UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2024-2025

Title : Identification of the crosstalk between metabolic and epigenetic processes in stem cell homeostasis and their involvement in fertility disorders and/or testicular cancer as well as in their chemoresistance.

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Summary: Understanding the mechanisms that drive stem cell fate decision is of major importance with clinical in the etiology of diseases such as infertility or cancer as well as in regenerative medicine and tissue rehabilitation after cancer therapy. Growing evidence show that metabolic pathways influence epigenetic changes associated with lineage commitment, specification, and self-renewal. In the other way round, epigenetic is also important in metabolic decision. However, the interplay between metabolism and epigenetics in deciding the fate of spermatogonial stem cells (SSC) remains largely unexplored. The study of SSC that self-renew while giving rise to differentiated germ cells appears as a useful strategy to decipher the mechanisms involved in stem cell homeostasis associated with cell fate specification and outcome of potential diseases. Our goal is to decipher the metabolic-epigenetic interplays through the study of "candidate genes" identified using RNAseq approaches. We will take advantage of genetically engineered mouse models in combination with cell culture experiments either treated by pharmacological agents or modified by genome editing (Crispr/CAS9). Our objectives are: **1/** to analyze the role of yet unidentified genes in the etiology of fertility disorders or germ cell cancers; **2/** to study the interaction between metabolic-epigenetic pathways in germ cell homeostasis and chemoresistance; and **3/** to transpose these data on human. The data obtained will shed light on the gene networks that drive stem cell fate and help to better understand the interaction between cellular metabolism and epigenetics for regulating stem cell homeostasis, cell state and differentiation capacity. This work should allow defining biomarkers of stem cell alterations leading to germ cell cancer, fertility disorders and/or transgenerational inheritance of disease to offspring. This project might also offer opportunities to develop new therapeutics in regenerative medicine following anti-cancer treatment.

Methodologies (key words) : Modèles murins, culture cellulaire, transduction virale, transfection transitoire, transplantation CSS tumorales, histologie/Imagerie, biologie moléculaire.

Publications of the research group on the proposed topic (3 max.)

1- Thirouard et al. *"Identification of a Crosstalk among TGR5, GLIS2, and TP53 Signaling Pathways in the Control of Undifferentiated Germ Cell Homeostasis and Chemoresistance."* **Adv. Sci (Weinh)** 2022 Apr 18; e2200626. doi: 10.1002/advs.202200626.
2- Thirouard et al. "*Analysis of the Reversible Impact of the Chemodrug Busulfan on Mouse Testes*.", ***Cells***, vol. 10 (9), 2021.
3- Baptissart et al. "*Multigenerational impacts of bile exposure are mediated by TGR5 signaling pathways.*", ***Scientific reports***, vol. 8 (1), pp. 16875, 2018.