Diabetes Type I - Stem Cells Transplantation a Choice Therapy

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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

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function. The proposal that the beta cells which lost in type 1 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 be 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 Edmonton 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.

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**Bibliography**


Services,


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