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PROTEIN FOLDING

Chaperone embrace

Heat-shock protein-70 (HSP70) proteins are molecular chaperones that participate in many cellular processes, such as protein folding, transport across membranes, prevention of protein aggregation and degradation. HSP70 activity is regulated by nucleotide-exchange factors (NEFs), which accelerate the release of ADP from the HSP70 nucleotide-binding domain (NBD), allowing ATP binding; this causes the release of the substrate and facilitates protein folding. But how do NEFs induce nucleotide release? Two groups now provide insights by describing the crystal structure of HSP70 in complex with members of the HSP110 family of NEFs.

HSP110 proteins are homologues of the HSP70 proteins that can bind and stabilize unfolded proteins but are unable to fold proteins independently of HSP70. To investigate the role of HSP110 in protein folding, Polier and colleagues obtained the 2.3 Å resolution of Sse1 (the yeast HSP110) in complex with the NBD of human HSP70, whereas Schuermann and colleagues obtained the crystal structure of Sse1 with the nearly full-length heat-shock protein-70 cognate (HSC70; the bovine HSP70 homologue). The general domain organization of Sse1 corresponds to that of canonical HSP70 proteins, which consist of an N-terminal NBD and substrate-binding structures — a β-sandwich domain and a C-terminal three-helix bundle domain (3HBD). A notable feature of both structures is that the NBD of HSP70 is embraced by the NBD and the 3HBD of Sse1. The extensive interactions between the two proteins lead to the opening of the nucleotide-binding cleft of HSP70 and the release of bound ADP from HSP70.

Schuermann and colleagues also observed a pore that is formed by subdomains of the Sse1 and HSC70 NBDs, and that connects the NBDs to the solvent outside of the complex. The authors suggest that this pore might allow nucleotides to enter and exit the complex. Interestingly, the Sse1–HSC70 complex structure contains ADP in the HSC70 NBD and therefore is a snapshot of the complex in its 'pre-ADP-release' state. Instead, in the crystal structure by Polier and colleagues, ADP is not present, and therefore this structure is a snapshot of the complex in its 'post-ADP-release' state.

Next, the two teams designed structure-based mutants of Sse1 and HSP70, and confirmed that the interactions in the endogenous complex are similar to those observed in the crystal structures. Polier and colleagues also used an *in vitro* assay to test whether Sse1 contributes to HSP70-assisted folding of a model substrate. They found that the NEF activity of Sse1 is essential for this function. Sse1 mutants with severely reduced NEF activity failed to rescue the lethality of a yeast strain that lacks Hsp110 proteins, highlighting the importance of this domain for the folding function.

Together, these findings demonstrate that HSP110 proteins control nucleotide exchange on HSP70 chaperones, which is essential for protein folding.

Francesca Cesari

> "…HSP110 proteins control nucleotide exchange on HSP70 chaperones…"

ORIGINAL RESEARCH PAPERS Polier, S. *et al.* Structural basis for the cooperation of Hsp70 and Hsp110 chaperones in protein folding. *Cell* 13 June 2008 (doi:10.1016/j.cell.2008.05.022) | Schuermann, J. P. *et al.* Structure of the Hsp110:Hsc70 nucleotide exchange machine. *Mol. Cell* 12 June 2008 (doi:10.1016/j.molcel.2008.05.006)