STUDYING THE ROLE OF BROWN FAT IN FRIEDREICH'S ATAXIA

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Friedreich's ataxia (FRDA), is a genetic disorder caused by expansions of GAA repeats in intron 1, associated with locus-specific chromatin changes leading to transcriptional silencing of *frataxin* gene (FXN) and consequent deficiency of mitochondrial protein frataxin (FXN). In this PhD program, we want to characterize whether an altered activity of brown adipose tissue (BAT) occurs and this event is a contributing factor in the severity of the disease. In particular, we intend to unravel whether thermogenic function is impaired in terms of defective mitochondrial and lipolytic activity as well as adipogenesis. BAT is a high oxidative tissue displaying elevated levels of triglyceride (TGs) and mitochondria. Starting from TGs degradation and oxidation of fatty acids, BAT produces heat via the uncoupling protein 1. Increased energy dissipation through BAT has beneficial effects on overall body metabolism. FXN is involved in maintenance of iron homeostasis and oxidative efficiency of mitochondria; however, the impact of its deficiency on BAT activity is completely unknown. FRDA patients frequently develop diabetes mellitus, and accumulation of intracellular TGs is found in many cells and tissues, thus implying defective BAT activity and utilization of lipids. Sodium butyrate is a physiologically produced short chain fatty acid functioning inhibitor of class I and II histone deacetylases. Butyrate promotes modification of chromatin structure by deacetylation of proteins, including histones and transcription factor, is induced leading to enhancement of gene transcription. Butyrate also, plays a pivotal role in cell proliferation, differentiation, energy metabolism and the maintenance of tight junctions as well as pathogenesis of diabetes mellitus, as it enhances lipolysis and thermogenic cascade in adipocytes. In this study we will use a commercially available mouse model of FRDA. After evaluation of body metabolic parameters by metabolic chambers and blood biochemical tests (e.g. glycaemia, lipid profile, OGTT), we will determine BAT morphology and activity (e.g. by assaying uncoupling respiration, thermogenic and lipolytic proteins). Adipogenesis will be also studied in mouse-derived brown adipocytes precursors. Importantly, we will test if supplementation with butyrate might restore FXN expression and BAT function ultimately halting disease progression. Hopefully, the results obtained performing this research, will recognize BAT as a target to combat metabolic disturbances observed in FRDA and suggest butyrate as a valuable and safe molecule to be employed for future clinical research.