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Transplantation of placenta-derived mesenchymal stem cells in type 2 diabetes: a pilot study.

Jiang R, Han Z, Zhuo G, Qu X, Li X, Wang X, Shao Y, Yang S, Han ZC.

Source

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Abstract

Mesenchymal stem cells (MSC) have been used in clinical trials for severe diabetes, a chronic disease with high morbidity and mortality. Bone marrow is the traditional source of human MSC, but human term placenta appears to be an alternative and more readily available source. Here, the therapeutic effect of human placenta-derived MSC (PD-MSC) was studied in type 2 diabetes patients with longer duration, islet cell dysfunction, high insulin doses as well as poor glycemic control in order to evaluate the safety, efficacy and feasibility of PDMSC treatment in type 2 diabetes (T2D). Ten patients with T2D received three intravenous infusions of PDSC, with one month interval of infusion. The total number of PDSC for each patient was (1.22-1.51) × 10(6)/kg, with an average of 1.35 × 10(6)/kg. All of the patients were followed up after therapy for at least 3 months. A daily mean dose of insulin used in 10 patients was decreased from 63.7±18.7 to 34.7±13.4 IU (P<0.01), and the C-peptide level was increased from 4.1 ±3.7 ng/mL to 5.6 ±3.8 ng/mL (P<0.05) respectively after therapy. In 4 of 10 responders their insulin doses reduced more than 50% after infusion. The mean levels of insulin and C-peptide at each time point in a total of 10 patients was higher after treatment (P<0.05). No fever, chills, liver damage and other side effects were reported. The renal function and cardiac function were improved after infusion. The results obtained from this pilot clinical trial indicate that transplantation of PD-MSC represents a simple, safe and effective therapeutic approach for T2D patients with islet cell dysfunction. Further large-scale, randomized and well-controlled clinical studies will be required to substantiate these observations.

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Placental Growth Factor Contributes to Micro-Vascular Abnormalization and Blood-Retinal Barrier Breakdown in Diabetic Retinopathy

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Abstract Objective

There are controversies regarding the pro-angiogenic activity of placental growth factor (PGF) in diabetic retinopathy (DR). For a better understanding of its role on the retina, we have evaluated the effect of a sustained PGF over-expression in rat ocular media, using ciliary muscle electrotransfer (ET) of a plasmid encoding rat PGF-1 (pVAX2-rPGF-1).

Conclusion: This is the first demonstration that sustained intraocular PGF production induces vascular and retinal changes similar to those observed in the early stages of diabetic retinopathy. PGF and its receptor Flt-1 may therefore be looked upon as a potential regulatory target at this stage of the disease.

Abstract

Placental tissue holds great promise as a source of cells for regenerative medicine due to its plasticity, and easy availability. Human placenta-derived mesenchymal stem cells (hPDMSCs) have the potential to differentiate into insulin-producing cells. Upon transplantation, they can reverse experimental diabetes in mice. However, it is not known whether culture-expanded undifferentiated hPDMSCs are capable of restoring normoglycemia upon transplantation in streptozotocin (STZ)-induced diabetic mice. Hence we prepared long-term cultures of hPDMSCs from the chorionic villi of full-term human placenta. Flow cytometry analyses and immunocytochemistry study revealed bonafide mesenchymal nature of the isolated hPDMSCs. These cultures could differentiate into adipogenic, oesteogenic, chondrogenic, and neuronal lineages on exposure to lineage-specific cocktails. Furthermore, we showed that hPDMSCs can form islet-like cell clusters (ILCs) on stepwise exposure to serum-free defined media containing specific growth factors and differentiating agents. qRT-PCR showed the expression of insulin, glucagon, and somatostatin in undifferentiated hPDMSCs and in ILCs. Differentiated ILCs were found to express human insulin, glucagon, and somatostatin by immunocytochemistry. Additionally, ILCs also showed abundance of pancreatic transcription factors ngn3 and isl1. Both undifferentiated hPDMSCs and ILCs exihibited insulin secretion in response to glucose. Transplantation of hPDMSCs or ILCs derived from hPDMSCs in STZ-induced diabetic mice led to restoration of normoglycemia. Our results demonstrate, for the first time, reversal of hyperglycemia by undifferentiated hPDMSCs and ILCs derived from hPDMSCs. These results suggest human placenta-derived MSCs as an alternative source for cell replacement therapy in diabetes.

Keywords: human placenta-derived stem cell, diabetes, mesenchymal stem cell, transplant, beta-cell, islet, differentiation, macrocapsule, immunoisolation

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[Age-related features of immunocompetent cells of human placenta associated with diabetes mellitus].

[Article in Russian]

Durnova AO, Poliakova VO, Pal'chenko NA.

Abstract

The immune-competent cells of placenta play the important role in protection of developing fetus against infectious agents; but their dysfunction can lead to development of placental insufficiency that affects health both fetus and mother. The aim of this study was the comparative analysis of presence of immune competent cells in villous chorion of mature placenta, taken from women with diabetes of different age groups. In our study we found three subpopulations of immune cells in villous chorion of mature placenta: natural killer cells (NK), B-lymphocytes and macrophages. Prevailing subpopulation are macrophages, they are detected 1,8 times more often than B-lymphocytes, and 2,3 times more often than NK. The quantity of immune competent cells in groups with diabetes of various types is different. Thus, the greatest number of macrophages was detected in group with diabetes type II of middle age (29-35 years)-- 4.62 +/- 0.93%, B-lymphocytes in group of women with diabetes type I of younger age (18-28 years)--2.50 +/- 0.30%, NK-cells in group with diabetes type I of younger age--1.98 +/- 0,42%. Analysis of received data showed the differences in expression of markers of

immune cells in women of different age groups, which brings about the conclusion of various reactance of immune system of women with diabetes depending on age.

PMID:

21033374

[PubMed - indexed for MEDLINE]

Abstract

Placental tissue holds great promise as a source of cells for regenerative medicine due to its plasticity, and easy availability. Human placenta-derived mesenchymal stem cells (hPDMSCs) have the potential to differentiate into insulin-producing cells. Upon transplantation, they can reverse experimental diabetes in mice. However, it is not known whether culture-expanded undifferentiated hPDMSCs are capable of restoring normoglycemia upon transplantation in streptozotocin (STZ)-induced diabetic mice. Hence we prepared long-term cultures of hPDMSCs from the chorionic villi of full-term human placenta. Flow cytometry analyses and immunocytochemistry study revealed bonafide mesenchymal nature of the isolated hPDMSCs. These cultures could differentiate into adipogenic, oesteogenic, chondrogenic, and neuronal lineages on exposure to lineage-specific cocktails. Furthermore, we showed that hPDMSCs can form islet-like cell clusters (ILCs) on stepwise exposure to serum-free defined media containing specific growth factors and differentiating agents. qRT-PCR showed the expression of insulin, glucagon, and somatostatin in undifferentiated hPDMSCs and in ILCs. Differentiated ILCs were found to express human insulin, glucagon, and somatostatin by immunocytochemistry. Additionally, ILCs also showed abundance of pancreatic transcription factors ngn3 and isl1. Both undifferentiated hPDMSCs and ILCs exihibited insulin secretion in response to glucose. Transplantation of hPDMSCs or ILCs derived from hPDMSCs in STZ-induced diabetic mice led to restoration of normoglycemia. Our results demonstrate, for the first time, reversal of hyperglycemia by undifferentiated hPDMSCs and ILCs derived from hPDMSCs. These results suggest human placenta-derived MSCs as an alternative source for cell replacement therapy in diabetes.

Keywords: human placenta-derived stem cell, diabetes, mesenchymal stem cell, transplant, beta-cell, islet, differentiation, macrocapsule, immunoisolation

J Cell Mol Med. 2011 Mar;15(3):612-24. doi: 10.1111/j.1582-4934.2010.01034.x.

MafA promotes the reprogramming of placenta-derived multipotent stem cells into pancreatic islets-like and insulin+ cells.

Chiou SH, Chen SJ, Chang YL, Chen YC, Li HY, Chen DT, Wang HH, Chang CM, Chen YJ, Ku HH.

Source

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Abstract

MafA is a pancreatic transcriptional factor that controls β-cell-specific transcription of the insulin gene. However, the role of MafA in the regulation of pancreatic transdifferentiation and reprogramming in human stem cells is still unclear. In this study, we investigate the role of MafA in placenta-derived multipotent stem cells (PDMSCs) that constitutively expressed Oct-4 and Nanog. PDMSCs were isolated and transfected with MafA using a lentivector. Our results showed that overexpression of MafA in PDMSCs significantly up-regulated the expression of pancreatic development-related genes (Sox17, Foxa2, Pdx1 and Ngn3). Microarray analysis suggested that the gene expression profile of MafA-overexpressing PDMSCs was similar to that of pancreas and islet tissues. MafA increased the expression levels of the mRNAs of NKx2.2, Glut2, insulin, glucagons and

somatostatin, and further facilitated the differentiation of PDMSCs into insulin(+) cells. The glucose-stimulated responses to insulin and c-peptide production in MafA-overexpressing PDMSCs were significantly higher than in PDMSCs with vector control. Our results indicated that MafA-overexpressing PDMSCs were more resistant to oxidative damage and oxidative damage-induced apoptosis than PDMSCs carrying the vector control were. Importantly, the expression of MafA in PDMSCs xenotransplanted into immunocompromised mice improved the restoration of blood insulin levels to control values and greatly prolonged the survival of graft cells in immunocompromised mice with STZ-induced diabetes. In summary, these data suggest that MafA plays a novel role in the reprogramming of stem cells into pancreatic β-progenitors, promotes the islet-like characteristics of PDMSCs, as well as functionally enhances insulin production to restore the regulation of blood glucose levels in transplanted grafts.

PMID:

20158571

[PubMed - indexed for MEDLINE]

J Long Term Eff Med Implants. 2010;20(3):219-50.

Stem cells: a new paradigm in medical therapeutics.

Mankikar SD.

Source

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Abstract

Even though the stem cells have been studied for decades, only during the past few years has there been an overwhelming proliferation of publications covering isolation, cultivation and utilization of the body's master cells. This paper attempts to summarize the recent studies in the field of stem cells. A number of studies have reported the existence of multipotent stem cells in the cord, cord blood, placenta, bone marrow, brain, heart, teeth, skin, liver, hair follicles and many other tissues and organs, giving rise to cell types other than their tissue of origin. Increased therapeutic use of stem cells has resulted in scientific methods of collection, testing, processing and storage of these cells, with minimal cell damage and differentiation. Cell expansion, bioreactors and tissue engineering are employed extensively to improve the cell dose and outcome. Stem cell infusion, transplantation and implantation are accepted curative therapies for many malignant and non-malignant conditions. Stem cell therapies also provide alternative solutions for the repair and regeneration of various tissues and organs. There has been a dramatic improvement in the understanding of immunosuppressive properties of stem cells on various immune cell types. Stem cells are found to secrete angiogenic cytokines that increase neovascularization. They bring the promise of curing a disease state as these cells normally regenerate tissues in a healthy organism. Stem cell transplantation, in isolation or in combination with other procedures, has been found to be effective. Stem cell therapy is also seen as a possible alternative for the treatment of different diseases such as juvenile diabetes, amyotrophic lateral sclerosis, cerebral palsy, stroke, spinal cord injury and Parkinson's disease. Regenerative medicine using human stem cells is one of the new and promising fields for treating various intractable diseases and damaged organs.

PMID:

21395520

[PubMed - indexed for MEDLINE]

Biochem Biophys Res Commun. 2007 Jun 1;357(2):414-20. Epub 2007 Apr 3.

Placenta-derived multipotent stem cells induced to differentiate into insulin-positive cells.

Chang CM, Kao CL, Chang YL, Yang MJ, Chen YC, Sung BL, Tsai TH, Chao KC, Chiou SH, Ku HH.

Source

Department of Obstetrics and Gynecology, Taipei, Taiwan.

Abstract

In the present study, we successfully isolated PDMSCs from human placental tissues. The RT-PCR results show that PDMSCs preserved the genetic characteristics of the primitive embryonic stage--Oct-4 and Nanog. By using serum-free medium supplemented essential growth factors and induction medium culture for 4 weeks, a monolayer of spindle-like PDMSCs gradually formed 3D spheroid bodies (SB-PDMSCs). By using real-time RT-PCR, early mRNA expressions of Pdx1, as well as the Sox17 and Foxa2 genes, were observed to be significantly activated in SB-PDMSCs, followed by the expression of mature pancreas-related genes (insulin, glucagon, and somatostatin). The high insulin content of SB-PDMSCs was further confirmed by ELISA assay, and the glucose dependency was demonstrated by the corresponding insulin secretion level. In a transplantation study of streptozotocin-pretreated nude mice, the restoration of normoglycemia in the SB-PDMSC treated group was further observed. In conclusion, these results indicate that PDMSCs are an excellent source for the induced differentiation of well-functioning insulin-positive cells. The potential of these insulin producing cells derived from PDMSCs was also demonstrated functionally by the demonstration of secreted insulin in vitro and effective control of blood glucose levels in vivo.

PMID:

17433254

[PubMed - indexed for MEDLINE]

Am J Pathol. 2004 February; 164(2): 457–466. PMCID: PMC1602274

Impairment in Ischemia-Induced Neovascularization in Diabetes

Bone Marrow Mononuclear Cell Dysfunction and Therapeutic Potential of Placenta Growth Factor Treatment

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Accepted October 17, 2003.

Other Sections▼

Abstract

Materials and Methods

Results

Discussion

References

Abstract

Mechanisms that hinder ischemia-induced neovascularization in diabetes remain poorly understood. We hypothesized that endogenous bone marrow mononuclear cell (BM-MNC) dysfunction may contribute to the abrogated postischemic revascularization reaction associated with diabetes. We first analyzed the effect of diabetes (streptozotocin, 40 mg/kg) on BM-MNC pro-angiogenic potential in a model of surgically induced hindlimb ischemia. In nondiabetic animals, transplantation of BM-MNCs isolated from nondiabetic animals raised the ischemic/nonischemic angiographic score, capillary number, and blood flow recovery by 1.8-, 2.7-, and 2.2-fold, respectively, over that of PBS-injected nondiabetic animals ($P < 0.05$). Administration of diabetic BM-MNCs also improved the neovascularization reaction in ischemic hindlimbs of nondiabetic mice but to a lesser extent from that observed with nondiabetic BM-MNC transplantation. In diabetic mice, injection of nondiabetic BM-MNCs was still more efficient than that of diabetic BM-MNCs. Such BM-MNC dysfunction was associated with the impairment of diabetic BM-MNC capacity to differentiate into endothelial progenitor cells (EPCs) in vitro and to

participate in vascular-like structure formation in a subcutaneous Matrigel plug. Placenta growth factor (PlGF) administration improved by sixfold the number of EPCs differentiated from diabetic BM-MNCs in vitro and enhanced ischemic/nonischemic angiographic score, capillary number and blood flow recovery by 1.9-, 1.5- and 1.6-fold, respectively, over that of untreated diabetic animals ($P < 0.01$). Endogenous BM-MNC pro-angiogenic potential was affected in diabetes. Therapeutic strategy based on PlGF administration restored such defects and improved postischemic neovascularization in diabetic mice.

Dokl Biol Sci. 2001 Jul-Aug;379:319-21.

Prolongation of the normoglycemic period in animals with acute experimental diabetes by means of various types of tissue transplantation.

Kulikov AV, Sukhikh GT, Arkhipova LV, Smirnova GN, Poltavtseva RA, Tret'yak TM, Kulikova LI, Chailakhyan LM.

Source

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12918363

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