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Institut Pasteur de Lille

[Graduate School “Biologie-Santé” de Lille]

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FUNCTIONAL ANALYSIS OF REGULATORY T CELL HETEROGENEITY IN METABOLIC LIVER DISEASE USING SINGLE-CELL ASSAYS

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Summary of thesis project
Metabolic dysfunction-associated steatotic liver disease (MASLD) is a highly prevalent chronic liver disease with marked interindividual variability in disease severity and progression. While metabolic factors such as overnutrition are central drivers of disease development, immune mechanisms are increasingly recognised as key contributors to liver inflammation and fibrosis. However, it remains unclear why immune responses differ so strongly between individuals and how this variability contributes to disease outcome.

Regulatory T cells (Tregs) play a central role in controlling immune activation and inflammation, yet their functional role in MASLD is still poorly defined in humans. In particular, whether Treg suppressive capacity differs between individuals with MASLD and healthy donors, and how this variability relates to disease severity, remains largely unexplored.

The aim of this Ph.D. project is to investigate interindividual heterogeneity in human Treg function in MASLD using a targeted single-cell functional approach. The project will focus on assessing the suppressive capacity and phenotypic properties of Tregs from peripheral blood samples of MASLD patients and healthy donors.

First, the Ph.D. student will establish and apply a single-cell Treg suppression assay based on autologous PBMC co-cultures. Tregs will be isolated by flow cytometry, reintroduced into PBMCs at defined ratios, and immune responses will be assessed after stimulation. Functional readouts will include proliferation and activation of multiple immune cell populations measured at single-cell resolution using spectral flow cytometry. This approach allows the functional impact of Tregs to be quantified in a physiologically relevant immune context.

Second, the student will analyse the resulting high-dimensional cytometry data to quantify Treg suppressive activity across donors and conditions. Data analysis will be performed using established R-based workflows to identify differences in immune responses between MASLD patients and healthy controls. The emphasis will be on data quality control, visualisation, and biologically guided comparisons rather than on the development of new computational methods.

Overall, this project is designed as a focused and feasible three-year Ph.D. project combining experimental human immunology with targeted single-cell data analysis. It will provide the student with solid training in functional immune assays, spectral flow cytometry, and practical data analysis, while addressing an important and clearly defined question in human metabolic liver disease.

Keywords
Regulatory T cells**,** Immune heterogeneity**,** Metabolic liver disease (MASLD)**,** Functional immune assays**,** Spectral flow cytometry**,** Single-cell data analysis, Immune regulation,

VASCULAR INTEGRITY THROUGH MITOCHONDRIAL IMPORT OF PROTEINS MEDIATED BY CHCHD4

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Summary of thesis project

The CHCHD4 mitochondrial import pathway is responsible for the import of proteins containing cysteine motifs, thereby linking signaling encoded by the nuclear genome to mitochondrial function. It plays a crucial role in cellular processes such as mitochondrial respiration, redox signaling, and stress response. Consequently, its dysregulation has been associated with various pathologies. However, the role of this pathway in angiogenesis remains unexplored, representing a major gap in our understanding of vascular regulation and tissue homeostasis, particularly in organs where vascular growth determines oxygen supply and metabolic flexibility.

This project aims to elucidate how CHCHD4 couples mitochondrial regulation to the metabolic fate of endothelial cells (ECs) and thereby influences tissue homeostasis through the regulation of vascularization. Through metabolic studies and spatial transcriptomic analyses, applied to in vitro and in vivo models of CHCHD4 deficiency in ECs, we will define the metabolic and molecular networks linking the CHCHD4 import pathway to endothelial function and the control of angiogenesis.

Our results will provide insight into how the endothelial CHCHD4 mitochondrial import pathway coordinates angiogenesis and the interaction between ECs and the surrounding tissue during physiological adaptation as well as under pathological conditions. They will also provide a foundation for identifying CHCHD4 and its substrates as potential therapeutic targets in diseases characterized by impaired vascularization and mitochondrial dysfunction.

Keywords

Mitochondrial homeostasis, Metabolic flexibility, Endothelial metabolism, Vascular remodelling

REMODELLING OF ADIPOSE TISSUE FOLLOWING WEIGHT LOSS: A STUDY OF THE CELLULAR MEMORY OF OBESITY

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Summary of thesis project

Adipose tissue (AT) is a key organ in energy and metabolic homeostasis. In situations of chronic calorie excess, such as in obesity, it undergoes pathological remodelling characterised by adipocyte hypertrophy, insulin resistance and low-grade inflammation. These alterations contribute to major complications such as metabolic dysfunction-associated steatohepatitis (MASLD). Weight loss (WL) improves these parameters, but is frequently followed by weight regain and metabolic relapse, suggesting the existence of a 'cellular memory of obesity'. The mechanisms involved remain poorly understood. This project aims to identify the cellular and molecular alterations in AT that persist after WP and to assess their impact during weight regain.

Using a mouse model of obesity and MASLD, we will analyse systemic metabolic adaptations as well as those of AT and the liver at the single-cell level. These data will enable us to construct a cellular atlas of AT and the liver, and to identify persistent cellular states and pathological mediators. The identified mechanisms will then be validated in vitro in cellular models (adipocytes, macrophages) for targeted functional analysis. The objective is to identify new therapeutic targets that sustainably enhance the metabolic benefits of weight loss.

Keywords
Obesity, Adipose tissue, Weight loss

IMPACT OF LIVER FIBROSIS ON THE DEVELOPMENT OF ATHEROSCLEROSIS: PATHOPHYSIOLOGICAL MECHANISMS AND THERAPEUTIC TARGETS

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Summary of thesis project

Liver fibrosis is a major complication of MASLD (Metabolic dysfunction–Associated Steatotic Liver Disease), the leading cause of chronic liver disease, affecting nearly 30% of the global population. Characterised by excessive accumulation of lipids in the liver, often associated with obesity, type 2 diabetes, dyslipidaemia and hypertension, MASLD encompasses a spectrum ranging from simple steatosis to metabolic steatohepatitis (MASH), which can progress to fibrosis, cirrhosis and hepatocellular carcinoma. Cardiovascular disease is the leading cause of death in MASLD patients, and the risk increases with the severity of liver fibrosis. Clinical studies show that a high liver fibrosis score (FIB-4 or NAFLD fibrosis score) is associated with the occurrence of cardiovascular events, independently of metabolic syndrome. However, the mechanisms linking liver fibrosis to atherosclerosis remain unknown, and no specific marker can explain this link.

The aim of this PhD project is to investigate, for the first time, the causal role of liver fibrosis in cardiovascular complications associated with NASH, particularly in the development of atherosclerosis. To this end, the project will utilize a new mouse model developed in the laboratory that combines liver fibrosis and atherosclerosis, enabling a direct assessment of the impact of liver fibrosis on the development of atherosclerosis. Targeted hepatic gene therapy strategies using AAV vectors will enable the selective modulation of fibrosis in the liver and the analysis of its remote effects on the heart. Metabolomic analyses of plasma will identify systemic variations in mediators of liver–heart communication, which will then be validated in humans.

This novel inter-organ approach aims to develop new diagnostic and therapeutic avenues to prevent or reduce cardiovascular risk in patients with NASH.

Keywords
Fibrosis, Atherosclerosis, Mice model, AAV

DOES THE NUCLEAR RECEPTOR FXR IN THE INTESTINE PLAY A ROLE IN THE PATHOPHYSIOLOGY OF ACUTE-ON CHRONIC LIVER DISEASE (ACLF)?

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Summary of thesis project

BACKGROUND: Acute-on-Chronic Liver Failure (ACLF) occurs in patients with pre-existing chronic liver disease, where the decompensation of cirrhosis, following an acute trigger resulting in liver neutrophil recruitment, leads to major hepatic and extra-hepatic complications (encephalopathy, kidney failure and cardiovascular events). Overall, ACLF is associated with systemic inflammation, multi-organ failure and a high short-term mortality rate which arises from the portal hypertension aggravation. We have already shown that mice deficient for the nuclear receptor FXR in their intestine (^{int}FXR KO mice) fed for 24 weeks with a Metabolic-Associated SteatoHepatitis (MASH)-inducing diet developed some common characteristics to ACLF patients: altered intestinal barrier, gut dysbiosis, bile acid pool changes and hepatic neutrophil recruitment (article under review).

PROBLEMATIC: The lack of treatment and of satisfying preclinical models hinders the care of ACLF patients. In this thesis project, we will study whether there is a role of FXR in the intestine for the development of ACLF and its multi-organ complications.

METHODOLOGIES: To achieve our goal, ^{int}FXR KO and control FXR floxed mice will be submitted to a chronic treatment of thioacetamide (inducer of chronic liver disease) for 12 weeks and then to a high fat, sucrose, cholesterol diet as acute trigger. *In vivo* functional tests and chemical assays will be performed to compare the ACLF development and the multi-organ failure in the 2 genotypes. Integrative omics will be conducted to elucidate the underlying mechanisms potentially governed by the intestinal FXR deficiency. Gender effect and the human relevance will be explored, and potential new drugs will be tested to validate their efficacity.

EXPECTED RESULTS: By using the ^{int}FXR KO mouse model, we expect to identify and validate new pathophysiological pathways of ACLF and its multi-organ complications, and to participate in the discovery of potential new pharmaceutical targets and new drugs.

Keywords

Nuclear receptor FXR, Liver chronic disease, ACLF, Intestine-liver axis, Multi-organ failure, Cardio-metabolic diseases

ECM-DRIVEN NUCLEAR MECHANISMS GOVERNING EPITHELIAL FATE IN LIVER DISORDER

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Summary of thesis project

Biliary diseases such as Primary Sclerosing Cholangitis and Alagille syndrome are characterized by progressive bile duct injury, fibrosis, and ultimately liver failure. These disorders primarily affect cholangiocytes, the epithelial cells lining the bile ducts, which can display remarkable plasticity during chronic liver damage. However, the mechanisms controlling cholangiocyte fate decisions and their transition toward regenerative or pathological states remain poorly understood.
Emerging evidence suggests that the extracellular matrix (ECM) plays a central role in regulating epithelial identity. Laminin-rich environments maintain biliary differentiation, whereas loss of laminin contact promotes cholangiocyte migration and acquisition of hepatocyte-like features. **This project aims to determine how ECM-dependent mechanical cues regulate cholangiocyte fate through nuclear mechanotransduction**.

We hypothesize that ECM composition governs cholangiocyte identity by mechanically constraining nuclear architecture and chromatin organization, thereby regulating transcriptional accessibility and enabling or restricting epithelial fate transitions. To test this hypothesis, we will first define how ECM-dependent nuclear mechanotransduction reshapes chromatin organization to control cholangiocyte fate. We will then determine how ECM-driven nuclear mechanics regulate nucleocytoplasmic transport and gate transcriptional programs. Finally, we will focus on establishing whether ECM-induced nuclear remodeling enables mutation-associated transcriptional programs and induces mechanical memory. Altogether, we hope to decipher how ECM-dependent nuclear mechanotransduction controls epithelial identity, providing a unifying framework to understand cholangiocyte plasticity in regeneration and disease that may uncover new strategies to modulate epithelial fate through microenvironmental targeting rather than genetic intervention.

Keywords

Extracellular matrix (ECM), Nuclear mechanotransduction, Cholangiocyte plasticity, Chromatin organization, Liver regeneration

ROLE OF FAT10 IN THE MECHANISM OF RESISTANCE TO PPAR-ALPHA AGONISTS IN THE TREATMENT OF MASH

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Summary of thesis project

Metabolic and fatty liver disease (MASLD), formerly known as NAFLD, is the leading cause of chronic liver disease in Western countries. It encompasses a continuum ranging from simple steatosis (MASL) to steatohepatitis (MASH), which can progress to serious complications such as cirrhosis or hepatocellular carcinoma. MASH is closely linked to metabolic syndrome, particularly obesity and type 2 diabetes, which are two major risk factors with a high prevalence among these patients. Management relies primarily on weight loss through lifestyle and dietary measures or bariatric surgery, a highly invasive technique limited to certain patients, which justifies the search for new therapeutic options. In this context, certain molecules already used to treat diabetes, dyslipidaemia or hypertension are currently being evaluated. Among these, PPARα agonists are of particular interest due to their role in improving lipid metabolism, inflammation and fibrosis. Nevertheless, their effects remain variable, suggesting the existence of resistance mechanisms that limit their efficacy.

An emerging player in this regulatory process is FAT10/UBD, a protein related to ubiquitin that is involved in protein degradation and stabilization is up-regulated in chronic inflammatory conditions. Our recent work shows that FAT10 is overexpressed in NASH and that it interferes with PPARα activity in the liver, reducing its ability to regulate lipid metabolism. This interaction could explain resistance to PPARα agonists in the treatment of NASH. The PhD project aims to demonstrate whether modulating FAT10 expression via a genetic or pharmacological approach in hepatocytes can restore the efficacy of therapies targeting PPARα in in vitro and in vivo models, which could open up new avenues for improving therapeutic options involving the use of PPARα agonists in the treatment of MASH.

Keywords
MASLD, MASH, PPARa, FAT10/UBD, Therapy, Nuclear receptors