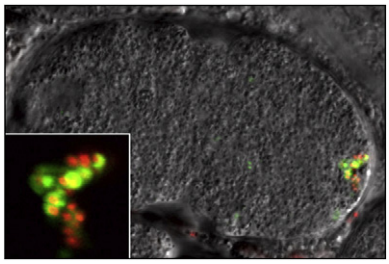
Cell

Mitochondria: Form and Function

Famous as "powerhouses of the cell," mitochondria also trigger apoptosis, regulate cell growth, and integrate stress responses. This issue's Select highlights recent studies that investigate mitochondrial form and function, providing new insight into how these organelles change their numbers, remodel their shapes, and divide their membranes.



Shortly after fertilization, autophagosomes (green) coalesce around the site of sperm penetration and selectively engulf paternal mitochondria (red). Image courtesy of K. Sato.

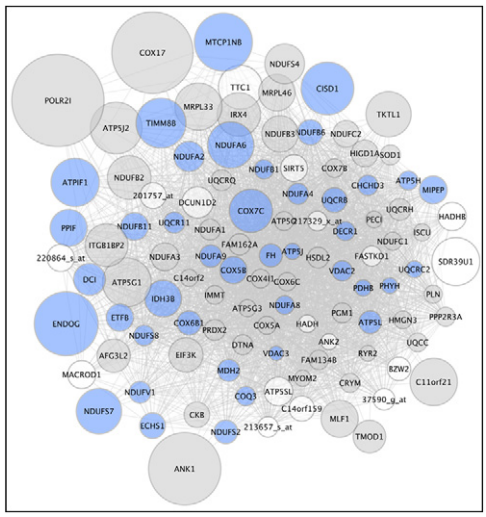
Maternal Recycling for Paternal Mitochondria

After an egg is fertilized, the resulting zygote contains both maternal and paternal mitochondria. With few exceptions, however, mitochondrial DNA (mtDNA) is transmitted solely through the maternal lineage. How do cells dispose of paternal mitochondria? New research from two independent groups provides evidence that paternal mitochondria are actively and rapidly degraded by autophagy, a highly regulated process that digests and recycles intracellular components. Sato and Sato (2011) follow fluorescently labeled paternal mitochondria in newly fertilized *C. elegans* oocytes and simultaneously monitor autophagosome formation. Immediately after fertilization, maternal autophagosome membranes accumulate near the site of sperm entry and appear to engulf paternal mitochondria. As embryogenesis proceeds, mitochondria and autophagosomes disperse throughout the cytosol, with maternal autophagosomes associating specifically with paternal mitochondria. Time-lapse microscopy reveals that paternal mitochondria are engulfed by maternal autophagosomes, which are subsequently degraded by lysosomes. In a related study, Al Rawi et al. (2011) examine recently fertilized oocytes from *M. musculus* and *C. elegans*, providing evidence that maternal autophagy of paternal mitochondria is an evolutionarily conserved event. Previous reports show that ubiquitin marks mitochondria in mammalian sperm, and it is likely that this signal is read by the maternal autophagy machinery in mice. However, the identity of the signal that marks paternal mitochondria for destruction in *C. elegans* remains unknown. To begin to address this question, Sato and Sato (2011) examine the fate of paternal mitochondria in embryos lacking autophagy. In these embryos, paternal mitochondria persist, but they maintain their compact, granular morphology and do not increase in number. Whether this distinct structure or a heretofore-unidentified sperm-specific mark underlies their selective elimination is a question for the future.

Sato, M., and Sato, K. (2011). Science. Published online October 13, 2011. 10.1126/science.121033.
Al Rawi, S., et al. (2011). Science. Published online October 27, 2011. 10.1126/science.1211878.

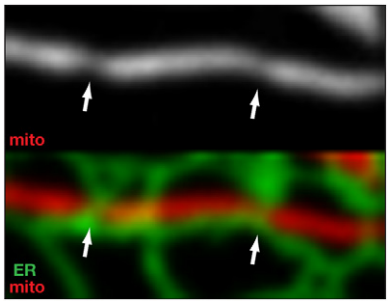
One Nuclease Makes You Smaller

The mitochondrial protein Endonuclease G (ENDOG) was originally reported to drive mitochondria-mediated apoptosis. Now, in a study examining the genetic basis for left ventricular mass (LVM) cardiac hypertrophy, McDermott-Roe et al. (2011) provide evidence that ENDOG boosts biogenesis of mitochondria and stimulates both synthesis and transcription of mtDNA. LVM cardiac hypertrophy predicts sudden death due to heart failure and is associated with obesity and type 2 diabetes. Taking advantage of integrative genetic approaches in the rat, McDermott-Roe and colleagues dissect the quantitative trait locus (QTL) for blood-pressure-independent LVM cardiac hypertrophy, linking loss-of-function alterations in the *Endog* locus to LVM hypertrophy. Without ENDOG function, cardiomyocytes contain elevated levels of the AMP-activated protein kinase and reactive oxygen species, both known to stimulate cell growth. These same cells have impaired respiration, most likely due to decreased mitochondrial mass and lower mtDNA content. The authors next analyze genome-wide coexpression data to infer how ENDOG functions in the human heart. They find that expression of *Endog* clusters with other mitochondrial and metabolic genes. They also provide mechanistic insight into how loss of ENDOG activity precipitates cardiac hypertrophy and mitochondrial dysfunction, exploring how the *Endog* locus is regulated. ERRα and PGC1α, two transcription factors known to work together for mitochondrial biogenesis and function, directly control ENDOG expression. Previous reports suggest that ENDOG plays key roles in mtDNA replication and mtRNA processing, and the authors now show that ENDOG directly binds mtDNA in a manner similar to TFAM, an mtDNA transcription factor that also participates in mtDNA synthesis and repair. Interestingly, deletion of TFAM also causes cardiac hypertrophy and heart failure. These findings clearly connect defects in mitochondrial function with enhanced cell growth, a phenomenon initially described in cancer cells and now linked to cardiac hypertrophy.



The ENDOG coexpression gene network from the human heart contains many mitochondrial genes (blue). Image courtesy of E. Petretto and S. Cook.

McDermott-Roe, C., et al. (2011). Nature 478, 114–118.



Before mitochondria (red) divide, they are constricted (arrows) by ER tubules (green).

An ER Noose for Mitochondria

Large, elongated mitochondria are sandwiched between myofibrils in sperm, whereas small, spherical mitochondria cluster together in sperm. In most other cell types, long, thin mitochondria extend throughout the cytoplasm. Regardless of their different shapes and sizes, all mitochondria undergo fusion and division.

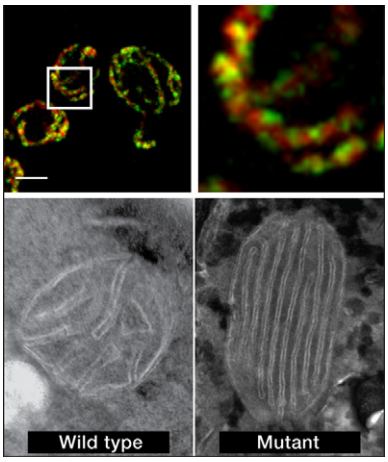
Now, with high-resolution imaging techniques, Friedman et al. (2011) reveal a surprising connection between the endoplasmic reticulum (ER) and mitochondrial division. They show that ER tubules encircle and constrict mitochondria, marking sites of future mitochondrial division events. First, with 3D reconstructions of yeast cell tomographs, the authors show that physical connections between the two organelles correlate with mitochondrial constrictions. Next, with time-lapse confocal microscopy, they observe the assembly of ER collars around mitochondria in growing yeast cells. These events clearly constrict mitochondria and presage organelle scission. The authors then turn their attention to mammalian cells, asking whether a similar phenomenon occurs in cultured kidney cells. Again, they find that organelle division sites are almost always marked by contact with ER tubules. Moreover, Friedman and colleagues show that ER-mediated constriction of mitochondria precedes Dnm1/Drp1 binding to the mitochondrial surface, an event previously associated with the final stages of mitochondrial scission. Because physical contacts between the ER and mitochondria mediate key steps in phospholipid biosynthesis and calcium signaling, these studies raise the intriguing possibility that local changes in membrane composition and/or calcium regulate mitochondrial constriction, influencing where division occurs. As one of the protein complexes linked to mitochondrial morphology and dynamics is also known to mediate ER-mitochondria contact sites, it will be interesting to learn whether it participates in ER-mediated mitochondrial constriction or if an undiscovered mode of membrane remodeling is involved in the first steps of mitochondrial division.

Friedman, J., et al. (2011). Science 334, 358–362.

The IMPORTance of Mitochondrial Organization

Although mitochondrial outer membranes make intimate connections with the ER, mitochondrial inner membranes have their own complicated relationships. The inner membrane (IM) consists of at least three morphologically distinct subregions—boundary membranes, cristae, and cristae junctions. These domains remodel in response to stress and the cell's metabolic needs. Now, two recent studies independently identify a large protein complex that regulates IM morphology and organization.

Hoppins et al. (2011) take a systematic approach, surveying over 600,000 pair-wise genetic interactions to generate a high-density quantitative genetic interaction map (MITO MAP). The analysis of this large dataset unveils new relationships between many different proteins that influence the form and function of mitochondria. In one example, the authors mine MITO MAP, discovering an Fcj1-containing complex that organizes the mitochondrial IM. Previous studies linked the IM-localized Fcj1/mitofilin protein to cristae morphology. Now, with biochemical and functional experiments, Hoppins and colleagues show that Fcj1 serves as an IM scaffold upon which a multimeric structure assembles. This structure encases the boundary membrane and, at specific sites, contacts the outer membrane. Deconvolution microscopy shows that this organizing structure contains both punctate and filamentous features, which are reminiscent of the bacterial cytoskeletal protein MreB. Given the similarities between these oligomeric protein structures, it is tantalizing to speculate that the Fcj1 complex and MreB may perform analogous functions.



The Fcj1 complex anchors an extended and heteromorphous scaffold along the mitochondrial inner membrane (top, image courtesy of J. Nunnari). Without the Fcj1 complex, cristae membranes elongate, often separating from the boundary membrane (bottom, image courtesy of K. Pfanner, K. von der Malsburg, and I. van der Klei).

Focusing specifically on Fcj1/mitofilin, von der Malsburg et al. (2011) purify Fcj1 and its associated proteins from yeast mitochondria and identify the components by mass spectrometry. In addition to the large Fcj1-associated protein complex that organizes the mitochondrial IM, they also uncover a key role for Fcj1 in mitochondrial protein import. Specifically, the efficient import of nuclear-encoded proteins destined for the intermembrane space (IMS) relies on a link between the TOM40, the channel portion of the outermembrane translocon, and Mia40, the IMS component required for import and assembly of IMS proteins. Fcj1 provides this link. von der Malsburg and her colleagues conclude that Fcj1 performs two separate functions—one in membrane organization and one in import. Coupling of these two processes, although likely, must rely on other proteins.

Hoppins, S., et al. (2011). J. Cell. Biol. 195, 323–340.
von der Malsburg, K., et al. (2011). Dev. Cell 21, 694–707.

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