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Mitochondria help dynamins get a grip

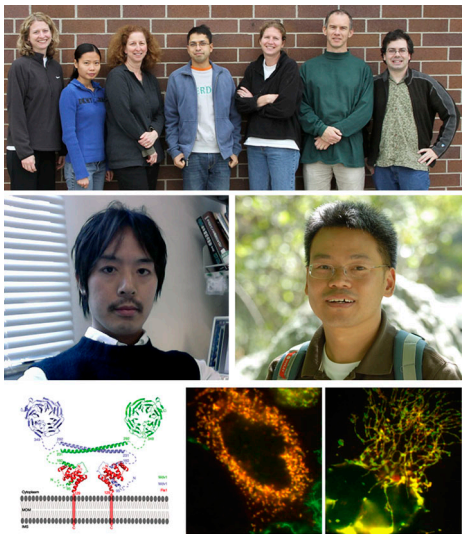
Pair of studies clarifies how organelles attract enzymes that promote their fission.

The dynamin-like GTPases spur mitochondria to break up. Two papers (1, 2) reveal new details about the molecular platforms that position these mitochondria-splitting proteins on the organelles.

In yeast, the dynamin-like GTPase Dnm1 dismembers mitochondria by settling on the outer surface of the mitochondrial membrane and polymerizing into spirals that cleave the organelle (3). Two other proteins construct a landing pad for Dnm1. An anchor known as Fis1 embeds in the membrane and is linked to Dnm1 by the adaptor Mdv1, which operates as a dimer. Researchers are still working out the architecture of Mdv1 to understand its mitochondria-severing capabilities. A previous study nailed down the configuration of the Mdv1 N terminus (4). Now, Koirala et al. (1) have determined the structure of the molecule's midsection, which is composed of multiple repeats of seven amino acids.

The researchers found that in an Mdv1 dimer, the middle segments are arranged in a coiled-coil conformation, with the two helices running in opposite directions. From crystal structures, the team built a model that depicts the Mdv1 dimer as an "X" shape. The N-terminal feet of the "X" latch onto Fis1, whereas the C-terminal caps hook up with Dnm1. The angled pieces are the coiled coils, which cross in the middle of the coupled molecule.

By tinkering with the coils, Koirala et al. discovered that their length and amino acid sequence help determine Mdv1's function. Removing some of the seven-amino acid repeats from the coil impaired mitochondrial fission. The team also replaced the Mdv1 coil with one of about the same length but with a different amino acid sequence; this modified version was poor at promoting mitochondrial division. Moreover, the altered Mdv1 molecules formed a weaker connection to Fis1, suggesting that the coil helps solidify this interaction.



TOP ROW IMAGE COURTESY OF ERIC TAYLOR. MIDDLE ROW IMAGES COURTESY OF HIDENORI OTERA (LEFT) AND YINGJIE WU (RIGHT).

Focal Point

Two research teams probed how mitochondria engage fission-promoting, dynamin-related GTPases. In yeast cells, Mdv1 helps capture the GTPase Dnm1. (Top row) Janet Shaw (third from left), Sajjan Koirala (fourth from left), and colleagues determined the structure of the middle portion of Mdv1. Their structure (bottom left, from (1)) shows two Mdv1 molecules (green and purple) with their coils overlapping. (Middle row) Hidenori Otera (left), Chunxin Wang (right), and colleagues (not shown) found that human mitochondria rely on the protein Mff to capture the dynamin-related GTPase Drp1. The bottom row images (from (2)) show that overexpressing Mff breaks up mitochondrial networks (middle), but not when Drp1 is missing (right).

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Now that scientists have a clearer picture of Mdv1's tertiary organization, "we can start to make predictions about how Dnm1 is recruited to the membrane and starts to form spirals," says senior author Janet Shaw. She adds that the next target for the field is to elucidate the structure of Mdv1's C terminus, by itself and in combination with Dnm1.

Although human cells carry equivalents of Fis1 and Dnm1—known as hFis1 and Drp1—they use a different anchoring setup, Otera et al. (2) show.

Researchers already knew about one difference—mammals don't appear to have genes for adaptor proteins like Mdv1. Another possible discrepancy is the role of hFis1. Evidence that it forms part of the receptor for Drp1 is equivocal: some studies suggest that Drp1 can attach to mitochondria in cells lacking hFis1 (5). So Otera and colleagues tested whether Drp1 connects to mitochondria in human cells via an alternative protein known as mitochondrial fission factor or Mff (6).

The team found that knocking down Mff with RNAi prevented Drp1's recruitment and disrupted mitochondrial fission, causing the organelles to stick together and form abnormal networks. However, depleting hFis1 had no impact on mitochondrial structure. Boosting cells' production of either protein spurred mitochondria to fragment, but increasing levels of Mff had a much stronger effect.

Otera et al. also showed that Drp1 attaches to Mff on the mitochondrial surface. Because of this attraction, the researchers could trick Drp1 into abandoning the organelles. In cells engineered to produce a version of Mff that lodged in the plasma membrane, Drp1 followed Mff to its new location.

The results suggest that mammals rely on Mff rather than hFis1 for recruiting their version of dynamin to the mitochondrial membrane. "hFis1 is dispensable for mitochondrial fission," says senior author Katsuyoshi Mihara, but that doesn't mean it has no role. hFis1 might join in after Drp1 has already coupled to Mff. Researchers don't know how Drp1 splits up mitochondria, so a key question is how Mff contributes to that task.

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3. Bleazard, W., et al. 1999. *Nat. Cell Biol.* 1:298–304.
4. Zhang, Y., and D.C. Chan. 2007. *Proc. Natl. Acad. Sci. USA.* 104:18526–18530.
5. Wasiak, S., et al. 2007. *J. Cell Biol.* 177:439–450.
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