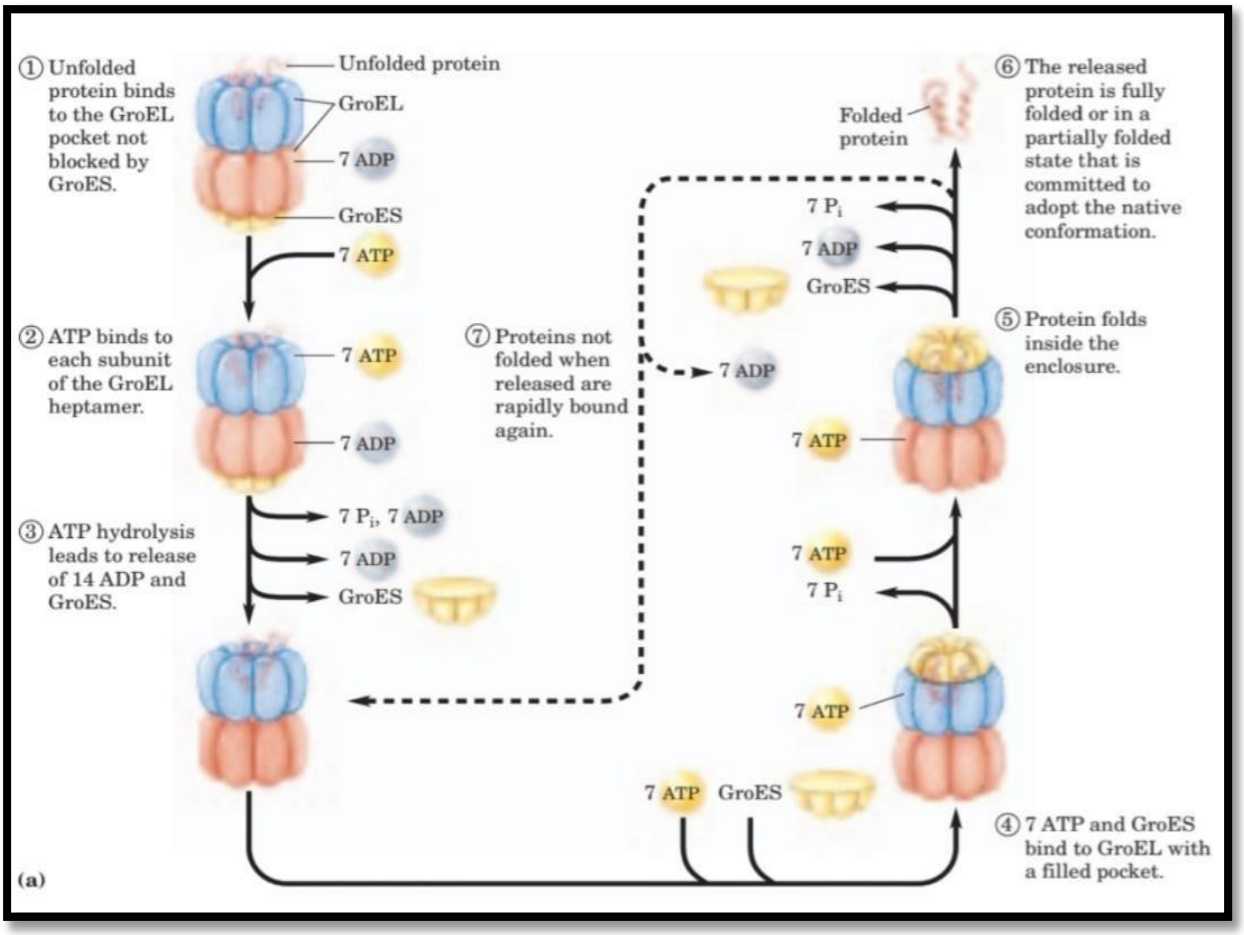
- Hsp70 proteins also block the folding of certain proteins that must remain unfolded until they have been translocated across Membranes. Some chaperones also facilitate the quaternary assembly of oligomeric proteins.
- The Hsp70 proteins bind to and release polypeptides in a cycle that also involves several other proteins (including a class called Hsp40) and ATP hydrolysis.
- Illustrates chaperone- assisted folding as elucidated for the chaperones DnaK and DnaJ in E. coli, homologs of the eukaryotic Hsp70 and Hsp40.

- DnaK and DnaJ were first identified as proteins required for in vitro replication of certain viral DNA molecules (hence the “Dna” designation).
- Chaperones in protein folding. The cyclic pathway by which chaperones bind and release polypeptides is illustrated for the E. coli chaperone proteins DnaK and DnaJ, homologs of the eukaryotic chaperones Hsp70 and Hsp40.
- The chaperones do not actively promote the folding of the substrate protein, but instead prevent aggregation of unfolded peptides.
- For a population of polypeptides, some fraction of the polypeptides released at the end of the cycle are in the native conformation.
- The remainder are rebound by DnaK or are diverted to the chaperonin system.

Hsp60

- Like Hsp70, Hsp60 chaperone proteins also have the ability to bind to exposed hydrophobic residues to form aggregates that are stable but inactive. These proteins are not involved in preventing aggregation, but instead function to quarantine and isolate unfolded proteins. The isolation also prevents the polypeptide chain from aggregating into clumps with other chains within the cytoplasm.
- Hsp 60 contains 14 different proteins components. These proteins form two rings, each made of 7 proteins, which are placed on top of each other. Unfolded proteins within these rings are then able to fold without aggregating with other unfolded proteins and without interference from Hsp70.

MECHANISM OF Hsp 60



- HSP60 homologs are found in all organisms investigated and can be divided into two groups: GroEL of eubacteria, mitochondrial HSP60 of eukaryotes, and plastid Rubisco subunit binding protein of plants are classified to group I, while chaperonins of archaebacteria and chaperonin containing TCP-1 (CCT) of eukaryotic cytosol are classified to group II.
- HSP60 family members play essential roles in recovery of denatured proteins under stress conditions and also in protein synthesis during cell growth and survival.
- The GroEL subunits are arranged as two stacked heptameric rings with a central cavity where folding takes place. The GroES subunits form a single heptameric ring that binds to one of the GroEL rings regulating its function.
- ADP is tightly bound to the subunits in the ring adjacent to GroES and with lower affinity in the opposite ring. Unfolded protein binds to GroEL ring opposite to GroES and triggers ADP dissociation from GroEL subunits. This in turn results in the release of GroES. ADP–ATP exchange weakens the affinity for the bound protein.
- GroES rebinds GroEL in the ATP state and may cover the ring that contains the bound substrate. Cooperative ATP hydrolysis releases the substrate protein for folding in the ring cavity. GroES binding becomes stabilized in the regained ADP state, and partially folded protein may reassociate for another round of interaction.