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GENE THERAPY

# Reprogramming α-cells reverses diabetes

Autoimmune destruction of insulin (INS)-producing pancreatic β-cells, resulting in persistent hyperglycaemia, underlies the pathogenesis of type 1 diabetes. Preserving and restoring functional β-cell mass is therefore a fundamental objective of diabetes therapy. Writing in *Cell Stem Cell*, Gittes and colleagues report the successful conversion of endogenous mouse α-cells into functional β-like cells, which reversed autoimmune diabetes in mice.

Accumulating evidence indicates that the β-cell possesses limited potential for regeneration in adult humans, therefore the possibility of reprogramming other cell types — to become glucose-responsive, INS-secreting β-like cells — is being actively pursued. Pancreatic α-cells may represent a promising source of β-cells owing to several reasons, including their developmental similarity to β-cells, their location in the pancreatic islet, the fact that they commonly undergo hyperplasia in diabetic animals and patients, and the finding that a significant decrease in α-cells in mice does not affect normal glucose metabolism.

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Gittes and colleagues therefore set out to convert α-cells into β-like cells through the forced expression of the key β-cell transcription factors, pancreatic and duodenal homeobox 1 (PDX1; necessary for pancreatic development — including β-cell maturation, proliferation and function) and MAFA (which binds to the INS promoter to regulate INS expression and β-cell metabolism).

First, the authors treated a transgenic mouse model that allows lineage tracing of α-cells with the β-cell toxin alloxan (ALX), to destroy the majority of β-cells and induce hyperglycaemia. One week later they infused an adeno-associated virus (AAV) carrying PDX1 and MAFA expression cassettes (AAV-PM) through the pancreatic duct. ALX-induced hyperglycaemia was corrected within 2 weeks in mice receiving the AAV-PM. In addition, β-cell mass was significantly increased in the mice, while α-cell mass was decreased. The regenerated $INS^+$ cells were found to derive almost exclusively from α-cells and had a similar gene expression profile to normal β-cells.

Importantly, AAV-PM induced prolonged glucose control: in hyperglycaemic non-obese diabetic (NOD) mice, a single infusion of AAV-PM increased $INS^+$ cell mass and led to durable euglycaemia for approximately 4 months, in contrast to control mice which exhibited continuously increasing blood glucose and died within 5 weeks.

Finally, the authors investigated whether human α-cells may similarly be reprogrammed into functional $INS^+$ cells. Human islets were treated with streptozotocin to destroy β-cells, and then treated with AAV-PM to trigger α-cell to β-cell conversion. The cells were then transplanted into ALX-treated hyperglycaemic NOD mice. Within 1 week, the mice exhibited significantly lower blood glucose levels and improved glucose tolerance. The grafts were harvested 4 weeks after transplantation, and were found to have significantly higher INS content and $INS^+$ cell numbers than control mice.

This study has demonstrated the feasibility of endogenous α-cell to β-cell conversion. The approach is currently being tested in non-human primates.

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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* https://doi.org/10.1016/j.stem.2017.11.020 (2018)



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