

## Review Article

# Mesenchymal Stem Cells: Rising Concerns over Their Application in Treatment of Type One Diabetes Mellitus

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Type 1 diabetes mellitus (T1DM) is an autoimmune disorder that leads to beta cell destruction and lowered insulin production. In recent years, stem cell therapies have opened up new horizons to treatment of diabetes mellitus. Among all kinds of stem cells, mesenchymal stem cells (MSCs) have been shown to be an interesting therapeutic option based on their immunomodulatory properties and differentiation potentials confirmed in various experimental and clinical trial studies. In this review, we discuss MSCs differential potentials in differentiation into insulin-producing cells (IPCs) from various sources and also have an overview on currently understood mechanisms through which MSCs exhibit their immunomodulatory effects. Other important issues that are provided in this review, due to their importance in the field of cell therapy, are genetic manipulations (as a new biotechnological method), routes of transplantation, combination of MSCs with other cell types, frequency of transplantation, and special considerations regarding diabetic patients' autologous MSCs transplantation. At the end, utilization of biomaterials either as encapsulation tools or as scaffolds to prevent immune rejection, preparation of tridimensional vascularized microenvironment, and completed or ongoing clinical trials using MSCs are discussed. Despite all unresolved concerns about clinical applications of MSCs, this group of stem cells still remains a promising therapeutic modality for treatment of diabetes.

## 1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease leading to beta cell destruction and lowered insulin production [1]. Insulin administration, as the standard treatment strategy for type 1 diabetes, cannot exactly mimic the physiologic secretion of insulin in the body [2].

To date, pancreatic and islet transplantation have been shown to be relatively effective therapeutic options [3, 4]. However, complications associated with the transplantation procedure, the need for life-long immunosuppressant therapy, with its adverse side effects, and the difficulty of obtaining transplant material and organ donations have restricted these treatment modalities [5].

Therefore, looking for other therapeutic options which can resemble islet cell function with limited complications

seems crucial. Among all kinds of stem cells, mesenchymal stem cells (MSCs) have been shown to be an interesting therapeutic option due to their immunomodulatory properties and their potential for in vitro differentiation into insulin-secreting cells.

This review summarizes the main features of mesenchymal stem cells as well as their use in the treatment of diabetes mellitus.

## 2. History and Sources

Fibroblast-like cell colonies from bone marrow were first isolated by Friedenstein and his colleagues in 1976 [6]. Later on, Caplan called these cells "mesenchymal stem cells" (MSCs) based on their features [7]. Bone marrow-derived

MSCs (BMMSCs) are multipotent, nonhematopoietic stromal cells capable of adhering to cell culture surface as well as having long-term self-renewal and multilineage differentiation capacities [8–10]. However, the term “multipotent mesenchymal stromal cells” is currently being used for this population of cells [11].

MSCs can also be isolated from various tissues and organs such as placenta, cord blood, umbilical cord Wharton’s jelly, pancreas, and adipose tissue [12–22].

### 3. Differentiation Capacities

A large number of studies have demonstrated that bone-marrow-derived MSCs have the potential to differentiate into mesodermal, ectodermal, and endodermal tissues including bone [23, 24], muscle [25, 26], neurons [27], hepatocytes [28] as well as skin [29–34], cardiomyocytes [35–38], and other tissues [9, 39–42]. In addition to angiogenesis promotion, several experimental studies have revealed that MSCs are able to differentiate into insulin-producing cells (IPCs) as well [43–48].

### 4. Markers

To date, there is no specific marker or group of markers to identify MSCs. As a result, this group of cells has been identified according to the combination of their surface markers and functional characteristics. Generally, MSCs express Stro-1 [49–51], CD105 (SH2) [52], CD73 (SH3/4) [53], CD90, CD146, and CD200 [54], in addition to some cell adhesion molecules including integrins ( $\alpha$  and  $\beta$ ) [55], intercellular adhesion molecule-1 and intercellular adhesion molecule-2 (ICAM-1 and ICAM-2), vascular cell adhesion molecule-1 (VCAM-1), lymphocyte function-associated antigen-3 (LFA-3), CD72, and activated leucocyte-cell adhesion molecule (ALCAM) [8, 56–61].

The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (ISCT) introduces minimal criteria to standardize human MSCs definition. First, MSCs must be adherent to the surface of standard plastic culture vessels. Second, MSCs must express CD105, CD73, and CD90, but they do not express CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR surface molecules [8, 62, 63]. Third, MSCs must be able to differentiate into osteoblasts, adipocytes, and chondroblasts in vitro [64].

In other species, MSCs have different patterns of surface antigens expression. However human MSCs from different sources do not present the same surface antigens expression patterns, which makes it difficult to compare the studies in this regard, but minimal criteria of ISCT are common in all of them.

### 5. Secretive Properties

*5.1. Cytokines and Growth Factors.* It has been shown in different studies [65–70] that MSCs naturally synthesize various cytokines and growth factors which are mainly influenced by

local microenvironments around them [71, 72] including M-CSF, IL-6, IL-11, IL-15, stem cell factor (SCF) [73], insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), transforming growth factor- $\beta$  (TGF- $\beta$ ), and hepatocyte growth factor (HGF) [74]. These trophic mediators not only promote the survival of surrounding cells [74] but also play important roles in MSCs regenerative/regulatory properties both in vitro and in vivo [67, 70, 75–77].

In Berman et al.’s study, they cotransplanted allogeneic MSCs intraportally with islets in cynomolgus diabetic monkeys. The results showed that MSCs significantly enhanced islet function and engraftment in one month after transplantation. They concluded that MSCs can provide immunomodulatory, revascularization, and regenerative cytokines [78].

In another study, coculture of MSCs with human islets from cadaveric donor improved islet’s insulin secretory function in vitro. The authors believed that increased amount of trophic cytokines secreted by MSCs resulted in this improvement [79, 80].

With respect to these properties, further studies must be done to understand the underlying mechanisms and clarify the role of various growth factors in beta cell neogenesis and regeneration.

*5.2. MSCs-Derived Microvesicles.* Microvesicles (MVs) are microparticles for cell to cell communication released from different cell types, as well as from MSCs [81–83]. MVs are released to the extracellular space throughout budding and blebbing of plasma membrane [81, 84–87]; therefore they have surface characteristics of the MSCs such as CD29, CD44, and CD73 [88]. They also contain biologically active molecules such as proteins, lipids, mRNA, and microRNA [84, 89]. When MVs are transferred to recipient cells via membrane fusion or internalization, the cargo can alter the transcription, proliferation, and immunoregulation of target cells, resulting in functional and phenotypic changes [87, 88, 90]. MVs functions are specific regarding cellular source [87]. Recent findings indicated that MSCs-derived MVs (MSCs-MVs) have regenerative effects in several disease models [88, 91, 92]. In Favaro et al.’s study, they cocultured MSCs-MVs with type 1 diabetic patient’s peripheral blood mononuclear cells (PBMCs). They showed that IFN $\gamma$  level decreased in stimulated PBMCs and TGF- $\beta$ , IL-10, IL-6, and prostaglandin E2 (PGE2) levels increased. Furthermore, MVs increased FoxP3+ regulatory T cells (Tregs) population in stimulated PBMCs [91]. Another study also demonstrated that MSCs-MVs can induce tolerogenic phenotype through induction of programmed death-ligand 1 (PD-L1), TGF- $\beta$ , IL-10, and Tregs [93]. Although MSCs-MVs could represent a new therapeutic strategy, in clinical application of MVs, some issues such as persistency of the biologic effects, disease specificity, homing, and biodistribution must be clarified.

### 6. MSCs Application in Experimental Studies and Differentiation to IPCs

*6.1. Bone Marrow.* Bone marrow is an important source of easily accessible adult stem cells, and bone marrow transplantation is considered to be effective for the treatment of

autoimmune type 1 diabetes. However, there is a great debate on the fate of transplanted bone marrow stem cells (BMCs) [94].

In 2003, Ianus et al. demonstrated that grafted mouse BMMSCs could differentiate into endocrine pancreatic cells *in vivo* spontaneously [95]. In contrast, additional studies failed to support these findings [96–98].

In other words, there was no evidence of bone marrow cells becoming IPCs in the pancreas of the recipient mice transplanted with GFP (green fluorescent protein) expressing bone marrow. However, it was difficult to rule out the possibility that the GFP gene was inactivated or that GFP-labeled cells were destructed as they engrafted into islets [99]. Moreover, this discrepancy might be due to diabetes etiology and/or stage as well as differences in mouse strains, mouse models, and experimental designs among research groups [100].

Other studies showed that both mouse [101] and human [99] BMMSCs ameliorated hyperglycemia in streptozotocin (STZ)-treated mice by inducing regeneration of endogenous pancreatic islets.

However, the exact mechanisms underlying the therapeutic effects of these cells have not been clearly defined. Some studies suggest that transdifferentiation of MSCs into IPCs might partly play a role in relieving hyperglycemia [95, 102–104].

On the other hand, this idea has been contradicted in another study [96] or attributed to cell fusion [105]. Xu et al. also hypothesized that MSCs transplantation into diabetic animals may prevent apoptosis of injured pancreatic beta cells and enhance regeneration of endogenous progenitor cells through paracrine actions such as angiogenic, cytoprotective, anti-inflammatory, mitogenic, and antiapoptotic effects [65].

It has been also reported that manipulation of culture conditions could induce low levels of insulin in rodent BMMSCs [102, 106–108]. However, the stability of this phenotype was unclear.

In 2009, Chang et al. transplanted male porcine BMMSCs to diabetic female pigs by direct injections into pancreas. As a result, insulin levels increased from day 14. The histological analysis revealed that newly formed islets were smaller than normal islets. In the same study, it was shown that MSCs adopt beta cell fate in diabetic pancreatic microenvironment without obvious immune rejections [109].

Gabr and colleagues differentiated human BMMSCs (hBMMSCs) into IPCs from healthy and diabetic donors. Differentiation was carried out in a 3-stage procedure with glucose-rich medium containing several activation and growth factors. Results did not show apparent differences in the rate of growth or differentiation between cells from the same donor or between cells from different donors with or without diabetes. IPCs expressed transcription factors and genes of pancreatic hormones similar to pancreatic islets. Their *in vivo* study in nude diabetic mice resulted in the control of their diabetic status for 3 months [110].

In a recent study, Ouyang et al. induced rat BMMSCs to differentiate into IPCs with various growth factors and small molecules through 3-step protocols. They concluded that, in their comparative study, aminopyrrole derivative compound

XW4.4 revealed the best activity among them and differentiated cells exhibited morphological and functional characteristics of IPCs and expression of pancreatic endocrine cell marker genes [111].

**6.2. Adipose Tissue.** Adipose tissues isolated from human lipoaspirates are also called adipose-derived stromal cells (ADSCs) with several priorities over other sources in the way that they can be accessed easily in large amounts and possess differentiation capacities similar to BMMSCs [112].

Moreover, several experimental studies have revealed that ADSCs even have greater proliferation, differentiation, and immunomodulatory potencies compared with BMMSCs [113–117].

In the studies by Timper et al. [118] and Eberhardt et al. [119] human adipose tissue-derived MSCs (AD-MSCs) from four donors were expanded in a fibroblast growth factor-containing medium. These cells expressed stem cell markers including *Isl1* mRNA, which is essential for the generation of pancreatic islet cells. Moreover, they observed upregulation of transcription factors *Ipfl*, *Isl1*, and *Ngn3* and islet gene insulin, glucagon, and somatostatin, in addition to the expression of C-peptide in differentiated cells.

Chandra et al. showed that AD-MSCs from murine epididymis could differentiate into insulin-producing aggregates under a ten-day inductive protocol. Differentiated cells expressed *PDX1*, *Ngn3*, *NeuroD*, *Pax4*, *Glut2*, and secreted insulin and C-peptide in accordance with glucose levels. Secretory granules in the cells cytoplasm were confirmed by electron microscopy. Normoglycemic state was restored 2 weeks after intraperitoneal transplantation into diabetic mice [120].

In a recent study by Karaoz et al., it was demonstrated that AD-MSCs differentiate into IPCs after 38-day coculture with islet cells. Insulin and C-peptide production were confirmed by ELISA and immunostaining. After cotransplantation of IPCs and islet cells under kidney capsule, hyperglycemic state was recovered in diabetic rats. Moreover, it was revealed that combination of differentiated AD-MSCs and islet cells resulted in better recovery from diabetes compared to islets transplants alone or cotransplantation of islets and differentiated BMMSCs [121].

Taken together with the advantages that harvesting and producing AD-MSCs appear to be more practical and less invasive in humans compared with BMMSCs, this population of MSCs can be considered as an alternative source of IPCs.

**6.3. Human Placenta-Derived MSCs.** In 2010, for the first time, Kadam et al. [45] introduced Human Placenta-Derived MSCs (hPDMSCs) as another alternative source for cell replacement therapy in diabetes.

They showed that hPDMSCs isolated from human chorionic villi of full-term placenta can form islet-like cell clusters (ILCs) on stepwise exposure to serum-free defined media containing specific growth factors and differentiating agents.

Differentiated ILCs were found to express human insulin, glucagon, and somatostatin by immunocytochemistry. Transplantation of hPDMSCs or ILCs derived from



hPDMSCs in STZ-induced diabetic mice led to restoration of normoglycemia. Their results demonstrated reversal of hyperglycemia by undifferentiated hPDMSCs and ILCs derived from hPDMSCs.

However, to evaluate hPDMSCs characteristics and their differentiation potentials, more studies should be carried out before their application in clinical trials.

**6.4. Human Cord Blood.** Human umbilical cord blood (UCB) as another source of MSCs has the potential to develop into IPCs. This issue has been indicated in several *in vivo* studies [122, 123].

Human UCB mononuclear-cell injections into the orbital plexus of obese B6.Y Lep(ob) mice, with spontaneous development of type 2 diabetes, improved blood glucose levels and survival rates and led to normalization of glomerular hypertrophy and tubular dilatation [122]. Furthermore, improved glycaemic profiles associated with histological improvement of insulinitis were obtained after intravenous (IV) administration of hUCB-MSCs to 25 NOD type 1 diabetic mice with insulinitis [123]. Later on, Yoshida et al. [124] investigated the *in vivo* capacities of hUCB-derived cells to generate IPCs. Thus, they transplanted hUCB cells into NOD/SCID- $\beta_2m^{\text{null}}$  mice and as a result they found IPCs of human origin in recipient pancreatic islets. However, the number of hUCB cells that transdifferentiated into IPCs and the rate of such an event need to be more investigated. Comparing the results of two studies by Bieback et al. [125] and Koblas et al. [126] the proportion of IPCs derived from hUCB per total number of islet cells was less than that of BM-derived IPCs. However, under diabetic conditions, the demand for the neogenesis of IPCs might increase and the rate of hUCB cells differentiation could become higher in order to compensate for the regeneration of beta cell mass. Moreover, the stem cell type in hUCB responsible for generation of IPCs remains unclear. Since MSCs isolated from cord blood [125] and hUCB-derived USSCs (unrestricted somatic stem cells) have rather the same cell markers and properties as MAPCs (multipotent adult progenitor cells) [126], it should be considered that MSCs might account for the differentiation of hUCB cells towards a beta cell phenotype.

The presence of mesenchymal stem or progenitor cells in hUCB was also indicated by other studies. They revealed that mononuclear adherent cells, isolated from UCB, display a BMMSCs-like immunophenotype and differentiation capacities [19, 115, 127]. Pessina et al. demonstrated that UCB cells exhibit genes essential for differentiation into pancreatic endocrine tissue (Isl1, PDX1, Pax4, and Ngn3), after culture in a medium supplemented with no specific cytokines or growth factors except fetal calf serum [127].

Prabakar et al. differentiated UCB-MSCs towards glucose-responsive IPCs by a stepwise culture protocol. They reported that differentiated cells express pancreas-specific transcription factors such as PDX1, Nkx6.1 and Isl1, Ngn3, and NeuroD1. UCB-MSCs-derived IPCs released insulin and C-peptide in response to a glucose challenge both *in vitro* and *in vivo* [128].

Since UCB-MSCs are available rather in large amounts, possess low risk for immune rejection [129], and have

increased capacities for expansion and differentiation into IPCs, this source of MSCs can be considered as an alternative option for treatment of diabetes [130].

**6.5. Wharton's Jelly MSCs.** Not only do MSCs in hUCB have the potential to differentiate into IPCs, but also MSCs residing in umbilical cord Wharton's jelly (WJ) share the same capability.

In 2008, Chao et al. [131] could successfully differentiate WJ-MSCs into IPCs through a four-step protocol. They also transplanted the IPCs into the liver of the diabetic mice. The authors demonstrated the expression of insulin in response to physiological glucose levels, as well as secretion of C-peptide and expression of pancreas-specific genes PDX1, Nkx2.2, HLXB-9, and Glut-2 [131, 132]. Later on, Wu and colleagues [133] compared the differentiative ability of WJ-MSCs and BMMSCs in obtaining an IPCs phenotype. Both cellular types were able to form islet-like clusters on the first day in a preconditioned culture medium. In addition, the researchers found a higher expression of PDX1 in differentiated WJ-MSCs compared with the differentiated BMMSCs. Secretion of insulin and mRNA expression of insulin and C-peptide were higher in the differentiated WJ-MSCs [133].

In a study by He et al., WJ-MSCs, infected with PDX1 gene carrying recombinant adenovirus and then treated with inductive factors, could differentiate into IPCs *in vitro*. They showed that the differentiated cells expressed  $\beta$ -cell related genes like PDX1, Ngn3, Glut2, and Nkx6.1 and were able to respond to high concentrations of glucose [134].

In another study, Tsai et al. demonstrated that WJ-MSCs differentiate into IPCs through a three-stage inductive protocol. They also showed that  $\beta$ -cell related genes were expressed in both differentiated cells and  $\beta$ -like cells transplanted into the liver of STZ-induced diabetic rats through portal vein. As a result, blood glucose levels were significantly reduced 4 weeks after transplantation [135].

Wang et al. could also differentiate WJ-MSCs into IPCs with an inductive medium. They evaluated differentiated cells *in vitro* in response to the glucose challenge test. After retroorbital injection of IPCs into NOD mice they found that IPCs containing human C-peptide and human nuclei were located in the liver. They concluded that differentiated IPCs from human WJ-MSCs could alleviate hyperglycemia in diabetic mice [48]. These promising data suggest that WJ-MSCs possess the ability, both *in vitro* and *in vivo*, to differentiate into insulin-secreting cells.

Due to more similarities of hUCB-MSCs, hPDMSCs, and WJ-MSCs to embryonic stem cells (ESCs) [127, 136, 137], these groups of MSCs should be considered as potential cell therapy options rather than BMMSCs.

With respect to the outstanding differentiation and immunomodulatory capacities of WJ-MSCs, conducting a banking system for both autologous and allogenic transplantation of these cells should be taken into consideration.

**6.6. Pancreatic Stem Cells.** It has been suggested by several studies that pancreatic stem or progenitor cells existing within pancreatic duct cells are able to differentiate and

migrate to form new islets during both organogenesis and regeneration. However, it is worth asking whether these cells are MSCs or not. Seeberger et al. [138] demonstrated that stem cells isolated from pancreas can differentiate into osteogenic, chondrogenic, and adipogenic lineages as well as expressing PDX1, Pax4, and Ngn3 transcription factors. Their preliminary data also suggest that these cells have the potential to derive beta cells. Another group [139] successfully isolated pancreatic stem cells from adult human pancreatic duct; these cells not only express nestin and PDX1 but also exhibit the identical markers of MSCs. In an earlier study by Gershengorn et al. [140], it was shown that fibroblast-like cells residing in pancreas are multipotent cells capable of reversible endoderm mesoderm transition (EMT) just like MSCs. However, further research revealed that EMT does not underlie the appearance of fibroblast-like cells in mouse islet cultures but that fibroblast-like cells appear to represent MSC-like cells akin to MSCs isolated from bone marrow [141].

Although there are some restrictions for harvesting pancreatic MSCs, more studies should be done to reveal the underlying mechanisms of their differentiation into beta cells and consequently suggest better differentiation protocols.

## 7. Immunomodulatory Properties of MSCs

Mesenchymal stem cells have been shown to have presumptive plasticity potential to differentiate into multiple lineages and their ability to escape immune recognition and immunomodulatory potentials have received great interest in regenerative and transplantation medicine [46, 142–144]. To date, evidences show that MSCs have immunomodulatory effects on T lymphocytes (T cells), B lymphocytes (B cells), dendritic cells (DCs), and natural killer cells (NK cells). Although the exact underlying mechanism of such effect has not been fully elucidated, these intriguing properties make MSCs a new alternative therapy for autoimmune disorders such as T1DM.

**7.1. MSCs Interaction with T Cells.** Multiple *in vivo* and *in vitro* studies have illustrated that MSCs can impair proliferative activities of T cells as well as their function [66, 67, 75, 145–158]. MSCs express surface adhesion molecules, such as VCAM, ICAM-1, ALCAM, and LFA3, and a number of integrins, which are essential for the interaction with T cells [57, 60, 61]. MSCs do not express MHC class II and other costimulatory molecules, such as CD80 (B7-1), CD86 (B7-2), CD 40, and CD 40L that induce T cells anergy [8, 55, 66, 75, 159, 160]. MSCs inhibit the cyclin D2 expression irreversibly and arrest T cells in G0/G1 phase of the cell cycle [151, 161]. Anergic state can be reversed partially with the addition of exogenous IL-2 [162]. MHC class II can be expressed on MSCs surface in presence of INF $\gamma$  in inflammatory conditions [55, 155]. In spite of MHC class II antigen expression and IL-2 addition, MSCs can inhibit allogeneic T cells proliferation in mixed lymphocyte cultures [66, 75, 145, 150, 160].

Several studies revealed that MSCs increase the number of CD4+ and CD25+ regulatory T cells, favored Foxp3 and

CTLA4 expression, and suppress function of other T cells subpopulations [67, 81, 152, 163]. Beyth et al. showed that depletion of CD25+ cells from the purified CD4+ T cells did not prevent MSC-mediated inhibition [156].

Many studies have shown that the immunomodulatory effects of MSCs are mediated by soluble factors. These factors include TGF- $\beta$ , HGF [66, 164], PGE2 [67], and IL-10 [94, 142, 156]. Nicola et al. demonstrated that inhibition of TGF- $\beta$  and HGF restores T cells proliferation [66], although contrary evidences showed that supernatants of MSCs were unable to suppress proliferation [60, 142]. However, another study that used semipermeable Transwells system revealed contrary results [165].

It was illustrated that MSCs express indolamine (IDO) protein and exhibit functionally active IDO after stimulation with INF $\gamma$  that catalyzes the conversion from tryptophan to kynurenine and inhibits T cell proliferation [146, 154, 166–170]. In contrast, another study showed that addition of tryptophan or usage of IDO inhibitor did not reverse suppressive effects of IDO [75]; therefore they exhibited that IDO and tryptophan depletion have partial roles in MSCs immunomodulatory effects [166]. In addition, production of PGE2 has been found to be one of the probable soluble factors that MSCs secrete to inhibit T cells proliferation [67]. However, PGE2 inhibition in MSCs and mitogen activated PBMCs coculture or MSCs and antibody stimulated PBMCs coculture was contradictory [75, 151].

Expression of other factors such as IL-10 [156], nitric oxide (NO) [171], HLA-G [163, 172, 173], heme oxygenase-1 [142, 154, 174], and stromal cell-derived factor-1 (SDF-1) [175] by MSCs has shown some effects on their immunosuppressive characteristics.

However, some controversies still remain in this regard. One explanation is that the effect of soluble factors on MSC-induced immunosuppression depends on the type of stimuli received by MSCs (e.g., allogeneic determinants, membrane-bound proteins, mitogens, and cytokines).

Krampera et al. demonstrated that the cell contact is required for MSCs inhibitory effects and inhibitory activity was abrogated when MSCs were added to the T cell cultures in a Transwells system or when MSCs were replaced by MSCs culture supernatant [145]. Augello et al. showed that the B7-H1/PD-1 pathway was involved in cell contact mechanism [176].

**7.2. MSCs Interaction with Dendritic Cells (DCs).** Dendritic cells (DCs) are the most important antigen-presenting cells [177]. Several studies have demonstrated that MSCs can inhibit differentiation, maturation, and the function of DCs [67, 156, 157, 178]. Some studies showed that MSCs suppress monocyte-derived DCs differentiation with cell contact mechanism [157, 178]. However, other studies confirmed that, at a higher MSC/monocyte ratio, DCs differentiation can also be suppressed by soluble factors [67, 156, 157, 179, 180].

MSCs have been found to suppress expression of HLA-DR, CD1a, CD40, CD80, and CD86 during DCs differentiation and also suppress CD40, MHC class I, and the maturation marker CD83 during the maturation process of DCs [152, 156, 157, 164]. Moreover, MSCs reduced endocytosis

capability and IL-2, IL-12, and TNF- $\alpha$  production of DCs, as well as increasing secretion of IL-10 and the ability to stimulate T lymphocyte proliferation [67, 156, 157, 178]. MSCs can also reverse the mature DCs into an immature phenotype [157].

Another study showed that MSCs coculture with DCs inhibits antigen presentation and DCs migration to attractive chemokines [179, 181].

**7.3. MSCs Interaction with B Cells.** In addition to T cell suppression, proliferation of stimulated B cells was also suppressed by MSCs [151]. Deng et al. showed that after coronary artery ligation MSCs could effectively inhibit the proliferation of B cells in a dose-dependent manner [182]. But at very low doses stimulating effects were observed [182, 183]. MSCs also decrease B cells activation and immunoglobulin secretion [182, 183]. B cell proliferation was arrested in the G0/G1 phase of the cell cycle by MSCs similar to T cells. One of the MSCs major mechanisms of B cell suppression is soluble factors. MSCs significantly downregulated CXCR4, CXCR5, and CCR7 chemokine receptors of B cells [183].

**7.4. MSCs and Natural Killer (NK) Cells.** Some studies demonstrated that MSCs are not recognized by NK cells [149]. Also, it has been reported that MSCs inhibit the proliferation of NK cells in a dose-dependent manner [151, 152, 166, 184]. Spaggiari et al. showed that MSCs suppress the proliferation of resting NK cells in response to IL-2 or IL-15 [185]. It has been also demonstrated that, in contrast to freshly isolated NK cells, activated NK cells by IL-2 that produced INF $\gamma$  could efficiently lyse autologous and allogeneic MSCs [61, 149]. After upregulation of MHC I expression in MSCs by INF $\gamma$  treatment, MSCs failed to induce NK cells to produce INF $\gamma$  so that the cytolytic activity was reduced [164, 185].

**7.5. In Vivo Studies of Immunomodulation.** Intravenous (IV) injection of MSCs was shown to prolong the survival of allogeneic skin graft in baboons [147]. Allogeneic MSCs could also engraft in bone without rejection in immunocompetent mice, but lymphocytic infiltration was seen at the periphery of the newly formed bone and inside the cartilaginous matrix [148]. IV administration of MSCs can ameliorate new onset encephalomyelitis (EAE) in the model of multiple sclerosis (MS) [159, 186]. Augello et al. reported that the occurrence of severe, irreversible damage to bone and cartilage in model of rheumatoid arthritis was prevented with a single injection of allogeneic MSCs [187]. In contrast, another group explained that MSCs did not have beneficial effect on this model [188]. In dystrophic experimental model, allogeneic and xenogeneic MSC infusions lead to muscle regeneration without host immune response [189]. Saito et al. [190] detected infused xenogeneic MSCs in bone marrow of immunocompetent rats undergoing coronary artery ligation. In other experimental studies Brdu labeled MSCs were detected at lesion territory in traumatic brain injury rat models [191, 192]. MSC infusion increased the success rate of the clinical outcome after hematopoietic stem cell transplantation (HSCT) [193]. Phase I clinical trials revealed the feasibility and safety of MSCs use

in HSCT [194]. Le Blanc et al. showed that injection of MSCs improved the clinical outcome in the patient with treatment-resistant grade IV acute graft-versus-host disease (GVHD) of the gut and liver [195]. Moreover, many studies have demonstrated that MSCs were valuable choice for allogeneic HSCT in patients suffering from acute GVHD [76, 196–198]. Contrarily, some studies reported that allogeneic MSCs trigger memory T cells, CD8+T cells, natural killer T (NKT), and NK infiltrating cells response and are thought to be immunogenic [199, 200].

In patients with Hurlers' syndrome, infused MSCs did not provoke alloreactive T cells response or GVHD [201].

Moreover, it has been revealed in phases I and II clinical trials that MSCs are a safe, feasible, and valuable option in treatment of Crohn's disease and its complications [202–205].

Several experimental studies demonstrated that allogeneic or syngeneic BMMSCs could prevent or revert autoimmune diabetes in diabetic animals [99–101, 206–209].

Bassi et al. reported that administrated AD-MSCs reversed hyperglycemia in NOD mice. The underlying mechanisms were induction of regulatory T cells and reduction of CD4+ Th1 response as well as decrease in INF $\gamma$  levels [210].

In a type 1 diabetes model, combination of allogeneic MSCs and sex-mismatched bone marrow cells resulted in normalization of blood glucose and serum insulin levels by T cells suppression [211].

Madec et al. revealed that MSCs could induce IL-10-producing regulatory T cells and suppress beta-cell-specific T cell responses in vitro and in NOD mouse [212].

Various and contrary outcomes might be related to different inflammatory microenvironments, different MSCs isolation and expansion methods, and use of non-well-characterized cells. Furthermore, in different microenvironments, MSCs utilize different mechanisms to exert immunosuppressive function.

Thus, it should be taken into consideration that animal models are not exactly equal to their human counterparts and, in different species, MSCs have different functions [213].

However, according to the contrasting results, more studies should be carried out before MSCs are applied as a therapeutic modality for T1DM.

## 8. MSCs Transplantation Routes

In experimental studies using MSCs for the purpose of glycemic control in diabetic animal models, various routes have been utilized for cell transplantation.

Banerjee et al. [214] and Sumi et al. [215] showed that transdifferentiation of MSCs into IPCs is feasible by intravenous injections. Ezquer et al. [100] observed that BMMSCs given intravenously contribute to the regeneration of the pancreas and kidney in an animal model of T1DM.

In two individual studies, despite different transplantation routes, similar results were obtained. In both studies, rat BMMSCs were successfully differentiated to islet-like cells and could alleviate hyperglycemia in diabetic rats after being transplanted subcutaneously [107] or given through portal vein [216]. Direct injections into pancreas [109], liver [131],



217], and orbital plexus [122], intracardiac infusion [99], and injection under the renal capsule [218] are the other ways introduced as MSCs delivery routes in diabetic models. In some clinical trials, also, MSCs were transplanted via intra-arterial route [219].

Liver is currently the site of choice for clinical islet transplantation, but due to its anatomic, immunologic, and physiologic properties it does not provide the optimal microenvironment for islet cells homing [220–223].

Another site that can be also considered for transplantation is the striated muscle because of its accessibility and angiogenesis potency [136, 224, 225]. Svensson and colleagues showed that muscles provide three times more blood vessels for engrafted islet than renal subcapsular region [226].

However, there is no evidence to confirm which modality is more effective in glycemic control or obtains fewer complications.

To define the best route of transplantation, specific studies should be designed to track MSCs homing.

### **9. Combination Therapy: Is It More Effective Than MSCs Transplantation Alone?**

Transplantation of allogeneic or syngeneic BMMSCs, alone or in combination with hematopoietic stem cells (HSCs), was performed on both STZ-induced diabetic mice and NOD models, improving glycaemia and renal lesions as the results [99, 216]. More recently, in a model of murine STZ-induced diabetes, blood glucose and serum insulin levels were normalized following concomitant transplantation of BM cells with syngeneic or semiallogeneic MSCs, via a single injection. In this study, regeneration of recipient-derived pancreatic insulin-secreting cells was attributed to the immunosuppressive effects of MSCs on the beta-cell-specific T lymphocyte response [211]. Urbán et al. also indicated that neither BMCs nor MSCs transplantation was effective alone. They also illustrated that no donor-derived beta cells were found in the recovered animals so that successful treatment of diabetic animals was not due to the reconstitution of the damaged islet cells from the transplant but due to graft initiated endogenous repair process as well as disappearance of beta-cell-specific T lymphocytes from diabetic pancreas [211].

It has been also shown that combined transplantation of BMMSCs and the islets improved the graft function, probably because of revascularization enhancement by MSCs [227].

Controversial results in these studies might be due to their different designs, cell expansion methods, and the characterized cells transplanted in the animal models of diabetes mellitus.

### **10. Single or Multiple MSCs Transplantation: Which Is More Effective?**

Banerjee et al. [214] successfully treated STZ-induced diabetes with multiple infusions of BM cells but did not suggest a mechanism for the recovery. Furthermore, Lee et al. [99] reported that repeated transplantation of human MSCs

could induce pancreatic islets and renal glomeruli repair in NOD/SCID mice suffering from STZ-induced diabetes. In a more recent study by Ho et al. [228], it was demonstrated that, compared to single intravenous transplantation, which only transiently decreased hyperglycemia, multiple MSC transplantations effectively restored blood glucose homeostasis. In their study, multiple human MSC transplantations ( $4.2 \times 10^7$  cells/kg each time) were performed intravenously at 2-week intervals into STZ-induced diabetic mice for 6 months. They described that multiple transplantations were essential to restore and maintain glucose homeostasis through decreasing systemic oxidative stress in the early stage and insulin production in the late stage.

However, according to our unpublished clinical trial results, repeated MSCs administration in patients with no response to the first intravenous transplantation revealed no advantages.

Thus, before the second course of transplantation, diabetic patients general condition as well as their immunological state must be evaluated and the optimum dose of MSCs should be defined.

### **11. Are Diabetic Patients' MSCs Suitable Candidates for Treatment of Diabetes?**

In a study by Dong et al. [229], allogeneic diabetic MSCs transplanted intravenously could initiate endogenous pancreatic regeneration by neogenesis of recipient islets. Thus, it was concluded that diabetic MSCs retain their stemness and potential to induce pancreatic regeneration on transplantation.

Moreover, Sun et al. [230] showed that BMMSCs from (both type 1 and type 2) diabetic patients also can differentiate into IPCs under appropriate conditions (18 days, three-stage protocol) *in vitro*. Their results provide the direct evidence for the feasibility of using patients' own BMMSCs as a source of IPCs for beta cell replacement therapy.

Some studies stated that prolonged exposure to hyperglycemia facilitates and enhances MSCs differentiation potency to IPCs [110, 218, 231, 232]; however, BMMSCs yielding in addition to their potency decreases throughout the life in normal population. Moreover, several studies have shown that hyperglycemic state and underlying defective microenvironment in diabetic patients impair MSCs function [46, 106, 233–236]. Therefore, considering another source of MSCs for cell based therapies in diabetic patients seems to be of great advantage.

In addition, duration of diabetes and MSCs potency are other important issues that must be taken into account before stem cell transplantation in a patient.

### **12. Role of Genetic Manipulation in MSCs Administration for Treatment of Diabetes Mellitus**

Xu et al. [217] showed that murine BMMSCs harboring human insulin gene could relieve diabetes for up to 6 weeks by intrahepatic administration in animal models.

Boumaza et al. [206] demonstrated that autologous BMMSCs can be administered to promote PDX1 and insulin protein expression locally in the pancreas and provide sustained systemic levels of insulin to treat or cure diabetes in the STZ-induced diabetic rats. Thus, blood-derived autologous MSCs can be carefully generated *ex vivo* and infused prior to the onset of full-blown diabetes to prevent beta cell damage and to modulate autoreactive T cell activation, while avoiding potential complications and cost for islet transplantation and long-term immunosuppression.

Lin et al. [237] revealed that rat BMMSCs transplantation followed by IV injection of recombinant lentiviruses encoding 2 different small hairpin RNAs (shRNAs) for specific interference with neurogenin 3 (Ngn3) could lower blood glucose by increasing beta cell mass compared with sham operated controls.

In the same year, Zhu et al. [238] demonstrated that experimental diabetes in beagle dogs could be relieved effectively for up to 16 weeks by intrahepatic autotransplantation of BMMSCs expressing human insulin. In a study by Moriscot et al. [103] it was indicated that by infection with adenoviruses coding for several transcription factors of the beta cell developmental pathway and coculture with islet tissue or islet-conditioned medium hBMMSCs are able to differentiate into insulin-expressing cells. In two other studies [218, 231] it was presented that pancreatic duodenal homeobox 1 (PDX1) gene-modified hBMMSCs can be differentiated into functional IPCs. Karnieli et al. [218] transfected MSCs with PDX1 and transplanted them under the renal capsule of STZ-diabetic SCID mice. After 5 weeks, glucose levels reduced from above 300 to 200 mg/dL. However, 6–8 weeks after transplantation an abnormal response to the glucose tolerance test was noted.

In a more recent study in 2012, Milanesi et al. [239] examined the ability of hBMMSCs genetically modified to transiently express VEGF or PDX1 to reverse diabetes. As a result, hBMMSCs expressing VEGF and PDX1 reversed hyperglycemia in more than half of the diabetic mice and induced overall improved survival and weight maintenance in all mice. However, recovery was sustained only in the mice treated with hBMMSCs-VEGF. Furthermore, *de novo* beta cell differentiation from human cells was observed in mice in both cases, treated with either hBMMSCs-VEGF or hBMMSCs-PDX1.

Taken collectively, MSCs can be differentiated into IPCs by genetic manipulation, but whether this strategy is a safe modality in clinical applications needs further investigations.

Hence, there are still serious concerns about the safety and the efficacy of manipulated cells as well as unresolved ethical issues regarding their use in the prospective gene therapy.

### 13. MSCs and Biomaterial Composites in Diabetes

In islet transplantation approach, one potential strategy to overcome immune rejection and lifelong use of immunosuppressive drugs is islet encapsulation with semipermeable

biomaterials [240–242]. Immunoprotective biomaterials can be used in islet encapsulation to create a permselective membrane around a group of islet cells. This type of device is called a bioartificial pancreas [242]. Despite the improvement of islet cell survival and efficacy rates, one of the obstacles is oxygenation limitation which results in loss of islets [241, 243–246].

There are some studies that used various biomaterials for encapsulation of or a scaffold for islet beta cells, ESCs-derived IPCs, and even xenogeneic islet cells [242, 243, 246–252].

Some other studies used the composition of biomaterials and MSCs in treatment of diabetes complications.

Chandra et al. encapsulated AD-MSCs-derived insulin-producing aggregates (ICAs) with alginate calcium and then transplanted them into peritoneal cavity. After 2 weeks, diabetic mice retained normoglycemic state. After 4 weeks, the transplanted capsules were removed, and ICAs showed cellular integrity, viability, and functionality [120].

In another study, Ngoc et al. firstly differentiated mouse BMMSCs and human UCMSCs into IPCs under three-step inductive protocol. In the next step they encapsulated IPCs in an alginate membrane. Finally they transplanted these capsules into peritoneal cavity. Simultaneously, they transplanted unencapsulated IPCs into diabetic mice through intraportal route. They showed that allogeneic and xenogeneic encapsulated IPCs had more survival than IPCs alone. Also encapsulation prevents immune response to xenogeneic and especially to allogeneic IPCs. Moreover hyperglycemic state improvement was observed in both xenogeneic and allogeneic encapsulated IPCs recipients [253].

Vériter et al. covered porcine islet cell scaffold composite with MSCs and demonstrated that MSCs can improve oxygenation of encapsulated islet cells with an increase of vascularization in the periphery of the bioartificial pancreas [254].

However, cotransplantation of MSCs and biomaterials, with the aim of preparing a more appropriate tridimensional microenvironment for beta cells transplantation and preventing immune rejection, should be evaluated more before being applied in cell-based therapies.

### 14. Application of MSCs in Human Studies

Although MSCs have tremendous therapeutic potentials, limitations such as lack of a standardized protocol to expand them, poor engraftment, limited differentiation under *in vivo* conditions, malignant transformation, and unwanted release of cytokines need to be overcome to enhance their clinical utility [5].

Risk of tumor induction is the issue that should be always taken into great consideration. Spontaneous malignant transformation of MSCs [209, 255–257] and promotion of tumor development and growth [148] are possible mechanisms accounting for their tumor formation potential.

In contrast to *in vitro* studies, spontaneous transformation has not been noted in clinical trials using human MSCs to date [256, 257]. The significant inhibitory effects of MSCs on the proliferation and function of major immune cells



populations may also play an important role in favoring cancer development and/or progression, as well as in helping preexisting non-MSC-derived tumors escape immune surveillance [148, 258, 259].

However, there are several clinical trials under way that might reveal the safety of MSCs administration in type one diabetic patients in the near future.

Trivedi and colleagues administrated ADSCs-derived IPCs, prepared in xenogeneic-free condition, in combination with HSCs into 11 insulin dependent patients without any immunosuppressive agents. Their study revealed promising results such as reduction in exogenous insulin requirement, increase in C-peptide levels, and having no episodes of diabetic ketoacidosis and host immune response. None of patients showed any unwanted effects [260].

Vanikar et al. cotransplanted AD-MSCs-derived IPCs and cultured bone marrow intraportally to 11 conditioned patients who irradiated and received anti-T and anti-B cells antibodies. They followed up patients for 23 months and exogenous insulin requirement and HbA1c level of patients decreased over this period, but insulin independency occurs in any patient. C-peptide give raised over follow up and any unwanted effects and ketoacidosis did not observe in patients [261]. However, complete insulin independency did not occur in their study, but safety and effectiveness of ADSCs-based cell therapy in diabetes have been shown. Thus, longer follow-ups must be done to demonstrate long-term safety and efficacy of the administered cells.

In another clinical study done by Hu et al., long-term efficacy of IV administration of WJ-MSCs in 15 new onset type 1 diabetic patients was assessed. They followed up the patients for their insulin requirements and HbA1c and C-peptide levels for 24 months after transplantation. Three patients became insulin independent in the end of the follow-up period. In other patients, insulin requirements and HbA1c levels decreased significantly in comparison to the control group. Also, C-peptide levels increased significantly in patients undergoing WJ-MSCs transplantation. They did not report any acute or chronic side effects or ketoacidosis in transplantation group while in control group ketoacidosis appeared in 3 patients [262].

Chen and coworkers infused autologous bone marrow mononuclear stem cells (including MSCs and HSCs) into pancreas through splenic artery. They reported beneficial effects of stem cell transplantation on insulin requirements and HbA1c and C-peptide levels of the patients. The authors have not published the whole data yet [263].

In our unpublished clinical study, we transplanted autologous BMMSCs intravenously to new onset type 1 diabetic patients without any immunosuppressive therapy. After 3 months, the patients who still required exogenous insulin to maintain blood glucose levels in normal ranges received another infusion. Six months after the first infusion, two patients became insulin independent and, in some patients, beneficial effects on their insulin requirements and C-peptide and HbA1c levels were seen. The rest of the patients did not benefit from the transplantations. However, no acute or chronic complications related to MSCs transplantation have been observed in the patients so far.

There are also some ongoing clinical trials (registered at <https://www.clinicaltrials.gov/>) in which MSCs from autologous or allogeneic sources are being transplanted to patients with T1DM (Table 1).

For instance, in Osiris clinical study, investigators are performing allogeneic MSCs transplantation on patients with T1DM to assess its safety and efficacy.

## 15. Conclusion

Although islet transplantation has opened new horizons in the treatment of T1DM, scarcity of supply, long-term immunosuppressive therapies, and rejection of grafted cells have restricted its application in the clinical setting. MSCs, as discussed previously, have great immunomodulatory and multilineage differentiation capacities. According to their accessible sources, it can be assumed that there would be unlimited sources for IPCs. However, there are still serious concerns about clinical application of MSCs.

One of the important issues regarding MSCs transplantation is the adequate number of differentiated or undifferentiated cells necessary to keep plasma glucose levels within normal ranges. However, sustained euglycemia might be disproportionate to the number of injected cells due to MSCs transdifferentiation into IPCs in vivo [264].

Another important issue is the evaluation of immunomodulatory effects of differentiated cells. It should be discussed more clearly at which stage of MSCs differentiation into IPCs they retain their immune suppressive effects. It has been suggested that undifferentiated MSCs can be used in T1DM treatment based on their immunosuppressive properties [142].

Minimum or no application of immunosuppressive drugs is favorable for MSCs or IPCs derived from MSCs because of their attenuating effects on the cells or their fatal complications in the recipients [136].

Nevertheless, more investigations are necessary to define the minimum dosage of immunosuppressants which does not alter the differentiation potency of combined MSCs to prevent even minor immune system response in the recipients.

One other concern about undifferentiated MSCs is their differentiation potency to unwanted tissues. Long-term cultivations and more cell passages to improve differentiation efficacy of MSCs can induce mutations and cell transformations [257].

According to some studies done on murines, MSCs, especially in allogeneic transplantation, might lead to tumor formation [148, 265, 266]. However, contrary studies revealed that MSCs inhibit tumor growth both in vitro and in vivo [267, 268].

Another issue, expected to be clarified soon, is the well characterization of markers expressed by MSCs to prevent immunological response in recipients. In addition, using autologous serum or serum-free and xenogeneic-free culture conditions should also be taken into account particularly in the clinical settings because fetal bovine serum (FBS), instead, can induce immune and allergic response especially in repeated administrations [269].

TABLE 1

| Study   | Year | Identifier  | Site/principal investigator                 | Intervention   | Status/enrollment                   |
|---|------|-------------|---|--|-------------------------------------|
| “Treatment of Patients with Newly Onset of Type 1 Diabetes with Mesenchymal Stem Cells Phase I/II”                          | 2010 | NCT01068951 | Uppsala University Hospital                 | Autologous transplantation of the patients’ own mesenchymal stem cells (approximately $2 \times 10^6$ cells/kg body weight) intravenously  | Completed 2013; 20 patients         |
| “PROCHYMAL (Human Adult Stem Cells) for the Treatment of Recently Diagnosed Type 1 Diabetes Mellitus (T1DM) Phase I”        | 2008 | NCT00690066 | Mesoblast International Sàrl                | Intravenous infusion of ex vivo cultured adult human mesenchymal stem cells (PROCHYMAL)  | Completed 2011; 63 patients         |
| “Umbilical Mesenchymal Stem Cells and Mononuclear Cells Infusion in Type 1 Diabetes Mellitus Phase I/II”                    | 2011 | NCT01374854 | Fuzhou General Hospital                     | Infusion of $1 \times 10^6$ /kg UCMSCs through pancreatic artery along with mononuclear cells by interventional therapy and another administration of same dose of UCMSCs one week after intervention                              | Active, not recruiting; 44 patients |
| “Autologous Transplantation of Mesenchymal Stem Cells for Treatment of Patients with Onset of Type 1 Diabetes Phase II/III” | 2010 | NCT01157403 | Lu Debin, Third Military Medical University | Autologous transplantation of bone marrow mesenchymal stem cells (approximately $2.5 \times 10^6$ cells/kg body weight) intravenously  | Recruiting; 80 patients             |
| “Safety and Efficacy of Mesenchymal Stem Cells in Newly Diagnosed Type 1 Diabetic Patients Phase I/II”                      | 2010 | NCT01322789 | University of Sao Paulo                     | Intravenous mesenchymal stem cell infusion; four consecutive intravenous infusions 1 week apart followed by 4 consecutive infusions 1 month apart  | Recruiting; 10 patients             |
| “Cotransplantation of Islet and Mesenchymal Stem Cell in Type 1 Diabetic Patients Phase I/II”                               | 2008 | NCT00646724 | Fuzhou General Hospital                     | Cotransplantation of islet and mesenchymal stem cell; islet of allograft and MSCs of autograft   | Recruiting; 30 patients             |
| “Human Menstrual Blood-Derived Mesenchymal Stem Cells Transplantation in Treating Type 1 Diabetic Patients Phase I/II”      | 2011 | NCT01496339 | S-Evans Biosciences Co., Ltd.               | $1 \times 10^6$ /kg MenSCs are infused through pancreatic artery or intravenous infusion once a week by the 4 consecutive therapies  | Recruiting; 50 patients             |
| “Stem Cell Therapy for Type 1 Diabetes Mellitus Phase I/II”   | 2010 | NCT01143168 | Cellonis Biotechnology Co.                  | First transplantation: on day 0, ABM-MNCs + UCMSCs through pancreas artery; second transplantation: on day $7 \pm 1$ , ABM-MNCs + UCMSCs intravenously; third transplantation: on day $14 \pm 2$ , ABM-MNCs + UCMSCs intravenously | Active, not recruiting; 24 patients |
| “Mesenchymal Stem Cells to Intervene in the Development of Type 1 Diabetes: A Blinded Randomized Study Phase II”            | 2014 | NCT02057211 | Uppsala University Hospital                 | Autologous mesenchymal stem cell transplantation   | Recruiting; 50 patients             |

ABM-MNCs: autologous bone marrow mononuclear cells, UCMSCs: umbilical cord mesenchymal stem cells, and MenSCs: menstrual blood-derived mesenchymal stem cells.

For broad application of MSCs in treatment of T1DM in the future, more clinical studies with various sources of MSCs, larger population of patients undergoing transplantation, and longer monitoring duration are required to determine safety and efficacy of this novel therapeutic approach. Additionally, utility of biomaterials, growth factors, and improvement of oxygen carriers should also be evaluated in further studies.

## Conflict of Interests

The authors declare no potential conflict of interests.

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## References

- [1] T. L. van Belle, K. T. Coppieters, and M. G. von Herrath, "Type 1 diabetes: etiology, immunology, and therapeutic strategies," *Physiological Reviews*, vol. 91, no. 1, pp. 79–118, 2011.
- [2] D. M. Nathan, P. A. Cleary, J.-Y. C. Backlund et al., "Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes," *The New England Journal of Medicine*, vol. 353, no. 25, pp. 2643–2653, 2005.
- [3] A. C. Gruessner, D. E. R. Sutherland, and R. W. G. Gruessner, "Long-term outcome after pancreas transplantation," *Current Opinion in Organ Transplantation*, vol. 17, no. 1, pp. 100–105, 2012.
- [4] R. M. Jamiolkowski, L. Y. Guo, Y. R. Li, S. M. Shaffer, and A. Naji, "Islet transplantation in type I diabetes mellitus," *The Yale Journal of Biology and Medicine*, vol. 85, no. 1, pp. 37–43, 2012.
- [5] P. Chhabra and K. L. Brayman, "Stem cell therapy to cure type 1 diabetes: from hype to hope," *Stem Cells Translational Medicine*, vol. 2, no. 5, pp. 328–336, 2013.
- [6] A. J. Friedenstein, U. F. Gorskaja, and N. N. Kulagina, "Fibroblast precursors in normal and irradiated mouse hematopoietic organs," *Experimental Hematology*, vol. 4, no. 5, pp. 267–274, 1976.
- [7] A. I. Caplan, "Mesenchymal stem cells," *Journal of Orthopaedic Research*, vol. 9, no. 5, pp. 641–650, 1991.
- [8] M. F. Pittenger, A. M. Mackay, S. C. Beck et al., "Multilineage potential of adult human mesenchymal stem cells," *Science*, vol. 284, no. 5411, pp. 143–147, 1999.
- [9] D. J. Prockop, "Marrow stromal cells as stem cells for non-hematopoietic tissues," *Science*, vol. 276, no. 5309, pp. 71–74, 1997.
- [10] A. J. Friedenstein, K. V. Petrakova, A. I. Kurolesova, and G. P. Frolova, "Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues," *Transplantation*, vol. 6, no. 2, pp. 230–247, 1968.
- [11] E. M. Horwitz, K. le Blanc, M. Dominici et al., "Clarification of the nomenclature for MSC: the International Society for Cellular Therapy position statement," *Cytotherapy*, vol. 7, no. 5, pp. 393–395, 2005.
- [12] D. A. de Ugarte, K. Morizono, A. Elbarbary et al., "Comparison of multi-lineage cells from human adipose tissue and bone marrow," *Cells Tissues Organs*, vol. 174, no. 3, pp. 101–109, 2003.
- [13] C. Campagnoli, I. A. G. Roberts, S. Kumar, P. R. Bennett, I. Bellantuono, and N. M. Fisk, "Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow," *Blood*, vol. 98, no. 8, pp. 2396–2402, 2001.
- [14] W. A. Noort, A. B. Kruisselbrink, P. S. In't Anker et al., "Mesenchymal stem cells promote engraftment of human umbilical cord blood-derived CD34<sup>+</sup> cells in NOD/SCID mice," *Experimental Hematology*, vol. 30, no. 8, pp. 870–878, 2002.
- [15] A. Erices, P. Conget, and J. J. Minguell, "Mesenchymal progenitor cells in human umbilical cord blood," *British Journal of Haematology*, vol. 109, no. 1, pp. 235–242, 2000.
- [16] P. S. In't Anker, S. A. Scherjon, C. Kleijburg-van der Keur et al., "Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta," *Stem Cells*, vol. 22, no. 7, pp. 1338–1345, 2004.
- [17] C. G. Fan, F. W. Tang, Q. J. Zhang et al., "Characterization and neural differentiation of fetal lung mesenchymal stem cells," *Cell Transplantation*, vol. 14, no. 5, pp. 311–321, 2005.
- [18] L.-L. Lu, Y.-J. Liu, S.-G. Yang et al., "Isolation and characterization of human umbilical cord mesenchymal stem cells with hematopoiesis-supportive function and other potentials," *Haematologica*, vol. 91, no. 8, pp. 1017–1028, 2006.
- [19] R. S. Tuan, G. Boland, and R. Tuli, "Adult mesenchymal stem cells and cell-based tissue engineering," *Arthritis Research & Therapy*, vol. 5, no. 1, pp. 32–45, 2003.
- [20] M.-S. Tsai, J.-L. Lee, Y.-J. Chang, and S.-M. Hwang, "Isolation of human multipotent mesenchymal stem cells from second-trimester amniotic fluid using a novel two-stage culture protocol," *Human Reproduction*, vol. 19, no. 6, pp. 1450–1456, 2004.
- [21] R. Sarugaser, D. Lickorish, D. Baksh, M. M. Hosseini, and J. E. Davies, "Human umbilical cord perivascular (HUCPV) cells: a source of mesenchymal progenitors," *Stem Cells*, vol. 23, no. 2, pp. 220–229, 2005.
- [22] H.-S. Wang, S.-C. Hung, S.-T. Peng et al., "Mesenchymal stem cells in the Wharton's jelly of the human umbilical cord," *Stem Cells*, vol. 22, no. 7, pp. 1330–1337, 2004.
- [23] S. P. Bruder, A. A. Kurth, M. Shea, W. C. Hayes, N. Jaiswal, and S. Kadiyala, "Bone regeneration by implantation of purified, culture-expanded human mesenchymal stem cells," *Journal of Orthopaedic Research*, vol. 16, no. 2, pp. 155–162, 1998.
- [24] S. P. Bruder, N. Jaiswal, and S. E. Haynesworth, "Growth kinetics, self-renewal, and the osteogenic potential of purified human mesenchymal stem cells during extensive subcultivation and following cryopreservation," *Journal of Cellular Biochemistry*, vol. 64, no. 2, pp. 278–294, 1997.
- [25] G. Ferrari, G. Cusella-De Angelis, M. Coletta et al., "Muscle regeneration by bone marrow-derived myogenic progenitors," *Science (New York, NY)*, vol. 279, no. 5356, pp. 1528–1530, 1998.
- [26] M. C. Galmiche, V. E. Koteliansky, J. Briere, P. Herve, and P. Charbord, "Stromal cells from human long-term marrow cultures are mesenchymal cells that differentiate following a vascular smooth muscle differentiation pathway," *Blood*, vol. 82, no. 1, pp. 66–76, 1993.
- [27] D. Woodbury, E. J. Schwarz, D. J. Prockop, and I. B. Black, "Adult rat and human bone marrow stromal cells differentiate into neurons," *Journal of Neuroscience Research*, vol. 61, no. 4, pp. 364–370, 2000.
- [28] B. E. Petersen, W. C. Bowen, K. D. Patrene et al., "Bone marrow as a potential source of hepatic oval cells," *Science*, vol. 284, no. 5417, pp. 1168–1170, 1999.



- [29] A. Hermann, R. Gastl, S. Liebau et al., "Efficient generation of neural stem cell-like cells from adult human bone marrow stromal cells," *Journal of Cell Science*, vol. 117, no. 19, pp. 4411–4422, 2004.
- [30] T. Ito, A. Suzuki, E. Imai, M. Okabe, and M. Hori, "Bone marrow is a reservoir of repopulating mesangial cells during glomerular remodeling," *Journal of the American Society of Nephrology*, vol. 12, no. 12, pp. 2625–2635, 2001.
- [31] H. Nakagawa, S. Akita, M. Fukui, T. Fujii, and K. Akino, "Human mesenchymal stem cells successfully improve skin-substitute wound healing," *British Journal of Dermatology*, vol. 153, no. 1, pp. 29–36, 2005.
- [32] M. Rojas, J. Xu, C. R. Woods et al., "Bone marrow-derived mesenchymal stem cells in repair of the injured lung," *The American Journal of Respiratory Cell and Molecular Biology*, vol. 33, no. 2, pp. 145–152, 2005.
- [33] G. V. Silva, S. Litovsky, J. A. R. Assad et al., "Mesenchymal stem cells differentiate into an endothelial phenotype, enhance vascular density, and improve heart function in a canine chronic ischemia model," *Circulation*, vol. 111, no. 2, pp. 150–156, 2005.
- [34] G. Cavallari, E. Olivi, F. Bianchi et al., "Mesenchymal stem cells and islet cotransplantation in diabetic rats: improved islet graft revascularization and function by human adipose tissue-derived stem cells preconditioned with natural molecules," *Cell Transplantation*, vol. 21, no. 12, pp. 2771–2781, 2012.
- [35] M. Alvarez-Dolado, R. Pardal, J. M. Garcia-Verdugo et al., "Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes," *Nature*, vol. 425, no. 6961, pp. 968–973, 2003.
- [36] K. Fukuda, "Development of regenerative cardiomyocytes from mesenchymal stem cells for cardiovascular tissue engineering," *Artificial Organs*, vol. 25, no. 3, pp. 187–193, 2001.
- [37] D. Hakuno, K. Fukuda, S. Makino et al., "Bone marrow-derived regenerated cardiomyocytes (CMG cells) express functional adrenergic and muscarinic receptors," *Circulation*, vol. 105, no. 3, pp. 380–386, 2002.
- [38] D. Orlic, "Adult bone marrow stem cells regenerate myocardium in ischemic heart disease," *Annals of the New York Academy of Sciences*, vol. 996, pp. 152–157, 2003.
- [39] S. Kadiyala, R. G. Young, M. A. Thiede, and S. P. Bruder, "Culture expanded canine mesenchymal stem cells possess osteochondrogenic potential in vivo and in vitro," *Cell Transplantation*, vol. 6, no. 2, pp. 125–134, 1997.
- [40] J. E. Dennis, A. Merriam, A. Awadallah, J. U. Yoo, B. Johnstone, and A. I. Caplan, "A quadripotential mesenchymal progenitor cell isolated from the marrow of an adult mouse," *Journal of Bone and Mineral Research*, vol. 14, no. 5, pp. 700–709, 1999.
- [41] R. G. Young, D. L. Butler, W. Weber, A. I. Caplan, S. L. Gordon, and D. J. Fink, "Use of mesenchymal stem cells in a collagen matrix for achilles tendon repair," *Journal of Orthopaedic Research*, vol. 16, no. 4, pp. 406–413, 1998.
- [42] H. A. Awad, D. L. Butler, G. P. Boivin et al., "Autologous mesenchymal stem cell-mediated repair of tendon," *Tissue Engineering*, vol. 5, no. 3, pp. 267–277, 1999.
- [43] J. Jiang, M. Au, K. Lu et al., "Generation of insulin-producing islet-like clusters from human embryonic stem cells," *Stem Cells (Dayton, Ohio)*, vol. 25, no. 8, pp. 1940–1953, 2007.
- [44] Y. Zhang, W. Shen, J. Hua et al., "Pancreatic islet-like clusters from bone marrow mesenchymal stem cells of human first-trimester abortus can cure streptozocin-induced mouse diabetes," *Rejuvenation Research*, vol. 13, no. 6, pp. 695–706, 2010.
- [45] S. Kadam, S. Muthyala, P. Nair, and R. Bhonde, "Human placenta-derived mesenchymal stem cells and islet-like cell clusters generated from these cells as a novel source for stem cell therapy in diabetes," *The Review of Diabetic Studies*, vol. 7, no. 2, pp. 168–182, 2010.
- [46] R. Anzalone, M. L. Iacono, T. Loria et al., "Wharton's jelly mesenchymal stem cells as candidates for beta cells regeneration: extending the differentiative and immunomodulatory benefits of adult mesenchymal stem cells for the treatment of type 1 diabetes," *Stem Cell Reviews and Reports*, vol. 7, no. 2, pp. 342–363, 2011.
- [47] H.-Y. Li, Y.-J. Chen, S.-J. Chen et al., "Induction of insulin-producing cells derived from endometrial mesenchymal stem-like cells," *Journal of Pharmacology and Experimental Therapeutics*, vol. 335, no. 3, pp. 817–829, 2010.
- [48] H.-S. Wang, J.-F. Shyu, W.-S. Shen et al., "Transplantation of insulin-producing cells derived from umbilical cord stromal mesenchymal stem cells to treat NOD mice," *Cell Transplantation*, vol. 20, no. 3, pp. 455–466, 2011.
- [49] P. J. Simmons and B. Torok-Storb, "Identification of stromal cell precursors in human bone marrow by a novel monoclonal antibody, STRO-1," *Blood*, vol. 78, no. 1, pp. 55–62, 1991.
- [50] P. J. Simmons, S. Gronthos, A. Zannettino, S. Ohta, and S. Graves, "Isolation, characterization and functional activity of human marrow stromal progenitors in hemopoiesis," *Progress in Clinical and Biological Research*, vol. 389, pp. 271–280, 1994.
- [51] P. J. Simmons and B. Torok-Storb, "CD34 expression by stromal precursors in normal human adult bone marrow," *Blood*, vol. 78, no. 11, pp. 2848–2853, 1991.
- [52] F. P. Barry, R. E. Boynton, S. Haynesworth, J. M. Murphy, and J. Zaia, "The monoclonal antibody SH-2, raised against human mesenchymal stem cells, recognizes an epitope on endoglin (CD105)," *Biochemical and Biophysical Research Communications*, vol. 265, no. 1, pp. 134–139, 1999.
- [53] F. Barry, R. Boynton, M. Murphy, S. Haynesworth, and J. Zaia, "The SH-3 and SH-4 antibodies recognize distinct epitopes on CD73 from human mesenchymal stem cells," *Biochemical and Biophysical Research Communications*, vol. 289, no. 2, pp. 519–524, 2001.
- [54] B. Delorme, J. Ringe, N. Gallay et al., "Specific plasma membrane protein phenotype of culture-amplified and native human bone marrow mesenchymal stem cells," *Blood*, vol. 111, no. 5, pp. 2631–2635, 2008.
- [55] M. K. Majumdar, M. Keane-Moore, D. Buyaner et al., "Characterization and functionality of cell surface molecules on human mesenchymal stem cells," *Journal of Biomedical Science*, vol. 10, no. 2, pp. 228–241, 2003.
- [56] M. K. Majumdar, M. A. Thiede, J. D. Mosca, M. Moorman, and S. L. Gerson, "Phenotypic and functional comparison of cultures of marrow-derived mesenchymal stem cells (MSCs) and stromal cells," *Journal of Cellular Physiology*, vol. 176, no. 1, pp. 57–66, 1998.
- [57] P. A. Conget and J. J. Minguell, "Phenotypical and functional properties of human bone marrow mesenchymal progenitor cells," *Journal of Cellular Physiology*, vol. 181, no. 1, pp. 67–73, 1999.
- [58] R. J. Deans and A. B. Moseley, "Mesenchymal stem cells: biology and potential clinical uses," *Experimental Hematology*, vol. 28, no. 8, pp. 875–884, 2000.

- [59] D. A. de Ugarte, Z. Alfonso, P. A. Zuk et al., "Differential expression of stem cell mobilization-associated molecules on multi-lineage cells from adipose tissue and bone marrow," *Immunology Letters*, vol. 89, no. 2-3, pp. 267-270, 2003.
- [60] G. Chamberlain, J. Fox, B. Ashton, and J. Middleton, "Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing," *Stem Cells*, vol. 25, no. 11, pp. 2739-2749, 2007.
- [61] K. Le Blanc, "Immunomodulatory effects of fetal and adult mesenchymal stem cells," *Cytotherapy*, vol. 5, no. 6, pp. 485-489, 2003.
- [62] K. Turnovcova, K. Ruzickova, V. Vanecek, E. Sykova, and P. Jendelova, "Properties and growth of human bone marrow mesenchymal stromal cells cultivated in different media Expansion of MSC in different media," *Cytotherapy*, vol. 11, no. 7, pp. 874-885, 2009.
- [63] M. L. Weiss, S. Medicetty, A. R. Bledsoe et al., "Human umbilical cord matrix stem cells: preliminary characterization and effect of transplantation in a rodent model of Parkinson's disease," *Stem Cells*, vol. 24, no. 3, pp. 781-792, 2006.
- [64] M. Dominici, K. Le Blanc, I. Mueller et al., "Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement," *Cytotherapy*, vol. 8, no. 4, pp. 315-317, 2006.
- [65] Y.-X. Xu, L. Chen, R. Wang et al., "Mesenchymal stem cell therapy for diabetes through paracrine mechanisms," *Medical Hypotheses*, vol. 71, no. 3, pp. 390-393, 2008.
- [66] M. D. Nicola, C. Carlo-Stella, M. Magni et al., "Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli," *Blood*, vol. 99, no. 10, pp. 3838-3843, 2002.
- [67] S. Aggarwal and M. F. Pittenger, "Human mesenchymal stem cells modulate allogeneic immune cell responses," *Blood*, vol. 105, no. 4, pp. 1815-1822, 2005.
- [68] G. Xu, Y. Zhang, L. Zhang, G. Ren, and Y. Shi, "The role of IL-6 in inhibition of lymphocyte apoptosis by mesenchymal stem cells," *Biochemical and Biophysical Research Communications*, vol. 361, no. 3, pp. 745-750, 2007.
- [69] F. Djouad, L.-M. Charbonnier, C. Bouffi et al., "Mesenchymal stem cells inhibit the differentiation of dendritic cells through an interleukin-6-dependent mechanism," *Stem Cells*, vol. 25, no. 8, pp. 2025-2032, 2007.
- [70] A. E. Aksu, E. Horibe, J. Sacks et al., "Co-infusion of donor bone marrow with host mesenchymal stem cells treats GVHD and promotes vascularized skin allograft survival in rats," *Clinical Immunology (Orlando, Fla)*, vol. 127, no. 3, pp. 348-358, 2008.
- [71] S. P. Dormady, O. Bashayan, R. Dougherty, X.-M. Zhang, and R. S. Basch, "Immortalized multipotential mesenchymal cells and the hematopoietic microenvironment," *Journal of Hematology and Stem Cell Research*, vol. 10, no. 1, pp. 125-140, 2001.
- [72] A. Björklund and O. Lindvall, "Cell replacement therapies for central nervous system disorders," *Nature Neuroscience*, vol. 3, no. 6, pp. 537-544, 2000.
- [73] A. I. Caplan and J. E. Dennis, "Mesenchymal stem cells as trophic mediators," *Journal of Cellular Biochemistry*, vol. 98, no. 5, pp. 1076-1084, 2006.
- [74] S. Ohnishi, T. Yasuda, S. Kitamura, and N. Nagaya, "Effect of hypoxia on gene expression of bone marrow-derived mesenchymal stem cells and mononuclear cells," *Stem Cells*, vol. 25, no. 5, pp. 1166-1177, 2007.
- [75] W. T. Tse, J. D. Pendleton, W. M. Beyer, M. C. Egalka, and E. C. Guinan, "Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation," *Transplantation*, vol. 75, no. 3, pp. 389-397, 2003.
- [76] B. Maitra, E. Szekely, K. Gjini et al., "Human mesenchymal stem cells support unrelated donor hematopoietic stem cells and suppress T-cell activation," *Bone Marrow Transplantation*, vol. 33, no. 6, pp. 597-604, 2004.
- [77] S. Itakura, S. Asari, J. Rawson et al., "Mesenchymal stem cells facilitate the induction of mixed hematopoietic chimerism and islet allograft tolerance without GVHD in the rat," *The American Journal of Transplantation*, vol. 7, no. 2, pp. 336-346, 2007.
- [78] D. M. Berman, M. A. Willman, D. Han et al., "Mesenchymal stem cells enhance allogeneic islet engraftment in nonhuman primates," *Diabetes*, vol. 59, no. 10, pp. 2558-2568, 2010.
- [79] K. S. Park, Y. S. Kim, J. H. Kim et al., "Influence of human allogeneic bone marrow and cord blood-derived mesenchymal stem cell secreting trophic factors on ATP (adenosine-5'-triphosphate)/ADP (adenosine-5'-diphosphate) ratio and insulin secretory function of isolated human islets from cadaveric donor," *Transplantation Proceedings*, vol. 41, no. 9, pp. 3813-3818, 2009.
- [80] K.-S. Park, Y.-S. Kim, J.-H. Kim et al., "Trophic molecules derived from human mesenchymal stem cells enhance survival, function, and angiogenesis of isolated islets after transplantation," *Transplantation*, vol. 89, no. 5, pp. 509-517, 2010.
- [81] L. Biancone, S. Bruno, M. C. Derogibus, C. Tetta, and G. Camussi, "Therapeutic potential of mesenchymal stem cell-derived microvesicles," *Nephrology Dialysis Transplantation*, vol. 27, no. 8, pp. 3037-3042, 2012.
- [82] A. N. Patel, V. Vargas, P. Revello, and D. A. Bull, "Mesenchymal stem cell population isolated from the subepithelial layer of umbilical cord tissue," *Cell Transplantation*, vol. 22, no. 3, pp. 513-519, 2013.
- [83] H.-C. Zhang, X.-B. Liu, S. Huang et al., "Microvesicles derived from human umbilical cord mesenchymal stem cells stimulated by hypoxia promote angiogenesis both in vitro and in vivo," *Stem Cells and Development*, vol. 21, no. 18, pp. 3289-3297, 2012.
- [84] V. Muralidharan-Chari, J. W. Clancy, A. Sedgwick, and C. D'Souza-Schorey, "Microvesicles: mediators of extracellular communication during cancer progression," *Journal of Cell Science*, vol. 123, part 10, pp. 1603-1611, 2010.
- [85] S. Mathivanan, H. Ji, and R. J. Simpson, "Exosomes: extracellular organelles important in intercellular communication," *Journal of Proteomics*, vol. 73, no. 10, pp. 1907-1920, 2010.
- [86] B. György, T. G. Szabó, M. Pásztói et al., "Membrane vesicles, current state-of-the-art: emerging role of extracellular vesicles," *Cellular and Molecular Life Sciences*, vol. 68, no. 16, pp. 2667-2688, 2011.
- [87] C. Théry, M. Ostrowski, and E. Segura, "Membrane vesicles as conveyors of immune responses," *Nature Reviews Immunology*, vol. 9, no. 8, pp. 581-593, 2009.
- [88] S. Bruno, C. Grange, M. C. Derogibus et al., "Mesenchymal stem cell-derived microvesicles protect against acute tubular injury," *Journal of the American Society of Nephrology*, vol. 20, no. 5, pp. 1053-1067, 2009.
- [89] M. Z. Ratajczak, M. Kucia, T. Jadczyk et al., "Pivotal role of paracrine effects in stem cell therapies in regenerative medicine: can we translate stem cell-secreted paracrine factors and microvesicles into better therapeutic strategies," *Leukemia*, vol. 26, no. 6, pp. 1166-1173, 2012.

- [90] F. Collino, M. C. Deregibus, S. Bruno et al., "Microvesicles derived from adult human bone marrow and tissue specific mesenchymal stem cells shuttle selected pattern of miRNAs," *PLoS ONE*, vol. 5, no. 7, Article ID e11803, 2010.
- [91] E. Favaro, A. Carpanetto, S. Lamorte et al., "Human mesenchymal stem cell-derived microvesicles modulate T cell response to islet antigen glutamic acid decarboxylase in patients with type 1 diabetes," *Diabetologia*, vol. 57, no. 8, pp. 1664–1673, 2014.
- [92] K. Sabin and N. Kikyo, "Microvesicles as mediators of tissue regeneration," *Translational Research*, vol. 163, no. 4, pp. 286–295, 2014.
- [93] A. Mokarizadeh, N. Delirezh, A. Morshedi, G. Mosayebi, A.-A. Farshid, and K. Mardani, "Microvesicles derived from mesenchymal stem cells: potent organelles for induction of tolerogenic signaling," *Immunology Letters*, vol. 147, no. 1-2, pp. 47–54, 2012.
- [94] M. Liu and Z. C. Han, "Mesenchymal stem cells: biology and clinical potential in type 1 diabetes therapy," *Journal of Cellular and Molecular Medicine*, vol. 12, no. 4, pp. 1155–1168, 2008.
- [95] A. Ianus, G. G. Holz, N. D. Theise, and M. A. Hussain, "In vivo derivation of glucose-competent pancreatic endocrine cells from bone marrow without evidence of cell fusion," *The Journal of Clinical Investigation*, vol. 111, no. 6, pp. 843–850, 2003.
- [96] J. B. Choi, H. Uchino, K. Azuma et al., "Little evidence of transdifferentiation of bone marrow-derived cells into pancreatic beta cells," *Diabetologia*, vol. 46, no. 10, pp. 1366–1374, 2003.
- [97] A. Lechner, Y.-G. Yang, R. A. Blacken, L. Wang, A. L. Nolan, and J. F. Habener, "No evidence for significant transdifferentiation of bone marrow into pancreatic beta-cells in vivo," *Diabetes*, vol. 53, no. 3, pp. 616–623, 2004.
- [98] J. Taneera, A. Rosengren, E. Renstrom et al., "Failure of transplanted bone marrow cells to adopt a pancreatic  $\beta$ -cell fate," *Diabetes*, vol. 55, no. 2, pp. 290–296, 2006.
- [99] R. H. Lee, M. J. Seo, R. L. Reger et al., "Multipotent stromal cells from human marrow home to and promote repair of pancreatic islets and renal glomeruli in diabetic NOD/scid mice," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 46, pp. 17438–17443, 2006.
- [100] F. E. Ezquer, M. E. Ezquer, D. B. Parrau, D. Carpio, A. J. Yañez, and P. A. Conget, "Systemic administration of multipotent mesenchymal stromal cells reverts hyperglycemia and prevents nephropathy in type 1 diabetic mice," *Biology of Blood and Marrow Transplantation*, vol. 14, no. 6, pp. 631–640, 2008.
- [101] D. Hess, L. Li, M. Martin et al., "Bone marrow-derived stem cells initiate pancreatic regeneration," *Nature Biotechnology*, vol. 21, no. 7, pp. 763–770, 2003.
- [102] D.-Q. Tang, L.-Z. Cao, B. R. Burkhardt et al., "In vivo and in vitro characterization of insulin-producing cells obtained from murine bone marrow," *Diabetes*, vol. 53, no. 7, pp. 1721–1732, 2004.
- [103] C. Moriscot, F. De Fraipont, M.-J. Richard et al., "Human bone marrow mesenchymal stem cells can express insulin and key transcription factors of the endocrine pancreas developmental pathway upon genetic and/or microenvironmental manipulation in vitro," *Stem Cells*, vol. 23, no. 4, pp. 594–603, 2005.
- [104] C. Chang, D. Niu, H. Zhou, F. Li, and F. Gong, "Mesenchymal stem cells contribute to insulin-producing cells upon microenvironmental manipulation in vitro," *Transplantation Proceedings*, vol. 39, no. 10, pp. 3363–3368, 2007.
- [105] Q.-L. Ying, J. Nichols, E. P. Evans, and A. G. Smith, "Changing potency by spontaneous fusion," *Nature*, vol. 416, no. 6880, pp. 545–548, 2002.
- [106] S.-H. Oh, T. M. Muzzonigro, S.-H. Bae, J. M. LaPlante, H. M. Hatch, and B. E. Petersen, "Adult bone marrow-derived cells trans differentiating into insulin-producing cells for the treatment of type I diabetes," *Laboratory Investigation*, vol. 84, no. 5, pp. 607–617, 2004.
- [107] L.-B. Chen, X.-B. Jiang, and L. Yang, "Differentiation of rat marrow mesenchymal stem cells into pancreatic islet beta-cells," *World Journal of Gastroenterology*, vol. 10, no. 20, pp. 3016–3020, 2004.
- [108] K. S. Choi, J.-S. Shin, J.-J. Lee, Y. S. Kim, S.-B. Kim, and C.-W. Kim, "In vitro trans-differentiation of rat mesenchymal cells into insulin-producing cells by rat pancreatic extract," *Biochemical and Biophysical Research Communications*, vol. 330, no. 4, pp. 1299–1305, 2005.
- [109] C. Chang, X. Wang, D. Niu, Z. Zhang, H. Zhao, and F. Gong, "Mesenchymal stem cells adopt  $\beta$ -cell fate upon diabetic pancreatic microenvironment," *Pancreas*, vol. 38, no. 3, pp. 275–281, 2009.
- [110] M. M. Gabr, M. M. Zakaria, A. F. Refaie et al., "Insulin-producing cells from adult human bone marrow mesenchymal stem cells control streptozotocin-induced diabetes in nude mice," *Cell Transplantation*, vol. 22, no. 1, pp. 133–145, 2013.
- [111] J. Ouyang, W. Huang, W. Yu et al., "Generation of insulin-producing cells from rat mesenchymal stem cells using an aminopyrrole derivative XW4.4," *Chemico-Biological Interactions*, vol. 208, no. 1, pp. 1–7, 2014.
- [112] P. A. Zuk, M. Zhu, P. Ashjian et al., "Human adipose tissue is a source of multipotent stem cells," *Molecular Biology of the Cell*, vol. 13, no. 12, pp. 4279–4295, 2002.
- [113] Y. J. Kim, H. K. Kim, H. K. Cho, Y. C. Bae, K. T. Suh, and J. S. Jung, "Direct comparison of human mesenchymal stem cells derived from adipose tissues and bone marrow in mediating neovascularization in response to vascular ischemia," *Cellular Physiology and Biochemistry*, vol. 20, no. 6, pp. 867–876, 2007.
- [114] C. Pendleton, Q. Li, D. A. Chesler, K. Yuan, H. Guerrero-Cazares, and A. Quinones-Hinojosa, "Mesenchymal stem cells derived from adipose tissue vs bone marrow: in vitro comparison of their tropism towards gliomas," *PLoS ONE*, vol. 8, no. 3, Article ID e58198, 2013.
- [115] S. Kern, H. Eichler, J. Stoeve, H. Klüter, and K. Bieback, "Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue," *Stem Cells*, vol. 24, no. 5, pp. 1294–1301, 2006.
- [116] S. M. Melief, J. J. Zwaginga, W. E. Fibbe, and H. Roelofs, "Adipose tissue-derived multipotent stromal cells have a higher immunomodulatory capacity than their bone marrow-derived counterparts," *Stem Cells Translational Medicine*, vol. 2, no. 6, pp. 455–463, 2013.
- [117] R. H. Lee, B. Kim, I. Choi et al., "Characterization and expression analysis of mesenchymal stem cells from human bone marrow and adipose tissue," *Cellular Physiology and Biochemistry*, vol. 14, no. 4–6, pp. 311–324, 2004.
- [118] K. Timper, D. Seboek, M. Eberhardt et al., "Human adipose tissue-derived mesenchymal stem cells differentiate into insulin, somatostatin, and glucagon expressing cells," *Biochemical and Biophysical Research Communications*, vol. 341, no. 4, pp. 1135–1140, 2006.
- [119] M. Eberhardt, P. Salmon, M.-A. von Mach et al., "Multipotent nestin and Isl-1 positive mesenchymal stem cells isolated from human pancreatic islets," *Biochemical and Biophysical Research Communications*, vol. 345, no. 3, pp. 1167–1176, 2006.



- [120] V. Chandra, S. G. S. Phadnis, P. D. Nair, and R. R. Bhonde, "Generation of pancreatic hormone-expressing islet-like cell aggregates from murine adipose tissue-derived stem cells," *Stem Cells*, vol. 27, no. 8, pp. 1941–1953, 2009.
- [121] E. Karaoz, A. Okcu, Z. S. Ünal, C. Subasi, O. Saglam, and G. Duruksu, "Adipose tissue-derived mesenchymal stromal cells efficiently differentiate into insulin-producing cells in pancreatic islet microenvironment both *in vitro* and *in vivo*," *Cytotherapy*, vol. 15, no. 5, pp. 557–570, 2013.
- [122] N. Ende, R. Chen, and A. S. Reddi, "Transplantation of human umbilical cord blood cells improves glycemia and glomerular hypertrophy in type 2 diabetic mice," *Biochemical and Biophysical Research Communications*, vol. 321, no. 1, pp. 168–171, 2004.
- [123] N. Ende, R. Chen, and A. S. Reddi, "Effect of human umbilical cord blood cells on glycemia and insulinitis in type 1 diabetic mice," *Biochemical and Biophysical Research Communications*, vol. 325, no. 3, pp. 665–669, 2004.
- [124] S. Yoshida, F. Ishikawa, N. Kawano et al., "Human cord blood-derived cells generate insulin-producing cells *in vivo*," *Stem Cells*, vol. 23, no. 9, pp. 1409–1416, 2005.
- [125] K. Bieback, S. Kern, H. Klüter, and H. Eichler, "Critical parameters for the isolation of mesenchymal stem cells from umbilical cord blood," *Stem Cells*, vol. 22, no. 4, pp. 625–634, 2004.
- [126] T. Koblas, S. M. Harman, and F. Saudek, "The application of umbilical cord blood cells in the treatment of diabetes mellitus," *The Review of Diabetic Studies*, vol. 2, no. 4, pp. 228–234, 2005.
- [127] A. Pessina, B. Eletti, C. Croera, N. Savalli, C. Diodovich, and L. Gribaldo, "Pancreas developing markers expressed on human mononucleated umbilical cord blood cells," *Biochemical and Biophysical Research Communications*, vol. 323, no. 1, pp. 315–322, 2004.
- [128] K. R. Prabakar, J. Domínguez-Bendala, R. Damaris Molano et al., "Generation of glucose-responsive, insulin-producing cells from human umbilical cord blood-derived mesenchymal stem cells," *Cell Transplantation*, vol. 21, no. 6, pp. 1321–1339, 2012.
- [129] E. Gluckman, H. E. Broxmeyer, A. D. Auerbach et al., "Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling," *The New England Journal of Medicine*, vol. 321, no. 17, pp. 1174–1178, 1989.
- [130] L. Vija, D. Farge, J.-F. Gautier et al., "Mesenchymal stem cells: stem cell therapy perspectives for type 1 diabetes," *Diabetes and Metabolism*, vol. 35, no. 2, pp. 85–93, 2009.
- [131] K. C. Chao, K. F. Chao, Y. S. Fu, and S. H. Liu, "Islet-like clusters derived from mesenchymal stem cells in Wharton's jelly of the human umbilical cord for transplantation to control type 1 diabetes," *PLoS ONE*, vol. 3, no. 1, p. e1451, 2008.
- [132] J. P. Palmer, "C-peptide in the natural history of type 1 diabetes," *Diabetes/Metabolism Research and Reviews*, vol. 25, no. 4, pp. 325–328, 2009.
- [133] L.-F. Wu, N.-N. Wang, Y.-S. Liu, and X. Wei, "Differentiation of wharton's jelly primitive stromal cells into insulin-producing cells in comparison with bone marrow mesenchymal stem cells," *Tissue Engineering—Part A*, vol. 15, no. 10, pp. 2865–2873, 2009.
- [134] D. He, J. Wang, Y. Gao, and Y. Zhang, "Differentiation of PDX1 gene-modified human umbilical cord mesenchymal stem cells into insulin-producing cells *in vitro*," *International Journal of Molecular Medicine*, vol. 28, no. 6, pp. 1019–1024, 2011.
- [135] P.-J. Tsai, H.-S. Wang, Y.-M. Shyr et al., "Transplantation of insulin-producing cells from umbilical cord mesenchymal stem cells for the treatment of streptozotocin-induced diabetic rats," *Journal of Biomedical Science*, vol. 19, no. 1, article 47, 2012.
- [136] N. El-Badri and M. A. Ghoneim, "Mesenchymal stem cell therapy in diabetes mellitus: progress and challenges," *Journal of Nucleic Acids*, vol. 2013, Article ID 194858, 7 pages, 2013.
- [137] K. Tateishi, J. He, O. Taranova, G. Liang, A. C. D'Alessio, and Y. Zhang, "Generation of insulin-secreting islet-like clusters from human skin fibroblasts," *The Journal of Biological Chemistry*, vol. 283, no. 46, pp. 31601–31607, 2008.
- [138] K. L. Seeberger, J. M. Dufour, A. M. J. Shapiro, J. R. T. Lakey, R. V. Rajotte, and G. S. Korbutt, "Expansion of mesenchymal stem cells from human pancreatic ductal epithelium," *Laboratory Investigation*, vol. 86, no. 2, pp. 141–153, 2006.
- [139] H.-T. Lin, S.-H. Chiou, C.-L. Kao et al., "Characterization of pancreatic stem cells derived from adult human pancreas ducts by fluorescence activated cell sorting," *World Journal of Gastroenterology*, vol. 12, no. 28, pp. 4529–4535, 2006.
- [140] M. C. Gershengorn, A. A. Hardikar, C. Wei, E. Ceras-Raaka, B. Marcus-Samuels, and B. M. Raaka, "Epithelial-to-mesenchymal transition generates proliferative human islet precursor cells," *Science*, vol. 306, no. 5705, pp. 2261–2264, 2004.
- [141] L. G. Chase, F. Ulloa-Montoya, B. L. Kidder, and C. M. Verfaillie, "Islet-derived fibroblast-like cells are not derived via epithelial-mesenchymal transition from Pdx-1 or insulin-positive cells," *Diabetes*, vol. 56, no. 1, pp. 3–7, 2007.
- [142] R. Abdi, P. Fiorina, C. N. Adra, M. Atkinson, and M. H. Sayegh, "Immunomodulation by mesenchymal stem cells: a potential therapeutic strategy for type 1 diabetes," *Diabetes*, vol. 57, no. 7, pp. 1759–1767, 2008.
- [143] B. Larjani, E. N. Esfahani, P. Amini et al., "Stem cell therapy in treatment of different diseases," *Acta Medica Iranica*, vol. 50, no. 2, pp. 79–96, 2012.
- [144] P. Fiorina, J. Voltarelli, and N. Zavazava, "Immunological applications of stem cells in type 1 diabetes," *Endocrine Reviews*, vol. 32, no. 6, pp. 725–754, 2011.
- [145] M. Krampera, S. Glennie, J. Dyson et al., "Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide," *Blood*, vol. 101, no. 9, pp. 3722–3729, 2003.
- [146] J. Plumas, L. Chaperot, M.-J. Richard, J.-P. Molens, J.-C. Bensa, and M.-C. Favrot, "Mesenchymal stem cells induce apoptosis of activated T cells," *Leukemia*, vol. 19, no. 9, pp. 1597–1604, 2005.
- [147] A. Bartholomew, C. Sturgeon, M. Siatskas et al., "Mesenchymal stem cells suppress lymphocyte proliferation *in vitro* and prolong skin graft survival *in vivo*," *Experimental Hematology*, vol. 30, no. 1, pp. 42–48, 2002.
- [148] F. Djouad, P. Plence, C. Bony et al., "Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals," *Blood*, vol. 102, no. 10, pp. 3837–3844, 2003.
- [149] I. Rasmusson, O. Ringdén, B. Sundberg, and K. Le Blanc, "Mesenchymal stem cells inhibit the formation of cytotoxic T lymphocytes, but not activated cytotoxic T lymphocytes or natural killer cells," *Transplantation*, vol. 76, no. 8, pp. 1208–1213, 2003.
- [150] K. le Blanc, L. Tammik, B. Sundberg, S. E. Haynesworth, and O. Ringdén, "Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex," *Scandinavian Journal of Immunology*, vol. 57, no. 1, pp. 11–20, 2003.
- [151] S. Glennie, I. Soeiro, P. J. Dyson, E. W.-F. Lam, and F. Dazzi, "Bone marrow mesenchymal stem cells induce division arrest

- energy of activated T cells," *Blood*, vol. 105, no. 7, pp. 2821–2827, 2005.
- [152] R. Maccario, M. Podestà, A. Moretta et al., "Interaction of human mesenchymal stem cells with cells involved in allo-antigen-specific immune response favors the differentiation of CD4<sup>+</sup> T-cell subsets expressing a regulatory/suppressive phenotype," *Haematologica*, vol. 90, no. 4, pp. 516–525, 2005.
- [153] E. Klyushnenkova, J. D. Mosca, V. Zernetkina et al., "T cell responses to allogeneic human mesenchymal stem cells: immunogenicity, tolerance, and suppression," *Journal of Biomedical Science*, vol. 12, no. 1, pp. 47–57, 2005.
- [154] H. K. Salem and C. Thiernemann, "Mesenchymal stromal cells: current understanding and clinical status," *Stem Cells*, vol. 28, no. 3, pp. 585–596, 2010.
- [155] K. le Blanc, C. Tammik, K. Rosendahl, E. Zetterberg, and O. Ringdén, "HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells," *Experimental Hematology*, vol. 31, no. 10, pp. 890–896, 2003.
- [156] S. Beyth, Z. Borovsky, D. Mevorach et al., "Human mesenchymal stem cells alter antigen-presenting cell maturation and induce T-cell unresponsiveness," *Blood*, vol. 105, no. 5, pp. 2214–2219, 2005.
- [157] X.-X. Jiang, Y. Zhang, B. Liu et al., "Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells," *Blood*, vol. 105, no. 10, pp. 4120–4126, 2005.
- [158] C. Li, W. Zhang, X. Jiang, and N. Mao, "Human-placenta-derived mesenchymal stem cells inhibit proliferation and function of allogeneic immune cells," *Cell and Tissue Research*, vol. 330, no. 3, pp. 437–446, 2007.
- [159] E. Zappia, S. Casazza, E. Pedemonte et al., "Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy," *Blood*, vol. 106, no. 5, pp. 1755–1761, 2005.
- [160] C. Götherström, O. Ringdén, C. Tammik, E. Zetterberg, M. Westgren, and K. Le Blanc, "Immunologic properties of human fetal mesenchymal stem cells," *The American Journal of Obstetrics and Gynecology*, vol. 190, no. 1, pp. 239–245, 2004.
- [161] J.-A. Kim, S. Hong, B. Lee et al., "The inhibition of T-cells proliferation by mouse mesenchymal stem cells through the induction of p16INK4A-cyclin D1/cdk4 and p21waf1, p27kip1-cyclin E/cdk2 pathways," *Cellular Immunology*, vol. 245, no. 1, pp. 16–23, 2007.
- [162] R. H. Schwartz, "T cell anergy," *Annual Review of Immunology*, vol. 21, pp. 305–334, 2003.
- [163] Z. Selmani, A. Naji, I. Zidi et al., "Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce CD4<sup>+</sup> CD25<sup>high</sup> FOXP3<sup>+</sup> regulatory T cells," *Stem Cells*, vol. 26, no. 1, pp. 212–222, 2008.
- [164] P. A. Sotiropoulou, S. A. Perez, A. D. Gritzapis, C. N. Baxevanis, and M. Papamichail, "Interactions between human mesenchymal stem cells and natural killer cells," *Stem Cells*, vol. 24, no. 1, pp. 74–85, 2006.
- [165] A. J. Nauta and W. E. Fibbe, "Immunomodulatory properties of mesenchymal stromal cells," *Blood*, vol. 110, no. 10, pp. 3499–3506, 2007.
- [166] M. Krampera, L. Cosmi, R. Angeli et al., "Role for interferon- $\gamma$  in the immunomodulatory activity of human bone marrow mesenchymal stem cells," *Stem Cells*, vol. 24, no. 2, pp. 386–398, 2006.
- [167] R. Meisel, A. Zibert, M. Laryea, U. Göbel, W. Däubener, and D. Dilloo, "Human bone marrow stromal cells inhibit allogeneic T-cell responses by indoleamine 2,3-dioxygenase-mediated tryptophan degradation," *Blood*, vol. 103, no. 12, pp. 4619–4621, 2004.
- [168] A. L. Mellor and D. H. Munn, "Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation?" *Immunology Today*, vol. 20, no. 10, pp. 469–473, 1999.
- [169] D. H. Munn, E. Shafizadeh, J. T. Attwood, I. Bondarev, A. Pashine, and A. L. Mellor, "Inhibition of T cell proliferation by macrophage tryptophan catabolism," *The Journal of Experimental Medicine*, vol. 189, no. 9, pp. 1363–1372, 1999.
- [170] G. Frumento, R. Rotondo, M. Tonetti, G. Damonte, U. Benatti, and G. B. Ferrara, "Tryptophan-derived catabolites are responsible for inhibition of T and natural killer cell proliferation induced by indoleamine 2,3-dioxygenase," *The Journal of Experimental Medicine*, vol. 196, no. 4, pp. 459–468, 2002.
- [171] K. Sato, K. Ozaki, I. Oh et al., "Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells," *Blood*, vol. 109, no. 1, pp. 228–234, 2007.
- [172] A. Nasef, N. Mathieu, A. Chapel et al., "Immunosuppressive effects of mesenchymal stem cells: involvement of HLA-G," *Transplantation*, vol. 84, no. 2, pp. 231–237, 2007.
- [173] G. la Rocca, R. Anzalone, S. Corrao et al., "Isolation and characterization of Oct-4<sup>+</sup>/HLA-G<sup>+</sup> mesenchymal stem cells from human umbilical cord matrix: differentiation potential and detection of new markers," *Histochemistry and Cell Biology*, vol. 131, no. 2, pp. 267–282, 2009.
- [174] D. Chabannes, M. Hill, E. Merieau et al., "A role for heme oxygenase-1 in the immunosuppressive effect of adult rat and human mesenchymal stem cells," *Blood*, vol. 110, no. 10, pp. 3691–3694, 2007.
- [175] K. Le Blanc, I. Rasmusson, C. Götherström et al., "Mesenchymal stem cells inhibit the expression of CD25 (interleukin-2 receptor) and CD38 on phytohemagglutinin-activated lymphocytes," *Scandinavian Journal of Immunology*, vol. 60, no. 3, pp. 307–315, 2004.
- [176] A. Augello, R. Tasso, S. M. Negrini et al., "Bone marrow mesenchymal progenitor cells inhibit lymphocyte proliferation by activation of the programmed death 1 pathway," *European Journal of Immunology*, vol. 35, no. 5, pp. 1482–1490, 2005.
- [177] J. Banchereau, F. Briere, C. Caux et al., "Immunobiology of dendritic cells," *Annual Review of Immunology*, vol. 18, pp. 767–811, 2000.
- [178] W. Zhang, W. Ge, C. Li et al., "Effects of mesenchymal stem cells on differentiation, maturation, and function of human monocyte-derived dendritic cells," *Stem Cells and Development*, vol. 13, no. 3, pp. 263–271, 2004.
- [179] Y.-J. Jung, S.-Y. Ju, E.-S. Yoo et al., "MSC-DC interactions: MSC inhibit maturation and migration of BM-derived DC," *Cytotherapy*, vol. 9, no. 5, pp. 451–458, 2007.
- [180] L. Chen, W. Zhang, H. Yue et al., "Effects of human mesenchymal stem cells on the differentiation of dendritic cells from CD34<sup>+</sup> cells," *Stem Cells and Development*, vol. 16, no. 5, pp. 719–731, 2007.
- [181] K. English, F. P. Barry, and B. P. Mahon, "Murine mesenchymal stem cells suppress dendritic cell migration, maturation and antigen presentation," *Immunology Letters*, vol. 115, no. 1, pp. 50–58, 2008.
- [182] W. Deng, Q. Han, L. Liao, S. You, H. Deng, and R. C. H. Zhao, "Effects of allogeneic bone marrow-derived mesenchymal stem

- cells on T and B lymphocytes from BXSB mice," *DNA and Cell Biology*, vol. 24, no. 7, pp. 458–463, 2005.
- [183] A. Corcione, F. Benvenuto, E. Ferretti et al., "Human mesenchymal stem cells modulate B-cell functions," *Blood*, vol. 107, no. 1, pp. 367–372, 2006.
- [184] J. M. Ryan, F. P. Barry, J. M. Murphy, and B. P. Mahon, "Mesenchymal stem cells avoid allogeneic rejection," *Journal of Inflammation (London, England)*, vol. 2, article 8, 2005.
- [185] G. M. Spaggiari, A. Capobianco, S. Becchetti, M. C. Mingari, and L. Moretta, "Mesenchymal stem cell-natural killer cell interactions: evidence that activated NK cells are capable of killing MSCs, whereas MSCs can inhibit IL-2-induced NK-cell proliferation," *Blood*, vol. 107, no. 4, pp. 1484–1490, 2006.
- [186] E. Gerdoni, B. Gallo, S. Casazza et al., "Mesenchymal stem cells effectively modulate pathogenic immune response in experimental autoimmune encephalomyelitis," *Annals of Neurology*, vol. 61, no. 3, pp. 219–227, 2007.
- [187] A. Augello, R. Tasso, S. M. Negrini, R. Cancedda, and G. Pennesi, "Cell therapy using allogeneic bone marrow mesenchymal stem cells prevents tissue damage in collagen-induced arthritis," *Arthritis and Rheumatism*, vol. 56, no. 4, pp. 1175–1186, 2007.
- [188] F. Djouad, V. Fritz, F. Apparailly et al., "Reversal of the immunosuppressive properties of mesenchymal stem cells by tumor necrosis factor  $\alpha$  in collagen-induced arthritis," *Arthritis & Rheumatism*, vol. 52, no. 5, pp. 1595–1603, 2005.
- [189] A. Shabbir, D. Zisa, M. Leiker, C. Johnston, H. Lin, and T. Lee, "Muscular dystrophy therapy by nonautologous mesenchymal stem cells: muscle regeneration without immunosuppression and inflammation," *Transplantation*, vol. 87, no. 9, pp. 1275–1282, 2009.
- [190] T. Saito, J.-Q. Kuang, B. Bittira, A. Al-Khalidi, and R. C.-J. Chiu, "Xenotransplant cardiac chimera: immune tolerance of adult stem cells," *The Annals of Thoracic Surgery*, vol. 74, no. 1, pp. 19–24, 2002.
- [191] M. Bakhtiary, M. Marzban, M. Mehdizadeh et al., "Combination of stem cell mobilized by granulocyte-colony stimulating factor and human umbilical cord matrix stem cell: therapy of traumatic brain injury in rats," *Iranian Journal of Basic Medical Sciences*, vol. 14, no. 4, pp. 327–339, 2011.
- [192] S. J. Hashemian, M. Tondar, and B. Laribi, "Intravenous injection of human umbilical cord matrix stem cell (Wharton jelly stem cell) provides functional recovery in a rat model of traumatic brain injury," *Yakhteh Medical Journal*, vol. 12, no. 1, pp. 87–96, 2010.
- [193] O. N. Koç, S. L. Gerson, B. W. Cooper et al., "Rapid hematopoietic recovery after coinfusion of autologous-blood stem cells and culture-expanded marrow mesenchymal stem cells in advanced breast cancer patients receiving high-dose chemotherapy," *Journal of Clinical Oncology*, vol. 18, no. 2, pp. 307–316, 2000.
- [194] H. M. Lazarus, S. E. Haynesworth, S. L. Gerson, N. S. Rosenthal, and A. I. Caplan, "Ex vivo expansion and subsequent infusion of human bone marrow-derived stromal progenitor cells (mesenchymal progenitor cells): implications for therapeutic use," *Bone Marrow Transplantation*, vol. 16, no. 4, pp. 557–564, 1995.
- [195] K. Le Blanc, I. Rasmusson, B. Sundberg et al., "Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells," *The Lancet*, vol. 363, no. 9419, pp. 1439–1441, 2004.
- [196] H. M. Lazarus, O. N. Koc, S. M. Devine et al., "Cotransplantation of HLA-identical sibling culture-expanded mesenchymal stem cells and hematopoietic stem cells in hematologic malignancy patients," *Biology of Blood and Marrow Transplantation*, vol. 11, no. 5, pp. 389–398, 2005.
- [197] M. Sundin, O. Ringdén, B. Sundberg, S. Nava, C. Götherström, and K. le Blanc, "No alloantibodies against mesenchymal stromal cells, but presence of anti-fetal calf serum antibodies, after transplantation in allogeneic hematopoietic stem cell recipients," *Haematologica*, vol. 92, no. 9, pp. 1208–1215, 2007.
- [198] O. Ringdén, M. Uzunel, I. Rasmusson et al., "Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease," *Transplantation*, vol. 81, no. 10, pp. 1390–1397, 2006.
- [199] A. J. Nauta, G. Westerhuis, A. B. Kruisselbrink, E. G. A. Lurvink, R. Willemze, and W. E. Fibbe, "Donor-derived mesenchymal stem cells are immunogenic in an allogeneic host and stimulate donor graft rejection in a nonmyeloablative setting," *Blood*, vol. 108, no. 6, pp. 2114–2120, 2006.
- [200] N. Eliopoulos, J. Stagg, L. Lejeune, S. Pommey, and J. Galipeau, "Allogeneic marrow stromal cells are immune rejected by MHC class I- and class II-mismatched recipient mice," *Blood*, vol. 106, no. 13, pp. 4057–4065, 2005.
- [201] O. N. Koç, J. Day, M. Nieder, S. L. Gerson, H. M. Lazarus, and W. Krivit, "Allogeneic mesenchymal stem cell infusion for treatment of metachromatic leukodystrophy (MLD) and Hurler syndrome (MPS-IH)," *Bone Marrow Transplantation*, vol. 30, no. 4, pp. 215–222, 2002.
- [202] D. García-Olmo, M. García-Arranz, D. Herreros, I. Pascual, C. Peiro, and J. A. Rodríguez-Montes, "A phase I clinical trial of the treatment of crohn's fistula by adipose mesenchymal stem cell transplantation," *Diseases of the Colon and Rectum*, vol. 48, no. 7, pp. 1416–1423, 2005.
- [203] G. M. Forbes, M. J. Sturm, R. W. Leong et al., "A phase 2 study of allogeneic mesenchymal stromal cells for luminal crohn's disease refractory to biologic therapy," *Clinical Gastroenterology and Hepatology*, vol. 12, no. 1, pp. 64–71, 2014.
- [204] W. Y. Lee, K. J. Park, Y. B. Cho et al., "Autologous adipose tissue-derived stem cells treatment demonstrated favorable and sustainable therapeutic effect for crohn's fistula," *Stem Cells*, vol. 31, no. 11, pp. 2575–2581, 2013.
- [205] F. De La Portilla, F. Alba, D. García-Olmo, J. M. Herrerías, F. X. González, and A. Galindo, "Expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of complex perianal fistula in Crohn's disease: results from a multicenter phase I/IIa clinical trial," *International Journal of Colorectal Disease*, vol. 28, no. 3, pp. 313–323, 2013.
- [206] I. Boumaza, S. Srinivasan, W. T. Witt et al., "Autologous bone marrow-derived rat mesenchymal stem cells promote PDX-1 and insulin expression in the islets, alter T cell cytokine pattern and preserve regulatory T cells in the periphery and induce sustained normoglycemia," *Journal of Autoimmunity*, vol. 32, no. 1, pp. 33–42, 2009.
- [207] W. Zhao, Y. Wang, D. Wang et al., "TGF- $\beta$  expression by allogeneic bone marrow stromal cells ameliorates diabetes in NOD mice through modulating the distribution of CD4<sup>+</sup> T cell subsets," *Cellular Immunology*, vol. 253, no. 1-2, pp. 23–30, 2008.
- [208] M. Jurewicz, S. Yang, A. Augello et al., "Congenic mesenchymal stem cell therapy reverses hyperglycemia in experimental type 1 diabetes," *Diabetes*, vol. 59, no. 12, pp. 3139–3147, 2010.
- [209] P. Fiorina, M. Jurewicz, A. Augello et al., "Immunomodulatory function of bone marrow-derived mesenchymal stem cells in experimental autoimmune type 1 diabetes," *Journal of Immunology (Baltimore, Md : 1950)*, vol. 183, no. 2, pp. 993–1004, 2009.



- [210] È. J. Bassi, P. M. M. Moraes-Vieira, C. S. R. Moreira-Sá et al., "Immune regulatory properties of allogeneic adipose-derived mesenchymal stem cells in the treatment of experimental autoimmune diabetes," *Diabetes*, vol. 61, no. 10, pp. 2534–2545, 2012.
- [211] V. S. Urbán, J. Kiss, J. Kovács et al., "Mesenchymal stem cells cooperate with bone marrow cells in therapy of diabetes," *Stem Cells*, vol. 26, no. 1, pp. 244–253, 2008.
- [212] A. M. Madec, R. Mallone, G. Afonso et al., "Mesenchymal stem cells protect NOD mice from diabetes by inducing regulatory T cells," *Diabetologia*, vol. 52, no. 7, pp. 1391–1399, 2009.
- [213] G. Ren, J. Su, L. Zhang et al., "Species variation in the mechanisms of mesenchymal stem cell-mediated immunosuppression," *Stem Cells*, vol. 27, no. 8, pp. 1954–1962, 2009.
- [214] M. Banerjee, A. Kumar, and R. R. Bhonde, "Reversal of experimental diabetes by multiple bone marrow transplantation," *Biochemical and Biophysical Research Communications*, vol. 328, no. 1, pp. 318–325, 2005.
- [215] S. Sumi, Y. Gu, A. Hiura, and K. Inoue, "Stem cells and regenerative medicine for diabetes mellitus," *Pancreas*, vol. 29, no. 3, pp. e85–e89, 2004.
- [216] X.-H. Wu, C.-P. Liu, K.-F. Xu et al., "Reversal of hyperglycemia in diabetic rats by portal vein transplantation of islet-like cells generated from bone marrow mesenchymal stem cells," *World Journal of Gastroenterology*, vol. 13, no. 24, pp. 3342–3349, 2007.
- [217] J. Xu, Y. Lu, F. Ding, X. Zhan, M. Zhu, and Z. Wang, "Reversal of diabetes in mice by intrahepatic injection of bone-derived GFP-murine mesenchymal stem cells infected with the recombinant retrovirus-carrying human insulin gene," *World Journal of Surgery*, vol. 31, no. 9, pp. 1872–1882, 2007.
- [218] O. Karnieli, Y. Izhar-Prato, S. Bulvik, and S. Efrat, "Generation of insulin-producing cells from human bone marrow mesenchymal stem cells by genetic manipulation," *Stem Cells*, vol. 25, no. 11, pp. 2837–2844, 2007.
- [219] A. Bhansali, V. Upreti, N. Khandelwal et al., "Efficacy of autologous bone marrow-derived stem cell transplantation in patients with type 2 diabetes mellitus," *Stem Cells and Development*, vol. 18, no. 10, pp. 1407–1416, 2009.
- [220] H. A. Russ, E. Sintov, L. Anker-Kitai et al., "Insulin-Producing cells generated from dedifferentiated human pancreatic beta cells expanded in vitro," *PLoS ONE*, vol. 6, no. 9, Article ID e25566, 2011.
- [221] W. Bennet, C.-G. Groth, R. Larsson, B. Nilsson, and O. Korsgren, "Isolated human islets trigger an instant blood mediated inflammatory reaction: implications for intraportal islet transplantation as a treatment for patients with type 1 diabetes," *Uppsala Journal of Medical Sciences*, vol. 105, no. 2, pp. 125–133, 2000.
- [222] D. J. van der Windt, R. Bottino, A. Casu, N. Campanile, and D. K. C. Cooper, "Rapid loss of intraportally transplanted islets: an overview of pathophysiology and preventive strategies," *Xenotransplantation*, vol. 14, no. 4, pp. 288–297, 2007.
- [223] B. O. Roep, I. Stobbe, G. Duinkerken et al., "Auto- and allo-immune reactivity to human islet allografts transplanted into type 1 diabetic patients," *Diabetes*, vol. 48, no. 3, pp. 484–490, 1999.
- [224] B. M. Prior, H. T. Yang, and R. L. Terjung, "What makes vessels grow with exercise training?" *Journal of Applied Physiology*, vol. 97, no. 3, pp. 1119–1128, 2004.
- [225] G. Christoffersson, J. Henriksnäs, L. Johansson et al., "Clinical and experimental pancreatic islet transplantation to striated muscle: establishment of a vascular system similar to that in native islets," *Diabetes*, vol. 59, no. 10, pp. 2569–2578, 2010.
- [226] J. Svensson, J. Lau, M. Sandberg, and P.-O. Carlsson, "High vascular density and oxygenation of pancreatic islets transplanted in clusters into striated muscle," *Cell Transplantation*, vol. 20, no. 5, pp. 783–788, 2011.
- [227] T. Ito, S. Itakura, I. Todorov et al., "Mesenchymal stem cell and islet co-transplantation promotes graft revascularization and function," *Transplantation*, vol. 89, no. 12, pp. 1438–1445, 2010.
- [228] J. H. Ho, T.-C. Tseng, W.-H. Ma et al., "Multiple intravenous transplantations of mesenchymal stem cells effectively restore long-term blood glucose homeostasis by hepatic engraftment and  $\beta$ -cell differentiation in streptozocin-induced diabetic mice," *Cell Transplantation*, vol. 21, no. 5, pp. 997–1009, 2012.
- [229] Q.-Y. Dong, L. Chen, G.-Q. Gao et al., "Allogeneic diabetic mesenchymal stem cells transplantation in streptozotocin-induced diabetic rat," *Clinical and Investigative Medicine*, vol. 31, no. 6, pp. E328–E337, 2008.
- [230] Y. Sun, L. Chen, X.-G. Hou et al., "Differentiation of bone marrow-derived mesenchymal stem cells from diabetic patients into insulin-producing cells in vitro," *Chinese Medical Journal*, vol. 120, no. 9, pp. 771–776, 2007.
- [231] Y. Li, R. Zhang, H. Qiao et al., "Generation of insulin-producing cells from PDX-1 gene-modified human mesenchymal stem cells," *Journal of Cellular Physiology*, vol. 211, no. 1, pp. 36–44, 2007.
- [232] H. Kajiyama, T. S. Hamazaki, M. Tokuhara et al., "Pdx1-transfected adipose tissue-derived stem cells differentiate into insulin-producing cells in vivo and reduce hyperglycemia in diabetic mice," *The International Journal of Developmental Biology*, vol. 54, no. 4, pp. 699–705, 2010.
- [233] G. P. Fadini, S. Sartore, M. Schiavon et al., "Diabetes impairs progenitor cell mobilisation after hindlimb ischaemia-reperfusion injury in rats," *Diabetologia*, vol. 49, no. 12, pp. 3075–3084, 2006.
- [234] K. A. Gallagher, Z.-J. Liu, M. Xiao et al., "Diabetic impairments in NO-mediated endothelial progenitor cell mobilization and homing are reversed by hyperoxia and SDF-1 $\alpha$ ," *The Journal of Clinical Investigation*, vol. 117, no. 5, pp. 1249–1259, 2007.
- [235] L. Shin and D. A. Peterson, "Impaired therapeutic capacity of autologous stem cells in a model of type 2 diabetes," *Stem Cells Translational Medicine*, vol. 1, no. 2, pp. 125–135, 2012.
- [236] N. S. El-Badri, A. Hakki, A. Ferrari, R. Shamekh, and R. A. Good, "Autoimmune disease: is it a disorder of the microenvironment?" *Immunologic Research*, vol. 41, no. 1, pp. 79–86, 2008.
- [237] P. Lin, L. Chen, N. Yang, Y. Sun, and Y. X. Xu, "Evaluation of stem cell differentiation in diabetic rats transplanted with bone marrow mesenchymal stem cells," *Transplantation Proceedings*, vol. 41, no. 5, pp. 1891–1893, 2009.
- [238] S. Zhu, Y. Lu, J. Zhu et al., "Effects of intrahepatic bone-derived mesenchymal stem cells autotransplantation on the diabetic Beagle dogs," *The Journal of Surgical Research*, vol. 168, no. 2, pp. 213–223, 2011.
- [239] A. Milanese, J.-W. Lee, Z. Li et al., " $\beta$ -Cell regeneration mediated by human bone marrow mesenchymal stem cells," *PLoS ONE*, vol. 7, no. 8, Article ID e42177, 2012.
- [240] E. C. Opara, S.-H. Mirmalek-Sani, O. Khanna, M. L. Moya, and E. M. Brey, "Design of a bioartificial pancreas(+)," *Journal of Investigative Medicine*, vol. 58, no. 7, pp. 831–837, 2010.
- [241] R. A. Pareta, A. C. Farney, and E. C. Opara, "Design of a bioartificial pancreas," *Pathobiology*, vol. 80, no. 4, pp. 194–202, 2013.

- [242] J. Beck, R. Angus, B. Madsen, D. Britt, B. Vernon, and K. T. Nguyen, "Islet encapsulation: strategies to enhance islet cell functions," *Tissue Engineering*, vol. 13, no. 3, pp. 589–599, 2007.
- [243] D. M. Salvay, C. B. Rives, X. Zhang et al., "Extracellular matrix protein-coated scaffolds promote the reversal of diabetes after extrahepatic islet transplantation," *Transplantation*, vol. 85, no. 10, pp. 1456–1464, 2008.
- [244] Y. Lai, D. Schneider, A. Kiszun et al., "Vascular endothelial growth factor increases functional  $\beta$ -cell mass by improvement of angiogenesis of isolated human and murine pancreatic islets," *Transplantation*, vol. 79, no. 11, pp. 1530–1536, 2005.
- [245] M. Brissova and A. C. Powers, "Revascularization of transplanted islets: can it be Improved?" *Diabetes*, vol. 57, no. 9, pp. 2269–2271, 2008.
- [246] K. R. Knight, Y. Uda, M. W. Findlay et al., "Vascularized tissue-engineered chambers promote survival and function of transplanted islets and improve glycemic control," *The FASEB Journal*, vol. 20, no. 3, pp. 565–567, 2006.
- [247] H. Blomeier, X. Zhang, C. Rives et al., "Polymer scaffolds as synthetic microenvironments for extrahepatic islet transplantation," *Transplantation*, vol. 82, no. 4, pp. 452–459, 2006.
- [248] R. F. Gibly, X. Zhang, M. L. Graham et al., "Extrahepatic islet transplantation with microporous polymer scaffolds in syngeneic mouse and allogeneic porcine models," *Biomaterials*, vol. 32, no. 36, pp. 9677–9684, 2011.
- [249] T. Saito, K. Ohashi, R. Utoh et al., "Reversal of diabetes by the creation of neo-islet tissues into a subcutaneous site using islet cell sheets," *Transplantation*, vol. 92, no. 11, pp. 1231–1236, 2011.
- [250] D. Y. Lee, S. J. Park, J. H. Nam, and Y. Byun, "A new strategy toward improving immunoprotection in cell therapy for diabetes mellitus: long-functioning PEGylated islets in vivo," *Tissue Engineering*, vol. 12, no. 3, pp. 615–623, 2006.
- [251] J. A. Giraldo, J. D. Weaver, and C. L. Stabler, "Enhancing Clinical Islet Transplantation through Tissue Engineering Strategies," *Journal of Diabetes Science and Technology*, vol. 4, no. 5, pp. 1238–1247, 2010.
- [252] G.-H. Mao, G.-A. Chen, H.-Y. Bai, T.-R. Song, and Y.-X. Wang, "The reversal of hyperglycaemia in diabetic mice using PLGA scaffolds seeded with islet-like cells derived from human embryonic stem cells," *Biomaterials*, vol. 30, no. 9, pp. 1706–1714, 2009.
- [253] P. K. Ngoc, P. van Phuc, T. H. Nhung, D. T. Thuy, and N. T. M. Nguyet, "Improving the efficacy of type 1 diabetes therapy by transplantation of immunoisolated insulin-producing cells," *Human Cell*, vol. 24, no. 2, pp. 86–95, 2011.
- [254] S. Vériter, N. Aouassar, P.-Y. Adnet et al., "The impact of hyperglycemia and the presence of encapsulated islets on oxygenation within a bioartificial pancreas in the presence of mesenchymal stem cells in a diabetic Wistar rat model," *Biomaterials*, vol. 32, no. 26, pp. 5945–5956, 2011.
- [255] D. Rubio, J. Garcia-Castro, M. C. Martín et al., "Spontaneous human adult stem cell transformation," *Cancer Research*, vol. 65, no. 8, pp. 3035–3039, 2005.
- [256] M. Miura, Y. Miura, H. M. Padilla-Nash et al., "Accumulated chromosomal instability in murine bone marrow mesenchymal stem cells leads to malignant transformation," *Stem Cells*, vol. 24, no. 4, pp. 1095–1103, 2006.
- [257] J. Tolar, A. J. Nauta, M. J. Osborn et al., "Sarcoma derived from cultured mesenchymal stem cells," *Stem Cells*, vol. 25, no. 2, pp. 371–379, 2007.
- [258] M. P. de Miguel, S. Fuentes-Julián, A. Blázquez-Martínez et al., "Immunosuppressive properties of mesenchymal stem cells: advances and applications," *Current Molecular Medicine*, vol. 12, no. 5, pp. 574–591, 2012.
- [259] Z. Han, Y. Jing, S. Zhang, Y. Liu, Y. Shi, and L. Wei, "The role of immunosuppression of mesenchymal stem cells in tissue repair and tumor growth," *Cell and Bioscience*, vol. 2, no. 1, article 8, 2012.
- [260] H. L. Trivedi, A. V. Vanikar, U. Thakker et al., "Human adipose tissue-derived mesenchymal stem cells combined with hematopoietic stem cell transplantation synthesize insulin," *Transplantation Proceedings*, vol. 40, no. 4, pp. 1135–1139, 2008.
- [261] A. V. Vanikar, H. L. Trivedi, S. D. Dave, and U. G. Thakkar, "Cotransplantation of adipose tissue-derived insulin-secreting mesenchymal stem cells and hematopoietic stem cells: a novel therapy for insulin-dependent diabetes mellitus," *Stem Cells International*, vol. 2010, Article ID 582382, 5 pages, 2010.
- [262] J. Hu, X. Yu, Z. Wang et al., "Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus," *Endocrine Journal*, vol. 60, no. 3, pp. 347–357, 2013.
- [263] L. Chen, J. Dong, W. Hou et al., "Sustained effect of autologous bone marrow mononuclear cell transplantation in patients with diabetes 12 month follow-up," *Transplantation*, vol. 86, no. 2S, p. 162, 2008.
- [264] S. M. Phadnis, M. V. Joglekar, M. P. Dalvi et al., "Human bone marrow-derived mesenchymal cells differentiate and mature into endocrine pancreatic lineage in vivo," *Cytotherapy*, vol. 13, no. 3, pp. 279–293, 2011.
- [265] F. Djouad, C. Bony, F. Apparailly, P. Louis-Pence, C. Jorgensen, and D. Noël, "Earlier onset of syngeneic tumors in the presence of mesenchymal stem cells," *Transplantation*, vol. 82, no. 8, pp. 1060–1066, 2006.
- [266] M. Studeny, F. C. Marini, R. E. Champlin, C. Zompetta, I. J. Fidler, and M. Andreeff, "Bone marrow-derived mesenchymal stem cells as vehicles for interferon- $\beta$  delivery into tumors," *Cancer Research*, vol. 62, no. 13, pp. 3603–3608, 2002.
- [267] A. Y. Khakoo, S. Pati, S. A. Anderson et al., "Human mesenchymal stem cells exert potent antitumorigenic effects in a model of Kaposi's sarcoma," *The Journal of Experimental Medicine*, vol. 203, no. 5, pp. 1235–1247, 2006.
- [268] Y.-R. Lu, Y. Yuan, X.-J. Wang et al., "The growth inhibitory effect of mesenchymal stem cells on tumor cells in vitro and in vivo," *Cancer Biology & Therapy*, vol. 7, no. 2, pp. 245–251, 2008.
- [269] J. L. Spees, C. A. Gregory, H. Singh et al., "Internalized antigens must be removed to prepare hypoimmunogenic mesenchymal stem cells for cell and gene therapy," *Molecular Therapy*, vol. 9, no. 5, pp. 747–756, 2004.