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Review Article

Various Chemical Strategies & Mediators that Improve Beta-Cell Function Through Regeneration and Reprogramming

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Abstract

β cell mass is defined as the total weight of cells in the pancreas and is determined by the balance between death [apoptosis/necrosis] and birth [proliferation of existing cells and neogenesis/ deformation] as well as the volume of individual cells [atrophy/hypertrophy]. Deficiency in beta cells causes diabetes. Type 1 Diabetes [T1D] and Type 2 Diabetes [T2D] are defined as blood hyperglycemia caused by an absolute or relative deficiency of pancreatic β cells. β cell mass regeneration is a potential therapeutic strategy for the recovery of damaged β cells. So far, many chemical compounds have been identified and used to improve the function of beta cells, each of which participates in various stages, including increased transcription and growth factors, proliferation, differentiation of other cells into beta cells, and neogenesis. In this paper, we comprehensively review these strategies and then discuss the various factors involved in regulating the regeneration of β cells in physiological or pathological conditions such as mediators, transcription factors, and signaling pathways. We will discuss potential medications and possible solutions to improve β cell regeneration.

Keywords: Pancreas; β cell; Chemical strategies; Regeneration

Introduction

The pancreas plays an essential role in the metabolism and consumption of energy [1]. The principal part of the pancreatic islets is β cell [2]. β cell mass is defined as the total weight of cells in the pancreas and is determined by the balance between death [apoptosis/necrosis] and generation [proliferation of existing cells and neogenesis/deformation] as well as the volume of individual cells [atrophy/hypertrophy] [3]. Pancreatic β cells are primarily responsible for the transcription of the gene-encoded insulin and subsequently processing and secreting insulin in response to increased extracellular glucose concentrations [4]. The deterioration of β cell function over time creates a vicious cycle in which metabolic abnormalities because of insulin secretion, which exacerbates most metabolic disorders [5]. Various types of stimulants such as Islet Amyloid Polypeptide [IAPP], cytokines, cholesterol, or high levels of glucose and lipids in the blood, can disrupt ER hemostasis and lead to oxidative and ER stress, inflammation, and apoptosis of pancreatic β cells. Glucose concentration is the major determinant for the regulation of β-cell mass and function. In animal models and humans, chronic hyperglycemia is associated with alterations in β-cell mass and function [6]. High-fat diet-induced obesity in mice is also accompanied by impressive increases in islet cell mass. Experimentally induced insulin resistance, such as liver-specific knockout of insulin receptors, induces up to a tenfold increase in β-cell mass [7]. Type 1 Diabetes [T1D] and Type 2 Diabetes [T2D] are defined as blood hyperglycemia caused by an absolute or relative deficiency of pancreatic β cells. Complications of diabetes can affect major organs of the body. The function of pancreatic β cells is part of the root cause of type 1 and type 2 diabetes. Pancreatic β cell regeneration is a potential strategy for β cell expansion or neogenesis. β cell mass regeneration is a potential therapeutic strategy for the recovery of damaged β cells.

Interest in β cell health in recent years has led researchers to hope that different treatment strategies on these cells may reduce the need for insulin or eliminate the need for insulin injections in general. However, the fundamental challenge is still to try to find ways to improve the function of pancreatic β cells.

In this paper, we comprehensively review these strategies and then discuss the various factors involved in regulating the regeneration of β cells in physiological or pathological conditions such as mediators, transcription factors, and signaling pathways. We will discuss potential medications and possible solutions to improve β cell regeneration.

Pancreatic β-cell Dysfunction

Beta-cell dysfunction has profound metabolic consequences, leading to high blood sugar and eventually diabetes. In diabetes, decreased cell function is associated with impaired insulin secretion of stimulated glucose [GSIS] and decreased cell mass [8]. Acute GSIS loss is associated with significant changes in beta-cell phenotype and changes in gene and protein expression [9]. High levels of glucose, Advanced Glaciation End-products [AGEs], proinflammatory cytokines, free fatty acids, and other lipid intermediates are increased [10]. These factors are toxic to cells and may activate several stress response pathways, including oxidative stress and Endoplasmic Reticulum [ER], mitochondrial dysfunction, apoptosis, and necrosis

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[11]. Pancreatic -cell failure resulting from -cell death or dysfunction is a crucial event in the development of diabetes. Death of cells in type 1 diabetes is mainly due to immune cell death of apoptosis. In this process (Figure 2), -cell apoptosis, initiated by inflammatory cytokines such as IL-1 and IFN-γ, is considered important [12]. Type 2 diabetes, hallmarked by underlying insulin resistance, is also characterized by defects in glucose-responsive insulin secretion in addition to an eventual decline in -cell mass. Evidence suggests that the loss of -cells [apoptosis] in type 2 diabetes is in response to a combination of oxidative stress and Endoplasmic Reticulum [ER] stress [13]. A transient increase in glucose levels in the physiological range causes insulin secretion and potentially beneficial signals. In contrast, long-term hyperglycemic blood sugar impairs the function of beta cells and alters cell mass [14]. The likely mechanisms of early cell demise include mitochondrial dysfunction, oxidative stress, ER stress, dysfunctional triglyceride/FFA [TG/FFA] cycling, and glucolipotoxicity. In insulin-resistant states, pancreatic islets usually respond by increasing insulin secretion to maintain normalization, a process that compensates for cells.

Intrinsic and extrinsic pathways are considered as two general routes for the activation of apoptosis. The former is activated by stress factors including growth factor deprivation, cell cycle disturbance, and DNA damage, which lead to the mitochondrial release of cytochrome C and subsequent stimulation of caspase-9. The latter begins with the cell death receptors and the associated activation of caspase-8. Finally, both pathways stimulate effector caspases [3,6,7], which target the substrates that promote DNA fragmentation and cell death.

Cells Regeneration

Some evidence suggests that the cell mass is dynamic and able to make adaptive changes in response to different secretory demands. Several recent studies have shown that human cells retain some of their ability to regenerate, even at the end of life [15]. Cells mass regeneration is a potential treatment strategy to improve cell loss. Cell regeneration occurs through endogenous or exogenous complement regeneration (Figure 1A), such as cell transplantation. Many strategies are involved in the reconstruction of cells, including: *in vivo* stimulation of existing cell replication, reprogramming of other pancreatic cells to differentiate into cells, *in vitro* differentiation of induced Pluripotential Stem [iPS] cells into new cells, and generation of human islets from genetically engineered pigs [16]. The two major mechanisms for cell replenishment are a replication of existing beta cells and differentiation of new cells from non- islet cells, pancreatic, and extra-pancreatic cells including stem/progenitor cells [i.e., cell neogenesis from non-beta cells] [17]. Both cell replication and neogenesis contribute to the expansion of cell mass that requires external stimuli such as hormones and growth factors [18]. Apart from the pancreas tissue, the liver, intestines, and stomach are also involved in the conversion to beta cells (Figure 1B). Self-regeneration [self-renewal or self-replication] is the cell's ability to replicate division without loss of identity or functional potential [19]. In rodents, new cells are more derivative than existing cells. In other words, under physiological conditions, the self-regeneration of cells is the main mechanism for the normal circulation of cells [20]. In adult mice, in a physiological state, and after partial pancreatectomy, existing cells rather than stem/ progenitor cells generated new cells [21], i.e., cell self-replenishment was preferred to cell neogenesis (from non-cells). However, in normal adult monkeys, for steady-state cell mass to prevail, the majority of newly forming cells were derived independent of cell self-replenishment, i.e., from cell neogenesis [from non-cells] [22]. In comparison with the rodent pancreas, the human pancreas has a significant population of extra-islet cells that scattered throughout the exocrine tissue, suggesting that neogenesis may occur in physiological states [23]. Therefore, cell self-replenishment may be the primary mechanism for maintaining cell populations in rodents but not in humans. Under the physiological state, the primary mechanism for replenishing cells in humans likely derived from cell neogenesis from non- cells [24]. Pancreatic Duodenal Homeobox-1 [PDX1] is a key transcription factor for pancreas development and mature -cell function [25]. It also plays a pro-survival role in adult -cells, so its partial deficiency increases -cell apoptosis, leading to decreased -cell mass and diabetes in rodents and humans [26]. Previous studies have reported that -cells have a capacity for increased proliferation in response to increased insulin demands [27]. The pancreas, liver, kidneys, and salivary glands are thought to be tissues with "permanent cells" that divide shortly after birth. This early study showed the flexibility and limitation of these organs, and many early researchers preferred to focus on islet performance instead of expanding them.

The pancreatic cells, the site of insulin production in adults, have only a limited capacity for regeneration. However, some substances, such as glucose, essential amino acids, insulin, and growth hormone, have been reported to stimulate some -cell proliferation in fetal, neonatal, or adult islands [28]. Various pancreatic regeneration models have been developed in both mice and rats to study -cell regeneration in vivo. The number of cells in the islets at birth is mainly produced by the proliferation and differentiation of pancreatic progenitor cells, a process called neogenesis. Shortly after birth, cell neogenesis stops, and a small proportion of cells in cycling can still expand the number of cells to compensate for the increased need for insulin, albeit at a slower rate. Low capacity for overgrowth in adults is too limited to result in extensive tissue damage leading to significant reconstruction. It is important to regulate the need for cell mass through glucose and hormonal effects on the proliferation of cells, size, apoptosis, and under specific conditions regulating the neogenesis of precursor cells. Intolerance to changes in the body, pregnancy, insulin sensitivity in the surrounding tissue, or tissue damage may lead to chronic blood sugar or diabetes [29]. Adequate transplantation of pancreatic cells can normalize blood sugar levels and may prevent the devastating effects of diabetes [30]. An alternative method for cell transplantation could be to induce an increase or regeneration of endogenous cells in the pancreas by growth factors and mediators. It seems that in the absence of major external stimuli, the cell population has only very little potential for regeneration. This is probably due to the limited capacity of cell proliferation [31] and the fact that neogenesis from precursor cells is not easily reactivated. However, under certain conditions where major external stimuli are applied, the expansion of cell regenerative resuscitation can be extended [32]. Such regenerative growth may be otherwise a precursor/precursor activation [33]. Unlike highly proliferative tissues such as the intestines, skin, or hematopoietic

Table 1: Chemical compounds identified and used to control the function and regeneration of β cells.

Chemical strategies	Pathway	Effect
IDE1 and IDE2	TGF-β pathway stimulating Smad2 phosphorylation	Modulates proliferation
ILV (Indolactam V)	(PKC) signaling	Increase PDX1, FOXA2, NKX6.1, HNF6, and PTF1A, Increase regeneration
Nicotinamide	Similar to EGF	Increase PDX1, NKX6.1 produce mature β cells
Andrographolide & C1037	Oxidative stress pathway block	Neogenesis, protective, up-regulating of PDX-1 expression
Betatrophin	Increase cell cycle regulators, cell cycle transcription factors such as E2F1 / 2, Increase β cell mass	The proliferation of β cells,
GSK3b (glycogen synthase kinase 3)	PI 3-kinase/Akt pathway	Increase proliferation & differentiation,
Inhibition of DYRK1A, SMAD, and Trithorax	(TGFbSF)/SMAD signaling	Increase proliferation, β cell numbers, β cell differentiation markers
ALK5iII	Unknown	Increase PDX1, NKX6.1, MafA blocking stress in β cells & restoring β cell functions
Puerarin (daidzein 8-C-glucoside)	activates GLP-1R signaling in β cells, Activates β-catenin and STAT3	Inhibit β-cell death, increase neogenesis, increase exendin-4
Glucagon receptor (GCGR) antagonist	GLP-1	Increase alpha cell mass ,alpha-to-beta conversion
Inhibitor (roscovitin)	inhibition of notch signaling	Increase formation and regeneration, increase duct-derived β-cells
Dipeptidyl Peptidase-4 Inhibitor	cAMP/PKA signal pathways, MAPK, epidermal growth factor, PKAB, and PKC	β-cell function, inhibits apoptosis, increase
Adenosine	adenosine signaling	Regulating β cell mass. increase β-cell survival, increase proliferation, neogenesis and regeneration
Geniposide T-cell factor 7-like 2 (TCF7L2)	catenin / TCF7L2 pathway, Wnt / β Catenin, (GLP-1R) signals	Increase survival and regeneration, conversion from ductal epithelial cell to β cell
Cyclin D2	cell cycle regulator	Increase β cell growth and β cell regeneration
sirtuin 1 (SIRT1)	AMP activated kinase protein(AMPK)	Increase differentiation Increase NGN3
T cell factor 7-like 2 (TCF7L2)	Wnt signaling	Increase β cell proliferation, growth & regeneration, protection against apoptosis and increase β cell survival
TBK1/IKKε TANK-binding kinase 1, Inhibitors of noncanonical IκB kinases	cAMP, PKA	Increase proliferation, regeneration
Ghrelin EGF/gastrin	EGF pathway	Increase β cell mass, neogenesis and regeneration
Proteins (GH, PRL)	Akt1 / PKB, Cdk4	Increase β -cell mass and increase (HGF) in β cells
Berberine	AMP-activated protein kinase	Increase insulin expression, β cell regeneration, antioxidant enzyme activity and decrease lipid peroxidation
Tetrabenazine (TBZ)	cAMP	Differentiation, Pdx1, Ngn3

TGF-β: Transforming Growth Factor Beta; PDX1: Pancreatic Duodenal Homeobox-1; FOXA2: Forkhead Box; Protein A2; GLP-1: Glucagon-Like Peptide-1; CAMP: Cyclic Adenosine Monophosphate; GH: Growth Hormone; PRL: Prolactin; PKB: Protein Kinase B; Cdk4: Cyclin-dependent kinase 4; Ngn3: Neurogenin 3; EGF: Epidermal Growth Factor; PKC: Protein Kinase C.

system, the pancreas, especially the endocrine chamber, has a low turnover rate under physiological conditions. However, under high metabolic demand such as pregnancy [physiological condition] or obesity [pathological condition], the pancreas can adapt to increasing its -cell mass, mainly by self-proliferation, cell hypertrophy, and increased insulin synthesis and secretion. The rate of loss of cells and glycemic status appears to play an important role in the regeneration of cells. This feature distinguishes other cells from cells, while non-glycemic conditions induce - cell self-replication [34]. Figure 3 depicted some important signaling pathways that play an effective role in beta-cell proliferation and lead to improved and increased beta-cell regeneration.

Recently, various strategies and methods for stimulating the regeneration of cells have been evaluated, but they have not been suitable for clinical applications. So far, many chemical compounds have been identified and used to improve the function of beta cells, each of them participates in various stages, including increased transcription and growth factors, proliferation, differentiation of other cells into beta cells, and neogenesis (Table 1).

The Mediators for Pancreatic Cells Regeneration

GABA & Artemisinin

The γ-Aminobutyric Acid [GABA] is a product of decarboxylation of the amino acid glutamate-mediated by the synthesizing enzyme Glutamic Acid Decarboxylase [GAD] [35]. Although GABA is a major inhibitory neurotransmitter of the brain, it is produced at high levels in pancreatic islets -Cells store GABA in synaptic-like micro-vesicles. It has been demonstrated that -cells mainly express the $GABA_B$ receptor [$GABA_BR$] and the $GABA_A$ receptor [$GABA_AR$] and produce GABA through GAD [36]. Extracellular glutamate, the precursor of GABA, enters -cells through the Glutamate Transporter-1 [GLT-1], where it is converted to GABA by the GAD enzyme and then stored in synaptic-like microvesicles. GABA signals through the $GABA_BR$ expressed by -cells, thus increasing insulin release, protecting -cells from STZ-induced apoptosis, and stimulating -cell proliferation. Baclofen and muscimol, both agonists of the $GABA_BR$, have the same effects. T cells are sensitive to GABA due to the presence of GABAAR on the cell surface. GABA has a significant effect on T cells by reducing the production of inflammatory cytokines [IL-1, IL-2, IL-6, IL-12,

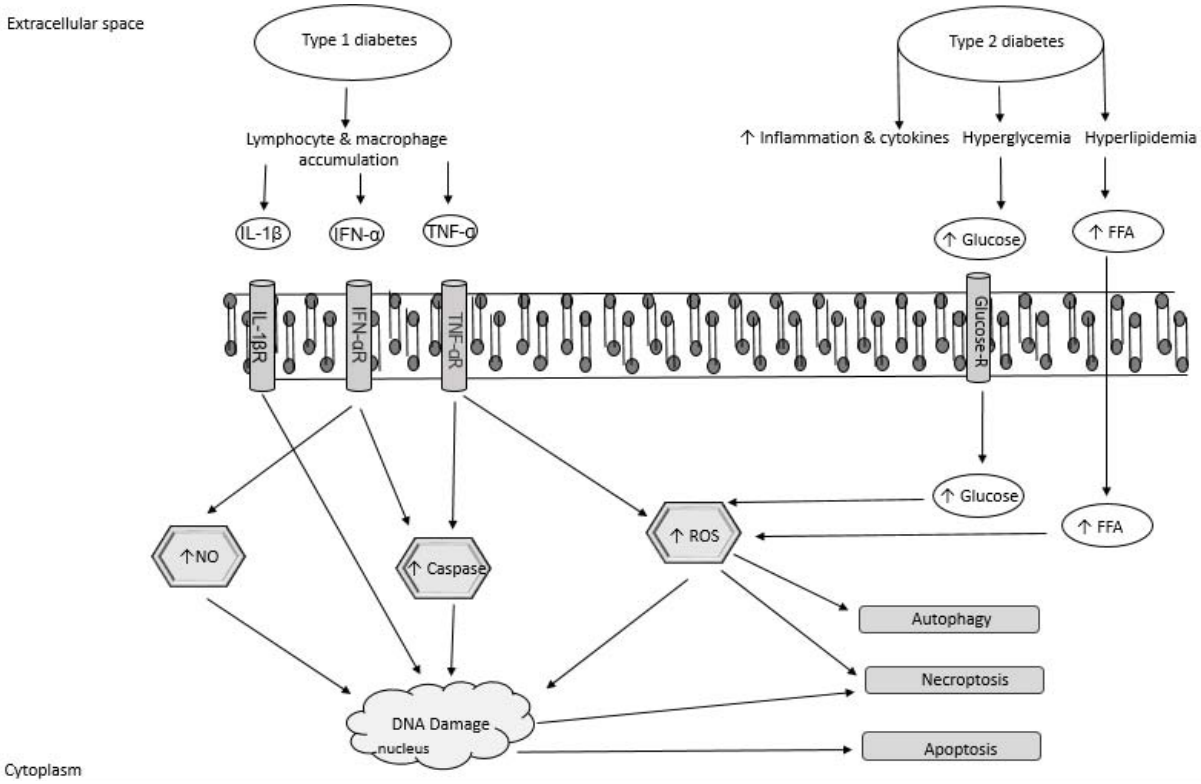

Figure 1: Type 1 diabetes is mostly caused by immune factors: IL-1β, IFN-α, TNF-α by binding to their receptors, cause accumulation [NO, caspase, ROS], and damage to cellular DNA. In type 2 diabetes, an increase in the concentration of glucose and fatty acids after binding of these substances to their receptors on the membrane of beta cells increases oxidative stress. Eventually, beta cells undergo autophagy, necrosis, and apoptosis, and lose their ability to secrete blood glucose-regulating hormones.

and IL-17] and inhibiting or reducing T cell proliferation. GAD is targeted by autoreactive T cells and specific anti-GAD antibodies [37]. There are two exciting advances in the conversion of α cells to cells. Collombat laboratory reports that GABA can induce α-to -like cellular conversion within the body [38]. After treatment with these two drugs, -like cell mass increases with the loss of α cells. GABA down-regulated Arx expression in α cells increased the proliferation of cells in the duct and revitalized the endocrine growth program. Meanwhile, Kubicek's laboratory showed that artemisinins could also convert α cells to cells both in vivo and *in vitro* [40]. Artemisinins increase the expression of insulin protein in α cells and increase the gephyrin protein, which enhances GABA receptor signaling. These beta- cells can reverse hyperglycemia.

Long-term GABA administration can result in significant cell hyperplasia that involved activation of a neogenic-like program within the pancreatic ducts and impair cell function.

GABA and the antimicrobial agent, which are active in the GABA pathways, can drive alpha-cell phenotype toward a cell-like phenotype. GABA signaling can program a-like cells to -like cells. This can be done by performing GABA on the GABAA receptor complex or by the antimalarial drug Artemether binding to Gephyrin, a protein associated with the GABA-A receptor complex. This leads to a decrease in glucagon expression and an increase in PAX4 and insulin expression. Treatment with GABA or Artemether leads to extensive neogenesis by forming more and larger islets. This is accompanied by an increase in the proliferation of epithelial cells. Stimulation of GABA pathways can stimulate cell regeneration [40]. The combined oral GABA and DPP-4 inhibitor prevents cell damage and regenerates cells. Two pathways have also been shown to mediate GABA function in maintaining cell mass [41]. The combination of GABA and sitagliptin was superior in increasing cell mass. This combination also increases the number of small islets, Ki67, and counting PDX1-cells. Also, they reduced the number of cells in the tunnel. Altogether, that leads to an increase in the proliferation of cells and reducing in apoptosis. The administration of Sitagliptin indeed increases the plasma GLP-1 levels [40]. Arx and Pax4 are key transcription factors involved in the conversion α cell to cell. Compounds that can induce Pax4 or inhibit Arx expression in α cellular classes lead to the identification of the class of artemisinin antimalarial drug class [for example, artemether]. They induce the conversion of α to cells through activation of GABA-A receptor signaling in α cells [42]. Wang et al., have shown that GABA therapy can restore the cell mass. Enhanced cell replication appears to depend on growth and survival pathways involving Akt activation. Some studies have also suggested that GABA induces trans differentiation of α cells into cells. GABA protects cells from damage and significantly reduces their apoptosis under various conditions. Partially, the anti-apoptotic effects depend on the increased activity of sirtuin-1 and the activity of Klotos. Both can inhibit the activation of the NF-κB inflammatory pathway. GABA (or GABAnergic drugs) can be combined with other antidiabetic drugs to make it more effective [43].

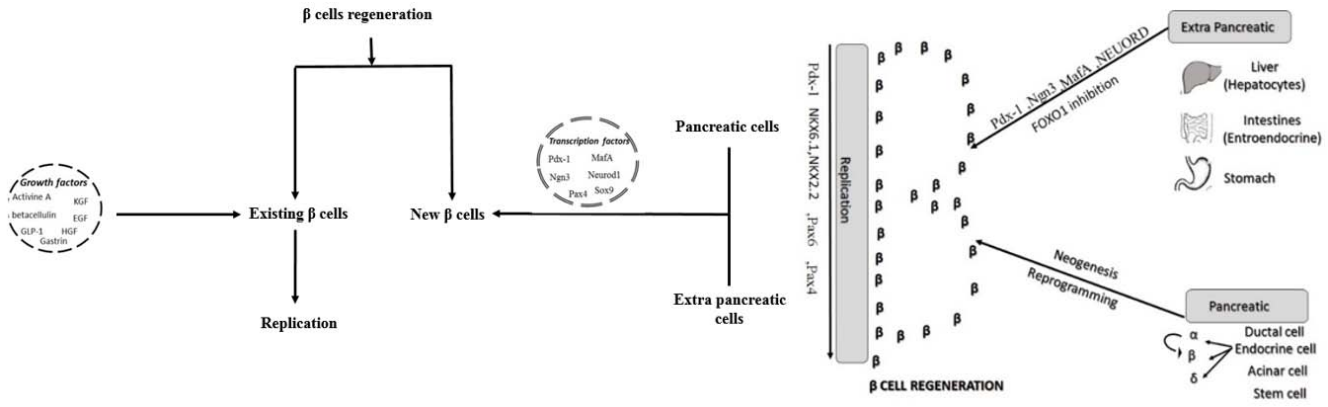

Figure 2: The mediators & major mechanisms for pancreatic β cell regeneration, Regeneration of pancreatic beta cells can occur both the production of new beta cells, and the replacement of existing beta cells. New beta cells can be produced both by converting different types of pancreatic cells to beta cells and by converting certain extra-pancreatic tissues [liver, intestines, and stomach]based on many transcription factors, including PDX1, NKX6.1, MafA, and NGN3. Hepatocyte cells in liver tissue and enteroendocrine cells in intestinal tissue can produce new beta cells. Several growth factors such as activin A, betacellulin, GLP-1, etc. are involved in the transformation of existing beta cells and cause the replacement of existing cells with functional beta cells. Beta cells in the pancreas can also become functional beta cells under the influence of several factors. All endocrine cells [alpha, delta, etc.], duct cells, and acinar cells present in the pancreas can become beta cells under the influence of growth factors. The most important factors include Pdx1, Ngn3, mafA, etc. Meanwhile, alpha cells become more beta-converting.

Clusterin & Exendin-4

Exendin-4 [Ex4], as the Glucagon-Like Peptide-1 [GLP-1] receptor agonist, has a stimulating function in the secretion of insulin and also plays a role in cell neogenesis [44]. Ex4 expression enhances the pdx-1 transcription factor, stimulates pancreatic duct cell differentiation, as well as cell proliferation and differentiation. These changes lead to an increase in cell mass [45]. Clusterin is a disulfide-linked heterodimer glycoprotein expressed ubiquitously in a wide variety of tissues. Clusterin is considerable in tissue regeneration, differentiation, and the death of apoptotic cells in damaged tissues. During pancreas development, Clusterin is expressed in both α and -cells. Up to now, two isoforms of Clusterin as the cytoprotective secreted-Clusterin [sCLU], and a prodeath factor Nuclear-Clusterin [nCLU] have been reported [46]. Ex4 treatment promotes the proliferation of pre-existing cells as the formation of new cells, as well as the differentiation and neogenesis of pancreatic duct cells [47]. Treatment with GLP-1 or Ex4 increases pdx-1 expression in ductal epithelium and exocrine tissues. Therefore, GLP-1 increases the activity of the pdx-1 promoter and also differentiates the epithelium of the duct into cells and reorganizes the cell in the islets. Various studies of rodents have shown that following chronic administration of both GLP-1 and GLP-1 receptor agonists, the neogenesis of the islets occurs with an increasing number of a small islet [48]. Findings suggested that Ex4 therapy showed a relationship between pdx-1 and the state of islet proliferation. The secreted clusterin stimulated the differentiation of cells from duct cells by the paracrine effect. After damaging islets, the Clusterin expression increased significantly in α cells. It is suggested that increasing the expression of Clusterin in α cells, in the early stages of damage, stimulates cell proliferation through a paracrine. It has been suggested that clusterin can act as a signal molecule for the RAS-ERK signaling mechanism in differentiation and proliferation [49]. Clusterin expression was increased in the pancreas regeneration in endocrine cells [50]. These results show that Ex4 treatment regulates cell clusters by regulating clusterin, which may be effective in proliferating cells and neogenesis.

Glucose & Glucokinase

In addition to the factors described in cells that act on the cell's autonomy, several reports suggest that systemic or circulatory factors can regulate the replication and mass of cells. Glucose itself is a -cell mitogen. Injection of glucose into rodents causes a slight increase in the proliferation of cells [51]. And glucokinase deficiency significantly reduces the compensatory proliferation of pancreatic cells in some areas [52]. Also, the genetic elimination of glucokinase in cells can reduce the rate of proliferation, while drug activation of this enzyme doubles the proliferation [53]. Several hormones, including insulin, placental lactogen, and prolactin, are also involved in regulating the mass of cells [54]. After using most of the cells in mice and inducing compensatory proliferation, the researchers found that the cells regulated their proliferation rate according to the rate of glycolysis. Accordingly, GCK-deficient mice cannot reduce cell proliferation by -cell proliferation, whereas GCK-activating compounds increase this proliferation. Further evidence of the importance of GCK [55] in cell proliferation was provided by the identification of a rare species [V91L] in the human glucokinase gene, in which the affinity for GCK for glucose was more than 8.5-fold [56]. Experiments clearly show that the rate of proliferation of adult cells inside the body and their regeneration due to injury is controlled by systemic factors. Local factors, such as the presence of dead cells or the architecture of disturbed islets, appear to play only a minor role. Thus, the control of the number of cells is similar to that of other systematically controlled tissues such as blood [such as red blood cells] [57]. Glucose is the chief systemic factor that controls the proliferation of cells. Glycolysis is the main stimulus for cells. Dropping the level of blood glucose [in the normal or abnormal state] due to exogenous insulin administration may decline the proliferation of cells because of reduced workload. Glucokinase activators can have beneficial effects on the number of cells [58]. Cells regulate their proliferation rate according to the glycolysis rate. Glucose metabolism is required for stimulation of cell proliferation. Glucokinase controls the cell function, proliferation, and survival [52]. Glucose has effects on growth and survival by activation of Insulin Receptor Substrate 2 [IRS-2], a protein in the

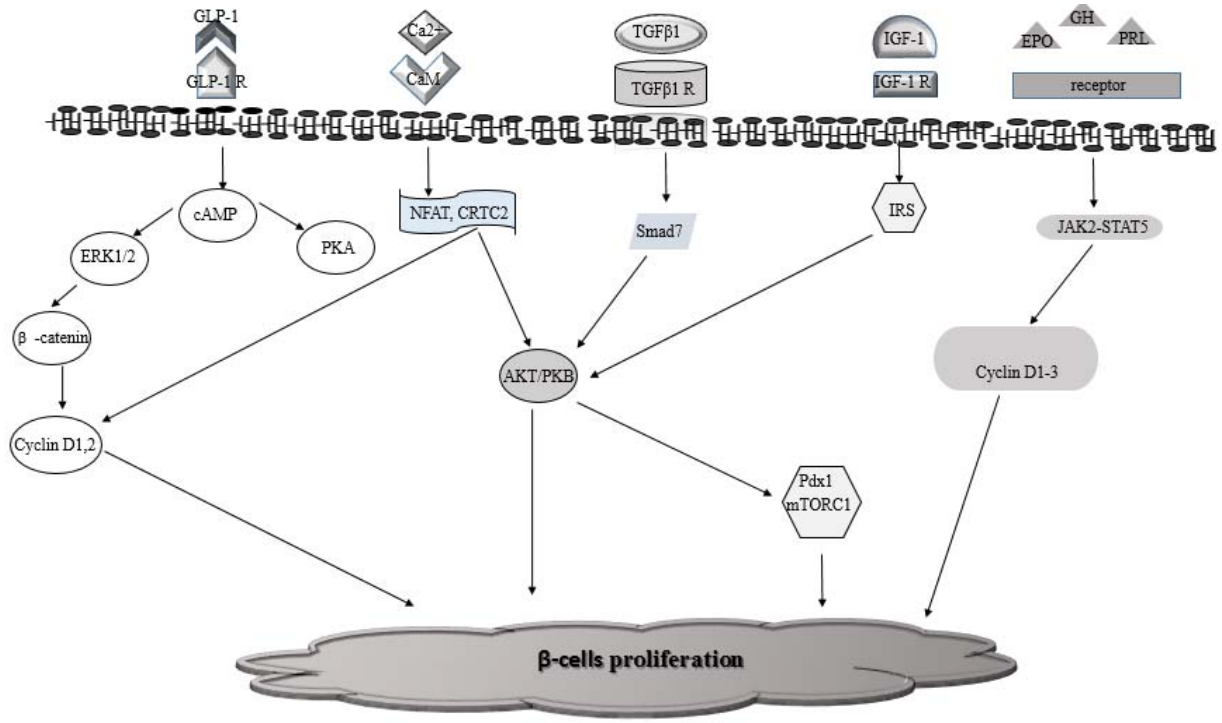

Figure 3: Signal pathways that play an important role in pancreatic beta-cell proliferation. Binding of GLP-1, IGF-1, TGFβ, Ca2+, and hormones to their respective receptors serves an important role in β-cell proliferation. GLP-1 binds to GLP-1R to activate cAMP-PKA, and it also acts via ADAM proteins to trigger the secretion of BTC that acts upon ErbB1/2. IGF-1, TGFβ, Ca2+, and hormones are involved in beta cell proliferation by activating AKT / PKB and mTOR complexes.

Insulin/insulin-like Growth Factor I [IGF-I] signaling pathway.

GLP1

In NOD mice, cells are destroyed by a spontaneous immune response that leads to type 1 diabetes. Suppression of the immune system in combination with GLP-1 [analog] therapy can repair normoglycemia and improve the histology of the islands [18]. Intracellular effects of soluble mediators are interceded mainly by interacting with specific receptors that bind extracellular signals to gene expression modulation. The GLP-1 signaling path is activated after connecting to its receptor GLP-1R and EGFR transmission. The effects of GLP-1 on cells are generally mediated by the cAMP signaling pathway. GLP-1 enhances glucose-secreted insulin secretion, enhances the function of -pancreatic cells by promoting neogenesis and proliferation, and by reducing apoptosis signals, increases antioxidant defenses, enhances insulin gene transcription, mRNA stability and biosynthesis increases Pdx-1 expression -1 and binds Pdx-1 to the insulin promoter. Exendin- 4, a GLP-1R agonist, enhances UPR gene expression in response to ER stress, stimulates GK expression, and prevents SERCA expression reduction [59]. Treatment with GLP1 or Exendin4 [Ex4], a long-acting analog of GLP1, promotes -cell regeneration [47].

GLP-1 and GLP-1R agonists have several physiological functions, especially in promoting -cell proliferation and neogenesis [60]. Ex4 could activate PI3K/AKT and suppress GSK3 [61]. That suggests the interaction between GLP-1 and Wnt signaling. The trans-differentiation of pancreatic ductal cells induced by exendin-4, Wnt/-catenin, and JAK2/ STAT3 might be downstream effectors of the GLP-1R signaling cascade [62]. Expression of GLP-1/IgG-Fc fusion protein enhances-cell mass. An important feature of GLP-1 is the enhancement of the mass of cells by promoting the growth of cells and preventing the death of cells. Both GLP-1/IgG-Fc and Ex4/IgG-Fc significantly increased islet-cell mass. The enhancement of -cell mass by GLP-1/IgG-Fc and Ex4/IgG-Fc was associated with an enhanced-cell function. Studies have shown that GLP-1 [or Ex4] increased-cell neogenesis [63]. GLP-1 is known to have potential effects in the regulation of the-cell mass through regeneration, differentiation, and neogenesis of pancreatic-cells [64]. However, GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase 4. The pancreatic a-cells are a target for GLP-1 action. GLP-1 promotes a-cell proliferation *in vitro* and *in vivo*. GLP-1 increases -cell regeneration by promoting a-to-cell transdifferentiation. GLP-1 can increase cells in the pancreas, and a cell can be a source of new cells. Ex4 increased the expression and secretion of Fibroblast Growth Factor 21 [FGF21] in cells. FGF21 increased the expression of pdx1 and neurogenin-3. These results suggest that a-cells can be a source of newly generated insulin-producing cells and that GLP-1 may act as a stimulus through autocrine signaling [65].

In pancreatic islets, GLP-1 also inhibits glucagon secretion, promotes cell proliferation, and protects cells from apoptosis [63]. Through binding to its receptor GLP-1R [66], GLP-1 promotes cell replication. That also prevents cell apoptosis via the activation of P13K/Akt and CREB-IRS2 signaling pathways. Liraglutide and Exenatide are examples of GLP-1 receptor agonists that improved-cell function. Treatment with liraglutide and exenatide can increase cell mass, stimulate cell proliferation, increase cell neogenesis, and inhibit cell apoptosis. The GLP-1 receptor is strongly expressed in the

cell membrane of the pancreas [67]. GLP-1 exerts acute effects on cell function by binding to the GLP-1 receptor.

Activin A and Betacellulin

Betacellulin is a member of the EGF family of growth factors [68]. Activin A and betacellulin have been reported to promote -cell regeneration by activation of both -cell replication and neogenesis [69]. Activin A and Betacellulin [BTC] appear to regulate the differentiation of pancreatic cells during adult cell development and regeneration. BTC belongs to the epidermal growth factor family. The expression of BTC is predominantly found in the pancreas and the intestine. BTC is found in endocrine precursor cells of the fetal pancreas and insulin-secreting cells [70,71]. It also has a mitogenic effect on undifferentiated human pancreatic epithelial cells [72]. These suggested that BTC plays a substantial role in regulating the growth and/or differentiation of pancreatic endocrine cells. Other studies [73] have shown that BTC improves glucose metabolism by promoting cell regeneration in diabetic animals.

Activin A, a member of the Growth Factor [TGF-b] family, regulates the growth and differentiation of many cell types [74] as well as the regulation of the pancreas and the determination of endocrine glands [75]. Activein A causes the expression of neurogenin 3 [76], a critical transcription factor in regulating the differentiation of endocrine cells [77]. It has been shown that the expression of activin A was up-regulated in the pancreatic duct during pancreatic regeneration and activin A regulates neogenesis of cells [78]. BTC and activin a likely promoted cell neogenesis from precursor cells located in the islets. Activin A and BTC therapy significantly increased the cell mass, size of islets, and promoted regeneration of cells. BTC, a member of the epidermal growth factor family, in combination with activin A, induces proliferation, differentiation, and convert an exocrine pancreatic cell line [AR42J] into insulin-expressing cells [79]. When administered systemically, BTC promoted the formation of new -cells. The combined treatment of activin A and BTC resulted in the regeneration of pancreatic -cells in neonatal STZ-treated rats.

Conclusion

Based on the studies collected in this article, it is concluded that pancreatic cells play an important role in maintaining blood glucose homeostasis by insulin secretion. Maintaining cell mass balance is essential for this role. Pancreatic cells can cause diabetes if they are damaged. Diabetes is on the rise around the world. Regenerating cells has shown its potential as a cure for the treatment of insulin-deficient diabetes. There is the ability to regenerate and improve the function of damaged pancreatic cells. Over the past few decades, studies on the regeneration of endogenous cells have suggested many ways to regenerate these cells. However, most of these solutions have only been used successfully in animals, and most of them have failed in humans. In this study, we collected various drugs and mediators involved in cell regeneration. According to the results of our study and the previous ones, we can conclude that the focus should be on regenerating cells and the functionality of new pancreatic cells to improve adaptability in clinical applications.

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