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Human β -cell regeneration: progress, hurdles, and controversy

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Abstract

Purpose of review—Therapies that increase functional β -cell mass may be the best long-term treatment for diabetes. Significant resources are devoted toward this goal, and progress is occurring at a rapid pace. Here, we summarize recent advances relevant to human β -cell regeneration.

Recent findings—New β -cells arise from proliferation of pre-existing β -cells or transdifferentiation from other cell types. In addition, dedifferentiated β -cells may populate islets in diabetes, possibly representing a pool of cells that could redifferentiate into functional β -cells. Advances in finding strategies to drive β -cell proliferation include new insight into proliferative factors, both circulating and local, and elements intrinsic to the β -cell, such as cell cycle machinery and regulation of gene expression through epigenetic modification and noncoding RNAs. Controversy continues in the arena of generation of β -cells by transdifferentiation from exocrine, ductal, and alpha cells, with studies producing both supporting and opposing data. Progress has been made in redifferentiation of β -cells that have lost expression of β -cell markers.

Summary—Although significant progress has been made, and promising avenues exist, more work is needed to achieve the goal of β -cell regeneration as a treatment for diabetes.

Keywords

dedifferentiation; human; islet; mitosis; mouse; neogenesis; pancreatic β -cell regeneration; proliferation; replication; transdifferentiation

INTRODUCTION

Diabetes is caused by reduced β -cell mass and function; significant effort around the globe is engaged in research toward therapies that increase β -cell mass. Hurdles include the inability to measure β -cell mass in living people, uncertainty as to how and when new β -cells are generated in the adult human, general lack of plasticity of adult β -cells, and insufficient understanding of pathways with potential to increase β -cell mass. Here, we summarize progress over the past 1–2 years, emphasizing studies with relevance to human β -cells.

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Conflicts of interest

There are no conflicts of interest.

Topics include advances in increasing β -cell proliferation, generating new β -cells from other cell types, and reclaiming β -cells lost to de-differentiation. Given space limitations, the important fields of generation of β -cells from stem cells, islet development, and β -cell survival are not covered. We have attempted to be complete; we sincerely apologize for recent advances that we fail to cite.

β -CELL PROLIFERATION IN RESPONSE TO NUTRIENTS AND PHYSIOLOGICAL DEMAND

Proliferation of β -cells varies across physiologies related to age, nutrition, pregnancy, and insulin sensitivity; learning what drives proliferation under these conditions may lead to therapeutic approaches to expand β -cell mass. Excess caloric intake increases β -cell mass in rodents. Recent autopsy data confirm prior findings that human β -cell mass is increased in obesity [1]. Human β -cells proliferate in response to obesity; transplanted human β -cell graft volume doubled in obese mice relative to lean mice, suggesting that not only do human β -cells proliferate in response to overnutrition *in vivo*, but that the proliferation results in meaningful expansion of β -cell mass [2^{''}]. In mice, β -cell proliferation begins within the first week of overnutrition, surprisingly, prior to the onset of insulin resistance [3].

This year, controversy emerged regarding the widely accepted concept that β -cell proliferative capacity is reduced with age. In humans, one study found that the β -cell population is set early in life [4], but β -cell mass was also found to be preserved in aging [1]. In mice, intriguingly, β -cells of old mice readily proliferated when exposed to a young mouse environment, suggesting that age-related proliferation decline is related to factors extrinsic to the β -cell [5]. Proliferative stimuli such as diphtheria-toxin-mediated β -cell ablation or glucokinase activation increased β -cell proliferation in old mice, reinforcing the possibility that β -cell regenerative capacity is retained in aging [6].

The advance that generated the greatest degree of excitement in this field this year was the identification of a liver-derived factor, termed betatrophin, which stimulates mouse β -cell proliferation in response to insulin resistance [7^{''}]. Another group also implicated a liver-derived circulating factor [8]. Consistent with this, local islet insulin concentration was found to be insufficient to explain the mitogenesis seen in hyperinsulinemic conditions [9]. It should be noted that another study, however, found that betatrophin was not required for glucose homeostasis in the mouse [10]. Although betatrophin levels were increased in some individuals with T1D [11], whether betatrophin can drive human β -cell proliferation remains unknown.

Hyperglycemia drives β -cell proliferation in a variety of model systems, including in-vivo engrafted human β -cells [12–14]. Activating glycolysis increases proliferation by reducing the duration of the quiescent phase of the cell cycle [5,6,15]. Glucose-induced proliferation requires a glucose-responsive transcription factor, carbohydrate response element binding protein (ChREBP), described below. Glucose was also found to regulate expression of long noncoding RNAs that map to T2D risk loci [16]; the significance of this remains uncertain. In one study, lipids were found to prevent glucose-induced proliferation by induction of cell

cycle inhibitors, although this is controversial [17,18]. More studies are needed to learn if these data have relevance to human diabetes.

The therapeutic potential of incretins to increase β -cell mass in people with diabetes remains controversial [19]. Two studies showed that incretins have a proliferative effect on human β -cells [20,21]. In rodents, Glp-1 action at the pancreas is required for the proliferative effect of Glp-1 [22], and the insulin granule SNARE Vamp8 was found to restrain proliferation induced by Glp-1 [23]. The exciting potential of incretin therapy was overshadowed this year, however, by a concerning report linking incretin use with pancreatic neoplasia [24^{''}]. Although valid criticisms of this work have been raised [25], and studies in rodents have not shown the same effect [26], further studies are needed to determine the safety of these agents.

β -CELL PROLIFERATION IN RESPONSE TO GROWTH FACTORS AND SIGNALING

Building on a long line of evidence that secreted factors acting through cell surface receptors can be mitogenic to β -cells, hepatocyte growth factor was required for β -cell regeneration in mice in response to pregnancy, partial pancreatectomy, and auto-immunity [27,28]. TGF- β family factor Nodal increased human β -cell proliferation [29]. A novel peptide derived from the nerve growth factor-responsive gene, *VGF*, preserved β -cell mass in Zucker diabetic fatty rats [30]. Blocking fas receptor activation increased human β -cell proliferation [31]. Two groups described GPCR-linked β -cell proliferative stimuli, which are of particular interest given the general tractability of these receptors to manipulation by small molecules [32,33]. Wnt signals promoted human β -cell proliferation in an mTOR-dependent manner [34^{''}], and SFRP5, a Wnt inhibitor, blocked rat β -cell proliferation [35].

Recent studies suggest that blood vessels may play only a small role in regulating β -cell mass in the adult rodent. Although short-term exposure to vascular endothelial growth factor (VEGF) increased β -cell proliferation, long-term exposure had the opposite effect [36]. Capillaries dilate in response to insulin resistance, which may increase islet function, but new angiogenesis was not seen during islet compensation [37]. Most surprising, reduction in islet vascularization, by inhibition or genetic ablation of VEGF, had no impact on β -cell mass or even function [38^{''},39^{''}]. On the contrary, neural tissue may promote β -cell growth; co-culture with neural crest cells increased β -cell proliferation [40], and the neurotransmitter gamma-Aminobutyric acid was shown to increase human β -cell proliferation, survival, and function [41].

NUCLEAR FACTORS REGULATING β -CELL PROLIFERATION

When glucose levels increase, the glucose-responsive transcription factor ChREBP translocates to the nucleus where it regulates genes [42,43]. ChREBP can have both positive and negative impact on β -cell mass. ChREBP is required for glucose-stimulated rodent and human β -cell proliferation [44], but ChREBP is also implicated in glucotoxicity by inducing TXNIP, mediator of islet inflammation and apoptosis [45,46]. Nuclear ChREBP was

observed in β -cells from diabetic, but not nondiabetic, individuals [42]; whether this indicates attempted regeneration or ongoing β -cell loss is unclear.

Other nuclear factors promoting β -cell mass are emerging. ZBED6 (zinc finger BED domain-containing protein 6) increases β -cell proliferation [47]. CRTC2 (creb regulated transcriptional coactivator), activated by glucose, promotes β -cell mass and function and may preserve islet function in the context of calcineurin-based immunosuppression [48]. In a cautionary work, overexpression of HNF4a (hepatocyte nuclear factor) was found to increase the number of human β -cells in early S-phase of the cell cycle, but a DNA damage response was activated, resulting in cell cycle arrest [49]. Another study found that long-term labeling with thymidine analogs inhibited mouse β -cell proliferation [50]. These studies emphasize the importance of demonstrating an actual increase in β -cell number rather than reliance on surrogate measures.

Important advances continue in the study of human β -cell cycle machinery. Analysis of the intra-cellular localization of critical cell cycle regulators found that proproliferative factors were excluded from the nucleus; the only regulators present in the nucleus were inhibitors [51,52]. Overexpression of cell cycle activators was sufficient to increase human β -cell proliferation [53].

NONCODING RNAS AND EPIGENETICS

MicroRNAs (miRNAs), small noncoding RNAs that regulate translation or message stability, play a role in metabolic homeostasis [54]. In mice, proliferative miRNAs were expressed in compensating islets during obesity and insulin resistance, but apoptotic miRNAs were found in decompensating islets in diabetes [55]. One particular miRNA, miR-338-3p, was decreased in rodent islets during pregnancy and obesity, regulated by estradiol and Glp-1; reducing miR-338-3p was sufficient to increase β -cell proliferation and survival *in vitro* and *in vivo* [56]. A second miRNA, miR-7a, regulates β -cell proliferation by targeting members of the mTOR signaling pathway [57].

Less is known about long noncoding RNAs (lncRNAs), although these make up a large proportion of the genome. In humans, some lncRNAs were found to be islet-specific, glucose-regulated, and dysregulated in islets from individuals with T2D. Many lncRNAs map to T2D susceptibility loci, suggesting a possible role for lncRNAs in the development of diabetes [16].

Transcription is also regulated through epigenetic modification. DNA methylation profiling of human islets showed distinct patterns in islets from individuals with T2D compared with nondiabetic individuals, with concordant mRNA expression changes. T2D-specific methylation sites were not present in blood cells from the same individuals, nor in nondiabetic islets exposed to high glucose [58]. β -cell differentiation genes were differentially methylated in α and β -cells, with a more stem-like signature found in α cells [59]. Pdx-1 methylation in human islets correlated negatively with pdx-1 expression, insulin secretion, and glycosylated hemoglobin [60].

GENERATION OF β -CELLS FROM OTHER CELL TYPES: EXOCRINE OR GUT CELLS

Transdifferentiation refers to the generation of new β -cells from another differentiated cell type. Lineage tracing with Ptf1a, expressed only in acinar cells in adulthood, found that some exocrine cells expressed β -cell markers after pancreatic duct ligation; exocrine-to-endocrine conversion was promoted by prior elimination of endogenous β -cells with streptozotocin [61[¶]]. Overexpression of Pdx1, Ngn3, and MafA in a transformed exocrine cell line suppressed exocrine markers and increased endocrine markers [62]; on the contrary, Hedgehog signaling inhibited exocrine to β -cell transformation [63]. Remarkably, deletion of FoxO1 in Ngn3+ cells resulted in glucose-responsive insulin-secreting cells in the gut, which expanded in number when pancreatic β -cells were eliminated using streptozotocin [64].

GENERATION OF β -CELLS FROM DUCTAL OR ALPHA CELLS

The presence of insulin-positive cells in or near ductal epithelium in adult mice and humans suggests that β -cells may arise from ducts as they do during embryogenesis. TCF7L2, Wnt signaling effector, and T2D risk locus, promotes β -cell mass and proliferation in rodents [65,66]. TCF7L2 expression correlated with compensatory islet expansion in mice, and TCF7L2 overexpression in isolated human exocrine tissue increased duct cell proliferation and formation of small islet cell clusters [67]. Ngn3, which initiates duct to endocrine differentiation during development [68], was sufficient to shift human ductal cells toward a neuroendocrine fate, but insufficient to reprogram into a full endocrine phenotype [69,70]. When Pdx1 was deleted specifically from ducts in mice, endocrine cell mass was unaffected but β -cell function was impaired, suggesting that pdx-1 is needed for full β -cell maturation [71]. In zebrafish, overnutrition led to the generation of new β -cells derived from ductal cells [72]. Alpha cells may represent a reservoir of pre- β -cells in the adult [73]; alpha cells had reversible epigenetic suppression of β -cell genes, and treating human islets with a methyltransferase inhibitor resulted in partial alpha-to- β reprogramming [59^{¶¶}]. On the contrary, genetic ablation of alpha cells failed to impact β -cell homeostasis in mice [74]. In human tissue, Pax4 and MafA were, surprisingly, found to be expressed in alpha cells in one study [75[¶]], but MafA was restricted to β -cells in another [76].

Two studies found that injecting stem cells, derived from cord blood or bone marrow, into the adult mouse increased endogenous β -cell regeneration; the source of new β -cells was not the stem cells themselves [77,78].

CONTROVERSY REGARDING NEOGENESIS CONTINUES

In contrast to some of the above reports, several mouse studies failed to find evidence that new β -cells are generated from other cell types in the adult, even after regenerative stimuli including β -cell ablation, pregnancy, partial pancreatectomy, and pancreatic duct ligation [79^{¶¶},80,81]. Histological studies on human tissue continue to report insulin-expressing cells in ducts, isolated β -cells in the pancreatic parenchyma, and small islet clusters [82], considered to be the evidence of neogenesis, although examples of these are readily

observable in mice as well. As lineage tracing cannot be performed in humans, whether neogenesis occurs in adult human pancreas is unlikely to be definitively resolved soon.

β-CELL DEDIFFERENTIATION: CAN THEY BE RECLAIMED?

In a critical recent observation, mice with diabetes resulting from the ablation of FoxO1 in β-cells lost β-cell mass, not because of cell death but because of dedifferentiation [83]. Some β-cells reverted to alpha cell phenotype, resulting in hyperglucagonemia, which worsens diabetes [84]. Nkx6.1 is necessary for β-cell differentiation in adult mice; its deletion caused delta cell fate [85]. Human data support the concept that β-cell dedifferentiation contributes to T2D pathogenesis: individuals with impaired glucose tolerance had increased frequency of islet cells coexpressing multiple hormones, hormone along with progenitor markers, or hormone along with vimentin [82,86]. Morphological changes in β-cells and increased alpha cells were also observed in monkeys on a high-fat diet [87]; this finding was corrected by resveratrol.

Expanding human β-cells *ex vivo* has been limited by dedifferentiation. β-cells in cultured human islets readily transformed to alpha cells [88]; islet isolation itself induced an inflammatory response and expression of progenitor markers, suggesting dedifferentiation occurs during isolation [89]. Extracellular matrix may be important; growing purified human β-cells on laminin partially prevented epithelial-mesenchymal transition [90]. Wnt signaling not only induced human β-cell proliferation but also dedifferentiation; treating with rho/ROCK inhibitors, or a novel thiazolidine-dione, allowed β-cells to maintain or regain differentiation markers [34,91]. Another group reported successful ex-vivo expansion of human β-cells, which dedifferentiated during culture but were redifferentiated by modulating notch signaling, and corrected hyperglycemia when transplanted into diabetic mice [92].

TECHNICAL ADVANCES RELEVANT TO β-CELL REGENERATION

Small molecule screens for inducers of human β-cell proliferation would facilitate discovery of novel therapeutics; progress has been made in adapting primary human islet culture for high-throughput screening [93]. Understanding human β-cell biology has been hampered by inability to isolate pure populations of β-cells. Using bioinformatics analysis of expression databases, cell surface proteins labeling islet cell types were identified, and two were useful for sorting islet cells by flow cytometry [94]. Also, notable is a new transgenic mouse that allows sorting actively proliferating cells from tissues using a cyclin B1-GFP fusion protein, which could be used to isolate proliferating β-cells [95]. Finally, toward better understanding of human endocrine pancreas, a study of autopsy specimens has catalogued islet size, architecture, and distribution in nondiabetic and diabetic individuals [96].

CONCLUSION

Meaningful human β-cell regeneration is a crucial goal in the fight against diabetes. Significant progress has been made toward the generation of new β-cells through proliferation or transdifferentiation from other cell types, while maintaining insulin secretory

capacity. Controversies still exist, and therapies that can be safely applied to patients remain, for the moment, beyond reach. Much work remains to be done toward this important goal.

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KEY POINTS

- Human β -cell regeneration is an important goal toward relieving the patient burden of diabetes.
- Adult human β -cells, although only minimally proliferative at baseline, can be induced to proliferate by a variety of stimuli, both *in vitro* and *in vivo*.
- Under certain conditions, β -cells can be generated from other cell types, including endocrine, exocrine, ductal, and even intestinal cells.
- Loss of β -cell differentiation markers occurs in diabetes; approaches to retain or restore β -cell phenotype may prove useful tools.