Protein quality control: knowing when to fold

A report from Judith Frydman's group, published in the 3 June issue of *Cell* (121, 739–748; 2005), shows that distinct chaperone pathways control the decision between either folding or degrading cytoplasmic proteins.

Misfolded proteins can be refolded or they can be degraded by the ubiquitin–proteasome pathway. Protein chaperones are important for both processes. In the endoplasmic reticulum (ER), two different chaperones sort proteins into folding or degradation pathways. But what determines the fate of cytoplasmic proteins?

Addressing this question in yeast with a mutant von Hippel–Lindau (VHL) protein that is folding-defective and unstable, Frydman and colleagues showed that the chaperones Hsp70, Hsp90 and Sti1 are required for VHL degradation, whereas the VHL folding chaperone TriC is not. So, as in the ER, the decision to fold or degrade cytosolic proteins is directed by different chaperones. Hsp70 stands out in this group because it acts in both normal VHL folding and in degradation, although it's unclear why this is the case. How is the target shunted from one pathway to another? The authors speculate that Sti1, which is known to bridge Hsp70 and Hsp90, might be key for switching between a re-folding complex containing Hsp70 and a second complex containing Hsp70, Hsp90, Sti1 and other proteins that facilitate VHL proteolysis.

Misfolded proteins are thought to undergo futile cycles of refolding before they are finally degraded. So, in this way, chaperones passively assist degradation by preserving the protein in a soluble form. The Frydman group finds that even in the absence of Sti1 and Hsp90, misfolded VHL remains soluble, leading to the conclusion that these chaperones have an active function in degradation.

Regulation of VHL folding and degradation by distinct chaperones.

Another surprising possibility to emerge from these studies is that these Hsp90 complexes, in addition to their established functions in activating protein kinases and steroid receptors, may also have unanticipated functions in quality-control decisions.

Finally, how might Hsp90 facilitate degradation? The authors speculate that Hsp90 might recruit the ubiquitination apparatus or deliver VHL to the proteasome. Both possibilities are consistent with other work that shows that Hsp90 binds to ubiquitinating enzymes and to the proteasome. Alternatively, Hsp90 may generate a specific conformation of VHL that is amenable for ubiquitination and degradation. These are not mutually exclusive possibilities and, indeed, it may turn out that Hsp90 facilitates degradation in multiple ways.

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