Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING II

Induction of Apolipoprotein A1 Gene Expression by the Rare Sugar Allulose

Shrina Parekh, MD.
University of Florida, JACKSONVILLE, FL, USA.

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Apolipoprotein A-I (apo A-I) is the primary protein component of high-density lipoprotein (HDL) and has many well documented properties which promote cardiovascular health. However, clinical trials designed to increase HDL levels by preventing its catabolism have failed in their primary endpoints in decreasing the risk of cardiovascular disease. Alternative strategies to increase de-novo apo A-I production may be more attractive. We recently demonstrated that the rare sugar allulose decreases oxidative stress and endoplasmic reticulum stress in both endothelial cells and hepatocytes. During these studies we demonstrated that allulose also induces apo A-I secretion by HepG2 cells. Apo A-I, albumin, and SP1 levels were measured by Western blot. Apo A-I and glyceraldehyde-3-phosphate (GAPDH) mRNA levels were measured by quantitative real-time polymerase chain reaction. The effect of allulose on apo A-I promoter activity was measured using transient transfection assays with several plasmids containing various segments and mutations in the apo A-I gene promoter. Apo A-I protein and mRNA levels in cells treated with allulose increased more than two-fold in a dose-dependent manner. These changes were due to the ability of allulose to induce apo A-I gene promoter activity. Using a series of deletion constructs, an allulose-response element was identified in the apo A-I gene promoter and the transcription factor SP1. The rare sugar allulose may have novel anti-atherogenic properties, in part, by increasing HDL levels.

Thyroid

THYROID DISORDERS CASE REPORTS II

Thyroid Dysfunction in a Patient with Malignant Melanoma Treated with Immune Checkpoint Blockade

Shaveta Gupta, M.D., Ngwe Yin, MD.
UCSF, Fresno, CA, USA.

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Thyroid Dysfunction in a Patient with Malignant Melanoma Treated with Immune Checkpoint Blockade

Background: Thyroid dysfunction is a known immune-related adverse event associated with immune checkpoint inhibitor therapy.

Clinical Case: 48 year old female, newly diagnosed with metastatic melanoma started on combination immune checkpoint inhibitor therapy with Ipilimumab and Nivolumab. Her baseline thyroid function tests were normal. 6 weeks after the first cycle, she was found to have TSH of 0.010IU/ml with FT4 3.33IU/ml. Patient was started on Prednisone for 2 weeks and beta-blocker for symptom control by oncology team and referred to endocrine clinic for further evaluation. She was diagnosed with thyroiditis. TSI and thyroid uptake scan were not checked as there was no clinical suspicion for Graves disease in the absence of ophthalmopathy and thyroid enlargement. Serial TFTs were obtained which showed improvement. However, 4 weeks later, patient developed overt hypothyroidism (TSH 11.800IU/ml, FT4 0.68IU/ml) for which therapy with levothyroxine was started.

Conclusion: Our case emphasizes the importance of close monitoring of patients receiving Immune Checkpoint Inhibitor Therapy for prompt diagnosis and management of the thyroid disorders to prevent complications such as thyroid storm or myxedema coma. Per the ASCO guidelines, Brahmer et al recommends monitoring TFTs every 4 to 6 weeks from the start of the therapy and every 2-3 weeks after the diagnosis to detect conversion of thyroiditis and hyperthyroidism to hypothyroidism. In the combination therapy, the median time to onset of hyperthyroidism and hypothyroidism after first treatment was 21 and 63 days and transition time from hyperthyroidism to hypothyroidism was 42 days.

Reference: (1) Characterization of Thyroid Disorders in Patients Receiving Immune Checkpoint Inhibition Therapy Lee et al
(2) Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer et al