# Fiche sujet de thèse

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## Titre de la thèse :

Role of MLKL in hepatocellular carcinoma development in NASH

## 3 mots-clés :

Necroptosis, Cancer, In vivo

## Unité/equipe encadrante :

IRSET – U1085 / Team 2

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## Contexte socioculturel et scientifique (env. 10 lignes) :

The liver is the fifth organ most affected by cancer and is the third leading cause of cancer-related deaths. Between 85 and 90% of primary liver cancers are derived from hepatocytes. Its etiologies range from infections with a hepatotropic viruses such as HBV and HCV, to aflatoxin poisoning or to alcohol overdose. Besides, nowadays, the evolution to a sedentary lifestyle, also accompanied by more caloric diet intakes, is responsible for the emergence of a new silent epidemic in human. Indeed, non-alcoholic fatty liver diseases (NAFLD) would affect nearly a quarter of the world’s population, with some geographical disparity. These cover a spectrum of hepatic disorders ranging from benign steatosis to inflammatory status, defined as non-alcoholic steatohepatitis (NASH), responsible for the development of fibrosis that will eventually worsen, leading to cirrhosis and even hepatocellular carcinoma (HCC) with high rates of morbidity and mortality. NASH will gradually become the first therapeutic indication of liver transplantation in developed countries. No curative treatment is available to cure form HCC. Only a kinase inhibitor, Sorafenib, is used in therapy but only allows to increase the life expectancy of patients by a few months more.

## Hypothèses et questions posées (env. 8 lignes) :

A general hallmark of cancer cells is their ability to evade from programmed cell death such as apoptosis or necroptosis. However, the literature suggests that necroptosis may have the particularity to display complex impacts on cancer development (Liu et al., Cell Stress 2019) with a tumor suppressor role during the initial phase of tumor development and a promoting role in late tumor development. On liver cancer, it is only known that necroptosis microenvironment may drive the lineage commitment rather towards intrahepatic cholangiocarcinomas (Seehawer et al., Nature 2018). To decipher the involvement of necroptosis on HCC emergence and expansion, mice depleted for MLKL, the executor of necroptosis, in liver parenchymal cells (MLKL\(^{LPC-KO}\)) or in all cells (MLKL\(^{−/−}\)) will be enrolled in parallel with their WT littermates in the NASH-HCC model occurring in diabetic individuals.

## Grandes étapes de la thèse (env. 12 lignes) :

Our team has already established the MLKL\(^{LPC-KO}\) mouse line. These mice age normally, without spontaneously developing any pathologies. The breeding of this mouse line includes wild-type littermates (MLKL\(^{+/+}\)) which will serve as pathology induction controls since they share the same genetic background. In parallel, we are actually establishing the total knockout murine line (MLKL\(^{−/−}\)) on the same genetic background that will also serve to decipher the role of necroptosis during HCC development. Data from the literature indicate that these last mice are viable healthy mice. In one part of the work, the PhD student will apply the experimental protocol for the in vivo development of HCC in the different mice lines. Mice, at pups stage, will be injected with a drug that destroys pancreatic beta cells to induce a type-I diabetes. After weaning, mice will be switched on a high-fat diet (HFD). Then, pathology will set and progressively worsens. Our previous experiments showed that a liver steatosis develops after 2 weeks of HFD, then the disease switches to an inflammatory state (hepatitis) at 4 weeks of HFD that is responsible for fibrosis establishment at 8 weeks of HFD and finally to hepatic tumor emergence from 8 weeks of HFD. Then, the evolution of tumors could be followed until 12 to 16 weeks of HFD. Collected samples (blood, spleen, liver) will be analysed with different complementary methodological approaches to define the specific physiopathological patterns obtained in the different mouse strains. In a second part of the work, MLKL will be studied in samples taken in tumor and non-tumor parts of livers issued from a cohort of patients with HCC developed on various aetiologic background including NASH.

## Compétences scientifiques et techniques requises par le candidat (2 lignes) :

Have followed theoretical training integrating cell and molecular biology and eventually oncology. Theoretical skills, and eventually practical, on murine models would be a supplementary advantage.

## 3 publications de l’équipe d’accueil relatives au domaine (5 dernières années) :


## Collaborations nationales et internationales :

With clinicians : Pr. Zucman-Rossi J. (Centre Cordelier Paris) and Pr. Boursier J. (CHU Angers) who established biobanks of human HCC samples, respectively issued from different aetiologies or specifically from NASH patients.