

Bone and Mineral Metabolism

BONE DISEASE FROM BENCH TO BEDSIDE

Physical and Cognitive Functioning Before and Six Months After Initiating Enzyme Replacement Therapy for an Adult with Hypophosphatasia: A Case Study

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We present changes on physical therapy (PT), occupational therapy (OT), and speech-language pathology (SLP) assessments for a patient pre- and 6 months post-initiation of recombinant alkaline phosphatase therapy for hypophosphatasia (HPP).

Our patient is a 30-year-old male diagnosed with pediatric onset HPP at the age of 28. Features of his HPP include skull deformities and scoliosis noted as a toddler, early loss of primary dentition with the root intact prior to the age of 4, severe bone and muscle pain described as “severe growing pain”, and fatigue as a teenager. He was noted to have arthritis in his feet requiring surgical fusion, which was complicated by nonunion. By the age of 30, he required the use of assistive devices for ambulation due to fatigue and pain. Biochemistry was notable for ALP 17U/L (40-150), serum PLP 241 mcg/L (5-50), urine phosphethanolamine 47 nmolmgCr (0-27), and genetic testing demonstrated a variant of undetermined significance of *ALPL* genet (Het. C.1364G>A p.Gly455Asp).

PT and OT assessments included a thorough musculoskeletal and neurologic examination, as well as functional testing of mobility, balance, motor control, and activity of daily living tasks. After 6 months of enzyme replacement therapy (ERT), the patient's scores on measures of body structure and function were grossly unchanged or diminished (muscle strength). However, activity-based measures of functional performance generally improved on ERT. Performance on the Five Times Sit to Stand Test (FTSTS), gait speed, Functional Gait Assessment, Sensory Organization Test, and Six-Minute Walk Test (6MWT) improved. His most significant improvements were on the FTSTS and 6MWT; his FTSTS improved from 15.4 seconds to 9.1 seconds, surpassing the cut-off for falls risk (12s), while his 6MWT improved from 1,228 feet to 1,541 feet, surpassing the minimal detectable change for individuals with osteoarthritis (201 ft).

Cognitive testing revealed improvement in delayed memory (e.g., word-list recognition, story-retell) on the Repeatable Battery of the Assessment of Neuropsychological Status from baseline (7thtile) to 6 months post therapy (47thtile). He also demonstrated improvement in Trail Making Part A [TM A, cognitive processing speed] & TM B (executive functioning) from baseline (45s, 49s) to 6 months post therapy (21s, 38s). Mean performance on TM A&B for adults 25-34 yrs is 24.4s±8.71 and 50.7s±12.4, respectively. Overall, the patient demonstrated improvement in delayed memory, cognitive processing speed and executive functioning on ERT. Additionally, while his performance on bedside

impairment-based testing generally declined or remained unchanged, his performance on standardized functional assessments improved on ERT. These functional improvements in physical and cognitive domains likely enable the patient to more fully participate in life roles to improve quality of life.

Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

Analysis of Divergent Long Noncoding RNAs in Estrogen-Regulated Transcription

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The role of long noncoding RNAs (lncRNAs) in cancer biology are just beginning to be elucidated and recent studies have shown that they could be therapeutic targets. In a previous study, combining powerful techniques, Global Run-On sequencing (GRO-seq) and subcellular fractionation RNA-seq in breast cancer cells identified a large number of estrogen-regulated unannotated long noncoding RNAs. Analysis of gene expression data from hundreds of samples representing 13 different tissue types including both cancer and normal tissue, revealed that many lncRNAs are differentially expressed in various cancers. Furthermore, a large number of lncRNAs are divergent transcripts and show distinct expression patterns across molecular subtypes of cancer. In functional assays, knockdown of selected lncRNA, such as lncRNA67, inhibits the growth of breast cancer cells. Amplified expression of lncRNA67 in luminal-subtype of breast cancer correlates with clinical outcome. lncRNA67 has now been fully annotated (transcription start and stop site, 5' cap, polyA tail, and exon/intron structure), and cloned. Our preliminary molecular analyses indicate that lncRNA67 plays a critical role in ER-dependent and -independent pathways. Collectively, our results suggest that lncRNAs are an integral component of cancer biology.

Thyroid

THYROID NEOPLASIA AND CANCER

Determining Novel Therapeutic Targets Using an in Vitro Model of TRb Tumor Suppression in Anaplastic Thyroid Cancer

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Anaplastic thyroid cancer (ATC) is one of the most lethal endocrine cancers, with an average survival time of six months after diagnosis. These aggressive tumors are characterized by rapid local extension, distant metastasis, and resistance to radioactive iodine therapy and mainstream chemotherapy. There are very limited treatment options for this aggressive form of thyroid cancer, highlighting a need for a deeper understanding of its mechanisms for development of more effective therapies.

Loss of expression of the thyroid hormone receptor beta (TR β) via epigenetic silencing is common amongst solid tumors, including ATC. Despite its recognized role as a tumor suppressor, the mechanisms underlying TR β tumor suppressor activity remain uncharacterized. We previously created a stable ATC cell line with constitutive re-expression of TR β (SW-TR β). These stable cells exhibit a slower baseline growth rate than both the corresponding parental cell line (SW1736) and the stable empty vector control cell line (SW-EV). Since the effects of thyroid hormone treatment on the growth of cancer cells remain unclear, we investigated changes in growth rates of these cells in response to hormone treatment (triiodothyronine (T₃) 10⁻⁸M). While T₃ had no effect on SW-EV cells, the addition of hormone significantly slowed the growth of the SW-TR β cells after two days. With longer exposure to T₃ (five days), the SW-TR β cells exhibited an apoptotic phenotype. We confirmed that the observed cell death was due to induction of apoptosis by assessing caspase 3 cleavage by immunoblot. The parental SW1736 cell line harbors a deleterious p53 truncating mutation, which is maintained in our stable cell lines. Therefore, we hypothesize that this T₃-induced apoptosis is occurring through an alternate, p53-independent, signaling pathway. This prompted us to examine RNA-seq data obtained from these cell lines under similar conditions to identify potential regulators of this response. Interestingly, pathway analysis revealed decreased CDK4/6-mediated cell cycle progression and activation of JAK1/STAT1 signaling upon T₃ treatment. These are novel mechanisms by which activation of T₃-TR β signaling can slow tumor growth and promote apoptosis in p53-deficient cancer cells. Furthermore, these pathways represent novel therapeutic targets specifically for ATC with potential high impact clinical applications.

Adipose Tissue, Appetite, and Obesity NEURAL MECHANISMS OF OBESITY

POMC Expression in GABAergic Neurons Suppresses NPY Overexpression and Restores Food Intake in Obese Mice

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Hypothalamic arcuate proopiomelanocortin (Arc-POMC) neurons are involved in different physiological processes such as the regulation of energy balance, glucose homeostasis and stress induced analgesia. Since these neurons heterogeneously express different biological markers and project to many hypothalamic and extrahypothalamic areas, it is proposed that Arc-POMC neurons could be classified into different subpopulations having diverse physiological roles. The

aim of the present study was to characterize the contribution of the subpopulation of Arc-POMC neurons co-secreting gamma-aminobutyric acid (GABA) neurotransmitter in the control of energy balance. Arc-Pomc expression restricted to GABAergic-POMC neurons was achieved by crossing a reversible Pomc-deficient mouse line (arcPomc^{-/-}) with a tamoxifen-inducible Gad2-CreER transgenic line. Tamoxifen treatment of arcPomc^{-/-}:Gad2-CreER mice at P60 resulted in Pomc expression in ~25 % of Arc-POMC neurons and ~23 % of Pomc mRNA levels, compared to Gad2-CreER control mice. Rescued mice normalized food intake, glycemia and fasting-induced hyperphagia, and significantly reduced body weight. Energy balance was also improved in arcPomc^{-/-}:Gad2-CreER mice treated with tamoxifen at P25. Distribution analysis of rescued POMC immunoreactive fibers revealed that the DMH is a major target site of GABAergic-POMC neurons. Interestingly, the expression of the orexigenic neuropeptide Y (NPY) in the DMH was increased in arcPomc^{-/-} obese mice but completely restored after Pomc rescue in arcPomc^{-/-}:Gad2-CreER mice. Finally, we performed stereotactic intracerebral injections of fluorescent retrobeads into the DMH followed by in situ hybridization for Gad1 and found that ~75 % of Arc-POMC neurons projecting to the DMH are GABAergic. In conclusion, in the present study we show that the expression of Pomc in the subpopulation of Arc-GABAergic-POMC neurons is sufficient to maintain normal food intake. In addition, we found that DMH-NPY expression is negatively correlated with Pomc expression in GABAergic-POMC neurons, suggesting that food intake may be regulated by an Arc-GABAergic-POMC --> DMH-NPY pathway.

Steroid Hormones and Receptors STEROID AND NUCLEAR RECEPTORS

The Role of Chromatin-Associated LncRNA161 in Estrogen-Dependent Transcription

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Abstract: Long noncoding RNAs (lncRNAs) have been identified to play a role in the progression of many different types of cancer. Some biological processes that are involved with lncRNA include but are not limited to chromatin organization, transcriptional and post-transcriptional gene expression, and protein and transcript trafficking. When lncRNAs are aberrantly expressed, disruption in the biological processes can cause tumor proliferation and progression leading to cancers. Studies have shown the role of lncRNAs in association with breast cancers. While estrogen receptor alpha positive (ER α +) breast cancer responds well to anti-estrogen treatment, the cancer can become