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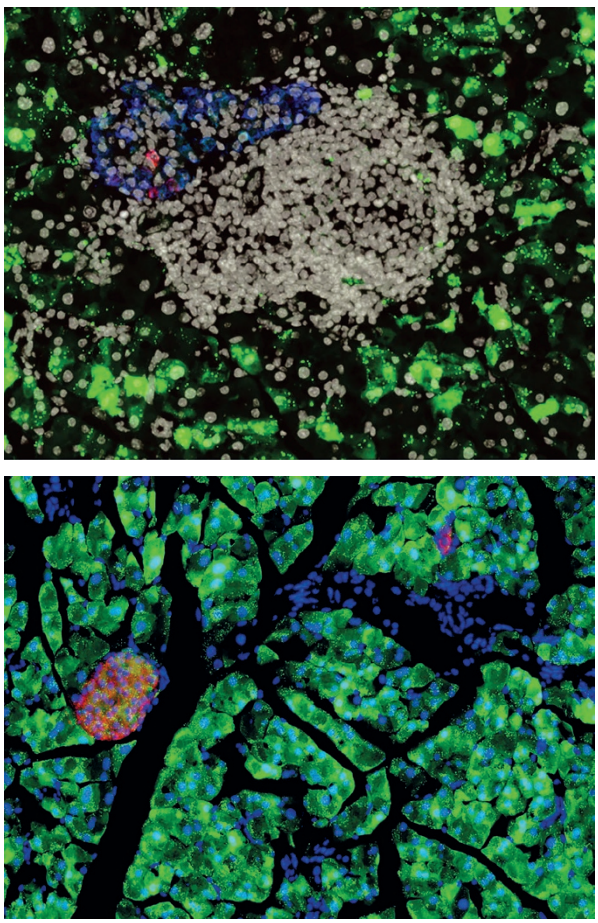
GENE THERAPY

Autoimmune diabetes reversed in mice

> “functional insulin-producing cells can be generated from human α-cells using this viral vector method”

A key goal of diabetes mellitus research is to preserve and restore β-cell function, with β-cell replacement receiving a lot of attention. However, these efforts have not yet led to viable treatments for patients. A new study published in *Cell Stem Cell* indicates that gene therapy could be used to reprogramme pancreatic endocrine cells and reverse autoimmune diabetes.



The top panel shows an islet with insulin (red) and glucagon (blue) cells in an autoimmune nonobese diabetic mouse after viral treatment. The bottom panel shows an intact islet after treatment of a wild-type mouse rendered diabetic by a β-cell toxin called alloxan. Images courtesy of Xiangwei Xiao.

George Gittes and colleagues were using viral vectors infused into the pancreatic duct to try and label duct cells for lineage tracing, when they decided to insert transcription factors instead. “This serendipitously resulted in transformation of α-cells into β-cells,” explains Gittes. As a result of this chance finding, the researchers conducted a series of further experiments to explore the effects of this transdifferentiation.

The investigators developed an adeno-associated virus that carries *Pdx1* and *MafA* expression cassettes — for transcription factors required for pancreatic development and that regulate the expression of *INS* (which encodes insulin) and β-cell metabolism, respectively. The viral vector was then infused through the pancreatic ducts of nonobese diabetic (NOD) mice and mice with β-cell-toxin-induced diabetes mellitus.

Delivery of the viral vector resulted in normalization of glucose levels in the toxin-treated mice, with an increase in the number of cells producing insulin. Lineage tracing demonstrated that these new cells were derived mainly from α-cells. NOD mice that received the viral vector early after the onset of hyperglycaemia (blood levels of glucose of 200 mg/dl) achieved euglycaemia for an average of 4 months. However, the treatment was less successful if started after blood levels of glucose had reached 400 mg/dl. Immunohistological analysis of the NOD mice that received the treatment early showed that the cell mass of insulin-producing cells had increased. In addition, electron micrographs showed that some of these cells contained insulin and glucagon granules. Given that the α-cells produce glucagon, this finding provides further support for the suggestion that the new insulin-producing cells are derived from α-cells.

Next, Gittes and colleagues treated human islets with streptozotocin to ablate the β-cells, followed by *in vitro* treatment with the viral vector. In culture, cells positive for both insulin and glucagon were detected after 3 days; the mass of α-cells had also decreased by 35%. The islets were also transplanted into NOD/SCID (severe combined immunodeficient) mice that had been treated with a β-cell toxin, which resulted in reduced blood levels of glucose and improved glucose tolerance. The islets were harvested 4 weeks after transplantation and were found to have an increased β-cell mass and insulin content. The researchers suggest that these results indicate that functional insulin-producing cells can be generated from human α-cells using this viral vector method.

“We suspect that the autoimmunity in the NOD mice might have eventually recurred; however, in normal mice, the new β-cells persisted for the life of the mouse,” explains Gittes. “These results are the first evidence of reversal of autoimmune diabetes without immunosuppression or transgenic approaches.” Gittes and colleagues are confident the techniques used in their study are translatable to humans and are currently assessing the approach in non-human primates with a view to applying for FDA approval for clinical trials in patients with type 1 or type 2 diabetes mellitus.

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ORIGINAL ARTICLE Xiao, X. *et al.* Endogenous reprogramming of alpha cells into beta cells, induced by viral gene therapy, reverses autoimmune diabetes. *Cell Stem Cell* **22**, 78–90.e4 (2018)