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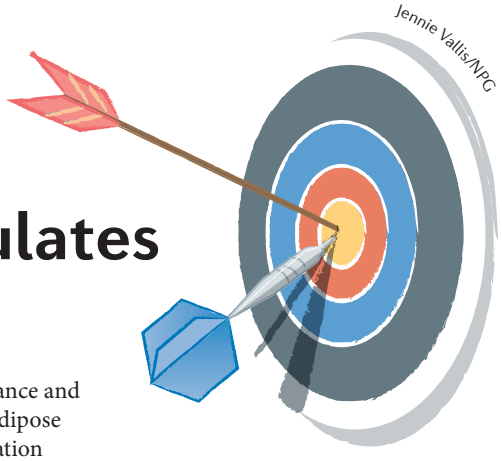

DIABETES

Incretin pathway regulates β-cell survival

Newly published data have shown that the incretin hormone glucose-dependent insulinotropic polypeptide (GIP) promotes β-cell function and survival via regulation of *TCF7* expression. This mechanism is distinct from that of glucagon-like peptide-1 (GLP-1), and highlights the potential therapeutic benefits of dual incretin agonism.

Incretins are produced by intestinal cells, and their actions include augmentation of glucose-stimulated insulin secretion (GSIS) by pancreatic β cells. GLP-1-receptor agonists such as exenatide and liraglutide are established treatments for type 2 diabetes mellitus (T2DM). Less is known about the mechanism of action of GIP than about GLP-1. In wild-type mice, GIP promotes GSIS, but is also involved in accretion of adipose tissue; blocking GIP signalling can prevent obesity and insulin resistance resulting from a high-fat diet (HFD).

In a study led by Jonathan Campbell and Daniel Drucker, the role of GIP signalling in β cells was investigated by the generation of mice with deletion of the gene encoding the GIP receptor (GIPR) specifically in adult β cells. The mice had improved glucose tolerance and GSIS at 18 weeks, and less adipose tissue than controls. Stimulation of insulin levels in these mice by HFD or insulin replacement caused weight gain and worsening of glucose tolerance and GSIS, indicating that the effect of GIP on adiposity and insulin resistance in wild-type mice is indirect and results from stimulation of insulin release from β cells.

Gipr$^{-/-}$ β cells exhibited sensitivity to apoptosis and a reduction in expression of *Tcf7*, which encodes T cell-specific transcription factor-1 (TCF1). By contrast, *Tcf7* expression was not affected in pancreatic islets from *Glp1r*$^{-/-}$ mice.

In a *Tcf7*$^{-/-}$ knockout mouse strain, GSIS and glucose tolerance were found to be impaired in 12-week-old mice fed an HFD or 18-week-old animals fed a low-fat diet. Expression of human *TCF7* in islets was lower in individuals with obesity than in lean controls, and lower still in individuals with T2DM. Treatment of human islets with GIP increased *TCF7* expression, and in mice a similar effect was dependent on extracellular signal-regulated kinase activity, but independent of cAMP. *TCF7* knockdown with small interfering RNA (siRNA) treatment reduced GSIS in response to GIP, and also significantly increased numbers of apoptotic β cells compared with controls.

> “Expression of human *TCF7* in islets was lower in individuals with obesity than in lean controls”

The results demonstrate a new pathway for incretin activity involving GIP and TCF1. “The TCF1 protein is a powerful regulator of β-cell function and survival,” explains Drucker. “GIP-directed therapies might have a chance to benefit islets through mechanisms distinct from pathways activated by GLP-1.” This approach is now being explored. “Multiple companies have GIP-containing co-agonists about to enter the clinic or in clinical trials, and early data look encouraging,” concludes Drucker.

Robert Phillips

ORIGINAL ARTICLE Campbell, J. E. *et al.* TCF1 links GIPR signaling to the control of beta cell function and survival. *Nat. Med.* http:dx.doi.org/10.1038/nm.3997