RESEARCH SUBJECTS OF MASTER 2 BIOLOGY-HEALTH COURSE PRECISION HEALTH EGID LABORATORIES – 2021-2022

UMR 1011

TEAM 1

Role of intestinal epithelial nuclear receptor FXR in the Non Alcoholic Fatty Liver Disease complication of Type 2 Diabetes

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The importance of the intestine and its crosstalk with the liver in the development of Type 2 diabetes (**T2D**) and Non-Alcoholic Fatty Liver Diseases (**NAFLD**) has received increasing attention. Notably, the **dysregulation of intestinal endocrine and immune functions** play a central role in metabolic diseases and **disruption of intestinal permeability** worsens T2D and NAFLD. **FXR** is a nuclear receptor expressed in metabolic tissues such as intestine, liver, adipose tissue and pancreas. FXR regulates energy metabolism *via* the modulation of bile acid synthesis, and lipid and glucose metabolism. Our preliminary results show that FXR deficiency restricted to intestinal epithelial cells impacts on gut immune system, even if mice are submitted to a normal chow diet.

We have submitted, for 24 weeks, C57Bl/6 mice deficient for FXR only in the epithelial cells of their intestine (**intFXR KO mice**) and their control littermates to a control or a **NAFLD-inducing diet**.
The M2 internship period will be devoted to the **processing of the samples we collected during the diet and at sacrifice**. intFXR KO mice and their control littermates will be characterized on chow and NAFLD-inducing diet regarding progression of the hepatic pathology (body weight monitoring, plasma ASAT/ALAT by ELISA, qPCR and histology of the liver) in relation to intestinal health (gut histology and immunofluorescence) and gut permeability (serum IgA by ELISA). The study of the intestinal immune system and the immune cell recruitment will be performed in small intestine and colon (biocomputing and statistical analysis of immunophenotyping data generated at the sacrifice, qPCR, and immunofluorescence).

This program should strengthen the preclinical proof-of-concept of FXR as a potential pharmacological target for the treatment of diabetes and its NAFLD complication.

The nuclear receptor Rev-Erbα: a new player in intestinal dietary lipid metabolism?

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Obesity and diabetes are multifactorial chronic diseases whose etiology is an imbalance between energy intake and expenditure. Significant abnormalities of intestinal functions, including overproduction of triglyceride-rich lipoproteins, accompany these metabolic disorders and contribute to the development of atherosclerosis and fatty liver disease (NAFLD). The nuclear receptor Rev-Erbα integrates the biological clock with metabolism in major organs. Based on our current work, we hypothesize that Rev-Erbα in the gut is a key molecular player in the orchestration of dietary lipid metabolism, as well as in the control of lipoprotein production.

This M2 project is focused on studying, in *ex vivo* organoid (or mini-gut) models from human and murine origin, the mechanisms involved in the control by Rev-Erbα of the intestinal postprandial lipidemic response. The inhibition in enteroids of the expression of candidate target genes, coupled with the use of inhibitors of biological processes (lipophagy, vesicular trafficking…) will allow to elucidate the molecular mechanisms. The link with the clinic will be achieved by using pharmacological modulators of Rev-Erbα.

The approaches used are based on cell and molecular biology techniques (gene and protein expression analysis, indirect immunofluorescence, gene invalidation and overexpression…). This project is based on an important work of cell culture and image analysis.

Caracterisation of the metabolic effects of TGR5 activation in the gut: study in a murin model using a pharmacological tool

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Background - The intestine is an organ contributing to metabolic and inflammatory homeostasis via 1/ its nutrient absorption function, 2/ its metabolically active commensal flora, 3/ its barrier function, by controlling permeability, 4/ its enteroendocrine function, by synthesising and secreting signalling molecules, and 5/ its homeostatic function, through the immune cells it contains. TGR5 is a G protein-coupled membrane bile acid receptor expressed by different cell types involved in the regulation of metabolic homeostasis, in particular the incretin glucagon-like-peptide-1 (GLP-1)-producing enteroendocrine cells, known for its beneficial effects on metabolic homeostasis.A pharmacological tool was developed, consisting of a pharmacophore conferring agonist activity on the murine TGR5 receptor and a kinetophore that reduces its intestinal absorption and targets the actions of the molecule in the distal part of the intestine when administered orally.

Hypothesis - Activation of TGR5 in the gut could lead to improved metabolic homeostasis, reduced food intake and improved glucose tolerance.

Objective - In M2, our objective will be to analyse the metabolic effects and their molecular mechanisms of selective activation of the TGR5 receptor in the gut by a selective agonist, BDM72881.

Methods - In male C57BL6 mice, the effects of acute administration of the compound BDM72881 will be evaluated by measuring food intake and energy expenditure (metabolic cages), neuronal activation (immunohistochemistry), functional test to assess metabolic homeostasis (OGTT), as well as the determination of peptides co-secreted with GLP-1 (ELISA multiplex).
This master 2 project could lead to a thesis project which will evaluate more globally the role of TGR5 in the intestine on endocrine function.

Key words - TGR5 receptor, enteroendocrine function, incretins, gastrointestinal peptides, metabolic homeostasis, pharmacological approach, biochemical analyses, histological analyses, gene expression measurement.

Pathophysiological role of amino acids involved in the one carbon metabolism in NAFLD: analysis of the molecular mechanisms of the variations observed in a cohort of patients.

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Context: NAFLD (Non Alcoholic Fatty Liver Disease), a major public health issue, is the hepatic complication of the metabolic syndrome and is highly associated with diabetes and obesity. NAFLD is a progressive pathology characterized by liver damage due to an accumulation of triglycerides in the liver or isolated steatosis (NAFL Non-Alcoholic Fatty Liver). In case of associated inflammation, NAFL evolves into steatohepatitis (NASH Non-Alcoholic Steato Hepatitis). Possible complications of NAFLD are fibrosis, cirrhosis and hepatocellular carcinoma. The mechanisms inducing NASH from NAFL are still poorly understood. Through a cohort study, we have demonstrated in NASH patients a specific metabolic plasma profile involving changes in the amino acids involved in one carbon metabolism (1C metabolism). This metabolism regulates methylation, which can lead to epigenetic changes. In order to understand the molecular mechanisms underlying the plasma variations observed in NASH patients, we wish to study these modulations in a mouse model in which NASH is induced by a specific diet. The literature reports that activation of the nuclear receptor PPARα by fenofibrate in a mouse model and in humans leads to a increase of one intermediates metabolite of one carbon metabolism, homocysteine (Luc et al., 2004). Since the expression of PPARα is itself decreased in NASH (Francque et al., 2015), we hypothesize that PPARα may be one of the regulators of one carbon metabolism in NASH.

Objective: The project aims to analyze plasma and hepatic amino acid variations as well as gene expression variations in a diet-induced mouse model of NASH with control of the expression and/or activity of PPARα.

Methods: The mouse models used will show diet-induced NASH with either genetic inactivation of PPARα (total Ko or specific Ko in hepatocytes) or pharmacological activation of PPARα (by fibrates). Targeted metabolomics analyses by mass spectrometry will be performed on plasma and liver samples from these models. Depending on the metabolome results, gene expression analyses in the

liver by Q-PCR or transcriptomic analysis will identify the genes responsible for the metabolic variations observed.

Collaborations: This work will be carried out in collaboration with Dr Joël Haas and Pr Anne Tailleux (UMR1011 team 1).

Keywords: NAFLD, mouse model, PPARα, amino acids, metabolism, metabolomics.

FASTRIP- Targeting strategy for the inhibition of FAT10/PPAR interaction to treat NASH

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Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming the most common liver disease affecting 80% of the obese population. NAFLD is initiated by the accumulation of fat in the liver (steatosis) which evolves to non-alcoholic steato-hepatitis (NASH). NASH is a risk factor for disabling and deadly liver diseases, such as cirrhosis and hepatocellular carcinoma (HCC), as well as cardiovascular disease. Currently, there is no drug treatment to limit the severity of NASH. In this context, it is important to well characterize the molecular mechanisms responsible for the development and progression of this pathology in order to provide preventive and/or therapeutic solutions.

The results of the UMR1011 laboratory revealed an involvement of FAT10/UBD, in NASH progression. FAT10 is a member of the eukaryotic ubiquitin-like protein family not or poorly expressed in normal tissues, which expression is increased in inflammatory context. FAT10 contains two UBL domains allowing covalent interaction (FATylation) through ligases (USE1 and UBA6), or non-covalent interaction, leading its substrates to proteasomal or lysosomal degradation. Transcriptomic analysis showed a high increase of FAT10 expression in the liver of NASH patients, which correlated positively with steatosis, fibrosis, ballooning scores, and also NASH severity. Interestingly, FAT10 overexpression was associated with a decrease in the expression of the peroxisome proliferator activated receptor-α (PPARα), a nuclear receptor controlling lipid metabolism and inflammation, as well as a down-regulation of the PPARα-signaling pathway. Our results suggest that FAT10 may modulate NASH progression by interacting with PPARα and promoting its deactivation highlighting FAT10/ PPARα interaction as a new potential target to treat NASH.

In this context, the objective of this project is:
(1) **to well characterize the type of physical interaction between FAT10 and PPARα**
(2) **to develop a cellular assay for analyzing the impact of FAT10/ PPARα interaction on PPARα activity**
(3) **to transfer the assay on the U1177 screening platform** for miniaturization and automation to increase the throughput.
(4) **to perform the screening of 30 000 compounds of the U1177 library** to identify molecules inhibiting FAT10/PPARα interaction.
The Master 2 project will be involved in the part 1) and 2) of this project. We expect to identify new molecules disrupting FAT10/PPARα interaction that could enter a drug discovery program to ultimately lead to an optimized candidate for a proof of concept in murine model of

NASH developed in the UMR1011 laboratory. The results should highlight additional mechanisms of the NASH development and lead to the identification of new therapeutic tools for this disease.

Characterization of cardiac remodeling during the development of NAFLD (Non Alcoholic Fatty Liver Disease) : focus on the role of myocardial immune cells.

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NAFLD (*Non Alcoholic Fatty Liver Diseases*) are hepatic manifestations of the metabolic syndrome associated with obesity and type 2 diabetes. The term NAFLD refers to the progressive succession of the NAFL (*Non Alcoholic Fatty Liver*) stage characterized by the presence of hepatic steatosis, followed by the NASH (*Non Alcoholic Steato-Hepatitis*) stage characterized by the presence of **hepatic steatosis and inflammation**. In the long term, NASH can lead to **hepatic fibrosis**, ultimately leading to cirrhosis or cancer. These chronic hepatic pathologies have no treatment to date, and **numerous epidemiological studies report an increased risk of developing cardiovascular pathologies such as atherosclerosis, heart failure or arrhythmia** in these patients. However, **the mechanisms linking NAFLD to cardiac pathologies are imperfectly understood**.

Our initial results suggest a **deregulation of the innate immunity** induced by NAFLDs, favoring the development of intracardiac inflammatory foci and fibrosis in the atria and ventricles. The project consists in characterizing these mechanisms in a **mouse pre-clinical model**. The description of **hepatic and cardiac phenotypes** will be based on macroscopic observations, functional cardiac stimulation tests, histological analyses, gene and protein expression analyses and complete immunophenotyping. These data will reinforce the clinical studies carried out on myocardial biopsies obtained during cardiac surgery and the post-operative follow-up of patients from a Lille cohort generated at the Heart-Lung Institute (POMI-AF: NCT03376165).

Impact of time of day on perioperative immuno-inflammatory response and myocardial remodeling after cardiac surgery

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Aortic valve stenosis is the most common cardiac valvular pathology. This valvulopathy is responsible for a chronic obstacle to the ejection of the left ventricle (LV). Faced with this high afterload, the LV adapts by increasing its muscle mass. This initially adaptive remodeling contributes to the development of intra-myocardial fibrosis and an alteration in the relaxation and compliance of the

LV. **Myocardial remodeling thus becomes maladaptive** and leads to **heart failure**. Aortic valve replacement (AVR) is the only therapeutic option.

Pre-clinical studies establish a link between circadian rhythm, inflammation and cardiac remodeling. We have recently demonstrated that aortic valve replacement (AVR) is associated with **fewer complications when performed in the afternoon vs. morning**. We hypothesize that the **biological clock modulates intraoperative immune cell recruitment** and thus the healing process and myocardial reverse remodeling after AVR. We wish to complement our clinical observations with a **pre-clinical study in a mouse model**.

We will perform a **transcriptome and epigenome on circulating leukocytes after surgery** in the morning vs. afternoon to determine the **impact of circadian rhythm on the systemic inflammatory response**. We will analyze **intra-myocardial inflammatory cell populations** using a complete immunophenotyping. Finally, we will define the impact of REV-ERBα nuclear receptor and clock gene signaling on leukocyte epigenetic signatures and cardiac remodeling in this animal model.

TEAM 3

Characterization of dendritic cell (DC) and T cell (T) interactions in non-alcoholic steatohepatitis (NASH)

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Background. NASH or "fatty liver disease" is a pathology whose incidence has increased dramatically worldwide and for which there is currently no pharmacological treatment. We have shown (Haas et al. Nat. Metab. 2019), in humans and in an animal model, that this metabolic pathology is associated with profound changes in the immune system affecting in particular subpopulations of DCs (cDC1 and cDC2) and cytotoxic CD8 LTs. These alterations are potentially causal in the pathology but the functional mechanisms involved, including interactions between DC and LT, remain unknown and these populations have not been precisely characterized.

Aim. The aim of the Master 2 is to analyze the phenotypic and functional characterization of CD8 (and CD4) T cells populations.

Methods. In a mouse model of NASH induced by diet, the hepatic CD8 and CD4 T lymphocyte populations will be characterized by various techniques: flow cytometry, RNA-seq on single cells (with a particular analysis of the metabolic pathways and of the antigenic receptor of the T lymphocytes - TCR-), measurements of intracellular metabolism (Seahorse). Depending on the results obtained, interactions with DCs could be evaluated in functional assays.

Collaboration. This work will be performed in collaboration with Dr Joël Haas (UMR1011 Team 1).

Keywords. NASH, T lymphocytes, DC, metabolism, scRNA-seq, bioinformatics, functional test

TEAM 4

Transcriptional control of hepatic cell phenotypic plasticity

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The liver exerts instrumental metabolic functions which need to be constantly adjusted to the nutritional and energy status of the body. We have recently identified that the hepatic transcriptome is controlled by a functional interplay between the chromatin structure, the epigenome and several transcriptional regulatory complexes. In this context, we are seeking to identify how transcriptional regulators interact with the chromatin to ensure specificity and appropriate levels of liver gene expression. We are also interested in the perturbation of these mechanisms in the context of liver dysfunction. We propose a Master 2 internship on this topic for a student interested in the elucidation of the molecular mechanisms of transcriptional regulation.

TEAM 5

Brown adipose tissue from embryo to adult: implications in metabolic diseases

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Brown adipose tissue represents a new therapeutic target for the treatment of metabolic diseases. When activated by different stimuli such as exposure to cold, brown adipose tissue metabolizes about 20% of the daily energy intake. Some of the glucose taken up by brown adipocytes is stored as glycogen. However, little is known about the role of glycogen and its fate in brown adipocytes. We recently published a paper showing that glycogen dynamics (formation and degradation) is essential for the formation of lipid droplets during brown adipocytes differentiation.

The objective of this project is to study glycogen metabolism in brown and beige adipocytes, in order to determine whether its metabolism may represent a potential target for improving brown adipose tissue activity in the context of metabolic diseases.

This study will be based on experiments in the mouse model, during development and in adults under different pathophysiological conditions. During the M2R, the student will carry out experiments in histology (tissue sections, staining, immunoshistochemistry, microscopy), cell biology (cell culture, immunohistofluorescence, confocal microscopy), molecular biology (RNA

extraction, RTqPCR) and metabolism (biochemical assays). This project aims to initiate a thesis project.

UMR 1283

Role of cell cycle and inflammation regulators in the dedifferentiation of pancreatic β cells during type 2 diabetes and aging.

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Type 2 diabetes is characterized by high blood sugar and develops due to insufficient ability of pancreatic beta cells to produce insulin. The incidence and susceptibility to type 2 diabetes increases with age, but the underlying mechanism(s) in beta cells that contribute to this increased susceptibility have not been fully understood. In this project, we propose to study the role of inflammation in the loss of function of pancreatic beta cells during aging and/or diabetes. The goal of this research project will be to assess the relationship between inflammation, differentiation and plasticity of pancreatic β cells using in vitro strategies, but also mouse models genetically modified specifically in certain tissues and allowing lineage tracing. We thus hope, through this project, to identify new targets responsible for the premature aging of insulin-producing cells in order to develop original therapeutic strategies that will constitute the future treatments.

Epigenomic reprogramming of pancreatic β cells during type 2 diabetes.

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Pancreatic β cells, the sensor of circulating glucose levels, control insulin secretion through a finely regulated process. Dysfunctions of this cell type, associated with a decrease in the number of ß cells are at the origin of metabolic pathologies such as type 2 diabetes. Recent studies have shown a plasticity of these cells leading to a loss of their function associated with the development of type 2 diabetes. Our preliminary results show that the epigenome plays a key role in this cellular reprogramming. The aim of this master's 2 research project will be to study the epigenomic mechanisms involved in the plasticity of pancreatic β cells using in vitro and ex vivo strategies. These data will provide a better understanding of the mechanisms of ß cell dysfunction during the development of diabetes.

Role of the purinergic pathway in metabolic homeostasis and the development of type 2 diabetes.

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Type 2 diabetes (T2D) is characterized by high levels of blood glucose. Pancreatic β-cell dysfunction plays a major role in the pathogenesis of T2D. Restoration of β cell mass and function has therefore become an area of intensive research necessary for the generation of novel anti-diabetic drugs. Our research program aims to decode the specific role of the purinergic pathway within β cells under physiological and pathophysiological conditions. By combining Pamgene technology, high throughput sequencing, mouse models, Cripsr/Cas9 and studies on mouse and human islets, this project will aim to dissect the processes regulated by the P2Y pathway and its pharmacological modulation in the control of metabolic homeostasis and will allow us to identify new pharmacological targets for the treatment of metabolic diseases.

UMR 1190

The Role of Pancreatic Stone Protein / Regenerating Protein (PSP/reg) in islet cell regeneration and diabetogenesis (M2 Precision Health).

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Scientific background: Pancreatic islet dysfunction and demise, are key characteristics of type 1 diabetes (T1D), type 2 diabetes (T2D), and HNF1A-MODY, respectively. Pancreatic Stone Protein / Regenerating Protein (PSP/reg) is regulated at the transcription level by HNF1A and physiologically secreted from rat pancreatic acinar cells. Upon focal or systemic extra-pancreatic inflammation, such as sepsis, PSP/Reg is strongly increased, but also highly elevated in the serum of T1D, TD2, and HNF1A-MODY patients. Although, PSP/reg is regulated by HNF1A and is induced in islets and the liver in diabetic mice, the mechanisms involved remain largely unknown. Moreover, after decades of research, whether PSP/reg protein expression in alpha, beta or delta cells under hyperglycaemic conditions, remains an enigma.

Hypothesis and aims: Since the *PSP/reg* gene is inducible by hyperglycaemia and secreted, we hypothesize that its gene product may function as a mitogenic, trophic, and/or an antiapoptotic factor in the endocrine pancreas. The aims of this study are **1)** to determine PSP/reg protein expression in liver and islet tissues extracted from normoglycemic vs. hyperglycaemic subjects, **2)** to measure PSP/reg and pancreatic hormone secretion from isolated islets from diabetic mouse models and human islets treated with a proinflammatory cocktail of cytokines (known to alter glucose-stimulated hormone secretion) in the presence or absence of recombinant PSP/reg.

Materials & Methods: Dual immunofluorescent techniques will be utilized to assess PSP/reg specific expression in the liver and pancreas using unique liver tissue sections encompassing grafted donor islets from a T1D patient, who underwent surgery for a non-malignant disease, and pancreatic and

liver and pancreatic sections from T2D patients and mouse models of T1D, T2D and HNF1A-MODY, which are already existing in our laboratory. PSP/reg and pancreatic hormone secretion from normoglycemic vs. hyperglycaemic mouse and human islets treated with or without recombinant PSP/reg will be assessed by islet perifusion and ELISA techniques.

Expected Results: We anticipate (**1**) to observe PSP/reg protein expression in the liver and precise its localization in pancreatic islet of mouse and human diabetic subjects; (**2**) to report whether recombinant PSP/reg protein can improve alterations in glucose-stimulated hormone secretion.

The student will be trained and supervised in advanced cell and molecular biology techniques by expert technical staff in our laboratory and will work closely with an international team of post-docs, and Ph.D. students, and the PI daily.

Articles related to the topic : Bonner et al, Diabetes, 2010 ; Bacon et al., BMC Endocrine Disorders, 2012 ; Kyithar & Bonner, Journal of Translational Medicine, 2013; Bonner, C. Endocrine, 2015.