Title
Diabetic β Cells: To Be or Not To Be?

Journal
Cell, 150(6)

ISSN
0092-8674

Authors
Puri, Sapna
Hebrok, Matthias

Publication Date
2012-09-01

DOI
10.1016/j.cell.2012.08.021

Peer reviewed

HHS Public Access

Author manuscript

Cell. Author manuscript; available in PMC 2015 December 28.

Published in final edited form as:

Cell. 2012 September 14; 150(6): 1103–1104. doi:10.1016/j.cell.2012.08.021.

Diabetic β Cells: To Be or Not To Be?

Sapna Puri[1] and **Matthias Hebrok**[1,*]

[1]Diabetes Center, Department of Medicine, University of California, San Francisco, San Francisco, CA 94143, USA

Abstract

β cell dysfunction with subsequent apoptosis is considered a significant contributor to the development of type 2 diabetes. Emerging data from Talchai et al. suggest β cell dedifferentiation as an alternative mechanism of insulin insufficiency that might be more amenable to intervention in at least a subset of patients.

Type 2 diabetes (T2D) is characterized by a steady decline in insulin secretion from pancreatic β cells, resulting in poorly regulated blood glucose levels that cause long-term complications in patients. It is widely accepted that β cells undergo premature programmed cell death as a consequence of exhaustion caused by unsustainable demands and that this naturally results in a reduction in circulating insulin (Chang-Chen et al., 2008). Talchai and colleagues now present an alternative scenario to explain compromised β cell function by demonstrating that adult murine β cells are modified in their differentiation state under conditions of physiological stress and assume a more progenitor-like state that permits conversion to other pancreatic endocrine cell types (Talchai et al., 2012).

Pancreatic β cells are highly sophisticated cells that respond to increases in blood glucose concentration with a rapid and commensurate release of insulin. Numerous physiological demands, including aging, pregnancy, and obesity, introduce stresses on the ability of the β cell to maintain normoglycemia. Talchai et al. now demonstrate that, under certain conditions of cellular stress, the β cell relies on a specific transcription factor for maintenance of cellular identity. FoxO1, a member of the FoxO family of transcription factors, has previously been implicated in integrating cellular responses to physiological stress and regulation of β cell mass (Buteau and Accili, 2007). The current study reports that ablation of *FoxO1* in murine β cells has little effect when the demand on β cells is low. In contrast, loss of the factor in β cells exposed to sustained stress results in a profound reduction of insulin-producing cells. Surprisingly, this reduction is not due to accelerated β cell death but, rather, is caused by the dramatic deconstruction of the mature β cell state. Transcription factors that activate insulin gene expression are missing, together with processing enzymes required for the production of the mature hormone and granules normally storing the insulin peptides in high concentrations. In short, FoxO1-deficient β cells are stripped of all functional attributes by unraveling the differentiation process that the cells have gone through during development. Remarkably, the mutant β cells may have

*Correspondence: mhebrok@diabetes.ucsf.edu.

regressed back along their original differentiation path, as they now express markers that are normally observed in multipotent endocrine progenitors. In other words, β cells have stepped back in ontogenic time to assume a stage similar to the one they progressed through during organ development (Figure 1).

Though it is unlikely that the differentiation state assumed by the *FoxO1* null cells is identical to the embryonic progenitor state found within the developing pancreas, dedifferentiated β cells can express other endocrine hormones. Also, plasticity of fate within the endocrine lineage has been recorded in mouse models of β cell depletion or ectopic expression of key regulatory factors (Collombat et al., 2007; Thorel et al., 2010). Importantly, decreased FoxO1 expression, reduction in the number of insulin-producing cells, and the presence of glucagon-expressing cells that are also positive for β cell markers were detected in other mouse models of T2D that are not driven by the genetic loss of *FoxO1*.

The findings described by Talchai and coworkers are important, as they beg the question of whether a compromised, dedifferentiated β cell (instead of β cell death) might be the culprit in a subset of T2D cases. Does cellular dedifferentiation provide β cells with an advantage to cope with the high demand posed by certain physiological conditions? For instance, during endoplasmic reticulum (ER) stress, mechanisms that are designed to ensure restoration of cellular functions can also initiate cell destruction if the underlying causes are not resolved (Oslowski and Urano, 2011). β cells are foremost hormone-producing cells, and this capacity to generate enough insulin can be exhausted under certain physiological conditions. Dedifferentiation, defined by reduction of all components of the insulin sensing, production, and secretion machinery as seen upon FoxO1 elimination, would dramatically reduce the need to perform at full capacity and might provide a shorter path to regeneration once the demand is reduced, as happens after pregnancy. In contrast, unabated demand caused by obesity and insulin resistance would prevent regeneration and result in further regression away from a mature β cell state.

If this scenario is correct, then the disabled β cells could present a window of opportunity during T2D progression when it might be possible to reverse this state and regain fully functional cells. In fact, transient loss of the β cell differentiation state has previously been noted upon inappropriate activation of the Hedgehog signaling pathway normally excluded from adult β cells (Landsman et al., 2011). Thus, conditions likely exist during which β cells possess the capacity to regenerate. Whether such transient states occur during T2D progression and whether β cell regeneration is possible remains to be explored.

A critical question not addressed is the relevance of the reported findings to the human condition. A prediction stemming from the current analysis would be that, in a subset of human T2D patients with mild hyperglycemia, nuclear FOXO1 expression would be present in insulin-positive cells. Islets of patients with longstanding disease should be devoid of both insulin and FOXO1. Furthermore, it would need to be tested whether “α-like” cells that express some β cell markers can be found in human T2D islets. Talchai and colleagues have observed hyperglucagonemia in *FoxO1* mutant mice; however, it is not clear whether this is caused by the fact that the glucagon-positive cells derived from β cells are functionally

compromised hybrids due to the inappropriate expression of β cell transcription factors. Additional questions concern the significance of the appearance of the pluripotency marker Oct4. Is the transcription factor expressed purely as a consequence of FoxO1 activity, or does it play a functional role in hindering the differentiation of the β cell? Similarly, the scant appearance of mesenchymal markers (that costain with glucagon-positive cells) raises more questions. Do the dedifferentiating β cells undergo an epithelialto-mesenchymal transition prior to adopting an α cell fate? Is there a requirement for this step to occur?

With ~79 million adult Americans considered as pre-diabetic, it is imperative that we obtain a complete picture of how the disease develops and how we can interfere with its progression. The establishment of transient and potentially reversible dedifferentiation of β cells as a contributor to T2D might open up new avenues for therapeutic intervention.

Acknowledgments

This work was supported by an NIH grant (DK60533) and by funds from The Leona M. and Harry B. Helmsley Charitable Trust.

REFERENCES

Buteau J, Accili D. Diabetes Obes. Metab. 2007; 9(Suppl 2):140–146. [PubMed: 17919188]

Chang-Chen KJ, Mullur R, Bernal-Mizrachi E. Rev. Endocr. Metab. Disord. 2008; 9:329–343. [PubMed: 18777097]

Collombat P, Hecksher-Sørensen J, Krull J, Berger J, Riedel D, Herrera PL, Serup P, Mansouri A. J. Clin. Invest. 2007; 117:961–970. [PubMed: 17404619]

Landsman L, Parent A, Hebrok M. Proc. Natl. Acad. Sci. USA. 2011; 108:17010–17015. [PubMed: 21969560]

Oslowski CM, Urano F. Curr. Opin. Cell Biol. 2011; 23:207–215. [PubMed: 21168319]

Talchai C, Xuan S, Lin HV, Sussel L, Accili D. Cell. 2012; 150:1223–1234. this issue. [PubMed: 22980982]

Thorel F, Népote V, Avril I, Kohno K, Desgraz R, Chera S, Herrera PL. Nature. 2010; 464:1149–1154. [PubMed: 20364121]

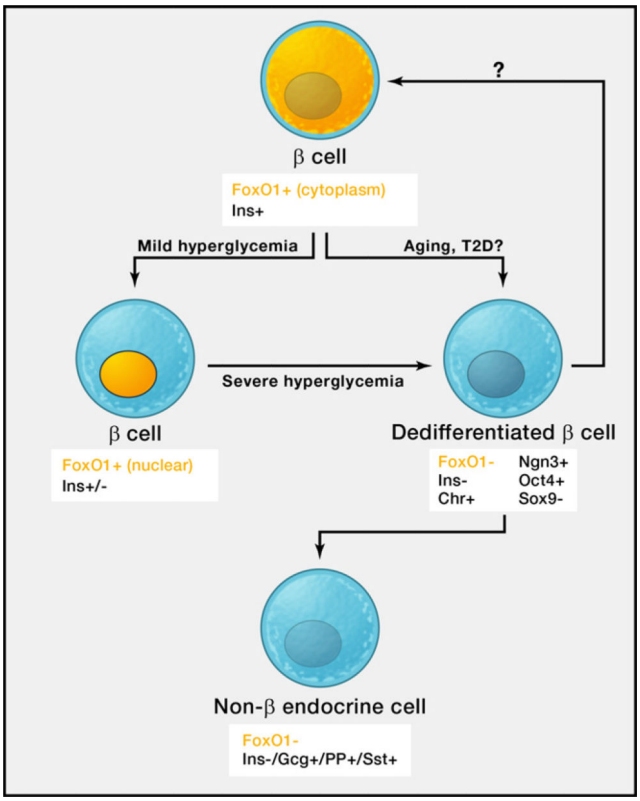

Figure 1. FoxO1 Plays a Role in Maintaining β Cell Identity

Under normoglycemic conditions, FoxO1 primarily localizes to the cytoplasm in mature, insulin-producing β cells. Under conditions of mild hyperglycemia, FoxO1 is seen to partially localize to the nucleus, with an observable reduction in insulin staining. In mouse models that exhibit severe hyperglycemia, FoxO1 is greatly diminished in the β cell, along with reduced insulin. Similarly, genetic ablation of FoxO1, combined with physiological stressors such as aging, leads to islets lacking FoxO1 and insulin expression that continue to be populated by endocrine cells as ascertained by chromogranin positivity. These dedifferentiated β cells re-express, at least transiently, Ngn3, Oct4, and L-myc, suggesting a more progenitor-like state. Lineage tracing demonstrates that a fraction of the remaining endocrine cells are derived from β cells that have repressed the β cell program. Whether such a mechanism of dedifferentiation occurs in human disease remains to be seen. Finally, a reversal of fate, from the dedifferentiated β cell into a fully functional β cell instead of other endocrine cell types, would potentially have great therapeutic value.