UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

# Track « Integrative Biology, Physiopathologies »

**Proposal for a Master 2 internship** – 2024-2025

***Title*** : The *Myc* oncogene as a transcriptional amplifier of sex dimorphism in the adrenal gland


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***Summary*** :
Benign or malignant adrenocortical lesions have a greater prevalence in women. The reasons for this sexual dimorphism (SD) remain unexplained but different mouse genetic models recreate this prevalence bias and suggest a hormonal cause rather than a chromosomal one. Indeed, the female mice show a bigger adrenal cortex with faster cell renewal, a better capacity to mobilise the progenitor cells and a greater production of corticosterone than males. Experiments using gonadectomies and hormone substitution or sex reversal models, have shown that the core of this SD depends on the inhibitive action of androgens. To elucidate the mechanisms mobilised by androgen signalling in the physiological or pathological manifestations of SD, we have performed the genetic inactivation of the androgen receptor (AR) in the postnatal adrenal cortex of mice. These experiments established that the targeted loss of AR in male mice is sufficient to induce a feminisation of the adrenal gland in most aspects of the cortex homeostasis and endocrine function. RNA-seq was performed on the adrenals of wild-type and AR deficient mice to identify common differentially expressed genes (DEG) influenced by both sex and AR. Using bioinformatic prediction tools, we identified transcription factors (TF) potentially enriched within promoter regions of members of this DEG list. Among these TF, cMyc oncogene whose expression is repressed by AR, appears to be the best candidate to support SD of the adrenal genetic program. The project will aim at testing this hypothesis *in vivo* by monitoring cMyc expression during development and functional differentiation of the adrenal gland using Myc-EFGP knock-in mice and by exploring the consequences of its invalidation using *Myc* floxed allele and adrenal-specific Cre drivers. This project is supported by ANR2023 ADD-SEX grant.


***Methodologies (key words) :*** handling (genetically-modified) mice, hormonal manipulation and dosage, immunohistology, microscopic imaging, gene expression analyses, omic data analysis

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


- Dumontet *et al.* PKA signalling drives reticularis differentiation and sexually dimorphic adrenal cortex renewal. JCI Insight. 2018 Jan 25;3(2). pii: 98394. doi: 10.1172/jci.insight.98394.
- Grabek *et al.* The adult adrenal cortex undergoes rapid tissue renewal in a sex-specific manner. Cell Stem Cell. 2019 Aug 1;25(2):290-296.e2. doi: 10.1016/j.stem.2019.04.012.
- Wilmouth *et al.* Sexually dimorphic activation of innate antitumor immunity prevents adrenocortical carcinoma development. Sci Adv. 2022 Oct 14;8(41):eadd0422. doi: 10.1126/sciadv.add0422.