the JAK2-STAT3 transduction mechanism. STAT3 is a latent transcription factor activated upon phosphorylation, which triggers its homodimerization and nuclear translocation. Evidence, however, for JAK2-independent, STAT3-dependent leptin receptor signaling mechanisms exist. FAK (focal adhesion kinase, Ptk2) and Pyk2 (protein tyrosine kinase 2b, Ptk2b) are a subset of nonreceptor protein tyrosine kinases and comprise the focal adhesion kinase family. FAK and Pyk2 are implicated in the regulation of cytokine receptor signaling. Furthermore, Pyk2 knockout mice have an obesity prone phenotype. Here, we studied the role of the focal adhesion kinases in leptin receptor signaling using genetic and pharmacological approaches. We found that overexpression of Pyk2 or FAK increased STAT3 phosphorylation (activation). Overexpression of a FAK or Pyk2 construct with impaired kinase activity, however, attenuated STAT3 phosphorylation, suggesting the increase in STAT3 phosphorylation is largely dependent upon kinase activity of FAK/Pyk2. Treatment of cells with a small molecule dual inhibitor of FAK and Pyk2 (PF431396) attenuated leptin-induced STAT3 phosphorylation in a mouse hypothalamic cell line. Importantly, this effect is independent of JAK2, as PF treatment of two independent JAK2-deficient cell lines exhibited similar attenuation of leptin-induced STAT3 phosphorylation. To assess the physiological relevance of FAK/Pyk2 in leptin receptor signaling *in vivo*, we administered PF compound to the lateral ventricle of 24-hour fasted lean wild-type mice followed by peripheral leptin administration. Intracerebroventricular (ICV) administration of PF suppressed the anorectic effect of leptin as evidenced by impaired inhibition of food intake upon refeeding. Accordingly, analysis of total hypothalamic lysates from these mice showed ICV PF impaired leptin-induced STAT3 phosphorylation. Taken together, these data suggest that Pyk2 and/or FAK play a role in leptin signal transduction.

# Thyroid

## THYROID CANCER CASE REPORTS II

### *Lower Extremity Leiomyosarcoma Metastatic to a Benign Thyroid Nodule*

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**MON-454**

**Background:** Metastases to the thyroid gland from non-thyroidal malignancies have been reported in 1.4-3% of patients undergoing thyroid surgery for malignant thyroid tumors, but only 4% of these are due to sarcomas[1]. Metastases in a pre-existing thyroid nodule are even more rare. We present a patient with a lower extremity leiomyosarcoma that metastasized to a pre-existing benign thyroid nodule.

**Clinical Case:** A 70-year-old woman was referred to the Thyroid Nodule Clinic for a 5 cm thyroid nodule replacing most of the right thyroid lobe. Twenty years earlier the patient had a left thyroid lobectomy for a benign nodule. One year before presentation, she was diagnosed with a high grade lower extremity leiomyosarcoma with lung metastases and started on treatment. A large right thyroid nodule pressing on the trachea was incidentally found on an initial chest CT performed for sarcoma staging. On PET-CT, the nodule was not FDG-avid. On ultrasound, the thyroid nodule was solid and heterogeneous, iso- to hyperechoic with smooth margins, inspissated colloid and grade 3 vascularity. Fine needle aspiration (FNA) of the nodule showed benign cytology (Bethesda II). The patient did not have local compressive symptoms and decided not to undergo surgical removal of the nodule.

The thyroid nodule was initially stable on periodic follow-up CT scans and thyroid ultrasounds. However, a thyroid ultrasound performed 2.5 years later showed a change in the nodule echogenicity without change in size. The nodule had become hypoechoic, heterogeneous and well-defined with grade 2 vascularity. FNA revealed a poorly differentiated malignant spindle cell neoplasm, similar to biopsies of other metastatic sites, supporting a diagnosis of metastatic high grade sarcoma. The patient underwent a right thyroidectomy; pathology revealed a 4.1 cm metastatic sarcoma with multifocal angioinvasion with tumor present at the surgical margin. Follow-up neck ultrasounds showed no evidence of local recurrence, while the patient was receiving chemotherapy for pulmonary metastases. The patient died 3 years later due to a massive pulmonary embolism.

**Conclusion:** To our knowledge, this is the first report of a lower extremity leiomyosarcoma metastatic to a benign thyroid nodule. Although metastasis of an extra-thyroidal malignancy to a pre-existing benign thyroid nodule is very rare, patients with thyroid nodules and a history of malignancy should have regular surveillance of the nodule by ultrasound, and any changes in the nodule features concerning for malignancy should be evaluated with FNA of the nodule.

1. Chung, A. Y., Tran, T. B., Brumund, K. T., Weisman, R. A., & Bouvet, M. (2012). Metastases to the thyroid: a review of the literature from the last decade. *Thyroid*, *22*(3), 258-268.

# Reproductive Endocrinology

## BASIC MECHANISMS IN REPRODUCTION: FROM BEGINNING TO END

### *Modeling Uterine Disorders Utilizing Adult Uterine Stem Cells*

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**OR20-04**

Endometriosis and uterine fibroids (leiomyomas) are benign gynecological disorders affecting 5-15% of women of reproductive age. They cause a wide range of symptoms including

mild to severe pelvic pain and infertility. Due to a paucity of proper study models, hormonal and cellular mechanisms driving the pathology of endometriosis and fibroid development and growth remain unclear. Therefore, in the current study, we established 3D spheroid/organoid cultures from human uterine epithelial and Stro-1+/CD44+ myometrial stem cells and also from cells isolated from normal proliferative phase endometrium. Uterine organoid cultures were derived from endometrial epithelial and myometrial cells isolated from women who were not receiving exogenous hormones at the time of laparoscopy or hysterectomy. They were embedded in Matrigel, and grown in culture media. To determine whether spheroids/organoids were responsive to steroid hormones, the cultures were treated in presence or absence of estradiol (E2), progesterone (P4) or the combination (E2+P4) in serum free culture media. Time-dependent spheroid/organoid-growth curves and morphological analyses were used to define growth characteristics of endometrial and myometrial organoids. Subsequently, immunohistochemical colocalization of steroid hormone receptors (estrogen receptor alpha (ER-α) and progesterone receptor (PR-A\B), alpha smooth muscle actin (α-SMA; myometrial cell marker), vimentin (stromal cell marker) and E-cadherin (endometrial epithelial cell marker) was assessed. Epithelial organoids expressed only E-cadherin in the absence of hormonal treatment. Myometrial organoids expressed α-SMA and vimentin. No expression of E-cadherin was observed in myometrial organoids. However, we observed the expression of ER-α and PR-A\B when organoids were treated with E2+P4 in a time-dependent manner. Stro-1+/CD44+ myometrial stem cells differentiated into α-SMA and fibroblast/stromal cells and response to sex hormones. These findings suggest human uterine organoid cultures retained their characteristic cellular responses to E2+P4 and could be maintained long-term in *ex vivo* culture. Thus, the current 3D uterine organoid systems show high expansion capacity with retention of phenotypical and functional properties, which can be used for uterine pathophysiological studies, drug discoveries and drug repositioning.

# Thyroid

## THYROID DISORDERS CASE REPORTS III

### *Impaired Sensitivity to Thyroid Hormone - A Diagnostic and Therapeutic Challenge*

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**MON-478**

**Background:** Impaired sensitivity to thyroid hormone refers to any process that negatively affects its action, including defects in its transport, metabolism and action on the receptor. Resistance to thyroid hormone due to beta-receptor mutations (RTH-beta) is the most common form of this entity and is characterized by reduced response of peripheral tissues to the action of thyroid hormone. The genetic variability of cofactors involved in the action of thyroid hormone explains the heterogeneity of resistance among affected individuals. Generally, patients with this disorder, have increased levels of free T4 and free T3 in association with normal or high TSH. **Clinical case:** 11-year-old boy, with personal history of Attention-deficit/hyperactivity disorder (ADHD). A pediatric endocrinology consultation was requested to evaluate abnormalities in his thyroid function tests. A few months earlier, his father was referred to endocrinology consultation because of thyroid function tests abnormalities: TSH - 3.01 µIU / mL (N: 0.35 - 4.94); Free T4 1.7 ng / dL (N: 0.7-1.48); Free T3 4.77 pg / mL (N: 1.71-3.71). Initially, two diagnostic hypotheses were considered: central hyperthyroidism or impaired sensitivity to thyroid hormone. The adult underwent pituitary magnetic resonance, which raised the hypothesis of a pituitary microadenoma, and TRH stimulation test, whose result was strongly suggestive of the second diagnostic possibility. A genetic study was requested and the presence of the c700 G> A variant (p. Ala 324 trh) in the THRB gene was identified, which confirmed the most likely hypothesis. At the time of the pediatric endocrinology consultation, the 11-year-old boy had the results of his lab tests: TSH - 6.67 µIU / mL (N: 0.35 - 5); T4L 2.27 ng / dL (N: 0.88-1.58); T3L 7.79 pg / mL (N: 2-4.20). Given his perfect height and weight evolution and the absence of symptoms suggestive of hypo or hyperthyroidism, it was decided not to start any medication, keeping only periodic surveillance. **Conclusion:** This case exemplifies unusual thyroid function tests. This discordance between serum thyroid hormone and TSH concentrations should raise the possibility of impaired sensitivity to thyroid hormone. In this condition, patients may present with symptoms of hypo or hyperthyroidism and the etiology of thyroid function tests abnormalities are not easily recognized. This can lead to misdiagnosis and consequently unnecessary treatment.

# Diabetes Mellitus and Glucose Metabolism

## CLINICAL AND TRANSLATIONAL STUDIES IN DIABETES

### *Are Hospitals Doing Enough in Caring for Patients with Diabetes?Results of a Landmark Survey: Current State of Inpatient Diabetes Care and Glycemic Management*

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**MON-664**

BACKGROUND

On average, 1 of every 3 hospitalized patients — the majority with diabetes — requires insulin to control blood glucose during their stay. Although widely prescribed and absolutely necessary, insulin is inherently dangerous: 50% of all medication errors involve insulin, including 1/3 of all fatal medication errors. Results of a nationwide survey indicate that prioritization of glycemic control is lacking, which hinders high reliability and increases risk of morbidity and mortality.

METHODS