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From damage to repair: how pancreatic structure shapes regenerative strategies

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Abstract

The pancreas, an organ of the digestive system, is mainly divided into two parts: the exocrine and the endocrine pancreas, each composed of different cells with various functions. In case of dysfunction or loss of β-cells, the natural consequence is to develop a disease such as type 1 diabetes, which is the result of autoimmune destruction of these cells, or type 2 diabetes, which is the result of peripheral tissue resistance to insulin. At present, the available treatment is composed of an pharmacological intervention in form of lifelong administration of insulin, and only limited alternative treatment options exist. However, emerging regenerative therapies, aim to replenish functional β-cells by stimulating proliferation of healthy ones, or by generating new ones through neogenesis from progrenitor populations or transdifferentiation from other mature cell types. This review lists those current regenerative strategies for diabetes, highlighting various approaches, lessons and studies. It discusses regeneration of β-cells, bioengineering methods with transplantation based methods.

Running title: Regeneration strategies in the pancreas

Keywords: pancreas; β-cells regeneration; transdifferentiation; transplantation α-cells; insulin; endocrine islets of Langerhans

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Introduction

Most of the time when considering damage to the pancreas or pancreatic cells, like in diabetes mellitus or in pancreatic cancer, it is commonly understood as an irreversible process. However, pancreatic regeneration has emerged as a key area of research due to its potential implications in treating diseases such as listed above. This article will focus on the current understanding of the mechanism of underlying pancreatic regeneration, with particular emphasis on the structural and cellular characteristics that influence regenerative potential. The pancreas is mainly divided into the exocrine and the endocrine pancreas. In short, the endocrine pancreas makes up about 85% of the pancreas and is composed of acinar and ductal cells, while the endocrine pancreas consists of Islets of Langerhans, which make up to 1-2% of the whole pancreas and it is composed of α-cells, β- cells, δ-cells and PP cells [1,2,3] In case of a dysfunction or loss of the β-cells, which are responsible for the insulin production, in the Islets of Langerhans, the natural consequence is the development of diseases such as type 1 diabetes [4], which results from an autoimmune- mediated destruction based on genetic or environmental factors, therapeutic intervention is required. The standard therapeutic approach for diabetes focuses on controlling blood glucose levels through pharmacological agents and insulin replacement therapy. However, these strategies do not 3restore endogenous pancreatic function; they merely compensate for its loss. Emerging regenerative approaches aim to replenish functional β-cells, either by stimulating the proliferation of existing β-cells or by generating new ones through neogenesis and transdifferentiation – from progenitor populations or by reprogramming other mature cell types [4].

Material and methods

Eligible criteria

This review focused on studies investigating mechanisms and strategies for pancreatic regeneration in humans and experimental models. Eligible publications included original research articles, clinical studies, and review papers that provided data on β-cell regeneration, islet neogenesis, stem cell– derived pancreatic cells, transdifferentiation, and molecular pathways regulating pancreatic repair. Studies were considered eligible if they met the following criteria:

- published in peer-reviewed scientific journals,available in English,
- focused on pancreatic regeneration at the cellular, molecular, or therapeutic level,
- employed experimental, preclinical, or clinical approaches related to pancreas recovery.

Studies were excluded if they:

- focused exclusively on non-pancreatic tissues,
- were limited to unrelated endocrine or metabolic processes without pancreatic implications,
- were conference abstracts, editorials, or reports without sufficient methodological detail.

Data sources and search strategy

The literature search was performed using PubMed, Scopus, and Google Scholar databases. The search covered studies published between 2000 and 2025, reflecting both the early experimental discoveries in β-cell regeneration and the more recent advances in stem cell and gene therapy research.

Study selections and data analysis

The identified publications were screened by title and abstract for relevance. Eligible full--text articles were reviewed in detail. Information extracted included study type (experimental, preclinical, clinical, or review), model system used, regeneration strategy investigated, molecular pathways studied, and main outcomes related to pancreatic repair or functional recovery.

Findings were synthesized and organized thematically into sections covering cellular and molecular mechanisms, regenerative therapies, and translational perspectives.

Type 1 and type 2 diabetes – understanding the differences

In order to approach and develop potential therapies for the regeneration of the human pancreas, it is important to firstly understand the underlying differences between type 1 and type 2 diabetes and how the pathological pathways differ in β-cell loss (T1D) and in β-cell dysfunction and remodelling (T2D). The following paragraph will focus on these differences and the anatomy of the pancreas.

The pancreas is located retroperitoneally in the abdomen, posteriorly to the stomach. In a healthy adult person it approximately weighs 100g, with a length of 14 to 25 cm [2]. Anatomically, the pancreas is composed of the head, which is located in the curve of the duodenum, the body, which extends across the midline, posteriorly to the stomach and anteriorly to the vertebral column, and the tail, which reaches toward the left upper quadrant, near the spleen. Looking closer at the pancreas, we can

distinguish between two morphologically and functionally different components: the exocrine function, which has a digestive role, and the endocrine function, the hormonal role [1].

The dominant portion of the pancreatic tissue is concentrated on the exocrine function. This includes the acinar and ductal cells. Acinar cells make up about 85% of the pancreas, they produce and secrete digestive enzymes such as amylase, lipase, proteases and bicarbonate. These enzymes flow through the ductal cells into the pancreatic duct and then in the duodenum to support the digestion by breaking down fats, proteins and carbohydrates for absorption [1,2].

On the other hand, the endocrine aspect of the pancreas is composed of Islets of Langerhans, which make up to 1-2% of the whole pancreas and are responsible for the hormone production. These Islet cells are divided into α- cells (about 20% of the endocrine pancreas) which produce glucagon, β- cells (40-60% of the endocrine cells), which produce insulin, δ-cells (around 4%), 4which produce somatostatin, PP cells (~1%), which produce pancreatic polypeptide and ε-cells (less than 1%), which produce ghrelin [1].

According to the World Health Organisation in 2022 about 830 million people worldwide lived with diabetes. About 9 million people are affected by type 1 diabetes, which is also known as insulin-dependent, juvenile or childhoodonset. T1D can appear at any age but as the name states most people are affected in childhood or adolescence and the pharmacological intervention in form of daily administration of insulin is required. Unfortunately, unlike T2D, this is not a preventable process, it is an autoimmune endocrine disorder in which T-cells eliminate insulin producing β-cells in the islets of Langerhans [5]. This has been described as a heterogeneous process, which means that β-cells loss in all islets of the pancreas follow a mosaic pattern. Some islets contain more functional β-cells (insulin +) than other islets (insulin-), where the β-cells are completely reduced in number [2]. With time, the insulin – islets are larger in number than the insulin + islets, which in other words means that the pancreas does not produce enough insulin for glucose uptake by the human tissues [2]. Other endocrine cells, such as α- and δ-cells, types remain undamaged.

In comparison to type 2 diabetes, type 1 diabetes affects only a small portion of people. Most individuals with diabetes – approximately 95% worldwide according to the World Health Organization in 2022 – are affected by type 2 diabetes, a preventable condition in which β-cells gradually lose function and which involves tissue insulin resistance of the peripheral tissues [6]. T2D is preventable because it is the result of risk factors such as being overweight or obese, physical inactivity and an unhealthy diet which can all lead to hyperglycaemia which further works in favour of tissue insulin resistance. From the histological point of view there is no typical histological structure in T2D because the islet architecture remains relatively intact compared to T1D [2]. However, several structural changes accompany the β-cells such as the following:

Increased amyloid deposition- majority of people living with T2D show an increase of islet amyloid deposition, however its role in diabetes has not yet been established back in 2020 [2]. In recent publications it is shown that increased islet amyloid polypeptide deposition can lead to endoplasmic reticulum stress, which in short leads to the upregulation of CHOP, a protein 5involved in apoptosis, and in this case in apoptosis of the β-cell [6]. β-cell apoptosis leads us to the next structural change.

Reduced β-cell mass- it is not possible to determine if a person loses β-cells throughout their lives as every individual is born with a different β-cell mass. However, autopsy studies of individuals who lived with T2D have shown that they contained about 40% less β-cells than a person living without T2D [2]. Other studies propose that the β-cell mass is lost due to dedifferentiation of β-cells, where β-cell-defining transcription factors are lost as a consequence of glucotoxicity [6]. Another possible cause for the loss of β-cell mass is the transdifferentiation, which means that β-cells can undergo a process in which they terminally differentiate into another cell type, however more studies on humans are needed [6]. Another possible cause for β-cell dysfunction and loss of mass is mitochondrial dysfunction where, as a consequence of elevated ROS, β-cell stop functioning or undergo apoptosis. The same happens in elevated levels of Thioredoxin-interacting protein (TXNIP), which promotes β- cell apoptosis.

Increased pancreatic fat content- pancreatic fat content increases with age but does not continue to do so with T2D [2], on the other hand obesity is often accompanied by T2D. T2D is not the reason for increased pancreatic fat content but it belongs to its profile. Overall increased body fat mass leads to increased fatty acids in the blood and inflammation that work in favour of T2D [6].

Understanding these structural and functional distinctions is therefore critical for designing effective regenerative approaches tailored to the underlying pathology of each diabetes type.

Lessons from pancreatic regenerative biology

Pancreatic regeneration relies on a variety of intrinsic and extrinsic mechanisms, and lessons from both animal models and human studies reveal how β-cells can be replenished despite the structural challenges imposed by diabetes.

Several animal studies have demonstrated the natural regeneration of β-cells in young rodents after suffering a β-cell loss through replication, which declines with age [1]. However, the replication of β-cell can be induced in adult rodents in pregnancy or obesity. A genetic lineage tracing in mice showed that these replicated cells were originating from pre-existing β-cells. Unfortunately, in humans this process is much less clear [1].

A recent review reveals strategies to stimulate β-cells replications as a potential regenerative therapy for diabetes. Molecular mechanisms controlling the β-cell cycle, including the transcription factors, growth signals, and signalling pathways were discussed as a potential therapeutic targets to enhance β-cell proliferation. The limited proliferative capacity of adult β-cells is emphasized, along with strategies to overcome this limitation. The authors note that modulating β-cell replication could form part of future regenerative therapies, but further research is needed to ensure functional maintenance and safety [12].

Another possible way to regenerate β-cells is by the process of transdifferentiation, which is the conversion of one mature cell into another mature cell. Several studies show different methods to obtain this transdifferentiation of one cell grup into β-cells.

When it comes to the pancreas, it is possible for α-cells, which produce glucagon, to undergo the process of transdifferentiation into β-cells. This process is controlled by regulating transcription factors, such as Dnmt1, Arx, Pdx1, MafA, and Nkx6 and signalling pathways. In experimental models, it improves glycemic control, however clinical challenges still remain, such as the stability and functionality of these new β-cells [13].

The next source suggest that repressing miR-23a, a type of microRNA, may promote transdifferentiation by increasing the secretion of SDF- 1α (stromal cell-derived factor-1). SDF-1α is a chemokine which plays a fundamental role in β-cell development, survival and regeneration. By enhancing the secretion of SDF- 1α there is a higher number of α- to β- cell transdifferentiation. This was 8also confirmed by in vitro and in vivo experiments which show an increase in number of β- cells and improvement in insulin secretion. Therefore these findings suggest a potential therapeutic target in treatment of diabetes [14].

The same process was demonstrated in on mice that underwent induction of β-cell loss using streptozotocin (STZ), a compound that selectively damages insulin-producing β-cells, resulting in a 30–40% reduction in β-cell mass in neonates and adults (different dosages of STZ were given to the animals). The modest β-cell loss induced α- to β-cell transdifferentiation in both neonatal and adult mice. Neonates showed a larger number of bi-hormonal cells (expressing both insulin and glucagon), indicating a higher initial transdifferentiation activity. However, adults exhibited more fully transdifferentiated insulin+ cells and were able to partially restore β-cell mass, whereas neonates did not, despite evidence of transdifferentiation. The results suggest that neonatal islets exhibit greater plasticity, whereas adult islets demonstrate a higher capacity for partial functional β-cell recovery, highlighting a complex relationship between age, plasticity, and regenerative capacity [15].

In contrast to purely genetic or developmental approaches, Karakose et al. (2024) used a pharmacological strategy, treating human pancreatic islets with regenerative compounds such as DYRK1A inhibitors, alone to in combination with other agents [16]. DYRK1A also known as dual tyrosine-regulated kinase 1A which plays an important role in cell cycle regulation, neurodevelopment and differentiation. In the context of pancreatic islet cells it serves as a negative regulator of cell proliferation, maintaining β-cell at a resting state under normal conditions [17]. This intervention in form of DYRK1A inhibitors induced a distinct population of 'cycling α-cells' that entered the cell cycle and displayed transcriptional signatures consistent with a transition toward β-cell identity. These findings suggest that drug-induced activation of α-cells could provide a practical therapeutic avenue to promote β-cell renewal in diabetes [16].

Similar studies have been demonstrated on a mouse model of human islet xenotransplantation using a combination of harmine (a DYRK1A inhibitor) and exendin-4 (a GLP-1 analog). This combination leads to a safe expansion of human β-cells in vivo. The therapy increased β-cell mass and proliferation, as well as improved insulin secretion. The findings suggest a potential clinical application of the combined therapy in diabetes [18].

In addition to β-cell replication and transdifferentiation there is neogenesis, the formation of new mature cells, in this context mature β-cells, from progenitor or precursor cells, which are usually undifferentiated or multipotent.

RSPO1 (R-spondin 1) is a strong inducer of β-cell neogenesis in the pancreas. In experimental models, RSPO1 stimulated the formation of new β-cells and improved insulin secretion by activating the Wnt/β-catenin pathway. Those findings suggest a potential application of RSOP1 as a regenerative therapy for diabetes [19].

Next, the use of an THR-123 (an ALK3/BMPR1A receptor agonist) induces β- cell renewal in situ. In preclinical models, it increases β-cell mass and functionality, improving insulin secretion. The mechanism involves activation of BMP signalling pathways and the findings indicate a potential pharmacological application in diabetes therapy [20].

Strategies for β-cell regeneration

Building on the biological insights into pancreatic regeneration, multiple therapeutic strategies have been explored to restore β-cell mass and function in diabetes, ranging from pharmacological and molecular interventions to advanced cellular, bioengineering, and transplantation- based approaches.

The first approach to be considered is pharmacological and molecular therapy. Some pharmacological compounds stimulate the β-cell proliferation and regeneration in both T1D and T2D, several of which were discussed above [16,18]. These mechanisms include effects on transcription factors, signalling pathways and epigenetic regulation using DYRK1A inhibitors (like harmine), GLP-1 receptor agonists (like exendin-4), adenosine kinase (ADK), Salt inducible kinases (SIKs) and glucokinase (GK). These molecular insights identify promising therapeutic targets for restoring β-cell mass. However, this strategy requires further validation before clinical application [21].

The second approach incudes cellular and bioengineering methods with transplantation--based strategies. Recent advances in stem cell--derived (SCislets) highlight their potential as a sustainable cell source for diabetes therapy.

In the context of T2D, SC-islets have been shown to restore β-cell mass, enhance insulin secretion, and modulate insulin sensitivity, although disease specific challenges such as lipotoxicity, inflammation, and insulin resistance may limit their effectiveness. There is still a need for clinical studies and for developing methods to protect cells from metabolic stress [22]. Proof of concept studies further demonstrated an improvement of glycaemic control after transplantation of differentiated stem cells into pancreatic insulin secreting β-cells [23]. Recent advances in differentiation protocols have enhanced the generation of mature β-cells and recreated more physiological islet--like structures, but key hurdles remain, including long-term stability, immune rejection, and oncogenic risks, which highlight the need for further optimization before clinical application [24]. Importantly, one of the landmark studies in the field showed that metabolically mature and functional islets derived from human stem cells can exhibit glucose responsiveness and insulin secretion comparable to native islets, with in vivo studies confirming restoration of normoglycemia in diabetic models [25].

Tissue engineering approaches aim to further enhance the survival and functionality of transplanted cells. Han et al. (2021) presented the concept of a bioartificial vascular pancreas (BVP), the aim was to ensure proper vasculature to the islets of the pancreas, which is crucial for its survival and function after transplantation [26]. By combining biomaterials, cells, and vascular networks, preliminary results suggest that the BVP may improve the long-term functionality of β-cells, offering a complementary strategy to SC-islets for achieving effective and durable cell replacement therapy [26].

As transplantation was mentioned, several islet transplantation studies, including allogeneic, xenogeneic, and stem-cell-derived sources, represent a cornerstone of β-cell replacement therapy. Xenogeneic pancreatic islet transplantation (mainly porcine islets), as an alternative to the limited number of human donors, has shown in preclinical studies and early clinical trials the possibility of maintaining insulin secretion after transplantation [27]. Other strategies in β-cell replacement, including allogeneic islet transplantation, stem cell–derived islets, and organoids, have demonstrated the potential to restore pancreatic metabolic control even in rare cases as for instance in Wolfram syndrome [28,29]. Current advances address key challenges such as donor scarcity, immune rejection, and long-term graft survival through improvements in cell isolation, alternative sources, and immunomodulatory strategies [30-32]. The choice of implantation site also plays a crucial role in graft function and survival, with vascularization, tissue microenvironment, and surgical accessibility influencing outcomes; personalized strategies are therefore recommended [33]. Innovative approaches, as in immunomodulatory nanoparticle–treated spleens, have shown promise in promoting immune tolerance and maintaining long-term islet function in preclinical models [34]. However, main challenges remain, including immunological rejection, the risk of transmission of animal viruses in xenotransplantation (e.g., PERV), and ensuring lon-

g-term functionality. Collectively, these studies highlight that combining alternative cell sources, optimized implantation sites, and immune protection strategies are essential to maximize the safety, durability, and efficacy of clinical islet transplantation.

Considering that T1D is an autoimmune mediated process it is also important to consider the immunological barriers in all presented strategies. Mu-u-min et al. (2025) identified this problem of immunological rejection of transplanted β- cells and discussed strategies to evade immune rejection, included β-cell encapsulation by a semi-permeable membrane that shields them from immune cells while still allowing insulin secretion, genetic modifications, such as HLA deletion to silence immune recognition markers, and immunomodulatory approaches to induce tolerance in the recipient's immune system towards transplanted β-cells. Ongoing and planned clinical trials aim to test these strategies, emphasizing the need to balance immune protection with maintaining β-cell functionality [35].

Structure-informed regeneration: how organization shapes repair

After examining lessons from regenerative biology and strategies for β-cell regeneration, another equally important aspect is the structural and microenvironmental organization of pancreatic islets. Understanding this organization is essential for β-cell function, survival, and regenerative potential, while also highlighting the critical role of extracellular matrix (ECM) components, scaffold design, and vascular support in both experimental and clinical islet therapies [36].

Firstly, it is important to highlight the importance of pancreatic islet architecture. Smaller islets exhibit better vascularization and survival, improving insulin secretion and glycemic control while larger islets are prone to hypoxia and necrosis, reducing transplant efficacy. This indicated the need for standardisation of islet isolation and selection in transplantation procedures, as islet architecture shows a critical impact on therapy success [37].

Complementing these findings, scaffold-free tissue engineering approaches have demonstrated that preserving native islet organization alone can enhance β-cell function and survival, emphasizing that structural arrangement is as crucial as size for therapeutic outcomes [38].

Beyond architecture, the ECM is a key component necessary for β-cell survival and function. When designing biomimetic scaffolds for islet transplantation, the proper ECM components should be recreated as it may improve longtherm graft functionality [39]. Nonetheless, the proper composition of ECM is not only a key scaffold supporting β-cells but it also holds a signalling role, supporting β-cell differentiation and survival. Building on this, recent strategies have focused on the use of decellularized ECM (dECM) and its integration with biomaterials or bioactive factors to recreate a physiological microenvironment for transplanted islets. Such approaches aim to not only improve cell survival and insulin secretion but also to enhance the long-term stability and functionality of bioengineered pancreatic constructs [40].

Additionally, hydrogels have proven to not only be a promising tool for encapsulating pancreatic islets, providing both structural support and immunoprotection while allowing the exchange of nutrients, oxygen, and hormones [41]. Going further, pancreas-derived hydrogel, which was created through the process of decellularization (dECM), was able to recreate the ECM microenvironment specific to pancreatic endocrine cells. In vitro models showed improved differentiation, survival and better insulin secretion of hiPSCendocrine cells than compared to conventional hydrogels [42]. Combining dECM with curcumin offers an anti-inflammatory and antioxidant effect, further enhancing survival and insulin secretion [43]. On the other hand, functionalized GLP-1 hydrogels also enhance insulin secretion, proliferation and protection against apoptosis in β-cells [44].

Advanced bioengineering strategies have also explored 3D biomimetic matrices to study β-cell function and insulin secretion, demonstrating the importance of scaffold mechanical properties and porosity for cell survival and functionality [45]. Integrating vascular networks into these constructs further improves graft outcomes, as shown in vascularized endocrine pancreas models using hiPSC-derived cells, which exhibit glucose-responsive insulin secretion and enhanced survival [46]. Collectively, these approaches reflect a convergence of ECM recreation, hydrogel engineering, and vascular integration as key factors in designing functional bioartificial pancreatic tissues [36].

Yet, a successful islet transplantation is also determined by the quality of vascularisation. Many biomaterials enhance revascularization after islet transplantation including hydrogels, nanomaterials, bioactive coatings, and porous scaffolds [47]. Migliorini & Nostro, (2024) discussed the interaction between vascular and immune systems in islet transplantation and 3D islet models, highlighting the importance of vascular integration for graft function and survival [48].

Future perspectives

After quite a long description and comparison of various studies and past articles it is time to look ahead. The future of β-cell replacement and regenerative therapy for diabetes will rely on the integration of pharmacological, cellular, and bioengineering approaches, with a focus on personalized and clinically translatable solutions.

Bioengineering and its advances allow the recreation of endocrine niches for β-cells, while considering the importance of interactions with the ECM, endothelial cells, and stromal cells for islet survival and function. This provides the foundation for recreating physiologically relevant microenvironments that support β-cell survival and function [49].

Regenerative strategies, including endogenous regeneration, transdifferentiation, neogenesis and cell-based therapies, offer additional opportunities to enhance β-cell regeneration, however clinical barriers, like immunological, technical, and regulatory still hinder therapy implementation [50].

Islet transplantation still needs to address challenges such as limited donor availability, immunosuppression, and long-term graft survival. New approaches that are encapsulation, stem cells as an islet source, and gene editing lead to opportunities and barriers that need to be addressed to increase accessibility and therapy efficacy [51,52].

Piemonti (2025) describes the current stage of β-cell replacement therapy development in type 1 diabetes as the "final mile" of development – close to routine clinical application. However, as noted before, the main barriers remain: immunosuppression, limited cell availability, and long-term functional stability but it is necessary to translate promising experimental results into clinical practice [53].

Conclusions

This review explored current strategies for β-cell regeneration and replacement in diabetes therapy using various approaches starting with lessons taken from animal studies, which focused on the residual regenerative capacity by β-cell replication [1].

Mentioned lessons were talking about gaining β-cells by transdifferentiation form other cell sources, like α-cells, by controlling the regulation of transcription factors and signalling pathways [13], by repressing miR-23a [14], or by a pharmacological approach using DYRK1A inhibitors [16]. Others approached neogenesis as a potential source for β-cells either by using RSPO1 [19] or by the use of THR-123 [20].

Then several strategies of β-Cell regeneration were mentioned: Pharmacological: by DYRK1A inhibitors (like harmine), GLP-1 receptor agonists (like exendin-4), adenosine kinase (ADK), Salt- inducible kinases (SIKs) and glucokinase (GK) [21].

Bioengineering methods with transplantation-based strategies: among which were cell-derived (SC-islets) as a sustainable cell source for diabetes therapy [22-25]; a bioartificial vascular pancreas (BVP) to ensure proper vasculature to the islets of the pancreas [26] and strategies to evade immune rejection [35].

Last but not least, the whole organization was described to gain the full potential of regeneration of the pancreas, starting with islet architecture [37], ECM composition [39, 40], hydrogels to encapsulate pancreatic islets [41-44] and leading to the importance of proper vasculature [47].

Although many obstacles remain, translating these promising results into clinical practice could potentially benefit millions of people living with diabetes.

Ethical approval

This was a descriptive review. No human or animal subjects were involved in this research.

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Conflict of interest

The authors declare no conflict of interest.

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