World Journal of Gastroenterology

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World J Gastroenterol 2024 October 28; 30(40): 4339-4353

DOI: 10.3748/wjg.v30.i40.4339

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Advancing diabetes management: Exploring pancreatic beta-cell restoration's potential and challenges

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Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade B
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Aydin S

Received: July 27, 2024
Revised: September 5, 2024
Accepted: September 24, 2024
Published online: October 28, 2024
Processing time: 80 Days and 10.2 Hours

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Abstract

Diabetes mellitus, characterized by chronic hyperglycemia due to insulin deficiency or resistance, poses a significant global health burden. Central to its pathogenesis is the dysfunction or loss of pancreatic beta cells, which are responsible for insulin production. Recent advances in beta-cell regeneration research offer promising strategies for diabetes treatment, aiming to restore endogenous insulin production and achieve glycemic control. This review explores the physiological basis of beta-cell function, recent scientific advancements, and the challenges in translating these findings into clinical applications. It highlights key developments in stem cell therapy, gene editing technologies, and the identification of novel regenerative molecules. Despite the potential, the field faces hurdles such as ensuring the safety and long-term efficacy of regenerative therapies, ethical concerns around stem cell use, and the complexity of beta-cell differentiation and integration. The review highlights the importance of interdisciplinary collaboration, increased funding, the need for patient-centered approaches and the integration of new treatments into comprehensive care strategies to overcome these challenges. Through continued research and collaboration, beta-cell regeneration holds the potential to revolutionize diabetes care, turning a chronic condition into a manageable or even curable disease.

Key Words: Diabetes therapies; Beta cell regeneration; Regenerative medicine; Stem cell therapy; Gene editing; Molecular therapeutics

Core Tip: Diabetes, a disease of uncontrolled blood sugar, arises from the loss or dysfunction of insulin-producing beta cells within the pancreas. While traditional management focuses on external insulin, cutting-edge research explores restoring these beta cells. Strategies include stem cell therapy, gene editing, and discovering molecules that promote beta cell growth. However, ensuring safety, overcoming biological complexities, and navigating the ethics of stem cell use present challenges. Through continued research, funding, and a patient-centered approach, beta-cell restoration offers the potential to move diabetes care from management to a possible cure.

Citation: Abdalla MMI. Advancing diabetes management: Exploring pancreatic beta-cell restoration's potential and challenges. *World J Gastroenterol* 2024; 30(40): 4339-4353
URL: https://www.wjgnet.com/1007-9327/full/v30/i40/4339.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i40.4339

INTRODUCTION

Diabetes mellitus encompasses a group of metabolic disorders characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The two primary forms are type 1 and type 2 diabetes. Type 1 diabetes, although less common, is primarily an autoimmune condition where the body's immune system attacks and destroys pancreatic beta cells, leading to an absolute insulin deficiency. This form of diabetes typically manifests in childhood or adolescence but can occur at any age[1]. By contrast, type 2 diabetes, which accounts for approximately 90%-95% of all diabetes cases globally, is primarily driven by insulin resistance, coupled with a relative insulin deficiency due to beta-cell dysfunction. It is often associated with obesity, sedentary lifestyle, and genetic factors, and typically presents in adults, although its incidence is increasing among younger populations[2].

Recently, a newer concept known as type 3 diabetes has emerged, which is closely associated with Alzheimer's disease and is characterized by insulin resistance and deficiency specifically in the brain. This hypothesis suggests that the brain's inability to properly utilize insulin could contribute to cognitive decline, adding a neurodegenerative aspect to the complexity of diabetes. Although type 3 diabetes is not yet universally recognized as a formal classification, its implications for both neurodegenerative and metabolic disorders highlight the multifaceted nature of diabetes and the potential overlap in pathophysiological mechanisms[3].

Given the central role of pancreatic beta cells in insulin production, both forms of diabetes could potentially benefit from beta-cell regeneration therapies. For type 1 diabetes, restoring beta-cell mass could replace the destroyed cells, thereby re-establishing endogenous insulin production[4]. In type 2 diabetes, enhancing the function and quantity of beta cells could alleviate insulin deficiency and improve glycemic control, particularly in patients with significant beta-cell loss or dysfunction[5,6]. Although type 3 diabetes involves insulin resistance in the brain rather than beta-cell dysfunction, improving overall insulin signaling and management of glucose metabolism could indirectly support cognitive health and reduce the risk of neurodegenerative diseases[7]. Understanding the underlying pathophysiological mechanisms of the different diabetes subtypes is essential for developing effective therapeutic strategies. Table 1 provides a summary of the pathophysiological pathways in type 1, type 2, and type 3 diabetes.

Recent research has shifted focus toward regenerative medicine as a promising avenue for diabetes management. The restoration of pancreatic beta cells, which are pivotal in insulin secretion, has emerged as a key target for therapeutic intervention. This approach aims to reestablish endogenous insulin production, potentially transforming diabetes from a chronic condition to a manageable or even curable disease[4,6]. Several innovative strategies are being explored to achieve beta-cell regeneration, including stem cell therapy, gene editing technologies, and the discovery of novel regenerative molecules. Stem cell therapy involves differentiating stem cells into insulin-producing beta cells, offering the potential to replenish the beta-cell population in diabetic patients[8-10]. Gene editing technologies, such as clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR-associated protein 9 (CRISPR-Cas9), provide precise tools to correct genetic defects and enhance beta-cell function, paving the way for personalized medical solutions[11-13]. Additionally, researchers are identifying small molecules and growth factors that can stimulate the proliferation and survival of existing beta cells[14-16].

However, translating these scientific advancements into clinical practice presents significant challenges. Ensuring the safety and long-term efficacy of regenerative therapies is paramount. Ethical concerns, particularly regarding the use of stem cells, must be addressed. Moreover, the complexity of beta-cell differentiation and integration within the existing cellular environment adds another layer of difficulty[17,18]. This review delves into beta-cell function's physiological basis, highlights the recent scientific advancements, and discusses the challenges in translating these findings into clinical applications. Through continued research and interdisciplinary collaboration, the goal of turning diabetes into a manageable or curable condition appears increasingly attainable.

PHYSIOLOGICAL BASIS OF BETA-CELL FUNCTION

Pancreatic beta cells, located within the islets of Langerhans, play a crucial role in maintaining glucose homeostasis by producing and secreting insulin in response to high blood glucose levels. The intricate processes governing beta-cell

Table 1 Key pathophysiological pathways in type 1, type 2, and type 3 diabetes

Pathway	Type 1 diabetes	Type 2 diabetes	Type 3 diabetes (Alzheimer's disease)
Insulin production	Autoimmune destruction of pancreatic beta cells leads to absolute insulin deficiency	Insulin resistance in peripheral tissues leads to compensatory hyperinsulinemia, followed by beta-cell dysfunction and relative insulin deficiency	Insulin resistance and deficiency in the brain contribute to impaired glucose metabolism and cognitive decline
Immune system involvement	Autoimmune response targeting beta cells, involving T cell-mediated destruction	Chronic low-grade inflammation contributes to insulin resistance and beta-cell dysfunction	Possible involvement of neuroinflammation and immune dysregulation contributing to neurodegeneration
Glucose metabolism	Hyperglycemia due to lack of insulin, resulting in impaired glucose uptake by cells	Hyperglycemia due to insulin resistance and inadequate compensatory insulin secretion by beta cells	Impaired glucose metabolism in the brain leads to reduced energy supply and cognitive impairment
Beta-cell function	Progressive loss of beta-cell mass due to autoimmune attack	Gradual decline in beta-cell function due to chronic insulin resistance, oxidative stress, and inflammation	Not directly related to beta cells, but brain insulin signaling impairment is a key factor
Associated complications	Ketoacidosis, retinopathy, nephropathy, neuropathy, cardiovascular disease	Retinopathy, nephropathy, neuropathy, cardiovascular disease, non-alcoholic fatty liver disease	Cognitive decline, memory loss, dementia, potential overlap with Alzheimer's disease
Therapeutic targets	Insulin replacement therapy, immunomodulation, beta-cell regeneration	Insulin sensitizers, lifestyle modifications, beta-cell support and regeneration, and anti-inflammatory agents	Improving brain insulin sensitivity, neuroprotective agents, and management of cognitive decline

function are fundamental to understanding diabetes pathophysiology and developing regenerative therapies[19]. Beta cells synthesize insulin, a peptide hormone essential for glucose uptake in tissues such as muscle and adipose tissue. Insulin secretion is tightly regulated by blood glucose levels through a series of well-coordinated steps. Glucose enters beta cells *via* glucose transporter type 2 and is metabolized through glycolysis and the citric acid cycle, leading to an increase in the ATP/ADP ratio. This metabolic shift closes ATP-sensitive potassium channels, resulting in cell membrane depolarization. The subsequent opening of voltage-gated calcium channels allows an influx of calcium ions, which triggers the exocytosis of insulin-containing granules[4,15,20]. Figure 1 presents an overview of beta cell function and insulin secretion.

Beyond glucose, several other factors influence beta-cell function and insulin secretion. Incretins such as glucagon-like peptide-1 (GLP-1) enhance insulin secretion in a glucose-dependent manner, linking nutrient intake to insulin release [21]. Additionally, neural and hormonal signals, including parasympathetic innervation and hormones like somatostatin and leptin, modulate beta-cell activity[22-24]. The beta-cell mass and function are dynamically regulated by several mechanisms. Beta cells have the capacity to proliferate in response to metabolic demands and can undergo apoptosis under stress conditions. Under normal physiological conditions, beta-cell turnover in adults is relatively low, with an estimated replication rate of about 0.5%-1% per day[25,26]. However, this rate can increase significantly in response to metabolic stressors such as pregnancy, obesity, or insulin resistance, reflecting the plasticity of beta cells to adapt to changing metabolic needs[27].

Several key pathways and factors regulate beta-cell proliferation and survival. One of the primary mechanisms involves cell cycle regulators, such as cyclins and cyclin-dependent kinases[28]. Cyclin D2, for instance, is crucial for beta-cell replication and its expression is upregulated in response to increased metabolic demands. This ensures that beta cells can proliferate adequately to meet the body's insulin requirements[29]. Another critical regulatory mechanism is the nutrient-sensing pathway, particularly the mechanistic target of the rapamycin (mTOR) pathway. This pathway plays a significant role in regulating beta-cell growth and function. Activation of mTOR complex 1 promotes beta-cell proliferation and insulin secretion in response to nutrients and growth factors, highlighting the importance of nutrient availability in beta-cell dynamics[30,31]. Growth factors also play a vital role in beta-cell proliferation and survival. Insulin-like growth factor 1 and hepatocyte growth factor are notable stimulators[32,33]. These growth factors activate signaling pathways such as phosphoinositide 3-kinase/protein kinase B, which enhance beta-cell mass and function. Their role in beta-cell biology underscores the potential of growth factor-based therapies for diabetes[34].

Transcription factors are essential for beta-cell development, identity, and function. Key transcription factors, including pancreatic and duodenal homeobox 1 (PDX1), NK6 homeobox 1, and V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA), are critical in these processes. PDX1 is vital for pancreatic development and beta-cell maturation, while NK6 homeobox 1 and MAFA maintain beta-cell identity and regulate insulin gene expression[35-37]. These factors ensure the maintenance of the differentiated state and regulate genes involved in insulin synthesis and secretion, making them indispensable in beta-cell physiology.

Beta-cell apoptosis can be triggered by various stressors, including endoplasmic reticulum (ER) stress, oxidative stress, and pro-inflammatory cytokines[38]. The intrinsic apoptotic pathway, involving mitochondrial outer membrane permeabilization and activation of caspases, is a significant route for beta-cell death under these conditions[39]. Understanding these pathways is crucial for developing interventions to prevent beta-cell loss in diabetes[39]. Figure 2 presents an overview of the factors influencing beta-cell function and insulin secretion.

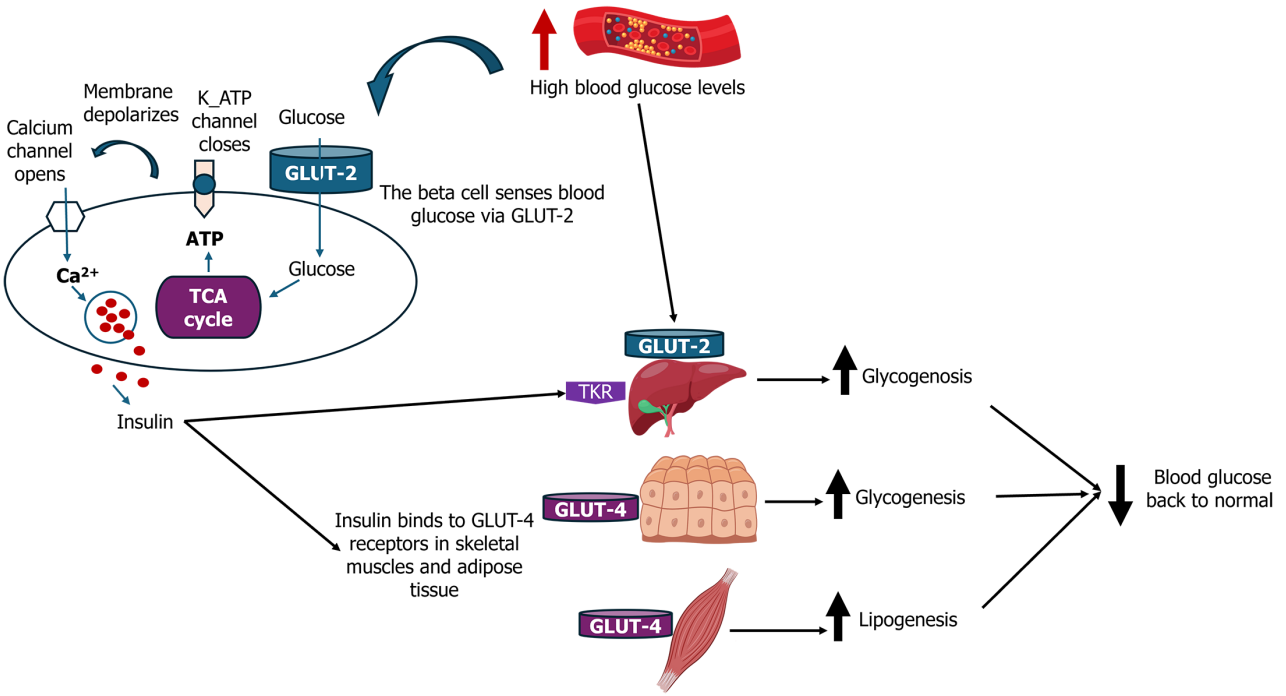

Figure 1 Overview of beta-cell function and insulin secretion. ATP: Adenosine triphosphate; Ca^{2+}: Calcium ion; GLUT-2: Glucose transporter 2; GLUT-4: Glucose transporter 4; K_ATP: Adenosine triphosphate-sensitive potassium channel; TCA cycle: Tricarboxylic acid cycle.

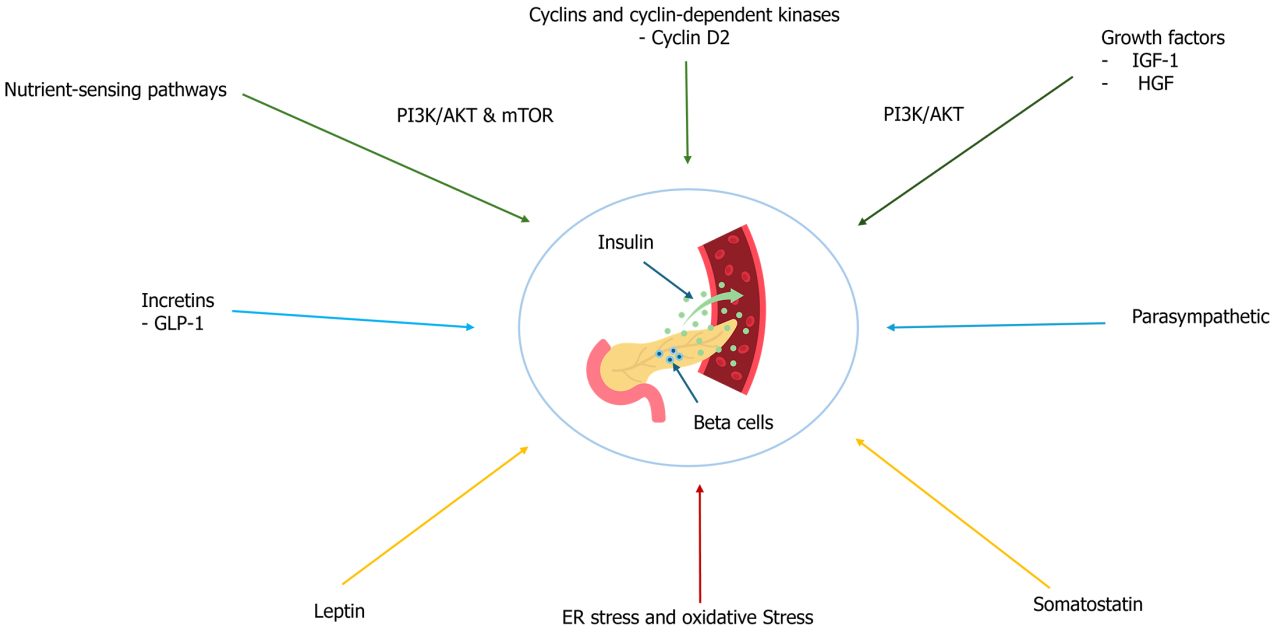

Figure 2 Factors influencing beta-cell function and insulin secretion. The green arrow refers to the promotion of beta-cell proliferation. The red arrow refers to promoting beta-cell apoptosis. The blue arrow indicates stimulation of insulin release. The orange arrow indicates inhibiting insulin secretion. AKT: Protein kinase B; ER: Endoplasmic reticulum; GLP-1: Glucagon-like peptide 1; HGF: Hepatocyte growth factor; IGF-1: Insulin-like growth factor 1; mTOR: Mechanistic target of rapamycin; PI3K: Phosphoinositide 3-kinase.

Autophagy, a cellular degradation process, plays a protective role in beta cells by removing damaged organelles and proteins. Proper regulation of autophagy is essential for beta-cell health, and its dysregulation can contribute to beta-cell dysfunction and the progression of diabetes. This highlights the importance of maintaining autophagic balance for beta-cell survival and function[40,41]. Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs such as microRNAs (miRNAs), also play significant roles in modulating beta-cell gene expression and function. These epigenetic changes can affect beta-cell proliferation, survival, and insulin secretion, emphasizing the importance of epigenetic regulation in beta-cell biology[42,43]. Understanding these modifications offers new avenues for therapeutic interventions aimed at preserving or restoring beta-cell function.

MECHANISMS OF BETA-CELL DYSFUNCTION IN DIABETES

In type 1 diabetes, the autoimmune destruction of beta cells leads to an absolute insulin deficiency[1]. Pro-inflammatory cytokines such as interleukin 1 beta, tumor necrosis factor alpha, and interferon gamma play a significant role in inducing beta-cell apoptosis, exacerbating beta-cell loss[44]. The regenerative capacity of beta cells is severely compromised due to the ongoing immune-mediated destruction, preventing effective beta-cell mass restoration[45].

Conversely, in type 2 diabetes, chronic metabolic stress, such as hyperglycemia and lipotoxicity, contributes to beta-cell dysfunction and increased apoptosis[46,47]. Although beta cells initially attempt to compensate by proliferating, the regenerative capacity diminishes over time, leading to progressive beta-cell failure[48,49]. Furthermore, beta-cell dedifferentiation, where beta cells lose their differentiated phenotype and insulin-secretory capacity, and/or trans-differentiation where beta cells differentiate into other islet hormone-producing cells are other contributing factors in type 2 diabetes[50,51]. This process further impairs insulin secretion and exacerbates hyperglycemia[52].

Beta cells are highly active in insulin synthesis, making them particularly susceptible to ER stress. Prolonged ER stress can lead to beta-cell apoptosis, contributing to both type 1 and type 2 diabetes[53,54]. Additionally, chronic hyperglycemia can result in the overproduction of reactive oxygen species, leading to oxidative stress. This oxidative damage can impair beta-cell function and induce apoptosis[55]. Inflammatory pathways also play a significant role in beta-cell dysfunction. In type 2 diabetes, low-grade chronic inflammation can contribute to insulin resistance and beta-cell failure [56].

In type 3 diabetes, the beta-cell dysfunction extends beyond the pancreas. It involves insulin resistance within the brain, leading to cognitive decline and neurodegeneration[3]. Although the primary pathology is related to neuronal insulin resistance, beta-cell dysfunction and impaired insulin signaling in the brain also contribute to the disease process. This highlights the broader systemic implications of insulin resistance and the potential role of beta-cell dysfunction in neurodegenerative diseases[7]. While the exact mechanisms remain under investigation, there is evidence that similar pathways, such as oxidative stress, inflammation, and impaired insulin signaling, contribute to both beta-cell dysfunction and neurodegeneration in type 3 diabetes[57].

MiRNAs have emerged as important regulators of beta-cell function and mass, influencing key processes such as beta-cell proliferation, apoptosis, and insulin secretion. MiRNAs are small, non-coding RNAs that play crucial roles in the post-transcriptional regulation of gene expression. MiRNAs exert their effects by binding to the 3′ untranslated regions of target mRNAs, leading to either mRNA degradation or inhibition of translation[43]. Among the miRNAs studied, miR-375 is one of the most extensively researched in the context of beta-cell biology. It is highly expressed in pancreatic beta cells and has been shown to regulate insulin secretion and beta-cell proliferation. Overexpression of miR-375 can lead to beta-cell apoptosis by downregulating anti-apoptotic genes such as B-cell lymphoma 2, while its inhibition has been found to promote beta-cell proliferation, indicating its potential as a therapeutic target for diabetes[43,58]. Other miRNAs, such as miR-7, miR-9, and miR-124a, have also been implicated in regulating beta-cell function[59]. For example, miR-7 has negatively regulated insulin secretion by targeting key genes involved in the insulin signaling pathway, such as paired box 6 and mTOR[60]. Dysregulation of miR-7 expression has been associated with impaired beta-cell function in type 2 diabetes[61]. Similarly, miR-9 has been linked to the modulation of glucose-stimulated insulin secretion and beta-cell proliferation, acting through pathways involving one cut homeobox 2 and sirtuin 1[62].

MiRNAs are also implicated in beta-cell dedifferentiation and transdifferentiation, which are particularly relevant in the context of type 2 diabetes. For instance, alterations in miRNA expression profiles have been associated with the loss of beta-cell identity and the conversion of beta cells into other endocrine cell types, contributing to the progressive decline in beta-cell function observed in diabetes[51]. Given their regulatory role in beta-cell biology, miRNAs represent promising therapeutic targets for diabetes treatment. Modulating the expression of specific miRNAs could potentially restore beta-cell function, enhance insulin secretion, and prevent beta-cell apoptosis, offering new avenues for diabetes management. However, further research is needed to fully understand the complex interactions between miRNAs and their target genes in the context of beta-cell dysfunction and to develop safe and effective miRNA-based therapies[59]. Additionally, the immune system's interaction with beta cells is also crucial, particularly in type 1 diabetes, where immune cells specifically target and destroy beta cells. Understanding the mechanisms of this immune-mediated attack is essential for developing interventions to protect and restore beta-cell mass[9,63].

Beta-cell communication within islets and the overall islet architecture play vital roles in synchronized insulin secretion [64]. Gap junctions and paracrine signaling within the islets ensure coordinated insulin release, highlighting the importance of maintaining islet integrity for optimal beta-cell function[65]. Understanding the physiological basis of beta-cell function has paved the way for innovative therapeutic strategies. Regenerative approaches aim to restore or replace beta-cell mass and function. This includes the use of stem cells to generate insulin-producing cells, gene editing techniques to enhance beta-cell resilience and function, and small molecules to promote beta-cell proliferation and survival[10,12,14,66]. Recent studies have highlighted the potential of reprogramming non-beta cells within the pancreas into functional beta cells. For instance, alpha cells and exocrine cells have been experimentally converted into insulin-producing cells, offering a potential endogenous source for beta-cell regeneration[67,68]. These advances underscore the importance of a detailed understanding of beta-cell physiology in developing effective treatments for diabetes.

RECENT SCIENTIFIC ADVANCEMENTS IN BETA-CELL REGENERATION

Advancements in beta-cell regeneration hold significant promise for transforming the treatment of diabetes. These approaches aim to restore the population of insulin-producing beta cells, which are diminished or dysfunctional in

diabetic patients. Cutting-edge research has focused on three primary strategies: Stem cell therapy, gene editing technologies, and the identification of novel regenerative molecules. Each of these strategies offers unique pathways to enhance beta-cell mass and function, potentially revolutionizing diabetes management and offering new hope for patients[69]. Figure 3 provides a visual summary of these strategies, highlighting their mechanisms in the context of beta-cell regeneration for diabetes treatment.

Stem cell therapy

Stem cell therapy represents a promising frontier in the quest for effective diabetes treatments, particularly for regenerating pancreatic beta cells. Various types of stem cells have been explored for this purpose, including mesenchymal stem cells (MSCs), human embryonic SCs (hESCs), and induced pluripotent SCs (iPSCs). These cells have the potential to differentiate into insulin-producing beta cells, offering a potential solution for restoring endogenous insulin production in diabetic patients[70,71].

MSCs: MSCs can be derived from multiple sources, including bone marrow, adipose tissue, umbilical cord blood, and dental pulp[72]. They are known for their immunomodulatory properties and ability to differentiate into various cell types, including beta cells[73]. MSCs also secrete growth factors that support beta-cell survival and function. These characteristics make MSCs a versatile and promising option for cell-based therapies aimed at diabetes treatment[74-76].

hESCs: hESCs, derived from the inner cell mass of blastocysts, have the potential to differentiate into any cell type, including beta cells[77]. Recent advances have focused on deriving functional beta cells from hESCs through carefully controlled culture conditions and the introduction of specific growth factors and signaling molecules. These protocols mimic the natural developmental pathways of pancreatic cells, ensuring that the derived beta cells exhibit characteristics similar to native beta cells, such as glucose-stimulated insulin secretion[10,78,79]. The differentiation process typically requires several weeks to months, and the exact duration can vary across different species and experimental conditions [70,71,80].

iPSCs: iPSCs are generated by reprogramming adult somatic cells to a pluripotent state, giving them the ability to differentiate into various cell types, including beta cells[81]. iPSCs offer the advantage of being derived from the patient's own cells, potentially reducing the risk of immune rejection. However, there are ongoing challenges related to the efficiency and consistency of iPSCs in differentiating into fully functional beta cells. Conflicting results in the literature highlight the need for further comparative studies to determine the most effective source of stem cells for beta-cell regeneration[82,83].

Stem cells can be transplanted into various sites within the body, to regenerate beta cells and restore insulin production. Common transplantation sites include the liver, where cells can integrate into the existing vasculature and receive appropriate signals for insulin secretion, and the subcutaneous space, where encapsulated stem cells can be protected from immune attack while providing systemic insulin release[76,84,85]. Most stem cell research related to beta-cell regeneration is currently in the preclinical stage, involving animal models. These studies have shown significant improvements in glucose regulation and reductions in the need for exogenous insulin upon transplantation of stem cell-derived beta cells. However, the translation to human clinical trials is still in its early stages, with ongoing trials assessing the safety and efficacy of these therapies in humans[71,86,87]. Several clinical trials have been registered on ClinicalTrials.gov over the past decade, focusing on both type 1 and type 2 diabetes. These trials are being conducted in various locations, including the United States, Canada, Europe, China, and other parts of Asia. Notable trials include the VC-01 and VC-02 trials by ViaCyte, which involve subcutaneous transplantation of hESC-derived pancreatic progenitor cells encapsulated in devices designed to protect from immune rejection[75,88].

Despite the promising advancements, several challenges remain in stem cell-based therapies. These include ensuring the long-term survival and functionality of transplanted beta cells, preventing immune rejection, and avoiding potential complications such as tumorigenesis. The risk of incomplete differentiation leading to undifferentiated cells that could form tumors, and achieving consistent glucose responsiveness in derived beta cells, are significant concerns. Strategies to address these issues involve encapsulating beta cells in biocompatible materials to protect them from immune attack and genetically modifying stem cells to reduce their immunogenicity[89,90]. In summary, stem cell therapy for beta-cell regeneration holds substantial promise but also faces numerous challenges. Ensuring the consistent and safe differentiation of stem cells into functional beta cells, addressing immune rejection, and mitigating the risk of complications are critical areas that require further research.

Gene editing technologies

Gene editing technologies, particularly CRISPR-Cas9, have revolutionized genetic engineering and opened new avenues for beta-cell regeneration in diabetes treatment. These technologies enable precise genome modifications, allowing researchers to correct genetic defects, enhance cellular functions, and explore gene functions. Various gene editing tools have been developed and applied to beta-cell regeneration with varying degrees of success[91].

CRISPR-Cas9: CRISPR-Cas9 is the most widely known and utilized gene editing tool due to its simplicity, efficiency, and versatility[92,93]. It uses a guide RNA to target specific DNA sequences and the Cas9 nuclease to create double-strand breaks. These breaks are repaired by the cell's natural repair processes, allowing for targeted gene modifications[94]. One promising application of CRISPR-Cas9 in beta-cell regeneration is correcting mutations associated with monogenic forms of diabetes, such as maturity-onset diabetes of the young[95]. By targeting specific mutations in beta-cell genes, CRISPR-Cas9 can restore normal function and improve insulin secretion. Additionally, this technology has been used to knock out genes that inhibit beta-cell proliferation, thereby enhancing the regenerative capacity of these cells[91,96].

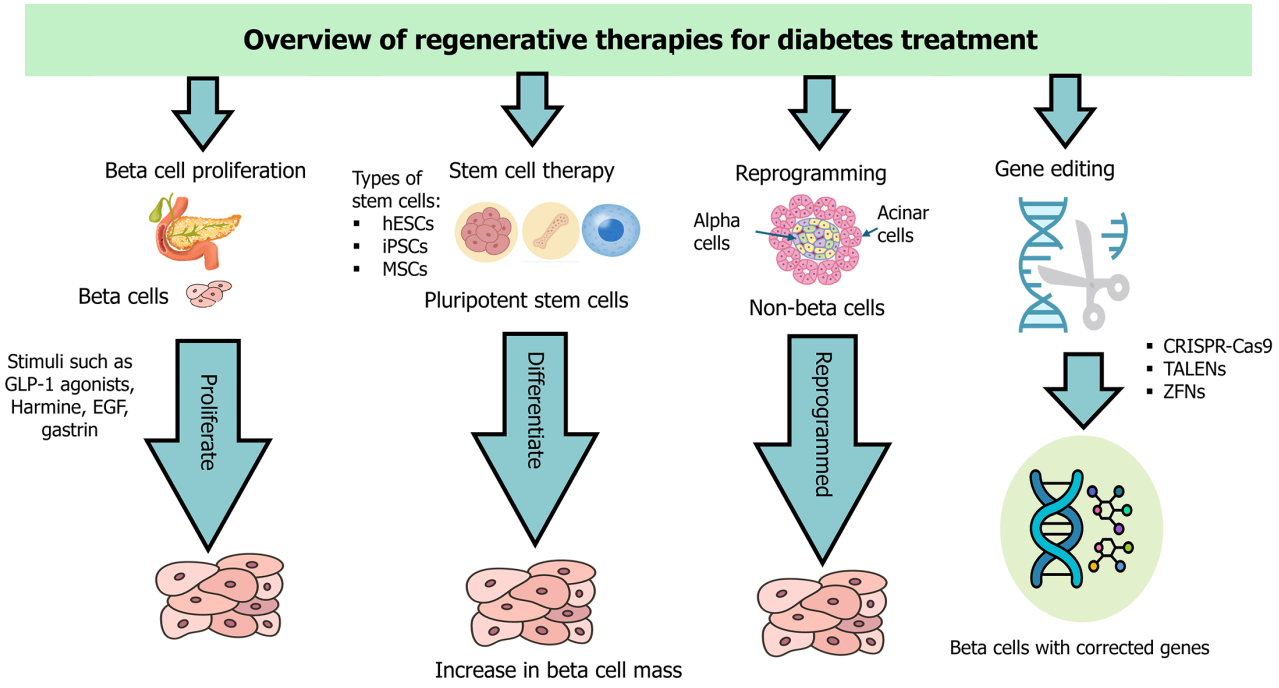

Figure 3 Overview of regenerative therapies for diabetes treatment. Cas9: CRISPR-associated protein 9; CRISPR: Clustered regularly interspaced short palindromic repeats; EGF: Epidermal growth factor; hESCs: Human embryonic stem cells; GLP-1: Glucagon-like peptide-1; iPSCs: Induced pluripotent stem cells; MSCs: Mesenchymal stem cells; TALENs: Transcription activator-like effector nucleases; ZFNs: Zinc finger nucleases.

Further advancements involve modifying beta cells to express molecules that confer resistance to apoptosis or immune-mediated destruction. Such as modifying beta cells to overexpress anti-apoptotic genes can enhance their survival under stress conditions, improving beta-cell transplantation outcomes[34]. However, a recent study demonstrated the successful application of CRISPR-Cas9 in primary human islets, efficiently targeting both protein-coding exons and non-coding regulatory elements, this approach led to the acute loss of key beta-cell regulators such as PDX1 and potassium inwardly rectifying channel, subfamily J, member 11 (KIR6.2), significantly impairing beta-cell function. While promising, translating these findings to clinical applications requires addressing off-target effects, delivery methods, and ensuring long-term safety and efficacy[96].

Zinc finger nucleases: Zinc finger nucleases (ZFNs) are engineered proteins that bind to specific DNA sequences and induce double-strand breaks. They were among the first gene editing tools developed and have been used in various research and therapeutic contexts. ZFNs have targeted beta-cell genes, but their design is complex and less flexible compared to CRISPR-Cas9, limiting their widespread adoption[97,98]. Despite these limitations, ZFNs have shown potential in enhancing beta-cell function by targeting genes involved in insulin production and secretion[97].

Transcription activator-like effector nucleases: Transcription activator-like effector nucleases are engineered proteins that function similarly to ZFNs but offer higher specificity and fewer off-target effects[99]. They bind to specific DNA sequences and induce double-strand breaks, facilitating targeted gene modifications. Transcription activator-like effector nucleases have shown promise in enhancing beta-cell function by targeting genes critical for beta-cell survival and insulin secretion. However, their construction is more challenging and time-consuming compared to CRISPR-Cas9[100].

CRISPR-Cpf1 (also known as CRISPR-Cas12a): Cpf1 is another CRISPR-associated protein with unique properties compared to Cas9. It recognizes different protospacer adjacent motif sequences and creates staggered cuts in DNA, which can be advantageous for certain types of gene editing. Cpf1 also processes its own guide RNAs, simplifying the CRISPR system's design and application for beta-cell gene editing. This tool has shown promise in editing beta-cell genes, offering an alternative to Cas9 with potentially different advantages and limitations[101].

Prime editing: Prime editing is a newer gene editing technology that uses a modified Cas9 protein fused to a reverse transcriptase. This system allows for precise DNA modifications without inducing double-strand breaks, enabling targeted insertions, deletions, and base substitutions with high accuracy and fewer off-target effects. Prime editing holds promise for correcting beta-cell gene mutations and enhancing beta-cell function[102,103].

Base editing: Base editing allows the direct conversion of one DNA base into another without causing double-strand breaks. This method uses a modified Cas9 protein fused to a deaminase enzyme to achieve targeted base changes, making it particularly useful for correcting point mutations in beta-cell genes. Base editing has shown potential in correcting genetic mutations that impair beta-cell function[102]. Gene editing holds significant promise but remains largely experimental, with most research in animal models. While studies demonstrate the feasibility of correcting genetic defects and enhancing beta-cell function, translating these findings to human trials is challenging. Ensuring safety and precision is

critical due to potential off-target effects, which could lead to tumorigenesis or immune reactions[104,105]. Several preclinical studies show promising results in improving beta-cell function and survival through gene editing. However, clinical trials are needed to validate these findings and assess long-term safety and efficacy. Currently, a few early-phase trials in the United States, China, and Europe investigate CRISPR-Cas9 for various genetic disorders, with limited focus on diabetes or beta-cell regeneration[106-108]. Challenges in gene editing include achieving high efficiency and specificity in targeting beta-cell genes, avoiding off-target effects, and ensuring the edited cells can be safely and effectively integrated into the patient's pancreas. Ethical considerations surrounding the use of gene editing, particularly in human embryos or germline cells, must be carefully addressed to gain public trust and regulatory approval[105,109].

Gene editing technologies offer a more targeted approach to correcting genetic defects and enhancing beta-cell function compared to stem cell therapy, which focuses on generating new beta cells from pluripotent or multipotent cells. Both approaches face challenges related to safety, efficacy, and immune rejection, but gene editing holds the potential for permanent correction of genetic defects, providing long-lasting solutions for diabetes management[110].

Novel regenerative molecules

The discovery of novel regenerative molecules that stimulate beta-cell proliferation and enhance its function is crucial for diabetes treatment. These molecules include small molecules, peptides, and growth factors targeting pathways involved in beta-cell development, maintenance, and regeneration. High-throughput screening has identified several small molecules that promote beta-cell proliferation by activating key signaling pathways such as wingless/integrated (Wnt) and β-catenin signaling (Wnt/β-catenin), Hedgehog, and Notch signaling. Notable examples include harmine, a dual-specificity tyrosine-(y)-phosphorylation regulated kinase 1a inhibitor, and γ-secretase inhibitors that modulate notch signaling to enhance beta-cell regeneration[111].

Peptides and growth factors also play significant roles in beta-cell regeneration. Betatrophin was initially reported to stimulate beta-cell proliferation, but subsequent studies have cast doubt on its efficacy, highlighting the complexities and controversies in this area of research[112]. By contrast, GLP-1 analogs, such as exenatide and liraglutide, are more established and known to promote beta-cell survival and proliferation by enhancing insulin secretion and reducing apoptosis[38]. Additionally, reprogramming molecules, which convert other pancreatic cell types, such as alpha cells, into beta-like cells, offer another innovative approach to increasing beta-cell mass. Factors such as PDX1, neurogenin 3, and MAFA induce such reprogramming, although the efficiency and stability of the reprogrammed cells remain areas of active investigation[113].

Recent studies have identified additional molecules, such as epidermal growth factor and gastrin, which synergistically promote beta-cell regeneration in preclinical models[114,115]. However, not all identified molecules are effective, and there is ongoing controversy regarding the reproducibility and translation of some findings from animal models to humans[116]. Extensive experimental and preclinical studies evaluate the efficacy and safety of these regenerative molecules. *In vitro* studies, using isolated pancreatic cells, assess the effects on beta-cell proliferation and function, measuring cell proliferation, insulin secretion, and gene expression. Numerous studies show promise in enhancing beta-cell regeneration. Preclinical *in vivo* studies with animal models, such as diabetic mice or rats, evaluate the therapeutic potential, studying effects on beta-cell mass, glucose homeostasis, and overall metabolic health. For instance, GLP-1 analogs have improved beta-cell function and reduced blood glucose levels in diabetic mice[117]. These studies also assess potential side effects and long-term safety, optimizing dosage, administration route, and treatment duration to ensure maximal efficacy with minimal adverse effects[117,118].

A recent systematic review on the combination therapy of SGLT2 inhibitors and GLP-1 receptor agonists demonstrated significant improvements in glycemic control, weight reduction, and blood pressure management without increasing the incidence of adverse events, including genital and urinary infections, in patients with T2DM or obesity. This evidence supports the therapeutic potential of these molecules in diabetes management and highlights their safety and efficacy profiles. Given the importance of enhancing beta-cell function and survival, the positive outcomes associated with GLP-1 receptor agonists make this combination therapy a relevant and promising strategy in the context of regenerative treatments for diabetes[119].

The administration of regenerative molecules varies based on their type and pharmacokinetic properties. Common routes include intravenous injection for peptides and growth factors, subcutaneous injection for molecules such as GLP-1 analogs, and oral administration for small molecules[119]. Localized delivery to the pancreas can enhance local effects and reduce systemic side effects. The duration for these molecules to show effects can range from days to weeks, depending on the specific molecule and model used[120].

Despite promising results, significant challenges and controversies exist with regenerative molecules. Reproducibility across studies and species is a major concern, and translating preclinical successes to clinical applications has proven difficult, with many molecules failing to show the same efficacy in human trials. Long-term safety and potential off-target effects remain critical areas of concern, requiring rigorous testing and validation to address these issues[116]. Table 2 summarizes the key distinctions between various regenerative approaches for diabetes treatment, highlighting their mechanisms of action, advantages, challenges, and examples.

CHALLENGES IN TRANSLATING FINDINGS TO CLINICAL APPLICATIONS

Translating the promising results of regenerative molecule studies into clinical applications faces significant challenges that must be addressed to effectively treat diabetes.

Table 2 Comparison of regenerative approaches for diabetes treatment

Regenerative approach	Mechanism of action	Advantages	Challenges	Examples	Ref.
Beta-cell regeneration and novel regenerative molecules	Stimulates proliferation, enhances function, and supports survival of existing beta cells	Potential for restoring endogenous insulin production and enhancing beta-cell mass	Reproducibility, safety concerns, and challenges in achieving efficient beta-cell proliferation	GLP-1 analogs, EGF, gastrin, Harmine (DYRK1A inhibitor)	[111,114-116,119]
Stem cell therapy	Differentiates stem cells into beta-like cells	Can potentially replace lost beta cells	Ethical concerns, risk of tumorigenesis, and immune rejection	hESCs, iPSCs	[89,124,125]
Gene editing	Corrects genetic defects in beta cells	Precise genetic modifications	Off-target effects, ethical concerns	CRISPR-Cas9, TALENs, ZFNs	[116,121,123]
Reprogramming molecules	Converts other pancreatic cell types into beta-like cells	Increases beta-cell mass	Efficiency and stability of reprogrammed cells remain areas of investigation	PDX1, NGN3, MAFA	[113]

CRISPR-Cas9: Clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9; DYRK1A: Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A; EGF: Epidermal growth factor; GLP-1: Glucagon-like peptide 1; hESCs: Human embryonic stem cells; iPSCs: Induced pluripotent stem cells; MAFA: V-Maf musculoaponeurotic fibrosarcoma oncogene homolog A; NGN3: Neurogenin 3; PDX1: Pancreatic and duodenal homeobox 1; TALENs: Transcription activator-like effector nucleases; ZFNs: Zinc finger nucleases.

Safety and long-term efficacy

Ensuring the safety and long-term efficacy of regenerative therapies is paramount. While preclinical studies show promise, translating these results to humans has been difficult. Many regenerative molecules that are effective in animal models fail in human trials[121-123]. Potential off-target effects pose risks, such as tumorigenesis or immune reactions. Long-term studies are needed to evaluate the sustained benefits and risks of these therapies, ensuring beta-cell regeneration does not introduce new health issues[124].

Ethical concerns

The ethical implications of regenerative approaches, particularly those involving stem cells and gene editing, must be carefully considered.

Stem cell research ethics: The use of hESCs remains one of the most contentious ethical issues in regenerative medicine. The primary ethical dilemma arises from the process of deriving hESCs, which involves the destruction of human embryos. This has sparked intense moral debates regarding the status of the embryo and the ethical acceptability of such research[125]. In the United States, the Dickey-Wicker Amendment prohibits federal funding for research that involves the creation or destruction of human embryos, reflecting the ongoing ethical and legal struggle to balance scientific progress with respect for human life[125]. While this regulation aims to protect ethical standards, it also constrains the potential of hESC research to advance regenerative therapies for conditions like diabetes.

Although iPSCs offer an alternative as they are derived from adult cells and do not require the destruction of embryos, they are not entirely free from ethical challenges. Concerns about genetic manipulation during the reprogramming process, potential genetic instability, and the risk of tumorigenesis highlight the need for careful ethical scrutiny and long-term safety evaluations. The use of iPSCs may bypass the ethical issues associated with hESCs, but it introduces new questions about the consequences of genetic alterations and the broader implications of manipulating human cells at a fundamental level[124,126,127].

Gene editing ethics and medicolegal implications: Gene editing technologies also raise significant ethical and medicolegal concerns. The possibility of germline editing, where genetic modifications could be passed down to future generations, presents profound ethical dilemmas[128]. The case of CRISPR-edited embryos in China, which led to international outcry, exemplifies the risks and ethical questions surrounding gene editing[129]. This case underscored the urgent need for global ethical standards and regulatory oversight to govern the use of such powerful technologies.

Medicolegal concerns are equally pressing. Ensuring that patients provide fully informed consent is critical, especially when the long-term risks of gene editing are not fully understood[130]. There is also the issue of liability - who bears responsibility if unforeseen complications arise from gene-editing interventions? The literature emphasizes the necessity of establishing clear legal frameworks that not only protect patient rights but also ensure that researchers and clinicians are held accountable for the outcomes of these cutting-edge treatments[131].

Complexity of beta-cell differentiation and integration

Differentiating stem cells into functional beta cells and ensuring their proper integration into the patient's existing cellular architecture remains highly complex. Achieving the precise conditions for beta-cell differentiation *in vitro* does not guarantee success *in vivo*. Newly formed beta cells must produce insulin effectively, respond to glucose levels, and integrate seamlessly with the host's immune system to avoid rejection. Additionally, the pancreatic microenvironment and interactions between various cell types add layers of complexity that are challenging to replicate and control[132].

INTERDISCIPLINARY COLLABORATION AND COMPREHENSIVE CARE STRATEGIES

Effective diabetes management, particularly when incorporating regenerative therapies, necessitates a coordinated, interdisciplinary approach involving various healthcare professionals[133]. For example, a patient with type 2 diabetes struggling to maintain glycemic control may benefit from a care team comprising an endocrinologist, a dietitian, a diabetes educator, and a psychologist. This collaborative approach addresses the patient's medical, nutritional, and psychological needs, leading to improved health outcomes[134].

In a more advanced scenario, a patient with type 1 diabetes considering beta-cell regeneration therapy would work with an interdisciplinary team including an endocrinologist, a transplant surgeon, and a genetic counselor. The team discusses potential risks and benefits, with the genetic counselor providing insights into how the patient's genetic profile might influence the therapy's success. The active involvement of the patient and their family ensures a patient-centered, fully informed care strategy[133]. The advancement of regenerative medicine for diabetes demands integrating the expertise of various specialists to address the complexities of beta-cell regeneration. Collaborative research networks and cross-disciplinary training are essential for accelerating discovery and enhancing innovation in diabetes care[135].

Patient-centered approaches are essential for aligning diabetes therapies with individual needs, involving patients in research, and developing personalized treatment plans[136]. Integrating regenerative therapies into comprehensive care strategies, which include lifestyle interventions, continuous monitoring, and support systems, enhances effectiveness and ensures holistic patient management[137]. Personalized treatment plans, informed by genetic profiles and disease progression, optimize efficacy and minimize adverse effects[138,139]. Educating patients about their condition and emphasizing treatment adherence empowers them to actively manage their condition[140,141]. Additionally, utilizing digital health tools and data analytics enhances diabetes management, leading to improved health outcomes and quality of life[142,143].

CONCLUSION

Integrating regenerative therapies into diabetes treatment represents a promising frontier in medical science. Beta-cell regeneration, in particular, offers the potential to restore endogenous insulin production and achieve long-term glycemic control. By fostering interdisciplinary collaboration and adopting patient-centered approaches, scientific advancements can be effectively translated into practical, safe, and personalized treatments. Comprehensive care strategies that include personalized treatment plans, multidisciplinary support, lifestyle interventions, patient education, and technological integration are essential for maximizing the benefits of regenerative therapies. Addressing the challenges of safety, long-term efficacy, ethical concerns, and the complexity of beta-cell differentiation and integration is crucial. Through these efforts, the aim is to improve health outcomes and enhance the quality of life for individuals with diabetes.

FOOTNOTES

Author contributions: Abdalla MMI conducted the research and wrote the manuscript.

Conflict-of-interest statement: The author has no conflicts of interest to declare.

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S-Editor: Wang JJ
L-Editor: Filipodia
P-Editor: Chen YX

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