

Mitochondrial maps reveal new connections to poorly understood diseases

August 4 2016



Dave Pagliarini, director of metabolism for the Morgridge Institute for Research and UW-Madison associate professor of biochemistry. Credit: Morgridge Institute for Research

Mitochondria are the engines that drive cellular life, but these complex machines are vulnerable to a wide range of breakdowns, and hundreds of their component parts remain a functional mystery.

Dave Pagliarini, director of metabolism for the Morgridge Institute for Research and UW-Madison associate professor of biochemistry, is working to identify the more than 200 proteins associated with mitochondria that currently have no defined function. Completing this process will give science a complete map of mitochondrial function and help discover the origins of more than 150 poorly understood diseases associated with mitochondria.

New features of that map are taking shape today. Two related studies led by the Pagliarini Lab, published consecutively in today's (Aug. 4) issue of the journal *Molecular Cell*, identify functions for three little-known mitochondrial proteins that play either a direct or potential role in disease.

Mitochondria are tiny organelles that exist in all human cells except red blood cells and consume about 95 percent of oxygen people breathe in order to manufacture adenosine triphosphate (ATP), the chemical currency of the cell. Mitochondrial diseases strike about 1 in 4,000 people and there are currently no licensed therapies available, beyond treatments with vitamins and supplements.

"We began by trying to learn something about what these proteins do by understanding what other proteins they physically interact with," says Pagliarini. To do this, Pagliarini's group partnered with Josh Coon's laboratory, a group that specializes in mass spectrometry and [protein analysis](#). Using the Coon Lab's cutting edge spectrometry techniques, they gained clues about the functions of uncharacterized proteins by mapping their interactions with known ones.

"In our first paper, we found about 2,000 interactions that we think are particularly robust, out of more than 100,000 total," he says. "These top 2 percent of interactions are really telling us something about [protein function](#) and will be very useful to the research community in the years

ahead."

The studies already helped assign function to three previously unknown proteins. The first one plays a key role in the assembly of complex I, the first of a series of protein complexes used to create ATP. Complex I deficiencies represent the largest class of inborn errors of metabolism. The team revealed that complex I does not function when missing this protein.

"Patients with complex I deficiencies are unable to turn sugar and other sources of fuel into energy," says Brendan Floyd, a UW-Madison MD-PhD student and co-author. "They can't make ATP and complete other processes. Symptoms can be very wide-ranging, from severe inborn diseases that are fatal, to effects later in life related to the inability to grow properly or exercise."

Floyd says the team confirmed this finding by examining the case of a patient with a complex I disorder. That patient appeared to have a deficiency in the protein the team identified.

Two other newly defined proteins are players in the production and use of coenzyme Q, a molecule that is essential to energy production within all cells. Coenzyme Q has been called the "spark plug" of the cell since all fuels being broken down by mitochondria to produce ATP rely on its action.

Inborn coenzyme Q deficiencies can lead to brain and muscular disorders, and coenzyme Q can be in lower quantities in people with cancer, diabetes, heart conditions, Parkinson's and other diseases.

Floyd says the identification of protein function can be an essential first step in the eventual quest to develop therapies. Protein function discoveries in the past 20 years have been the impetus for therapies for

cystic fibrosis, and the ability to inhibit certain types of protein expression is at the heart of cholesterol-lowering statin drugs.

The second paper identified a link between a protein used in coenzyme Q synthesis and the development of cerebellar ataxia, which leads to abnormalities in balance, gait and eye movement. An international collaboration with H el ene Puccio and colleagues in France was key for this work. The researchers found that this protein is required for assembling other coenzyme Q-related proteins into a complex inside mitochondria. By working with Craig Bingman, a protein crystallographer in the Department of Biochemistry at UW-Madison, the team also captured new snapshots of this protein in action.

Jonathan Stefely, a Morgridge postdoctoral research associate and co-author, says the research will continue for many more missing steps in the pathway that produces coenzyme Q. This molecule can only be produced in the body and does not come from diet. "If we know the biochemical functions of proteins throughout this pathway, we might be able to design therapies or drugs that bypass a dysfunctional step in coenzyme Q production," he says.

Pagliarini says these findings only scratch the surface of what useful information may be found in their protein interaction database, which is public and available to the research community. This initial project focused on 50 uncharacterized proteins that, based on literature searches, showed some likelihood of being associated with human disease. "We hope that researchers around the world will use our data to further understand how these mitochondrial protein work, thereby giving us a chance to fix them when they malfunction," says Pagliarini.

Provided by Morgridge Institute for Research

Citation: Mitochondrial maps reveal new connections to poorly understood diseases (2016, August 4) retrieved 23 April 2024 from <https://medicalxpress.com/news/2016-08-mitochondrial-reveal-poorly-understood-diseases.html>

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