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Structure watch

A DRAMATIC WAY TO REMODEL

Molecular chaperones, such as heat-shock protein-90 (Hsp90), are ATP-driven molecular machines that facilitate the correct folding of client proteins. New structural studies show how dramatic conformational changes that occur during the Hsp90 reaction cycle might be coupled to client-protein remodelling.

Hsp90 proteins comprise three domains that are connected by hinge regions, and they form dimers through their C-terminal domains (CTDs). Shiau *et al.* determined the structure of the *Escherichia coli* Hsp90 orthologue HtpG in the nucleotide-free, ATP-analogue-bound and ADP-bound states. Each of the HtpG states adopts distinct conformations, and the conformational changes induced by nucleotide binding are far more dramatic compared with the previously published findings with yeast Hsp90. The hinge regions between the N-terminal domain (NTD) and the middle domain (MD) as well as between the MD and the CTD are thought to enable this conformational flexibility.

In the nucleotide-free state, the NTD, MD and CTD of the HtpG monomer each present hydrophobic surface areas into a large V-shaped cleft formed by the dimer. The authors propose that this state is probably most optimal for binding client proteins. The addition of ATP leads to changes in the conformation of the NTD and MD. The dimer changes to a more compact ATP-bound state in which the distance between the NTDs decreases and the so-called 'ATP lid' loop structure moves over the bound nucleotide. This more compact configuration is likely to affect client-protein remodelling. Nucleotide hydrolysis results in the very compact ADP-bound state that is expected to release the client protein, thereby resetting the chaperone for binding a new client protein.

The first glimpse of Hsp90 in complex with a client protein was recently provided by Vaughan *et al.* They expressed and purified a complex of yeast Hsp90 in complex with the co-chaperone Cdc37 and the client protein Cdk4, and demonstrated a 2:1:1 ratio for the Hsp90–Cdc37–Cdk4 complex. Taken together with previous data, the authors suggest the formation of an initially symmetric interaction between dimeric Hsp90 and dimeric Cdc37 carrying the client protein, after which a Cdc37 molecule is released. Electron-microscopy data indicate that Cdk4 adopts a lobe-shaped extended conformation when bound to the NTD and MD on the outside of one Hsp90 monomer. Cdc37 is thought to be bound to the NTD of the other Hsp90 monomer. The orientation of Cdk4 relative to Hsp90 provides a possible mechanism by which ATP-dependent changes in the conformation of the NTD and MD of Hsp90 might be coupled to the remodelling of the client protein.

REFERENCES Shiau, A. K. *et al.* Structural analysis of *E. coli* hsp90 reveals dramatic nucleotide-dependent conformational rearrangements. *Cell* **127**, 329–340 (2006) | Vaughan, C. K. *et al.* Structure of an Hsp90–Cdc37–Cdk4 complex. *Mol. Cell* **23**, 697–707 (2006)

FURTHER READING Ali, M. M. U. *et al.* Crystal structure of an Hsp90–nucleotide–p23/Sba1 closed chaperone complex. *Nature* **440**, 1013–1017 (2006)