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REVIEW

Transplantation of stem cells from umbilical cord blood as therapy for type I diabetes

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Abstract

In recent years, human umbilical cord blood has emerged as a rich source of stem, stromal and immune cells for cell-based therapy. Among the stem cells from umbilical cord blood, CD45+ multipotent stem cells and CD90+ mesenchymal stem cells have the potential to treat type I diabetes mellitus (T1DM), to correct autoimmune dysfunction and replenish β-cell numbers and function. In this review, we compare the general characteristics of umbilical cord blood-derived multipotent stem cells (UCB-SCs) and umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs) and introduce their applications in T1DM. Although there are some differences in surface marker expression between UCB-SCs and UCB-MSCs, the two cell types display similar functions such as suppressing function of stimulated lymphocytes and imparting differentiation potential to insulin-producing cells (IPCs) in the setting of low immunogenicity, thereby providing a promising and safe approach for T1DM therapy.

Keywords Type 1 diabetes mellitus · Umbilical cord blood · Mesenchymal stem cells · Multipotent stem cells · Immunomodulation · Insulin-producing cells

Introduction

Type 1 diabetes mellitus (T1DM) is generally considered to have an autoimmune etiology, occurring as a consequence of irreversible and organ-specific immune destruction of the insulin-producing pancreatic β cells in the islets of Langerhans (Bluestone et al. 2010; Atkinson et al. 2014). β cells play a critical role in glucose homeostasis by sensing blood glucose and releasing insulin to maintain physiologic glucose levels within a relatively narrow range (Bluestone et al. 2010). Once these cells are lost due to autoimmune destruction, T1DM patients lose control over blood glucose, resulting in hyperglycemia (Willcox and Gillespie 2016). Lifelong, exogenous, daily insulin injections are presently the primary life-sustaining treatment for millions of patients. Nevertheless, insulin injection by itself does not establish effective control over the underlying autoimmunity and cannot reverse β cell destruction or aid in cell regeneration (Zhao et al. 2012).

Most clinical research on T1DM therapy focuses on two challenging issues: how to modify the pancreatic microenvironment to overcome the underlying T cell-mediated autoimmune dysfunction and restore immune homeostasis (Chatenoud et al. 2012) and how to preserve residual β cells or replace damaged β cells by transplanting exogenous insulin-producing cells (Bruni et al. 2014). Although allogeneic islet cell transplantation has recently emerged as a promising potential treatment for T1DM, it is still hampered by challenges including a shortage of transplant donors, a propensity for immunological rejection and the necessity for

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long-term immunosuppression (Xv et al. 2017; Hematti et al. 2013). Recent studies have suggested that transplantation of umbilical cord blood (UCB)-derived stem cells may have the potential to treat T1DM by controlling autoimmune dysfunction and replenishing β cell function (Zhao et al. 2012; Reddi et al. 2015, 2010; Haller et al. 2008; Mabed 2011; Sahraneshin et al. 2015; Van Pham et al. 2014). This review article focuses on the introduction of stem cells derived from umbilical cord blood and summarizes the use of these cells as an ideal source for T1DM therapy.

Umbilical cord blood is an important stem cell source

Umbilical cord blood (UCB) plays important roles for the transport of nutrients and oxygen between mother and fetus. Because it is free from ethical complications and easy to isolate without invasive methods, human umbilical cord blood (hUCB) has become a precious medical product. Since hUCB was first reported as an efficacious source of sufficient cells for clinical hematopoietic reconstitution to cure a patient with Fanconi disease in 1989 (Gluckman et al. 1989), a growing number of reports have demonstrated that hUCB is a rich source of naive cells and pluripotent cells (Koblas et al. 2005; Jaing 2014), including about 40% monocytes (macrophage precursors), 40% lymphocytes, 10% neutrophils and other leukocytes and 10% stem cells and progenitor cells (Jaing 2014). The stem cell/progenitor fraction consists of umbilical cord blood-derived $CD34^+$ hematopoietic stem cells (UCB-HSCs) (Almici et al. 1995; Broxmeyer et al. 1989), $CD90^+$ umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs) (Bieback et al. 2004), umbilical cord blood-derived endothelial stem cells (UCB-ESCs) (Murohara et al. 2000) and $CD34^-CD45^+$ umbilical cord blood-derived multipotent stem cells (UCB-SCs) (Zhao et al. 2006, 2010).

In recent years, numerous publications have described various strategies of utilizing cord blood cells to exert beneficial therapeutic effects for diabetes treatment. Among cord blood cells, $CD45^+$ UCB-SCs and $CD90^+$ UCB-MSCs have similar characteristics, including differentiation potential and immunoregulatory potential. Both of these two cell types can be cultured from the mononuclear cell fraction, which is isolated from umbilical cord blood using standard Ficoll Hypaque techniques. However, the influence of subsequent cell culture conditions, including the culture medium, fetal bovine serum (FBS) or its substitutes, O_2 and CO_2 concentrations and the specific stimuli used (e.g., antibodies, cytokines) results in production of stem cells with different capabilities (shown in Fig. 1). For UCB-MSCs, most of the studies chose DMEM-low glucose medium or MEM-α medium supplemented with 10–20% FBS, with or without L-glutamine, EGF, β-FGF and other supporting cytokines, under 37 °C CO_2 incubator with saturated humidity and 5% CO_2 (Goodwin et al. 2001; Kern et al. 2006; Jin et al. 2013; Salazar et al. 2009; Erices et al. 2003). However, culturing UCB-SC using RPMI 1640 medium supplemented with a low percentage (7%) of FBS and incubated under higher than usual CO_2 content (8%), yields UCB-SCs with different surface markers measured by flow analysis (Table 1) (Zhao et al. 2006, 2012, 2013b; Li et al. 2012). In the remainder of this review, we compare and discuss the general characteristics of UCB-SCs and UCB-MSCs and elaborate upon their therapeutic potential for T1DM.

Umbilical cord blood-derived mesenchymal stem cells

MSCs are defined as undifferentiated cells that are capable of long-term in vitro expansion and have multi-lineage differentiation potential (Jiang et al. 2002; Dominici et al. 2006). MSCs have been isolated from multiple human tissues, including bone marrow (BM-MSCs), umbilical cord blood (UCB-MSCs) and adipose tissue (AD-MSCs). Although most reports have focused on BM as a major source of MSCs, limitations posed by decreases in differentiation and proliferation potential of BM-MSCs with age have led to increased interest in an alternative source of MSCs that do not demonstrate such senescent properties. UCB has been studied as a potential source for isolation and therapeutic applications of MSCs due to its greater proliferative potential, high cell yields and relative ease of collection in comparison with BM-MSCs (Kim et al. 2010; Davies et al. 2017). Comparative analysis of characteristics of human BM-MSCs and UCB-MSCs revealed that UCB-MSCs possess common characteristics similar to BM-MSCs, as defined by the proposed International Society for Cellular Therapy (ISCT) criteria (Jin et al. 2013; Dominici et al. 2006), including plastic adherent typical fibroblastoid population morphology, multi-lineage differentiation potential to several cell types such as osteoblasts, adipocytes, chondrocytes and other cell types and positive staining for a set of MSCs marker proteins including CD29, CD44, CD73, CD90, CD105, CD106 and HLA-class I, while lacking hematopoietic markers including CD14, CD34 and CD45 and CD133 (Bieback et al. 2004; Jin et al. 2013).

Moreover, compared with BM-MSCs, UCB-MSCs are able to generate more primitive and progenitor cells, show higher immunosuppressive activity, demonstrate increased cell proliferation and clonality and display a significantly lower expression of senescence markers (Jin et al. 2013; Barachini et al. 2009; Kögler et al. 2006; Markov et al. 2007), which make them clinically advantageous in treating T1DM. Furthermore, UCB-MSCs lack expression of major histocompatibility II (MHC-II) and co-stimulatory molecules CD80 (B7-1), CD86 (B7-2) and CD40 (Hematti et al. 2013), thus retaining low immunogenicity. Retrieval of UCB-MSCs is completed through a fast, simple and painless procedure that poses no risks to the donor, in comparison with retrieval of BM-MSCs, which must be obtained through an invasive, albeit generally safe surgical procedure. Additionally, the

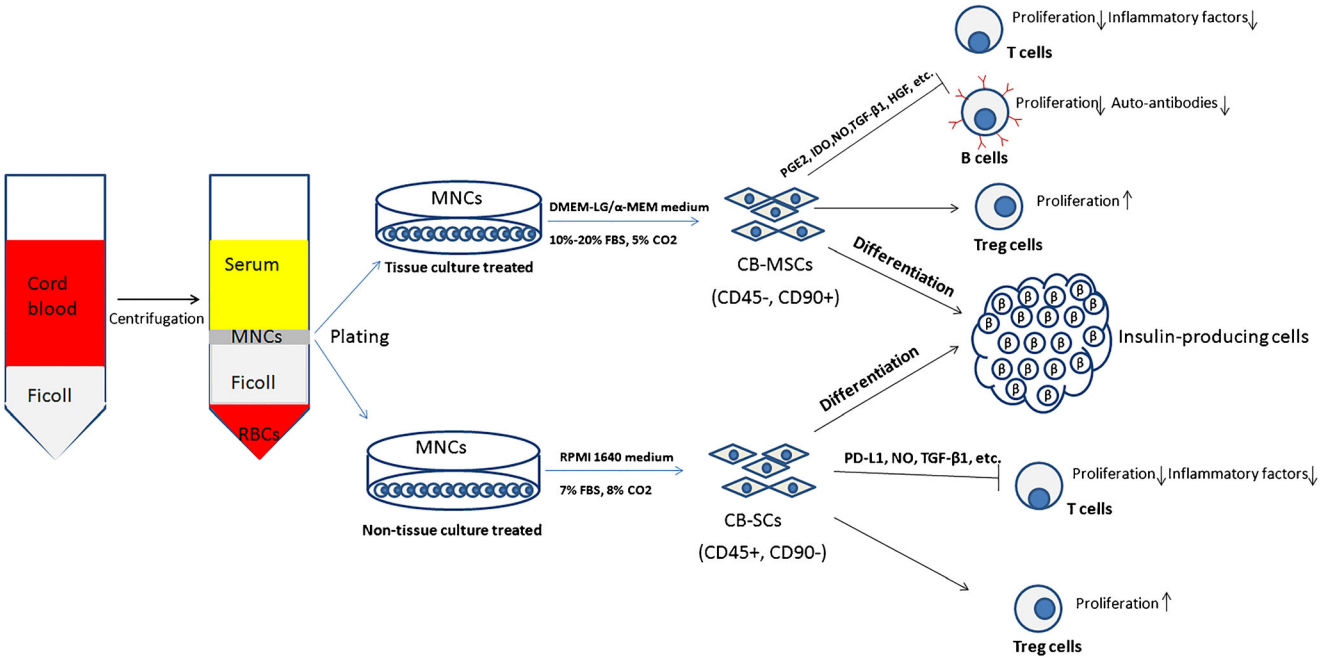

Fig. 1 Cord blood mesenchymal stem cells (UCB-MSCs) and multipotent stem cells (UCB-SCs) isolated from umbilical cord blood and their therapeutic potential for T1DM

noninvasive nature of UCB-MSC retrieval makes this source of cells more accessible than BM-MSCs, allowing for greater possibility of UCB-MSC banking and potentially lower cost of cultivation. Cumulatively, these features provide advantages for development of UCB-MSCs as off-the-shelf products for clinical applications (Kim et al. 2010), including providing immunomodulation and stromal support for transplantation of naked or encapsulated allogeneic β-cells or stem cells in T1DM therapy.

Immunomodulation properties of UCB-MSCs for T1DM

Cell-based therapies utilizing UCB-MSCs have been spotlighted as a promising tool for the treatment of a wide range of patients with neurodegenerative, autoimmune, liver and severe acute graft-versus-host and other immune-related diseases (Shin et al. 2016; Chang et al. 2011; Wang et al. 2013). UCB-MSCs have multiple immunomodulatory effects on both innate and adaptive immune cells, such as T lymphocytes, B lymphocytes, dendritic cells (DCs) and natural killer (NK) cells. UCB-MSCs exert immune suppressive action on lymphocyte proliferation, inhibit pro-inflammatory cytokine release and also induce peripheral tolerance (Shin et al. 2016; Kang et al. 2017; Wang et al. 2009; Oh et al. 2008). The mechanistic details of immunomodulation by UCB-MSCs are still unclear but direct cell-to-cell contact, paracrine actions by soluble factors and generation of regulatory T (Treg) cells have been reported to be crucial for the immunomodulatory ability of MSCs (Shin et al. 2016; Kang et al. 2017). Several reports confirmed that UCB-MSCs pre-activated by immune cells mediate immunosuppression through the secretion of prostaglandin E2 (PGE-2) (Kim et al. 2013, 2015), interleukin (IL)-10 (Kim et al. 2013), transforming growth factor-beta 1 (TGF-β1) (Kim et al. 2015), indoleamine-2,3-dioxygenase (IDO) (Lee et al. 2017b), nitric oxide (NO) (Sato et al.

Table 1 Cell surface marker expression in UCB-MSC and UCB-SC

Cell surface marker	UCB-MSCs	UCB-SCs	Reference
CD 45	–	+	Zhao et al. 2006; Kern et al. 2006; Koblas et al. 2009
CD 117	–	+	Zhao et al. 2006; Kern et al. 2006; Koblas et al. 2009
CD 133	–	±	Jaing 2014; Zhao et al. 2010; Kern et al. 2006; Koblas et al. 2009
CD 90	+	–	Zhao et al. 2006; Kern et al. 2006; Koblas et al. 2009

Cell surface marker expression measured by flow cytometry (positive expression of marker is indicated by +, lack of expression is indicated by – and variable expression is indicated by ±)

2007), and hepatocyte growth factor (HGF) (Lee et al. 2017a), which can widely inhibit the activation of immune cells.

The efficacy of MSC-based immunomodulatory cell therapy has emerged as a promising strategy in treating T1DM. MSCs have the ability to reduce inflammatory damage to islets in the early peritransplant period, attenuate autoimmunity through secreting regulatory cytokines to control autoreactive T cells and alloreactive effector CD4+ and CD8+ T cells and suppress insulitis through multifaceted immunomodulatory effects (Abdi et al. 2015; Hu et al. 2015). Recent studies have shown that human UCB-MSCs could represent a viable inhibition of pathogenic immune cells of T1DM patients (Montanucci et al. 2016) and transplantation of UCB-MSCs exerts immunomodulatory effects in autoimmune diabetic patients to improve the $CD4^{+}CD25^{hi}FoxP3^{+}$ Treg cell level, partly recover islet function and at least temporarily reverse overt hyperglycemia (Li et al. 2013; Haller et al. 2011). Other reports demonstrate that due to their immunosuppressive and protective properties, UCB-MSCs possess the ability to prevent diabetic renal injury in diabetic rats (Park et al. 2012), promote the epithelialization of ulcerated tissue in diabetic foot ulcers (Zhao et al. 2013a) and improve diabetic wound healing (Jung et al. 2018).

Clinical success has been demonstrated in transplantation of BM-MSCs for treatment of a variety of immune conditions including graft-versus-host disease (GVHD), systemic lupus erythematous (SLE) and T1DM (von Bonin et al. 2009; Le Blanc et al. 2008; Kebriaei et al. 2009; Wang et al. 2014; Li et al. 2016). However, the marked decrease in senescent properties of UCB-MSCs implies a more promising source of immune regulation. Clinically, UCB-MSCs have been used to treat severe acute GVHD with minimal to no side effects and successful long-term suppression of immune response (Wu et al. 2011) In addition, preliminary studies have demonstrated safety and efficacy of UCB-MSC administration in the treatment of active and refractory SLE, with no adverse effects considered to be directly related to UCB-MSC treatment (Wang et al. 2014). Use of UCB-MSCs in SLE demonstrated improvement of serologic markers as well as normalization of clinical features (Sun et al. 2010). Preliminary clinical trials investigating UCB-MSCs in the treatment of T1DM also demonstrate promise. In one double-blind study, researchers reported clinical safety and restoration of function of β cells for newly onset T1DM (Hu et al. 2013). Patients were infused with either UCB-MSCs or saline and followed for a total of 24 months. The treatment group exhibited significantly lower postprandial glucose and HbA1c measurements at all time points compared to the control group and demonstrated higher C-peptide levels. Another study demonstrated moderate improvement of metabolic function in T1DM patients treated concurrently with UCB-MSC and autologous bone marrow mononuclear cell (aBM-MNC) transplantation (Cai et al. 2016). Patients treated with both UCB-MSCs and aBM-MNC were followed at 3-month intervals for 1 year and compared to controls. Results at 1 year follow-up demonstrated significant increases in both C-peptide and insulin levels in treated individuals in contrast to decreased C-peptide and insulin levels in controls. Both studies demonstrated safety and efficacy of treatment with UCB-MSCs; however, larger trials and longer duration of follow-up are necessary.

Differentiation of insulin-producing cells from UCB-MSCs

In addition to their immunomodulatory effects, several research reports have described that MSCs can be induced to differentiate into insulin-producing cells (IPCs) under defined conditions, which could represent an ideal source of β cell generation for replacement therapy (Phuc et al. 2011). Hisanaga et al. (2008) refined a simple and effective protocol based on the combination of conophylline and betacellulin-delta4 in inducing differentiation of murine BM-MSCs into IPCs containing insulin-containing secretory granules. The differentiated cells also gained the ability to respond to high concentrations of glucose and secrete mature insulin, thereby markedly reducing the plasma glucose levels of streptozotocin (STZ)-treated diabetic mice.

Several studies have demonstrated that UCB-MSCs display the potential to differentiate into IPCs either in vitro or in vivo. Gao et al. (2008a) used a differentiation system based on extracellular matrix gels to differentiate human UCB-MSCs into IPCs in vitro. The authors also used a combination of various factors including retinoic acid, nicotinamide, epidermal growth factor and exendin-4 to differentiate UCB-MSCs into islet-like cells, which expressed pancreatic β cell markers and could synthesize and secrete functional islet proteins. However, the differentiated cells did not respond to glucose challenge very well (Gao et al. 2008b). Hu et al. (2009) also used the extracellular matrix gel to differentiate human UCB-MSCs into insulin-producing cells but they found the differentiated cells did not have the ability to reduce hyperglycemic levels in diabetic mice. Prabakar et al. (2012) showed differentiation protocols based on stepwise culture conditions to differentiate UCB-MSCs towards glucose-responsive IPCs and found the differentiated cells expressed pancreas-specific transcription factors and released insulin and C-peptide in response to a glucose challenge both in vitro and in vivo. Bhandari et al. (2011) showed that a simple serum-free protocol to induce different sources of MSCs, including UCB-MSCs, led to differentiation into pancreatic endocrine cells within a week. Phuc et al. (2011) established a new method to induce PDX-1 expression in UCB-MSCs by mRNA transfection, which significantly improved the differentiation effect of MSCs into IPCs. The in vivo differentiation potential of UCB-derived stem cells into pancreatic β cells has been confirmed only by Yoshida et al. (2005) and Koblas et al. (2009)

using the immunodeficient mouse as the recipient, despite the average successful differentiation of hUCB-derived insulin-producing cells still occurring at a rather low rate. Overall, these data suggest that human cord blood may be a promising source of islet cells for the treatment of T1DM.

Umbilical cord blood-derived multipotent stem cells

As UCB-MSCs and UCB-multipotent stem cells (UCB-SCs) possess many similar characteristics (including differentiation potential and immunoregulatory potential), several reports may have conflated these two different cell types. Although both of these cell types can be isolated from mononuclear cells of UCB, Zhao et al. (2006, 2010) identified UCB-SC as a unique type of stem cell by virtue of its capability to attach to a plastic surface of non-tissue cultured-treated Petri dishes and subsequent different cultural conditions (Fig. 1), with additional differences in their surface markers (a battery of negative and positive markers is shown in Table 1).

UCB-MSCs generally lack hematopoietic cell markers (CD45, CD34, CD117, CD14 and CD11b); platelet and endothelial cell adhesion molecules (CD31); and embryonic-like stem cell marker (CD133) but they express variable levels of CD13, CD105 (SH2), CD73 (SH3/4), CD44, CD90/Thy-1 and CD49 (Kern et al. 2006; Jin et al. 2013; Secco et al. 2009; Cappellesso-Fleury et al. 2010). However, UCB-SCs display similar embryonic and hematopoietic markers including leukocyte common antigen CD45 and stem cell factor receptor CD117 (Zhao et al. 2006; Li et al. 2012) and CD133 (variable) (Jaing 2014; Zhao et al. 2010) but remained negative for CD3, CD11b/Mac-1, CD20, CD34 and CD90/Thy-1 surface antigens (Zhao et al. 2006; Li et al. 2012). Similar to UCB-MSCs, UCB-SCs displayed very low immunogenicity as indicated by expression of a very low level of major histocompatibility complex (MHC) antigens and immune response-related co-stimulating molecules CD40, CD80 and CD86 (Zhao et al. 2006, 2007).

Immune-suppression of UCB-SC for T1DM

Similar to the immune-modulation effect of UCB-MSCs, UCB-SCs exerted immune suppression on stimulated CD4+ T cells and CD8+ T cells. Mechanistic studies revealed that the membrane-expressed protein programmed death receptor-1 ligand 1 (PD-L1) and soluble factor nitric oxide (NO) contributed to the T cell suppression induced by UCB-SC (Zhao et al. 2007). He et al. (2016) also discovered that UCB-SCs could increase the proportion of Tregs in peripheral lymphocytes and could improve the pathology and cognitive impairment of AD model mice. Zhao et al. (2013a, b) found UCB-SCs could reverse the functional defects of CD4+CD62L+Tregs, leading to prevention of diabetes onset and the reversal of overt diabetes in an autoimmune-mediated diabetic non-obese diabetic (NOD) mouse model. In addition, the control of diabetes correlated with systemic immune alterations, including restoration of Th1/Th2 cytokine balance in blood, as well as local regulation in pancreatic islets through a unique distributional pattern of TGF-β1 ("a TGF-β1 ring") that may protect islet β cells against infiltrated lymphocytes (Zhao et al. 2009, 2010). Based on the experimental results obtained, this group used the UCB-SCs to develop a strategy called "Stem Cell Educator therapy" (Zhao et al. 2012; Li et al. 2015), which is a closed-loop system that circulates a patient's blood through a blood cell separator, separates the lymphocytes and briefly co-cultures them with adherent UCB-SCs before returning the educated lymphocytes (but not the UCB-SCs) to the T1DM patient's blood circulation. Co-culture with UCB-SCs, which express an autoimmune regulator (AIRE), induces immune tolerance and re-educates the lymphocytes. The authors applied the "Stem Cell Educator" in a clinical study in humans and found that this therapy could provide lasting reversal of autoimmunity, as evidenced by improved C-peptide levels, reduced HbA1c values and decreased insulin daily requirement in patients with long-standing T1DM with or without residual pancreatic function (Zhao et al. 2012, 2013b; Sordi et al. 2017). A recent follow-up study assessed the safety and efficacy of this treatment administered twice in patients with T1DM and followed for 56 months (Delgado et al. 2015). Treatment was well tolerated in all subjects and improvement of B cell function was observed in those subjects with residual B cell mass. The stem cell educator therapy demonstrates the potential to mitigate the challenges posed by memory T cells in the pathogenesis of autoimmune disease.

Differentiation of insulin-producing cells from UCB-SCs

UCB-SCs had the potential to differentiate into functional IPCs in STZ-induced diabetic Balb/c nude mice. Denner et al. (2007) first investigated the differentiation potential of UCB-SC lineages to produce C-peptide and insulin in vitro. The transplanted UCB-SCs had the capacity to correct hyperglycemia, as indicated by the production of human C-peptide in mouse plasma (Zhao et al. 2006). Sun et al. (2015) also developed a strategy for inducing functional pancreatic endocrine cells from UCB-SCs through regulation of the c-Met/HGF axis by combining hypoxia and HGF treatment. They found that significantly greater amounts of C-peptide and insulin were released from the differentiated cells than from undifferentiated cells after incubation with a range of glucose concentrations. Importantly, transplantation of these differentiated cells could reverse the hyperglycemia of STZ-induced diabetic mice.

Conclusions and future studies

Cells derived from umbilical cord blood may represent an important biological resource for β cell generation, as well

as a source of immune-modulatory cells for T1DM therapy. We highlighted the main similarities and differences of UCB-SCs and UCB-MSCs. Human umbilical cord blood has great potential as a rich source of stem cells, including UCB-MSCs and UCB-SCs, which can be readily isolated from umbilical cord blood without ethical problems.

The properties of weak immunogenicity and strong immunoregulation make these cells promising for treating T1DM. UCB-MSCs possess characteristics similar to other sources of MSCs, including multiple immunomodulatory effects on both innate and adaptive immune cells differentiation potential into the insulin-producing cells, and low immunogenicity under certain biological conditions, which provide advantages for development of off-the-shelf products for clinical application in treating T1DM.

There are some differences in surface marker expression between UCB-SCs and UCB-MSCs, such as CD45, CD90, CD117 and CD133. However, both cell types possess immunomodulatory and regenerative capacity, as UCB-SCs also display the immune suppression effect on stimulated lymphocytes, differentiation potential to IPCs and low immunogenicity, which are therapeutic features similar to UCB-MSCs.

To conclude, through promising data from preclinical studies and clinical research, the therapeutic transplantation of umbilical cord blood-derived stem cells, whether UCB-MSCs or UCB-SCs, may represent safe and effective treatment for T1DM patients.

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