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The Role of Mesenchymal Stem Cells in Diabetes Mellitus

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Abstract

Diabetes mellitus is a disease characterized by progressive destruction of the beta cells in the pancreatic islets of Langerhans. The current primary treatment is changing the life style and insulin injection. However, this therapy cannot provide sustained physiological glycemic control. Pancreas or islet cell transplantation would be the preferred treatment options. However, the lack of donor tissue immunoincompatibility, cell rejection and using long term immunosuppression are the major barriers to their widespread use.

Mesenchymal stem cells (MSC) hold promising therapy in regenerative medicine. MSCs are residing many adult and fetal tissue such as in the bone marrow, adipose tissue, umbilical cord blood, and Wharton jelly of the umbilical cord. MSCs, with self-renewal capacity and transdifferentiation potential are an attractive unlimited cell source for treating diabetic patients. On the other hand, MSCs have well characterized immunomodulatory properties that can suppress inflammatory damage and immune-mediated rejection and by secreting paracrine factors and deposition of the extracellular matrix improve the engraftment of pancreatic islets in micro-environmental niche. Here, we review the properties of MSCs and some of the recent clinical studies using MSCs as a new therapeutic option in the treatment of diabetic patients.

Keywords

Diabetes, Insulin, Beta cell, Stem cell, Islet

Introduction

Diabetes has become one of the most common chronic diseases in the world. The prevalence of diabetes was globally estimated to be 4.4% in 2030 and the total number of patients will be increased to 366 million [1].

Type 2 diabetes mellitus (T2DM) comprises 90% of all causes of diabetes and is characterized by a combination of peripheral insulin resistance and progressive beta-cell dysfunction. The routine treatments for T2DM include insulin sensitizers with exogenous insulin supply, but these drugs temporarily ameliorate hyperglycemia, and ultimately progressive beta cell dysfunction happens [2].

Type 1 diabetes mellitus (T1DM) comprises 10% of all causes of diabetes and is characterized by T cell-mediated destruction of insulin-producing cells in the pancreatic islets [1] during childhood. This autoimmune process (insulitis) is mainly mediated by CD4+ cells, CD8+ T cells, as well as proinflammatory cytokines, such as interleukin (IL)-2 and tumor necrosis factor (TNF)-a [3]. The patients are usually treated with exogenous insulin therapy. Nevertheless, a good metabolic control is not feasible and episodes of hypoglycemia and hyperglycemia frequently happen. Tight glycemic control is very important in diabetic patients [4]. But unfortunately, even with improved insulin formulations, the use of new infusion systems as well as continuous glucose monitoring, keeping tight control in the normal range is not possible. Therefore, chronic small vessel complications, such as retinopathy, nephropathy, and neuropathy occur [4,5].

Whole pancreas transplantation is another option for treatment, but it is associated with several limitations, such as major surgery, shortage of donors and organ rejection after transplantation. Islet cell transplantation is an alternative non invasive procedure in which the insulin secreting cells have physiological responses to the blood glucose levels [6]. The Edmonton group in 2000 established the "Edmonton Protocol" and demonstrated sustained long-term insulin-independence [6,7]. The islet cells are isolated from cadaveric donors [7,8], and injected into the recipient's portal vein. Instant blood-mediated inflammatory reactions, alloimmune reaction to transplanted cells and diabetogenic effect of immunosuppressive drugs reduced the initial beta cell mass and many patients require repeated episodes of cell transplantation [7,9].

Due to these limitations, the implantation of stem cells from embryonic or adult sources may be another potential treatment for diabetes [10,11]. Stem cells are characterized by their potential of self-renewal and multilineage differentiation. Therefore, they represent an alternative and unlimited source for differentiation toward islet cells.

Cell sources for generation of insulin producing cells (IPCs)

Previous *in vitro* studies showed that different types of stem cells such as embryonic stem cells [ESCs] [12], induced pleuripotent stem cells (iPS) [13], and mesenchymal stem cells (MSCs) [14] had been successfully differentiated into insulin-producing cells.

For differentiation of cells toward insulin producing cells, it is essential to pay attention to the native process of islets generation; and, the embryonic stem cell (ESC) differentiation protocols are

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useful models for understanding the molecular mechanism [15-17]. In this way, after establishment of pancreatic endoderm, inhibition of Notch signaling leads to further endocrine differentiation and, subsequently, maturation of endocrine precursors toward specialized insulin-producing cells occurs [18].

Nuclear reprogramming of adult somatic tissue leads to generation of autologous and patient-specific induced pluripotent stem (iPS) cells [13,19]. Differentiation of the skin fibroblast derived iPS cells toward insulin-producing islet-like clusters has been investigated. This cluster showed C-peptide and insulin expression, but the level of C-peptide secretion was lower compared with adult human islets. It was proposed that this low efficacy is in relation to differentiation procedure [20]. The generation of glucose responsive and functional islets requires silencing of stemness programs as well as the induction of stage specific transcription factors [21].

Routine differentiation protocols directing ESCs or iPS toward islets needs a variety of expensive cytokines and inhibitors. Due to the significance of microRNAs [miR] in islet development, such as miR-375 and Mir-7, their overexpression promotes pancreatic endocrine differentiation [22-24].

Different sources of MSCs, such as the umbilical cord blood, bone marrow and human pancreatic islet, have been investigated for differentiation to β-cells [25-27]. Wharton' jelly MSCs can be an important source for pancreatic islets generation due to possession of stem cell properties and easy achievement without ethical problems compared with embryonic and bone marrow stem cells. Transformation of Wharton' jelly MSCs into the islet-like cell clusters by neuron-conditioned medium has been analyzed. These clusters demonstrated insulin release and functional stability *in vivo* [28]. The researchers transfected MSCs by Pdx1 mRNA and induced them to differentiate by soluble factors. Strong expression of β-cells specific genes, Pdx1, Ngn3, Nkx6, and insulin, and the production of C-peptide and insulin were observed. The results of this study showed that induction of cells after transfection exhibits a better differentiation outcome than induction alone [29].

Generation of pancreatic islets from pancreatic progenitor cells has been also reported [30]. There are controversial studies about the existence of pancreatic progenitor cells [31]. It is speculated that progenitor cells are located within the basement membrane of common pancreatic ducts and they have the potential to differentiate and secrete insulin [30,31]. The differentiation of pancreatic progenitor cells derived from human fetal tissues was done by co-culture with liver stromal cells, devoid of growth factors. The examination of produced cells revealed the expression of important markers and functionality of the cells [32].

Mesenchymal Stem Cell with Dual Magic Function

MSCs are multi-potent, self-renewing cells that are isolated from different tissues, such as the bone marrow, adipose tissue [33], amniotic fluid [34], and umbilical cord blood [35]. The cells have a great multiplication potency and can be expanded in culture for several passages without losing their properties [36]. The International Society for Cellular Therapy has introduced criteria for defining these cells. MSCs adhere to plastic in culture plates and express cell surface markers, such as CD105, CD73, and CD90 and do not express CD45, CD34, CD14 or CD11b, CD79a, or CD19 and HLADR [37,38]. MSCs have been characterized for their ability to differentiate toward osteoblasts, adipocytes, and chondrocytes [39]. However, MSCs have also differentiated into endodermal and ectodermal lineages, including neural cells [40], hepatocytes [41], and insulin-producing cells [42].

Besides their differentiation potential toward insulin producing cells, MSCs contributed to repair processes through the secretion of pro-angiogenic molecules and formation of new blood vessels [43]. MSCs have well known unique immunomodulatory properties on T cells, B cells, dendritic cells and NK cells. The cells affect the role of regulatory T cells and autoreactive T cells by secreting several regulatory cytokines, such as IFN-γ, TGF-β, IL-4 and IL-10 [44].

MSCs also have an anti-inflammatory effect which is important in maintaining peripheral tolerance [45]. The cells express intermediate levels of MHC class I molecules but not the MHC class II which is important for rejection. Therefore, cell implantation across MHC barriers is possible. After cellular injury, these cells are able to migrate and settle in the injured tissues after systemic intravenous delivery [46].

After intravenous injection and migration to damaged tissues local over-expression of chemokines such as VCAM-1, SDF, MCP-1, CX3CL1-CX3CR1 and CXCL12-CXCR4 has been documented [47,48]. It seems that transplanted MSCs change the tissue microenvironment that supports the survival of damaged cell and inhibit the immune responses that accelerate the regeneration of homing recipient cells [47,48].

According to their immunomodulatory capacity, MSCs have been tried in clinical trials in treatment of steroid-refractory acute GVHD [49,50] and autoimmune diseases, such as multiple sclerosis, systemic lupus erythematosus [51] Crohn's disease [52] and Diabetes type 1 [53]. The results of these human trial revealed that repeated infusion of MSCs is safe and effective for treatment of at least a percentage of patients [54].

The immunomodulatory properties and paracrine effect of MScs on regeneration of resident beta cells was confirmed in differerent animal studies [55-57]. In diabetic patients.

In clinical trial database (http://www.clinicaltrials.gov) by April 2014, 28 human trials using MSC for diabetic patients were documented. In 8 projects, the trial was conducted on type 2 diabetic patients and in 20 studies, MSCs was transplantated to T1DM patients. The efficacy of these cells was also evaluated on chronic diabetic complications, such as diabetic foot. The MSCs were derived from the umbilical cord, outologous bone marrow and Prochymal Commercial drug [58-65].

The results of published clinical trials on stem cell transplantation in both diabetes type 1 and type 2 is summarized in table 1.

In an ongoing study, 21 patients with T1DM received outologous umbilical MSC infusions through the pancreatic artery. They believed that MSCs may change the local environment that promotes beta cell regeneration. They found that outologous UCB infusion was safe but failed to preserve C-peptide for a long time [58].

In another project, Hu et al. evaluated the long-term effects of the Wharton's jelly-derived MSCs on 29 patients with newly onset T1DM. The authors found that this treatment can restore the function of islet cells over a longer time [59].

The efficacy of autologous bone marrow mononuclear cells in the treatment of type 2 diabetes mellitus was also evaluated by this group and suggested that the implantation of autologous bone marrow mononuclear cells was safe and effective [60].

Mesples and co-workers used co-transplantation of MSCs and outologous HSCs stem cells in three T1DM patients. The bone marrow derived mononuclear cells were directly injected into the patient's liver paranchyma. During a long term follow-up, a significant increase in pancreatic secretion of C-peptide was documented [61]. In another clinical trial, twenty adult patients with newly diagnosed type 1 diabetes received MSC treatment. Residual β-cell function was analyzed with C-peptide in response to a mixed-meal tolerance test (MMTT). They found that autologous MSC treatment can contribute to the disease progression and preserve islet cell function [62].

Kong and colleagues used the umbilical cord derived MSCs for 18 patients with type 2 diabetes mellitus. The cells were transfused intravenously. They concluded that the umbilical cord derived MSCs transfusion was safe and it effectively alleviated blood glucose, and the C-peptide level was increased [63]. Another study was performed to evaluate the effect of combined autologous skin fibroblasts on biodegradable collagen membrane (Coladerm) in combination with outologous bone marrow derived mesenchymal stem cells for treatment of chronic non-healing wound in diabetic patients. They found that the wound size decreased and the vascularity of the

Table 1: Clinical trials of MSC therapy for diabetes

	Type of Diabetes	Type of transplanted cells	Follow-up	Outcome	Reference
1	Newly diagnosed T1DM (n=20) NCT01068951	Autologous MSC	blood C-peptide level in response to a mixed-meal tolerance test (MMTT) during 1-year follow-up	preserved or even increased C-peptide peak value in TX group loss in both C-peptide peak values in control group	[62]
2	Newly onset T1DM (n=29)	Wharton's jelly-derived mesenchymal stem cells	both the HbA1c and C peptide level during next 21 months	Better level of both HbA1c and C peptide	[59]
3	T1DM (n=15)	Autologous umbilical cord blood infusion followed by 1 year of supplementation with vitamin D and docosahexaenoic acid	C-peptide level; CD4/CD8 ratio	The absolute rate of C-peptide decline was slower in treated subjects but failed to reach significance. CD4/CD8 ratio remained stable in treated subjects.	[58]
4	T1DM (n=3)	Autologous bone marrow stem cell (liver puncture)	HbA1c ,c-peptide level, Islets Cells Antibody (ICA), Glutamic Acid Decarboxylase (GAD) and insulin antibody	In two treated patients: negative value in ICA, GAD and anti insulin antibody levels, with an increased levels of c peptide and decreased levels of HbA1c.	[61]
5	T1DM (n=15); median diabetic history was 8 years	Stem Cell Educator (Separated lymphocytes from the peripheral whole blood co-cultured with adherent cord blood-derived multipotent stem cells. returned to the patient's circulation	Blood C-peptide, HbA1c, daily dose of insulin. Immunological monitoring during 40 weeks	markedly improve C-peptide levels, reduce the HbA1C values, decrease the daily dose of insulin increased expression of co-stimulating molecules (CD28 and ICOS), increases in the number of CD4+CD25+Foxp3+ Tregs, and restoration of Th1/Th2/Th3 cytokine balance	[66]
6	T1DM (n=15) NCT00315133	Autologous nonmyeloablative hematopoietic stem cell transplantation	Decrease in insulin requirement	became insulin free with normal levels of glycated hemoglobin A(1c) (HbA(1c)) during a mean 18.8-month follow-up	[67]
7	T1DM NCT00690066	PROCHYMAL® (Ex Vivo Cultured Adult human mesenchymal stem cells)	both the HbA1c and C peptide level	The study is Finished in 2014 but the data is not published	https:// clinicaltrials.gov
8	T2DM (n=18)	Umbilical cord MSC	FPG, PBG, HbA1c, C-peptide, and Treg were followed up in the first, third, and sixth month	FBG and PBG of the patients in TX group were significantly reduced. Plasma C-peptide levels and Treg cell number in the TXgroup were numerically higher but did not reach significance ($p > 0.05$).	[63]
9	T2DM with triple oral antidiabetic drug failure and requiring insulin ≥0.4 IU per kg per day (n=21)	Autologous bone marrow-derived stem cell	End point: a reduction in insulin requirement by ≥50% from baseline while maintaining HbA1c <7% 12 months	significant decrease in the insulin dose requirement along with an improvement in the stimulated C-peptide levels	[68]
10	T2DM with failure of triple oral antidiabetic drugs, and on insulin (>0.7 U/kg/day) (n=10)	Autologous bone marrow-derived stem cell	Decrease in insulin requirement by ≥50%	Significant reduction in insulin requirement (60% of patients), significant improvement in glucagon-stimulated C-peptide level	[69]
11	Diabetic patients with critical limb ischaemia (n=7)	Autologous mesenchymal stem cells (MSCs), from granulocyte-colony-stimulating factor (G-CSF)-mobilised peripheral blood	neurological signs, wound healing and the rate of lower-limb amputation	Pain was significantly reduced; ankle-brachial index and the pulse strength were significantly improved; , lower limb amputation	[70]
12	T2DM (n=118)	Autologous bone marrow mononuclear cells (injected into the patient's pancreas)	HbA1c and C-peptide level	HbA1c and C-peptide in TX group were significantly improved	[60]
13	T2D (n=10)	human placenta-derived MSC		Decreased daily mean dose of insulin Increased –peptide level, renal function and cardiac function were improved	[71]
14	T2D critical limb ischemia and foot ulcer **(n=41)**	Bonemarrow mesenchymal stem cells (BMMS), Bonemarrow-derived mononuclear cells	improvements in limb perfusion	painless walking time ;ankle-brachial index, transcutaneous oxygen pressure were more improved in BMMS group	[72]
15	T2DM for >5 years with failure of triple oral antidiabetic drugs, and on insulin (> or = 0.7 U/ kg/day) (n=10)	Autologous bone marrow-derived stem cell	End point: a reduction in insulin requirement by ≥50% from baseline and improvement in glucagon-stimulated C-peptide levels	Significant reduction in insulin requirement, significant improvement in both fasting and glucagon-stimulated C-peptide level	[73]

T2DM: Type 2 Diabetes Mellitus; T1DM: Type 1 Diabetes Mellitus; FPG: Fasting Plasma Glucose; PBG: Postprandial Blood Glucose; regulatory T cells: Treg; Treated Group: TX group; HbA1C: Glycated Hemoglobin A1C

dermis increased [64]. Dave and colleagues conducted another study on 10 insulin dependent diabetic patients with co-infusion of *in vitro* autologous adipose tissue-derived MSC-differentiated insulin-secreting cells (ISC) with hematopoietic stem cells (HSC). The results were promising and they suggested that this combination therapy offered a better long term control of hyperglycemia in patients [65].

Overall, in T1DM, the authors claimed that MSC therapy was safe and promising tool to intervene in disease progression and preserve function of β-cell. In type 2 diabetic patients MSC therapy was well tolerated, and this strategy effectively alleviated blood glucose level. In diabetic patients with critical limb ischemia, MSC therapy, accelerated the wound healing processes and decreased the rate of lower limb amputation [58-72].

In conclusion, the combination of immunomodulatory activity and tissue regenerative potential of MSCs as well as their differentiation capacity to islet like cells has attracted significant scientific and clinical interest.

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