

New role for alpha cells as a source for new beta cells

The endocrine pancreas consists of the islets of Langerhans, which contain clusters comprising at least five types of cells: glucagon-producing α -cells, somatostatin-producing δ -cells, pancreatic polypeptide-producing (PP)-cells, ghrelin-producing ϵ -cells and insulin-producing β -cells. An inadequate mass of functioning pancreatic β -cells is a common feature of both type 1 and type 2 diabetes. Increasing the mass of functioning pancreatic β -cells can be viewed as a new strategy in the treatment of diabetes.

The mass of functioning pancreatic β -cells is determined by a balance between the ratio of regeneration and death of pancreatic β -cells. Enhancement of β -cell regeneration is one strategy to increase β -cells mass. Although β -cell regeneration is probably accounted for by β -cell replication and neogenesis, β -cell replication to increase β -cells mass solely occurs under a physiological setting, at least in mice¹. In contrast, neogenesis or transdifferentiation of β -cells is reported in cultured cells derived from the pancreas^{2,3}. In addition, new β -cells are formed from endocrine precursor cells in a murine pancreatic duct ligation model⁴. Accordingly, in certain tissue injury models, neogenesis of β -cells can occur *in vivo*. However, the pancreatic duct ligation model shows an inflammatory reaction in the pancreas. Such inflammation should be circumvented before one can apply the pancreatic duct ligation model to clinical treatment. For example, viral-mediated expression of transcription factors important for β -cell differentiation in pancreatic exocrine cells can reprogram the cell fate from non- β -cell to β -cells⁵. However, the use of viral vectors also induces an

inflammatory reaction and thus should be avoided. Induction of β -cell neogenesis or transdifferentiation without the associated inflammatory reaction would be helpful in increasing β -cell mass. In this regard, the recent study of Thorel *et al.*⁶ is intriguing. In their study, they used a transgenic mouse model of diphtheria-toxin-induced acute selective β -cell ablation. This method chemically destroyed more than 99% of β -cells in adult mice. Then, they kept the mice alive by insulin administration and followed β -cell regeneration in the pancreas of these mice. In that study, they used the lineage-tracing

method to identify the fate of the cells that express or previously expressed glucagon. They found that most regenerated β -cells arose from cells that expressed glucagon, not from the limited number of residual β -cells after destruction by diphtheria toxin. In contrast, this event was not observed when only half of the β -cells were destroyed. Thus, these experiments provided evidence for transdifferentiation of α -cells to β -cells and that such process occurred only when β -cells were specifically and almost completely destroyed.

During fetal pancreatic development, glucagon is the earliest peptide hormone

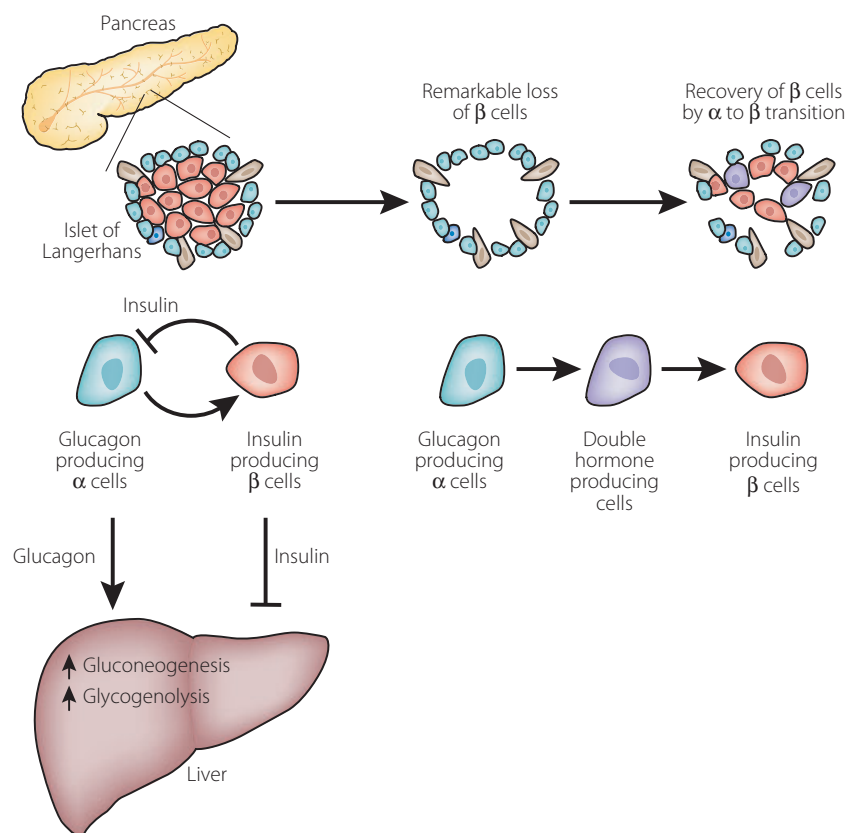


Figure 1 | Under physiological states, glucagon counteracts the effect of insulin. Glucagon secretion is affected by insulin and insulin secretion is affected by glucagon. Thorel *et al.*⁶ showed the new role of glucagon producing α -cells. When β -cells are completely destroyed, new β -cells can be generated from pre-existing α -cells.

*Corresponding author. Hirotaka Watada
Tel: +81-3-5802-1579 Fax: +81-3-3813-5996
E-mail address: hwatada@med.juntendo.ac.jp
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present at appreciable levels in the pancreatic primordial. These cells sometimes co-express insulin. Thus, it was proposed previously that all islet cell types seem to arise from glucagon-positive cells⁷. In fact, exogenous Pdx-1 expression in α -cell-derived cell lines induces endogenous expression of some β -cell-specific genes^{8,9}, suggesting the likelihood of α - to β -cell transition. However, the results of lineage tracing analysis showed that adult α - and β -cells are derived from cells that have never transcribed insulin or glucagon¹⁰. Accordingly, during the fetal pancreatic development process, adult β -cells are not derived from glucagon-expressing cells.

In contrast, Thorel *et al.*⁶ provided clear evidence for α to β transition in adult mice. Intriguingly, several recent studies have also provided *in vivo* evidence of plasticity of α -cell differentiation into β -cells. For example, Menin is a well-known tumor suppressor gene. Mutation of this gene causes multiple endocrine neoplasia type 1 (MEN1), characterized by multiple endocrine tumors affecting the parathyroid, anterior pituitary and endocrine pancreas. As expected, disruption of β -cell-specific menin in mice induces insulinomas. In contrast, ablation of α -cell-specific menin induces the appearance of cells that share the characteristics of both α - and β -cells in young mice. Eventually, growth of not only glucagonomas, but also a large number of insulinomas, was noted in the pancreas of the mutant mice¹¹. In addition, ectopic expression of Pax4, a transcription factor essential for differentiation of β -cells, was reported to cause reprogramming of the cell fate of α -cells into β -cells¹².

Under physiological states, hypoglycemia induces glucagon secretion to counteract the action of insulin, predominantly in the liver. Although insulin inhibits hepatic gluconeogenesis and glycogenolysis, glucagon promotes hepatic gluconeogenesis and glycogenolysis, and ultimately increases blood glucose levels to counter hypoglycemia. Similar to the relationship between the actions of glucagon

and insulin, the secretion of insulin and glucagon affects each other. Indeed, insulin suppresses glucagon secretion from α -cells and glucagon stimulates insulin secretion from pancreatic β -cells. In addition, blocking the early expression of glucagon prevents β -cell differentiation in the early embryonic pancreas.

Taken together, these facts show that the physiological role of α -cells is to maintain glucose homeostasis in collaboration with β -cells. Transdifferentiation of α - to β -cells would definitely be helpful in maintaining glucose homeostasis as a long-term compensatory reaction, should a substantial loss of β -cells occur. In the meantime, we should consider the plasticity of α - to β -cells as a new role for α -cells to maintain glucose homeostasis (Fig. 1).

There are still many unsolved questions regarding the plasticity of α - to β -cells. Why is the transdifferentiation of α - to β -cells active only when β -cell counts are substantially low? What kind of signal(s) regulates the transdifferentiation of α - to β -cells? Clarification of the signal involved in this phenomenon should help resolve the mechanism that controls the transdifferentiation of α -cells to β -cells. Augmentation of β -cell mass by enhancing α -cell differentiation into β -cells is an innovative therapeutic strategy in diabetes.

Hiroataka Watada*

Department of Medicine, Metabolism & Endocrinology, Juntendo University Graduate School of Medicine, Tokyo, Japan

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