Chaperones just prepare proteins for folding on their own

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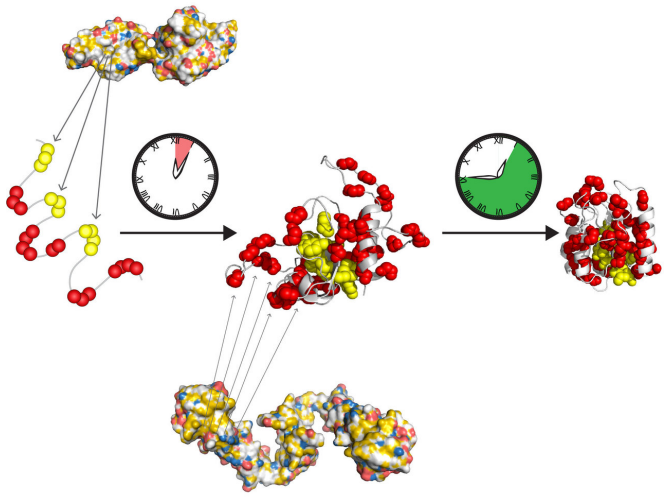

The molecular chaperones Hsp70 and Hsp90 form a fast-acting relay team to prepare proteins to fold into their active state on their own. Hsp70 recognizes short hydrophobic stretches (yellow), exposed in the unfolded protein. Hsp90 acts downstream from Hsp70 and facilitates forming the folding intermediate, which slowly turns into the native state, free of further chaperone action. Credit: Tania Morán Luengo and Stefan Rüdiger, Utrecht University

Cellular proteins are produced as long chains of amino acids that must fold precisely into their final shape. The key players in this folding process are the so-called molecular chaperones, protein helpers that make sure this process is successful. Researchers from Utrecht University, in close collaboration with colleagues from Heidelberg University, have at last uncovered how the two most important chaperone families, Hsp70 and Hsp90, cooperate in this folding process. Surprisingly, it turns out they do not actively assist in the folding, as scientists had long assumed. Instead, they simply prepare the proteins for spontaneous, productive folding. This breakthrough in understanding the functioning of the Hsp70-Hsp90 cascade will be published in *Molecular Cell* on 3 May.

Incorrectly folded proteins can result in serious diseases such as cystic fibrosis and many neurodegenerative diseases like Alzheimer's. Scientists have long known that Hsp70 and Hsp90 play a key role in this folding process, and that Hsp90 acts downstream of Hsp70. However, the actual mechanism by which they fold a protein has remained enigmatic.

Ph.D. candidate Tania Morán Luengo from Utrecht University has recently demonstrated that the chaperone Hsp70 binds to the young protein, protecting it while also preventing it from folding. Then Hsp90 breaks the Hsp70 block, which allows the protein to continue folding into the correct state all by itself. This discovery signaled the surprising end of the longstanding belief that chaperones fold proteins.

Research leader Dr. Stefan Rüdiger from Utrecht University got a glimpse of this novel idea while preparing to teach a course about the subject. Hsp70 binds to hydrophobic amino acids, protecting them from sticking together until they are hidden inside the final protein structure. He realised that the way Hsp70 binds to its substrates therefore could not contribute to protein folding, but rather inhibits it instead.

The researchers then set out to analyse the folding process, observing that concentrations of Hsp70 in the range of those present in our cells inhibited protein folding. "This inferred that Hsp70 is not a promoter, but in fact an effective inhibitor of the folding process," Rüdiger explains. His group teamed up with the laboratory of Prof. Matthias Mayer at Heidelberg University to test this hypothesis experimentally. They demonstrated that the presence of Hsp90 at this point is critical for the folding process to occur. Hsp90 enables the protein to break out of the Hsp70 deadlock to fold in its right shape on its own.