Master Biologie Moléculaire et Cellulaire 'BMC',
Université de Paris - *UFR Sciences du Vivant*

Parcours : **Biologie et Développement Cellulaires 'BDC'**
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Fiche de Projet de Stage M2, Année 2022-2023

Unité INSERM, CNRS ou Université : Centre de Recherche des Cordeliers INSERM UMR 1138 **Intitulé Equipe :** Proliferation, Stress and Liver Physiopathology **ED d'appartenance :** BioSPC **Responsable de l'Equipe :** Chantal Desdouets	**Responsable du Stage :** Chantal Desdouets **Contacts** chantal.desdouets@inserm.fr Tém 01 44 27 24 77

Titre du projet : Fatty liver disease, DNA damage accumulation driver of disease progression ?

Résumé du Projet de Stage (en 300 mots maximum, mots clés en gras)
Caloric excess and sedentary lifestyle have led to a global epidemic of obesity and metabolic syndrome. The hepatic consequence of metabolic syndrome and obesity, nonalcoholic fatty liver disease (NAFLD), is estimated to affect up to one-third of the adult population in developed countries. This spectrum of liver disease ranges from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis. Alarmingly, NAFLD is clearly fueling the rising incidence and prevalence of liver cancer in many countries. NAFLD is a complex disease with multiple parallel hits. One of the main mechanisms in NAFLD pathogenesis is hepatocyte lipotoxicity that produce a cascade of stress-induced responses including release of reactive oxygen species (ROS) and recruitment of immune cells. Importantly, NAFLD also strongly affects the balance between cellular death and compensatory proliferation. This process is a main driver for the emergence of proliferative damaged hepatocytes and tumorigenesis.
Our laboratory demonstrated that livers from NASH patients displayed a dramatic enrichment of DNA damage stigmata. In fact, NAFLD hepatocytes display hallmarks of replication stress, including slow replication fork progression and the activation of an DNA Damage Response (DDR) checkpoint (ATR/ATM signaling). Importantly, oxidative stress was evidenced as a key player. Indeed, antioxidant treatment was sufficient to: (1) dampen ROS level in murine NAFLD damaged liver, (2) reduce the percentage DNA damage NAFLD hepatocytes.
The project of the M2 student is now to unveil how DNA damage hepatocytes behave in a fatty liver and what could be their relevance during disease progression. Specifically, this project will: (1) The consequence of ATM deletion on liver tumorigenesis under NASH settings. (2) How deletion of ATM impact on metabolism reprograming during NAFLD development. The experimental strategy is mainly based on the use of relevant mouse models mimicking different stages of NAFLD disease. CRISPR/Cas9 in vivo technology is already developed to induce ATM deletion. The M2 student will benefit from a highly collaborative environment within the team and will acquire and use differents technological approaches (e.g. primary culture of hepatocytes, dynamic metabolic approaches, multispectral imaging, in situ digital histology).
Keywords : Liver, Non-alcoholic steatohepatitis, Cell proliferation, DNA damage, Replication stress, Metabolism
Publications de l'équipe, relatives au stage proposé
Gentric G, et al. (2015). Oxidative stress promotes pathologic polyploidization in nonalcoholic fatty liver disease. J. Clin. Invest. 2015. 125, 981-992.
Donne et al., (2020). Polyploidy in liver development, homeostasis and disease. Nat Rev Gastroenterol Hepatol. 17 (7): 391-405.
Donne et al. (2022). Replication stress triggered by nucleotide pool imbalance drives DNA damage and cytosolic DNA sensing pathway activation in non-alcoholic fatty liver disease Develpmental Cell *in press*.