Published in final edited form as:

Nature. 2010 April 22; 464(7292): 1132–1133. doi:10.1038/4641132a.

DIABETES FORUM Extreme makeover of pancreatic α -cells

Kenneth S. Zaret

Institute for Regenerative Medicine, Department of Cell and Developmental Biology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA. zaret@upenn.edu

Morris F. White

Howard Hughes Medical Institute, Division of Endocrinology, Children's Hospital Boston, and at the Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA. morris.white@childrens.harvard.edu

Abstract

Most insulin-secreting pancreatic β -cells are irreplaceably lost in type 1 diabetes. In a mouse model, pancreatic α -cells seem to sacrifice their identity to replenish the low stock of β -cells¹. Two experts discuss what this means for understanding the basic cell biology involved and its relevance to treating diabetes.

Pancreatic α - and β -cells are normally very stable: the cells live for a year or more, and when they divide, α -cells make α -cells and β -cells make β -cells. However, various types of damage to the pancreas and other internal organs can cause unexpected changes in cell type. In rats, for example, a toxic diet can cause liver cells to form in the pancreas² and intestinal cells to form in the liver³. Also, chronic tissue damage such as that caused by stomach-acid reflux into the oesophageal epithelium can lead to similar abnormal cell-type changes, as well as cancer⁴. For the most part, these 'transdifferentiation' phenomena have remained at the fringes of cell biology, largely because the events are rare and the initiating cells in which the conversions occur were not identified. Thorel and colleagues' study¹ provides a notable advance because the authors were able to genetically mark and follow the conversion of α -cells to β -like cells under conditions of extreme damage to the pancreatic β -cells (Fig. 1). Their observations set the stage for dissecting and controlling the cell-conversion process.

Is the generation of β -like cells from α -cells, after extreme β -cell damage, a mechanism of last resort that has evolved for the animal's survival? In times of starvation, animals may eat food far outside their normal diet. Toxic substances that are thereby ingested could acutely damage vital organs, favouring extreme mechanisms of regeneration that might result in cells that are only partially functional. Alternatively, could it be that the emergence of the β -like cells reflects an inherent plasticity of the differentiated state that, although fascinating to biologists, has no true physiological advantage?

In either case, understanding the signals that elicit such regeneration could provide unexpected insight into ways of manipulating cell differentiation for regenerative therapy. Specifically, defining the crucial extracellular components that initiate and maintain α -cell to β -cell conversion, as well as the necessary response pathways within the α -cell, should allow the conversion process to be enhanced by adding appropriate agonists of β -cell fate and antagonists of α -cell fate. (Such information might be more easily gleaned from *in vitro* assays of the α - to β -cell conversion.) The relevant signalling pathways would probably include those involved in the initial selection of α - and β -cells from their common progenitors during development, and pathways associated with sensing local damage and triggering inflammatory responses in the relevant tissue.

Thorel and colleagues' approach to cell reprogramming differs strikingly from those used previously^{5,6}, which typically involved virus-mediated introduction of regulatory genes to short-circuit a differentiated state and convert cells directly to another fate. The use of viral vectors can lead to unwanted inflammatory effects, which themselves may facilitate cell conversion⁷. It is important, therefore, to understand the signalling milieu in both of these contexts^{1,5,6}. Such information could help to enhance the generation of β -cells from stem cells, rather than from their sister α -cells. Until there is a cure for type 1 diabetes, we are not in a position to reject any unforeseen means by which β -cells can be regenerated.

Pancreatic β -cells secrete insulin, a hormone that is essential for the maintenance of physiological levels of blood glucose. In diabetes, β -cells are destroyed (type 1 diabetes) or their numbers and function are insufficient to compensate for insulin resistance (type 2 diabetes). Both types of diabetes result in abnormally high blood glucose levels and can cause kidney, eye and nerve damage, as well as cardiovascular disease.

Finding ways to restore the pancreatic β -cell population in patients with type 1 diabetes, or replace dysfunctional β -cells in patients with type 2 disease, is a challenging problem of top clinical priority. The transplantation of donor islets of Langerhans might eventually work, but this strategy is impractical in the near future, because high-quality donor islets are in short supply and have a limited useful lifespan after transplantation. So new ways to come up with healthy β -cells and cure diabetes are under investigation in laboratories around the world; these approaches include inducing the generation of β -cells from embryonic stem cells, the replication of existing β -cells and the conversion of other pancreatic cells into functional β -cells⁸.

There has been progress on all fronts, especially in identifying transcriptional programs and signalling cascades that can be exploited to make β -cells from stem cells⁹. But Thorel *et al.*¹ avoided investigating elaborate cell-based or pathway-based strategies for coaxing stem cells into β -cells. Instead, they carefully manipulated mice to show that mammals facing a fatal shortage of β -cells due to damage to the islets can restore them naturally by converting pre-existing glucagon-producing α -cells into insulin-producing cells — at least when an autoimmune response typical of type 1 diabetes is out of the picture. The process is slow, taking nearly five months before there are sufficient numbers of β -cells to control glucose levels. And no cell division is involved, as all the new β -cells come from pre-existing α -cells.

Previous experiments¹⁰, in which most of the pancreas was surgically removed to approximate β -cell deficiency, indicated that β -cell regeneration occurs by the replication of pre-existing β -cells. So what determines the pathway to regeneration? The transdifferentiation process observed by Thorel *et al.* might arise because α -cells are completely spared the damage inflicted by the diphtheria toxin, whereas β -cells are almost totally destroyed. But even so, it seems odd that, once new β -cells have been made from the conversion of α -cells, β -cell replication doesn't take over to further expand their repertoire. Eventually, it might also be important to replace the converted/depleted α -cells to maintain a correct glucagon–insulin ratio.

Although some of the new cells seem to produce both insulin and glucagon, suggesting that the conversion is difficult to achieve completely (Fig. 1), Thorel and colleagues' result is truly surprising. It reveals a previously unknown flexibility in the functioning of the pancreas in relation to hormone secretion, with the potential for exploiting it to cure diabetes. Indeed, an ideal solution would be to produce an oral medicine that could orchestrate this process¹ reproducibly and quickly in humans, and drive the total conversion to β -cells to avoid problems created by the co-secretion of insulin and glucagon.

The possibility of pursuing this work¹ as a starting point for research into alternative therapies for diabetes is especially intriguing, because, in patients with diabetes, α -cells are usually healthy and abundant. So the inter-conversion of α - to β -cells could provide a revolutionary approach to curing diabetes. But we're not there yet, and tough roadblocks lie ahead before such an approach becomes feasible.

As with all strategies, the destruction of new β -cells through autoimmunity in patients with type 1 diabetes will need to be managed. And it remains to be seen whether sufficient β -cells differentiate and survive in patients to cure their diabetes for life. Let us hope that Thorel and colleagues' work sparks other studies to achieve such a cure.

References

1. Thorel F, et al. *Nature*. 2010; 464:1149–1154. [PubMed: 20364121]
2. Rao MS, et al. *Am. J. Pathol.* 1989; 134:1069–1086. [PubMed: 2470253]
3. Elmore LW, Sirica AE. *Cancer Res.* 1993; 53:254–259. [PubMed: 7678071]
4. Slack JM. *Nature Rev. Mol. Cell Biol.* 2007; 8:369–378. [PubMed: 17377526]
5. Davis RL, Weintraub H, Lassar AB. *Cell*. 1987; 51:987–1000. [PubMed: 3690668]
6. Zhou Q, Brown J, Kanarek A, Rajagopal J, Melton DA. *Nature*. 2008; 455:627–632. [PubMed: 18754011]
7. Wang AY, Ehrhardt A, Xu H, Kay MA. *Mol. Ther.* 2007; 15:255–263. [PubMed: 17235302]
8. Borowiak M, Melton DA. *Curr. Opin. Cell Biol.* 2009; 21:727–732. [PubMed: 19781928]
9. German MS. *Nature Biotechnol.* 2008; 26:1092–1093. [PubMed: 18846076]
10. Dor Y, Brown J, Martinez OI, Melton DA. 2004. *Nature*. 429:41–46. [PubMed: 15129273]

THE PAPER IN BRIEF

- Thorel *et al.*¹ (page 1149 of this issue) chemically destroyed more than 99% of β -cells in adult transgenic mice (Fig. 1).
- The mice were kept alive with insulin treatment, and β -cell regeneration was studied.
- Replication of the rare surviving β -cells could not account for the regenerated population.
- Instead, the new β -cells arose from direct reprogramming of pancreatic α -cells.

Figure 1. A helping hand from α -cells

The islets of Langerhans in the pancreas contain both insulin-secreting β -cells and glucagon-secreting α -cells. Insulin lowers the level of glucose circulating in the bloodstream, whereas glucagon has the opposite effect. Thorel *et al.*¹ used diphtheria toxin to destroy almost all pancreatic β -cells in mice. The authors' cell-lineage tracing indicates that, following treatment with insulin over time, a population of α -cells passes through a bihormonal step (producing both insulin and glucagon; green cells) before becoming new β -cells.