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PRESS RELEASE (2025/2/25)

More than meets the eye: an adrenal gland tumor is more complex than previously thought

New research uncovers the hidden diversity of adrenal gland tumors, shedding light on how they cause unusual medical symptoms and paving the way for new drug treatments.

Fukuoka, Japan – Kyushu University researchers have uncovered a surprising layer of complexity in aldosterone-producing adenomas (APAs)—adrenal gland tumors that drive high blood pressure. Using cutting-edge analysis techniques, they discovered that these tumors harbor at least four distinct cell types, including ones that produce cortisol, the body's main stress hormone. Published in the week beginning 24 February in *PNAS*, their findings not only explain why some patients with APAs develop unexpected health issues, like weakened bones, but also pave the way toward new treatment strategies.

"Currently, the only way to cure APAs is through surgery to remove the tumor, and this hasn't changed for decades," says first author of the study, Assistant Professor Maki Yokomoto-Umakoshi, from the Department of Endocrine and Metabolic Diseases at Kyushu University Hospital. "To develop new treatment models, such as drug treatments, we urgently need to understand how these tumors work at the molecular level, and how the different cell types interact with each other."

APAs are benign (non-cancerous) tumors that develop on the adrenal glands—small glands on top of the kidneys that produce important hormones, such as aldosterone, cortisol and sex hormones. Due to their location, APAs are a major cause of primary aldosteronism, a condition in which excessive production of the hormone aldosterone leads to high blood pressure. Primary aldosteronism is responsible for about 5–10% of high blood pressure cases, and patients with APAs have a higher risk of heart and blood vessel problems compared to people with common high blood pressure.

"Without proper treatment, patients can develop serious health problems like heart disease, diabetes, and bone weakness," adds Yokomoto-Umakoshi.

In this study, the researchers focused on APAs caused by changes in a gene called *KCNJ5*. This mutation, which accounts for around 40-70% of all cases of these tumors, is typically associated with larger tumors that form at a younger age, as well as more severe symptoms that cannot simply be explained by overproduction of aldosterone. However, the cellular makeup of *KCNJ5* tumors, as well as which other hormones the tumors might secrete, has previously proven difficult to study.

To gain a deeper understanding of APAs, the research team, led by Professor Yoshihiro Ogawa from Kyushu University and in collaboration with Osaka University, Kyoto University, and the University of Tokyo, applied a combination of advanced techniques, providing the first comprehensive view of APAs in unprecedented detail. The researchers were able to map where different cell types were located within these tumors, and how they work together.

Furthermore, the techniques allowed the researchers to reveal diverse genetic variation within different regions of APAs and identify exactly which hormones the tumors were producing.

The study revealed that APAs are more complex than previously thought, consisting of at least four distinct cell types. The tumor starts with cells that respond to stress, which can then develop into either cells that make aldosterone, or cells that make cortisol. The cortisol-producing cells can then further develop into stromal-like cells that help the tumor to grow.

The researchers also discovered that special immune cells called lipid-associated macrophages were more abundant within the tumor, with a potential role in influencing hormone production and tumor growth.

"Overall, these tumors contain diverse hormone-producing cells that can affect patient's health in different ways—not just through high blood pressure, but also through other symptoms caused by excess cortisol, like bone weakness," explains Yokomoto-Umakoshi.

In the future, the researchers plan to use these techniques to extend their analysis to other types of APAs, as well as to other tumors that produce excess hormones. They also hope that their current findings help set the stage for developing future drug treatments for APAs.

"Now we understand more about APAs, it opens up promising new treatment strategies, such as directly targeting lipid-associated macrophages or excess cortisol," concludes Yokomoto-Umakoshi.

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For more information about this research, see "Multiomics analysis unveils the cellular ecosystem with clinical relevance in aldosterone-producing adenomas with KCNJ5 mutations" Maki Yokomoto-Umakoshi, Masamichi Fujita, Hironobu Umakoshi, Tatsuki Ogasawara, Norifusa Iwahashi, Kohta Nakatani, Hiroki Kaneko, Tazuru Fukumoto, Hiroshi Nakao, Shojiro Haji, Namiko Kawamura, Shuichi Shimma, Masahide Seki, Yutaka Suzuki, Yoshihiro Izumi, Yoshinao Oda, Masatoshi Eto, Seishi Ogawa, Takeshi Bamba, Yoshihiro Ogawa, *PNAS*, https://doi.org/10.1073/pnas.2421489122

About Kyushu University

Founded in 1911, Kyushu University is one of Japan's leading research-oriented institutes of higher education, consistently ranking as one of the top ten Japanese universities in the Times Higher Education World University Rankings and the QS World Rankings. The university is one of the seven national universities in Japan, located in Fukuoka, on the island of Kyushu—the most southwestern of Japan's four main islands with a population and land size slightly larger than Belgium. Kyushu U's multiple campuses—home to around 19,000 students and 8000 faculty and staff—are located around Fukuoka City, a coastal metropolis that is frequently ranked among the world's most livable cities and historically known as Japan's gateway to Asia. Through its VISION 2030, Kyushu U will "drive social change with integrative knowledge." By fusing the spectrum of knowledge, from the humanities and arts to engineering and medical sciences, Kyushu U will strengthen its research in the key areas of decarbonization, medicine and health, and environment and food, to tackle society's most pressing issues.

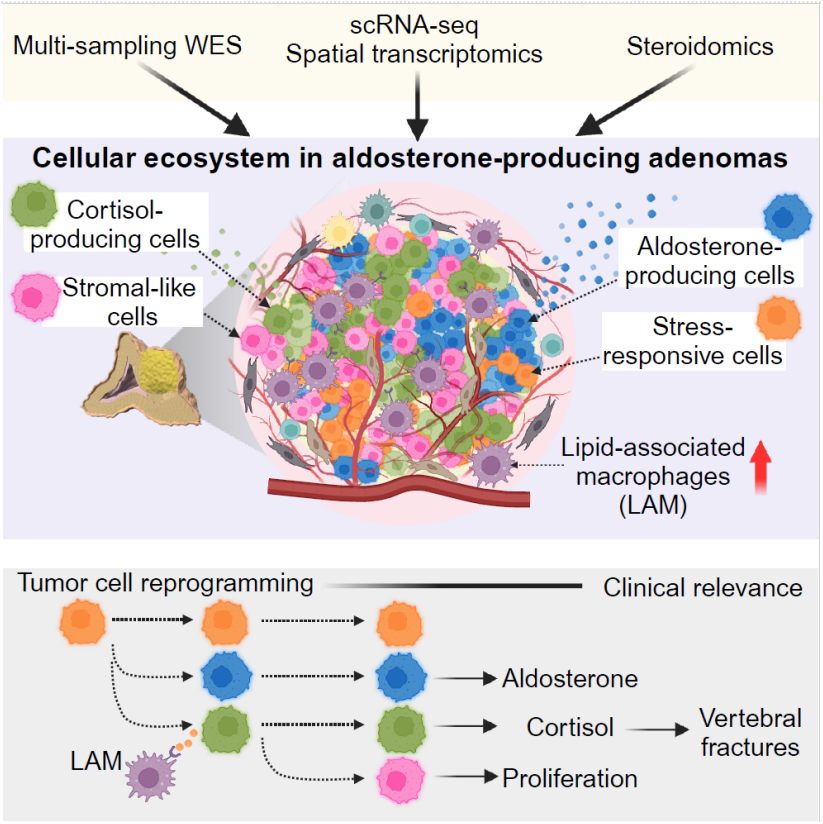

Fig. 1. A study that used a combination of advanced techniques has revealed that APAs contain four different cell types and overproduce both aldosterone and cortisol. Lipid-associated macrophages are also more abundant within these tumors and may place a role in hormone production and tumor growth. This figure was created using BioRender (https://app.biorender.com/).

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