COLLEGE DOCTORAL BRETAGNE SCIENCES DE LA VIE ET DE LA SANTE

Year 2022-2023

# THESIS TOPIC

| **Subject N° (to be completed by the ED):** | **FUNDING:** ☒ **Requested** ☐ **Acquired** | **Funding origin:** |
|---|---|---|
| Thesis title: immune response and oxidative stress characterization by imaging in the liver of patients with metabolic associated fatty liver disease (MAFLD) | | 3 keywords: immunity<br>Image analysis<br>Metabolic associated fatty liver disease |
| Research Unit / team: **Irset /** Infection, Immunité, Facteurs environnementaux du Foie | | |
| Director's name:<br>**Michel Samson (director)** et Céline Raguenes-Nicol (co-supervisor) | | Phone number: 02 23 23 58 57<br>Email address: michel.samson@univ-rennes.fr<br>Year of HDR : 2001 |

Socio-economic and scientific context (approximately 10 lines):

Metabolic associated fatty liver diseases now affect 25% of the world population and have become the 1st cause of chronic liver disease and the 1st cause of hepatocellular carcinoma (HCC). Steatosis evolves into steatohepatitis where hepatic inflammation and hepatocytes suffering are added, and which itself can degenerate into cirrhosis and HCC. The only current treatment is then liver transplantation. Liver diseases were usually classified according to their alcoholic (ALD) or non-alcoholic (NASH) origin. However, hepatic steatosis often has a mixed origin with moderate alcohol consumption and the presence of metabolic disorders (obesity, diabetes, etc.). The impact of alcohol consumption on the mechanisms of carcinogenesis in MAFLD patients remains to be explored. Epidemiological studies suggest a more than additive effect on the risk of HCC in patients with metabolic disorders and alcohol consumption. The co-existence of the two risk factors may potentially induce more carcinogenic mechanisms than those induced by each of these factors alone, notably involving oxidative stress and immune cell infiltration.

Working hypothesis and aims (approximately 8 lines):

This project will contribute to the identification of new signatures in the pathophysiology and progression of MAFLD and HCC. It will compare liver damage in cohorts of patients suffering from MAFLD with no, moderate or excessive alcohol consumption. Especially, the analyzed features will be

i) research of markers of cell death, steatosis, fibrosis, inflammation and oxidative stress *in situ*.

ii) fine mapping and phenotyping of the immune cell infiltrate and the blood capillary network in the liver.

iii) research of predictive biomarkers in sera, such as cytokines and chemokines levels and markers of oxidative stress

Main milestones of the thesis (approximately 12 lines):

The thesis student will have at disposal a bank of biological samples from MAFLD patients from the University Hospital of Angers. The patients are stratified according to alcohol consumption.

The first step will be to finalize a panel of hyperplex markers of immune cells and oxidative stress by the innovative histochemistry technology "CellDIVE". The only equipment currently available in France is in Rennes. The panel of 24 staining on a single tissue section will allow a detailed spatial analysis of the cohort samples. This will require the development of an image analysis process using machine learning bioinformatics tools.

Other more classical methods of exploration by RT-qPCR, ELISA, and multiplex ELISA by flow cytometry, or RNAscope will also be used.

A global analysis of the mass data produced will be able to highlight characteristic signatures of the different profiles of the cohort.

Scientific and technical skills required by the candidate (2 lines):
Skills are required in immunology, oncology, image analysis and bio-informatic.

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

Filliol A, Piquet-Pellorce C, **Raguénès-Nicol C**, Dion S, Farooq M, Lucas-Clerc C, Vandenabeele P, Bertrand M JM, Le Seyec J and **Samson M**. RIPK1 protects hepatocytes from Kupffer cells-mediated TNF-induced apoptosis in mouse models of PAMP-induced hepatitis. 2017. ***J Hepatol.*** Jun;66(6):1205-1213.

Simoes Eugénio M, Farooq M, Dion S, Devisme C, **Raguenes-Nicol C**, Piquet-Pellorce C, **Samson M**, Dimanche-Boitrel MT and Le Seyec J. Hepatocellular carcinoma emergence in diabetic mice with non-alcoholic steatohepatitis depends on diet and is delayed in liver exhibiting an active immune response. 2020. ***Cancers***. Jun 8;12(6):E1491.

Farooq, M.; Hameed, H.; Dimanche-Boitrel, M.-T.; Piquet-Pellorce, C.; **Samson, M.;** Le Seyec, J. Switching to Regular Diet Partially Resolves Liver Fibrosis Induced by High-Fat, High-Cholesterol Diet in Mice. 2022. ***Nutrients***. *14*, 386.

National and international collaborations:
This project is part of the Grand Ouest **GO-NASH** hospital-university federation associating clinicians and academic researchers. Jérome Boursier (CHU Angers, for the GO-NASH consortium). Julien Edeline (CHU Rennes) ; Valérie Paradis (Hôpital Paris).

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