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β-CELL PROTECTION AND REGENERATION: EMERGING THERAPEUTIC STRATEGIES FOR TYPE 2 DIABETES MELLITUS

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease characterised by insulin resistance, loss of β-cell function over time and a reduction in the number of functional β-cells which leads to inadequate insulin production and increased blood glucose levels. The available antidiabetic drugs are effective at controlling glycaemic levels but have limited ability to prevent β-cell loss and disease progression. Thus, the preservation and regeneration of pancreatic β-cells has become a promising therapeutic approach to the long-term disease modification. This review summarizes pancreatic β-cell biology in terms of islet architecture, development of the β cell, insulin biosynthesis and mechanisms that govern and regulate β cell homeostasis. It also reviews the key mechanisms involved in β-cell dysfunction in T2DM including glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, inflammation, dedifferentiation and apoptosis. Special attention is given to novel therapeutic approaches which aim to preserve and regenerate β-cell function such as incretins, β-cell proliferation and redifferentiation, stem cell and cellular reprogramming, gene editing and molecular therapeutics, and islet transplantation involving tissue engineering. Furthermore, recent limitations in the clinical translation of regenerative therapies are presented, and future perspectives of precision medicine and targeting of β-cells are discussed. Together, these developments offer novel possibilities to restore insulin production, maintain functional β-cell mass and enhance long-term clinical results, thus offering promising disease-modifying strategies for management of T2DM.

KEYWORDS: Type 2 diabetes mellitus, Pancreatic β-cells, β-cell regeneration, β-cell protection, Insulin secretion, Incretin-based therapy, Stem cell therapy, Cellular reprogramming, Gene editing, Islet transplantation, Tissue engineering, Regenerative medicine.

INTRODUCTION

Despite the significant improvements in glucose-lowering treatments, type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder, with a progressive decline in pancreatic β-cell function and mass. Clinical data suggest that at diagnosis there are already significant β-cell dysfunctions and additional metabolic stress causes further loss of the β-cell resulting in poor insulin secretion and progressive hyperglycaemia.[1] While currently available antidiabetic therapies, such as metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, and insulin, can achieve sufficient

glycaemic control and help prevent diabetes-related complications, they fail to prevent a progressive loss of functional β-cell mass. Preservation and restoration of endogenous β-cells have thus become major therapeutic targets for the restoration of long-term glycaemic control and reducing disease progression.[2]

The pathogenesis of insulin resistance to T2DM is primarily due to impaired ability of the pancreatic β-cell to keep up with the greater insulin requirements imposed by insulin resistance in the skeletal muscle, adipose tissue and liver. The progressive failure of β-cell function occurs many years before you're diagnosed with the disease and is a continuing process even while you are being treated, emphasising the need to preserve the integrity, survival and insulin-secretory function of these cells.[3]

Previously pancreatic β-cells were thought to have limited regeneration capacity and to be terminally differentiated. With the advent of improved developmental biology, molecular genetics and lineage tracing techniques, however, it has been shown that β-cells have some residual regenerative capacity.[4] In physiological situations (pregnancy, obesity, and raised metabolic demand), β-cells are capable of proliferation, and pancreatic endocrine cells show remarkable plasticity under specific pathological and experimental conditions, and can transdifferentiate or redifferentiate. This has led to a great deal of research focused on identifying molecular mechanisms that can promote the regeneration of endogenous β-cells while maintaining their functional maturity.[5]

Advances in technology have revolutionized the understanding of the biology of the pancreatic islet, especially single-cell RNA sequencing, spatial transcriptomics, and high resolution imaging. These strategies have identified distinct subpopulations of β-cells with variable insulin secretion, proliferative capacity, stress resistance and survival, suggesting that there is substantial functional heterogeneity. In addition, the interplay between the cells of the islet (e.g., the β-cells, the α-cells, the δ-cells, the endothelial cells, the immune cells, and the extracellular matrix) is crucial in the regulation of insulin secretion, islet homeostasis, tissue remodeling, and regenerative responses, and it is important to preserve the entire microenvironment of the islet and not just the β-cells.Another key concept is that of β-cell dedifferentiation, where differentiated insulin-producing β-cells cease to be specialized without undergoing apoptosis.[6] This is a reversible adaptive response to the chronic metabolic stress and may represent a therapeutic approach to restoring β cells to their proper identity by targeting key transcription factors.

Current approaches to regeneration target the protection of existing β-cells, as well as the restoration of β-cell mass, by reducing oxidative stress, inflammation, apoptosis, mitochondrial dysfunction and endoplasmic reticulum stress and maintaining cell identity and insulin-secretory function. Stimulating endogenous β-cell proliferation, activation of pancreatic progenitor cells, transdifferentiation of non-β endocrine cells, stem cell-derived β-like cells, islet transplantation, tissue engineering approaches, genetic manipulation techniques and cellular reprogramming are all regenerative strategies.[7] Signaling pathways like PI3K/Akt, AMPK, mTOR, Wnt/β-catenin, transforming growth factor-β (TGF-β), Hippo/YAP, Notch, and FOXO1 have been identified as key regulators of β-cell proliferation, survival, metabolism, and regeneration, alongside key transcription factors and molecular regulators like pancreatic and duodenal homeobox-1 (PDX-1), NK6 homeobox 1 (NKX6.1), musculoaponeurotic fibrosarcoma oncogene homolog A (MafA), forkhead box protein O1 (FOXO1), dual-specificity tyrosine-regulated kinase 1A (DYRK1A), and menin. Such in-depth knowledge of these molecular networks will enable the development of targeted regenerative therapies that will be able to maintain the function of β-cells and change the natural course of T2DM.[8]

2. Pancreatic β-Cell Biology

2.1 Pancreatic Islet Architecture and Cellular Composition

The pancreas is a bi-functional organ made up of an exocrine part (95–98%) capable of secreting digestive enzymes and an endocrine part (2–5%) that secretes hormones that control glucose homeostasis. The endocrine pancreas is made up of the islets of Langerhans, which are clusters of cells scattered throughout the pancreatic parenchyma and are very vascular. They constitute a very small portion of the pancreas, but the islets are crucial to the maintenance of metabolic homeostasis, regulating the secretion of several hormones.[9]

There are five types of endocrine cells in the pancreatic islets, each having a physiological function. The major population is the β-Cells (50-70%) which secretes the main hormone involved in the regulation of glucose uptake and metabolism: Insulin. The α-cells (20–40%) produce glucagon which triggers increased glucose production from the liver during hypoglycaemia. 5-10% of the cells are 5-cell (δ-cells) that secrete somatostatin, which affects insulin and glucagon secretion. Pancreatic polypeptide (PP) cells secrete pancreatic polypeptide which controls gastrointestinal and exocrine pancreatic function (1–5%); ε-cells secrete ghrelin, a hormone which regulates appetite and energy balance (<1%).[10]

Pancreatic islets have highly organized architecture to facilitate efficient communication between endocrine cells via paracrine signaling, gap junctions, neural inputs, close association with endothelial cells, extracellular matrix components, and resident immune cells. They are extensively vascularised to allow speedy glucose sensing and hormone release into the circulation.[11] Disruption of

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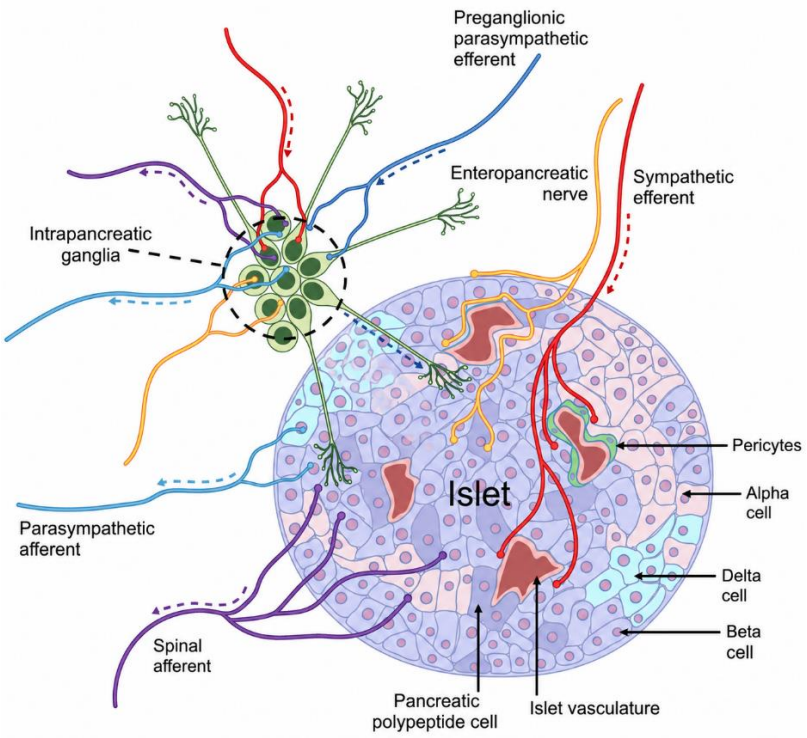
this specialised islet microenvironment disrupts insulin secretion, affects the survival of the β-cells and is a factor in the gradual progressive diabetic β-cell dysfunction that defines Type 2 diabetes mellitus. Hence, knowledge of the structure and cell composition of the pancreatic islet is essential to the formulation of strategies that aim at maintaining and regenerating functional β-cell mass.[12]



2.2 Development and Maturation of Pancreatic β-Cells

The development of pancreatic β-cells from the definitive endoderm is a tightly regulated process that involves several signaling pathways and transcription factors during embryonic development. Formation of the pancreas starts as the dorsal and ventral pancreatic buds develop from the endoderm of the foregut, which eventually fuse to create the adult pancreas. Signaling pathways such as FGF, BMP, Hedgehog, Wnt, and Notch direct the differentiation of multipotent pancreatic progenitor cells to endocrine and exocrine lineages, and are involved in early pancreatic specification.[13]

The master regulators of pancreatic development and β-cell differentiation are pancreatic and duodenal homeobox-1 (PDX1) among the key transcription factors. Neurogenin-3 (NGN3) is the trigger for commitment to the endocrine lineage, and successive members of the family of genes, PAX4, NKX2.2, NKX6.1, NeuroD1, ISL1, and MafA, successively control β-cell specification, maturation, and capacity to produce insulin.[14]

β-cells are generated during the embryonic period but undergo a lot of postnatal maturation. The mature β-cells develop a higher mitochondrial activity, higher expression of glucose transporters and ion channels, and efficient glucose stimulated insulin secretion (GSIS). Recent studies further show that the transcriptional movements of the β-cell are dynamic and that there is a certain functional plasticity of the β-cells, which allows them to adapt to metabolic stress and, under certain conditions, regenerate. The results have laid the ground work for regenerative approaches to restore functional β-cell mass in T2DM.[15]

Developmental stage	Major Regulators	Function
Definitive endoderm	Activin/Nodal	Pancreatic lineage initiation
Pancreatic progenitor	PDX1, PTF1A, SOX9	Pancreatic bud formation
Endocrine progenitor	NGN3	Endocrine lineage commitment
Immature β- cell	PAX4, NKX2.2, NKX6.1, NeuroD1	Cell differentiation
Mature β-cell	MafA, PDX1	Insulin synthesis, glucose sensing, GSIS

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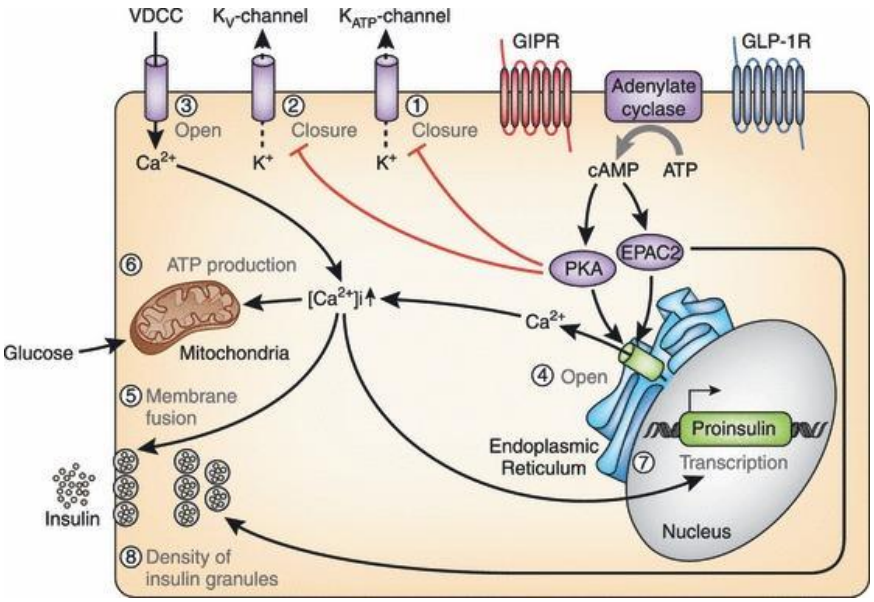
2.3 Insulin Biosynthesis and Glucose-Stimulated Insulin Secretion

Insulin is produced, stored, and secreted in a regulated fashion by pancreatic β-cells to maintain glucose homeostasis. The biosynthesis of insulin starts with the transcription of INS gene into preproinsulin, which is then processed to proinsulin in the endoplasmic reticulum. Within the secretory granules, proinsulin is converted to mature insulin and C-peptide by prohormone convertases (PC1/3, PC2) and carboxypeptidase E, and stored until stimulated to be secreted.

Glucose is the most important stimulus for insulin secretion.[16] It is imported into β-cells by either GLUT1 (humans) or GLUT2 (rodents) and then phosphorylated by glucokinase, which results in the production of ATP via glucose metabolism. This leads to more ATP/ADP, which causes closure of ATP-sensitive potassium (KATP) channels, resulting in membrane depolarization and opening of voltage-dependent Ca^{2+} channels. Increased calcium entry causes SNARE-dependent fusion of insulin granules with the plasma membrane and insulin is released into the blood.[17]

There are two phases of insulin secretion, the first a rapid phase which corresponds to the release of stored insulin, and the second a prolonged phase which is dependent on continued insulin synthesis and granule mobilization. In addition to glucose, insulin secretion is stimulated by incretins (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)), amino acids, fatty acids, autonomic nerve signals, and paracrine islet interactions. Defect in insulin biosynthesis, insulin-sensing, mitochondrial metabolism, and/or stimulus–secretion coupling are responsible for impaired insulin secretion and eventual.[18]



2.4 Regulation of β-Cell Mass and Homeostasis

Maintenance of pancreatic β-cell mass depends on the balance of cell proliferation, neogenesis, cell hypertrophy, apoptosis, and cell plasticity to ensure sufficient insulin production to meet metabolic needs. In response to physiological conditions, including growth, pregnancy and obesity, β-cells adapt and expand their functional capacity and, to a lesser degree, their numbers. Growth factors, hormones, nutrients and signaling pathways regulate these adaptive responses.[19]

In adults, the main mechanism for maintaining β-cell mass is by proliferation of β-cells, which is driven by cell-cycle proteins such as cyclins, cyclin-dependent kinases (CDKs), transcription factors, including PDX1, FOXO1 and NKX6.1. The contribution of β-cell neogenesis to adult is more modest, although it is very important during the embryonic development. On the other hand, the progressive loss of β-cells in Type 2 diabetes mellitus is caused by excessive apoptosis stimulated by glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum stress, and inflammation.[20]

3. Mechanisms of β-Cell Dysfunction in Type 2 Diabetes Mellitus

Importance to the progression of insulin resistance to chronic hyperglycaemia. Early, the β-cells begin to respond to insulin resistance by increasing insulin production and release. Eventually, however, the adaptive mechanisms are impaired by chronic metabolic stress and result in dysfunction of insulin secretion, loss of β-cell identity, and gradual decrease in functional β-cell mass. In the case of T2DM, β-cell dysfunction is caused by a plethora of interconnected mechanisms such as glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, chronic inflammation, and impaired autophagy and β-cell dedifferentiation, which are different from the primary autoimmune destruction of β-cells seen in Type 1 diabetes. These disease processes

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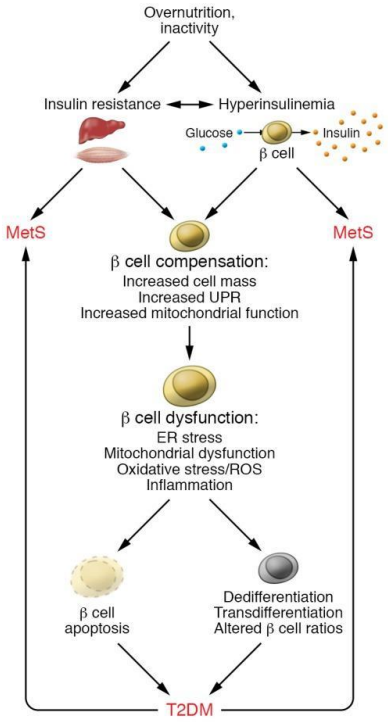
impair the biosynthetic function of insulin, glucose sensing, and stimulus–secretion coupling, which results in failure of β-cells and disease progression.[21]



4. Current Therapeutic Approaches for β-Cell Preservation

Treatment goals for type 2 diabetes mellitus (T2DM) focus mainly on improving glycaemic control by increasing insulin sensitivity, increasing insulin secretion, decreasing hepatic glucose production or increasing urinary glucose excretion. While these treatments can help lower blood sugar and decrease diabetes-related complications, they do not halt the gradual loss of pancreatic β-cell mass and function. Some antidiabetic drugs, however, have β-cell protection properties, including their ability to decrease metabolic stress and maintain insulin secretory reserve.[22]

4.1 Metformin

Metformin is the initial drug of choice for T2DM because it is effective and free from serious side effects. It turns on AMP-activated protein kinase (AMPK) which inhibits glucose production in the liver and enhances insulin sensitivity. Metformin indirectly protects the function of β-cells by reducing glucotoxicity and oxidative stress, but with little ability to restore lost β-cells.[23]

4.2 Incretin-Based Therapies

The GLP-1 receptor agonists (such as liraglutide and semaglutide) and DPP-4 inhibitors (such as sitagliptin and linagliptin) improve glucose-dependent insulin secretion by increasing the activity of incretins. These agents can evert the decline in β-cell function by boosting the survival of β-cells, decreasing apoptosis and decreasing oxidative stress. They do mostly preserve existing β-cells, however, and not restore β-cell mass.[24]

4.3 SGLT2 Inhibitors

SGLT2 inhibitors act by causing glucose to be excreted in the urine, which reduces blood glucose levels. They lower the glucose toxicity, enhance insulin sensitivity and lower the metabolic load from the β-cells. These drugs have beneficial effects on the cardiovascular and renal system, but have moderate effects on the direct regeneration of β-cells.[25]

4.4 Thiazolidinediones and insulin therapy

Thiazolidinediones (TZDs) have anti-insulin lipotoxic and anti-stress effects on β-cells and enhance insulin sensitivity by activation of PPAR-γ. In late T2DM, insulin therapy may be necessary to get glycaemic control and to give “temporary” β-cell rest. Both treatments, however, do not restore functional β-cell mass or reverse the progression of the disease.[26]

Current antidiabetic treatments are mostly aimed at preserving rather than regenerate β-cells. The restrictions have led to the development of regenerative approaches that seek to restore endogenous insulin production and for long-term disease modification.[27]

5. Emerging Strategies for β-Cell Regeneration

5.1 β-Cell Regeneration Through Proliferation and Redifferentiation

A progressive loss of functional β-cell mass is one of the hallmarks of Type 2 diabetes mellitus (T2DM) and is the reason for the decrease in insulin secretion, resulting in chronic hyperglycaemia. For this reason, approaches that favour β-cell regeneration have received much attention as they aim to attack the underlying cause of the disease

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instead of merely reducing blood glucose.[28] Among the two key mechanisms of β-cell regeneration, β-cell proliferation and β-cell redifferentiation are the two mechanisms.

Proliferation of the β-cells is the growth of existing β-cells to boost functional β-cell mass; this is called as β-cell proliferation. The ability of human β-cells to proliferate is limited in adults, but can be induced when there is an increase in metabolic demands. This process is controlled by Cyclin D1/D2, CDK4/6, growth factors (IGF-1, HGF, EGF) and signaling pathways (PI3K/Akt, mTOR, Wnt/β-catenin) that all contribute to growth, survival, and insulin secretion in β-cells.[29]

Besides cell proliferation, β cell redifferentiation is another promising way of regeneration. In T2DM, mature β-cells can dedifferentiate, losing the insulin-producing phenotype, through decreased expression of insulin-specific transcription factors like PDX1, MafA, NKX6.1 and NeuroD1. This process is potentially reversible, unlike a process of apoptosis.[30] Re-activating these transcription factors and changing developmental pathways such as Notch, Hippo/YAP and TGF-β can restore β-cell identity and insulin secretory function. Together, these regeneratory strategies provide some hope for restoring the natural insulin production and slowing the disease process in T2DM.[31]

5.2 Stem Cell and Cellular Reprogramming

Stem cell-based therapy has been proven to be a promising regeneration therapy for pancreatic β-cell mass restoration in Type 2 diabetes mellitus (T2DM). Whereas traditional treatments primarily focus on the glycaemic effect, stem cell therapy was a new approach designed to replace impaired or destroyed insulin-producing β-cells with new ones. Patient-specific cells such as embryonic stem cells (ESCs) have the potential to develop into functional β-like cells with unlimited life and self-renewal, and induced pluripotent stem cells (iPSCs) are cells derived from adult somatic cells that are patient-specific and have fewer ethical concerns and less risk of immune rejection.[32] Indirectly, MSCs play a role through the release of growth factors, cytokines and extracellular vesicles which help to lower inflammation, repair tissue damage, and increase the survival of β-cells.[33]

Another promising approach is to reprogramme mature pancreatic α-cells, ductal cells and acinar cells into insulin producing β-cells. It involves specific transcription factors like PDX1, NGN3, MafA, and PAX4 that are important for the expression of specific genes in β-cells and for the recovery of insulin secretion.[34] The benefit of cellular reprogramming is that it uses cells from within the body reducing the need for donor tissue. In experimental studies, these techniques have proven promising, but issues of incomplete maturation of β-cells, poor long-term survival, immune rejection and potential for tumour formation are all challenges. However, the continued developments of stem cell biology, gene editing, and tissue engineering will further enhance the potential for these regenerative therapies to restore insulin production and reduce the course of T2DM.[35]

5.3 Gene Editing and Molecular Therapeutics

Gene editing and molecular therapeutics are now emerging as novel means for the restoration of β-cell function and promotion of regeneration in T2DM. These strategies are different from the traditional therapies, which mainly focus on managing hyperglycaemia, as they focus on the molecular and genetic mechanisms responsible for the dysfunction of the β-cells.[36] The use of the CRISPR/Cas9 technique allows precise modification of genes that play a role in the development of β-cells, insulin secretion and β-cell survival, which could allow genetic defects to be corrected and the ability to regenerate to be improved. At the same time, the epigenetic regulation of genes related to β-cell proliferation, apoptosis, insulin biosynthesis, and glucose metabolism is controlled by RNA-based therapeutics such as small interfering RNAs (siRNAs), microRNAs (miRNAs), and long non-coding RNAs (lncRNAs). In experimental studies, modulation of these non-coding RNAs has been observed to be beneficial for the survival of β-cells and to restore insulin secretory function.[37]

Another key point is epigenetic regulation, including DNA methylation, histone modification, and chromatin remodeling of the genetic sequence that shape the identity and function of β-cells. These epigenetic changes may be reversible and could restore normal β-cell function and slow the progress of the disease. In recent years, the efficiency and specificity of molecular therapeutics has also been enhanced by the development of new gene delivery systems such as lipid nanoparticles and viral vectors.[38] While these strategies are mostly in the preclinical and early clinical phases, they are potential precision medicine approaches with the potential to restore functional β-cells, maintain endogenous insulin production and offer lifelong therapeutic benefits for T2DM patients.[39]

5.4 Incretin-Based Therapies for β-Cell Protection

Preservation of pancreatic β-cell function is an important strategy in the management of Type 2 diabetes mellitus and incretins are playing a role in this. When food is consumed, the intestine releases two incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which stimulates glucose-dependent insulin secretion. But these hormones are easily broken down by the enzyme dipeptidyl peptidase-4 (DPP-4).[40] This has been addressed by the development of drugs called GLP-1 receptor agonists (GLP-1RAs) and DPP-4 inhibitors which help to increase the incretin activity and enhance β-cell function.[41]

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The GLP-1 receptor agonists (LIR) such as liraglutide, semaglutide and dulaglutide increase insulin levels, decrease glucagon levels, slow gastric emptying and reduce appetite. They also activate intracellular signaling pathways, including cAMP/PKA, PI3K/Akt and CREB, leading to increased β-cell survival, insulin gene expression, decreased oxidative stress, and inhibition of apoptosis. DPP-4 inhibitors, like sitagliptin, linagliptin, enhance the production of GLP-1 by inhibiting its degradation, improving glucose responsive insulin production and maintaining β-cell function.[42]

Recent studies have shown that incretin-based therapies have the potential to also induce β-cell proliferation and inhibit β-cell dedifferentiation to help preserve functional β-cell mass. While they do not regenerate β-cells, these treatments do slow down the gradual deterioration of β-cells, and they are an important long-term treatment strategy for T2DM that can help modify the disease.[43]

5.5 Islet Transplantation and Tissue Engineering

Islet transplantation involves replacing damaged pancreatic β-cells with functional islets from a donor, and is considered a promising means of restoring endogenous insulin production in patients with severe diabetes.[44] The islets are usually transplanted into the portal vein of the liver and they grow in and begin producing glucose-responsive insulin. This can lead to better glycaemic control, lower insulin dose, and a lower risk of hypoglycaemia. Its wide use is hampered by a shortage of donor organs, immune rejection, the need for lifelong immunosuppressive therapy, and impaired function of the graft over time.[45]

To surmount these constraints, a novel approach in the field of bioengineering, known as tissue engineering, has been developed for creating bioengineered pancreatic tissues. The biomaterial-based scaffolds, hydrogels, and 3D bioprinting offer a conducive microenvironment that improves islet survival, vascularization, and long-term function following transplantation. Further, encapsulations technologies encapsulate the transplanted islets in semi-permeable biomaterials that facilitates the passage of oxygen, nutrients, glucose and insulin and prevents immune attack against the cells.[46] These advances have made it possible to decrease systemic immunosuppression and increase graft survival. Recent studies also have investigated the potential for integration of β-like cells derived from stem cells with tissue-engineered scaffolds to create artificial pancreatic tissue. These strategies are largely experimental at this time, but ongoing advances in biomaterials, bioengineering and transplantation medicine have great potential for restoring β-cell mass and achieving long-term glycaemic control in patients with Type 2 diabetes mellitus (T2DM).[47]

Current challenges in clinical application:

Although great strides have been made, there are a number of limits that prevent the effective clinical use of β-cell regenerative therapies. The main challenges of islet transplantation are immune rejection, inadequate vascularization, limited long-term survival of islet β-cells and lack of sufficient donor organs. The use of stem cell therapy is also fraught with challenges of inadequate maturation to adult β-cells, the risk of tumor formation, and the uncertainty of efficacy. Likewise, long-term safety and ethical issues must be evaluated and off-target mutations must be carefully considered in the case of gene editing using CRISPR/Cas9. Moreover, the cost of regeneration therapies, complex manufacturing processes and strict regulatory requirements remain to be a factor that prevents broad clinical application of these therapies.

Future Perspectives

Future studies are warranted to develop safe, effective and individualized regenerative therapies to restore the function of the endogenous β-cells. New developments in the fields of gene editing, stem cell engineering, biomaterials, tissue engineering, artificial intelligence, and single-cell transcriptomics will help enhance β-cell regeneration and therapeutic accuracy. Combination treatments that combine pharmacologic and regenerative therapies might offer greater protection to the β-cells, stimulate their regeneration and improve long-term glycaemic regulation. Ongoing multidisciplinary research and proper designed clinical trials will be crucial to bring these innovative therapies into clinical practice and eventually provide disease-modifying therapies that can maintain or regenerate functional β-cell mass in patients with T2DM.

CONCLUSION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder which result in progressive loss of pancreatic β-cell mass and function, and impaired insulin secretion and chronic hyperglycaemia. The present antidiabetic treatments successfully treat hyperglycaemia, but they are not able to halt the progressive reduction in functional β-cells. Thus, attempts to protect and regenerate the β-cells have become attractive targets for modifying disease process and not just maintaining hyperglycaemia. In recent years, new therapeutic approaches have been developed to target β-cells, such as the use of incretins, the stimulation of β-cell proliferation and redifferentiation, stem cell and cellular reprogramming, gene editing and islet transplantation combined with tissue engineering. These strategies have proven to have great promise for maintaining β-cell function and restoring endogenous insulin production. Current limitations of their clinical use include immune rejection, limited long-term survival of the graft, safety and/or high treatment cost. Combining precision medicine, advanced biomaterials, and molecular therapeutics could speed up the progress towards effective disease-modifying therapies in the future. In summary, β-cell protection and regeneration is a promising area for achieving better long-term results in the treatment of T2DM.

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DISCUSSION

The current treatment of Type 2 diabetes mellitus (T2DM) such as metformin, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones and insulin all help to reduce glycaemic control, but do not halt the progressive loss of **β-cell mass and function**. The only treatments that are currently known to work primarily inhibit metabolic stress and help maintain the existing β-cells, but they do not restore them and so do not impact disease progression.

Several novel regenerative strategies, such as β-cell proliferation and redifferentiation, stem cell therapy, gene editing, and islet transplantation, have been explored to restore insulin-producing function of endogenous β-cells. While the idea has been successful in preclinical and early clinical trials, its broad use is hampered by issues of immune rejection, long-term graft survival, safety and treatment cost.

Additional studies are required to gain deeper insight into the molecular mechanisms of β-cell regeneration, to increase the safety and efficacy of regenerative therapies, and to demonstrate the clinical long-term benefit of these therapies on a large scale. The advancement of precision medicine, advanced biomaterials and molecular therapeutics can help propel the development of effective disease-modifying treatments for T2DM, which can ultimately drive better patient outcomes.

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