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Stem Cell Therapy for Islet Regeneration

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1. Introduction

Diabetes mellitus is an endocrine disorder characterised by inadequate production or use of insulin, resulting in abnormally high blood glucose levels. High blood glucose leads to the formation of reactive advanced glycation end-products (Feldman et al., 1997), which are responsible for complications such as blindness, kidney failure, cardiovascular disease, stroke, neuropathy and vascular dysfunction. Diabetes mellitus is classified as either type 1 or type 2. Type 1 diabetes mellitus (insulin-dependent diabetes mellitus) results from the autoimmune destruction of the pancreatic beta cells, whereas type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus) results from insulin resistance and impaired glucose tolerance.

Approximately 7.8% (23.6 million people) of the US population has been diagnosed with diabetes mellitus, and another 57 million people are likely to develop diabetes mellitus in the coming years (American Diabetes Association, 2007). The number of people with diabetes mellitus is set to continue to rapidly increase between now and 2030, especially in developing countries.

Over the last decade, a new form of treatment called islet transplantation therapy was thought to provide good patient outcomes; however, few islets are available for transplantation. Typically, the pooled islets isolated from two pancreases are enough to treat a single patient. Since the enormous potential of stem cells was discovered, it was hoped that they would provide the most effective treatment for diabetes mellitus. Over the past two decades, hundreds of studies have looked at the potential of stem cell therapy for treating diabetes mellitus. Successful stem cell therapy would eliminate the cause of the disease and lead to stable, long-term results; hence, the term “pancreatic regeneration” was coined. The hypothesis was that stem cells could regenerate the damaged pancreas. After careful consideration of the aetiology of diabetes mellitus, scientists have put forward two general treatment strategies: stem cell therapy to treat the autoimmune aspect of the disease, and stem cell therapy to treat the degenerative aspect of the disease. In this review, we focus on stem cell-based therapies aimed at islet regeneration through stem cell or insulin-producing cell (IPC) transplantation. We will also discuss the latest strategies for treating both type 1 and type 2 diabetes mellitus using stem cell therapy, along with the (initially promising) results.

2. Islet regeneration by cell replacement

2.1 Stem cell sources

Many different types of stem cells have been used in the research, testing and treatment of diabetes mellitus, including stem cells that can be used to regenerate pancreatic islets, e.g. embryonic stem cells, adult stem cells and infant stem cells (umbilical cord stem cells isolated from umbilical cord blood).

2.1.1 Embryonic stem cells

Human embryonic stem cells (ESCs) were first isolated at the University of Wisconsin-Madison in 1998 by James Thomson (Thomson et al., 1998). These cells were established as immortal pluripotent cell lines that are still in existence today. The ESCs were derived from blastocysts donated by couples undergoing treatment for infertility using methodology developed 17 years earlier to obtain mouse ESCs. Briefly, the trophectoderm is first removed from the blastocyst by immunosurgery and the inner cell mass is plated onto a feeder layer of mouse embryonic fibroblasts (Trombunson et al., 2001; 2002). However, cells can also be derived from early human embryos at the morula stage (Strelchenko et al. 2004) after the removal of the zona pellucida using an acidified solution, or by enzymatic digestion by pronase (Verlinsky et al., 2005). Nowadays, ESCs can be isolated from many different sources (Fig. 1).

ESCs are pluripotent, which means that they can differentiate into any of the functional cells derived from the three germ layers, including beta cells or insulin-producing cells (IPCs). The differentiation of ESCs into IPCs is prerequisite for their use as a diabetes mellitus treatment, and may occur either *in vivo* (after transplantation) or *in vitro* (before transplantation). *In vivo* differentiation is based on micro environmental conditions at the graft site, whereas *in vitro* differentiation requires various external factors that induce the phenotypic changes required to produce IPCs. This means that diabetes mellitus can be treated either by direct transplantation of ESCs, or by indirect transplantation of IPCs that have been differentiated from ESCs. However, Naujok et al. (2009) showed that ESCs could modify gene expression and exhibit a phenotype similar to that of islet cells when transplanted into the pancreas only if they are first differentiated *in vitro*, and that *in vitro* differentiation is a prerequisite for successful *in vivo* differentiation (Naujok et al., 2009). Moreover, using ESCs for pancreatic regeneration carries with it the risk of tumour formation after transplantation.

Therefore, the *in vitro* differentiation of ESCs into IPCs is necessary before they can be used to treat diabetes mellitus. Studies looking at the *in vitro* differentiation of ESCs into IPCs were first performed in 2001 using mouse cells (Lumelsky et al., 2001). However, the results could not be repeated in subsequent studies (Rajagopal et al., 2003; Hansson et al., 2004; Sipione et al., 2004). Researchers then developed a strategy for selecting ESCs expressing genes related to pancreatic cells (e.g. nestin), and successfully generated IPCs from these ESCs (Soria et al., 2000; Leon-Quinto et al., 2004). Other workers succeeded in creating IPCs from ESCs using gene transfer (Blyszczuk et al., 2003; Schroeder et al., 2006), or phosphoinositol-3 kinase inhibitors (Hori et al., 2002). The differentiation of ESCs into IPCs usually involves differentiation into embryoid bodies. This relatively long process comprises two phases: the embryoid body stage (4–5 days) and the differentiation stage (30–40 days). In 2005, Shi et al. decreased the time taken for this differentiation process to 15 days (Shi et al., 2005).

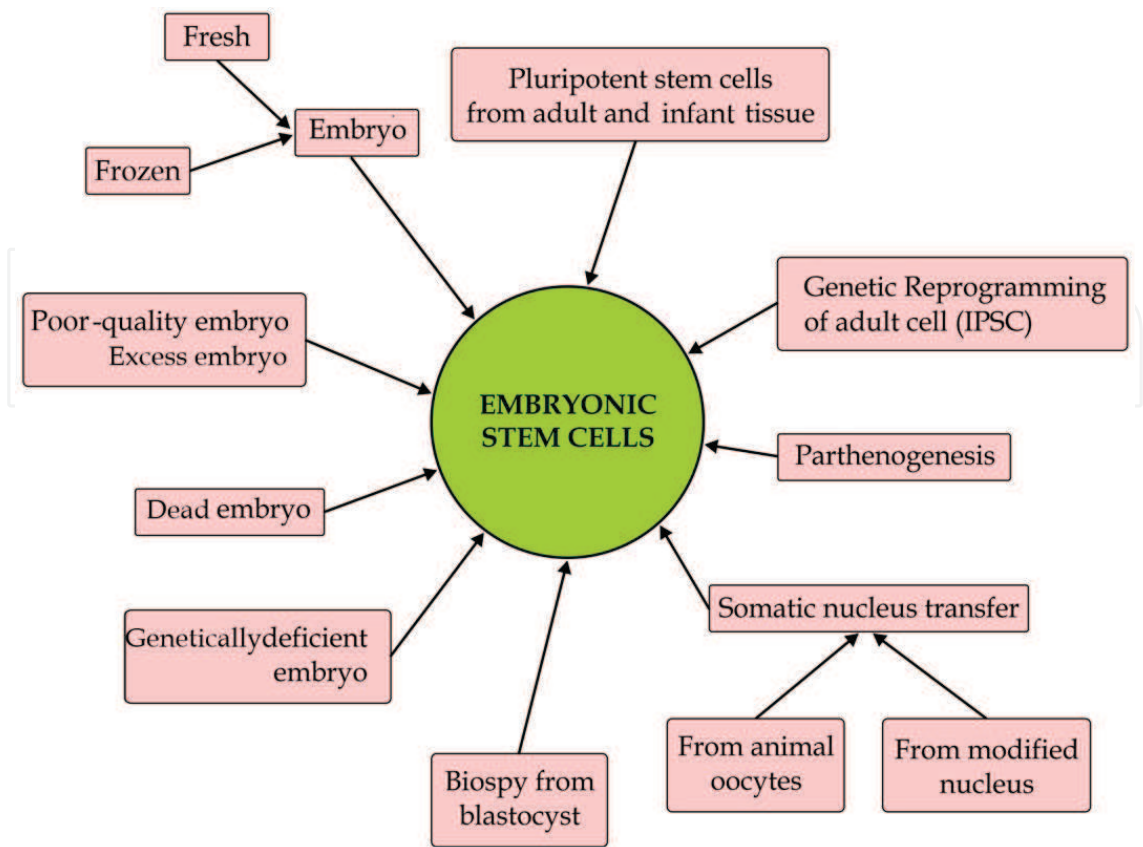


Fig. 1. ESC sources. ESCs can be isolated from fresh, frozen, dead, excess and genetically deficient embryos, by parthenogenesis and somatic nucleus transfer, from biopsies, and from pluripotent stem cells obtained from adult tissues.

In 2001, Assady et al. reported that IPCs could be generated by spontaneous differentiation of human ESCs. Although the IPC number and insulin content of these cells was low, this was the first proof-of-principle experiment indicating that human ESCs were a potential source of β -like cells. Recent reports from D'Amour et al. and Kroon et al. described the differentiation of pancreatic lineage cells from human ESCs *in vitro*. To date, many groups have reported the *in vitro* generation of IPCs from human ESCs (D'Amour et al., 2006; Jiang et al., 2007; Jiang et al., 2007).

2.1.2 Induced pluripotent stem cells

First created by Takahashi et al. (2007) and Yu et al. (2007), induced pluripotent stem cells (iPSCs) are a new source of embryonic-like stem cells, and are considered a technical breakthrough in stem cell research. iPSCs have several advantages over ESCs. One major advantage is that iPSCs can be created from any cell-type; thus, creating patient-specific stem cells (Park et al., 2008; Dimos et al., 2008). Similar to ESCs, iPSCs can differentiate into many different cell types, including neurons (Dimos et al., 2008; Chambers et al., 2008), heart muscle cells (Zhang et al., 2009) and insulin-secreting cells (Tateishi et al., 2008; Zhang et al., 2009).

iPSCs can be created from many different cell types via a simple process. First-generation iPSCs are obtained by transferring four genes (*Oct-3/4*, *Sox-2*, *c-Myc* and *Klf4*; Shinya Yamanaka et al., 2006) or *Oct-3 / 4*, *Sox-2*, *Nanog* and *LIN28* into mice. Second-generation

IPSCs are derived using only *Oct-3/4*, *Sox-2* and *Klf4*, because *c-Myc* is an oncogene (Nakagawa et al., 2008). Third-generation IPSCs are generated using only two genes, *Oct-3/4* and *Sox-2*, and the histone deacetylase inhibitor, valproic acid (VPA) (Danwei Huangfu et al., 2008).

A recent study shows that IPSCs can be successfully created from adult fibroblasts derived from type 1 diabetic patients (Rene'Maehr et al., 2009). These cells were differentiated into IPCs and used to successfully treat diabetic rats (Alipio et al., 2010).

2.1.3 Pancreatic stem cells

A recent report by Harry Heimberg's group (Heimberg et al., 2008) describes the existence of pancreatic stem cells in mice. In their most recent study, Heimberg's group ligated the ducts that secrete pancreatic enzymes in adult mice. The result was a doubling in the number of beta cells within two weeks. Also, the pancreases of the experimental animals began to produce more insulin; evidence that the newly generated beta cells were functional (Xu et al., 2008). Another research team showed that the production of new beta cells was dependent on the gene *neurogenin 3* (*Ngn3*), which plays a role in the pancreas during embryonic development, and successfully isolated and established a murine pancreatic stem cell line (Noguchi et al., 2008; 2009).

Human pancreatic stem cells have also been successfully differentiated into IPCs (Noguchi et al., 2010). Islet cells were isolated from the pancreases of human donors using the Ricordi technique modified by the Edmonton protocol. The isolated cells were then cultured in media specifically designed for mouse or human pancreatic embryonic stem cell culture. The cells were differentiated for 2 weeks in induction media containing exendin-4, nicotinamide, keratinocyte growth factor, PDX-1 protein, or protein BETA2/NeuroD. However, according to Davani et al. (2007), human islet precursor cells derived from human pancreases exhibit the properties of mesenchymal stem cells (MSCs) in that they adhere to plastic, express CD73, CD90 and CD105, and differentiate *in vitro* into adipocytes, chondrocytes, and osteocytes. Davani et al. also identified a rare population of CD105+/CD73+/CD90+ cells in adult human islets that express low levels of insulin mRNA (Davani et al., 2007).

2.1.4 Mesenchymal stem cells

MSCs are multipotent stem cells that can differentiate into a variety of cell types, such as osteoblasts (bone cells), chondrocytes (cartilage cells) and adipocytes (fat cells) (Anna et al., 2008). This cell type was first discovered in 1924 by the cell morphologist Alexander A. Maximo, who described a type of cell within the mesenchyme that develops into various types of blood cell. Ernest A. McCulloch and James E. Till first revealed the clonal nature of marrow cells in 1963 (Becker et al., 1963; Siminovitch et al., 1963). Subsequently, *ex vivo* clonogenic assays were used to examine the potential of multipotent marrow cells (Friedenstein et al., 1974, 1976). In these assays, stromal cells or MSCs were used as colony-forming unit-fibroblasts (CFU-f). The characteristics of MSCs are as follows: they adhere to culture vessels; they have a fibroblast-like shape; they express Stro-1, CD133, CD29, CD44, CD90, CD105 (SH2), SH3, SH4 (CD73), c-kit, CD71, and CD106; and they can differentiate into specialised cells, e.g. bone, cartilage and fat.

MSCs have been isolated from many different tissues, including bone marrow (Oyajobi et al., 1999; Majumdar et al., 2000; Prockop et al., 2001; Smith et al., 2004; Titorencu et al., 2007;

Wolfe et al., 2008; Gronthos and Zannettino et al., 2008; Phadnis et al., 2011; Bao et al., 2011), adipose tissue (Katz et al., 2005; Baptista et al., 2009; Caviggioli et al., 2009; Baer et al., 2010; Bruyn et al., 2010; Estes et al., 2010; Tucker, Bunnell, 2011), peripheral blood (Kassis et al., 2006), umbilical cord blood (Erices et al., 2000; Rosada et al., 2003; Hutson et al., 2005; Reinisch et al., 2007; Bieback and Klüter et al., 2007; Perdikogianni et al., 2008; Zhang et al., 2011), banked umbilical cord blood (Phuc et al., 2011), umbilical cords (Cutler et al., 2010; Farias et al., 2011), umbilical cord membranes (Deuse et al., 2010; Kita et al., 2010), umbilical cord veins (Santos et al., 2010), Wharton's jelly from the umbilical cord (Zeddou et al., 2010; Peng et al., 2011), placenta (Miao et al., 2006; Battula et al., 2007; Huang et al., 2009; Semenov et al., 2010; Pilz et al., 2011), decidua basalis (Macias et al., 2010; Lu et al., 2011), the ligamentum flavum (Chen et al., 2011), amniotic fluid (Feng et al., 2009; Choi et al., 2011, Shuang-Zhi et al., 2010), amniotic membrane (Chang et al., 2010; Marongiu et al., 2010), dental pulp (Agha-Hosseini et al., 2010; Karaöz et al., 2010; Yalvac et al., 2010; Spath et al., 2010), chorionic villi from human placenta (Poloni et al., 2008), foetal membranes (Soncini et al., 2007), menstrual blood (Meng et al., 2007; Hida et al., 2008; Musina et al., 2008; Kyurkchiev et al., 2010), and breast milk (Patki et al., 2010) (Fig. 2).

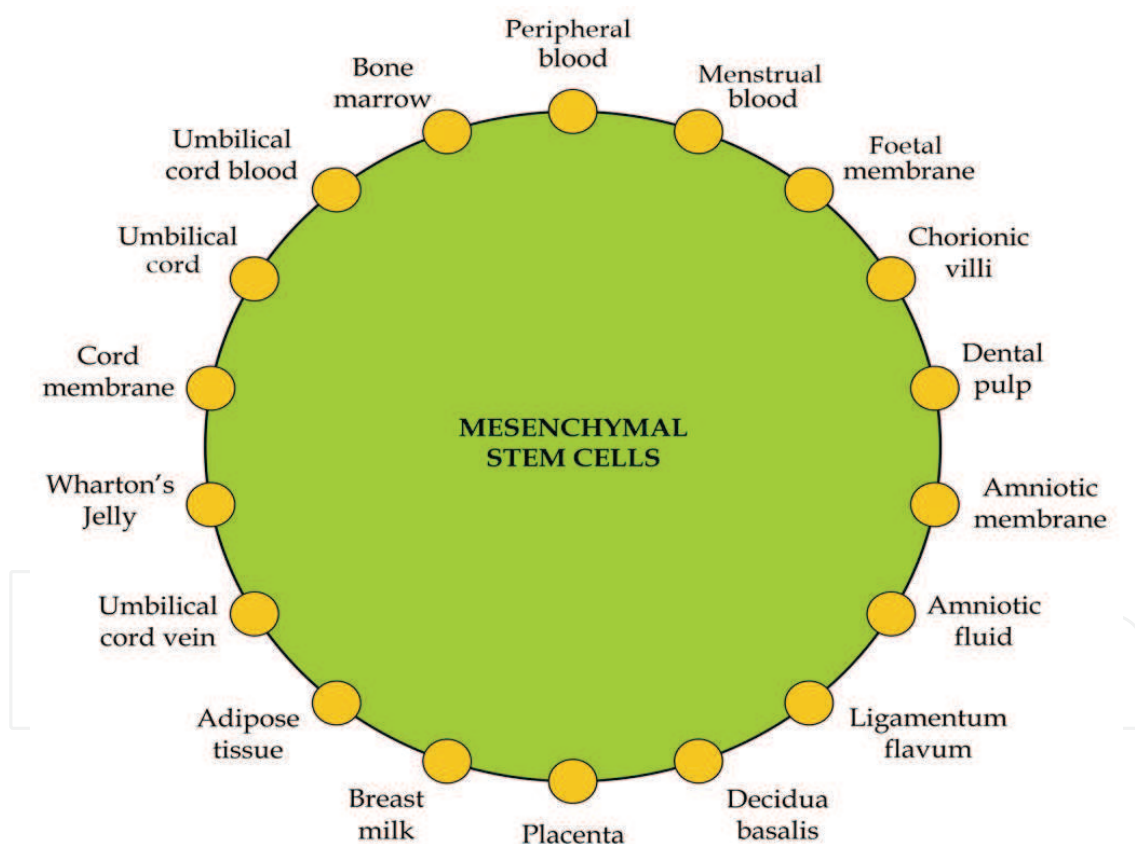


Fig. 2. Sources of MSCs. MSCs can be derived from several adult or infant tissues.

MSCs have been successfully differentiated into IPCs *in vitro* and can reduce blood glucose levels in both animals and humans after transplantation. The *in vitro* differentiation of MSCs into IPCs requires certain substances combined with medium stress. Most successful protocols for the differentiation of MSCs into IPCs used nicotinamide and/or exendin-4 inducers. Changes in the glucose concentration within the culture medium are necessary to

trigger this process. MSCs are commonly cultured in low glucose medium to initiate differentiation before they can be induced to differentiate into IPCs by nicotinamide. In some studies, epidermal growth factor (EGF) was added to the culture medium during the IPC maturation phase in addition to nicotinamide. Currently, IPCs can be generated from MSCs obtained from human umbilical cord blood (Gao et al., 2008; Parekh et al., 2009; Wang et al., 2010), banked human umbilical cord blood (Phuc et al., 2011), placenta (Kadam et al., 2010), bone marrow (Sun et al., 2007; Xie et al., 2009; Phadnis et al., 2011), menstrual blood (Li et al., 2010), amniotic fluid (Trovato et al., 2009), Wharton's jelly (Chao et al., 2008; Wu et al., 2009), amnion (Kadam et al., 2010), and adipose tissue (Chandra et al., 2009). Other studies report the successful use of transgenesis to differentiate MSCs into IPCs, or up-regulation of genes (mainly *PDX-1* or *betacellulin*) related to signalling pathways that trigger this process (Karnieli et al., 2007; Li et al., 2007; Li et al., 2008; Hisanaga et al., 2008; Limbert and Seufert., 2009; Yuan et al., 2010; Paz et al., 2011). Moreover, coating the tissue culture flasks with substrates such as fibronectin or laminin can also induce MSCs to differentiate into IPCs (Moriscot et al., 2005; Chang et al., 2008; Gao et al., 2008; Lin et al., 2010; Lin et al., 2011).

2.1.5 Other sources

Recent reports suggest that pancreatic duct cells, liver cells, spleen cells, and other cell types have the ability to differentiate into islet cells. Although it is difficult to differentiate adult cells into insulin-producing pancreatic cells, some researchers have shown evidence of pancreatic duct regeneration in mouse models. When gastrin was injected into mice to induce acinar cells to differentiate into duct cells, these cells became a cellular substrate for the formation of new beta cells, similar to the effects seen in rats receiving glucose injections (Weir and Bonner-Weir et al., 2004).

Liver cells originating from the endothelium may also be candidates for this specialised insulin-secreting role (Meivar-Levy et al., 2006). Yang et al. (2002) reported that exposure to high glucose concentrations caused oval cells in the liver to differentiate into cells with a phenotype similar to that of pancreatic islet cells (Yang et al., 2002). Another strategy involves the *in vivo* gene transfer of the *pdx-1* gene into liver cells using an adenovirus vector to induce endogenous *pdx-1* gene expression. *Pdx-1*, along with other beta cell genes, is associated with insulin secretion (Zalzman et al., 2005; Sapir et al., 2005; Shternhall-Ron et al., 2007; Aviv et al., 2009; Gefen-Halevi et al., 2010; Meivar-Levy and Ferber, 2010). Similar to *pdx-1*, *betacellulin* and *neuro-D* expression by liver cells yielded sufficient insulin-producing cells in a streptozocin (STZ)-induced diabetic mouse model. These techniques not only induce liver cells to differentiate into beta cells, but also create new islets within the liver itself (Kojima et al., 2003). Other studies showed that human foetal liver cells transfected with *telomerase* and *pdx-1* can produce insulin and release it into the body. These cells cured diabetes mellitus when transplanted into immuno-deficient diabetic mice.

Fibroblasts are a relatively new source of islets and are easily isolated from skin. In a recent study, 61 single-cell-derived dermal fibroblast clones were established from human foreskin using a limiting dilution technique. These cells were able to differentiate into islet-like clusters when induced using pancreatic-inducing medium and several hormones, including insulin, glucagon and somatostatin, were detectable at both the mRNA and protein levels after induction. Moreover, transplantation of these islet-like clusters resulted in the release of insulin in response to glucose *in vitro* (Bi et al. 2010).

2.2 Stem cell transplantation strategies

2.2.1 Transplantation methods

Transplantation of stem cells/IPCs to treat diabetes mellitus has been investigated in both animal models and humans. Many different types of stem cells have been tested using different methods. Cells can be grafted underneath the kidney capsule (Rackham et al., 2011; Figliuzzi et al., 2009; Ito et al., 2010; Lin et al., 2009; Kodama et al., 2009; Kodama et al., 2008; Zhang et al., 2010; Ohmura et al., 2010; Xiao et al., 2008; Berman et al., 2010), delivered via intra-peritoneal injection (Boroujeni et al., 2011; Chandra et al., 2009; Koya et al., 2008; Shao et al., 2011; Kadam et al., 2010; Phuc et al., 2011; Lin et al., 2009) or intra-portally (Shyu et al., 2011; Trivedi et al., 2008; Li et al., 2010; Wu et al., 2007; Longoni et al., 2010; Itakura et al., 2007), grafted into the liver (Chao et al., 2008; Zhu et al., 2009; Xu et al., 2007; Chen et al., 2009; Wang et al., 2010) or injected into the tail vein (Dinarvand et al., 2010; Koblas et al., 2009; Kajiyama et al., 2010; Jurewicz et al., 2010) (Fig. 3). However, there is little research comparing the efficiency of these methods. Chen et al. (2009) showed that transplantation of stem cells into the liver produces better results than transplantation into the renal capsule. Although diabetes mellitus is caused by destruction of the beta cells within the pancreatic islets, no studies have attempted transplantation directly into the pancreas. This is because the pancreas is very sensitive organ and is vulnerable to mechanical intervention.

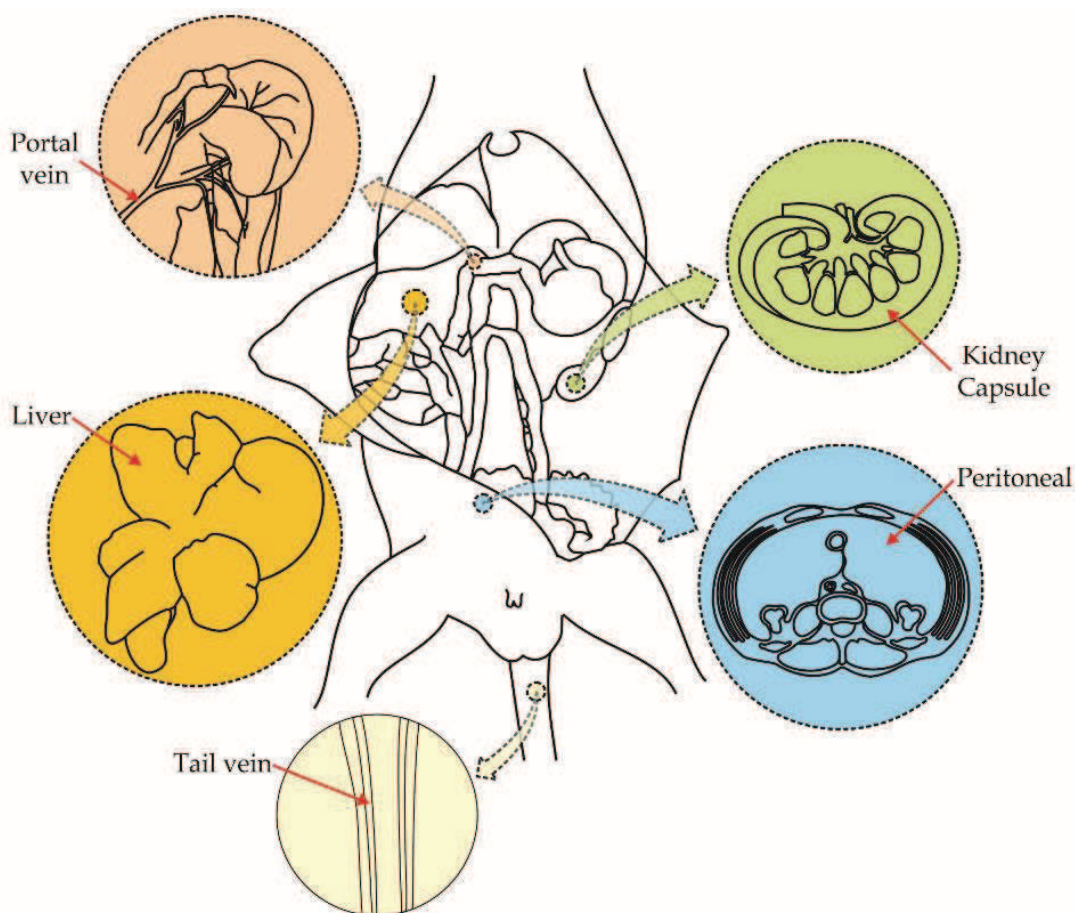


Fig. 3. Methods of stem cell/IPC transplantation. Stem cells or IPCs can be transplanted via the tail vein, intraperitoneally, under the kidney capsule, into the liver, or via the portal vein.

2.2.2 Stem cell transplantation

Unlike IPC transplantation, the mechanisms underlying islet regeneration and the reductions in blood glucose levels seen in diabetic patients require further study. The main questions that need to be answered are: 1) what role do grafted stem cells play in the regeneration of pancreatic islets? 2) How will stem cells behave when grafted into the body rather than the pancreas?

One type of stem cell that has been used to treat diabetes mellitus and investigated extensively in animal models is MSCs. Almost all research on MSC transplantation shows that *in vitro* or *in vivo* transplantation of MSCs results in a reduction of blood glucose levels, weight gain and increased longevity. However, MSCs can play multiple roles. Grafted stem cells can move into the pancreatic islets and differentiate into IPCs (Sorvi et al., 2005; Sordi, 2009). In an *in vitro* model using MSCs derived from human bone marrow and pancreatic islets, Sorvi et al. (2005) demonstrated crosstalk between MSCs and pancreatic cells mediated by various chemokines and their receptors. A minority of BM-MSCs (2–25%) express chemokine receptors (CXC receptor 4 [CXCR4], CX3C receptor 1 [CX3CR1], CXCR6, CC chemokine receptor 1 [CCR1], and CCR7) and, accordingly, show chemotactic migration in response to chemokine CXC ligand 12 (CXCL12), CX3CL1, CXCL16, CC chemokine ligand 3 (CCL3), and CCL19. These factors, released from the islets, were then able to attract MSCs. Moreover, MSCs were detected within the pancreatic islets of mice injected with green fluorescent protein (GFP)-positive MSCs (Sorvi et al., 2005). This result was subsequently confirmed in 2009 by Sordi, who hypothesised that the crosstalk between MSCs and pancreatic islets was driven by the CXCR4-CXCL12 and CX3CR1-CX3CL1 axes (Sordi, 2009). Movement of MSCs into the pancreas after transplantation was also confirmed by Lin et al. (2009) and Phadnis et al. (2011). Using bone marrow-derived MSC transplantation coupled with down-regulation of neurogenin 3 (Ngn3) induced by a recombinant lentivirus encoding two different small hairpin RNAs (shRNAs) for specific interference, they showed the successful engraftment of MSCs. In addition, they found that the endogenous pancreatic stem cells differentiated into IPCs and played a major role in reversing hyperglycaemia (Lin et al., 2009). However, there are cases in which stem cells derived from human umbilical cord blood also move into the pancreas and differentiate into IPCs in immunocompromised diabetic animals without improving hyperglycaemia (Koblas et al., 2009). Hasegawa et al. (2007) used Nos3 (-/-) mice as a model of impaired bone marrow-derived cell mobilisation and showed that the hyperglycaemia-improving effects of bone marrow transplantation were inversely correlated with the severity of myelo-suppression and delays in peripheral white blood cell recovery. Thus, stem cell mobilisation is critical for bone marrow transplantation-induced beta cell regeneration after injury. Therefore, they suggested that, during bone marrow transplantation, grafted cells first move into the recipient's bone marrow and, subsequently, into the injured periphery to regenerate the recipient's pancreatic beta cells (Hasegawa et al., 2007).

Another study showed that MSCs display immunomodulatory functions. MSCs prevented beta-cell destruction and development of diabetes mellitus by inducing regulatory T cells (Madec et al., 2009). Thus, MSC transplantation may prevent islet cell destruction by the immune system seen in type 1 diabetes mellitus and the pancreatic islets can be gradually restored. The result was a decrease in blood sugar levels and weight gain. While in a more recent study, it is said that MSCs protected islets from hypoxia/reoxygenation (H/R)-induced injury by decreasing apoptosis and increasing the expression of HIF-1 α , HO-1, and COX-2 mRNA. The MSCs induced the expression of anti-apoptotic genes, thereby enhancing resistance to H/R-induced apoptosis and dysfunction (Lu et al., 2010).

The use of ESCs for treating diabetes mellitus is limited because of high levels of tumour formation. So there were a few researches using the ESCs for treating diabetes mellitus. In one study, pancreatic cell ontogeny within ESCs transplanted into the renal capsule of STZ-induced mice resulted in pancreatogenesis *in situ* or beta cell neogenesis. Immunohistochemistry was performed on excised pancreatic tissues using antibodies against stage- and lineage-specific pancreatic markers. Twenty-one days post-transplantation, PDX-1+ pancreatic foci appeared in the renal capsule, which expressed exocrine enzymes (amylase) and endocrine hormones (insulin, glucagon, and somatostatin). These multi-hormonal endocrine cells, a characteristic of beta cell regeneration, suggested possible divergence from embryonic islet cell development (Kodama et al., 2008). In another study, Kodama et al. (2009) showed that transplanted ESCs could migrate into the injured pancreas. Cell tracing analysis showed that significant beta cell neogenesis occurred 2 to 3 weeks after injury. Importantly, whereas pancreas-localised ESC or their derivatives were found adjacent to the sites of regeneration, neogenic pancreatic epithelia, including Ngn3+ cells, were endogenous. Transplantation efficiency was confirmed by enhanced endogenous regeneration and increased beta cell differentiation from endogenous progenitor cells (Kodama et al., 2009).

2.2.3 Transplantation of differentiated stem cells

Based on the successful transplantation of beta cells, or pancreatic islets, for the treatment of diabetes mellitus (Ris et al., 2011; Wahoff et al., 1995; 1996), transplantation of IPCs differentiated from stem cells is seen as a promising therapy for diabetic patients, particularly in light of the lack of tissue donors and the many side effects of insulin injections. Unlike stem cells, transplanted IPCs produce insulin directly. IPC transplantation using different grafting methods has been studied in mouse models. Routes of administration include the portal vein, intra-peritoneal injection, the liver, the tail vein, and the kidney capsule. IPCs, differentiated from bone marrow-derived MSCs, were successfully allografted into the portal vein in a rat model of diabetes mellitus. After transplantation, the IPCs migrated into the liver where they expressed islet hormones, resulting in reduced glucose levels between Days 6 and 20 post-injection (Wu et al., 2007). Xenotransplantation of IPCs derived from fresh or banked human umbilical cord blood into diabetic mice also showed positive results. These IPCs, transplanted via the portal vein (Wang et al., 2010) or intraperitoneally (Phuc et al., 2011), reduced the blood glucose levels in diabetic mice. When IPCs were grafted into the portal vein, human C-peptides were detected in the mouse livers by immunohistochemistry (Wang et al., 2010). Similar to these results, xenotransplantation of IPCs differentiated from the Wharton's jelly from human umbilical cords restored normoglycaemia, body weight and a normal glucose tolerance test, indicating that the cells are functional when grafted via the portal vein (Kadam et al., 2010) or liver (Chao et al., 2008).

Zang et al. (2010) injected IPCs differentiated from human islet-derived progenitor cells under the renal capsule of immunodeficient mice. One month later, 19/28 mice transplanted with progenitor cells and 4/14 mice transplanted with IPCs produced human C-peptide that was detectable in the blood. This indicates that the *in vivo* environment further facilitates the maturation of progenitor cells. Moreover, 9/19 mice transplanted with progenitor cells, and 2/4 mice transplanted with IPCs, secreted C-peptide in response to glucose (Zang et al., 2010). Allotransplantation of IPCs differentiated from islet progenitor cells produced similar results (Shyu et al. 2011). In this study, progenitor cells cultured in matrigel differentiated into IPCs following transplantation into diabetic mice.

ESCs were also differentiated into IPCs and used to treat diabetes mellitus in animal models. After transplantation, these cells did not induce teratoma formation in STZ-induced mice and treatment reduced blood glucose levels to almost normal levels (Kim et al., 2003). Another study indicated that ESCs could differentiate into IPCs; however, transplantation of these pancreatic progenitor clusters into STZ-induced mice failed to reverse the hyperglycaemic state. This indicates that ESCs can differentiate into pancreatic progenitor cells and commit to a pancreatic islet cell fate, but are unable to perform the normal functions of beta cells (Chen et al., 2008). While most studies have focused on experimental treatments using IPC transplantation, another study used liver cells (rather than IPCs) to treat diabetes mellitus. Hepatic cells were differentiated from bone marrow-derived MSCs. Transplantation of syngeneic hepatic cells into STZ-induced mice cured their diabetes mellitus. Treatment of mice with hyperglycaemia and islet cell destruction resulted in repair of the pancreatic islets. Blood glucose levels, intra-peritoneal glucose tolerance tests, and serum insulin levels recovered significantly in the treated group. In addition, both body weight and the number of islets were significantly increased (Dinarvand et al., 2010).

2.2.4 Stem cell gene therapy

Due to their properties of self-renewal and capacity for multipotent differentiation, stem cells are thought to be the best vector for delivering genes and therapeutic gene-coded proteins into the body. Gene transfer experiments that cause stem cells to differentiate into beta cells, or that transfer specific genes coding for insulin, have also been conducted in recent years. There are several possible reasons why the use of stem cell gene therapies can be used to treat diabetes mellitus. However, no study has compared the difference between IPCs produced by chemical induction and those derived from gene transfer. Some researchers hypothesise that the key is the genetic transfer of the signalling pathways related to differentiation from stem cells into IPCs, which will create IPCs more similar to stem cells *in vivo*. Others argue that genetic modifications, e.g. *PDX-1*, *betacellulin*, or *Neuro-D* transfer, induce cells to differentiate into beta cells, while yet others suggest that the efficiency of IPC transplantation is low because IPCs are mature, specialised cells. For long-term effectiveness, a source of insulin with a long-term regenerative capacity is needed. Early studies by Xu et al. (2007), looking at transferring insulin into MSCs, showed that the resulting MSCs did express human insulin. The body weight of diabetic mice treated with these MSCs increased by 6% within 6 weeks of treatment, and average blood glucose levels were 10.40 \pm 2.80 mmol/l (Day 7) and 6.50 \pm 0.89 mmol/l (Day 42), compared with 26.80 \pm 2.49 mmol/l (Day 7) and 25.40 \pm 4.10 mmol/l (Day 42) in untreated animals ($p < 0.05$). Experimental diabetes mellitus was effectively relieved for up to 6 weeks after intrahepatic transplantation of murine MSCs expressing human insulin (Xu et al., 2007). In other studies, STZ-treated mice transplanted with *Pdx1*-transduced adipose tissue-derived MSCs (*Pdx1*-MSCs) showed significant decreases in blood glucose levels and increased survival compared with control mice (Lin et al., 2009; Kajiyama et al., 2010).

2.2.5 Transplantation of immuno-isolated IPCs

Transplantation IPCs offers a potential cell replacement therapy for patients with type 1 diabetes mellitus. However, because of the inadequate number of cells obtained from donors, other stem cell sources have drawn significant attention from many research groups. The efficacy of these approaches is limited because they typically necessitate the administration of immunosuppressive agents to prevent rejection of transplanted cells. The

use immunosuppressive drugs can have deleterious side effects, such as increased susceptibility to infection, liver and kidney damage, and an increased risk of cancer. In addition, immunosuppressive drugs may have unexpected effects on the transplanted tissues. For example, some reports have shown that cyclosporine can inhibit insulin secretion by pancreatic cells.

Immuno-isolation is a promising technique that protects the implanted tissues from rejection. One of the most common immuno-isolation techniques is to encapsulate cells within a semi-permeable membrane, such as alginate, that physically protects the grafts from the host's immune cells while simultaneously allowing nutrients and metabolic products to diffuse into or out of the capsule. To achieve this, the cells are encapsulated within a hydrogel or alginate membrane using gravity, electrostatic forces, or coaxial airflow to form the capsule. Allogeneic and xenogeneic transplantation of encapsulated islets of Langerhans restores normal blood glucose levels in mice (Dufrane et al., 2006; Fan et al., 1990; Omer et al., 2003), dogs (Soon-Shiong et al., 1992a,b; 1993) and non-human primates (Sun et al., 1996) with diabetes mellitus induced by autoimmune diseases or chemical injury, without on the need for immunosuppressive agents. In most of these studies, transplantation was via intraperitoneal injection of islet cells. However, Dufrane et al. (2006) recently reported the generation of encapsulated porcine islets using a Ca-alginate material. These capsules were implanted under the kidney capsule of nondiabetic *Cynomolgus* monkeys. The implanted porcine islets survived for up to 6 months after implantation without immunosuppression, even in animals injected with porcine IgG. Moreover, C-peptide was detected in 71% of the animals. After 135 and 180 days, the explanted capsules still synthesised insulin and responded to glucose stimulation (Dufrane et al., 2006).

In another study, transplantation of alginate-encapsulated IPCs from an embryo-derived mouse embryo progenitor-derived insulin-producing-1 (MEPI-1) cell line lowered hyperglycaemia in immuno-competent, allogeneic diabetic mice. After transplantation, hyperglycaemia was reversed and was followed by a 2.5-month period of normal to moderate hypoglycaemia before relapse. Relapse occurred within 2 weeks in mice transplanted with non-encapsulated MEPI-1 cells. Blood glucose levels, insulin levels, and the results of an oral glucose tolerance test all correlated directly with the number of viable cells remaining in the capsules in the transplanted animals (Shao et al., 2011). Moreover, encapsulation of IPCs differentiated from amnion-derived MSCs, or adipose tissue-derived MSCs in polyurethane-polyvinyl pyrrolidone macrocapsules, or IPCs in calcium alginate, resulted in the restoration of normoglycaemia without immunorejection (Chandra et al., 2009; Kadam et al., 2010) in diabetic rats

2.2.6 Co-transplantation of stem cells and IPCs

Allogeneic islet/IPC transplantation is an efficient method for maintaining normal glucose levels and for the treatment of diabetes mellitus. However, limited sources of islets/IPCs, high rates of islet/IPC graft failure and the need for long-term immunosuppression are major obstacles to the widespread application of these therapies. To overcome these problems, co-transplantation of pancreatic islets/IPCs and adult stem cells is considered as a potential target for the near future. In fact, new results suggest that co-transplantation of stem/precursor cells, particularly MSCs, and islets/IPCs promotes tissue engraftment and beta cell/IPC survival. This theory proposes that stem cells also act as "feeder" cells for the islets, supporting graft protection, tissue revascularisation, and immune acceptance (Sordi et al., 2010).

Overcoming the loss of islet mass is important for successful islet transplantation. Adipose tissue-derived stem cells (ADSCs; referred to as MSCs by some authors) have angiogenic and anti-inflammatory properties. Co-transplantation of ADSCs and islets into mice promotes survival, improves insulin secretion by the graft, and reduces the islet mass required for treatment (Ohmura et al., 2010). In another study, MSCs derived from adipose tissue were differentiated into IPCs and co-transplanted with cultured bone marrow cells into 11 diabetic patients (7 male, 4 female; disease duration, 1–24 years; age range, 13–43 years). Their mean exogenous insulin requirements were 1.14 units/kg BW/day, the mean glycosylated haemoglobin (Hb1Ac) level was 8.47%, and the mean c-peptide level was 0.1 ng/mL. All the patients received successful transplants and the mean follow-up period was 23 months. The results showed a decreased mean exogenous insulin requirement of 0.63 units/kgBW/day, a reduced Hb1Ac of 7.39%, and raised serum c-peptide levels (0.38 ng/mL). The patients reported no diabetic ketoacidosis events and a mean weight gain of 2.5 kg on a normal vegetarian diet and physical activity (Vanikar et al., 2010). However, a previous report indicated that similar results were obtained with undifferentiated MSC-derived adipose tissue co-transplanted with cultured bone marrow. In this study, human adipose tissue-derived MSCs were transfused along with unfractionated cultured bone marrow into five insulinopenic diabetic patients (2 male, 3 female; age range, 14–28 years; disease duration, 0.6 to 10 years) being treated with human insulin (14–70 U/d). The patients had postprandial blood sugar levels between 156 and 470 mg%, Hb1Ac levels of 6.8% to 9.9%, and c-peptide levels of 0.02 to 0.2 ng/mL. After successful transplantation, all patients showed a 30% to 50% reduction in their insulin requirements along with a 4–26-fold increase in serum c-peptide levels during a mean follow-up period of 2.9 months (Trivedi et al., 2008).

After transplantation, MSCs appear to play an immunomodulatory role, thereby promoting graft acceptance. In a cynomolgus monkey model, allogeneic MSCs were co-transplanted with islets intra-portal on postoperative Day 0 and intravenously with donor marrow on postoperative Days 5 and 11. Increased co-transplantation efficiency was associated with increased numbers of regulatory T-cells in the peripheral blood, indicating that co-transplantation of MSCs and islets may be an important method of enhancing islet engraftment and, thereby, decreasing the number of islets required (Berman et al., 2010). Co-transplantation may also downregulate the production of pro-inflammatory cytokines. These results also suggest that MSCs may prevent acute rejection and improve graft function after portal vein pancreatic islet transplantation (Longoni et al., 2010), or that they may induce haematopoietic chimerism and subsequent immune tolerance without causing graft-versus-host disease (Itakura et al., 2007). Moreover, MSC-stimulated graft vascularisation and improved islet graft function are both associated with co-transplanted islets (Figliuzzi et al. 2009; Ito et al. 2010). In addition, interleukin (IL)-6, IL-8, vascular endothelial growth factor-A, hepatocyte growth factor, and transforming growth factor-beta were detected at significant levels in MSC culture medium. These are trophic factors secreted by human MSCs that enhance the survival and function of the islets after transplantation (Park et al., 2010).

3. Islet regeneration by immune correction

There is increasing evidence suggesting that both autoimmune and autoinflammatory mechanisms are involved in the development of type 1 and type-2 diabetes mellitus. Type 1 diabetes mellitus is currently treated with anti-inflammatory drugs and immunosuppressive and immunomodulatory agents. However, despite their profound effects on immune

responses, these drugs do not induce clinically significant remission in certain patients. In recent years, stem cells have come to be regarded as the best treatment for autoimmune disorders, including type 1 diabetes mellitus.

In a phase 1/2 study of autologous non-myeloablative haematopoietic stem cell (HSC) transplantation, C-peptide levels were detected in 23 type 1 diabetes mellitus patients (age range, 13–31 years). During a 7–58 month follow-up (mean, 29.8 months; median, 30 months), 20/23 patients with no previous history of ketoacidosis and not receiving corticosteroids were found to be insulin free. Twelve patients maintained normal blood glucose levels for up to 31 months (range, 14–52 months). Eight patients suffered a relapse and resumed insulin injections at a lower dose (0.1–0.3 IU/kg). No mortality was reported. Thus, C-peptide levels increased significantly and the majority of patients achieved insulin independence with good glycemic control (Couri et al., 2009).

In another study, bone marrow from *gfp* transgenic mice was isolated and transplanted into diabetic mice. Repair of diabetic islets was evidenced by a reduction in hyperglycaemia, an increase in the number of islets, and altered pancreatic histology. Transplanted cells in the recipient pancreases expressed CD34 (an HSC marker), but not *insulin*, *PDX-1*, *Ngn3*, *Nkx2.2*, *Nkx6.1*, *Pax4*, *Pax6*, or CD45. It was concluded that BM-derived cells, especially HSCs, were able to repair islets by stimulating the proliferation of beta cells and the differentiation of pancreatic stem cells; however, they could not differentiate into beta cells or IPCs (Gao et al., 2008). Chamson-Reig et al. (2010) used a *Vav-iCre* double transgenic mouse model to investigate the use of HSC transplantation for the treatment of type 1 diabetes mellitus. Only haemopoietic lineage cells expressed the *Vav1* gene promoter, evidenced by expression of a *R26R*-enhanced yellow fluorescent protein (YFP) reporter gene. Between postnatal Days 2 and 4, mice were injected with either STZ or vehicle (control). Mice were sacrificed between Days 10 and 130 and the pancreases examined by immunofluorescence microscopy. The results showed that approximately 30% of YFP-positive cells within the islets co-stained for the endothelial cell marker, CD31. The number of haemopoietic-derived cells and the proportion of CD31-positive cells significantly increased 21 and 40 days after STZ treatment respectively. This indicates that haemopoietic lineage cells promote intra-islet angiogenesis following beta cell loss due to STZ treatment, which supports a partial recovery of the islets (Chamson-Reig et al., 2010). Huang et al. (2010) demonstrated that the role of bone marrow transplantation was to supply a source of very small embryonic-like cells that exist in the bone marrow without the need for HSCs. The authors concluded that these very small embryonic-like cells mobilise to the injured pancreatic tissue and contribute to beta cell regeneration after bone marrow transplantation (Huang et al., 2010).

The initial results of some studies investigating the treatment of type 2 diabetes mellitus show that transplantation of stem cells produces good results. Intra-bone marrow-bone marrow transplantation plus thymus transplantation can be used to treat type 2 diabetes mellitus by normalising the T cell imbalance. Recipient *db/db* mice showed increases in body weight, reduced blood glucose levels, and a reduction in plasma IL-6 and IL-1 β levels 7 weeks after transplantation. More importantly, treatment resulted in the restoration of normal CD4/CD8 ratios, increased plasma adiponectin levels, improved insulin sensitivity, and an increase in the number of insulin-producing cells. Furthermore, expression of pancreatic pAKT, pLKB1, pAMPK and HO-1 increased after transplantation. In short, this treatment normalises T cell subsets, and restores cytokine balance and insulin sensitivity in the *db/db* mouse model (Li et al. 2010).

The results from some preclinical or clinical trials to treat type 1 and type 2 diabetes were summarized in Table 1.

Species	Diabetic	Kind of Stem cell/IPCs	Transplantation methods	Auto/Allo/Xenograft	Immunosuppression	Effects	References
Mouse	1;STZ	MSC (Human endometrium)	N/A	Xeno	Yes	Restore blood glucose levels	Li et al., 2010
Rat	1;STZ	Proliferating islet Cells (Rat)	Portal vein	Allo	None	Restore euglycemia, weight gain for up to 130 days	Li et al., 2010
Mouse	NOD	MSCs (BM)	Tail vein	Allo	None	Long-term reversal of hyperglycemia (reduce blood glucose from week 2-12)	Jurewicz et al., 2010
Rat	1;STZ	Pancreatic stem cell (Human fetal pancreatic tissues)	Kidney capsule	Xeno	None	Reduce blood glucose levels; prolong the life time	Xiao et al., 2008
Rat	1;STZ	MSCs (BM)	Tail vein	Allo	None	Reduce blood glucose level up to 45 days	Dong et al., 2008
Dog	1;STZ	Insulin expressing- MSCs (dog bone)	Liver	Auto	None	Reversal of hyperglycemia for up to 16 week	Zhu et al., 2009
Mouse	1;STZ	MSCs + Islets	Kidney capsule	Syngenic	None	92% of mice reverting to normoglycaemia, (42% islets alone) after 1 month	Rackham et al., 2011
Rat		MSCs + Islets	Kidney capsule	Syngenic	None	Normoglycemia maintained until killing	Figliuzzi et al., 2009
Mouse	NOD SCID	MSCs + Islets	Renal capsule	Allo	None	Reversed diabetes in 8/8; (3/10 in control)	Ito et al., 2010
Rat	1;STZ	BM-MSC	Kidney capsule	Allo	None	Increasing beta-cell mass	Lin et al., 2009
Mouse	1;STZ	ESCs	Kidney capsule	Allo	None	Beta cell neogenesis occurred between 2 to 3 weeks	Kodama et al., 2009

Table 1. The results of some preclinical and clinical experiment about treating diabetes type 1 & 2 by stem cell/IPCs transplantation.

4. Conclusion

Taking into account all the currently available results (Table 1), we can expect that diabetes mellitus will be successfully treated using stem cell therapy in the near future. However, questions regarding the survival of the cells after grafting and improvements in the vitality and maintenance of cellular function after transplantation remain to be answered. On the basis of evidence supporting the many advantages of bone marrow transplantation, umbilical cord blood transplantation, and HSC therapy for blood-related diseases, the strategy of HSC/BM/UCB may produce several positive results in the coming years and become the treatment of choice for both type 1 and type 2 diabetes mellitus. Although more difficult, ESCs or adult stem cell-derived IPC transplantation are also important treatments for diabetes mellitus, especially when HSCs are in short supply.

5. References

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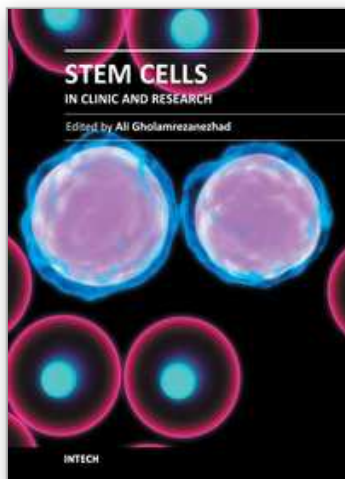
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Based on our current understanding of cell biology and strong supporting evidence from previous experiences, different types of human stem cell populations are capable of undergoing differentiation or trans-differentiation into functionally and biologically active cells for use in therapeutic purposes. So far, progress regarding the use of both in vitro and in vivo regenerative medicine models already offers hope for the application of different types of stem cells as a powerful new therapeutic option to treat different diseases that were previously considered to be untreatable. Remarkable achievements in cell biology resulting in the isolation and characterization of various stem cells and progenitor cells has increased the expectation for the development of a new approach to the treatment of genetic and developmental human diseases. Due to the fact that currently stem cells and umbilical cord banks are so strictly defined and available, it seems that this mission is investigational more practical than in the past. On the other hand, studies performed on stem cells, targeting their conversion into functionally mature tissue, are not necessarily seeking to result in the clinical application of the differentiated cells; In fact, still one of the important goals of these studies is to get acquainted with the natural process of development of mature cells from their immature progenitors during the embryonic period onwards, which can produce valuable results as knowledge of the developmental processes during embryogenesis. For example, the cellular and molecular mechanisms leading to mature and adult cells developmental abnormalities are relatively unknown. This lack of understanding stems from the lack of a good model system to study cell development and differentiation. Hence, the knowledge reached through these studies can prove to be a breakthrough in preventing developmental disorders. Meanwhile, many researchers conduct these studies to understand the molecular and cellular basis of cancer development. The fact that cancer is one of the leading causes of death throughout the world, highlights the importance of these researches in the fields of biology and medicine.

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