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Review Article

Adult Stem Cells and Diabetes Therapy

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Abstract

The World Health Organization estimates that diabetes will be the fourth most prevalent disease by 2050. Developing a new therapy for diabetes is a challenge for researchers and clinicians in field. Many medications are being used for treatment of diabetes however with no conclusive and effective results therefore alternative therapies are required. Stem cell therapy is a promising tool for diabetes therapy, and it has involved embryonic stem cells, adult stem cells, and pluripotent stem cells. In this review, we focus on adult stem cells, especial human bone marrow stem cells (BM) for diabetes therapy, its history, and current development. We discuss prospects for future diabetes therapy such as induced pluripotent stem cells which have popularity in stem cell research area.

Keywords: Diabetes; Islet β-cell; Bone marrow; Stem cell therapy; Induced pluripotent stem cells

Introduction

Diabetes Mellitus (DM) is a condition where hyperglycemia is caused by islet β-cell function deficiency (type I) and inadequate insulin secretion and/or the context of insulin resistance (type II) [1]. The prevalence of DM is consistently rising throughout the world [2]. Type 1 DM is caused by an autoimmune response to the β-cells, which physiologically release insulin in the pancreas and has two phases. The first phase is insulitis, where the islets are destroyed by a mixed population of leukocytes. The second phase is diabetes, when most β-cells have been injured. There is no longer adequate insulin production to control blood glucose levels, resulting in hyperglycemia [3]. Type 2 DM consists of two main problems: the insufficient production of insulin from the pancreas and the resistance of body cells to normal or even high levels of insulin [4].

To restore pancreatic β-cell function, recently developing stem cell research provides a great potential. Stem cells are the cells capable of regeneration through division and differentiation into multi-lineage cells [5]. There are three categories of stem cells: embryonic stem cells, induced pluripotent stem cells (iPSCs) and adult stem cells. Embryonic stem cells are derived from embryos and can differentiate into cells of the three germ layers [6]. iPSCs have the unique abilities of self-renewal and differentiation into many types of cell lineages. These are generated from somatic cells using various transcription factors [7]. Adult stem cells are able to regenerate themselves and differentiate into the major specialized cell types of the tissue or organ. Their primary role in living organism is to maintain and repair local tissue [8]. Hematopoietic adult BM, one type of adult stem cells, has the ability to transdifferentiate into the classical embryonic germ cell layers: ectoderm, mesoderm, and endoderm [9]. Recent studies have used BM and its derived stem cells as a source to repair injuries of the heart [10,11], neuron [10,12], and muscle [10,13].

In previous reports, the potential of differentiation of embryonic stem cells and iPSCs into pancreatic-like cells has been shown *in vitro* [14,15]. Others have also reported that insulin-producing cells can be generated from pancreatic ductal cells, hepatic oval cells, umbilical cord blood stem cells, and neural progenitor cells [14]. However, BM is transdifferentiated into a variety of lineages because it is a rich source of Mesenchymal Stem Cells (MSCs), and more available than the other type of stem cells [14]. In this short review, we focus on how adult stem cells and bone marrow cells affect beta cell function and their potential role in diabetes therapy.

Islet transplantation

After the discovery of immunosuppressive agents, islet transplantation is considered as a feasible clinical choice and provides a promising cure for type 1 diabetes [16]. The Edmonton protocol is the standard for islet transplantation. This protocol requires at least two donors per transplant [17]. However, the limited source of islets, low islet survival rate, and poor islet function post transplantation are significant obstacles to routine islet cell transplantation [2]. The low survival rate and poor islet function is in part due to the islet isolation process, which destroys the supportive microenvironment [18].

Studies have examined the mechanism by which islets perish and lose function during transplantation. Human islet transplantation has not been used as the standard of care for the treatment of type 1 DM due to the fact that islets die and lose function during the isolation process. More than 60% of the pancreatic islet tissue undergoes apoptosis [19]. The apoptotic pathways in islet cells are stimulated by the changes of the islet microenvironment due to the loss of vasculature and their sensitivity to hypoxic conditions [19].

External vascular support of Endothelial Progenitor Cells (EPCs), which is in islet transplants, is lost during the process of islet isolation [20]. Following *in vitro* culture, loss of vascular support affects their dedifferentiation, apoptosis, and necrosis [20,21]. Their survival rates are unsatisfactory in islets post-isolation because of vascularization damage throughout the islet isolation process [17].

Two types of apoptosis may occur during islet transplantation. The first type is the pro-apoptotic proteins released from islet cells as a result of DNA damage and mitochondria toxin production. The second type is the response to inflammation caused by pre-inflammatory cytokines such as IL-1β, TNF-α, and IFN-ϒ. Transplanted islets will be damaged and lose viability due to the apoptosis,

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There are several studies attempting to develop methods and materials to maintain islet function during isolation. Johansson et al. found that formation of composite EPC-MSC islets can enhance the adherence of the EPCs to the islets and revascularization of the EPCs. Proteases from MSCs contribute to EPC migration [20]. Upregulation of the expression of angiopoietin and Vascular Endothelial Growth Factor (VEGF) in EPCs contribute to an increase in angiogenesis and stabilization of the vasculature. This was performed by MSCs [20,22].

Effect of BM to islet transplantation

Previous studies show that BM cells have the ability to repair non hematopoietic tissues, including CNS, renal, pulmonary, and skin tissue [17]. BM may even play a role in tissue regeneration in these organs [17]. Luo et al. established that the rate of apoptosis, apoptosis related inflammatory factors, extra cellular ATP accumulation, and ATP receptor P2X7R expression reduced in co-cultured human islets with human BM versus only human islets culture. It is shown that BM co-cultured with human pancreatic islets can inhibit β-cell apoptosis and promote insulin positive cells [19].

BM contains all type of BM subpopulation, including EPCs. BM containing EPCs are capable of revascularization. EPCs from BM can protect islet β-cells from injury caused by hypoxia and apoptosis. BM has an anti-apoptotic effect by decreasing IL-1β and ATP levels and consequently releases them into the extracellular matrix. Thus, islets are protected from apoptosis by these anti-apoptotic effects and revascularization. This takes place even in long term *in vitro* culture conditions.

A damaged human islet is repaired when human islets are co-cultured with BM [17]. Levels of insulin release are enhanced from islets in long term co-culture with BM. It was demonstrated that the first 6 days of a islet-BM co-culture resulted in a monolayer surrounding the islet structure. Eventually insulin response to glucose was enhanced. This improvement continues to be found in long term culture.

On the other hand, islet-only cultures rapidly lose their morphology within the first week. The islet cells undergo degeneration of their monolayer forms and undergo apoptosis in long term culture. They showed spikes of insulin levels on days 15 and 28 due to leakage of intercellular insulin from dying β-cells. Basal insulin release levels gradually decreased. No viable islet cells were found after 6 months islet only culture [17].

Pancreatic islet β-cell growth is supported by BM *in vivo*, which may be manipulated to generate new β-cells *in vitro* [23,24]. BM cells may repair human islets which are injured from the isolation process. BM has various subpopulations which may play different roles. For instance, BM-derived MSCs possess the ability to differentiate into multiple lineages including adipogenic [10,25], osteogenic [10] [26], and chondrogenic tissues [10,27]. Alternatively, BM can develop a biological scaffold microenvironment. Meanwhile EPCs, which is the other type of BM subpopulation, produces undergo angiogenesis and vascularization [9].

In spite of the evidence for BM subpopulation differentiation into β-cells, mice studies have not been consistent. In a previous study of mice, injection of only EPCs into injured pancreas increased the number of donor and recipient EPCs, but there was no evidence for EPCs differentiation into β-cells [10,28]. It is not surprising that EPCs can promote revascularization. It enhances the islet microenvironment that was damaged from the islet isolation process. Recent research demonstrated human islet survival and function are improved by allogenic BM for more than six months [17]. It shows that regeneration is achieved by a synergy between angiogenesis and paracrine factor. Luo et al. examined two major subpopulations of BM, MSCs and EPCs, and found that they influence human islet β-cell survival and function [10]. The BM and its derivatives MSCs and EPCs have considerably different impacts on β-cell population under similar culture conditions even if obtained from the same donor. Islet injury is repaired by MSCs and EPCs, but they cannot increase the β-cell population since β-cell related transcription factors are not activated. Nevertheless, the effect of co-cultured BM on human islet β-cell regeneration has not been observed in other BM subpopulations. Only BM has the capability of improving β-cell regeneration [10].

Future of stem cell therapy for diabetes

iPSCs are a novel source of cell therapy for diabetes, as well as other multigenic diseases. iPSCs are reprogrammed from patient cells by transcription factors. For instance, three transcription factors (OCT4, SOX2, and KLF4) regenerate iPSCs from patient fibroblast [29]. These iPSCs begin acting as β-like cells and release insulin. Transplantation of homologus pancreatic islets is problematic due to immune rejection. Therefore, stem cell therapy with autologous iPSCs is a favorable treatment for diabetes [30].

Alipio et al. showed that iPSCs differentiated into β-like cells that were similar to the endogenous insulin-secreting cells in mice. iPSCs can differentiate into insulin-secreting cells *in vitro* [4]. *In vivo*, iPSCs reduce high glucose level in the diabetic mouse model [4].

An alternative cell source is human umbilical cord-derived mesenchymal stem cells (UCMSCs). UCMSCs can be easily isolated from the umbilical cord [31]. They have considerably more pluripotency than adult stem cells. They express the pluripotency markers OCT4, SOX2, and c-MYC. In contrast to embryonic stem cells, transplanted USMSCs are not associated with tumors. Also they are inherently immune-suppressive and available for use as a cell source with few ethical disputes. Therefore, USMSCs harbor a great potential for diabetes treatment [32].

Conclusion

Adult stem cells derived from BM are potential cells for diabetes therapy. BM can suppress inflammation and inhibit apoptosis in transplanted islets. It initiates revascularization and differentiation to β-cells in diabetic pancreases. Transplantation of allogenic BM does not cause immune rejection in recipient. Thus, BM derived stem cell therapy is a promising therapeutic strategy for treatment of diabetes. Other types of stem cells like iPSCs and USMSCs are also being developed for diabetes treatment.

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