International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 09, Issue 11, November 2024,
https://doi.org/10.23958/ijirms/vol09-i11/1992

Review Article

Overcoming Endoplasmic Reticulum Stress in iPSC-Derived Beta Cells: Advancing Therapies for Diabetes

Amália Cinthia Meneses do Rêgo [1], Ph.D., Irami Araújo-Filho [1,2], Ph.D.

[1]Institute of Teaching, Research, and Innovation, Liga Contra o Câncer - Natal - Brazil; Full Professor of the Postgraduate Program in Biotechnology at Potiguar University (UnP) - Natal/RN - Brazil.
[2]Full Professor, Department of Surgery, Potiguar University. Ph.D. in Health Science/ Natal-RN - Brazil.

*Corresponding author: Prof. Dr. Irami Araújo-Filho, MD, Ph.D.; *irami.filho@uol.com.br*

Received 20 September 2024; Accepted 26 October 2024; Published 01 November 2024

Abstract

Pancreatic beta cell dysfunction is a central feature of diabetes mellitus, where prolonged metabolic stress contributes to cell failure and death. A significant driver of this dysfunction is endoplasmic reticulum (ER) stress, which leads to impaired insulin secretion and beta cell loss. The recent development of induced pluripotent stem cells (iPSCs) offers an innovative approach to generating patient-specific beta cells, presenting a potential breakthrough in diabetes treatment. However, a significant challenge remains iPSC-derived beta cells are particularly vulnerable to ER stress, which hampers their functionality and survival after transplantation. This review provides a detailed analysis of the effects of ER stress on iPSC-derived beta cells, focusing on the molecular mechanisms that trigger the unfolded protein response (UPR) a crucial pathway activated to manage protein misfolding and cellular stress. The review examines current therapeutic strategies to alleviate ER stress, including pharmacological agents and genetic interventions designed to modulate the UPR to improve beta cell resilience and function in diabetic conditions. By synthesizing recent findings, this review highlights critical gaps in the research and proposes future directions to optimize iPSC-derived beta cell therapies. Addressing ER stress is crucial to unlocking the full therapeutic potential of these cells, paving the way for more effective and long-lasting diabetes treatments. This article aims to capture the current state of research and inspire further exploration into overcoming one of the most significant barriers in beta cell replacement therapy.

Keywords: ***endoplasmic reticulum stress, induced pluripotent stem cells, pancreatic beta cells, unfolded protein response, diabetes mellitus.***

Introduction

Diabetes mellitus, a chronic metabolic disorder, is characterized by the progressive dysfunction and failure of pancreatic beta cells, leading to impaired glucose regulation. In type 1 diabetes (T1D), autoimmune destruction of beta cells results in absolute insulin deficiency, while in type 2 diabetes (T2D), a combination of insulin resistance and gradual beta cell dysfunction contributes to hyperglycemia [1-3].

Current therapies, including insulin replacement, manage the symptoms but do not address the underlying loss of functional beta cells. The advent of stem cell-based therapies, particularly through induced pluripotent stem cells (iPSCs), offers a promising solution by generating insulin-producing beta cells. However, despite the potential of iPSCs in treating diabetes, several challenges remain, with endoplasmic reticulum (ER) stress emerging as a critical factor in beta cell dysfunction and death [2-4].

The ER is essential for protein synthesis, folding, and quality control, particularly in insulin-producing beta cells, where high insulin production creates a significant demand on the ER. During periods of cellular stress such as increased metabolic demand or exposure to inflammatory cytokines, the ER can become overwhelmed, leading to an accumulation of misfolded proteins [3-5].

This triggers the unfolded protein response (UPR), which is designed to restore ER homeostasis. However, when ER stress is prolonged or excessive, the UPR can lead to apoptosis. In the context of diabetes, beta cells are highly susceptible to ER stress, which accelerates their dysfunction and loss, worsening the disease. Understanding and mitigating ER stress in iPSC-derived beta cells is therefore crucial for improving the efficacy of stem cell-based therapies for diabetes [4-6].

iPSCs present an exciting opportunity to generate patient-specific beta cells, reducing the risk of immune rejection and providing an abundant source of insulin-producing cells. These cells are derived from reprogrammed somatic cells and can be differentiated into various cell types, including pancreatic beta cells. However, beta cells derived from iPSCs often exhibit functional immaturity and heightened sensitivity to stress, particularly ER stress [5-7].

This vulnerability limits their therapeutic potential, as they must be able to endure the demands of insulin production and metabolic fluctuations in diabetic patients. Addressing ER stress in iPSC-derived beta cells is therefore a major objective in advancing the field of diabetes therapy [6-8].

The objective of this review is to explore the current understanding of ER stress in iPSC-derived beta cells and discuss potential strategies to overcome this challenge, thereby enhancing the viability and functionality of these cells for therapeutic applications in diabetes. By examining the molecular mechanisms of ER stress, potential therapeutic interventions, and innovative bioengineering approaches, this review aims to highlight key areas for future research and development [7-9].

ER stress is a well-known contributor to beta cell dysfunction in diabetes. In iPSC-derived beta cells, which are expected to handle high insulin production, the ER is under significant strain to fold large amounts of insulin protein. Failure to properly manage this process can activate apoptotic pathways, compromising the survival and function of these cells [8-10].

Although iPSC-derived beta cells have shown promise in producing insulin, they remain vulnerable to ER stress under diabetic conditions, mirroring the challenges seen in endogenous beta cells. Therefore, strategies aimed at reducing or preventing ER stress are critical to improving the therapeutic success of beta cell replacement therapies [9-11].

One promising approach to managing ER stress involves modulating the UPR pathways. Under normal conditions, the UPR works to alleviate ER stress by enhancing protein-folding capacity, slowing protein translation, and promoting the degradation of misfolded proteins [10]. However, prolonged activation of the UPR can lead to cell death. Finding a balance between promoting cell survival and maintaining ER function is essential for the success of iPSC-derived beta cell therapies. By fine-tuning the UPR, researchers hope to enhance the resilience of these cells to stress without compromising their insulin-producing capabilities [11-13].

Molecular chaperones, proteins that assist in the folding of nascent polypeptides and the maintenance of ER function, also offer a potential solution to ER stress in iPSC-derived beta cells. Enhancing the activity of these chaperones could improve the cells' ability to handle the high protein-folding demands of insulin production, thereby reducing ER stress [12-14]. Chaperones such as BiP/GRP78 have been identified as key regulators of the ER stress response, and their upregulation in stem cell-derived beta cells could provide a protective mechanism against stress-induced apoptosis [13-15].

In addition to molecular interventions, pharmacological agents that alleviate ER stress have shown promise in preclinical studies. Chemical chaperones, such as tauroursodeoxycholic acid (TUDCA) and 4-phenylbutyrate (4-PBA), have been found to reduce ER stress and improve beta cell survival [14-16].

These compounds work by stabilizing protein folding and reducing stress signals within the ER. Incorporating these agents into the treatment regimen for iPSC-derived beta cells could enhance their functionality and increase their longevity post-transplantation, particularly in the challenging metabolic environments characteristic of diabetes [15-17].

Another critical factor in managing ER stress is the microenvironment where iPSC-derived beta cells are grown. Traditional 2D culture systems often fail to replicate the complex architecture and signaling cues in vivo, leading to increased ER stress [16-18].

Advances in 3D culture systems and bioengineered scaffolds offer more physiologically relevant environments, promoting the maturation of beta cells and reducing ER stress. By mimicking the native pancreatic microenvironment, these technologies could enhance the maturation and function of iPSC-derived beta cells, making them more robust for clinical applications [17-19].

The role of oxidative stress in conjunction with ER stress is also an important area of investigation. ER stress is often accompanied by generating reactive oxygen species (ROS), which can further damage cells. By targeting both ER and oxidative stress, researchers can develop combined therapeutic strategies to improve the survival and function of iPSC-derived beta cells. When used with ER stress modulators, antioxidants may synergistically protect beta cells from the dual insults of protein misfolding and oxidative damage [18-20].

Genetic engineering techniques, such as CRISPR/Cas9, offer additional avenues for mitigating ER stress in iPSC-derived beta cells. By editing genes that regulate ER function and the UPR, researchers can develop beta cell lines more resistant to stress-induced apoptosis. This approach enhances the functionality of iPSC-derived beta cells and increases their resilience in the diabetic microenvironment. Genetically modified beta cells with enhanced ER resilience could significantly advance the development of durable, long-lasting cell-based therapies for diabetes [19-21].

The differentiation protocols that generate beta cells from iPSCs are also being refined to improve their functionality and stress tolerance. Current protocols often result in immature beta cells that lack full glucose responsiveness [12]. By optimizing these protocols and incorporating strategies that enhance ER function, researchers can produce more robust beta cells capable of handling the demands of insulin production in vivo. These improvements are crucial for ensuring the success of stem cell-based therapies in clinical settings [20-22].

Ultimately, the long-term viability of iPSC-derived beta cell therapies depends on their ability to withstand the metabolic stresses of the diabetic environment. Transplanted beta cells must survive and continue functioning effectively, secreting insulin in response to glucose fluctuations [23]. Enhancing ER resilience, along with strategies to optimize differentiation and protect against oxidative stress, will be vital to the success of these therapies [24].

This review aims to provide a comprehensive overview of the current understanding of ER stress in iPSC-derived beta cells and explore potential strategies to overcome this challenge. By addressing ER stress, researchers can significantly improve the viability and functionality of these cells, bringing stem cell-based therapies for diabetes closer to clinical reality.

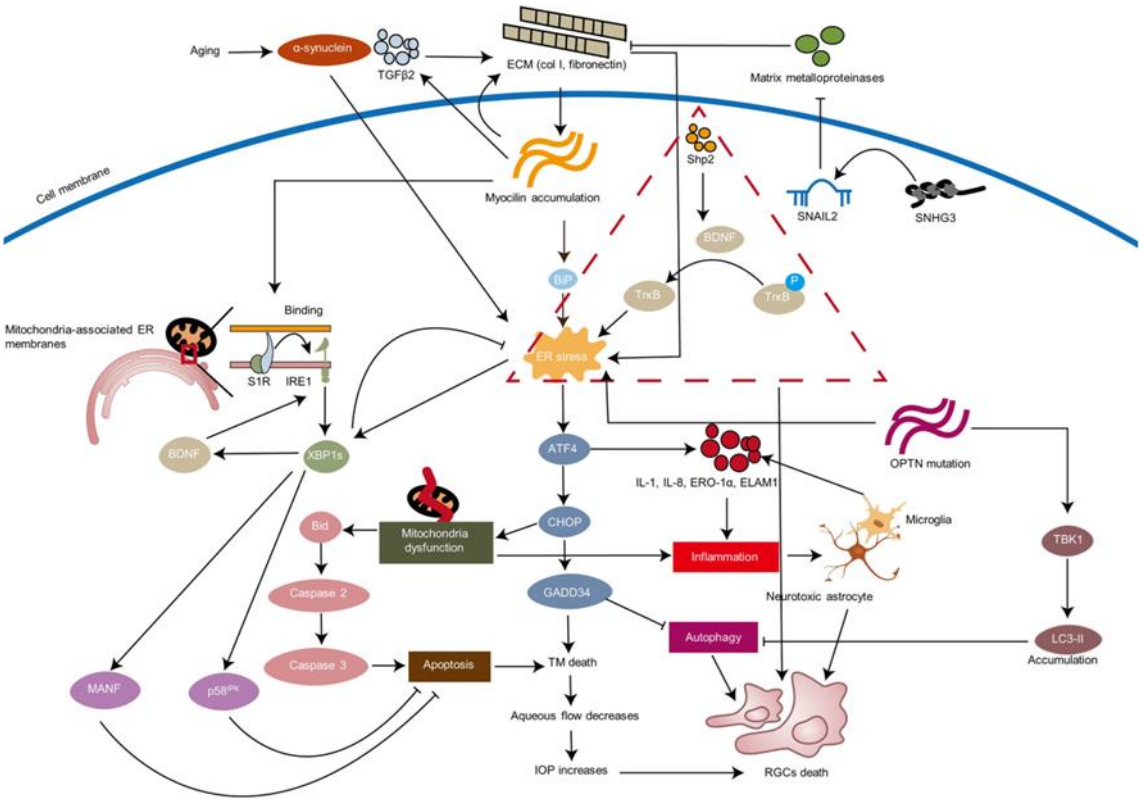

Figure 1: This figure illustrates the cellular mechanisms involved in endoplasmic reticulum (ER) stress and its link to mitochondrial dysfunction, inflammation, and cell death pathways. Aging and α-synuclein accumulation trigger TGFβ2, leading to extracellular matrix (ECM) remodeling, myocilin accumulation, and ER stress. The unfolded protein response (UPR) is activated, engaging key proteins such as BiP, XBP1s, and ATF4. ER stress induces mitochondrial dysfunction via the activation of caspases and the Bid pathway, leading to apoptosis. Inflammation is exacerbated by cytokines such as IL-1 and IL-8, with contributions from microglial activation. The accumulation of LC3-II and impaired autophagy further intensify neurotoxicity and retinal ganglion cell (RGC) death.

Source: Chen X, Shi C, He M, Xiong S, Xia X. Endoplasmic reticulum stress: molecular mechanism and therapeutic targets. Signal Transduct Target Ther. 2023 Sep 15;8(1):352. doi: 10.1038/s41392-023-01570-w.

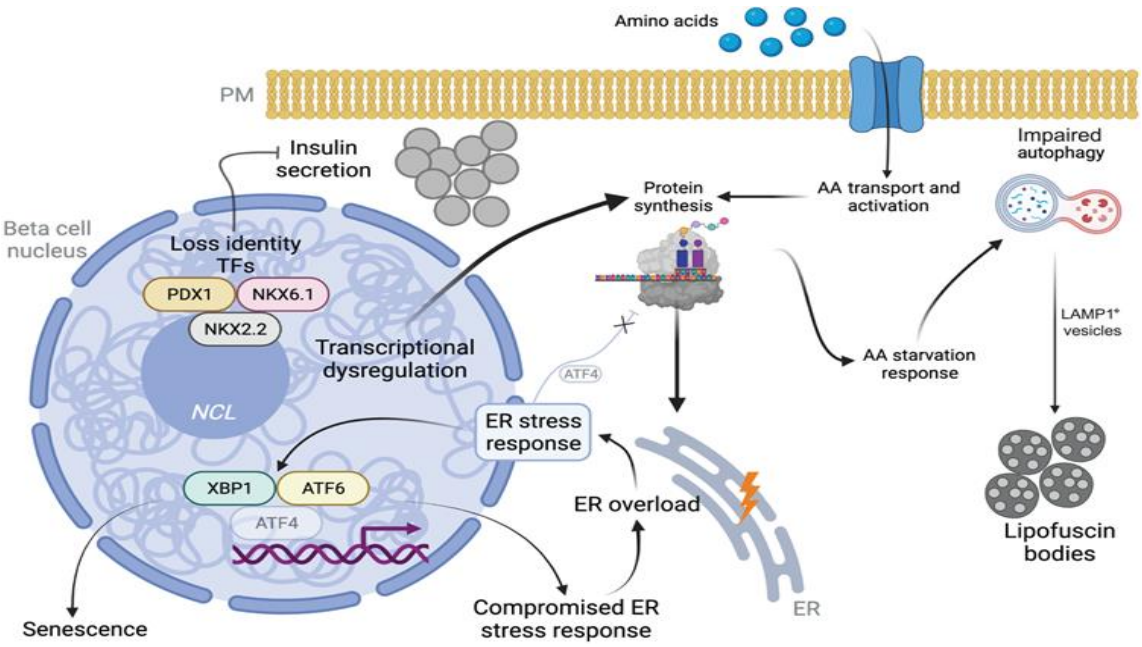

Figure 2: This figure illustrates the cellular and molecular pathways leading to ER stress in pancreatic beta cells, with a focus on transcriptional dysregulation and autophagy impairment. Key transcription factors (TFs) like PDX1, NKX6.1, and NKX2.2 lose function, contributing to beta cell identity loss and impaired insulin secretion. The accumulation of unfolded proteins in the ER triggers an ER stress response mediated by ATF6 and XBP1. This stress is exacerbated by impaired autophagy, leading to amino acid starvation, lipofuscin body formation, and the accumulation of LAMP1+ vesicles. Persistent ER overload compromises the ER stress response, contributing to beta cell senescence and dysfunction in protein synthesis, exacerbating metabolic dysregulation in diabetes.

Source: Shrestha S, Erikson G, Lyon J, Spigelman AF, Bautista A, Manning Fox JE et al. Aging compromises human islet beta cell function and identity by decreasing transcription factor activity and inducing ER stress. Sci Adv. 2022 Oct 7;8(40):eabo3932. doi: 10.1126/sciadv. abo3932.

Methods

This comprehensive review was conducted to explore the impact of endoplasmic reticulum (ER) stress in induced pluripotent stem cell (iPSC)-derived pancreatic beta cells and its implications for diabetes mellitus therapies. A systematic search of relevant literature was performed across multiple databases, including PubMed, Scopus, Embase, Web of Science, SciELO, and Google Scholar, from the databases' inception to the present. The search strategy was designed using specific MeSH terms and keywords such as: "Endoplasmic Reticulum Stress," "Induced Pluripotent Stem Cells," "Pancreatic Beta Cells," "Unfolded Protein Response," and "Diabetes Mellitus." Boolean operators (AND, OR) were applied to refine the search results and optimize the identification of studies that explored cellular stress mechanisms, therapeutic implications, and strategies for mitigating ER stress in iPSC-derived beta cells. The review included a range of study designs, including randomized controlled trials, cohort studies, case-control studies, cross-sectional analyses, case series, systematic reviews, meta-analyses, and preclinical studies that evaluated ER stress and the unfolded protein response (UPR) in iPSC-derived pancreatic beta cells. These studies focused on identifying mechanisms by which ER stress affects beta cell function and insulin secretion, as well as therapeutic approaches to alleviate this stress in the context of diabetes treatment. The inclusion criteria were based on relevance to the study's objectives, emphasizing mechanisms of ER stress, its role in beta cell dysfunction, and therapeutic strategies for enhancing the resilience of iPSC-derived beta cells. Two independent reviewers screened titles and abstracts to ensure the study selection was unbiased and comprehensive. Any discrepancies between the reviewers were resolved through discussion or, if needed, by consultation with a third reviewer. The reviewers were blinded to the study details during selection to minimize potential biases. Data extraction followed a standardized process, collecting essential information such as study design, population characteristics, interventions, and outcomes relevant to ER stress and its effects on iPSC-derived pancreatic beta cells. A thematic analysis was employed to synthesize the findings, organizing results into central themes such as the molecular pathways involved in ER stress, the activation of the UPR, the role of autophagy, and the effects of ER stress on beta cell viability and insulin secretion. The analysis also focused on therapeutic interventions to reduce ER stress in diabetes, exploring potential pharmacological and genetic strategies for improving beta cell function. This review aims to provide a comprehensive overview of the current understanding of ER stress in iPSC-derived pancreatic beta cells. It will focus on identifying knowledge gaps and suggesting future research directions to improve diabetes therapies.

Results and Discussion

Stem cell-based therapies have revolutionized the potential for treating diabetes mellitus, mainly through induced pluripotent stem cells (iPSCs) that generate patient-specific insulin-producing beta cells. This approach can address type 1 and type 2 diabetes by replacing or regenerating lost or dysfunctional beta cells. However, despite this promise, several significant barriers remain [25-27].

Among these, endoplasmic reticulum (ER) stress is one of the most critical challenges that must be addressed to improve the survival, functionality, and overall therapeutic efficacy of iPSC-derived beta cells. This comprehensive discussion delves deeper into the current understanding of ER stress in these cells, explores the gaps that remain in research, and highlights emerging strategies to overcome this challenge for clinical applications [26-28].

Beta cells are specialized for the high-volume production and secretion of insulin, a protein that must be properly folded and processed in the ER to function correctly. Under normal physiological conditions, the ER ensures the correct folding, trafficking, and secretion of insulin and other proteins. However, under metabolic stress such as chronic hyperglycemia and inflammation associated with diabetes, the ER becomes overwhelmed by the demand for insulin production, accumulating misfolded proteins [27-29].

This triggers ER stress and activates the unfolded protein response (UPR), a signaling network to restore ER homeostasis. While the UPR can be beneficial in the short term by enhancing protein folding capacity and reducing protein synthesis, prolonged activation leads to cell death through apoptosis. This dynamic is particularly problematic for beta cells derived from iPSCs, which are often more immature and less capable of handling such stress than their endogenous counterparts [28-30].

One of the critical reasons for the focus on ER stress in iPSC-derived beta cells is the vulnerability of these cells to the metabolic conditions they face post-transplantation. Even though iPSC-derived beta cells can be programmed to produce insulin, they often lack full maturation, making them highly sensitive to the environmental stressors of the diabetic milieu, such as elevated glucose levels and oxidative stress [29-31].

Studies have shown that beta cells derived from iPSCs are prone to ER stress and apoptosis under these conditions, limiting their potential as a long-term treatment option. This vulnerability underscores the need to develop strategies that can modulate ER stress responses and enhance the resilience of these cells in the harsh metabolic environment of diabetic patients [30-32].

Researchers have explored several therapeutic strategies to address ER stress in iPSC-derived beta cells, including modulating the UPR. The UPR is a complex signaling network comprising three primary pathways: IRE1, PERK, and ATF6. These pathways reduce the burden of misfolded proteins by enhancing the ER's capacity for protein folding, slowing overall protein synthesis, and promoting the degradation of misfolded proteins [31-33].

However, if ER stress is not resolved, these pathways initiate apoptotic signaling, mainly through upregulating pro-apoptotic factors like CHOP. Therefore, therapeutic strategies that fine-tune the UPR-activating its protective aspects without triggering cell death are critical for improving the viability of iPSC-derived beta cells. Researchers are exploring both pharmacological and genetic approaches to achieve this delicate balance [32-34].

Molecular chaperones play a central role in maintaining ER function by assisting in the proper folding of proteins. Chaperones such as BiP/GRP78 are integral to the UPR's ability to prevent the accumulation of misfolded proteins within the ER. Enhancing the expression or activity of these chaperones has been shown to mitigate ER stress and improve beta cell survival [33-35].

In iPSC-derived beta cells, this approach promises to boost their resilience to the high insulin production demands placed on them after transplantation. Small molecules or gene-editing technologies could be employed to upregulate chaperones, providing a buffer against ER stress and enabling beta cells to function more effectively in the diabetic environment [18]. Additionally, increasing chaperone activity may facilitate the maturation process of iPSC-derived beta cells, making them more functionally similar to adult beta cells [36].

Pharmacological interventions have also been a research focus to alleviate ER stress in beta cells. Chemical chaperones, such as tauroursodeoxycholic acid (TUDCA) and 4-phenylbutyrate (4-PBA), have been shown to stabilize protein folding and reduce ER stress in various cellular models [37-39].

These compounds hold significant potential in the context of stem cell-derived beta cell therapies, as they could protect beta cells from the metabolic and oxidative stress encountered post-transplantation [40]. These pharmacological agents in the early stages after beta cell transplantation could be precious, as this is when the cells are most vulnerable to environmental stressors. Moreover, combining chemical chaperones with other therapeutic agents, such

as antioxidants or anti-inflammatory drugs, may offer a multifaceted approach to protecting iPSC-derived beta cells and enhancing their long-term viability [41,42].

The culture environment in which iPSC-derived beta cells are developed is another critical factor in their ability to handle ER stress. While useful for basic research, traditional two-dimensional (2D) culture systems do not accurately replicate the pancreatic islet's complex three-dimensional (3D) architecture or the mechanical and biochemical cues that beta cells experience in vivo [43-45].

Beta cells grown in 2D culture environments are often immature and more susceptible to ER stress because they lack the supportive signals needed for proper development and function. Recent advances in bioengineering, including creating 3D culture systems and biomimetic scaffolds, have provided new opportunities to enhance the maturation and function of iPSC-derived beta cells [36]. By mimicking the 3D microarchitecture of the pancreatic niche, these systems can reduce ER stress and promote better beta cell maturation. 3D culture systems may enhance cell-to-cell interactions and signaling, which is essential for maintaining proper beta cell function and insulin secretion [46,47].

The role of oxidative stress in exacerbating ER stress has been another area of active investigation. In beta cells, the accumulation of misfolded proteins in the ER can lead to the generation of reactive oxygen species (ROS), which causes further cellular damage. This creates a cycle in which oxidative stress and ER stress feed into each other, ultimately leading to beta cell dysfunction and death [48].

Addressing both oxidative and ER stress through combined therapeutic strategies may offer a more comprehensive solution for preserving the function of iPSC-derived beta cells. Antioxidant therapies, combined with interventions aimed at modulating the UPR and enhancing the chaperone function, could help protect beta cells from the dual insults of oxidative damage and protein misfolding [49,50].

Genome-editing technologies, particularly CRISPR/Cas9, offer another promising avenue for reducing ER stress in iPSC-derived beta cells. By selectively targeting genes involved in the UPR and ER homeostasis, it may be possible to create beta cell lines more resistant to ER stress-induced apoptosis [14].

This could include knocking out pro-apoptotic genes like CHOP or upregulating genes that enhance protein folding and degradation. Genome editing can potentially improve the function of iPSC-derived beta cells and strengthen their resilience to the metabolic challenges associated with diabetes [44]. This approach represents a significant advancement in developing durable, long-term solutions for diabetes treatment, as it allows for the precise manipulation of cellular stress pathways [51,52].

Another critical challenge that must be addressed is the functional immaturity of iPSC-derived beta cells. Despite improvements in differentiation protocols, these cells often lack the full glucose responsiveness and insulin-secreting capacity of mature beta cells. Immature beta cells are more prone to ER stress and are less capable of managing the demands of insulin production in vivo [53,54].

Optimizing differentiation protocols to produce more mature and stress-resistant beta cells is essential for enhancing their therapeutic potential. This could involve fine-tuning growth factors, signaling molecules, and culture conditions to promote beta cell maturation and ensure that the cells are better equipped to handle the metabolic pressures of diabetes [9,55].

The long-term success of iPSC-derived beta cell therapies also depends on the ability of these cells to maintain their function in the host environment over time. Transplanted beta cells must survive and continue to secrete insulin in response to fluctuations in blood glucose levels [18,22].

Enhancing the ER resilience of these cells will be a crucial component of ensuring their long-term viability. However, ER stress is not the only challenge transplanted beta cells face. Immune rejection, inflammatory damage, and metabolic overload are also significant threats to the survival and function of beta cells in the diabetic milieu [33,56].

Future therapeutic strategies must integrate multiple approaches, including immune modulation, metabolic support, and ER stress reduction, to create a supportive environment for beta cell survival. Encapsulation technologies, for example, may provide a physical barrier that protects beta cells from immune attack while allowing for the exchange of nutrients and insulin [57,58].

The future of iPSC-derived beta cell therapies lies in integrating these various strategies. Pharmacological agents, genetic modifications, bioengineering techniques, and advanced culture systems must be combined to create a comprehensive approach to overcoming ER stress and improving beta cell viability [25,52].

Importantly, future research must continue to investigate the molecular mechanisms that underlie ER stress in beta cells, as these pathways may reveal new therapeutic targets. By addressing ER stress's root causes and enhancing iPSC-derived beta cells' resilience, researchers can bring stem cell-based therapies closer to clinical reality [39,45].

ER stress is one of the most pressing challenges in developing iPSC-derived beta cell therapies for diabetes. While significant progress has been made in understanding the molecular pathways involved in ER stress and identifying potential therapeutic interventions, many gaps remain [13,26].

The ability to modulate the UPR, enhance molecular chaperone activity, and optimize the culture and transplantation environment will be vital to improving the viability and function of iPSC-derived beta cells [30]. As research in this field continues to evolve, there is great potential for stem cell-based therapies to revolutionize diabetes treatment, offering hope for millions of individuals worldwide. By integrating pharmacological, genetic, and bioengineering approaches, researchers can overcome the challenges posed by ER stress and unlock the full potential of iPSC-derived beta cell therapies [59,60].

Impact of the Inflammatory Microenvironment on ER Stress

A critical aspect often underexplored in the discussion of ER stress is the inflammatory microenvironment that exists in individuals with diabetes, especially in T1D. Chronic inflammation, characterized by elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IFN-γ, can exacerbate ER stress in beta cells [38,61].

These cytokines directly disrupt ER homeostasis, accumulating misfolded proteins, worsening ER stress, and accelerating apoptosis. Understanding the impact of inflammation on iPSC-derived beta cells is crucial, as the diabetic environment is inherently inflammatory. Anti-inflammatory interventions, combined with strategies to mitigate ER stress, could significantly improve the success of beta cell transplantation. Targeting pathways like NF-κB, activated by inflammatory cytokines and contributing to ER stress, offer a promising approach to protect transplanted cells from inflammatory damage [54,62].

Autophagy and Its Role in Regulating ER Stress

Autophagy, the process by which cells degrade damaged organelles and misfolded proteins, is closely linked to the regulation of ER stress. When the UPR is unable to resolve ER stress, autophagy can be activated to help clear misfolded proteins and restore cellular homeostasis. However, if autophagy is impaired, the accumulation of damaged proteins in the ER can exacerbate ER stress [63-65].

In the context of iPSC-derived beta cells, enhancing autophagic pathways may offer a therapeutic strategy to mitigate ER stress and protect cells from apoptosis. Studies suggest that stimulating autophagy in beta cells can reduce ER stress and improve cell survival, making autophagy modulation a promising adjunct to therapies targeting the UPR [66-68].

Engineering Cells for Enhanced Resistance to ER Stress

Another promising approach involves the genetic engineering of iPSC-derived beta cells to enhance their resistance to ER stress. Using technologies like CRISPR/Cas9, researchers can edit genes involved in the UPR and ER stress pathways to create more resilient cells under conditions of metabolic stress [69-72].

For instance, downregulating pro-apoptotic factors like CHOP or upregulating protective chaperones like BiP/GRP78 could significantly improve the survival of beta cells. Researchers are exploring the potential of expressing ER stress-resistant variants of insulin or other proteins that beta cells produce, which could reduce the burden on the ER and mitigate stress. Genetic engineering promises to create a new generation of beta cells that are more durable and capable of withstanding the challenges posed by the diabetic microenvironment [72-74].

Pharmacological Approaches to Alleviate ER Stress

Pharmacological interventions targeting ER stress have also shown significant potential. Chemical chaperones such as tauroursodeoxycholic acid (TUDCA) and 4-phenylbutyrate (4-PBA) have been extensively studied for their ability to improve protein folding and reduce ER stress [75].

These compounds stabilize protein folding and lessen the activation of UPR signaling pathways. Their application in iPSC-derived beta cells could enhance the resilience of these cells, particularly in the early stages post-transplantation when the cells are most vulnerable to stress [46].

In addition to chemical chaperones, researchers are investigating small molecule inhibitors of specific UPR pathways (such as IRE1α or PERK) that may selectively modulate the stress response without triggering apoptosis. Combining pharmacological agents with other strategies, such as antioxidant therapies, could provide a multi-pronged approach to protecting beta cells [57].

Differences in ER Stress Between Type 1 and Type 2 Diabetes

An important consideration that has not been fully explored is how the distinct pathophysiologies of T1D and T2D may impact ER stress and iPSC-derived beta cell therapies. In T1D, the autoimmune destruction of beta cells is the primary driver, whereas in T2D, insulin resistance and metabolic overload are the key contributors [76].

The diabetic microenvironment in T2D, characterized by chronic hyperglycemia and lipotoxicity, imposes different stressors on beta cells, which may exacerbate ER stress differently than T1D [12].

This distinction suggests that therapeutic strategies for reducing ER stress may need to be tailored to the specific type of diabetes. For instance, in T2D, targeting metabolic overload and lipotoxicity in combination with ER stress modulation may be more effective, whereas in T1D, immunomodulation combined with ER stress reduction may be critical for success [31,48].

Role of 3D Culture Systems and Bioengineering in Reducing ER Stress

The importance of the cellular microenvironment cannot be overstated. While useful for preliminary studies, traditional two-dimensional (2D) culture systems fail to mimic the complex architecture, and dynamic interactions present in the in vivo pancreatic islet [76].

Beta cells cultured in 2D systems are often immature and more susceptible to ER stress. Developing three-dimensional (3D) culture systems and biomimetic scaffolds has shown promise in reducing ER stress by providing a more physiological environment. 3D systems support more natural cell-cell interactions, extracellular matrix signaling, and mechanical cues, critical for proper beta cell function and maturation [27,50].

3D cultures systems have been shown to enhance insulin secretion and reduce the susceptibility of beta cells to stress. Incorporating 3D bioengineered platforms into the differentiation and maturation processes of iPSC-derived beta cells could significantly improve their functionality and reduce ER stress [14].

Oxidative Stress and Its Relationship with ER Stress

Oxidative stress and ER stress are often intertwined, creating a feedback loop that exacerbates beta cell dysfunction. In beta cells, oxidative stress occurs when reactive oxygen species (ROS) production overwhelms the cell's antioxidant defenses. The accumulation of misfolded proteins in the ER can trigger the production of ROS, which, in turn, exacerbates ER stress by damaging cellular structures [48,71].

Both ER and oxidative stress through combined therapeutic strategies may offer a more comprehensive solution for preserving the function of iPSC-derived beta cells. Antioxidant therapies, such as using N-acetylcysteine (NAC) or other ROS-scavenging molecules, could help mitigate oxidative damage and, when combined with interventions targeting the UPR, provide dual protection against cellular stress [33,72].

Challenges in Translating iPSC-derived Beta Cell Therapies to Clinical Practice

While significant advances have been made in addressing ER stress in iPSC-derived beta cells, several barriers to clinical translation remain. One of the most pressing challenges is ensuring the patient's long-term survival and functionality of transplanted beta cells [11,74].

The immune response is a significant obstacle, particularly in T1D, where the autoimmune destruction of beta cells is crucial. Strategies such as immune encapsulation are being explored, which involve encasing beta cells in a semi-permeable membrane that allows for the diffusion of nutrients and insulin but blocks immune cell infiltration [22,34].

Costs and scalability are significant considerations for the large-scale production of iPSC-derived beta cells. Ensuring that the cells can be produced consistently, efficiently, and at a viable scale for widespread clinical use remains a significant challenge [55].

Animal Models and Preclinical Studies

Animal models, particularly non-obese diabetic (NOD) mice, have been instrumental in advancing the understanding of beta cell transplantation and ER stress. These models allow researchers to investigate the immune response, ER stress, and other metabolic challenges in a controlled setting [43,51].

However, there are limitations to these models, and findings in mice do not always translate directly into human physiology. Continued refinement of preclinical models, including developing humanized mouse models and more accurate large animal models, will be critical for bridging the gap between laboratory research and clinical application [19,66].

Emerging Technologies and the Role of Artificial Intelligence

The incorporation of artificial intelligence (AI) and machine learning (ML) into the study of stem cell biology offers exciting new possibilities for optimizing beta cell differentiation protocols and predicting cell functionality [64,76].

AI could be used to analyze vast datasets generated from experiments to identify the optimal conditions for reducing ER stress and enhancing beta cell maturation. AI-driven models could predict how beta cells respond to environmental stressors, allowing researchers to fine-tune therapeutic interventions more precisely [56].

Conclusion

ER stress remains one of the most significant challenges in developing iPSC-derived beta cell therapies for diabetes. Addressing this issue requires a multifaceted approach, including modulating the UPR, enhancing molecular chaperone activity, employing pharmacological agents, optimizing the culture environment, and leveraging genetic engineering to create more stress-resistant cells.

The inflammatory microenvironment and oxidative stress and tailoring therapies to the specific challenges of T1D and T2D are essential for improving outcomes. While progress has been made, there are still gaps in understanding how to fully mitigate ER stress and its downstream effects in iPSC-derived beta cells.

By continuing to explore these areas and incorporating cutting-edge technologies like AI, researchers can bring stem cell-based therapies closer to clinical reality, offering hope to millions of individuals with diabetes worldwide. Integrating multiple strategies will be vital to unlocking the full potential of iPSC-derived beta cells, leading to a durable, long-term solution for diabetes management.

Declarations

For manuscripts that do not involve human or animal data, tissues, or participants, such as a scientific review article, it is appropriate to state "Not applicable" in the ethics approval and consent section. This is because review articles synthesize and analyze previously published information rather than collecting new data directly from humans or animals. Consequently, there is no requirement for ethics committee approval or obtaining informed consent, as the work does not involve direct interaction with participants or the handling of sensitive data or biological material from human or animal sources.

Authors' contributions

ACMR conceptualized the study, conducted the literature review, and drafted the initial manuscript. IAF critically reviewed and revised the manuscript, providing expertise on the implications of endoplasmic reticulum stress and beta cell functionality. ACMR and IAF jointly contributed to the analysis and interpretation of the recent advancements in iPSC-derived beta cell therapies for diabetes. Both authors read and approved the final manuscript, ensuring accuracy and coherence with the study's objectives.

Funding Statement

This study was fully funded by the authors, with no external financial support or grants involved.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgments

The authors thank the Federal University of Rio Grande do Norte, Potiguar University, and Liga Contra o Cancer for supporting this study.

References

[1] Memon B, Abdelalim EM. Toward Precision Medicine with Human Pluripotent Stem Cells for Diabetes. Stem Cells Transl Med. 2022 Jul 20;11(7):704-714. doi: 10.1093/stcltm/szac030.

[2] Abdelalim EM. Modeling different types of diabetes using human pluripotent stem cells. Cell Mol Life Sci. 2021 Mar;78(6):2459-2483. doi: 10.1007/s00018-020-03710-9.

[3] Leavens KF, Alvarez-Dominguez JR, Vo LT, Russ HA, Parent AV. Stem cell-based multi-tissue platforms to model human autoimmune diabetes. Mol Metab. 2022 Dec; 66:101610. doi: 10.1016/j.molmet.2022.101610.

[4] Youngblood RL, Sampson JP, Lebioda KR, Shea LD. Microporous scaffolds support assembly and differentiation of pancreatic progenitors into β-cell clusters. Acta Biomater. 2019 Sep 15; 96:111-122. doi: 10.1016/j.actbio.2019.06.032.

[5] Burgos JI, Vallier L, Rodríguez-Seguí SA. Monogenic Diabetes Modeling: In Vitro Pancreatic Differentiation From Human Pluripotent Stem Cells Gains Momentum. Front Endocrinol (Lausanne). 2021 Jul 6; 12:692596. doi: 10.3389/fendo.2021.692596.

[6] Memon B, Younis I, Abubaker F, Abdelalim EM. PDX1-/NKX6.1+ progenitors derived from human pluripotent stem cells as a novel source of insulin-secreting cells. Diabetes Metab Res Rev. 2021 Jul;37(5). doi: 10.1002/dmrr.3400.

[7] Fonoudi H, Ansari H, Abbasalizadeh S, Larijani MR, Kiani S, Hashemizadeh S, Zarchi AS, Bosman A, Blue GM, Pahlavan S, Perry M, Orr Y, Mayorchak Y, Vandenberg J, Talkhabi M, Winlaw DS, Harvey RP, Aghdami N, Baharvand H. A Universal and Robust Integrated Platform for the Scalable Production of Human Cardiomyocytes From Pluripotent Stem Cells. Stem Cells Transl Med. 2015 Dec;4(12):1482-94. doi: 10.5966/sctm.2014-0275.

[8] Memon B, Abdelalim EM. Differentiation of Human Pluripotent Stem Cells into Pancreatic Beta-cell Precursors in a 2D Culture System. J Vis Exp. 2021 Dec 16;(178). doi: 10.3791/63298.

[9] Braverman-Gross C, Benvenisty N. Modeling Maturity Onset Diabetes of the Young in Pluripotent Stem Cells: Challenges and Achievements. Front Endocrinol (Lausanne). 2021 Feb 22; 12:622940. doi: 10.3389/fendo.2021.622940.

[10] Diane A, Al-Shukri NA, Bin Abdul Mu-U-Min R, Al-Siddiqi HH. β-cell mitochondria in diabetes mellitus: a missing puzzle piece in the generation of hPSC-derived pancreatic β-cells? J Transl Med. 2022 Apr 9;20(1):163. doi: 10.1186/s12967-022-03327-5.

[11] Zhou Z, Ma X, Zhu S. Recent advances and potential applications of human pluripotent stem cell-derived pancreatic β cells. Acta Biochim Biophys Sin (Shanghai). 2020 Jul 10;52(7):708-715. doi: 10.1093/abbs/gmaa047.

[12] Balboa D, Otonkoski T. Human pluripotent stem cell-based islet models for diabetes research. Best Pract Res Clin Endocrinol Metab. 2015 Dec;29(6):899-909. doi: 10.1016/j.beem.2015.10.012.

[13] Loo LSW, Lau HH, Jasmen JB, Lim CS, Teo AKK. An arduous journey from human pluripotent stem cells to functional pancreatic β cells. Diabetes Obes Metab. 2018 Jan;20(1):3-13. doi: 10.1111/dom.12996.

[14] Lim LY, Ching C, Kong D, Chan SY, Teo AKK. Generating pancreatic beta-like cells from human pluripotent stem cells. Methods Cell Biol. 2022; 170:127-146. doi: 10.1016/bs.mcb.2022.02.011.

[15] Amirruddin NS, Low BSJ, Lee KO, Tai ES, Teo AKK. New insights into human beta cell biology using human pluripotent stem cells. Semin Cell Dev Biol. 2020 Jul; 103:31-40. doi: 10.1016/j.semcdb.2019.11.004.

[16] Yang S, Cho Y, Jang J. Single cell heterogeneity in human pluripotent stem cells. BMB Rep. 2021 Oct;54(10):505-515. doi: 10.5483/BMBRep.2021.54.10.094.

[17] Jiang Y, Chen C, Randolph LN, Ye S, Zhang X, Bao X, Lian XL. Generation of pancreatic progenitors from human pluripotent stem cells by small molecules. Stem Cell Reports. 2021 Sep 14;16(9):2395-2409. doi: 10.1016/j.stemcr.2021.07.021.

[18] Chen T, Wang F, Wu M, Wang ZZ. Development of hematopoietic stem and progenitor cells from human pluripotent stem cells. J Cell Biochem. 2015 Jul;116(7):1179-89. doi: 10.1002/jcb.25097.

[19] Liu H, Li R, Liao HK, Min Z, Wang C, Yu Y, Shi L, Dan J, Hayek A, Martinez Martinez L, Nuñez Delicado E,

Izpisua Belmonte JC. Chemical combinations potentiate human pluripotent stem cell-derived 3D pancreatic progenitor clusters toward functional β cells. Nat Commun. 2021 Jun 7;12(1):3330. doi: 10.1038/s41467-021-23525-x.

[20] Yanagihara K, Liu Y, Kanie K, Takayama K, Kokunugi M, Hirata M, Fukuda T, Suga M, Nikawa H, Mizuguchi H, Kato R, Furue MK. Prediction of Differentiation Tendency Toward Hepatocytes from Gene Expression in Undifferentiated Human Pluripotent Stem Cells. Stem Cells Dev. 2016 Dec 15;25(24):1884-1897. doi: 10.1089/scd.2016.0099.

[21] Bose B, Katikireddy KR, Shenoy PS. Regenerative medicine for diabetes: differentiation of human pluripotent stem cells into functional β-cells in vitro and their proposed journey to clinical translation. Vitam Horm. 2014;95:223-48. doi: 10.1016/B978-0-12-800174-5.00009-0.

[22] Loo LSW, Vethe H, Soetedjo AAP, Paulo JA, Jasmen J, Jackson N, Bjørlykke Y, Valdez IA, Vaudel M, Barsnes H, Gygi SP, Raeder H, Teo AKK, Kulkarni RN. Dynamic proteome profiling of human pluripotent stem cell-derived pancreatic progenitors. Stem Cells. 2020 Apr;38(4):542-555. doi: 10.1002/stem.3135.

[23] George MN, Leavens KF, Gadue P. Genome Editing Human Pluripotent Stem Cells to Model β-Cell Disease and Unmask Novel Genetic Modifiers. Front Endocrinol (Lausanne). 2021 Jun 2; 12:682625. doi: 10.3389/fendo.2021.682625.

[24] Tesařová L, Simara P, Stejskal S, Koutná I. Haematopoietic developmental potential of human pluripotent stem cell lines. Folia Biol (Praha). 2014;60 Suppl 1:90-4.

[25] Agrawal A, Narayan G, Gogoi R, Thummer RP. Recent Advances in the Generation of β-Cells from Induced Pluripotent Stem Cells as a Potential Cure for Diabetes Mellitus. Adv Exp Med Biol. 2021;1347:1-27. doi: 10.1007/5584_2021_653.

[26] Tan LS, Chew RSE, Ng NHJ, Teo AKK. Protocol for the generation of pancreatic and hepatic progenitors from human pluripotent stem cells for gene regulatory assays. STAR Protoc. 2021 Apr 19;2(2):100471. doi: 10.1016/j.xpro.2021.100471.

[27] Simonson OE, Domogatskaya A, Volchkov P, Rodin S. The safety of human pluripotent stem cells in clinical treatment. Ann Med. 2015;47(5):370-80. doi: 10.3109/07853890.2015.1051579.

[28] Hamazaki T, El Rouby N, Fredette NC, Santostefano KE, Terada N. Concise Review: Induced Pluripotent Stem Cell Research in the Era of Precision Medicine. Stem Cells. 2017 Mar;35(3):545-550. doi: 10.1002/stem.2570.

[29] Wang X, Sterr M, Burtscher I, Chen S, Hieronimus A, Machicao F, Staiger H, Häring HU, Lederer G, Meitinger T, Cernilogar FM, Schotta G, Irmler M, Beckers J, Hrabě de Angelis M, Ray M, Wright CVE, Bakhti M, Lickert H. Genome-wide analysis of PDX1 target genes in human pancreatic progenitors. Mol Metab. 2018 Mar; 9:57-68. doi: 10.1016/j.molmet.2018.01.011.

[30] Memon B, Abdelalim EM. Highly Efficient Differentiation of Human Pluripotent Stem Cells into Pancreatic Progenitors Co-expressing PDX1 and NKX6.1. Methods Mol Biol. 2022; 2454:351-363. doi: 10.1007/7651_2020_323.

[31] Memon B, Abdelalim EM. Stem Cell Therapy for Diabetes: Beta Cells versus Pancreatic Progenitors. Cells. 2020 Jan 23;9(2):283. doi: 10.3390/cells9020283.

[32] Gaertner B, Carrano AC, Sander M. Human stem cell models: lessons for pancreatic development and disease. Genes Dev. 2019 Nov 1;33(21-22):1475-1490. doi: 10.1101/gad.331397.119.

[33] Tan LS, Chen JT, Lim LY, Teo AKK. Manufacturing clinical-grade human induced pluripotent stem cell-derived beta cells for diabetes treatment. Cell Prolif. 2022 Aug;55(8). doi: 10.1111/cpr.13232.

[34] Zhu Z, Li QV, Lee K, Rosen BP, González F, Soh CL, Huangfu D. Genome Editing of Lineage Determinants in Human Pluripotent Stem Cells Reveals Mechanisms of Pancreatic Development and Diabetes. Cell Stem Cell. 2016 Jun 2;18(6):755-768. doi: 10.1016/j.stem.2016.03.015.

[35] Chmielowiec J, Borowiak M. In vitro differentiation and expansion of human pluripotent stem cell-derived pancreatic progenitors. Rev Diabet Stud. 2014 Spring;11(1):19-34. doi: 10.1900/RDS.2014.11.19.

[36] Patterson M, Chan DN, Ha I, Case D, Cui Y, Van Handel B, Mikkola HK, Lowry WE. Defining the nature of human pluripotent stem cell progeny. Cell Res. 2012 Jan;22(1):178-93. doi: 10.1038/cr.2011.133.

[37] Ghazizadeh Z, Kao DI, Amin S, Cook B, Rao S, Zhou T, Zhang T, Xiang Z, Kenyon R, Kaymakcalan O, Liu C, Evans T, Chen S. ROCKII inhibition promotes the maturation of human pancreatic beta-like cells. Nat Commun. 2017 Aug 21;8(1):298. doi: 10.1038/s41467-017-00129-y.

[38] Steyer B, Cory E, Saha K. Developing precision medicine using scarless genome editing of human pluripotent stem cells. Drug Discov Today Technol. 2018 Aug; 28:3-12. doi: 10.1016/j.ddtec.2018.02.001.

[39] Nostro MC, Keller G. Generation of beta cells from human pluripotent stem cells: Potential for regenerative medicine. Semin Cell Dev Biol. 2012 Aug;23(6):701-10. doi: 10.1016/j.semcdb.2012.06.010.

[40] Millman JR, Pagliuca FW. Autologous Pluripotent Stem Cell-Derived β-Like Cells for Diabetes Cellular Therapy. Diabetes. 2017 May;66(5):1111-1120. doi: 10.2337/db16-1406.

[41] Memon B, Karam M, Al-Khawaga S, Abdelalim EM. Enhanced differentiation of human pluripotent stem cells into pancreatic progenitors co-expressing PDX1 and NKX6.1. Stem Cell Res Ther. 2018 Jan 23;9(1):15. doi: 10.1186/s13287-017-0759-z.

[42] Balboa D, Saarimäki-Vire J, Otonkoski T. Concise Review: Human Pluripotent Stem Cells for the Modeling of Pancreatic β-Cell Pathology. Stem Cells. 2019 Jan;37(1):33-41. doi: 10.1002/stem.2913.

[43] Balboa D, Iworima DG, Kieffer TJ. Human Pluripotent Stem Cells to Model Islet Defects in Diabetes. Front Endocrinol (Lausanne). 2021 Mar 22; 12:642152. doi: 10.3389/fendo.2021.642152.

[44] Cnop M, Toivonen S, Igoillo-Esteve M, Salpea P. Endoplasmic reticulum stress and eIF2α phosphorylation: The Achilles heel of pancreatic β cells. Mol Metab. 2017 Jul 12;6(9):1024-1039. doi: 10.1016/j.molmet.2017.06.001.

[45] Cierpka-Kmiec K, Wronska A, Kmiec Z. In vitro generation of pancreatic β-cells for diabetes treatment. I. β-like cells derived from human pluripotent stem cells. Folia Histochem Cytobiol. 2019;57(1):1-14. doi: 10.5603/FHC.a2019.0001.

[46] Bartolomé A. Stem Cell-Derived β Cells: A Versatile Research Platform to Interrogate the Genetic Basis of β Cell Dysfunction. Int J Mol Sci. 2022 Jan 2;23(1):501. doi: 10.3390/ijms23010501.

[47] Abdelalim EM, Bonnefond A, Bennaceur-Griscelli A, Froguel P. Pluripotent stem cells as a potential tool for disease modelling and cell therapy in diabetes. Stem Cell Rev Rep. 2014 Jun;10(3):327-37. doi: 10.1007/s12015-014-9503-6.

[48] Pagliuca FW, Millman JR, Gürtler M, Segel M, Van Dervort A, Ryu JH, Peterson QP, Greiner D, Melton DA. Generation of functional human pancreatic β cells in vitro. Cell. 2014 Oct 9;159(2):428-39. doi: 10.1016/j.cell.2014.09.040.

[49] Tabar V, Studer L. Pluripotent stem cells in regenerative medicine: challenges and recent progress. Nat Rev Genet. 2014 Feb;15(2):82-92. doi: 10.1038/nrg3563.

[50] Rostovskaya M, Bredenkamp N, Smith A. Towards consistent generation of pancreatic lineage progenitors from human pluripotent stem cells. Philos Trans R Soc Lond B Biol Sci. 2015 Oct 19;370(1680):20140365. doi: 10.1098/rstb.2014.0365.

[51] Maxwell KG, Millman JR. Applications of iPSC-derived beta cells from patients with diabetes. Cell Rep Med. 2021 Apr 20;2(4):100238. doi: 10.1016/j.xcrm.2021.100238.

[52] Carrasco M, Wang C, Søviknes AM, Bjørlykke Y, Abadpour S, Paulo JA, Tjora E, Njølstad P, Ghabayen J, Nermoen I, Lyssenko V, Chera S, Ghila LM, Vaudel M, Scholz H, Ræder H. Spatial Environment Affects HNF4A Mutation-Specific Proteome Signatures and Cellular Morphology in hiPSC-Derived β-Like Cells. Diabetes. 2022 Apr 1;71(4):862-869. doi: 10.2337/db20-1279.

[53] Sackett SD, Rodriguez A, Odorico JS. The Nexus of Stem Cell-Derived Beta-Cells and Genome Engineering. Rev Diabet Stud. 2017 Spring;14(1):39-50. doi: 10.1900/RDS.2017.14.39.

[54] Schroeder IS. Potential of pluripotent stem cells for diabetes therapy. Curr Diab Rep. 2012 Oct;12(5):490-8. doi: 10.1007/s11892-012-0292-5.

[55] Soria B, Gauthier BR, Martín F, Tejedo JR, Bedoya FJ, Rojas A, Hmadcha A. Using stem cells to produce insulin. Expert Opin Biol Ther. 2015;15(10):1469-89. doi: 10.1517/14712598.2015.1066330.

[56] Jacobson EF, Tzanakakis ES. Who Will Win: Induced Pluripotent Stem Cells Versus Embryonic Stem Cells for β Cell Replacement and Diabetes Disease Modeling? Curr Diab Rep. 2018 Oct 20;18(12):133. doi: 10.1007/s11892-018-1109-y.

[57] Choudhury S, Surendran N, Das A. Recent advances in the induced pluripotent stem cell-based skin regeneration. Wound Repair Regen. 2021 Sep;29(5):697-710. doi: 10.1111/wrr.12925.

[58] Santana A, Enseñat-Waser R, Arribas MI, Reig JA, Roche E. Insulin-producing cells derived from stem cells: recent progress and future directions. J Cell Mol Med. 2006 Oct-Dec;10(4):866-83. doi: 10.1111/j.1582-4934.2006.tb00531.x.

[59] Zhang P, Munier JJ, Wiese CB, Vergnes L, Link JC, Abbasi F, Ronquillo E, Scheker K, Muñoz A, Kuang YL, Theusch E, Lu M, Sanchez G, Oni-Orisan A, Iribarren C, McPhaul MJ, Nomura DK, Knowles JW, Krauss RM, Medina MW, Reue K. X chromosome dosage drives statin-induced dysglycemia and mitochondrial dysfunction. Nat Commun. 2024 Jul 2;15(1):5571. doi: 10.1038/s41467-024-49764-2.

[60] Pan G, Mu Y, Hou L, Liu J. Examining the therapeutic potential of various stem cell sources for differentiation into insulin-producing cells to treat diabetes. Ann Endocrinol (Paris). 2019 Feb;80(1):47-53. doi: 10.1016/j.ando.2018.06.1084.

[61] Domínguez-Bendala J, Lanzoni G, Klein D, Álvarez-Cubela S, Pastori RL. The Human Endocrine Pancreas: New Insights on Replacement and Regeneration. Trends Endocrinol Metab. 2016 Mar;27(3):153-162. doi: 10.1016/j.tem.2015.12.003.

[62] Southard SM, Kotipatruni RP, Rust WL. Generation and selection of pluripotent stem cells for robust differentiation to insulin-secreting cells capable of reversing diabetes in rodents. PLoS One. 2018 Sep 5;13(9). doi: 10.1371/journal.pone.0203126.

[63] Bejoy J, Farry JM, Peek JL, Cabatu MC, Williams FM, Welch RC, Qian ES, Woodard LE. Podocytes derived from human induced pluripotent stem cells: characterization, comparison, and modeling of diabetic kidney disease. Stem Cell Res Ther. 2022 Jul 26;13(1):355. doi: 10.1186/s13287-022-03040-6.

[64] Houbracken I, Bouwens L. The quest for tissue stem cells in the pancreas and other organs, and their application in beta-cell replacement. Rev Diabet Stud. 2010 Summer;7(2):112-23. doi: 10.1900/RDS.2010.7.112.

[65] Chen F, Li T, Sun Y, Liu Q, Yang T, Chen J, Zhu H, Shi Y, Hu YP, Wang MJ. Generation of insulin-secreting cells from mouse gallbladder stem cells by small molecules in vitro. Stem Cell Res Ther. 2019 Sep 23;10(1):289. doi: 10.1186/s13287-019-1407-6.

[66] Yang D, Patel S, Szlachcic WJ, Chmielowiec J, Scaduto D, Putluri N, Sreekumar A, Suliburk J, Metzker M, Balasubramanyam A, Borowiak M. Pancreatic Differentiation of Stem Cells Reveals Pathogenesis of a Syndrome of Ketosis-Prone Diabetes. Diabetes. 2021 Oct;70(10):2419-2429. doi: 10.2337/db20-1293.

[67] Rajaei B, Massumi M, Wheeler M. Glucose-Responsiveness of Pancreatic β-Like (GRP β-L) Cells Generated from Human Pluripotent Stem Cells. Curr Protoc Hum Genet. 2019 Jan;100(1). doi: 10.1002/cphg.71.

[68] Jeon K, Lim H, Kim JH, Thuan NV, Park SH, Lim YM, Choi HY, Lee ER, Kim JH, Lee MS, Cho SG. Differentiation and transplantation of functional pancreatic beta cells generated from induced pluripotent stem cells derived from a type 1 diabetes mouse model. Stem Cells Dev. 2012 Sep 20;21(14):2642-55. doi: 10.1089/scd.2011.0665.

[69] Lu S, Kanekura K, Hara T, Mahadevan J, Spears LD, Oslowski CM, Martinez R, Yamazaki-Inoue M, Toyoda M, Neilson A, Blanner P, Brown CM, Semenkovich CF, Marshall BA, Hershey T, Umezawa A, Greer PA, Urano F. A calcium-dependent protease as a potential therapeutic target for Wolfram syndrome. Proc Natl Acad Sci U S A. 2014 Dec 9;111(49). doi: 10.1073/pnas.1421055111.

[70] Mercier I, Jasmin JF, Pavlides S, Minetti C, Flomenberg N, Pestell RG, Frank PG, Sotgia F, Lisanti MP. Clinical and translational implications of the caveolin gene family: lessons from mouse models and human genetic disorders. Lab Invest. 2009 Jun;89(6):614-23. doi: 10.1038/labinvest.2009.23.

[71] Chan XY, Black R, Dickerman K, Federico J, Lévesque M, Mumm J, Gerecht S. Three-Dimensional Vascular Network Assembly From Diabetic Patient-Derived Induced Pluripotent Stem Cells. Arterioscler Thromb Vasc Biol. 2015 Dec;35(12):2677-85. doi: 10.1161/ATVBAHA.115.306362.

[72] Ma S, Viola R, Sui L, Cherubini V, Barbetti F, Egli D. β Cell Replacement after Gene Editing of a Neonatal Diabetes-Causing Mutation at the Insulin Locus. Stem Cell Reports. 2018 Dec 11;11(6):1407-1415. doi: 10.1016/j.stemcr.2018.11.006.

[73] El Khatib MM, Ohmine S, Jacobus EJ, Tonne JM, Morsy SG, Holditch SJ, Schreiber CA, Uetsuka K, Fusaki N, Wigle DA, Terzic A, Kudva YC, Ikeda Y. Tumor-Free Transplantation of Patient-Derived Induced Pluripotent Stem Cell Progeny for Customized Islet Regeneration. Stem Cells Transl Med. 2016 May;5(5):694-702. doi: 10.5966/sctm.2015-0017.

[74] Rajaei B, Shamsara M, Amirabad LM, Massumi M, Sanati MH. Pancreatic Endoderm-Derived From Diabetic Patient-Specific Induced Pluripotent Stem Cell Generates Glucose-Responsive Insulin-Secreting Cells. J Cell Physiol. 2017 Oct;232(10):2616-2625. doi: 10.1002/jcp.25459.

[75] Kishida T, Ejima A, Yamamoto K, Tanaka S, Yamamoto T, Mazda O. Reprogrammed Functional Brown Adipocytes Ameliorate Insulin Resistance and Dyslipidemia in Diet-Induced Obesity and Type 2 Diabetes. Stem Cell Reports. 2015 Oct 13;5(4):569-81. doi: 10.1016/j.stemcr.2015.08.007.

[76] Park TS, Zimmerlin L, Evans-Moses R, Thomas J, Huo JS, Kanherkar R, He A, Ruzgar N, Grebe R, Bhutto I, Barbato M, Koldobskiy MA, Lutty G, Zambidis ET. Vascular progenitors generated from tankyrase inhibitor-regulated naïve diabetic human iPSC potentiate efficient revascularization of ischemic retina. Nat Commun. 2020 Mar 5;11(1):1195. doi: 10.1038/s41467-020-14764-5.