

Role of mitochondrial antioxidant defense systems in fatty acid β -oxidation defects

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Mitochondrial fatty acid oxidation (FAO) plays a pivotal role in energy homeostasis, namely during periods of fasting or metabolic stress. FAO defects are a group of inherited metabolic disorders that encompass at least twelve distinct enzyme or transporter deficiencies, and can present with a wide range of clinical symptoms with various degrees of severity. Besides recent advances, many doubts still remain on the degree and characteristics of mitochondrial dysfunction on FAOD and its contribution to the clinical phenotype.

Mitochondria are major sources of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that play key functions in cellular homeostasis. However, when ROS/RNS load increases and/or the antioxidant systems are not working properly they lead to mitochondrial dysfunction and ultimately to cellular death. Due to the importance and relation of oxidative stress with disease, it's important to understand how mitochondrial antioxidant defense system adapts and contribute to FAOD. The authors applied a large scale, organelle specific, proteomics approach to characterize mitochondrial proteome of patients with multiple acyl-CoA dehydrogenation deficiency and long chain 3-hydroxy acyl-CoA dehydrogenase deficiency.

It was observed that several antioxidant proteins, namely MnSOD and peroxiredoxins are over-represented in the patients, in response to increased oxidative stress. Our data, point out that in the most severe presentations of FAOD the mitochondrial antioxidant defense system is overexpressed, but it is most probably overloaded since it cannot avoid molecular lesions on mitochondria. This observation is in contrast with the less severe presentations of FAOD, like SCAD, where the downregulation/inhibition of the antioxidant defense system has been reported to play a key role on disease progression and symptoms output.