

# Mitochondria, from cell death to proliferation

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Mitochondrial signaling cascades have been implicated in the activation of programmed cell death and, more recently, control of cell proliferation. A nuclear gene encoding a mitochondrial Krebs-cycle protein, fumarate hydratase, is now shown to act as a major tumor-suppressor gene.

The list of diseases that involve mitochondrial dysfunction has been growing steadily for the past decade or so. The first to be discovered were several rare disorders, characterized by inefficient energy production and caused by mutations in mitochondrial DNA<sup>1</sup>. One of the many clinical features of these diseases is tissue necrosis<sup>2</sup>, which was attributed to the fact that mitochondrial dysfunction can lead to necrotic and apoptotic cell death<sup>3</sup>. It later became clear that mitochondria participate in many normal apoptotic

processes. Moreover, mitochondria-controlled apoptosis is considered to be a crucial event in many genetic and non-genetic diseases<sup>4</sup>.

Mitochondrial abnormalities have been described in tumor and cancer tissues, but it has been generally thought that these anomalies are a consequence rather than the cause of tumor formation. Within the past two years, two types of brain tumor—hereditary and sporadic cases of paraganglioma, and pheochromocytoma—were found to be caused by muta-

tions in three nuclear genes encoding subunits of succinate dehydrogenase, a Krebs-cycle enzyme<sup>5–7</sup>. But these conditions are so rare that few people seriously considered that mitochondrial dysfunction could lead to aberrant cell proliferation as well as cell death. That should change with the report on page 406 of this issue<sup>8</sup>, in which three groups, led by Ian Tomlinson, Richard Houlston and Lauri Aaltonen, find that mutations in another nuclear gene encoding mitochondrial Krebs-cycle protein are frequently associated with tumor formation.

## Lessons from fibroids

The consortium refined the locus for dominantly inherited uterine fibroids, skin leiomyomata (a benign tumor composed of smooth muscle and fibrous tissue) and renal cell cancer to chromosome 1q42.3–q43. Subsequent mutation screening in the fumarate hydratase (*FH*) gene disclosed causative mutations in approximately 60% of the cases (24/42). The gene acts as a typical tumor suppressor, with loss of the functional allele occurring in benign smooth muscle tumors (including skin leiomyomata and uterine fibroids) and renal cell cancer. This finding is of obvious importance in view of the high incidence and associated morbidity of uterine fibroids, which account for nearly

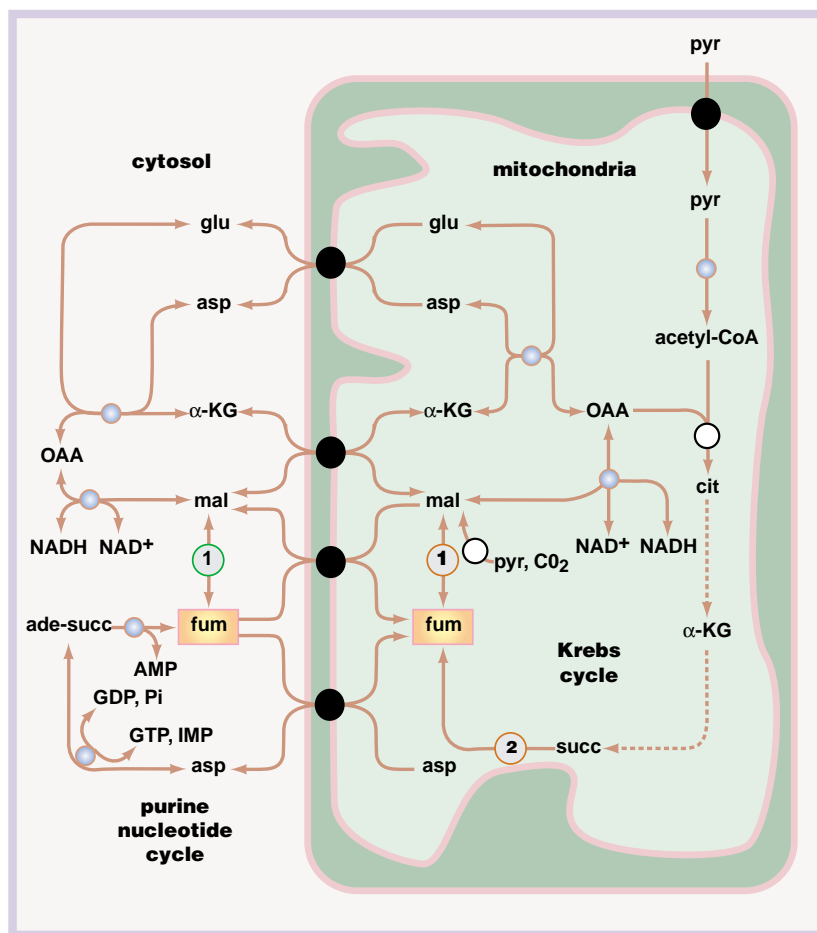
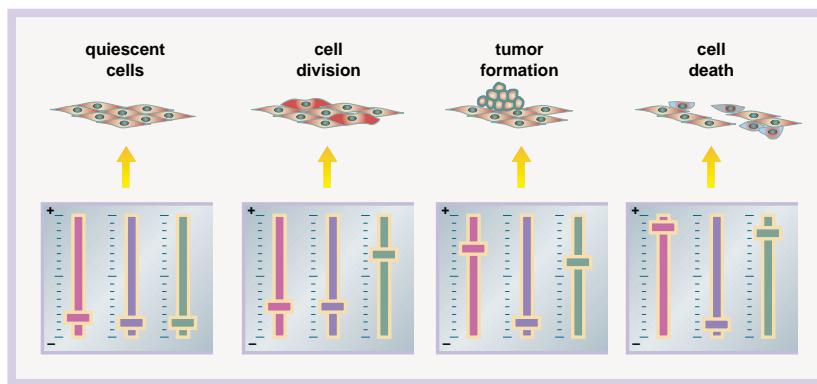


Fig. 1 The intricate metabolism of fumarate in mammalian cells. The single translation product of *FH* is distributed between the cytosol and mitochondria in most mammalian cells and catalyzes the reversible hydration of fumarate into malate (1). In mitochondria, the enzyme is part of the Krebs cycle and the fumarate produced by the succinate dehydrogenase (2) is not excreted by mitochondria. However, fumarate may be taken up from the cytosol in exchange for malate or aspartate. In the cytosol, the enzyme would be involved in the purine nucleotide cycle. Dark symbols indicate mitochondrial carriers; open symbols designate enzymes. ade-succ, adenylyl-succinate; asp, aspartate; cit, citrate; fum, fumarate; glu, glutamate; a-KG, a-ketoglutarate; malate, malate; OAA, oxaloacetate; pyr, pyruvate; succ, succinate.

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**Fig. 2** Cell proliferation, cell death and the mitochondrion. A complex set of parameters are constantly regulated by the activity of mitochondria, signaling cell proliferation or cell death. Among these, superoxides represent a major factor known to regulate the expression of a number of nuclear genes. According to this scheme, severe fumarate hydratase or succinate dehydrogenase deficiency would trigger increased superoxide production by the mitochondria, resulting in tumor formation or cell death *in vivo*. The red cursor indicates superoxide and radical oxygen species production, the blue cursor indicates redox status and the green cursor indicates mitochondrial membrane potential.



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25% of all healthcare-related expenditure in Western gynecology departments. It also adds a new and important category in the already long list of primary mitochondrial disorders.

The mechanism through which loss of fumarate hydratase function leads to tumor formation remains to be determined. Fumarate hydratase is distributed in both the cytosol and the mitochondrial matrix compartment, except in the brain, where the enzyme is only present in mitochondria. The mitochondrial enzyme catalyzes the freely reversible hydration of fumarate into malate in the Krebs cycle, whereas the physiological role of the cytosolic isoform is as yet unknown. As Tomlinson *et al.*<sup>8</sup> show, enzymatic activity is abolished in uterine fibroids, skin leiomyomata and renal cancer cells, presumably leading to an accumulation of fumarate in both cell compartments. This suggests that tumor formation may be caused by the abnormal accumulation of fumarate.

### Superoxides: for better or for worse?

It is tempting, however, to associate the study by Tomlinson *et al.*<sup>8</sup> with those that disclosed a tumor-suppressor role for the three succinate dehydrogenase genes<sup>5–7</sup>. In these studies, fumarate was not found to accumulate. Both fumarate hydratase and succinate dehydrogenase are constitutively active in the Krebs cycle and work in concert to metabolize succinate and fumarate (Fig. 1). Accordingly, it has been observed that severely defective fumarate hydratase activity causes a blockade of succinate oxidation in intact mitochondria, presumably because of the accumulation of fumarate<sup>9</sup>. So, a similar mechanism might well be at work in both fumarate hydratase- and succinate dehydrogenase-related tumor formation. The blockade of succinate dehydrogenase, resulting from mutant

protein subunits, or as a secondary effect of the accumulation of fumarate caused by *FH* mutation, could lead to a decrease in the superoxide-scavenging activity of the respiratory chain. This could, in turn, cause superoxide overproduction, which may lead to tumor formation.

Several different mechanisms have been proposed to trigger mitochondrial-dependent apoptosis in cells<sup>3</sup>. In attempting to resolve both cell death and proliferation into a single model, one can take a relatively unsophisticated view (Fig. 2), where a low level of superoxides, together with nitric oxide, would be required for normal cell function<sup>10</sup>. Increasing superoxide amounts would signal increased cell proliferation<sup>11</sup>, and an overwhelming excess of superoxides would trigger apoptosis<sup>12</sup>. According to this naive view, the fine-tuning of mitochondrial superoxide production would be of tremendous importance for the fate of the cell, and superoxides (or one or more of their derivatives) would have a central role in communication between mitochondria and the nucleus.

Further questions arising from the discovery of fumarate hydratase as a tumor suppressor either mirror or amplify questions already raised by the description of succinate dehydrogenase genes as tumor-suppressor genes. First, all of these are typical housekeeping genes, present and functional in all human tissues and cells. Why, then, should the tumor-restricted loss of the functional allele be favorable for cell proliferation in a given tissue? Second, children with Leigh syndrome (necrosis of specific brain territories, namely brainstem, basal ganglia thalamus and spinal cord, causing encephalopathy) or encephalomyopathy (encephalopathy plus skeletal muscle involvement), which are caused by deleterious mutations of genes encoding succinate dehydrogenase or fumarate hydratase, do

not have tumors, nor do their heterozygous relatives<sup>9–13</sup>. Why should this be? Two possibilities, discussed by Tomlinson *et al.*<sup>8</sup>, are that tumors may have been overlooked if benign, or that young affected individuals carrying homozygous mutations might have died before tumors developed.

It is also clear that tumors in those carrying a mutated *FH* allele cannot solely be due to the secondary blockade of succinate dehydrogenase. For example, the tissue distribution of fumarate hydratase-related tumors is restricted to smooth muscle, whereas paraganglioma and pheochromocytoma (the tumors associated with succinate dehydrogenase gene mutations) are found in the brain. It should also be noted that succinate dehydrogenase is present only in mitochondria, whereas fumarate hydratase is found in both mitochondria and the cytosol. This implies that additional dysfunction may well have participated in tumor formation in fumarate hydratase mutants. Even though the mechanism behind tumor formation in these two different mutants is still unknown, we can now agree on the importance of mutant housekeeping and mitochondrial proteins in the pathogenesis of common tumor types. □

- Wallace, D.C. *Annu. Rev. Biochem.* **61**, 1175–1212 (1992).
- Munnich, A. & Rustin, P. *Am. J. Med. Genet.* **106**, 4–17 (2001).
- Kroemer, G. & Reed, J.C. *Nature Med.* **6**, 513–519 (2000).
- Reed, J.C. *Trends Mol. Med.* **7**, 314–319 (2001).
- Baysal, B.E. *et al. Science* **287**, 848–851 (2000).
- Nieman, S. & Muller, U. *Nature Genet.* **26**, 268–270 (2000).
- Astuti, D. *et al. Am. J. Hum. Genet.* **69**, 49–54 (2001).
- Tomlinson, I.A.P. *et al. Nature Genet.* **30**, 406–410 (2002).
- Bourgeron, T. *et al. J. Clin. Invest.* **93**, 2514–2518 (1994).
- Droge, W. *Physiol. Rev.* **82**, 47–95 (2002).
- Oberley, L.W. *Antioxid. Redox Signal* **3**, 461–472 (2001).
- Gerome, V. *et al. Hum. Mol. Genet.* **10**, 1221–1228 (2001).
- Bourgeron, T. *et al. Nature Genet.* **11**, 144–149 (1995).

