

Regeneration of Pancreas Gland

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Abstract

Diabetes mellitus is a hyperglycemic syndrome characterized by a reduced production of insulin or of insulin action and a relative or absolute increase of glucagon, the main insulin counterregulatory hormone. The disease courses with mutilating chronic complications. The inability to produce or to respond to insulin, a hormone synthesized by pancreatic β -cells, leads to diabetes. There is an excruciating need of finding new approaches to protect or restore these cells once they are lost. The first rudimentary attempt to transplant the pancreas occurred in 1894 before insulin was isolated by Banting, Best and Collip in 1921. Current research is focusing on β -cell regeneration in the human pancreas, this probably being one of the most controversial aspects of research on DM1. As a more general definition, we may state that β -cell regeneration corresponds to the formation of new β -cells whether or not these cells were actually lost. The potential mechanisms of β -cell regeneration are the proliferation of these specific cells, their neogenesis from non- β -cell precursors, and their trans-differentiation from α -cells. There are favorable and unfavorable arguments regarding the ability of the human pancreas to regenerate β -cells within the context of DM1 and in other pathological conditions such as resections, fibrocystic disease and neoplasia. The enigma continues regarding whether the function of β -cells persists in diabetic patients through regeneration or neogenesis maintained in T1D. In this paper we discuss the history of Diabetes knowing from Insulin Discovery until α - cell transdifferentiating.

Keywords: *Regeneration; Trans Differentiation; Beta-Cell; Pancreas Islet; Pancreas Gland*

Introduction

The age of the earth is based on radioactive dating calculated from meteorites that fell on the planet, since the earth's surface is constantly changing or under destruction, so that it is difficult to determine this age precisely. At the end of the 19th century, the French scientist Henri Becquerel [1] discovered radioactivity and a method for the calculation of the earth's age based on the half-life of the radioactive elements of terrestrial and extraterrestrial minerals. The age of the earth was then calculated as 4.54×10^9 years \pm 1%. Based on uranium atoms that are decomposed into the lead atoms found in minerals.

The Earth has 7 billion inhabitants. The primates arose 70 million years ago. The chimpanzee, the common ancestor of man, appeared 25 million years ago.

The first hominids appeared on the Earth between 3 and 1 million years, the first representatives of modern man appeared 200 thousand years ago and intelligent human beings thousand years ago. Since the appearance of Homo Sapiens, the biped primate that arose in Africa 200,000 year ago, more than 108 billion people have lived on the Earth.

The current calendar for the counting of time started during the Christian era, more than 2000 years ago.

The saga for survival of the human species has suffered several drawbacks and natural selection has permitted the survival of lineages more resistant to the adversities at the expense of others.

The development of the health area with notions of hygiene, vaccination and preventive and curative medicines has permitted a marked increase in life expectancy, leading to the novel specialty called geriatrics. Today it is difficult to delimit the range of the population that can be defined as old and consequences have arisen with human aging, with people starting to live with new diseases typical of senescence.

There has been an increase in degenerative diseases and their consequences and in other previously non-existing diseases. Man has constantly sought to improve his knowledge in order to obtain early diagnoses, especially involving solid organs, looking for a cure by means of conventional treatments and later by means of transplant of the affected organs.

Pancreas

In the history of transplants, Adam was the first donor (Genesis 2:21-2) [2]. In the modern era, transplants were first performed in the 1980's, involving non-regenerable organs. Transplantation of an organ did not provide a cure but represented the hope for survival.

Diabetes mellitus is a hyperglycemic syndrome characterized by a reduced production of insulin or of insulin action and a relative or absolute increase of glucagon, the main insulin counterregulatory hormone. The disease courses with mutilating chronic complications.

The inability to produce or to respond to insulin, a hormone synthesized by pancreatic β -cells, leads to diabetes. There is an excruciating need of finding new approaches to protect or restore these cells once they are lost.

The first rudimentary attempt to transplant the pancreas occurred in 1894 before insulin was isolated by Banting, Best and Collip in 1921 [3].

The first pancreas/kidney transplant involved a patient with type 1 Diabetes Mellitus (DM1) with terminal nephropathy. In the 1990 decade, the joint pancreas/kidney transplants registered in the International Pancreas Transplant Registry (IPTR) reached a total of 6000 surgeries [4].

Modern pancreas transplantation started in 1972 when Ballinger and Lacy [5] reversed Diabetes Mellitus in rodents, in 1990, Scharp, *et al.* [6] obtained insulin independence for 30 days in a patients with DM1. Since then, the best 50% results obtained for human transplant recipients were observed in pancreatectomized patients [7].

In 2000, Shapiro, *et al.* reported that a series of pancreatic islet transplants in 7 patients with DM1 led to exogenous insulin independence for one year in all of them [8].

Along the 2000 decade, the Faculty of Medicine of Ribeirão Preto in the state of São Paulo, Brazil, became a pioneer in the treatment of DM1 with stem cell transplantation. These cells are known to have the potential for self-renewal and for the differentiation into more mature cells *in vitro* and in man, being able to reduce the onset to the typical complications of this disease [9-11].

Current research is focusing on β -cell regeneration in the human pancreas, this probably being one of the most controversial aspects of research on DM1 [12].

As a more general definition, we may state that β -cell regeneration corresponds to the formation of new β -cells whether or not these cells were actually lost [12].

The potential mechanisms of β -cell regeneration are the proliferation of these specific cells, their neogenesis from non- β -cell precursors, and their trans-differentiation from α -cells [12-15]. There are favorable and unfavorable arguments regarding the ability of the human pancreas to regenerate β -cells within the context of DM1 and in other pathological conditions such as resections, fibrocystic disease, and neoplasias [16,17].

The accepted view was that Langerhans islets might repopulate the pancreas during adult life through the reactivation of ductal progenitor cells. During the last decade, this theory was contested by the notion that pancreatic regeneration does not involve progenitors and might occur through the duplication of pre-existing mature cells [16,18,19].

These conclusions about pancreatic regeneration are not categorical, especially in view of emerging evidence that progenitor lines are less homogeneous and that cellular changes are more dynamic than previously thought. Thus, these two hypotheses about regeneration are not mutually exclusive.

Adult tissues are thought to harbor two populations of “dormant” and “actively dividing” stem cells. Quiescent stem cells undergo rare asymmetric cell divisions (ACDs) through which they self-renew and give rise to tissue-committed “progenitors” of distinct fate and “progenitors” undergo symmetric cell divisions (SCDs) and clonal expansion. Quiescent stem cells have not been demonstrated in adult tissues [19,20].

Although adult β -cells were thought to differentiate up to term and therefore to be irreversibly quiescent, over the last few years it became clear that this is not true and more recent approaches have shown that various molecular classes are clearly able to induce human β -cell proliferation [21].

Thus, there are challenges in a rapidly moving field aiming to transfer cell regeneration therapy from the laboratory to clinical practice, from the bench to the bed [22-24].

The strategies for β -cell regeneration can be classified into two main categories: 1) *in vitro* regeneration using pluripotent stem cells and 2) *in vivo* reprogramming of non β -cells so that they will turn into β -cells [23,24].

β -Cell regeneration has been shown to be a potential cure of insulin-dependent DM. Much progress is still necessary and β -cell regeneration therapy is becoming closer to clinical reality, although still far from being used (SCDs) in practice [25].

Postnatal β -cell growth is largely attributed to the proliferation of these cells, a process that continuously declines with advancing age. To boost beta-cell proliferation to regenerate adequate function, there is the need to understand the signaling pathways that regulate β -cell proliferation so that practical strategies may be created to promote the process. Transforming growth-factor beta (TGF β) belongs to a signaling superfamily that governs pancreatic development and the regeneration of beta cells in pancreatic injury [22]. TGF β exerts these functions by activating the Smad protein pathway and, by crossing other pathways, the signaling pathway of the TGF β receptor also participates in the control of β -cell proliferation [26].

Human Multipotent Stromal Cells (hMSCs) are one of the most versatile types used in medicine because of their ability to respond to injury. However, *in vivo* transplantation models for the determination of the regenerative potency of hMSCs are long/slow, onerous and poorly productive processes. A high-throughput quantitative proteomics assay has been developed to screen β -cell regenerative potency from donors of hMSC lines (uncharacterized hMSC lines for β -cell regenerative clinical applications [27].

A niche of β -cell kept immature during pancreatic development has been recently discovered. These cells are denoted “virgin” β -cells since they do not stem from existing mature β -cells. They are exclusively found at the periphery of islets and are denoted neogenic niches of β -cell regeneration.

The pancreatic duct gland (PDG) compartment has been proposed as a potential stem cell niche of the endocrine and exocrine pancreas on the basis of its tubular structure surrounded by mesenchyme containing endocrine and exocrine epithelial cells [28].

Adenosine signaling via the A2a receptor has an important role in compensatory β -cell proliferation that could be harnessed pharmacologically in the future for β -cell expansion and for future diabetes therapy. These studies are being conducted on zebra fish, linking endogenously produced adenosine to β -cell proliferation [29].

Glucagon-like peptide 1 (GLP1) can increase pancreatic β -cells, and α -cells could be a source for new β -cell generation, playing an important role in α -cell transdifferentiation to generate new- β -cells, which might be mediated in part by fibroblast growth factor 21 (FGF21) in locations whether endogenous adenosine regulates β -cell proliferation, either in the basal state or in states of increased demand for insulin. Thus, studies could be conducted to determine whether endogenous adenosine regulates β -cell proliferation, either in the basal state or in states of increased demand for insulin, and to delineate the mechanisms involved [30-32].

Insulin-like growth factor binding-protein 1 (IGFBP1) potently promotes β -cell regeneration inducing α -to- β transdifferentiating by inhibiting, at least in part, IGF1 and appears to be conserved across species. A prospective human study showed that having high IGFBP1 levels reduces the risk of developing type-2 diabetes (T2D) by more than 85% [31,32].

Protease-activated receptor-2 (PAR2), a G-protein-coupled receptor, modulates transdifferentiation of islet cells in a cell-specific manner even in the absence of β -cells in murine and human type 1 diabetes (T1D) [33].

The mechanism of regeneration of the remnant pancreas after partial pancreatectomy is still unknown. The effect of siRNA against the collagen specific chaperone HSP47, which inhibits collagen secretion from activated pancreas stellate-cells (cPSCs) inducing their apoptosis, has been studied in the regeneration of the pancreatic remnant with favorable results [34].

There is evidence that transplantation of cadaveric β -cells could be an effective therapy for T1D. However, gauging the suitability of islet samples for clinical use remains a challenge. It is possible that previously classified genes in combination with other tests may complement the verification of islet quality before the clinical use of the islets in transplants [35].

The enigma continues regarding whether the function of β -cells persists in diabetic patients through regeneration or neogenesis maintained in T1D [36-38].

A compensatory increase in β -cell mass occurs during pregnancy to counter the associated insulin resistance and a failure in adaptation is thought to contribute to gestational diabetes. Insulin-expressing but glucose-transport-low (Ins+Glut2LO) progenitor cells are present in mouse and human pancreas, being predominantly located in extra-islet β -cell clusters and contribute to the regeneration of the endocrine pancreas following induced ablation. Ins+Glut2LO cells are likely to contribute to β -cell mass expansion during pregnancy [39].

Modulating molecular targets involved in β -cell fate maintenance or in general differentiation mechanisms can further potentiate this intrinsic cell plasticity, which leads to insulin production reconstitution [40]. In humans, insulinomas hold the “genomic recipe” for β -cell expansion. It was shown that most of the insulinomas studied had mutations, copy number variants and/or dysregulation of epigenetic modifying genes, coupled with co-expression of network modules associated with cell proliferation, revealing candidates for inducing β -cell proliferation [40]. Understanding the molecular complexity of insulinomas may be a valuable approach to the discovery of new drugs for the treatment of diabetes [41].

Conclusion

In spite of the fact that Diabetes History advanced a lot in knowing, there much to do to becomes these knowing in reality for the diabetic patient.

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