RESEARCH SUBJECTS OF MASTER 2 BIOLOGY-HEALTH COURSE PRECISION HEALTH
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UMR 1011

Role of the nuclear receptor Rev-erbα in angiogenesis

Supervisor **: B. Pourcet**– **Université de Lille INSERM U1011 Institut Pasteur de Lille CHU Lille EGID** – 01 rue du Pr Calmette – 0320877125 **benoit.pourcet@univ-lille.fr**

Atherosclerosis is a chronic inflammatory disease of large vessels triggered by the accumulation of cholesterol and leukocytes in the vascular wall. During atherogenesis, vascular wall thickening induces local hypoxia and promotes the *vasa vasorum* expansion by angiogenesis. This neovessels are however immature that promote leakage of lipids and leukocytes and contributes to plaque progression and rupture. The molecular and cellular mechanisms involved in the growth of the perivascular blood network are not known. Reducing its expansion could, however, represent an innovative therapeutic strategy in the treatment of these diseases. Our preliminary data suggest that the nuclear receptor Rev-erb-α controls angiogenesis and intraplaque neovascularization *ex vivo* and *in vivo*. This proposal aims to determine the impact of Rev-erb-α in angiogenesis using *in vivo* and *in vitro* approaches. For this, angiogenesis will be assessed *in vivo* by confocal and light sheet microscopy in *Rev-erbα*$^{-/-}$ mice and their control by analyzing the development of the vascular network of newborn retinas. The role of Rev-erb-α on angiogenic processes will then be analyzed *in vitro* using 3D spheroid models of cell competition. The pathways involved in angiogenesis will be assessed in tissues and cultured cells by WES and RT-qPCR. This M2R proposal aims to determine the impact of Rev-erb-α in angiogenesis during atherosclerosis and to define the molecular and cellular mechanisms involved.

RevErbα & IQGAP2 in the gut: a new axis in dietary lipid handling and in the control of postprandial lipemia?

Tutor **: Olivier BRIAND** – INSERM U1011 – EGID
Laboratoire JK, Pôle recherche Faculté de médecine, boulevard du Pr Jules Leclercq 59 Lille
Tel : 03 20 97 42 11 – fax : 03 20 97 42 01 – olivier.briand@univ-lille.fr

Nuclear receptors are transcription factors that modulate the expression of target genes in response to specific ligands. Among these, **Rev-Erbα** is highly expressed in the body and participates in energy homeostasis coordinating lipid, carbohydrate and bile acid metabolism with the biological clock. Increased magnitude and duration of post-meal hypertriglyceridemia, or **postprandial dyslipidemia**, is a cardiovascular risk factor because of its pro-atherogenic and inflammatory nature. In diabetic or obese patients, the **overproduction of chylomicrons by the intestine** is a major contributor of postprandial dyslipidemia. In our work, we demonstrated the control by Rev-Erbα of key steps of chylomicron metabolism in small intestinal epithelial cells (enterocytes).

IQGAP2, a player in lipid metabolism in the liver, is the gene most strongly regulated by Rev-Erbα as revealed by transcriptomic analysis in the Caco-2/TC7 cell line. The use of IQGAP2 ko mice and the silencing of IQGAP2 in vitro have shown that deficiency in this gene is associated with a defect in the activation of autophagy in response to a lipid challenge as well as with an exacerbated cellular storage of lipids.

These data suggest a role for IQGAP2 in the control exerted by Rev-Erbα in the enterocyte.

The project we propose for an M2 is part of the investigation of the molecular mechanisms by which the nuclear receptor RevErbα and the protein IQGAP2 control lipid turnover and lipophagy in enterocytes. We then plan, for a thesis project, to characterize this process in a genetically altered mouse model (RevErbα ko intestine-specific).

The approaches used are based on **cellular and molecular biology techniques** (gene and protein expression analysis, indirect immunofluorescence and video microscopy, protein half-life, gene invalidation and overexpression ...). This project is based on an important work **in cell culture** (filter culture of the human enterocyte line Caco-2/TC7 and murine and human intestinal organoids).

Evaluation of pharmacological therapies for NASH in a new preclinical mouse model of NASH/NAFLD

Supervisor: Dr Fanny Lalloyer, Inserm UMR 1011 - Institut Pasteur of Lille - University of Lille
Tel : +33320877996
Mail: fanny.lalloyer@univ-lille.fr

NAFLD (Non-Alcoholic Fatty Liver Disease) is the most common liver disease in the world, with a prevalence estimated at 25% of the general population, but reaching 80-90% in obese adults and 50-70% in patients with type 2 diabetes. This pathology has now become a veritable global “epidemic” whose incidence continues to increase, in parallel with the growing epidemic of obesity and diabetes. NAFLD is the hepatic expression of the metabolic syndrome and is characterized in its first stage by an excessive accumulation of fat in the liver, considered as benign steatosis, in the absence of excessive alcohol consumption. During the progression of NAFLD, simple steatosis can progress to NASH (Non-Alcoholic Steatohepatitis), diagnosed as a combination of steatosis, inflammation and ballooning of hepatocytes. In the worst cases, liver damage can progress to fibrosis, cirrhosis and hepatocellular carcinoma, which can lead to the death

of the patient. Currently, there is no approved therapeutic treatment for patients with NAFLD and NASH, the aggressive form of NAFLD.
In the laboratory, we developed a new mouse model which presents all stages of human NAFLD pathology (liver steatosis, inflammation, ballooning and fibrosis) under high fat diet for 12 weeks. The project aims to better understand NASH physiopathology and to test novel therapeutic targets for NASH in this model. Histological, biochemical and molecular analyzes will be carried out on the various technical platforms of the laboratory.

Role of FAT10/UBD on Mallory Denk Bodies formation in hepatocytes during NASH development

Pr. Réjane Paumelle-Lestrelin. UMR1011 « récepteurs nucléaires, maladies métaboliques et cardiovasculaires. rejane.lestrelin@univ-lille.fr
Non-alcoholic fatty liver disease (NAFLD) affects one third of the general population. NAFLDs are characterized by an intrahepatic accumulation of lipids (steatosis) progressing to non-alcoholic steatohepatitis (NASH) which can lead to the development of cirrhosis and hepatocellular carcinoma (HCC). To date, no effective medical treatment for NASH is available other than lifestyle change or weight loss surgery. Among the various mechanisms involved in the development and progression of NASH, the disruption of degradation pathways leading to the formation of Mallory Denk Bodies (MDB) appears to be a potential mediator of the progression of NASH to cirrhosis and HCC. However, the mechanisms leading to the formation of MDBs during NASH are not yet known. Our transcriptomic analysis of liver biopsies from obese patients with NASH show that the expression of FAT10/UBD correlates positively with the different histological grades of NAFLD. FAT10 is a protein of the “ubiquitin-like” family involved in FATylation processes regulating protein degradation. Interestingly FAT10 play a role in the formation of MDB induced by a chemical agent, DCC, in mice. The Master 2 project therefore aims to determine the role of FAT10 in the formation of Mallory bodies in hepatocytes, *in vitro*, in models of human hepatocytes and in vivo, in a mouse model developing NASH.

The role of the mitochondrial protein CHCHD4 in endothelial cell function

Tutor: Anna Rita Cantelmo, PhD, HDR
U1011 - Récepteurs Nucléaires, Maladies Métaboliques et Cardiovasculaires, Institut Pasteur de Lille - 1 Rue du Professeur Calmette - Lille Cedex - Tel: 03 20 33 70 78
email: anna-rita.cantelmo@univ-lille.fr

Mitochondria exert central functions in bioenergetics, metabolism, and apoptosis. The correct function of these organelles requires the import of > 1000 nucleus-encoded proteins as the mitochondrial genome provides only 13 proteins. A key component of the mitochondrial protein import machinery is the evolutionarily conserved AIF/CHCHD4 oxidoreductase that catalyzes the oxidative folding of targeted proteins after they cross the outer mitochondrial membrane. This mechanism is finely tuned and it is affected in disease.

Using a multidisciplinary approach, combining molecular and cellular biology, this project aims at i) studying the role and functional relevance of AIF/CHCHD4 in endothelial cells, and ii) characterizing the signaling pathways that impact on AIF/CHCHD4-dependent import pathway in angiogenesis in disease. The working hypothesis is that aberrant activity of this import pathway drives pathological angiogenesis. We will investigate angiogenic responses in healthy endothelial cells overexpressing CHCHD4 mimicking pathological endothelial cells.

The results generated with this project promise to provide unprecedented insights that will be useful for the development of novel therapeutic strategies for a variety of human diseases characterized by dysfunctional vasculature, such as cardiovascular disorders.