CREATIS
Centre de Recherche en Acquisition et Traitement de l'Image pour la Santé

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PhD thesis

Doctoral school: ED 205 EDISS de Lyon

Title: Multiparametric MRI for the staging of hepatic steatosis and understanding of Mitochondria-Endoplasmic reticulum interaction.

Laboratory: CREATIS- Team MAGICS, Lyon

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Scientific fields: *In vivo* MRI, mice
Keywords: liver steatosis, quantitative/parametric MRI

Medical context : Obesity is a major issue in developed countries with a high incidence on life expectancy. Hepatic steatosis is a frequently associated pathology and being able to stage and understand its development can greatly help in reversing it through drugs intake and/or changes in lifestyle. Disruption of hepatic Endoplasmic Reticulum (ER)-mitochondria contact sites has been recently associated with hepatic steatosis and insulin resistance [1]. Targeting ER-mitochondria interactions, particularly though nutritional changes, could be a new approach to fight against hepatic metabolic diseases. Accessing hepatic steatosis requires liver biopsies which is an invasive procedure. An alternative strategy could be the use of magnetic resonance imaging (MRI) which is a proven non-invasive diagnostic tool for soft tissues and in particular the liver [2-5].

Aims : To apply various non-invasive parametric MRI (newly acquired 7T and 11.7T preclinical MRIs) techniques on liver, pancreas and adipose tissue, of mice undergoing controlled diets. The aims are i) to correlate the obtained MRI measures with validated histological and biological biomarkers, thus improving liver steatosis diagnosis using multiparametric MRI, and ii) to analyze changes of hepatic ER-mitochondria interactions with nutritional changes and correlate it to lipid accumulation.

Description of the project methodology:

- Development of an advanced *in vivo* MRI protocol (MR spectroscopy, MR elastography , multi gradient-echo imaging, MR spectroscopic imaging and intra-voxel incoherent motion) on mice and lasting less than two hours.
- Three groups of 12 mice will be fed for 24 weeks either with a standard diet (SD), or with a high fat high sucrose diet (HFHSD) or with an HFHSD followed by a reversal to a SD the last 8 weeks. They will undergo

monthly MRI scans yielding, multiple imaging biomarkers (fat quantification and composition, viscoelastic parameters, diffusion and perfusion parameters). At the end of the protocol, in collaboration with J.Rieusset (CarMeN laboratory, Lyon), ER-mitochondria interactions will be measured by in situ proximity ligation assay on paraffin-embedded liver.

- Statistical analysis to compare/correlate all the obtained MR biomarkers with validated histological and biological biomarkers in collaboration with Jennifer Rieusset (CarMeN laboratory, Lyon).

Expected results:

- Understanding of MRI biomarkers through their correlation with proven biological and histological biomarkers.
- Identification of pertinent MR biomarkers for the staging of development and regression of liver steatosis in mice.
- Analysis of ER-mitochondria interactions yielding improved insight in molecular pathways of liver steatosis development.

Required skilss : Physics, signal/data processing, programming

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