Review

MOLECULAR METABOLISM

An update on pancreatic regeneration mechanisms: Searching for paths to a cure for type 2 diabetes

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ABSTRACT

Background: Over the last decades, various approaches have been explored to restore sufficient β-cell mass in diabetic patients. Stem cells are certainly an attractive source of new β-cells, but an alternative option is to induce the endogenous regeneration of these cells.
Scope of Review: Since the exocrine and endocrine pancreatic glands have a common origin and a continuous crosstalk unites the two, we believe that analyzing the mechanisms that induce pancreatic regeneration in different conditions could further advance our knowledge in the field. In this review, we summarize the latest evidence on physiological and pathological conditions associated with the regulation of pancreas regeneration and proliferation, as well as the complex and coordinated signaling cascade mediating cell growth.
Major conclusions: Unraveling the mechanisms involved in intracellular signaling and regulation of pancreatic cell proliferation and regeneration may inspire future investigations to discover potential strategies to cure diabetes.

Keywords Pancreas regeneration; Proliferation; Exocrine pancreas; Islet plasticity

1. INTRODUCTION

The adult human pancreas consists of two main glands composed of endocrine and exocrine tissues, with a very low percentage of vascular and nerve structures. The greater part of the pancreatic mass is the exocrine gland, responsible for the synthesis of digestive enzymes as well as their transport to the duodenum through a complex ductal system. Over 95% of the pancreas is composed of acinar and ductal cells, and their ability to proliferate in response to various stimuli make them attractive targets for in vivo β-cell regeneration (see Tables 1 and 2, Fig. 1).

The endocrine pancreas represents about 2% of the overall organ, organized into functional units called islets of Langherans including α, β, δ, ε and PP cells, which produce hormones mainly involved in regulating glucose homeostasis [1,2]. Absolute or relative deficit of functioning β-cells leads to diabetes and one of the major goals of diabetes research over the last decades has been to understand the mechanism regulating homeostasis and the development of the functional β-cell mass.

β-Cell mass is the total weight of β-cells in the pancreas and is determined by the balance between birth (replication of existing cells and neogenesis/transdifferentiation) and death (apoptosis/necrosis) of β-cells as well as single cell volume (atrophy/hypertrophy).

Two possible approaches to replenish β-cells are: 1) transplantation of cadaveric islets or β-cells derived from human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSC) and 2) induction of endogenous regeneration. The first option already represents a concrete strategy for β-cell replacement which is being explored in preclinical and clinical settings [4–6] However, transplantation of cadaveric islets or pancreas is limited by the availability of organ donors and the need for lifelong immunosuppression.

Additional issues still need to be addressed, i.e. inadequate cell differentiation, appearance of chromosomal abnormalities, islet encapsulation, delivery and long-term graft survival, function, and integration with the body [7], prior to large-scale clinical use of ESC or iPSC.

In addition, we believe that induction of endogenous regeneration is a fascinating approach to restore functioning β-cell mass and prevent diabetes onset.

Endogenous regeneration can follow two pathways: enhanced replication of existing β-cells and genesis of new β-cells from cells not expressing insulin, either by conversion from a differentiated cell type (transdifferentiation) or differentiation from progenitors (neogenesis) [3].

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Table 1 — Main factors involved in β-cell mass adaptive modifications during pregnancy. *Both PL and PRL act mainly through the prolactin receptor (PRLR) activating different molecular pathways, including JAK2/STAT5 and PI3K/AKT. These pathways regulate the expression of target genes involved in cell proliferation, expansion, death, such as Foxd3, FoxM1 and Menin1. Serotonin acts in a paracrine fashion contributing to β-cell expansion.*

	Animal studies	*Human studies*	*Effect*
Hormones			
Prolactin and placental lactogen	↑ β-cell serotonin secretion [48] ↑JAK2/STAT5 and PI3K-AKT-mTOR signaling pathway [49] ↓ Menin1 expression [42]		β-cell proliferation
Serotonin	Co-secreted with insulin by β-cells ↑β-cell expansion (paracrine action) [48]		B-cell expansion
Intracellular factors			
JAK2/STAT5 signalling	↑Pbk kinase [50]		β-cell proliferation
PI3K/AKT/mTOR signalling	↑β-cell growth and differentiation [66]		β-cell growth and differentiation
Foxd3	Maintain glucose homeostasis. ↑ β cell expansion [51]	Expressed in human islets [51]	β-cell expansion
FoxM1	cell-cycle transcription factor [52,53]		β-cell proliferation
Menin1	maintain cell cycle inhibitors p27 and p18 active [42]		β-cell proliferation (due to downregulation)
Others			
Hepatocyte growth factor (HGF)	decreased β-cell regeneration and increased β-cell apoptosis in c-Met KO mice [56]	Circulating HGF markedly increased during pregnancy [67]	mitogenic, antiapoptotic and insulinotropic agent for the β-cell
Micro-RNA	modulate β-cell gene expression [57,59]		β-cell differentiation, proliferation, survival
Macrophages	Pancreatic macrophages depletion compromises β-cell proliferation and leads to glucose intolerance [63]		β-cell proliferation

Table 2 — Genetic and epigenetic alterations of PDAC: PDAC is frequently characterized by activating K-RAS mutations, and by the inhibition of INK4, p53, and SMAD4 tumor suppressor genes [219]. Overexpression of tyrosine kinases receptors, such as FGFR, PDGFR and VEGFR, as well as their ligands is a common event in PDAC [220]. Insulin and IGF are both overexpressed in PDAC and have a similar function [229]. Genetic analysis reports that Notch, sonic Hedgehog and Wnt pathways are aberrantly activated [234]. Elevated COX-2 has been associated with pancreatic cancer cell proliferation [236] and tumor growth [216,237].

Genetic and epigenetic alterations of PDAC		
	Role	*References*
activating K-RAS mutations	Oncogene	[219]
inactivation of the INK4, p53, and SMAD4	Tumor suppressor genes	[219]
Overexpression of FGFR, PDGFR and VEGFR and their ligands	Tyrosine kinase receptors	[220—222]
Overexpression of IGF1 and IGF2	Induction of proliferation	[224]
High insulin receptor expression	Enhances PDA development	[225,226]
Notch, sonic Hedgehog and Wnt pathways aberrantly activated	Modulate cellular replication	[234]
Cox 2 overexpression	Induces cell proliferation	[235—237,239]

New insights suggest that β-cell regeneration could be responsible for β-cell mass regulation in various phases of life, particularly in early postnatal life, pregnancy, obesity and aging. Both exocrine cells, such as duct—lining or acinar cells, and endocrine cells, such as preexisting β-cells and intraislet precursor cells, could be involved in these molecular mechanisms [8,9]. It is worth noting that many mechanisms involved in pancreatic cell regeneration, possibly representing new opportunities for treatment of type 2 diabetes (T2D), are still unknown. Pancreas regeneration involves a complex and finely regulated cascade of signaling molecules mediating the regulation of compensatory cell growth. Starting from these assumptions, an in-depth analysis of physiologic and pathologic conditions, such as human pancreatic carcinoma and proliferative disease, may represent an effective way to unravel new molecules and mechanisms involved in the intracellular signaling and regulation of β-cell regeneration.

2. CONDITION-SPECIFIC MECHANISMS OF PANCREATIC CELL REGENERATION IN THE ENDOCRINE ORGAN

The islets of Langherans undergo several adaptations to new physiological conditions occurring during life. β-cell replication is the main mechanism leading to β-cell expansion in early childhood. However, β-cell proliferation rapidly declines and in adults β-cell division rate is very low [10—12]. Unlike young β-cells, adult β-cells show increased expression of cell cycle inhibitors such as p16INK4a, and a reduction in cell cycle activators including FoxM1, cyclins, and cyclin-dependent kinases, which determine a resistance to proliferation [13—15].
Under some circumstances, including obesity and pregnancy, β-cell mass adaptively increases in adults. In addition, endocrine hormones might be involved in β-cell mass homeostasis and turnover. It has been suggested that the gut-derived hormones gastrin, glucagon-like peptide 1 (GLP-1), as well as human placental lactogen (hPL) and

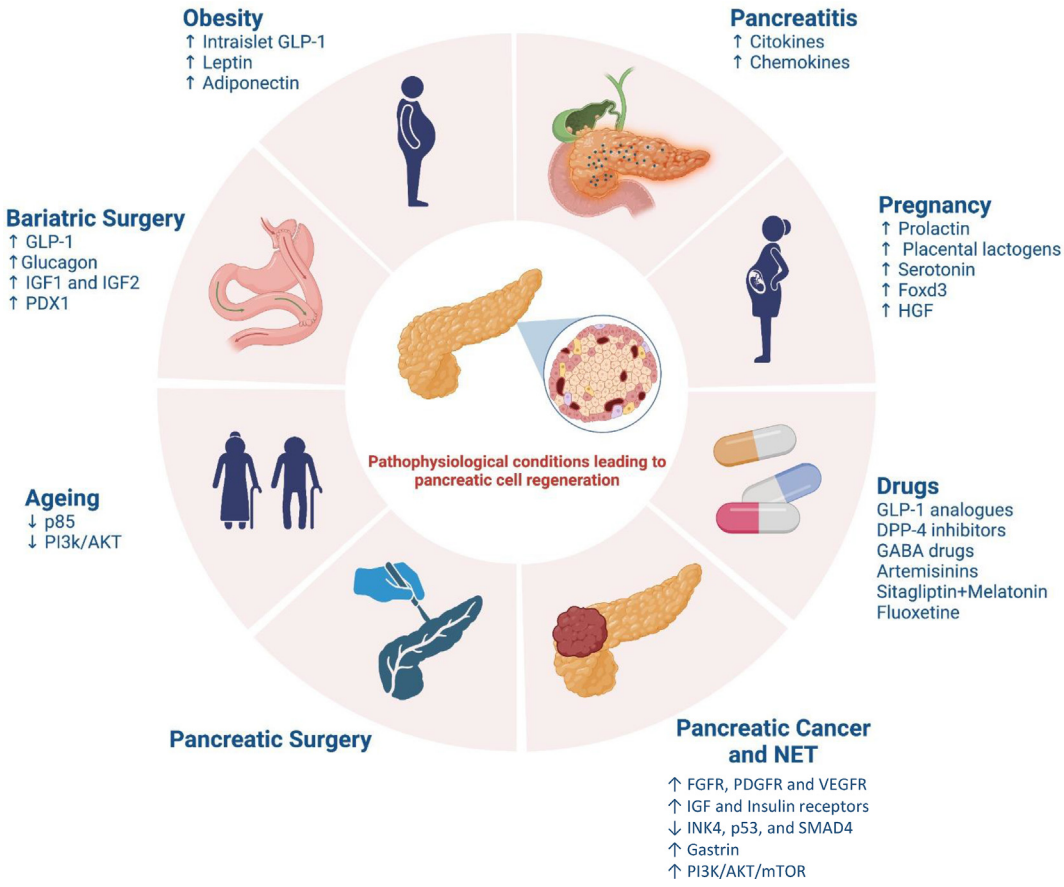

Figure 1: Pathophysiological conditions leading to pancreatic cell regeneration.

prolactin (PRL), enhance β-cell replication [16,17]. On the other hand, pathological conditions like insulinoma or nesidioblastosis can cause uncontrolled proliferation of β-cells [18,19]. All these observations have raised interest in the signaling pathways driving β-cell mass increase in the hope that the same signals could open new roads to β-cell regeneration in humans with diabetes [20]. In common with other cell types, replicating β-cells have an increased vulnerability to apoptosis, which is likely to limit the therapeutic value of inducing β-cell replication in the proapoptotic environment of T1D and T2D unless applied in conjunction with a strategy to suppress increased apoptosis.

2.1. Aging

It is well known that endocrine and exocrine secretions decrease progressively with aging [21]. However, in contrast to the atrophy of the exocrine pancreas, the endocrine organ remains relatively unchanged during aging [22,23]: In fact, it has recently been observed that β-cell mass remains relatively constant from the age of 20—100. Furthermore, there is no change in β-cell size and apoptosis rate, suggesting that in healthy individuals β-cell are longlived [11]. At the same time, increased β-cell nuclear size confirms the increased demand in glucose stimulated insulin secretion (GSIS) due to reduced insulin sensitivity [24].

Pancreatic growth is also attenuated by aging [25,26] and the replicative capacity of β-cells declines rapidly with age. Kulkarni et al. have demonstrated that transforming growth factor signaling-β (TGF-β),through the recruitment of Smad 3, induces Ink4α expression, leading to replicative decline in β-cells and that small molecule inhibitors of TGF-β signaling can be used to induce β-cell replication [27]. The same group also proved that aging reduces global m6A methylation. Since the latter phenomenon regulates β-cell biology and is critical to maintaining healthy cells, its alteration contributes to the pathogenesis of type 2 diabetes mellitus in humans [28]. Thus, therapeutic targeting of regulators of m6A in a β-cell specific manner might be a new way to counter decreased m6A levels in T2D islets and promote β-cell survival and function.

Further, activation of the PI3K/Akt pathway plays an important role in many endocrine functions, such as insulin signaling, insulin-stimulated glucose transport, and glycogen synthesis [28—30]. The activation of this pathway, which is essential for pancreatic duct cell differentiation into insulin-producing cells both in vitro and in vivo during pancreatic regeneration [31], is decreased in elderly subjects.

In addition, telomere shortening, a well-known characteristic of senescent cells, has been found to occur in the human pancreas (both exocrine and endocrine cells) during aging [32]. Cellular senescence is defined as a state of irreversible cell cycle arrest during which cells secrete proinflammatory cytokines and chemokines, known as the senescence-associated secretory phenotype (SASP). The latter negatively affects β-cell homeostasis [33] leading to chronic inflammation [34,35]. Moreover, senescent β-cells may contribute to the senescence of adjacent β-cells via secretion of SASP in a paracrine manner. Therefore, controlling chronic inflammation or suppressing senescent cells are considered two emerging potential therapeutic strategies for aging related diseases, including diabetes. Within the last two decades potential markers and molecular mechanisms of cellular senescence

have been discovered in pancreatic β cells [35], and senotherapy application in diabetes could represent a new treatment strategy which needs further investigation to evaluate potential clinical application.

2.2. Pregnancy

During pregnancy, the mother develops insulin resistance to shunt nutrients to the growing fetus. As a result, maternal islets of Langerhans undergo several changes to increase insulin secretion in order to maintain glucose homeostasis and prevent the development of gestational diabetes [36]. The change in maternal β-cell capacity results in the increase of the pool of maternal cells and in their ability to secrete insulin in response to glucose [37].

From the first observation in 1978 reporting an approx. 2.4 fold increase in β-cell mass in pregnant compared to non-pregnant women [38], pregnancy has been considered the strongest physiological stimulus inducing β-cell mass plasticity. Several studies have thus investigated the role of pregnancy in the regulation of β-cell mass both in rodents and humans. In pregnant rodents, proliferation of preexisting cells and their enhanced function [39] seem to be the main mechanisms of compensation, even if neogenesis cannot be excluded [40]. Butler et al. [41] found an increased number of β-cells in apparently new, small islets as well as insulin-positive cells within the ductal epithelium, rather than β-cell replication in existing islets, in pregnant women. Therefore, in humans β-cell neogenesis rather than β-cell replication seems to be the main mechanism behind this adaptive change, since no increase in mean size or in mean number of β-cells per islet were found.

However, analysis of pancreas samples from pregnant cadaveric donors may represent a limitation in the evaluation of pancreas morphology and proliferation. In fact, previous studies show that murine β-cells proliferate within a defined time window [20,42], which does not correspond to gestational age of the pancreata analyzed in human pregnancy. For these reasons, mechanisms of β-cell mass expansion during human pregnancy are still controversial. Moreover, based on current evidence, β-cell regeneration could be one of the mechanisms regulating pregnancy related β-cell expansion, even though it is strongly suggested that β-cell proliferation in humans is relatively low compared to animal models.

Furthermore, pregnancy associated hormones such as PRL, hPL, and human growth hormone (hGH) have been shown to be involved in the proliferation of β-cells in mice, rats and human islets, suggesting that β-cell proliferation could be involved in β-cell expansion during human pregnancy [43]. Although hormonal involvement in β-cell expansion during human pregnancy has not been investigated, several studies in animal models have suggested hormonal implication in pregnancy changes; thus, a similar regulation in human β-cells cannot be excluded. Increased β-cell proliferation during pregnancy is correlated with the rising of pituitary and placental lactogen levels [39] and treatment with PRL and PL efficiently drives β-cell proliferation and increases GSIS in vitro and in vivo in rodents [43,44]. Finally, β-cell modifications during pregnancy require an intact β-cell PRL receptor (PRLR) in mice [45,46]. This receptor is activated by the binding of both PRL and PL and its expression is induced in β-cells during pregnancy [47,48].

In addition, increased serotonin production by β-cells, which is normally secreted in response to PL signaling, has been proposed as an additional player contributing to β-cell expansion through a paracrine action [48].

The PRL receptor (PRLR) is a cytokine class-1 receptor and activates the JAK2-STAT intracellular pathway, as well as Ras/Rap/MAPK and PI3K/AKT/mTOR signaling cascades, which strongly influence cellular response by modulating concentrations of cytosolic and nuclear phosphatases [49]. Among the various effects, the activation of JAK2-STAT5 signaling induces the transcription of the gene coding for Pbk kinase which has a crucial role in the β-cell proliferation [50].

Further, Menin1 has also been indirectly described as modulator of the homeostasis of β-cell proliferation during pregnancy. This transcription factor is downregulated during pregnancy due to the effect of the PRL pathway and experimentally-induced expression of Menin1 during pregnancy leads to decreased β-cell proliferation and maternal hyperglycemia probably due to its effect on cell cycle inhibitors p27 and p18 [42].

In addition, studies suggest that transcription factor Forkhead box D3 (Foxd3), also expressed in human islets, plays a role in glucose homeostasis and β-cell expansion during pregnancy. Foxd3-mutant mice show decreased β-cell mass and proliferation as well as misregulation of genes regulating proliferation, Foxm1, Skp2, Ezh2, Akt2, and Cdkn1a [51]. Specific deletions in the gene encoding Foxd3, implicated in cell proliferation and stem cell regulation during embryogenesis, also reduced β-cell expansion during pregnancy, although β-cell mass was already decreased before pregnancy in these animals. Interestingly, expression of Foxd3 actually decreases during pregnancy [51]. By contrast, expression of the cell-cycle-associated transcription factor FoxM1 increases in mouse β-cells together with cell-cycle induction during pregnancy, and in mouse islets in vitro, in response to lactogens [52]. Selective deletions of the gene encoding FoxM1 reduced β-cell expansion both during normal postnatal growth [53] and in pregnant mice [52]. Finally, deletions of the β-cellular gene encoding nuclear receptor HNF4α also led to decreased β-cell proliferation and mass in pregnant mice [37].

Circulating hepatocyte growth factor (HGF) increases markedly during pregnancy in humans [54] and has been shown to exert mitogenic, antiapoptotic and insulinotropic effects on β-cells [55]. Demirci el al. [56] investigated the role of HGF in maternal β-cell adaptation during pregnancy and they observed decreased β-cell regeneration and increased β-cell apoptosis, associated with reduction in islet PRLRs levels, Stat5 nuclear localization and FoxM1 mRNA together with an upregulation of p27 in pancreata of pregnant HGF receptor (c-Met)-knockout mice, thus suggesting an essential role of HGF/c-Met signaling in maternal β-cell adaptation during pregnancy.

Beside lactogenic hormones, additional factors contribute to adaptive changes in β-cell mass, including steroid hormones and lipids, and, more recently, microRNAs [57]. Among them, miR-338-3p [58] is decreased in pregnancy and obesity by the activation of the G-coupled protein estrogen receptor GPR30 and the glucagon-like peptide 1 receptor, consequently enhancing β-cell proliferation and inhibiting apoptosis [37,59]. Further studies are required to investigate the role and relationship of estrogens and progesterone in mediating β-cell adaptations during pregnancy.

Conditions such as pregnancy and obesity are associated with a decreased sensitivity of target tissues to insulin and a consequent rise in insulin demand, initially compensated by increased β-cell function and mass [60,61]. In human pregnancy, the stimuli leading to β-cell mass expansion occur before the peak of decline in insulin sensitivity, which has been observed in the third trimester of pregnancy [62]. Collectively, these observations suggest that the increased insulin demand due to insulin resistance cannot be the major factor in β-cell mass expansion and that islet expansion during pregnancy anticipates worsening of insulin resistance.

Furthermore, recent studies suggesting an interplay between pancreatic macrophages and β-cells have revealed that depletion of pancreatic macrophages may compromise β-cell proliferation and lead

to glucose intolerance in animal models [63]. β-cell-derived placental growth factor (PIGF) recruits naïve macrophages and polarizes them towards an M2-like phenotype. These macrophages then secrete epidermal growth factor (EGF), which activates extracellular signal-regulated kinase 5 (ERK5) signaling in β-cells to promote gestational β-cell proliferation. On the other hand, activation of ERK5 signaling in β-cells enhances their PIGF production and secretion [63]. In addition, alpha cells seem to play an essential role in regulating metabolic homeostasis in pregnancy. It has recently been demonstrated that in mice alpha cells undergo several morphological and functional changes regulated by pregnancy hormones [64]. C57BL/6 mice models showed a significant increase in α-cell mass during pregnancy, possibly potentiating insulin secretion. Maternal pancreatic GLP-1 content was also significantly increased during pregnancy [65]. Therefore, several hormonal changes in humans induce islet remodeling to counteract the decrease in insulin sensitivity, and these changes differ significantly compared to animal models. As regards intracellular pathways, JAK2/STAT5 and PI3K-AKT-mTOR seem to have a crucial role in inducing β-cell proliferation also in pregnancy.
Additional factors contributing to adaptive changes in β-cell mass: HGF (hepatocyte growth factor), highly expressed in islet endothelial cells with mitogenic, antiapoptotic and insulinotropic effects on β-cells, MicroRNAs (miRNAs) modulating β-cell gene expression and macrophages, recruited by PIGF.

2.3. Obesity and insulin resistance

The natural history of β-cell failure in obesity-induced T2D can be divided into three steps: 1. cell compensatory hyperplasia and insulin hypersecretion, 2. Insulin secretory dysfunction and 3. Loss of β-cell mass. [68] In fact, obesity is associated with peripheral insulin resistance, a hallmark of T2D pathophysiology. To maintain euglycemia, β-cell secretory function has a compensatory phase during which insulin secretion rises. However, hyperglycemia appears when compensation mechanisms fail [69,70].
Obesity is strongly correlated with increased β-cell mass, as recently confirmed by Saisho et al. [22]. They suggested that 50% increase in β-cell mass is mainly due to an increased number of β-cells (hyperplasia) rather than β-cell hypertrophy. Neogenesis might be involved in β-cell mass expansion, but the source of possible new cells is still unknown [23]. These data confirm previous observations suggesting the presence of enlarged islets [71], increased pancreatic parenchymal volume [72] and β-cell area [73] in a few non diabetic obese patients.
The exact origin of potential new β-cells in insulin resistance is still being actively investigated. Replication, neogenesis and transdifferentiation (i.e. transdifferentiation of α-cells into β-cells and/or acinar/ductal transdifferentiation into insulin-producing cells) are all potential mechanisms [74—76], but it is still unclear which (if any) plays a dominant role in humans. While the main mechanism in adult rodents seems to be β-cell replication [77,78], in some human studies, neogenesis rather than enhanced replication seems to emerge as the most important mechanism. Yoneda et al. [79] reported increased numbers of single cells or small clusters of insulin + cells, bihormone-expressing cells and a greater percentage of insulin + cells in ducts in pancreas samples from subjects with impaired glucose tolerance (IGT) or newly diagnosed T2D compared to non-diabetic patients; no difference in proliferation (Ki67 expression) was observed. Similarly, our group reported an increased proportion of scattered insulin + cells and small islets and a 3-fold increase in cells co-expressing insulin and the duct marker cytokeratin 19 (CK19) in pancreas samples from insulin-resistant non-obese subjects compared to insulin-sensitive subjects; proliferation was not detectable, as observed by KI67 staining [74].
Bhushan et al. identified duct cells positive for immature β-cell markers in pancreas sections from pregnant humans and in individuals with T2D, therefore in physiological and in pathological states of insulin resistance [80]. Furthermore, inflammatory cytokines seem to stimulate ductal-to-endocrine cell reprogramming in human pancreatic ductal cells with implications for β-cell regeneration [81]. A fourth study, analyzing pancreas samples from organ donors, reported overall increased neogenesis (clusters of 3 or less insulin + cells) in obesity and T2D [61]. In addition, increased PCNA+(proliferating cell nuclear antigen)/insulin + cells were found in non-diabetic obese individuals, whereas decreased levels were detected in obese T2D subjects [3].
Therefore, pancreatic duct cells seem to serve as a pool for progenitors of both islet and acinar tissues after birth and during adulthood [82].
Another potential origin of new β-cells is the pool of α-cells. In fact, an increase in α-cells and insulin/glucagon double positive cells has been reported in insulin resistant humans [74,79].
It seems that the dysfunctional β-cells themselves are able to induce β-cell mass expansion [75].
A factor that seems to be crucial in islet remodeling is the intraislet production of incretin hormones [83]. Indeed, the presence of intraislet GLP-1 has several effects including the differentiation of progenitor cells into β-cells in the pancreatic duct epithelium [84,85], and the direct stimulation of proliferation and inhibition of apoptosis of β-cells [86—88].
In addition, liver-derived circulating factors such as HGF [89] and SerpinB1 have been recently demonstrated to potentiate β-cell proliferation in multiple species, including in human islets [90].
Insulin itself seems to contribute to β-cell proliferation and survival via an endocrine manner. Circulating insulin levels activate signaling proteins downstream of the insulin/IGF-1 receptors, including AKT, ERK and FoxO1. β-cells in mice with conditional disruption of functional insulin receptors (e.g. βIRKO) exhibit minimal activation of AKT pathways in response to glucose or insulin stimulation, in contrast to ERK and FoxO1 proteins, which were phosphorylated independently of insulin receptor signaling [91]. Furthermore, receptor-mediated insulin signaling promotes G0/G1 transition enhancing the FoxM1/PLK1/CENP-A pathway, thus increasing the expression of centromere protein A (CENP-A), which is required for chromosome segregation during the M-phase, necessary for adaptive β-cell proliferation [92].
In addition, obese subjects show higher levels of adipokines, which correlates positively with glucose and insulin levels, while correlating negatively with insulin sensitivity [93]. Leptin and adiponectin are the best known adipokines. Various studies have demonstrated that adipokines regulate β-cell proliferation, while leptin has been shown to induce proliferation of mouse and rat pancreatic β-cells [94] and to protect β-cells from the effects of lipid overload [95]. In fact, leptin-resistant mice exhibit greater β-cell mass loss on a high fat diet (HFD) [96]. Other adipokines regulating β-cell proliferation are irisin, visfantin and apelin [97]. However, proliferation has not been recognized as a crucial mechanism in response to obesity in human pancreata and to date, only a few studies have explored the possibility that some adipokines may influence other mechanisms, such as β-cell neogenesis from duct cells, increased β-cell size, and transdifferentiation from α-into β-cells. Various studies in streptozocin (STZ)-induced diabetic and HFD-fed mice have shown that apelin plays an important role in the regulation of pancreatic β-cell hyperplasia [98,99]. Considering the beneficial extrapancreatic effects of apelin-13 such as promotion of satiety, cellular glucose uptake, insulin sensitivity and cardiovascular effects, targeting the apelin-APJ axis could be an attractive future strategy for the treatment of diabetes.

In addition, IL-6 seems to have a role in the β-cell adaption to obesity. In fact, transgenic mice overexpressing IL-6 show islet hyperplasia and an increased number of extra- and intra-islet ducts, suggesting islet neogenesis [100].

Replication in humans probably plays a more significant role during childhood, in particular in the first five years of life [101,102] and childhood obesity might determine a greater increase in β-cell mass in adult life [103].

It has recently been suggested that cross talk between peripancreatic adipose tissue and β-cells [104] could be responsible for increased β-cell replication in obesity. Obesity, in fact, could induce specific changes in the expression profile of peripancreatic adipose tissue, leading to decreased IGFBP3 expression, consequently causing an increase in β-cell proliferation through a paracrine effect. Since insulin like growth factors (IGFs) are known to exert mitogenic effects on β-cells both in vitro [105] and in vivo [106,107], decreased IGFBP3 expression may act in a IGF1-dependent manner. Furthermore, it has been suggested that the glycerolipid/free fatty acid cycle plays a significant role in the regulation of β-cell mass and function [107]. In this cycle glucose and lipid metabolic pathways converge providing mediators of β-cell growth and proliferation, such as lysophosphatidic acid and phosphatidic acid respectively, activating PPARgamma and mTOR pathways [108]. Increased β-cell mass and increased lipogenesis have been observed in several T2D animal models, whereas obese Zucker fatty rats showed enhanced glycerolipid/free fatty acid cycle at high glucose levels, suggesting that an additional compensation is required for obesity [109,110]. The role of free fatty acids in β-cell proliferation is still under debate. Some studies suggest that they exert toxic effects on β-cell function and hence survival [111]; others postulate that in the context of obesity FFAs could stimulate β-cell proliferation [112]. Although studies in vivo have concluded that FFAs do not limit β-cell proliferation [113,114], recent findings suggest that higher levels of FFAs block glucose-mediated adaptive β-cell proliferation via induction of cell cycle inhibitors p16 and p18 [115] in vivo, introducing a new antiproliferative form of β-cell glucolipotoxicity.

In conclusion, obesity, like other conditions characterized by insulin resistance, is strongly correlated with β-cell mass expansion mainly due to increased β-cell number. In the compensatory phase, thanks to β-cell mass expansion, insulin secretion rises thereby maintaining euglycemia, while hyperglycemia and diabetes appear only when the compensation mechanisms fail and apoptosis and dedifferentiation begin to prevail on β-cell mass growth and overload. In fact, a number of studies have suggested a decreased β-cell mass in T2D compared to controls [116–119]. Our group has also recently clarified the role of beta-cell mass reduction in the pathogenesis of diabetes, suggesting that acute reduction of beta-cell mass induces hyperglicemia only in subjects with preexisting functional defects [120].

Thus, we believe that the increase of beta-cell functional mass is the only defense strategy against diabetes and that beta-cell regeneration could be used to treat diabetes in presence of preserved functionality and concomitant treatment of the dysfunctional milieu.

2.4. Pancreatectomy

Partial pancreatectomy in rodents has been used as a model to investigate adaptative changes in the β-cell mass. Several animal studies have suggested increased β-cell proliferation after varying rates of pancreatectomy: in fact, increased numbers of β-cells and increased β-cell proliferation have been observed in the residual pancreas of rodent models [121] after surgery.

Bhartiya et al. demonstrated that a novel population of very small embryonic-like stem cells (VSELs) is involved in the regeneration of adult mice pancreata after partial pancreatectomy. However, the existence of VSELs [122,123] is still controversial.

Hepatic growth factor seems to play an important part in β-cell regeneration after partial pancreatectomy in mice. In a study, mice undergoing partial pancreatectomy and receiving a daily dose of HGF showed an increased rate of β-cell proliferation, compared to placebo. Conversely, c-Met-knockout mice undergoing partial pancreatectomy showed reduced β-cell mass, glucose intolerance and decreased insulin secretion, when compared to wild type mice, after surgery [124].

By contrast, partial pancreatectomy in adult humans does not seem to cause the same effects. Merge et al. [125] suggested that after 50% pancreatectomy there was no increase in β-cell mass and in β-cell turnover in the pancreas. However, since β-cell proliferation in children is more active compared to adults, it cannot be excluded that 50% pancreatectomy could be differently compensated in childhood. In particular, children with hyperinsulinism undergoing subtotal pancreatectomy, showed improved glucose tolerance and a significantly lower risk of developing diabetes compared to adult patients [126], suggesting an increased rate of β-cell replication [127]. Therefore, aging is associated with significantly decreased pancreatic regeneration after partial pancreatectomy [128]. As there is a decreased age-dependent phosphorylation of Akt after partial pancreatectomy, this could possibly explain the loss of regeneration with aging [129].

An important source of β-cells after pancreatectomy seems to be ductal cells. Bonner-Weir et al. demonstrated that after partial pancreatectomy in adult rats, pancreatic duct cells undergo a reproducible dedifferentiation and expansion by forming transient areas of regeneration composed of proliferating ductules. These foci of regeneration reiterate aspects of embryonic pancreatic differentiation and within a few days rapidly differentiate into new lobules of pancreas containing both islets and acini [130,131].

Gittes et al. found small ductal branches, originating from larger ducts, in murine and young human islets but not in mature islets after partial pancreatectomy. Through lineage tracing they confirmed that pancreatic ductal cells can typically convert into new β-cells in normal young mice [132].

Although many controversial studies exist, it seems likely that the generation of new β-cells from ductal cells (neogenesis) occurs mainly in young subjects and that it is responsible for pancreas regeneration after partial pancreatectomy to a greater extent than enhanced replication [133,134,78].

From a clinical point of view the incidence of diabetes after partial pancreatectomy is about 10–25%. After pancreatic surgery most patients undergo a worsening of glucose tolerance evaluated by standard 75 g OGTT [74,135] and a significant reduction of insulin secretion evaluated by hyperglycemic clamp over 2 h followed by acute stimulation with L-arginine. Furthermore, the increase in the proinsulin to insulin ratio after physiological stimulation of insulin secretion is further amplified following acute β-cell mass reduction, showing a significant impairment of proinsulin processing, possibly due to increased β-cell workload and endoplasmic reticulum stress [136]. Even though the surgical procedure is the same in all subjects, only patients with previous insulin resistance, in whom islet remodeling and impaired β-cell function are already present, develop diabetes after surgery [137], suggesting that regeneration potential is still present in subjects with normal insulin sensitivity.

2.5. Bariatric surgery/nesidioblastosis

A consequence of the obesity epidemic is the increasing use of bariatric surgery as a therapeutic approach in patients with severe obesity. Bariatric surgery is the most effective method to achieve major, long term weight loss and consequent improvement of all obesity-related comorbidities in severely obese patients [138]. Although originally developed as a weight-reduction therapy, bariatric surgery has been reported to improve T2D and to reduce rates of cardiovascular disease and death [139]. In particular, recent evidence has suggested that these patients experience diabetes remission prior to significant weight loss through weight-independent mechanisms [140]. There is limited knowledge as to the physiological mechanisms underlying the considerable metabolic modifications occurring after bariatric surgery. Enteral signals stimulating β-cells certainly play an important role. In fact, the faster gastrointestinal (GI) transit determines a huge increase in GLP-1 secretion after meals and a significant modification in the distribution of GLP-1 producing L-cells throughout the intestine [141], which is associated with an enhanced GLP-1 effect on β-cell function [142,143]. The secretion of GIP is still a matter of debate: in Roux-en-Y gastric bypass (RYGB) patients postprandial GIP levels have been reported as increased, decreased or unchanged [144,145]; in Vertical Sleeve Gastrectomy (VSG) patients postprandial GIP levels have not been investigated, and lastly, reduced postprandial incretin levels have been found in biliopancreatic diversion (BPD) patients [140,146]. Furthermore, the role of GIP receptors on α-cells and β-cells in the modulation of islet function after surgery remains almost entirely unexplored [138].

The roles of α-cells and glucagon after surgery need further investigation. In fact, surprisingly, patients with RYGB, BPD, or VSG, as well as rodents with VSG [147], show a significant increase in circulating glucagon following meal ingestion [147—149] with a profile that closely follows the temporal pattern of GLP-1 secretion [150,151]. One hypothesis is that after RYGB enteroendocrine L-cells produce and secrete glucagon, but results could be invalid because of possible assay artifacts due to increased concentrations of cross-reacting proglucagon peptides [152].

Muscogiuri et al., studied the modifications of incretins, insulin and glucagon in patients undergoing pylorus-preserving pancreatoduodenectomy. After this surgical procedure, as after RYGB, there is an increase in GLP-1 secretion, a decrease in GIP secretion and an elevation of glucagon concentrations after meals. However, in contrast with bariatric procedures, this type of surgery is associated with impairment of glucose tolerance, which could be explained by the reduction in insulin secretory capacity due to the resection of the head of the pancreas.

A recent study by Douros et al. [147] shows that pancreatic islets isolated from VSG mice undergo intrinsic changes within a week of surgery leading to enhanced insulin sensitivity and unique changes in the transcriptomic profile compared to calorically restricted, weight-matched controls. It is unclear how the changes in GI anatomy are communicated to the islets to evoke these changes. However, Douros' study is only one of the studies which identify surgery as cause of the changes in β-cell responsiveness to glucose not linked to acute stimulation by gut factors [138].

Severe recurrent hyperinsulinemic hypoglycemia has been described as a consequence of RYGB surgery in a small series of patients [153,154]. The high rates of meal-induced insulin secretion in subjects with the hypoglycemia syndrome were initially attributed to increased GLP-1 secretion and action [153,155], but subsequent studies including greater numbers of subjects showed no significant differences in plasma GLP-1 [143]. However, inactivating GLP-1 receptor (GLP-1R) with GLP-1R antagonist exendin-(9—39) almost completely mitigates meal-induced hypoglycemia in symptomatic RYGB subjects [150,156], suggesting an increased sensitivity to GLP-1 as a mechanism behind the hyperinsulinemic hypoglycemia syndrome [138]. Histological examination of post-RYGB pancreatic samples from patients affected by severe recurrent hypoglycemia requiring partial or subtotal pancreatectomy, has suggested that nesidioblastosis could be the cause of this disorder. Nesidioblastosis is a rare condition characterized by cell differentiation and budding from the ductal epithelium to form new islets and by pathological proliferation of abnormal β-cells throughout the pancreas.

In fact, surgical samples have shown hypertrophic cells with enlarged and hyperchromic nuclei with some distinct nucleoli [18,19,157,158]. Furthermore, an increased expression of IGF2, IGF1R alpha and TGFβ r3 in pancreatic islets has also been described in nesidioblastosis pancreatic tissue compared to controls, confirming the important role played by growth factors and growth factor receptors in the pathogenesis. The possibility that islet cell growth after RYGB is involved in hypoglycemia is supported by the typical delay of 1—2 years before the appearance of symptoms. The syndrome can be corrected by further surgery, either by increasing gastric restriction [19] or reversing the RYGB [159]. Moreover, subjects with hypoglycemia after RYGB have comparable insulin secretion in response to IV glucose to subjects with no surgery [160], suggesting that there is no generalized β-cell hyperfunction [138].

However, the pathogenesis of nesidioblastosis is still unknown, and several mechanisms have been proposed including: β-cell hypertrophy developing during obesity; a severe manifestation of dumping syndrome; a previously unrecognized hyperinsulinemia syndrome, which becomes apparent after gastric bypass surgery; an inappropriate growth factor release or altered growth factor signal. In particular, the increase in gut hormones post gastric bypass and the confirmed role of gut hormones in triggering β-cell neogenesis and proliferation while inhibiting apoptosis leads to islet cell hyperplasia in rodents [86,161], suggesting this as a possible pathogenetic mechanism of nesidioblastosis. Given the known role of PDX1 in the regulation of islet growth [162], and its increased expression in nesidioblastosis, probably induced by GLP-1 hypersecretion, it has been recognized as a possible contributor to the development of nesidioblastosis. Reduced ghrelin levels after RYGB [163] have been considered mediators of nesidioblastosis due to their inhibitory effect on incretins [164]. Moreover, cases of underlying insulinoma have been described in patients with nesidioblastosis [165].

Therefore, even though bariatric surgery is widespread nowadays, further investigations are required to fully understand the mechanisms underlying bariatric surgery-induced diabetes remission and the pathogenesis of nesidioblastosis.

2.6. Pancreatic endocrine tumors (PETs)

Pancreatic Endocrine Tumors (PETs), arising from neoplastic islet cells [166], represent about 1% of all pancreatic neoplasms by incidence. Although about 15% are non-functional, most PETs are functional and have unique metabolic and clinical characteristics due to hormonal products of alpha, beta, delta, PP and epsilon cells. PETs occurs sporadically or can be part of a hereditary syndrome such as multiple endocrine neoplasia type 1 (MEN1 syndrome), Von Hippel Lindau disease (VHL), neurofibromatosis type 1 (NF-1), and tuberous sclerosis (TSC) [167].

mTOR represents a key factor in cell growth and in the integration of cellular inputs, such as growth factors, nutrients, energy status and hypoxia-induced stress, and it is also the main target of the alterations

occurring in these hereditary syndromes. Indeed, mTOR function is physiologically suppressed by neurofibromin and tuberin, encoded by NF1 and TSC1/2. Mutations of these genes cause loss of function [168]. In Von Hippel-Lindau disease (VHL), mTOR signaling has been found to be impaired due to hypoxia-induced factor (HIF)-dependent mTOR activation [169]. Mutations of MEN1 gene lead to deregulation of JunD, SMAD3, p27KIPl and P18INK4c, physiologically involved in a negative control cell cycle machinery and interaction with DNA repair mechanisms [170].

It is interesting to note that the surface of PET cells express several growth factors receptors, including EGFR overexpression and IGF1/IGF1R expression in gastrinomas, as well as HGF, SCF receptor c-Kit and VEGF [171]. The transductional PI3K/AKT/mTOR pathway seems particularly relevant. The above-mentioned factors PTEN, TSC complex, NF1 and menin, known to play a major role in the mTOR pathway, have a decreased activity in PETs, thus leading to overactivation of the mTOR pathway and increased cell growth and proliferation [172]. On the other hand, menin has been reported to play a negative role in AKT kinase activity, by reducing AKT proliferation and antiapoptosis [173]. Furthermore, there are studies suggesting that the AKT/mTOR pathway is involved in the growth and apoptosis of pancreatic β-cells. In fact, mice with constitutively active AKT protein or conditional deletion of TSC2 in β-cells have increased β-cell mass and size [174,175]. Analyzing human tumor samples and their cell cycle dysregulation, Guo et al. [176] also observed that cyclinD1 is overexpressed in 65% of sporadic PETs, together with activation of p38/MAPK and AKT pathways and downregulation of ERK.

Several studies [177,178] have reported increased islet size in pancreatic samples from patients with gastrinomas, and gastrin has been reported to produce an increase in β-cell mass and improvements in glucose control in rodent models of diabetes [179,180]. Collectively, these studies present the hypothesis that islet hyperplasia in gastrinomas might be due to the direct effect of gastrin on β-cells. On the other hand, islet hyperplasia and increased β-cell replication have been observed in islets close to gastrinomas but not in islets located >1 cm away from the tumor. It is therefore more likely that it is the local release of several growth factors produced by PET, (known to stimulate β-cell growth in vitro), rather than systemic gastrin release that leads to islet hyperplasia and increased replication [181].

Recently, Vasu et al. demonstrated that an injection of mesenchymal stromal/stem cells (MSC) expressing gastrin (gastrin-MSCs) caused a significant delay in hyperglycemia in non-obese diabetic (NOD) mice [182].

Therefore, PETs are characterized by the downregulation of cell cycle inhibitors. This can lead to cell proliferation and augmented expression of growth factor receptors.

2.7. Drugs and endocrine cell regeneration

Almost all antidiabetic drugs can protect β-cells by inhibiting β-cell apoptosis and dedifferentiation via correction of hyperglycemia and amelioration of inflammation and oxidative stress. Moreover, in type 1 diabetes, given the fundamental role of autoimmune damage, the administration of immunomodulating drugs can protect β-cells and decrease insulin requirements [183].

Another attractive approach is to identify drugs able to induce β-cell endogenous regeneration possibly via proliferation, differentiation of stem cells, and transdifferentiation of other intra or extra-islet cell types [183], as previously discussed.

Some drugs have been reported to exert protective effects on β-cells. The most studied are GLP-1 and GABA. GLP-1 and GABA promote the replication of β-cells, enhance the conversion of α to β-cells, and suppress immune reactions and cell apoptosis.

GABA promotes β-cell replication in grafted human islets by activating a calcium-dependent signaling pathway and the downstream PI3K/Akt and CREB-IRS2 signaling pathways [184]. The antidiabetic drug GLP-1 analogue exendin-4 stimulates human β-cell proliferation in juvenile, but not adult islets, and requires calcineurin/Nfat signaling [185].

GLP-1/exendin-4 has been reported to facilitate β-cell neogenesis from duct cells in streptozocin-induced T1D rats and in cultured human ducts [186]. The dipeptidyl peptidase 4 (DPP4) inhibitor vildagliptin, by inhibiting GLP-1 degradation, promotes β-cell neogenesis in streptozotocin-induced diabetic rodents [187,188].

GABA is an inducer of α to β-cell conversion in mice and human islets, which is useful information for clinical trials [189]. Artemisinins, which have already been clinically used for malaria treatment, improve glucose-stimulated insulin release, change gene profiles of human islets, and induce α to β transdifferentiation [190]. Various studies have shown that GLP-1 drugs (including GLP-1 analogs and DPP4 inhibitors) and other drugs that increase GLP-1 levels can induce phenotype conversion from α-cells to β-cells [191,192]. Another study has shown that dapagliflozin, a sodium-glucose cotransporter type 2 (SGLT2) inhibitor, also induces α to β-cell conversion in T2D mice [193].

Patel et al. recently demonstrated that a therapeutic combination of sitagliptin and melatonin has an additive effect in inducing mouse β-cell regeneration under glucotoxic stress, and in the human islet transplant mouse model [194].

Wagner et al. demonstrated that 5-iodotubercidin (5-IT), an adenosine kinase inhibitor increases human β-cell proliferation in vitro and in vivo by inhibiting the dual-specificity tyrosine phosphorylation—regulated kinase 1 A (DYRK1A) [76]. Harmine is another DYRK1A inhibitor able to induce β-cell proliferation in mouse and human islets [195].

Fluoxetine, a selective serotonin reuptake inhibitor, also seems to improve glucose homeostasis through direct effects on β-cells. In fact, the exposure of MIN6 β-cells or isolated mouse and human islets to the dose of 1 μmol/L fluoxetine significantly increased β-cell proliferation and protected islet cells from cytokine-induced apoptosis. In addition, 1 μmol/L fluoxetine induced rapid and reversible potentiation of glucose-stimulated insulin secretion in islets isolated from mice, and from lean and obese human donors [196].

There are, therefore, several agents with clinical potential, but further investigations are required since many differences have been found in regeneration mechanisms between humans and rodents.

3. CONDITION-SPECIFIC MECHANISMS OF PANCREAS CELL REGENERATION IN THE EXOCRINE COMPARTMENT

3.1. Aging

As reported in the previous section (Endocrine compartment: aging), pancreatic growth is reduced by aging and older age is associated with significantly decreased pancreatic regeneration after partial pancreatectomy [129]. The same study suggested a significantly decreased age-dependent phosphorylation of AKT after partial pancreatectomy, in part explaining the loss of regeneration with age [129]. Acinar cells from aged mice do not experience AKT activation or increased cell proliferation in response to IGF1 treatment in vitro. In particular, the study suggested that aging suppressed IGF-1-induced PI3K/Akt signaling without affecting IGF1 receptor activation, showing that intracellular modifications can lead to suppression of PI3K/Akt activation and loss of cell proliferation. Moreover, an unexpected decreased expression of p85, a PI3k regulatory subunit, seems to

cause the loss of PI3K/Akt activation, as confirmed in both mouse and human pancreas in vivo through immunohistochemical staining [197]. The attenuation of the PI3k/Akt signaling pathway has been shown to be a common phenomenon in multiple organs responding to several hormones and growth factors. A recent study conducted by Chen et al. investigated whether a specific reduction in Akt activity, induced by pharmacologic Akt inhibition or genetic inactivation of Akt1 isoform selectively in pancreatic acinar cells, is effective in ameliorating the onset and progression of acute pancreatitis. They demonstrated that systemic reduction of Akt activity decreased acinar proliferation and exacerbated acinar-to-ductal metaplasia (ADM), two critical events in the progression of pancreatitis. Moreover, the conditional inactivation of Akt1 in acinar cells resulted in reduced expression of 4 E-BP1, a multifunctional protein of great importance in cell proliferation and metaplasia [198]. These studies provide the basis for further investigating the potential of Akt1 activators to boost pancreatic regeneration. The modulation of the PI3K/AKT signaling pathway is a novel strategy to enhance β-cell function and survival, but further investigations are required to identify which of the PI3K/AKT pathway modulators enhance β-cell function and prevent β-cell death without inducing excessive β-cell proliferation, which may carry carcinogenic risks. One of these seems to be a parasite-derived protein, termed FhHDM-1 (*Fasciola hepatica* helminth defense molecule 1) [199].

It is known that telomere shortening occurs in the human pancreas during aging [32] as also in the pathogenesis of chronic diseases and in the limitation of organ regeneration due to several insults. Telomere dysfunction induces the activation of p53-checkpoint, which results in either apoptosis or p21-dependent cellular senescence [200,201]. Late generation telomerase knockout mice exhibited impaired exocrine pancreatic regeneration after acute pancreatitis. Interestingly, the impairment of pancreas regeneration seems to occur through a p53-independent pathway, possibly involving Chk1 [202]. On the other hand, previous studies on telomerase knockout mice have shown that telomere shortening affects regeneration of somatic tissue by activating p21-dependent cell cycle arrest [203].

3.2. Pancreatitis

Chronic pancreatitis (CP) is a progressive, destructive and inflammatory process of multifactorial etiology that leads to irreversible obliteration of exocrine and endocrine pancreatic tissue and to replacement of functional parenchyma by fibrotic tissue. Several theories have been advanced to explain the pathophysiology of CP. Various observations seem to suggest a close relationship between acute pancreatitis, recurrent acute pancreatitis and the development of CP. These events cause acinar cell injury accompanied by fibrosis with the switching of quiescent pancreatic stellate cells (PaSCs) to activated myofibroblast-like phenotype and pancreatic damage [204]. Frequent exposure to injurious factors leads to inflammatory response and the cytokines released attract a specific cellular infiltrate, whereas profibrotic cells including stellate cells set off the development of pancreatic fibrosis [205]. In response to activation mediated by cytokines, growth factors and reactive oxygen species (ROS), PaSCs acquire several functions, such as proliferation, synthesis, migration, and secretion of extracellular matrix components, as well as degradation of ECM (extracellular matrix) components [206,207].

Duct cells from the pancreata of patients with chronic pancreatitis have the capacity to differentiate into cells producing proteins normally associated with either pancreatic endocrine or exocrine tissue [208]. Comparing patients with chronic pancreatitis to controls, the ducts of patients with chronic pancreatitis had an increased number of proliferating cells and an increased number of insulin-, glucagon-, PDX1-, and amylase-positive cells. These findings suggest that ductal cells in the adult pancreas have the capacity to undergo altered differentiation (metaplasia) [209]. On the other hand, Schneider et al. [210] found no increase in β-cell turnover in CP patients, despite severe damage in the exocrine organ. The endocrine cells, therefore, seem to preserve an "immunoprivileged" status and active antiapoptotic program through the NF-kB pathway. It should also be noted that CP predisposes to the development of pancreatic cancer, through the increased risk of neoplastic transformation by increased genomic damage and cellular proliferation. Further, we should also highlight that this inflammatory environment, cytokines, chemokines and activated signaling pathway all play a role in the transformation of normal duct epithelium into metaplastic and early neoplastic lesions that could lead to pancreatic cancer [211,212].

In particular, NF-kB is one of the transcription factors whose persistent activation was found both in CP and pancreatic cancer [213,214]. Constitutive NF-κB activation promotes low-grade inflammation, producing a favorable environment for cancer development.

Further, signal transducer and activator of transcription 3 (Stat3), a transcription factor activated by cytokines such as IL-6 and growth factors, is a key mediator of inflammation and is constitutively active in 30—100% of human pancreatic adenocarcinoma samples [215].

Cox-2 is an enzyme upregulated during inflammation and in CP it is over-expressed in acinar, islet, and ductal cells. COX-2 has been linked to the development of pancreatic dysplasia and pancreatic ductal adenocarcinoma (PDAC).

Pathways such as Notch, Hedgehog, and Wnt-β catenin are activated in pancreatic tissues in CP during the regenerative response and dysregulation of these pathways has been linked to pancreatic tumorigenesis [205,216].

3.3. Pancreatic ductal adenocarcinoma (PDAC)

Long standing duct obstruction and ductal pressure caused by pancreatic fibrosis are considered responsible for activating signaling pathways promoting cellular transformation [205]. Although ductal pancreatic tumors and ductal preneoplastic lesion cells have long been thought to originate exclusively from pancreatic ductal cells, several recent studies, using linear tracing in mice, have shown that PDAC can arise from acinar cells [217]. In particular, murine acinar cells can dedifferentiate into embryonic progenitor-like phenotype, and consequently trigger a senescence program with concomitant activation of Ras and ERK, thus limiting their proliferative potential. Interestingly, the same pancreatic progenitor phenotype, expressing markers such as CpA1, Sox 9 and Hnf1b, is present in experimental models of chronic pancreatitis [218], suggesting that dedifferentiation could be involved in the physiopathology of PDAC. Since this type of tumor usually has a poor prognosis, many studies have focused on investigating the wide range of genetic and epigenetic PDAC-related alterations. PDAC is frequently characterized by K-RAS activating mutations, and by the inhibition of INK4, p53, and SMAD4 tumor suppressor genes [219]. Overexpression of tyrosine kinase receptors, such as FGFR, PDGFR and VEGFR, as well as their ligands is common in human pancreatic cancer [220]. In particular, FGF families have been shown to contribute to tumor cell proliferation in human pancreatic cell lines [221] and the crosstalk with VEGFs plays an important role in the promotion of tumor angiogenesis by mutually regulating their expression [222].

IGF signaling proteins are frequently overexpressed in pancreatic ductal adenocarcinoma, and promote proliferation, differentiation, and angiogenesis in many cancers [223]. In particular, as previously discussed, activation of IGF1 and IGF2 receptors leads to the activation of several transductional pathways such as PI3K/AKT and MAPK signaling pathways [224].

High IR (insulin receptor) expression has been found in pancreatic cancer tissues [225]. Insulin mainly activates two signal pathways: PI3K-AKT and ERK-MAPK. Based on these two signal pathways, insulin promotes PDAC development by mediating metabolic changes, crosstalk with IGF-1, strengthening drug resistance and creating a favorable tumor microenvironment (inflammation, fibrosis, and neoangiogenesis) [226]. When insulin binds to cancer cell insulin receptor (IR), it activates the PI3K-AKT signal pathway leading to upregulation of mTOR receptor through crosstalk with G protein-coupled receptors (GPCR) [227]. mTOR is a key regulator in pancreatic cancer glucose metabolism.

Both IR and IGF-1R belong to the tyrosine kinase receptor family. Due to the similar signal pathways activated by insulin and IGF-1, these two hormones have a similar function in pancreatic cancer. Recently, the crosstalk between insulin and IGF-1 has been attracting great attention. Firstly, both insulin and IGF-1 could promote each other's expression. In pancreatic cancer tissues, the tumor-associated fibroblast (TAF) produces IGF-1, which stimulates pancreatic islet β-cells to proliferate and secrete more insulin through a bidirectional microcirculation system in the pancreas [228]. Meanwhile, hyperinsulinemia stimulates human liver tissue to synthesize more IGF-1 in blood vessels and enhances the survival and proliferation of TAF.

Studies have revealed that insulin has a more substantial effect on the survival of cancer cells, while IGF-1 was more effective in the cell cycle and proliferation [229]. The crosstalk between insulin and IGF-1 sustains a balance between cell survival and proliferation in PDAC and the cooperation between insulin and IGF-1 can lead to drug resistance and reduced apoptosis.

In addition, IR and IGF1R can form hybrid receptors, which makes the understanding and targeting of IGF signaling pathway more complex [230]. Therefore, there is a tight correlation between insulin and pancreatic cancer. PDAC induces peripheral insulin resistance by producing factors influencing the sensitivity of peripheral tissues to insulin, possibly leading to hyperglycemia and diabetes [231,232]. Moreover, in subjects at high risk of PDAC insulin may have a tumorigenic effect [233].

Genetic analyses of human pancreatic cancer show that Notch, sonic Hedgehog and Wnt pathways were aberrantly activated, suggesting an important involvement of these signaling pathways in the development of pancreatic cancer [234]. Recently, COX-2 overexpression has also been described in pancreatic ductal adenocarcinoma, and could play an important role in oncogenesis and tumor progression [235]. Elevated COX-2 has been associated with pancreatic cancer cell proliferation [236] and tumor growth [216,237].

Taken together, these alterations contribute to increased expression of cyclin D1 and the loss of negative control over CDK 4/6, leading to unchecked proliferation. Moreover, the anti-proliferative function of TGFβ signaling is skipped by cancer cells, through inhibition of Smad activity by CDK4 [238].

Uncontrolled cellular proliferation is a sign of malignancy and should always be avoided. However, we do believe that understanding the molecular pathways at the root of oncogenesis, and identifying potential similarities and differences compared to pathways that characterize physiological and virtuous β-cell proliferation, as pregnancy and obesity, would be an excellent way to achieve possible therapeutic goals.

3.4. Vascular compartment

The finding of blood vessel signals during the early stages of pancreatic specification and endocrine differentiation suggest that blood vessels play a nurturing role, transporting secreted factors necessary for proper development of the epithelial ductal tree, endocrine cells and the mesenchyme sustaining them [240]. However, the crosstalk between the pancreas and its vasculature changes during the development and differentiation process. In fact, after the first few days of pancreatic budding during which blood vessels are required for endocrine specification, they are responsible for suppressing pancreatic branching and exocrine differentiation, demonstrating a surprising vascular suppression of pancreatic growth [241,242].

It is worth noting that islet microcirculation has peculiar features, such as a 5 times higher capillary density and 10 times more fenestrations compared to the exocrine tissue's microcirculation. These findings suggest that endothelial cells are involved in additional roles, such as induction of insulin gene expression, regulation of adult β-cell function, promotion of β-cell proliferation and secretion of growth factors [243]. However, it is also suggested that this interaction can be involved in the regulation of adaptive changes needed to face increased insulin demand during body growth, pregnancy and potentially insulin resistance [244]. It seems likely that endothelial cells and β-cells communicate via paracrine interactions; it has been suggested that purified endothelial cells from pancreatic islets can stimulate β-cell proliferation through secretion of connective tissue growth factor (CTGF) that, in turn, upregulates positive cell cycle regulators and other factors involved in β-cell proliferation, including β1-integrin and hepatocyte growth factor (HGF). VEGFa and insulin can trigger the release of HGF from endothelial cells which, in a co-culture system, stimulates rat β-cell proliferation [67,245].

Indeed, a study suggests that in pregnant rats the predominant expression of HFG in islet endothelium was closely associated with proliferating β-cells. In 2000, Garcia-Ocana et al. developed transgenic mice overexpressing HGF and concluded that in vivo HGF overexpression increased β-cell proliferation, number of islets, β-cell mass, as well as insulin production [246].

As previously discussed, HGF appears to be involved in the β-cell compensatory response to insulin resistance in pregnancy and obesity and to pancreatectomy. On the other hand, HGF/c-Met pathway plays a key role in the onset and progression of human cancers. Therefore, modulating endogenous HGF levels could generate unique therapeutic strategies for IR or diabetes, but these may be significantly limited by the cancer promoting properties of HGF.

Another factor produced by endothelial cells is thrombospodin-1 (TSP-1), a matricellular glycoprotein which, inducing the production of TGF-β, has a critical role in insulin production [247]. In a high glucose model, both overexpression of PKC and TGF-β1 regulate TSP-1 expression, and the glucose-induced increase of TSP-1 can synergistically facilitate TGF-β1 [248].

Endothelin-1 (ET-1) is a potent endothelium-derived vasoconstrictor. Studies have shown its ability to stimulate insulin secretion via ET(A) receptors in β-cells [249,250]. At the same time insulin can stimulate the expression and secretion of ET-1 in both bovines [251] and humans [252].

Collectively, these findings suggest that the vascular compartment is not only involved in the regulation of pancreas morphology during organogenesis and development but also in the proliferation of adult pancreatic islets.

Apart from the effect of endothelial cells on β-cells through paracrine mechanisms, β-cells can also secrete many proangiogenic factors promoting endothelial cell proliferation, influencing the function of endothelial cells, and increasing vascularization. Vascular endothelial

growth factor-A (VEGF-A) is a major contributor to proliferation, migration survival and permeability of endothelial cells. Angiopoietin-1 (Ang-1) is another factor secreted by β-cells that binds a specific receptor on endothelial cells. Insulin may also influence the function of endothelial cells since IR can be detected [253]. As previously discussed, insulin can be synergistic with VEGF-A in vivo and in vitro, which can induce endothelial cells to secrete HGF and enhance β-cell proliferation [67,254].

Therefore, there is a close interaction between β-cells and endothelial cells with a reciprocal signaling that is crucial both during development and in the adult pancreas.

Aging-decreased expression of p85, (a PI3k regulatory subunit), seems to cause loss of PI3K/Akt activation in response to IGF1, in both mouse and human pancreas [197]. Telomere shortening and dysfunction induce activation of p53-checkpoint, resulting in either apoptosis or p21-dependent cellular senescence [32].

Pregnancy, PRL and hPL activate JAK2-STAT intracellular pathway, and Ras/Rap/MAPK and PI3K/AKT/mTOR signaling [49], inducing β-cell serotonin secretion, which contributes to β-cell expansion [48]. The PI3k/AKT/mTOR pathway is also overactivated in Pancreatic endocrine tumors [172].

Expression of Foxd3, a transcription factor also expressed in human islets, with a role in glucose homeostasis [51] decreases during pregnancy. HGF markedly increases during pregnancy in humans and exerts mitogenic, antiapoptotic and insulinotropic effects on β-cells [67].

Obesity: intraislet GLP-1 plays a role in the stimulation of proliferation and inhibition of apoptosis of β-cells [88]. Adipokines e.g., leptin, and proinflammatory cytokines such as IL-6 contribute to β-cell proliferation [95].

Pancreatectomy: Several animal studies have suggested increased β-cell proliferation after different degrees of pancreatectomy [133]. In this condition HGF seems to be an important factor for β-cell regeneration [124].

Bariatric surgery: by stimulating β-cells, enteral signals have an important role in major metabolic changes. There is a huge increase in GLP-1 secretion after meals [141], an enhanced GLP-1 effect on β-cell function [142] and an increase in circulating glucagon levels after meals [149]. Increased expression of IGF2, IGF1Ralpha, TGFβ r3 and PDX1 in pancreatic islets is described in nesidioblastosis pancreatic tissue [157].

Drugs: GLP-1 RA, DPP4i and GABAergic drugs protect β-cells from apoptosis and induce β-cell endogenous regeneration. This is usually obtained via proliferation, differentiation of stem cells and transdifferentiation. GABA, artemisinins and dapagliflozin induce α-to-β cell conversion in mouse and human islets [189,190,193]. A therapeutic combination of sitagliptin and melatonin has an additive effect in inducing β-cell regeneration under glucotoxic stress [194]. Fluoxetine also seems to improve glucose homeostasis [196].

Chronic pancreatitis: inflammatory cytokines and chemokines play an important role in the transformation of normal duct epithelium into metaplastic and, subsequently, neoplastic tissue. NF-kB and Stat3 are two of the transcription factors active in CP [213–215].

Pancreatic ductal adenocarcinoma: is characterized by oncogene activating mutations, mutations contributing to tumor cell proliferation (KRAS, FGFR, PDGFR and VEGFR, IGF 1 and 2 and insulin receptor) and by inhibition of INK4, p53, and SMAD4 tumor suppressor genes [219,224].

4. SUMMARY

Over the past few years, significant efforts have been made to better understand the regeneration potential of β-cells, in order to exploit the plasticity of pancreatic cells to increase available sources of new β-cells.

Stem cells are certainly an attractive source of new β-cells, but another attractive option is to induce the endogenous regeneration of these cells.

We here present an overall view of pancreatic physiological and pathological conditions underlining their particular features in terms of cell regeneration. The increased number of cells positive to insulin, glucagon, PDX1, amylase in the ducts of patients with chronic pancreatitis, the involvement of IR and IGF1 receptor in the proliferation of PDCA, as well as PETs, islet hyperplasia observed in pregnancy and obesity and nesidioblastosis after bariatric surgery represent the most studied conditions from which we believe meaningful insights can be translated into the search for strategies to regenerate β-cells.

Pi3k/Akt/mTOR and JAK2/STAT5 pathways seem to have a crucial role in the regulation of endocrine pancreas regeneration, and we cannot rule out the impact of lactogens, hepatokines, adipokines and gut hormones in modulating β-cell regeneration, and thus β-cell mass. Further, greater focus should also be placed on the potential of antidiabetic agents and other drugs to induce β-cell proliferation, neogenesis and transdifferentiation, which can potentially improve β-cell functional mass in type 2 diabetes. Therefore, in future, a greater understanding of the molecular and hormonal mechanisms underlying the increase in β-cell mass, physiologically possible in pregnancy and obesity, could help to find new therapeutic strategies or boost current therapies.

Recent insights have shown that pancreatic cells establish continuous and close crosstalk by sharing regulatory pathways, molecules and signals, suggesting that the exocrine and endocrine organs cannot be considered separately. In this scenario, looking at the overall pancreas rather than focusing on a single cell type may be a successful choice to finding the right path to regenerate β-cells, and a cure for type 2 diabetes.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY

No data was used for the research described in the article.

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