UNIL | Université de Lausanne

Department of Biomedical Sciences

DBS SEMINAR

Tuesday, December 6th, 2022 – 12h15

Zoom Meeting and seminar room 6th floor, Bugnon 7

"New cell and animal models to decipher the molecular mechanisms of primary aldosteronism"

Prof. Sheerazed Boulkroun

Inserm, PARCC
Université Paris Cité
Paris, France

Host: Prof. Edith Hummler

Primary aldosteronism is the most common form of secondary hypertension, affecting up to 10% of hypertensive patients. It is responsible for treatment resistance and increased risk of cardiovascular complications. Over the past 10 years, important discoveries have been made regarding the genetic basis of aldosterone producing adenoma and familial forms of primary aldosteronism. In most cases, genetic abnormalities are found in genes coding for ion channels (*KCNJ5, CACNA1D, CACNA1H, CLCN2*) as well as ion pumps (*ATP1A1, ATP2B3*). They occur as somatic mutations in aldosterone producing adenoma and as germline mutations in familial forms of the disease. Mutations in these genes affect intracellular ion homeostasis and/or cell membrane potential, leading to increased intracellular calcium concentrations and activation of calcium signalling, which is the main regulator of aldosterone biosynthesis. In addition, double mutations in *CTNNB1* and *GNAQ/GNA11* have been identified in aldosterone producing adenoma presenting in puberty, pregnancy and menopause. Although the role of these mutations in regulating aldosterone biosynthesis has been clearly established, the mechanisms involved in proliferation and aldosterone producing adenoma formation still remain to be elucidated. The investigation of different animal models increased our knowledge on the molecular mechanisms underlying the development of PA. Hence the constitutive β-catenin activation in the adrenal cortex induces ectopic zona glomerulosa differentiation and dedifferentiation of the orthotopic zona fasciculata, resulting in hyperaldosteronism in 10-month-old mice. The deletion of *rarα* gene, coding for the retinoic acid receptor α, revealed that retinoic acid receptor signaling contributes to the normal morphology and functional zonation of the adrenal cortex. Finally, mice expressing a constitutively open ClC2 chloride channel, encoded by *CLCN2* gene, display typical features of human primary aldosteronism. To further our understanding of the molecular mechanisms involved, we have taken advantage of the recent development of chemogenetic tools to develop cell and animal models in which we can modulate intracellular calcium concentration "on demand" by modulating sodium entry, thus mimicking some mutations identified in primary aldosteronism. The characterization of the cell model revealed that sodium entry leads to cell membrane depolarization, calcium entry, stimulation of *CYP11B2* (coding for aldosterone synthase) expression and aldosterone biosynthesis. This cell model is a useful tool to decipher how alterations in intracellular ion balance and calcium signaling lead to the development of aldosterone producing adenoma.

References

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