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PROTEIN DEGRADATION

A proteasome for every occasion

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URLs
Ubp6
http://www.expasy.org/uniprot/P43593

Rpn4
http://www.expasy.org/uniprot/Q03465

> "…the composition of the proteasome is altered during periods of ubiquitin deficiency…"

Cells maintain a continuous free pool of ubiquitin that can be conjugated onto target proteins to mark them for degradation by the proteasome. Now, in *Cell*, Finley and colleagues show that the composition of the proteasome is altered during periods of ubiquitin deficiency to ensure that levels of free ubiquitin are maintained.

Several accessory proteins have recently been shown to associate transiently with the proteasome core to regulate proteasome activity and the rate of protein degradation. These accessory proteins include the de-ubiquitylating enzyme Ubp6, which trims ubiquitin from substrate proteins; it also acts non-catalytically to partially inhibit proteasome activity so that more ubiquitin can be retrieved from substrate proteins before they are degraded. Finley and colleagues show that yeast express a catalytically inactive mutant of Ubp6 at higher levels compared with wild-type Ubp6. Levels of cellular ubiquitin are reduced in the *ubp6* mutant, which is consistent with a function for Ubp6 in recycling ubiquitin from proteasome-destined cargoes. Increasing free ubiquitin levels in *ubp6*-mutant cells corrected the levels of mutant Ubp6, and depleting ubiquitin in wild-type yeast upregulated Ubp6 levels. Together, these findings highlight an inverse relationship between ubiquitin and Ubp6 levels.

So how are Ubp6 levels regulated? It has previously been shown that transcription of all subunits of the proteasome, including *ubp6*, is controlled by the transcription factor Rpn4. Rpn4 is efficiently degraded by the proteasome and, consequently, when proteasome activity is decreased (proteasome stress), Rpn4 degradation is reduced, which enables transcriptional activation. Ubp6 partially inhibits the proteasome, and because this function is maintained in the *ubp6* active-site mutant, this mutant also induces proteasome stress. The authors observed upregulation of proteasome levels by an Rpn4-dependent mechanism. Surprisingly, however, if ubiquitin deficiency was generated in a way that did not also induce proteasome stress, then Ubp6 levels were regulated by Rpn4-independent mechanisms and without an increase in the levels of other proteasome subunits.

It appears that there are two pathways of cellular regulation, which are activated in response to proteasome or ubiquitin stress and mediated by independent mechanisms. The authors argue that this is logical because "When ubiquitin levels are dangerously low, it would not be advantageous to increase proteasome levels, as this would exacerbate ubiquitin depletion". The identity of the ubiquitin sensor that switches on *ubp6* is unknown, but it could be a transcription factor that is normally rapidly ubiquitylated and degraded, and which therefore becomes stable when ubiquitin levels fall. Unusually, the degradation of Rpn4 is largely ubiquitin independent, which highlights its function as a dedicated proteasome sensor and, furthermore, rules it out as being the ubiquitin sensor.

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ORIGINAL RESEARCH PAPER Hanna, J. *et al.* A ubiquitin stress response induces altered proteasome composition. *Cell* **129**, 747–759 (2007)
FURTHER READING DeMartino, G. N. & Gillette, T. G. Proteasomes: machines for all reasons. *Cell* **129**, 659–662 (2007) | Pickart, C. M. & Cohen, R. E. Proteasomes and their kin: proteases in the machine age. *Nature Rev. Mol. Cell Biol.* **5**, 177–187 (2004)

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