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The Mighty MitoCarta—Online Mitochondrial Atlas Leads to Cause of Inherited Disease

Mitochondria are busy organelles. They participate in so many cellular tasks that trouble can ensue when they stop working, including neurodegenerative diseases, metabolic disorders, and organ failure, among other problems. Now, HHMI-supported scientists have created MitoCarta, an online atlas of more than 1,000 proteins that healthy mitochondria use to keep cells running smoothly—a tool that should help researchers understand what happens when things go wrong.

To demonstrate the power of MitoCarta, its creators have used the resource to identify a genetic mutation responsible for complex I deficiency, a rare, lethal metabolic disorder in infants. Their work is reported in the July 11, 2008, issue of the journal *Cell*.

“To really understand a system, you have to begin by identifying its individual components,” says Vamsi Mootha, a researcher at Massachusetts General Hospital (MGH) and recipient of a HHMI Early Career Physician Scientist award. “Eventually we want to know how all the components get assembled in healthy cells and how these processes go awry in disease.”

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Mootha led a team from MGH, Harvard Medical School, and the Broad Institute of the Massachusetts Institute of Technology and Harvard to create the MitoCarta. It is freely available at <http://www.broad.mit.edu/publications/MitoCarta/>.

Mitochondria are best known for their role as the center of energy metabolism. The organelles also integrate numerous other biochemical pathways and contribute to cellular balance, differentiation, and programmed cell death.

Given the many vital and complex functions of mitochondria, it is little wonder that their failure can trigger a range of diseases. The 50 known mitochondrial diseases combined affect a total of about two million Americans. Researchers suspect that breakdowns in mitochondria's function may be behind an even higher number of common conditions, from Alzheimer's disease to some forms of cancer and heart disease.

That is why biologists want to identify the proteins that make up mitochondria and understand their roles in health and disease. These proteins come from two sets of genes: Mitochondria carry their own small set of 13 genes, which are inherited only from the mother, and approximately 1,500 mitochondrial proteins come from genes in a cell's nucleus.

As a medical student, Mootha trained in mitochondrial physiology as an HHMI-NIH Research Scholar. Later, after completing his clinical training, he pursued postdoctoral training in genomics as an HHMI Physician Postdoctoral Fellow, which was when he began his quest to build a protein atlas for mitochondria.

Since launching his own laboratory at MGH in 2004, Mootha has specialized in studying rare mitochondrial diseases. He used two well established but laborious and often inaccurate protein analysis tools—mass spectrometry and green fluorescent protein tagging and microscopy—to identify new mitochondrial proteins systematically. Using his background in mathematics and computer science, Mootha integrated the vast amount of data generated from these approaches to construct the MitoCarta database of 1,098 proteins and their expression across 14 organs.

Of those proteins, scientists had pinpointed functions for less than 800. To learn more about what they do, Mootha developed methods to compare mitochondrial proteins for 500 different species whose genomes have been sequenced. That allowed him to trace the evolutionary history of specific proteins and predict their role in human mitochondria. They could also help identify unknown mutations leading to mitochondrial disorders.

To prove the system worked, Mootha and the team focused on a large assembly of proteins that mitochondria use to produce energy, called complex I (CI). Problems in the CI system, which is part of the electron transport system inside the cell, are the most common cause of a group of rare diseases, generally fatal in infancy, but they have also been implicated in Parkinson's disease, multiple sclerosis, and other more common conditions. Previous studies have shown that half of patients with CI deficiencies lack mutations in a known CI gene, which suggests that other genes are involved,

Mootha says.

Comparing the genomes of organisms from yeast to mammals, Mootha and his team searched for the 45 proteins known to make up CI. They then compared that expression pattern to other proteins in the MitoCarta to find similar patterns. They identified 19 proteins not previously known to be part of the CI system. After turning off those genes using small interfering RNA, the team found four genes that were important to CI activity within mitochondria. Using genetic samples from families with CI deficiency disorders, Mootha's lab identified the chromosomal location for a new CI defect and a single gene, C8orf38, as the culprit for the rare defect.

Mootha's lab is now using MitoCarta to seek out genes responsible for other CI disorders. "Already, we're identifying the culprits behind devastating rare CI deficiencies, but we're also excited about pursuing studies of more common diseases like Parkinson's and type 2 diabetes," Mootha says. "We hope other groups will make use of the MitoCarta as well."