Improving Management Strategies for Multiple Acyl-Coa Dehydrogenase Deficiency – Insights From Wet and Computational Research

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Background: Multiple Acyl-CoA dehydrogenase Deficiency (MADD, OMIM #231680), a rare disease from the group of IEM, is an autosomal recessively inherited disorder of fatty acid, amino acid and choline metabolism. MADD results from defects on electron transfer flavoprotein (ETF), and ETF:ubiquinone oxidoreductase (ETF:QO) proteins. These proteins are responsible for transferring electrons from at least 12 dehydrogenases to the respiratory chain, hence mutations on their genes will cause diminished mitochondria β-oxidation and impaired energy production.

Case Study/Methods: In recent years the development of newborn screening programs worldwide resulted in an increased number of MADD patients being identified. Interestingly, for milder forms the molecular mechanism that triggers disease symptoms is still unknown, and no effective therapy is established, thus, to make disease prognosis is highly challenging to clinicians. To fulfill this gap, we design a project integrating molecular, cellular and computational studies aiming to gain insights in disease molecular mechanism and symptoms development.

Results: Previously we have identified structural hotspots in ETF, and made a comprehensive characterization of three ETF variants [1]. Further, we resort to a ETF:QO bacterial homologue from *Rhodobacter sphaeroides* to characterize a riboflavin-responsive variant [2]. We have deepened our studies to MADD patient-derived fibroblasts and showed that these cells present an altered mitochondria morphology and mitochondria membrane potential diminished. Further, energy production is impaired as cells presented lower ATP content and higher ROS production. Currently, we are analyzing other ETF and ETF:QO MADD variants using biochemical, biophysical and structural methods. And we will complement our experimental data with *in silico* information on thermodynamic stability and evolutionary conservation.

[1] Henriques *et al* (2010) BBA-Mol Basis Disease

[2] Lucas *et al* (2020) BBA-Prot & Proteom