Profile N° (à remplir par VAS)
FUNDING: Ordinary doctoral contract (MEN)

Sheet abstract of thesis 2019

Disciplinary Fields: Health / Basic Biology / Bioinformatics

Thesis Title : (1-2 lines)

Impact of phenotypic fluidity in the heterogeneity and progression of hepatocellular carcinoma

3 keywords : (1 line) **ACRONYME *HepatoFluid***
Modelisation / Tumor heterogeneity / Molecular Pathology

Unit/Team of supervising : (1-2 lines)
Institut NUMECAN, Nutrition, Métabolismes et Cancer. INSERM U-1241-Université de Rennes 1, INRA

Name of the scientific director and co-director : (1 line)

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Socio-economic and scientific context : (10 lines)

Primary liver cancers, 90% of which are hepatocellular carcinomas (HCCs), are the 2nd cause of cancer-related death in the world. HCCs generally emerge in the context of chronic liver diseases resulting from viral infections, alcohol abuse, non-alcoholic steato-hepatitis or various genetic diseases. In France, HCC is one of the 3 deadliest cancers, with a median survival of 9.4 months and only 23% patient eligibility to potentially curative treatments. This is in contrast with a median survival of 50 months in populations benefiting from early detection of potentially curative treatments. In France, median survival and access to potentially curative treatments are subject to regional variations. The French region Brittany has a high HCC incidence, with a median survival of less than 9 months and access to potentially curative treatments in less than 22% of patients. These variations highlight the importance of early detection of HCC patients who are eligible to curative treatments (Bull Cancer 2017; 104 :752 ; J Hepatol 2017 ; 66 :537 ; Lancet 2016 ; 387 :2236; World J Gastroenterol 2018 ; 40:4536).

Assumptions and questions (8 lines)

Prediction of HCC aggressiveness and therapeutic management are based on morphologic criteria (tumor size and number, vascular invasion) revealed by imaging (Nat Rev Dis Primers 2016; 2:16018). However, HCC molecular heterogeneity is not taken into account for HCC staging and therapeutic management since liver biopsy is not routinely used for HCC diagnosis because of the risk of complications. Thus, further refinement of HCC patient management will come from the integration of HCC imaging and molecular data. Our previous study of over 1000 HCCs revealed a subclass that preserved normal liver metabolism and had the most favorable prognosis among all HCCs. These data suggested a fluidity of tumor phenotypes across tumor progression (Hepatology 2017; 66:1502). The **PhD work aims to study molecular, metabolic and imaging features of HCC phenotypic fluidity**.

The main steps of the thesis and demarche (10-12 lines)

We will study phenotypic fluidity in HCCs to pinpoint markers of tumor aggressiveness. Phenotypic fluidity is defined as the time-dependent evolution of tumor cell phenotypes within a single tumor. Our previous data are based on the analysis of over 1000 HCC patients. To answer our question, successive tumor biopsies across the steps of tumor progression would have been needed from each one of the patients in an HCC cohort. Obviously, this approach is not feasible for ethical reasons. Therefore, we set up a model of HCC phenotypic fluidity by integrating transcriptomic (microarray/RNAseq) profiles from human HCCs with transcriptomic data from a longitudinal model across HCC emergence and progression in mice. These profiles will be integrated with data obtained from Magnetic Resonance Imaging of mouse HCCs, from the study of tumor microenvironment across HCC progression as we previously described (Int J Biochem Cell Biol 2016; 81:195; Oncotarget 2016; 7:39026) and from the impact of mechanical forces on the emergence of cancer progenitor/stem cells with metabolic reprogramming.

Methodological and technical approaches considered (4-6 lines)

Methods and biological resources are available in our lab. *Human HCCs available*: transcriptomic (microarray / RNAseq) metabases with clinical annotations (R language) + paraffin-embedded/frozen in-house samples for independent validation (Hepatology 2017; 66:1502). *Mouse HCCs available*: longitudinal study, magnetic resonance imaging (MRI) followed by autopsy/histopathology >250 mice, >1000 samples (paraffin-embedded/frozen), >100 MRI files. *PhD candidate involvement*: transcriptomics, histopathology, study of tumor mechanical forces (biophysics), murine models of HCC, cell biology; energy metabolism, high-dimension data analyses.

Scientific and technical skills required by the candidate (2 lines)

Master 2 with strong background in human biology, physiopathology, molecular and cell biology, high dimensional data analysis, R language, biostatistics (Masters 2: Biology & Health, Bioinformatics & Health, Public Health).