Fussy mitochondria fuse in response to stress

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When cells become committed to apoptosis, they shatter their mitochondrial networks through the actions of the mitochondrial fission protein DRP1. Massive fragmentation of mitochondria facilitates simultaneous release of cytochrome c from all mitochondria within a cell, thus promoting further progression along the apoptotic pathway. In this issue, Tondera et al (2009) describe a new process with the opposite effect. When cells are subjected to modest levels of stress (well below levels needed to induce apoptosis), their mitochondria fuse to each other forming a closed network, similar to networks observed when mitochondrial fission is blocked. Stress-induced mitochondrial hyperfusion (SIMH), as this process was called, might counter stress by optimizing mitochondrial ATP production.

Mitochondria of healthy cells continually divide and fuse with each other (Okamoto and Shaw, 2005; Chan, 2006; Hoppins et al, 2007). Mitochondrial fission facilitates the redistribution of mitochondria in response to local changes in the demand for ATP and it allows for disposal of faulty mitochondrial fragments through mitophagy, whereas mitochondrial fusion promotes exchange of mtDNA and other vital components, thus reinvigorating the mitochondrial network. Mitochondrial fission and fusion processes are mediated by a series of dynamin family members. Fission is mediated by the dynamin-related protein DRP1. Mutations in the gene coding for this protein give rise to a highly interconnected network of mitochondria. Fusion is mediated by the dynamin-related proteins MFN1 and MFN2 at the mitochondrial outer membranes and the dynamin-related protein OPA1 at the mitochondrial inner membranes. Mutations in the genes coding for these proteins give rise to fragmented mitochondria, because fission still occurs while fusion is blocked. Mutations in the genes coding for the mitochondrial fusion proteins are also responsible for two human diseases. Patients with a heterozygous mutation in MFN2 develop a peripheral neuropathy called Charcot–Marie–Tooth disease (CMT-2A) and patients with heterozygous mutations in OPA1 develop dominant optic atrophy (DOA) through progressive loss of retinal ganglion cells. The severity of heterozygous mutations in humans and the lethality of homozygous mutations in mice show that mitochondrial fission and fusion processes are crucially important for cell survival (Chan, 2006; Davies et al, 2007).

The rates of mitochondrial fission and fusion vary between cell types and different growth conditions, but they are usually balanced within a cell. However, the rate of fission does increase markedly without a compensating increase in the rate of fusion when cells become committed to apoptosis (Suen et al, 2008). Increased fission in apoptotic cells coincides with the release of cytochrome c and mutations in the genes for the fission protein DRP1 can delay the release of cytochrome c, suggesting that apoptotic cytochrome c release is intimately connected with mitochondrial fission. Tondera et al (2009) now add a new twist to this plot with their discovery of a pathway that they call Stress-induced mitochondrial hyperfusion (SIMH) pathway. They show that treatments with low levels of toxic agents such as cycloheximide, UV irradiation or actinomycin D have the opposite effect of full-blown apoptosis-inducing treatments. Instead of inducing mitochondrial fragmentation as observed in apoptotic cells, these treatments cause mitochondria to fuse into a closed network, similar to networks observed in cells with mitochondrial fission defects (Figure 1). This closed network confers some degree of...
resistance to further insults, perhaps by increasing the robustness of mitochondria through exchange of crucial components.

One might ask whether the SIMH pathway merely reflects increased activity of the conventional fusion machinery or alternatively represents a deliberate switch to an alternative pathway. Tondera et al (2009) found three differences in protein requirements, suggesting mechanistic differences between SIMH pathway and conventional fusion. The first difference was observed with MFN1 and MFN2 knockout cells, which normally have fragmented mitochondria. Fragmentation in both cell types indicates that conventional mitochondrial fusion depends on the combined actions of MFN1 and MFN2. However, low levels of stress induce filamentous mitochondria in MFN2 knockout cells but not in MFN1 knockout cells, suggesting that SIMH pathway requires MFN1 but not MFN2 (Figure 1). Several years ago a specific requirement for MFN1 was noted when fusion was induced by the overexpression of OPA1 (Cipolat et al, 2004). Could this inducible fusion have been equivalent to SIMH? Conversely, MFN1 has not been linked with inducible fusion under either condition, but it was previously linked to Charcot–Marie–Tooth disease. The picture that is starting to emerge is that of dual requirements for MFN1 and MFN2 under normal conditions and additional dedicated functions of these proteins under special circumstances. MFN2 could, for example, affect axonal transport of mitochondria, as suggested in the Charcot–Marie–Tooth disease, although MFN1 can mediate mitochondrial fusion without help from MFN2 when cells are subjected to low levels of stress.

The second difference was discovered with OPA1. In un-stressed cells, certain isoforms of OPA1 are constitutively cleaved by the mitochondrial intermembrane space AAA protease YME1L (Griparic et al, 2007; Song et al, 2007). This cleavage generates the amino-terminal transmembrane segment to generate a short form of OPA1 (S-OPA1). Isoforms that are not cleaved by YME1L retain their amino-terminal transmembrane segment and are called the long form of OPA1 (L-OPA1).

Conventional fusion of mitochondrial inner membranes requires the combined actions of S- and L-OPA1 (Song et al, 2007). Tondera et al (2009) now show that L-OPA1, but not S-OPA1, is required for SIMH. A unique requirement for L-OPA1 is consistent with an earlier report in which it was shown that YME1L siRNA, which leads to accumulation of L-OPA1, also leads to a fused mitochondrial network (Griparic et al, 2007). The third difference was noted in the requirements for maintaining intact OPA1. Under adverse conditions, OPA1 is proteolytically inactivated by the actions of an as yet unknown protease (Griparic et al, 2007). This proteolytic inactivation occurs during apoptosis, but it also occurs when certain scaffolding proteins called prohibitins are not around (Merkwirth et al, 2008). Tondera et al (2009) now show that SIMH requires a different scaffolding protein, the stomatin-like protein SLP-2, to prevent proteolytic inactivation of OPA1. As the requirements for MFN1 and MFN2 at the mitochondrial outer membrane, the requirements for S- and L-OPA1 at the mitochondrial inner membrane and the scaffolding proteins required for maintaining the integrity of L-OPA1 are all different, one can conclude that there are important differences between SIMH pathway and conventional mitochondrial fusion, consistent with an alternative pathway.

Until now, mitochondrial fusion seemed like a monolithic problem begging for a biochemical solution. The discoveries of Tondera et al (2009) add nuance to this problem. What are the specialized functions of MFN1 and MFN2? Why does conventional fusion require S- and L-OPA1, whereas SIMH only needs L-OPA1? Why are different scaffolding proteins involved in OPA1 function? In addition to these mechanistic questions, there are also new questions about regulation. How do different forms of cellular stress converge on the mitochondrial fusion apparatus? Which protein modifications steer the fusion apparatus towards the conventional fusion process and which ones steer it towards SIMH? These types of questions will inevitably change the course of future experiments.

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