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Gene Therapy Applied to the Regeneration of Pancreatic Beta Cells: A Literature Review

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ANNOTATION

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease characterized by the destruction of pancreatic β-cells, which are responsible for insulin production. Conventional therapies, such as exogenous insulin replacement and pancreatic islet transplantation, are limited by immune rejection, the need for immunosuppressants, and reduced donor availability. In this context, gene therapy emerges as a promising alternative to restore pancreatic function and improve glycemic control. This study aimed to review the main gene therapy strategies applied to β-cell regeneration. The search was conducted in the PubMed, SciELO, and BVS databases, using Portuguese and English descriptors combined with Boolean operators. Fifteen original articles were included, investigating techniques such as the use of viral vectors, CRISPR/Cas9 gene editing, cellular reprogramming, and stem cell differentiation. The analyzed results demonstrate that alpha-to-beta-cell reprogramming, epigenetic modulation, directed stem cell differentiation, and ectopic insulin expression have shown significant outcomes in experimental and animal models, contributing to the restoration of endogenous insulin secretion. It is concluded that while advances indicate a promising path for the treatment of T1DM, further clinical studies are required to confirm the safety, efficacy, and applicability of these approaches in humans.

Keywords: Insulin-Secreting Cells; Gene Therapy; Pancreatic Endocrine Cells; Diabetes Mellitus, Type 1; Insulin; Pancreas

Abbreviations: T1DM: Type 1 Diabetes Mellitus; CDC: Centers for Disease Control; SciELO: Scientific Electronic Library Online; MSCs: Mesenchymal Stem Cells; hPSCs: Human Pluripotent Stem Cells; hASCs: Human Adipose-Derived MSCs; ADSCs: Adipose-Derived Stem Cells; GcgR: Glucagon Receptor; Btc: Betacellulin; Ngn3: Neurogenin3; HDAd: High-Capacity Adenoviral Vector

Introduction

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease characterized by the selective destruction of pancreatic β-cells, which are responsible for insulin production [1]. The total or near-total deficiency of this hormone impairs blood glucose regulation, resulting in persistent hyperglycemia. This metabolic imbalance can lead to severe complications such as microvascular and macrovascular lesions, neuropathies, nephropathies, and retinopathies. Furthermore, the absence of insulin predisposes patients to acute crises, such as diabetic ketoacidosis, which can be fatal. Therefore, the treatment of T1DM requires continuous administration of exogenous insulin and strict glycemic monitoring. However, to ensure effective metabolic control and reduce the risk of chronic complications, it is essential to adopt a multidisciplinary approach focused on health education, therapeutic adherence, and specialized clinical support [1]. T1DM is a global disease that affects millions of individuals. Historically, limited access to insulin represented a significant barrier to proper treatment, resulting in severe complications and high morbidity and mortality. Insulin plays a vital role in maintaining glycemic homeostasis and regulating energy metabolism. Its absence disrupts crucial cellular signaling pathways, leading to severe metabolic disorders. Thus, the exogenous administration of insulin is indispensable for the survival of individuals with T1DM, enabling partial restoration of metabolic functions and proper glucose utilization by the body [2].

It is estimated that, in 2021, approximately 304,000 children and adolescents under the age of 20 and around 1.7 million adults were living with T1DM in the United States of America (USA), according to

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data from the Centers for Disease Control and Prevention (CDC) [3]. In Brazil, the estimated total number of people with T1DM in 2024 was approximately 499,000, of whom about 99,000 were between 0 and 19 years old, making it a major national public health concern [4,5]. Among individuals with T1DM, many exhibit gastrointestinal manifestations, such as diabetes-associated enteropathy, a condition that can affect the entire gastrointestinal tract. The main symptoms include dysphagia, reflux, early satiety, nausea, abdominal pain, diarrhea, or constipation, occurring individually or in combination, and affecting multiple regions of the gastrointestinal system [6]. Before the advent of gene therapy, the treatment of T1DM faced numerous challenges. The persistent autoimmune destruction of pancreatic β-cells, essential for insulin production, limited the effectiveness of available therapeutic strategies. Conventional approaches included the use of exogenous insulin for glycemic control and β-cell transplantation, typically performed through pancreatic islet transplantation. However, these methods faced significant obstacles, such as recurrent immune rejection, even with the use of immunosuppressive drugs [7].

Attempts to induce β-cell regeneration from pancreatic progenitors proved largely ineffective, as the neogenesis of these cells in the adult pancreas is limited under physiological conditions. Nonetheless, even though these early experiments did not yield significant clinical results, they provided crucial insights into cellular mechanisms and underscored the necessity for more direct interventions to treat T1DM. While experimental strategies such as α-to-β-cell reprogramming have been explored, their clinical application significantly advanced only with the development of more robust approaches, such as intraductal viral infusion, facilitated by progress in gene therapy [7]. In this context, gene therapy has emerged as an innovative and promising approach for treating various genetic and autoimmune diseases, including T1DM. Recent studies [8] have demonstrated the use of CRISPR/Cas9 methodologies to identify genetic mutations and induce changes that confer β-cell resistance to autoimmune destruction, providing a potential avenue for innovative therapeutic interventions. It has also been reported that genetic modifications in human HEK-293T cells derived from normal human embryonic kidney cells transformed with adenovirus type 5 can reduce the activation of pro-apoptotic pathways, such as those associated with endoplasmic reticulum stress, thereby increasing the survival and functionality of β-cells [9].

Additionally, large-scale genetic screening has revealed that the inactivation of specific genes in T1DM models can enhance β-cell resistance to autoimmune destruction, favoring the restoration of glycemic control in experimental models. These advances underscore gene therapy's potential as an approach capable not only of restoring pancreatic function but also of mitigating the immunological challenges that compromise the survival of transplanted cells, thereby representing a significant step in the evolution of T1DM management and prevention strategies [8]. Therefore, the objective of this study was to evaluate the applications of gene therapy in the context of pancreatic β-cell regeneration, focusing primarily on cellular reprogramming mechanisms and considering current clinical studies reporting the efficacy of this technique in tissue regeneration and insulin production, which is an essential process for T1DM treatment.

Materials and Methods

Search Strategy

This study consists of a literature review. The following descriptors were used: "Insulin-Secreting Cells," "Gene Therapy," "Pancreatic Endocrine Cells," "Diabetes Mellitus, Type 1," "Insulin," and "Pancreas," all registered in the Health Sciences Descriptors (DeCs), as well as their corresponding translations in Portuguese. The databases consulted included PubMed (via MedLine), Scientific Electronic Library Online (SciELO), and Virtual Health Library (BVS). Boolean operators AND, OR, and NOT were applied to refine the searches and effectively evaluate the available articles within the selected platforms.

Inclusion Criteria

The inclusion criteria included articles published between 2015 and 2025, encompassing in vitro studies, human studies, and/or animal models. Furthermore, only articles employing gene therapy techniques (e.g., viral vectors and CRISPR/Cas9) and reporting outcomes related to β-cell function restoration, glycemic control, or a reduction in the need for exogenous insulin were included.

Exclusion Criteria

To ensure the relevance and focus of this review, articles not addressing gene therapy techniques or those unrelated to pancreatic β-cells were excluded. Studies focusing on cellular reprogramming for type 2 diabetes treatment were also excluded, as this condition is acquired and managed differently. Additionally, literature reviews, abstracts from scientific congresses, dissertations, and thesis were excluded.

Selection Criteria

The initial selection was based on screening titles and abstracts of the identified papers. Articles meeting the initial inclusion criteria underwent full-text analysis to confirm eligibility. This comprehensive evaluation, considering both previously defined inclusion and exclusion criteria, ensured the relevance and quality of the studies incorporated into this review (Figure 1).

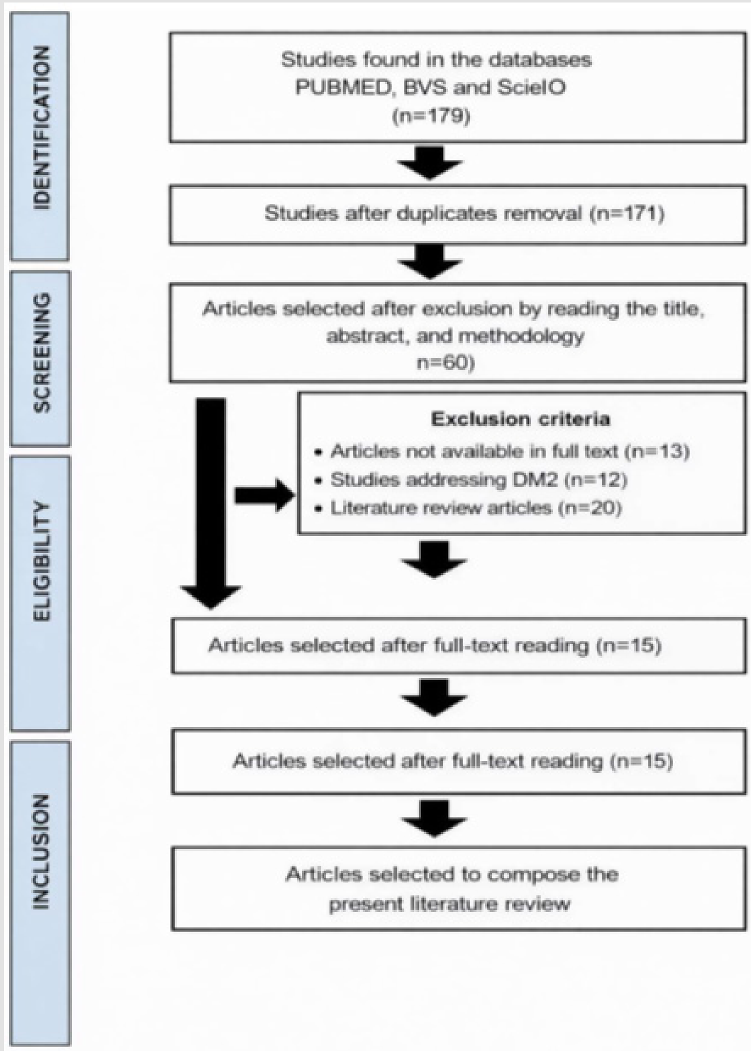

Figure 1: Process of identification, screening, eligibility, and inclusion of the studies selected for this literature review.

Results

A total of 15 articles were selected for this literature review. Table 1 presents an overview of the main findings of the selected studies, highlighting the methodology used, the experimental models (animal, human, or in vitro), as well as their key results and authors' conclusions.

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Table 1: Studies selected and included in the present review.

Author/Year	Methodology	Subjects	Results	Conclusion
Ukaha, et al. [1]	Study on β-cell regeneration from precursor cells and bone marrow cell transfer in mice with T1DM.	Animal model (mice)	The formation of new β-cells contributed to the reversal of established T1DM in mice.	Restoration of β-cells and pancreatic islet vascular integrity may represent a promising therapeutic approach for T1DM.
Al-Hasani, et al. [2]	Inhibition of EZH2 and regeneration of β-cells from pancreatic progenitor cells in T1DM.	Experimental model using post-mortem pancreatic tissue from a 13-year-old girl with T1DM.	EZH2 inhibition restored the expression of β-cell progenitor genes and increased insulin production in human pancreatic cells.	This study demonstrates the potential of epigenetic modulation to restore insulin production in individuals with T1DM, warranting further investigation.
Shuo You, et al. [6]	Hepatic Insulin Gene Therapy (HIGT) in diabetic dogs (AAV8).	STZ-induced diabetic mice	HIGT therapy normalized blood glucose levels and prevented functional and neurohistological alterations in mice.	Hepatic insulin gene therapy showed potential in preventing diabetic enteropathy.
Xiao, et al. [7]	Gene therapy involving the reprogramming of α-cells into pancreatic β-cells in mouse models.	Animal model (mice)	Reprogramming of α-cells into β-cells normalized glycemia in diabetic mice and prolonged β-cell survival in an autoimmune environment.	α-cell reprogramming may represent a novel therapeutic approach for endogenous insulin production in diabetes treatment.
Peng Yi, et al. [8]	CRISPR screening in type 1 diabetic mice.	Immunodeficient NOD mice	CRISPR screening identified the RNLS gene, whose inactivation increased β-cell resistance and improved glycemic control in T1DM models.	RNLS gene deletion is a promising therapeutic target to prevent β-cell loss in T1DM.
Li, et al. [9]	Used CRISPR/Cas9 and HDR to integrate an insulin gene into the genome of HEK-293T cells. These cells were cultured on different biomaterials (Cytopore I and GelMA) and tested *in vivo* in mice to evaluate insulin production and secretion.	STZ-induced diabetic C57BL/6 mice	Successful insulin gene integration enabled HEK-293T cells to produce human insulin. Treated mice demonstrated improved hyperglycemia and maintained insulin secretion for up to 48 hours post-implantation.	This study demonstrates that CRISPR/Cas9-modified cells can produce functional insulin and reverse hyperglycemia. The Cytopore I approach showed particular promise for long-term therapy with a low immune response and good biocompatibility.
Yaochite, et al. [10]	Experimental study using mesenchymal stromal cells (MSCs).	STZ-induced diabetic mice	T1D-MSCs and C-MSCs reversed hyperglycemia and improved β-cell function.	MSCs derived from T1DM patients retained immunomodulatory properties and therapeutic efficacy.
Memon & Abdelalim [11]	Analysis of cell therapies employing β-cells and pancreatic progenitors.	Newly diagnosed T1DM patients (23.2 ± 2.9 years, anti-GAD positive) and healthy individuals (33.1 ± 4.9 years) as controls	Pluripotent stem cells can generate functional β-cells, but maturation and efficiency remain challenges.	The use of encapsulated pancreatic progenitors may serve as a promising alternative to conventional transplantation.
Presa, et al. (2009)	Gene therapy using adipose-derived stem cells after differentiation on microcarriers.	STZ-induced type 1 diabetic mice	Increased insulin expression and alleviation of hyperglycemia after subcutaneous injection.	Microcarriers may enhance cell survival and hold potential for long-term cell therapy.
Gooch, et al. [13]	Clinical study using 3D pancreatic islet organoids and mesenchymal stromal cells.	Diabetic NOD mice and diabetic dogs	Redifferentiation of islet cells and restoration of normoglycemia without immunosuppression.	Neo-Islet therapy may significantly expand patient access to T1DM treatments by obviating the need for immunosuppression.
Shin, et al. [14]	Gene therapy using adenovirus expressing betacellulin for β-cell regeneration.	Animal model (STZ-induced diabetic mice)	Administration of recombinant betacellulin resulted in diabetes remission, restoring pancreatic β-cell mass, and normalizing blood glucose levels in mice.	Transient betacellulin expression regenerated sufficient β-cells for diabetes remission in animal models, indicating therapeutic potential.

Veres, et al. [15]	*In vitro* differentiation of pluripotent stem cells into pancreatic β-cells.	Not applicable (*in vitro* stem cell study)	Stem cell-derived β-cells secreted insulin in response to glucose and restored metabolic homeostasis in diabetes models.	Significant progress has been achieved in the use of stem cells for T1DM-related therapies.
Hogrebe, et al. [16]	Therapy using stem cell-derived islets.	Trials in mice and humans	Improved glycemic control and insulin production from stem cell-derived islets.	SC-islets show great potential for diabetes treatment, though challenges related to infection and vascularization remain.
Chang, et al. [17]	Gene therapy using adenovirus to induce islet neogenesis in NOD mice.	Diabetic NOD mice	50% of mice achieved sustained euglycemia and insulin recovery.	Proof-of-concept for diabetes reversal through islet neogenesis and protection against cytokine-mediated destruction.
May-Yun Wang, et al. [18]	Glucagon receptor (GcgR) antagonism in type 1 diabetic mouse models.	Type 1 diabetic NOD mice	Improved glycemia, increased β-cell mass, and recovery of insulin release in NOD mice.	Glucagon receptor blockade restores functional β-cell mass and improves glycemia in diabetes.

Discussion

Type 1 Diabetes Mellitus (T1DM) is characterized by absolute insulin deficiency and the consequent need for continuous exogenous replacement. Despite advances in insulin formulations and automated delivery systems, achieving ideal glycemic control remains a challenge. In this context, cellular and genetic therapies have emerged as promising alternatives, particularly those aimed at restoring endogenous insulin secretion through physiological mechanisms. However, a major obstacle to these approaches remains the host immune response, which can lead to cell rejection and necessitate the use of immunosuppressants [7,8]. Among the various strategies investigated to restore pancreatic function in T1DM, the combination of genetic engineering and biomaterials stands out. This approach not only seeks to induce insulin-producing cell formation effectively but also to protect these cells from immune responses, a significant barrier to clinical application. Therefore, the use of cell-encapsulation systems with biocompatible and semipermeable materials represents a promising solution to ensure both the survival and functionality of genetically modified cells [9]. Genetic engineering combined with biomaterials has emerged as an innovative alternative capable of yielding effective and safe techniques for T1DM treatment. Li Y. and collaborators [9] modified human HEK-293T cells to secrete functional insulin and encapsulated them in semipermeable biomaterials (CytoPore I and GelMA), creating a physical barrier against immune responses without impairing cell performance.

Among recent advances, gene-editing approaches stand out for enabling a better understanding of autoimmune destruction mechanisms in pancreatic β-cells. In this scenario, CRISPR/Cas9-based genetic screening represents a highly impactful tool. It employs extensive guide RNA libraries, allowing the systematic inactivation of thousands of genes in parallel to identify those whose absence influences β-cell survival or function [8]. In T1DM models, this technique allows researchers to determine which gene deletions confer greater β-cell resistance to immune-mediated attack. Cai and collaborators [8] applied the GeCKO v2 library in NIT-1 cells and NOD mice, conducting in vivo screening that identified the gene Renalase (RNLS) as a relevant target, as its inactivation protected pancreatic β-cells from autoimmune destruction. The results also demonstrated that modulating genes associated with β-cell vulnerability improved resistance to autoimmunity, thereby contributing to the reversal of hyperglycemia and slowing disease progression. These findings underscore CRISPR/Cas9's potential not only for genetic screening but also for identifying novel therapeutic targets for T1DM. Mesenchymal stem cells (MSCs) have attracted considerable interest due to their plasticity and immunomodulatory profile. These cells can be isolated from different tissues, including human adipose tissue, and possess the ability to differentiate into multiple lineages. Moreover, MSCs offer advantages such as easy collection, in vitro expansion, and low immunogenicity, making them promising candidates for therapeutic strategies aimed at restoring pancreatic function [10].

Yaochite JNU and collaborators [10] demonstrated that human adipose-derived MSCs (hASCs), when differentiated into β-like cells, significantly improved glycemic levels and produced human insulin in diabetic mice, confirming the therapeutic potential of these cells. Similarly, human pluripotent stem cells (hPSCs) can differentiate along two main pathways for pancreatic regeneration. The first leads to mature β-cells capable of secreting insulin but often limited by incomplete functional maturation or unwanted hormone production, thereby reducing therapeutic efficiency. The second path leads to pancreatic progenitor cells, which, although not fully functional initially, exhibit greater plasticity and the ability to organize into islet-like structures, facilitating better cellular interactions and integration into host tissues [11]. Consequently, a highly promising strategy for pancreatic β-cell regeneration involves directing hPSCs toward both mature β-cell and pancreatic progenitor stages. Memon B. and collaborators [11] argue that while mature β-cells face limitations related to incomplete functionality and undesired hormonal profiles, progenitor cells display greater differentiation potential and capacity to reconstruct pancreatic islet architecture, favoring beneficial cell interactions. Adipose-derived stem cells (ADSCs) can be harvested from the patient and reprogrammed in vitro. When genetically modified with insulin genes regulated by specific promoters, they can be induced to produce the hormone in a controlled manner. This strategy aims to create an autologous and immune-compatible source of insulin-producing cells, thereby reducing the risk of rejection [12].

The use of genetically modified ADSCs with insulin genes activated by specific promoters has been shown to significantly increase insulin production, highlighting the importance of directed differentiation and its combination with gene therapy [12]. Three-dimensional bioengineering has also emerged as a promising solution to overcome challenges associated with traditional pancreatic islet transplantation. In this context, "Neo-Islets" have been developed by combining mesenchymal stem cells (MSCs) with expanded pancreatic islet cells in culture [13]. This strategy both increases the availability of viable islets and creates a microenvironment conducive to immune tolerance. In animal models, Neo-Islets effectively restored normoglycemia without the need for immunosuppressants, representing a significant advance toward reducing donor scarcity and immunosuppression-related risks. Gene reprogramming strategies are among the most extensively studied in the T1DM field. Recent studies [2,7] have explored various mechanisms of cellular reprogramming to restore β-cell function. Xiao X. and collaborators [7] showed that introducing expression cassettes for the transcription factors Pdx1 and MafA can convert α-cells into functional β-cells, re-establishing insulin secretion in diabetic animal models. Complementarily, Al-Hasani K. and collaborators [2] demonstrated that the use of the epigenetic inhibitor GSK126, targeting the enzyme EZH2, reactivates silenced β-cell genes such as Ins, Pdx1, and Nkx6.1, thus enhancing transdifferentiation potential and opening new therapeutic avenues for pancreatic regeneration.

Beyond direct genetic modification and cell differentiation strategies, the role of vascular microenvironments in supporting pancreatic regeneration is crucial [1]. The vascular network not only provides nutrients and oxygen but also influences cell maturation and endocrine function through paracrine signaling. Recent evidence [1] highlights that vascular restoration can be essential for enhancing regenerative therapy outcomes and ensuring the long-term stability of newly generated β-cells. The influence of the pancreatic islet vascular environment is particularly relevant as β-cells depend heavily on their microenvironment for optimal development. Ukaha TK and collaborators [1] demonstrated that bone marrow cells can regenerate pancreatic blood vessels and induce β-cell formation from precursors, thereby strengthening the regenerative niche. Another key approach involves delivering insulin-encoding genes directly into host tissues. Viral vectors have proven effective in promoting the expression of growth and differentiation factors that improve glycemic control in experimental models. However, autoimmune responses remain a major limitation to maintaining long-term therapeutic effects [14]. Shin S. and collaborators [14] evaluated gene therapy for T1DM using a recombinant adenoviral vector (rAd-BTC) to induce Betacellulin expression, achieved normoglycemia in diabetic mice. While effective in chemically induced models, the results were less robust in autoimmune models, confirming that immune regulation remains a major barrier necessitating combination strategies.

To enhance the quality and functionality of lab-generated cells, recent efforts have focused on refining differentiation protocols. Veres A. and collaborators [15] identified the marker CD49a, which is capable of isolating highly pure β-cells from heterogeneous populations derived from human pluripotent stem cells. This selection improved insulin secretory function and therapeutic efficiency, marking a significant advancement toward the clinical production of β-cells for transplantation. Beyond pancreatic-targeted reprogramming, some gene therapy approaches focus on inducing insulin production in alternative tissues. This approach aims to bypass autoimmune β-cell destruction by utilizing other organs as insulin-secreting platforms. Among these, hepatic insulin gene therapy using AAV8 vectors has shown promise, improving glycemic control and preventing complications such as diabetic enteropathy, thus representing a physiological alternative to exogenous insulin administration [6]. Recent advances in cellular therapy have also highlighted the use of pluripotent stem cells as a source of functional human β-cells. This approach seeks to overcome donor shortages and provide renewable material for transplantation. Refining differentiation protocols has brought these cells closer to the physiological properties of native pancreatic islets [16]. Additionally, biotechnology-based techniques for generating human stem cell-derived islets (SC-islets) involve directed hPSC differentiation followed by transplantation, with or without immunoprotective encapsulation devices.

Clinical trials [16] with products such as VX-880 have shown improvements in insulin secretion and reductions in exogenous insulin needs, although challenges related to immune rejection and incomplete cell maturation still limit full therapeutic success. Another innovative direction explores pancreatic islet neogenesis within hepatic tissue. This strategy leverages the plasticity of liver cells to reprogram them into insulin-secreting endocrine cells, offering an alternative or complementary pathway to existing cell-replacement therapies [17]. Li R. and collaborators [17] investigated high-capacity adenoviral vector (HDAd)-based gene therapy to induce islet neogenesis in the livers of NOD mice. The combined delivery of Neurogenin3 (Ngn3) and Betacellulin (Btc) promoted hepatic cell differentiation into insulin-producing cells, while SOCS1 overexpression conferred immunological protection. Approximately 50% of treated animals achieved sustained euglycemia for over four months. Recent research has also explored the role of glucagon in T1DM pathophysiology. This hormone, secreted by α-cells, raises blood glucose levels by stimulating glycogenolysis and hepatic gluconeogenesis. In diabetes, dysregulated glucagon secretion exacerbates hyperglycemia, making it an attractive therapeutic target [18]. Wang MY and collaborators [18] developed an innovative approach based on glucagon receptor (GcgR) antagonism using the monoclonal antibody Ab-4. This intervention produced sustained glycemic improvement in T1DM mice, even after treatment cessation, and increased functional β-cell mass, suggesting α-to-β-cell transdifferentiation.

Complementary tests in non-human primates confirmed glycemic benefits, reinforcing this strategy's translational potential for human therapy. Overall, gene therapy and bioengineering strategies demonstrate significant progress in developing alternatives to conventional T1DM treatments. From α-to-β-cell reprogramming and hPSC-derived progenitors to hormonal receptor blockade and 3D structural bioengineering, all described techniques show potential for restoring endogenous insulin secretion and improving glycemic control in experimental models. Despite these promising results, challenges related to immune response, cell stability, and long-term safety persist. Consequently, future clinical translation will depend on further controlled trials confirming the efficacy, safety, and feasibility of these approaches in humans.

Conclusion

The gene therapy and cellular bioengineering strategies applied in the context of pancreatic β-cell regeneration in T1DM are crucially important innovative treatment approaches that aim not only at symptom management but also at improving the quality of life of these patients. Techniques such as the reprogramming of α-cells into β-cells, CRISPR/Cas9-mediated gene editing to confer autoimmune resistance, and the development of "Neo-Islets," which combine mesenchymal stem cells with expanded islets, represent substantial advances in T1DM treatment. These studies in experimental and animal models not only validate the restorative potential of endogenous insulin secretion but also demonstrate the possibility of reversing hyperglycemia in a manner that is more physiologically similar and longer-lasting compared to traditional treatments for symptom control. However, it is also important to acknowledge that significant challenges remain, such as the control of immune responses, the stability of the generated cells, and long-term safety, which still limit the clinical application of these therapies. Therefore, it is imperative that future research focuses on overcoming these barriers, expanding clinical trials, and exploring alternatives that enhance their efficacy and feasibility for human use.

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