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TOPIC HIGHLIGHT

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Mesenchymal stem cells help pancreatic islet transplantation to control type 1 diabetes

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Abstract

Islet cell transplantation has therapeutic potential to treat type 1 diabetes, which is characterized by autoimmune destruction of insulin-producing pancreatic islet β cells. It represents a minimal invasive approach for β cell replacement, but long-term blood control is still largely unachievable. This phenomenon can be attributed to the lack of islet vasculature and hypoxic environment in the immediate post-transplantation period that contributes to the acute loss of islets by ischemia. Moreover, graft failures continue to occur because of immunological rejection, despite the use of potent immunosuppressive agents. Mesenchymal stem cells (MSCs) have the potential to enhance islet transplantation by suppressing inflammatory damage and immune mediated rejection. In this review we discuss the impact of MSCs on islet transplantation and focus on the potential role of MSCs in protecting islet grafts from early graft failure and from autoimmune attack.

Key words: Mesenchymal stem cell; Islet transplantation; Type 1 diabetes; Vascularization; Immune modulation

Core tip: Type 1 diabetes is caused by a cell-mediated autoimmune destruction of pancreatic β cells. The transplantation of pancreatic islets provides a cure for this disorder. In this review, we first summarize the current knowledge on the pathogenesis of type 1 diabetes and on the therapeutic options for this disorder. Next we discuss the impact of mesenchymal stem cells on vascularization and immunomodulation of islet transplantation.

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INTRODUCTION

Type 1 diabetes results from the autoimmune destruction of insulin-producing pancreatic islet β cells and is usually diagnosed in children and young adults. β cell replacement therapies using either pancreas or islet transplantation represent a therapeutic alternative to the administration of exogenous insulin.

Islet transplantation is advantageous compared with whole pancreas transplantation because it is relatively non-invasive. However, a decline in islet cell survival, after transplantation, remains a significant obstacle in successful islet transplantation. It has been suggested that the complete lack of islet vasculature and hypoxic environment in the immediate post-transplantation period contribute to the acute loss of islet by ischemia[1]. Moreover, graft failure continues to occur because of

immunological rejection, despite the use of potent immunosuppressive agents.

Mesenchymal stem cells (MSCs) are non-hematopoietic multipotent stromal cells that can differentiate in a variety of tissues[2]. The ability of MSCs to secrete trophic and angiogenic factors may help to prevent early islet damage and assist islet engraftment. MSCs may also attenuate autoimmunity through their immunomodulatory properties while secreting cytokines to control autoreactive T cells. All these properties could be used for *in vivo* co-transplantation to improve islet engraftment[3]. Here we discuss the impact of MSCs on islet transplantation from both early graft failure and from autoimmune attack, to prevent immune rejection and promote long-term islet allograft survival.

PATHOGENESIS OF TYPE 1 DIABETES

Type 1 diabetes is a fast-growing global problem with enormous social, health, and economic consequences. This metabolic disorder is characterized by the irreversible destruction of insulin-secreting β cells. Death of the pancreatic β cells is associated with hyperglycaemia, which is the main determinant of long-term complications in diabetic patients. Exogenous insulin administration is required to control glucose levels in the blood. The pancreatic islets are the targets of an autoimmune assault, where islets are invaded by mononuclear cells that cause an inflammatory reaction called "insulitis", leading to loss of most of β cells. β cell death in the course of insulitis is probably caused by direct contact with activated macrophages and T-cells, and/or exposure to soluble mediators secreted by these cells, as cytokines, nitric oxide (NO), and oxygen free radicals[4].

Type 1 diabetes is a multifactorial disease where a genetic predisposition combines with environmental factors to induce the activation of the specific autoimmune destruction of β cells. Different known genetic risk factors can predict type 1 diabetes but autoantibodies are the most important preclinical markers. Autoantibodies include: islet cell autoantibodies, autoantibodies to insulin, autoantibodies to GAD (GAD 65), and autoantibodes to the tyrosine phosphatases IA-2 and IA-2β. In 85%-90% of patients affected by juvenile diabetes, these autoantibodies are detectable[5]. Several genetic loci have been associated with type 1 diabetes but the HLA (human leukocyte antigen) region, located on chromosome 6p, with its multiple genes is the strongest link to immune-mediated diabetes susceptibility. More than 200 identified genes are located in the HLA region, over half of which are predicted to be expressed[6]. Non-genetic factors also contribute to the risk of type 1 diabetes. This is supported by the fact that the overall concordance rate for type 1 diabetes among monozygotic twins is only about 10%-40%[7]. Environmental factors play a substantial role in the development of type 1 diabetes. They include specific infectious agents, dietary factors, perinatal factors, socioeconomic factors, and psychosocial factors[8].

THERAPEUTIC OPTIONS FOR TYPE 1 DIABETES

The treatment of type 1 diabetes mellitus includes different therapeutic approaches. The aim of clinical intervention is to arrest or prevent the β cell destruction due to autoimmunity, reverse this process and restore normal blood glucose level and immune homeostasis. Insulin therapy was the first therapy and represented the primary breakthrough treatment for type 1 diabetes, however, frequent hyper- and hypo-glycaemia episodes seriously affect the quality of life of these patients. Recent technological innovations such as insulin analogue formulation, devices for insulin delivery and glucose monitoring systems have allowed diabetic patients to improve their glycaemic control[9]. Intensive insulin therapies *via* insulin pens, subcutaneous or intraperitoneal insulin infusions using pumps reduce the onset and progression of diabetic complications, risks of hypo- or hyper-glycaemia, and increase the patient's quality of life.

β cell replacement is the only way to restore euglycaemia and ameliorate the progression of diabetic complications. Pancreas or pancreatic islet transplantation represents therapeutic alternatives to the administration of exogenous insulin to treat patients with type 1 diabetes. At the current time pancreas transplantation can produce long-term exogenous insulin independence, however, it remains a major surgical undertaking, associated with sizeable early morbidity and mortality, and with mandatory life-long immunosuppression[10]. Islet transplantation also offers glycaemic control and prevention of hyperglycaemia without the need for exogenous insulin administration[11]. As islets make up only 1%-2% of the pancreas, islet transplantation provides a much smaller transplant mass than whole pancreas transplant and is therefore a much less invasive procedure, and presents a smaller load of immunogenic tissue.

New therapeutic strategies for type 1 diabetes focus on three important points: residual β cell prevention, β cell restoration and β cell immune protection[12]. An achievable goal could be to develop a new cellular source for β cell. Different studies focus on immortalization and expansion of β cells from deceased donor pancreas[13,14], reprogramming or transdifferentiation of other pancreatic cells to β cells[15], differentiation from pancreatic progenitor cells in the adult pancreas[16] and differentiation and maturation from embryonic stem cells and induced pluripotential stem cells[17]. All these cellular sources appear promising in developing potential new candidates for beta-cell substitution and therapy for patients.

Immunoprotection strategies include immunomodulatory therapies and immunoisolation techniques. Immunotherapies aim to down-regulate the autoimmune

response to pancreatic self-antigens and arrest beta-cell destruction. Ideally, this type of technique would induce prolonged remission from type 1 diabetes and achieve a cure[18]. As regards the separation of implanted cells from the host immune system, this has been recognized as an experimental strategy to prevent immunorecognition, rejection and avoid lifelong immune suppression. A bioartificial pancreas tries to create a barrier to immune cells while allowing sufficient oxygen and nutrients transfer. Immunoisolation strategies facilitate islet transplantation without the need of immunosuppression[19].

Islet transplantation as a cure for type 1 diabetes

Transplantation of pancreatic islets is a less invasive procedure than pancreas transplantation, with a shorter hospital stay and lower morbidity. This therapeutic option is reserved for patients with severe glycaemic variability, progressive diabetic complications and life threatening hypoglycemia[19]. Successful islet transplantation was established in the early 70s in diabetic rats[20] and rhesus monkeys[21]. Najaran *et al*[22] reported the first significant case of human islet transplantation in patients with chronic pancreatitis. These patients underwent total or near total pancreatectomy, followed by autologous islet transplantation which prevented the development of diabetes. Thereafter, allograft was attempted in selected patients with type 1 diabetes. Unfortunately, out of the 237 allografts transplanted from 1990 to 1999, only 16% have resulted in insulin-independence for more than 1 week, and only 11% for more than 1 year[23]. Important progress was made thanks to improvements in techniques for isolating human islets[24,25] and to the availability of new and more effective immunosuppressive agents.

A positive turn in islet transplantation occurred in 2000, when James Shapiro and his colleagues treated 7 diabetic patients with severe hypoglycemia with allogeneic islets and a novel immunosuppressive regimen, obtaining insulin-independence in all the transplanted patients at a median follow-up period of 11.9 mo[11]. This success was due to several changes in the transplantation procedure, such as the large number of infused islets (from 2-4 donors for each recipient), an immunosuppressive regimen with inclusion of sirolimus and without glucocorticoids and the limited cold ischemia time of the recovered pancreases. A follow-up report monitored 65 transplant recipients for a period of 5 years. This study showed that 80% of the transplanted patients remained insulin-independent at 1 year, but only 10% retained an insulin-free status at 5 years. However partial graft function allowed improvement of glycaemic control with a decreased occurrence of hypoglycemic episodes. Recent results for islet transplantation demonstrate major improvement in outcomes. Analysis of transplantations performed by Collaborative Islet Transplant Registry (CITR) from 1999 to 2010 showed that the insulin independence rate at 3 years after transplantation increased from 27% in 1999-2003 to 44% in 2007-2010 and at 4 years approximately 90% of the grafts showed some degree of function[26].

All these studies indicated that islet transplantation is a promising strategy for treatment of type 1 diabetes. However, there are several challenges limiting widespread application. The disadvantages of the current approach is the limited supply and suboptimal yields of procurement and isolation of islets, graft failure and relatively high requirements to achieve prolonged insulin independence and glucose stability[27]. Poor vascularization and hypoxia of the transplanted islets[28], destruction by autoimmunity and allorejection[29] and exposure to the toxic effects of immunosuppressive agents[30] are thought to contribute to early graft failure. Better protection of the transplanted islets and improved immunosuppression are current strategies under investigation that could substantially advance islet transplantation as an acceptable alternative treatment. Mesenchymal stromal cells have been proposed to be one possible means to enhance islet transplantation protocols[31].

ROLE OF MSCS IN VASCULARIZATION AND IMMUNOMODULATION OF ISLET TRANSPLANTATION

MSCs are multipotent, self-renewing cells that reside mainly in the bone marrow, representing only 0.001%-0.01% of nucleated marrow cells. They can be also isolated from other tissues, including skeletal muscle[32], adipose tissue[33], amniotic fluid[34] and umbilical cord blood[35] and expanded for several passages without losing their self-renewing capacity[36,37]. The International Society for Cellular Therapy has defined criteria to define the MSC population, including adherence to plastic in culture, expression of cell surface markers, such as CD105, CD73 and CD90, and lack of expression of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR surface molecules[38]. MSCs have been well characterized for their ability to differentiate into several cell types of mesenchymal origin, such as osteoblasts, adipocytes and chondrocytes[38], but it has been also demonstrated that they have the capacity to differentiate into cell types of endodermal and ectodermal lineages, including lung epithelial cells[39], retinal pigment[40], skin[41], sebaceous duct cells[42], renal tubular cells[43], neural cells[44], hepatocytes[45] and insulin producing cells[46]. However, an intense debate about the contribution of MSCs to form functional tissue through transdifferentiation processes is still open[47]. Aside to their ability to differentiate into many types of cells, MSCs can also have a reparative effect through the migration to the site of injury[48] and the release of paracrine factors that affect cell migration, proliferation and survival of the surrounding cells[49]. In addition, MSCs have been shown to contribute to repair processes through the secretion of pro-angiogenic molecules, thus promoting the formation of new blood vessels *in vivo*[50]. Moreover, MSCs have

emerged as a useful cell population for immunomodulation therapy thanks to their ability to secrete a large amount of bioactive molecules that affect immune and inflammatory responses[51]. The combination of tissue regenerative potential and immunomodulatory or immunosuppressive activity has prompted therapeutic interest.

MSCs promote islet graft revascularization

Normally pancreatic islets have a rich vascular supply within the pancreas to support their metabolic activity and to facilitate rapid dispersal of secreted hormones. Large islets are supplied by 1-3 arterioles that penetrate the B cell-rich islet core and distribute into a dense network of sinusoidal capillaries connected to venules in the islet periphery[52]. Islets receive considerably more blood flow than surrounding pancreatic exocrine tissue[53] and islet capillaries are much more permeable than exocrine capillaries due to the presence of 10 times as many small pores within their endothelial cells[54]. Relatively strong expression of VEGF by islets is probably responsible for the high degree of vascularization and fenestration. Depletion of VEGF in β cells in mice reduces vascular density and permeability to the level of exocrine tissue and partly impairs insulin secretion[55]. The islet vasculature degenerates during the process of isolation and transplantation and the islets must initially rely on diffusion of oxygen and nutrients from the culture medium and from vessels in the transplant environment for their survival[56,57]. This condition leads to prolonged hypoxia that, at the early post-transplant stages, is considered a major reason for early islet graft loss. The vessel density and oxygen tension in transplanted islets are less than half compared with islets in the native pancreas[58]. Further compromising islet graft survival in this context is their vulnerability to oxidative stress, a consequence of relatively low expression of antioxidant enzymes[59]. Thus, transgenic islet expression of antioxidant enzymes, such as glutathione peroxidase, could be a possible solution. However, a potential drawback of this approach is that glutathione peroxidase removes H_2O_2, an inducer of VEGF synthesis[60], and thus may further impair islet graft revascularization. The net result of oxidative and other challenges is that more than 70% of islets transplanted intraportally fail to become stably engrafted[61].

VEGF is a multi-functional angiogenic regulator that stimulates blood vessel formation, endothelial cell survival and epithelial cell proliferation[62]. The receptors of VEGF are predominantly expressed on vascular endothelial cells[62] and are also expressed in pancreatic islets[63]. Several line of evidence indicates that insufficient expression of VEGF limits the rate and extent of islet graft revascularization. Transplanted islets show a significant reduction of VEGF expression at day 3-4 after transplantation[64] while an over expression of VEGF markedly improves the degree of revascularization and function of islet grafts. Mouse islets transfected with an adenovirus carrying the cDNA for the human $VEGF_{165}$ isoform were transplanted under the kidney capsule of diabetic nude mice. Vascular endothelial growth factor (VEGF) expression resulted in an increase in both islet graft mass and revascularization and, unlike vector-transfected grafts, rapidly returned recipient to stable normoglycaemia[65].

Several bone marrow subpopulations, such as endothelial progenitor cells and MSCs may be able to differentiate into one or more of the cellular compartments of the vascular bed[66,67]. MSCs are known to secrete VEGF and other growth factors and to enhance proliferation of endothelial cells and smooth muscle cells[68]. MSCs release a wide array of cytokines that support hematopoietic stem and progenitor cell development, as well as the secretion of other cytokines that are relevant to increasing blood flow to ischemic tissue[69]. Moreover, MSCs secrete several important arteriogenic cytokines, including VEGF and monocyte chemoattractant protein-1 (MCP-1). In mice undergoing distal femoral artery ligation, a model of hind limb ischemia, local injection of MSCs increased adductor muscle levels of VEGF and fibroblast growth factor (FGF) proteins compared with controls, and co-localization of VEGF and transplanted MSCs within adductor tissue was demonstrated[68].

Recently it has been reported that in animal models, MSCs are able to enhance survival and function of islet graft by increasing islet revascularization[70]. Consistent with these studies, our group showed that cultured MSCs express high level of VEGF and that transplantation of those MSCs elicited a robust host angiogenic response leading to neovascularization of syngeneic islet grafts in diabetic rats. This effect may serve to increase local perfusion of the islets and ameliorate their metabolic activity[71]. Similar results were obtained in a preclinical model by Berman *et al*[72] that demonstrated enhanced islet engraftment and function at 1 mo post-transplant in a cynomologus monkey model of allogeneic islet-MSCs transplantation. The authors hypothesized that MSCs enhance islet engraftment by staying in proximity to the islets at the time of cotransplantation, providing revascularization and regenerative signals. MSCs provided an important approach for enhancement of islet engraftment, thereby decreasing the numbers of islets needed to achieve insulin independence[72].

In summary, MSCs cotransplanted with islets in type 1 diabetic recipients can facilitate islet revascularization, engraftment and improved islet function: Consequently, the presence of MSCs permit to reduce the islet number required for reversal of diabetes. Therefore, cotransplantation of MSCs with islets could facilitate islet engraftment and improve islet graft function in clinical islet transplantation.

Immunomodulation of islet transplantation by MSCs

One of the most promising aspects of MSCs regards their dynamic role in modulating the immune system. MSCs are not only immunoprivileged cells, due to the low expression of class Ⅱ Major Histocompatibilty Complex (MHC-Ⅱ) and co-stimulatory molecules in their cell surface, but they also interfere with different

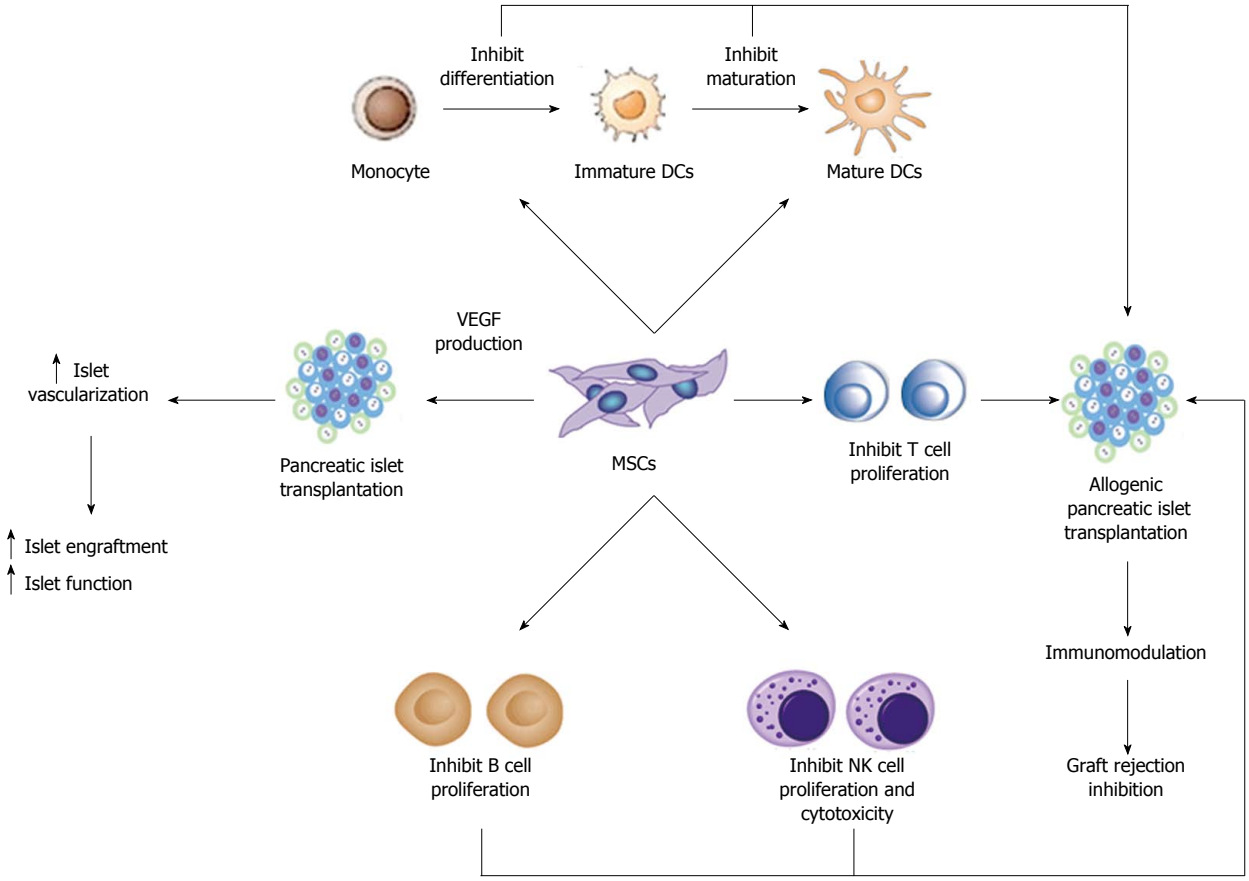

Figure 1 Schematic representation of the role of mesenchymal stem cells in islet transplantation. MSCs: Mesenchymal stem cells; VEGF: Vascular endothelial growth factor; DCs: dendritic cells.

pathways of the immune response by means of direct cell-to-cell interactions and soluble factor secretion. As schematically represented in Figure 1, it is well established that MSCs can exert immunosuppressive activity on T cells[73] and interfere with dendritic cell (DC) maturation[74]. Furthermore, MSCs may modulate natural killer (NK) cell cytotoxic activity, B cell proliferation and immunoglobulin production.

MSCs have been shown to suppress autoreactive T-cell responses in models of autoimmunity such as experimental autoimmune encephalomyelitis[75], collagen-induced arthritis[76] and autoimmune enteropathy[77]. Type 1 diabetes is one of the most prevalent autoimmune diseases in childhood. The effector mechanisms of immune-mediated destruction of islet β cells are complex, but an essential early event is the activation of islet cell antigen reactive T cells. Recently, the therapeutic benefit of MSCs has been evidenced in the treatment of type 1 diabetes. Lee *et al*[78] used immunodeficient recipient mice chemically induced by streptozotocin to study the effect of human MSCs in the development of diabetes. Infusion of hMSCs reduced glycaemic levels and increased peripheral insulin levels. In the pancreas of these mice the islets appeared larger compared with islets from untreated diabetic mice[78]. In experimental mouse models, intravenously infused MSCs are capable of migrating to pancreatic islets[48]. However, the role of MSCs in β cell replacement is controversial. Some evidence suggests the possibility that MSCs differentiate into islet β cells[48]. In addition, similar results were reported by Ezquer *et al*[79] in a model of streptozotocin-induced diabetes. Reversion of hyperglycemia and glycosuria was observed after injection of MSCs, with increased morphologically normal β pancreatic islets. Other reports have contradicted these findings suggesting that MSCs could be feeder cells for islet differentiation, proliferation and vascularization, but do not differentiate into β cells[80].

MSCs may also offer therapeutic opportunities in transplantation by directly targeting alloreactive T cells. MSCs are immunosuppressive *in vitro* and, in mixed-lymphocyte reactions, suppress T-cell proliferation[73] through soluble factors, including 2,3-dioxygenase (IDO), prostaglandin-E2 (PGE2), nitric oxide, transforming growth factor β (TGF β) and hepatocyte growth factor (HGF)[81,82]. Neutralizing antibodies against TGF β and HGF can restore the MSC-induced suppression of T cell proliferation[73]. In a model of allogenic pancreatic islet transplantation, the administration of MSCs resulted in the prolonged survival of islets and led to long-term stable normoglycemia[83]. In this study MSCs were colocalized at the graft site where they locally produced immunosuppressive matrix metalloproteinase-2 and-9 that block the activation and expansion of alloreactive T cells[83]. In a most recent paper, using

a rat model of streptozotocin induced diabetes, the authors found that MSCs significantly improved glycemic control and reduced graft infiltration by immune cells in either allogenic or syngeneic pancreatic islet transplantation[84]. They found that MSCs were effective when administrated either locally or systematically. The modulation of acute rejection that the authors observed after islet transplantation may indicate that soluble factors are released by MSCs to several organs after their systemic administration.

Additional studies revealed that MSCs might produce this anti-proliferative effect *via* induction of anergy in the T cell population[85], T cell tolerance[75], or by inducing proliferation of regulatory T cell populations[86]. Berman *et al*[72] first reported increased numbers of Treg in a MSC allogeneic islet transplant preclinical model. MSCs treatment significantly enhanced islet engraftment and function at 1 mo post-transplant, as compared with animals that received islets without MSCs. Additional infusions of donor or third-party MSCs resulted in reversal of rejection episodes and prolongation of islet function. Stable islet allograft function was associated with increased numbers of regulatory T-cells in peripheral blood[72].

The immune response is related not only to T cells, but to the interaction between DC cells and T cells[87]. DCs are antigen-presenting cells (APCs) capable of stimulating both naïve and memory T cells. MSCs affect the differentiation, maturation and function of DCs at different levels[74,88]. MSCs have also been shown to alter the cytokine secretion profile of DCs toward up-regulation of regulatory cytokines, such as IL-10, and down regulation of inflammatory cytokines such as IFNγ, IL-12 and TNFα, inducing a more anti-inflammatory or tolerant dendritic cell phenotype[74,89]. Studies in animal models suggest that DC based immunotherapeutic strategies might also be utilized to facilitate islet transplant tolerance[90,91]. Li *et al*[92] demonstrated that in mice with combined transplantation of pancreatic islets and MSCs, the expression of CD11c (DCs phenotype derived from monocytes) and CD83 (mature DCs phenotype) was down regulated markedly. This finding showed that MSCs inhibit the maturation of DCs and the stimulation of T cell was weakened, resulting in survival of transplanted pancreatic islets.

Autoimmunity also involves B cells by antibody production. The interaction between MSCs and B cells is not yet completely understood. However, co-culture experiments with these two cells using both mouse and human cells showed that MSCs inhibit B cell proliferation[93]. They also observed that MSCs affect chemotactic properties of B cells while B-cell co-stimulatory molecule expression and cytokine production were unaffected by MSCs.

Finally, NK cells are key effector cells of innate immunity. MSCs alter the function of NK cells by suppressing their proliferation, and cytotoxicity. Spaggiari *et al*[88] demonstrated that cytokine induced proliferation of freshly isolated NK cells was inhibited in the presence of MSCs.

Thanks to their interactions with many different types of immune cells, MSCs administrated in conjunction with islet cell transplantations could prevent immune rejection and promote long term islet allograft survival.

CONCLUSION

In summary, current data suggest that MSCs have the potential to aid in the treatment of type 1 diabetes and overcome some of the current limitations to islet transplantation. These cells may exert beneficial pro-angiogenic and immunomodulatory effects when co-transplanted with pancreatic islets. The pro-angiogenic effects result from the release of angiogenic factors from MSCs that have been shown to improve islet vascularization and graft function in islet transplantation. The immunomodulatory properties of MSCs may help in reducing inflammatory damage to the islets in the early peritransplant period. MSCs may also reduce autoimmunity through their capacity to inhibit T cell proliferation and suppress differentiation and maturation of dendritic cells.

These data encourage further preclinical co-transplantation of MSCs and pancreatic islets to improve the outcome of allogeneic islet transplantation in the treatment of type 1 diabetes. However, some key issues need to be addressed before MSC based therapies become a safe option for clinical studies. Most importantly, it is unclear if co-transplanted MSCs engraft and differentiate at the implantation site. Thus, the long-term stability of MSC activity and function after transplantation should be assessed *in vivo*. In addition, the selection of a suitable donor MSC source may differ if the treatment aims at modulating the autoimmune disease or enhancing pancreatic islet engraftment and vascularization. Therefore, whether autologous or allogeneic MSCs are suitable as a donor source should be selected according to the specific aim of the study.

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