

The chaperonin folding machine

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Chaperonins are versatile molecular machines that assist the folding of a wide range of substrate proteins. They harness an ATPase cycle to control access of non-native proteins to hydrophobic binding sites. ATP binding promotes large conformational changes that partially bury the hydrophobic sites and initiate the binding of a co-chaperonin, creating closed and open cavities. Non-native proteins progress towards the native fold during their confinement in these cavities, and are then released by the allosteric action of ATP.

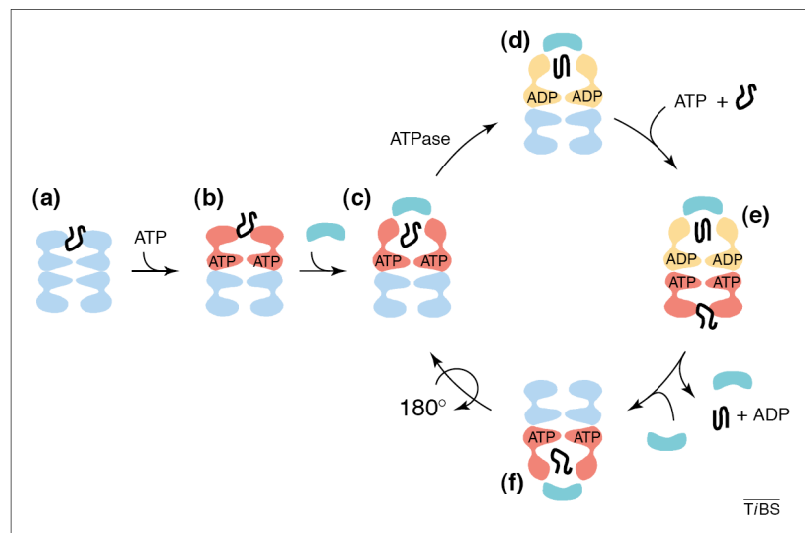


Fig. 1. GroEL ATPase and the folding cycle. The GroE complexes are shown as sections through the stacked-ring complexes. (a) GroEL has high affinity for non-native polypeptide substrate (black curved line). (b) ATP binds with positive co-operativity to one ring but negative co-operativity between rings, producing an altered conformation with reduced substrate affinity. (c) The ATP-bound ring rapidly binds GroES, simultaneously sequestering the hydrophobic binding sites and encapsulating the substrate in the folding chamber. There is a massive conformational change in the GroES-bound ring. (d) The substrate folds inside the chamber and ATP is hydrolysed. (e) ATP binding to the opposite ring primes the release of GroES and the trapped substrate. (f) A new substrate gets encapsulated. Adapted, with permission, from [14].

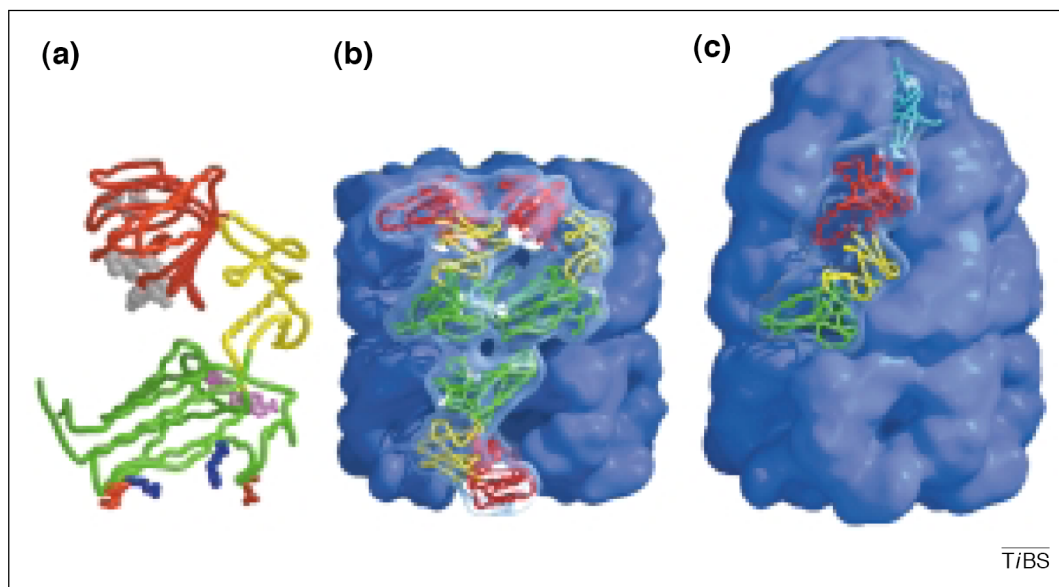


Fig. 2. Crystal structures of *Escherichia coli* GroEL (Hsp60) and its complex with ADP and GroES (Hsp10). (a) The three domains of the GroEL subunit are colour coded – green for the equatorial domain, yellow for the intermediate domain and red for the apical domain. The equatorial domain contains the nucleotide-binding site, shown occupied, as well as the two inter-ring contacts at the base of the molecule (negatively charged residues in red, positive in blue). The apical domain contains the hydrophobic binding sites (grey, space-filling representation) for non-native polypeptides. ATP is shown in pink. (b) The structure of the unbound GroEL 14-mer, with three subunits shown at the front [11]. The hydrophobic binding sites face into the end cavities. (c) The GroEL-ADP-GroES complex [12], with one GroEL subunit and one GroES subunit (cyan).