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DIABETES

Human iPSC-derived β-like cells rescue diabetic mice

Pancreatic islet transplantation holds promise as a potential cure for type 1 diabetes, but such donor islets are in short supply. Pluripotent stem cells provide a potential alternative source of pancreatic β-cells, but generating mature fully functional β-cells *in vitro* has been challenging. Now, writing in *Cell Metabolism*, Evans and colleagues demonstrate that overexpression of estrogen-related receptor-γ (ERRγ) in human induced pluripotent stem cell (iPSC)-derived β-like cells renders them capable of glucose-stimulated insulin secretion (GSIS) and reversing diabetes when transplanted into mice.

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β-cells functionally mature postnatally, including acquiring the ability to carry out GSIS. iPSC-derived β-like cells resemble fetal cells in their inability to secrete insulin in response to glucose, which has presented a major roadblock to their therapeutic application. Evans and colleagues therefore set out to identify crucial pathways required for GSIS.

To do this, they first compared the transcriptomes of islets isolated from mice at different time points during postnatal maturation. Genes involved in cell proliferation were found to be downregulated during islet maturation, whereas upregulated genes were associated with metabolic pathways, particularly glucose metabolism and ATP biosynthesis, including mitochondrial genes known to regulate GSIS. Notably, expression of ERRγ — a known mitochondrial gene regulator — was progressively induced during islet maturation.

Next, the authors investigated the potential role of ERRγ in the functional maturation of β-cells. They generated β-cell-specific ERRγ-knockout (βERRγKO) mice and found them to be glucose intolerant and unable to perform GSIS. Notably, the βERRγKO phenotype was exaggerated by metabolic stress after weaning and was phenocopied in both inducible β-cell-specific deletion and pancreatic-specific ERRγKO mouse models.

Further analysis of islets from the mouse models, including RNA sequencing and microarray studies, indicated that ERRγ is required to maintain mitochondrial function in functionally mature β-cells and also directly orchestrates many of the transcriptional changes that drive postnatal β-cell maturation.

The authors then investigated the effects of ERRγ overexpression in human iPSC-derived β-like cells. First, they optimized the differentiation protocol for producing insulin-positive β-like cells from human iPSCs, followed by adenoviral overexpression of ERRγ in these cells. The resultant 'iβeta' cells exhibited an altered expression profile of metabolic pathway genes similar to that seen in human islets and were capable of GSIS *in vitro*.

Finally, Evans and colleagues transplanted iβeta cells into the kidney capsule of mice that had been treated with streptozotocin — a model of type 1 diabetes. The iβeta cells began to lower blood glucose levels within days of transplantation, and levels were normalized within a few weeks, similar to mice receiving functional human or mouse islets. Importantly, approximately 50% of the iβeta cell recipient mice exhibited non-diabetic blood glucose levels at 2 months after transplantation, concomitant with a glucose-responsive phenotype, and improvements in the circadian regulation of glucose and lipid metabolism.

Together, these findings reveal a key role for ERRγ in β-cell metabolic maturation, and should accelerate the development of patient-specific glucose-sensitive insulin-producing β-cells.

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