Review Article

Stem Cell – Derived β – Cell Therapy in Diabetes – Advances in Regeneration, Maturation and Immune Protection

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterised by insufficient insulin production or impaired insulin action leading to persistent hyperglycaemia. Among available therapeutic approaches, regenerating functional pancreatic β-cells offers a promising strategy for achieving long-term glycemic control. Recent advances in stem cell biology have facilitated the differentiation of human pluripotent stem cells into β-like cells capable of sensing glucose and secreting insulin in a regulated manner. Despite notable progress, challenges remain including incomplete functional maturation, limited long-term engraftment, and immune-mediated destruction following transplantation. Encapsulation technologies and immune protective strategies have shown promise in shielding transplanted cells from host immunity while maintaining functionality. Furthermore, recent innovations in gene editing, small molecule modulation, and three-dimensional culture systems have improved β-cell maturation and functional performance. Preclinical studies demonstrate that stem cell-derived β cells can restore glycaemic control in diabetic models yet translation to clinical application necessitates overcoming hurdles in scalability, safety, and regulatory approval. This review summarizes current understanding of stem cell-derived β-cell therapy focusing on molecular mechanisms of differentiation strategies to enhance functional maturation approaches for immune protection and translational challenges. By integrating findings from recent studies, we highlight both the progress achieved and the gaps that remain in the field. Addressing these challenges will be critical to advancing β-cell replacement therapies towards routine clinical use and may pave the way for curative interventions in diabetes.

Keywords: Stem cells, β-cell regeneration, Diabetes therapy, Immune protection, Islet transplantation, Maturation, Translational medicine

INTRODUCTION

Diabetes mellitus is a global health concern affecting hundreds of millions worldwide and contributing to significant morbidity and mortality. The disease is primarily characterised by the progressive loss or dysfunction of pancreatic β cells leading to chronic hyperglycaemia and associated complications. Current therapeutic approaches including insulin replacement and pharmacological agents can manage glycaemia but fail to restore endogenous β-cell function, and long-term outcomes remain suboptimal. These limitations have motivated intense research into regenerative strategies aimed at replenishing functional β cells.[1-3]

Stem cell–derived β-cell therapy has emerged as a potential strategy to fulfill this unmet clinical need. Advances in pluripotent stem cell biology have enabled the in vitro differentiation of human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) into pancreatic progenitors and β-like cells capable of glucose-stimulated insulin secretion. This strategy provides a sustainable, patient-tailored source of functional β cells overcoming the limited availability of donor islets and minimising the risk of immune rejection when autologous cells are employed. Despite these advances several challenges impede clinical translation. Stem cell-derived β cells often exhibit incomplete maturation, limited functional longevity, and vulnerability to immune-mediated destruction following transplantation. Furthermore, variability in differentiation protocols and difficulties in achieving reproducible outcomes highlight the need for standardised approaches. Addressing these gaps is critical for moving β-cell replacement therapies from bench to bedside[4-12].

The aim of this review is to provide a comprehensive synthesis of recent developments in stem cell-derived β-cell therapy for diabetes. We focus on three core aspects - the molecular mechanisms underlying β-cell differentiation and maturation, current therapeutic strategies including immune protection and encapsulation and the translational challenges that must be overcome to achieve clinical success. By integrating findings from recent preclinical and clinical studies this review seeks to elucidate both the progress and the remaining research gaps, offering a roadmap for future investigations[13-15]

Current Therapeutic Strategies Using Stem Cell–Derived β Cells

Stem cell-derived β-cell therapy has emerged as a promising approach to restore functional insulin-producing cells in patients with diabetes. The primary strategy involves transplantation of differentiated β-like cells or pancreatic progenitors, aiming to replace lost endogenous β-cell mass and achieve regulated insulin secretion. Both autologous induced pluripotent stem cell (iPSC)-derived β cells and allogeneic human embryonic stem cell (hESC)-derived β

cells have been explored, with autologous cells offering reduced immunogenicity [4-7].

A major challenge in transplantation is immune-mediated rejection**.** Allogeneic β cells are vulnerable to both innate and adaptive immune responses, necessitating either immunosuppressive therapy or protective strategies [8-9].

Encapsulation technologies have gained attention as a solution, enclosing β cells in semipermeable biomaterials that allow nutrient and insulin exchange while shielding them from immune attack. Alginate-based microcapsules, hydrogel scaffolds, and conformal coatings have demonstrated long-term glycaemic control in preclinical models. Notably, Keymeulen et al. showed that encapsulated stem cell-derived β cells maintained glucose homeostasis in animal models over extended periods [10-12.]

In addition to encapsulation, immune-modulatory approaches are being investigated. Strategies include co-transplantation with regulatory T cells expression of immune checkpoint molecules, or genetic modification to reduce HLA expression. These methods combined with encapsulation or scaffold-based delivery create a protective environment that enhances graft survival [13-14].

Another critical aspect is functional maturation prior to transplantation. Stem cell-derived β cells initially display immature glucose-stimulated insulin secretion (GSIS), requiring additional in vitro or in vivo maturation strategies. Extended culture, metabolic conditioning and exposure to physiologically relevant glucose fluctuations have improved dynamic insulin responses. Scalable production of consistent, functionally competent β cells remains a key translational challenge [15-17].

Collectively, current therapeutic strategies integrate advances in stem cell biology, bioengineering and immunology to move β-cell replacement closer to clinical application. While promising challenges related to immune protection, functional maturation and large-scale reproducibility must be addressed before these therapies can become routine clinical practice [18-19].

Limitations and Challenges

Despite significant progress stem cell–derived β-cell therapy faces several critical limitations. Incomplete functional maturation remains a major issue as many β-like cells generated in vitro exhibit immature glucose-stimulated insulin secretion, limited dynamic response and incomplete metabolic coupling with fully mature β-cells resembling adult human islets still under investigation. Immune-mediated rejection is another barrier allogeneic cells are subject to adaptive and innate immune attacks, and immunosuppressive regimens increase infection and malignancy risk. Even autologous iPSC-derived cells may trigger immune responses due to aberrant antigen expression and although encapsulation and immunomodulatory strategies are promising, long-term viability, nutrient supply and insulin secretion remain challenging. Scalability and reproducibility are also problematic as producing clinically relevant β-cells with consistent quality and functionality is technically complex with batch variability, culture stress, and teratoma risk further complicating translation alongside stringent regulatory requirements. Finally, long-term engraftment and vascularization are unresolved issues insufficient integration into host tissue can limit cell survival and insulin responsiveness [20-23].

Future Prospects

Emerging strategies aim to overcome current barriers and enhance the translational potential of β-cell replacement therapy. Enhancing β-cell maturation and refining differentiation protocols are essential, with recent studies demonstrating that extended culture durations, metabolic conditioning and three-dimensional islet-like constructs markedly improve insulin secretion and the dynamics of glucose-stimulated insulin release. Additionally, gene editing tools such as CRISPR/Cas9 are being explored to enhance immune evasion, reduce HLA expression, and promote β-cell survival. Immune-protective innovations continue to evolve. Advanced encapsulation devices, conformal coatings and immunomodulatory scaffolds aim to provide long-term protection without systemic immunosuppression. Co-transplantation with regulatory T cells or mesenchymal stromal cells may further promote immune tolerance and enhance engraftment[24-26].

Clinical translation and scalability are receiving increasing attention. Strategies to produce large-scale, GMP-compliant β cells, combined with standardised differentiation protocols are underway to ensure reproducibility and safety. Early-phase clinical trials of stem cell-derived pancreatic progenitors have demonstrated safety and preliminary efficacy, providing encouragement for future studies. Finally, integration with bioengineering and artificial pancreas systems offers the potential for hybrid approaches that combine cellular therapy with continuous glucose monitoring and automated insulin delivery, potentially achieving more physiologic glycaemic control [27-28].

CONCLUSIONS

Stem cell-derived β-cell therapy represents a transformative approach for diabetes management. Advances in differentiation, maturation, and immune protection have propelled the field toward clinical translation[29].

Challenges remain including functional immaturity, immune rejection, limited engraftment, and scalability [30]. Addressing these through optimised differentiation protocols, immune-protective strategies and rigorous preclinical validation is essential. With continued innovation stem cell derived β-cell therapy holds promise as a durable, patient-specific and potentially curative treatment for diabetes.

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