into Membrane Topology and Protein Trafficking

Shahida Flores, MSc, Xingyu Zhang, B.Sc., ZiMing Cheng, MD, Patricia L. Dahia, MD,PHD.
Univ of TX Health Sci Ctr San Antonio, San Antonio, TX, USA.

SUN-138

TMEM127, a tumor suppressor gene in hereditary pheochromocytomas and paragangliomas, encodes for a poorly characterized, ubiquitous, transmembrane (TM) protein with no substantial identity to any other protein and no identifiable functional domains other than putative TM domains. The function and regulation of TMEM127 remain poorly defined which limits prediction of pathogenicity of germline *TMEM127* variants. Characterizing structure-function features of TMEM127 is relevant for understanding how dysfunction of this tumor suppressor can lead to inherited tumors. Moreover, a better understanding of TMEM127 functional domains and critical residues will increase our ability to identify pathogenic variants which will improve interpretation of genetic screening results and help guide clinical decisions for patients and their families. In this study, we investigated subcellular localization and steady-state levels of patient-derived, tumor-associated, germline *TMEM127* variants (n=21; 16 missense and 5 truncating/frameshift/indel variants). We used confocal immunofluorescence and immunoblot analysis of GFP-TMEM127 constructs expressed in HEK293T cells. Wild-type (WT) TMEM127 localized predominantly to endo-lysosomal vesicles (punctate) with some plasma membrane localization. The localization of variant TMEM127 proteins displayed three distinct patterns: punctate (similar to WT), diffuse (cytoplasmic), and plasma membrane only. All diffuse proteins, and a few punctate proteins, decreased at a faster rate than the WT suggesting instability. Variants resulting in diffuse proteins occurred within TM domains and indicated that membrane binding ability was lost. This observation, supported by *in silico* analysis and selective permeability assays, led us to conclude that TMEM127 is a four-TM protein, not a three-TM protein, as previously predicted, with a novel TM domain in the N-terminus. One variant with predominantly plasma membrane localization indicated that membrane binding ability was maintained but internalization capability was lost. We identified an atypical, extended acidic dileucine motif in the C-terminal which is responsible for TMEM127 internalization and showed that it is mediated by clathrin. Our findings provide novel insights into structure-function features of TMEM127 which will allow for better understanding of its physiological role and improved prediction of pathogenic variants.

Thyroid

THYROID DISORDERS CASE REPORTS II

Clinical Hypothyroidism Associated with Lutetium 177-DOTATATE Therapy for Metastatic Paraganglioma: A Novel Adverse Effect of Peptide Receptor Radionuclide Therapy

Sriram Gubbi, MD[1], Mohammad Al-Jundi, MD[2], Abhishek Jha, MD[2], Marianne Knue, CRNP[2], Joy Zou, RN[3], Jaydira Del Rivero, MD[3], Baris Turkbey, MD[3], Jorge A. Carrasquillo, MD[4], Karel Pacak, MD,PhD[2], Joanna Klubo-Gwiezdzinska, MD,PhD[1], Frank I. Lin, MD[3].
[1]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA, [2]Eunice Kennedy Shriver National Institute of Child and Human Development, National Institutes of Health, Bethesda, MD, USA, [3]National Cancer Institute, National Institutes of Health, Bethesda, MD, USA, [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA.

SAT-502

Background: Peptide receptor radionuclide therapy (PRRT) is a relatively novel, emerging therapy for the treatment of metastatic pheochromocytoma and paraganglioma (PPGL). Lutetium 177 (^{177}Lu)-DOTATATE (Lutathera ®) is a form of PRRT that is currently being evaluated for its treatment efficacy in metastatic PPGL. It acts by binding to somatostatin receptors 2 (SSTR2) which are present on PPGL and other tissues of neuroendocrine origin. Although subclinical thyroid dysfunction has been previously noted, development of clinical hypothyroidism post ^{177}Lu-DOTATATE therapy has not been reported to date. **Case:** A 29-year-old male with Beckwith-Weidemann syndrome and metastatic, succinate dehydrogenase subunit B (*SDHB)* germline mutation-positive paraganglioma with normal metanephrines was enrolled at our center under the ^{177}Lu-DOTATATE trial for the treatment of inoperable, metastatic PPGL (ClinicalTrials.gov NCT03206060). Prior to the first cycle of therapy, the patient underwent endocrine evaluation per protocol. He was noted to have suppressed thyroid stimulating hormone (TSH) of <0.01 mcIU/mL (normal: 0.27 - 4.2 mcIU/mL), and a normal free thyroxine (FT4) of 1.3 ng/dL (0.9 - 1.7 ng/dL), indicating subclinical hyperthyroidism. Thyroid auto-antibodies were not measured at that time point. The patient denied symptoms of hyper- or hypothyroidism. On physical examination, there was no thyromegaly or cervical lymphadenopathy. Serial monitoring of thyroid function tests (TFTs) was pursued. One month after the first cycle of ^{177}Lu-DOTATATE therapy, the patient complained of new onset fatigue and weight gain. The TSH had markedly increased (73.04 mcIU/mL), along with a reduction in FT4 levels (0.3 mg/dL). Mass spectrometry measures revealed a low total T4 (1.3 ng/dL; 4.9 - 10.5 ng/dL), and a low total T3 (57 ng/dL; 87 - 169 ng/dL). Thyroid peroxidase antibodies were >1000 IU/mL (0.0 - 34.9 IU/mL), and anti-thyroglobulin antibodies were 668 IU/mL (0.0-40.0 IU/mL). Weight-based levothyroxine therapy was initiated and the follow-up TFTs normalized. The baseline diagnostic Gallium 68-DOTATATE scan performed prior to PRRT demonstrated an increased diffuse uptake in the entire thyroid gland (maximum standardized uptake value: 14.3) and post-treatment SPECT-CT scan revealed similar increased, diffuse ^{177}Lu-DOTATATE uptake in the thyroid gland. The patient currently has stable metastatic disease and continues to be under ^{177}Lu-DOTATATE therapy. **Conclusion:** We report the first known case of clinical hypothyroidism post ^{177}Lu-DOTATATE therapy in a patient who likely had subclinical hyperthyroidism prior to treatment. The possible mechanism was development of thyroiditis. Further studies are necessary to evaluate the mechanisms of PRRT-induced endocrine abnormalities and their clinical implications.

Thyroid

THYROID DISORDERS CASE REPORTS III

An Extremely Rare Case of Urothelial Carcinoma Metastasizing to the Thyroid Gland

Massiell German, MD[1], Abhilasha Singh, MD[1], Yu Kuei Lin, MD[2], Vishnu Sundaresh, MD[1].
[1]University of Utah School of Medicine, Salt Lake City, UT, USA, [2]University of Michigan, Ann Arbor, MI, USA.