# MASTER 2 BMC
# PARCOURS GENOPATH
# ANNEE 2023-2024

**Titre du sujet de stage :**

EZH2-mediated epigenetic regulation of gene expression networks in liver cancer (Etude des mécanismes de régulations épigénétiques impliquant EZH2 dans le cancer du foie)

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**Sujet de stage :**

Hepatocellular carcinoma (HCC), the most frequent form of liver cancer, represents the fourth leading and fastest rising cause of cancer death worldwide. Major risk factors include chronic viral hepatitis B and C, ethanol consumption, and non-alcoholic fatty liver disease. Although the risk of developing HCC can be reduced by treatment of the underlying cause, e.g. by viral clearance, strategies to prevent cancer development in patients with advanced fibrosis and established cirrhosis are still lacking. Despite recent improvements, treatment options for HCC remain largely unsatisfactory.

Driving forces in hepatocyte transformation, HCC development and progression include chronic inflammation, DNA damage, epigenetic modifications, chromosomal instability and early neo-angiogenesis. Notably, the deregulation of signaling pathways and epigenetic changes are detected early in the natural history of HCC development, at the stage of cirrhosis. We are focusing on the role of enhancer of zeste homolog 2 (EZH2), a subunit of the polycomb repressive complex 2 (PCR2) in HCC development. The histone methyltransferase EZH2 is responsible for H3K27 trimethylation (H3K27me3), a mark that represses gene transcription. In cancer EZH2-PRC2 activation targets tumor suppressor gene expression but EZH2 also plays a role in activation of transcription, independently of PRC2. Our team aims to uncover the molecular mechanisms governing the roles of EZH2 in liver-derived cells contributing to deregulate gene expression in hepatocarcinogenesis. We have recently shown an interplay

between EZH2 and O-linked N-acetylglucosamine transferase (OGT) in hepatoma cells and uncovered that these proteins co-regulate cancer-associated genes in these cells. Of note, other regulatory factors that have been demonstrated to be O-GlcNAcylated and to interact with EZH2 could contribute to these regulatory processes.

The aim of this project is to assess target gene promoter occupancy by EZH2 and other proteins that could regulate its functions using ChIP experiments and to study the effect of pharmacological inhibitors/siRNA directed against those proteins found at target gene promoters on gene transcription. We will also assess how EZH2 target genes are involved in HCC.

The knowledge gained within this project will contribute to further decipher the molecular mechanisms underlying EZH2-mediated gene regulation as well as chronic liver disease and HCC development. A better understanding of these processes will help to design new therapeutic strategies.

**Technologies utilisées :** RNA-seq, RT-PCR, ChIP-seq, ChIP-qPCR, cell culture, functional studies (siRNA, pharmacological inhibitors), proximity ligation array, immunofluorescence

**Mots clés :** histone methyl transferase, O-GlcNAcylation, post-translational modification, epigenetics, liver cancer

**Publications d'intérêt :**

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