Overexpression of MAML1 in Human and Dogs with Cushing’s Disease

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Introduction

Background:
• Cushing’s disease (CD) – hypercortisolism caused by rare adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas (PA) that afflicts humans and dogs.
• Causes: weight gain, moon facies, myopathy, hirsutism, hypertension, infertility, hyperglycemia, emotional lability, poor concentration, fractures, immunosuppression
• Treatment include surgery, radiotherapy, and medication. However, poor side effects, often targets adrenal glands (not ACTH tumor/remainder), and 35% recurrence.
• Because CD is a rare tumor, research has been limited and yielded only a few dysfunctional genes.

Objective:
• Profile the genomic aberrations and abnormal gene expression of CD PA in humans and dogs that may spur the development of targeted pharmaceutical interventions.

Methods

Whole Exome Sequencing (WES) [Human, n=6]
To determine genetic variants in ACTH-secreting PAs

RNA-Seqencing (RNA-seq) [Human & Dog, n=6 & 7 ]
To determine differential gene expression in Cushing’s disease

Immunohistochemistry (IHC) [Human, n=31]
To confirm differentially expressed gene at the protein level

Results

Figure 2: Boxplot comparison of overexpressed genes in humans and dogs.

Figure 3: Immunohistochemistry for proteins suspected to be overexpressed in Cushing’s disease.

Conclusions

Highlights:
• WES (not shown): Non-synonymous changes in USP48 (p.M415I and p.M415V) and in GNAQ (p.T96S). Copy number gains were found in chromosomes 7, 12, 14 and a loss was reported in 19.
• RNA-seq: Differential RNA-seq showed eight genes (MAML1, MNX1, RASEF, TBX19, BIRC5, TK1, GLDC, FAM13B) to be significantly (P<0.05) overexpressed across human and canine corticotroph PA.
• IHC: Staining demonstrated Mastermind Like Domain Containing 1 (MAML1) to be positively (3+) expressed in the nucleus of ACTH-secreting tumor cells of human corticotroph PAs (22/31, 70.9%), but absent in healthy pituitary glands.

Discussion

• First insights into the comparative genomic characterization of human and dog corticotroph PA with respect to MAML1 overexpression, a finding of potential direct impact to the previously described TBX19, POMC and ACTH expression.
• Since MAML1 appears to stain exclusively for corticotrophic tumor cells as compared to TBX19 (may stain both normal and tumor corticotrophic cells), MAML1 staining may be helpful in diagnosing CD, particularly in microadenomas where tissue quantity may be limited.
• Our study also offers a rationale that corticotroph PA, although rare, may also be a heterogeneous disease from the genetic perspective and illustrates the potential use of the canine model in development of precision therapeutics.
• Studies suggest MAML1 has an inhibitory transcriptional co-activator role in regulating embryological NOTCH signaling in pituitary development, and recently another family gene (MAML3) has found to be associated to an adrenal neuroendocrine tumor through fusion function.
• Overall, the function of MAML1 is unclear, and to the best of our knowledge, this is the first report link to CD and encourages further functional investigation.

Acknowledgements

We appreciate the support of Emory University, Winship – Pathology Corelab services, specifically Dianne Alexis, MPH, who supported section histology and staining.

We appreciate the funding of the AI Lerner Chair Award, Department of Neurosurgery, Emory University School of Medicine.

References