capacity of these stem cell-derived neurons to fully mature and integrate into existing neural circuits of physiological relevance is unknown. This study systematically tested whether *Pomc* mRNA-positive cells newly generated from tanycyte precursors can differentiate into melanocortin-secreting POMC neurons, integrate into the normal anatomical projection pathways of these cells and rescue the obesity phenotype caused by the loss of *Pomc* expression in *ArcPomc*$^{fneo/fneo}$ mice. We generated an inducible compound genetic mouse model by crossing *RaxCreERT2* with the Cre-dependent *ArcPomc*$^{fneo/fneo}$ and *LSL-syp-tdTomato* alleles. *Rax* is expressed exclusively in postnatal tanycytes, thereby limiting tamoxifen-induced recombination of the two floxed alleles by CreERT2 to tanycytes. As expected, tamoxifen treatment of the mice at age 4–5 wk recapitulated endogenous *Rax* expression 16 wk later as observed by red fluorescent tdTomato expression in all tanycytes. In addition, Cre recombinase-mediated deletion of the floxed-neomycin cassette from the neuronal enhancer region of the *ArcPomc*^{fneo} alleles relieved their constitutive transcriptional silencing. Consequently, tamoxifen treatment consistently generated a significant number of newly generated POMC neurons from tanycytes (~10% of the POMC neurons in a WT mouse), identified by *Pomc* FISH and POMC/α-MSH immunofluorescence in the soma and established terminal projections to hypothalamic nuclei including the PVH and DMH involved in energy homeostasis. A subpopulation of these neurons also expressed the synaptophysin-tDTomato reporter. We performed serial body weight, food intake, body composition, oral GTT and insulin measurements with the *RaxCreERT2/+, ArcPomc*$^{fneo/fneo}$ mice and found no significant differences in any of these metabolic variables compared to untreated obese *ArcPomc*$^{fneo/fneo}$ mice. These data are consistent with previous studies from our lab suggesting that *Pomc* expression has to be at least ~30% of normal to mitigate the obesity phenotype in *Pomc*-null mice. In conclusion, we demonstrated that tanycytes are capable of generating mature *Pomc*-expressing neurons in the hypothalamus of adult mice. However, we propose that determining the underlying mechanisms involved in the generation of hypothalamic POMC neurons from tanycytes and interventions to increase their number, might lead to a novel approach to treat obesity. **Nothing to Disclose:** SG, GW, RML, MJL

Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

Distinct Molecular Phenotypes of Non-Diseased Breast Adipose Tissue of Pre-Menopausal Obese and Non-Obese Women May Underlie Differing Breast Cancer Risks

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SUN-126

Obesity is a major risk factor for many chronic diseases including postmenopausal breast cancer. Paradoxically, breast cancer susceptibility is inversely linked to obesity in pre-menopausal women. Adipose tissues are active endocrine organs that play major roles in tumor development and progression; however, fat depots at different anatomical sites are biologically and functionally distinct and their singular influence on breast epithelial biology remains unclear. To study the early events by which breast adiposity may provide a microenvironment predisposing normal breast epithelial cells to tumorigenesis, we collected breast tissue from pre-menopausal (n=10/group) non-obese (NO, BMI=27.6±0.8) and obese (O, BMI=44.5±2.8) women of comparable ages (NO: 36.1± 3.3; O: 40.0±2.0) with no breast cancer and undergoing elective breast reduction surgery. Breast adipose tissue and corresponding glandular cells were analyzed histologically and evaluated for expression of genes (adipokines, cytokines, steroid hormone signaling) by QPCR and proteins (proliferation, apoptosis, inflammation) by IHC. Adipocyte size distributions from NO and O breasts did not differ (P=0.9). However, adipose mRNA levels for pro-inflammatory cytokines (*IL-6, IL-8*, *CSF-1*, *MCP-1*) and adipokines (*LEP*, *CFD*) were higher for O than NO (P<0.05). *AdipoQ*, *ER*-α, and *ER*-β transcript levels were lower for O than NO (P<0.05), while those for *CYP19* and *PTGS2* showed reverse trends (O>NO, P<0.05). In the corresponding glandular cells, NO had higher mRNA levels for *IL-6*, *IL-8*, *ER*-α, and *ER*-β than O (P<0.05). Immunostaining with anti-Ki67 antibodies indicated that O glandular cells were 3-fold less proliferative than those for NO, consistent with their lower *Cyclin D1* mRNA levels (P<0.05). Galectin-1, a pro-fibrotic protein, showed predominant myo- vs. luminal epithelial localization, with staining intensities for O tending to be higher (P=0.07) than for NO. Perilipin immunostaining was specific for adipocytes and did not differ for O and NO. A non-targeted approach using a Human Cytokine Array (R&D Systems) was employed to further evaluate the inflammation status of O vs. NO adipose. The analyses confirmed the higher expression of *IL-8*, *Leptin* and *CFD* (by QPCR) in O vs. NO and identified C-reactive protein, EMMPRIN, Trefoil Factor-3, Cystatin-3 and Macrophage Migration Inhibitory Factor-1 as greater in O than NO (~2-fold). Our findings demonstrate marked differences in gene and protein expression patterns of O and NO breast adipose tissue, which were accompanied by a suppression of proliferation of O relative to NO breast epithelium. We speculate that early exposure of the breast epithelium to a highly inflammatory environment fueled by breast adiposity may promote a *senescent* state that confers protection from pre-menopausal breast cancer.

Bone and Mineral Metabolism

OSTEOPOROSIS: DIAGNOSIS AND CLINICAL ASPECTS

Denosumab Preserves Bone Mineral Density at the Knee in Persons with Subacute Spinal Cord Injury

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SUN-396

Despite clinical strides in the treatment of osteoporosis in several diverse medical conditions, the ability to maintain bone has proven to be exceedingly difficult in individuals with severe immobilization. Fifty to 60% of bone mineral density (BMD) at the epiphyseal and metaphyseal regions of the long-bones of the lower extremities may be lost over the first couple of years after spinal cord injury (SCI). Once a large amount of bone has been lost, it would be challenging to restore BMD, trabecular architectural integrity, and mechanical strength to provide protection against long-bone fractures of the lower extremities. Persons with neurologically complete forms of SCI have marked loss of BMD of the lower extremities, predisposing to fracture, especially at the knee. Denosumab, a commercially available human monoclonal antibody of the IgG_2 immunoglobulin isotype with a high affinity and specificity for binding RANKL to antagonize its action, may provide an immunopharmacological solution to the rapid progressive deterioration of sublesional bone after SCI. Twenty-six patients with motor-complete SCI [International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) grade A and B] were randomized to receive denosumab or placebo at baseline (BL), 6, and 12 months. Ten participants in the denosumab group and 8 participants in the placebo group completed the 18-month clinical trial [ClinicalTrials.gov (NCT01983475)]. Dual energy x-ray absorptiometry (DXA; Lunar Prodigy Advance, all software version 12.20.023; EnCORE, GE Medical Systems, Madison, WI) and peripheral quantitative computed tomography (pQCT; Stratec XCT 3000; STIM designs, Carmel, CA) imaging were performed. Within group paired analysis revealed a significant decrease for areal BMD (aBMD) from BL in the placebo group that started at month 3 for the distal femoral epiphysis (DFE), distal femoral metaphysis (DFM), and total hip (TH) and at month 6 for the femoral neck (FN), and at month 12 for the proximal tibial epiphysis (PTE); the loss in aBMD progressed to 18 months for all the skeletal regions of interest (ROI). At 18 months, the percent change at the ROI for the denosumab vs. placebo groups were: DFE (1.1% ± 7.5 vs. -30.0% ± 11.9, respectively, $p<0.001$ and $p<0.001$), DFM (1.2% ± 6.4 vs. -17.2% ± 14.2, $p<0.01$), TH (3.3% ± 8.7 vs. -25.6% ± 7.6, $p < 0.001$), and PTE (-1.7% ± 8.2 vs. -24.1% ± 12.3, $p<0.001$). At 18 months, pQCT at the 4% tibial region confirmed the DXA findings at proximal tibial; at the 38% tibial region, a trend toward loss of total volumetric BMD (vBMD) was observed (-0.7% ± 4.5 vs. -16.9% ± 20.0, $p<0.09$), but cortical vBMD was similar between the denosumab and placebo groups, suggesting trabecular loss at the tibial shaft. In summary, the findings suggest that denosumab, if treatment is initiated within 3 months of acute SCI, appears to be an efficacious approach to maintain BMD at the knee and hip regions.

Diabetes Mellitus and Glucose Metabolism

CLINICAL STUDIES IN OBESITY, DIABETES RISK, AND CARDIOVASCULAR OUTCOMES

Nattokinase to Improve Insulin Sensitivity and Weight Loss in Women with Obesity +/- Diabetes

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SAT-618

Background: Diabetes (DM) and obesity are related health issues which are increasing in prevalence. But not all obesity is related to DM. Women suffering from Lipedema are categorized as gynoid obese. Nattokinase (Natto) is an enzyme supplement that has been shown to degrade fibrin. Patients with obesity tend to have elevated clotting factors which can lead to adipose tissue hypoxia, impaired insulin signaling, and lead to insulin resistance. Research in fat disorders noted that fat biopsies from women with Lipedema likely had micro-clots, and patients with Lipedema treated with Natto reported a decrease in clothing size and fat distribution. Objective: Determine the effect of Natto on participants with Obesity and DM and in patients with Lipedema without DM. Materials and Methods: Group 1: Involved subjects with Obesity and DM. This was a double blinded, randomized controlled clinical trial over 3 months. A total of 17 female patients were recruited from a rural clinic. Nine received Natto 2,000 FU daily and eight received an identical placebo capsule daily. Fasting labs, questionnaires, bioimpedance, and anthropometric measurements were completed at Baseline and 3 months. Group 2: 42 women with Lipedema seen at a Fat Disorder Clinic. 21 received Natto and 21 did not. We compared for weight only from the day Nattokinase was started until follow-up, which varied from 4 months to 1 year 8 months. Results: Group 1: After 3 months, there was no difference in weight loss in both groups. Per Bioimpedance, more subjects lost water weight in the Natto group (63%) compared to Placebo (33%). More subjects in the Natto group had a decrease in HbA1c (43%) compared to Placebo (22%), with average decrease in the Natto group of 0.9%. Also, more subjects in the Natto group had lower fasting insulin levels (75% vs 22%), lower fasting glucose level (50% vs 22%) and lower HOMA index (63% vs 22%). Group 2: 57% of patients in the Natto group lost weight compared to only 33% of patients not on Natto. Conclusions: In participants with obesity and DM, regardless of weight loss, metabolic health improved after taking Natto for 3 months. Higher percentage of subjects in the treated group had improved HbA1c, fasting Insulin, glucose, and HOMA score. We hypothesize that if treatment time was beyond 3 months, further metabolic improvement would be noted, indicating that Natto could have potential as an adjunct to DM care. The difference in weight loss between Metabolic Obesity and Lipedema reflects the difference in adipose tissue, likely differing in etiology and pathophysiology. Further studies are needed to evaluate long term benefits of Natto, including larger and longer randomized controlled trials, and assessment of clotting factors.

Bone and Mineral Metabolism

BONE AND MINERAL CASE REPORTS I

*Out of Sight, out of Mind: PHEX 3'-UTR C.*231A>G X-Linked Hypophosphatemia in Adults: A Case Study of One Family Pedigree with a Widely Variable Phenotype*

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