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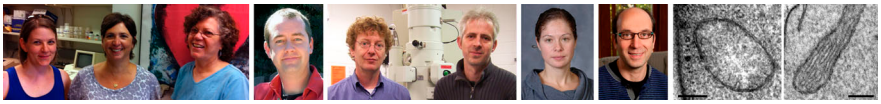
# Locating a mitochondrial scaffold on the map

A high-density genetic interaction map reveals a complex that organizes the mitochondrial inner membrane.

## Focal Point



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**A collaborative effort by researchers including (left to right) Suzanne Hoppins, Jodi Nunnari, Ann Cassidy-Stone, Sean Collins, Benedikt Westermann, Eric Hummel, Maya Schuldiner, and Jonathan Weissman resulted in the assembly of MITO-MAP, a systems-wide view of the interactions between yeast genes involved in mitochondrial and endoplasmic reticulum function. The map revealed the existence of a protein complex called MitOS that forms an extended scaffold-like structure to organize the mitochondrial inner membrane. Compared to a wild-type mitochondrion (second from right), mitochondria from cells lacking MitOS components have a single, large, inner membrane crista that wraps around itself in the matrix to form an onion-like structure (far right).**

The ability of mitochondria to perform numerous different functions is reflected in the organelle's complex architecture. The mitochondrial inner membrane, in particular, is organized into distinct regions that carry out specialized functions (1). Boundary regions are where the inner membrane contacts the outer membrane to facilitate protein import and respiratory complex assembly. Once assembled, respiratory complexes concentrate in cristae, inner membrane folds that project into the mitochondrial matrix. Connecting these two inner membrane regions are tubular structures called cristae junctions. Hoppins et al. uncover a protein complex that organizes the mitochondrial inner membrane into these distinct domains (2).

Jodi Nunnari, who works at the University of California, Davis, is interested in the various functions of mitochondria. "We're really interested in figuring out how they're all integrated with each other," she says, "but that system-wide view is hard to get at using classical cell biological approaches."

Nunnari therefore teamed up with several researchers, including Jonathan Weissman from the University of California, San Francisco, whose lab has helped develop methods to comprehensively map the interactions between large sets of yeast genes (3). "These approaches allow you to explore functions without envisioning, *a priori*, all the important processes of the cell," Weissman explains. "It removes personal bias from your analysis."

> **"We never would have seen this complex without taking this systems-wide view."**

Weissman is also interested in the physical and functional links between mitochondria and the endoplasmic reticulum. The researchers therefore quantified the interactions between 1,482 yeast genes encoding ER and mitochondrial proteins by mating single mutant strains to each other and measuring the growth of the resulting double mutants. Strong changes in growth indicate a significant interaction between the two alleles, and genes with similar interaction patterns—what Weissman describes as a "high-resolution phenotype"—are likely to share a common function.

The resulting interaction network, which the researchers named "MITO-MAP," showed that mitochondria and the ER generally have separate functions, though a protein complex called ERMES, which physically links the two organelles (4), helps them cooperate in phospholipid synthesis and mitochondrial DNA inheritance.

MITO-MAP also revealed the existence of a new protein complex within mitochondria themselves. A cluster of four genes—FCJ1, AIM5, AIM13, and AIM37—had similar interaction profiles with a variety of inner and outer membrane proteins. "We never would have seen this complex without taking this systems-wide view," Nunnari says. Immunoprecipitation experiments showed that the proteins encoded by these four genes interact physically with each other and that they form a complex with two other mitochondrial proteins, Mos1 and Mos2.

Fcj1 has previously been implicated in organizing the inner mitochondrial membrane (5), and yeast lacking any of the six complex members displayed dramatic changes in mitochondrial morphology. "Normally, cristae are dispersed throughout mitochondria," Nunnari explains. "In the mutants, you get one dominant crista that keeps growing and growing until it snaps off from the boundary membrane." This suggests that the Fcj1-containing complex, which the researchers called the mitochondrial organizing structure (MitOS), helps to specify and order the distinct regions of the mitochondrial inner membrane.

MitOS localized to the inner membrane, probably at boundary regions where it can also interact with outer membrane proteins. Yet individual MitOS subunits showed different staining patterns—some localized to filamentous structures, whereas others had a more punctate distribution. "MitOS is extended and heteromorphic," Nunnari says. "[The subunits] clearly interact with each other, but there's some sort of ordered assembly within a larger structure." It remains to be seen exactly how MitOS organizes the inner membrane, but Nunnari and colleagues think that it may act as a scaffold-like structure.

The information contained within MITO-MAP will enable the mitochondrial community to investigate plenty of other questions related to mitochondrial biology, as well. "That's going to be a blast for people," Nunnari says. "I think they'll be really eager to see it."

1. Frey, T.G., and C.A. Mannella. 2000. *Trends Biochem. Sci.* 25:319–324.
2. Hoppins, S. et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201107053.
3. Schuldiner, M., et al. 2005. *Cell*. 123:507–519.
4. Kornmann, B., et al. 2009. *Science*. 325:477–481.
5. Rabl, R., et al. 2009. *J. Cell Biol.* 185:1047–1063.