International Journal of Science and Research Archive

eISSN: 2582-8185

Cross Ref DOI: 10.30574/ijsra

Journal homepage: https://ijsra.net/

(Review Article)

Regenerative medicine for diabetes: Unraveling the impact of stem cells

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International Journal of Science and Research Archive, 2024, 11(01), 1917–1932

Publication history: Received on 04 January 2024; revised on 13 February 2024; accepted on 14 February 2024

Article DOI: https://doi.org/10.30574/ijsra.2024.11.1.0263

Abstract

Diabetes poses a significant health challenge, particularly in developing nations, with an alarming annual increase in cases. Current medications mainly focus on managing hyperglycemia and preventing complications associated with diabetes. However, the article underscores the potential of stem cells in advancing diabetes treatment, particularly in the generation of insulin-producing β-cells. It highlights the damage to these cells within the islet of Langerhans in diabetic patients, whether through autoimmune reactions in type 1 diabetes or inherent changes affecting β-cell function in type 2 diabetes. The article suggests that cell replacement strategies, such as islet transplantation, could offer therapeutic options for diabetes. Stem cells, capable of differentiating into specialized cells, are presented as a promising avenue for creating insulin-producing β-cells, aiming to restore normal insulin levels and providing a more comprehensive and long-term solution compared to current medications. While the potential is promising, it's essential to note that stem cell therapies are still in the experimental stage, necessitating further research and clinical trials to establish their safety and efficacy for widespread use in diabetes treatment.

Keyword: Diabetes; insulin-producing; β-cells. stem cell; Cell replacement

1. Introduction

Diabetes, a severe metabolic disorder characterized by elevated blood glucose levels (hyperglycemia), is a global health concern with a rising prevalence. Approximately 425 million people currently suffer from diabetes, and projections estimate that 629 million people could be affected by 2045. Both Type 1 (T1D) and Type 2 (T2D) diabetes result from an insufficient supply of functional insulin-producing β cells, leading to micro and macrovascular complications that contribute to morbidity and mortality. Conventional treatments, such as insulin, oral hypoglycemic agents, and islet transplantation, have limitations related to dosage precision, timing challenges, and the need for rare donors, along with the complexities of immunosuppressant therapy. These standard approaches fail to replicate the natural insulin secretion of healthy β cells, rendering them non-curative. Stem cell therapy emerges as a promising alternative, as stem cells possess the capacity to replace damaged cells, including dysfunctional insulin-producing β cells in the pancreas. Biologically, stem cells can divide, differentiate into specialized cell types, and self-renew. Extracted, prepared, and administered into the body, these cells can potentially repair damaged tissues, offering a novel avenue for diabetes treatment. Stem cells activated with specific growth factors before injection could develop into normal insulin-secreting cells, providing a more effective and potentially cost-saving alternative to drug-based treatments. This paper explores the potential of therapeutic stem cell treatment as a viable approach for managing diabetes.

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Table 1 Types of diabetes and its description

Diabetes Types	Description
Type 1 diabetes mellitus (T1DM)	The destruction of β-cells typically results in absolute insulin deficiency.
Type 2 diabetes mellitus (T2DM)	Insulin resistance can manifest in varying degrees, often coupled with prolonged insulin deficiency over the long term.
Gestational diabetes mellitus (GDM)	Pregnant women who have never had diabetes mellitus but encounter elevated blood glucose levels during pregnancy are often diagnosed with gestational diabetes.
Maturity-onset diabetes of the young (MODY)	The described rare form of diabetes, distinct from both type 1 and type 2 diabetes. This condition is strongly hereditary, caused by a mutation in a single gene. If a parent carries this gene mutation, there is a 50% chance that any child will inherit it, leading to the development of monogenic diabetes.
Latent autoimmune diabetes of the adult (LADA)	The disorder characterized by a gradual progression of autoimmune β-cell failure, despite the presence of islet antibodies at the time of diabetes diagnosis, is commonly referred to as latent autoimmune diabetes in adults (LADA).
Diseases of the exocrine pancreas	This category encompasses various conditions such as pancreatitis, trauma, infection, neoplasia, cystic fibrosis, hemochromatosis, pancreatectomy, and other factors that can impact the normal functioning of the pancreas.
Endocrinopathies	This category comprises conditions like acromegaly, Cushing's syndrome, glucagonoma, hyperthyroidism, somatostatinoma, and other endocrine disorders that can influence glucose metabolism and contribute to diabetes.
Drug- or chemical-induced diabetes	This category encompasses certain medical interventions, including immunotherapy, exogenous steroids, antipsychotic medications, statins, and other treatments that may have associations with the onset or aggravation of diabetes.
Infections	Congenital rubella and other viral infections have been suggested as potential factors contributing to the development of certain conditions or complications.
Uncommon forms of immune-mediated diabetes	In rare instances, diabetes has been linked to the use of new checkpoint inhibitor therapies, a class of medications commonly employed in cancer immunotherapy.
Stiff-man syndrome	The described condition is an autoimmune disorder affecting the central nervous system, typically characterized by elevated levels of glutamic acid decarboxylase [GAD] autoantibodies.

1.1. Stem cells and Diabetes

Stem cells represent undifferentiated cells in the human body with the unique capacity to transform into any cell type and undergo self-renewal. These cells are present in both embryos and adult tissues. There are two primary categories of stem cells: pluripotent stem cells, which can differentiate into any cell type within the body, and multipotent stem cells, which have a more limited differentiation potential, specializing in specific cell types. Stem cells, often referred to as "mother cells," play a crucial role in facilitating tissue regeneration and overall bodily growth. They replace damaged or dysfunctional cells across various tissues in the body. Over the years, stem cells have beutilized independently or in combination with other therapeutic approaches to address a diverse range of medical conditions.

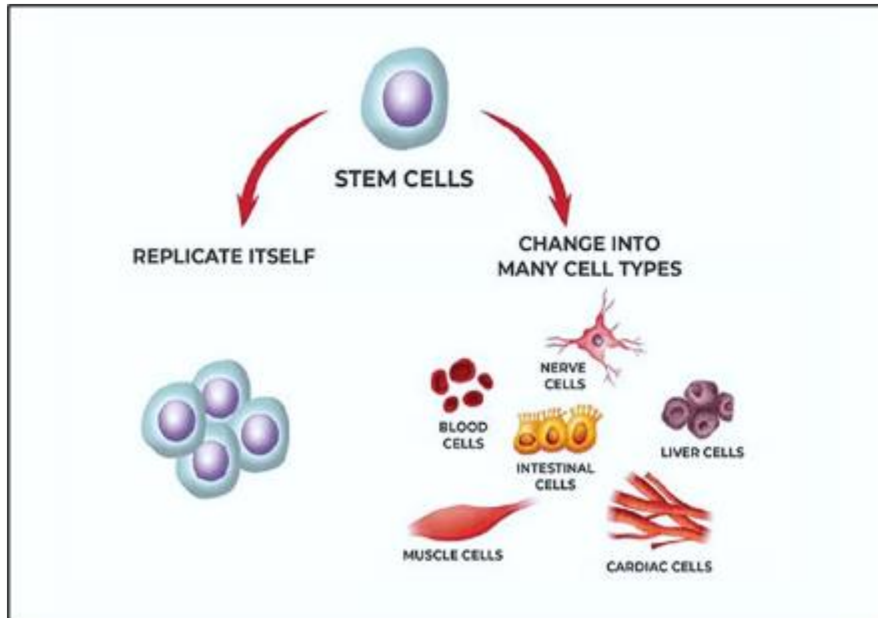

Figure 1 Stem Cells

Various stem cell models have been employed successfully for the in vitro differentiation of β-cells, including

- Embryonic stem cells,
- Induced pluripotent stem cells,
- Mesenchymal stem cells,
- Progenitor cells.

1.1.1. Embryonic stem cells

These stem cells are derived from embryos at a developmental stage of approximately four to five days during pregnancy, originating from the inner cell mass of the blastocyst. Alternatively, embryonic stem cells can be generated outside the body using in vitro fertilization (IVF). The blastocyst consists of two layers: the inner cell mass, also known as embryoblast, and the outer layer, referred to as trophoblast. Embryonic stem cells form within four to six days before implantation in the uterus. Subsequently, the outer cell mass contributes to the formation of the placenta, while the inner cell mass, a group of cells, undergoes differentiation to develop into all the structures of an adult organism.

The Embryonic Stem Cells Can Be Further Classified As:

- Totipotent Stem Cells: These cells have the remarkable ability to differentiate into all possible types of cells in the human body.
- Pluripotent Stem Cells: Derived from early embryos, these cells can differentiate into any cell type, offering a wide range of developmental possibilities.
- Multipotent Stem Cells: These cells can differentiate into closely related cell types. For example, hematopoietic stem cells can differentiate into both red and white blood cells.
- Oligopotent Stem Cells: Found in adult lymphoid or myeloid cells, oligopotent stem cells can differentiate into a limited number of distinct cell types.

Unipotent Stem Cells: These cells can produce only cells of their type. Despite being limited to a specific cell lineage, they possess the ability to renew themselves. An example is muscle stem cells.

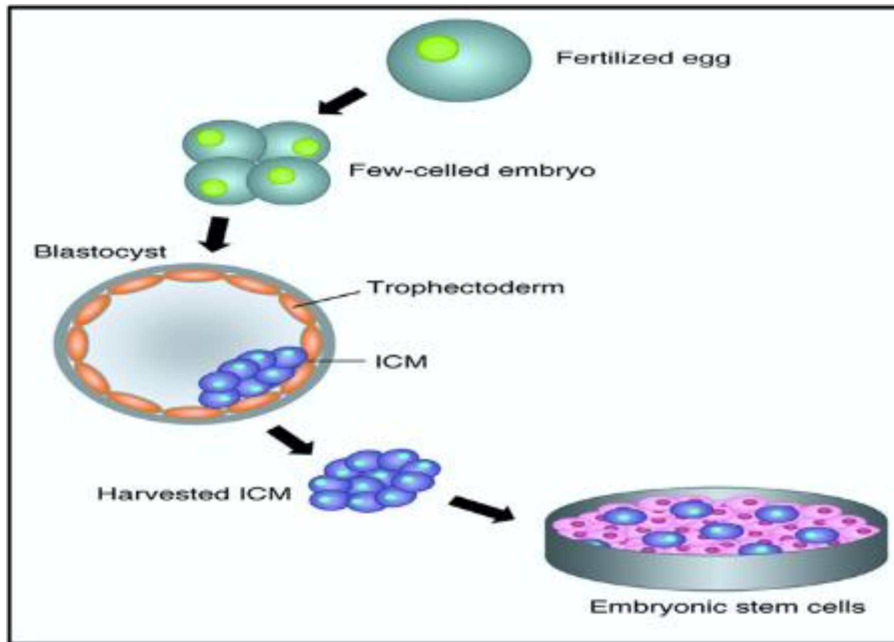

Figure 2 Embryonic Stem Cells (ICM: Inner Cell Mass)

1.1.2. Pancreatic Regeneration Through Embryonic Stem Cell

The optimal model for exploring pancreatic regeneration involves the use of embryonic stem cells (ESCs). Introducing pancreatic β cells, cultivated in vitro from pluripotent stem cells like embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs), has been suggested as an alternative therapeutic approach for diabetes. The fundamental protocol for the in vitro differentiation of mouse embryonic stem (ES) cells into insulin-producing cells involves a three-step process. This includes (i) the formation of embryoid bodies, (ii) the spontaneous differentiation of embryoid bodies into progenitor cells representing ecto-, meso-, and endodermal lineages, and (iii) the induction of differentiation of early progenitors into the pancreatic lineage. The differentiated cells can be obtained in approximately 33 days. Transgenic expression of PDX-1 (pancreatic and duodenal homeobox 1) and Nkx6.1 (NK6 homeobox 1) has been demonstrated to prompt the differentiation of ESCs into endocrine cells that express insulin, somatostatin, and glucagon. Incorporating growth factors and extracellular matrix elements, including laminin, nicotinamide, and insulin, facilitates the process

The induction of ESC-derived C-peptide/insulin-positive islet-like cell clusters, exhibiting insulin release upon glucose stimulation and expressing Pax4 (paired box gene), represents a significant advancement. Retinoic acid (RA) plays a crucial role in pancreatic development and is commonly employed to prompt pancreatic differentiation of ESCs. Direct addition of RA to activin A-induced human ESCs expressing CXCR4 leads to 95% of cells becoming positive for the pancreatic marker PDX-1H (pancreatic and duodenal homeobox 1). Animal studies have demonstrated that encapsulating human ESC-derived glucose-responsive mature β cells in alginate and transplanting them into a streptozotocin (STZ)-induced diabetic mouse model effectively regulates glycemic control. However, ethical concerns associated with ESCs have restricted their widespread clinical application. As an alternative, induced pluripotent stem cells have been proposed, possessing similar pluripotent characteristics to ESCs, thereby addressing ethical considerations.

The primary focus of research on embryonic pancreas development is to enhance our comprehension of the processes involved in the generation of β-cells under normal conditions. This entails not only unravelling the intricate networks of signalling pathways and transcription factors that govern cell-autonomous differentiation but also acquiring insights into epithelial-mesenchymal interactions and the influence of factors secreted by adjacent tissues that guide endocrine and β-cell development. The overarching goal is that, with the accumulation of this comprehensive information, it will be possible to integrate and reconstruct the embryonic differentiation program. This, in turn, could facilitate the ex vivo generation of therapeutic β-cells for potential clinical applications.

The pancreas, a sophisticated endoderm-derived organ, encompasses diverse cell types serving both endocrine and exocrine functions. The exocrine component, constituting over 90–95% of the pancreatic mass, houses acinar cells responsible for secreting digestive enzymes such as lipases, carbohydrases, and amylases. Additionally, ductal cells facilitate the transport of these enzymes into the duodenum. Despite comprising only 1–2% of the pancreatic cell

population, hormone-secreting endocrine cells play a vital role in maintaining euglycemia. Within the pancreas, the islets of Langerhans host five distinct endocrine cell types, with the insulin-producing β-cell dominating and constituting 60–80% of the islet. In rodents, and to a lesser extent in humans, β-cells are typically positioned at the centre of the islets, surrounded by other endocrine cell types. The proportion and arrangement of these cells in the adult pancreas, along with the morphological changes during pancreas development, have been extensively studied for over a century. More recently, driven by the advancements in transgenic mouse technology, substantial insights have been gained into the molecular mechanisms governing pancreas organogenesis and epithelial cell differentiation.

During vertebrate embryogenesis, the three primary germ layers—ectoderm, mesoderm, and endoderm—form through extensive cell migration during gastrulation. In the mouse, a favoured mammalian model for embryogenesis studies, a thin cup-shaped sheet of embryonic endoderm evolves into the primitive gut tube, which can be subdivided into distinct regions along the anterior-posterior axis. Each region possesses distinct developmental potential, typically giving rise to various endodermal organs, including the liver, lung, stomach, and pancreas. Specification of the pancreatic field occurs around embryonic day 8.5 (E8.5) in mice and around 3 weeks in humans. Initially, three pancreatic primordia emerge from the definitive gut epithelium: the first from the dorsal side, followed by two primordia on the ventral side. Due to their independent origin and distinct locations along the primitive gut tube, differences arise in the surrounding environment, timing, specificity of signalling pathways, and gene expression profiles guiding these processes. Shortly after formation, one of the ventral buds regresses, while the remaining ventral bud eventually fuses with the dorsal evagination during the gut tube's rotation around E12.5.Subsequently, the pancreatic epithelium undergoes significant growth and branches into the surrounding mesenchyme. Although glucagon-producing cells and a few cells coexpressing insulin and glucagon can be detected as early as E9.5, fully differentiated β-cells and other hormone-secreting cells become prominently evident around E13. Termed the secondary transition, this stage witnesses a substantial increase in endocrine cell numbers through the proliferation and subsequent differentiation of pancreatic progenitors.

The pancreas plays a pivotal role in systematically regulating glucose homeostasis, and its development involves a complex interplay of factors that influence stem cell differentiation into pancreatic progenitor cells, ultimately forming a fully functional organ. Consequently, most stem cell-based differentiation protocols aim to generate mature, single hormone-expressing, glucose-responsive human β-cells, drawing insights from studies on pancreatic development. Specific signals orchestrate the programming of insulin-producing β-cells. Transcription factors such as SRY (sex determining region Y)-box (Sox)17 and homeobox gene HB9 (Hlxb9) play crucial roles in endoderm formation during gastrulation. After foregut formation, fibroblast growth factor (FGF)-10, retinoic acid, SOX9, and hedgehog signalling pathways induce pancreatic development. Pancreatic specification and budding are driven by pancreas-specific transcription factors like pancreatic and duodenal homeobox 1 (Ptf-1a), pancreatic and duodenal homeobox 1, NK6 homeobox 1 (Nkx6.1), neurogenin-3 (Ngn-3), and mafA. These factors enable the endocrine formation and stimulate ISL LIM homeobox 1 (Isl-1), NK2 homeobox 2 (Nkx2.2), neurogenic differentiation factor (NeuroD), paired box gene (Pax)4, and Pax6 signalling, contributing to the formation of the islets of Langerhans. Throughout pancreatic development, transcription factors Sox17, hepatocyte nuclear factor (HNF)-6, and HNF-3beta (also known as forkhead box A2, Foxa2) are consistently expressed. Finally, FGF-10 and notch signaling-induced stem cell and pancreatic progenitor cell differentiation stimulate neogenesis, leading to the creation of β-cells.

1.1.3. Induced Pluripotent Stem

Induced pluripotent stem cells (iPS) are adult cells that undergo genetic reprogramming in the laboratory to acquire characteristics similar to embryonic stem cells. iPS cells possess the remarkable ability to differentiate into nearly all specialized cell types found in the body, making them a versatile resource for generating new cells for various organs or tissues. This quality positions them as valuable tools for disease modelling, with researchers globally exploring their potential to develop cures for severe diseases. Notably, iPS cells offer the advantage of being autologous, meaning they originate from the individual's cells, thereby minimizing the risk of immunological reactions or rejection when transplanted tissues derived from iPS cells are used.

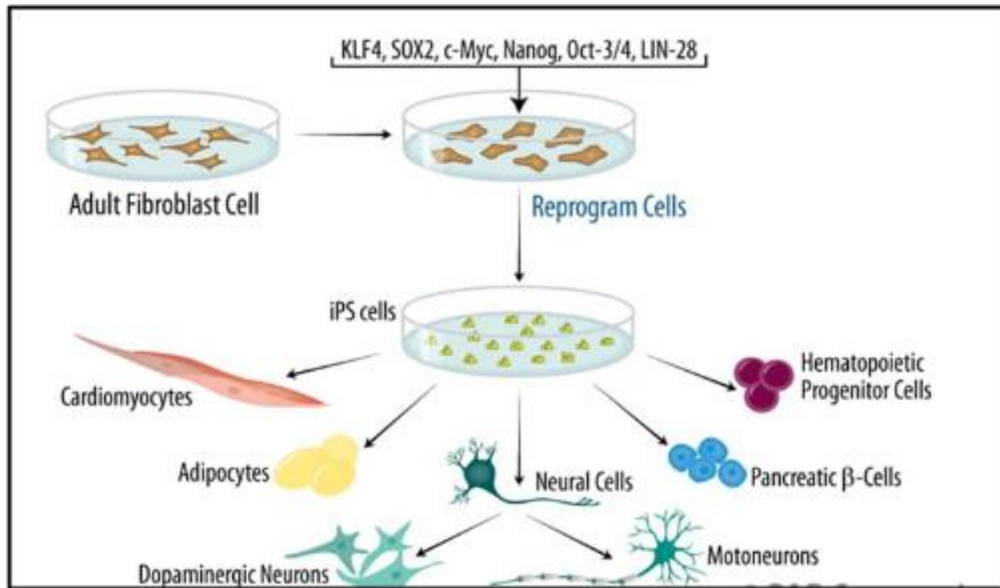

Figure 3 Induced Pluripotent Stem Cell

1.1.4. Pancreatic Regeneration Through Induced Pluripotent Stem Cell

Human induced pluripotent stem cells (iPSCs) are generated by reprogramming human somatic cells to acquire pluripotent properties. These iPSCs have proven to be a valuable source for deriving glucose-responsive β-like cells. Despite the complexity of β cell development, creating an efficient and reproducible β cell differentiation protocol has been challenging. A potential solution involves initiating differentiation from human iPSC-derived pancreatic progenitor cells expressing PDX-1 and SOX9, which exhibit prolonged proliferation potential and the ability to generate C-peptide-positive β cells. Another effective differentiation protocol involves supplementing factors related to epidermal growth factor (EGF), transforming growth factor β (TGF-β), thyroid hormone, retinoic acid (RA) signalling, and γ-secretase inhibition. This approach results in β cells capable of inducing Ca2+ flux in response to glucose, packaging insulin into secretory granules, and secreting insulin. Due to their unlimited replicative capacity (self-renewal) and pluripotency, iPSCs offer a promising avenue for differentiating into pancreatic endocrine lineage cells, specifically functional insulin-producing pancreatic β cells. Research has consistently reported positive outcomes in various in vitro studies using protocols that emulate the mechanisms of in vivo pancreas development to guide iPSC differentiation into functional β cells.

The first demonstration of generating functional β cells from induced pluripotent stem (iPS) cells was conducted by Tateishi and colleagues. Their study revealed that human dermal fibroblast-derived iPS cells, subjected to a four-stage serum-free in vitro differentiation process, could differentiate into functional islet-like clusters (ILCs) with mixed C-peptide+ and glucagon+ cells. Throughout the differentiation, iPS cells underwent stage-specific morphological changes resembling those observed in human embryonic stem cells (ESCs). Functional analysis, employing quantitative reverse transcriptase polymerase chain reaction (RT-PCR) and immunostaining, showed that the differentiated iPS cells expressed stage-specific genes and antigen markers at each developmental stage. These stages included definitive endoderm (Foxa2 and Sox17), pancreatic endoderm (Pdx1), exocrine/endocrine cells (NKX6.1, Ptf1, and Insulin), and insulin-producing cells (Insulin, C-peptide, and glucagon), mirroring the pattern observed in human ESCs. Notably, the iPS cell-derived ILCs exhibited the ability to secrete insulin in response to glucose stimulation, displaying a dose-dependent secretion pattern. However, Tateishi and colleagues noted clonal variability in the potential of iPS cells to differentiate into pancreatic endocrine lineage cells, and the efficiency of differentiation remained somewhat limited.

Maehr and colleagues have demonstrated the successful generation of induced pluripotent stem (iPS) cells from the skin fibroblasts of patients with Type 1 Diabetes (T1DM), referred to as DiPS. These patient-specific iPS cells can be further differentiated into insulin-producing and glucose-responsive cells. DiPS cells offer a patient-specific or autologous stem cell source, potentially resolving issues related to immune rejection that often hinder the transplantation of allogenic stem cells. Additionally, DiPS cells capture the genotypic abnormalities underlying T1DM, serving as a valuable disease model to investigate the pathological processes involved in T1DM development. Under a specific in vitro differentiation protocol, DiPS cells can differentiate into cells of the pancreatic endocrine lineage that stain positively for somatostatin, glucagon, insulin, and C-peptide. These differentiated cells also express specific gene markers of the pancreatic endocrine lineage, including insulin, Pdx1, Nkx2.2, glucagon, and somatostatin. Notably,

pancreatic endocrine cells derived from DiPS cells can secrete insulin in response to glucose stimulation in a dose-dependent manner. This approach holds promise for studying T1DM pathogenesis and exploring potential therapeutic interventions.

While many differentiation protocols for induced pluripotent stem (iPS) cells into the pancreatic endocrine lineage have low efficiency, leading to the production of pancreatic islet cells with immature characteristics, Zhang and colleagues have successfully developed a highly efficient differentiation protocol with a 25% efficiency for human embryonic stem cells (ESCs). This protocol yields functionally mature β-like cells resembling adult human pancreatic β cells. These cells co-express specific adult β cell transcription factors and functional markers in a pattern similar to adult β cells in vivo, including C-peptide, Pdx1, Glut2, MafA, Nkx6-1, Isl-1, and NeuroD. Importantly, these cells do not co-express somatostatin and glucagon, and they secrete insulin in response to glucose stimulation, exhibiting levels of secretion and a dose-dependent response comparable to adult human islet cells. Quantitative PCR-based gene expression profiling revealed that the pancreatic differentiation induced by this approach closely mirrors the key gene expression pattern of in vivo pancreas development. When adapted to iPS cells, this protocol induces the majority of iPS cells to differentiate into Pdx1+ pancreatic progenitor cells and further differentiate into functional islet cells expressing crucial β cell transcription factors and functional markers (Pdx1, MafA, Glut2, insulin, or C-peptide). The co-expression of PDX1 and C-peptide indicates the final mature stage of iPS cell differentiation towards pancreatic β cells. This protocol holds promise for advancing the efficiency and maturity of iPS cell-derived pancreatic cells for potential therapeutic applications.

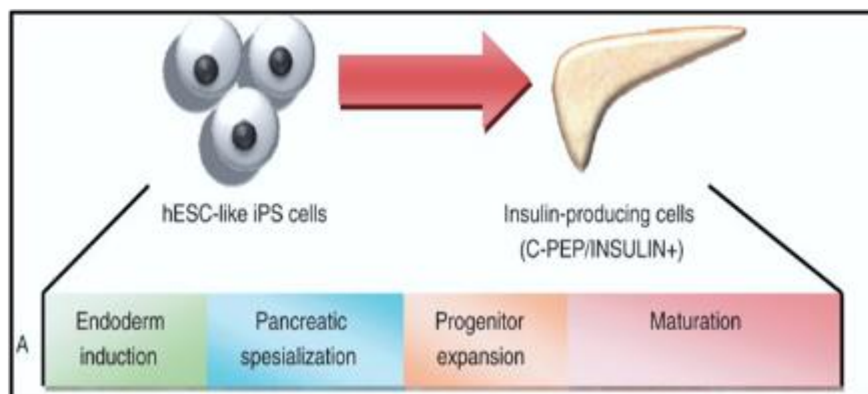

Figure 4 Pancreatic Regeneration Through Induced Pluripotent Stem Cell

1.1.5. Mesenchymal stem cells

Adult stem cells, particularly Mesenchymal stem cells (MSCs), present an appealing strategy for obtaining β cells in regenerative medicine. MSCs are characterized by their multi-potentialities, including self-renewal ability, pluripotency, low antigenicity, reduced toxicity, and ease of in vitro culture and expansion to obtain sufficient cells for therapeutic applications. These cells are found in various parts of the body, such as bone marrow, adipose tissue, amniotic fluid, umbilical cord blood, and placenta. Studies have demonstrated that MSCs from adipose tissue and placenta (PDMSCs) can be expanded for several passages without losing their self-renewal capacity.

The International Society for Cellular Therapy has established criteria for defining MSCs, which include their ability to adhere to plastic in culture, expression of cell surface markers CD105, CD73, and CD90, lack of expression of CD45, CD34, CD14 or CD11b, CD79a, or CD19, and HLADR surface molecules. Additionally, MSCs can differentiate into osteoblasts, adipocytes, or chondrocytes. Notably, MSCs have demonstrated the capacity to differentiate into cell types from endodermal and ectodermal lineages, including renal tubular cells, skin cells, neural cells, hepatocytes, and insulin-producing cells (IPCs).

1.1.6. Umbilical cord tissue-derived mesenchymal stem cells

The majority of umbilical cord tissue-derived stem cells (UC-MSCs) are located in the subcortical endothelium of the umbilical cord, the perivascular area, and Wharton's jelly. Studies suggest that approximately 1 × 10^6 UC-MSCs can be obtained from a 20 cm human umbilical cord. MSCs isolated from Wharton's jelly have demonstrated remarkable growth potential, with over 80 population doublings without signs of senescence, morphological changes, increased growth rate, or alterations in their ability to differentiate into neurons. research has indicated that xenotransplantation of post-differentiated human UC-MSCs, without the need for immunosuppressive therapy, does not lead to rejection.

This lack of immunogenicity may be attributed to the absence of major histocompatibility II and co-stimulatory molecules such as CD80 (B7-1), CD86 (B7-2), and CD40. Successful differentiation of human UC-MSCs into clusters of mature islet-like cells with insulin-producing capacity has been achieved by researchers. These islet cells showed an increase in insulin and other β-cell-related genes, including Pdx1, Hlxb9, Nkx2.2, Nkx6.1, and Glut-2. Furthermore, xenotransplantation of human pancreatic islet-like cell clusters effectively controlled hyperglycemia in diabetic rats.

In clinical studies, patients with newly diagnosed Type 1 Diabetes (T1D) who received repeated intravenous doses of allogeneic UC-MSCs showed improved islet cell preservation and a significant increase in postprandial C-peptide levels. However, C-peptide levels did not significantly change in patients with juvenile-onset T1D. The number of UC-MSCs contributed more significantly than other indicators to predicting clinical remission, emphasizing the importance of dose-dependent therapeutic efficacy. Therefore, future research should prioritize determining appropriate doses and courses for MSC transplantation.

UC-MSCs also show promise in treating chronic complications of Type 1 Diabetes (T1D), such as neuropathy, diabetic nephropathy (DN), and retinopathy. Studies have demonstrated that intraperitoneal injection of human UC-MSCs can mitigate renal injury in streptozotocin-induced diabetic mice. A study in China found that the combination of human UC-MSCs and resveratrol provided superior protection to renal podocyte function, resulting in reduced blood glucose levels and less renal damage compared to insulin administration alone. This suggests that the combination of resveratrol and human UC-MSCs could be an innovative approach for treating T1D, though further research in humans is needed to evaluate the effects of this combination on the management of DN.

In another study involving mice, UC-MSC therapy restored erectile function by suppressing toll-like receptor 4, alleviating corpora cavernosa fibrosis, and increasing the production of VEGF and endothelial nitric oxide synthase. One notable advantage of UC-MSCs is their abundance as a source of various stem cells that can be easily manipulated. They are collected at birth through the clamping and severing of the umbilical cord, and their use raises no ethical concerns since the collection process is non-invasive and utilizes material that would otherwise be discarded as waste.

1.1.7. Adipose tissue-derived mesenchymal stem cells

Adipose tissue-derived mesenchymal stem cells (ADSCs) are a subset of cells originating from the mesoderm during embryonic development, with subcutaneous adipose tissue being a clinically relevant and minimally invasive source. Focusing on white adipose tissue, which houses ADSCs, this tissue acts as a storage site for excess energy in the form of triglycerides. The extracted cell population of interest, known as processed lipoaspirate (PLA), contains a putative stem cell population found in the stromal compartments of adipose tissue.

Obtaining PLA requires lipoaspiration, a procedure that, while not adversely affecting ADSC function, can cause damage to mature adipocytes due to the vacuum process involved. Studies have demonstrated that successfully extracted PLA can differentiate in vitro into various cell lineages, showcasing multi-germ-line potential. ADSCs' ability to efficiently differentiate into insulin-producing cells (IPC) offers a novel approach to managing Type 1 Diabetes (T1D).

ADSCs present advantages over other stem cell sources, including a relatively painless harvesting procedure, high yields of harvested cells, and the absence of human leukocyte antigen-DR expression, allowing for transplantation without immunosuppression. Co-transplantation of insulin-secreting ADSCs has been explored as an alternative to lifelong insulin therapy. Studies have shown improved diabetic control and sustained improvements in blood sugar levels with the transplantation of autologous insulin-secreting ADSCs, offering a promising therapeutic avenue for achieving normoglycemia.

Beyond T1D, ADSC therapy has demonstrated efficacy in reducing complications such as diabetic nephropathy (DN) and end-stage renal disease (ESRD). Mechanisms involve the inactivation of nuclear factor kappa B pathways and the downregulation of VEGF-A, among others. However, the challenge remains in achieving complete independence from exogenous insulin. Further research is needed to enhance insulin production in IPC derived from ADSCs or modify cell signalling pathways to obtain a greater number of IPC for sustained T1D cure.

1.1.8. Bone marrow-derived mesenchymal stem cells

Bone marrow-derived mesenchymal stem cells (BM-MSCs) represent a subtype of adult stem cells abundantly found in bone marrow with low immunogenicity. Within the bone marrow stem cell population, they fall into two main categories: hematopoietic stem cells and MSCs. The advantage of sourcing these cells from the same individual lies in the potential reduction of rejection issues, presenting a viable therapy for Type 1 Diabetes (T1D).

BM-MSCs possess the capability to differentiate into functionally competent β-cells in vivo. Studies on non-obese diabetic (NOD) mice indicate the restoration of normal T cell and B cell function, suggesting that an allogeneic bone marrow transplant could prevent islet destruction and reinstate self-tolerance. The hypoimmunogenic and immunomodulatory properties of BM-MSCs make them an attractive therapeutic option for T1D.

A study examining Type 1 Diabetes (T1D) patients experiencing Diabetic Ketoacidosis (DKA) observed that Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs) preserved β-cell function in T1D patients. This preservation was evidenced by reductions in fasting and post-prandial C-peptide levels. Remarkably, one patient achieved a state of insulin independence for three months.

Research has shown that Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs) can alleviate the impact of metabolic and hepato-renal abnormalities, enhance lipid profiles, and improve carbohydrate and glycemic management. In diabetic rats, an eight-week treatment with BM-MSCs led to an improvement in lipid profiles compared to diabetic rats not treated with BM-MSCs. Furthermore, BM-MSCs therapy has been observed to ameliorate diabetes-related liver damage by promoting endogenous hepatocyte regenerative mechanisms and enhancing liver function.

BM-MSCs have demonstrated effectiveness in treating comorbidities of T1D, including diabetic nephropathy (DN), poor wound healing, and erectile dysfunction (ED). Research by Nagaishi et al. explored a novel approach of combining BM-MSCs with umbilical cord extracts from Wharton's Jelly to enhance therapeutic effects in ameliorating renal injury in T1D patients with DN. The study showed improvements in morphology and functionality of diabetes-derived BM-MSCs in vitro and a therapeutic impact on DN in vivo, suggesting potential benefits for patients with various diabetic complications. Additionally, BM-MSCs have been found to promote corneal epithelial wound healing by activating stem cells through a tumour necrosis factor-inducible gene 6-dependent mechanism. In a phase I pilot clinical trial, the treatment of ED in T1D patients with two consecutive intracavernous injections of autologous BM-MSCs was deemed safe and effective.

Suicide gene therapy is emerging as a potential therapeutic approach for Type 1 Diabetes (T1D). This strategy involves introducing suicide-inducing transgenes into the body via Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs). The suicide genes induce various processes, including the suppression of gene expression, production of intracellular antibodies blocking essential pathways, and transgenic expression of caspases and deoxyribonucleases. Ongoing clinical trials are exploring the use of stem cells, particularly BM-MSCs, as a delivery mechanism to restore damaged organs in individuals with T1D.

The concept of transplanting Bone Marrow-Derived Mesenchymal Stem Cells (BM-MSCs) offers hope to patients, with autologous BM-MSCs being particularly significant. Autologous BM-MSCs are easily obtained and can avoid graft rejection after transplantation, making them a favourable option compared to allogeneic BM-MSC transplantations, which may carry the risk of graft rejection and associated complications. For stem cell therapy to be most effective, early delivery of stem cells following a diagnosis of Type 1 Diabetes (T1D) is considered crucial compared to intervention at later stages.

1.1.9. Endometrium, dental pulp and conjunctival tissue-derived mesenchymal stem cells

Recent research indicates that Menstrual Blood-Derived Endometrial Stem Cells (MenSCs) hold therapeutic promise for treating Type 1 Diabetes (T1D) due to their high rates of proliferation, noninvasive collection method, and significant immunomodulatory activity. Transplantation of MenSCs and Umbilical Cord Mesenchymal Stem Cells (UC-MSCs) in T1D model mice resulted in a significant decrease in blood glucose and insulin levels, along with improvements in the morphology and function of the liver, kidneys, and spleen. A study in 2021 found that MenSCs expressed genes related to pancreatic β-cells, such as INSULIN, GLUT-2, and NGN-3, showcasing their potential to develop into pancreatic cells.

Dental Pulp-Derived Mesenchymal Stem Cells (DP-MSCs) are another unique type of MSC proposed for T1D treatment. DP-MSCs, derived from exfoliated human deciduous teeth, offer the advantage of being easily obtained with minimal donor injury. In a study by Mo et al., DP-MSCs demonstrated the ability to differentiate into pancreatic β-cells. However, further research is needed to establish optimal procedures for β-cell differentiation in vivo before advancing to larger-scale investigations.

An in vivo study demonstrated that conjunctiva-derived mesenchymal stem cells (C-MSCs) efficiently differentiated into pancreatic islet stem cells in both 2D cultures and 3D scaffolds under optimal induction conditions. C-MSCs exhibit a robust proliferative capacity, a spindle-shaped morphology, and a high potential for clonogenic differentiation, and are

readily available. However, further extensive in vitro studies are required to firmly establish the potential of C-MSCs as a treatment for Type 1 Diabetes (T1D).

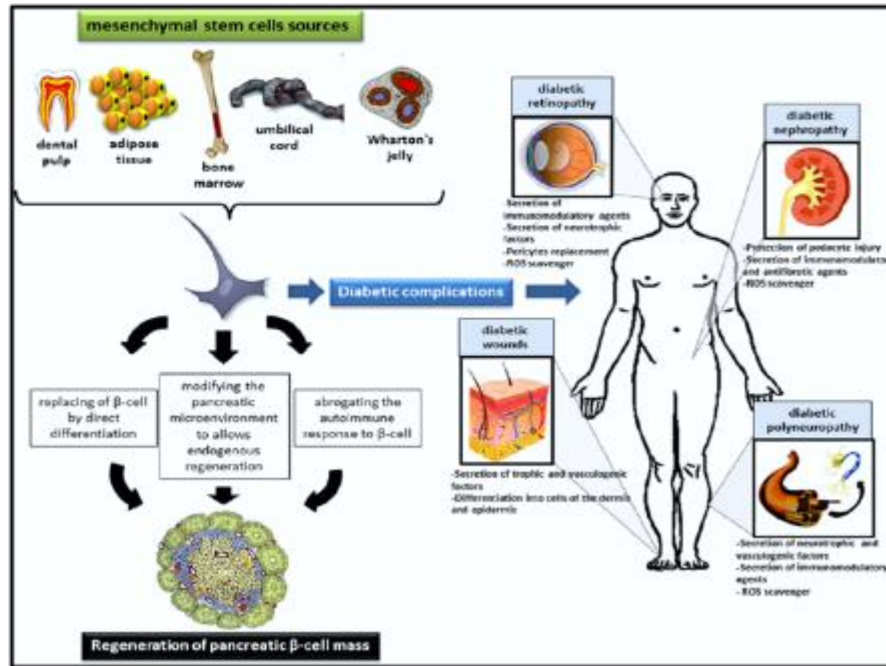

Figure 5 Pancreatic Regeneration Through Induced Mesenchymal Stem Cell

1.1.10. Progenitor cells

Identification of progenitor cells in the adult pancreas has garnered increasing attention due to their pancreatic lineage characteristics, allowing them to generate new functional β cells. In vitro, the induction of pancreatic progenitor cells to differentiate into islets, followed by transplantation into streptozotocin-induced mice, resulted in the direct migration of progenitor cells into the injured pancreas. Subsequently, these cells rapidly differentiated into insulin-producing cells (IPCs), leading to a reduction in glucose levels towards normoglycemia. A recent study highlighted the presence of progenitor cells expressing Ngn-3 in the ducts of the adult mouse pancreas. Despite Ngn-3 being expressed at extremely low levels in normal postnatal pancreatic tissues, ectopic expression of Ngn-3 in pancreatic ductal cells facilitated their conversion into IPCs. Additionally, treatment of human ductal and acinar cells with a combination of epidermal growth factor and gastrin induced neogenesis of islet β cells from the ducts, thereby increasing the functional β cell mass. Other studies explored co-transplantation approaches, where purified human non-endocrine pancreatic epithelial cells were combined with human fetal pancreatic tissue under the kidney capsule of immunodeficient mice. This led to the differentiation of these epithelial cells into endocrine cells, indicating that fetal cells provide supportive factors for the survival and differentiation of epithelial cells. Furthermore, stem cell-like cells with the capacity for ex vivo expansion and clone formation have been identified. These cells exhibit proliferative capabilities and can form cellular aggregates, displaying potential for endocrine and exocrine differentiation. While these findings suggest the existence of stem/progenitor cells within the pancreas, there is an urgent need for specific markers to isolate these cell populations.

2. Conclusion

The review article highlights the potential of stem cells as a novel therapy for diabetes, emphasizing their role in tissue repair, organ regeneration, and the creation of pancreatic beta cells. Stem cell therapy presents a promising avenue to address the limitations of current diabetes management, potentially eliminating the need for multiple daily insulin injections. The transplantation of stem cells can contribute to pancreas reform by providing paracrine effects and influencing cell differentiation. The positive results observed in human trials using various stem cells underscore the potential of stem cell therapy for diabetes. However, the article acknowledges the need for further extensive and well-controlled experiments to address limitations and refine the approach. Randomized human trials, comparative studies, and a deeper understanding of which stem cell types and methods yield optimal results are highlighted as areas for future research. Both embryonic and adult stem cells are recognized as valuable resources for differentiating into insulin-producing cells. Adult stem cells, in particular, are emphasized for their easy accessibility, reduced controversy, and potential to offer therapy to a broader patient population. The comfort of patients being treated with their tissues

is noted as a factor contributing to faster and more effective treatment. In conclusion, the article emphasizes the potential of stem cell therapy, particularly adult stem cells, as a promising resource for treating diabetes. It underscores the importance of ongoing clinical trials to validate and advance the progress in using stem cell therapy for diabetes treatment in the future.

Compliance with ethical standards

Acknowledgments

Authors will like to thank the all the co-authors for their constant support and guidance.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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