

 PROTEIN DEGRADATION

# Tipping the balance

A new protein that regulates ubiquitin homeostasis has been identified by Keiji Tanaka and co-workers. As described in *Cell*, Rfu1 (regulator of free ubiquitin chains 1) regulates the concentrations of monomeric ubiquitin and free ubiquitin chains by inhibiting the deubiquitylating enzyme (DUB) Doa4.

Cells that lack Rfu1 accumulate monomeric ubiquitin and have reduced levels of free ubiquitin chains, whereas overexpression of Rfu1 has the opposite effect. These results suggest that Rfu1 inhibits the production of monomeric ubiquitin and promotes the formation of free ubiquitin chains. Of the 19 DUBs in yeast, only Doa4 localizes to endosomes in which Rfu1 is also present. Lack of Doa4 causes accumulation of free ubiquitin chains and reduction of the monomeric ubiquitin pool, which is the opposite effect of Rfu1 depletion. Furthermore, Rfu1 interacts with Doa4 *in vitro* and *in vivo*, and recombinant Rfu1 inhibits the deubiquitylating activity of Doa4 *in vitro*. So, Rfu1 is an inhibitor of Doa4.

Cellular stress causes the accumulation of misfolded proteins that need to be rapidly ubiquitylated and degraded by the 26S proteasome. Notably, heat shock decreases Rfu1 and increases Doa4 protein levels, and reduces the levels of free ubiquitin chains, which are (at least in part) disassembled into monomeric ubiquitin by Doa4. Overexpression of Rfu1 inhibits the heat shock-induced disappearance of free ubiquitin chains. The authors propose that “free ubiquitin chains function as a ubiquitin reservoir that allows maintenance of monomeric ubiquitins at adequate levels under normal conditions and rapid supply for substrate conjugation under stress conditions”.

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**ORIGINAL RESEARCH PAPER** Kimura, Y. *et al.* An inhibitor of a deubiquitinating enzyme regulates ubiquitin homeostasis. *Cell* **137**, 549–559 (2009)