# β cell regeneration and novel strategies for treatment of diabetes (Review)

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**Abstract.** The etiology of diabetes is primarily attributed to the lack of functioning β cells, which in-turn leads to insulin deficiency or insulin resistance, and this ultimately leads to β cell dysfunction. Restoring the number and function of β cells is an effective means of improving or even curing diabetes. β cell regeneration is a potential method for increasing the number of functioning β cells. In addition to self-duplication of pancreatic β cells, β cells can be regenerated from embryonic stem cells, human induced pluripotent stem cells and pancreatic stem cells. Based on these mechanisms, proliferation and differentiation into functional β cells *in vitro* is one of the most promising strategies for treatment of diabetes. Although β cell regeneration has significant potential in the treatment of insulin-deficient diabetes, and significant progress has been made in this regard, there remains challenges which prevent its use in the clinic.

**Contents**



## 1. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by persistent hyperglycemia, which is primarily divided into type 1 diabetes (T1D) and type 2 diabetes (T2D). T1D and T2D are caused in whole or in part by an insufficient number of normally functioning pancreatic β cells (1-3). In T1D, insulin deficiency is caused by the immune destruction of β cells (4). T2D is usually caused by peripheral insulin resistance and/or β cell dysfunction (5). The factors that control the number of β cells include: i) Replication of existing β cells, ii) differentiation of new β cells from ducts and extra-islet precursor cells, iii) formation of new β cells from other endocrine cells and iv) β cell apoptosis (6). There are two general methods for supplementing β cells, replacement therapy by transplanting islets or β cells derived from human embryonic stem cells (hESCs)/induced pluripotent stem cells (iPSCs) and inducing endogenous regeneration (7). Although significant progress has been made in islet transplantation, their remain several challenges including the limited number of donors for human islets and immune suppression. Therefore, novel treatment options and/or means of increasing the number of functioning β cells are required (8). The regeneration of β cell masses may be useful for management of T1D and T2D. This review discusses the mechanisms of β cell regeneration and their potential in the treatment of diabetes.

## 2. The molecular mechanisms of β cell regeneration

Previous studies have shown that there are several internal and external factors related to the protection and regeneration of pancreatic β cells (8). The modification of different genes plays an important role in the regeneration of β cells.

*Self-duplication of pancreatic β cells*. The three cell sources that have been identified for β cell regeneration include β cell neogenesis from progenitor cells (9,10), replication of existing β cells (11,12), and transdifferentiation from α and δ islet cells (13,14). The insulin receptor substrate 2 (IRS2)/phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB or Akt) signaling pathway plays an important role in the regulation of the pancreatic β cell mass. Akt activates cyclin-dependent protein kinase (CDK4) to promote the G1/S transition of pancreatic islet β cell cycle and induce the proliferation of pancreatic β cells (11). In addition, a study found that inhibiting the expression of cell cycle inhibitor P57 with a lentiviral system encoding small hairpin RNA could promote β cell proliferation (15). An animal study found that selective inhibition of the expression of the specific transcription factor Arx in

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α cells could result in the transformation of α cells into β cells in mice of any age (16).

*Regenerating β cells from embryonic stem cells (ESC).* ESCs possess self-renewal ability and multi-directional differentiation potential. Therefore, human ESCs can be directed to differentiate into pancreatic β cells as an alternative approach for management of diabetes. To date, several key breakthroughs have been made in the efforts to obtain functional β cells from hESCs (17,18). The first key breakthrough was the development of the differentiation process that could transform hESCs into endocrine cells which could synthesize all the pancreatic hormones, including insulin, glucagon, somatostatin, pancreatic peptide and ghrelin (19). Studies have shown that *in vitro* hESC-derived pancreatic progenitor cells have the ability to spontaneously differentiate into functional β cells *in vivo*, thus transplantation of pancreatic progenitor cells has the potential to treat T1D (20,21). Pagliuca *et al* (22) developed an *in vitro* differentiation protocol, which could successfully induce hESCs (and iPSCs) into functional human β cells, that is, stem cell-derived β cells; this was also a key breakthrough in the study of obtaining functional β cells (22). Another study found that transplanting pancreatic progenitor cells derived from hESCs into streptozotocin-induced diabetic mice resulted in mice with β cells with relatively complete function and alleviation of a hyperglycemic state in the mice (20). However, there remains a major obstacle in translating these findings into clinical applications; safety issues. Due to the highly proliferative properties of stem cells, if not controlled, it can lead to the formation of tumors in the body (20). Placing transplanted cells in an encapsulation device can alleviate this problem. This device can not only allow for removal of the transplanted cells that grow into tumors, but also protect them from immune attack. Technologies to this effect have made substantial key advances in the past few years, allowing hESC-derived precursor cells to differentiate and function *in vivo* (23-25).

*Regenerating β cells from human (h)iPSCs.* In the past decade, researchers have developed methods to generate pancreatic cells from hPSCs (19-22). Studies have found that encapsulated pancreatic progenitor cells can mature into functional β cells that can reverse hyperglycemia in mice (23,24,26). At present, it is also possible to generate β-like cells from hPSCs, including hiPSCs from T1D patients (22,27,28). iPSCs derived from skin fibroblasts from T1D patients can generate functional β cells (28). iPSC-derived β cells from T1D patients possessed β cell markers, responded to glucose *in vitro* and *in vivo*, and prevented alloxan-induced diabetes. These characteristics are the same as those of stem cell-derived β cells derived from normal hiPSCs (28). *In vitro*, Pagliuca *et al* (22) used iPSCs to induce glucose-responsive mature β-like cells, which expressed the mature pancreatic β cell marker PDX1, regulated insulin secretion and improved blood sugar levels in mice (22). A study found that the epidermal cells of diabetic patients could be transdifferentiated into iPSCs, and then further differentiated into islet β-like cells with a functioning glucose response (29).

*Regenerating β cells from pancreatic stem cells.* In animal models, studies have found that pancreatic resection, catheter ligation, and chemical or genetically induced pancreatic injury can induce the regeneration of pancreatic β cells (9,30,31). The purified islets are cultured under various conditions, such that multipotent progenitor cells can be enriched and differentiated into islet cells (32-35). Lechner *et al* (33) used a three-step culture protocol to culture a monolayer of cells expanded from pancreatic islets, which resulted in the expansion of pancreatic islet cells *in vitro* and the differentiation of insulin-secreting cell clusters. In addition, several studies have attempted to obtain regenerative β cells from cultured pancreatic duct cells (36-38). The pancreatic ductal epithelial cells were isolated from non-obese diabetic mice and successfully differentiated into islet-like structures after *in vitro* culture, and when these islet-like structures were implanted in the kidney capsule, they reversed hyperglycemia in diabetic mice (39). Bonner-Weir *et al* (40) successfully expanded the adult human duct tissue and differentiated it into islet-like clusters that could secrete insulin after glucose stimulation (40).

Subsequently, the researchers further optimized the *in vitro* culture conditions and improved the differentiation protocol, resulting in notable progress. Membrane proteins such as CA19-9 and CD133, and growth factors such as epidermal growth factor (EGF), hepatocyte growth factor (HGF) and keratinocyte growth factor (KGF) were found to promote the differentiation of ductal cells into insulin-producing β cells (41-45). For example, the membrane proteins CA19-9 and CD133 enable duct-derived stem cells to be purified by flow cytometry (41-43). Furthermore, the ability of purified CA19-9+ ductal cells to spontaneously differentiate into insulin-producing β cells was increased after co-culture with pancreatic stromal cells (43). EGF, HGF and KGF can further stimulate the proliferation of human pancreatic duct-derived stem cells (44,45).

## 3. β cell regeneration and treatment strategies for diabetes

In recent years, researchers have explored the use of β cell regeneration techniques to treat diabetes in animal models and humans. Abdel Aziz *et al* (46) found that curcumin could inhibit the infiltration of lymphocytes into the islets of Langerhans and maintain the number of pancreatic islets and β cells. They also demonstrated that curcumin exerted a hypoglycemic effect by lowering fasting blood glucose (FBG) concentrations, and increasing serum insulin and C-peptide levels. Studies have found that *in vitro* expansion of human duct tissues and subsequent differentiation of pancreatic islet cells were observed after 3-4 weeks of pancreatic duct tissue culture. Additionally, insulin production increased significantly and functional islet-like structures were formed (32,40). Animal studies have found that using inducible diphtheria toxin A to ablate β cells or small molecule glucokinase activators can increase β cell proliferation in elderly mice by a factor of 2-3X (47). Pancreatic ducts can be used as β cell progenitors in adult mice. Mice expressing paired box 4 (Pax4) ectopically in glucagon-expressing cells can continuously form new α cells through ductal epithelial cells, and these can be transformed into β cells, allowing for repeated recovery from toxin-induced diabetes (16,48-50). There are multiple strategies to promote the process of transdifferentiation from pancreatic duct cells to β cells, including the transgene overexpression of IFN-γ

in β cells (51), the upregulated expression of TGF-α in the pancreatic duct (52), deletion of SCF-type E3 ubiquitin ligase substrate recognition component (also known as Fbw7) of the complex of SKP1, CUL1, and F-box protein (also known as SCF) type ubiquitin ligase (53) and ectopic expression of Pax4 in glucagon-positive cells (49).

Acinar cells are the most abundant pancreatic cell type and are a potential source of β cell regeneration. If the acinar cells are co-cultured with the growth factors EGF and leukemia inhibitory factor, the newly formed β cells can restore normoglycemia in the alloxan-induced diabetic mouse model (54). The transient cytokine mixture of EGF and ciliary neurotrophic factor activates the Stat3 signaling pathway in mice, causing the acinar cells to transform into β cells, which can reverse alloxan-induced diabetes (55).

A study found that human insulin can be detected 7 weeks after transplantation of pancreatic islet progenitor cells into an animal model, exhibiting a 17-fold increase in insulin production after 8 weeks, while the biomass of the encapsulated cells remained unchanged during this period. It was also shown that there was sufficient concentrations of human insulin in the encapsulated cells for 20 weeks after transplantation. These results indicate that the islet progenitor cells isolated from encapsulated hESCs hold significant promise as cell replacement therapies for insulin-dependent diabetes (24).

## 4. Challenges in β cell regeneration strategies for the treatment of diabetes

Using pluripotent stem cells, including hESCs and iPSCs, proliferation and differentiation into functional β cells *in vitro* is one of the most promising treatment strategies for diabetes. However, there remain considerable challenges regarding the regeneration of β cells *in vitro*, including host immune response-immune rejection of transplanted stem cell-derived β cells and autoimmunity against β cells, resulting in the loss of the original β cells in T1D recipients. However, hiPSC-derived β cells from T1D patients can be used as an autologous source of cell replacement therapy, thereby eliminating the problem of systemic immunosuppression (28). A study found that gene editing could be used to generate hPSCs that are 'invisible' to the immune system and can escape allogeneic rejection (56). This may allow cells to escape autoimmune destruction. Using animal models, progress has been made in inducing immune tolerance (17). The combination of β cell regeneration and immune tolerance induction can allow for long-term therapeutic benefits in patients with T1D. Finally, whether the results of animal models are suitable, and the developed methods are translatable to humans is also a question that needs to be further studied. Although some clinical trials have been performed, there remains a dearth of large-sample, multi-center prospective randomized controlled trials.

## 5. Conclusions

Restoring the number and function of pancreatic islet β cells in patients is potentially one the most effective means of curing diabetes. The use of β cell replacement therapy for human pancreatic islet transplantation faces several challenges, such as the limited number of donors and suppressing the host immune response to allow integration of the transplanted cells. Regenerating β cells from ESCs, hiPSCs and pancreatic stem cells may become a novel option for the treatment of diabetes.

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## Authors' contributions

QC conceived the subject of review. ZJ performed the literature search and was involved in drafting the manuscript. ML was involved in drafting the manuscript. HX and HY revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

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## Competing interests

The authors declare that they have no competing interests.

## References

1. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA and Butler PC: Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 52: 102-110, 2003.
2. Wang P, Fiaschi-Taesch NM, Vasavada RC, Scott DK, García-Ocaña A and Stewart AF: Diabetes mellitus-advances and challenges in human β-cell proliferation. Nat Rev Endocrinol 11: 201-212, 2015.
3. Campbell-Thompson M, Fu A, Kaddis JS, Wasserfall C, Schatz DA, Pugliese A and Atkinson MA: Insulitis and beta-cell mass in the natural history of type 1 diabetes. Diabetes 65: 719-731, 2016.
4. Burke GW III, Vendrame F, Virdi SK, Ciancio G, Chen L, Ruiz P, Messinger S, Reijonen HK and Pugliese A: Lessons from pancreas transplantation in type 1 diabetes: Recurrence of islet autoimmunity. Curr Diab Rep 15: 121, 2015.
5. Afelik S and Rovira M: Pancreatic beta-cell regeneration: Advances in understanding the genes and signaling pathways involved. Genome Med 9: 42, 2017.
6. Levine F and Itkin-Ansari P: Beta-cell Regeneration: Neogenesis, replication or both? J Mol Med (Berl) 86: 247-258, 2008.
7. Aguayo-Mazzucato C and Bonner-Weir S: Pancreatic β cell regeneration as a possible therapy for diabetes. Cell Metab 27: 57-67, 2018.
8. Benthuysen JR, Carrano AC and Sander M: Advances in beta cell replacement and regeneration strategies for treating diabetes. J Clin Invest 126: 3651-3660, 2016.
9. Xu X, D'Hoker J, Stangé G, Bonné S, De Leu N, Xiao X, Van de Casteele M, Mellitzer G, Ling Z, Pipeleers D, *et al*: Beta cells can be generated from endogenous progenitors in injured adult mouse pancreas. Cell 132: 197-207, 2008.

10. Li WC, Rukstalis JM, Nishimura W, Tchipashvili V, Habener JF, Sharma A and Bonner-Weir S: Activation of pancreatic-duct-derived progenitor cells during pancreas regeneration in adult rats. J Cell Sci 123 (Pt 16): 2792-2802, 2010.
11. Dor Y, Brown J, Martinez OI and Melton DA: Adult pancreatic beta-cells are formed by self-duplication rather than stem-cell differentiation. Nature 429: 41-46, 2004.
12. Teta M, Rankin MM, Long SY, Stein GM and Kushner JA: Growth and regeneration of adult beta cells does not involve specialized progenitors. Dev Cell 12: 817-826, 2007.
13. Thorel F, Népote V, Avril I, Kohno K, Desgraz R, Chera S and Herrera PL: Conversion of adult pancreatic alpha-cells to beta-cells after extreme beta-cell loss. Nature 464: 1149-1154, 2010.
14. Chera S, Baronnier D, Ghila L, Cigliola V, Jensen JN, Gu G, Furuyama K, Thorel F, Gribble FM, Reimann F and Herrera PL: Diabetes recovery by age-dependent conversion of pancreatic δ-cells into insulin producers. Nature 514: 503-507, 2014.
15. Avrahami D, Li C, Yu M, Jiao Y, Zhang J, Naji A, Ziaie S, Glaser B and Kaestner KH: Targeting the cell cycle inhibitor p57Kip2 promotes adult human β cell replication. J Clin Invest 124: 670-674, 2014.
16. Courtney M, Gjernes E, Druelle N, Ravaud C, Vieira A, Ben-Othman N, Pfeifer A, Avolio F, Leuckx G, Lacas-Gervais S, *et al*: The inactivation of Arx in pancreatic α-cells triggers their neogenesis and conversion into functional β-like cells. PLoS Genet 9: e1003934, 2013.
17. Lilly MA, Davis MF, Fabie JE, Terhune EB and Gallicano GI: Current stem cell based therapies in diabetes. Am J Stem Cells 5: 87-98, 2016.
18. Domínguez-Bendala J, Lanzoni G, Klein D, Álvarez-Cubela S and Pastori RL: The human endocrine pancreas: New insights on replacement and regeneration. Trends Endocrinol Metab 27: 153-162, 2016.
19. D'Amour KA, Bang AG, Eliazer S, Kelly OG, Agulnick AD, Smart NG, Moorman MA, Kroon E, Carpenter MK and Baetge EE: Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells. Nat Biotechnol 24: 1392-1401, 2006.
20. Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S, Young H, Richardson M, Smart NG, Cunningham J, *et al*: Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nat Biotechnol 26: 443-452, 2008.
21. Rezania A, Bruin JE, Riedel MJ, Mojibian M, Asadi A, Xu J, Gauvin R, Narayan K, Karanu F, O'Neil JJ, *et al*: Maturation of human embryonic stem cell-derived pancreatic progenitors into functional islets capable of treating pre-existing diabetes in mice. Diabetes 61: 2016-2029, 2012.
22. Pagliuca FW, Millman JR, Gürtler M, Segel M, Van Dervort A, Ryu JH, Peterson QP, Greiner D and Melton DA: Generation of functional human pancreatic beta cells in vitro. Cell 159: 428-439, 2014.
23. Bruin JE, Rezania A, Xu J, Narayan K, Fox JK, O'Neil JJ and Kieffer TJ: Maturation and function of human embryonic stem cell-derived pancreatic progenitors in macroencapsulation devices following transplant into mice. Diabetologia 56: 1987-1998, 2013.
24. Kirk K, Hao E, Lahmy R and Itkin-Ansari P: Human embryonic stem cell derived islet progenitors mature inside an encapsulation device without evidence of increased biomass or cell escape. Stem Cell Res 12: 807-814, 2014.
25. Vegas AJ, Veiseh O, Gürtler M, Millman JR, Pagliuca FW, Bader AR, Doloff JC, Li J, Chen M, Olejnik K, *et al*: Long-term glycemic control using polymer-encapsulated human stem cell-derived beta cells in immune-competent mice. Nat Med 22: 306-311, 2016.
26. Xie R, Everett LJ, Lim HW, Patel NA, Schug J, Kroon E, Kelly OG, Wang A, D'Amour KA, Robins AJ, *et al*: Dynamic chromatin remodeling mediated by polycomb proteins orchestrates pancreatic differentiation of human embryonic stem cells. Cell Stem Cell 12: 224-237, 2013.
27. Rezania A, Bruin JE, Arora P, Rubin A, Batushansky I, Asadi A, O'Dwyer S, Quiskamp N, Mojibian M, Albrecht T, *et al*: Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nat Biotechnol 32: 1121-1133, 2014.
28. Millman JR, Xie C, Van Dervort A, Gürtler M, Pagliuca FW and Melton DA: Generation of stem cell-derived beta-cells from patients with type 1 diabetes. Nat Commun 7: 11463, 2016.
29. Navarro-Tableros V, Gomez Y, Brizzi MF and Camussi G: Generation of human stem cell-derived pancreatic organoids (POs) for regenerative medicine. Adv Exp Med Biol 1212: 179-220, 2020.
30. Van de Casteele M, Leuckx G, Baeyens L, Cai Y, Yuchi Y, Coppens V, De Groef S, Eriksson M, Svensson C, Ahlgren U, *et al*: Neurogenin 3+ cells contribute to β-cell neogenesis and proliferation in injured adult mouse pancreas. Cell Death Dis 4: e523, 2013.
31. Lee SH, Hao E and Levine F: β-Cell replication and islet neogenesis following partial pancreatectomy. Islets 3: 188-195, 2011.
32. Gao R, Ustinov J, Korsgren O and Otonkoski T: In vitro neogenesis of human islets reflects the plasticity of differentiated human pancreatic cells. Diabetologia 48: 2296-2304, 2005.
33. Lechner A, Nolan AL, Blacken RA and Habener JF: Redifferentiation of insulin-secreting cells after in vitro expansion of adult human pancreatic islet tissue. Biochem Biophys Res Commun 327: 581-588, 2005.
34. Gershengorn MC, Hardikar AA, Wei C, Geras-Raaka E, Marcus-Samuels B and Raaka BM: Epithelial-to-mesenchymal transition generates proliferative human islet precursor cells. Science 306: 2261-2264, 2004.
35. Seaberg RM, Smukler SR, Kieffer TJ, Enikolopov G, Asghar Z, Wheeler MB, Korbutt G and van der Kooy D: Clonal identification of multipotent precursors from adult mouse pancreas that generate neural and pancreatic lineages. Nat Biotechnol 22: 1115-1124, 2004.
36. Bonner-Weir S, Toschi E, Inada A, Reitz P, Fonseca SY, Aye T and Sharma A: The pancreatic ductal epithelium serves as a potential pool of progenitor cells. Pediatr Diabetes 5 (Suppl 2): S16-S22, 2004.
37. Otonkoski T, Gao R and Lundin K: Stem cells in the treatment of diabetes. Ann Med 37: 513-520, 2005.
38. Corritore E, Lee YS, Sokal EM and Lysy PA: β-cell replacement sources for type 1 diabetes: A focus on pancreatic ductal cells. Ther Adv Endocrinol Metab 7: 182-199, 2016.
39. Ramiya VK, Maraist M, Arfors KE, Schatz DA, Peck AB and Cornelius JG: Reversal of insulin-dependent diabetes using islets generated in vitro from pancreatic stem cells. Nat Med 6: 278-282, 2000.
40. Bonner-Weir S, Taneja M, Weir GC, Tatarkiewicz K, Song KH, Sharma A and O'Neil JJ: In vitro cultivation of human islets from expanded ductal tissue. Proc Natl Acad Sci USA 97: 7999-8004, 2000.
41. Gmyr V, Belaich S, Muharram G, Lukowiak B, Vandewalle B, Pattou F and Kerr-Conte J: Rapid purification of human ductal cells from human pancreatic fractions with surface antibody CA19-9. Biochem Biophys Res Commun 320: 27-33, 2004.
42. Lee J, Sugiyama T, Liu Y, Wang J, Gu X, Lei J, Markmann JF, Miyazaki S, Miyazaki J, Szot GL, *et al*: Expansion and conversion of human pancreatic ductal cells into insulin-secreting endocrine cells. Elife 2: e00940, 2013.
43. Yatoh S, Dodge R, Akashi T, Omer A, Sharma A, Weir GC and Bonner-Weir S: Differentiation of affinity-purified human pancreatic duct cells to beta-cells. Diabetes 56: 1802-1809, 2007.
44. Rescan C, Le Bras S, Lefebvre VH, Frandsen U, Klein T, Foschi M, Pipeleers DG, Scharfmann R, Madsen OD and Heimberg H: EGF-induced proliferation of adult human pancreatic duct cells is mediated by the MEK/ERK cascade. Lab Invest 85: 65-74, 2005.
45. Hoesli CA, Johnson JD and Piret JM: Purified human pancreatic duct cell culture conditions defined by serum-free high-content growth factor screening. PLoS One 7: e33999, 2012.
46. Abdel Aziz MT, El-Asmar MF, Rezq AM, Mahfouz SM, Wassef MA, Fouad HH, Ahmed HH and Taha FM: The effect of a novel curcumin derivative on pancreatic islet regeneration in experimental type-1 diabetes in rats (long term study). Diabetol Metab Syndr 5: 75, 2013.
47. Stolovich-Rain M, Hija A, Grimsby J, Glaser B and Dor Y: Pancreatic beta cells in very old mice retain capacity for compensatory proliferation. J Biol Chem 287: 27407-27414, 2012.
48. Al-Hasani K, Pfeifer A, Courtney M, Ben-Othman N, Gjernes E, Vieira A, Druelle N, Avolio F, Ravassard P, Leuckx G, *et al*: Adult duct-lining cells can reprogram into β-like cells able to counter repeated cycles of toxin-induced diabetes. Dev Cell 26: 86-100, 2013.

49. Collombat P, Xu X, Ravassard P, Sosa-Pineda B, Dussaud S, Billestrup N, Madsen OD, Serup P, Heimberg H and Mansouri A: The ectopic expression of Pax4 in the mouse pancreas converts progenitor cells into alpha and subsequently beta cells. Cell 138: 449-462, 2009.
50. Pfeifer A, Courtney M, Ben-Othman N, Al-Hasani K, Gjernes E, Vieira A, Druelle N, Avolio F, Faurite B, Mansouri A and Collombat P: Induction of multiple cycles of pancreatic β-cell replacement. Cell Cycle 12: 3243-3244, 2013.
51. Gu D and Sarvetnick N: Epithelial cell proliferation and islet neogenesis in IFN-g transgenic mice. Development 118: 33-46, 1993.
52. Wang TC, Bonner-Weir S, Oates PS, Chulak M, Simon B, Merlino GT, Schmidt EV and Brand SJ: Pancreatic gastrin stimulates islet differentiation of transforming growth factor alpha-induced ductular precursor cells. J Clin Invest 92: 1349-1356, 1993.
53. Sancho R, Gruber R, Gu G and Behrens A: Loss of Fbw7 reprograms adult pancreatic ductal cells into α, δ, and β cells. Cell Stem Cell 15: 139-153, 2014.
54. Baeyens L, De Breuck S, Lardon J, Mfopou JK, Rooman I and Bouwens L: In vitro generation of insulin-producing beta cells from adult exocrine pancreatic cells. Diabetologia 48: 49-57, 2005.
55. Baeyens L, Lemper M, Leuckx G, De Groef S, Bonfanti P, Stangé G, Shemer R, Nord C, Scheel DW, Pan FC, *et al*: Transient cytokine treatment induces acinar cell reprogramming and regenerates functional beta cell mass in diabetic mice. Nat Biotechnol 32: 76-83, 2014.
56. Rong Z, Wang M, Hu Z, Stradner M, Zhu S, Kong H, Yi H, Goldrath A, Yang YG, Xu Y and Fu X: An effective approach to prevent immune rejection of human ESC-derived allografts. Cell Stem Cell 14: 121-130, 2014.