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β -cell dedifferentiation in diabetes is important, but what is it?

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Abbreviations: GSIS, glucose-stimulated insulin secretion; GLUT2, glucose transporter 2; MafA, v-maf musculoaponeurotic fibrosarcoma oncogene family A; PDX-1, pancreatic duodenal homeobox; Nkx6.1, NK6 homeobox 1; Pax6, paired box 6; HNF3b, HNF4a, and HNF1a, hepatocyte growth factor; Myc, myelocytomatosis oncogene; Oct4, POU domain transcription factor; Nanog, homeobox protein NANOG

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This commentary discusses the concept of β -cell dedifferentiation in diabetes, which is important but not well defined. A broad interpretation is that a state of differentiation has been lost, which means changes in gene expression as well as in structural and functional elements. Thus, a fully mature healthy β cell will have its unique differentiation characteristics, but maturing cells and old β cells will have different patterns of gene expression and might therefore be considered as dedifferentiated. The meaning of dedifferentiation is now being debated because β cells in the diabetic state lose components of their differentiated state, which results in severe dysfunction of insulin secretion. The major cause of this change is thought to be glucose toxicity (glucotoxicity) and that lowering glucose levels with treatment results in some restoration of function. An issue to be discussed is whether dedifferentiated β cells return to a multipotent precursor cell phenotype or whether they follow a different pathway of dedifferentiation.

Introduction

β -cell dedifferentiation is a term used to describe β cells with an altered phenotype that can lead to loss of key components responsible for optimal performance including insulin secretion. This loss of critical β -cell machinery leads to the dysregulated insulin secretion that is a fundamental part of the pathogenesis of both types 1 and 2 diabetes (T1D and T2D).¹ The word dedifferentiation has ambiguity because it means different things to different people (Fig. 1). Some

see dedifferentiation as a change in β -cell phenotype that regresses back toward the multipotent progenitor cell from which it originated.² However, one could also think of dedifferentiation as a loss of differentiated components resulting in cells with little resemblance to primitive immature β cells or their precursors. β -cell heterogeneity should be part of this discussion because it must be accompanied by variations in gene expression. While these changes are likely to be part of a normal life cycle or natural aging, it can be argued that these perhaps fluctuating changes could be considered modest alterations in dedifferentiation.

However dedifferentiation is defined, it is important because of its implications for β -cell function, birth, death, and regeneration, all of which contribute to the severity of the diabetic state. To appreciate the importance of differentiation or the lack thereof, we will discuss the concepts of “functional β -cell mass,” β -cell maturation and heterogeneity, and finally the meaning and impact of a loss of differentiation.

Functional β -Cell Mass

Differentiation and dedifferentiation are important concepts for our understanding of “functional β -cell mass.” Beta cell mass is a simple concept, it is just the weight of all of the β cells in the pancreas, which is directly proportional to β -cell volume. It cannot be precisely correlated with β -cell number because the size of individual β cells can vary.³ A key aspect of function is insulin secretion, which is more difficult to define as a number or

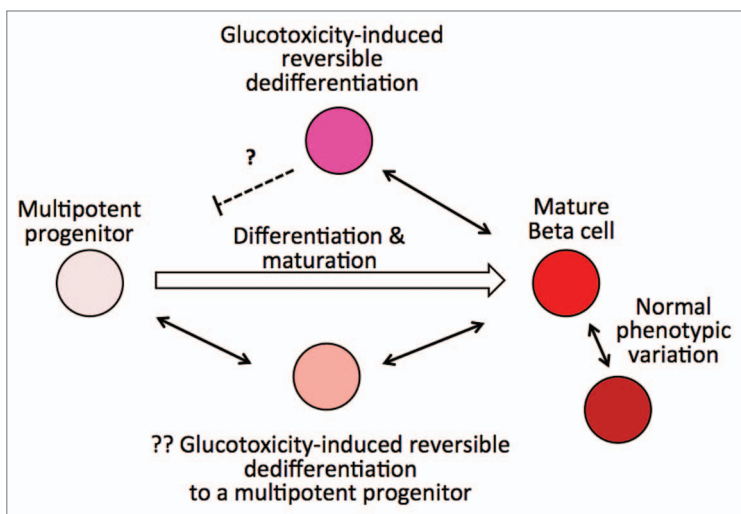


Figure 1. The differentiation state of a fully mature β cell can change with natural reversible events and during progression to death. The hyperglycemia of diabetes is thought to be the major determinant causing β cells to lose their differentiation (also termed dedifferentiation), which leads to dysfunctional insulin secretion. This process is also called glucose toxicity, which can be at least partially reversed by treatment of hyperglycemia. An unanswered question is whether the β cells in the diabetes revert toward a multipotent precursor phenotype or a separate reversible dedifferentiated state.

amount. One way to look at function is as glucose-stimulated insulin secretion (GSIS), realizing that the amount of GSIS will of course depend upon the strength of the stimulus and the timing of the response. Insulin responses to a meal will have even more variable complexities. Because optimal insulin secretion is dependent upon the unique differentiation of β cells, it is easy to see how loss or change of differentiation could result in impairment of insulin secretion in the absence of a change in β -cell mass, with the result being reduced functional β -cell mass.

Normal Differences in β -Cell Differentiation: β -Cell Maturation and Heterogeneity

Differentiation of β cells obviously changes as they develop from a multipotent precursor cell to full maturity.^{4,5} This process has been best mapped out in rodents and it is noteworthy that full function in terms of the benchmark GSIS takes over a month after birth to develop.⁶ While a population of β cells in adulthood may look the same with insulin immunostaining or by change of a glucose-induced NAD(P)H autofluorescence response during secretion,⁷

there is certainly a great deal of heterogeneity. There are now many studies showing notable differences between single β cells in terms of secretion, gene expression, and cell size.⁸⁻¹¹ The secretion differences have been particularly well demonstrated with the reverse hemolytic plaque assay.⁸ There must be a spectrum of change in β cells as they move from birth to death. β -cell biology would benefit enormously if these different stages could somehow be identified by markers. The study of fetal and neonatal β cells has provided a lot of information about the major phenotypic changes that occur^{4,5} and markers of aging are also being found such as p16.¹² There are other markers of aging that may prove valuable including senescence-associated β -galactosidase (SA- β gal)¹³ among others.^{14,15} These differences are, however, only the tip of the iceberg; we look forward to the identification of many more markers.

The adult pancreas provides even more examples of heterogeneity, which could be considered normal phenotypic variation (Fig. 1). A newly born β cell from neogenesis must have a very different phenotype than a new β cell resulting from self-duplication. Another example is the recent finding of populations of

less active islets that have low oxygen tension, less blood flow and presumably less insulin output.¹⁶ These might be considered “sleeping islets” because they can be awakened by increased demand for secretion as occurs in the pancreatic remnant left after partial pancreatectomy (PPx).

Glucotoxicity as a Cause of Dysfunctional Insulin Secretion

Almost 40 y ago, it was shown in humans that only a small increase of glucose levels was associated with a profound loss of acute GSIS.¹⁷ Subjects with fasting glucose levels a little above 100 mg/dl had reduced acute GSIS and once over 115 mg/dl the response was nil. This striking secretory defect, found when glucose levels were short of being diagnostic for diabetes, has now been confirmed in humans and animals by many studies. Because this change of function was so tightly tied to rising glucose levels, we were attracted to the concept of what is now called glucotoxicity. β cells normally see glucose concentrations maintained within a very narrow range of about 65–150 mg/dl, but when forced into an environment of even mild hyperglycemia their phenotype and function changes. To test this hypothesis we exposed β cells to hyperglycemia using several rat models including partial pancreatectomy,¹⁸ glucose infusion¹⁹ and the neonatal streptozocin,²⁰ and found marked β -cell dysfunction, most notably with GSIS, in all cases. Coupling these findings with earlier work looking at secretion changes in islets cultured in a high glucose environment, the glucotoxicity hypothesis was strengthened.²¹

Much has been written about lipotoxicity and glucolipotoxicity also contributing to the secretory dysfunction found in diabetes.¹ Unfortunately, almost all of the support for this hypothesis comes from in vitro experiments and as of yet there are no clearly convincing in vivo experiments showing that free fatty acid elevations in the pathophysiological range correlate with insulin secretory defects. As discussed in more detail elsewhere,¹ our view is that there is no persuasive evidence that either lipotoxicity or glucolipotoxicity

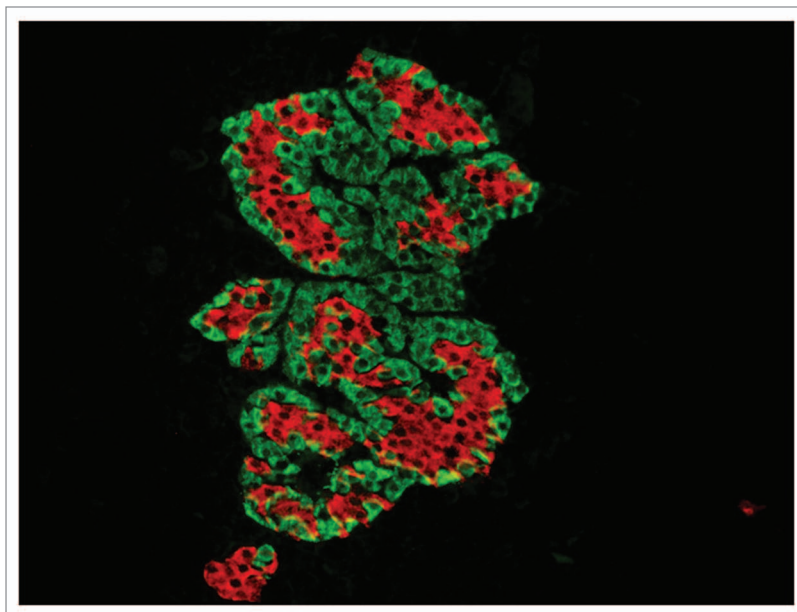


Figure 2. Baboons with chronic diabetes induced by streptozotocin were assessed for *in vivo* β -cell function, β -cell mass and insulin content after 5- 46 mo of diabetes.³⁶ When pancreatic β -cell mass was 40–50% of that of the control animals, fasting hyperglycemia was present and accompanied by dysfunctional insulin secretion. Pancreatic sections from 3 separate tissue blocks/ animal (5 diabetic and 2 control animals; average of 60 ± 14 islets per section) were immunofluorescently stained for insulin (red) and a cocktail of antibodies against non- β -cell hormones (glucagon, somatostatin, and pancreatic polypeptide) (green). The pancreatic cross sections were examined by 2 blinded observers. This islet was from baboon after 34 mo of diabetes. All islet cells in all animals (control and with chronic diabetes) were immunostained for insulin, non- β -cell hormones or both. No “empty” cells could be identified.

acting through high free fatty acid levels have adverse direct effects on β cells.¹ However, it is entirely possible that there are important derangements of lipid signaling within β cells.

Dysfunction of insulin secretion is a major contributor to the hyperglycemia of diabetes.²² Studies looking at maximal stimulation in subjects with T2D and controls using glucose infusions followed by stimulation with arginine or isoproterenol found that the insulin response in T2D was only about 15% of that of the control.^{23,24} Because the average reduction in β -cell mass in T2D is about 50% of normal,²⁵ it can be estimated that the secretory output of a given mass of β cells in the presence of hyperglycemia might be reduced to about 30% of normal. There is good reason to think that this loss of function is reversible because of the remarkable restoration of GSIS seen after bariatric surgery for T2D²⁶ and the improvement of insulin secretion seen after intensive insulin treatment in a number of studies.^{27,28}

β -Cell Dedifferentiation Following Surgical Reduction of β -Cell Mass

The rat partial pancreatectomy (PPx) model has proved particularly useful for studying changes in gene expression in β cells. After waiting 4 wk after surgery to minimize the confounding variables of early regeneration, islets were isolated from the remnant and studied for function and gene expression. These studies found gene expression changes that were similar to those found earlier in Zucker diabetic fatty rats.²⁹ Among the notable findings in the PPx model was reduction in expression of genes that are normally highly expressed in β cells including insulin I and II, GLUT2, glucokinase, mitochondrial glycerol phosphate dehydrogenase, and pyruvate carboxylase.^{3,30} Conversely we found increased expression of genes that are normal poorly expressed in β cells, some of which are considered to be “disallowed genes”^{31,32} including lactate dehydrogenase A and the monocarboxylic acid

transporters, as well as glucose-6-phosphatase and hexokinase I. There was also reduced expression of transcription factors that maintain β -cell identity including MafA, PDX-1, Nkx6.1, Pax6, HNF3b, HNF4a, and HNF1a.^{3,33} Another striking finding was a big increase in the expression of c-Myc, which may have contributed to β -cell phenotypic changes and the β -cell hypertrophy found in this model.

To show that these changes were not an artifact associated with surgery or regeneration, rats were kept normoglycemic with the administration of phlorizin during the last 2 wk of the 4-wk time period.^{3,30} This largely prevented the changes presumably caused by hyperglycemia. None of the findings suggested that lipotoxicity was responsible for these changes, as there were no alterations in plasma triglycerides, non-esterified fatty acids, or islet triglyceride levels.

The expression of many other genes were markedly changed in this model (some published, others not). These changes should receive more attention because they are associated with the marked dysfunction of insulin secretion, which is such an important concept for the pathophysiology and treatment of diabetes. A potentially important issue meriting mention concerns β cell susceptibility to autoimmune killing in T1D. In the PPx model there were major changes in the expression of stress genes, death pathways and other genes that are likely to make the β cell a moving target for the immune system as blood glucose levels climb.³⁴ Differences in the expression of these genes in β cells as glucose levels move from normal to mild and then to severe hyperglycemia, may lead to changes in susceptibility to immune damage as disease progresses.

β -Cell Dedifferentiation Found with FoxO1 Knock Out

A mouse model developed by Talchai et al. is more complicated in that two major forces were influencing β cells: the direct effects of the FoxO1 knockout and secondary effects of hyperglycemia.² In contrast, when β -cell mass is reduced surgically as in the PPx model, the effects of hyperglycemia should be the dominant

factor, without the added complexities inherent in models using β -cell toxins or genetic manipulation. The main findings of the FoxO1 knockout study were that there were changes of gene expression, some of which resembled those found in the PPx model. However, there were other findings either not found or not examined in the PPx model, most notably a population of cells thought to be dedifferentiated β cells having no insulin by immunostaining and expressing Neurogenin3, Oct4, Nanog and L-Myc. There was also some evidence that these dedifferentiated β cells can turn into α cells, as shown with lineage tracing. This led to the following provocative conclusion: “We propose that dedifferentiation trumps endocrine cell death in the natural history of beta cell failure and suggest that treatment of beta cell dysfunction should restore differentiation, rather than promoting beta cell replication.” The main point that “treatment... should restore differentiation” is in agreement with the conclusions of a lot of earlier work and our view is that this represents recovery from glucotoxicity as euglycemia is restored with treatment.

However, the following conclusions require scrutiny: “Dedifferentiated β cells reverted to progenitor like cells expressing Neurogenin3, Oct4, Nanog, and L-Myc. A subset of FoxO1-deficient beta cells adopted the alpha cell fate, resulting in hyperglucagonemia.” A key question is whether the changes in this FoxO1 mouse knockout can be found in human T2D. Detailed studies remain to be done but a recent report “did not detect any changes in Neurogenin3, Oct4, NANOG, or MYCL1 levels in human T2D islets”³⁵.

The possible presence of “empty beta cells” containing no insulin is of considerable interest but key questions are whether insulin immunostaining could have been obtained by using a higher concentration of primary antibody. Then, if empty β cells can be found, how many are there and what contribution might they make? We have reexamined sections obtained from our PPx rats and a baboon model of T2D induced by streptozotocin, and in spite of the chronic hyperglycemia, cannot find evidence for significant numbers

of such “empty” cells but it is possible that a very small number might have been missed. A section of an islet from the diabetic baboon model (Fig. 2) is an example of our failure to find such cells³⁶; details of the study are provided in the legend.

Questions must also be asked about how many α cells might have been generated from these dedifferentiated β cells. The presence of hyperglucagonemia is universally found in the diabetic state so it is difficult to attribute this to secreted glucagon from new α cells.

Summary

Altered β -cell differentiation associated with diabetes is now receiving a great deal of attention. The changes in β -cell phenotype are marked and are no doubt largely responsible for the impaired insulin secretion in T2D and the early stages of T1D. The changes are linked to and probably caused by hyperglycemia and there are good reasons to think that obtaining euglycemia with treatment will restore the normal phenotype of these β cells (Fig. 1). It is reasonable to use the term dedifferentiation to describe a loss of differentiated features. Some of these changes can be viewed as a move toward a more primitive state, but questions remain as to whether they can revert to true multipotent precursor cells and if so, what are the prospects for significant regeneration from whatever number of these cells might be present? We look forward to these questions being answered in the near future.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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