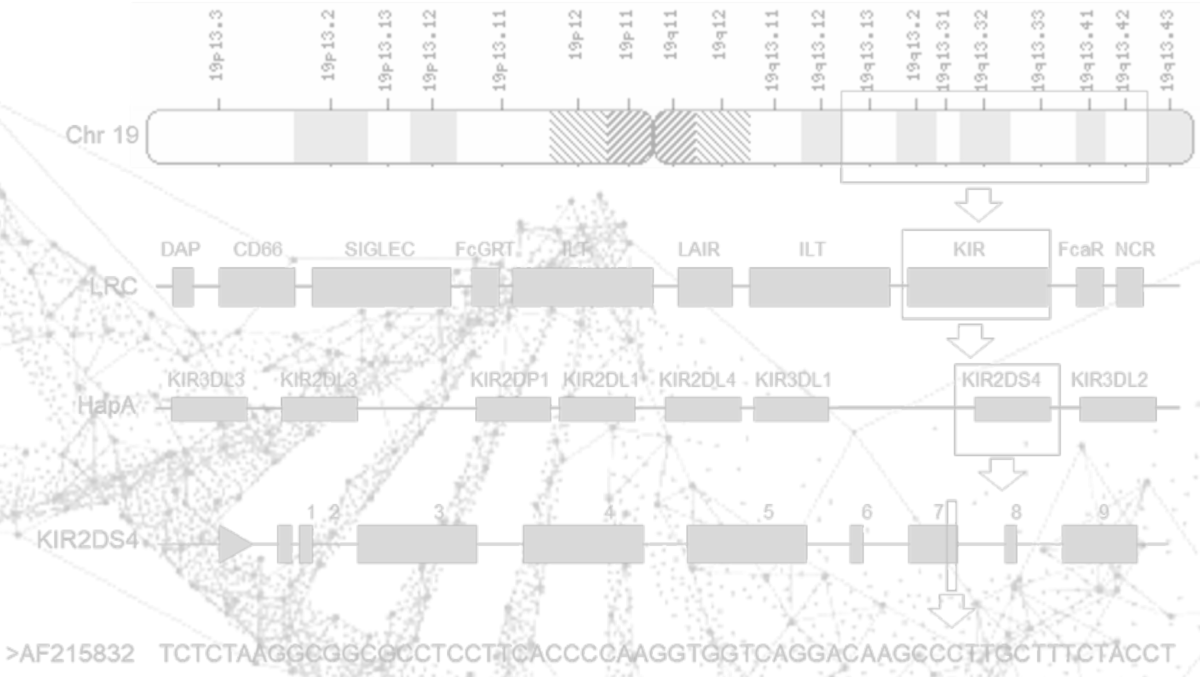

Chaperones

San Luis Potosi State University (UASLP) Mexico
Molecular Biology Course, Faculty of Medicine post-graduate program

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Viral & Human Genomics BSL-3 Laboratory

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Discovery and early history

Heat shock proteins discovered by Ferruccio Ritossa in 1962 in Drosophila, observing chromosomal puffing patterns in response to heat stress.

The term "chaperone" coined by Ron Laskey in 1978 while studying nucleosome assembly.

Alfred Tissières and Hugh Pelham in the 1980s characterized the heat shock response in detail and identified specific heat shock proteins, particularly HSP70.

Ellis and van der Vies (1991) formally defined molecular chaperones as proteins that assist in the folding of other proteins but are not part of the final functional structure.

Ferruccio Ritossa

Ron Laskey

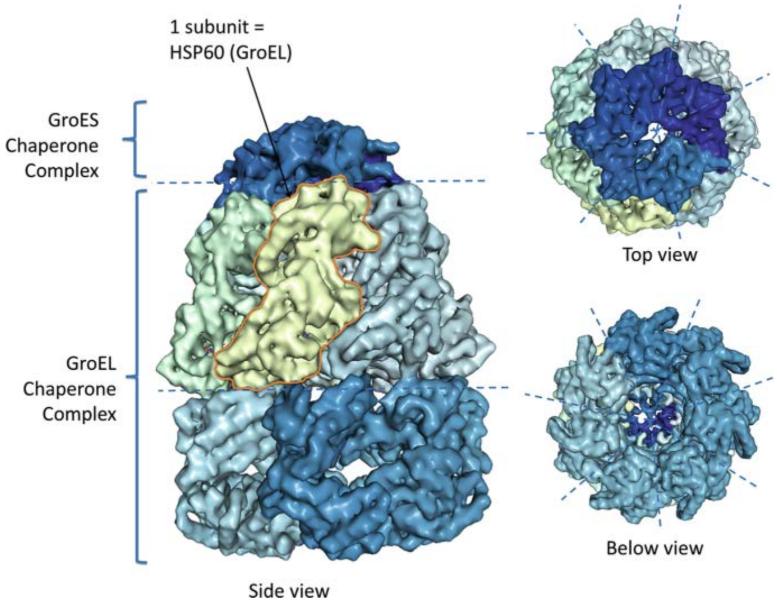
Discovery and early history

GroEL/GroES system discovered in E. coli by Georgopoulos and colleagues in the 1970s as essential for bacteriophage lambda assembly; later revealed as a chaperonin by Hemmingsen et al. in 1988.

HSP60 (chaperonin) family identified as homologues of bacterial GroEL, essential for mitochondrial protein folding.

HSP90 characterized as a major cytosolic chaperone involved in signal transduction and steroid hormone receptor maturation.

Small heat shock proteins (sHSPs) recognized as ATP-independent chaperones with roles in preventing aggregation.



Chaperones

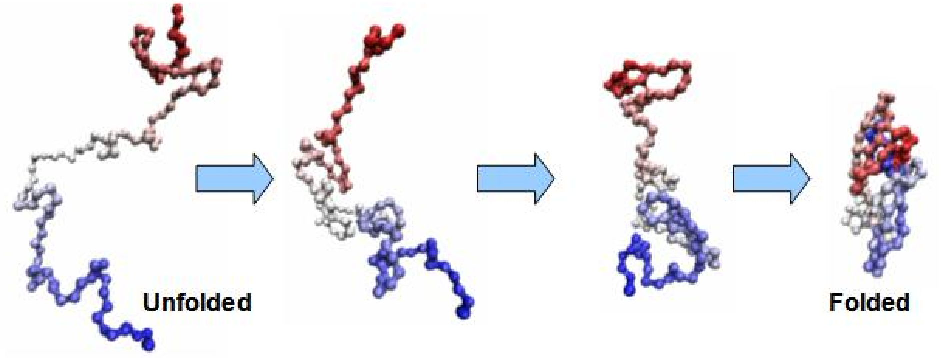
Proteins that assist the conformational folding or unfolding of large proteins or macromolecular protein complexes.

Function to assist large proteins in proper protein folding during or after synthesis, and after partial denaturation.

Chaperones are also involved in the translocation of proteins for proteolysis.

Chaperones

The reactivity of protein surfaces means that incorrect interactions may occur unless the process of folding a protein after translation is controlled.

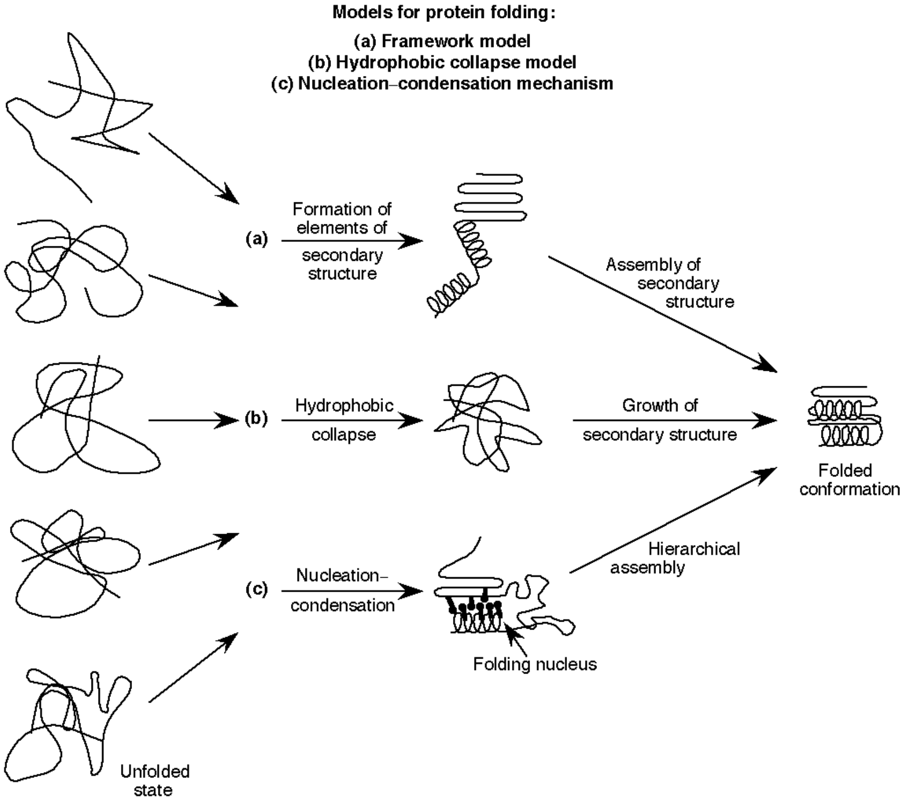


Some proteins are able to acquire their mature conformation spontaneously = Self assembly.

A test for this ability = denature the protein and determine whether it can then renature into the active form → implies that the internal interactions are intrinsically directed toward the right conformation.

Protein folding energy

When this does not happen, and alternative sets of interactions can occur, a protein may become trapped in a stable conformation **THAT IS NOT THE INTENDED FINAL FORM !**



Models for protein folding:

(a) Framework model
(b) Hydrophobic collapse model
(c) Nucleation–condensation mechanism

Protein folding energy

Proteins in this category cannot self-assemble. Their acquisition of proper structure requires the assistance of a chaperone.

Chaperones are proteins that mediate correct assembly by causing a target protein to acquire one possible conformation instead of others.

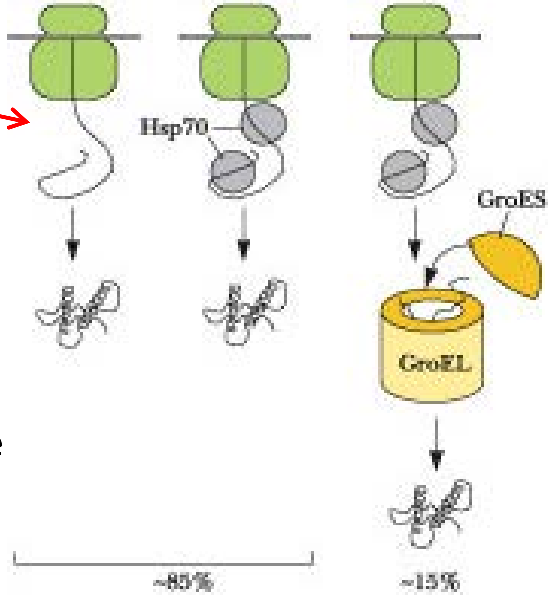
Accomplished by binding to reactive surfaces in the target protein that are exposed during the assembly process and preventing them from interacting.

Chaperones function by preventing formation of incorrect structures rather than by promoting formation of correct structures.

Initial acquisition of the correct conformation

The ability of chaperones to recognize incorrect protein conformations allows them to play two related roles concerned with protein structure:

- As a protein is synthesized it is in an unfolded form.
- Spontaneous folding then occurs as the emerging sequence interacts with regions of the protein that were synthesized previously.
- Chaperones influence the folding process by controlling the accessibility of the reactive surfaces.
- When a protein is denatured, new regions are exposed and become able to interact.
- These interactions are similar to those that occur when a protein (transiently) misfolds as it is initially synthesized.
- They are recognized by chaperones as comprising incorrect folds.
- Chaperones assist renaturation or degradation.



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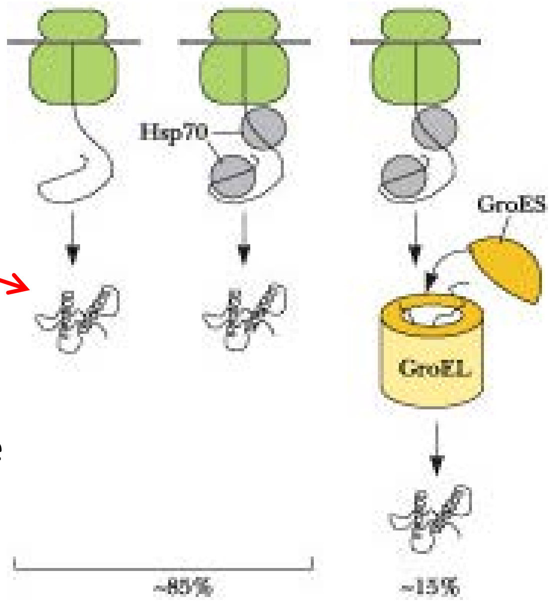

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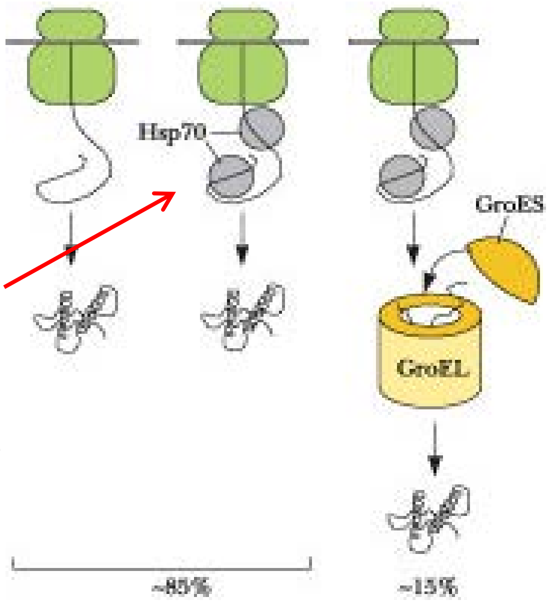

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- Spontaneous folding occurs as the emerging sequence interacts with regions of the protein that were synthesized previously.
- Chaperones influence the folding process by controlling the accessibility of the reactive surfaces.
- When a protein is denatured, new regions are exposed and can deleteriously interact.
- These interactions are similar to those that occur when a protein (transiently) misfolds as it is initially synthesized.
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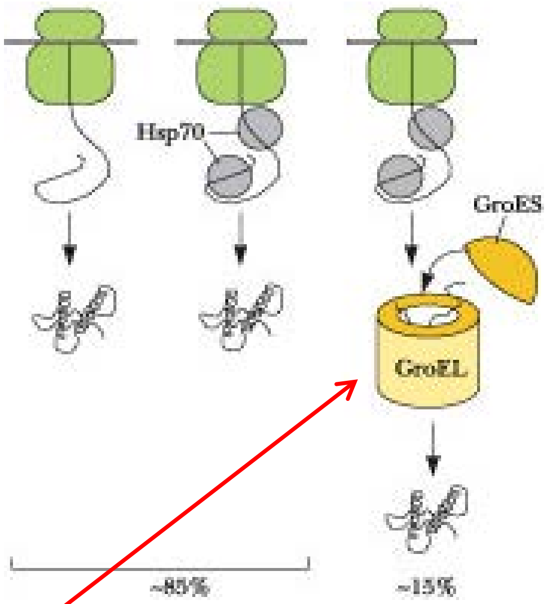


Cheperones in protein trafficking

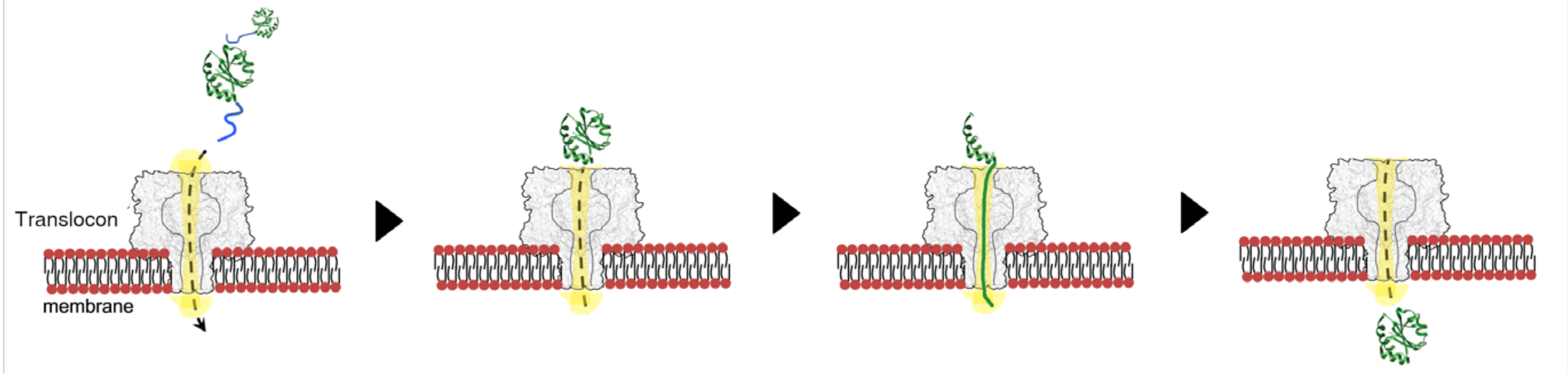
Chaperones also required to assist the formation of oligomeric structures and for the transport of proteins through membranes.

Protein folding is an important feature of membrane passage.

It may be necessary to maintain a protein in an unfolded state because of the geometry of passage.

Chaperones may prevent a protein from acquiring a conformation that would prevent passage through the membrane.

Once the protein has passed through the membrane, it may require another chaperone to assist with folding to its mature conformation.



Cheperone functional groups

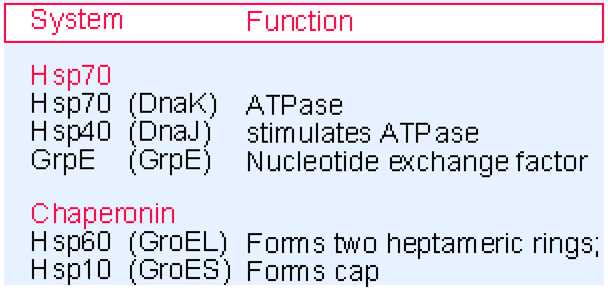
Two major groups of chaperones have been well characterized:

The Hsp70 system (Hsp70, Hsp40 & GrpE).

- Newly synthesized protein
- Proteins being transported through membranes
- Proteins denatured by stress.
- The name reflects their induction by heat shock.

The chaperonin system (Hsp10, Hsp60)

- Consists of a large oligomeric assembly.
- Also minimize the damage caused to proteins by heat denaturation.



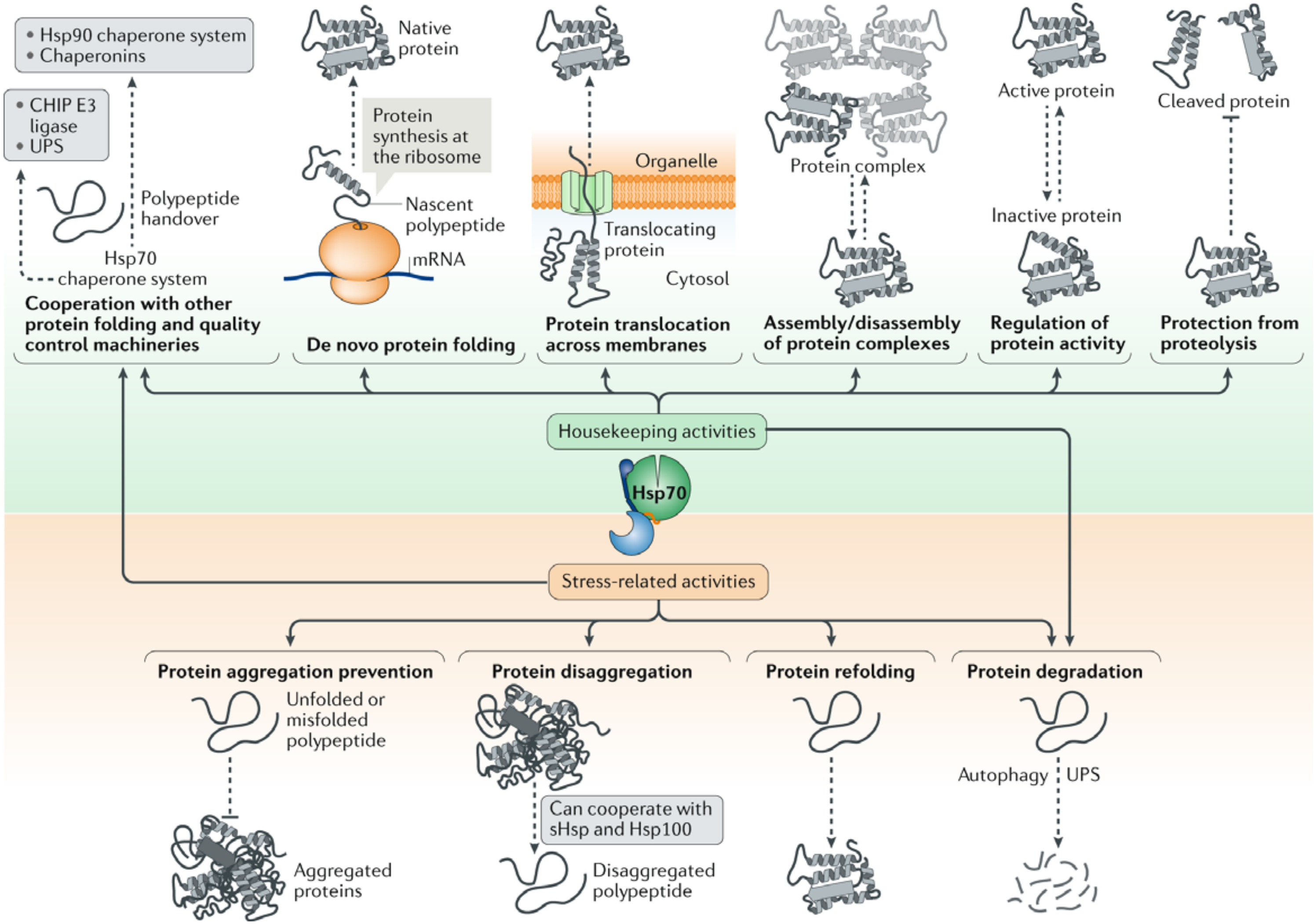
System		Function
Hsp70		
Hsp70	(DnaK)	ATPase
Hsp40	(DnaJ)	stimulates ATPase
GrpE	(GrpE)	Nucleotide exchange factor
Chaperonin		
Hsp60	(GroEL)	Forms two heptameric rings;
Hsp10	(GroES)	Forms cap

Prokaryotes

Eukaryotes

The Hsp70 system (Hsp70, Hsp40 & GrpE).

The Hsp70 family found in bacteria, eukaryotic cytosol, in the ER & in endosymbionts.



Rosenzweig R, et al. Nat Rev Mol Cell Biol. 2019 Nov

The Chaperonin system (Hsp60 & Hsp10 GroEL/ES).

Large (oligomeric) structure with a hollow cavity used for folding or degradation of proteins.

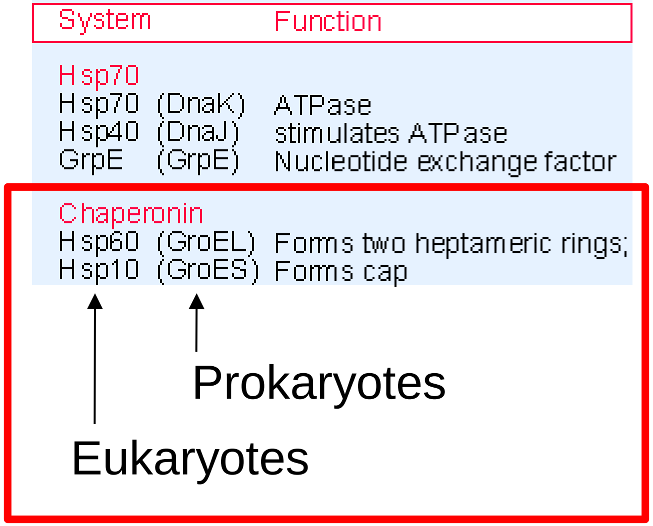
The typical structure is a ring of many subunits, forming a cylinder.

Target protein is placed in a controlled environment (cavity).

In folding, the closed environment prevents the target protein from wrong interactions with other proteins.

In the case of degradation, isolation makes for a more controlled process than would be possible in open cytosol.

The energy for these processes is provided by hydrolysis of ATP.



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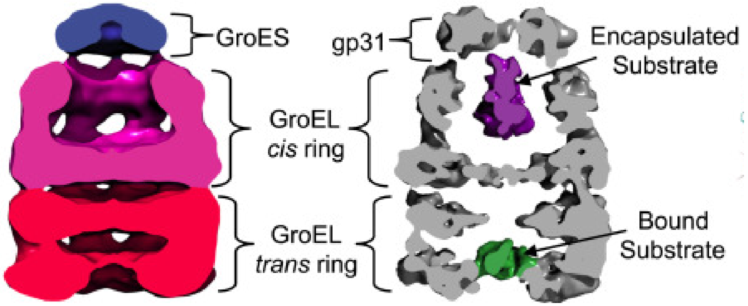


The Chaperonin system (Hsp60 & Hsp10 GroEL/ES).

GroEL (prokaryote) forms an oligomer of two rings, each comprising a hollow cylinder made of 7 subunits (heptamer).

Hsp60 (eukaryote) forms a large apparatus that consists of two types of subunit.

Top and bottom surfaces of the double ring are the same.

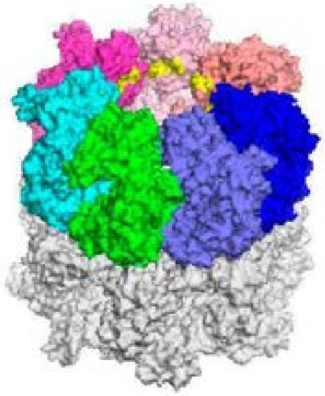
The central hole is blocked at the equator of each ring by the COOH ends of the subunits, which protrude into the interior.

GroES heptamer forms a dome that associates with one surface of the double ring.

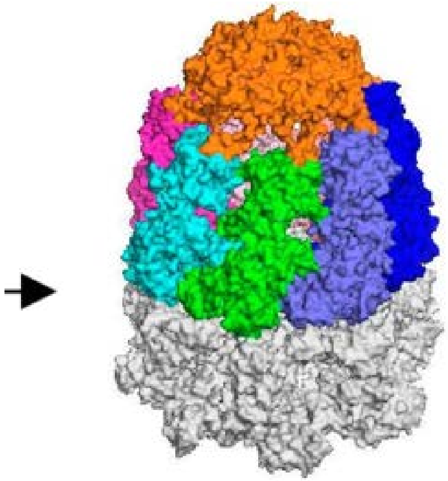
The entire GroEL/GroES structure has a mass ~10x106 daltons.

Comparable to a small ribosomal subunit.

GroEL sometimes called a chaperonin & GroES a co-chaperonin.



GroEL



GroEL-GroES-ADP

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