DIABETES

PRC2 in β-cell function

New research by J. Andrew Pospisilik and colleagues shows that patients with type 2 diabetes mellitus (T2DM) exhibit chromatin dysfunction and β-cell dedifferentiation, which is defined as the loss of cellular identity. The authors also report that mice with dysregulated Polycomb repressive complex 2 (PRC2), an epigenetic gene silencer, results in β-cell dedifferentiation and T2DM.

Previous rodent and human studies showed that β-cells are dedifferentiated in T2DM, but the underlying mechanisms remain unknown. Therefore, in the present study, the researchers investigated the role of epigenetic regulators in T2DM.

Using deep epigenome mapping and single-cell transcriptomics to analyse islet samples from mice fed chow and mice fed a high-fat diet (HFD), the researchers showed that a HFD triggers chromatin dysfunction and reduces levels of mature β-cell markers. Transcriptomic analyses of islet samples from patients with T2DM supported the mouse data, and immunostaining of these samples demonstrated that loss of PRC2 function results in chromatin dysfunction.

Next, the researchers generated a mouse model (βEEDKO) lacking PRC2 by knocking out Polycomb protein EED, a PRC2 subunit, expression in β-cells. The PRC2 function of β-cells from βEEDKO mice decreased over time and was lost in >90% of insulin-positive cells by 8 weeks of age. βEEDKO mice also had marked glucose intolerance and all βEEDKO animals developed T2DM by 25 weeks of age. Interestingly, the putative β-cells in the islets of βEEDKO mice were negative for all major islet endocrine hormones, including insulin. In addition, the βEEDKO cells exhibited reduced levels of mature β-cell markers, suggesting the loss of cellular identity. Finally, transcriptomic analyses of βEEDKO islets recapitulated the results from HFD-fed mice and humans.

The researchers conclude that PRC2 mediates stable β-cell function and identity through global gene silencing.

Ivone Leong

ORIGINAL ARTICLE Lu, T. T.-H. et al. The polycomb-dependent epigenome controls β cell dysfunction, dedifferentiation, and diabetes. *Cell Metab.* https://doi.org/10.1016/j.cmet.2018.04.013 (2018)

PCOS

Mechanism underlying beneficial effects of exercise in PCOS identified

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism and hyperinsulinaemia. Despite being one of the most common endocrine disorders in women of reproductive age, understanding of the disorder and effective treatments is still lacking. In a rat model of PCOS, researchers have now determined that exercise activates the phosphoinositide 3-kinase (PI3K)–protein kinase B (PKB, also known as AKT) pathway by reducing the expression of 5α-reductase type 1 (5αR1; an enzyme that regulates androgen levels).

Chuyan Wu and co-workers generated the rat model by injecting 21-day old Wistar female rats with testosterone propionate for 28 days, while feeding them a high-fat diet. The rats were then divided into seven groups: sedentary; sedentary and 5αR1 inhibitor (5αR1I); sedentary and 5αR2I; exercise; exercise and 5αR1I; exercise and 5αR2I; and control (no PCOS). The exercised rats swam for 120 min per day, 6 days a week for 2 weeks. At the end of the treatment period, blood and skeletal muscle samples were taken and Western blots were used to determine expression levels of 5αR and phosphorylation levels of PI3K and AKT.

The researchers found that the 'sedentary', 'sedentary and 5αR1I', 'sedentary and 5αR2I' and 'exercise and 5αR1I' groups had increased levels of 5αR1 compared with the control group. The expression of 5αR1 was reduced in the 'sedentary and 5αR1I', 'exercise', 'exercise and 5αR1I' and 'exercise and 5αR2I' groups compared with the sedentary group. In addition, the 'sedentary' and 'exercise and 5αR1I' groups had reduced phosphorylation of PI3K and AKT, whereas the 'exercise and 5αR2I' group had increased phosphorylation levels. The researchers therefore suggest that exercise activates the signalling pathways involved in glucose metabolism in the skeletal muscle of rats with PCOS by reducing the expression of 5αR1.

Claire Greenhill

ORIGINAL ARTICLE Wu, C. et al. Exercise activates the PI3K–AKT signal pathway by decreasing the expression of 5α-reductase type 1 in PCOS rats. *Sci. Rep.* **8**, 7982 (2018)

IN THE NEWS

Highlights from ECE2018

In May, the endocrinology community gathered in Barcelona, Spain, for the European Congress of Endocrinology 2018 (ECE2018). More than 3,000 delegates, from 90 different countries, attended 4 days of talks and lively debates organized by the European Society for Endocrinology.

Gerald Shulman from the Yale School of Medicine, USA, gave a fascinating plenary talk about his group's research on the cellular mechanisms linking insulin and nonalcoholic fatty liver disease. Other interesting plenary sessions discussed the role of gonadotropin-releasing hormone-expressing neurons in fertility and how retinal assessments could be used to identify patients with type 2 diabetes mellitus who are at risk of developing Alzheimer disease.

The European Hormone Medal winner, Ilpo Huhtaniemi (Imperial College London, UK), gave an insightful presentation on the highlights of his research career and his work in the hypothalamic–pituitary–gonadal axis. Additionally, Philippe Chanson (University Paris-Sud, France), winner of the Clinical Endocrinology Trust Award, gave an interesting talk about growth hormone treatments.

Of the many excellent symposiums, those on endocrine-disrupting chemicals (EDCs) were particularly popular, including an excellent talk from Cheryl Walker (Texas A&M University, USA) on the effect of EDCs on the epigenome in relation to adult onset diseases. Another session that generated much interest was the symposium on disorders of sexual development. Julie Bakker's (Liège Université, Belgium) presentation on the brain structure and function of prepubertal children and adolescents diagnosed with gender dysphoria was a highlight for me.

The 'for and against' debates were also popular and the debate on whether anti-Müllerian hormone is a primary marker of fertility was well attended. Another debate that drew the attention of many delegates was on whether the European Commission's guidelines on EDCs are sufficient to protect human health.

Overall, the meeting provided a great environment for endocrinologists from all disciplines to discuss their research and form new collaborations. We look forward to ECE2019, which will be held in Lyon, France.

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