DIABETES

New role for oestrogen-related receptor γ in β -cell maturation

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Generating functional pancreatic β cells has been a focus of diabetes research over the past few years, but this approach has faced many challenges. New findings published in *Cell Metabolism* show that oestrogen-related receptor γ (ERR γ , which regulates oxidative pathways in mitochondria) is required for post-natal maturation of β cells. These findings could affect the approach to generating functional human β -cell therapeutics *in vitro*.

During postnatal maturation, β cells gain the ability to secrete insulin in response to high levels of glucose. In order to identify which pathways are required for this response, the researchers compared the transcriptomes of isolated islets from mice during the maturation process. Genes associated with metabolic pathways (such as glucose metabolism and ATP biosynthesis) were found to be upregulated after maturation.

Interestingly, the expression of *Erry* increased progressively during the maturation of β cells. In addition, expression of *Erry* was approximately five times higher in adult β cells than in neonatal β cells.

Next, the researchers created a β -cell specific *Erry* knockout mouse (termed β ERR γ KO) by crossing *Erry*^{fl/fl} mice with rat insulin 2 promoter (RIP)-CRE mice. The β ERR γ KO mice were glucose intolerant compared with control mice (*Erry*^{fl/fl} mice or RIP-CRE mice), and the phenotype was exaggerated under conditions of metabolic stress (such as a diet high in sucrose and fat).

As ERR γ is known to regulate mitochondrial oxidative phosphorylation and metabolism in several tissues, the investigators questioned whether it was also required for mitochondrial function in the islets. ERR γ deletion in isolated islets diminished glucose responsiveness, the oxygen consumption rate and glucose-stimulated insulin secretion (GSIS); similar effects were seen with ERR γ knockdown in the rat β -cell line INS-1). "These results suggest that ERR γ regulation of β cell energy metabolism is required for GSIS," write the researchers.

Once the investigators had established the role of ERR γ in the maturation of β cells, they wanted to determine if overexpression of ERR γ could rescue GSIS function in β -like cells derived from induced pluripotent stem cells (iPSCs). The researchers used adenoviral ERR γ (Ad-ERR γ) or control (Ad-GFP) vectors to infect iPSC-derived β -like cells at day 22–25. Gene expression and functional analyses were then performed at days 25–30, using

human C-peptide levels as a surrogate marker of insulin. The Ad-ERR γ vector restored ERR γ expression, without affecting the intracellular levels of C-peptide. Importantly, the control cells did not secrete C-peptide in response to a glucose challenge, whereas cells infected with the Ad-ERR γ vector secreted C-peptide in a similar manner to isolated human islets.

A key question is whether these cells function *in vivo*. The researchers used NOD-SCID mice with streptozotocin-induced diabetes to address this question. iPSC-derived β -like cells infected with either Ad-ERR γ or Ad-GFP vectors were transplanted into the kidney capsules of the mice, and glucose levels were monitored. Importantly, blood glucose levels normalized in the mice that received cells containing the Ad-ERR γ vector and insulin-positive cells were detected in the kidneys 2 months after transplantation.

"These results demonstrate that increased oxidative mitochondrial metabolism driven by ERR γ expression may be exploited to potentiate GSIS function in human iPSC-derived β -like cells," write the authors. The researchers hope that their work will contribute to the development of functional β cells that can be used to treat patients with diabetes mellitus.

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ORIGINAL ARTICLE Yoshihara, E. et al. ERR γ is required for the metabolic maturation of therapeutically functional glucose-responsive β cells. *Cell Metab.* <http://dx.doi.org/10.1016/j.cmet.2016.03.005> (2016)

FURTHER READING Wang, P. et al. Diabetes mellitus—advances and challenges in human β -cell proliferation. *Nat. Rev. Endocrinol.* **11**, 201–212 (2015)