Neuroendocrinology and Pituitary

ADVANCES IN NEUROENDOCRINOLOGY

Sensory Neuron Metabolism Mediates Changes in Ovarian Function via LKB1

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Sensory Neuron Metabolism Mediates Changes in Ovarian Function via LKB1

Bi-directional communication between sensory neurons to peripheral tissue to mediate physiology has become an area of interest. Previous research on peripheral neuron control of ovarian function shows that lesioning the superior ovarian nerve resulted in decreased estradiol release from the ovary; but there has been little research on how sensory neurons affect ovarian physiology. Interestingly, the metabolic activity of sensory neurons that control ovarian and follicular function may have profound effects on tissues they innervate. LKB1 (Liver Kinase B1) is a metabolic kinase that regulates cell growth and polarity. When downregulated in cortical neurons *in vitro*, leads to shorter axons with less branching. Female mice with LKB1 removed from their peripheral sensory neurons have litters more often and increased litter sizes compared to wild-type mice, which led to the investigation into the mechanisms into the role of LKB1 in sensory neurons in ovarian function. $Na_v1.8cre\text{-}LKB1^{fl/fl}$ mice were used to assess the removal of LKB1 from Nav1.8-expressing neurons on the mechanisms behind reproductive viability. The estrus cycle was tracked by using vaginal lavage to collect cells from the vagina twice per day for ten days, and cytology was assessed to determine phase. Ovaries were collected from mice in all phases of the estrus cycle, sectioned at 8 micron thickness, stained with H&E. Follicle sizes and numbers were measured on 8 sections per ovary. Sensory innervation was measured by clearing whole ovary using ScaleS1 and using confocal microscopy to image through the whole tissue for sensory neurons tagged with tdTomato and DAPI. Our data indicate that Nav1.8-expressing neurons innervate the ovary from celiac ganglia, upper lumbar, and lower thoracic dorsal root ganglia. $Na_v1.8cre\text{-}LKB1^{fl/fl}$ mice have larger litters and breed more frequently compared to cre-negative litter mates (WT). $Na_v1.8cre\text{-}LKB1^{fl/fl}$ mice have larger ovaries, spend less time in proestrus, and have greater follicular turnover compared to WT mice. Phase-matched ovaries from $Na_v1.8cre\text{-}LKB1^{fl/fl}$ mice in proestrus show greater numbers of antral and degenerating follicles than WT mice, but similar numbers of immature follicles; however, the size of all follicles from $Na_v1.8cre\text{-}LKB1^{fl/fl}$ mice are smaller than follicles from WT mice. $Na_v1.8cre\text{-}LKB1^{fl/fl}$ mice have improved reproductive viability by increased follicular turnover rate, more mature follicles, and shortened estrus cycle length.

Neuroendocrinology and Pituitary

PITUITARY TUMORS I

Evading Death: Noxa in Cushing's Disease Pituitary Adenomas

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ntroduction: Recurrence of Cushing's disease (CD) caused by benign pituitary microadenomas are challenging clinical problems. Mechanisms underlying adenoma formation and recurrence remain unknown. *PMAIP1* gene codes for Noxa, a Bcl-2 homology 3 (BH3) pro-apoptotic protein frequently downregulated in malignant human tumors.[1-6] The role of dysregulated apoptosis remains largely unknown in benign tumors and in CD. We hypothesized that altered expression of Noxa protein is a pro-survival adaptation employed by CD adenomas.

Methods: Syngeneic human pituitary adenoma and adjacent normal gland pairs (n=2), and an additional CD adenoma were analyzed with RNAseq. 10 CD, 1 growth hormone (GH) and 1 non-functioning adenoma (NFPA) underwent immunohistochemical (IHC) analysis for Noxa expression, which was graded by a neuropathologist as 0=none, 1=light, 2=medium, 3=strong. Staining grade represents relative protein expression.

Results: Compared to adjacent normal pituitary tissue, we found that adenomas (n = 3) had a 3.76 fold increase in *PMAIP1* mRNA. However, there was attenuated Noxa IHC staining in adenomas compared to normal pituitary in 8 of 10 CD patients (2:3, respectively), but similar staining in 2 of 10 CD patients (2:2 and 2-3:2-3). In GH and NFPA, we found similar patterns of Noxa suppression in the adenomas compared to the normal gland.

Conclusion: Despite elevated *PMAIP1* (Noxa) gene expression in adenomas compared to adjacent normal gland in CD, protein expression was reduced in adenomas. This downregulation of Noxa protein expression may contribute to reduced apoptosis of tumor cells. These findings suggest that CD adenomas gain pro-survival advantage by downregulating Noxa protein at post-transcriptional or post-translational level.

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Bone and Mineral Metabolism

CLINICAL ASPECTS OF OSTEOPOROSIS AND VITAMIN D ACTION

Bone Quality and Strength in Obese Men with Type 2 Diabetes Mellitus Are Impaired and Negatively Influenced by Adiposity

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