iodine concentration. Suppurative thyroiditis (ST) often presents with fever, tachycardia, leukocytosis, tenderness, and euthyroid labs. However, when ST occurs with thyrotoxicosis, it can meet criteria for thyroid storm, which presents a diagnostic dilemma.
Clinical Case:
A 17 year old female with family history of Graves' disease presented to the ER with a sore throat. She was diagnosed with viral pharyngitis and treated with dexamethasone. Over the next 2 weeks, she developed fatigue, body aches, nausea, vomiting, and chills. She returned to the ER and was found to have tachycardia, hyperthyroidism [free T4 5.64 ng/dL (0.8 - 2.0 ng/dL), TSH <0.015 uIU/mL (0.5 - 4.5 uIU/mL)], and WBC 11 k/uL (3.5 - 11.5 k/uL). She was prescribed atenolol and referred to Endocrinology. Three days later she developed fever, diaphoresis, ear pain, vomiting, and abdominal pain. In the ER, she was febrile to 101.2°F with a heart rate (HR) of 117 BPM. Labs showed a free T4 6.14 ng/dL, TSH <0.015 uIU/mL, and WBC 20 k/uL. She was treated with methylprednisolone, propylthiouracil, and labetalol with improvement and transferred for concern of impending thyroid storm. Exam showed left-sided thyroid enlargement with tenderness. Thyroid ultrasound showed an enlarged heterogenous left thyroid lobe with 2 nodules, one 25 x 33 x 21 mm heterogenous and one 19 x 11 x 19 mm homogenous, without discrete abscess. That night she developed vomiting, hand tremors, HR in the 130's BPM, fever to 104.1°F, and a headache. Treatment was initiated with methimazole, SSKI drops, propranolol, and dexamethasone. Symptoms improved save persistent neck tenderness and dysphagia. CT neck demonstrated a left-sided 25 x 17 x 90 mm abscess with concern for 4th branchial apparatus abnormality. She underwent incision and drainage with drain placement. Cultures grew Streptococcus anginosus and Fusobacterium necrophorum. Broad spectrum antibiotics were started and later narrowed to ampicillin-sulbactam. Betablockers and methimazole were discontinued and thyroid labs nearly normalized by discharge [T4 11.8 mcg/dL (4.5-11.5 mcg/dL), free T4 2.0 ng/dL (0.8-2 ng/dL), and total T3 78 ng/dL (100-210 ng/dL)]. Thyroid auto-antibodies were negative.
Discussion:
In patients with ST, only 11% present with hyperthyroidism. Current thyroid storm scoring systems are sensitive but not specific so an acute bacterial infection with thyrotoxicosis can easily meet criteria. While ultrasound is standard for assessing for thyroid abscesses, in the setting of high clinical suspicion, further imaging with contrasted neck CT is warranted.

Adipose Tissue, Appetite, and Obesity

MECHANISMS AND TREATMENT OF OBESITY IN HUMANS

Amino Acid Signature of Abdominal Obesity in the TwinsUK Cohort

Ina Maltais-Payette, PhD student[1], Jinchu Vijay, PhD Student[2], Elin Grunberg, PhD[3], Andre Tchernof, PhD[1].
[1]CRIUCPQ, Quebec City, QC, Canada, [2]McGill University and Genome Quebec Innovation Centre, Montreal, QC, Canada, [3]Children's Mercy Hospitals and Clinics, Kansas University, MO, USA.

OR33-05

Background and aim: Metabolomic studies have shown that circulating amino acid levels are altered in the context of obesity. The branched-chain amino acids (BCAAs, namely leucine, isoleucine and valine) have been the most studied because of their consistent positive association with adiposity and their ability to prospectively predict type 2 diabetes and cardiovascular diseases (1). Circulating glutamate has been much less investigated, but some have shown that its specific association with central fat accumulation was stronger than that of BCAAs (2). This study aimed to evaluate the relationship between circulating glutamate and abdominal obesity and the impact of genetic factors on this association. **Methods:** In the TwinsUK cohort, we selected individuals for whom both metabolomics and DXA trunk fat measurements were available (n=4 665). We used linear regression to assess the correlation between glutamate level and trunk fat. Those with a trunk fat mass greater than 15 kg were considered abdominally obese. We compared the odds of presenting abdominal obesity in each circulating glutamate quintile with logistic regression models. Monozygotic twin pairs discordant for trunk fat were selected to identify analyte differences driven by non-genetic factors. All analyses were also performed with BCAAs for comparison. **Results:** Circulating glutamate was positively and significantly associated with trunk fat (β: 0.28, 95%CI: 0.26-0.31). Individuals in the highest circulating glutamate quintile had a more than 8-fold higher risk of being characterized by abdominal obesity compared to those in the lowest quintile (OR: 8.44, 95%CI: 6.17-11.55). In the 54 monozygotic twin pairs discordant for trunk fat, the heavier twin had significantly higher glutamate level compared to the leaner co-twin (p-value: 4.05e-07). In all these analyses, the results for glutamate were more significant than with any of the BCAAs. **Conclusion:** There is a positive relationship between circulating glutamate and trunk fat that is partially independent of genetic background. This often-overlooked metabolite might represent an interesting biomarker of abdominal obesity. **References:** (1) Newgard (2017). Metabolomics and Metabolic Diseases: Where Do We Stand? *Cell Metab, 25*(1), 43-56, (2) Kimberly et al. (2017). Metabolite profiling identifies anandamide as a biomarker of nonalcoholic steatohepatitis. *JCI Insight, 2*(9).

Tumor Biology

NOVEL REGULATORS OF BREAST CANCER PROGRESSION

The Androgen Receptor Is a Tumour Suppressor in Estrogen Receptor Positive Breast Cancer

Theresa E. Hickey, PHD[1], Luke Selth, PhD[1], Kee Ming Chia, PhD[2], Heloisa Milioli, PhD[2], Daniel Roden, PhD[2], Geraldine Laven-Law, BSc[1], Shalini Jindal, PhD[1], Mun Hui, MD[2], Esmaeil Ebrahimie, PhD[1], Stephen birrell, MBBS, PhD, FRACS[1], Suzan Stelloo, BSc[3], Elizabeth Caldon, PhD[2], Jessica Findlay-Schultz, PhD[4], Tarek Abdel_Fatah, MD, PhD[5], Ian Ellis, PhD[5], Wilbert Zwart, MSC[3], Carlo Palmieri, BSc, MB BS, PhD, FRCP[6], Carol Ann Sartorius, PHD[4], Alex Swarbrick, PhD[2], Elgene Lim, PhD[2], Jason S. Carroll, PHD[7], Wayne D. Tilley, BSC, PHD[1].

[1]DRMCRL, University of Adelaide, Adelaide, Australia, [2]Garvan Inst of Medical Research, Sydney, Australia, [3]Oncode Institute, Netherlands Cancer Institute, Amsterdam, Netherlands, [4]University of Colorado Anschutz Medical Center, Aurora, CO, USA, [5]University of Nottingham, Nottingham, United Kingdom, [6]University of Liverpool, Liverpool, United Kingdom, [7]CRUK Cambridge Institute, Cambridge, United Kingdom.

OR05-06

There is strong interest in targeting the androgen receptor (AR) in estrogen receptor (ER) positive breast cancer, but widespread confusion exits as to what therapeutic strategy - agonism or antagonism - is appropriate. Current understanding of AR predominantly stems from the field of prostate cancer, where AR is the key oncogenic driver and therapeutic target. An ensuing assumption is that AR promotes malignancy in breast cancer and should be therapeutically antagonised. However, compelling pre-clinical data to support this assumption is lacking. Since estrogen stimulates and androgen inhibits the development of normal breast tissue, we hypothesized that AR acts as a tumour suppressor in the breast and that AR agonism is the appropriate therapeutic strategy for ER-driven breast cancer. We tested this hypothesis using a large suite of cell line and patient-derived explant (PDE) and xenograft (PDX) models of breast cancer, including those that were resistant to current therapies and those harbouring genomic anomalies of *ESR1* associated with treatment-resistant disease. Across the diverse models we found compelling evidence that AR agonism, but not antagonism, potently and durably inhibited tumour growth. A signature of AR activity derived from the xenograft models positively predicted disease survival in multiple large clinical cohorts of ER+ breast cancer, out-performing other breast cancer-specific prognostic signatures. We also show that an AR agonist can be combined with current ER target therapies such as Tamoxifen or a CDK4/6 inhibitor to maximize growth inhibition. Mechanistically, agonist-bound AR opposed ER signalling by repositioning ER and the co-activator p300 in the chromatin landscape, resulting in down-regulation of cell cycle genes. Introduction of an AR DNA binding mutant had no effect on ER signalling or estrogen-stimulated growth in breast cancer cells. As part of this study, we have generated consensus AR cistromes representing ER+ breast cancer cell lines and ER+ tumours that provide a new understanding of AR activity and clearly show differences to those associated with prostate cancer cell lines and tumours. In conclusion, our data provides a compelling biological rationale for AR agonism as a therapeutic strategy in multiple, clinically relevant contexts of ER-positive breast cancer. These findings should dispel widespread confusion over the role of AR in ER-driven breast cancer, an issue that currently hinders progress in leveraging modern AR-targeted therapies (e.g. selective androgen receptor modulators) that lack the undesirable side-effects of androgens for clinical benefit.

Thyroid

THYROID DISORDERS CASE REPORTS II

Melanoma Treated with Pembrolizumab Leading to Thyroiditis and Subsequent Hypothyroidism

Heather Fishel, MD.
USC/William Jennings Dorn VA, Columbia, SC, USA.

SAT-477

Background: Pembrolizumab (PD-1) is an immune checkpoint inhibitor used for treating melanoma and has been associated endocrine immune-related adverse events.

Case Presentation: 76-year-old Caucasian male presented for evaluation of abnormal thyroid labs. Significant co-morbidities included recurrent melanoma, heart failure, atrial fibrillation, coronary artery disease, type 2 diabetes, hypertension. Patient's melanoma was being treated with Pembrolizumab. Further history revealed no family/personal history of thyroid disease but a history of mouth cancer treated with radiation over 30 years ago. He denied any recent glucocorticoid or biotin use. Symptoms included worsening fatigue, weight loss, and diarrhea. He was afebrile and vitally stable. Physical exam was unremarkable. Prior to this year, patient had normal thyroid labs. Recent thyroid labs showed TSH of 0.01 uIU/mL (normal 0.34-4.94 uIU/mL), confirmed with repeat labs a week later (TSH: < 0.01, Free T4: 2.23 ng/dL, normal Free T4: 0.7-1.48 ng/dL). There was a high suspicion that these labs were related to Pembrolizumab, but other etiologies were evaluated. Completed thyroid uptake and scan showed no evidence of increased activity (4-hour uptake: 1.6%, 24-hour update: 1.2%). Repeat thyroid labs indicated recovering thyroid function with a TSH: 0.14 uIU/mL, Free T4: 0.49 ng/dL, Free T3: 1.5 pg/mL (normal Free T3 2.3-4.2 pg/mL), TSI: 96% (normal < 140%), TPO Ab: 111 IU/mL (normal TPO Ab < 9 IU/mL). One month later thyroid tests resulted as TSH: 72.81 uIU/mL, Free T4: < 0.40. He was started on levothyroxine, which was titrated over several weeks.

Discussion: Pembrolizumab (PD-1) is an IgG4 programmed cell death 1-directed monoclonal antibody, whose mechanism of action is to inhibit cancer cells ability impede T-cell activation. However, because of this mechanism, some T-cells, will remain activated, leading to autoimmune diseases. PD-1 has been associated with thyroid dysfunction, with an incidence rate as high as 14-20%. The clinical presentation varies from isolated thyrotoxicosis to overt hypothyroidism. In our patient, he developed thyrotoxicosis with subsequent development of hypothyroidism. Generally, the timing of thyroid dysfunction after the initiation of PD-1 ranges from 3 to 40 weeks, with the median onset at week 6. Baseline TSH and free T4 should be obtained with rechecking of these labs monthly for the first 6 months. For patients who present with thyrotoxicosis, Grave's disease should be ruled out, and initial treatment should include beta-blockers. Hypothyroidism should be treated with levothyroxine with titration to normal thyroid function tests. What remains to be determined is the mechanism in which PD-1 causes thyroid dysfunction and if specific patient characteristics, such as thyroid antibodies, can be used to risk stratify the likelihood of a patient developing thyroid dysfunction.

Diabetes Mellitus and Glucose Metabolism

TYPE 2 DIABETES MELLITUS

Fournier's Gangrene and Diabetic Ketoacidosis Caused by Canagliflozin

George Alexiades Stamatiades, MD[1], Kinjal Kasbawala, B.S[2], Aristea Sideri Gugger, MD-PhD[1], Mehreen Elahee, MD[3], Sachin K. Majumdar, MD[1].