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ABSTRACTS

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Abstracts

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lactated women. Both the Disposition index and Matsuda index was improved in previously lactated women, suggesting improved β cell function in lactated women. In mice, after 3 weeks after delivery, lactating mice had improved glucose tolerance and increased β cell mass compared to non-lactating mice. Lactating mice maintained high serum prolactin levels for milk production, which induced serotonin production in β cell via PRLR-STAT5-TPH1 cascade. Similar to pregnancy, increased β cell serotonin facilitated β cell proliferation and enhanced β cell function. Amelioration of glucose tolerance and β cell function were maintained for several months after the cessation of lactation. However, these beneficial effects were diminished in β cell-specific *Tph1* knockout mice. In addition, we demonstrated a novel mechanism of 5-HT derivatives acting as a direct anti-oxidant to enhance β cell survival upon oxidative stress.

Conclusion: Serotonin contributes to the beneficial metabolic effects of lactation by enhancing β cell mass and function.

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In vitro and fully mature in vivo function of human induced pluripotent stem cell-derived beta cells

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Background and aims: Pancreatic β-cell failure is central in the pathogenesis of diabetes. *In vitro* differentiation of human induced pluripotent stem cells (iPSCs) into β-cells represents a novel cell source for diabetes research. Here we differentiated iPSC-β-cells and tested their function *in vitro* and *in vivo* in humanized mice.

Materials and methods: iPSCs were differentiated into β-cells using a 7-step protocol. Markers of β-cell development were assessed by qPCR and immunocytochemistry and compared to organ donor human islets. *In vitro* iPSC-β-cell function was assessed by static glucose- and forskolin (Fk, 10 μM)-stimulated insulin secretion. NOD-SCID mice were transplanted with iPSC-β-cells under the kidney capsule and underwent intraperitoneal glucose tolerance tests at 7, 14 and 20 weeks post-transplantation (n=8-13). At 21 weeks mice were injected with streptozotocin (STZ, 200 mg/kg) to selectively ablate the mouse β-cells, and glycemia was followed for 1 week before nephrectomy or *in situ* kidney perfusion (single-pass circuit through renal artery and vein, n=3), in order to evaluate *in vivo* function of the graft.

Results: iPSC-β-cells followed a proper developmental pathway as determined by gene expression. The yield of insulin-positive β-cells was comparable to that of human islets (44±3% versus 49±1%) as assessed by immunocytochemistry. iPSC-β-cells at stage 7 did not augment insulin release in response to glucose *in vitro* (16.7 mM versus 1.7 mM), but high glucose plus Fk increased insulin secretion by 4-fold ($p<0.001$). In transplanted mice, human C-peptide secretion was detectable at 7 weeks and grafts became glucose-responsive by 14-20 weeks. After STZ, transplanted mice maintained normoglycemia until graft removal by nephrectomy, when they became diabetic. *In situ* kidney perfusion showed marked human insulin secretion in response to glucose (20 mM) *in vivo*, and this was amplified by Fk (1 μM). Diazoxide (a K_{ATP} channel opener, 250 μM) fully inhibited insulin release, whereas gliclazide (K_{ATP} channel blocker, 25 μM) or high K^+ (30 mM) strongly stimulated insulin secretion.

Conclusion: *In vitro* differentiation generates iPSC-β-cells with mature β-cell characteristics but still lacking fully mature β-cell function. Transplantation and the *in vivo* environment boost their maturation to such an extent that they acquire the functional characteristics of adult human islets. This technology provides us with an unlimited supply of human β-cells that will be instrumental to study β-cell dysfunction and demise in diabetes.

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Diabetic condition upregulates insulin secreting capacity of human iPSC-derived pancreatic endocrine progenitor cells after implantation in mice

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Background and aims: Islet transplantation is a promising therapeutic option for patients with brittle type 1 diabetes, but does not meet clinical demand due to donor shortage. Stem cell-derived pancreatic cells have attracted interest as an alternative cell source. Given the difficulty in generating fully mature islets *in vitro* so far, host environment is an important factor to drive differentiation, cell-cycle and maintenance of implanted stem cell-derived pancreatic cells. The purpose of this study is to investigate whether host diabetic environment impacts the fate of pancreatic endocrine progenitor cells (EPCs) implanted in immunodeficient mice.

Materials and methods: EPCs were differentiated from human induced pluripotent stem cells (iPSCs) by reported differentiation protocols with some modifications, and then implanted into the kidney sub-capsular space of diabetic and non-diabetic NOD.CB17-Prkdcscid/J (NOD/SCID) mice. Status of cells was assessed by measuring plasma human C-peptide (hC-peptide) levels and by analyzing the explanted grafts.

Results: EPCs were comprised of >50% chromogranin A^+ ($CHGA^+$) cells and the majority of the cells expressed NKX6.1, indicating the potential to become β cells; few cells expressed insulin or glucagon. After implantation, plasma hC-peptide levels were higher in streptozotocin (STZ)-induced diabetic mice than in non-diabetic mice for 13 weeks, while the levels did not differ thereafter. The elevation of plasma hC-peptide levels was reproduced when EPCs were derived from another iPSC line or were implanted in genetically-induced diabetic Akita-NOD/SCID mice. These results suggest that the insulin secreting capacity of grafts is upregulated in a host diabetic environment. To clarify how the insulin secreting capacity of implanted cells is increased in host diabetic environment, cell mass and composition of explanted EPC grafts were analyzed. Appearance and weight of whole grafts were not different between diabetic and non-diabetic mice despite different plasma hC-peptide levels. In contrast, whole graft contents of insulin and glucagon were higher in the grafts from diabetic mice compared with those from non-diabetic mice by 3.1- and 4.1-fold, respectively. In addition, grafts from diabetic mice contained 3.0-fold more CHGA- and 3.7-fold more insulin-immunoreactivity areas. These results suggest that the host diabetic environment increases endocrine cells including insulin producing cells without affecting graft mass via facilitated hormone expression and endocrine cell commitment.

Conclusion: In this study, we demonstrated that diabetic condition upregulates the insulin secreting capacity of human iPSC-derived EPCs implanted in immune-deficient mice. These findings would provide important insights into postoperative diabetes care for cell therapy using stem cell-derived pancreatic cells in the future.

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