How Effective are Genetically Modified Islets and Other Sources of Insulin-Producing Cells for Treating Autoimmune Diabetes?

Anna Pehe*, Christina Baechle

German Center for Diabetes Research (DZD), Munich-Neuherberg, Germany

Corresponding Author*

Anna Pehe,

German Center for Diabetes Research (DZD), Munich-Neuherberg, Germany

Tel: 498934521063

E-mail: pehe.anna@geruni.org

Received: 28-Sep-2022, Manuscript No. jdm-22-20149; **Editor assigned:** 01-Oct-2022, PreQC No: jdm-22-20149(PQ); **Reviewed:** 08-Oct-2022, QC No. jdm-22-20149; **Revised:** 22-Oct-2022, Manuscript No jdm-22-20149(R); **Published:** 31-Oct-2022, DOI: 10.35248/2155-6156.1000960

Abstract

For those with type 1 diabetes, islet transplantation is a promising treatment that may offer real-time metabolic regulation of glucose and eventually lead to insulin independence. However, there are two significant issues that must be resolved: (1) poor immune responses, such as inflammation brought on by the islet isolation/transplantation method, recurrent autoimmunity, and outright rejection, might result in graft loss; and (2) a lack of organ donors. In animal models, a number of gene therapy strategies and pharmaceutical medications have been shown to increase the longevity of pancreatic islet grafts; nevertheless, the human applications require more research. The ex vivo production of insulin-secreting cells from various sources of stem/progenitor cells has also emerged as an appealing possibility in regenerative medicine as a substitute for pancreatic beta-cell replacement therapy. This paper reviews current approaches to generate functional insulin-secreting cells from stem/progenitor cells and focuses on the genetic modification of islets during transplantation therapy.

Keywords: Autoimmune; Type 1 diabetes; RXRα ligand; Diabetes; Cytotoxic chemicals; Pharmaceutical.

Introduction

Type 1 diabetes (T1D) is an autoimmune condition in which auto reactive T lymphocytes gradually kill insulin-producing cells in the pancreatic islets, resulting in hyperglycemia. Two million people in Europe and North America are affected by the illness, which accounts for around 10% of all instances of diabetes and most frequently affects those of European origin. Because the different populations have varying genetic susceptibility/resistance variables or levels of exposure to environmental triggers, there is a noticeable regional difference in the occurrence [1]. For example, a child in Finland (Northern Europe) has an approximately 80-fold higher risk of contracting the illness than a youngster in China (Eastern Asia). It is well known that the incidence of T1D is rising globally at a rate of 3% per year, and this sharp increase strongly suggests that environmental factors should be acting on susceptibility genes and influencing the T1D epidemiology as it changes [2].

For metabolic management in T1D patients, daily insulin therapy through injection or a pump is essential. However, this exogenous insulin supply has the potential to result in hypoglycaemic episodes and is unable to establish physiological control of blood glucose concentrations, Additionally a sizeable percentage of patients experience chronic and degenerative side effects like nephropathy, retinopathy, and vascular and heart disease [3]. The best course of action for T1D is replacement of the -cell mass, which is currently achieved through whole pancreas transplantation and islet transplantation. For diabetic patients who can achieve insulin independence from a single donor, complete pancreas transplantation is the usual treatment. Compared to whole-organ transplant therapy, which can result in thrombosis, pancreatitis, and peritonitis, pancreatic islet transplantation is a safer and less intrusive procedure. However, compared to pancreas transplantation, the main disadvantage of islet transplantation is the higher donor demand and lower 5-year insulin independence rate [4].

Compared to current therapies, transplantation therapy ought to offer a higher quality of life and assist prevent problems. Unfortunately, the main barriers to establishing insulin independence and long-term graft survival in this therapy are immune-mediated destruction and a lack of available donor organs for transplantation. Genetically altering islets to increase their resistance to immunological attack and rigorous research into other sources of insulin-secreting cells are being done in an effort to get around such issues. We will review the most recent research on immunomodulator therapy for islet transplantation in this paper, as well as look at alternate sources of insulin-secreting cells for cell replacement therapy [5].

Materials and Methods

Mechanisms of Islet Graft Rejection: Nonspecific Inflammation and T-Helper Cell Subset Contribution

Additionally, the isolation of the islets sets off a series of stressful events in the cells, including the induction of apoptosis or necrosis and the generation of proinflammatory chemicals, which have a detrimental effect on the viability and functionality of the islets. The generation of proinflammatory cytokines and chemokines by the islets is induced by transplantation procedures such collagenase-based islet isolation. It is toxic to islets and can cause the local generation of reactive oxygen species when islet-resident macrophages produce proinflammatory cytokines including interleukin-1 (IL-1) and tumour necrosis factor (TNF) (ROS). Contrarily, the production of acute islet allograft rejection depends on chemokine receptors such chemokine (C-C motif) receptor (CCR) 2 CCR5, and C-X-C chemokine receptor (CXCR)3, as well as their ligands. The inflammatory cytokines, chemokines, and ROS work as a team to attack the islets in the first place, which can result in apoptosis and loss of function [6].

Many concerns, including as the therapeutic medicines' inability to be locally targeted and the possibility that they may have impacts on other organs or tissues, leading to unforeseen side effects, can be resolved by the direct delivery of protective and therapeutic genes to islet grafts, Any vector system can modify islets ex vivo using gene therapy without endangering the receiver. Additionally, long-lasting, secure, and locally controlled gene expression can be achieved using graft-specific gene therapy. This makes ex vivo islet modification by gene transfer systems an appealing strategy to defend grafts from immune attack. However, great consideration should be given to the gene delivery methods used. In general, long-term gene expression does not include the use of immunogenic vectors that cannot elicit an immunological response from the host [7].

Techniques for Preventing Insult Inflammation and T-Cell-Mediated Immunity

Pancreatic cells in autoimmune diabetes experience inflammatory stress as a result of T-cell-mediated apoptosis. In the islet microenvironment, macrophages and/or dendritic cells create proinflammatory cytokines and free radicals that cause -cell destruction. To further stimulate other immune cells and hasten -cell death, activated T cells produce death receptors and release cytotoxic chemicals like granzyme B, perforin, or cytokines. It has

been shown that a number of preventive and therapeutic strategies, such as regulating T-cell activity and reducing inflammatory reactions in the islet microenvironment, can shield cells from immunological attack. Many gene targets that exhibit potent immunoregulatory and antiapoptotic effects have been introduced to the islets in an effort to protect them from immune attack. These methods include the creation of transgenic mice using islet-specific promoters to carry the desired genes, transfection or viral delivery of genes into the islets, and administration of recombinant proteins and medications.

Numerous methods have been demonstrated to enhance islet transplant performance and shield grafts from immune attack. Among these strategies are the blocking of co-stimulation signals by CTLA-4-Ig, the down regulation of Th1 responses by overexpression of galectin-9 (Chou et al., manuscript under revision), the overexpression of antiapoptotic and antioxidative molecules like B-cell lymphoma (Bcl)-2, TRX, and superoxide dismutase (SODs), the blocking of inflammatory cytokine signalling by overexpression of IL .

In conclusion, these techniques greatly lower islet graft apoptosis and increase graft survival in diabetes patients. However, there has been no success using these protective genes in transplantation therapy. Generally speaking, paracrine therapeutic targets would have more pronounced biological effects than membrane-bound or intracellular compounds. Furthermore, the effectiveness of gene delivery to the islets and the levels of target protein expression in the grafts' milieu are directly related to the protective effect. Therefore, using a "cocktail" therapy-for instance, combining antiapoptotic and anti-inflammatory genes-might have produced better results because they might have synergistic protective effects [8].

Alternative Sources of Insulin-Producing Cells: Insulin-Producing Cells Derived from Stem/Progenitor Cells for Cell Replacement Therapy

Despite being viewed as a "cure" therapy for diabetes, islet transplantation is impeded by the lack of donors for isolating islets. In-depth research is being done on a variety of other methods that can be used to obtain cells that secrete insulin. They consist of the following: (1) the creation of surrogate cells through genetic modification of non-endocrine cells to secrete insulin in response to glucose challenge, (2) the trans differentiation of non-endocrine stem/progenitor cells or mature cells to glucose-responsive adult tissues, (3) the controlled differentiation of islet stem/progenitor cells to produce large numbers of mature, functional islets, (4) the in vitro differentiation of stem cells to become insulin-secreting cells, and (5) the in vitro differentiation of stem cells [9].

Discussion

Stem cells can develop into several cell types and can reproduce themselves (self-renew). They are the perfect subject for regenerative medicine because of these qualities. Additionally, stem cells have potent immunosuppressive properties and have the capacity to secrete a variety of trophic substances that aid in the regeneration of injured tissues. As a result, stem cells have emerged as a desirable alternative cell source for the treatment of diabetes. Embryonic stem cells (ESCs), adult stem cells, and most recently iPSCs are all possible sources of stem cells that could be used to create insulin-producing cells.

Previous studies have shown that ESCs can be made to develop into tissue that secretes insulin and has features resembling those of pancreatic islets. Nevertheless, these cells are frequently insensitive to glucose or produce less insulin than endogenous cells, which is insufficient to control normoglycemia in diabetic recipients in a mouse model. Because animal studies have not advanced enough to support this strategy, ESCs have not yet been used therapeutically to treat diabetes mellitus in humans. For instance, the positive insulin staining of ESC-derived pancreatic-like tissue most likely results from uptake of insulin from the culture medium, and the intermediate stages involved in the differentiation pathway are complex and poorly understood [10].

Mesenchymal stromal cells (MSCs) and iPSCs, which have less limits or limitations due to ethical issues in the research and clinical contexts, have also become the perfect cell types for regeneration therapies in addition to ESCs made from embryos. Previous studies have shown that MSCs can be differentiated into clusters of cells resembling islets, and that these cell clusters can reverse the diabetic state in recipients who had been induced with streptozotocin (STZ) to become diabetic. Additionally, MSCs themselves possess potent cytoprotective and immunosuppressive properties. The cotransplantation of islets and MSCs results in better outcomes than islet transplantation alone, according to a number of lines of evidence. MSCs serve as feeder cells in cotransplantation therapy, promoting islet revascularization and enhancing graft function [11].

Recently, an intriguing alternative source of cells with pluripotent properties similar to ESCs has emerged: iPSCs made from reprogrammed somatic cells. This idea has been further investigated by creating islet-like clusters from iPSCs utilising human skin fibroblasts or cells from skin biopsies taken from T1D patients. These cells have the ability to secrete C-peptide and react to high glucose concentrations, indicating that functional cells may one day be produced from iPSCs. In subsequent research, transplantation of pancreatic beta-like cells produced from iPSCs corrected hyperglycemia in diabetic mice models. These results offer a preliminary proof of concept for the potential clinical use of iPSCs. Additionally, if iPSCs could be created from diabetic patients, they would share the recipient's genotype, preventing the issue of immune rejection. iPSCs are so promising for developing patient-specific regenerative therapies. Unexpectedly and shockingly, autologous iPSCs reprogrammed from foetal fibroblasts by viral or no viral genetic methods cause T-cell-dependent immunological responses and rejection in genetically similar animals. This is probably due to the iPSCs' aberrant antigen expression, which broke down peripheral tolerance. Additionally, there might be additional unidentified epigenetic variations between iPSCs and ESCs [12].

Conclusions

One of the conditions that respond best to cell replacement therapy is T1D. Since the development of the Edmonton protocol and the successful replication of this glucocorticoid-free immunosuppressive procedure, clinical studies of islet transplantation have demonstrated exceptional effectiveness. However, allograft rejection and recurring autoimmunity have a negative impact on this procedure's long-term success. Additionally, the lack of organ donors makes it difficult to treat T1D. Researchers have devised a variety of methods to control the negative immune reactions and have also looked at alternative sources of cells that secrete insulin in an effort to solve these issues. Using gene therapy, it is possible to change islets to create immunosuppressive chemicals that decrease T-cell response and make islet grafts resistant to inflammation-induced apoptosis. It is now a hopeful reality to employ stem cells to create functional, regenerative cells. Furthermore, employing pancreatic-like cells produced from iPSCs, it should be possible to create patient-specific, autologous cell replacement treatment based on current understanding of genomic cell reprogramming.

Although these proofs of concept for possible preclinical applications demonstrate a significant advancement in this field, the following considerations should be taken into account: (1) the persistence and levels of targeted gene expression in islets, (2) the potential for insertion mutagenesis (retroviruses and lent viruses) and host immunogenicity (adenoviruses) associated with the use of viral vectors for direct gene therapy, and (3) the effectiveness of differentiation of insulin-secreting cells from stem cells.

In conclusion, more research is needed to create the most effective immunoregulatory therapies for grafts and to produce stable and safe sources of cells that secrete insulin for clinical islet transplantation or cell replacement therapies.

Conflict of Interest

None

Acknowledgement

None

References

1. Gillespie KM (2006) Type 1 diabetes: pathogenesis and prevention. J Canadian Medical Association 175 (2):165-170.
2. Harjutsalo V, Sjöberg L, Tuomilehto J (2012) Time trends in the incidence

of type 1 diabetes in Finnish children: a cohort study. The Lancet 371(9626):1777-1782.

3. Berney T, Johnson PR (2010) Donor pancreata: evolving approaches to organ allocation for whole pancreas versus islet transplantation. Transplantation 90(3):238-243.
4. O'Connell PA, Pacheco-Silva A, Nickerson PW (1993) Unmodified pancreatic islet allograft rejection results in the preferential expression of certain T cell activation transcripts. J Immunology 150 (3):1093-1104.
5. Walsh PT, Strom TB, Turka LA (2004) Routes to transplant tolerance versus rejection: the role of cytokines. Immunity 20 (2):121-131.
6. Subudhi SK, Zhou P, Yerian LM (2004) Local expression of B7-H1 promotes organ-specific autoimmunity and transplant rejection. The Journal of Clinical Investigation 113(5):694-700.
7. Huang SH, Chu CH, Yu JC (2010) Transgenic expression of haem oxygenase-1 in pancreatic beta cells protects non-obese mice used as a model of diabetes from autoimmune destruction and prolongs graft survival following islet transplantation. Diabetologia 53 (11):2389-2400.
8. Cobb BS, Nesterova TB, Thompson E (2005) T cell lineage choice and differentiation in the absence of the RNase III enzyme Dicer. The Journal of Experimental Medicine 201(9):1367-1373.
9. Zhou X, Jeker LT, Fife BT (2008) Selective miRNA disruption in T reg cells leads to uncontrolled autoimmunity. Journal of Experimental Medicine 205(9):1983-1991.
10. Lu LF, Thai TH, Calado DP (2009) Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein. Immunity 30(1):80-91.
11. Yang ML, Ye L, Wang B (2015) Decreased miR-146 expression in peripheral blood mononuclear cells is correlated with ongoing islet autoimmunity in type 1 diabetes patients. Journal of Diabetes 7(2):158-165.
12. Grieco FA, Vendrame F, Spagnuolo I, Dotta F (2011) Innate immunity and the pathogenesis of type 1 diabetes. Seminars in Immunopathology 33(1):57-66.

Cite this article: Anna Pehe, Christina Baechle. How Effective are Genetically Modified Islets and Other Sources of Insulin-Producing Cells for Treating Autoimmune Diabetes? J Diabetes Metab, 2022, 13(10): 960.