ADRENAL GLAND

Mechanisms of β -catenin-induced adrenal hyperplasia

Somatic β -catenin gain-of-function (β cat-GOF) mutations are known to drive adrenal hyperplasia and are common in adrenal cortical carcinoma. A new study published in *Cell Reports* shows that adrenal hyperplasia induced by β cat-GOF results from a block in adrenal zonal transdifferentiation.

"The Wnt- β -catenin signalling pathway, which is a key regulator of cellular proliferation, has mostly been studied in rapidly cycling cell systems," explains corresponding author David Breault. However, the cells of the adrenal cortex have a fairly low proliferation rate, making this tissue an ideal system to study the effects of the Wnt- β -catenin signalling pathway, independently of cellular proliferation.

"A few years ago, our laboratory developed a mouse model that allows targeted expression of Cre recombinase specifically within the zona glomerulosa," describes Breault. "This tool provides us with the opportunity to directly study the effect of activating the Wnt- β -catenin pathway within the slowly cycling cells of the zona glomerulosa."

In this mouse model, β -catenin was stabilized specifically in cells of the zona glomerulosa, leading to constitutive activation of the Wnt- β -catenin pathway (β cat-GOF adrenals). Notably, mice with β cat-GOF adrenals showed expansion of the zona glomerulosa into the underlying region where the zona fasciculata normally resides. Furthermore, histomorphometric analysis of wild-type adrenals (β cat-WT) and β cat-GOF adrenals showed that this expansion was due to hyperplasia and not hypertrophy. Experiments using mT/mG double-fluorescent Cre-reporter mice showed that β cat-GOF adrenals have a functional block in the transdifferentiation of zona glomerulosa to zona fasciculata.

The identity of zona fasciculata cells is known to be negatively regulated by phosphodiesterases, via a block in cAMP/PKA signalling. In the adrenal gland, PDE2A in the zona glomerulosa induces phosphodiesterase activity. Of note, the researchers saw upregulated expression of *Pde2a* in β cat-GOF adrenals compared with controls. Further experiments showed inhibited cAMP/PKA signalling in the β -catenin-positive zona glomerulosa regions, suggesting a potential mechanism for the transdifferentiation block.

Chronic activation of the renin-angiotensin-aldosterone system (RAAS) is known to be associated with increased zona glomerulosa proliferation. A mouse model with ~5-fold increased RAAS activation was combined with the β cat-GOF adrenal model. This new model showed substantial adrenal hyperplasia leading to adrenomegaly.

"We plan to study the effect of chronic activation of the RAAS on the zona glomerulosa in patients carrying somatic and/or germ-line mutations in β -catenin," concludes Breault. "Finally, we plan to explore the interaction of β cat-GOF with other known regulators of adrenal function such as the p53-Rb pathway."

Shimona Starling

ORIGINAL ARTICLE Pignatti, E. et al. Beta-catenin causes adrenal hyperplasia by blocking zonal transdifferentiation. *Cell Reports*. **31**, 107524 (2020)

Artistic rendering of a β cat-GOF adrenal section showing accumulation of β -catenin (red) throughout the adrenal cortex. Nuclei shown in blue. Image was modified using Photoshop Oil Paint Filter. Image supplied courtesy of David T. Breault/Boston Children's Hospital

Credit: tenna/Getty

preference," adds Alex Sisti, the other co-lead author. These data provide insight into why artificial sweeteners, which were introduced into consumer products more than 40 years ago, have failed to substitute or reduce our appetite for sugar.

"Given the extraordinary effect of sugar in worldwide malnutrition, obesity, metabolic disorders and type 2 diabetes mellitus, identifying strategies to prevent our craving and consumption for sugar could have meaningful effects on human health," concludes corresponding author Charles Zuker.

Alan Morris

ORIGINAL ARTICLE Tan, H.-E. et al. The gut-brain axis mediates sugar preference. *Nature* **580**, 511–516 (2020)

This novel pathway is distinct from the taste circuits that operate from the tongue

Credit: Jennie Vallis/ Springer Nature Limited

for the progression of the disease," say Santin and Castellanos-Rubio.

The researchers hope that molecular characterization of the T1DM-associated SNPs in non-coding regions will aid the search for novel therapies for T1DM. "In the future, our research group aims to identify novel RNA molecules related to disease-associated variants involved in the development of diseases such as T1DM," conclude Santin and Castellanos-Rubio.

Claire Greenhill

ORIGINAL ARTICLE Gonzalez-Moro, I. et al. The T1D-associated lncRNA *Lnc13* modulates human pancreatic β cell inflammation by allele-specific stabilization of *STAT1* mRNA. *Proc. Natl Acad. Sci. USA* **117**, 9022–9031 (2020)

the impact of *Lnc13* in this process might be crucial for the progression of the disease