

Unraveling the "Autoimmune" Mystery of Graves' Disease - Joint collaboration between Taipei Veterans General Hospital and National Taiwan University Hospital

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Graves' Disease (GD) is the most common cause of hyperthyroidism, presenting as diffuse goiter, thyroid eye disease and symptoms of thyrotoxicosis, including palpitation, hand tremor, sweating, weight loss, insomnia, diarrhea, jaundice, muscle weakness etc. If left untreated, life-threatening thyroid storm and decompensated heart failure may occur. However, current treatment options are limited, with anti-thyroid drugs being the mainstay of therapy. While blocking thyroid hormone synthesis, anti-thyroid drugs does not target the "autoimmune" etiology of the disease. Therefore, relapses are common even after a complete course of therapy. Although rare, anti-thyroid drugs are also associated with severe side effects such as liver injury and agranulocytosis, which is defined by an absolute neutrophil count less than 500/mm³, causing the patient prone to serious infections. Traditionally, when the disease is active, physicians would suggest patients to decrease their daily iodine intake because this micronutrient is essential for thyroid hormone synthesis. However, the dietary restrictions are both inconvenient and uncertain as to their effect on disease control.

The research team of Dr. Pei-Lung Chen from the Department of Medical Genetics at National Taiwan University Hospital and Dr. Chun-Jui Huang from the Division of Endocrinology and Metabolism at Taipei Veterans General Hospital focused on unraveling the "autoimmune" mystery of Graves' disease and genetic profile of "antithyroid drug-induced agranulocytosis" for the past few years. They used the world's leading technologies - immunogenomic sequencing, HLA genotyping, spectral flow cytometry sorting of immune cells in blood, histologic staining and multiomics profiling of thyroid tissue sections, single-cell sequencing of immune cells in thyroid surgery specimens, and urinary iodine measurement - in an attempt to lift the veil on this mysterious and important autoimmune disease.

Under the support of the two hospital, more than 200 patients with Graves' disease have been enrolled in the research, and 23 patients who experienced the rare side effect

of "antithyroid drug-induced agranulocytosis" have also contributed. In 2015, the team led the world in identifying two "HLA genes" that increase the risk of "antithyroid drug-induced agranulocytosis" by nearly 50 times. Through the close and long-term collaboration between the two hospitals, it is expected that they will be able to penetrate deeper into the core of the disease-causing mechanism and unravel the mystery behind the immune mechanism. This understanding of the pathogenic mechanisms will help to develop new drugs to more effectively treat autoimmune disorders while minimizing the serious side effects, thus determining the most appropriate personalized therapy for the patient.