ASSIGNMENT (CLASS - 31.03.2020)
BIOMOLECULAR STRUCTURES

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Chaperone and Chaperonin Proteins

Why do we need them?

Protein in its native conformation usually has the lowest free energy, and given enough time, all proteins will eventually assume their correct fold. In most cases, proteins would require a very long time during which they get trapped in states that have a free energy which is higher than that of the native state, but lower than that of all neighbouring conformations. Unfolding such misfolded proteins therefore requires a high activation energy and hence is a slow process and not very feasible.

While some proteins can go from unstructured to folded all by themselves, not all proteins can do this and since many proteins don't fold by themselves.

What are Chaperones and Chaperonins?

Such proteins instead get help from proteins called chaperones and chaperonins.

Chaperone

Chaperones assist the appropriate noncovalent folding of proteins but are not components of the proteins formed are called chaperones. The function of chaperones is not structure-dependent. They inhibit the side reactions during self folding or control the speed of the process in a catalytic or non-catalytic manner.

Classes of chaperones

There are several classes categorised by molecular size, cellular compartment and function that cooperate in folding proteins. The largest chaperone families are Hsp90 (Hsp of apparent molecular weight 90 kDa), Hsp70, Hsp60, Hsp40 or DnaJ (40-kDa Hsps), and the small heat shock proteins (sHsps).

*(Hsp are proteins that are produced by cells in response to exposure to stressful conditions)

Chaperonins

Chaperonins allow ATP-dependent folding of proteins and unfold misfolded proteins using energy from ATP-hydrolysis to break offending bonds. The Hsp60 class of chaperones is also referred to as chaperonins. Chaperonins comprised a two ring structure which can either be homo – dimeric or hetero – dimeric.

Classes of chaperonins

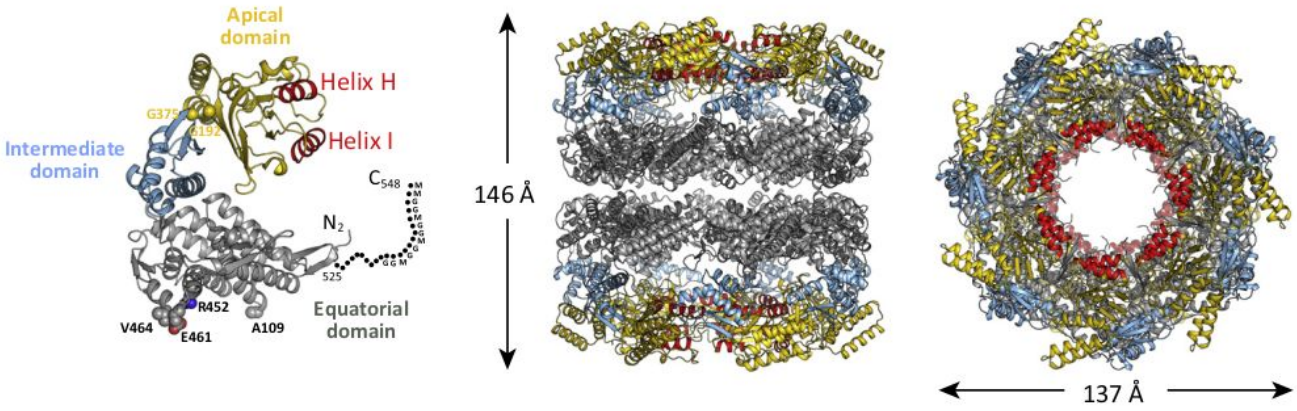
There are two classes of chaperonins based on the presence or absence of a co-chaperonin - Group I or Group II chaperonins. Group I chaperonins are prokaryotic and mainly include the bacterial heat shock proteins such as Hsp60 and prokaryotic GroEL. Group II chaperonins include the Archean and the eukaryotic chaperonins. Group I chaperonins usually consist of one repeating subunit, while group II chaperonins have a more complex structure.

GroEL/GroES System

GroEL along with its co-chaperone GroES is a folding chaperonin system in E.Coli. GroEL is a chaperonin and is found in many bacteria that is required for the proper folding of many proteins. It requires the lid-like co-chaperonin protein complex GroES.

Structures

GroEL

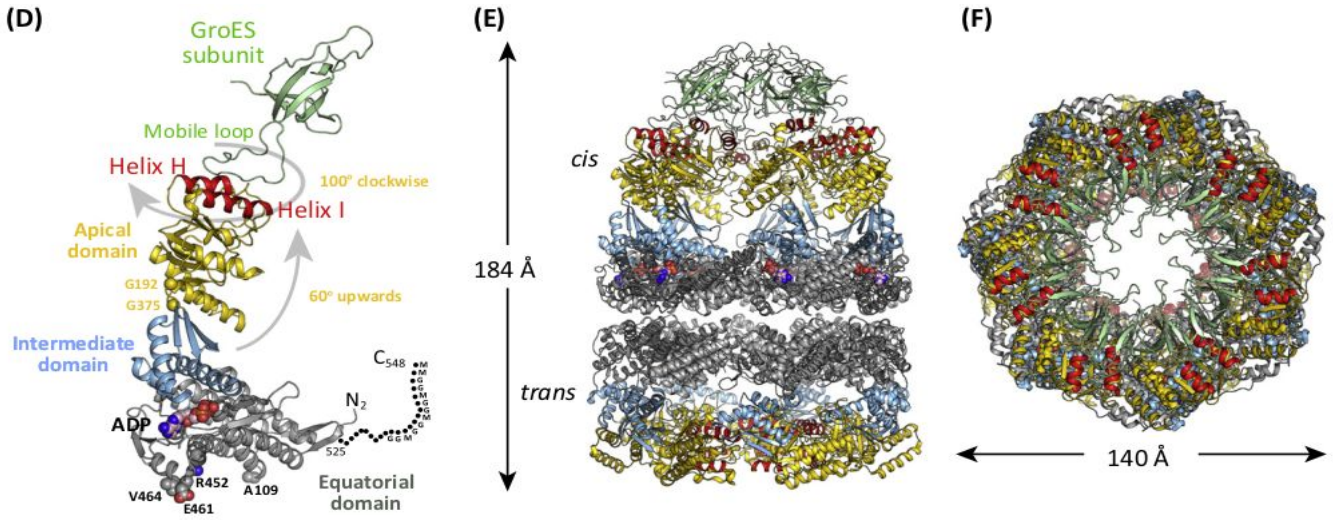


GroEL is a group I type of chaperonin present in EColi is a cylindrical complex of two seven membered rings of 57 kDa subunits. The two rings are stacked back-to-back in a staggered arrangement, with each subunit in one ring contacting two subunits in the opposite ring

Each subunit forms a u-shaped structure that contains three domains:

- Equatorial domain:
    - Contains nucleotide binding sites.
    - Provides all the intra- and inter-ring contacts between subunits.
    - It is ordered and largely helical.
- Apical domain:
    - Involved in poly-peptide binding
    - Contains the binding sites for GroES.
- Intermediate domain:
    - Connects the equatorial and apical domains
    - Binds the substrate protein

GroES

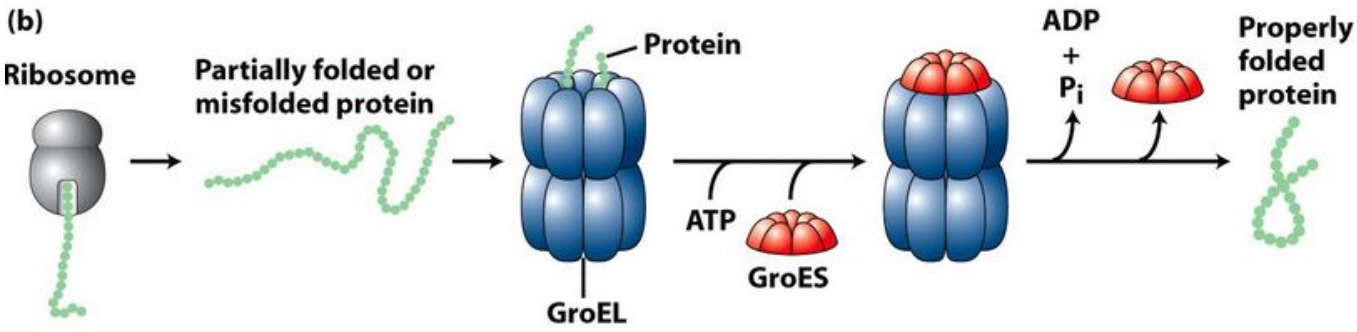


GroES is a dome-shaped seven membered ring of 10 kDa subunits that binds to the ends of the GroEL cylinder, forming the cage in which substrate protein is captured for folding. Each subunit is a core beta-barrel structure with two beta-hairpin loops.

*(Beta barrel: A beta-sheet composed of continuous repeats that twists and coils to form a closed toroidal structure)

*(Beta-hairpin: A motif involving two beta strands that look like a hairpin)

Reaction Cycle:



1. The Hydrophobic amino acids of the apical domain of the *trans* ring in an open GroEL capture non-native substrate proteins. (The acceptor state for non-native substrate protein is the nucleotide-free trans-ring of the GroEL–GroES complex)
2. ATP binds to the equatorial domain of a protein loaded ring and induces a conformational change in GroEL.
3. GroES is then able to bind to the apical domain, which releases the non-native substrate into the cavity. (The complex is now in its *cis* conformation)

4. ATP is hydrolyzed within the cis complex, which leads to binding of ATP to the other (unoccupied) trans GroEL ring. (The second ATP binding event releases GroES from the complex, and the substrate protein into the cell)