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

Iad Alhallak, BSc, Keith G. Wolter, MD, PHD, Frank A. Simmen, PHD, Richard Jon Ward, BSc, Stacy A. Petty, APRN, Rosalia CM Simmen, PHD.
Univ of Arkansas for Med Sciences, Little Rock, AR, USA.

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

William Alan Bauman, MD[1]*, Christopher M. Cirnigliaro, MS*[1]*, Michael F. La Fountaine, EdD*[1]*, Josh Hobson, MS*[1]*, Steven C. Kirshblum, MD*[2]*, Christin McKenna, MD*[3]*, Ann M. Spungen, EdD*[1]*.*
[1]James J. Peters VA Medical Center, Bronx, NY, USA, [2]Kessler Institute for Rehabilitation, East Orange, NJ, USA, [3]Kessler Institute for Rehabilitation, Bronx, NJ, USA.