UNIVERSITÉ Clermont Auvergne

MASTER BIOLOGIE SANTE

Track « Integrative Biology, Physiopathologies »

Proposal for a Master 2 internship – 2023-2024

Title : How does SUMOylation influence the functional patterning of the adrenal cortex?

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Summary :
Steroid hormones secreted by the adrenocortical gland (mineralo- & glucocorticoids), allow the adaptation of energy metabolism, blood pressure and immune response to the variations of the environment and the physiological demands. The quality of this response, and therefore the survival of the individual, is conditioned by the maintenance of the cortex structure in concentric zones specialized in the production of mineralocorticoids from the *zona Glomerulosa* (outer cortex) and glucocorticoids from the *zona Fasciculata* (inner cortex). Cortical zones are constantly renewed as a result of the recruitment of progenitor cells located at the periphery of the organ that first acquire a zG cell identity and then, as they migrate inward, transdifferentiate into a zF identity. This concentric patterning relies on the balanced actions of WNT/β-catenin (zG) and ACTH/PKA (zF) signaling pathways[1] and on the decreasing gradient of a posttranslational modification termed SUMOylation[2]. As a result, alteration of one of these players can lead to either tumor development or functional failure. Indeed, the excess of SUMOylation following ablation of the SENP2 de-SUMOylase in the cortex (*Senp2*^{cKO} mice), leads to the blockage of zG-to-zF transdifferentiation resulting in zF atrophy and lethal glucocorticoid deficiency[3]. Reasons for this blockage are still elusive but could include an alteration of PKA catalytic activity when SUMO pathway is upregulated. The aim of the project will be to explore the reciprocal influences of PKA and SUMO pathways using transient cell transfections and genetically engineered mouse models. Elucidation of these mechanisms is a key to understanding functional zonation of the adrenal cortex and its pathological deficits, and may provide a paradigm for understanding homeostatic maintenance of other organs.

Methodologies (key words) : *transient cell transfection of SUMOylating enzymes and PKA subunits; IP; WB ; kinase assays; confocal microscopy ; immunohistology ; targeted mutagenesis ; PCR*

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

1- Drelon et al. WNT signalling inhibition by PKA is involved in adrenal zonation and restrains malignant tumour development. Nat Commun. 2016 Sep 14;7:12751. doi:10.1038/ncomms12751
2- Dumontet et al. Hormonal and spatial control of SUMOylation in the human and mouse adrenal cortex. FASEB J. 2019 Sep;33(9):10218-10230. doi: 10.1096/fj.201900557R.
3- Dufour et al. Loss of SUMO-specific protease 2 causes isolated glucocorticoid deficiency by blocking adrenal cortex zonal transdifferentiation in mice. Nat Commun. 2022 Dec 21;13(1):7858. doi: 10.1038/s41467-022-35526-5.