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Metabolic Maturation and Clinical Translation of Stem Cell-Derived β-Cells in Diabetes Therapy

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Abstract

Effective treatment of diabetes requires functional pancreatic β cells capable of accurately regulating blood glucose levels. Although human Pluripotent Stem Cells (hPSCs) can be differentiated into insulin-producing cells, these cells often remain functionally immature and resemble fetal β cells. Increasing evidence suggests that the nutritional and metabolic environment plays an important role in β-cell maturation. This review explores how modulation of glucose, amino acids and fatty acids affects key metabolic pathways, with particular focus on the shift from mTOR-driven growth to AMPK-mediated maturation. Improving nutrient-sensing conditions during differentiation may enhance Glucose-Stimulated Insulin Secretion (GSIS), reduce the risk of hypoglycemia and strengthen the therapeutic potential of stem cell-derived β cells for diabetes treatment.

Keywords: Human Pluripotent Stem Cells Diabetes Therapy; Glucose-Stimulated Insulin Secretion

Abbreviations

AMPK: AMP-Activated Protein Kinase; GLUT1: Glucose Transporter 1; GSIS: Glucose-Stimulated Insulin Secretion; hPSC: Human Pluripotent Stem Cell; MSC: Mesenchymal Stem Cell; mTOR: Mechanistic (or mammalian) Target of Rapamycin; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus

Introduction

Diabetes mellitus is a chronic metabolic disease that affects millions of people worldwide and continues to increase in prevalence each year [1]. The disease is characterized by the body's inability to properly regulate blood glucose levels due to insufficient insulin production or impaired insulin action. In both Type 1 Diabetes (T1DM) and later stages of Type 2 Diabetes (T2DM), pancreatic β-cell dysfunction or loss plays a central role in disease progression [1-3]. For many individuals, this requires continuous blood glucose monitoring and management, placing a significant physical and psychological burden on patients over time. Current treatment strategies largely focus on insulin replacement or glucose management rather than addressing the underlying loss of functional β-cells [1,2,4].

Because of these limitations, regenerative medicine approaches have gained significant attention, particularly those involving stem cell-derived β-cells. Human Pluripotent Stem Cells (hPSCs), including embryonic stem cells and induced pluripotent stem cells, can be differentiated into insulin-producing β-like cells in a laboratory setting [5-7]. However, there is a significant hurdle: many of these cells fail to reach full functional maturity and often resemble fetal β-cells rather than adult ones [8-10]. They resemble β-cells in appearance but often do not function the same way as mature β-cells. This immaturity is a major barrier to clinical translation [10,11].

Recent evidence suggests that this lack of maturity may be influenced not only by genetic programming but also by the nutritional and metabolic environment in which stem cells are cultured [12-14]. Nutrients such as glucose, amino acids and fatty acids act as signaling molecules that regulate key pathways involved in β-cell metabolism and insulin secretion [15,16]. Essentially, what we "feed" these cells during their development might be just as important as their DNA. Understanding how nutrient signaling affects stem cell-derived β-cells may help improve differentiation protocols and therapeutic outcomes for patients everywhere [12,14,15].

This report reviews current research on how nutrient signaling contributes to the maturation of stem cell-derived pancreatic β-cells. Although hPSCs can be differentiated into insulin-producing cells, these cells often remain functionally immature and display fetal-like metabolic characteristics, which limits their glucose-stimulated insulin secretion and clinical potential [10,17,18]. This review focuses on how extracellular nutrients, including glucose, amino acids and fatty acids, influence key metabolic signaling pathways involved in β-cell maturation, with particular attention to the shift from mTOR-associated growth signaling toward AMPK-mediated maturation pathways [19,20]. Rather than emphasizing genetic modification or lineage specification strategies, this manuscript highlights metabolic and environmental factors that may improve β-cell functionality. By combining mechanistic insights with findings from preclinical and clinical studies, this work aims to identify nutrient-based approaches that could enhance therapeutic outcomes while reducing risks such as hypoglycemia in regenerative treatments for diabetes [12,15,21].

With this in mind, this review is guided by the following questions: Which nutrient sensing pathways regulate the maturation of stem cell derived pancreatic β-cells? How do specific nutrients, including glucose, amino acids and fatty acids, influence the balance between growth through mTOR and functional maturation through AMPK in these cells? What evidence exists that nutrient based strategies can improve β-cell functionality and support clinical applications for diabetes treatment.

Results and Discussion

Mature pancreatic β-cells are highly specialized metabolic cells that respond precisely to changes in blood glucose levels. They act as the body's natural sensor for sugar. Glucose enters β-cells through glucose transporters, primarily GLUT1 in humans and is processed by glucokinase, which acts as the cell's main glucose sensor [22]. This process leads to increased ATP production through mitochondrial oxidative phosphorylation [2,22]. As ATP levels rise, specific channels in the cell close, causing a change in the cell's electrical charge that ultimately triggers insulin secretion [2,22]. This tightly regulated process, known as stimulus-secretion coupling, is a hallmark of fully mature β-cells and is essential for maintaining normal glucose homeostasis (Fig. 1) [23].

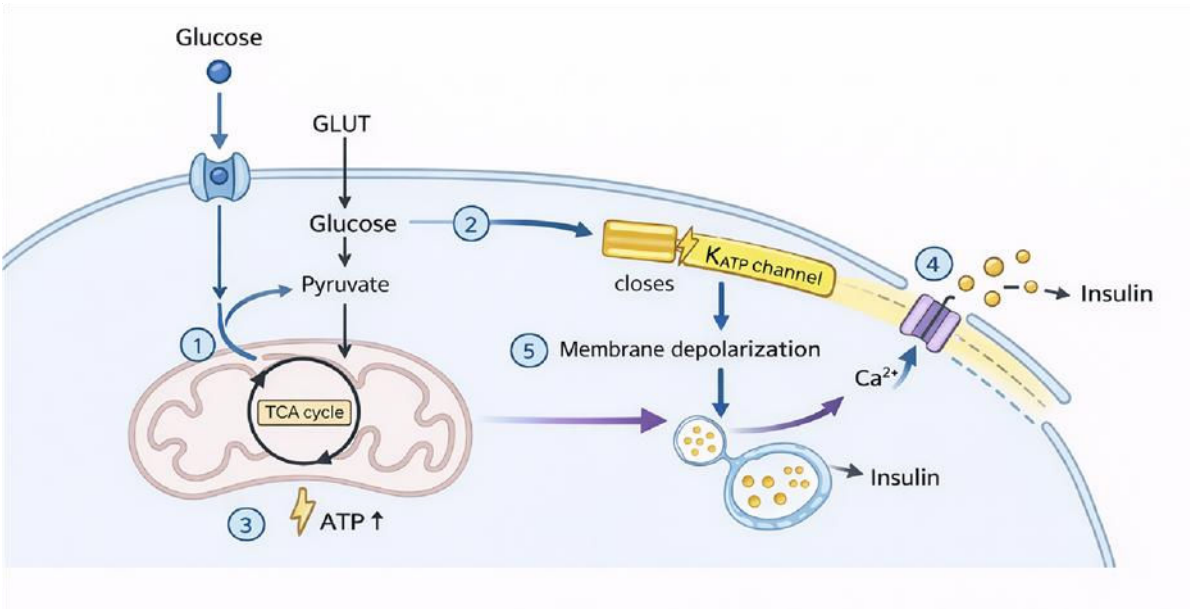

Figure 1: Overview of glucose-stimulated insulin secretion (GSIS) in mature pancreatic β-cells. Glucose metabolism increases ATP production, leading to closure of KATP channels, membrane depolarization, Ca^{2+} influx and insulin secretion. Adapted from [24].

In contrast, stem cell-derived β-cells often display immature metabolic features, including poor mitochondrial activity and inappropriate insulin secretion at low glucose levels [10,17,25].

Recent results from a phase 1/2 clinical trial using fully differentiated stem cell-derived islet cells (zimislecel, VX-880) showed restoration of natural insulin production, elimination of severe hypoglycemia and insulin independence in several participants. These findings provide strong evidence that metabolically mature stem cell-derived β-cells can function effectively in humans [26]. These defects are especially concerning for clinical use, as uncontrolled insulin release could lead to dangerous hypoglycemia [8,10]. Since glucose metabolism is central to β-cell function, improper nutrient conditions during differentiation may directly contribute to this immature phenotype [12,13].

Stem Cell-Derived β-cell Differentiation and Maturation

The differentiation of stem cells into β-cells is a multi-step process designed to mimic normal pancreatic development in an embryo. Stem cells are first directed to become definitive endoderm, followed by pancreatic progenitors, endocrine progenitors and finally insulin-producing β-cells [18,27]. Each stage requires specific signaling cues, including growth factors, transcription factors and metabolic inputs [18,27,28].

Nutrient availability plays an important role throughout this entire process. For example, glucose levels can influence how fast the cells grow and what lineage they choose, while amino acids activate growth-related signaling pathways such as mTOR [15, 16]. If nutrient conditions are not carefully controlled, cells may remain stuck in an immature, proliferative state-meaning they keep dividing instead of maturing into functional β-cells [9,14,29].

Transcription factors such as PDX1, MAFA and NKX6.1 are essential for maintaining adult β-cell identity, regulating insulin gene expression, glucose sensing and secretory capacity. β-cells do not simply fail under metabolic stress; their differentiated state is actively preserved by these transcriptional networks. Persistent exposure to high glucose, elevated fatty acids or inflammatory signals can disrupt these pathways, causing PDX1, MAFA and NKX6.1 to lose functionality. As a result, β-cells may gradually lose their mature characteristics and adopt progenitor-like or alternative endocrine states-a process referred to as dedifferentiation [30]. This shift compromises insulin secretion and emphasizes that β-cell dysfunction in type 2 diabetes reflects a continuum of stress-adaptive changes rather than immediate cell death.

Mesenchymal Stem Cells (MSCs) are also being explored as supportive cells. Although MSCs do not typically turn into β-cells, they secrete growth factors and cytokines that improve β-cell survival and help build blood vessels to deliver nutrients after a transplant [11,31,32]. These supportive effects further highlight how important the surrounding environment is for β-cell health (Fig. 2) [31,33,34].

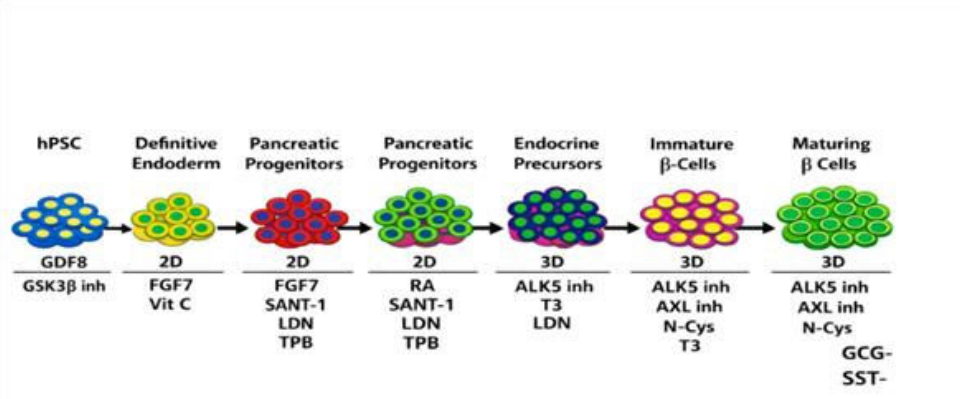

Figure 2: Directed differentiation of human pluripotent stem cells into pancreatic β-cells.

Schematic representation of the staged differentiation process from hPSCs to maturing β-cells, including key signaling factors and culture conditions at each step [35].

Potential Challenges and Solutions

- Mimicking the *In-vivo* Niche: Difficult to replicate the human body in a lab dish [11,36]
- Solution: Use endocrine cell clustering and 3D scaffolds to replicate pancreatic structure [33,37]
- Nutritional Stress: High nutrient levels can cause metabolic exhaustion [38,39]
- Solution: Monitor metabolic biomarkers and adjust nutrients to prevent toxicity [20,39,40]
- Immune Rejection: Transplanted cells may be attacked by the immune system [36,41]
- Solution: Use encapsulation devices to protect cells while allowing glucose sensing [42,43]

Role of Nutrition and Nutrient Signaling in β-cells Maturation (Fig. 3)

A. mTOR and AMPK Signaling Pathways

- mTOR promotes growth in nutrient-rich conditions but prolonged activation can block β-cell maturation [16,19,44]. AMPK promotes energy efficiency under low-energy conditions. A shift from mTOR- to AMPK-dominant signaling is required for functional maturation, influenced by nutrient availability, especially glucose and amino acids [12,15,19,20,46]

B. Macronutrients and Micronutrients

- Glucose: Chronic high glucose causes stress; natural levels support responsiveness [12,19]
- Amino acids: Excess leucine/arginine trap cells in immature states [15,16]
- Lipids: Saturated fats cause stress; unsaturated fats may protect [38,39]
- Micronutrients: Vitamin D and retinoic acid stabilize β-cell identity [47,48]

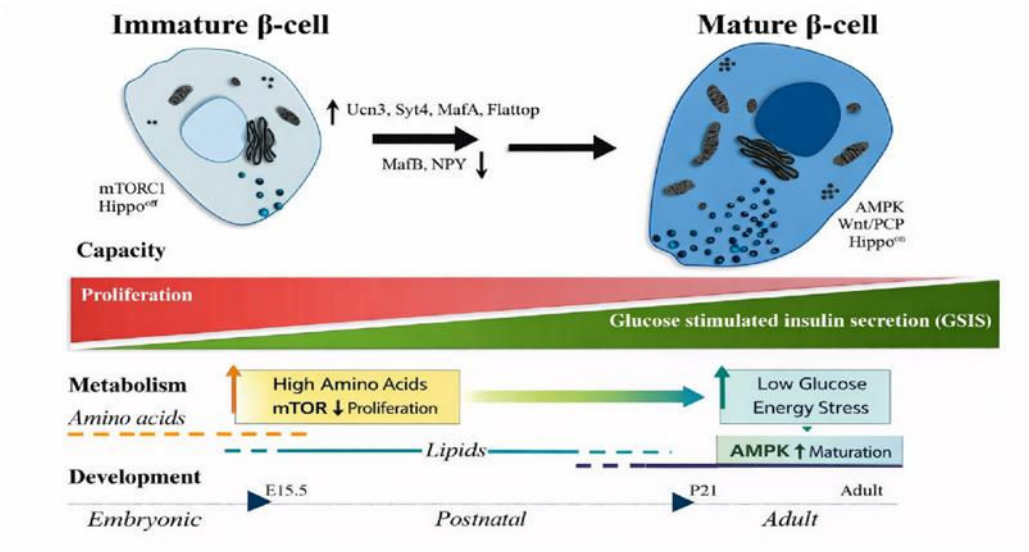

Figure 3: Metabolic and functional maturation of pancreatic β-cells. Schematic representation of the metabolic and functional maturation of pancreatic β-cells. The transition from immature to mature β-cells is depicted, highlighting changes in proliferative capacity, nutrient utilization and signaling pathways from mTORC1 to AMPK activation. Adapted from [49].

Clinical Applications of Stem Cell-Derived β-cells

Stem cell-derived β-cells are being tested in early clinical trials as a potential treatment for diabetes. Scientists are using protective devices or "pouches," to shield transplanted cells from the immune system while still allowing them to sense blood sugar and release insulin [21,42,43,50].

Early clinical results are promising. Some patients with type 1 diabetes showed better blood sugar control and needed less insulin after receiving encapsulated β-cells [21,42]. This shows that lab-grown β-cells can function in humans, although researchers are still studying how long they last and how consistent their insulin release is [42,50].

Clinical trials for stem cell-derived β-cell replacement generally use two main strategies: encapsulation for immune protection and systemic immunosuppression (Table 1). Encapsulation physically separates transplanted cells from immune attack while

still allowing them to sense glucose and secrete insulin. In a recent study, encapsulated stem cell-derived β-cells survived implantation and improved glucose control in patients with type 1 diabetes, showing that this approach is feasible [51]. Similarly, transplanting stem cell-derived pancreatic progenitors has been shown to produce glucose-responsive C-peptide, which suggests partial functional maturation *in-vivo* [52].

However, encapsulation results are mixed. While transplanted cells often survive, the amount of insulin released is sometimes not enough to fully replace external insulin therapy. This suggests that immune protection alone does not ensure complete β-cell maturation. One possible reason is that encapsulation devices can limit oxygen and nutrient diffusion, which may restrict how well the cell's function [33,53].

In contrast, immunosuppression can provide a more supportive metabolic environment for transplanted cells. In a recent phase 1/2 trial using fully differentiated stem cell-derived islet cells (zimislecel, VX-880), patients showed strong restoration of natural insulin production, elimination of severe hypoglycemia and large reductions in insulin use. Some participants even achieved insulin independence [26]. These findings suggest that stem cell-derived β-cells can achieve physiologic glucose-responsive insulin secretion in humans when full metabolic maturity is reached.

Overall, these trials suggest that long-term success depends not only on immune protection but also on the metabolic fitness of the transplanted cells. Ensuring proper nutrient signaling, healthy mitochondrial function and full β-cell maturation before transplantation may be key to improving clinical outcomes (Table. 1) [31,37,42,43].

Strategy	Example Studies	How It Protects Cells	Main Results	Biggest Drawbacks
Encapsulation delivery	Keymeulen, et al., 2024 [51]; Ramzy, et al., 2021 [52]	Protective device	Survival; glucose response	Low output; limited access
Immunosuppression delivery	Shapiro, et al., 2025 [26]	Systemic drugs	High insulin; independence	Lifelong risk

Table 1: Summary of clinical strategies for stem cell-derived β-cell transplantation. Overview of encapsulation and immunosuppression approaches, including example studies, how each method protects cells, key results and main limitations. Success does not only depend on immune protection. Transplanted cells must also be healthy and metabolically mature. Cells stressed from poor nutrient conditions in the lab may not survive or function properly in the patient [31, 37, 42, 43]. Ensuring cells are "fit" before and after transplantation is therefore critical [37, 42].

Takeaways from Clinical Trial

From these trials, it's clear that just keeping the β-cells safe from the immune system isn't enough. The cells also need to be healthy and fully matured to work well in the patient. Encapsulation devices do a good job of protecting cells while still letting them sense glucose and release insulin, but sometimes the insulin output isn't enough on its own. On the other hand, immunosuppression can create a better environment for the cells, letting them function closer to natural β-cells, though it comes with the risk of lifelong medication [21,42,43,50].

Healthy, metabolically mature cells survive longer and respond better to blood sugar changes. Making sure the cells are "fit" before transplant, with proper nutrients and energy metabolism, seems to be key for long-term success [31,37,42,43]. Patients in these studies often saw lower insulin requirements and better overall blood sugar control, which shows that lab-grown β-cells can really make a difference when they're in the right state. These trials highlight that combining stem cell biology with careful attention to nutrients and cell health may make regenerative diabetes treatments safe and effective (Fig. 4).

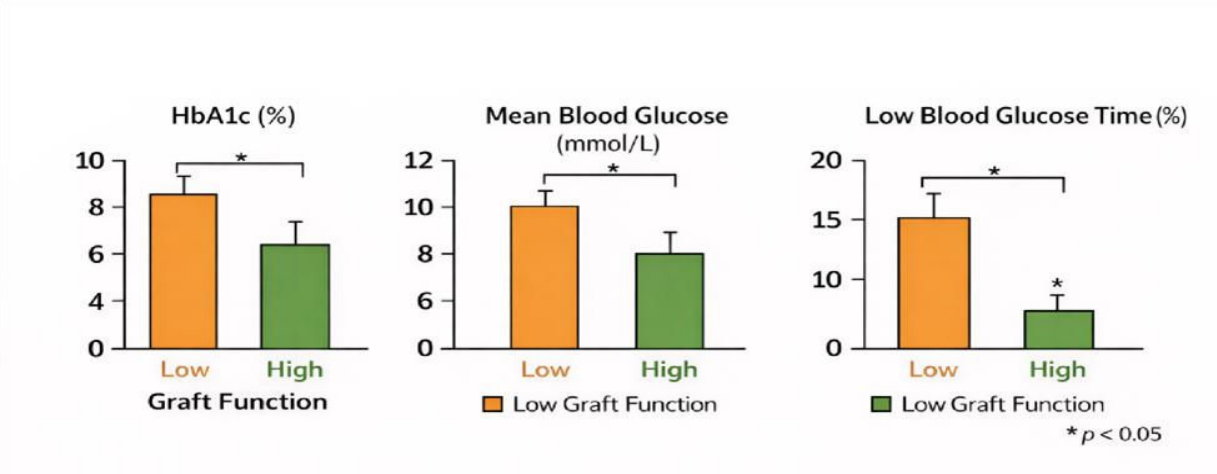

Figure 4: Impact of islet graft function on glycemic control following transplantation. Schematic representation of clinical outcomes comparing glycemic control between individuals with low vs high islet graft function. Adapted from [54].

Expected Results

Research suggests a direct link between the nutritional environment of a stem cell and its ability to become a mature β-cell. Carefully balancing glucose and amino acids may shift signaling from mTOR toward AMPK, producing cells that release insulin appropriately [19,20]. Adding specific micronutrients, such as vitamin D, during later stages of differentiation may help cells withstand transplantation stress [47,48]. Ultimately, a "nutrition first" approach to cell growth could reduce complications like hypoglycemia and improve long term blood sugar control [21,25,42,43]. Functional maturity would be assessed through glucose stimulated insulin secretion assays, metabolic profiling and mitochondrial function analyses.

Patient Impact

If this research is successful, the effect on patients with diabetes could be transformative. Right now, many patients live with the fear of sudden drops in blood sugar because lab-grown β-cells sometimes release insulin inappropriately [8, 10]. By maturing these cells properly through controlled nutrient signaling and optimizing their metabolic fitness, we can create a treatment that responds naturally to changes in blood glucose [12,15,26].

For patients, this means more than just better readings on a glucose monitor; it could reduce their dependence on insulin injections and lower the risk of long-term complications such as heart or kidney disease [1,2,42,43]. Early clinical trials have already shown that well-matured stem cell-derived β-cells can survive after transplantation, sense glucose correctly and improve glycemic control [51, 52]. Successfully transplanting functional, nutritionally optimized β-cells could give patients a level of independence and peace of mind, knowing their body is once again regulating itself more naturally [21,42,43].

Research Gaps and Future Directions

Even though significant progress has been made in producing stem cell-derived β-cells, important gaps remain in understanding how nutrient signaling affects their maturation and long-term function [36,41]. Many studies focus on genetic factors and growth signals during differentiation, but fewer examine how nutrients such as glucose, amino acids and lipids influence whether these cells become fully mature and functional β-cells [14,15,19]. Because β-cells are highly metabolic, this represents a critical area for future research, especially considering that clinical trials have shown variable outcomes depending on the functional maturity of the transplanted cells [26,51,52].

One major goal is to better define how nutrient requirements change at different stages of β-cell development. While higher nutrient levels may support early cell growth through mTOR signaling, prolonged exposure to high glucose or excess amino acids can prevent proper maturation [15,16,19,44]. Optimizing the timing and levels of nutrients to promote energy sensing through AMPK could enhance functional maturation, ensuring that cells are capable of robust glucose stimulated insulin secretion and mitochondrial activity before transplantation [10,17,25]. This directly addresses findings from encapsulation trials, where cells often survived implantation but did not release enough insulin to fully replace external therapy [51,52].

Another key direction is integrating nutrient optimization with transplantation strategies. Encapsulation devices protect transplanted β-cells from immune attack, but their success also depends on the health and resilience of the cells at the time of implantation [42,43]. β-cells that are metabolically stressed from suboptimal nutrient conditions *in-vitro* may be less likely to survive or function properly, as suggested by studies showing variable glucose responses in encapsulated grafts [33,53]. Trials using immunosuppression and fully differentiated islet cells demonstrated that when cells reach full metabolic maturity, they can achieve physiologic insulin secretion, eliminate severe hypoglycemia and even lead to insulin independence [26]. Future research should explore how precise nutrient control during differentiation can maximize these functional outcomes.

Conclusion

Stem cell-derived β-cells offer a promising way to treat diabetes by addressing the root cause of the disease rather than just managing symptoms. Although significant progress has been made in creating insulin producing cells from stem cells, many of these cells still do not function like adult human β-cells. One major reason for this appears to be the nutritional and metabolic environment in which the cells develop. Nutrition does more than provide energy. Glucose, amino acids and fatty acids act as signals that guide β-cells growth, maturation and how the cells respond to glucose. If these nutrient signals are not balanced correctly, stem cell-derived β-cells may remain immature, release insulin at the wrong time or fail to survive after transplantation. The recent clinical trials show how important this is. Encapsulated cells can survive implantation and improve glucose control in patients, but only fully mature cells, as seen in the immunosuppression-based trial with fully differentiated islet cells, provide strong insulin response and can even allow some patients to stop insulin therapy. This shows that protecting cells from the immune system is not enough. The cells also need to be healthy and trained by nutrients to work properly. Understanding how nutrient sensing pathways such as mTOR and AMPK respond to different conditions can help improve lab protocols and produce β-cells that behave more like adult cells. Adjusting nutrient levels during differentiation and supporting the cells with the right metabolic environment after transplantation could improve long term function, reduce problems like insulin release at the wrong time and make treatments safer for patients.

Significance of the Study

This research is important because it focuses on a factor that is often overlooked in stem cell-based diabetes therapies: nutrition. Many studies focus on genetic programming and growth factors to produce β-cells from stem cells, but fewer examine how nutrient availability and metabolic signals influence whether these cells become fully functional. Since β-cells are highly metabolic by nature, understanding how nutrients affect their development is especially important. By studying how nutrient signaling pathways such as mTOR and AMPK influence stem cell-derived β-cells, this project may help explain why many lab grown β-cells remain immature. Identifying the specific nutritional conditions that support proper β-cell maturation could improve differentiation protocols and make stem cell-based treatments safer and more effective. This work also has direct clinical relevance. If the nutritional environment affects β-cell survival and function after transplantation, strategies to optimize nutrients or metabolism could be used alongside regenerative therapies to improve patient outcomes. Optimizing these nutrient sensing mechanisms may increase glucose stimulated insulin secretion, reduce the risk of hypoglycemia and improve the long-term effectiveness of stem cell-derived β-cell therapies for diabetes.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

Not applicable.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions

All authors contributed equally to this paper.

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