DIABETES

Targeting PTP1B in islet grafts

Credit: GlobalP/Getty

One of the main reasons that attempts to treat type 1 diabetes mellitus with transplanted pancreatic islets have been unsuccessful is that islet grafts undergo deficient vascularization, which leads to graft loss. Now, Ramon Gomis, Rosa Gasa and colleagues show that the protein tyrosine phosphatase 1B (PTP1B) is a potential therapeutic target to improve islet graft vascularization.

PTP1B is known to inhibit phosphorylation of vascular endothelial growth factor A (VEGFA) and vascular endothelial cadherin, which are important factors in angiogenesis. To investigate PTP1B importance in islet grafts, the researchers used a PTP1B-deficient mouse model (PTP1B$^{-/-}$). Notably, islets isolated from PTP1B$^{-/-}$ mice showed a decreased rate of endothelial cell loss in vitro, as compared with islets from wild-type animals.

In vivo experiments showed that PTP1B$^{-/-}$ mouse islets could be successfully transplanted into a diabetic mouse model. Transplantation resulted in normalized plasma glucose and insulin levels. Of note, the eye was used as the site of islet engraftment, as it represents an immune privileged and highly vascular location and it is easily and non-invasively imaged in living animals.

Further analysis of transplanted PTP1B$^{-/-}$ islets showed that compared with islets derived from wild-type animals, the PTP1B$^{-/-}$ islets grafted into diabetic mice had improved revascularization and survival rates. Moreover, islets from PTP1B$^{-/-}$ mice that were cultured in vitro in nutrient-deprived conditions or were transplanted into diabetic mice had increased VEGFA production.

Importantly, in vitro interfering RNA experiments in islets obtained from human donors showed that silencing PTP1B can increase expression of VEGFA and improve islet graft revascularization.

"From a translational point of view, it will be exciting to test non-genetic approaches to inhibit PTP1B in islets," explains Gasa. "It will also be interesting to investigate whether stem cell-derived β-cells respond similarly to PTP1B inhibition, as improved vascularization together with the use of patient-derived inducible pluripotent stem cells as a cell source might greatly improve the chances of successful and long-term maintenance of the transplant."

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ORIGINAL ARTICLE Figueiredo, H. et al. Targeting pancreatic islet PTP1B improves islet graft revascularization and transplant outcomes. *Sci. Transl Med.* **11**, eaar6294 (2019)

OBESITY

Mechanistic insights into overeating

Rachel Perry, Gerald Shulman and colleagues have identified glucocorticoid stimulation of Agouti-related protein (AgRP) neurons as a potential therapeutic target for overeating under conditions of leptin deficiency. These new data could have implications for the development of therapeutics that aim to treat hyperphagia (excessive eating) in patients with hypoleptinaemia.

Leptin is a hormone secreted by adipocytes. "It has been known since the discovery of leptin that leptin deficiency leads to massive hyperphagia and obesity in rodents as well as in humans; however, it is not known how leptin suppresses food intake," explains lead author Perry. "In our study, we wanted to understand whether leptin suppresses food intake directly (by altering the regulation of appetite by the central nervous system) and/or indirectly."

The team studied rats and mice under three conditions: starvation, diabetic ketoacidosis and hypoglycaemia. To examine the specific role of leptin and glucocorticoids on appetite in these animal models, Perry and colleagues infused them with leptin, with or without corticosterone. The team also generated mice with a genetic modification that decreased corticosterone action in AgRP neurons to test whether these neurons mediated the effects of hypoleptinaemia-driven increases in corticosterone to promote food intake.

Perry and colleagues found that in starvation and diabetic ketoacidosis, glucocorticoids, which are found in increased

METABOLISM

Microbiota supplements to improve metabolic health

Commensal microbiota in the gastrointestinal tract contribute to the regulation of host metabolic health. In addition, complex metabolic diseases are associated with imbalances in microbiome composition. For instance, obesity and type 2 diabetes mellitus are correlated with decreased abundance of the commensal bacterium *Akkermansia muciniphila*. A new clinical study by Patrice Cani and co-workers now explores the feasibility, safety and tolerability of administering *A. muciniphila* to humans to reduce the risk factors that characterize the metabolic syndrome.

Prior to this study, translational research in rodents by Cani's group and others had indicated that increasing *A. muciniphila* abundance might be a promising therapeutic strategy to enhance metabolic health. "We found that the bacteria were reinforcing the gut barrier leading to the blockage of gut permeability," explains Cani. "This improved glucose tolerance and enhanced the efficiency of using fat and glucose in metabolic tissues."

The researchers have now undertaken a randomized, double-blind, placebo-controlled pilot study in 32 volunteers with obesity and insulin resistance. The study participants were administered either live or pasteurized *A. muciniphila*, or placebo, daily for 3 months.

The primary end points of the study were safety, tolerability and readouts of metabolic health. Secondary outcomes were intestinal barrier function and gut microbiota composition. The researchers found that, following the 3-month regimen, study participants who were given the bacteria had improved insulin sensitivity, reduced plasma levels of total cholesterol and decreased plasma levels of biomarkers for liver dysfunction and inflammation compared with the placebo group. In addition, body weight