Nature Reviews Molecular Cell Biology | AOP, published online 18 April 2013; doi:10.1038/nrm3569

PhotoDisc/Getty Images \ Lisa Zador

POST-TRANSLATIONAL MODIFICATION

A SUMO protease for stress protection

During cell stress, the unfolded protein response (UPR) triggers protective signalling that allows cell adaptation and survival. Here, Guo *et al.* show that during oxygen and glucose deprivation (OGD), the UPR reduces the levels of the deSUMOylating enzyme SENP3 (sentrin-specific protease 3) to promote cell survival, and that SENP3 recovery contributes to cell death upon reoxygenation.

Cell stress upregulates protein SUMOylation, and this has been proposed to mediate a protective response. Consistent with this, the authors observed that OGD (an *in vitro* model of ischaemia) increased the levels of SUMO2 (small ubiquitin-related modifier 2) and SUMO3 conjugation in cultured rat cortical neurons and HEK293 cells, and that this correlated with decreased levels of SENP3. The UPR kinase PERK is known to be activated during ischaemia, and, using *Perk*$^{-/-}$ mouse embryonic fibroblats (MEFs), Guo *et al.* showed that this kinase is required for the reduction in SENP3 levels during OGD. Moreover, they observed that SENP3 degradation was directly mediated by the lysosomal protease cathepsin B *in vitro*, and cathepsin B (*Ctsb*)$^{-/-}$ MEFs did not degrade SENP3 during OGD despite PERK activation.

Next, the authors sought to determine the effects of SENP3 degradation during ischaemia. They observed that overexpression of SENP3 reduced the levels of cytochrome *c* in mitochondria, and that this effect required dynamin-related protein 1 (DRP1). DRP1 is known to regulate cytochrome *c* release through mitochondrial fission, which promotes cell death, and SUMOylation of DRP1 influences its association with the mitochondrial membrane. The authors found that knockdown of SENP3 in HEK293 cells increased DRP1 SUMOylation, and expression of a DRP1 mutant that cannot be SUMOylated (DRP1^{R}4KR) led to increased release of cytochrome *c* from mitochondria. The authors hypothesized that deSUMOylation of DRP1 by SENP3 allows its association with the mitochondrial membrane, thus increasing cytochrome *c* release and promoting cell death. Indeed, DRP1 colocalization with mitochondria was reduced upon SENP3 knockdown. Moreover, using live imaging analysis and fluorescence recovery after photobleaching (FRAP), they showed that DRP1^{R}4KR cycled more slowly between the mitochondria and the cytoplasm, and this mutant also had increased association with the mitochondria in fractionation analysis.

> “Rapid reduction in SENP3 levels … would promote cell survival”

What is the consequence of DRP1 deSUMOylation by SENP3? Overexpression of the SUMO protease increased mitochondrial fission in HeLa cells, and also altered mitochondrial morphology in primary cortical neurons. Mitochondrial fission was also increased in cultured neurons expressing DRP1^{R}4KR. On the basis of their findings, the authors propose that SENP3 promotes mitochondrial fission and thereby cytochrome *c* release through deSUMOylation of DRP1.

The above observations suggest that the rapid reduction in SENP3 levels during OGD would promote cell survival. However, most cell damage is known to occur post-ischaemia, during reoxygenation of a tissue. Guo *et al.* observed that SENP3 levels recovered during this period, so they asked what effects this might have. They saw that knockdown of SENP3 or DRP1 prevented the induction of cell death that normally occurs upon reoxygenation of HEK293 cells or cortical neurons; this protective effect of SENP3 was lost when DRP1^{R}4KR was overexpressed. The SENP3-mediated deSUMOylation of DRP1 therefore seems to promote cell death during recovery from ischaemia.

Thus, the triggering of rapid SENP3 degradation in response to ischaemic stress constitutes a protective pathway that promotes cell survival. As the restoration of SENP3 levels upon reoxygenation can contribute to cell death, a better understanding of how the UPR targets SENP3 may offer an opportunity to reduce post-ischaemic injury.

Alison Schuldt

ORIGINAL RESEARCH PAPER Guo, C. *et al.* SENP3-mediated deSUMOylation of dynamin-related protein 1 promotes cell death following ischaemia. *EMBO J.* 22 Mar 2013 (doi:10.1038/emboj.2013.65)

FURTHER READING Hickey, C. M., Wilson, N. R. & Hochstrasser, M. Function and regulation of SUMO proteases. *Nature Rev. Mol. Cell Biol.* **13**, 755–766 (2013)