Talk

Mitochondria and liver disease

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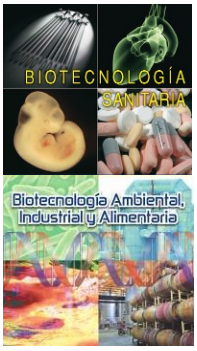

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ABSTRACT

Motivation:

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of pathologies, from simple steatosis to steatohepatitis with fibrosis and inflammation. Steatosis is characterized by a hepatic fat content. Efficient drug treatments are still lacking [1]. Hepatic lipid accumulation is associated with mitochondria dysfunction, which may favor the progression of the disease. Tricarboxylic acid cycle (TCA) and oxidative phosphorylation are key metabolic pathways of mitochondria. Succinate dehydrogenase (SDH), that consists of four subunits (A-B-C-D), is involved in the TCA cycle (oxidises succinate to fumarate) and in the electron transport chain (provides electrons to complex III and enables the reduction of ubiquinone to ubiquinol) [2]. Previous work in the laboratory showed that NAFLD is characterized by decreased levels of the subunit D of SDH (SDHD).

The aim of this Master's Thesis (TFM) is to analyse the impact of SDHD levels in the progression of NAFLD in an experimental mouse model.

Methods:

For this purpose, male C57BL/6J mice were fed a methionine-choline deficient diet (MCDD), a NASH-inducing diet [3], and control diet (CD) for 4 and 6 weeks. Two weeks after the start of the diets, adeno-associated virus (AAV) encoding SDHD (AAV-SDHD) or control (AAV-renila) were injected intravenously. Mice were sacrificed and serum, livers and pancreas were obtained. Serum alanine transaminase (ALT) and aspartate transaminase (AST) were determined. Livers and pancreas were dissected out and fixed in formalin for hematoxylin & eosin and Sirius red staining (for liver fibrosis). For cryosections, livers were frozen in OCT compound to perform Oil Red staining (for intracellular lipids) and SDH activity. Mouse livers were flash-frozen in liquid nitrogen, and homogenized in RIPA buffer for proteins and RNAzol for RNA. Western blots were achieved to analyze protein levels and mRNA was reverse transcribed into cDNA. Quantitative real-time PCR was performed using SYBR green PCR master mix. Relative RNA expression for pro-inflammatory cytokines, macrophages, fibrosis and mitochondrial genes were normalized using two different housekeeping genes (cyclophilin and Rlpo).

REFERENCES

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