the association of adrenal insufficiency with NLRP1 mutation. Furthermore, the symptoms of
adrenal insufficiency and myopathy can overlap making it difficult to delineate. While so far
most studies have dealt with mitochondrial myopathies due to deletions or point mutations in the
mitochondrial deoxyribonucleic acid (DNA), a new field of investigation is that of syndromes
due to mutations in the nuclear DNA.

Thyroid

THYROID CANCER CASE REPORTS I

Combined Treatment with Laser Ablation and Tyrosin Kinase Inhibitors. a Novel Multimodality Approach to Locally Advanced Thyroid Cancer?

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SUN-485

Background. Direct loco-regional treatments are considered for local control of cervical metastasis of thyroid cancer. In our feasibility study, laser ablation was employed for initial debulking of an unresectable radioiodine-refractory thyroid cancer in a combined treatment with tyrosin kinase inhibitors (TKI).

Clinical case. On June 2016, a 69-year-old woman underwent partial resection of a papillary thyroid cancer with extensive tracheal infiltration. On August 2016, whole body scan performed after 131-I treatment (8140 MBq) demonstrated nearly absent thyroid bed uptake. Due to progressive increase of the cervical mass, the patient experienced dysphonia and dysphagia and, after multidisciplinary consultation, was treated with laser ablation (LTA). After local anesthesia, two 300 nm fiberoptics were inserted into the lesion through 21G spinal needles. Two illuminations with 4-watt output power and 3600 Joules energy delivery were peformed with a diode-laser source. LTA resulted in rapid mass volume decrease (28 x12 x16 mm, 2.8 mL, vs 52 x 29 x 29 mm, 22.7 mL) and improvement of pressure symptoms that lasted 6 months. In May 2017, due to initial regrowth of the tumor mass, the patient started therapy with Lenvatinib, at 10-24 mg/day. The cervical tumor burden remained controlled until April 2019, when occurred rapid disease progression and death of the patient.

Discussion. These preliminary results suggest that locally-advanced unresectable and radioiodine-refractory thyroid tumors can be managed with preliminary LTA mass debulking, for rapid control of local disease, followed by long-term TKI treatment.

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Genetics and Development (including Gene Regulation)

G PROTEIN-COUPLED RECEPTOR SIGNALING IN ENDOCRINE SYSTEMS: NOVEL MECHANISMS IN HEALTH AND DISEASE

Ovarian Follicle Survival Is Determined by Follicle-Stimulating Hormone Receptor (FSHR) and Estrogen Receptor (GPER) Heteromers

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Mechanisms regulating the selection of antral ovarian follicles are poorly understood and supposed to rely on low estrogen levels, decline of follicle-stimulating hormone (FSH) levels and receptor (FSHR) expression. These concepts are challenged *in vitro*, where apoptosis of human granulosa cells (hGLC) and transfected cell lines is induced by high doses of FSH or FSHR overexpression, while estrogens induce anti-apoptotic signals via nuclears and a G protein-coupled estrogen receptor (GPER). Therefore, *in vitro* data suggest that antral follicle selection may be driven by underestimated, FSH/FSHR-dependent apoptotic signals due to transiently maximized FSHR expression and overload of cAMP signalling, prevailing on estrogen-dependent signals. Here we demonstrate how FSHR/GPER physical interaction rescue ovarian follicles from FSH-mediated death. 10 nM FSH induces high intracellular levels of cAMP, measured by bioluminescence resonance energy transfer (BRET), and apoptosis in cultured hGLC under conditions where GPER levels are depleted by siRNA. This result was confirmed in transfected HEK293 cells overexpressing FSHR. Using BRET, photo-activated localization microscopy (PALM) and bioinformatics prodiction, we also demonstrate FSHR/GPER heteromers at the cell surface. The role of FSHR/GPER heteromers may be relevant to inhibit FSH-induced death signals, since increasing GPER expression levels in HEK293 cells co-expressing FSHR results in displacement of the Gαs-protein to FSHR, blockade of FSH-induced cAMP production and inhibition of apoptosis. However, in HEK293 cells coexpressing GPER/FSHR, FSH-induced activation of the anti-apoptotic AKT-pathway via a Gβγ-dependent mechanism, as demonstrated by Western blotting in cells treated using the inhibitor gallein. Inhibition of both FSH-induced cAMP production and apoptosis was lost when FSHR is coexpressed together with a mutant GPER, unable to

heteromerize with FSHR, as well as in KO HEK293 cells unable to produce a molecular complex associated with GPER inhibiting cAMP. GPER/FSHR coexpression is confirmed in secondary follicles from paraffin-embedded tissues of human ovary by immunohistochemistry, suggesting that FSHR-GPER heterodimers could be physiologically relevant *in vivo* for inhibiting cAMP-linked apoptosis. Most importantly, FSHR and GPER co-expression correlates in hGLC from FSH-normo-responder women undergoing assisted reproduction, while it is not in hGLC from FSH-poor-responders, where increasing *FSHR* mRNA levels do not correspond to increasing *GPER* mRNA levels. We demonstrate that death signals in atretic follicles are delivered through overexpressed FSHR and inhibited by FSHR/GPER heteromerization, activating anti-apoptotic pathways. This finding unveils a novel working model of the physiology of dominant follicle selection and the relationship between FSH and estrogens.

Bone and Mineral Metabolism

CLINICAL ASPECTS OF OSTEOPOROSIS AND VITAMIN D ACTION

Vitamin D Metabolism in Patients with Acromegaly: A Case-Control Pilot Study

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MON-390

Objective: to study the differences in the metabolism of vitamin D and calcium-phosphorus metabolism in patients with an active phase of acromegaly in comparison with healthy individuals. Materials and methods: The study included 8 patients with an active acromegaly, median age 36.5 ± 6.25 years, BMI 27.9 ± 1.95 kg/m2, IGF-1 907.3 ± 239 ng/ml, as well as 8 conditionally healthy individuals selected by age, sex and level of 25(OH)D determined by the immunochemiluminescent method (DEQAS certified). All participants were tested for calcium-phosphorus metabolism, PTH, and vitamin D metabolites by HPLC/MS-MS (25(OH)D3, 25(OH)D2, 3-epi-25(OH)D3 and 24,25(OH)2D3) before oral administration of 150 000 IU of an aqueous solution of cholecalciferol and 7 days after administration. Results: In the Acromegaly group, on the 7th day after taking the drug, there was a statistically significant increase in 25(OH)D3 (89.8 ± 10.5 vs. 54.1 ± 14.8 nmol/L), 3-epi-25(OH)D3 (9.0 ± 2.6 vs. 3.3± 1.1 nmol/L) and 24,25(OH)2D3 (8.3 ± 1.9 vs. 6.4 ± 2.1 nmol/L), and a decrease of 25(OH)D2 (0.8 ± 0.2 vs. 1.1 ± 0.3 nmol/L) and a ratio of 24,25(OH)2D3 to 25(OH)D3 (0.1 ± 0.02 vs. 0.13 ± 0.03). A statistically significant increase in albumin-adjusted calcium was also noted (2.39 ± 0.14 vs. 2.31 ± 0.13 mmol/L). The medians of the levels of PTH and phosphorus initially were 27.1 ± 13.5 pg/ml and 1.6 ± 0.3 mmol/l and did not change by day 7 after taking the drug; creatinine and magnesium levels also remained the same. The level of calcium-creatinine ratio in a single portion of urine (CCR) was initially within the reference interval for all patients, its median did not change by day 7, however, in two patients there was a clinically insignificant increase higher than the upper limit of the reference interval; the phosphorus-creatinine ratio in a single portion of urine increased significantly. In the control group, after taking cholecalciferol similar changes in the levels of the studied vitamin D metabolites were observed, the levels of PTH also remained the same, however, there were no changes in the median biochemical parameters of blood and urine by day 7 after drug intake. Among the studied vitamin D metabolites, there were initially no significant differences between the groups; on day 7 a difference was recorded for the level of 3-epi-25(OH)D3 (9.0 ± 2.6 in the Acromegaly group vs. 18.8 ± 8.9 nmol/L in the control group). Among the biochemical parameters in the Acromegaly group higher levels of ionized blood calcium (1.14 ± 0.05 vs 1.1 ± 0.03 mmol/L), blood phosphorus (1.61 ± 0.26 vs 1.15 ± 0.09 mmol/L) and CCR were observed. Conclusion: Loading dose of cholecalciferol in patients with acromegaly is associated with less production of 3-epi-25(OH)D3, and results in lower inactive fraction of vitamin D than in healthy controls. More studies are needed to evaluate the effect of 1.25(OH)2D3 level on calcium-phosphorus metabolism in acromegaly.

Genetics and Development (including Gene Regulation)

G PROTEIN-COUPLED RECEPTOR SIGNALING IN ENDOCRINE SYSTEMS: NOVEL MECHANISMS IN HEALTH AND DISEASE

USP8 Genetic Variants May Contribute to the Development of Bilateral Adrenal Hyperplasia and ACTH-Independent Cushing Syndrome

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Background: Bilateral adrenocortical hyperplasias (BAHs), including primary pigmented nodular adrenocortical disease (PPNAD), isolated micronodular adrenocortical disease (iMAD) and primary macronodular adrenocortical hyperplasia (PMAH), are rare causes of ACTH-independent Cushing syndrome (CS). PPNAD and iMAD usually present in children or adolescents as multiple small (<1cm), cortisol-producing adrenocortical nodules. On the other hand, PMAH is most frequently identified in older patients with multiple large adrenal nodules. Most patients with PPNAD have *PRKAR1A* mutations whereas patients with PMAH may harbor variants in other genes (*ARMC5, MC2R, GNAS, APC, MEN1).* Even though several genes have been associated with ACTH-independent CS, there are still cases that the genetic cause has not been elucidated.

Clinical cases: Herein, we present two unrelated patients with ACTH-independent CS that harbor *USP8* gene variants. *USP8* is mainly known for being mutated in Cushing disease but as a deubiquitinase it may be involved into the Wnt/β-Catenin signaling pathway.

The first patient was diagnosed with BAH on prenatal ultrasound (26 gestational week) and subsequently required