can extend ATC patient survival, drug resistance and tumor reoccurrence often develop (2). Therefore, there is a critical need for more effective targeted therapies for ATC. Although the cell signaling landscape of ATC tumors is well described, very little is known about tumorigenic adaptations in ATC cellular metabolism. Tumors exhibit an increased consumption of glucose compared to normal tissues to fuel tumor progression. Some cancers meet this high glucose requirement by storing and breaking down glycogen. In our studies here, we show for the first time that normal thyroid, PTC, FTC, and ATC cells express genes necessary for glycogen metabolism. We confirm these observations in patient samples in normal thyroid and thyroid cancer patient samples via immunofluorescence in tissue microarrays. Furthermore, we detect intracellular glycogen stores in cell lines representing normal thyroid, PTC, FTC, and ATC cells. Importantly, we demonstrate that glycogen phosphorylase inhibitors result in accumulation of intracellular glycogen and induce subsequent apoptosis in ATC cells. We further show that glycogen phosphorylase inhibitors synergize with kinase inhibitors such as sorafenib and buparlisib to decrease ATC cell viability. Our work establishes glycogen metabolism as a novel metabolic process in thyroid cells that is associated with thyroid cancer dedifferentiation and provides insight to the effectiveness of inhibiting glycogen metabolism as a therapeutic strategy in ATC.

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Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Triple Negative Breast Cancer is Dependent on the Lysosomal Cholesterol Transporter NPC1

Kathleen O'Neill, BS.
University of Colorado - Anschutz, Aurora, CO, USA.

Background: Triple Negative Breast Cancer (TNBC) is an aggressive subtype of breast cancer (BC) with peak rate of metastasis within the first few years post diagnosis and few targeted therapies. Normal epithelial cells and estrogen receptor alpha (ER) positive BC express the microRNA-200c (miR-200c), a potent suppressor of epithelial-to-mesenchymal transition (EMT). However, miR-200c is silenced or lost in TNBC, allowing aberrant expression of genes conferring a de-differentiated, non-epithelial phenotype that confers invasive and chemo-resistant properties. Recent literature demonstrated that EMT also promotes altered tumor cell metabolism. **Hypothesis:** We postulate that EMT reversal in TNBC will reveal selective advantages and identify novel therapeutic vulnerabilities. **Methods:** We used restoration of miR-200c as a tool to identify selective advantages conferred by EMT. In addition to driving global metabolic changes, miR-200c-repressed key cholesterol metabolism genes that support the uptake of dietary cholesterol, which is delivered via low-density-lipoproteins (LDL) and processed by the lysosomal cholesterol transporter, Niemann-Pick Type C1 (NPC1). Manipulation of NPC1 by genetic and pharmacological means was used to determine if and how TNBC are reliant on this pathway. **Results:** We determined that *NPC1* is overexpressed in TNBC relative to ER+BC (*Nature* Metabric P<0.0001). Restoration of miR-200c directly targets the *NPC1* 3'UTR and represses *NPC1* by two-fold (p=0.01). While silencing of *NPC1* in ER+ BC cells led to slowed proliferation, TNBC cell lines died within 48-72 hours. NPC1 is associated with mitochondrial dysfunction and mTOR suppression. Intracellular cholesterol homeostasis is critical for cell survival and is carefully regulated, but how these homeostatic mechanisms adapt during tumor progression is poorly understood. **Conclusions:** This study demonstrates that while mesenchymal-like TNBC cells do not require exogenous cholesterol from the microenvironment, this cancer type is sensitive to the loss of NPC1. Overall, this work identifies NPC1 as a novel target in TNBC and sheds light on how lysosomes and mitochondria interact to sense cholesterol and drive cell survival.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Using Multimodal Functional Imaging in the Management of SDHx-Related Pheochromocytoma and Paraganglioma

Gemma White, BSc[1], Samantha Anandappa, MBBS, MRCP (UK)[2], Michael Masucci, BSc[3], Fahim-Ul Hassan, MBBS, MSc, MRCP, FRCP[2], Louise Breen, RN[2], Mamta Joshi, MRCP (UK)[2], Barbara McGowan, MA, MBBS, MRCP, PhD[2], Jonathan Hubbard, MBBS, MD, FRCS[2], Rupert Obholzer, MA, MBBS, FRCS[2], Philip Touska, MBBS, MRCS, FRCR[2], Louise Izatt, MA, MB BChir, PhD, FRCP[2], Anand Velusamy, MBBS, MRCP (UK)[2], Paul Carroll, MA, MD, MRCPI, FRCP[2].
[1]Barts and The London School of Medicine and Dentistry, London, United Kingdom, [2]Guys and St Thomas' NHS Trust, London, United Kingdom, [3]King's College London, London, United Kingdom.

Background: Succinate Dehydrogenase *(SDH)* subunit pathogenic variants predispose to Pheochromocytoma and Paraganglioma (PPGL). Functional imaging harnesses the innate receptor expression and the aberrant cellular pathways in PPGLs to improve diagnostic accuracy & guide treatments, including nuclear medicine therapies. Currently commonly available functional imaging modalities include ^{18}F-FDG PET, ^{123}I-MIBG and ^{68}Ga-DOTATATE. **Aims**: To analyze the use of ^{123}I-MIBG, ^{18}F-FDG PET and ^{68}Ga-DOTATATE in patients harboring *SDHB* & *SDHD* pathogenic variants and determine the detection rates for both primary tumors and metastatic sites of disease. **Methods:** Retrospective review of patient records and imaging reports allowed tumor characteristics and imaging features of 21 patients with *SDH*-related PPGL to be recorded. Contrast enhanced CT/MRI were used as control to calculate the sensitivity of each functional imaging modality. Avidity of the primary lesion and metastatic deposits were used to calculate detection rates.

^{123}I-MIBG imaging was available for 22 primary tumors (8 *SDHB*, 14 *SDHD*), ^{18}FDG-PET for 24 (9 *SDHB*, 15 *SDHD*) and ^{68}Ga-DOTATATE for 6 (2 *SDHB*, 4 *SDHD*) respectively. **Results:** 29 PPGLs (primary and metastases, 13 *SDHB*, 16 *SDHD*) were identified in 21 patients. ^{123}I-MIBG detected 14/22 (64%) primary tumors; 5/8 (63%) *SDHB* and 9/14 (64%) *SDHD*-related PPGL. According to tumor location, 3/3 PCCs, 6/8 HNPGLs and 4/11 non-HNPGLs demonstrated ^{123}I-MIBG avidity. Both^{18}F-FDG PET and ^{68}Ga-DOTATATE detected all PPGLs imaged; 24 (9 *SDHB*, 15 *SDHD*) and 6 (2 *SDHB*, 4 *SDHD*) respectively, demonstrating 100% sensitivity in the detection of the primary PPGL in all the above locations. 6 metastatic deposits (located in bone, lungs, liver and local lymph nodes) in 4 patients were imaged using all 3 modalities (3 *SDHB*, 1 *SDHD*), all of which were avid on ^{18}F-FDG PET and ^{68}Ga-DOTATATE whereas only 50% demonstrated avidity on ^{123}I-MIBG imaging. **Discussion:** Recent guidelines promote preferential use of ^{68}Ga-DOTATATE and ^{18}F-FDG PET as initial functional imaging modalities in *SDHx*-related disease over ^{123}I-MIBG. The results from our patient cohort indicate superior sensitivity (100%) for detection of SDHx-related disease with FDG and Dotatate compared with MIBG. In contrast to the current literature, a high proportion (75%) of HNPGLs in our series demonstrated MIBG avidity. Further prospective studies are needed to further evaluate these and various other novel tracers to inform diagnostic and therapeutic strategy in PPGLs arising from *SDHx* and various other germline and somatic pathogenic variants.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

VERU-111: An Oral Tubulin Inhibitor That Suppresses Taxane-Sensitive and Taxane-Resistant Breast Cancer

Shanshan Deng, PhD, Raisa I. Krutilina, PhD, Deanna Parke, MS, Hao Chen, PhD, Duane D. Miller, PhD, Wei Li, PhD, Tiffany Nicole Seagroves, PhD.
The University of TN Health Science Center, Memphis, TN, USA.

Triple negative breast cancer (TNBC) patients have poorer overall prognosis relative to patients diagnosed with other molecular subtypes due to rapid onset of drug resistance to conventional chemotherapies and increased risk of visceral metastases. The microtubule inhibitor paclitaxel (Taxol, a taxane) is a frontline therapy for advanced breast cancer. We evaluated in TNBC models the preclinical safety and efficacy of a novel, potent, and orally bioavailable tubulin inhibitor, VERU-111, a tubulin inhibitor targeting the colchicine binding site. VERU-111 showed potent anti-proliferative and anti-migratory activity against several taxane-sensitive and taxane-resistant TNBC breast cancer cell lines. Based on these observations, taxane-resistant HER2+ cell lines were generated, and were also found to be responsive to VERU-111 treatment. *In vivo*, orally administered VERU-111 inhibited MDA-MB-231 tumor growth in a dose-dependent manner with antitumor potency similar to paclitaxel, and repressed metastases originating from the mammary fat pad or following tail vein injection. In contrast, in a MDA-MB-231 paclitaxel-resistant (TxR) subline, tumor growth was refractory to paclitaxel whereas VERU-111 significantly inhibited primary tumor growth and reduced lung and liver metastases. VERU-111 was then tested in a luciferase-labeled, multidrug resistant patient-derived xenograft (PDX) TNBC model. VERU-111 significantly inhibited HCI-10 PDX tumor growth and suppressed the expansion of axillary lymph node metastases present prior to initiation of therapy while suppressing lung, liver, bone and kidney metastases at study endpoint. Moreover, in contrast to paclitaxel, VERU-111 therapy did not cause a significant decrease in mouse body weight during treatment. Evaluation of efficacy of VERU-111 in taxane-sensitive and -resistant HER2+ xenograft models is in progress. Overall, we conclude that VERU-111 is a new generation orally bioavailable tubulin inhibitor that potently inhibits the growth of taxane-sensitive *and* taxane-resistant breast cancers with reduced adverse side effects relative to paclitaxel. Importantly, VERU-111 is well-tolerated in patients as evaluated in phase I/II clinical trials for advanced prostate cancer patients (NCT03752099). We propose that VERU-111 will be an effective second line therapy for patients with advanced breast cancer who progress on taxane-based therapeutic regimens.

Tumor Biology

TUMOR BIOLOGY CASE REPORTS

A Case of Non-Islet Cell Tumor Hypoglycemia in Metastatic Solitary Fibrous Tumor

Lakshmi Priyanka Mahali, MD[1], Beatrice Wong, MD[2].
[1]Montefiore medical center, bronx, NY, USA, [2]MONTEFIORE MEDICAL CENTER, Staten Island, NY, USA.

Introduction: Insulin like growth factor (IGF-2) mediated hypoglycemia secondary to solitary fibrous tumor (SFT), also known as Doege-Potter syndrome is a rare paraneoplastic syndrome. The tumor cells produce large amounts of high molecular weight IGF 2 precursor protein called "big IGF-2" which binds to insulin and IGF receptors in liver, muscle and other peripheral tissues. This causes reduced gluconeogenesis and increased uptake of glucose by the muscle and other tissues leading to hypoglycemia. Big IGF-2 also exerts central negative feedback of growth hormone causing reduction of IGF-I production. Most SFTs are benign and localized (approximately 78-88%). As a result, tumor excision alone would often lead to resolution of the hypoglycemia. We present a case of metastatic SFT with multiple metastasis managed with oral prednisone.
Clinical Case: A 44-year-old man with metastatic SFT presented with bilateral humeral fractures. He has known metastatic disease to the brain, lung, liver, bony lytic lesions over a course of eleven years. It has progressed despite multiple chemotherapy and radiation therapies. Prior to admission, he had multiple syncopal episodes associated with fasting hypoglycemia. He reported capillary blood glucose values ranging between 30-50 mg/dl during these episodes which would improve after drinking juice or eating candy. There was no history of diabetes mellitus or use of oral hypoglycemic agents or insulin. On admission, he had a capillary blood glucose value of less than 20 mg/dl, which was confirmed by a serum glucose value of 18 mg/dl on basic metabolic panel. His renal, liver and thyroid function