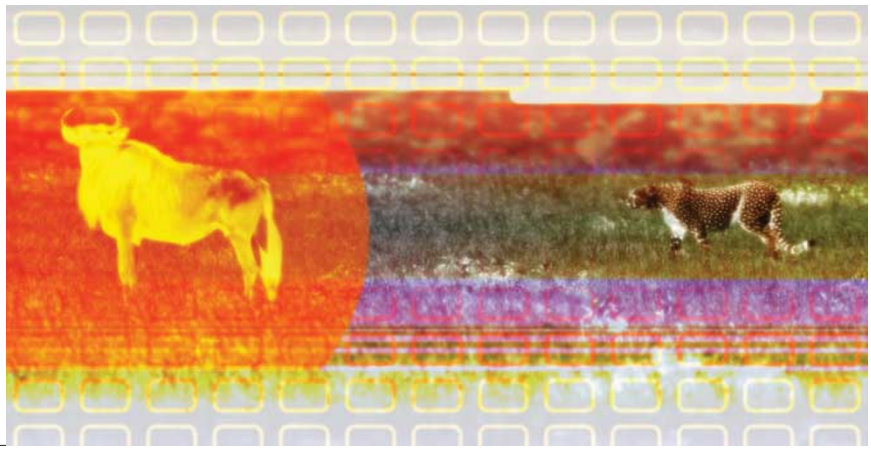
HIGH-LIGHTS



APOPTOSIS

Inactivity can be deadly

The mutant mouse *mnd2* (motor neuron degeneration 2) — a model of inherited neuromuscular disease — shows signs of muscle wasting and neurodegeneration, and dies by the time it reaches 40 days old. The neurodegeneration combines features of necrosis and apoptosis, and early mitochondrial degeneration has been observed in striatal neurons, which are particularly sensitive to the effects of the *mnd2* mutation. However, the molecular basis of the *mnd2* disorder has been unclear. Now, though, in *Nature*, Alnemri, Meisler and colleagues provide new insights.

The authors showed that the *mnd2* disorder is caused by the missense mutation Ser276Cys (where Ser is serine and Cys is cysteine) in the protease domain of Omi. Omi is a nuclear-encoded mitochondrial serine protease that is usually found in the mitochondrial intermembrane space. However, during apoptosis, Omi is released from mitochondria, and it subsequently binds, inhibits and degrades inhibitor of apoptosis (IAP) proteins.

Alnemri, Meisler and co-workers showed that the Ser276Cys mutation does not affect the levels, maturation or IAP-binding activity of Omi. It does, however, markedly reduce its protease activity. The PDZ domain of Omi normally limits substrate access to the active site, and the authors found that deleting this domain partially restored activity in the mutant protein. This indicates that the Ser276Cys mutation somehow impairs substrate access or binding to Omi's active site.

So, how does a lack of Omi protease activity affect cell viability? The authors showed that, after treatment with stress-inducing agents, more *mnd2* mouse embryonic fibroblasts (MEFs) than wild-type MEFs could be stained for markers of apoptosis and necrosis. This indicates that a loss of Omi protease activity increases sensitivity to stress-induced cell death.

Finally, Alnemri, Meisler and colleagues showed that *mnd2*-mutant cells are more susceptible to Ca^{2+}-induced mitochondrial-permeability transition and mitochondrial-membrane permeabilization, which leads to apoptosis and necrosis. The Ser276Cys mutation in Omi somehow seems to promote the Ca^{2+}-induced activation of the mitochondrial permeability transition pore.

This work has clarified the molecular basis of the *mnd2* disorder, and the authors suggest that their data are explained by two distinct functions for Omi. First, Omi has a role in mitochondrial homeostasis under normal physiological conditions, perhaps as a sensor of unfolding stresses (bacterial members of the same protein family are quality-control proteases that are needed to survive various cell stresses). Second, Omi has a role outside mitchondria in apoptosis under apoptotic conditions. They propose that the Ser276Cys mutation compromises the normal mitochondrial function of Omi (for example, it might result in defective protein quality control in mitochondria). It now remains to be seen whether any human neurodegenerative disorders are caused by spontaneous mutations in Omi.

Rachel Smallridge

URLs
Omi
http://us.expasy.org/cgi-bin/nicezprot.pl?Q9JIY5
PDZ domain
http://www2.ebi.ac.uk/interpro/IEntry?ac=IPR001478

References and links

ORIGINAL RESEARCH PAPER Jones, J. M. *et al.* Loss of Omi protease activity causes the neuromuscular disorder of *mnd2* mutant mice. *Nature* 8 Oct 2003 (doi:10.1038/nature02052)

WEB SITES
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