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Islet Transplantation: Potential Role of Stem Cells

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Abstract

Type 1 diabetes mellitus is due to the loss of pancreatic islet β cells, and islet transplantation is a promising therapy. However, sustaining pancreatic β cell function and survival is challenge for successful islet transplantation. Stem cells can be used to increase the supply of pancreatic islet β cells and sustain β cell survival. In this review, we briefly summarize how various types of stem cells can be used to either differentiate into functional β cells or to improve the microenvironment of an islet to support β cell. Special attention is paid towards the contribution of bone marrow mesenchymal stem cells to sustain human islet β cell.

Keywords: Stem cells; Diabetes mellitus; Transplantation; Insulin; Induced pluripotent stem cells; Mesenchymal stem cells

Introduction

Diabetes mellitus type 1 is characterized by insulin deficiency due to autoimmune destruction of the pancreatic islets. Usually presenting in childhood, these patients usually rely on insulin therapy. It is possible to treat diabetes mellitus type 1 with islet transplantation [1]. Transplanted islet tissue more closely mimics the physiology of the lost islets, and patients no longer require multiple daily insulin injections. Transplantation, however, is limited by the supply and viability of islets [2]. Islets are limited not only by the availability of donors, but by the tissue viability after procurement. In fact, the Edmonton protocol used for islet transplantation requires two set of donors for one recipient [3].

Stem cells offer a way to improve the supply of pancreatic islets [3]. This review focuses on ways various stem cells can be used to increase available β cells and improve the viability of islet β cell after procurement. Stem cells could be differentiated *in vitro* into cells capable of glucose stimulated insulin secretion and subsequently transplanted. Alternatively, certain types of stem cells once transplanted may improve the β cell function of the recipient. This case does not involve differentiation but rather support of the islets through a paracrine effect and through improving the microenvironment of the β cell.

Transplanted islet β cell survival and function require a supportive microenvironment, which consists of the microvasculature [4], the endogenous adult stem cells, and pro-apoptotic factors and cytokines [5]. After procurement, this microenvironment is compromised, resulting in apoptosis of at least 60% of the islets [3]. In fact, if islets are transplanted intact with the pancreas as opposed to islets alone, patients are less likely to need insulin therapy [5].

Stem Cells Can Trans-Differentiate into β-Like Cells

The most direct way to address the limited supply of pancreatic islets is trans-differentiation. Embryonic stem cells, derived from embryos can differentiate into insulin producing cells by over-expressing embryonic transcription factors [6]. Embryonic stem cells lowered hyperglycemia in mice with immunosuppression [7,8]. Unfortunately, they are associated with tumor formation [9]. This method is not autologous and has the risk of immune-rejection.

Induced pluripotent stem cells (iPSCs) are derived from various somatic cells, induced by transcription factors [10]. Mouse and human studies have converted iPSCs into β-like cells both *in vitro* and *in vivo* [11,12]. iPSCs have the advantage of being essentially autologous since the cells are from the patient-self [13,14] (**Figure 1**).

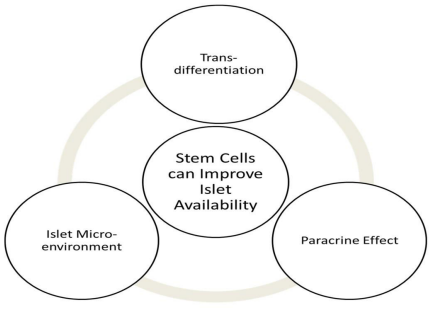

Figure 1 Potential role of stem cells

Adult stem cells generally reside within the organ into which they differentiate [15,16]. In particular, bone marrow mesenchymal stem cells (BM-MSCs) can be used to create insulin-producing cells [17-20]. BM-MSCs are of particular interest because patients with diabetes mellitus who incidentally receive a bone marrow transfusion can improve β cell function. This has been observed in multiple clinical studies [21-23].

Umbilical cord-derived mesenchymal stem cells (UCMSCs) are another source of stem cells [24]. They are more pluripotent than adult stem cells and are not as tumor-genic as embryonic stem cells. They have a lower likelihood of immune-rejection [25,26]. One study demonstrated their differentiation into insulin producing cells [27]. Another demonstrated that injection of UCMSCs into diabetic mice improved hyperglycemia and restored islet β cell function [28]. A recent type of stem cell, amniotic fluid-derived stem cells (AFSC) is an emerging type of stem cell [29]. AFSCs were shown to differentiate into insulin-producing cell *in vitro* [30].

Stem Cells Can Improve Islet β Cell Function through a Paracrine Effect

An indirect method by which stem cells can improve the availability of pancreatic islet β cell is by stimulating the patients' pancreatic islets through a paracrine effect or by improving the islets' microenvironment [2]. Studies demonstrate that stem cells co-cultured with islets improve their viability and function [31,32]. It is in the experience of this lab that islets co-cultured with BM-MSCs have improved morphology [33].

Stem cells address aspects of the microenvironment. Mesenchymal stem cells can promote revascularization through angiopoietin and vascular endothelial growth factor [32,34,35]. Some studies suggest that bone marrow mesenchymal stem cells lower apoptosis by lowering apoptotic factors, such as IL-1β [4,5,35,36]. Mesenchymal stem cells also have an immunosuppressive effect [31]. Amniotic fluid stem cells prevent β cell injury by increasing vascular endothelial growth factor A expression and activating the insulin receptor/Pi2K/Akt pathway [37].

The obvious medical application of stem cell studies is to produce β cells that are transplantable or to improve the viability of islet β cells after procurement. Stem cell supporting β cell longevity *in vitro* could now be used to elucidate the microenvironments necessary for cellular growth and development. This would have applications towards tissue regeneration for diabetes therapy.

Conclusion

Islet transplantation is a treatment that would obviate the need for multiple daily insulin injections. The limited supply of islets can be addressed by stem cells. There are multiple ways by which stem cell can contribute to improve islet transplantation: Stem cells transdifferentiate into β cells to increase β cell supplies, improve the microenvironment of islet to support β cell function and survival *in vivo*.

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