COLLEGE DOCTORAL BRETAGNE SCIENCES DE LA VIE ET DE LA SANTE

Year 2022-2023

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin: Région Bretagne - INSERM**
Thesis title: Role of cytochromes P450 in metabolic-associated fatty liver disease and insulin resistance		3 keywords: Insulin resistance NAFLD Cytochrome P450
Research Unit / team: INSERM U1317 NuMeCan (Nutrition, Metabolisms and Cancer), EXPRES team		
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Socio-economic and scientific context (approximately 10 lines):

The increasing prevalence of obesity favors the occurrence of type 2 diabetes (T2D) and metabolic-associated fatty liver disease also called NAFLD. This pathology is among the most frequent chronic liver disease and constitutes a major public health issue. In subjects with NAFLD or T2D, the expression and activity of several xenobiotic metabolizing enzymes (XME) such as some cytochromes P450 (CYP) are altered. Notably, CYP2E1 activity is increased in human NAFLD and experimental rodent models of diabetes and obesity, as well as other XME such as CYP3A4, CYP1A2. CYPs are responsible for the biotransformation of endogenous substrates, such as ketone bodies and fatty acids, and exogenous compounds including drugs. It should be noted that the metabolism of most of the above compounds by CYP2E1 generates toxic metabolites in both the endoplasmic reticulum and mitochondria due to its dual location within the cell. However, the precise mechanisms involved in CYP2E1 alteration and more broadly of XME are not fully characterized, nor their contributions to the development of insulin resistance and/or the progression of NAFLD.

Working hypothesis and aims (approximately 8 lines):

This project aims to explore the role of XME, including CYP2E1 in the pathophysiology of NAFLD and the development of insulin resistance. The identification of the main factors and associated pathways responsible for the alteration of XME expression and activity observed in human obesity and NAFLD is important to better understand the pathophysiological situations associated with an alteration of these enzymes. We suspect that CYP2E1 induction as well as other CYP alteration play a role in oxidative stress, NAFLD progression and the development of insulin resistance.
Ultimately, these investigations will provide a better understanding of XME role in the pathophysiology of NAFLD and this study may contribute to an improvement of the medical management of patients suffering from NAFLD by proposing specific nutritional and therapeutic recommendations that would limit the onset of metabolic syndrome and/or the aggravation of steatosis.

Main milestones of the thesis (approximately 12 lines):

This PhD project involves 4 complementary research objectives:
1/ To identify the molecular mechanisms involved in the alteration of XME in vitro, on liver cells in 2D and 3D culture. The effect of hormones and endogenous molecules (fatty acids, cytokines), whose concentrations can be disturbed during obesity and NAFLD, on the expression and activity of XME with altered profile reported in human studies (CYP2E1, CYP3A4/5, CYP1A2, UGT2B7, SULT1A) will be measured. 2/ To specifically evaluate the consequences of hepatic CYP2E1 induction on insulin sensitivity and NAFLD progression in vitro. The role of CYP2E1 induction on oxidative stress, insulin sensitivity and metabolism will be studied. 3/ To determine the subcellular localization of CYP2E1 and its effect on mitochondrial functions, oxidative stress and inflammation. Mitochondrial functions, reticulum stress as well as insulin sensitivity and NAFLD progression upon differential subcellular localization of CYP2E1 will be evaluated, in order to elucidate the specific role of CYP2E1 in these subcellular compartments. 4/ To determine in vivo in mice the effect of a diet enriched in CYP modulating fatty acids on the occurrence of NAFLD and associated metabolic alterations. Based on the results obtained in objective 1, the impact of certain fatty acids on the development of NAFLD and metabolic syndrome will be evaluated in vivo.

Scientific and technical skills required by the candidate (2 lines):

Knowledge on lipid and glucose metabolism.
Cell culture, molecular biology, microscopy

3 publications from the team related to the topic (last 5 years):

Massart, J., Begriche, K., Hartman, J. H. & Fromenty, B. Role of Mitochondrial Cytochrome P450 2E1 in Healthy and Diseased Liver. Cells 11, (2022).

Massart J, Begriche K, Corlu A, Fromenty B. Xenobiotic-Induced Aggravation of Metabolic-Associated Fatty Liver Disease. Int. J. Mol. Sci. 2022, 23(3): 1062.

Allard J, Bucher S, Massart J, Ferron PJ, Le Guillou D, Loyant R, Daniel Y, Launay Y, Buron N, Begriche K, Borgne-Sanchez A, Fromenty B. Drug-induced hepatic steatosis in absence of severe mitochondrial dysfunction in HepaRG cells: proof of multiple mechanism-based toxicity. Cell Biol. Toxicol. 2021;37:151-175.

National and international collaborations:

Dr Jessica Hartman, Medical University of South Carolina, USA