IN THE NEWS

A hand-me-down from Dad

"Mitochondria may not be inherited solely through the maternal line", reported *New Scientist* (23 August 2002). The discovery stands to overturn decades of "accepted biological wisdom" and "could have huge implications for evolutionary biology and biochemistry".

Until now, paternal mitochondria were thought to be destroyed during conception, leaving only maternal mitochondria to be inherited. But, when sequencing the mitochondrial DNA from a 28-year-old patient, Marianne Schwartz and John Vissing from the University Hospital Rigshospitalet in Copenhagen unexpectedly found that a large percentage of the patient's mitochondria came from his father.

These findings, published in the *New England Journal of Medicine*, outline the first case of paternal mitochondrial inheritance. The patient, who suffers from extreme fatigue during exercise, appeared to be clinically healthy. But, Schwartz and Vissing identified two mutations in his mitochondrial DNA which were found to map to his father and not, as expected, to his mother. "Muscle biopsies showed that about 90 per cent of his mitochondria came from his father. However, the mitochondria in his blood, hair roots and fibroblasts came entirely from his mother"(*New Scientist*).

The researchers believe that paternal inheritance of mitochondria will probably remain a rare event. It is clear that these findings need to be confirmed, but for many evolutionary biologists, and for those scientists interested in metabolic diseases, these surprising results will force a re-evaluation of ideas.

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APOPTOSIS

Death theory turned on its head

Apoptosis can be initiated in many ways — two of which are cytokine-induced or stress-induced. Both rely on the activity of caspases; proteases that signal the cell's downfall. Although the final curtain is drawn on the cell in both scenarios, the performance has always been thought to be quite different for the two cases. That was, until a report by Lazebnik's group in *Science*, which implies that both modes of apoptosis can proceed through conceptually similar pathways.

Stress-induced death, which is mediated by stimuli such as DNA damage, depends on the outcome of the balance of activities of Bcl-2-family members on mitochondrial integrity; permeabilization of the mitochondrial membrane releases proteins such as cytochrome *c* that can act together with Apaf-1 to activate caspase-9, as well as other caspase-independent executioners. In this case, mitochondria take on a central role. In cytokine-induced death, however, mitochondria act more passively as 'amplifiers' — caspase activation results from autocatalytic processing, and mitochondria serve merely to amplify the caspase signal. However, data from Lazebnik's group imply that DNA damage induces caspases to control mitochondrial permeability, rather than vice versa.

They chose to study caspase-2 in IMR90E1A cells (cells transformed with the E1A oncogene, which facilitates the activation of caspase-9). Using small interfering RNA (siRNA), they ablated the function of caspase-2 and, to their surprise, found that this inhibited DNA-damage-induced apoptosis to a similar degree as silencing of Apaf-1 function. As this pointed to a role for caspase-2 in apoptosis, the authors restored the function of caspase-2 to see whether this restored sensitivity to apoptosis by cytotoxic agents. To prevent the ectopically expressed caspase-2 from being destroyed by siRNA, silent mutations — that is, changes in the nucleotide sequence that do not affect the amino acid that is produced — were introduced. Consistent with the highly specific nature of siRNA, expression of this construct wasn't silenced, and the result was that wild-type caspase-2, but not a proteolytically impaired version, restored sensitivity to apoptosis.

Looking more closely at the mitochondrial aspect, Lazebnik's group saw that, in the absence of caspase-2 expression, cytochrome *c* was not released from mitochondria. Furthermore, even in the absence of proteolytic processing of caspases 3, 7 and 9, caspase-2 was still cleaved, indicating that it is probably activated before them, and that, in these cells at least, it is needed to permeabilize mitochondria. Extending the analysis to five other human tumour cell lines showed that two of these required caspase-2 for cytochrome *c* release, one did not, and two others couldn't be evaluated due to technical difficulties.

Taking a step further back in the pathway to look at the earliest detectable change, treatment with caspase-2 siRNA prevented the translocation of the Bcl-2-family member Bax from the cytoplasm to the mitochondria. This therefore indicates that a crucial function of caspase-2 is to move Bax to mitochondria, presumably inducing subsequent mitochondrial permeabilization.

The implications of this study are widespread — from the possibility that Bcl-2-family members sequester molecules that are required for the activation of caspases, to helping us understand how Bax is activated. And importantly, this study highlights that "even the basic pathways of apoptosis are not sufficiently understood to allow the efficient modulation of apoptosis to a therapeutic end".

Katrin Bussell

References and links

ORIGINAL RESEARCH PAPER Lassus, P., Opitz-Araya, X. & Lazebnik, Y. Requirement for caspase-2 in stress-induced apoptosis before mitochondrial permeabilization. *Science* **297**, 1352–1354 (2002)

WEB SITE

Encyclopedia of Life Sciences: http://www.els.net
Apoptosis: molecular mechanisms

NOTE ADDED IN PROOF

A related manuscript can be found in *Nature*: Marsden, V. S. *et al.* Apoptosis initiated by Bcl-2-regulated caspase activation independently of the cytochrome *c*/Apaf-1/caspase-9 apoptosome. *Nature* (in the press).