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Induce Mesenchymal Stem Cells Differentiation into Insulin-Producing Cells: Mini-Review

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Abstract

Islet transplantation is an ideal treatment to cure diabetes. As shortage of donors is an insurmountable obstacle, the generation of insulin-producing cells to replace islet cell may be a promising approach. Mesenchymal stem cells (MSCs) that possesses great differentiation potential to other types of cells become an attractive source for generation of insulin-producing cells (IPCs). Many methods such as gene transfection and gene editing were used to induce MSCs differentiation into insulin-producing cells. We review the new progress in this field, advantages and drawbacks of insulin-producing cells in clinical application.

Keywords: Mesenchymal stem cell; Insulin-producing cells; islet; Diabetes

Abbreviations: DM: Diabetes Mellitus; T1DM: Type 1 Diabetes Mellitus; MSCs: Mesenchymal Stem Cells; IPCs: Insulin-Producing Cells

Mini Review

Diabetes mellitus (DM) is a global health concern with about 300 million individuals worldwide. The number of people suffered from DM may increase to more than 600 million by 2045 [1]. Type 1 diabetes mellitus (T1DM) patients, whose islets are destroyed by an autoimmune-mediated response, account for 5% of all diabetic patients. However, the existent treatments for the diabetes have kinds of drawbacks. Traditional exogenous insulin injections could maintain blood glucose level, but it could not reverse the chronic complications of diabetes, and there is a risk of hypoglycemia, which sometimes is lethal. Pancreatic transplantation may cure diabetes, but severe surgical trauma and life-long oral immunosuppressive drugs limit the use of pancreatic transplantation. Islet transplantation is an alternative treatment since it's less invasive. However, the implementation of islet transplantation is also limited by limited islet availability and immune rejection. Mesenchymal stem cells (MSCs)-based therapy for T1DM has been the focus of many research over the past several decades. MSCs could be obtained from many types of tissue, including the bone marrow, fetal annexes, adipose tissue, dental tissues, skeletal muscle tissue, liver tissue, lung tissue, menstrual blood and pancreatic tissue [2-8]. The application of MSCs with the advantages of wide availability, negligible teratogenic risks, nonimmunogenic, differentiation potential to islet-like cell and immunoregulation may provide more competitive treatments comparing with other ones [9,10]. Therefore, MSCs are a promising option for therapy for T1DM.

Many literatures have reported that MSCs could be induced differentiation into insulin producing cells (IPCs). Tan found that pancreatic MSCs could differentiate into IPCs by the two-step induction method [11]. Zhang considered that pancreatic MSCs could be functionally induced into IPCs with the optimized three-step protocol [12]. Both Zhang & Gabr [13,14] reported that bone marrow-derived MSCs were differentiated into IPCs. Adipose tissue-derived MSCs could also be differentiated into IPCs [15,16]. Van and Tasi found that IPCs differentiated from umbilical cord blood-derived MSCs could treat streptozotocin-induced diabetic rats [17,18]. The methods of inducing MSCs differentiation into IPCs include the following: firstly, gene transfection or gene editing. The most commonly used genes such as pancreatic and duodenal homeobox 1 (Pdx1), neuronal differentiation 1 (Neurod1) and Mafa were transfected into MSCs singly or in combination by plasmid or vector [19-21]. These genes play a crucial role in pancreatic organogenesis and β cell function. The other genes such as neurogenin-3 (NGN3) and paired box 4 (PAX4) are also

key for differentiation and maturation of islet cells [22,23]. Thi Do transfected porcine bone marrow derived MSCs with the insulin gene and generated IPCs which can improve hyperglycemia in streptozotocin-diabetic pig [24].

Recently many researchers pay more attention to microRNAs (miRNAs) which also play vital roles in the generation of IPCs from stem cells. Because miR-375, which is specific and most abundant miRNA in islets, contributes to the development of β cells [25], many researchers attach more importance to it. Jafarian reported that IPCs were generated from bone marrow derived MSCs by transfection with both miR-375 and anti-miR-9 [26]. Bai et al. [27] induced umbilical cord derived MSCs differentiation into IPCs by transfection with miR-375 and miR-26a. Zhao discovered a novel mouse miRNA which significantly promoted the differentiation of bone marrow derived MSCs into IPCs *in vitro* [28]. The breakthrough in genome editing makes it possible to induce endogenous human insulin transcription using the dCas9-VP160 transcriptional activator in human cells [29]. The CRISPR/Cas9 gene editing system identified the role of several transcription factors involved in pancreatic embryonic development [30], such as PDX1 and PTF1A, which are associated with several deficiencies in pancreatic agenesis. Secondly, directed differentiation. Currently, differentiation of stem cells into IPCs *in vitro* is being done using specific culture protocols. Generally speaking, cells were cultured in glucose-rich media with different growth and activation factors, which imitate the microenvironment *in vivo* for islet cell differentiation [31]. Gabr provided a 3-step differentiation protocol for inducing hBM-MSCs differentiation into IPCs [14]. Ikemoto developed a simple protocol for differentiating IPCs from adipose derived MSCs with a 2-step protocol [32]. Three-dimensional (3D) culture is thought to better mimic the *in vivo* microenvironment, so Takeuchi and Khorsandi employed 3D culture to improve bone marrow/adipose derived MSCs differentiation into IPCs [16,33]. Although great achievements have been obtained in this field, there are still some drawbacks. Firstly, the use of viral vectors faces risk of oncogene transactivation and spreading virus to human during clinical translation. The application of gene editing to human also faces huge ethical challenges. Secondly, directed differentiation protocols that induce MSCs to generate IPCs *in vitro* are expensive, difficult, time-consuming and less efficient. Thirdly, although the generated IPCs could reverse hyperglycemia in streptozotocin-diabetic animals, they may be destroyed by the existing antibodies that have damaged the native β cells in T1DM after transplantation and could not function anymore.

Conclusion

In summary, there is still a long way to go before differentiated IPCs from MSCs could be transplanted to human. The MSCs-derived IPCs should be able to control blood glucose level and should not be suspected of being teratogenic and tumorigenic, and they should avoid the damage by the antibodies in transplant recipients and function for a long time. Only when these standards are met, MSC-derived IPCs may be used in clinical practice on a large scale.

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