UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2023-2024

Title : Identification of the molecular mechanisms involved in the etiology of testicular cancer and of their chemoresistance.

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Summary: Testicular germ cell tumors (TGCT) are the most frequently diagnosed cancer in young men (15-39 years old). The incidence of TGCT has been increasing throughout Europe over the last 30 years. A better understanding of etiological factors of TGCT is a major challenge for improving screening and identifying new diagnostic or prognostic markers, especially for the 10-20% aggressive and metastatic forms of TGCT, which may develop chemoresistance leading to patient death. The accepted etiology for TGCT suggests that a delayed maturation of gonocytes to spermatogonia, causes germ cell neoplasia in situ (GCNIS). This is sustained by the fact that, as fetal germ cell, GCNIS and seminomas exhibit low levels of DNA methylation and permissive chromatin structure associated with high transcriptional and proliferative activity. This highlights the main role of stem cell fate in the process of tumor development.
We recently demonstrated that modulations of bile acid signaling alter spermatogonial stem cell (SSC) pool establishment and germ cell chemosensitivity. Based on the results obtained by our team through RNAseq analyzes of germ cells treated with busulfan, cisplatin or 5-Fluorouracil and using, during the internship, mouse models and drug-modulated cell cultures anti-cancer drugs or modified by genome editing (Crispr/CAS9), our objectives are: **1/** to analyze the role of bile acid signaling pathways in the etiology of TGCT; **2/** to study the interaction between metabolic-epigenetic pathways in the chemoresistance of TGCT; **3/** to study these pathways in in vivo models of TCGT in mouse; and **4/** to transpose these data on human samples.
The data obtained will define gene networks involved in the etiology of TGCT and will help to decipher the molecular mechanisms associated with the aggressiveness and/or the chemoresistance of TCGT.

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.