department, he was tachycardic at 116 bpm, widened pulse blood pressure of 131/50 mmHg with normal respiratory rate 24 BR/min. He had diffused and significant muscle weakness on his all extremities including grip strength.
His potassium was 1.6 mmol/L (3.5 - 5.2) and magnesium 1.6 mmol/L (1.6-2.3). The rest of his chemistry panel was unremarkable. He had EKG changes consistent with hypokalemia with U waves, also revealing atrial rhythm with first degree AV block, intraventricular conduction delay, and QTc prolongation at 588 (<450). His chest x-ray was normal. Normal saline was
administered, and potassium replacement was given with 40 mEq of KCl followed by D5 NS with 40 meq/L KCl at maintenance. He continued taking atenolol and methimazole. He was also given an IV dose of magnesium. His muscle strength returned completely and potassium level returned to normal range at 4.6 mmol/L after 24 hours of treatment.
Conclusion: TPP is a rare cause of acute paralysis and can lead to cardiac arrhythmia and death without accurate diagnosis and prompt treatment. Our case should raise awareness of this disorder among pediatricians, emergency department physicians and endocrinologists. Acute paralysis with hypokalemia should also prompt the physician to consider evaluating thyroid function as a differential diagnosis in young Asian men.

Tumor Biology

NOVEL REGULATORS OF BREAST CANCER PROGRESSION

Lethal ERα-Dependent Hyperactivation of the Unfolded Protein Response Induces Complete Regression Without Recurrence of Primary and Metastatic Breast Cancer

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OR05-05
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. To target metastatic ERα positive breast cancer, 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, 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 for 4-6 months without additional treatment was common, tumors that did recur remained fully sensitive to ErSO re-treatment. Consistent with the essential nature of the 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. These xenograft studies used human cancer cells in mice that lack a functional immune system 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 immune cell activators, robustly activated mouse and human macrophages and increased macrophage migration. Moreover, use of ErSO is not limited to breast cancer. ErSO rapidly kills ERα positive ovarian and endometrial cancer cells that do not require estrogen for growth. ErSO's potent activity against advanced primary and metastatic ERα-positive breast cancers represents a paradigm shift in leveraging ERα for anticancer efficacy.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS I

Severe Primary Hyperparathyroidism, Hypercalcemic Crisis, Acute Pancreatitis and Fatality: Complications of Atypical Parathyroid Adenoma, a Case Report

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SAT-352
Background: Atypical parathyroid adenomas (APAs) are a controversial and rare entity. These tumors show some features of carcinomas including adherence to adjacent structures, banding fibrosis, mitotic activity, and tumor cells trapped within capsule; however, they lack definitive capsular, vascular, or perineural invasion. Patients are often asymptomatic, or have vague symptoms such as fatigue. Studies and literature have reported that the elevation in parathyroid hormone (PTH) and calcium levels in APAs are intermediate between those of adenomas and carcinomas, and that the clinical course is generally benign. **Clinical Case:** A 41-year old woman with diabetes mellitus, Hashimoto's thyroiditis, and obesity was noted to have mild asymptomatic hypercalcemia during routine tests performed at an outside hospital several months prior to presentation. A few weeks prior to presentation, she started complaining of anorexia, nausea, vomiting and abdominal pain. At the time of presentation, she was critically-ill with

a picture of severe acute pancreatitis. Laboratory tests showed hypercalcemia (13.9 mg/dL, normal 8.5-10.6 mg/dL) and elevated lipase (1134 U/L, normal 13-60 U/L); however, a magnetic resonance cholangiopancreatography showed no biliary obstruction. Further testing revealed markedly elevated PTH (>5000 pg/ml, normal 15-65 pg/ml), and subsequent neck ultrasound showed a solitary mass on the left side of the neck. Despite maximum medical treatment, the patient continued to rapidly decompensate and passed away rapidly. Autopsy examination revealed a picture of severe acute pancreatitis including a markedly enlarged necrotic pancreas (360 grams, normal: 60-100 grams), extensive omental fat necrosis, ascites, and dusky discoloration of the abdominal organs. A well-circumscribed mass (6.6 x 3.5 x 1.5 cm) was found on the superior aspect of the left thyroid lobe. The tumor showed parathyroid cell proliferation admixed with banding fibrosis, no unequivocal invasion into the surrounding capsule, blood vessels or perineural spaces, and no evidence of lymph node involvement or distant metastasis, consistent with a diagnosis of APA. Her cause of death was the left neck APA and its associated sequelae of significant hypercalcemia and acute pancreatitis. **Conclusion:** This patient had asymptomatic hypercalcemia for months prior to presentation with PTH/hypercalcemic crisis, highlighting the importance of ruling out primary hyperparathyroidism in the assessment of patients with asymptomatic hypercalcemia. While it's generally appreciated that parathyroid carcinomas usually cause more profound hypercalcemia and are more likely to cause fatality from metabolic complications, and that APAs follow a generally more benign course, this case shows that APAs can grow into significantly large lesions and could follow a severe and abrupt clinical course if not surgically removed.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

Single-Cell Sequencing Identifies Novel Regulators of Thyrotrope Populations and POU1F1-Independent Thyroid-Stimulating Hormone Expression

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OR16-05

We implemented single-cell RNA sequencing (scRNAseq) technology as a discovery tool to identify factors enriched in differentiated thyrotropes. Thyroid-stimulating hormone (TSH) is produced in the pars distalis of the anterior pituitary (AP) and primarily acts on the thyroid gland to regulate metabolism through T3/T4. However, TSH is also produced by cells in the pars tuberalis (PT), which is comprised of a thin layer of cells that extends rostrally from the pars distalis along the pituitary stalk to the median eminence in the hypothalamus. TSH produced by PT thyrotropes acts on hypothalamic tanycytes to regulate seasonal reproduction. PT thyrotropes likely descend from rostral tip thyrotropes that arise at e12.5 of mouse development, which transcribe the TSH beta subunit (*Tshb*) without detectable expression of the transcription factor POU1F1. POU1F1 is required for *Tshb* transcription in thyrotropes of the adenohypophysis, and it acts synergistically with GATA2 to drive cell fate. The molecular mechanisms driving *Tshb* expression independently of *Pou1f1* in PT thyrotropes are unclear.
Thyrotropes are the least abundant endocrine cell-type in the pituitary gland. We used genetic labeling and fluorescence-activated cell sorting (FACS) to enrich for thyrotropes for single-cell sequencing. We performed scRNAseq on 7-day-old GFP-positive pituitary cells from *Tshb-Cre; R26-LSL-eYFP* and intact whole pituitaries, recovering more than 15,000 cells altogether. We observe two distinct populations of cells expressing *Tshb*. The larger thyrotrope population has approximately twenty fold higher levels of *Tshb* and five fold higher *Cga* transcripts than the smaller population, and they are also distinguished by expression of *Pou1f1*, TSH-releasing hormone receptor (*Trhr*), and deiodinase 2 (*Dio2*), consistent with expectations for AP thyrotropes. The smaller thyrotrope population does not express *Pou1f1,* but those cells are characterized by expression of TSH receptor (*Tshr*) and melatonin receptor 1A (*Mtnr1a*), consistent with expectations for PT thyrotropes. They express mildly increased levels of *Eya3* and *Six1*, although these genes are expressed in other cell-types including AP thyrotropes, stem cells, and gonadotropes. They have two-fold higher levels of *Gata2* transcripts and uniquely express the transcription factor *Sox14.* SOX14 is a SoxB2 family transcription factor that counteracts the transcriptional activity of SoxB1 family members, such as *Sox2.* In conclusion, our scRNAseq has identified novel markers of PT thyrotropes and unveils novel insights into the similarities and differences in the development and function of pituitary thyrotrope subpopulations.

Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

Familial 46, XY Complete Female External Sex Development with a Non-Mosaic Inherited SRY Gene Variation

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SUN-712

Abstract
Context: SRY, an architectural transcription factor containing a SOX-related high-mobility group (HMG) box, initiates testis formation in the mammalian bipotential gonadal ridge. Inherited human SRY mutations can be associated with differences in sexual differentiation (DSD) with variable phenotypes in a family.