

THESIS TOPIC

Subject N° (to be completed by the ED):	FUNDING: <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Acquired	Funding origin: ARED and INSERM Grants
Thesis title: Role of fatty acids in the induction of hepatic cytochrome P450 2E1 (CYP2E1): involvement in the pathogenesis of non-alcoholic steatohepatitis (NASH) related to obesity		3 keywords: CYP2E1 / Fatty acids/ NASH
Unit/Team : UMR INSERM U1241- NuMeCan (Nutrition Métabolismes et Cancer) - Team EXPRES (Exogenous and Endogenous Stress and Pathological Responses in Hepato-gastrointestinal Diseases), Rennes		
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<u>Socio-economic and scientific context (approximately 10 lines):</u> <p>The higher incidence of metabolic liver diseases is mainly related to the increased prevalence of obesity and metabolic syndrome that promote hepatic fat accretion and occurrence of steatosis. Although simple fatty liver is a benign condition, it can evolve in the long term to nonalcoholic steatohepatitis (NASH) in 10 to 20% of patients. In some individuals, NASH can further progress to more serious liver diseases such as fibrosis, cirrhosis and hepatocellular carcinoma. These liver diseases, also called collectively nonalcoholic fatty liver diseases (NAFLD), are among the most common chronic liver diseases worldwide and constitute a major public health concern in our modern societies. This is why many studies are still underway to better understand the pathophysiology of NASH, with a particular focus on the mechanisms involved in the worsening of steatosis into steatohepatitis.</p>		
<u>Working hypothesis and aims (approximately 8 lines):</u> <p>Although the pathophysiologic mechanisms of NASH related to obesity are complex, several studies have highlighted the role of cytochrome P450 2E1 (CYP2E1). Indeed, CYP2E1 has emerged as an important actor in the progression of steatosis to NASH by promoting oxidative stress. Numerous studies reported that induction of hepatic CYP2E1 may be consequent to various factors including ketones bodies, insulin resistance and fatty acids (FAs). Regarding these latter molecules, our recent <i>in vitro</i> investigations have shown that CYP2E1 induction in response to a FA treatment is complex and is not specific to the steatosis context but rather linked to the action of some specific FAs. This thesis project aims to understand the involvement of CYP2E1 in the pathophysiology of NASH by seeking in particular the mechanisms of induction of this cytochrome by some FAs and the deleterious consequences of such induction at the hepatocyte level.</p>		
<u>Main milestones of the thesis (approximately 12 lines):</u> <p>Since induction of hepatic CYP2E1 could contribute to the worsening of steatosis into NASH, we recently performed <i>in vitro</i> investigations on a human hepatoma cell line (HepaRG cells) to evaluate the impact of different classes of FAs (saturated, monounsaturated and polyunsaturated FAs) on the induction of CYP2E1 and on hepatic steatosis. This work allowed us to identify three FAs promoting the induction of hepatic CYP2E1. Furthermore, we noticed that increased expression and activity of hepatic CYP2E1 with these specific FAs is not systematically correlated to the degree of steatosis. Considering these results, the thesis project will aim to continue and deepen these investigations to better understand the causes and consequences of the induction of hepatic CYP2E1 in the aggravation of steatosis into NASH. To this end, the thesis will be organized around four major axes including <i>in vitro</i> and <i>in vivo</i> investigations. [1] Identification in HepaRG cells of the molecular mechanisms involved in the induction of CYP2E1 after one week of treatment with AGs. [2] Evaluation of the consequences of CYP2E1 induction on mitochondrial function, oxidative stress and inflammation. [3] Biochemical characterization of the different lipid species, and in particular those that can play a deleterious role in the hepatocyte at the mitochondrial level. [4] Determination in mice of the effects of a hyperlipidic diet enriched</p>		

with a FA inducing CYP2E1, in particular regarding the occurrence of steatohepatitis and further characterization of the associated metabolic alterations.

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

Master 2 with background in biology, physiopathology, nutrition and strong skills in molecular and cell biology. Skills in mouse experimentation will also be appreciated.

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

- Bucher S, Le Guillou D, Allard J, Pinon G, Begriche K, Tête A, Sergent O, Lagadic-Gossmann D, Fromenty B. Possible involvement of mitochondrial dysfunction and oxidative stress in a cellular model of NAFLD progression induced by benzo[a]pyrene/ethanol co-exposure. **Oxid. Med. Cell. Longev.** **2018**; 2018: 4396403.
- Bucher S, Jalili P, Le Guillou D, Begriche K, Rondel K, Martinais S, Zalko D, Corlu A, Robin MA, Fromenty B. Bisphenol A induces steatosis in HepaRG cells using a model of perinatal exposure. **Environ. Toxicol.** **2017**, 32: 1024-1036.
- Michaut A, Le Guillou D, Moreau C, Bucher S, McGill MR, Martinais S, Gicquel T, Robin MA, Jaeschke H, Fromenty B. A cellular model to study drug-induced liver injury in nonalcoholic fatty liver disease: application to acetaminophen. **Toxicol. Appl. Pharmacol.** **2016**, 292: 40-55.

National and international collaborations:

National collaborations (main)

- Pr Valérie Paradis, Département de Pathologie, Hôpital Beaujon, Clichy, France (since 2005 - 3 articles).
- Dr Gilles Labbe, Sanofi, Investigative Toxicology, Alfortville (since 2008 - 3 articles).
- Dr Annie Borgne-Sanchez, MITOLOGICS, Hôpital Robert Debré, 48 Bd Sérurier, Paris (since 2011 - 3 articles).
- Dr Daniel Zalko, UMR1331 Toxalim (Research Centre in Food Toxicology), Université de Toulouse, INRA, Toulouse (since 2017 - 2 articles).
- Dr Dominique Lagadic-Gossmann, UMR_S 1085, Inserm, EHESP, IRSET (Institut de recherche en santé, environnement et travail) Université de Rennes, Rennes (since 2018 - 3 articles).

International collaborations

- Dr Viviane Trak-Smayra, Pathology Department, Saint-Joseph University, Beirut, Lebanon (since 2011 - 3 articles).
- Pr Hartmut Jaeschke, Department of Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, Kansas City, KS, USA (since 2012 - 2 articles).
- Dr Juliette Legler, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands (since January 2019, in the frame of the European project GOLIATH).
- Dr Angel Nadal, CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM) and Institute of Bioengineering, Miguel Hernández University of Elche, Elche, Alicante, Spain (since January 2019, in the frame of the European project GOLIATH).