statistically different expression induced by T3, including known response genes such as *Tshb*, *Hr* and *Gh*. Responses were impaired in *Thrb*-KO mice. T3 induced recruitment of TRb binding, chromatin opening and specific histone acetylation marks. **Conclusion:** Most T3 response genes in pituitary depend to some extent upon TRb. T3-dependent chromatin modifications indicate properties of TRb-dependent enhancer regions and a critical role for TRb in transcriptional regulation of pituitary function.

Thyroid

THYROID HORMONE METABOLISM AND ACTION

Urine Proteomic Analysis of Differences Between Patients With Hyperthyroidism Before and After Carbimazole Treatment

Afshan Masood, MBBS MD.
King Saud University, Riyadh, Saudi Arabia.

Background: Hyperthyroidism, characterised by increased circulating thyroid hormone (TH) levels, alters the body's metabolic and systemic haemodynamic balance and directly influences renal function However, the underlying mechanisms and metabolic implications of these changes are not well understood. **Objective:** In the present study we aimed to study the changes occurring in the urinary proteome of patients with hyperthyroidism before and after treatment. The levels of the excreted proteins in the urine were studied using an untargeted 2D DIGE MALDI TOF proteomic approach with network analysis. **Methods:** The study included 9 age matched patients with mean age 38.6 ± 12.1 years with newly diagnosed hyperthyroidism. The patients were evaluated at baseline and after receiving treatment with carbimazole. Urine samples were obtained from the same patient at baseline (hyperthyroid state) with serum FT4 levels of 35.4 + 9.9 pmol/L and TSH 0.014 + 0.014 mIU/L (mean + SD), and post treatment with anti-thyroid drugs (euthyroid state) with levels of FT4 17.0 + 2.8 pmol/L and TSH 0.6 + 0.5 mIU/L (mean + SD). **Results:** Alterations in the abundance of urinary proteins, analyzed by Progenesis software, revealed statistically significant differential abundance in a total of 40 spots corresponding to 33 proteins, 26 up and 7 down (≥1.5-fold change, ANOVA, $p \leq 0.05$). The proteins identified in the study are known to regulate processes related to cellular metabolism, transport, acute phase response. The urinary proteins upregulated with hyperthyroidism included serotransferrin, transthyretin, serum albumin, ceruloplasmin, α1B glycoprotein, syntenin-1, nesprin, and glutamilnyl peptide cyclotransferase while the 3 notable down regulated proteins were plasma kallikrein, protein glutamine gamma-glutamyl transferase and serpin B3. Bioinformatic analysis using Ingenuity Pathway Analysis (IPA) identified dysregulation of pathways related to cellular compromise, inflammatory response, cellular assembly and organization and identified the involvement of the APP and AKT signaling pathways via their interactions with interleukins as the central nodes. **Conclusion:** The urine proteomic profiling between the hyperthyroid and euthyroid states demonstrates alteration in the protein levels involved in acute phase response and in maintaining an individual's haemodynamic state.

Tumor Biology

EMERGING MECHANISMS AND THERAPIES IN ENDOCRINE-RELATED TUMOR BIOLOGY

ERa-Dependent Lethal Hyperactivation of the Anticipatory Unfolded Protein Response Induces Complete Regression Without Recurrence of Advanced Breast Cancer

Darjan Duraki, BS Biochemistry[1], Matthew Boudreau, BS[1], Lawrence Wang, BS[1], Chengjian Mao, PhD[1], Bingtao Tang, PhD[1], Liqian Ma, BS[1], Edward Roy, PhD[1], Timothy Fan, DVM, PhD[1], Ben Ho Park, MD, PhD[2], Erik Russell Nelson, BSc,PhD[3], Paul Hergenrother, PhD[1], David J. Shapiro, PhD[4].
[1]University of Illinois at Urbana-Champaign, Urbana, IL, USA, [2]Vanderbilt University Medical Center, Nashville, TN, USA, [3]University of Illinois at Urbana-Champaign, Champaign, IL, USA, [4]University of IL, Urbana, IL, USA.

Metastatic estrogen receptor α (ERα) positive breast cancer is presently incurable and most patients die within 7 years. From a medicinal chemistry program, we identified a novel small molecule that acts through ERα to kill breast cancer cells and often induces complete regression without recurrence of large, therapy-resistant primary breast tumors and of lung, bone, and liver metastases. We exploited our finding that estrogen-ERα activates an extranuclear tumor-protective, signaling pathway, the anticipatory unfolded protein response (UPR). We repurposed this tumor protective pathway by targeting it with the small molecule, ErSO. ErSO kills cancer cells by acting non-competitively through ERα to induce lethal hyperactivation of the anticipatory UPR (a-UPR), triggering rapid necrotic cell death. Using luciferase to image primary tumors and metastases containing lethal ERαD538G and ERαY537S mutations seen in metastatic breast cancer, oral and injected ErSO exhibited unprecedented antitumor activity. In mouse xenografts bearing large breast tumors, oral and injected ErSO induced complete regression (>115,000 fold mean regression) in about 45% of mice (18/39). Although durable response without treatment for 4-6 months was common, tumors that did recur remained fully sensitive to ErSO re-treatment. Consistent with the essential nature of the a-UPR pathway targeted by ErSO, in more than 100 tumor-bearing mice, we have never seen an ErSO-resistant tumor. In just 7 days, oral ErSO induced complete regression of most lung, bone, and liver metastases. ErSO is well-tolerated in mice and blood-brain-barrier penetrant. Injected ErSO induced profound regression of challenging brain tumors. On average, ErSO-treated tumors were >180-fold smaller than vehicle-treated tumors. Moreover, use of ErSO is not limited to breast cancer. With its unique mechanism of action through the a-UPR, ErSO eradicated orthotoptic ERα positive ovarian tumors that do not require estrogen for growth. These xenograft studies used human cancer cells in immune compromised mice and therefore did not exploit the known ability of inducers of necrotic cell death to activate immune cells and induce immunogenic cell death. Notably, medium from breast cancer cells killed by ErSO contained high levels of the established immune cell activators, HMGB1 and ATP, robustly activated mouse and human macrophages and increased macrophage migration. ErSO's potent activity against advanced primary and metastatic ERα-positive breast cancers represents a paradigm shift in leveraging ERα for anticancer efficacy.