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Cell-based Therapy for Treatment of Diabetes Mellitus: Can the Agonists of Growth Hormone-releasing Hormone Make a Contribution?

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Abstract

Beta cell replacement, to supply the body with cells producing insulin, is considered as one of the most important alternative approaches to the treatment of diabetes. Transplantation of human islets and the resulting progressive improvement of clinical results confirm the approach as a positive trend in this field. Recent progress in beta cell differentiation, deriving from many types of pluripotent stem cells, has potentially provided an unlimited source of β cells for research and clinical applications. Novel approaches are needed to make cell-based therapy more safe, reproducible and long-lastingly efficient. As an example, pretreatment of the islet cells with agonists of growth hormone-releasing hormone improves cell proliferation and metabolic functions and, facilitates engraftment of islets after transplantation in rodents. Here, we review current progress in islet transplantation and the studies using stem cell-derived insulin-producing β cells as therapeutic options in the treatment of diabetes.

Keywords

Diabetes, Islet transplantation, Mesenchymal stem cells, Embryonic stem cells, Induced-pluripotent stem cells, Beta cells, Growth hormone-releasing hormone agonists

Introduction

Diabetes currently affects more than 300 million people worldwide; this number is set to rise dramatically [1]. Permanently elevated blood glucose levels are the key indicator of this metabolic disorder. Type 1 diabetes (T1D) is an autoimmune disease in which insulin-producing β cells within the pancreatic islets are irreversibly destroyed, resulting in deficient insulin production. Type 2 diabetes (T2D) is a disease in which the pancreas produces insufficient amounts of insulin, due to progressive loss of β cells; systemic tissues may also become resistant to normal or even high levels of insulin. Severe complications, such as blindness, kidney failure, limb amputation and heart attack arise as a consequence of the long-term damage of tissues, caused by high levels of blood sugar. In both T1D and T2D the supply of insulin-producing tissue/cells is inadequate. Cell-based therapies are strategies to overcome this and thus reduce the dependence on exogenous insulin in diabetic patients. The main strategy is thus the development of such cell therapies to treat diabetes by the production of sufficient numbers of pancreatic endocrine cells that can function as primary islets.

The progress in pancreatic islet transplantation achieved over the past decade suggests that diabetes can be improved by replacing deficient β cells with new, functional, insulin-producing cells [2-4]. These techniques, while effective, are hindered by immune rejection as well as by the lack of adequate supplies of primary tissues for such transplantation. Generation of functional β cells from other sources is needed, therefore, to overcome the islet shortage. Over the past several years, stem cell therapy, especially that using mesenchymal stem cells (MSCs) [5,6], embryonic stem cells (ESCs) [7,8] and induced pluripotent stem cells (iPSCs) [9,10], as sources of engineered insulin-producing cells, has provided alternative approaches to islet transplantation. Recent findings of the beneficial effects of agonists of growth hormone-releasing hormone (GHRH) on the functions of β cells may also provide new approaches to their application in T1D and T2D diabetes [11-14].

Herein, we outline the progress, in animal studies and in human clinical trials, in the generation of β cells from different types of stem cells and also in the progress in methodology for infusion of islets and stem cell derived β cells intra-corporeally for the treatment of diabetes.

Islet Transplantation

One emerging alternative to whole organ pancreatic transplantation is transplantation of isolated pancreatic islet cells. This process is based on the enzymatic isolation of pancreatic islets

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from pancreata procured from cadaver donors. The islets obtained are infused into the liver of the recipient through a percutaneous catheterization of the portal venous system. This procedure for islet cell transplantation (ICT) is considered to be minimally invasive, and allows the selective transplantation of a population of insulin-producing cells. ICT can be considered an alternate option in the restoration of glucose homeostasis in a subset of T1D patients with unstable glycemic control and with frequently severe hypoglycemia which has failed correction by standard intensive insulin therapy [3].

The ICT method was first developed in the 1970s. These initial efforts with ICT showed that the treatment reduced the occurrence of diabetic complications, however, the long-term outcome was unsatisfactory. The results were improved remarkably, in 2000, by the demonstration of Shapiro et al. [15], that the key to success of islet transplantation lay in the quality and the mass of the islets used, as well as the immunosuppressive regimen. By using an improved, "Edmonton Protocol", the destruction of islets, caused by rejection and recurrent autoimmune disease, was reduced. Further, the report by the Collaborative Islet Transplant Registry for allogeneic islet transplantation performed during the years 1999 to 2010, indicated that the rate of recipients achieving insulin-independence for 3 years showed increasing stability, from only 10% before 1999 to 44% in the years from 2007-2010 [16,17]. Using potent application of immunotherapy, a higher rate of insulin-independence can thus be achieved [18,19]. Increased levels of C-peptide and reduction of glycated hemoglobin, (Hb-A1c), attested to the increasing durability of islet graft function. However, the limitation of transplantable pancreatic donor material is still a major hurdle. To meet the demand for islet transplantation, a potential alternative is the use of animal sourced islets. The use of pancreatic islets obtained from pigs has emerged as a practical alternative to the use of human tissues, due to their greater availability and physiologic similarities to human islets. Long-term graft survival, in non-human primates, of porcine islets isolated from adult, neonatal or genetically engineered pigs has been reported [20-22]. Infusion of adult porcine islets resulted in normoglycemia in immunosuppressed, diabetic, non-human primates [23].

Minimization of attack by the host's immune system is a critical issue in achieving efficient islet engraftment. Immunosuppressive therapy, however, itself causes undesirable side effects. Despite many preclinical and clinical trials, there is still not a single standard immunosuppressive regimen that can be used to suppress acute and chronic immune reactions, with lower toxicity, to grafted islets.

An islet encapsulation technology to treat diabetes, another conceptual option, has been developed. By trapping islets into man-made devices, a physical barrier between the islet cells and the immune system is created, thus allowing normal physiologic function of encapsulated islet cells. The system has been tested in several experimental models [24]. A pilot trial for safety and efficacy to treat patients with T1D is in progress [3]. A "bioartificial pancreas" has also been developed which consists of macrochambers specifically engineered for islet transplantation and survival. The subcutaneously implantable device allows for a controlled and adequate oxygen supply and is specially designed to afford immunologic protection of its contained donor islets against the host's immune system. This has made possible long-term glycemic control in diabetic rats and minipigs [12,25]. A breakthrough was reported in that a human patient, suffering from TD1, received an implanted bioartificial pancreas and experienced persistent graft function, with regulated insulin secretion and preservation of islet morphology and function, without the need for immunosuppression, for ten months [26]. This system/concept opens up an entirely new, fundamental strategy for the therapy of diabetes, by providing an avenue for future approaches using xenotransplantation. A clinical trial, using a "DIABECELL" device, which incorporates neonatal porcine islets encapsulated in alginate microcapsules, is also in progress [3]. DIABECELL has been safely transplanted in both healthy and diabetic animals. Following DIABECELL transplants, the requirement for daily insulin was significantly reduced in diabetic mice, rats, rabbits, dogs and non-human primates.

Designing a procedure to specifically isolate islets, with high cellular yields and minimal damage, is another critical issue in the success of islet transplantation [2]. Strategies to robustly condition pancreatic islets, such as promotion of cell growth and metabolic function, are particularly important [27,28]. Numerous studies have reported efforts to improve the survival of islets by preventing the loss of islet cell viability and function during and following the transplantation period, in animal diabetic models. To this end growth hormone (GH), and various growth factors such as insulin-like growth factor-1 (IGF-1) and, glucagon-like peptide (GLP-1) were studied for their ability to stimulate proliferation and survival of pancreatic β cells [29-32]. Pharmaceutical screening to identify new drugs that can improve β cell function, survival, proliferation, or all of those, is another important possibility for improving the maintenance of functional islet cells for transplantation. For example, in mouse models of diabetes, the efficacy of islet transplantation can be substantially improved by the preconditioning of islets with kinase Ce (PKCe) activator [33]. Recently, agonists of growth hormone-releasing hormone (GHRH) were found to significantly improve β cell survival, growth and metabolic function, and to increase expression of cellular insulin, IGF-1 and vascular endothelial growth factor (VEGF); they also stimulated insulin secretion in response to glucose challenge *in vitro*. Pretreatment of rat islets with GHRH agonists also improves the *in vivo* engraftment and the metabolic function of islets following the transplantation into streptozotocin (STZ)-induced diabetic mice [11,13,14]. Pretreatment with GHRH agonists also significantly enhanced function of rat islets encapsulated in bioartificial macrochambers after implantation into diabetic rats [12]. The pretreatments led to a reduction of the islet mass necessary for normoglycemic metabolic control in diabetic animals [12,14]. VEGF has been reported to play a critical role in development of β cells, and is itself also associated with the survival of islets *in vivo* following transplantation [34,35]. We can speculate that the beneficial effects of GHRH agonists on the functions of β cells may provide an improved approach to ICT. Clinical trials of oral caspase inhibitor to prevent apoptosis of islets, and Sitagliptin, a drug to increase the amount of GLP-1, are already in progress in T1D patients after islet transplantation [3].

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) represent a stem cell population that can be isolated from a variety of adult tissues. MSCs exhibit a great capacity of self-renewal in culture, and also the potential of multipotent differentiation. Human MSCs exhibit low immunogenicity, thereby making them important and promising candidates for allogeneic cell therapy. MSCs have the potential to supply growth factors and cytokines, and the ability to selectively target into those injured tissues requiring repair [36,37]. Furthermore, MSCs are an abundantly available cell source and can be obtained from patients for use in autologous transplantation. MSCs are currently being evaluated in various pre-clinical and clinical studies and offer significant potential as a novel cellular therapy for tissue regeneration and repair, immune disorders, diabetes, and related complications [38].

In vitro differentiation of MSCs into insulin producing cells is well documented. Using multistep differentiation protocols, MSC-derived insulin-producing cells can be obtained from a variety of human adult tissues [5,39] including bone marrow [40,41], adipose tissue [42,43], umbilical cord or its blood [44,45], endometrium [46]. Numerous studies have reported the potential improvement of diabetes by transplantation of MSCs in T1D diabetic mice [6,47-50], rats [51] and miniature pigs [52]. Infusion of MSCs derived from bone marrow or umbilical cord improved the hyperglycemia and raised blood insulin levels in T2D mice [53]. The infusion of MSCs not only promoted β-cell function, but also ameliorated insulin resistance in T2D rats [53]. MSCs can also improve the secretion of a variety of trophic factors such as IGF-1 and VEGF. VEGF is known to play a key role in cell engraftment and MSC-mediated vasculogenesis [54,55]. Co-transplanting bone marrow cells concurrent with islet transplantation also significantly improves islet engraftment in

diabetic mice [56,57]. Transplantation with MSCs also ameliorated damages in cardiac dysfunction [54,58,59], renal failure [49,60,61], dysfunctional wound healing and limb ischemia [62,63], in diabetic animal models.

Preliminary and preclinical studies of infusions, using human MSCs derived from bone marrow, umbilical cord, cord blood or placenta, to treat patients with T1D and T2D have yielded promising data. The treatment is shown to be safe and well tolerated; reduction of insulin dependence is observed. Studies have further indicated that autologous bone marrow MSCs preserve β cell function in patients with recent-onset T1D [64,65]. In the management of T2D, they partially restore the function of islet beta-cells, maintaining blood glucose homeostasis, increasing levels of C-peptide [66,67] and improving wound healing in diabetic patients with critical limb ischemia [68]. The infusion of multipotent stem cells, derived from umbilical cord blood, remarkably improves C-peptide levels, reduces Hb-A1c values, decreases the required median daily doses of insulin in patients with T1D [69]; it also ameliorated metabolic control and reduced inflammation markers in patients with T2D [70]. Wharton's jelly–derived MSCs (WJ-MSCs, isolated from the umbilical cord with a high yield of "young cells") or MSCs derived from adipose tissue or placenta can also be used in the treatment of new-onset T1D [71,72], and T2D [73,74].

The abundantly available sources of MSCs for transplantation, and their low immunogenicity and immune-modulatory properties, give MSCs advantages over islets in cell based therapy. Animal studies and pilot clinical trials have demonstrated the effectiveness of MSCs in the treatment of T1D and T2D. However, despite the success of differentiation of human MSCs *in vitro* into functional pancreatic β cells, the rate of trans-differentiation was considered low [75,76], and the duration of functional maintenance *in vivo* is difficult to evaluate. The absence of standardized protocols for the expansion and generation of insulin secreting cells still leads to inconsistent clinical outcomes. MSCs do not pose the risk of producing teratomas, but their substantial expression of chemokines may have hidden risks for the promotion of tumor growth and metastasis. Karyotypic changes might also appear after long-term continuation in culture [37]. Nevertheless, transplantation of MSCs ameliorates the progress of diabetes and, perhaps, may have unique potential when used in combination with ICT [3,6,56,57]. Recently it has been reported that agonists of GHRH promote survival of cardiac myocytes and cardiac stem cells *in vitro* [77-79], reverse remodeling after myocardial infarction *in vivo* [77,78], accelerate wound healing [80] and augment the production of VEGF in mouse or human MSCs [55]. These interesting finding may provide a new insight into the use of agonists of GHRH for the potential tissue repair function of MSCs. The use of GHRH agonists may improve the efficacy of MSCs based therapy of diabetes.

Embryonic Stem Cells

The most significant aspect of the use of cell therapies to treat diabetes is the potential for the production of sufficient numbers of pancreatic endocrine cells that can function similarly to primary islets. Human embryonic stem cells (ESCs) derived from the inner cell mass of a blastocyst can proliferate extensively *in vitro*, be maintained indefinitely as an undifferentiated cell line, and have the potential to differentiate into derivatives of any of the three germ layers [81,82]. One advantage of applications using ESC-derived cells is that ESCs are not as immunologically potent as allogeneic adult cells; the use of ESCs therefore provides a promising alternative cell source for the cellular treatment of diabetes. Many studies have been reported wherein both mouse and human ESCs may differentiate into insulin-secreting cells [83-85]. By using strategies mimicking embryonic pancreatic organogenesis, human ESCs can be induced to differentiate *in vitro* into endocrine cells capable of synthesizing pancreatic hormones [86]. After implantation into diabetic mice, these cells efficiently generate glucose-responsive cells, exhibit the properties of functional β cells after engraftment, and prevent STZ-induced hyperglycemia [87]. Furthermore, by using defined cell surface markers, enriched populations of pancreatic endoderm cell types can be differentially separated, and give rise to all pancreatic lineages after transplantation into mice [88]. A scalable system for the production of functional pancreatic progenitors from human ESCs has been developed; these cells, upon implantation, efficiently protect against diabetes in mice [89,90]. This system has provided a robust methodology for manufacturing pancreatic progenitors for use in clinical trials. The very first-in-human trial using human ESC-derived pancreatic precursor cells to treat patients with T1D is now under way [7,91]. The cells are encapsulated in a drug delivery system developed by the Encaptra Company. The system is placed under the patient's skin to protect from the recipient's immune cells [91]. Recently, two groups independently reported that, by using a multiple-stage induction protocol, they efficiently converted human ESCs into insulin producing cells *in vitro* [92,93]. The cells displayed glucose-stimulated insulin secretion similar to that of human islets [92]. Xenotransplantation of these cells efficiently reverses diabetes in mice. *In vitro* expansion of these cells provides a promising alternative to using pancreatic progenitor cells and would overcome donor islet shortages. ESCs are a favorable source for cell based therapy, however, in addition to ethical issues, safety is a major concern because the possible contamination by undifferentiated cells is a hidden risk for the formation of teratomas or other tumors [94]. There is now a growing recognition that differentiated cells derived from ESCs are mostly immature [95]. These cells thus can mimic embryonic development and adopt phenotypes that resemble fetal or neonatal cells which, with the hidden danger of genetic mutagenesis, could lead to tumor formation. More studies, with long-term observation, are required to understand the mechanisms involved and their significance.

Induced Pluripotent Stem Cells

The exciting discovery of induced pluripotent stem cells (iPSCs), in 2006, opened a new possibility in generating replacement cell based therapy for disease treatment [96]. Forced expression of four defined key transcription factors can program mouse somatic cells, such as fibroblasts, into iPSCs. IPSCs resemble ESCs with their infinite self-renewal capacity and great potential to differentiate into a wide variety of cell types. Success in generation of iPSCs from human somatic cells was soon reported [97,98]. Un-differentiated iPSCs can be maintained as cell lines; this, therefore, provides great promise for disease modeling and for allowing the generation of personalized stem cells for autologous cell therapies [9,99].

Mouse skin fibroblast-derived iPSCs were able to differentiate into β-like cells, similar to normal, endogenous insulin-secreting cells, and thereby reverse hyperglycemia in diabetic mice [100]. iPSCs have been generated from patients suffering from T1D and T2D [101-103]. Insulin-producing cells have then been generated *in vitro* from iPSCs by directed differentiation, using small molecules and growth factors in culture [104,105]; these produced a nearly 25% yield of insulin-positive cells [106]. Recently, a stratagem for large-scale production of functional human β cells from human iPSCs *in vitro* has been demonstrated. By using sequential modulation of multiple signaling pathways found in the development of the pancreas, in a three-dimensional cell culture system, mono-hormonal insulin-producing and glucose-responsive cells were generated [105,107]; with reproducible protocols an approximately 50% yield could be obtained [93,108]. These cells also responded to multiple, sequential high-glucose challenges and thus functionally protected mice from diabetes. Therefore, this technique may allow us to produce large numbers of β cells *in vitro* for therapeutic application.

An advantage of using iPSCs is the absence of ethical concerns. The technology allows the generation of autologous cells for cell-replacement therapy. The somatic origin of iPSCs has minimized, but however, not eliminated, some of the challenges that have hampered the development of human ESC-based therapies. As with ESCs, a major obstacle to the use of iPSCs is the safety issue; the risk of teratoma formation can be substantial [109,110]. An improved understanding of the molecular mechanisms of cellular reprogramming is necessary in order to overcome these barriers before the so-called "next-generation stem cells" can be safely applied in patients with diabetes.

Transdifferentiation

Several studies have shown that β cells can be generated from other cell types of endodermal origin, without requiring transit though a pluripotent stage. Introduction of pancreatic transcription factor *in vivo* induced liver cells to express pancreatic endocrine-related genes including those for insulin production, without affecting normal hepatic function, and resulted in prevention of chemically induced hyperglycemia in mice [111,112]. A strategy of re-expressing key developmental regulators *in vivo* can reprogram differentiated pancreatic exocrine cells into cells resembling β cells in respect in size, shape, ultrastructure and expression of those genes essential for β cell functions [113-115]. Pancreatic ductal structures may also contain precursor cells that can yield insulin-producing cells. Ductal tissue from human pancreas can be isolated in large scale, expanded and directed to differentiate into glucose responsive islet tissue *in vitro* [116,117]. The expression of a single transcription factor in mouse pancreatic α cells induced them to re-differentiate towards a β cell fate; α cell-mediated regeneration of the β cell mass ameliorated hyperglycemia and extended lifespan [118]. These studies presented additional concepts and protocols for production of pancreatic β cells.

The application of the GHRH agonists in the Treatment of Diabetes

Hypothalamic GHRH stimulates production and release of growth hormone (GH) from the pituitary gland, exerts some of its effects through the GH/IGF-1 axis, and also directly affects extra-pituitary cells expressing GHRH receptors by activating them. GHRH receptor(s) have been detected in pancreatic β cells, cardiac stem cells and MSCs from different species [11-14,55,77-80]. It has been proposed that the activation of signal pathways (such as MAPK/ERK, PI3K/AKT, and cAMP/PKA), triggered by the interaction between GHRH agonists and the receptors on β cells, plays an important role in the stimulation of metabolic function of pancreatic β cells [14]. The GHRH-GHRH receptor complex may enable signal transduction independently or in cooperation with other pathways, likely the IGF-1 signaling pathway, in the regulation of development and function of pancreatic β cells. The beneficial effects of GHRH agonists on the metabolic function of pancreatic β cells may provide approaches to cell based therapy for treatment of diabetes.

Conclusion

In conclusion, strategies to supply the body with cells producing insulin are considered as the most important alternative approaches to the treatment of diabetes. The progress in the transplantation of pancreatic islets that has been achieved suggests that clinical diabetes can be improved by the replacement of deficient beta cells with new, functional cells. Generation of functional β cells from stem cells offers an attractive method of restoring islet cell mass. The use of MSCs, ESCs and iPSCs as sources for engineered insulin secreting cells, has provided an alternative approach to the use of islet transplants. Recent success in the generation of mono-hormonal, insulin-producing and glucose-responsive cells from human ESCs and iPSCs provides an enormous potential source of β cells for therapeutic usage. Beneficial effects of GHRH agonists and other hormonal and growth agents on the proliferation and function of β cells and on the engraftment of islets after transplantation, suggest that these classes of compounds might also improve the function of the insulin-producing-cells derived from ESCs, iPSCs and other cell types of endodermal origin, but further studies are required. The development and application of encapsulation technology to circumvent immune rejection by recipients may enable us to reduce or eliminate the necessity of immunosuppressive drugs. Progress in these areas opens up new avenues for the treatment of both T1D and T2D.

References

1. Holliday EG (2013) Hints of unique genetic effects for type 2 diabetes in India. Diabetes 62: 1369-1370.
2. Lehmann R, Spinas GA, Moritz W, Weber M (2008) Has time come for new goals in human islet transplantation? Am J Transplant 8: 1096-1100.
3. Bruni A, Gala-Lopez B, Pepper AR, Abualhassan NS, Shapiro AJ (2014) Islet cell transplantation for the treatment of type 1 diabetes: recent advances and future challenges. Diabetes Metab Syndr Obes 7: 211-223.
4. Maffi P, Secchi A2 (2015) Clinical results of islet transplantation. Pharmacol Res 98: 86-91.
5. El-Badri N, Ghoneim MA (2013) Mesenchymal stem cell therapy in diabetes mellitus: progress and challenges. J Nucleic Acids 2013: 194858.
6. Azarpira N, Kaviani M, Salehi S (2015) The role of mesenchymal stem cells in diabetes mellitus. Int J Stem Cell Res Ther 2: 1.
7. Bouwens L, Houbracken I, Mfopou JK (2013) The use of stem cells for pancreatic regeneration in diabetes mellitus. Nat Rev Endocrinol 9: 598-606.
8. Moore SJ, Gala-Lopez BL, Pepper AR, Pawlick RL, Shapiro AJ1 (2015) Bioengineered stem cells as an alternative for islet cell transplantation. World J Transplant 5: 1-10.
9. Wu SM, Hochedlinger K (2011) Harnessing the potential of induced pluripotent stem cells for regenerative medicine. Nat Cell Biol 13: 497-505.
10. Johannesson B, Sui L, Freytes DO, Creusot RJ, Egli D4 (2015) Toward beta cell replacement for diabetes. EMBO J 34: 841-855.
11. Ludwig B, Ziegler CG, Schally AV, Richter C, Steffen A, et al. (2010) Agonist of growth hormone-releasing hormone as a potential effector for survival and proliferation of pancreatic islets. Proc Natl Acad Sci USA 107: 12623-12628.
12. Ludwig B, Rotem A, Schmid J, Weir GC, Colton CK, et al. (2012) Improvement of islet function in a bioartificial pancreas by enhanced oxygen supply and growth hormone releasing hormone agonist. Proc Natl Acad Sci USA 109: 5022-5027.
13. Schubert U, Schmid J, Lehmann S, Zhang XY, Morawietz H, et al. (2013) Transplantation of pancreatic islets to adrenal gland is promoted by agonists of growth-hormone-releasing hormone. Proc Natl Acad Sci USA 110: 2288-2293.
14. Zhang X, Cui T, He J, Wang H, Cai R, et al. (2015) Beneficial effects of growth hormone-releasing hormone agonists on rat INS-1 cells and on streptozotocin-induced NOD/SCID mice. Proc Natl Acad Sci USA 112: 13651-13656.
15. Shapiro AM, Lakey JRT, Ryan EA, Korbutt GS, Toth E, et al. (2000) Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 343: 230-238.
16. Alejandro R, Barton FB, Hering BJ, Wease S; Collaborative Islet Transplant Registry Investigators (2008) 2008 Update from the Collaborative Islet Transplant Registry. Transplantation 86: 1783-1788.
17. Barton FB, Rickels MR, Alejandro R, Hering BJ, Wease S, et al. (2012) Improvement in outcomes of clinical islet transplantation: 1999-2010. Diabetes Care 35: 1436-1445.
18. Bellin MD, Barton FB, Heitman A, Harmon JV, Kandaswamy R, et al. (2012) Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes. Am J Transplant 12: 1576-1583.
19. Rickels MR, Liu C, Shlansky-Goldberg RD, Soleimanpour SA, Vivek K, et al. (2013) Improvement in β-cell secretory capacity after human islet transplantation according to the CIT07 protocol. Diabetes 62: 2890-2897.
20. Hering BJ1, Wijkstrom M, Graham ML, Hårdstedt M, Aasheim TC,, et al. (2006) Prolonged diabetes reversal after intraportal xenotransplantation of wild-type porcine islets in immunosuppressed nonhuman primates. Nat Med 12: 301-303.
21. Thompson P, Badell IR, Lowe M, Cano J, Song M, et al. (2011) Islet xenotransplantation using gal-deficient neonatal donors improves engraftment and function. Am J Transplant 11: 2593-2602.
22. Bottino R, Wijkstrom M, van der Windt DJ, Hara H, Ezzelarab M, et al. (2014) Pig-to-monkey islet xenotransplantation using multi-transgenic pigs. Am J Transplant 14: 2275-2287.
23. Shin JS, Kim JM, Kim JS, Min BH, Kim YH, et al. (2015) Long-term control of diabetes in immunosuppressed nonhuman primates (NHP) by the transplantation of adult porcine islets. Am J Transplant 15: 2837-2850.
24. Scharp DW, Marchetti P (2014) Encapsulated islets for diabetes therapy: history, current progress, and critical issues requiring solution. Adv Drug Deliv Rev 67-68: 35-73.
25. Neufeld T, Ludwig B, Barkai U, Weir GC, Colton CK, et al. (2013) The efficacy of an immunoisolating membrane system for islet xenotransplantation in minipigs. PLoS One 8: e70150.
26. Ludwig B, Reichel A, Steffen A, Zimerman B, Schally AV, et al. (2013) Transplantation of human islets without immunosuppression. Proc Natl Acad Sci USA 110: 19054-19058.
27. Lakey JR, Burridge PW, Shapiro AM (2003) Technical aspects of islet preparation and transplantation. Transpl Int 16: 613-632.
28. Fotino N, Fotino C, Pileggi A (2015) Re-engineering islet cell transplantation. Pharmacol Res 98: 76-85.

29. Rhodes CJ, White MF (2002) Molecular insights into insulin action and secretion. Eur J Clin Invest 32 Suppl 3: 3-13.

30. Ma F, Wei Z, Shi C, Gan Y, Lu J, et al. (2011) Signaling cross talk between growth hormone (GH) and insulin-like growth factor-I (IGF-I) in pancreatic islet β-cells. Mol Endocrinol 25: 2119-2133.

31. Li Y, Hansotia T, Yusta B, Ris F, Halban PA, et al. (2003) Glucagon-like peptide-1 receptor signaling modulates beta cell apoptosis. J Biol Chem 278: 471-478.

32. Nielsen JH, Galsgaard ED, Møldrup A, Friedrichsen BN, Billestrup N, et al. (2001) Regulation of beta-cell mass by hormones and growth factors. Diabetes 50 Suppl 1: S25-29.

33. Hamilton D, Rugg C, Davis N, Kvezereli M, Tafti BA, et al. (2014) A preconditioning regimen with a PKCÉ› activator improves islet graft function in a mouse transplant model. Cell Transplant 23: 913-919.

34. Brissova M, Shostak A, Shiota M, Wiebe PO, Poffenberger G, et al. (2006) Pancreatic islet production of vascular endothelial growth factor-A is essential for islet vascularization, revascularization,and function. Diabetes 55: 2974-2985.

35. Zhang N, Richter A, Suriawinata J, Harbaran S, Altomonte J, et al. (2004) Elevated vascular endothelial growth factor production in islets improves islet graft vascularization. Diabetes 53: 963-970.

36. Sordi V, Malosio ML, Marchesi F, Mercalli A, Melzi R, et al. (2005) Bone marrow mesenchymal stem cells express a restricted set of functionally active chemokine receptors capable of promoting migration to pancreatic islets. Blood 106: 419-427.

37. Kode JA, Mukherjee S, Joglekar MV, Hardikar AA (2009) Mesenchymal stem cells: immunobiology and role in immunomodulation and tissue regeneration. Cytotherapy 11: 377-391.

38. Patel DM, Shah J, Srivastava AS (2013) Therapeutic potential of mesenchymal stem cells in regenerative medicine. Stem Cells Int 2013: 496218.

39. Wu XX, Shao JZ, Xiang C (2014) Generation of pancreatic β cells from mesenchymal stem cells to treat type 1 diabetes. OA Stem Cells 2: 5.

40. Sun Y, Chen L, Hou XG, Hou WK, Dong JJ, et al. (2007) Differentiation of bone marrow-derived mesenchymal stem cells from diabetic patients into insulin-producing cells in vitro. Chin Med J (Engl) 120: 771-776.

41. Bhansali A, Upreti V, Khandelwal N, Marwaha N, Gupta V, et al. (2009) Efficacy of autologous bone marrow derived stem cell transplantation in patients with type 2 diabetes mellitus. Stem Cells Dev 18: 1407-1416.

42. Timper K, Seboek D, Eberhardt M, Linscheid P, Christ-Crain M, et al. (2006) Human adipose tissue-derived mesenchymal stem cells differentiate into insulin, somatostatin, and glucagon expressing cells. Biochem Biophys Res Commun 341: 1135-1140.

43. Dave SD, Vanikar AV, Trivedi HL (2012) Ex vivo generation of glucose sensitive insulin secreting mesenchymal stem cells derived from human adipose tissue. Indian J Endocrinol Metab 16 Suppl 1: S65-69.

44. Prabakar KR, Domínguez-Bendala J, Molano RD, Pileggi A, Villate S, et al. (2012) Generation of glucose-responsive, insulin-producing cells from human umbilical cord blood-derived mesenchymal stem cells. Cell Transplant 21: 1321-1339.

45. Chao KC, Chao KF, Fu YS, Liu SH (2008) Islet-like clusters derived from mesenchymal stem cells in Wharton's Jelly of the human umbilical cord for transplantation to control type 1 diabetes. PLoS One 3: e1451.

46. Santamaria X, Massasa EE, Feng Y, Wolff E, Taylor HS (2011) Derivation of insulin producing cells from human endometrial stromal stem cells and use in the treatment of murine diabetes. Mol Ther 19: 2065-2071.

47. Hess D, Li L, Martin M, Sakano S, Hill D, et al. (2003) Bone marrow-derived stem cells initiate pancreatic regeneration. Nat Biotechnol 21: 763-770.

48. Jurewicz M, Yang S, Augello A, Godwin JG, Moore RF, et al. (2010) Congenic mesenchymal stem cell therapy reverses hyperglycemia in experimental type 1 diabetes. Diabetes 59: 3139-3147.

49. Lee RH, Seo MJ, Reger RL, Spees JL, Pulin AA, et al. (2006) Multipotent stromal cells from human marrow home to and promote repair of pancreatic islets and renal glomeruli in diabetic NOD/scid mice. Proc Natl Acad Sci USA 103: 17438-17443.

50. Gabr MM, Zakaria MM, Refaie AF, Ismail AM, Abou-El-Mahasen M, et al. (2013) Insulin-producing cells from adult human bone marrow mesenchymal stem cells control streptozotocin-induced diabetes in nude mice. Cell Transplant 22: 133-145.

51. Tsai PJ, Wang HS, Shyr YM, Weng ZC, Tai LC, et al. (2012) Transplantation of insulin-producing cells from umbilical cord mesenchymal stem cells for the treatment of streptozotocin-induced diabetic rats. J Biomed Sci 19: 47.

52. Tang K, Xiao X, Liu D, Shen Y, Chen Y, et al. (2014) Autografting of bone marrow mesenchymal stem cells alleviates streptozotocin-induced diabetes in miniature pigs: real-time tracing with MRI in vivo. Int J Mol Med 33: 1469-1476.

53. Si Y, Zhao Y, Hao H, Liu J, Guo Y, et al. (2012) Infusion of mesenchymal stem cells ameliorates hyperglycemia in type 2 diabetic rats: identification of a novel role in improving insulin sensitivity. Diabetes 61: 1616-1625.

54. Zhang N, Li J, Luo R, Jiang J, Wang JA (2008) Bone marrow mesenchymal stem cells induce angiogenesis and attenuate the remodeling of diabetic cardiomyopathy. Exp Clin Endocrinol Diabetes 116: 104-111.

55. Gomes SA, Rangel EB, Premer C, Dulce RA, Cao Y, et al. (2013) S-nitrosoglutathione reductase (GSNOR) enhances vasculogenesis by mesenchymal stem cells. Proc Natl Acad Sci USA 110: 2834-2839.

56. Sakata N, Chan NK, Chrisler J, Obenaus A, Hathout E (2010) Bone marrow cell cotransplantation with islets improves their vascularization and function. Transplantation 89: 686-693.

57. Oh BJ, Oh SH, Jin SM, Suh S, Bae JC, et al. (2013) Co-transplantation of bone marrow-derived endothelial progenitor cells improves revascularization and organization in islet grafts. Am J Transplant 13: 1429-1440.

58. Khan M, Ali F, Mohsin S, Akhtar S, Mehmood A, et al. (2013) Preconditioning diabetic mesenchymal stem cells with myogenic medium increases their ability to repair diabetic heart. Stem Cell Res Ther 4: 58.

59. Ammar HI, Sequiera GL, Nashed MB, Ammar RI, Gabr HM, et al. (2015) Comparison of adipose tissue- and bone marrow- derived mesenchymal stem cells for alleviating doxorubicin-induced cardiac dysfunction in diabetic rats. Stem Cell Res Ther 6: 148.

60. Ezquer F, Ezquer M, Simon V, Pardo F, Yanez A, et al. (2009) Endovenous administration of bone marrow-derived multipotent mesenchymal stromal cells prevents renal failure in diabetic mice. Biol Blood Marrow Transplant 15: 1354-1365.

61. Lv S, Cheng J, Sun A, Li J, Wang W, et al. (2014) Mesenchymal stem cells transplantation ameliorates glomerular injury in streptozotocin-induced diabetic nephropathy in rats via inhibiting oxidative stress. Diabetes Res Clin Pract 104: 143-154.

62. Kwon DS, Gao X, Liu YB, Dulchavsky DS, Danyluk AL, et al. (2008) Treatment with bone marrow-derived stromal cells accelerates wound healing in diabetic rats. Int Wound J 5: 453-463.

63. Amin AH, Abd Elmageed ZY, Nair D, Partyka MI, Kadowitz PJ, et al. (2010) Modified multipotent stromal cells with epidermal growth factor restore vasculogenesis and blood flow in ischemic hind-limb of type II diabetic mice. Lab Invest 90: 985-996.

64. Mesples A, Majeed N, Zhang Y, Hu X (2013) Early immunotherapy using autologous adult stem cells reversed the effect of anti-pancreatic islets in recently diagnosed type 1 diabetes mellitus: preliminary results. Med Sci Monit 19: 852-857.

65. Carlsson PO, Schwarcz E, Korsgren O, Le Blanc K4 (2015) Preserved Î²-cell function in type 1 diabetes by mesenchymal stromal cells. Diabetes 64: 587-592.

66. Hu J, Li C, Wang L, Zhang X, Zhang M, et al. (2012) Long term effects of the implantation of autologous bone marrow mononuclear cells for type 2 diabetes mellitus. Endocr J 59: 1031-1039.

67. Wang ZX, Cao JX, Li D, Zhang XY, Liu JL, et al. (2015) Clinical efficacy of autologous stem cell transplantation for the treatment of patients with type 2 diabetes mellitus: a meta-analysis. Cytotherapy 17: 956-968.

68. Lu D, Chen B, Liang Z, Deng W, Jiang Y, et al. (2011) Comparison of bone marrow mesenchymal stem cells with bone marrow-derived mononuclear cells for treatment of diabetic critical limb ischemia and foot ulcer: a double blind, randomized, controlled trial. Diabetes Res Clin Pract 92: 26-36.

69. Zhao Y, Jiang Z, Zhao T, Ye M, Hu C, et al. (2012) Reversal of type 1 diabetes via islet β cell regeneration following immune modulation by cord blood-derived multipotent stem cells. BMC Med 10: 3.

70. Zhao Y, Jiang Z, Zhao T, Ye M, Hu C, et al. (2013) Targeting insulin resistance in type 2 diabetes via immune modulation of cord blood-derived multipotent stem cells (CB-SCs) in stem cell educator therapy: phase I/II clinical trial. BMC Med 11: 160.

71. Hu J, Yu X, Wang Z, Wang F, Wang L, et al. (2013) Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus. Endocr J 60: 347-357.

72. Thakkar UG, Trivedi HL, Vanikar AV, Dave SD (2015) Insulin-secreting adipose-derived mesenchymal stromal cells with bone marrow-derived hematopoietic stem cells from autologous and allogenic sources for type 1 diabetes mellitus. Cytotherapy 17: 940-947.

73. Jiang R, Han Z, Zhuo G, Qu X, Li X, et al. (2011) Transplantation of placenta-derived mesenchymal stem cells in type 2 diabetes: a pilot study. Front Med 5: 94-100.

74. Liu X, Zheng P, Wang X, Dai G, Cheng H, et al. (2014) A preliminary evaluation of efficacy and safety of Wharton's jelly mesenchymal stem cell transplantation in patients with type 2 diabetes mellitus. Stem Cell Res Ther 5: 57.

75. Gabr MM, Zakaria MM, Refaie AF, Khater SM, Ashamallah SA, et al. (2015) Differentiation of human bone marrow-derived mesenchymal stem cells into insulin-producing cells: Evidence for further maturation *in vivo*. Biomed Res Int. 2015: 575837.

76. Carlsson PO, Korsgren O, Le Blanc K (2015) Mesenchymal stromal cells to halt the progression of type 1 diabetes? Curr Diab Rep 15: 46.

77. Kanashiro-Takeuchi RM, Takeuchi LM, Rick FG, Dulce R, Treuer AV, et al. (2012) Activation of growth hormone releasing hormone (GHRH) receptor stimulates cardiac reverse remodeling after myocardial infarction (MI). Proc Natl Acad Sci USA 109: 559-563.

78. Kanashiro-Takeuchi RM, Tziomalos K, Takeuchi LM, Treuer AV, Lamirault G, et al. (2010) Cardioprotective effects of growth hormone-releasing hormone agonist after myocardial infarction. Proc Natl Acad Sci USA 107: 2604-2609.

79. Florea V, Majid SS, Kanashiro-Takeuchi RM, Cai RZ, Block NL, et al. (2014) Agonists of growth hormone-releasing hormone stimulate self-renewal of cardiac stem cells and promote their survival. Proc Natl Acad Sci USA 111: 17260-17265.

80. Dioufa N, Schally AV, Chatzistamou I, Moustou E, Block NL, et al. (2010) Acceleration of wound healing by growth hormone-releasing hormone and its agonists. Proc Natl Acad Sci USA 107: 18611-18615.

81. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, et al. (1998) Embryonic stem cell lines derived from human blastocysts. Science 282: 1145-1147.

82. Hoffman LM, Carpenter MK (2005) Characterization and culture of human embryonic stem cells. Nat Biotechnol 23: 699-708.

83. Soria B, Roche E, Berná G, León-Quinto T, Reig JA, et al. (2000) Insulin-secreting cells derived from embryonic stem cells normalize glycemia in streptozotocin-induced diabetic mice. Diabetes 49: 157-162.

84. Lumelsky N, Blondel O, Laeng P, Velasco I, Ravin R, et al. (2001) Differentiation of embryonic stem cells to insulin-secreting structures similar to pancreatic islets. Science 292: 1389-1394.

85. Segev H, Fishman B, Ziskind A, Shulman M, Itskovitz-Eldor J (2004) Differentiation of human embryonic stem cells into insulin-producing clusters. Stem Cells 22: 265-274.

86. D'Amour KA, Bang AG, Eliazer S, Kelly OG, Agulnick AD, et al. (2006) Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells. Nat Biotechnol 24: 1392-1401.

87. Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, et al. (2008) Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells *in vivo*. Nat Biotechnol 26: 443-452.

88. Kelly OG, Chan MY, Martinson LA, Kadoya K, Ostertag TM, et al. (2011) Cell-surface markers for the isolation of pancreatic cell types derived from human embryonic stem cells. Nat Biotechnol 29: 750-756.

89. Schulz TC, Young HY, Agulnick AD, Babin MJ, Baetge EE, et al. (2012) A scalable system for production of functional pancreatic progenitors from human embryonic stem cells. PLoS One 7: e37004.

90. Agulnick AD, Ambruzs DM, Moorman MA, Bhoumik A, Cesario RM, et al. (2015) Insulin-producing endocrine cells differentiated in vitro from human embryonic stem cells function in macroencapsulation devices *in vivo*. Stem Cells Transl Med 4: 1214-1222.

91. Ilic D, Devito L, Miere C, Codognotto S3 (2015) Human embryonic and induced pluripotent stem cells in clinical trials. Br Med Bull 116: 19-27.

92. Rezania A, Bruin JE, Arora P, Rubin A, Batushansky I, et al. (2014) Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nat Biotechnol 32: 1121-1133.

93. Pagliuca FW, Millman JR, Gürtler M, Segel M, Van Dervort A, et al. (2014) Generation of functional human pancreatic β cells in vitro. Cell 159: 428-439.

94. Gordeeva OF, Nikonova TM (2013) Development of experimental tumors formed by mouse and human embryonic stem and teratocarcinoma cells after subcutaneous and intraperitoneal transplantations into immunodeficient and immunocompetent mice. Cell Transplantat 22: 1901-1914.

95. Hrvatin S, O'Donnell CW, Deng F, Millman JR, Pagliuca FW, et al. (2014) Differentiated human stem cells resemble fetal, not adult, β cells. Proc Natl Acad Sci USA 111: 3038-3043.

96. Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126: 663-676.

97. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, et al. (2007) Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131: 861-872.

98. Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, et al. (2007) Induced pluripotent stem cell lines derived from human somatic cells. Science 318: 1917-1920.

99. Jang J, Yoo JE, Lee JA, Lee DR, Kim JY, et al. (2012) Disease-specific induced pluripotent stem cells: a platform for human disease modeling and drug discovery. Exp Mol Med 44: 202-213.

100. Alipio Z, Liao W, Roemer EJ, Waner M, Fink LM, et al. (2010) Reversal of hyperglycemia in diabetic mouse models using induced-pluripotent stem (iPS)-derived pancreatic beta-like cells. Proc Natl Acad Sci USA 107: 13426-13431.

101. Maehr R, Chen S, Snitow M, Ludwig T, Yagasaki L, et al. (2009) Generation of pluripotent stem cells from patients with type 1 diabetes. Proc Natl Acad Sci USA 106: 15768-15773.

102. Kudva YC, Ohmine S, Greder LV, Dutton JR, Armstrong A, et al. (2012) Transgene-free disease-specific induced pluripotent stem cells from patients with type 1 and type 2 diabetes. Stem Cells Transl Med 1: 451-461.

103. Teo AK, Windmueller R, Johansson BB, Dirice E, Njolstad PR, et al. (2013) Derivation of human induced pluripotent stem cells from patients with maturity onset diabetes of the young. J Biol Chem 288: 5353-5356.

104. Kunisada Y, Tsubooka-Yamazoe N, Shoji M, Hosoya M (2012) Small molecules induce efficient differentiation into insulin-producing cells from human induced pluripotent stem cells. Stem Cell Res 8: 274-284.

105. Raikwar SP, Kim EM, Sivitz WI, Allamargot C, Thedens DR, et al. (2015) Human iPS cell-derived insulin producing cells form vascularized organoids under the kidney capsules of diabetic mice. PLoS One 10: e0116582.

106. Zhang D, Jiang W, Liu M, Sui X, Yin X, et al. (2009) Highly efficient differentiation of human ES cells and iPS cells into mature pancreatic insulin-producing cells. Cell Res 19: 429-438.

107. Pellegrini S, Ungaro F, Mercalli A, Melzi R, Sebastiani G, et al. (2015) Human induced pluripotent stem cells differentiate into insulin-producing cells able to engraft in vivo. Acta Diabetol 52: 1025-1035.

108. Greggio C, De Franceschi F, Figueiredo-Larsen M, Gobaa S, Ranga A, et al. (2013) Artificial three-dimensional niches deconstruct pancreas development in vitro. Development 140: 4452-4462.

109. Miura K, Okada Y, Aoi T, Okada A, Takahashi K, et al. (2009) Variation in the safety of induced pluripotent stem cell lines. Nat Biotechnol 27: 743-745.

110. Kanemura H, Go MJ, Shikamura M, Nishishita N, Sakai N, et al. (2014) Tumorigenicity studies of induced pluripotent stem cell (iPSC)-derived retinal pigment epithelium (RPE) for the treatment of age-related macular degeneration. PLoS One 9: e85336.

111. Ferber S, Halkin A, Cohen H, Ber I, Einav Y, et al. (2000) Pancreatic and duodenal homeobox gene 1 induces expression of insulin genes in liver and ameliorates streptozotocin-induced hyperglycemia. Nat Med 6: 568-572.

112. Ber I, Shternhall K, Perl S, Ohanuna Z, Goldberg I, et al. (2003) Functional, persistent, and extended liver to pancreas transdifferentiation. J Biol Chem 278: 31950-31957.

113. Zhou Q, Brown J, Kanarek A, Rajagopal J, Melton DA (2008) In vivo reprogramming of adult pancreatic exocrine cells to beta-cells. Nature 455: 627-632.

114. Li W, Nakanishi M, Zumsteg A, Shear M, Wright C, et al. (2014) In vivo reprogramming of pancreatic acinar cells to three islet endocrine subtypes. Elife 3: e01846.

115. Klein D, Álvarez-Cubela S, Lanzoni G, Vargas N, Prabakar KR, et al. (2015) BMP-7 Induces Adult Human Pancreatic Exocrine-to-Endocrine Conversion. Diabetes 64: 4123-4134.

116. Gmyr V, Kerr-Conte J, Vandewalle B, Proye C, Lefebvre J, et al. (2001) Human pancreatic ductal cells: large-scale isolation and expansion. Cell Transplant 10: 109-121.

117. Lysy PA, Weir GC, Bonner-Weir S (2013) Making β cells from adult cells within the pancreas. Curr Diab Rep 13: 695-703.

118. Collombat P, Xu X, Ravassard P, Sosa-Pineda B, Dussaud S, et al. (2009) The ectopic expression of Pax4 in the mouse pancreas converts progenitor cells into alpha and subsequently beta cells. Cell 138: 449-462.