Mitochondrial Dynamics in Disease

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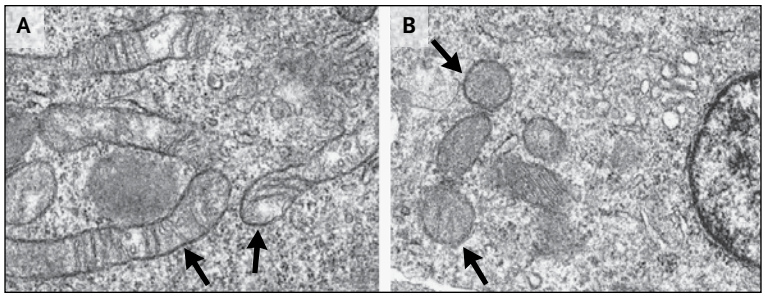
Mitochondria are subcellular organelles that coordinate numerous metabolic reactions, including those of the respiratory complexes that produce the ATP that powers cellular reactions. They have often been depicted as static, with a kidney-bean shape, but there is a growing appreciation of their dynamic nature.[1,2] Moreover, they are strikingly varied in structure, ranging from small, spherical particles to long, interconnected filaments. Mitochondria are also highly motile and constantly move in a directed manner along cytoskeletal tracks within cells.

An individual mitochondrion is not an autonomous organelle. The hundreds of mitochondria within a typical cell undergo continual cycles of fusion and fission (see the video, available with the full text of this article at www.nejm.org). Because mitochondria have an outer lipid membrane as well as an inner one, each fusion event requires the coordinated fusion of the membranes. Not only do the membranes of two mitochondria merge, but so do their contents, including the matrix compartment that contains mitochondrial DNA (see diagram). Conversely, a fission event causes a single mitochondrion to become two. Because of these complementary processes, the identity of any individual mitochondrion is transient.

Distinct protein complexes mediate these remodeling processes. For mitochondrial fusion, three mitochondrial enzymes that hydrolyze guanosine



Control of Mitochondrial Shape by Fusion Defects.

Panel A shows mitochondria (arrows) in wild-type fibroblasts from mouse embryos. Panel B shows mitochondria (arrows) in fibroblasts lacking Mfn2. Because of reduced mitochondrial fusion, the mitochondria in these cells are fragmented into small spheres, in contrast to the long tubules observed in the wild-type cells. Micrographs courtesy of Hsiuchen Chen and J. Michael McCaffery.

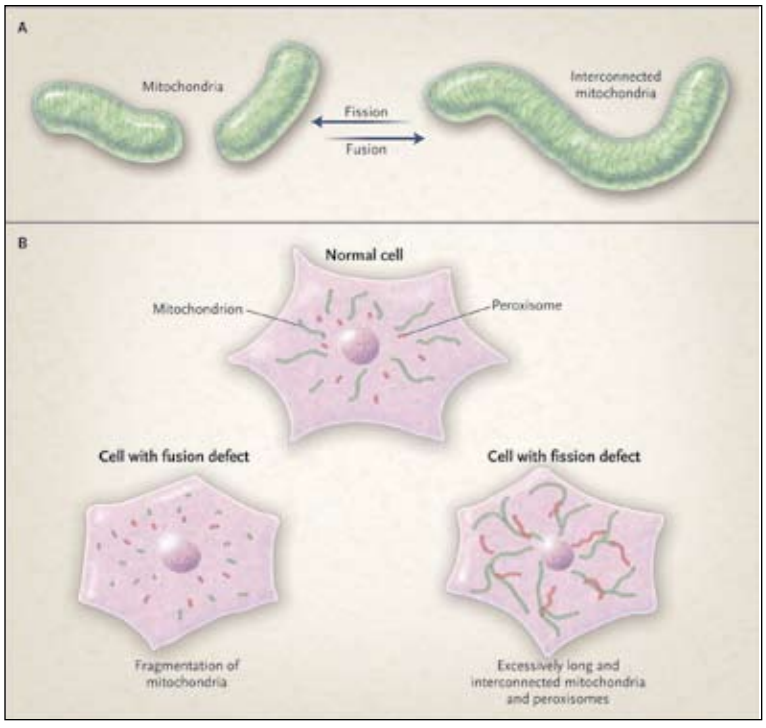
triphosphate (guanosine triphosphatases, or GTPases) are required. Two of these GTPases (the mitofusin 1 and 2 proteins MFN1 and MFN2) are embedded in the outer mitochondrial membrane and mediate the tethering of mitochondria with each other during the fusion process. A third GTPase (called the optic atrophy 1 protein, or OPA1) is located in the intermembrane space and is probably involved in the fusion of the inner mitochondrial membranes. For mitochondrial fission, yet another GTPase, called dynamin-like protein 1 (DLP1) or dynamin-related protein 1 (DRP1), is required. To mediate mitochondrial fission, DLP1 must be recruited from the cytoplasm to the surface of the mitochondrion, where it is thought to assemble into large oligomeric complexes that use GTP hydrolysis to constrict mitochondrial tubules (in the transverse dimension) during fission. Not much is known about the mechanism through which DLP1 is recruited to mitochondria, although it is established that FIS1, an outer-membrane protein, is critical to DLP1-mediated fission. Both DLP1 and FIS1 are also required for the fission of peroxisomes, organelles involved in oxidative reactions that are important for the catabolism of fatty acids and hydrogen peroxide.

Intuitively, it is easy to imagine how mitochondrial fusion and fission can change the morphologic characteristics of mitochondria. Fusion results in fewer and longer mitochondria, whereas fission results in more and shorter mitochondria (see diagram and micrograph). Indeed, genetic studies indicate that cells with mutations in the genes required for mitochondrial fusion have fragmented mitochondria instead of the tubular mitochondrial network observed in normal cells. Similarly, cells with mutations in genes required for mitochondrial fission have excessively elongated and interconnected mitochondria because of unopposed fusion. Peroxisomal shape is also controlled by fission; the role of fusion is less clear.

Mitochondrial dynamics are now a focus of cell biologists, but are these processes physiologically and clinically important? Recent developments indicate that they are. In this issue of the *Journal*, Waterham et al. (pages 1736–1741) describe a human disorder caused by a mutation affecting DLP1. An infant carrying this mutation had microcephaly and metabolic aberrations and died at 37 days of age. These events show that fission processes have widespread physiological functions essential to life.

Previous studies have shown that mitochondrial fission precedes apoptosis, a form of programmed cell death.[3] Perhaps the fragmentation of mitochondria, through fission, facilitates the release of mitochondrial proteins and metabolites that trigger cell death. Whether any of the diverse clinical signs reported by Waterham et al. are related to a defect in apoptosis, however, is unclear.

As for mitochondrial fusion, several observations indicate that it is a process of broad physiological importance. Mice with mutations in *Mfn1*, *Mfn2*, or *Opa1* have greatly reduced mitochondrial fusion and do not survive past the middle of gestation. Cells lacking mitochondrial fusion show impaired respiratory activity. The mitochondria of such cells have heterogeneous properties, indicating that mitochondrial fusion is important for maintaining a healthy, homogeneous mitochondrial population. In addition, fusion causes mitochondrial genomes to become mixed. Since diseases caused by mutations in mitochondrial DNA have a progressive course that is dependent on the segregation of pathogenic



Control of Morphologic Characteristics of Mitochondria and Peroxisomes.

Mitochondria undergo fusion, which results in the merging of the outer and inner membranes as well as the mixing of the mitochondrial contents (Panel A). Conversely, fission results in the division of mitochondria. Panel B shows the effects of defects in fusion or fission on organelle shape. A normal cell typically contains tubular mitochondria and spherical or rodlike peroxisomes. The steady-state shape of mitochondria is the result of a careful balance between fusion and fission, which can be perturbed by mutations. Mutations in genes required for mitochondrial fusion result in the fragmentation of mitochondria, owing to ongoing fission in the absence of fusion. The disruption of proteins required for mitochondrial fission results in mitochondria that are excessively long and interconnected. In extreme cases, the mitochondria form tangles that tend to collapse around the nucleus. Since molecules involved in fission are shared between mitochondria and peroxisomes, such defects also cause elongation of peroxisomes, as found by Waterham et al.

mitochondrial DNA, fusion may influence clinical outcome.

Defects in mitochondrial fusion cause neurodegenerative disease. Charcot–Marie–Tooth disease type 2A, an autosomal dominant neuropathy of long peripheral nerves, is caused by mutations in *MFN2*. Moreover, dominant optic atrophy, the most commonly inherited optic neuropathy, is caused by mutations in *OPA1*. This apparent sensitivity of neurons to defects in mitochondrial dynamics probably depends on the special requirements of neurons for mitochondrial function. An ultrastructural hallmark of the synapse is the presence of abundant mitochondria, which maintain calcium homeostasis and levels of ATP production that, in turn, are critical to nerve transmission. Neurons have extraordinarily long cellular processes, and tight control of mitochondrial dynamics is probably necessary for distributing active mitochondria to dendrites and axon terminals. Given the important roles of mitochondrial dynamics in human physiologic processes, it would not be surprising to find additional diseases caused by mutations in genes that control mitochondrial fusion and fission.

A video is available with the full text of this article at www.nejm.org.

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2. Okamoto K, Shaw JM. Mitochondrial morphology and dynamics in yeast and multicellular eukaryotes. Annu Rev Genet 2005;39:503-36.
3. Youle RJ, Karbowski M. Mitochondrial fission in apoptosis. Nature Rev Mol Cell Biol 2005;6:657-63.