	Principal Investigator	Kyushu University, Faculty of Medical Sciences, Professor	
		OGAWA Yoshihiro	Researcher Number: 70291424
Project Information	Project Number : 22H04993	Project Period (FY) : 2022-2026	
	Keywords : adrenal gland, scRNA-seq, steroidomics, machine learning		

Purpose and Background of the Research

● Outline of the Research

The endocrine organ, which secretes bioactive hormones in response to a variety of environmental cues, is involved in the maintenance of our body's homeostasis. Whatever the cause, unbalanced hormone secretion results in the disruption of stress response, thereby leading to a variety of age-related diseases. Although much effort has been made to discover a novel hormone and to elucidate the mechanism of its action, and its functional and medical application, there are few comprehensive studies to understand the entire picture of a particular endocrine organ with different kinds of endocrine cells.

The adrenal gland plays a critical role in the integration of stress response. The adrenal cortex is composed of three functionally and histologically distinct zones, which secrete aldosterone, cortisol, and androgens, while adrenal medulla secretes catecholamines. Environmental cues such as ageing and chronic stress might induce adrenal histopathological alteration and tumorigenesis, thus leading to unbalanced hormone secretion and/or a variety of age-related diseases. However, how the adrenal gland secretes multiple hormones in a coordinated fashion, how adrenal tumors occur as a result of somatic driver mutations, and how the otherwise balanced hormone secretion is disrupted are poorly understood. On the other hand, the findings obtained from clinical studies with human samples are to be validated by animal studies with careful consideration of marked species-differences in adrenal function and histology.

In this study, we conduct basic and clinical studies in a bidirectional manner, to understand the molecular mechanisms underlying age- and stress-associated adrenal alteration and its pathological consequences, through state-of-the-art analytical methods.

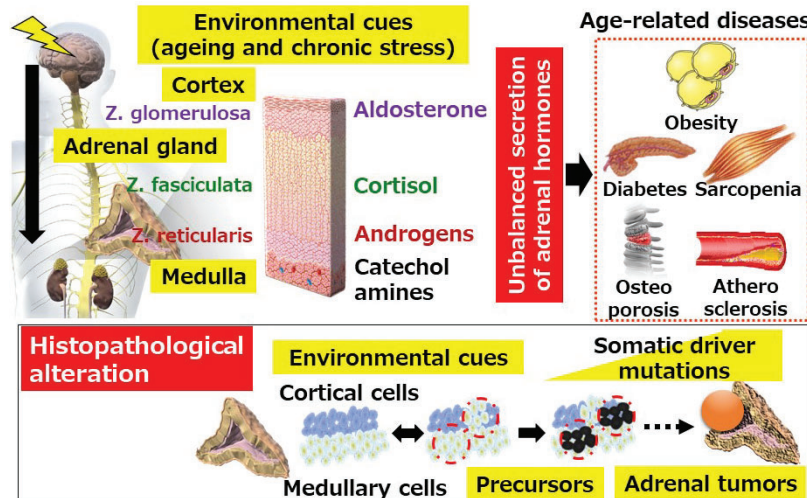


Figure 1. Image of the whole project

● Single cell RNA sequencing (scRNA-seq) analysis of human adrenal tissues

We conducted scRNA-seq analysis of normal human adrenal tissues and identified clusters corresponding to cells from three functionally and histologically adrenocortical zones (z. glomerulosa, z. fasciculata, and z. reticularis) and medullary cells. By the trajectory analysis, we found that the precursors of aldosterone-producing adenoma (aldosterone-producing cell cluster (APCC)) are derived from z. glomerulosa cells at single cell resolution.

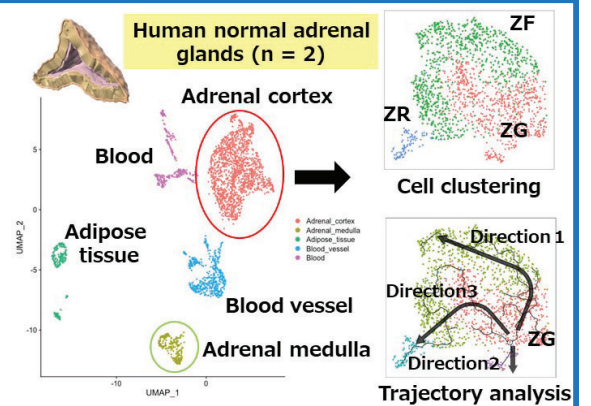


Figure 2. scRNA-seq analysis of human adrenal tissues

Expected Research Achievements

On the assumption that the adrenal gland is a key organ responsible for the a variety of age-related diseases, we address the molecular mechanism underlying the functional and histological alteration of adrenal tissues in response to a variety of environmental cues, unbalanced adrenal hormone secretion, and its pathological consequences.

(a) Molecular mechanism underlying adrenal tumorigenesis:

We conduct scRNA-seq and whole genome sequencing analysis of human adrenal tissues, adrenal tumors (aldosterone- and cortisol-producing tumors, and pheochromocytoma), and their precursors to elucidate the sequence of events during the course of tumorigenesis; how adrenal tumors occur from normal tissues via the precursors, as a result of somatic driver mutations in response to environmental cues.

(b) Hormone-producing cell diversity and heterogeneity in adrenal tumors:

By combining the newly-developed comprehensive steroidomics, imaging mass spectrometry, spatial transcriptomics, and whole genome sequencing analysis, we visualize hormone-producing endocrine cells *in situ* to elucidate their diversity and heterogeneity in normal adrenal tissues and adrenal tumors, and even in the precursors.

(c) Pathophysiologic role of unbalanced production of adrenal hormones:

We use steroidomics analysis to elucidate the steroid hormone profiles in healthy subjects at different ages and in patients with adrenal tumors. We also conduct machine learning-based analysis of the correlation of adrenal hormone profiles with the disease severity and treatment outcome, to obtain new diagnostic and therapeutic clues.

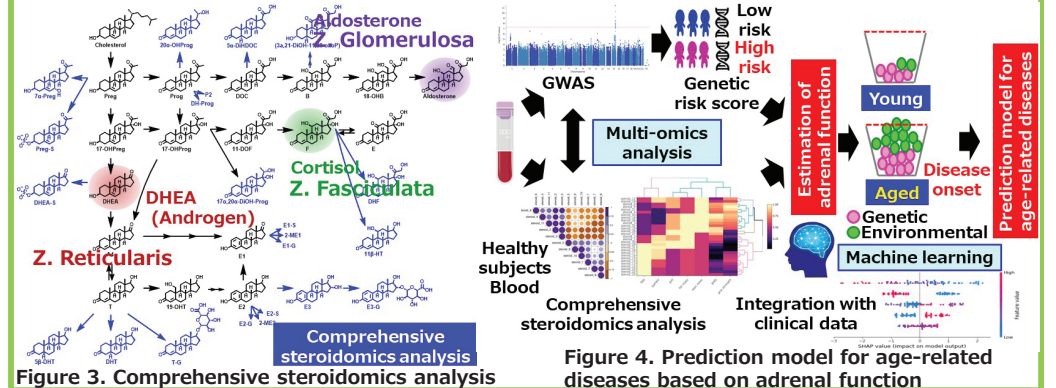


Figure 3. Comprehensive steroidomics analysis

Figure 4. Prediction model for age-related diseases based on adrenal function