ISSN 2475-5451

Research Article

International Journal of Diabetes & Metabolic Disorders

Developing a Beta Cell Vaccine in the Pancreatic Beta Cell Restoring Therapy for Treating Type First Diabetes

Ashwin Singh Chouhan[1]* and Narpat[2]

[1,2]*Jai Narain Vyas University, India*

***Corresponding Author**
Ashwin Singh Chouhan, Jai Narain Vyas University, India.

Submitted: 2023 May 05; **Accepted**: 2023 June 08; **Published**: 2023 June 21

Citation: Ashwin, S. C., Narpat. (2023). Developing a Beta Cell Vaccine in the Pancreatic Beta Cell Restoring Therapy for Treating Type First Diabetes. *Int J Diabetes Metab Disord, 8*(2), 372-376.

Abstract

Gene transfer and biotechnology can develop new beta cells in the human body. Regenerative mechanisms under physiological and pathological conditions, factors involved in stimulation of regeneration, and potential pharmaceutical drugs are discussed. Replication is mediated by mitogenic signaling pathways and upstream activators. These mechanisms also involve upstream activators of mitogenic signaling pathways, including nutrients (glucose, calcium), epidermal and platelet-derived GFs (Glp1, Gip), and hormones (leptin, estrogen, prolactin, and progesterone).

Keywords: Beta Cell, Pancreases, Type First Diabetes, Gene transfer, Biotechnology.

1. Introduction

The exocrine pancreas is composed of acinar and ductal cells that secrete digestive enzymes. The endocrine pancreas is composed of five different hormone-secreting cell types that include glucagon-secreting α cells, insulin-producing β cells, somatostatin-releasing δ cells, ghrelin-releasing ε cells, and pancreatic polypeptide (PP)-secreting cells. These cells aggregate to form the islets of Langerhans, which are intermingled with the intra-islet microvascular network and play an essential role in regulation of blood glucose levels by directly secreting insulin and glucagon into the bloodstream[1,2]. Recently, numerous strategies and technologies for producing human insulin-secreting cells have emerged, including in vivo stimulation of existing β cell replication, reprogramming of other pancreatic cells to differentiate into β cells, in vitro differentiation of induced pluripotential stem (iPS) cells into new β cells, and generation of human islets from genetically engineered pigs [3,4]. For example, strategies for enhancing replication of residual β cells have been successful in rodent but not in humans. As such, it is critical to determine the causes for limited success of clinical trials, and to determine possible strategies for improving cell therapy for T1D. In this review, we summarize advanced strategies and approaches for endogenous β cell regeneration, discuss regenerative mechanisms under physiological and pathological conditions, focus on various factors involved in stimulation of regeneration, and discuss promising potential pharmaceutical drugs.

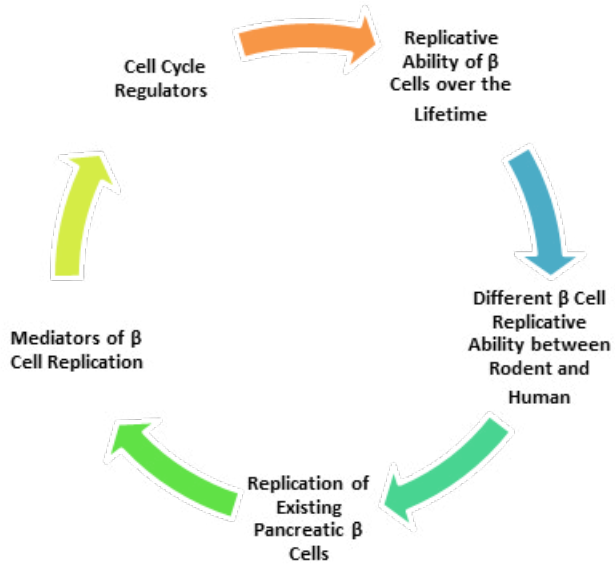

Figure 1: Beta Cell Regeneration Therapy

1.1 Replication of Existing Pancreatic β Cells

Pancreatic β cells replicate readily in the fetal and neonatal stages. However, this ability to replicate rapidly declines after these stages. Furthermore, this ability to replicate is different in rodents and humans. Proliferation of β cells is precisely controlled by cell cycle regulators and circulating soluble factors. Studies have shown that many mutagenic agents could stimulate β cell replication in young rodents, but not in humans. However, using high-throughput chemical screening, a series of inhibitors of DYRK1A-NFAT, GSK3, and NF-κB signaling pathways were shown to increase human pancreatic β cell replication, suggesting that these inhibitors have unique potential for treatment of diabetes.

1.2 Replicative Ability of β Cells Over the Lifetime

During embryonic development, insulin-positive β cells appear at approximately embryonic day 13.5 in mice or during weeks 8–9 in humans. During the fetal period, β cells are mainly generated by differentiation of endocrine progenitor cells [5]. During the late gestational and neonatal stages, β cells are generated by replication of existing β cells [6,7]. The rate of β cell replication reduces after weaning, and the renewal capacity of β cells becomes limited during adulthood or late adolescence. Nevertheless, β cell mass, which is determined on the basis of cell numbers and individual cell volumes, correlates in a linear fashion with body weight throughout the lifespan of an organism [5,8]. For example, in rats, the number and size of β cells expands with body weight during the first few months of life. The rate of β cell replication then progressively declines, to 1% in young rats (1 month of age), and <0.2% in adults (3~7 months) [8]. In aging rats (15~20 months), β cell mass primarily increases through increased cell size [9]. In healthy rodents, individual β cells have long lifespans, and replication of mature β cells is limited during adulthood [5,10]. Under some physiological or pathological conditions, rates of β cell proliferation are elevated. For example, β cells proliferate adaptively in response to pregnancy or obesity via self-replication [11,14]. Moreover, in young rodents, β cell proliferation can be induced by increased metabolic demands or β cell deficiency resulting from tissue injury [8,15].

1.3 Different β Cell Replicative Ability between Rodent and Human

Human and rodent islets have distinct structural and molecular characteristics [16]. Replicative ability of human and rodent β cells have common and different features. For example, β cell mass increases during the earlier stages of life and declines with aging in both species. Adaptive β cell proliferation during pregnancy and obesity occurs extensively in rodents, but is limited in humans [17]. Pregnancy-associated insulin resistance induces amplified insulin production to maintain glucose homeostasis. In rodents, elevated insulin production is accompanied by increased β cell numbers mediated by lactotrophic hormones [13,14,18]. Humans also exhibit a compensatory increase in insulin secretion. New β cells originate from other pancreatic cell lineages and existing β-cells. Moreover, β cell proliferation mediated by lactotrophic hormones or other mitogenic stimuli is limited in humans [19]. In addition, obesity-induced insulin resistance is associated with dramatic expansion of β cell mass in several rodent models, but not in human islets [20]. Various mutagenic agents, hormones, and growth factors (GFs) such as Glp-1, Gip-1, exendin-4, prolactin, Hgf, and Igf-1 stimulate β cell proliferation in rodents but not in humans [21-27].

1.4 Mediators of β Cell Replication

- **Cell Cycle Regulators**

β cell replication is mediated by multiple mitogenic signaling pathways such as Irs–Pi3k–Akt, Gsk3, mTor, ChREBP/cMyc,

Ras/Raf/Erk, and Nfats. These mechanisms also involve upstream activators of mitogenic signaling pathways, including nutrients (glucose, calcium), epidermal and platelet-derived GFs (Glp1, Gip), and hormones (leptin, estrogen, prolactin, and progesterone). Mitogenic signals stimulate quiescent β cells to re-enter the cell cycle by regulating the expression of downstream cell cycle regulators such as cyclins, cyclin-dependent kinases (Cdks), cell-cycle inhibitors, and E2F factors [28-33]. For example, exendin-4 and glucagon-like peptide 1 (Glp-1) exert mitogenic effects on β cell proliferation by activating cell cycle activators (cyclin A and Cdk1) and proliferation-activating transcription factors (TFs) through the cAMP-dependent calcineurin/Nfat pathway [24,25,34-37]. Menin is an endocrine tumor suppressor that suppresses β cell proliferation by epigenetically promoting the expression of the cell-cycle inhibitors p27 and p18 or by inhibiting K-Ras signaling [38-40]. Moreover, Ezh2 mediates increased trimethylation of p16INK4a and p19Arf by H3K27, which epigenetically represses Ink4a/Arf production and contributes to proliferation of pancreatic β cells [40-41].

2. Method and Material

We conducted this review by observing the different types of reviews, as well as conducting and evaluating literature review papers.

3. Conclusion

In our review, we concluded that The endocrine pancreas is composed of five different hormone-secreting cell types that include glucagon-secreting α cells, insulin-producing β cells, somatostatin-releasing δ cells, ghrelin-releasing ε cells, and pancreatic polypeptide (PP)-secreting cells. Recently, numerous strategies and technologies for producing human insulin-secreting cells have emerged, including in vivo stimulation of existing β cell replication, reprogramming of other pancreatic cells to differentiate into β cells, in vitro differentiation of induced pluripotential stem (iPS) cells into new β cells, and generation of human islets from genetically engineered pigs.

Acknowledgment: We grateful thanks to all the sincere and extremely helpful friends for their support and help for the completion of work. Last but not the least, we thankful to all those who cooperated and helped me directly or indirectly to carry out this work.

Ethical Approval: - Ethical approval was not required for this letter. All data used is publicly accessible.

Funding: - There were no external sources of funding for this research.

Data Availability Statement: We do not wish to share our data before we have thoroughly analyzed. All data sources described in the study are directed at the corresponding author.

Financial Support and Sponsorship: Nil.

Conflicts of Interest: All authors are declaring that they have no conflicts of interest.

Authors' Contribution

The first author developed the proposal, and then collected and analyzed the data under supervision of respective advisers. The rest of authors undertook the literature search and review, and gave constructive comments and guidance to work with the main author with respect to the research objective.

References

1. Butler, A. E., Janson, J., Bonner-Weir, S., Ritzel, R., Rizza, R. A., & Butler, P. C. (2003). β-cell deficit and increased β-cell apoptosis in humans with type 2 diabetes. Diabetes, 52(1), 102-110.
2. Matveyenko, A. V., & Butler, P. C. (2008). Relationship between β-cell mass and diabetes onset. Diabetes, Obesity and Metabolism, 10, 23-31.
3. Zhou, Q., & Melton, D. A. (2018). Pancreas regeneration. Nature, 557(7705), 351-358.
4. Aguayo-Mazzucato, C., & Bonner-Weir, S. (2018). Pancreatic β cell regeneration as a possible therapy for diabetes. Cell metabolism, 27(1), 57-67.
5. Finegood, D. T., Scaglia, L., & Bonner-Weir, S. (1995). Dynamics of β-cell mass in the growing rat pancreas: estimation with a simple mathematical model. Diabetes, 44(3), 249-256.
6. Dor, Y., Brown, J., Martinez, O. I., & Melton, D. A. (2004). Adult pancreatic β-cells are formed by self-duplication rather than stem-cell differentiation. Nature, 429(6987), 41-46.
7. Meier, J. J., Butler, A. E., Saisho, Y., Monchamp, T., Galasso, R., Bhushan, A., ... & Butler, P. C. (2008). β-cell replication is the primary mechanism subserving the postnatal expansion of β-cell mass in humans. Diabetes, 57(6), 1584-1594.
8. Montanya, E., Nacher, V., Biarnés, M., & Soler, J. (2000). Linear correlation between beta-cell mass and body weight throughout the lifespan in Lewis rats: role of beta-cell hyperplasia and hypertrophy. Diabetes, 49(8), 1341-1346.
9. Bock, T., Pakkenberg, B., & Buschard, K. (2003). Increased islet volume but unchanged islet number in ob/ob mice. Diabetes, 52(7), 1716-1722.
10. Teta, M., Long, S. Y., Wartschow, L. M., Rankin, M. M., & Kushner, J. A. (2005). Very slow turnover of β-cells in aged adult mice. Diabetes, 54(9), 2557-2567.
11. Gargani, S., Thévenet, J., Yuan, J. E., Lefebvre, B., Delalleau, N., Gmyr, V., ... & Kerr-Conte, J. (2013). Adaptive changes of human islets to an obesogenic environment in the mouse. Diabetologia, 56, 350-358.
12. Butler, A. E., Cao-Minh, L., Galasso, R., Rizza, R. A., Corradin, A., Cobelli, C., & Butler, P. C. (2010). Adaptive changes in pancreatic beta cell fractional area and beta cell turnover in human pregnancy. Diabetologia, 53, 2167-2176.
13. Rieck, S., & Kaestner, K. H. (2010). Expansion of β-cell mass in response to pregnancy. Trends in Endocrinology & Metabolism, 21(3), 151-158.

14. Kim, H., Toyofuku, Y., Lynn, F. C., Chak, E., Uchida, T., Mizukami, H., ... & German, M. S. (2010). Serotonin regulates pancreatic beta cell mass during pregnancy. Nature medicine, 16(7), 804-808.
15. Nir, T., Melton, D. A., & Dor, Y. (2007). Recovery from diabetes in mice by β cell regeneration. The Journal of clinical investigation, 117(9), 2553-2561.
16. Dai, C., Brissova, M., Hang, Y., Thompson, C., Poffenberger, G., Shostak, A., ... & Powers, A. C. (2012). Islet-enriched gene expression and glucose-induced insulin secretion in human and mouse islets. Diabetologia, 55, 707-718.
17. Georgia, S., & Bhushan, A. (2004). β cell replication is the primary mechanism for maintaining postnatal β cell mass. The Journal of clinical investigation, 114(7), 963-968.
18. Xu, Y., Wang, X., Gao, L., Zhu, J., Zhang, H., Shi, H., ... & Wu, X. (2015). Prolactin-stimulated survivin induction is required for beta cell mass expansion during pregnancy in mice. Diabetologia, 58, 2064-2073.
19. Baeyens, L., Hindi, S., Sorenson, R. L., & German, M. S. (2016). β-Cell adaptation in pregnancy. Diabetes, Obesity and Metabolism, 18, 63-70.
20. Linnemann, A. K., Baan, M., & Davis, D. B. (2014). Pancreatic β-cell proliferation in obesity. Advances in nutrition, 5(3), 278-288.
21. Menge, B. A., Tannapfel, A., Belyaev, O., Drescher, R., Muller, C., Uhl, W., ... & Meier, J. J. (2008). Partial pancreatectomy in adult humans does not provoke β-cell regeneration. Diabetes, 57(1), 142-149.
22. Saisho, Y., Butler, A. E., Manesso, E., Elashoff, D., Rizza, R. A., & Butler, P. C. (2013). β-cell mass and turnover in humans: effects of obesity and aging. Diabetes care, 36(1), 111-117.
23. Chen, H., Kleinberger, J. W., Takane, K. K., Salim, F., Fiaschi-Taesch, N., Pappas, K., ... & Stewart, A. F. (2015). Augmented Stat5 signaling bypasses multiple impediments to lactogen-mediated proliferation in human β-cells. Diabetes, 64(11), 3784-3797.
24. Fusco, J., Xiao, X., Prasadan, K., Sheng, Q., Chen, C., Ming, Y. C., & Gittes, G. (2017). GLP-1/Exendin-4 induces β-cell proliferation via the epidermal growth factor receptor. Scientific reports, 7(1), 9100.
25. Buteau, J., Foisy, S., Joly, E., & Prentki, M. (2003). Glucagon-like peptide 1 induces pancreatic β-cell proliferation via transactivation of the epidermal growth factor receptor. Diabetes, 52(1), 124-132.
26. Tella, S. H., & Rendell, M. S. (2015). Glucagon-like polypeptide agonists in type 2 diabetes mellitus: efficacy and tolerability, a balance. Therapeutic advances in endocrinology and metabolism, 6(3), 109-134.
27. Stamateris, R. E., Sharma, R. B., Kong, Y., Ebrahimpour, P., Panday, D., Ranganath, P., ... & Alonso, L. C. (2016). Glucose induces mouse β-cell proliferation via IRS2, MTOR, and cyclin D2 but not the insulin receptor. Diabetes, 65(4), 981-995.
28. Kulkarni, R. N., Mizrachi, E. B., Ocana, A. G., & Stewart, A. F. (2012). Human β-cell proliferation and intracellular signaling: driving in the dark without a road map. Diabetes, 61(9), 2205-2213.
29. Bernal-Mizrachi, E., Kulkarni, R. N., Scott, D. K., Mauvais-Jarvis, F., Stewart, A. F., & Garcia-Ocaña, A. (2014). Human β-cell proliferation and intracellular signaling part 2: still driving in the dark without a road map. Diabetes, 63(3), 819-831.
30. Stewart, A. F., Hussain, M. A., García-Ocaña, A., Vasavada, R. C., Bhushan, A., Bernal-Mizrachi, E., & Kulkarni, R. N. (2015). Human β-cell proliferation and intracellular signaling: part 3. Diabetes, 64(6), 1872-1885.
31. Rieck, S., Zhang, J., Li, Z., Liu, C., Naji, A., Takane, K. K., ... & Kaestner, K. H. (2012). Overexpression of hepatocyte nuclear factor-4α initiates cell cycle entry, but is not sufficient to promote β-cell expansion in human islets. Molecular endocrinology, 26(9), 1590-1602.
32. Cozar-Castellano, I., Fiaschi-Taesch, N., Bigatel, T. A., Takane, K. K., Garcia-Ocana, A., Vasavada, R., & Stewart, A. F. (2006). Molecular control of cell cycle progression in the pancreatic β-cell. Endocrine reviews, 27(4), 356-370.
33. Huang, C., Snider, F., & Cross, J. C. (2009). Prolactin receptor is required for normal glucose homeostasis and modulation of β-cell mass during pregnancy. Endocrinology, 150(4), 1618-1626.
34. Song, W. J., Schreiber, W. E., Zhong, E., Liu, F. F., Kornfeld, B. D., Wondisford, F. E., & Hussain, M. A. (2008). Exendin-4 stimulation of cyclin A2 in β-cell proliferation. Diabetes, 57(9), 2371-2381.
35. Fujitani, Y. (2018). How does glucagon-like peptide 1 stimulate human β-cell proliferation? A lesson from islet graft experiments. Journal of Diabetes Investigation, 9(6), 1255-1257.
36. Dai, C., Hang, Y., Shostak, A., Poffenberger, G., Hart, N., Prasad, N., ... & Powers, A. C. (2017). Age-dependent human β cell proliferation induced by glucagon-like peptide 1 and calcineurin signaling. The Journal of clinical investigation, 127(10), 3835-3844.
37. Heit, J. J., Apelqvist, Å. A., Gu, X., Winslow, M. M., Neilson, J. R., Crabtree, G. R., & Kim, S. K. (2006). Calcineurin/NFAT signalling regulates pancreatic β-cell growth and function. Nature, 443(7109), 345-349.
38. Chamberlain, C. E., Scheel, D. W., McGlynn, K., Kim, H., Miyatsuka, T., Wang, J., ... & German, M. S. (2014). Menin determines K-RAS proliferative outputs in endocrine cells. The Journal of clinical investigation, 124(9), 4093-4101.
39. Karnik, S. K., Hughes, C. M., Gu, X., Rozenblatt-Rosen, O., McLean, G. W., Xiong, Y., ... & Kim, S. K. (2005). Menin regulates pancreatic islet growth by promoting histone methylation and expression of genes encoding p27 Kip1 and p18 INK4c. Proceedings of the National Academy of Sciences, 102(41), 14659-14664.
40. Karnik SK, Chen H, McLean GW, Heit JJ, Gu X, Zhang AY, et al.. Menin controls growth of pancreatic beta-cells in pregnant mice and promotes gestational diabetes mellitus. Science (2007) 318:806–9.

41. Chen, H., Gu, X., Su, I. H., Bottino, R., Contreras, J. L., Tarakhovsky, A., & Kim, S. K. (2009). Polycomb protein Ezh2 regulates pancreatic β-cell Ink4a/Arf expression and regeneration in diabetes mellitus. Genes & development, 23(8), 975-985.