therapy-resistant tumors. Progesterone receptors (PR) are known drivers of normal stem and breast CSCs. Our objective was to define novel signaling pathways governing cell fate transitions involved in driving therapy resistance in ER+ breast cancer. We reported that cytoplasmic complexes composed of steroid receptor (SR) co-activators, PELP1 and SRC-3, drive breast CSC outgrowth. SRC-3 knockdown abrogated PELP1-induced CSC expansion and target genes required for cell survival, suggesting an essential role for PELP1/SRC-3 complexes. PELP1 also forms a signaling and transcriptional complex with ER and PR-B. Phospho-PR species are key mediators of stemness in ER+ breast cancer models. Accordingly, PR knockdown and antiprogestins disrupted PELP1/SRC-3 complexes and blocked PELP1-induced breast CSC outgrowth. Mammary stem cell (MaSC) populations were increased *in vivo* in MMTV-tTA;TRE-cyto-PELP1 transgenic mice as well as in MMTV-tTA;TRE-hPR-B mice. To better understand PELP1-mediated pathways, we performed RNA-seq on MCF-7 PELP1+ models grown in tumorsphere conditions to enrich for CSC populations (ALDH+, CD44+/CD24-). Cytoplasmic PELP1-expressing cells had a different global gene profile relative to WT PELP1 (i.e. nuclear). Gene sets associated with stem cell biology, hypoxic stress, and cancer metabolism were differentially regulated, including members of the glycolytic bi-functional kinase/phosphatase PFKFB family. Seahorse metabolic phenotyping demonstrated cytoplasmic PELP1 influences metabolism by increasing both glycolysis and mitochondrial respiration. Cytoplasmic PELP1 interacted strongly with PFKFB3 and PFKFB4, and inhibition of PFKFB3 or PFKFB4 kinase activity blocked PELP1-induced tumorspheres and protein-protein interactions with SRC-3. Additionally, antiprogestin and PFKFB inhibitors were synergistic when combined with ER+ targeted therapies. These aspects of PELP1/SRC-3 biology were phenocopied in therapy resistant models (tamoxifen resistant [TamR], paclitaxel resistant [TaxR]). Together, our data suggest that PELP1, SRC-3, PR, and PFKFBs form complexes that reprogram cellular metabolism to drive breast CSC expansion. Identifying the mechanisms that regulate recurrent ER+ tumor cell populations will enable specific targeting within heterogeneous breast tumors and may lead to the development of non-ER targets that can be used in combination with endocrine treatments to overcome therapy resistance.

Adrenal

ADRENAL MEDICINE — CLINICAL APPLICATIONS AND NEW THERAPIES

Morning ACTH Levels as a Reliable Biomarker for Excluding Autonomous Cortisol Secretion in Incidetally Discovered Adrenal Adenomas. A Prospective Cohort

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Adrenal incidentalomas are common with a prevalence of 3-10% and in up to 30% of cases may have probable autonomous cortisol secretion. Hypercortisolism is associated with substantial cardiometabolic morbimortality and can physiologically decrease ACTH levels.

Objective: To determine the sensitivity, specificity, and positive and negative predictive values of ACTH levels in evaluating autonomous cortisol secretion in a prospective cohort of incidentally discovered adrenal adenomas.

Methods: We prospectively evaluated 224 consecutive adult subjects with incidentally discovered adrenal masses on computed tomography. Finally, 168 participants with radiographic adenoma criteria underwent systematic hormonal assessment, including measurements of morning cortisol and ACTH on day 1, and a 1 mg dexamethasone suppression test (DST) on day 2. Hypercortisolism was excluded if the DST was < 1.8 mcg/dL. Autonomous cortisol secretion was defined as a DST > 5.0 mcg/dL and DST levels of 1.8-5.0 mcg/dL were considered to be possibly autonomous hypercortisolism. We evaluated the correlation of ACTH levels with clinical, radiographic, and endocrine variables. In order to identify the most sensitive threshold value for diagnosing autonomous cortisol secretion, we determined ROC curves and negative likelihood ratio (NLR). Concordance of repeated ACTH was assessed using Bland Altman analysis.

Results: The characteristics of the cohort were mean age 56 (+/- 11.8) years, 76% female, adenoma size 19 (+/- 7) mm, and 13% bilateral adenomas. Mean ACTH was 15 (+/- 11) pg/ml (range 5-72) and the mean DST was 2.2 (+/- 3.0) ug/dL (range 0.4-25.9). Fifty-four (32%) participants had a DST ≥1.8mcg/dL and 13 (8%) a DST≥5.0 mcg/dL. We found no correlation between ACTH levels and age, gender or body mass index. ACTH was inversely associated with adrenal adenoma diameter (r=-3.3 p=0.002) and volume (r=-2.9 p=0.008). There was an inverse association between ACTH and DST values (r=-3.1 p=0.01). In the subgroup of patients with a second ACTH measurement we found high concordance, with mean difference of 0.16+/-3.6 pg/ml (p=0.83). ROC analysis showed that an ACTH ≥20 pg/ml had a sensitivity of 98% to exclude hypercortisolism, with a negative predictive value of 97% and a negative likelihood ratio of 0.06. The only case with DST≥1.8 and ACTH≥20 had Cushing´s phenotype with both an adrenal adenoma and a pituitary ACTH-producing adenoma. Systematic evaluation of morning cortisol and ACTH allowed the detection of 5 cases of false negative low DST values due to the use of non-oral corticosteroids.

Conclusion: In this cohort, an ACTH ≥20pg/ml excluded autonomous cortisol secretion with excellent sensitivity and negative predictive value, providing strong reassurance that there is no clinically relevant hypercortisolism. Therefore, subjects with a normal DST and ACTH ≥20pg/ml should be candidates for relaxed surveillance.

Thyroid

THYROID DISORDERS CASE REPORTS I

Rapid Resolution of Hyperthyroidism Induced Hepatic Dysfunction with Methimazole

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