Metabolomic signature for improving management of a rare metabolic disorder

Place of work/: BioISI Mass Spectrometry Facility - Chemistry for bilogical systems Group, BioISI - FCUL

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MSc thesis project proposal

Inborn errors of metabolism (IEM) are group of genetic disorders described as rare yet having a high impact in society. Multiple acyl-coA dehydrogenase deficiency (MADD), a rare metabolic disorder, is caused by defects in ETF or ETF:QO proteins which form a key control point of the mitochondria β-oxidation pathway. In Portugal MADD diagnosis made through the Portuguese newborn screening program (Teste do Pézinho), but disease prognosis is challenging due to the heterogeneous clinical phenotypes and age onset.
We hypothesize that β-oxidation impairment will impact other pathways as well as to contribute to global cellular dysfunction, and these effects will be genotype related.
Our goal is to use metabolomics to complement previous cellular studies on mitochondria quality as an ultimate phenotypic tool to differentiate mild phenotypes in MADD. Here, we will use high resolution mass spectrometry and post-hoc bioinformatic analysis to discover metabolomic/lipidomic fingerprint of MADD patient-derived fibroblasts. Moreover, changes in metabolic profile will be followed-up in cells with altered growth conditions aiming to reconstitute healthy physiological function of mitochondria.
Finally, we expect to identify putative biomarkers for development of further quantitative diagnostic assays for assessment mitochondrial function in MADD.
The MSc project will proceed through the following steps:
1) optimization of the metabolite extraction and sample preparation procedure for discovery metabolomis and lipidomics.
2) optimization of chromatographic conditions for maximum separation efficiency for lipidomics and central metabolome analysis.
3) Analysis will be performed on the state-of-the-art Bruker UPLC-ESI-QTOF IMPACT II mass spectrometry equipment in data dependent acquisition mode.
4) Multivariate statistical analysis as well as metabolic pathway analysis will be performed on in-house software platform (Metaboscape by Bruker) and online R-based platform (Metaboanalyst).
5) Successful candidate will be create a fibroblast specific database of annotated metabolites that will be used in further experiments.
The work will be developed at BioISI mass spectrometry facility using high resolution UPLC/QTOF mass spectrometer in the laboratory dedicated exclusively to the proteomics/metabolomics sample preparation under the supervision of Dr Vukosava Torres, and co-supervision of Drª Bárbara Henriques. This project is part of an ongoing BioISI internal collaborative project lead by the supervisor and, a project financed by the Fundação para a Ciência e Tecnologia lead by the co-supervisor.