DISCOVERY MEDICINE

Mesenchymal Stem Cell-Based Therapy for Type 1 Diabetes

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Abstract: Diabetes has increasingly become a worldwide health problem, causing huge burden on healthcare system and economy. Type 1 diabetes (T1D), traditionally termed "juvenile diabetes" because of an early onset age, is affecting 5~10% of total diabetic population. Insulin injection, the predominant treatment for T1D, is effective to ameliorate the hyperglycemia but incompetent to relieve the autoimmunity and to regenerate lost islets. Islet transplantation, an experimental treatment for T1D, also suffers from limited supply of human islets and poor immunosuppression. The recent progress in regenerative medicine, especially stem cell therapy, has suggested several novel and potential cures for T1D. Mesenchymal stem cell (MSC) based cell therapy is among one of them. MSCs are a type of adult stem cells residing in bone marrow, adipose tissue, umbilical cord blood, and many other tissues. MSCs, with self-renewal potential and transdifferentiation capability, can be expanded *in vitro* and directed to various cell lineages with relatively less efforts. MSCs have well-characterized hypoimmunogenicity and immunomodulatory effect. All these features make MSCs attractive for treating T1D. Here, we review the properties of MSCs and some of the recent progress using MSCs as a new therapeutic in the treatment of T1D. We also discuss the strength and limitations of using MSC therapy in human trials.

Introduction

Diabetes affected 25.8 million people of all ages and cost $245 billion in North American in 2012, according to the recent National Diabetes Factsheet published by the American Diabetes Association, and the numbers are quickly building up. Type 1 diabetes (T1D) which comprises 5~10% of the total diabetic population, is characterized by an early onset age and low serum insulin level. T1D is a chronic autoimmune disease that involves the progressive destruction of pancreatic β-cells, ultimately resulting in the loss of insulin production and secretion (Chhabra and Brayman, 2013). Daily insulin injection provides the most effective glycemic control for T1D patients. However, insulin injection leads to poor and drastic glycemic control and fails to address the complications such as ketoacidosis, nephropathy, high blood pressure, foot diseases, etc., caused by constant hyperglycemia. Islet transplantation, on the other hand, holds the potential to be an optimal and permanent therapy for T1D in a limited number of patients when insulin therapy fails (Shapiro *et al.*, 2000). However, the shortage of pancreas donors and the inadequate means to prevent immune rejection remain two major hurdles to expand this protocol worldwide. Therefore, the need for an effective cell replacement strategy from renewable sources for curing T1D persists.

The increase in the prevalence of T1D at an earlier onset age calls for a novel and more effective treatment. Stem cell therapy, an intervention strategy introducing stem cells into damaged tissues to treat diseases or injuries, has attracted great attention as a powerful tool for both basic biological research and novel therapeutics. Among all the stem cells, mesenchymal stem cells (MSCs) are quite promising. This cell therapy offers a solution to the problems associated with islet transplantation. MSCs have well-characterized self-renewal potential and transdifferentiation capability. MSCs are widely accessible from bone marrow, adipose tissue, umbilical cord blood, and many other tissues. Besides, MSCs hold tissue-homing capacity and immunomodulatory effect, suggesting their potential in treating T1D. Hereby, we briefly summarize the recent progress using MSC-based cell therapy for T1D from two aspects — MSCs as a suppression immunotherapy to prevent the onset of T1D and MSCs as a regenerative medicine to regenerate insulin-producing cells. Hopefully, this review may shed some useful insights into the development of novel therapy for T1D.

Mesenchymal Stem Cells as an Immunotherapy

T1D is an autoimmune disease, characterized by the recognition and destruction of insulin-producing pancreatic β cells by the autoreactive host immune system. To permanently cure T1D, the autoreactive host immune system must be addressed first before any attempts in islet replacement or regeneration. Diabetes clinics have been making progress using depleting antibodies against T cells but the diabetes remission is transient. Moreover, these antibodies do not discriminate between T cells normally required for maintaining immunity and the autoreactive T cells. Therefore, T cells involved in maintaining normal immune function are also going to be depleted, causing various complications (Cobbold *et al.*, 1984).

The immunomodulatory effect of MSCs has been explored to prevent immune diseases in the past decades. Recent clinical trials have demonstrated powerful immunomodulatory effects of the MSCs to treat graft-versus-host diseases (Le Blanc *et al.*, 2004). MSCs are hypoimmunogenic, lacking the necessary surface markers such as HLA-DR, CD14, CD80, and CD86 to activate the host immune system (Ryan *et al.*, 2005). MSCs hold homing capacity, which will guide them to the injured mesenchymal tissue, representing a good vehicle to deliver therapeutic proteins. In contrast to depleting antibodies, MSCs mainly work on the antigen-presenting stage and subsequent T-cell-activation stage by secreting soluble factors (Bartholomew *et al.*, 2002; Wu *et al.*, 2013). Although the factors are unknown, hepatocyte growth factor (HGF), IL-10, and indoleamine 2,3-dioxygenase (IDO) may play a role as indicated by the study regarding lymphocyte/MSC mixture (Meisel *et al.*, 2004). Therefore, MSCs offer more selectivity and specificity on hyperreactive T cells instead of compromising the whole-body immunity during the onset of T1D. In a recently published clinical trial, MSCs injected through liver puncture successfully reduced the levels of islet cell antibodies (ICA), glutamic acid decarboxylase (GAD), and insulin antibodies of two patients in 12 months, suggesting well tolerance and immunomodulatory effect (Mesples *et al.*, 2013).

Besides exerting immunomodulatory effect by themselves, MSCs were also demonstrated to be capable of recruiting and increasing immunosuppressive cells of host immunity. For example, human umbilical cord blood derived MSCs increased CD4+CD25+Foxp3+ regulatory T cells (Tregs), restored Th1/Th2 cytokine balance in blood, and induced apoptosis of infiltrated leukocytes in pancreatic islets in NOD mice with T1D (Zhao *et al.*, 2009). In an advanced humanized mouse model with human islet transplantation, human bone marrow derived MSCs demonstrated similar capability by increasing Tregs and causing immune tolerance of transplanted human islets (Wu *et al.*, 2013). The ability of

MSCs to “educate” immunosuppressive cells has been recently translated into a clinical trial (NCT01350219). The preliminary results showed that a single treatment with the umbilical cord blood derived MSCs provided lasting reversal of autoimmunity that allows regeneration of islet beta cells and improvement of glycemic control in subjects with long-standing T1D (Zhao *et al.*, 2009). Although the data must be explained with caution due to the limited number of patients at this stage, the results did implicate the unique potential of MSCs for autoimmune diseases and regenerative medicine.

In preclinical studies, the potential of MSCs as a novel immunotherapy was further enhanced by genetic modifications. For example, MSCs genetically engineered to express the soluble tumor necrosis factor (TNF) receptor II into NOD/SCID mice resulted in decreased serum TNF-α and inflammation (Liu *et al.*, 2013). Similarly, MSCs genetically engineered to express IL-1 receptor antagonist (IL-1Ra) prevented the inflammation in the sites of islet transplantation and helped the graft survival (Panakanti and Mahato, 2009; Wu *et al.*, 2011). However, caution should be exercised as these genetically modified MSCs usually acquired some gene aberrations, which may lead to MSC transformation and tumorigenicity after several passages. A recent study may provide some useful information about how to selectively eliminate the genetically modified MSCs after the therapeutic purpose was achieved (Martinez-Quintanilla *et al.*, 2013).

Mesenchymal Stem Cells to Regenerate Insulin-producing Cells

Human islet transplantation and many preclinical studies regarding human islets have been limited by the shortage of pancreas donors. While MSCs are known to differentiate into osteocyte, chondrocyte, and adipocyte natively, MSCs could also transdifferentiate into other cell types including insulin-producing cells under certain circumstances. Many research groups have been working on the generation of insulin-producing cells from the transdifferentiation of MSCs *in vitro*. Moreover, the crosstalk between MSCs and pancreas in diabetic animals has been revealed in some reports, even though the detailed mechanism is unclear. MSCs express a set of chemokine receptors, which may play critical roles in the pancreas homing/regeneration (Sordi *et al.*, 2005). Systemic administration of MSCs increased β-cell mass and reverted hyperglycemia in streptozotocin-induced diabetic mice (Ezquer *et al.*, 2008). However, it is not clear whether MSCs can directly transform into β cells. The up-to-date cell lineage tracing studies from Douglas Melton’s group once suggested that new β cells can only be generated from the pre-existing β cells instead of MSCs (Dor *et al.*, 2004). The authors concluded that MSCs merely served as a “tropic mediator” to support islet function in an indirect manner such as promoting angiogenesis (Dor *et al.*, 2004). However, some reports did show that insulin-producing β cells can be regenerated from the transdifferentiation of α cells, pancreatic duct cells, and acinar cells (Furuya *et al.*, 2013; Kopp *et al.*, 2011; Thorel *et al.*, 2010).

Although *in vivo* studies did not favor MSCs as a source of insulin-producing β cells, many successful attempts have been made to transdifferentiate MSCs into insulin-producing cells *in vitro*. Chen *et al.* (2004) first reported *in vitro* transdifferentiation of rat MSCs into functional insulin-producing islet-like cells that actively controlled blood glucose level in diabetic rats. Pancreatic and duodenal homeobox 1 (Pdx-1) is one of the most critical factors involved in the transdifferentiation of MSCs to β cells (Karnieli *et al.*, 2007; Li *et al.*, 2007). Then, other transcription or soluble factors such as neurogenin 3 (Ngn3), paired box gene 4 (Pax4), aristaless related homeobox (Arx), glucagon-like peptide-1 (GLP-1), and epidermal growth factor (EGF) were identified to play a role in the regeneration of β cells (Blyszczuk *et al.*, 2003; Bonner-Weir and Weir, 2005; Kroon *et al.*, 2008; Limbert *et al.*, 2011). Further studies demonstrated that MSCs also had the potential to transdifferentiate into glucagon and somatostatin expressing cells, suggesting the possibility of using MSCs as a sole source of “artificial” human islets *in vitro* (Timper *et al.*, 2006). Several groups even reported the formation of islet-like clusters from *in vitro* cultured MSCs given proper stimulation (Chao *et al.*, 2008; Gao *et al.*, 2008). However, these reports should be accepted with caution because: 1) most of these studies failed to regenerate a functional islet as a whole that composes of α cells, β cells, other cell-types and functional vasculature and therefore they may disturb the insulin/glucagon balance after transplantation; and 2) most of these studies failed to generate sufficient amount of islets for human transplantation and the long-term stability and tumorigenicity of these genetically modified insulin-producing cells are unknown. Recently, progress in tissue engineering suggested that a biocompatible scaffold might be necessary for the *in vitro* generation of artificial islets with functional vasculature from stem cells (Aloysious and Nair, 2013).

Strength and Weakness of Mesenchymal Stem Cells

MSCs can be isolated from multiple tissues. They can be easily expanded and genetically modified *in vitro*. They are hypoimmunogenic cells and well-tolerated in many animal studies and limited human trials. All these features make MSCs a good candidate for future cell therapy. Moreover, the current treatment options for T1D such as insulin injection and islet transplantation are only replacement therapies, which target hyperglycemia and associated complications but clearly hold no hope to cure T1D without proper immunotherapy to correct the autoreactive host immune system and islet regeneration to replenish the lost islets. With strong evidence of immunomodulatory effect and transdifferentiation potential, MSCs are well-equipped to address these two issues (**Figure 1**).

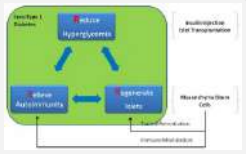

Figure 1. Triangular approaches of curing type 1 diabetes (T1D). There are three key components to treat T1D: to reduce hyperglycemia, to relieve autoimmunity, and to regenerate lost islets. While current treatment options such as insulin injection and islet transplantation can treat hyperglycemia and associated complications, they cannot relieve autoimmunity and replenish lost insulin-producing islets. Stem cell therapy, especially mesenchymal stem cell (MSC) based cell therapy, has the potential to resolve the remaining issues and eventually leads to an ultimate cure for T1D.

However, several issues remain unsolved to translate MSCs from bench to bedside. First of all, stem cell therapy is a mild therapy and may not be efficacious to reverse autoimmunity of T1D alone. A co-administration of immunosuppressive drugs may be necessary to prevent the acute autoimmunity. Secondly, MSCs need the guidance of “homing” factors to reach the desired sites of action, but most of the homing factors, especially the homing factors toward pancreas, are still unknown. Moreover, MSCs injected intravenously suffered from a “pulmonary first pass effect” and were likely to be sequestered in the lungs (Fischer *et al.*, 2009). This issue must be overcome to move any cell therapy into the clinics. Thirdly, contamination can be a potential concern for the manufacture of MSCs in large quantity. Maintaining the stem-cell like properties and avoiding the tumorigenicity and immunogenicity of MSCs in the manufacturing process can be another concern. Finally, the cost-effectiveness analysis of stem cell therapy versus current immunosuppressive regimens should be explored and discussed.

Conclusion

Recent studies have demonstrated MSC as a powerful tool for both biological research and regenerative medicine. MSCs are relatively easy to isolate, expand, and genetically manipulate while retaining their immunomodulatory effect and stem-cell like properties. Although safety concerns regarding developing MSCs, especially genetically modified MSCs, as a novel regenerative medicine should not be ignored, future in-depth mechanistic studies may help us to overcome the scientific and manufacturing hurdles and eventually pave the way for the first cell therapy to treat and even cure T1D.

Disclosure

The authors report no conflicts of interest.

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