Neuroendocrinology and Pituitary

NEUROENDOCRINOLOGY AND PITUITARY BASIC RESEARCH ADVANCES

Tissue-Specific Tumorigenesis in Multiple Endocrine Neoplasia Type I

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While a germline heterozygous mutation in the *MEN1* gene predisposes tumor formation in the endocrine pancreas, parathyroid glands and anterior pituitary, this tissue-specific tumorigenesis is not dependent on *MEN1* mutations alone. In fact, a homozygous deletion of *Men1* in the entire pancreas of a mouse results in tumor formation only in the endocrine pancreas, not in the exocrine pancreas, suggesting an endocrine tissue-specific mechanism. The *MEN1* gene encodes the menin protein, which interacts with chromatin associated protein complexes, therefore engaging in epigenetic control mechanisms. Recognizing menin's participation in epigenetic regulation led to an investigation of whether the pathogenesis of MEN1 syndrome may be related to epigenetic changes in the affected endocrine tissues. Indeed, MEN1-associated endocrine cell types exhibit various menin-dependent epigenetic mechanisms. In fact, a significant increase in methylated DNA loci was observed in MEN1 human parathyroid tumors when compared to human parathyroid adenomas and carcinomas without known *MEN1* mutations. Subsequent studies revealed that loss of menin results in increased activity of DNA methyltransferase 1 (Dnmt1). Our studies have shown that *Dnmt1* is transcriptionally regulated by the menin-interacting protein Rbbp5. While menin normally functions to suppress Rbbp5 activity, loss of menin activates Rbbp5, thus upregulating *Dnmt1* expression, causing global DNA hypermethylation and subsequent tumorigenesis in MEN1-target endocrine tissues. In order to assess the behavior of Rbbp5 in both MEN1-target tissues and non-target tissues, Rbbp5 protein expression was analyzed in both MEN1-target tissues (endocrine pancreas, anterior pituitary, parathyroid) and non-MEN1-target tissues (kidney, lung, liver, brain, heart) of wild-type (WT) mice. We confirmed that Rbbp5 protein expression is ubiquitous throughout all of these WT mouse tissues. Since Rbbp5 is a transcriptional activator responsible for enhanced *Dnmt1* gene expression, and the loss of menin causes *Dnmt1* overexpression solely in MEN1-target tissues, we assessed whether Rbbp5 binds preferentially in a tissue-specific manner to the *Dnmt1* promoter. We determined the presence of Rbbp5 on the *Dnmt1* promoter in MEN1-target tissues (WT mouse endocrine pancreas, normal human parathyroid, WT mouse pituitary) and the absence of Rbbp5 on the *Dnmt1* promoter in non-MEN1-target tissues (WT mouse liver, WT mouse kidney, WT mouse lung). These results confirmed that Rbbp5 does exhibit MEN1-target-tissue-specific occupancy at the *Dnmt1* promoter. This endocrine-specific localization of Rbbp5 to the *Dnmt1* promoter suggests the presence of additional tissue-specific factors (with tissue-specific expression or interactions/activity) that must be validated and tested further.

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Transcriptome of Distinct LH and FSH Cells Reveals Different Regulation Unique to Each Cell Type

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From mammals to fish, gametogenesis and sexual maturation are driven by LH and FSH, the two gonadotropic hormones temporally secreted from the pituitary. Teleost fish are an excellent model for addressing the unique regulation and function of each gonadotropin hormone since, unlike mammals; they synthesize and secrete LH and FSH from distinct cells. By performing cell specific transcriptome analysis of double-labelled transgenic Nile tilapia (*Oreochromis niloticus*) expressing GFP and RFP in LH or FSH cells, respectively, we identified genes specifically enriched in each cell type. Though GnRH is considered the main neuropeptide regulating LH and FSH, we found that each LH and FSH cell express unique GPCR signature that reveals the direct regulation of additional metabolic and homeostatic hormones (like cholecystokinin, somatostatin and glutamate). Moreover, some of those GPCRs were conserved also in gonadotrophs of mammals (like PACAP receptor, Adropin receptor and GABBA receptor). Next, we had exploited the unique behavior of Nile tilapia where a behavioral hierarchy is created between males, to compare the gene expression in the pituitary and brain of dominant (reproducing) males to a subordinate (non-reproducing) males. By combining the two transcriptome sets we had identified novel players in the hypothalamic regulation of the HPG axis, and revealed how brain aromatase (*cyp19a1b*), that is enriched specifically in LH cells, is the key factor in regulating the activity of LH and FSH cells in dominant reproducing fish. Thereby, unraveling novel mechanisms in the differential regulation of LH and FSH. The research was funded by the Israel Science Foundation (ISF) no. 1540/17.

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NEUROENDOCRINOLOGY AND PITUITARY CASE REPORTS

"An Unexpected Pit" - Ectopic Pituitary Adenoma

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Background: Ectopic pituitary adenomas (EPAs) are exceedingly rare neoplasms, comprising about 0.5% of all pituitary adenomas. These are often misdiagnosed radiologically, while the correct diagnosis requires high index of suspicion on pathology and immunohistochemistry analysis. **Clinical Case:** 62-year-old female presented to the