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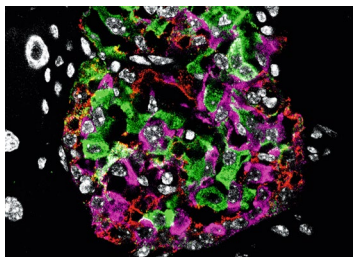
DIABETES

Restoring β-cells



The image shows a pancreatic islet from a mouse with streptozotocin-induced diabetes mellitus, with staining for the most frequent cell types in these islets. White stains for the cell nucleus (DAPI staining). β-cells (insulin) are stained green, α-cells (glucagon) are red and δ-cells (somatostatin) are in magenta. Image courtesy of Heiko Lickert, Institute for Diabetes and Regeneration at the Helmholtz Center Munich, Germany.

Dedifferentiation of β-cells is thought to be a major mechanism underlying β-cell loss and dysfunction in type 1 and type 2 diabetes mellitus; however, whether this process could be targeted pharmacologically was unknown. New research demonstrates that β-cell dedifferentiation can be targeted to restore β-cell function in mice with streptozotocin-induced diabetes mellitus.

Previous papers have shown that a GLP1–oestrogen conjugate can reverse the metabolic syndrome in mice and that oestrogen has positive effects on β-cells. "Hence, in our current study we hypothesized that the targeted delivery of oestrogen to GLP1R-expressing pancreatic β-cells could achieve additional metabolic benefits to stop or revert diabetes mellitus progression," explain authors Stephan Sachs and Heiko Lickert. The authors treated mice with multiple low doses of streptozotocin to induce diabetes mellitus while allowing some β-cells to survive. The mice were then divided into treatment groups to receive: a GLP1–oestrogen conjugate; GLP1; oestrogen; a long-acting pegylated insulin analogue (PEG-insulin); or a combination of GLP1–oestrogen and PEG-insulin. "Using single-cell RNA sequencing (scRNA-seq), we show that the surviving β-cells after the initial streptozotocin treatment dedifferentiate into a dysfunctional state," explain Sachs and Lickert. This data also allowed the researchers to compile a detailed transcriptomic landscape of dedifferentiated β-cells.

The scRNA-seq data also demonstrated that the PEG-insulin treatment and combined treatment of GLP1–oestrogen and PEG-insulin led to redifferentiation of β-cells. Furthermore, this redifferentiation resulted in functional β-cell recovery and remission of diabetes mellitus in the mouse model. "Combining GLP1–oestrogen with PEG-insulin therapy achieved superior metabolic benefits compared with the mono-treatments, normalizing glycaemia and glucose tolerance, increasing pancreatic insulin content and increasing the number of β-cells," say Sachs and Lickert. The combination therapy also meant that the dose of insulin could be reduced, mitigating the adverse effects of insulin treatment. "We could also show that GLP1–oestrogen, but not GLP1 or oestrogen alone, increases human β-cell function when human pancreatic islets are exposed to cytokine stress, which is known to impair human β-cell function," explain Sachs and Lickert. The researchers hope that their work will pave the way for future studies in this area and ultimately the development of novel therapies to regenerate β-cells and result in diabetes mellitus remission.

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ORIGINAL ARTICLE Sachs, S. et al. Targeted pharmacological therapy restores β-cell function for diabetes remission. *Nat. Metab.* **2**, 192–209 (2020)