

Stem Cell Strategies for Pancreatic β -cell Regeneration: From Bench to Bedside

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Pancreatic β cells are exquisite endocrine cells that control glucose homeostasis. Under physiological conditions, mammals maintain a dynamic β -cell mass throughout life in response to various demands for insulin. Critical β -cell mass is kept in delicate balance by β -cell replication, neogenesis, hypertrophy, and apoptosis.¹ Various insults that disturb this balance result in the loss of β -cell mass, which is the common denominator in all forms of diabetes. Optimal therapy is the reconstitution of the functional β -cell mass to maintain euglycemia.

At present, several strategies are under investigation for replenishing functional β -cell mass: allo-islet transplantation, stem cell-derived insulin-producing cells for transplantation, and stimulation of endogenous β -cell regeneration in the diabetic pancreas. Islet transplantation has recently been demonstrated as an efficient therapy for patients with type 1 diabetes;² however, immune rejection, recurrent autoimmune attack against transplanted islets, and the lack of donor islets restrict its application in clinical practice. In recent years, many investigators have focused on stem cells as a potentially inexhaustible source for islet cells.³⁻⁶ Developing a simple, reliable procedure to obtain autologous stem cell-derived insulin-producing cells for transplantation or to promote endogenous pancreatic regeneration would alleviate the major limitations of islet availability and allogeneic rejection. This issue of *Endocrinology Rounds* discusses the successes and failures of the current approaches in stem-cell strategies for pancreatic β -cell regeneration in light of future clinical applications.

Sources of stem cells for β cells

Stem cells are self-renewing progenitor cells that can differentiate into one or more specialized cell types. For transplantation therapy in patients with diabetes, stem cell-derived β cells should have the following essential properties:

- insulin gene expression
- appropriate post-translational modification and processing of insulin through the regulatory secretory pathway
- glucose-sensitive insulin production and release within the physiological range
- unlimited availability *in vitro*.

In practice, however, fully functional islets have not yet been derived from stem cells. Several strategies and different stem-cell sources for β -cell substitution have been proposed.

Embryonic stem cells

Embryonic stem cells (ESCs) are pluripotent cells derived from the inner-cell mass of preimplantation embryos. They have the ability to self-renew, giving rise to new pluripotent stem cells, and to differentiate into cells of endodermic, mesodermic, and ectodermic origin and, thereafter, into cells that are specific for the various tissues in the body.



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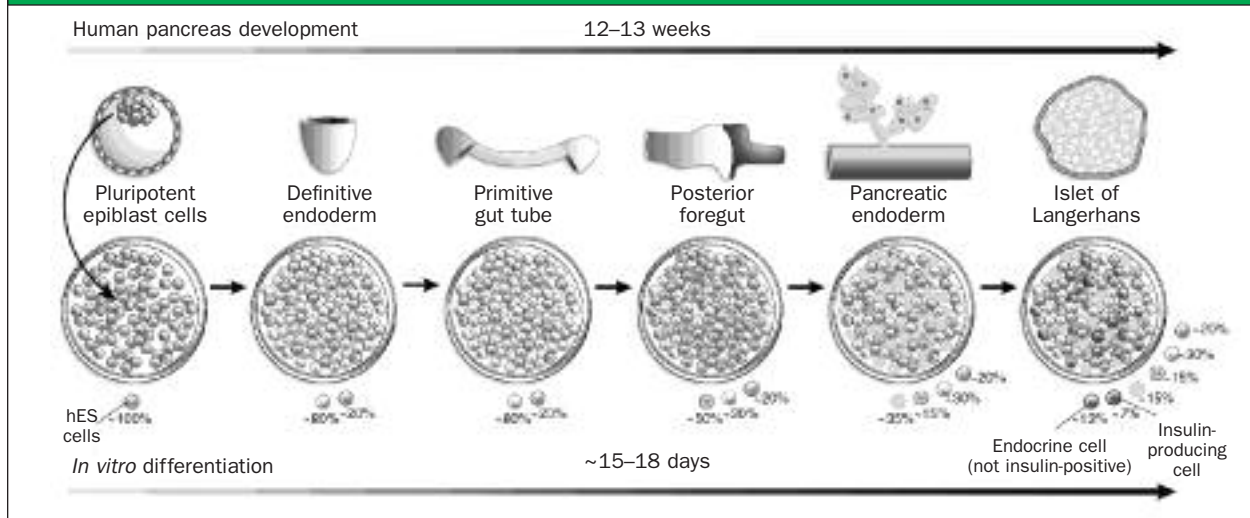
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Figure 1: Directed differentiation of human embryonic stem cells to insulin-producing cells by mimicking embryonic development¹³



hES = human embryonic stem. Reprinted by permission from Macmillan Publishers Ltd: *Nature Biotechnology*. 2006;24(12):1481-1483, copyright 2006.

Beginning in 2000, many groups reported the differentiation of insulin-producing cells from mouse and human ESCs *in vitro*;⁷⁻¹⁰ however, inefficiency of differentiation, low-insulin content of the insulin-producing cells, and uptake of exogenous insulin from the medium, limited further study *in vivo*.^{11,12} These unsuccessful early attempts focused attention on improving the understanding of normal embryonic development. This suggested the possibility of a more plausible approach by directing ESCs through a process that mimics normal pancreatic development (Figure 1).¹³ In 2006, D'Amour et al¹⁴ developed a 5-stage protocol for efficiently differentiating human ESCs to endocrine hormone-expressing cells through a series of endodermal intermediates resembling those that occur during pancreatic development *in vivo*. The insulin content of the insulin-expressing cells approaches that of adult islets; however, C-peptide release by these cells was suboptimal in response to glucose. The following year, Jiang et al¹⁵ described a novel, serum-free protocol to generate insulin-producing islet-like clusters (ILCs) from human ESCs grown under feeder-free conditions. The ESC-derived ILCs expressed multiple endocrine hormones and produced C-peptide in response to glucose stimulation *in vitro*. Recently, Kroon et al¹⁶ assessed the competence of human ESC-derived pancreatic endoderm to produce functional endocrine cells *in vivo*. With glucose stimulation of mice implanted with the endoderm, serum levels of human insulin and C peptide were similar to those of mice that received ~3,000 human islets. In addition, the insulin-expressing cells generated after the engraftment exhibited many properties of functional β cells, including expression of critical β -cell transcription factors, appropriate processing

of proinsulin, and the presence of mature endocrine secretory granules.

There are considerable ethical concerns regarding the use of human ESCs. The generation of individual patient-specific ESC-derived β cells for transplantation purposes requires therapeutic cloning of human ESCs. Therapeutic cloning involves taking the nucleus from a somatic cell of a patient, inserting it into an enucleated human egg, and allowing it to develop into a blastocyst. The inner-cell mass of the blastocyst is used to generate pluripotent ESC lines, which can be expanded *in vitro* to produce the billions of cells required for transplantation therapy. Some other considerations in the use of human ESCs are:

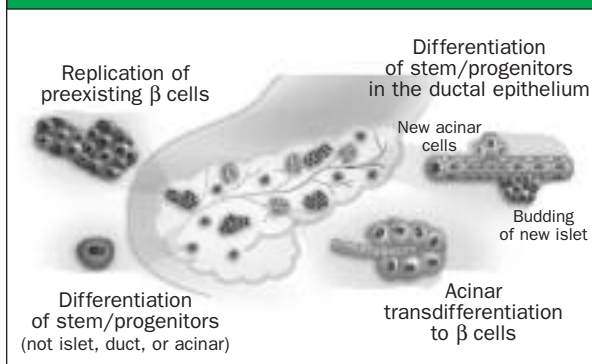
- the lack of biphasic insulin secretion
- tumourigenicity (eg, animals develop tumours when transplanted with ESC-derived insulin-producing cells)¹⁷
- increased mutation rates in adult donor cells and incorrect reprogramming of somatic cell nuclei
- recurrence of autoimmunity.

Therefore, it is advisable to perform detailed efficacy studies on ESCs before proposing these cells as a suitable source of insulin-producing cells in the treatment of diabetes.

Adult stem cells

Adult stem cells are often known as tissue-specific stem cells, since they have a lower plasticity compared with ESCs; however, recent data suggest that some adult stem cells have the ability to transdifferentiate (ie, generate a progeny belonging to a tissue lineage different from the one of origin) under certain conditions. The possibility that new β cells could be generated from adult stem cells would avoid the potential ethical problems associated with the use of ESCs.

Figure 2: New sources of pancreatic β cells²²



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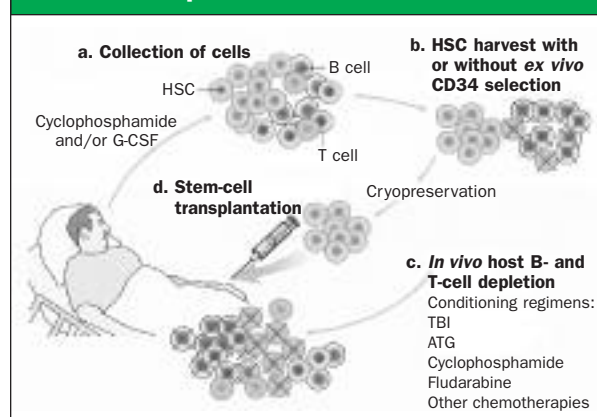
Pancreatic stem/progenitor cells

Stem/progenitor cells with the potential to differentiate into insulin-producing cells *in vitro* and/or *in vivo* have been found in pancreatic islets, pancreatic ducts, and pancreatic acinar cells (Figure 2).¹⁸⁻²² Data from both *in vivo* and *in vitro* experiments support the hypothesis that islet neogenesis in the mature pancreas emanates from ductal cells. Bonner-Weir et al²⁰ cultured human ductal cells as a monolayer overlaid with an extracellular matrix preparation, and observed the formation of "islet buds" containing CK19-expressing cells, as well as insulin-positive cells. Although these studies provided convincing evidence that ductal cells contribute to islet neogenesis in the adult pancreas *in vitro*, the low proportions of differentiating cells suggested that either the methods were as yet inefficient, or that only a specific subpopulation of ductal cells are true islet progenitors. Nevertheless, with the success of the Edmonton protocol for islet transplantation, the presence of islet progenitor (ductal-epithelial) cells may improve the long-term metabolic outcome.²³

Hepatic stem cells

During embryogenesis, both the liver and ventral pancreas appear to arise from the same cell population located within the embryonic endoderm. It could be assumed that the epithelial cell populations within the pancreas and liver might share common stem-cell populations. Yang et al²⁴ used *in vitro* proliferation of hepatic oval cells to obtain islet-like clusters that could express several endocrine hormones, including insulin. Their *in vivo* study described the successful reversal of diabetes in streptozotocin-treated nonobese diabetic mice with severe combined immunodeficiency (NOD-SCID). Herrera et al²⁵ isolated and characterized a population of human liver stem cells that were phenotypically different from oval cells; these cells revealed self-renewing capability and multi-lineage differentiation potential, including insulin-producing islet-like structures.

Figure 3: Autologous hematopoietic stem-cell transplantation³⁷



HSC=hematopoietic stem cells; G-CSF=granulocyte colony-stimulating factor; TBI=total body irradiation; ATG=antithymocyte globulin. Reprinted by permission from Macmillan Publishers Ltd: *Nature*. 2005;435(7042):620-627, copyright 2005.

Bone marrow stem cells

In the past few years, several studies have indicated that bone marrow transplantation could prevent or restore hyperglycemia in rodent models.^{26,27} In fact, serious debates have focused on the fate of transplanted bone marrow cells and whether they undergo cell fusion or transdifferentiation into pancreatic β cells, or if they induce endogenous pancreatic regeneration *in vivo* by stimulating neovascularization.²⁸⁻³⁰

In addition to the subgroup of adult stem cells from bone marrow, hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and endothelial progenitor cells (EPCs) have been identified. They have been shown to promote β -cell regeneration through different mechanisms. Beilhack et al³¹ employed a purified HSC fraction of the bone marrow to test whether the development of hyperglycemia could be prevented in NOD mice. The data demonstrated that purified HSC grafts block the development of autoimmune diabetes, and illuminated how HSC grafts alter thymic and peripheral T-cell responses against auto- and alloantigens. Mathews et al³² provided evidence that bone marrow-derived EPCs could be recruited to the pancreas further to islet injury. Although bone marrow-derived EPCs contribute to neovascularization, they do not differentiate into insulin-expressing cells. As for bone marrow MSCs, they have revealed multiple differentiation potency, as well as immunoregulatory and trophic properties. As a result, MSCs appear to be a very promising tool for regenerative and immunoregulatory cell therapy. Several *in vitro* and *in vivo* studies have provided direct evidence that bone marrow MSCs are capable of reprogramming to become functional insulin-producing cells.³³⁻³⁵ These data indicated that bone marrow MSCs could be manipulated towards a pathway of pancreatic endocrine cell lineage differentiation to form islet-like

cells *in vitro*. Portal vein transplantation of these islet-like cells was able to alleviate hyperglycemia in diabetic rats.³⁶ Moreover, bone marrow MSCs could improve the survival of islets *in vitro* and lengthen the function of islet grafts *in vivo*.

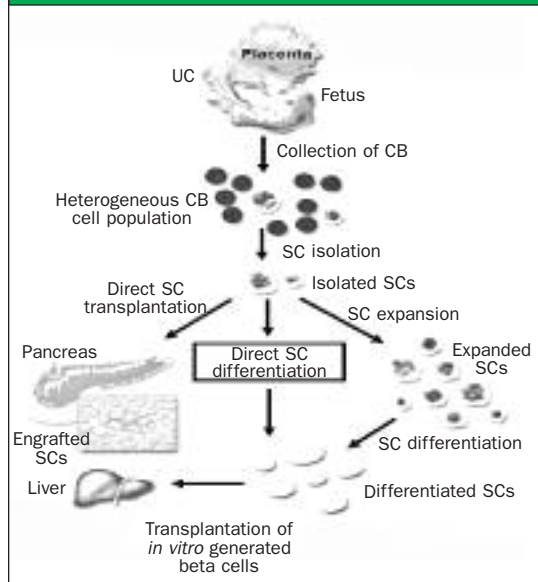
Recently, autologous HSC transplantation has been applied in the treatment of severe autoimmune diseases (Figure 3).³⁷ Voltarelli et al³⁸ used high-dose immunosuppression followed by autologous nonmyeloablative hematopoietic stem-cell transplantation (AHSCT) to treat 15 newly diagnosed type 1 diabetic patients. During 7–36 (mean 18.8) months of follow-up, 14 patients became free of insulin injections. At 6 months after AHSCT, mean total area under the C-peptide response curve was significantly greater than pre-treatment values and stabilized at 12 and 24 months; as well, antiglutamic acid decarboxylase antibody levels decreased after 6 months. Serum levels of hemoglobin A_{1c} were maintained at <7% in 13 of 14 patients. The only severe acute adverse effect was culture-negative bilateral pneumonia in 1 patient and late endocrine dysfunction (hypothyroidism or hypogonadism) in 2 others; there was no mortality. These data have demonstrated a promising potency; however, the study still had some limitations:

- The study design did not include a randomized control group.
- The duration of follow-up for all patients undergoing AHSCT was insufficient to determine whether the apparent improvement in C-peptide levels was sustained.
- It is unknown whether the beneficial effects of AHSCT are due to immune reconstitution, or to alteration of the immune-mediated β -cell destruction, or to regeneration of β cells.
- There is also a well-known “honeymoon” period of relative remission after the onset of type 1 diabetes that complicates the interpretation of these results.³⁹

Spleen stem cells

In 2003, Kodama et al⁴⁰ demonstrated a reversal of diabetes in NOD mice with end-stage disease after administering live, labeled, donor male splenocytes, which rapidly differentiated into islet and ductal epithelial cells within the pancreas. Their results suggested a role for complete Freund’s adjuvant (CFA) together with the injection of donor splenocytes to eliminate autoimmunity and restore stable normoglycemia. The return of endogenous insulin secretion was accompanied by the reappearance of pancreatic β cells that were engrafted and transdifferentiated from CD45-mesenchymal precursors in the spleen.

Figure 4: Possible methods of generating umbilical cord blood stem cell-derived β cells⁴⁴



UC=umbilical cord; SC=stem cell; CB=cord blood
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However, three more recent studies utilizing similar, although not identical, treatment regimens have failed to show engraftment of donor splenocytes; further reports suggest that CFA treatment in the absence of donor splenocytes is sufficient to reinstate normoglycemia with β -cell regeneration.^{41–43} To date, no lineage studies have demonstrated the transdifferentiation of splenic cells into hormone-producing cells in the pancreatic islets of Langerhans.

Umbilical cord blood stem cells

A variety of different stem cell types have been identified within umbilical cord blood (UCB), including HSCs, MSCs, ESCs, and a not yet fully characterized population of multipotent cells.⁴⁴ Investigators have made use of these stem cells to examine whether they can promote endogenous β -cell regeneration in a diseased or damaged pancreas. One research group found that intravenous transplantation of a mononuclear cell (MNC) fraction of the human UCB in NOD mice resulted in a significant lowering of blood-glucose levels and a significant reduction of insulinitis.⁴⁵ Beneficial effects are also found in type 2 diabetes; after transplantation of human UCB-MNCs in obese mice with spontaneous development of type 2 diabetes, the mice experienced beneficial effects on blood-glucose levels, survival, and renal pathology.⁴⁶ Similar to the benefits observed in bone marrow transplantation studies, the mechanisms engendering these improvements remain unclear.

A recent report demonstrated that following the intravenous transplantation of human UCB into NOD-SCID mice, insulin-producing cells of human origin were found in mouse islets.⁴⁷

Thus, UCB offers another option for stem-cell therapy in diabetes mellitus. The most challenging task will be the directing of cell fate toward a β -cell phenotype (Figure 4). There are 2 strategies worth testing:

- The simpler approach is the direct transplantation of cultivated stem cells or partially differentiated precursor cells. UCB cells have the capacity to migrate to various tissues and could be applied for this purpose; however, the exact mechanisms that drive the homing of manipulated cells in the pancreas and determine the phenotype of the potentially engrafted cells are not yet known.
- An alternative approach may be the *in vitro* generation of pancreatic precursors or mature β cells. The employment of exogenous factors that have been shown to be effective in β -cell differentiation could provide desirable outcomes.

Recently, Haller et al⁴⁸ embarked on a pilot study to document the safety and potential efficacy of autologous UCB infusion in 15 subjects with type 1 diabetes. Preliminary observations suggest that autologous UCB transfusion is safe and provides some slowing in the loss of endogenous insulin production. Increased regulatory T-cell populations may be found in the peripheral blood of subjects >6 months after cord blood infusion. It is clear that prolonged follow-up and additional mechanistic research are urgently needed to determine whether UCB-derived stem cells can be added to the options for safe and effective therapies in type 1 diabetes.

Conclusions

The utility of stem cells in diabetes therapy depends on their ability to promote β -cell regeneration. The apparent major mechanisms involved include immunomodulation, revascularization, support of endogenous β -cell regeneration, and differentiation into insulin-producing cells. Successful achievement of these goals may result in a cure for diabetes. Although, at the present time, research on stem cells for potential treatment of diabetes is still in its early stages, we believe that the evidence presented here gives some reasons for optimism. Therefore, future investigations of stem-cell therapeutic approaches to provoke endogenous islet regeneration for their insulin contribution would be worthwhile.

Dr. Wu is a postdoctoral fellow in Dr. Woo's laboratory.

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