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The emerging role of the mitochondrial fatty-acid synthase (mtFASII) in the regulation of energy metabolism

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Abstract

Malonyl-CoA synthetase (ACSF3 gene product) catalyzes the first step of the mitochondrial fatty acid biosynthesis (mFASII). Mutations in ACSF3 cause CMAMMA a rare inborn error of metabolism. The clinical phenotype is very heterogeneous, with some patients presenting with neurologic manifestations. In some children, presenting symptoms such as coma, ketoacidosis and hypoglycemia are suggestive of an intermediary metabolic disorder. This may indicate a role for mFASII in the regulation of energy homeostasis and metabolic flexibility.

We have performed comprehensive metabolic phenotyping, SILAC-based proteomics and lipidomics in fibroblasts from CMAMMA patients in order to investigate the role of mFASII in the regulation of mitochondrial energy regulation.

Mutations in ACSF3 resulted in reduced mitochondrial respiration and glycolysis due a lower lipoylation degree. In contrast, fatty acid oxidation was upregulated as compensatory mechanism to address the required energy need. The concentration of ceramides and phospholipids was also significantly reduced in patient

fibroblasts whereas we observed a significant upregulation of sphingomyelin and cardiolipins with subsequent shift of the fatty acids species.

Our studies in fibroblasts showed that mFASII is indeed important in the regulation of energy metabolism and metabolic flexibility linking glycolysis and fatty acid oxidation. Moreover, we showed that defect in this pathway also affects the total cellular lipid composition with possible consequences on signal transduction.

Biography

Zeinab Wehbe is a postdoctoral researcher at the Department of Pediatric Hematology and Oncology, University of Freiburg, Germany since 2020. She received a bachelor's degree in biochemistry and life science from the faculty of science, University of Saint-Joseph, Lebanon in 2013, a master's degree in molecular biology and genetics in 2015 and a PhD in metabolic flexibility from the University of Freiburg, Germany in 2019.