Opening Up the Group II Chaperonins

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A new study in this issue of *Structure* (Huo et al., 2010) reports the crystal structure of a group II chaperonin in the open state, providing unprecedented levels of detail for the domain movements that result from ATP hydrolysis and a clearer picture of the protein folding mechanism mediated by chaperonins.

Protein folding mediated by chaperones is critical for the survival and proper function of cells. Impaired protein folding has been implicated in a wide range of diseases, including the amyloidoses (such as Alzheimer's disease, familial amyloid cardiomyopathy, or polyneuropathy—type II diabetes), prion-related diseases (such as Creutzfeld-Jakob disease), and cancer. Elucidating the molecular basis of protein folding by chaperones is therefore essential toward understanding the overall protein folding process.

Divided into two classes, the chaperonins are oligomeric molecular chaperone complexes that facilitate protein folding in an ATP-dependent manner. The conserved chaperonin structure is cylindrical and comprised of two back-to-back rings (Figure 1). Each subunit consists of three domains. An equatorial domain binds ATP and provides interring contacts; an apical domain at each end of the chaperonin binds and contains the protein to be folded; and an intermediate hinge domain connects the equatorial and apical domains. Much of the structural work to date has been concerned with the group I chaperonins, which include the widely studied GroEL, and the various conformational states associated with their protein folding mechanism have been characterized by structural techniques that include electron microscopy and X-ray crystallography. The group I chaperonins are characterized by a cofactor (GroES) that closes the protein folding chamber in the presence of ATP. In contrast, the group II chaperonins have been less extensively studied, although several recent reports have begun to shed light on their three-dimensional structure and function. Unlike their group I counterparts, the group II chaperonins lack the GroES cofactor and are instead distinguished by a built-in lid at the tip of the apical domains.

Until very recently, structures of group II chaperonins were only available in the closed state from *Thermoplasma acidophilum* and *Thermococcus sp.* KS-1 (Shomura et al., 2004; Ditzel et al., 1998). Despite this, nucleotide-bound structures from both studies showed the location of the nucleotide binding site and how domain movements might occur. A recent electron microscopy study of the *Methanococcus maripaludis* chaperonin (MmCpn) by Zhang et al. (2010) reported a 4.3 Å atomic model of the closed state built directly from the single particle cryo-EM density map, which is a significant technical achievement and may provide a powerful tool for determining models of large macromolecular structures. The authors also reported a model of the open state to ~8 Å resolution, which, although lower, was sufficient to show the local conformational changes triggered by ATP hydrolysis that lead to ring closure. A separate study by Pereira et al. (2010) reported the crystal structures of MmCpn in the closed state at 3.3 Å resolution, and the crystal structure of MmCpn in the open state at 6 Å resolution. Whereas the group I chaperonins tend to exhibit a similar conformation of the equatorial domains between open and closed states, the group II chaperonin structural models determined by Zhang et al. (2010) and Pereira et al. (2010) show that the three domains of each subunit reorient as a single rigid body, undergoing a large anticlockwise rotation as a result of ATP hydrolysis and creating a large hydrophilic surface inside the folding chamber.

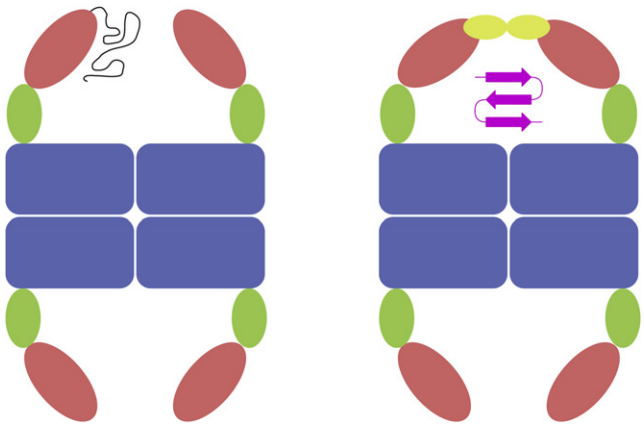

Figure 1. Schematic Showing the Open (left) and Closed (right) States of the Chaperonin
Blue represents the equatorial domain, green represents the intermediate domain, and red represents the apical domain. Yellow represents the GroES cofactor in group I chaperonins or the lid (part of the apical domain) in the group II chaperonins. The black line in the open state represents the unfolded substrate. The magenta cartoon in the closed state represents the folded substrate.

In their elegant study reported in this issue of *Structure*, Huo et al. (2010) have determined the crystal structure of a thermosome (group II chaperonin) from *Acidianus tengchongensis* in the open state at 3.7 Å, representing the highest resolution structure of an open state group II chaperonin to date. The first detailed crystal structure of

a thermosome in the open state is therefore of interest and will help to complete our understanding of the mechanism of group II chaperonins. From their structural analysis of the open state, they show a rotation of ~30° of the apical and lid domains relative to the closed state, providing the clearest picture yet of the domain movements resulting from ATP hydrolysis. The authors additionally report electron microscopy reconstructions for both the open and closed states of the thermosome. This work provides a nice complement to the recent reports on group II chaperonins by Zhang et al. (2010) and Pereira et al. (2010), and builds upon their impressive work by providing a substantially higher resolution structure of the group II chaperonin in the open state.

REFERENCES

Ditzel, L., Lowe, J., Stock, D., Stetter, K.-O., Huber, H., Huber, R., and Steinbacher, S. (1998). Cell *93*, 125–138.

Huo, Y., Hu, Z., Zhang, K., Wang, L., Zhai, Y., Zhou, Q., Lander, G., Zhu, J., He, Y., Pang, X., et al. (2010). Structure *18*, this issue, 1270–1279.

Pereira, J.H., Ralston, C.Y., Douglas, N.R., Meyer, D., Knee, K.M., Goulet, D.R., King, J.A., Frydman, J., and Adams, P.D. (2010). J. Biol. Chem *285*, 27958–27966.

Shomura, Y., Yoshida, T., Iizuka, R., Maruyama, T., Yohda, M., and Miki, K. (2004). J. Mol. Biol. *335*, 1265–1278.

Zhang, J., Baker, M.L., Schroder, G.F., Douglas, N.R., Reissmann, S., Jakana, J., Dougherty, M., Fu, C.J., Levitt, M., Ludtke, S.J., et al. (2010). Nature *463*, 379–384.

The Talin FERM Domain Is Not So FERM

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The structure of the head domain of talin, an intracellular activator of integrin membrane adhesion receptors, has been solved by Elliott et al. (2010). A FERM domain can be identified in the head from sequence comparisons but, rather than having a compact structure of three subdomains, it has linear arrangement of four subdomains.

FERM domains are found in numerous proteins located at the cytoplasmic face of the plasma membrane (Fehon et al., 2010). The FERM name derives from its presence in four proteins: band four-point one, ezrin, radixin, and moesin. Other important FERM-containing proteins include focal adhesion kinase (FAK) and Janus kinase (JAK). FERM domains have around 300 amino acids with three subdomains, usually called F1, F2, and F3. Several structures of FERM domains have been solved; there is some variation, especially in linker regions and loop insertions, but all previous structures have had a relatively compact clover-leaf structure with intimate contacts between all three subdomains (Figure 1). In this issue, the crystal structure of the N-terminal head of talin is reported (Elliott et al., 2010). This has an unexpected structure with a linear, rather than a clover-leaf, arrangement of subdomains.

Talin is an intracellular protein that is a key player in the activation of integrins, large heterodimeric membrane-spanning adhesion receptors (Campbell and Ginsberg, 2004). Talin has an N-terminal head region and an elongated 220 kDa helical rod that combine to link the cytoplasmic tail of the β-integrin subunit with the actin cytoskeleton (Critchley, 2009). The head contains a FERM domain with clear sequence similarities to other FERM proteins, although the F1 subdomain has a 30-residue insertion and some of the linker regions are different. The talin FERM domain is also preceded by an "F0" subdomain, recently shown to have an ubiquitin-like fold, similar to F1 (Goult et al., 2010). The 30-residue insertion in F1 is largely unstructured, but it has helical propensity and can be removed without perturbing the core structure of F1 (Goult et al., 2010). Many unsuccessful attempts have been made to obtain structures of the intact

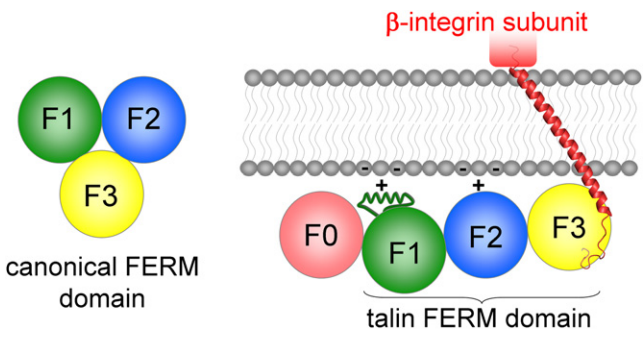

Figure 1. Subdomain Arrangements in FERM Proteins
An illustration of the clover-leaf arrangement of subdomains observed in previous FERM structures (left) and the novel arrangement found in the FERM domain from the talin head (right). Positive patches on the F1 and F2 subdomains can interact with negatively charged membranes. F3 binds the cytoplasmic tail of the integrin β-subunit (Anthis et al., 2009) and F0-F3 then act in synergy to activate integrins.