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Fatty acid increases performance of cellular powerhouse – Fundamentally new biological signaling pathway discovered

Scientists from the German Cancer Research Center (DKFZ) have discovered an entirely new control mechanism that regulates the function of mitochondria, the powerhouses of the cell. Surprisingly, a fatty acid is playing a key role in this process. The scientists have now reported in the journal *Nature* that using fatty acid as a food additive improved disease symptoms in flies that suffer from Parkinson's-like symptoms due to dysfunctional mitochondria.

Mitochondria are essential to all higher forms of life. Every animal and plant depends on these small intracellular structures. Mitochondria have multiple tasks: Since they generate most of the cell's biochemical energy, they are referred to as the powerhouses of the cell. In addition, they are responsible for producing and breaking down amino acids and fats. They also regulate cellular death, called apoptosis.

As a result, the spectrum of diseases that are linked to mitochondrial defects is wide, ranging from severe muscular and nervous disorders to neurodegenerative diseases as well as all symptoms of aging.

"It was by pure chance that we discovered this completely new control mechanism of mitochondrial function," says first author Deniz Senyilmaz, who works in Aurelio Teleman's group at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ). In collaboration with colleagues from Cambridge, Teleman and his team had planned to investigate the metabolism of long-chain fatty acids. For this purpose, the researchers bred flies whose cells were unable to produce stearic acid, a fatty acid that is composed of 18 carbon atoms. Animals with this defect did not develop beyond the pupal stage and were not viable afterwards.

Teleman and his team were curious to find out why this happened. They then discovered a highly complex biological control mechanism that regulates the fusion – as well as fragmentation – of mitochondria and, hence, the performance of these organelles.

The key element in this control mechanism is the transferrin receptor, which binds stearic acid. "For the first time in biological research, we have found out that stearic acid, which up until now has been believed to be simply a metabolic product, also has signaling function," says Teleman. The researchers demonstrated that mitochondrial control via stearic acid works not only in flies but also in the HeLa human cancer cell line.

When the researchers added stearic acid to fly food, the animals' mitochondria fused; when they kept fatty acid levels low, the organelles fragmented. "If using stearic acid as a food additive improves the performance of normal mitochondria, then it might do the

same in pathogenically dysfunctional mitochondria," Teleman explained, describing their experimental approach.

The researchers studied flies that exhibit Parkinson's-like symptoms resulting from a mitochondrial defect in the PINK and Parkin proteins and are recognized as a model system for studying this neurodegenerative disease. When the affected animals were fed stearic acid with their food, their motor skills and energy balance improved and they survived for much longer.

"This opens up the fascinating possibility of using a food additive to alleviate symptoms in patients with mitochondrial disease," says Teleman. "However, this still is a dream of the future, because we do not yet know whether human cells respond in the same way as fly cells do to increased quantities of stearic acid in the diet. Our diet naturally contains much more stearic acid than fly food does. Therefore, a further increase might not make any more difference."

Deniz Senyilmaz, Sam Virtue, Xiaojun Xu, Chong Yew Tan, Julian L Griffin, Aubry K. Miller, Antonio Vidal-Puig, and Aurelio A. Teleman: Regulation of mitochondrial morphology and function by Stearoylation of TfR1. *Nature* 2015, DOI: 10.1038/nature14601

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 3,000 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

Contact:

Dr. Stefanie Seltmann
Head of Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2854
F: +49 6221 42 2968
presse@dkfz.de

Dr. Sibylle Kohlstädt
Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2843
F: +49 6221 42 2968
Email: presse@dkfz.de