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RESEARCH ARTICLE

PANCREATIC STEM CELLS: THE HOPE (SOURCES – MARKER EXPRESSION– PROMISING APPLICATIONSIN REGENERATIVE MEDICINE)

Areej, M. Alshehri[1], Rasha, A. Alshali[1], Rania, Magadmi[2] and Laila M. Aboul- Mahasen[1]

[1]Clinical Anatomy Department, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[2]ClinicalPharmacology Department, Faculty of Medicine, King Abdulaziz University, Saudi Arabia

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**Corresponding author:*
Areej, M. Alshehri

ABSTRACT

The potential of stem cells in regenerative medicine to combat diabetes is an excitingpurpose. From beta cell replacement to immune modulation and vascular regeneration, stem cell-based approaches offerhope for more effective treatments and a potential cure for this widespread metabolic disorder. As research in this field continues to advance, stem cell therapies may revolutionize the management of diabetes, offering new possibilities for improved quality of life for patients.In this review, although some significant technical hurdles remain, stem cells offer great hope for patients with diabetes. This review will provide insightson the sources and marker expression of pancreatic stem cells. The data are collected about the potential use of pancreatic stem cells (PSC)-derived islets for treating and understanding types of DM. Induced pluripotent stem cells (iPSCs), are promising for the treatment of diabetes owing to their self-renewal capacity and ability to differentiate into functional β-cells.Type 2 diabetes patients might benefit from the transplantation of cells expanded from their own duct cells since they would not need any immunosuppression.

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INTRODUCTION

Stem cells are fundamental components of the human body essential for development and tissue repairing. They are undifferentiated cells and have the unique ability of self-renewal and differentiation into many types of specialized cells. Thus, they provide valuable therapeutic applications in repairing and regenerating the damaged tissues.

Types of stem cells based on their potency: This is the classification of stem cells according to the degree to which the stem cells are able to differentiate into different cell types. Figure 1 (Majo, *et al*. 2008) shows the four types of stem cells as follows:

- **Totipotent**stem cells can differentiate into all cell types. They are the resultant first few cells that are derived from the zygote division **(Morgani *et al.* , 2013).**
- **Pluripotent**stem cells can differentiate into nearly all cell types as the embryonic stem cells and cells that are derived from the mesoderm, endoderm, and ectoderm germ layers that are formed in the beginning stages of embryonic stem cell differentiation (**Hanna *et al*., 2010**).
- **Unipotent**stem cellshave restricted capability to produce only their own cell type, but they do selfrenewal , for example the muscle stem cells in adults (**SchölerH. R.,2016)**
- **Multipotent** stem cells can differentiate into a closely associated cells family. For example, the hematopoietic (adult) stem cells that are capable to turn into platelets or red and white blood cells (Zhao and Mazzone, 2010).
- **Oligopotent** stem cells can differentiate into few cells such as adult myeliod or lymphoid stem cells **(Shah., 2021**).

Types of stem cells based on their sources

There are many types of stem cells, each have its unique properties and can be classified according to their source as follow:

Embryonic Stem Cells (ESCs): They are multipotent stem cells derived from the inner cell mass of a developing embryo.They have a wonderfulcapability of differentiating into any type of cells in the human body. Research on ESCs supports promising potential applications for tissue repair and regenerative medicine (Thomson, 1998 and Mahla,2016).

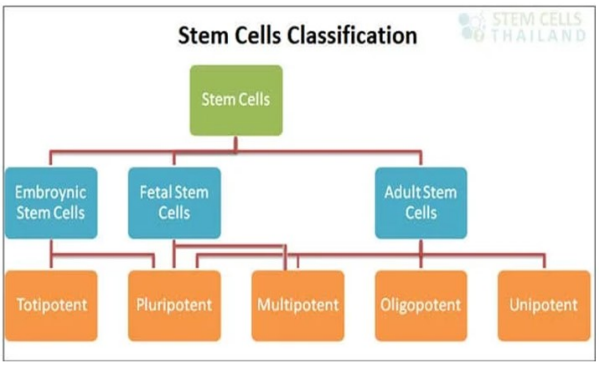

Figure 1. Stem cells types based on their potency and differentiation (Majo, etal. 2008)

Adult stem cells (ASCs): They are multipotent or **totipotent**undifferentiated cells found in different tissues and organs in adults. However, they have less differentiation potential than ESCs and mainly contribute to tissue repair and maintenance as they can differentiate only to the same adult tissue. They can renew themselves or generate new cells that can replenish dead or damaged tissues. They are divided into several subtypes.

Subtypes of adult stem cells

Mesenchymal Stem Cells (MSCs): they are multipotent stem cells found in variable tissues, including bone marrow, adipose tissue, and umbilical cord. They can differentiate into cell types such as bone, cartilage, and fat cells. They are used in regenerative medicine, especially treating osteoarthritis and tissue injuries and cancer therapies (Hmadcha, 2020).

Hematopoietic Stem Cells (HSCs):they are found in bone marrow and blood. They can differentiate into all types of blood cell; thus, they are crucial for blood-related therapies like bone marrow transplants (Mosaad, 2014)

Neural Stem Cells (NSCs): They are specialized stem cells foundmainly in the central nervous system. NSCs can differentiate into neurons, astrocytes, and oligodendrocytes. Therefore, they have high potential to treat neurodegenerative diseases and spinal cord injuries (Zakrzewski, 2019).

Epithelial Stem Cells (EpSCs): They are specified during development and are controlled by epithelial-mesenchymal interactions. They give rise to many cell linings like the skin, uterus, intestines, cornea, hair follicles and respiratory tract (Ferraces-Riegas, 2022).

Induced Pluripotent Stem Cells (iPSCs): They are artificially reprogrammed cells derived from adult somatic cells by introducing specific transcription genes and factors to be converted into iPSCs. iPSCs possess pluripotency similar to ESCs, exhibiting their potential for disease modeling, drug testing, and specific therapies **(**Ye and Swingen, 2013). Induced pluripotent stem cells (iPSCs), are promising for the treatment of diabetes owing to their self-renewal capacity and ability to differentiate into functional β-cells (Feng,*et al*. 2024).

Sources of pancreatic isletstem/Progenitor cells

Pancreatic progenitor cells are multipotent stem cells originating from the developing foregut endoderm which have the ability to differentiate into the lineage specific progenitors responsible for the developing pancreas (Ku, 2008 andNoguchi, 2010).

Pancreatic tissue as a source of islet progenitor/stem cells

Many researchers looked for islet-like stem cells from adult pancreatic tissue. They had discovered a population of stem-like cells within both the adult pancreas islets and pancreatic ducts. These cells do not express the marker typical of ductal cells, so they are unlikely to be ductal cells. Instead, they express a marker called nestin, which is typically found in developing neural cells. The nestin-positive cells do not express markers typically found in mature islet cells. However, depending upon the growth factors added, the cells can differentiate into different types of cells, including liver, neural, exocrine pancreas, and endocrine pancreas, judged by the markers they express, and can be maintained in culture for up to eight months **(Zulewski, H., *et al*., 2001).**

Ductal cells as a source of islet progenitor /stemcells

Another promising source of islet progenitor cells lies in the cells that line the pancreatic ducts. Some researchers believed that multipotent stem cells were intermingled with mature, differentiated duct cells, while others believed that the duct cells themselves could undergo a differentiation, or a reversal to a less mature type of cell, which could then differentiate into an insulin-producing islet cell (Itkin-Ansari, *et al*., 2000).

Mature duct cells that have undergone dedifferentiation or regression serve as the primary progenitor source for pancreatic development and regeneration. Two pathways are involved in a significant regeneration: replication of pre-existing differentiated cells, either acinar or endocrine; and the growth of ductules to create regeneration foci that subsequently differentiate into islets and acini to produce entire new pancreatic lobes. The growth of the duct epithelium and the differentiation into acini and islets are the first two steps of this second neogenic route, which occurs quickly within a week (Bonner-Weir and Sharma2002). Bonner-Weir, *et al*., (2008), reported that when ductal cells isolated from adult human pancreatic tissue were cultured, they could be induced to differentiate into clusters that contained both ductal and endocrine cells. Type 2 diabetes patients might benefit from the transplantation of cells **expanded** from their own duct cells since they would not need any immunosuppression.

Intra-islet stem cells as a source of islet progenitor /stem cells: It has been proposed that intra-islet stem cells might serve as an extra source of new islet cells in addition to the replication of differentiated islet cells (Murtaugh, *et al*. 2005).

Embryonic development of pancreas

Two evaginations in the posterior foregut, one dorsal and one ventralgrow into the adult organ's head and tail, respectively, to form the mammalian pancreas. The expression of the homeodomain transcription factor Pdx1(Pancreatic and duodenal homeobox 1) in the cells that will evaginate to create the pancreatic buds is the earliest indication of pancreatic development in mice, occurring at embryonic day 8.5.These undifferentiated progenitor cells then start to express the digesting enzyme Cpa1 (Zhou *et al*., 2007 and Ku, 2008).The

Pdx1+/Ptf1a+(pancreas associated transcription factor 1a) progenitor cells (Fig. 2)are the source of nearly all mature pancreatic cells, including acini, ducts, and islets, Furthermore, mutations in either of these genes almost eliminate pancreatic development and differentiation (Murtaugh and Hopinke, 2008and Sarkar *et al*., 2008).

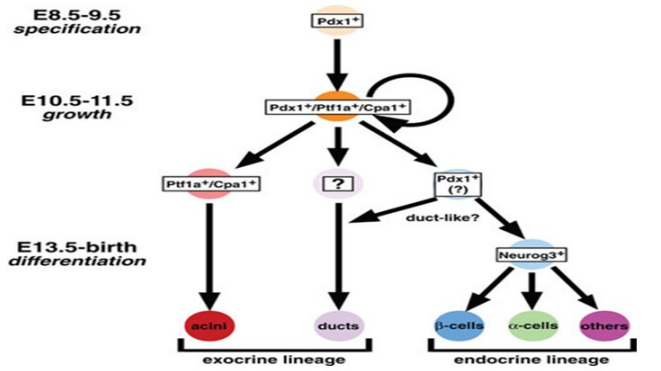

Figure 2. Pancreatic lineages in the mouse. Studies performed in mice have helped in the lineage tracing of progenitors (Murtaugh and Hopinke, 2008)

Expression of the transcription factor Pdx1, which identifies the progenitors of all exocrine and endocrine cell types, is the earliest indication of pancreatic specificity inside the foregut endoderm. The transcription factor Ptf1a and the digesting enzyme Cpa1 are also expressed by multipotent progenitor cells as the embryonic organ develops. Before differentiation, these progenitors are then divided into several sub-lineages. Whereas islet cells develop from precursors that momentarily express the transcription factor Neurog3, acinar cells develop from precursors that exhibit high amounts of Ptf1a and Cpa1 (Bhushan, *et al*. 2001; Murtaugh, 2005 and Ku, 2008).

Common Marker expression of the pancreatic stem cells

Pax-8: Pax proteins are a family of transcriptional regulators, control the growth of different cells during mammalian development and play important roles in cell proliferation, organogenesis, tissue differentiation, and resistance to apoptosis. Studies have shown that nine Pax genes mainly exist in mice and humans (Pax-1 to Pax-9). Pax-8 is essential to the differentiation of cells and the generation of tissues throughout embryonic development and plays a key role in maintaining the appropriate functionof several organs after birth. Of note, in normal human tissues, Pax-8 was consistently noted in the thyroid, kidney, lymphoid cells, and pancreatic islet cells, as well as epithelial cells of the endocervix, endometrium, and fallopian tube in women, and the seminal vesicle and epididymis in men. Regarding subcellular localization, the intracellular expression of Pax-8 was mostly concentrated in the nucleus (Kakun, *et al*. , 2022 and Zhou *et al*. 2024)

CK19: Cytokeratin19 (CK19) positive epithelial cells are progenitors for islet cells and ductal cells. In a study on stem cell expression markers, CK-19 is a marker of transformation from pancreatic duct epithelial cells to stem cells (Gao *et al*., 2003, Banerjee andBhonde, 2003). Islet cells were derived from duct-like precursor cell masses, which arisefrom the ductal embryonic buds of islet cells (Hao *et al*., 2006)).

NCAM-1 (CD56): Neural cell adhesion molecule (NCAM) belongs to the immunoglobulin superfamily of CAMs (cell adhesionmolecules). NCAM was originally characterised as a homophilic cell adhesion molecule (Maestro *et al*.2000) that mediates the homophilic binding between cells and between cell and matrix. CD56 is a neural cell adhesion molecule expressed by pancreatic duct epithelium and islet cell of pancreas (Bonner-Weir and Sharma 2002and Nugali, *et al*. 2016).

PDX-1: Pancreatic PDX-1 expression becomes progressively restricted during development as it is believed to play a role in the regulation of IN gene transcription (Fernandes *et al*. 1997).While the PDX-1 protein is expressed in the embryonic pancreatic ducts,shortly after birth, it is re-expressed in the ducts; it is the same protein that others have suggested as a marker for the adult progenitor cells(Bonner-Weir and Sharma 2002, Noguchi *et al*., 2003 and Fujimoto and Polonsky , 2009).

Nestin: The intermediate filament nestin has been used as a marker for neural stem cells and was recently reported in scattered cells in the islets and pancreatic ducts.Nestin Positive cells isolated from the rat and human islets could be expanded in culture and were found by RT-PCR to express liver, pancreatic exocrine and endocrine genes, leading to the suggestion that they were multipotent tissue stem cells.They proliferate and express nestin. When they become confluent, they form spheroid clusters and express cytokeratin-19 and neural cell adhesion molecule (NCAM). In the pancreas, nestin-positive cells are also numerous, being not just in islets but also in the stroma of the pancreatic ducts and common in the connective tissue surrounding the acini (Bonner-Weir and Sharma 2002 and Trucco 2005).

Pancreatic regeneration: Re-growth or re-differentiation?

β-cells, may be destroyed experimentally by many ways. However, after being injured surgically, chemically, or transgenically, the pancreas and its β-cells may regenerate at least somewhat, often enough to cure hyperglycaemia (Bouwens and Rooman, 2005). After partial pancreatectomy, the exocrine pancreas can regenerate, but it seems to do so to a lesser extent than the β-cells.Remnant duct and/or acinar cells seem to return to a more progenitor-like condition; for instance, their proliferation rate rises and Pdx1 expression is significantly increased (Jensen *et al*., 2005 and Desai *et al*., 2007).

Pancreatic growth as an indication of adult progenitor/stem cells: It has been proposed that islet differentiation, namely B-cell differentiation, is the "default pathway" of embryonic pancreatic development. After birth, during normal growth, and through the mass of B cells keeps growing as an adult. Due to both the creation of a new islet and its extension, the islet's size has grown.It has been proposed that intra-islet stem cells might serve as an extra source of new islet cells in addition to the replication of differentiated islet cells. Certain human disorders, including severe liver disease and recently diagnosed type 1 diabetes, have been linked to increased neogenesis. Insulin-producing B cells in adult rats have been identified as consisting of only 0.1% of the ductal cells, but elevated neogenesis has been observed in several experimental settings(Murtaugh, *et al*. 2005)

"True stem cells" are very mobile and possess the limitless capacity to self-renew and specialize into distinct cell lineages when exposed to the right local environmental stimuli, sometimes referred to as growth factors or morphogens.

Human and rat islets have yielded putative **intra-islet stem cells** that express the neural stem cell marker nestin. Following partial pancreatectomy, a mature duct cell in the regenerating rat pancreas may regress with replication to a less differentiated cell (possibly comparable to an embryonic pancreatic duct cell) that regains the potential to differentiate into an islet, acinar, or mature duct cell; these cells' phenotypic differentiation is guided by outer cues or morphogens. (Murtaugh, *et al*. 2005))

Nestin-positive cells from the pancreas: dispersed cells in the islets and pancreatic ducts were shown to have the intermediate filament nestin, which has been employed as **a marker** for neural stem cells. It was proposed that the nestin-positive cells extracted from the rat and human islets were multipotent tissue stem cells since they could proliferate in vitro and were shown by RT-PCR to express exocrine, endocrine, and hepatic genes (Lumelsky, 2001)

Other putative intra-islet stem cells: After employing the toxin streptozotocin to destroy the majority of the B cells, many researchers discovered another intra-islet precursor cell in the B-cell regeneration. A repopulation occurred in certain animals following the death of the B cell core, beginning with cells expressingPDX-1 and somatostatin and progressing to cells expressing both PDX-1 and insulin. They did not develop into actual insulin-positive cells, though, and there were relatively few somatostatin/insulin-positive cells. (Guz,2001 and Ebrahim, 2022).

Uses of Stem Cells in Regenerative Medicine: Stem cells can regenerate damaged or degenerated tissues. For instance, Mesenchymal stem cells (MSCs) have been utilized to repair bone, cartilage, and muscle tissues, offering potential treatments for conditions of permanent damaged tissues, atrophies and injuries including degenerative neurological diseases, heart conditions, GIT damages or inflammations, bone, some solid tumor cancers and diabetes mellitus (Zhao, *et al*., 2016).

Uses of Stem Cells in diabetes mellitus:A hopein Regenerative Medicine

Diabetes mellitus (DM) is a common metabolic disorder characterized by a disturbance in the metabolism of carbohydrates, fat and proteins, resulting in uncontrolled hyperglycemia. DM is classified by the World Health Organization (WHO) according to etiological criteria into three common clinical types: type 1, type 2 and type 3(WHO, 2024). Type 1 is the insulin dependent diabetes mellitus (IDDM), which is common in children due to autoimmune destruction of insulin-producing cells (IPCs), pancreatic β cells, leading to absolute insulin hormone deficiency. Type 2 is the non-insulin dependent diabetes mellitus (NIDDM), which is the most co
Type 3 is known as gestational diabetes that affects pregnant mothers and can be resolved after delivery. Both type 2 and type 3 are characte

Employing Stem Cells in Type 1 Diabetes: The remarkable ability of stem cells to differentiate into functional cells makes them suitable modalities for treating several diseases such as diabetes.Pancreatic ducts of the pancreas contain endocrine stem cells. In the regenerating rat pancreas, after partial pancreatectomy, a mature duct cell can revert with replication to a less differentiated cell that regains the potential to differentiate into an islet, acinar, or mature duct cell (Bonner-Weir and Sharma 2002). The identification of a progenitor for all differentiated pancreatic cell types has wide implications for a potential generator of new islets for replenishment therapy for diabetes mellitus. (Bonner-Weir, S. 2008 and Kh and Haider, 2021).

Regeneration of insulin precursors cells of the pancreas, β cells, is one of the methods to help in maintaining the regulation of blood glucose in diabetic patients. Pancreatic islet transplantation was a well-established strategy and has allowed weaning from insulin treatment in some patients with T1DM. Islet cells from doners are seeded in a non-physiological environment where a little amount will be able to adapt and survive, then these cells are transplanted clinically as a minimally invasive procedure alternative to pancreas transplantation (Ahearn, *et al*., 2015). However, two major issues have limited the use of this treatment modality. First, the shortage of organ donors is the major limiting factor. Second, islet transplants require lifelong immunosuppressive regimens to minimize rejection, which is not only expensive but generally reduces the patient's quality of life due to drug-induced side effects. Therefore, there is a compelling need to develop potential alternative therapies for the treatment of type 1 DM. (Raikwar, S. P., & Zavazava, 2009). Another concern is the reemerging autoreactive T cells that destroy not only the patient's residual islets and block β-cell regeneration, but also the newly transplanted donor islets and eventually causing chronic graft rejection (Pugliese,2017). If additional renewable sources of insulin producing cells (IPCs) can be generated, diabetes management could significantly be improved. Derivation of IPCs from ESCs and iPSCs offer a novel innovative treatment for type 1 diabetes(Maxwell, K.G. and. Millman, 2021). However, there are major challenges associated with the identification and monitoring of ESCs undergoing differentiation into IPCs.

This is further worsened because the currently available protocols for this differentiation are labor intensive, expensive and time consuming. Another remarkablelimitation is that the final yield of IPCs is still very low (≤ 1% of the final cell population).In addition, the amount of insulin produced by each IPC compared to that produced by a single islet appears to be less than a tenth based on our estimates.The efficiency of ESC differentiation into IPCs can be significantly enhanced by the generation of stable ESC lines expressing key transcription factors involved in the development of pancreatic β cells. There is a crucial need to identify various molecular markers defining multiple stages of pancreatic development including cell-specific markers of pancreatic stem/progenitor cells.(Raikwar, S. P., & Zavazava, 2009). The next approach to maximize the generation of IPCs using ES cells involves a combination of in vitro partial differentiation of ES cells followed by in vivo differentiation and maturation of the precursors into IPCs post transplantation in streptozotocin induced diabetic mice.Therefore, research efforts have been directed to the final steps of in vitro differentiation, aiming at production of a second proportion of functional and mature β-cells and integration of interdisciplinary fields to generate efficient cell therapy strategies capable of reversing the clinical outcome of T1D (Silva, *et al*., 2022).

Recently, insulin expressing cells from mouse stem cells have been generated. In addition, the cells self-assemble to form structures, which closely resemble normal pancreatic islets and produce insulin. Researchers need to investigate how to optimize conditions for insulin production with the aim of providing a stem cell-based therapy to treat diabetes by replacing the constant need for insulin injections.

Promising Employing Stem Cells in Type 2 Diabetes

Liu et al. (2021). delve into the promising applications of stem cells in the context of Type 2 diabetesas follow:

Beta Cell Replacement Therapy: One of the primary approaches in regenerative medicine for T2DM is the generation of insulin-producing beta cells from stem cells. Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) can be differentiated into functional beta-like cells. Transplantation of these cells into patients could potentially restore proper insulin secretion, effectively treating the disease (Hamad, *et al*., 2021; Salib, *et al*. 2022 and Cui. *et al*. 2024).

Modulating Immune Response: Mesenchymal stem cells (MSCs) have immunomodulatory properties. In T1&2DM, immune dysfunction and inflammation play a significant role. MSCs can help modulate the immune response, reducing inflammation and preserving pancreatic beta cells. Clinical trials are exploring MSC-based therapies for T1DM (Refaie, A. F.,*et al*.2021 andParis, *et al*. 2022)

Vascular Regeneration: T2DM often leads to vascular complications. Endothelial progenitor cells (EPCs) derived from stem cells can promote vascular regeneration and improve blood flow, potentially mitigating the vascular complications associated with diabetes (Liew, *et al*. 2008) Kh and Haider,(2021) mentioned that here is continuous advance in the uses of pluripotent stem cells following the new less stringent legislation regarding the use of embryonic stem cells (ESCs).

This led to the beginning of the protocols for the reprogramming of somatic cells to achieve pluripotency reminiscence of ESCs. Induced pluripotent stem cells (iPSCs) may provide an alternative renewable source of patient-specific β-cells for transplantation to support an inefficient intrinsic repair mechanism.

CONCLUSION

There is a recent advance in the uses of pluripotent stem cells following the restricted use of embryonic stem cells (ESCs).*Induced pluripotent stem cells* (iPSCs) may provide an alternative renewable source of patient-specific β-cells for transplantation to support an inefficient intrinsic repair mechanism. Finally, weappreciate the published data defining the possibility to use the exogenous stem cells for replacement of nonfunctional pancreatic β-cells to normalize insulin production.Type 2 diabetes patients might benefit from the transplantation of cells expanded from their own duct cells since they would not need any immunosuppression.

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