THESIS TOPIC

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<th>Subject N° (to be completed by the ED):</th>
<th>FUNDING:</th>
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<td>Thesis title:</td>
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<tr>
<td>Study of the inflammatory, adipogenic and hepatic steatosis mechanisms mediated by excessive dietary linoleic acid</td>
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<td>Metabolic impact</td>
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<td>Pathophysiology</td>
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Unit / team: UMR 1241 NuMeCan, team EXPRES

Supervisor’s name: Vincent Rioux/Karima Begriche/Ronan Thibault

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Socio-economic and scientific context (approximately 10 lines):
In France, more than 50% of the population is overweight or obese. This overload pathology has an inflammatory component and is often associated with insulin resistance, type 2 diabetes (metabolic syndrome) and chronic non-alcoholic liver disease (NAFLD, including steatosis and steatohepatitis). Lipid nutrition, at the quantitative level (energy overload) and especially at the qualitative level of the fatty acid composition of the diet, is a very important component in the genesis of these pathological processes. The nutritional prevention of metabolic syndrome and hepatic steatosis is therefore a major societal public health issue. It is in this context that the NuMeCan EXPRES team is studying the biological effects of dietary fatty acids. More specifically, bibliographical data and recent results from the team suggest the deleterious nature, on the development of metabolic and hepatic diseases, of an excessive intake of linoleic acid (C18: 2 n-6 or LA), which is consumed at a level much higher than the needs in the Western diet. The objective of this thesis is to study the impact of excessive dietary linoleic acid on inflammation, adiposity and hepatic steatosis and to describe the metabolic mechanisms involved.

Working hypothesis and aims (approximately 8 lines):
Linoleic acid (LA) is an essential fatty acid, precursor of polyunsaturated fatty acids (PUFAs) of the ω6 family, the main animal derivative of which is arachidonic acid (C20: 4 n-6 or ARA). In humans, epidemiological studies have correlated excess LA intake with the prevalence of adiposity and overweight. In mice, the transgenerational pro-adipogenic role of LA has been confirmed. In rats, our results demonstrate that excessive intake in moderately enriched diets leads to systemic and vascular (aorta) inflammation and the development of hepatic steatosis. Finally, in the HepaRG cell model, LA appears to be both pro-steatosis and inducer of cytochrome P450 2E1 (CYP2E1), a potential factor in the aggravation of steatosis towards steatohepatitis. The biochemical mechanisms associated with these metabolic alterations are however poorly understood. The direct or indirect roles of LA via its active derivatives such as OXLAMS (Oxidized Linoleic Acid Metabolites, 9- and 13-HODE), its conjugate (t10, c12-CLA, produced by the intestinal microbiota), or the best-known derivatives ARA (eicosanoids, endocannabinoids), are suspected. The regulation of the enzymatic pathways producing these derivatives (phospholipases A2, cyclooxygenases, lipoxigenases, epoxidase and hydroxylase activities of cytochromes P450, etc.) will be studied and characterized.

Main milestones of the thesis (approximately 12 lines):
The thesis will first include cellular studies on hepatocytes, HepaRG and adipocytes incubated with different concentrations of linoleic acid alone or in mixture (for example with PUFAs of the ω3 family). OXLAMS derivatives (commercial or chemically synthesized by collaboration) and the main oxygen mediators from ARA will also be tested. The lipogenic, steatotic, CYP2E1 inducing and pro-inflammatory effects of these molecules will be studied. Secondly, in vivo nutritional studies on the rodent model will be carried out. Different normo- and hyper-caloric diets (LA dose-effect with varying amounts of lipids and carbohydrates) will be applied. Mouse models deficient for the enzymatic players involved (PLA2, COX, LOX, CYPs including CYP2E1), a possible deficit in the energy use of fatty acids by β-oxidation, or an overabundant influx of free fatty acids from adipose tissue, itself overloaded and inflamed.

Scientific and technical skills required by the candidate (2 lines):
The candidate should have skills in biochemistry, cell and molecular biology. Knowledge in nutritional physiology will also be important.

FUNDING:

3 publications from the team related to the topic (last 5 years):
Linoleic acid overconsumption alters offspring gut and adipose tissue homeostasis in young but not older adult rats, *Nutrients* 12 (2020) 3451.

**National and international collaborations:**

This subject will first of all require local collaborations within the NuMeCan Institute (EXPRES team, Karima Begriche co-supervisor; EAT team, Gaëlle Boudry and Ronan Thibault; METHER team, gastro-hepato-enterologist clinicians and H2P2 platform). At the national level, an analytical collaboration with the Metatoul platform (Toulouse) will be set up (lipidomics). Collaboration with the “Synthesis of Bioactive Lipids” team (Thierry Durand) UMR CNRS 5247 Montpellier is also planned. At the international level, the collaboration already initiated with Nathalie Delzenne (UC Louvain) will be continued.