Nature Reviews Endocrinology | Published online 23 Jun 2017; doi:10.1038/nrendo.2017.82

DIABETES

Why β cells fail in T2DM

> "…HDAC inhibitors could be a viable approach for patients with T2DM…"

Impaired insulin secretion has long been recognized as a key feature in the pathogenesis of type 2 diabetes mellitus (T2DM), with loss of β-cell mass and defective β-cell function both proposed to be the cause. Now, in new research, mature adult β cells are shown to dedifferentiate to a less functional phenotype with progression of T2DM. The findings potentially reconcile the opposing views on how insulin secretion becomes impaired in T2DM by suggesting that the functional β-cell mass reduces.

Using microarrays and co-expression network analysis, Rosengren and colleagues genetically profiled pancreatic islets from 123 human donors, 41 of whom had T2DM. The team identified a module of 168 genes with islet-specific open chromatin that was associated with T2DM-associated traits (diabetes status, levels of HbA_{1c} and insulin secretion). Comparison of the module with publicly available microarray data sets revealed high similarity between the T2DM signature and that of artificially dedifferentiated human islets, suggesting that the module is characteristic of an immature β-cell phenotype.

Analysis of transcription factor binding sites in the 168 genes revealed a large number of putative SOX5 binding sites. Knockdown of *Sox5* in rat insulinoma cells (INS-1 832/13) induced gene expression changes similar to those seen in donors with T2DM (that is, decreased expression of the 168 genes) and had marked effects on insulin secretion, including reductions in depolarization-evoked Ca^{2+} influx and β-cell exocytosis. By contrast, overexpression of *Sox5* increased expression of the 168 genes. Moreover, overexpression of *SOX5* in human islets isolated from donors with T2DM improved glucose-stimulated insulin secretion. Overall, the findings suggest that levels of SOX5 are suppressed in T2DM, which results in decreased expression of genes in the module and resultant loss of β-cell secretory capacity.

Finally, as the module contained genes with open chromatin, the team investigated the potential of the histone deacetylase (HDAC) inhibitor valproic acid to remodel the chromatin of the 168 genes and thus restore β-cell function. Treatment of INS-1 832/13 cells with valproic acid markedly increased *Sox5* mRNA levels and stimulated both insulin secretion and expression of most genes in the module, thereby recapitulating the effects of *Sox5* overexpression.

"Targeting β-cell dedifferentiation with HDAC inhibitors could be a viable approach for patients with T2DM," suggests Rosengren. "As HDAC inhibitors are already used to treat diseases such as epilepsy, these agents could be repurposed to treat T2DM." However, Rosengren acknowledges that the potential beneficial effects on glucose control need to be balanced against the adverse effects of HDAC inhibitors.

David Holmes

ORIGINAL ARTICLE Axelsson, A. S. *et al.* Sox5 regulates beta-cell phenotype and is reduced in type 2 diabetes. *Nat. Commun.* **8**, 15652 (2017)