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DIABETES

Fasting and β cell regeneration

> …a fasting-mimicking diet (FMD) can promote the regeneration of insulin-producing β cells…

The reprogramming of pancreatic β cells to restore insulin production has been proposed as a potential therapeutic strategy for type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). New research published in *Cell* now suggests that a fasting-mimicking diet (FMD) can promote the regeneration of insulin-producing β cells and reverse diabetes mellitus in mouse models of T1DM and T2DM.

"We developed a FMD that causes changes in factors such as insulin-like growth factor 1 (IGF1), glucose and ketone bodies that were similar to changes caused by water-only fasting," explains Valter Longo, the lead investigator. During 4-day FMD cycles, mice received 50% of their daily caloric intake on day 1 and 10% on days 2–4, and this was followed by 're-feeding' (up to 10 days of *ad libitum* feeding between cycles). In mouse models of T1DM and T2DM with insulin deficiency and severe hyperglycaemia, the researchers demonstrated that six to eight cycles of FMD and re-feeding could restore insulin-producing β cell mass and normalize blood levels of glucose.

To identify the genes regulating FMD-induced β cell regeneration, pancreatic gene expression was measured. "The cycles of the FMD followed by normal feeding in these mice increased the expression of a set of genes normally expressed during fetal development," explains Longo. Marked upregulation of *Foxo1* and its transcriptional targets were initially observed post FMD, followed by induction of endocrine progenitor marker *Ngn3* (neurogenin 3). This metabolic reprogramming led to the generation of insulin-producing β cells in the mouse models.

Similar effects were observed *ex vivo* in primary pancreatic islets from humans with T1DM. Importantly, fasting-mimicking conditions induced expression of *NGN3* and promoted insulin production. This pancreatic regeneration was found to be primed by a reduction in levels of IGF1, and consequent dampening of downstream protein kinase A (PKA) and mechanistic target of rapamycin (mTOR) activity.

Overall, the findings suggest that a short-term FMD can promote *NGN3*-driven lineage reprogramming to restore insulin production by β cells and systemic glucose homeostasis in mouse models of T1DM and T2DM. "These results provide the first demonstration of an intervention that causes a highly coordinated cellular reprogramming leading to the generation of specialized and functional cells," concludes Longo. "In addition to performing clinical trials on the effect of the FMD on both T1DM and T2DM, we will test its effects on other organs and systems in mice".

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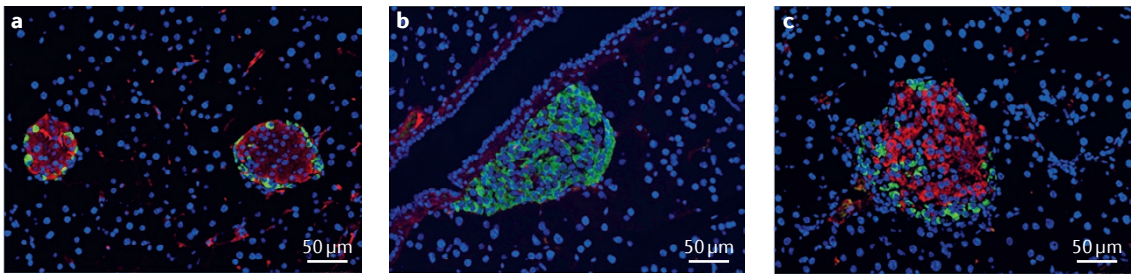
ORIGINAL ARTICLE Cheng, C.-W. *et al.* Fasting-mimicking diet promotes Ngn3-driven β-cell regeneration to reverse diabetes. *Cell* **168**, 775–788 (2017)



Immunostaining of insulin (red), glucagon (green) and DAPI stained nuclei (blue) in normal murine pancreatic islets (**a**), and in damaged pancreatic islets derived from mouse models of type 1 diabetes mellitus (T1DM) fed a normal diet (**b**) or cycles of a fasting-mimicking diet (**c**). Image courtesy of V. Longo, University of Southern California, USA.