Stem Cell Transplantation in the Treatment of Type 1 Diabetes Mellitus: From Insulin Replacement to Beta-Cell Replacement

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Type 1 diabetes mellitus (T1DM) is an autoimmune disease that attacks pancreatic β-cells, leading to the destruction of insulin-related islet β-cells. Islet β-cell transplantation has been proven as a curative measure in T1DM. However, a logarithmic increase in the global population with diabetes, limited donor supply, and the need for lifelong immunosuppression restrict the widespread use of β-cell transplantation. Numerous therapeutic approaches have been taken to search for substitutes of β-cells, among which stem cell transplantation is one of the most promising alternatives. Stem cells have demonstrated the potential efficacy to treat T1DM by reconstitution of immunotolerance and preservation of islet β-cell function in recent research. cGMP-grade stem cell products have been used in human clinical trials, showing that stem cell transplantation has beneficial effects on T1DM, with no obvious adverse reactions. To better achieve remission of T1DM by stem cell transplantation, in this work, we explain the progression of stem cell transplantation such as mesenchymal stem cells (MSCs), human embryonic stem cells (hESCs), and bone marrow hematopoietic stem cells (BM-HSCs) to restore the immunotolerance and preserve the islet β-cell function of T1DM in recent years. This review article provides evidence of the clinical applications of stem cell therapy in the treatment of T1DM.

Keywords: type 1 diabetes mellitus, stem cell, β-cell, immunotolerance, transplantation

1 INTRODUCTION

Diabetes mellitus (DM) characterized by hyperglycemia, caused by insufficient insulin secretion or insulin resistance, is a group of chronic metabolic diseases. According to the International Diabetes Federation (IDF), the global adult diabetes population will exceed 537 million by 2021, and more than three-fourths of people with diabetes live in low- and middle-income countries, indicating that
diabetes disproportionately affects the poor (http://www.diabetesatlas.org/). Diabetes is classified into four types: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and monogenic diabetes mellitus (1–5). T1DM is an autoimmune disease, where autoreactive T cells attack pancreatic β-cells, leading to insulitis-related islet β-cell destruction, which results in an absolute lack of insulin secretion causing hyperglycemia, abnormal glucose metabolism, and lifelong dependence on exogenous insulin. The majority of T1DM patients have poor blood glucose control and large blood sugar fluctuation. Chronic hyperglycemia results in the development of serious complications associated with diabetes, such as microvascular and macrovascular complications, reducing the quality of life and causing a considerable economic burden on T1DM patients and the society (6). The incidence rate of T1DM is increasing every year around the world (7, 8). Although there is evidence that a combination of genetic susceptibility and environmental factors can increase the risk of immune disorder in T1DM patients, the exact etiology of the impaired immune system in T1DM is still unclear. More scientific efforts are needed to prevent β-cell loss and improve the quality of life in T1DM.

2 THE DIFFICULTIES OF INSULIN REPLACEMENT AND β-CELL REPLACEMENT IN T1DM

At present, the treatment and preventive options for T1DM are limited, mainly through insulin replacement therapy. T1DM cannot be cured; patients must rely on exogenous insulin injections for the rest of their lives to maintain glycemic control. Lente and NPH insulin were the only effective methods for the treatment of T1DM in the past (9, 10). In recent years, novel approaches to insulin treatment, such as the introduction of glycosylated hemoglobin assays (HbA1c) and continuous glucose monitoring (CGM), have been used, and the effectiveness of basal/bolus therapy using portable continuous subcutaneous insulin infusion (CSII) pumps and closed-loop artificial pancreas system has been demonstrated. Artificial pancreas combining CGM with CSII pumps could automatically administer an appropriate insulin dose via a dosing algorithm. Some randomized controlled trials proved that the artificial pancreas system could efficiently adjust the glycemic index by automatically delivering exogenous insulin with dosing algorithms based on sensor glucose levels (11). However, the lag time of glycemia detected by CGM and the risk of hypoglycemia and infections limit the application of artificial pancreas, and some of the patients with unawareness of hypoglycemic events such as brittle type T1DM are not qualified to use the artificial pancreas (12, 13). Also, insulin replacement therapy can only supplement the missing insulin and cannot fundamentally restore the function of the pancreas. Although these achievements can better manage blood glucose and large blood sugar fluctuation in T1DM, they can hardly prevent the occurrence of a series of complications, including microvascular, macrovascular, and neuropathy complications (14, 15). As a result, many adjunctive therapies, such as dietary and weight management, nutrition therapy, physical activity and exercise, and some drugs used to treat T2DM, have been proposed to treat T1DM, which alleviate blood glucose fluctuation and reduce the lifetime risk of complications to some extent, but their effectiveness is limited. Therefore, it is very important to develop better technology and equipment for diagnosis and treatment options to prevent T1DM (16–18).

β-Cell replacement has also been proven as a curative measure in T1DM, which may be achieved through pancreas or islet transplantation in selective candidates (19). Pancreatic transplantation has the potential of re-establishing physiologic-regulated insulin production, obviously decreasing the risk of hypoglycemic unawareness and finally decreasing the lifetime risk of mortality from severe hypoglycemic complications (20). Since 2000, β-cell replacement through intrahepatic isolated islet transplantation has proven efficacious, indicating that islet transplantation is also an important option in the treatment of T1DM (21). Compared with the artificial pancreas system, islet transplantation and pancreatic transplantation were the better options to relieve the symptom of T1DM patients with unawareness of hypoglycemic events such as brittle type T1DM for a long time (22). T1DM patients can be clinically alleviated through improved control of the levels of blood glucose and restored awareness of hypoglycemia, resulting in the prevention of several life-threatening complications associated with diabetes, such as diabetic foot, microvascular and macrovascular diseases, kidney failure, nerve damage, and blindness (23). During the process of pancreatic or islet transplantation, both the autoimmune and alloimmune systems are still major threats to increase the transplantation risk. Patients treated with cell replacement therapies require immunosuppressive drugs as life-long treatment, and in many cases, these drugs lead to toxicities and side effects that made the adoption of this treatment strategy limited to only the most severe disease cases, inhibiting the widespread adoption of pancreatic or islet transplantation therapies in T1DM (24).

Besides the immune problem, the logarithmic increase in the global population of people with diabetes, the limited donor supply, and the need for lifelong immunosuppression restrict its widespread use (25). Numerous therapeutic approaches have been reported to solve this problem, including the search for β-cell substitutes, porcine islet xenotransplantation, and stem cell transplantations, which present solutions to the donor shortage and may be the most likely alternatives (26, 27).

Although the artificial pancreas system and pancreatic transplantation in T1DM can normalize and improve glycemic control in T1DM, the application of artificial pancreas systems and pancreatic transplantation is still limited due to their shortage. To solve the problem, stem cell transplant is a promising new strategy for patients with T1DM. There are many advantages of stem cells in the treatment of T1DM: first of all, stem cells such as bone marrow-derived stem cells (MSCs) can easily be obtained from bone marrow, umbilical cord blood, adipose tissue, etc. compared with islet and pancreas; secondly,
the pluripotent stem cells could differentiate into β-cells and increase the secretion of insulin; thirdly, stem cells can moderate the immunome effect by inhibiting T-cell proliferation and reduce the inflammatory response, which can protect β-cells from autoimmune attack; and finally, stem cells can secrete cytokines by paracrine effects to enhance the antioxidant and proliferation ability of cells, which can help improve the survival of β-cells. To better understand the constitution of immunotolerance and preservation of islet β-cell function, we reviewed the progression of stem cells in recent years and tried to provide support for the clinical applications of stem cell therapy in the treatment of T1DM, especially in the brittle type T1DM.

3 STEM CELL TRANSPLANTATION THERAPY FOR T1DM

Stem cells are undifferentiated cells capable of self-renewal, giving rise to virtually any tissue or organ (28–33). Stem cells can be grouped into four broad categories based on their origin: adult stem cells (ASCs), fetal stem cells (FSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs). iPSCs and ESCs are pluripotent stem cells (PSCs), whereas ASCs are unipotent or oligopotent (34–36). PSCs, such as human-induced PSCs (iPSCs) and human embryonic stem cells (ESCs), offer a reproducible source of human cells at a very early developmental stage with the potential to form any cell type in the adult body (37–39). iPSCs, human cord blood-derived multipotent stem cells (CB-SCs), hematopoietic stem cells (HSCs), and MSCs were used for the preservation of β-cells by islet protection and regeneration, and another potent function of stem cells is the ability to re-establish peripheral tolerance toward β-cells through remodeling of the immune response as well as through inhibition of autoreactive T-cell function (40, 41). In general, stem cells can increase the mass of islets by the ability of differentiation to β-cells-like organoids, and reconstitute immunotolerance by inhibiting the immune response of T cell and Th1 cells through TGF-β and inflammatory pathways (Figure 1). As T1DM is featured as an autoimmune disease by activating immune cells to attack and destroy pancreatic β-cells, the immunomodulatory properties of stems cells and its potential ability of differentiation into insulin-producing cells should be considered when using stem cell therapy for T1DM treatment.

3.1 MSC Transplantation in T1DM

MSCs are one of the best candidate cells used as cell therapy for T1DM. MSCs are fibroblast-like, multipotent stromal, non-hematopoietic cells that could easily be sourced from various tissues, including adipose tissue, bone marrow, and umbilical cord blood (42). MSCs rapidly undergo mesodermal lineage differentiation, such as adipocytes, myoblasts, cardiomyocytes, chondrocytes, and β-cell-like cells (43–45). The bone marrow and umbilical cord blood could be separated over a gradient of Percoll by density gradient centrifugation to collect the MNCs, and the MNCs were washed with PBS and transferred to a 100-mm culture dish to induce MSCs. The redundant tissues such as arteries and veins were removed from the adipose tissue, human umbilical cord, etc. The region of the remaining adipose or human umbilical cord tissues was diced into small fragments and seeded into a 100-mm culture dish to collect the MSCs. The induced MSCs were stored in liquid nitrogen and cultured for up to five passages for transplantation via intravenous injection. The characteristics of MSCs were defined by the International Society for Cell Therapy (ISCT) as follows: adherence to plastic; expression of the surface molecules CD73, CD90, and CD105 in the absence of CD34, CD45, HLA-DR, and CD14 or CD11b and CD79a or CD19; and the capacity for differentiation to adipocytes, osteoblasts, and chondroblasts in vitro (46). The potential of MSCs as a cell-based therapy in the treatment of immunologic disorders has been well established (47). MSCs can alter the microenvironment in tissues and promote existing β-cell survival and regeneration, resulting in increased β-cell mass and normal blood glucose recovery (48–51). Injection of bone marrow MSCs into diabetic mice can increase insulin levels and downregulate hyperglycemia; the exosomes derived from human umbilical cord stem cells (hUCMSCs) can enhance insulin sensitivity (52). Similarly, monotherapy with human umbilical cord MSCs reverses autoimmunity, promotes islet cell regeneration, and improves blood glucose control (53–55).

The allogeneic MSCs have been attempted in clinical trials, which can improve the level of insulin and C-peptide and reduce blood glucose. Although MSC xenotransplantation was not used in the clinics, several pieces of evidence showed that human-derived MSCs could alleviate the diabetic symptom through β-cell-like organoid differentiation and immunomodulation in NOD mice, rats, and monkeys, while far-red light, gene editing, and other modifications could enhance the function of MSCs in a T1DM animal model, indicating that the intervening and xenograft MSCs are the potential option for T1DM treatment.

3.1.1 Immunomodulatory Ability of MSCs

MSCs can protect β-cell, increase the secretion of insulin, and reduce glycemia in patients with T1DM by regulating the immune system. The application of MSCs in eliminating autoimmune diseases has been fully proven in an animal model, and MSCs have a wide range of regulatory effects on immune cells. Domouky et al. showed that MSCs could reduce hyperglycemia in diabetic rats on day 15 (56). The inhibition of T-cell proliferation in islets and the presence of increased Treg in T1DM were features of MSCs’ autoimmune properties (57). Shigemoto-Kuroda et al. developed T1DM mouse models for autoimmune diseases and discovered that MSCs could suppress type 1 helper T cell (Th1) development and delay the onset of T1DM in mice. CD4+ cells were found in significant numbers in the islets of mice treated with PBS, while fewer CD4+ cells were found in the islets of MSC-treated mice. The level of insulin in plasma was increased by MSC treatment, and there was a significant reduction in the production of IL-12, IFN-γ, p70, and tumor necrosis factor (TNF) (58). Bassi et al. isolated MSCs from epididymal fat tissue from 8-week-old male Balb/c mice and characterized through immunophenotyping its capacity to prevent the proliferation of CD4+ T cells (59, 60). Treatment of NOD mice with MSCs attenuated hyperglycemia of early-onset
autoimmune diabetes and increased amylin levels, reflective of autoimmune diabetes improvement; reduced the amount of inflammatory cell infiltration, maintaining insulin expression in pancreatic islets by suppressing the Th1 immune response in the pancreas; and promoted the high expression of active TGF-β1 (60). Meanwhile, syngeneic MSCs were detected for a significantly longer period, albeit with diminishing persistence in immune-deficient mice model (61). In another study, van Megen et al. found that activation of MSCs can take up and process antigen and increase HLA-DR expression and immune inhibitory markers, while their metabolic profile was maintained without enhancing T-cell proliferation. MSCs can also enhance immunosuppressive capacity without stimulating alloreactive T cells (62). In an in-vitro study, Montanucci et al. provided preliminary evidence that immunoisolatory microcapsule-hHUCMS (CpS-hUCMS) may represent a functional biohybrid artificial system, where molecular products can induce effective immunomodulatory effects in vitro and in T1DM patients, making it possible to further clarify their therapeutic potential in humans (63). Montanucci et al. isolated and microencapsulated human umbilical cord Wharton jelly-derived mesenchymal stem cells (hUCMS) for

**FIGURE 1** | The possible mechanism of stem cells in the treatment of T1DM. Stem cells were used for the reconstitution of immunotolerance through activating T regulatory cells (Treg) and inhibiting T and Th1 cells, and they could also be used for the preservation and regeneration of β-cells.
xenograft (TX) in a spontaneous T1DM mouse model (NOD mice). At 10 days of TX, Treg cells did not increase, while at 216 days of TX, CD4\(^{+}\) CD25 high cells increased in terms of both percentage and number. Further research found that at 216 days of TX, only the mild T1DM NOD mice presented sustained and full alleviation of hyperglycemia, while no alleviation of hyperglycemia was observed in severe T1DM NODs. These findings suggested that the successful hUCMS therapy approach for the treatment of T1DM in NOD mice depended on the stage of the T1DM disease process, with severe T1DM NODs exhibiting a continuous decrease in residual \(\beta\)-cell mass (64). All these results provide encouraging first steps in the clinical translation of the use of preactivated MSCs as a cellular immune intervention therapy, which helps to treat inflammatory and autoimmune disorders, including T1DM.

3.1.2 Islet Protection and Regeneration Ability of MSCs

MSCs can increase the mass of islets and the survival of \(\beta\)-cells by differentiation to \(\beta\)-cell-like cells. MSCs rapidly undergo mesodermal lineage differentiation to \(\beta\)-cell-like cells, and the transdifferentiation of MSCs into insulin-producing cells was successfully attempted in vitro, with the pancreatic and duodenal homeobox 1 (PDX-1), the key marker that was present in the transdifferentiation of MSCs to insulin-producing cells (65). Chen et al. successfully differentiated MSCs into pancreatic islet \(\beta\)-cell-like cells by pre-inducing in L-DMEM with 10 mmol/L nicotinamide and 1 mmol/L \(\beta\)-mercaptoethanol for 24 h and re-inducing in serum-free H-DMEM with 10 mmol/L nicotinamide and 1 mmol/L mercaptoethanol for another 10 h. These induced islet \(\beta\)-cell-like cells with similar morphological characters to pancreatic islet cells and promoted the transcription, translation, and excretion of insulin, which could effectively control the level of blood glucose in diabetic rats (66).

Similar results were reported by several other groups that islet-like clusters can be formatted in vitro by cultured MSCs given the appropriate procedure (67, 68). Human umbilical cord Wharton jelly cells (hUCWJCs) are a subtype of MSCs, which were transplanted into a T1DM mouse model with renal damage, and the therapeutic effect of transplantation was evaluated. It was found that hUCWJCs can promote the level of C-peptide and insulin in mice, which certified the potential of intraperitoneal injection of hUCWJCs and the ability of hUCWJCs to migrate to damaged tissues to enhance the secretion of insulin from non-pancreatic local cells (69).

3.1.3 MSC Transplantation in Clinical Trials

MSCs have been used in human clinical trials, showing that stem cell transplantation has beneficial effects on T1DM. In an open-label, non-randomized, parallel-armed prospective study, Lu et al. enrolled 53 participants including 33 adult-onset (≥18 years) and 20 juvenile-onset T1DM (ChiCTR2100045434). The results revealed that an intravenous dose of allogeneic UC-MSCs was safe in patients with newly diagnosed T1DM at 12 months of follow-up, which probably led to better islet \(\beta\)-cell protection compared with standard treatment alone during the first year after diagnosis (70). Cai et al. proved that transplantation of UC-MSCs was safe and associated with moderate improvement of metabolic measures in patients with established T1DM too (NCT01374854) (50). Another clinical trial revealed that MSC injection through liver puncture could successfully decrease the levels of insulin, islet cells, and glutamic acid dehydrogenase (GAD) antibody in two patients within 1 year, with a decreased concentration of blood glucose and HbA1c and increased concentration of C-peptide, indicating immune regulatory cell tolerance (71).

3.2 HSC Transplantation in T1DM

The conception of HSCs was generated in the 1950s with the discovery that intravenously injected bone marrow cells could rescue irradiated mice from lethality through re-establishing blood cell production (72). The ability to manage expansion and the characteristics of self-renewal of the hematopoietic compartment while maintaining the capacity for differentiation into HSCs were demonstrated (72, 73). Peripheral hematopoietic stem cells are mobilized with cyclophosphamide and granulocyte colony-stimulating factors. Leukapheresis using a continuous-flow blood cell separator was initiated when the rebounding CD34\(^{+}\) cells reached 10 cells/μL. Apheresis was continued daily until the number of harvested progenitor cells reached a minimum of 3.0 × 10\(^6\) CD34\(^{+}\) cells/kg body weight. Unmanipulated peripheral blood stem cells were frozen in 10% dimethyl sulfoxide in a rate-controlled freezer and stored in the vapor phase of liquid nitrogen (74). Then, the collected cells were injected intravenously. HSCs have proven to be safe in human subjects and have been widely utilized as an effective treatment for hematological malignancies (75). Recently, HSCs have been used in T1DM for the suppressed function of the immune system response in both in-vitro and in-vivo studies.

3.2.1 Immunomodulatory Ability of HSCs

Immunomodulatory activity is the most important ability of HSCs in patients with T1DM. HSCs can inhibit the occurrence of T1DM (76–78). Patients with recent-onset T1DM have been triumphantly reverted to euglycemia by autologous hematopoietic stem and progenitor cell transplantation (AHSC), and modulation of autologous hematopoietic stem and progenitor cells (HSPCs) with prostaglandins (PGs) in vitro enhances their immunoregulatory properties through increasing the expression of the immune checkpoint-signaling molecule PD-L1 (79). Wang et al. demonstrated a lower proportion of proliferating T conventional cells (Tcon) and a higher absolute number and percentage of Treg cells in pancreatic lymph nodes from resistant mice among the younger recipients compared to the rapid progressors among the older recipients, and older NOD mice progressed more rapidly to the end stage of diabetes (80). Although mixed chimerism with MHC-matched non-autoimmune donor bone marrow (BM) transplants did not prevent T1DM in NOD mice models, induction of either mixed or complete chimerism with MHC-mismatched BM transplants inhibited T1DM in the same mice (81). This limited the translational applications of HSCs to reshape the autoimmune response by myeloablative agents/approaches. The genetically modified HSCs were used to overcome the disadvantage. Ex-vivo
genetic manipulation of NOD HSCs to encode proinsulin and transgenically target MHC class II could successfully prevent T1DM onset (78, 82). The increased CXCL12 (SDF-1) level in bone marrow-derived HSCs of NOD mice is considered to change the transport of HSCs and peripheral dendritic cells, which is conducive to the occurrence of T1DM (78, 83).

3.2.2 HSC Transplantation in Clinical Trials
D’Addio et al. enrolled 65 individuals with newly diagnosed T1DM in three independent clinical trials, where the patients transplanted with HSCs showed enhanced C-peptide levels at 6 months after treatment compared with baseline, and the immune system showed an overall stabilization in the remaining follow-up period (84). Gu et al. performed a parallel-assignment, phase-II prospective, non-randomized trial, in which 20 patients were treated only with insulin injections and 20 received autologous hematopoietic stem cell therapy (AH SCT). The results demonstrated the beneficial effects of AH SCT in patients with recent-onset T1DM by increasing the concentration of C-peptide and inducing insulin independence, and the safety and good tolerability of AH SCT compared with conventional intensive insulin therapy was also certified (77). Another clinical trial in Ning’s research also proved that AH SCT was safe without a reduction in the diversity of T-cell receptor (TCR) repertoires, and TCR repertoires tended to be more stable after AH SCT (85). The clinical trial data also showed significant direct correlations between HSPC levels and the coefficient of variation of glucose levels or time in hypoglycemia, which were weaker in patients with long-standing diabetes than in those with short-term diabetes (86). HSC transplantation improves glycated hemoglobin levels in a time-dependent manner (87).

3.3 ESC and iPSC Transplantation in T1 DM
ESCs and iPSCs are PSCs that can regenerate the islet β-cells and immune cells through differentiating, which helps to increase the mass of β-cells. D’Amour et al. firstly proved that ESC-derived β-cells could be successfully generated through the in-vitro recapitulation of pancreatic islets and β-cell physiological development by stepwise application of specific factors (88, 89). iPSCs, reprogrammed from somatic cells, have a similar ability to differentiate and proliferate like ESCs. iPSCs collected from the umbilical cord at birth have the potential for self-renewable multipotency and can differentiate into various lineages such as islets (31, 59, 90). Hence, iPSCs provide a promising platform to produce insulin-secreting cells in vitro. However, the utilization of ESCs and iPSCs is less due to law restrictions in many countries, so there is little clinical research on ESCs and iPSCs.

3.3.1 Islet Protection and Regeneration Ability of ESCs and iPSCs
Transplantation of ESCs or iPSCs in T1DM can regenerate the islet β-cells and increase β-cell mass through differentiating to insulin-producing cells (iPSCs), pancreatic progenitors, islet organoids, and interspecific pancreatic chimeras, which benefited the treatment of T1DM. Rezania et al. cultured iPSCs expressing key markers of mature β-cells such as insulin in vitro and obtained cells which have functional similarities to human islets; the iPSCs rapidly reversed hyperglycemia in streptozotocin (STZ)-induced diabetic mice through increasing the level of insulin and C-peptide when transplanted in vivo (91). iPSCs can be generated from the skin fibroblasts of T1DM patients. These iPSCs can differentiate into pancreatic cell lineages and generate T1DM SC β-cells, making autologous stem cell-derived pancreatic progeny transplantation for T1DM possible (92). Korytnikov and Nastro isolated hPSCs successfully in a lab and then transplanted them to mice models to monitor their developmental potential in vivo, and they found that mice transplanted with multipotent pancreatic progenitor cells can form all pancreatic lineages in vivo (93). Nadav et al. used single-cell RNA sequencing of differentiating β-cells and revealed that ESC differentiation toward the mature β-cell phenotype can be tracked at each stage through monitoring the expression of markers identifying each intermediate progenitor, such as the β-cell marker insulin, endocrine precursor marker neurogenin 3, NK6 homeobox (NKK6.1), and PDX-1 (89, 94). They also proved that WNT inhibition and bone morphogenetic protein (BMP) activation could modulate the ratio of progenitors and endocrine cells, which shed light on a possible gene editing target for ESC differentiation toward the mature β-cells (89).

3.3.2 Immunomodulatory Ability of ESCs and iPSCs
Haque et al. characterized autoantigen-specific naturally occurring Treg-like iPSC-Tregs and proved that adoptive transfer of ovalbumin (OVA)-specific iPSC-Tregs greatly suppressed autoimmunity in the mouse model preventing the β-cells from destruction. These tissue-associated Tregs can effectively inhibit the migration and activity of the pathogenic immune cells and accumulate in the diabetic pancreas causing T1DM by downregulating the production of proinflammatory cytokine IFN-γ and suppressing the expression of ICAM-1 (95). Another report declared that pancreatic endoderm derived from hESCs can generate functional insulin-producing cells in vivo regardless of the presence of innate lymphoid cell elements, and the combination of CTLA4Ig and anti-CD40L mAbs can block hESC-PE graft rejection in immunocompetent mice, while regulatory T cells were not needed for the tolerance during hESC-PE transplantation (96).
To increase the function of stem cells, it is very important to sustain the regeneration and differentiation ability of stem cells and prevent the programmed death of stem cells in vivo (30, 97). Several approaches and conditions, including far-red light, genetic engineering, biological material scaffolds, nanofiber tubular, combination treatment with insulin or other drugs, microcapsules, and co-transplantation with more than one type of stem cells, were utilized to promote the survival, differentiation, and immunomodulatory ability of stem cells in vivo and in vitro. These preclinical attempts tried to derive pancreas islet cells, increase the number and function of Tregs, ameliorate the function of islets, and prevent β-cells more effectively (Table 1). Also, stem cells have been used in human clinical trials, which showed that stem cell transplantation had beneficial effects on T1DM, with no obvious adverse reactions (Table 2). Recently, an allogeneic, gene-edited, immune-evasive, stem cell-derived therapy for the treatment of T1DM was approved in Canada for clinical trial application (CTA)
| Type   | Donor | Recipient | Pretreatment condition                            | Doses                          | Effect                                                                                                                                  | Pathway/target/mechanism                                                                 | Year/reference |
|--------|-------|-----------|--------------------------------------------------|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|----------------|
| hESCs  | Human | Mice      | Aggregates of hESC-derived PP with rat-derived MV in hydrogels | N/A                           | Accelerate the normalization of glycemia and persist long-term and promote beta-cell maturation                                        | Improve the survival of PP cells by reducing hypoxia and apoptosis                        | 2021 (98)      |
| hMSCs  | Human | Mice      | Far-red light-activated human islet-like designer | N/A                           | Improve glucose tolerance, sustain blood glucose control, and attenuate both oxidative stress and development of multiple diabetes-related complications in the kidneys | Sustain fine-tuned secretion of insulin                                                  | 2021 (99)      |
| hPSCs  | Human | In vitro  | PD-L1 overexpression and HLA class I knockout by genome engineering | N/A                           | Provide protection from diabetes-specific immune recognition                                                                             | Abrogate human diabetogenic CD8 T cells in activation                                    | 2021 (100)     |
| hPSCs  | Human | In vitro  | Superporous agarose scaffolds                     | N/A                           | Enhance the function of the bioartificial pancreas                                                                                     | Sustain insulin production                                                              | 2021 (101)     |
| hESC   | Human | Mice/dog  | Nanofibrous encapsulation                        | 2,500 cluster cells/mouse     | Corrected glucose levels immediately (within a week)                                                                                   | Sustain the survival of human SC-β cells in immunodeficient mice and immunocompetent mice and dogs | 2021 (102)     |
| hBM-cMSCs | Human | Rhesus monkey | Combined therapy with liraglutide | 1.5 x 10^6/kg | Reduce FBG and HbA1c                                                                                                                   | Immunomodulation by increased Tregs, IL-4, IL-10, and TGF-β1 and decreased IL-6 and IL-1β | 2021 (103)     |
| ADMSCs | Human | Mice      | Co-culture with MIN6 cells                        | 0.5 x 10^6/mouse              | Provide protection to MIN6 cells from streptozotocin                                                                               | AKT and ERK pathway                                                                      | 2021 (43)      |
| MSCs   | Human | Mice      | Generated human alpha-1 antitrypsin-engineered MSCs | N/A                           | Increased self-renewal, better migration, and multilineage differentiation abilities                                                     | Upregulate the expression of WNT3A, KDR, ICAM 1, VIM1, MMP2, and IGF1                   | 2021 (104)     |
| hUCMS and hIDCs | Human | Mice | Co-microencapsulation of hUCMS and hIDC in AG | 1 x 10^6 hIDC + 1 x 10^6 hUCMS/1.3 ml AG | Reverse the recent onset hyperglycemia in mice                                                                                          | Couple the immunoregulatory activities of hUCMS and insulin production by hIDC           | 2020 (105)     |
| MSCs   | Human | Rats      | Combined therapy with insulin                     | 2 x 10^6 MSCs/kg              | Decrease blood glucose level                                                                                            | Regulate the expression of leptin receptor, neuropeptide Y, and mielanoctin-4 receptor   | 2020 (106)     |
| ADMSCs | Human | Mice      | Co-transplant with neonatal porcine islets        | 1 x 10^6 MSCs/mouse           | Improve glucose tolerance and stimulate serum porcine insulin                                                                     | Secrete anti-inflammatory and proangiogenic factors                                     | 2019 (107)     |
| MSCs   | Mice   | Mice      | Allograft                                         | 1 x 10^6 MSCs/mouse           | More effective in induction of immunosuppressive effects                                                                          | Reduce the inflammatory cytokines and increase inflammatory cytokine                     | 2020 (108)     |

(Continued)
| Type | Donor | Recipient | Pretreatment condition | Doses | Effect | Pathway/target/mechanism | Year/reference |
|------|-------|-----------|------------------------|-------|--------|--------------------------|---------------|
| ESCs | Mice  | Mice      | MHC-mismatched         | N/A   | Prevent insulitis and T1D development | Increase the number and function of Tregs | 2019 (109) |
| HSPCs | Human | Murine    | Overexpression PD-L1 by genome engineering | 1 x 10^6/mouse | Inhibit the autoimmune response and revert diabetes | PD-L1/PD-1 pathway | 2017 (110) |
| hESCs | Human | Mice      | Allograft              | 1 x 10^6/mouse | Enhance insulin secretion and enhance immunosuppression | CXCL12 pathway | 2019 (111) |
| HSPCs | Human | Mice      | Modulation with prostaglandins | 1 x 10^5/mouse | Abrogate the autoreactive T-cell response | PD-L1 pathway | 2018 (79) |
| MSCs | Mice  | Mice      | Allograft              | 2 x 10^5/mouse | Decrease blood glucose and glycosylated hemoglobin levels | Inhibit the proliferation of T lymphocytes to induce immune tolerance | 2017 (112) |
| iPSCs | Human | Mice      | MHC-mismatched         | N/A   | Significantly improve the yield of PDX-1^+ and NKX6.1^+ cells | Rescue and generate the islet-like compact cell clusters | 2017 (113) |
| MSCs | Mice  | Mice      | Allograft              | 2 x 10^5/mouse | Improve insulin levels and suppress adverse immune responses | IFN-γ/IL-4 pathway | 2017 (114) |
| hESCs | Human | In vitro  | Overexpression TGF-β by genome engineering | 5 x 10^6/mouse | Increase cell proliferation and pancreatic differentiation. | TGF-β signaling | 2016 (115) |
| MSCs | Rats  | In vitro  | Co-encapsulation within GLP-1 ligand-functionalized polyethylene glycol hydrogel | N/A | Improve islet function and stimulate cell survival | GLP-1 promotes the stimulation of insulin gene transcription, islet growth, and neogenesis | 2017 (116) |
| ADMSCs | Mice | Mice      | Allograft              | 1 x 10^6/mouse | Intrasplenic administration improves β-cell mass and insulin production | Increase pancreatic TGF-β levels | 2015 (117) |

hESCs, human embryonic stem cells; PP, pancreatic progenitors; hMSCs, human mesenchymal stem cells; hPSCs, human pluripotent stem cells; hBM-cMSCs, human clonal mesenchymal stem cells; FBG, fasting blood glucose; ADMSCs, adipose tissue-derived MSCs; N/A, not applicable; MSCs, mesenchymal stem cells; WNT3A, Wnt family member 3A; KDR, kinase insert domain receptor; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion protein 1; MMP2, matrix metalloproteinase-2; IGF-1, insulin-like growth factor; iPS, induced pluripotent stem cells; hUCMSCs, human umbilical cord-derived mesenchymal stem cells; hIDCs, pancreatic islet-derived insulin-producing cells; AG, sodium alginate; HSPCs, hematopoietic stem and progenitor cells; PD-L1, programmed death ligand 1.
### TABLE 2 | Stem cell treatment of T1DM in human clinical trials.

| Type | Case | Transplantation method | Observation | Effect | Side effect | Number of clinical trials | Year/ reference |
|------|------|------------------------|-------------|--------|-------------|---------------------------|----------------|
| MSCs | 27 (MSC-treated); 26 (control) | The MSC-treated group received repeat transplantation with an interval of 3 months, and each time for 1.0 x 10^6 cells/kg was given. | Participants were followed up at 3, 6, and 12 months and yearly afterward | HbA1c levels decreased and C-peptide was significantly increased in the MSC-treated group | Had mild fever after MSC infusion | ChiCTR2100045434 | 2021 (70) |
| ASCs | 8 (ASC treated); 5 (control) | | | | | NCT03920397 | 2020 (118) |
| AHSCT | 20 (AHSCT); 20 (control) | HSCs were mobilized and collected from peripheral blood by leukapheresis and cryopreserved. Cells were injected intravenously after conditioning with CTX (200 mg/kg) and rabbit ATG (4.5 mg/kg) | Participants were followed up at 3, 6, 12, 18, 24, 36, and 48 months | Stability of C-peptide, better glucose control, and lower insulin requirement | Transient headache (n = 8), mild local infusion reactions (n = 7), tachycardia (n = 4), and abdominal cramps (n = 1) | NCT00807651 | 2018 (77) |
| CB-SCs | 15 | CB-SC-treated mononuclear cells (interaction for 2~3 h) were returned to the patient’s blood circulation via a dorsal vein in the hand with physiological saline; after 3 months, subjects received a similar second treatment | Follow-up visits were scheduled 2, 8, 12, 18, 26, 40, and 56 weeks after treatment for clinical assessments and laboratory tests | Improved fasting C-peptide levels, reduced daily dose of insulin, increased Tregs, and reduced HbA1c | | NCT01350219 | 2015 (119) |
| UC-MSCs | 21 (UC-MSCs); 21 (control) | The dorsal pancreatic artery or its substitute was identified, and 60~80 ml BM-MNCs (106.8 x 10^6/kg) plus 30~50 ml UC-MSCs (1.1 x 10^6/kg) were sequentially infused within 30 min | N/A | HbA1c levels decreased, FBG decreased, and insulin dose requirements reduced | | NCT01374854 | 2016 (50) |
| CB-SCs | 12 (with CB-SCs educated); 3 (without CB-SCs educated) | The collected lymphocytes were transferred into the device for exposure to allogeneic CB-SCs for 2~3 h, then were returned to the patient’s circulation via a dorsal vein in the hand under gravity flow control (2 to 3 ml/min) with physiological saline | Follow-up visits were scheduled 4, 12, 24, and 40 weeks after treatment for clinical assessments and laboratory tests | Improved fasting C-peptide levels, reduced daily dose of insulin, increased Tregs, and reduced HbA1c | | NCT01350219 | 2012 (120) |
| ASCs | 7 (ASCs + VIT D); 4 (VIT D); 6 (control) | Allogenic ASC (1 x 10^6 cells/kg) and cholecalciferol 2,000 UI/day for 6 months | Participants were followed up at T0 and after 1, 3, and 6 months | Improved fasting C-peptide levels and reduced HbA1c level | Four patients developed local thrombophlebitis within the first week and two had transient mild eye floaters during infusion, with no subsequent visual abnormalities. One patient developed central retinal vein occlusion at T3, with complete resolution at T6 | NCT03920397 | 2021 (121) |

T1DM, type 1 diabetes mellitus; BMI, body mass index; SCs, stem cells; MSCs, mesenchymal stem cells; hESCs, human embryonic stem cells; ASCs, adipose stem cells; HSCs, hematopoietic stem cells; BM-MSCs, bone marrow-derived mesenchymal stem cells; HbA1c, glycosylated hemoglobin assays; FBG, fasting blood glucose; Treg, T regulatory; hUCMS, human umbilical cord matrix stem cells; sBCs, stem cell-derived pancreatic beta-like cells; ADMSCs, adipose tissue-derived MSCs; CB-SCs, human cord blood-derived multipotent stem cells; UC-MSCs, umbilical cord mesenchymal stromal cells; VIT D, vitamin D; N/A, not applicable.
(CRISPR Therapeutics and ViaCyte, Inc. to start clinical trial of the first gene-edited cell replacement therapy for the treatment of T1DM, retrieved on November 16, 2021). This CRISPR therapeutics offered novel β-cell replacement therapies to address unmet T1DM needs. All these efforts are aimed at better promoting the effectiveness of stem cells, which proved to be a more viable option for the treatment of T1DM, lessening the suffering of the patients.

4 CONCLUDING REMARKS

In recent research, stem cell therapy has demonstrated itself as a rapidly expanding and potentially limitless source of β-cells to arrive at a cure for T1DM by reconstitution of immunotolerance and differentiation into islet β-cell clusters. As the immunosuppression affected the effect of transplantation of stem cells, stem cell intervention before transplantation could help preserve β-cells and remodel the immune response. However, several challenges, such as the ethical problem of autologous and allogeneic stem cells used to preserve the function of β-cells, still need resolution. Although research into β-cell replacement derived from stem cells is increasing every year, we must make more efforts in the future on the intervention with stem cell transplantation, which can help achieve remission of T1DM by β-cell replacement.

AUTHOR CONTRIBUTIONS

X-XW reviewed the literature, wrote the manuscript, and created the descriptive figures. X-MH and QZ edited the tables and figures. D-YZ and S-YZ assisted in the literature review. MK edited the manuscript. KX and R-HY revised the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Campbell MR. Review of Current Status of Molecular Diagnosis and Characterization of Monogenic Diabetes Mellitus: A Focus on Next-Generation Sequencing. *Expert Rev Mol Diag* (2020) 20(4):413–20. doi: 10.1080/14737159.2020.1730179
2. Miller KM, Herrmann J, Foster N, Hofer SE, Rickels MR, Danne T, et al. Longitudinal Changes in Continuous Glucose Monitoring Use Among Individuals With Type 1 Diabetes: International Comparison in the German and Austrian DPP and U.S. T1D Exchange Registries. *Diabetes Care* (2020) 43(1):e1–2. doi: 10.2337/dc19-1214
3. Quansah DY, Gross J, Gilbert L, Pauchet A, Horsch A, Benhalima K, et al. Cardiometabolic and Mental Health in Women With Early Gestational Diabetes Mellitus: A Prospective Cohort Study. *J Clin Endocrinol Metab* (2022) 107(3):e996–e1008. doi: 10.1210/clinem/dgab791
4. Vinuela A, Varshney A, van de Bunt M, Prasad RB, Asplund O, Bennett A, et al. Genetic Variant Effects on Gene Expression in Human Pancreatic Islets and Their Implications for T2D. *Nat Commun* (2020) 11(1):4912.
5. Wang J, Lv B, Chen X, Pan Y, Chen K, Zhang Y, et al. An Early Model to Predict the Risk of Gestational Diabetes Mellitus in the Absence of Blood Examination Indexes: Application in Primary Health Care Centres. *BMC Pregnancy Childbirth* (2021) 21(1):814. doi: 10.1186/s12884-021-04295-2
6. Pang H, Luo S, Xiao Y, Xia Y, Li X, Huang G, et al. Emerging Roles of Exosomes in T1DM. *Front Immunol* (2020) 11:593348. doi: 10.3389/fimmu.2020.593348
7. Rosell Rask S, Bjerre M, FGF21 and Glycemic Control in Patients With T1D. *Endocrine* (2019) 65(3):550–7. doi: 10.1007/s12020-019-02027-3
8. Terrazzano G, Bruzzaniti S, Rubino V, Santopaofo M, Patuelli AT, Giovanazzi A, et al. T1D Progression Is Associated With Loss of CD3(+) CD56(+) Regulatory T Cells That Control CD8(+) T Cell Effector Functions. *Nat Metab* (2020) 2(2):142–52. doi: 10.1038/s42255-020-0173-1
9. Katasarou A, Gudbjornsodottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, et al. Type 1 Diabetes Mellitus. *Nat Rev Dis Primers* (2017) 3:17016. doi: 10.1038/nrdp.2017.16
10. Owens DR. Insulin Preparations With Prolonged Effect. *Diabetes Technol Ther* (2011) 13 Suppl 1:S5–14. doi: 10.1089/dia.2011.0068
11. Haidar A, Legault L, Matteau-Pelletier L, Messier V, Dallaire M, Ladouceur M, et al. Outpatient Overnight Glucose Control With Dual-Hormone Artificial Pancreatic, Single-Hormone Artificial Pancreas, or Conventional Insulin Pump Therapy in Children and Adolescents With Type 1 Diabetes: An Open-Label, Randomised Controlled Trial. *Lancet Diabetes Endocrinol* (2015) 3(8):595–604. doi: 10.1016/S2213-8587(15)00141-2
12. Garg SK, Weinzimer SA, Tamborlane WV, Buckingham BA, Bode BW, Bailey TS, et al. Glucose Outcomes With the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults With Type 1 Diabetes. *Diabetes Technol Ther* (2017) 19(3):155–63. doi: 10.1089/dtt.2016.0421
13. Nijhoff MF, de Koning EJP. Artificial Pancreas or Novel Beta-Cell Replacement Therapies: A Race for Optimal Glycemic Control? *Curr Diabetes Rep* (2018) 18(11):110. doi: 10.1007/s11892-018-1073-6
14. Nally LM, Sherr JL, Van Name MA, Patel AD, Tamborlane WV. Pharmacologic Treatment Options for Type 1 Diabetes: What’s New? *Expert Rev Clin Pharmacol* (2019) 12(5):471–9. doi: 10.1080/17512433.2019.1597705
15. Yan WT YY, Hu XM, Ning WY, Liao LS, Lu S, Zhao W, et al. Do Pyroptosis, Apoptosis, and Necroptosis (PAN)optosis Exist in Cerebral Ischemia? Evidence From Cell and Rodent Studies. *Neural Regener Res* (2022) 17(8):1761–8. doi: 10.4103/1673-5374.331539
16. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 Diabetes. *Lancet* (2014) 383(9911):69–82. doi: 10.1016/S0140-6736(13)60591-7
17. Gregg EW, Cheng YJ, Srinivasan M, Lin J, Geiss LS, Albright AL, et al. Trends in Cause-Specific Mortality Among Adults With and Without Diagnosed Diabetes in the USA: An Epidemiological Analysis of Linked National Survey and Vital Statistics Data. *Lancet* (2018) 391(10138):2430–40. doi: 10.1016/S0140-6736(18)30314-3
18. Rawshani A, Sattar N, Franzen S, Rawshani A, Hattersley AT, Svensson AM, et al. Excess Mortality and Cardiovascular Disease in Young Adults With Type 1 Diabetes in Relation to Age at Onset: A Nationwide, Register-Based Cohort Study. *Lancet* (2018) 392(10146):477–86. doi: 10.1016/S0140-6736(18)31506-X
19. Chiang JL, Kirkman MS, Laflé LM, Peters AL. Type 1 Diabetes Sourcebook: Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. *Diabetes Care* (2014) 37(7):2034–54. doi: 10.2337/dc14-1140
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20. Ryan AJ, O’Neill HS, Duffy GP, O’Brien FJ. Advances in Polymeric Islet Cell Encapsulation Technologies to Limit the Foreign Body Response and Provide Immunomodulation. Curr Opin Pharmacol (2017) 36:66–71. doi: 10.1016/j.coph.2017.07.013

21. Vantyghem MC, de Koning EJP, Pattou F, Rickels MR. Advances in Beta-Cell Replacement Therapy for the Treatment of Type 1 Diabetes. Lancet (2019) 394(10205):1274–85. doi: 10.1016/S0140-6736(19)31334-0

22. Gruessner RW, Sutherland DE, Kandaswamy R, Gruessner AC. Over 500 Solitary Pancreas Transplants in Nonuremic Patients With Brittle Diabetes Mellitus. Transplantation (2008) 85(1):42–7. doi: 10.1097/TP.0b013e31800296820. 46978.3

23. Abdulreda MH, Rodriguez-Diaz R, Cabrera O, Caicedo A, Berggren PO. The Different Faces of the Pancreatic Islet. Adv Exp Med Biol (2016) 936:31–24. doi: 10.1007/978-3-319-39824-2_2

24. Sneddon JB, Tang Q, Stock P, Bluestone JA, Roy S, Desai T, et al. Stem Cell Therapies for Treating Diabetes: Progress and Remaining Challenges. Cell Stem Cell (2018) 22(6):810–23. doi: 10.1016/j.stem.2018.05.016

25. Coe TM, Markmann JF, Rickert CG. Current Status of Porcine Islet Cell Replacement Therapy for Type 1 Diabetes. Cell Transplant (2010) 19(4):485–500. doi: 10.3727/096389410X12465051586120

26. Liang CC, Shaw SW, Huang YH, Lee TH. Human Amniotic Fluid Stem Cells can Improve Cerebral Vascular Remodelling and Neurological Function After Focal Cerebral Ischaemia in Diabetic Rats. J Cell Mol Med (2021) 25(21):10185–96. doi: 10.1111/jcm.16956

27. Zhang Q WX, Hu XM, Zhao WJ, Ban XX, Huang YX, Yan WT, et al. Targeting Programmed Cell Death to Improve Stem Cell Therapy: Implications for Treating Diabetes and Diabetes-Related Diseases. Front Cell Dev Biol (2021) 9:809656. doi: 10.3892/fcd.2021.809656

28. Wu SJ, Zheng XM, Liu LF, Li NN, Mao HA, Huang L, et al. Effects of Primary Microglia and Astrocytes on Neural Stem Cells in In Vivo and In Vivo models of ischemic stroke. Neurological Regener Res (2021) 16(9):1677–85.

29. Sultan N, Amin LE, Zaheer AR, Grawish ME, Scheven BA. Dental Pulp Stem Cells Stimulate Neuronal Differentiation of PC12 Cells. Neurological Regener Res (2021) 16(9):1821–3. doi: 10.4103/1673-5374.306089

30. Hu XM, Li ZX, Zhang DY, Yang YC, Fu SA, Zhang ZQ, et al. A Systematic Summary of Survival and Death Signalling During the Life of Hair Follicle Stem Cells. Stem Cell Res Ther (2021) 12(1):453. doi: 10.1186/s13287-021-02577-y

31. Francese R, Fiorina P. Immunological and Regenerative Properties of Cord Blood Stem Cells. Clin Immunol (2010) 136(3):309–22. doi: 10.1016/j.clim.2010.04.010

32. Hu XM, Zhang Q, Zhou RX, Wu YL, Li ZX, Zhang DY, et al. Programmed Cell Death in Stem Cell-Based Therapy: Mechanisms and Clinical Applications. World J Stem Cells (2021) 13(3):386–415. doi: 10.4225/12.42251841

33. Yang R, Liu F, Wang J, Chen X, Xie J, Xiong K. Epidermal Stem Cells in Wound Healing and Their Clinical Applications. Stem Cell Res Ther (2019) 10(1):229. doi: 10.1186/s13287-019-01312-z

34. Ilic D, Polak JM. Stem Cells in Regenerative Medicine: Introduction. Br Med Bull (2011) 98:117–26. doi: 10.1093/bmb/ddr012

35. Bongso A, Richards M. History and Perspective of Stem Cell Research. Adv Exp Med Biol (2004) 539:1.1145

36. Yang R, Yang S, Zhao JY, Hu X, Chen J, Huang L, et al. Umbilical Cord Mesenchymal Stromal Cell With Autologous Bone Marrow Cell Transplantation in Established Type 1 Diabetes: A Pilot Randomized Controlled Open-Label Clinical Study to Assess Safety and Impact on Insulin Secretion. Diabetes Care (2016) 39(1):149–57. doi: 10.2337/dci15-0171

37. Domouky AM, Hegab AS, Al-Shahat A, Raafat N. 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. J Autoimmun (2008) 31(4):393–402. doi: 10.1016/j.jaut.2008.10.004

38. Boumaza I, Ocana A, 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. J Autoimmun (2008) 31(4):393–402. doi: 10.1016/j.jaut.2008.10.004

39. Shigenoto-Kuroda T, Oh YJ, Kim DK, Jeong HJ, Park SY, Lee HJ, et al. MSC-Derived Extracellular Vesicles Attenuate Immune Responses in Two Autoimmune Murine Models: Type 1 Diabetes and Uveoretinitis. Stem Cell Rep (2017) 8(5):1214–25. doi: 10.1016/j.stemcr.2017.04.008
59. Abdi R, Fiorina P, Adra CN, Atkinson M, Sayegh MH. Immunomodulation by Mesenchymal Stem Cells: A Potential Therapeutic Strategy for Type 1 Diabetes. Diabetes (2008) 57(7):1759–67. doi: 10.2337/db08-0180
60. Bassi EJ, Moraes-Vieira PM, Moreira-Sa CS, Almeida DC, Vieira LM, Cunha CS, et al. Immune Regulatory Properties of Adipogenic Derived Mesenchymal Stem Cells in the Treatment of Experimental Autoimmune Diabetes. Diabetes (2012) 61(10):2534–45. doi: 10.2337/db11-0844
61. Gerace D, Martiello-Wilk R, Habib R, Ren B, Nassif NT, O’Brien BA, et al. Ex Vivo Expansion of Murine MSC Impairs Transcription Factor-Induced Differentiation Into Pancreatic Beta-Cells. Stem Cells Int (2019) 2019:1395301. doi: 10.1155/2019/1395301
62. van Megen KM, van ’t Wout ET, Lages Motta J, Dekker B, Nikolic T, Roep BO. Activated Mesenchymal Stromal Cells Process and Present Antigens Regulating Adaptive Immunity. Front Immunol (2019) 10:6964. doi: 10.3389/fimmu.2019.006941
63. Montanucci P, Alunno A, Basta G, Bistoni O, Pescara T, Cateri S, et al. Restoration of T Cell Subsets of Patients With Type 1 Diabetes Mellitus by Microencapsulated Human Umbilical Cord Wharton Jelly-Derived Mesenchymal Stem Cells: An In Vitro Study. Clin Immunol (2016) 163:34–41. doi: 10.1016/j.clim.2015.12.002
64. Montanucci P, Pescara T, Alunno A, Bistoni O, Basta G, Calafore R. Remission of Hyperglycemia in Spontaneously Diabetic NOD Mice Upon Transplant of Microencapsulated Human Umbilical Cord Wharton Jelly-Derived Mesenchymal Stem Cells (UCMS/C). Xenotransplantation (2019) 26 (2):12476. doi: 10.1111/xen.12476
65. Karmieli O, Izhar-Prato Y, Bulvik S, Efraïm S. Generation of Insulin-Producing Cells From Human Bone Marrow Mesenchymal Stem Cells by Genetic Manipulation. Stem Cells (2007) 25(11):2837–44. doi: 10.1634/ stemcells.2007-0164
66. Chen LB, Jiang XG, Yang L. Differentiation of Rat Marrow Mesenchymal Stem Cells Into Pancreatic Islet Beta-Cells. World J Gastroenterol (2004) 10 (20):3016–20. doi: 10.3748/wjg.v10.i20.3016
67. Gao F, Wu DQ, Hu YH, Jin GX, Li GD, Sun TW, et al. Induction of Robust Diabetes Resistance and Prevention of Recurrent Type 1 Diabetes Following Islet Transplantation by Gene Therapy. J Immunol (2007) 179(10):6762–9. doi: 10.4049/jimmunol.179.10.6762
68. Gu B, Miao H, Zhang J, Hu J, Zhou W, Gu W, et al. Clinical Benefits of Autologous Haematopoietic Stem Cell Transplantation in Type 1 Diabetes. Diabetes Metab (2018) 44(4):341–5. doi: 10.1016/j.diabet.2017.12.006
69. Pastore I, Assi E, Ben Nasr M, Bolla AM, Maestroni A, Usuelli V, et al. Hematopoietic Stem Cells in Type 1 Diabetes. Front Immunol (2021) 12:694118. doi: 10.3389/fimmu.2021.694118
70. Ben Nasr M, D’Addio F, Malvandi AM, Faravelli S, Castillo-Leon E, Usuelli V, et al. Prostaglandin E2 Stimulates the Expansion of Regulatory Hematopoietic Stem and Progenitor Cells in Type 1 Diabetes. Front Immunol (2018) 9:1387. doi: 10.3389/fimmu.2018.01387
71. Wang N, Rajasekaran N, Hou T, Macabas C, Mellins ED. Immunological Basis for Rapid Progression of Diabetes in Older NOD Mouse Recipients Post BM-HSC Transplantation. PLoS One (2015) 10(5):e0128494. doi: 10.1371/journal.pone.0128494
72. Racine J, Wang M, Zhang C, Lin CL, Liu H, Todorov I, et al. Induction of Mixed Chimerism With MHC-Mismatched But Not Matched Bone Marrow Transplants Results in Thymic Deletion of Host-Type Autoreactive T-Cells in NOD Mice. Diabetes (2011) 60(2):555–64. doi: 10.2337/db10-0827
73. Xiong J, Chen W, Zhao J, Jia L, Zou L, Xu L, et al. One Repeated Transplantation of Bone Marrow Genetically Engineered to Express Proinsulin II Protects Against Autoimmune Insulitis in NOD Mice. J Gene Med (2006) 8 (11):1281–90. doi: 10.1002/jgm.968
74. Leng Q, Nie Y, Zou Y, Chen J. Increased CXCL12 Expression in the Bone Marrow of NOD Mice Is Associated With Altered T Cell and Stem Cell Trafficking and Diabetes Development. BMC Immunol (2008) 9:51. doi: 10.1186/1471-2172-9-51
75. D’Addio F, Valderrama Vasquez A, Ben Nasr M, Franek E, Zhu D, Li L, et al. Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in New-Onset Type 1 Diabetes: A Multicenter Analysis. Diabetes (2014) 63 (9):3041–6. doi: 10.2337/db14-0129
76. Zhang J, Hu M, Wang B, Gao J, Wang L, Li L, et al. Comprehensive Assessment of T-Cell Repertoire Following Autologous Hematopoietic Stem Cell Transplantation for Treatment of Type 1 Diabetes Using High-Throughput Sequencing. Pediatr Diabetes (2018) 19(7):1229–37. doi: 10.1111/pedi.12728
77. Boscari F, D’Anna M, Bonora BM, Tresso S, Cappellari R, Avogaro A, et al. Effects of Glucose Variability on Hematopoietic Stem/Progenitor Cells in Patients With Type 1 Diabetes. J Endocrinol Invest (2021) 44(11):119–26. doi: 10.1007/s40618-020-01278-6
78. Snarski E, Szmurlo D, Halaburda K, Krol M, Urbanowska E, Milczarczyk A, et al. An Economic Analysis of Autologous Hematopoietic Stem Cell Transplantation for Treatment of Type 1 Diabetes Using High-Throughput Sequencing. Pediatr Diabetes (2018) 19(7):1229–37. doi: 10.1111/pedi.12728
79. Loretelli C, Assi E, Seelam AJ, Ben Nasr M, Fiorina P. Cell Therapy for Type 1 Diabetes. Expert Opin Biol Ther (2020) 20(8):887–97. doi: 10.1080/14712598.2020.1748596
80. Tyndall A, Walker UA, Cope A, Dazzi F, De Bari C, Fibbe W, et al. Immunomodulatory Properties of Mesenchymal Stem Cells: A Review Based on an Interdisciplinary Meeting Held at the Kennedy Institute of Rheumatology Division, London, UK, 31 October 2005. Arthritis Res Ther (2007) 9(1):301. doi: 10.1186/1475-9916-9-1
81. Rezania A, Bruin JE, Arora P, Rubin A, Batuhashi I, Asadi A, et al. Reversal of Diabetes With Insulin-Producing Cells Derived In Vitro From Human Pluripotent Stem Cells. Nat Biotechnol (2005) 23(12):1534–41. doi: 10.1038/nbt.1163
82. Loretelli C, Assi E, Seelam AJ, Ben Nasr M, Fiorina P. Cell Therapy for Type 1 Diabetes. Expert Opin Biol Ther (2020) 20(8):887–97. doi: 10.1080/14712598.2020.1748596
83. Carboni O, Navari M, Grandis A, Battistini S, Angioni A, et al. Cultivation of Human Embryonic Stem Cells to Definitive Endoderm. Nat Biotechnol (2003) 21(12):1382–3. doi: 10.1038/nbt.1133
84. Maehr R, Chen S, Snitow M, Ludwig T, Yagasaki L, Goland R, et al. Induction of Mixed Chimerism With MHC-Mismatched But Not Matched Bone Marrow Transplants Results in Thymic Deletion of Host-Type Autoreactive T-Cells in NOD Mice. Diabetes (2011) 60(2):555–64. doi: 10.2337/db10-0827
85. Zhu C, Ishikami S, Wang P, Zhao H, Li H. Optimal Design and Fabrication of Mixed Chimerism With MHC-Mismatched But Not Matched Bone Marrow Transplants Results in Thymic Deletion of Host-Type Autoreactive T-Cells in NOD Mice. Diabetes (2011) 60(2):555–64. doi: 10.2337/db10-0827
86. Korytnyk R, Nostro MC. Generation of Polychromatotic and Multipotent Pancreatic Progenitor Lineages From Human Pluripotent Stem Cells. Methods (2016) 101:56–64. doi: 10.1016/j.ymeth.2015.10.017
87. Zhu C, Ishikami S, Wang P, Zhao H, Li H. Optimal Design and Fabrication of Multichannel Helical Long-Period Fiber Gratings Based on Phase-Only Sampling Method. Opt Express (2019) 27(3):2281–91. doi: 10.1364/ OE.27.002281
95. Haque M, Lei F, Xiong X, Das JK, Ren X, Fang D, et al. Stem Cell-Derived Tissue-Associated Regulatory T Cells Suppress the Activity of Pathogenic Cells in Autoimmune Diabetes. JCI Insight (2019) 4(7):e126471. doi: 10.1172/jci.insight.126471

96. Sotz GL, Yadav M, Lang J, Kroon E, Kerr J, Kadoya K, et al. Tolerance Induction and Reversal of Diabetes in Mice Transplanted With Human Embryonic Stem Cell-Derived Pancreatic Endoderm. Cell Stem Cell (2015) 16(2):148–57. doi: 10.1016/j.stem.2014.12.001

97. Yan WT, Lu S, Yang YD, Ning WY, Cai Y, Hu XM, et al. Research Trends, Hot Spots and Prospects for Necroptosis in the Field of Neuroscience. Neural Regener Res (2021) 16(8):1628–37.

98. Aghazadeh Y, Poon F, Sarangi F, Wong FTM, Khan ST, Sun X, et al. Microvessels Support Engraftment and Functionality of Human Islets and hESC-Derived Pancreatic Progenitors in Diabetes Models. Cell Stem Cell (2021) 28(11):1936–1949.e1938. doi: 10.1016/j.stem.2021.08.001

99. Yu G, Zhang M, Gao L, Zhou Y, Qiao L, Yin J, et al. Far-Red Light-Activated Human Islet-Like Designer Cells Enable Sustained Fine-Tuned Secretion of Insulin for Glycemic Control. Mol Ther J Am Soc Gene Ther (2022) 30(1):341–54. doi: 10.1016/j.ymthe.2021.09.004

100. Castro-Gutiérrez R, Alkanani A, Mathews CE, Michels A, Russ HA. Protecting Stem Cell-Derived Pancreatic Beta-Like Cells From Diabetogenic T Cell Recognition. Front Endocrinol (2021) 12:707881. doi: 10.3389/fendo.2021.707881

101. Nalbandian R, Guerin RE, Goloborgorsky R, Blaha C, Munnpangi P, Santandreu A, et al. Superporous Agarose Scaffolds for Encapsulation of Adult Human Islets and Human Stem-Cell-Derived β Cells for Intravascular Bioartificial Pancreas Applications. J Biomed materials Res Part A (2022) 109(12):2438–48. doi: 10.1002/jbm.a.37236

102. Wang X, Maxwell KG, Wang K, Bowers DT, Flanders JA, Liu W, et al. A Pilot Study in Recent-Onset Type 1 Diabetes Patients. Stem Cell Ther (2021) 8(3):31. doi: 10.1007/sctm.20-0122

103. Montanucci P, Pescara T, Greco A, Leonardi G, Marini L, Basta G, et al. Combined Therapy of Mesenchymal Stem Cells With a GIP-1 Receptor Agonist, Liraglutide, on an Inflammatory-Mediated Diabetic Non-Human Primate Model. Life Sci (2021) 276:119374. doi: 10.1016/j.lfs.2021.119374

104. Song L, Gou W, Wang J, Wei H, Lee J, Strange C, et al. Overexpression of Alpha-1 Antitrypsin in Mesenchymal Stromal Cells Improves Their Intrinsic Biological Properties and Therapeutic Effects in Nonobese Diabetic Mice. Stem Cells Trans Med (2021) 10(2):320–31. doi: 10.1002/sctm.20-0122

105. Montanucci P, Pescara T, Greco A, Leonardi G, Marini L, Basta G, et al. Microencapsulation of Human Umbilical Cord-Derived Mesenchymal Stem and Pancreatic Islet-Derived Insulin Producing Cells in Experimental Type 1 Diabetes. Diabetes-Metabolism Res Rev (2021) 37(2):e3372. doi: 10.1002/dmr.3372

106. Sarvestani FS, Zare MA, Saki F, Kooheypa F, Al-Abdullah IH, Azarpira N. Neural Regener Res (2017) 16(2):148–157. doi: 10.1172/jactbio.2016.02.025

107. Bai T, Nazli C, Okcu A, Duruksu G, Karaoz E, Kızılıl S. Mesenchymal Stem Cells and Ligand Incorporation in Biomimetic Poly(Ethylene Glycol) Hydrogels Significantly Improve Insulin Secretion From Pancreatic Islets. J Tissue Eng Regener Med (2017) 11(3):694–703. doi: 10.1002/tem.1965

108. Yaschitz JN, Caliari-Oliveira C, de Souza LE, Neto LS, Palma PV, Covas DT, et al. Therapeutic Efficacy and Blood Distribution of Allogeneic Mesenchymal Stem Cells Delivered by Intrasplenic and Intrapancreatic Routes in Streptozotocin-Induced Diabetic Mice. Stem Cell Ther (2015) 6(1):31. doi: 10.1016/j.sctt.2015.01.007 – 1

109. Araujo DB, Dantas JR, Silva KR, Souto DL, Pereira MFC, Moreira JP, et al. Allogeneous Adipose Tissue-Derived Stromal/Stem Cells and Vitamin D Supplementation in Patients With Recent-Onset Type 1 Diabetes Mellitus: A 3-Month Follow-Up Pilot Study. Front Immunol (2020) 11:993. doi: 10.3389/fimmu.2020.00993

110. Delgado E, Perez-Basterrechca M, Suarez-Alvarez B, Zhou H, Revuelta EM, Garcia-Gala JM, et al. Modulation of Autoimmune T-Cell Memory by Stem Cell Educator Therapy: Phase 1/2 Clinical Trial. EbioMedicine (2015) 2(12):2024–36. doi: 10.1016/j.ebiom.2015.11.003

111. Zhao Y, Jiang Z, Zhao T, Ye M, Hu C, Yin Z, et al. Reversal of Type 1 Diabetes via Islet Beta Cell Regeneration Following Immune Modulation by Cord Blood-Derived Multipotent Stem Cells. BMC Med (2012) 10:3. doi: 10.1186/1711-7015-10-3

112. Dantas JR, Araujo DB, Silva KR, Souto DL, de Fatima Carvalho Pereira M, Luiz RR, et al. Adipose Tissue-Derived Stromal/Stem Cells + Cholecalciferol: A Pilot Study in Recent-Onset Type 1 Diabetes Patients. Arch Endocrinol Metab (2021) 65(3):342–51. doi: 10.20945/2359-399700000368

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