was stopped at week 24. The main outcome measure was clinical response versus non-response to a 24-week MMI treatment defined as biochemical euthyroidism versus persistent hyperthyroidism at week 24 and/or relapse at weeks 36, 48, and 96. TSAb was reported as percentage of specimen-to-reference ratio (cut-off SRR% <140). Blocking activity was defined as percent inhibition of luciferase expression relative to induction with bovine TSH alone (cut-off >40% inhibition).
Results
Forty-four patients responded to MMI of whom 43% had Graves' orbitopathy (GO) while 56 were non-responders (66% with GO, p<0.01). At baseline, undiluted serum TSAb but not thyroid binding inhibiting immunoglobulins (TBII) differentiated between thyroidal GD only versus GD+GO (p<0.001). Further, at baseline responders demonstrated marked differences in diluted TSAb titers compared with non-responders (p<0.001). All patients with a TSAb dilution titer above three did not respond to MMI treatment. In contrast, TBII dilution titers did not differentiate between responders and non-responders to MMI and serum samples became TBII negative already at low dilutions. During treatment, serum TSAb levels decreased markedly in responders (p<0.001) but increased in non-responders (p<0.01). In contrast, TBII strongly decreased in non-responders (p=0.002). All non-responders at week 24 and/or those who relapsed during the 72-week follow-up were TSAb positive at week 24. A shift from TSAb to TBAb was noted in eight patients during treatment and/or follow-up and led to remission.
Conclusions
Serum TSAb levels are a biomarker for and mirror severity of GD. Their increase during MMI treatment is a marker for on-going disease activity. TSAb dilution analysis had additional predictive value.

Adrenal

ADRENAL - HYPERTENSION

Cosyntropin Stimulation on Adrenal Venous Sampling Obscure Surgically Curable Primary Aldosteronism

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Context: While it has been shown that ACTH stimulation during adrenal venous sampling (AVS) for primary aldosteronism (PA) leads to correct lateralization, others showed opposite results. Whether to use ACTH stimulation during AVS for the subtype diagnosis of PA remains unsolved. **Objectives:** Our purpose of this study is to evaluate the clinical implications of ACTH stimulation during AVS in terms of surgical outcomes. **Design and settings:** Among JRAS cohort, we allocated 314 patients with both basal and ACTH-stimulated AVS data who underwent adrenalectomy to 3 groups: basal lateralization index (LI)≥2 with ACTH-stimulated LI ≥4 on the ipsilateral side (Unilateral (U) to U group, n=245); basal LI <2 with ACTH-stimulated LI ≥4 (n=15); basal LI≥2 with ACTH-stimulated LI <4 (U to Bilateral (B) group, n=54). We compared surgical outcomes among the groups. **Results:** Compared with the U to U group, the U to B group had poor clinical and biochemical outcomes and low rates of adrenal adenoma as a pathological finding. All patients in the U to Bgroup with clinical and biochemical benefits however had adrenal adenoma as a pathological finding and could be well differentiated from those with poor surgical outcome via basal LI, but not ACTH-stimulated LI. A receiver operating characteristic curve analysis demonstrated that the cut-off value of 8.3 showed the specificity of 84% for the prediction of good surgical outcome in U to B group.These results were similar even when we defined each group based on a cut-off value of 4 for basal LI. Although, the basal plasma aldosterone concentration (PAC) in the adrenal veins on both dominant and non-dominant sides among patients with better surgical outcome in the U to B group were not significantly different from those in the U to U group, there was a significant difference in the ACTH-stimulated PAC on the dominant side. **Conclusions:** We demonstrated novel findings showing that patients in the U to B group were shown to be comprised of 2 groups with good and poor surgical outcomes, and basal LI was useful in identifying PA patients with good surgical outcome in U to B group. The low expression level of MC2R receptor on aldosterone-producing adenoma (APA) might be the explanation of the weak response in aldosterone level in a proportion of surgically curable APA cases. These findings point to the important fact that ACTH stimulation on AVS obscure surgically curable cases of PA.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

Metabolic Effects Of Hypothalamic Pomc Neurons Generated Postnatally From Tanycytes On A Pomc Null Genetic Background

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Hypothalamic proopiomelanocortin (POMC) neurons are an integral part of the central melanocortin system and regulate feeding and energy balance in vertebrates. Tanycytes are radial glial-like cells lining the third ventricle that contain a subpopulation of adult stem cells, which can differentiate under specific circumstances into glia and neurons, including POMC neurons. However, the

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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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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