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Stem cell therapy: Differentiation potential of insulin producing cells from human adipose derived stem cells and umbilical cord MSCs

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Abstract

Diabetes mellitus is a huge burden for several countries. No matter type I or type II diabetes, the insufficient of insulin causes the dysfunction of regulating blood sugar and leads to hypoinsulinemia and life threatening ketoacidosis. To our knowledge, no effective treatment to cure diabetes and most diabetic patients still need to rely on the long-term injection of insulin. Herein, we summarized new finding and advantageous resource for regenerative medicine with the possibility to be employed in diabetes treatments. We also discuss the differentiation potentials of human adipose derived stromal cells (hADSCs) and human umbilical cord derived mesenchymal stem cells (hUCMSCs) and give rise to a new hope of treatment in the future.

1. Introduction

1.1. Diabetes

Diabetes Mellitus is one of major diseases causing heavy burden of many countries and people around the world (1). Both type 1 and type 2 diabetes are due to a reduction in beta-cell function and mass which lead to hyperglycemia (elevated blood sugar). In type I diabetes, autoimmune response causes the destruction of the beta cell itself severely and results in a reduced beta-cell mass to lead to marked hypoinsulinemia and potentially life threatening ketoacidosis (2, 3). In type II diabetes, the deficiency is relative, although functionally insufficient to maintain blood glucose levels within the normal range (2, 3). Accordingly, it is important to understand how beta-cell mass is maintained during life, not just as a biological conundrum, but as a forerunner for minimizing beta-cell loss and devising the best strategy for beta-cell regeneration as potentially curative treatment of diabetes. Recently, one of effective therapies of diabetes mellitus is islet transplantation which was reported in 2001(4). However, the amount of islet cells from the patients is insufficient for transplantation (5). Following years, several approaches of acquiring islet cells have been studied to reach sufficient

number, including differentiation from embryonic stem cells (ESCs) (6-9), mesenchymal stem cells (MSCs) (10-12), islet precursor, biliary epithelial cells (13), and trans-differentiation from duct cells (14).

1.2. Mesenchymal Stem Cells derived from Adipose Tissues and Umbilical Cord

With regard to ethical issues of ESCs, MSCs are more considerable as cell source for cell therapy. In addition, sufficient amount of cell numbers, high extension rate, immunomodulation, and multipotency of MSCs promote MSCs as a suitable population in differentiation of insulin producing cells (IPCs) for autologous transplantation (15-21). MSCs can be isolated from several organs and tissues such as bone marrow, dental pulp, adipose tissues, and umbilical cords. Within limit invasions, hADSCs are easy to harvest sufficient amount of cells with high proliferation potential, and multipotency (22, 23). Moreover, the fetus source of MSCs, hUCMSCs, was also considered as highly potential of differentiation in many aspects (5, 24-26). Both stem cells have been introduced that differentiate into lineage of three germ layers, neuron, hepatocyte, cardiomyocyte, and insulin producing cells (22, 24-28). Human adipose derived stem cells were as mesenchymal stem cells have features of self-renewal, long-term viability and multilineage differentiation potential (27). hADSCs were first isolated from adipose tissue after liposuction surgery by Zuk et al. in 2002 (22). According to previous studies, ADSCs have better colony forming unit-fibroblast (CFU-F) and high proliferation rate than bone marrow stromal cells (BMSCs)(27). Moreover, hADSCs as BMSCs were able to be induced to differentiate into multilineage cell types, including osteogenesis, chondrogenesis, adipogenesis, myogenesis, and neurogenesis (22, 27). Due to the multilineage potential of hADSCs, recently, more researches focused on the differentiation of insulin producing cells to search for the possible treatment of diabetes mellitus (28). Timper et al. had shown that hADSCs differentiated into insulin producing cells in vitro (28), however, in vivo differentiation is still looking forward to being proven by animal model in the near future.

Wharton's jelly cells (WJCs), umbilical cord derived mesenchymal stem cells, is a primitive stromal population which display the characteristics of MSCs (25, 26, 29, 30). hUCMSCs grow as adherent cells with mesenchymal morphology, self-renewing and express cell surface markers displayed by MSCs (25, 26, 29, 30). Moreover, hUCMSCs are able to differentiate into bone, cartilage, adipose, muscle, and neural cells (25, 26, 29-32). Like other stromal cells, hUCMSCs support the expansion of other stem cells, such as hematopoietic stem cells, show the property of immunosuppression (33). When hUCMSCs compare with bone marrow MSCs, hUCMSCs have greater expansion capability and faster growth in vitro. UC-MSCs have been reported that are therapeutic in several different pre-clinical animal models of human disease such as neurodegenerative

disease, cancer, and heart disease (25, 29, 30). Since hUCMSCs expand faster and to a greater extent than adult derived MSCs, these findings suggest that hUCMSCs are a primitive stromal cell population with therapeutic potential.

1.3. Development and Differentiation of Beta Cells to Therapeutic Potential in Type 1 Diabetes: In Vitro and in Vivo Studies

A series of transcription factors in utero enacts differentiation of multipotent pancreatic progenitors, capable of exocrine, ductal or endocrine differentiation, to terminally differentiated into islet cell lineages, including beta-cells (34). The embryonic pancreas is composed of branching duct-like structures made up of epithelial cells that express the transcription factor, pancreas-duodenal homeobox 1 (Pdx1)(34). Expressing neurogenin 3 (Ngn3), a basic helix-loop-helix transcription factor control a part of these cells within the centre of the embryonic pancreas commit to an endocrine cell fate (35). Lack of Ngn3 leads to an absence of islets (36); its ectopic expression over-commits cells prematurely to an endocrine cell fate (37). A series of further transcription factors lie downstream of Ngn3 to differentiate endocrine precursors to beta-cells. Characterization of promoter and enhancer regions has demonstrated direct regulation by Ngn3 of target genes, such as neurod1, paired domain homeobox gene 4 (Pax4), NK family member Nkx2.2 and insulinoma associated 1 (Ia1), all of which when inactivated impair differentiation, downstream of Ngn3, to a beta-cell fate (38-42). Ectopic expression of NGN3 in adult ductal cells, either carcinoma cell lines or preparations of fresh adult pancreatic cells, has also been shown to recapitulate something similar to this normal beta- cell differentiation program enacted during fetal development (43, 44).

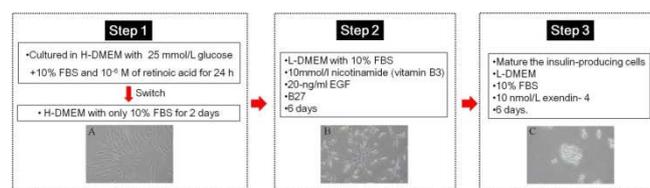


Figure 1. Schematic representation illustrating the differentiation protocol followed to differentiate the UCMSC to IPC. (A) After step 1 incubation, spindle-shaped cells colony formation could be observed. (B) After step 2 incubation, cells were aggregated and clustered. (C) In the final step of IPC maturation, islet-like cluster was formed.

The origin of beta cells is able to derive from several approaches, including differentiation from islet stem cells and progenitors (2, 27, 28, 45), differentiation from embryonic stem cells (ESCs)(3), and differentiation from mesenchymal stem cells (MSCs)(28, 46). However, isolation of islet stem cells and progenitors is difficult from patients for therapeutic purpose. On the other hand, the source of customized ES cells for patients cannot be derived easily, despite ES cells have pluripotency to differentiate

many cell types. According to the consideration of autologous transplantation and derivation of stem cell resources, mesenchymal stem cells are a considerable cell source to apply in the differentiation of insulin producing cells. Therefore, we modified the differentiation approach followed by Gao et al. (46) (Figure1). Moreover, we also summarized the previous studies for the therapeutic effects of UMSC and embryonic stem cells-derived IPC on type 1 diabetes (24, 47, 48) (Table 1).

1.4. Comparison of Effectiveness of Various Coating Surface in IPC Differentiation

Coating surface in differentiation of MSCs and ESCs

Table 1. Summary of MSC treatment protocols for animal models of diabetes.

Year	Authors	Model	Type	Location	Time	Method
2008	Chao et al. ⁽²⁴⁾	SD rat 200-250 g (n=6)	hUMSCs	Liver	7 weeks	STZ: 50 mg/kg/day for 2 days (>400 mg/dL) 2×10 ⁶ cells with a 22 [#] needle slowly injected into liver parenchyma
2008	Chen et al. ⁽⁴⁷⁾	C57BL/6 mice 7-8 weeks (n=5)	Mouse ESCs	Kidney capsule	25 days	STZ: 50 mg/kg/day for 5 days (>270 mg/Dl) 5×10 ⁶ cells were injected into the renal capsule
2009	Mao et al. ⁽⁴⁸⁾	SCID mice 6-8 weeks (n=9)	Human ESCs	Kidney capsule	7 weeks	STZ: 180 mg/kg (>300 mg/Dl) 8×10 ⁶ cells were injected into a microinjector under kidney capsule

2. Conclusion

Based on previous studies suggesting the multipotency of hADSCs and hUCMSCs, both of them would be a good source for differentiation into insulin producing cells and give rise to a possible treatment of diabetes by cell therapy. Moreover, hADSCs are adult tissues whereas hUCMSCs are fetal tissues. Comparing these two types of stem cells would be interesting in this study to understand the potential differences between adult and fetal stem cells for the future clinic application. Furthermore, IPCs function in animal model and new transplantation sites of STZ null mice will be addressed in this study as well.

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