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REVIEW ARTICLE

Co-transplantation of mesenchymal stem cells and endothelial cells with islet grafts: A strategy to improve post-tx engraftment of pancreatic islets

Raza Ali Naqvi[1*], Amar Singh[2*] Afsar Naqvi[1], Priyadarshini M[3], Devanjan Dey[2]

[1]Department of Periodontics, College of Dentistry, University of Illinois at Chicago, Chicago, IL, United States.
[2]Department of Surgery, University of Minnesota, Minneapolis, MN, United States.
[3]Department of Medicine, College of Medicine, University of Illinois at Chicago, Chicago, IL, United States.
[*]E-mail: naqvi@uic.edu
[*]singh423@umn.edu

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ABSTRACT

Though islet transplantation is now being considered as a gold standard to cure type 1 diabetes in patients without the threat of unaware hypoglycemia and severe hypoglycemia episode, post-transplantation islet loss due to the loss of intra-islet vasculature during the islet isolation process compromises the full functionality of the transplanted islet mass. Therefore, besides instant blood-mediated inflammatory reaction (IBMIR) induced loss within the first 60 minutes in intraportal vein, two weeks avascular window, prior to adequate vascularization, is responsible for further loss of islets due to hypoxia induced necrosis. Burgeoning evidences demonstrated that using omentum or kidney capsules we can overcome the IBMIR. This review first summarizes the post - transplantation islet loss till day 14 due to the absence of islet vascularization and then elucidates the methods used to restore the post-IBMIR islet loss. Co-transplantation of mesenchymal stem cells and endothelial cells with the islets appeared to be a better approach to overcome the challenges in islet transplantation.

Keywords: Type 1 diabetes (T1D), Islet transplantation, Co-transplantation, Mesenchymal stem cells (MSCs), Endothelial cells (ECs), Instant blood mediated immune reaction (IBMIR), Post-transplantation islet loss.

1. Introduction

Autoimmune destruction of insulin-producing beta cells in the pancreas and resultant hyperglycemia are the salient features of this devastating type 1 diabetes (T1D)[1]. The exact etiology and pathogenesis of this disease is ironically unknown. Global burden of Type 1 diabetes is increasing rapidly. Recently, Gregory et al, reported ~8.4 million individuals worldwide with type 1 diabetes with various age groups: 1·5 million aged ≤ 20 years, 5·4 million aged 20–59 years, 1·6 million aged ≥60years, in 2021[2]. Although genetic predisposition suggested more than 40 loci at different chromosomes are associated with T1D predisposition, the majority of genetically predisposed individuals do not necessarily show overt T1D[3-5].

Though insulin is considered a life savior drug to treat T1D patients with overt hyperglycemia, insulin-induced iatrogenic hypoglycemia has emerged as a real challenge to this treatment modality[6,7]. Human islet allo-transplantation under Edmonton's immunosuppressive protocol turn out to be a medical miracle as 7/7 patients in this treatment achieved irreversible insulin independence for 5 years. This protocol is based on steroid-free immune suppressive regimens[8]. Results of this protocol were successfully reproduced in multi-centric international trials in 2006 and it has been widely accepted as state-of-art technology to treat type 1 diabetics[9]. In this protocol, Tacrolimus (Tac) is regarded as a mainstay immunosuppressant to prevent islet specific post transplantation auto- and allo immunity. Prolonged exposure to Tac (calcineurin inhibitor) eventually leads to 1) nephrotoxicity[10], 2) impairment in insulin secretion and biosynthesis[11], 3) mitochondrial arrest[12] and 4) decrease in post-transplant vascularization[13]. To overcome the deleterious effects of Tac, Shapiro's group supplemented the islets with antiaging glycopeptide (AAGP)[14]. AAGP supplementation significantly improved islet survival (Tac^+ vs. Tac^+AAGP, 31.5% vs. 67.6%,), augmented insulin secretion (area under the curve: Tac^+ vs. Tac^+AAGP, 7.3 vs. 129.2 mmol/L/60 min), ameliorated oxidative stress, enhanced insulin exocytosis, reduced apoptosis, and improved engraftment in mice[14]. Furthermore, the use of pig islets has promised to resolve islet donor shortages with good quality islets[15-18]. Long-term survival of both adult pig islets[18] and neonatal pig islets promised to solve most of the issues pertaining to insufficient cadaveric islets[19] but PERV virus epidemiology in pigs is yet to be resolved to apply this hyperglycemia curing regimen in the clinic in the future[20] (Figure 1).

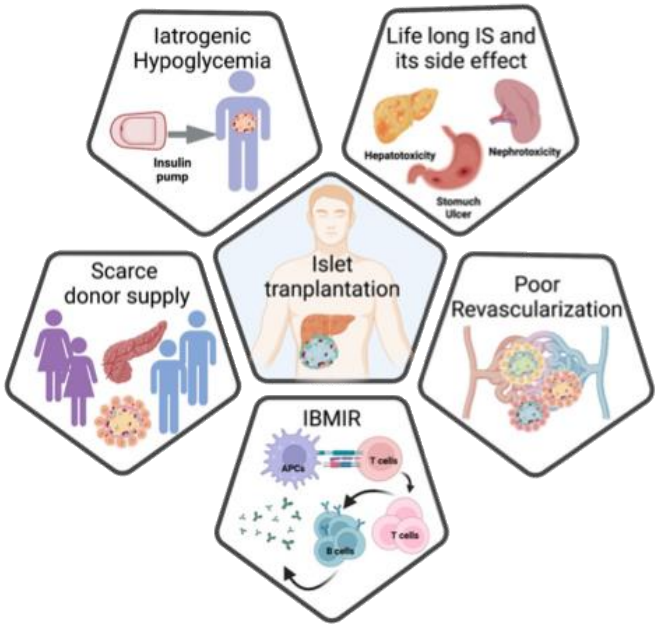

Figure 1: Illustration of islet transplantation and current challenges: Insulin dysregulation-Iatrogenic hypoglycemia, life-long immune suppression and its side effect, poor revascularization, instant blood mediated inflammatory reaction (IBMIR) and scarce donor supply.

Despite the aforementioned attributes of islet allo- and xeno- transplantation loss of a significant number of islets during intraportal infusion of islets by IBMIR is a real challenge[8]. The majority of patients undergoing islet transplantation require more than two donors to achieve insulin independence, leading to an immense shortage of donor supply. Also multistep islet isolation process (tissue dissociation, and prolonged enzymatic digestion) results in the loss of vascularization inducing islet-endothelial cells, thereby leaving the isolated islet avascular till the induction of neo-vascularization in the islet-recipient. This results in further loss of islets due to hypoxia-induced necrosis and as a result, islet transplants recipients fail to achieve long-term insulin independence[8,9]. Therefore, new therapies are urgently needed to tackle these challenges. In recent years, co-delivery of islets with accessory cells, mesenchymal stem cells, and endothelial cells along with biomaterial-based encapsulation and delivery strategies have been proposed and show significant advantages in improving the outcome of islet transplantation.

In this review, we first discuss the current challenges in islet transplantation mainly highlighting the poor engraftment of transplanted islet mass and then we detail various cell delivery strategies used in islet transplantation to overcome this issue in a comprehensive way.

2. Poor engraftment of islet graft

Owing to recent advancements in islet isolation and immunosuppression regimens, pancreatic islet transplantation holds great promise for a long-term cure of T1D without recurrent hypoglycemic episodes[8,9,18]. Ironically, 60-70% of islet mass is lost during the initial days of transplantation, and normoglycemia is maintained by 20-30% leftover islets[21]. To maintain the optimal delivery of oxygen and other necessary nutrients for sufficient dispersal of secreted hormones, pancreatic islets maintain exceptional glomerular-like angioarchitecture with a high blood perfusion rate: 5–7 ml $min^{-1} \cdot g^{-1}$ tissue[22,23]. The disruption of islet endothelium and endogenous islet-angioarchitecture during the islet isolation process led to the purified transplantable islets as an avascular entity[24-27]. Thus, there is a crucial need for rapid vascularization for the survival and engraftment of the islets to maintain normoglycemia in T1D patients.

To improvise the post-transplantation vascularization, D. Menger's group has made commendable efforts. The group has have transplanted pancreatic islets onto the vascular bed of striated muscles in the dorsal skinfold chamber in the Syrian golden hamsters' model. Both in iso- and xeno-islets, the first signs of re-vascularization appeared on 2-4 days post-tx[28]. Early vascularization in this study was characterized by: 1) the presence of sinusoidal vessels and, the protrusion of capillary sprouts from the venular segments, 2) post capillary venules of the striated muscle vascular bed (which further branched and eventually formed an initial microvascular network). Later in the same year, O Korsgren's group in Sweden further substantiated these findings. They have transplanted fetal porcine islet-like cell clusters (ICC) and used laser-Doppler flowmetry and Hsp70 levels (beta cell stress) as read-outs of initiation of revascularization[29]. They have demonstrated that revascularization of subcapsular ICC graft was initiated rapidly within 3 days post-tx with the concomitant lowering of Hsp70 levels[29]. Furthermore, it was demonstrated by Davalli et al., that post-tx re-vascularization begins on day 3 and peaks on day 14[30]. Therefore, the transplanted islets were in an avascular state till day 14 and succumb to undergo beta cell necrosis[30]. The potential of this newly formed vascular bed to meet the requirements of highly metabolically active beta cells is still a matter of debate[24,26]. Carlsson et al, demonstrated poor revascularization in transplanted islets, which could *in-turn* effect compromise the metabolic and insulin release by beta cells. This group observed mean pO_2 in native pancreatic islets as ~40 mmHg vs pO_2 of ~5 mmHg in revascularized islets irrespective of transplantation site[26]. These studies suggest that revascularization is critical for islet transplant success, Poor revascularization are the key reasons of post-tx islet loss (Figure 2).

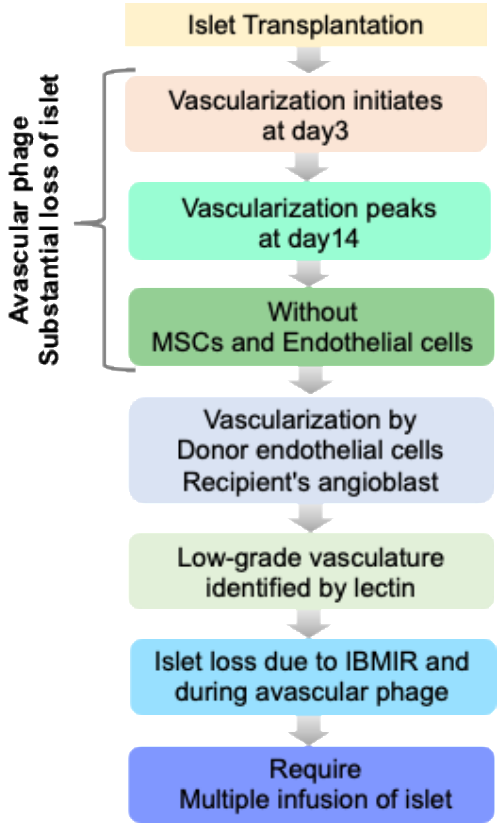

Figure 2: Schematics of effect of loss of vasculature on post-tx islet engraftment.

3. Strategies to improve the vascularization of the islet graft

Poor revascularization in transplanted islets results in insufficient oxygen and nutrient supply, accumulation of waste, and worsening ischemia and hypoxia, ultimately leading to islet cell death and graft failure. This challenge has raised concerns about islet transplantation as a viable therapy for reversing T1D[8,9]. Various strategies have been developed to enhance revascularization, including conjugating pro-angiogenic factors like VEGF and PDGF, inhibiting anti-angiogenic factors, implanting vascularization-promoting devices, and co-culturing or co-transplanting islets with blood-network-promoting cells such as mesenchymal stem cells (MSCs) and endothelial cells[31-36]. These approaches aim to restore beta cell function in T1D patients by facilitating rapid and efficient revascularization of islet grafts. (Figure 3).

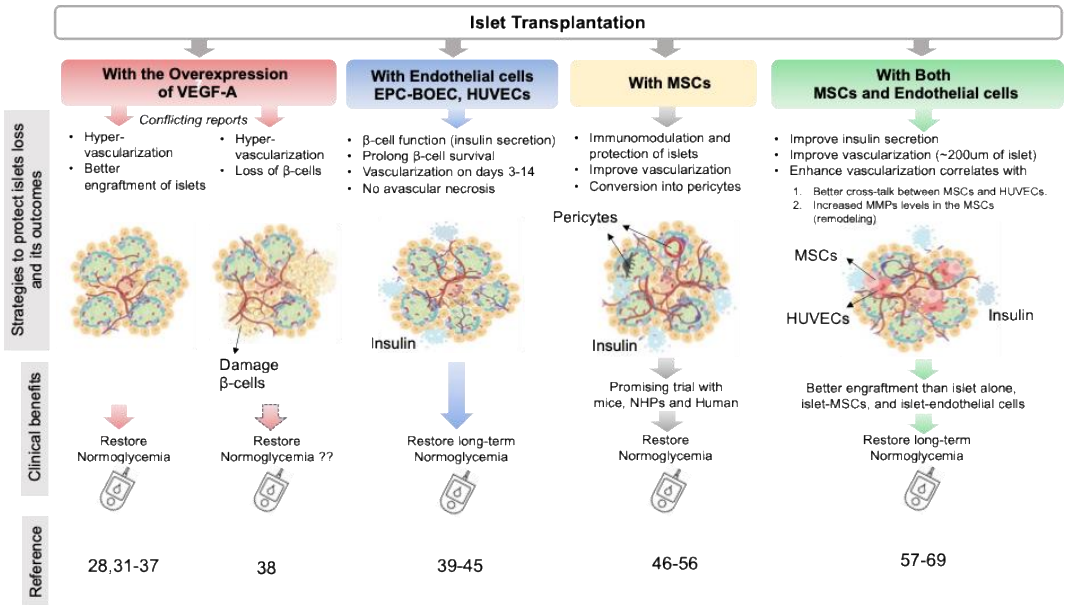

Figure 3: Overview of various strategies used to improve the vascularization and engraftment of transplanted islets

3.1 OVER EXPRESSION OF VEGF FROM DONOR ISLETS

Though sequence of events orchestrating the re-vascularization are not known, pericellular proteolysis, sprouting or migration/proliferation of endothelial cells (EC), formation of new capillaries, and maturation of blood vessels are considered as few prime steps towards vascularization.[31] In native pancreas, VEGF produced by crosstalk of endothelial and endocrine cells is responsible for the glomerular vasculature formation[32,33]. Early and later stages of pancreas development require different extent of VEGF expression[34-36]. inactivation of VEGF-A (either in endocrine progenitors or differentiated β cells) is responsible for loss of intra-islet capillary density, vascular permeability and islet function (no need). Interestingly, we have come across confounding studies on over expression of VEGF-A. Lammert and colleagues have reported that pancreas-wide overexpression of VEGF-A from early development to adulthood results in pancreatic hyper- vascularization, β cell mass expansion and islet hyperplasia[33]. In this pursuit, Zhang et al., reported that transplantation of murine islets containing human VEGF165 cDNA (by adenoviral-mediated gene delivery system) in the kidney capsule of streptozotocin (STZ)-induced diabetic mice were associated with restoring normoglycemia. These islets demonstrated augmented microvasculature and elevated insulin content[37]. Furthermore, Brissova et al. reported that though increased VEGF-A production plays a pivotal role in β cell regeneration, transiently increased VEGF-A production in adult β cells increases the intra-islet endothelial cells activation but also β cell loss at the same time[38].Thus, these pieces evidence suggest VEGF-A expression is a double-edged sword in the process of islet vascularization, which needs to be fine-tuned in accordance with the microenvironment.

3.2. CO-TRANSPLANTATION OF ENDOTHELIAL CELLS IMPROVES VASCULARIZATION

Brissova et al., demonstrated that both donor and recipient's endothelial cells populations were involved in the process of post-tx revascularization[39] In-depth analysis of transplanted islets further revealed that some vessels were lined with donor endothelial cells, while others with recipient endothelial cells. They found no evidence of developing chimeric blood vessels in the human islet graft transplanted in the mouse[39]. Multiple evidence also demonstrated the role of circulatory epithelial progenitor cells (EPC) in enhancing neovascularization in various clinical settings[40,41]. Also, Mathews et al., demonstrated migration and homing $EGFP^+$ bone marrow cells in the pancreas of mice injured with STZ.

In this pursuit, the Park's group in Korea co-transplanted 7,000 islet equivalents (IEQ) pig islets into the renal capsules of diabetic nude mice- with and without vascularization promoting human cord blood–derived endothelial progenitor cells (EPCs; 5×10^5) isolated from umbilical cord blood obtained from normal births [43]. Islet-EPC group, in this study, maintained normoglycemia (<200 mg/dL) on day 11, whereas the blood glucose in islet only group never restored normoglycemia. Also, mice transplanted with EPC demonstrated higher porcine insulin level (21.5 ± 2.0 ng/mL) under fasting as compared to the islet alone group (12.2 ± 2.6 ng/mL). Interestingly, the islet-EPC group revealed high vascular density from day 3 to day 14 as compared to the islet-only group.[43] In a separate study, Coppens et al., co-transplanted 5×10^5 Human blood outgrowth endothelial cells (BOEC) with a different number of pig islets in kidney capsules to restore normoglycemia in severe combined immunodeficiency (SCID) mice.[44] Interestingly, this group demonstrated that mice transplanted marginal mass of islets i.e. 50 and 75 islets exhibited stable normoglycemia on day 7 post-tx. To evaluate the islet vascularization dynamics, i.v. injection of biotinylated Lycopersicon esculentum (LE) lectin was used 10 minutes before the animals were scarified and biotinylated LE was detected with streptavidin conjugated with Alexa-fluor-555. Till day 3 post-tx, lectin injection did not show any increase in functional blood vessels through islets but the mean vessel volume of co-transplanted islets (islets + blood outgrowth

endothelial cells; BOEC) was doubled on day 28 post-tx. Importantly, they also observed a significant decrease in cell-death area in the islet+BOEC group on day 4 as compared to islet alone, (0.93± vs. 10.82±5.37%)[44], thereby suggesting the role of BOEC in post-tx islet protection. This observation was further corroborated by Quaranta et al. This group showed the survival and function of marginal islets (700 IEq) upon co-transplantation with endothelial progenitor cells (EPCs) (5×10^5 EPCs in the portal vein) in syngeneic rats[45]. Therefore, co-transplantation of endothelial cells with islets, 1) protects islet beta cells, 2) decreases the need for islet mass to restore normoglycemia, 3) facilitates rapid and improved vascularization as compared to islet alone groups.

3.3 .CO-TRANSPLANTATION OF MESENCHYMAL STROMAL CELLS ALSO GETTING ATTENTION

In addition to endothelial cells, mesenchymal stem cells (MSCs) are adult progenitor cells and have been reported to play a major role in tissue repair[46,47]. Tang et al., reported that transplantation of autologous MSCs decreased cardiomyocytes apoptosis, and concomitant increased blood vessel density and blood flow in a mice model of myocardial infarction[48]. These observations were corroborated by Kim et al., in a separate study suggesting the inefficiency of endothelial cells to rescue cardiac functions in absence of bone marrow (BM) derived MSCs[49]. However, the dose of MSCs to be used for angiogenesis is very important as at higher doses these cells are proven cytotoxic to endothelial cells (ECs)[48].

Furthermore, Figliuzzi et al., revealed the role of MSCs (1×10^6) in rescuing the hyperglycemia in diabetic Lewis rats transplanted with 2000 islets (never reverted hyperglycemia in islet alone group) in the kidney capsule. 2000 islets + MSCs group successfully helped to achieve good glucose control until nephrectomy. Vascular density for islet + MSCs was found remarkably higher than islet alone cases (1459 ± 66 capillaries/mm^2 vs. 1002 ± 55 capillaries/mm^2)[50]. In the same way, Itoh et al., et al., also co-transplanted a marginal number of islets with MSCs to restore the hyperglycemia in the kidney capsule of LEW rats. Interestingly, all 8/8 recipients were able to restore normoglycemia with two-fold high density of vasculature on day 7[51]. The study by Rackham et al., further reported that co-transplantation of MSCs with islets in kidney capsules takes less time to reverse normoglycemia than islet alone (7±2 days islet + MSCs vs. 17±2 days islet alone). Interestingly, in immunohistochemistry islet + MSCs deciphered intact islet like architecture viz. endocrine area separated by extensive areas of non-endocrine tissue[52].

Importantly, in addition to their role in re-vascularization, MSCs are good tools to embargo inflammation within and surrounding the non-endocrine tissue of the recipient after transplantation. In a study, Solari et al., transplanted marginal islet mass with MSCs in the omentum of a rat model. In addition to achieving normoglycemia, surprisingly, T- cells obtained from the recipients showed significantly less production IFN-γ and TNF-α upon ex-vivo activation. Also, the T cell population showed a significantly higher fraction of $CD4^+$ IL-10^+ subsets[53]. Ben Nasr et al., systemically injected autologous and heterologous MSCs in allo-islet transplanted diabetic mice recipients and their data showed that allo-islet recipients treated with autologous MSCs from bone marrow showed Th2 skewing. However, even the systemic treatment of autologous MSCs could only delay the rejection process[54]. In addition to mice model studies, the Norma S. Kenyon group performed allotransplantation of islets in non-human primates[55]. They reported that MSC-islet co-transplantation in hepatic portal vein showed no difference in fasting C-peptide values between ones treated with delayed rapamycin and anti-CD154 and those that began treatment with rapamycin before allo-islet transplant. Grippingly, the graft destabilization is found to be linked with the decreased proportion of $FoxP3^+$ T regs in the recipients, as more MSC infusion on graft dysfunction resulted in an increase in Tregs and also graft stabilization in terms of restoring fasting C-peptide levels[56].

Apart from preclinical studies, MSCs are also getting clinical attention as these cells are presently being evaluated in clinical trials for the treatment of type 1 and type 2 diabetes, diabetes complications, and other diseases (clinicaltrials.gov). In this study, more than 1,000 humans have been tested for MSCs infusion and no adverse effects were reported[55]. In a recent clinical trial, Wang et al., evaluated the safety and efficacy of co-transplantation of autologous MSCs and islets in patients undergoing total pancreatectomy and islet auto transplantation (TP-IAT). Interestingly, one in 3 patients who received both islets and MSCs (1x 10^6 per kg) were found to be insulin free compared with 22.2% and 20.0% of historical control patients (islet only) at 6 and 12 months, respectively. Also, MSC infused patients required less daily insulin than historical controls on a postoperative day 2 (10.7 ± 4.5 U vs. 22.0 ± 18.7 U, MSC: control, p = .02) and day 3 (5.3 ± 6.1 U vs. 18.7 ± 19.1 U, p = .04). Additionally, the daily requirement for exogenous insulin was turned out to be lower in MSC group at 6 months. More specifically, 9.3 ± 8.1 U vs. 18.1 ± 21.5 U in MSC+ islets vs. islet only. However, after 6 more months i.e. after 12 months this figure was found to be increased in both but still found to be less in individuals' undergone intraportal MSCs infusion (16.7 ± 15.0 U vs. 20.7 ± 23.1U). Therefore, all these data affirm the clinical use of MSCs to induce rapid revascularization and improve the function of co-transplanted islets[56].

3.4. CO-TRANSPLANTATION OF MESENCHYMAL STROMAL CELLS WITH ENDOTHELIAL CELLS

Based on the above reports we can say the crux of islet therapy would lie in re-vascularization. Matsumoto et al., developed a ground-breaking 3D culture method and demonstrated that mesenchymal cells, undifferentiated endothelial cells, and endoderm are required for the orchestration of events that eventually lead to the initiation of 3D liver bud condensation.[57] Later on, Takebe et al. have shown that this culture system allows the crosstalk of multiple progenitors cells in 4D (spatiotemporal) manner in order to develop a functional bud, ready to be transplanted with bright chances of getting successful engraftment[58-60]. Johansson et al., also revealed that endothelial cells have tendency to initiate vascularization which was eventually improved and augmented by the addition of MSCs[61]. The group demonstrated that only one day after the addition of MSCs, there was a threefold increase in the islet surface covered by ECs. Briefly, the total number of sprouts coming out from EC-MSC islets was higher than that in the control or EC islets. Also, they visualized the induction of sprouts in a paracrine manner. On the other hand, disruption of sprouting over time in EC-islets, pinpoints the pivotal role of MSCs in vascularization[61]. In a different study, Ghajar et al., unraveled that the positive stimulatory effect of MSCs on angiogenesis in three-dimensional fibrin was partly as a result of degradation of the fibrin matrix by proteases produced by the MSCs. This potential may be seen as role of MSCs in tissue remodeling and resultant vascularization into dense micro-organs such as islets[62].

In this pursuit, Buitinga et al., seeded the islets in nonadherent agarose microwell chips as described previously[63-65] and added MSCs and HUVECs on the micro-well chip. Interestingly, to maximize the angiogenic potential of these cells they incubated agarose chips with (endothelial growth medium (EGM-2) for 8 h and then transplanted these MSC-EC-islet clusters subcutaneously in Matrigel plugs in the back of 8-week-old male NMRI-nu mice (Harlan). A total of 9 plugs were implanted containing every 200 islets in each mouse. Quantitative assessment of vascularization within 200 µm of islets revealed the following trend: 7% of the islets in the control group, 19%, hMSC-islets and 32%, HUVEC–hMSC-islets, respectively. However, we still do not have a very clear picture of how do hMSCs and HUVECS improve vascularization. Evidence of secreting a multitude of factors by MSCs and HUVECs viz. vascular endothelial growth factor, bFGF, and MMPs, which are in fact involved in endothelial cell survival, tip cell migration, proliferation, endothelial tubulogenesis, and/or vascular maturation[66-69] and dramatic increase of

many of them during HUVEC/HMSC co-cultures compelled us to believe their pivotal role in improving imminent engraftment after islet transplantation. Importantly, differentiation of hMSCs in pericyte[70] is another factor that made us believe in the role of MSCs in endothelial cell-mediated vascularization. Now, studies on the co-transplantation of islets co-cultured with MSCs and HUVECs at various transplantation sites are needed to see a clear picture of the role of these cells in the engraftment of the islet graft.

4. Future perspectives

Though islet transplantation is the best suited treatment modality to reverse hypoglycemia, severing intra islet vasculatures, and vasculature inducing cells (islet endothelial cells) during the process of getting islet isolation is a real irony towards the successful engraftment, function, and survival of the transplanted islets. Co-transplantation of MSCs and endothelial cells turned out to be the unsurpassed remedy to deal with the problem of inducing neo-angiogenesis in the islets. By virtue of inducing self-condensation, MSCs help islets and endothelial cells to form a real islet-like entity that is proangiogenic and shown to induce intra-islet vasculature and therefore forms a conducive microenvironment for survival and glucose-stimulated insulin secretion in the transplantation setting. Based on this, the islet-MSC-endo complex in a well-described ratio, will act as a NEO-ISLET to restore hyperglycemia in Type 1 diabetes patients. (Figure 3). Similar to islets, MSCs and HUVECs derived from HLA- matched/ mismatched individuals might elicit the mild immune response, that we have to test, whether we have test- whether we have to increase the doses of current immunosuppression regimen based on Edmonton protocol or not.

5. Conclusion

This review highlights the critical challenges and advancements in pancreatic islet transplantation for treating T1D. Despite the promising outcomes achieved through the Edmonton protocol and advancements in immunosuppressive regimens, the loss of islets due to poor vascularization remains a significant barrier. Co-transplantation of mesenchymal stem cells (MSCs) and endothelial cells has emerged as a viable strategy to enhance revascularization, reduce hypoxia-induced islet loss, and improve long-term graft survival. These accessory cells not only support neo-angiogenesis but also provide immunomodulatory benefits, fostering a conducive microenvironment for islet engraftment. Emerging technologies, such as bioengineered neo-islets and prevascularized scaffolds, further strengthen the prospects of successful transplantation. However, addressing immune compatibility issues and ensuring the scalability of these approaches remain critical. As researchers continue to explore the integration of MSCs and endothelial cells, it is imperative to optimize their therapeutic ratios and delivery methods. In conclusion, advancing islet transplantation techniques, supported by innovative co-transplantation strategies, holds great promise for transforming the treatment landscape for T1D, improving patient outcomes, and addressing the global challenge of donor islet scarcity.

Conflict of Interest:

The authors declare that there are no conflicts of interest.

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Authors' Contributions:

RN, AS,: Conceptualized and wrote the manuscript, and created the figure. MP, AB, and DD: Review the manuscript. RN and AS: Contributed equally.

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