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Researchers examine metabolism in defective cells

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University of Alberta researchers are taking a closer look at how two metabolic pathways interact to increase the lifespan of cells with mitochondrial defects. Magnus Friis is the lead author of the study, which was published online on April 10 and will be published in the April 24 issue of *Cell Reports*.

Mitochondria produce energy for cells through oxidative metabolism, but the process produces toxic byproducts that can accumulate and cause defects in the cell's mitochondria. These defects, in turn, affect the cell's ability to generate energy and can potentially lead to cell death and are associated with aging and various neurological diseases.

Friis, a postdoctoral fellow in Mike Schultz's biochemistry lab, examined how dietary changes at the cell level can affect cell health. He exposed normal and defective yeast cells to two different energy sources: glucose, the preferred sugar of cells, and raffinose, a natural sugar found in vegetables and whole grains.

"[The dietary intervention] is a general shift in what we're feeding the cells to get them to do something different with their whole nutrient metabolism," Friis noted. "There are signaling pathways that allow a cell to sense its environment and co-ordinate events to allow the cell to adapt to what's going on. In this case, [cells are responding to] which nutrients are available."

Friis and Schultz examined two nutrient signaling pathways called the

AMPK pathway and the retrograde response. AMPK responds to energy deficits in the cell by down-regulating energy consuming processes, which are often associated with cell growth, and up-regulating energy producing processes. The retrograde response pathway is specific to the yeast used in the study and supplies key amino acids to the cell by changing the metabolic process of the mitochondria.

When activated individually, neither the AMPK pathway nor the retrograde response provided substantial benefits to cells with damaged mitochondria. When activated simultaneously, clear benefits became evident.

"We looked at the effect activating both pathways had on maintenance of cellular viability in what's called a chronological aging experiment," Friis said. "Even when they had defective mitochondria, the cells with the retrograde response and AMPK simultaneously activated during growth were able to live as long as cells with normal mitochondrial function."

Working in collaboration with John Paul Glaves, a postdoctoral fellow in Bryan Sykes' lab, and Tao Huan, a PhD student in Liang Li's lab, Friis measured the molecules produced during the metabolic process. They found that the defective cells had higher levels of branched chain amino acids and trahelose, a carbohydrate found in yeast that can serve an energy source, similar to glycogen in human cells.

"By activating AMPK, we've removed certain blocks in metabolism. With the retrograde response, we've changed the amino acid metabolism in a way that allowed the cells to accumulate storage carbohydrates, which stabilize their function," Friis said.

Activated AMPK and retrograde response pathways allow the cell to accumulate a storage carbohydrate, which can be metabolize normally

despite mitochondrial defects that affect the cell's metabolism. The additional energy stabilizes cell function and prevents premature cell death often caused by defects in mitochondria.

"No matter how many people are working on the problem in humans, mitochondrial disorders are too complicated to figure out the nuts and bolts without the work that Magnus is doing," Schultz said. "This research opens the concept, a new concept on how to deal with these metabolic problems."

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