HIGHLIGHTS

DIFFERENTIATION

Time to change jobs?

At present, 150 million people worldwide are diabetic and, in *Current Biology*, Slack and colleagues now provide a possible alternative treatment for insulin-dependent diabetes. In embryonic development, the liver and pancreas are made from adjacent regions of endoderm, and they've managed to change the job of differentiating or differentiated liver cells by converting them into pancreatic cells.

The transcription factor Pdx1 probably determines the difference between the pancreas and the liver but, in previous studies that overexpressed *Pdx1* in various sites, no ectopic pancreas was produced. This led Slack and co-workers to suggest that suitable Pdx1 binding partners might be missing in the tissues studied, so they designed a modified active form of Pdx1 that does not require such partners.

The modified Pdx1 consisted of the VP16 activation domain from *Herpes simplex* virus fused to the carboxyl terminus of Xlhbox8 (the *Xenopus laevis* Pdx1 homologue). The mouse transthyretin (*TTR*) promoter — which directs expression to the liver — was used to control *Xlhbox8–VP16* expression and, to simplify visualization, the transgene included green fluorescent protein (GFP) under the control of the *elastase* promoter, which marks pancreatic differentiation.

Xenopus tadpoles containing the *TTR–Xlhbox8–VP16:elastase–GFP* transgene initially developed normally but, after 5 days, Slack and colleagues could see fluorescence in an area normally occupied by liver. In this area, they detected the presence of *insulin* and *glucagon* messenger RNAs (products of pancreatic endocrine cells) and of *amylase* mRNA (a product of pancreatic exocrine cells), which indicates the presence of differentiated pancreas that contains both exocrine and endocrine tissues.

When the authors looked at the expression of endogenous *TTR* mRNA in the transgenic tadpoles, they found that this liver-specific marker is quickly downregulated in the ectopic pancreas. Furthermore, they showed that the liver is already differentiating before the expression of the transgene is induced, which indicates that this conversion is 'transdifferentiation', rather than a change of developmental pathway in the embryo.

So, could liver cells be made to change jobs in humans? It seems the answer is yes, because when Slack and co-workers transfected the transgene into the human liver cell line HepG2, they found that most of the differentiated liver cells that received the construct converted into pancreatic cell types.

Expression of *Xlhbox8–VP16* is only transient in the liver, because *TTR* expression is downregulated as the conversion to pancreas occurs. However, once established, the ectopic pancreas persists. This procedure, which requires no permanent genetic change, could therefore represent an important discovery in the hunt for new treatments for insulin-dependent diabetes.

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References and links

ORIGINAL RESEARCH PAPER Horb, M. E. *et al.* Experimental conversion of liver to pancreas. *Curr. Biol.* **13**, 105–115 (2003)

FURTHER READING Tosh, D. & Slack, J. M. W. How cells change their phenotype. *Nature Rev. Mol. Cell Biol.* **3**, 187–194 (2002)