MON-491

Introduction: Most thyroid cancers (TC) are due to mutually exclusive somatic driver mutations. *NTRK* fusions are rare oncogenic drivers in papillary TC (PTC), poorly differentiated TC (PDTC) and anaplastic TC (ATC), estimated to be in 2.3% of all TC. However, the clinical presentation and behavior of TRK-fusion TC remains largely unknown. **Methods / Case Presentation:** Using institutional databases, we identified all TC patients (pts) with an NTRK fusion reported on somatic testing performed by a CLIA-certified laboratory. Data from the medical records were collected. The objective of this study was to investigate the clinical and pathological features of TC pts whose tumors harbored an NTRK fusion. **Results / Discussion:** We identified 36 TC pts with somatic *NTRK* fusions. Fusion testing was generally done in pts with advanced or radioactive iodine refractory (RAI-R) disease. Median age at diagnosis was 27.4 years (range 4–75 years), 21 (58%) were female and 16 (44%) were pediatric. 28/36 (78%) pts had PTC, 2/36 (5%) PDTC and 6/36 (17%) ATC. There were a total of 12 (33%) *NTRK1*, 24 (67%) *NTRK3*, and no *NTRK2* fusions. In ATC and PDTC pts *NTRK3* was the most common *NTRK* fusion 7/8 (87%). In PTC pts, 11 (39%) had *NTRK1* and 17 (61%) had *NTRK3*. In the adult pts *NTRK3* was more common 17/20 (85%) (Odds Ratio 7.2, P=0.013), however, in pediatric pts rate of *NTRK1* and *NTRK3* were similar. One pt had additional mutations along with the *NTRK* fusion, an ATC pt with multiple mutations including *BRAF* V600*E*. Of the 30 PTC/PDTC pts, 23 (77%) had distant metastases (mets). 14 (38%) pts had distant mets at diagnosis and 11 (69%) pediatric pts had distant mets. Lung 21 (70%) and bone 9 (30%) were the most common distant mets sites. In the PTC pts with distant mets, 9 (41%) had RAI-avid and 11 (50%) had RAI-R disease. In the entire cohort of 36 pts, 17 (53%) were on a systemic therapy of whom 11 pts were PTC. *NTRK* directed was the most common systemic therapy 16 (94%). All PTC pts were alive with a median time from diagnosis of 46 months (Interquartile 1–3: 25–118 months). Four ATC and one PDTC pts had died at the time of the analysis. **Conclusions**: In this study we confirmed that *NTRK* fusions occur primarily in PTC but also in less differentiated tumors. Most were young pts but *NTRK* fusions were identified in tumors from adults as old as 75 years. *NTRK1* and *NTRK3* were the most common *NTRK* fusions with *NTRK3* being more common in adults. In thyrocyte-derived TC pts, *NTRK* fusions are mutually exclusive genetic events that occur in pts of all ages and varying histologies. Given the availability of NTRK targeted therapy, consideration should be given to testing for *NTRK* fusions in advanced thyroid cancer pts, especially those in whom prior genetic testing did not identify an oncogenic driver.

Adipose Tissue, Appetite, and Obesity

NEURAL MECHANISMS OF OBESITY

Characterization of Dual Projection Patterns of Refeeding-Activated Neurons in the Parasubthalamic Nucleus

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SAT-605

We have observed that following a fast, animals terminate their food intake within 2h after refeeding accompanied by a pattern of neuronal activation as identified by c-fos immunostaining that involves a number of brain regions associated with the regulation of food intake including the nucleus tractus solitarius (NTS), parabrachial nucleus (PBN), central nucleus of the amygdala (CEA), hypothalamic arcuate and paraventricular nuclei, and bed nucleus of the stria terminalis. We also observed striking c-fos activation in the posterior-lateral hypothalamus called the parasubthalamic nucleus or PSTN, raising the possibility that it may also be an important anorectic center in the brain. To establish how the PSTN is integrated into the CNS, we performed dual-label retrograde tract tracing studies to characterize whether refeeding-activated PSTN neurons project to one, or more than one target area in the CNS. Adult, Sprague-Dawley rats received dual stereotaxic injections of Alexa Fluor 488- and Alexa Fluor 555-conjugated cholera toxin β subunit (CTB; 0.1%, 0.5–1 μl volume) into the 1) PBN and NTS, 2) PBN and CEA and 3) NTS and CEA. After 7–12 days, the animals were fasted for 24 h and then given free access to food for 2 h before euthanasia by transcardial perfusion with 4% paraformaldehyde. Brains with successful dual injections were further processed for c-fos immunohistochemistry. The results showed that 26.5±3.8% of PSTN neurons projecting to the PBN also project to the CEA, and 34.6±7.6% of PSTN neurons that project to the CEA also project to the PBN. In addition, 20.2±2.7% of PSTN neurons that project to the PBN also project to the NTS, and 38.1±9.7% of PSTN neurons that project to the NTS also project to the PBN. Furthermore, 35.0±12.5% of PSTN neurons that project to the CEA project to the NTS and 37.1±4.0% of PSTN neurons that project to the NTS project to the CEA. Finally, up to 15% of the neurons with dual projections to the PBN and CEA contained c-fos after refeeding; up to 18% of the neurons with dual projections to the PBN and NTS contained c-fos; and up to 30% of neurons with dual projections to the NTS and CEA contained c-fos. We conclude that a large number of PSTN neurons have more than one projection site within the brain, thus the PSTN appears to have the capability of simultaneously communicating information about appetite to several, major feeding-related sites within the brain, presumably to terminate feeding.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

Chronic Treatment Of Juvenile Hypothalamic Pomc-deficient Mice With RM-493 Prevents The Development Of Obesity

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SAT-299

Arc-*Pomc* knockout mice have a disruption of the two neural enhancers for the *Pomc* (proopiomelanocortin) gene, resulting in selective loss of *Pomc* gene expression in the

arcuate nucleus of the hypothalamus. This gene targeting strategy leaves pituitary *Pomc* expression unaffected. These mice are hyperphagic starting at weaning, and develop progressive obesity, infertility and insulin resistance over their lifetime. RM-493 (setmelanotide) is a melanocortin-4 receptor agonist that has shown promise in treating humans with *Pomc* null mutations. In this preclinical study, we investigated the effects of chronic RM-493 treatment using subcutaneously implanted osmotic minipumps in two groups of male mice: Arc-*Pomc* knockout mice, fed regular chow throughout the study period, and their wildtype counterparts, fed a 45% high-fat diet. Each of these groups of mice was randomized into three treatment cohorts at weaning: one that was given RM-493 throughout the entire study period (4–24 weeks of age, "RM-493" group), one that was given RM-493 only for the first 4 weeks of the study (4–8 weeks of age, "switch" group) and then switched to vehicle, and one cohort that received vehicle for the entire study ("vehicle" group). We serially measured body weight, food intake, body composition, glucose tolerance, insulin tolerance, and several measures of metabolism using the Comprehensive Lab Animal Monitoring System, including oxygen consumption, energy expenditure, ambulatory activity and lipid and glucose oxidation.

Among other results, at the end of the study (24 weeks of age), Arc-*Pomc* knockout mice in the RM-493 group weighed significantly less than either the switch or vehicle groups ($p<0.05$). Arc-*Pomc* knockout mice on RM-493 also had higher energy expenditure when compared to the switch and vehicle groups ($p<0.05$). In addition, RM-493 improved the glucose-insulin index for Arc-*Pomc* knockout mice ($p<0.05$). According to our preliminary results, wildtype mice on high-fat diet, treated chronically with RM-493, did not differ in any of these measurements from their switch and vehicle groups.

We conclude that the obesity syndrome caused by a loss of hypothalamic *Pomc* expression was completely blocked by RM-493 treatment started before the onset of obesity, with no apparent desensitization to the drug's action over 20 weeks. However, the beneficial effects of a single month's treatment were steadily reversed within one month after switching to vehicle treatment. In contrast to the dramatic effects of RM-493 in the genetic obesity syndrome, at this time, there does not appear to be any phenotypic changes in wild-type mice with RM-493 administration on the development of obesity or secondary metabolic disruptions in response to high-fat diet consumption.

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

Diabetic Amyotrophy; A Rare Cause of Muscle Weakness

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MON-674

Background: Diabetic amyotrophy is a rare complication of type 2 diabetes mellitus. There is little existing evidence contributing to projected outcomes for patients recovering from diabetic amyotrophy.Clinical Case: A 42 year-old man presented with lower extremity muscle pain and progressive proximal muscle weakness over 8 months. He developed asymmetrical muscle weakness in the lower extremities with diffuse pain and sensitivity to touch. He also had 80 pounds weight loss, diarrhea, and erectile dysfunction over the same time period. He had a past medical history of asthma, chronic migraines, and type II diabetes mellitus with A1c 7.1. His medications included high dose prednisone to treat his chronic migraines and asthma. Exam revealed generalized muscle atrophy, asymmetric proximal weakness, areflexia, with sensory loss in bilateral lower limbs.ESR, CRP, ANA, anti-HMG CoA reductase, CK, aldolase, SPEP, and myomarker panel were all within normal limits. Treponema pallidum and Bartonella serologies were negative. CSF evaluation was not suggestive of any demyelinating or neuromuscular disease. Full body STIR MRI demonstrated muscle edema in abductor, gluteus minimus, and paraspinal muscles bilaterally. EMG testing revealed acute to subacute active asymmetrical polyradiculoneuropathy and evidence of chronic proximal myopathy.Based on clinical presentation, EMG findings, and lack of evidence to support alternative diagnoses, he was diagnosed with diabetic amyotrophy and was started on IVIG and methylprednisolone with improvement in pain but very minimal improvement in weakness. Unfortunately, the expected clinical course following a diagnosis of diabetic amyotrophy is one of minimal improvement with treatment, as was the case in our patient.Conclusion: Diabetic amyotrophy is a rare complication of type 2 diabetes mellitus which typically presents with muscle weakness followed by severe pain in the thighs, hips, and buttocks. Compared with other neurologic complications of diabetes, amyotrophy is relatively uncommon, affecting approximately 1 percent of patients. This low prevalence and the broad differential for proximal muscle weakness makes it challenging to diagnose. It remains a diagnosis of exclusion, though EMG studies showing polyradiculoneuropathy in the proximal leg musculature is suggestive. Clinical improvement is slow and often incomplete. Physical and occupational therapy are a mainstay of treatment which may also include IVIG and steroids aimed at treating associated pain. Endocrinologists should have a high clinical suspicion for diabetic amyotrophy in the appropriate clinical context. When considering the diagnosis and discussing treatment options with patients, this case highlights the important role of endocrinologists discussing expectations associated with projected outcomes while attempting to manage diabetic amyotrophy.

Neuroendocrinology and Pituitary

CASE REPORTS IN UNUSUAL PATHOLOGIES IN THE PITUITARY

Lymphocytic Hypophysitis Mimicking Tolosa Hunt Syndrome

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SUN-286

Introduction:

Lymphocytic hypophysitis often presents with headache, hypopituitarism and visual disturbance, the latter from