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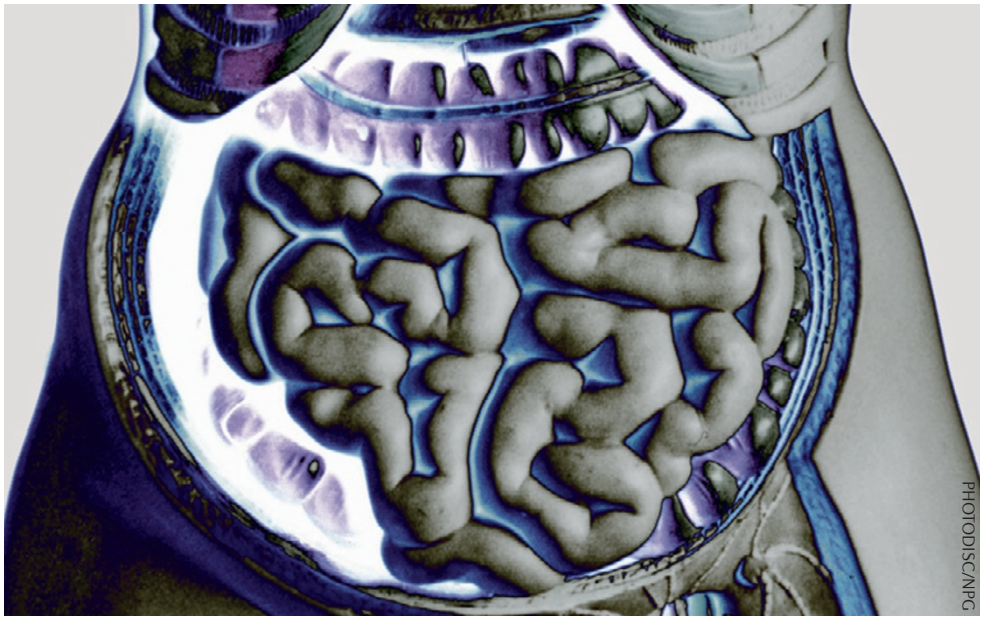

DEVELOPMENTAL BIOLOGY

Re-evaluating gut insulin instinct

Tissue types that take on very different biological roles in adults often originate from a shared precursor, the fate of which can be determined by the transcription factors it expresses. In a recent study, Talchai *et al.* found that by ablating one such transcription factor, forkhead box protein O1 (FOXO1), in mouse enteroendocrine progenitors, gut cells took on key characteristics of pancreatic β-cells, including insulin production.

Endocrine progenitors that express Neurog3 are found in the embryonic pancreas, where they go on to develop into all known pancreatic cell types, and in the adult stomach and intestines, where they give rise to most of the cells of the enteroendocrine system. The authors here sought to determine the role of FOXO1 in Neurog3$^+$cells in the gut. The targeted deletion of *Foxo1* in Neurog3$^+$ enteroendocrine precursors in mice (Neurog3–Cre-driven *Foxo1* knockouts (NKO)) led to the repression of HES1, a Notch-signalling transcription factor that restricts endocrine plasticity of Neurog3$^+$ cells in development.

When the authors examined the fate of the *Foxo1* ablated cells they found, to their surprise, the presence of pancreatic hormone-producing cells in the neonatal gut, including cells that produce insulin (gut Ins$^+$ cells). Furthermore, this insulin was bioactive in the regulation of blood glucose *in vivo* and was secreted in response to glucose in experiments on gut Ins$^+$ cells *in vitro*. Such regulated release of insulin has thus far been difficult to produce in embryonic-stem-cell-derived insulin-producing cells.

The regenerative capacity of the NKO gut Ins$^+$ cells was then tested in a model of diabetes that was induced by treating mice with the toxin streptozotocin. Administration of streptozotocin to NKO and wild-type mice caused hyperglycaemia, which was initially controlled with insulin administration. Following withdrawal of insulin, all of the wild-type mice died, whereas 75% of NKO mice survived; furthermore, NKO mice showed near-normal glucose tolerance. This effect was attributed to restoration of the gut Ins$^+$ cells after ablation by streptozotocin, indicating much potential for cell-based therapy in type 1 diabetes.

The authors then further probed the molecular mechanisms involved in the development of the gut Ins$^+$ cells. Marker analysis showed a derepression of the β-cell programme in the gut of NKO mice. In addition, lineage tracing showed that the gut Ins$^+$ cells arise by a cell-autonomous manner, suggesting that FOXO1 acts as a cell-autonomous repressor of pancreatic endocrine fate — potentially through altered Notch signalling and WNT signalling.

The plasticity of enteroendocrine cells shown here, and the ability to modulate the insulin production of gut Ins$^+$, raises improved prospects for the development of cell-based therapies for type 1 diabetes.

Hannah Stower

ORIGINAL RESEARCH PAPER Talchai, C. *et al.* Generation of functional insulin-producing cells in the gut by *Foxo1* ablation. *Nature Genet.* 7 Feb 2012 (doi:10.1038/ng.2215)