PROTEIN FOLDING

Quality control

It seems that distinct chaperone pathways actively determine whether a cytosolic protein is folded or degraded. Previous studies using artificial or damaged protein substrates indicated that chaperones have a passive, non-specific function in protein degradation, keeping non-native polypeptides soluble to prevent aggregation and facilitate sampling by the ubiquitin–proteasome system. However, reporting in *Cell*, Frydman and colleagues now show that the folding and degradation of a cytosolic protein — the von Hippel–Lindau (VHL) tumour suppressor — are mediated by different chaperone pathways.

VHL folding is mediated by 70-kDa heat-shock protein (Hsp70) and the chaperonin TRiC/CCT, and is linked to the assembly of VHL into a native complex with elongin-B and elongin-C (elongin-BC). Mutations in mammalian VHL that block the assembly of the native VHL–elongin-BC complex disrupt folding and lead to VHL degradation by the proteasome.

Frydman and co-workers first established that VHL quality control proceeds similarly in yeast. Continuing in yeast, they then asked whether Hsp70 and TRiC/CCT are required for VHL degradation. By studying the degradation of a VHL mutant that cannot bind elongin-BC, or the degradation of wild-type VHL in the absence of elongin-BC, they showed that the Hsp70 Ssa1 is specifically required for VHL folding and degradation, but that TRiC/CCT is required for VHL folding only.

They also showed that the Ssa1 cofactor Sti1 is required for VHL degradation. In the absence of Sti1, VHL remained soluble, but was not degraded. This indicated an active role for Sti1 in VHL quality control. Sti1 can form a bridging complex between Hsp70 and Hsp90, and Frydman and colleagues showed that Hsp90 is not required for VHL folding, but is needed for its degradation. Loss of Hsp90 didn't affect VHL solubility or its association with Hsp70 and TRiC/CCT, but a specific Hsp90 complex mediated the degradation of misfolded VHL. This complex contained Hsp70, Sti1, Hsp90 and the Hsp110 chaperone Sse1.

This work has provided important insights into the quality control decisions that are made for cytosolic proteins. Two distinct chaperone pathways mediate VHL folding and degradation. Newly synthesized VHL is folded by Hsp70 and TRiC/CCT. Misfolded VHL is transferred from Hsp70 to Hsp90 with the assistance of Sti1, and a specific Hsp90 complex then facilitates VHL degradation by the proteasome. A hierarchy of chaperone interactions seems to determine the fate of VHL — an initial association between newly translated VHL and TRiC/CCT favours folding, whereas failure to fold leads to Hsp90 binding and VHL degradation.

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References and links

ORIGINAL RESEARCH PAPER McClellan, A. J., Scott, M. D. & Frydman, J. Folding and quality control of the VHL tumor suppressor proceed through distinct chaperone pathways. *Cell* **121**, 739–748 (2005)

FURTHER READING Young, J. C. *et al.* Pathways of chaperone-mediated protein folding in the cytosol. *Nature Rev. Mol. Cell Biol.* **5**, 781–791 (2004)

WEB SITE

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