EUROPEAN ACADEMIC RESEARCH
Vol. I, Issue 12/ March 2014

ISSN 2286-4822
www.euacademic.org

Impact Factor: 3.1 (UIF)
DRJI Value: 5.9 (B+)

Diabetes Type I - Stem Cells Transplantation a Choice Therapy

IJAZ MALOOK[1]
MUHAMMAD ILYAS
ZIA UR REHMAN
NOOR MUHAMMAD
Department of Biotechnology and Genetic Engineering
Kohat University of Science and Technology
Kohat, Pakistan
MUHAMMAD MUDASAR ASLAM
Department of Botany
Kohat University of Science and Technology
Kohat, Pakistan
IRFAN MALOOK
Department of Pharmacy
Kohat University of Science and Technology
Kohat, Pakistan
SHEEBA KANWAL
Department of Zoology
Abdul Wali khan University
Mardan, Pakistan
MUHAMMAD JAMIL
Department of Biotechnology and Genetic Engineering
Kohat University of Science and Technology
Kohat, Pakistan

Abstract:

Diabetes is a group of diseases which creates peculiarly high level of glucose in blood due to gradual destruction of beta cells by body own immune system. Regardless of advancement in accepting the original disease mechanisms for type 1 diabetes, there is still a scarcity of efficient therapies for diabetes. In current existence researchers have been trying to find out ways for replacement of beta cells or beta cell

[1] Corresponding author: ijazmalook@yahoo.com

function. The proposal that the beta cells which lost in type1 diabetes possibly will be replaced by stem cell transplantation approaches using different stem cells sources and mechanisms. Stem cell therapy is one of the most promising treatments in near future and it is predictable that this kind of therapy can improve the basic health care of diabetic patients. The development and demarcation of stem cells from any origin have considerable potential to overcome the deficiency of insulin producing Beta cells. This article summarizes the contemporary research work on the function of some of the stem cells originated from different origins on curing type 1 diabetes mellitus.

Key words: Diabetes, Auto Immune Disorder, Pancreatic Stem Cells, Cell Therapy, Neogenesis

Introduction

Diabetes mellitus is a hyperglycemic, glucose metabolic syndrome that is caused by the destruction of Beta cells of pancreas that in general produced insulin which control blood glucose level. As type I diabetes mellitus *T1DM* is an auto immune disorder common in young ones and children's in which body owns immune system is accountable for the demolition of pancreatic cells concerned with insulin secretion, in this disease auto reactive T cells destroy the beta islet of pancreas for which the main antigen was recognized as enzyme of the islet Glutamic acid decarboxylase (Medical microbiology & immunology 7th edition). Diabetic influence nearly 346 million people worldwide and this ratio are thought to reach 4 billion in 2030 (Liu et al. 2013). At the moment there is no therapy for diabetic person and they are absolutely insulin dependent which they receive a number of times in a day with regular monitoring of blood glucose level. Recurrent monitoring of blood glucose level is important for Diabetic patients to reduce normal complications with diabetes as cardiovascular diseases and retinopathy (Bethesda et al. 2013).There are problems with the current approaches of the treatments

because insulin usually fails to control blood glucose level to optimal position (The Diabetes Control and Complications Trial Research Group 1993). Common genetic and environmental factors are thought to involved in *T1DM* but still the main reason are unknown, clinical symptoms of *T1DM* appears late and 60 to 80% of beta cell have been destroyed at time of diagnosis (Notkins et al. 2001). The main genetic risk is due to HLA genes localized at 6p21 chromosome (Stuchlikova et al., 2006) Even though contemporary medicine play a substantial progression in the handling of diabetes, still exogenous application of insulin is required for managing of *T1DM* and *T2DM*, and increasing occurrence of infection as hypoglycemia, ketoacidosis, chronic complications, along with renal, retinal, cardiovascular, nervous and cerebro vascular problems (Nathan et al., 2005). It is also possible to treat *T1DM* by transplanting whole pancreas or even islet cells into the patient from a donor, this can enable the individual to regain power of controlling body glucose level and no need of further insulin injection is needed (Insulin Production in the Human Pancreas diagram 2001). Though pancreas and pancreatic islet transplantation have made amazing advancement in establishment of body own insulin secretion system (Berney et al. 2010, Fridell et al. 2010), however shortage of the donor organs and the use of immune suppressant slowed down its wide expansion. Therefore different cell based therapies targeting stem cells transplantation is a choice therapy for *T1DM*.

Possible Approaches for *T1DM* Therapy

There is so many possible approaches used for type 1 Diabetes mellitus *T1DM,* but everyone take some sort of constraint. Replacement of Beta cells of pancreas in individual, cellular replacement therapy, whole organ transplantation and transplantation of isolated pancreatic islets, in these the transplantation of pancreatic islets was ineffective for a long

period, but Edmonten protocol create a new hope in this type of therapy, but still this protocol face a lot of challenges as limited donor islets, 2 to 4 different pancreatic islets for a single individual and less percentage of infected patient can be treated (Shapiro et al., 2000).

Choice stem cells therapies for Diabetes mellitus type 1

The choice stem cell for Beta cells replacement includes pancreatic stem cells *PSCs*, hepatic stem cells *HSCs*, embryonic stem cells *ESCs* and induced pluripotent stem cells *IPSCs*.

Progenitor or Pancreatic stem cells

Pancreatic stem cells or progenitor cells are located in the ductal tissues of pancreas which are involved in generation of insulin producing cells; these cells are also researched in lab conditions (Noguchi 2007, 2008; Gioviale 2009). Pancreatic tissue show boosts proliferative commotion and regenerate Beta cells (Zorina 2003). Immunological rejection is the leading problem against stem cells therapy but the use of adult stem cells solve this problem, because immunological responses is not produced against the use of adult stem cells of the same individual. Beside these culturing of adult stem cells is difficult in lab conditions, so researcher are interested in the use of pre existing cell instead of putative pancreatic stem cells for the regeneration of Beta cells after birth (Dor et al. 2004). Insulin producing Beta cells are also obtained from endocrine progenitors (Xu et al., 2008). Publish work reported that Adult stem cells from bone marrow (Xie et al. 2009), pancreas (Seaberg et al. 2004), liver (Yang et al. 2002), umbilical cord blood (Sun et al. 2007), Wharton's jelly (Chao et al. 2007), placenta Chang et al. 2007), embryonic stem cells (Damour et al. 2006) and induced pluripotent stem cells (Maehr et al. 2009) have high pluripotency having ability to differentiate into insulin producing cells.

Beta cell Renaissance and Replication in adult pancreas from alpha cells

Published data showed that possibility is present to replace the infected or defective beta cell lines by regenerating new beta cells to overcome the deficiency of insulin from adult cells (Gordon et al. 2011). As in Rodent study model shows beta cells posse's strong ability for replication (Bruning et al. 1999). By destroying beta cells in mice the remaining islet glucagon-secreting alpha cells appeared to presume a beta cell phenotype and were able to reestablish glucose levels to normal after many months, so this interesting phenomenon is of considerable importance that ectopic creation of Pax4 in progenitor cells of mouse pancreas can escort to consequent renovation of alpha cells to beta bells (Collomb et al. 2009).

Neogenesis

It has been hypothesized that the progression of postnatal neogenesis is a recapitulation of islet maturity in fetal life, and that the pancreatic duct epithelium could be enthused therapeutically to make new-fangled islets (Bonner Weir et al. 2010). One loom would be to build up a medication that would kindle the progression of neogenesis with in a patient's pancreas. Another advance would involve directed differentiation of duct cells into innovative islets *in vitro* that could then be transplant (Bonner Weir et al. 2000, Yatoh et al. 2007)

Stem Cells from Bone Marrow, mesenchymal cells and cell fusion mechanism

This was researched that bone marrow transplantation helps in maintaining blood glucose level, and surveillance was better, as in islets bone marrow derived cells had differentiated into endothelial cells and occasionally into insulin secreting cells (Hess et al. 2003). Mesenchymal stem cells (MSC,s) was obtained from human adult tissues and were utilized to

differentiate into insulin producing cells type, some other important MSC,s are fibroblast (Tateishi et al. 2008), Bone marrow (Karnieli et al. 2007), liver cells (Sapir et al. 2005), endometrium (Santamaria et al., 2011) but among these bone marrow is the dominant source of MSC,s because of its greater ability to self replicate and differentiated both in vivo and in lab conditions, essay to culture and maintain its pluripotentiality (Pittenger et al. 1999). Cell fusion has been recommended as a method of clear alteration of bone marrow resultant cells into an extramedullary phenotype (Theise et al. 2003, Kofman et al. 2004).

Embryonic and Induced Pluripotent Stem Cells

Human embryonic stem cells (ESCs) have the capacity to become wholly mature beta cells (Kroon et al. 2008). Efforts to undeviating the discrimination of (iPSCs) cells to mature islet cells are also making progress but have not yet had the accomplishment of ESCs (Alipio et al., 2010). Concerns are present about the epigenetic changes in these cells and this is undergoing passionate exploration. Embryonic stem cells possess high proliferative capacity and are used for the proliferation of three developmental germs layers, researchers are succeeded in producing pancreatic epithelial cell or insulin producing Beta cells from rodent and mice embryonic stem cells (Josue et al. 2007). Induced pluripotent stem cells possess the power to use for diabetes therapy, IPSC can be generated in invitro from spermatogonial stem cells by growing in culture medium supplemented with proper growth factors these IPSC then further differentiated into 3 germ lines (Golestaneh et al. 2009).

Hepatic stem cells

Liver and pancreas instigate from the endoderm and having common progenitor cells, it has been hypothesize that liver cells can be used as an alternative source of beta cells (Zaret et al.

2008). There is no data available till date which show that modified hepatic cell propagate in vitro and can reach an adequate number of efficient cells for transplantation therapy. On the other hand, these liver tissues still have excellent scenario, and are not contentious like pancreatic stem cells. Due to their strong regenerative ability and easy collection by biopsy make these cells an ideal source for transdifferentiation (Liu et al., 2013).

Adipose and Placenta derived stem cells for T1DM

Adipose *ADSC* and placenta *PDSC* derived stem cells have the ability to produce insulin producing beta cell lines which have the ability to restore blood glucose level (Timper et al. 2006, Kadam et al. 2010).

Transdifferentiation toward stem cell therapy for T1DM

According to the published research work researcher failed to observe transdifferentiation of bone marrow stem cells and embryonic stem cells to insulin producing pancreatic beta cells (Dong et al. 2008). Stem cell therapy here implies the substitute of diseased or vanished cells from progeny of pluripotent or multipotent cells. Embryonic stem cells and adult stem cells have been used to engender substitute Beta cells or restore beta cell functioning. Embryonic stem cells can be differentiated into insulin producing cells by manipulating culture environment (Mehboob et al. 2014).

Conclusion

Regenerative cell therapy is one of the research fields which have the utmost advance in the last years. In this review we focus on some of the progresses in stem cells therapy for type 1 diabetes mellitus to imitate or to rejuvenate the shattered beta cells to overcome the dearth of insulin, such acquaintance of the

stem cells may escort to the development of the new curative strategies that help in the restoring beta cells function. Stem cell study makes the ways to innovative therapies and paths to improve understanding about the pathophysiology of the diabetes and advancement with stem cell biology has been exciting and scenario for the hope are very stirring.

Abbreviations

Pancreatic stem cells **PSCs**, Hepatic stem cells **HSCs**, Embryonic stem cells **ESCs**, Induced pluripotent stem cells **IPSCs**, Type 1 Diabetes mellitus **T1DM**, Type 2 Diabetes mellitus **T2DM**, Adipose derived stem cell **ADPS**, Placenta derived stem cell **PDSC**, Mesenchymal stem cells **MSC**.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

The authors are grateful to the Department of Biotechnology and Genetic Engineering, Kohat University of Science and Technology, Kohat.

Bibliography

Alipio, Z., W. Liao, E.J. Roemer, M. Waner, L.M. Fink, D.C. Ward, and Y. Ma. 2010. "Reversal of hyperglycemia in diabetic mouse models using induced-pluripotent stem (iPS)-derived pancreatic beta-like cells." *Proc Natl Acad Sci U S A* 107:13426-13431.

Berney, T. and P.R. Johnson. 2010. "Donor pancreata: evolving approaches to organ allocation for whole pancreas versus islet transplantation." *Transplantation* 90: 238–243.

Bethesda, M.D. 2013. "Stem Cells and Diabetes" In *Stem Cell Information* [World Wide Web site]. National Institutes of Health, U.S. Department of Health and Human

Services,
http://stemcells.nih.gov/info/scireport/pages/chapter7.aspx>

Bonner-Weir, S., W.C. Li, L. Ouziel-Yahalom, L. Guo, G.C. Weir, and A. Sharma. 2010. "Beta-cell growth and regeneration: replication is only part of the story." *Diabetes* 59:2340-2348.

Bonner-Weir, S., M. Taneja, G.C. Weir, K. Tatarkiewicz, K.H. Song, A. Sharma, and J.J. O'Neil. 2000. "In vitro cultivation of human islets from expanded ductal tissue." *Proc Natl Acad Sci U S A*: 97:7999-8004.

Bruning, J.C., J. Winnay, S. Bonner-Weir, S.I. Taylor, D. Accili, and C.R. Kahn. 1999. "Development of a novel polygenic model of NIDDM in mice heterozygous for IR and IRS-1 null alleles." *Cell* 88:561-572.

Chang, C.M., C.L. Kao., Y.L. Chang., M.J. Yang., and Y.C. Chen. 2007. "Placenta derived multipotent stem cells induced to differentiate into insulin-positive cells." *Biochem Biophys Res Commun* 357: 414-420.

Chao, K.C., K.F. Chao., Y.S. Fu., and S.H. Liu. 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-e1458.

Collombat, P., X. Xu, P. Ravassard, B. Sosa-Pineda, S. Dussaud, N. Billestrup, O.D. Madsen, P. Serup, H. Heimberg, and A. Mansouri. 2009. "The ectopic expression of Pax4 in the mouse pancreas converts progenitor cells into alpha and subsequently beta cells." *Cell* 138:449-462.

D'Amour, K.A., A.G. Bang, S. Eliazer, O.G. Kelly, and A.D. Agulnick. 2006. "Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells." *Nat Biotechnol* 11: 1392-1401.

Dor, Y., J. Brown., O.I. Martinez., D.A. Melton. 2004. "Adult

pancreatic beta-cells are formed by self-duplication rather than stem-cell differentiation." *Nature* 429: 41-46.

Fridell, J.A., J. Rogers., R.J. Stratta. 2010. "The pancreas allograft donor: current status, controversies, and challenges for the future." *Clin Transplant*: 24: 433–449.

Gioviale, M.C., G. Damiano., G. Montalto., G. Buscemi., M. Romano. 2009. "Isolation and culture of beta-like cells from porcine Wirsung duct." *Transplant Proc* 41: 1363-1366.

Golestaneh, N., M. Kokkinaki, and D. Pant. 2009. "Pluripotent stem cells derived from adult human tests." *Stem Cells Dev* 18: 1115–1126.

Gordon, C. W., C. Claudia and B. Susan. 2011. "Stem cell approaches for diabetes: towards beta cell replacement." *Genome Medicine* 3:61.

Hess, D., L. Li, M. Martin. 2003. "Bone marrow-derived stem cells initiate pancreatic regeneration." *Nat Biotechnol* 21**:** 763–70.

Josue, K. and I. B. Mfopou. 2007. "Milestones of pancreatic Beta cell differentiation from embroyonic stem cell." *Advances in gene, Molecular and cell therapy*. Global Science Books.

Kadam, S.S. and R.R. Bhonde. 2010. "Islet neogenesis from the constitutively nestin expressing human umbilical cord matrix derived mesenchymal stem cells." *Islets* 2: 112-120.

Karnieli, O., Y. Izhar-Prato, S. Bulvik, and S. Efrat. 2007. "Generation of insulin-producing cells from human bone marrow mesenchymal stem cells by genetic manipulation." *Stem Cells* 25(11): 2837–2844.

Kofman, A., N.D. Theise, and M.A. Hussain. 2004. "Paradigms of adult stem cell therapy for type 1 diabetes mellitus in mice." *Eur J Endocrinol* 150: 415–19.

Korbling, M., R.L. Katz, and A. Khanna. 2002. "Hepatocytes and epithelial cells of donor origin in recipients of

peripheral blood stem cells." *N Engl J Med* 346: 738–46.

Kroon, E., L.A. Martinson, K. Kadoya, A.G. Bang, O.G. Kelly, S. Eliazer, H. Young, M. Richardson, N.G. Smart, J. Cunningham, A.D. Agulnick, K.A. D'Amour, M.K. Carpenter, and E.E. Baetge. 2008. "Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo." *Nat Biotechnol* 26:443-452.

Lee, S.H., E. Hao, A.Y. Savinov, I. Geron, A.Y. Strongin, and P. Itkin-Ansari. 2009. "Human beta-cell precursors mature into functional insulin-producing cells in an immunoisolation device: implications for diabetes cell therapies." *Transplantation* 87: 983-991.

Levinson, Warren and Ernest Jawetz. *Medical microbiology & immunology* by 7th Edition.

Liu, X. F., Y. F. Wang., Y. L. Li. 2013. "Research status and prospect of stem cells in the treatment of diabetes mellitus" *Sci China Life Sci* 56: 306–312.

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

Mehboob, A. H. and D.T. Neil. 2004. "Stem-cell therapy for diabetes mellitus." 364: 203–05.

Nathan, D. M., P. A. Cleary., J. Y. Backlund. 2005. "Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes.' *N Eng J Med* 353: 2643–2653.

Noguchi, H. 2007. "Stem cells for the treatment of diabetes." *Endocr J* 54: 7-16.

Noguchi, H., S. Matsumoto., M. Ueda., S. Hayashi., N. Kobayashi. 2008. "Method for isolation of mouse pancreatic stem cells." *Transplant Proc* 40: 422- 433.

Notkins, A. I., Kernmark, A. 2001. "Auto immune type I diabetes: resolved and un resolved issue" *J Clin Invest*

108: 1247 – 1252.

Pittenger, M.F., A. M. Mackay, and S. C. Beck. 1999. "Multilineage potential of adult human mesenchymal stem cells." *Science* 284 (5411): 143–147.

Qing, Y.D., L. Chen, Q.G. Guan, W. Lei, S. Jun, C. Bo, X. Yu-Xin, and S. Lei. 2008. "Allogeneic diabetic mesenchymal stem cells transplantation in streptozotocin-induced diabetic rat." *Clin Invest Med* 31(6): 328-337.

Santamaria, X., E. E. Massosa, and Y. Feng. 2011. "Derivation of insulin producing cells from human endometrial stromal stem cells and use in the treatment of marine diabetes." *Molecular Therapy* 19: 2065–2071.

Sapir, T., K. Shternhall, and I. Meivar-Levy. 2005. "Cell-replacement therapy for diabetes: generating functional insulin-producing tissue from adult human liver cells." *Proceedings of the National Academy of Sciences of the United States of America* 102(22): 7964–7969.

Seaberg, R.M., S.R. Smukler., T.J. Kieffer., G. Enikolopov, and Z. Asghar. 2004. "Clonal identification of multipotent precursors from adult mouse pancreas that generate neural and pancreatic lineages." *Nat Biotechnol* 22: 1115-1124.

Shapiro, A.M. 2000. "Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen." *N Engl J Med* 343(4): 230-8.

Stuchlikova, M., D. Kantarova, D. Michalkova., L. Barak., M. Bue. 2006. "Association of HLA – DPBI alleles with type I diabetes mellitus in Sovak population, *Bratisl lek listy*. 107(3): 73 – 75.

Sun, B., K.H. Roh., S.R. Lee, Y.S. Lee., and K.S. Kang. 2007. "Induction of human umbilical cord blood derived stem cells with embryonic stem cell phenotypes into insulin producing islet-like structure." *Biochem Biophys Res Commun* 354: 919-923.

Tateishi, K., J. He, O. Taranova, G. Liang, A. C. D'Alessio, and Y. Zhang. 2008. "Generation of insulin-secreting islet-like clusters from human skinfibroblasts." *The Journal of Biological Chemistry* 283(46): 31601–31607.

The Diabetes Control and Complications Trial Research Group. 1993. "The effect of intensive Treatment of diabetes on the development and progression of long-term complications in Insulin dependent diabetes mellitus." *New England Journal of Medicine* 329: 977-986.

Theise, N.D., and Wilmut, I. 2003. "Cell plasticity: flexible arrangement." *Nature* 425**:** 21.

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

Winslow, Terese. 2001. *Insulin Production in the Human Pancreas' diagram*. (assisted by Lydia Kibiuk). Cell images courtesy of Harry Heimberg. Diabetes injection image. London: Wellcome Library.

Xie, Q.P., H. Huang., B. Xu., X. Dong., and S.L. Gao. 2009. "Human bone marrow mesenchymal stem cells differentiate into insulin-producing cells upon microenvironmental manipulation in vitro." *Differentiation* 77: 483-491.

Xu, X., J. D'Hoker., G. Stange., S. Bonne., and N. De Leu. 2008. "Beta cells can be generated from endogenous progenitors in injured adult mouse pancreas." *Cell* 132: 197–207.

Yang, L., S. Li., H. Hatch., K. Ahrens., and J.G. Cornelius. 2002. "In vitro transdifferentiation of adult hepatic stem cells into pancreatic endocrine hormone producing cells." *Proc Natl Acad Sci* 99: 8078-8083.

Yatoh, S., R. Dodge, T. Akashi, A. Omer, A. Sharma, G.C. Weir, and S. Bonner-Weir. 2007. "Differentiation of affinity-

purified human pancreatic duct cells to beta-cells." *Diabetes* 56:1802-1809.

Zaret, K.S. and M. Grompe. 2008. "Generation and regeneration of cells of the liver and pancreas." *Science* 322: 1490–1494.

Zorina, T.D., V.M. Subbotin., S. Bertera. 2003. "Recovery of endogenous _ cells function in the NOD model of autoimmune diabetes." *Stem Cells* 21**:** 377–88.