Stat5a serine phosphorylation regulates Stat5a nuclear activity in a non-canonical fashion, contributing to its role in mammary oncogenesis. As shown in a tissue microarray (TMA), human breast cancer tissues express both pS726- and pS780-Stat5a. Nuclear Allred score for pS726-Stat5a increases two-fold with increasing tumor grade, with no difference in staining associated with estrogen or progesterone receptor (ER, PR) status, nor other clinical characteristics. Likewise, patient derived xenograft (PDX) tumors of various molecular subtypes express pS726- and pS780-Stat5a. Phosphorylation of S726-Stat5a is PRL-responsive *in vitro*. Pharmacologic inhibition of ERK1/2 prevents this phosphorylation, uncovering a novel pathway in which ERK1/2 mediates Stat5a activity in response to PRL in breast cancer. To examine the functional significance of Stat5a serine phosphorylation *in vitro*, we have performed Stat5a knockdown (KD) in the breast cancer cell line MCF7. Following Stat5a KD, cells were rescued with phospho-site specific Stat5a mutant constructs. Characteristics of breast cancer examined in these mutation-carrying cells, including anchorage-independent growth and proliferation, show distinct phenotypes compared to controls. PRL-induced expression of the CISH gene is significantly decreased up to 65% in the mutation-carrying cells compared to wild type Stat5a. Mechanistic studies will examine the ability of these Stat5a mutants to undergo nuclear translocation and interact with other transcription factors. Collectively, these studies have the potential to provide novel insights into the role of the non-canonical pathway of Stat5a activation in breast cancer pathogenesis.

Diabetes Mellitus and Glucose Metabolism

DIABETES DIAGNOSIS, TREATMENT AND COMPLICATIONS

The Impact of Age on Outcomes of Hyperosmolar Hyperglycemia Among Adult Patients with Diabetes. from the National Inpatient Sample.

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SUN-625

Objective: There is paucity of literature on the impact of age on outcomes hyperosmolar hyperglycemic state (HHS) among adult patients with diabetes. The aim of the study was to evaluate the effect of age on the outcome of patients admitted for the management of HHS. Methodology: The National Inpatient Sample (NIS) was queried for all patients who were admitted with a diagnosis of HHS during the years 2005-2014. The primary outcomes of the study were all-cause mortality, acute myocardial infarction (MI), and acute stroke. The secondary outcomes were acute kidney injury (AKI), rhabdomyolysis, acute respiratory failure (ARF), need for mechanical ventilation (MV) length of stay (LOS), and total cost of stay. Results: Overall, 188,725 patients were admitted for HHS. Mean age was 55.9, standard error of the mean (SEM): 0.1. Majority were of middle age. Females were (43.9%), Caucasians were 37.4% while African Americans were 35.2%. Total mortality was 1.1%, MI was 1.3% and stroke was 1.1%. Most common secondary outcome was AKI seen in 31.3% followed by ARF seen in 2.9% of total. The mean cost was 7887 $ (SEM: 84.6) and mean LOS was 4.1 days (SEM: 0.03). Young age was defined as age ≤ 35 years, middle age was > 35 and ≤ 65 years, old age was > 65 years. Mortality was 0.3 %, 0.6%, 2.5% in young, middle and older aged groups respectively. Similarly, higher age correlated with increased risk for MI, stroke and all secondary outcomes. On multivariable analysis, age was an independent predictor for all adverse outcomes. Compared to young patients, middle and older age groups had higher odds for mortality with adjusted odds ratio (aOR) 2.23 [95%CI:1.10-4.52], p=0.03 and aOR 7.35 [95%CI: 3.27-16.53], p<0.001 respectively, higher risk for stroke with aOR 9.32 [95%CI: 2.92-29.7], p<0.001 and aOR 17.46 [95%CI:5.23-58.3], p<0.001 and higher risk for MI aOR 5.18 [95%CI:2.15-12.51], p<0.00 and aOR 5.80 [95%CI:2.27-14.80], p<0.00 for middle and older age groups respectively. In addition, compared to the younge age group, the risk for rhabdomyolysis, AKI, ARF, MV, total cost and LOS was significantly higher among middle and older age groups respectively. Conclusion: Age is an important determinant for adverse outcomes among patients with hyperosmolar hyperglycemic sate.

Tumor Biology

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

Nuclear PDCD4 Expression Predicts Good Clinical Outcome in Luminal A-Like and Luminal B-Like Breast Cancer Subtypes

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SUN-122

Hormone receptor-positive (HR+, estrogen and/or progesterone receptor-positive) and HER2-negative breast cancer (BC) subtype is a biologically heterogeneous entity that comprises 70% of BCs. This subtype includes both luminal (Lum) A- and B-like subtypes, which have differences in prognosis and sensitivity to endocrine therapies. The development of biomarkers guiding treatment decisions in these settings is required. Tumor suppressor PDCD4 (programmed cell death 4), which can be found both in the nucleus (NPDCD4) or the cytoplasm (CPDCD4), inhibits

tumor growth and metastasis, and its loss is associated with poor prognosis in solid tumors. To explore the clinical relevance of PDCD4 in BC, we analyzed its expression by immunohistochemistry in a cohort of 619 patients with primary invasive BC. We found that 34.7% of patients showed NPDCD4 and 21.3% showed CPDCD4. NPDCD4 positivity, but not CPDCD4, was associated with lower clinical stage (P = 0.0003), with presence of more differentiated tumors (P = 6.4x10-6), and with estrogen and progesterone receptor (PR) expression (P = 9.2x10-9 and P = 2.8x10-9, respectively). Kaplan-Meier analysis revealed that NPDCD4 expression was associated with a longer overall survival (OS) and disease-free survival (DFS) in LumA-like (P = 0.008 and P = 0.028, respectively) and LumB-like (P = 0.004 and P = 0.012, respectively) subtypes. Interestingly, patients with LumB-like tumors displaying NPDCD4 presented estimated OS and DFS rates similar to the ones observed in patients with LumA-like tumors also expressing NPDCD4, indicating that its presence improves the clinical outcome of LumB-like patients. Multivariate Cox regression analysis identified NPDCD4 as an independent predictor of good clinical outcome in both LumA-like (HR: 0.45, 95% CI 0.22-0.96, P = 0.038) and LumB-like (HR: 0.28, 95% CI 0.10-0.80, P = 0.018) subtypes. We validated our results by *in silico* analysis using expression data from the METABRIC cohort. Bioinformatics analysis of BC cells from the Cancer Cell Line Encyclopedia revealed a positive correlation between PDCD4 and PR expression (P = 0.015). Since LumB-like tumors present a higher risk of resistance to endocrine therapy and both PR and PDCD4 levels in this subtype are lower than in the LumA-like one, we postulated that the presence of PR may modulate PDCD4 expression. Silencing of PR expression in HR+ cells decreased PDCD4 protein levels while reconstitution of PR in a PR-null cell line increased them, confirming PR requirement for PDCD4 modulation. In line with PDCD4 physiological function, its knockdown increased cell migration capability of HR+ BC cells, whereas its restoration led to a decrease in cell migration of HR-negative BC models. Our findings identified NPDCD4 positivity as a novel biomarker of clinical outcome in LumA- and B-like subtypes and revealed PDCD4 reconstitution as a novel therapeutic strategy in BC.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS II

Debilitating Neuropsychiatry Symptoms in Pancreatic Insulinoma Co-Secreting Serotonin and IGF-1

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MON-911

Background:
Insulinoma is the most common type of functioning pancreatic neuroendocrine tumor (NET). Polyhormonal secretions from the NET, giving rise to distinct clinical symptoms such as carcinoid symptoms are rare. **Clinical Case:** We report a 68-year-old woman who presented with four months history of recurrent diaphoresis, palpitations, tremors and chest tightness. These were associated with episodic paroxysms of flushing and diarrhoea. The physical examination was unremarkable. She was a well-nourished woman with BMI of 28 kg/m^2. Initial laboratory tests ruled out any renal, liver abnormalities with normal cortisol and thyroid function test. Further evaluation confirms insulin mediated hypoglycaemia with low random blood sugar 2.5 mmol/l (4.4-7.8) and failure to suppress C-peptide, 1092 pmol/L (298-2350) and insulin levels, 12.7 mU/L (3-25). Urine 5-HIAA was markedly elevated 2430.37 µmol/day (3.66-42.89) with borderline elevation of serum chromogranin A level 122 ng/mL (27-94). IGF-1 was also raised at 416 ug/L (91-282). Two months later she presented with new onset of delirium, incoherence, agitation and restlessness independent of her hypoglycaemic events. These symptoms deteriorated and fluctuates throughout the day with period of normalcy in between. This has led to requirement of a full time caregiver for her. Cranial CT excluded any brain pathology. We are faced with a diagnostic challenge to localize the primary lesion as radiological imaging so far were normal. GALLIUM-68 PET CT showed physiological uptake in the uncinate process of the pancreas (SUVmax 14.4). Endoscopic ultrasound of the pancreas was normal. An intra-arterial calcium stimulation test with hepatic venous sampling (ASVS) confirms a lesion at the head of pancreas with two times increment of insulin from baseline at the gastroduodenal artery distribution. Despite elimination of hypoglycaemic events with Diazoxide 100mg twice daily, her neuropsychiatric symptoms persisted. We postulate that this might be from excessive peripheral production of serotonin by the pancreatic carcinoid tumour or a niacin deficiency state because of metabolic diversion of its precursor, tryptophan. **Conclusion:**
This case highlights the occurrence of debilitating neuropsychiatry manifestations in a likely neuroendocrine tumour arising from the head of pancreas secreting insulin, serotonin and IGF-1.

Adrenal

ADRENAL MEDICINE — CLINICAL APPLICATIONS AND NEW THERAPIES

Over 14% of Inpatients with Euvolemic Hyponatremia Have Undiagnosed Adrenal Insufficiency

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OR25-04

Background- The commonest cause of euvolemic hyponatremia (EvHNa) is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The diagnosis of SIADH requires the exclusion of secondary adrenal insufficiency (AI) and untreated hypothyroidism. Studies have suggested about 4% of unselected patients presenting to the emergency room with EvHNa have undiagnosed SAI.[1] Among patients admitted to specialized endocrine units this prevalence maybe as high as 20%.[2] *Objective-* To study the prevalence of undiagnosed AI among inpatients with EvHNa admitted to general medical wards. *Methods-* This