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# Beta-Cell Function and Failure

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## 1. Introduction

### 1.1. Beta cells ( $\beta$ -cells)

Beta cells are a type of cell in the pancreas located in the so-called islets of Langerhans. They make up 65-80% of the cells in the islets.

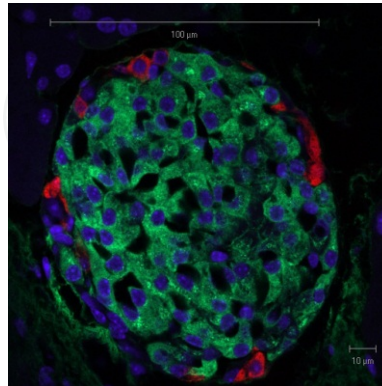
The Islets diameter is about 50 to 300 micrometers. They are composed of several types of cells. At least 70 percent are beta cells, which are localized in the core of the islet. These cells are surrounded by alpha cells that secrete glucagon, smaller numbers of delta cells that secrete somatostatin, and PP cells or F cells that secrete pancreatic polypeptide. All of the cells communicate with each other through extracellular spaces and through gap junctions. This arrangement allows cellular products secreted from one cell type to influence the function of downstream cells. As an example, insulin secreted from beta cells can suppress glucagon secretion.

A neurovascular bundle containing arterioles and sympathetic and parasympathetic nerves enters each islet through the central core of beta cells. The arterioles branch to form capillaries that pass between the cells to the periphery of the islet and then enter the portal venous circulation.

## 2. Beta cells functions

Insulin is synthesized as preproinsulin in the ribosomes of the rough endoplasmic reticulum in the beta cells (fig 1). Preproinsulin is then cleaved to proinsulin, which is transported to the Golgi apparatus where it is packaged into secretory granules located close to the cell membrane. Proinsulin is cleaved into equimolar amounts of insulin and C-peptide in the secretory granules. The process of insulin secretion involves fusion of the secretory granules with the cell membrane and exocytosis of insulin, C-peptide, and proinsulin

Insulin is a hormone that controls the blood glucose concentration. The liver maintains the base-line glucose level, but the beta cells can respond quickly to spikes in blood glucose by releasing some of its stored insulin while simultaneously producing more. The response time is very quick.



**Figure 1** Mouse pancreatic islet as seen by light microscopy. Beta cells can be recognized by the green insulin staining. Glucagon is labeled in red and the nuclei in blue

Apart from insulin, beta cells release C-peptide, a consequence of insulin production, into the bloodstream in equimolar amounts. C-peptide helps to prevent neuropathy and other symptoms of diabetes related to vascular deterioration. Measuring the levels of C-peptide can give a practitioner an idea of the viable beta cell mass.

Beta-cells also produce amylin, also known as IAPP, islet amyloid polypeptide. Amylin functions as part of the endocrine pancreas and contributes to glycemic control. Amylin's metabolic function is now somewhat well characterized as an inhibitor of the appearance of nutrient [especially glucose] in the plasma. Thus, it functions as a synergistic partner to insulin. Whereas insulin regulates long-term food intake, increased amylin decreases food intake in the short term.

GABA ( $\gamma$  amino butyric acid) is produced by pancreatic beta cell. GABA released from beta cells can act on GABA<sub>A</sub> receptor in the  $\alpha$  cells, causing membrane hyperpolarization and hence suppressing glucagon secretion. An impaired insulin-Akt-GABA<sub>A</sub> receptors glucagon secretory pathway in the islet may be an underlying mechanism for unsuppressed glucagon secretion, despite hyperglycemia, in diabetic subjects. Some studies demonstrated that beta cells also express GABA<sub>A</sub> receptors, forming an autocrine GABA signaling system. However, the role of this autocrine GABA signaling in the regulation of beta cell functions remains largely unknown.

Zinc is needed by over 300 enzyme systems. Some of those are involved with the metabolism of blood sugar and are so important that a lack of zinc, in and of itself, can cause type I or type II diabetes.

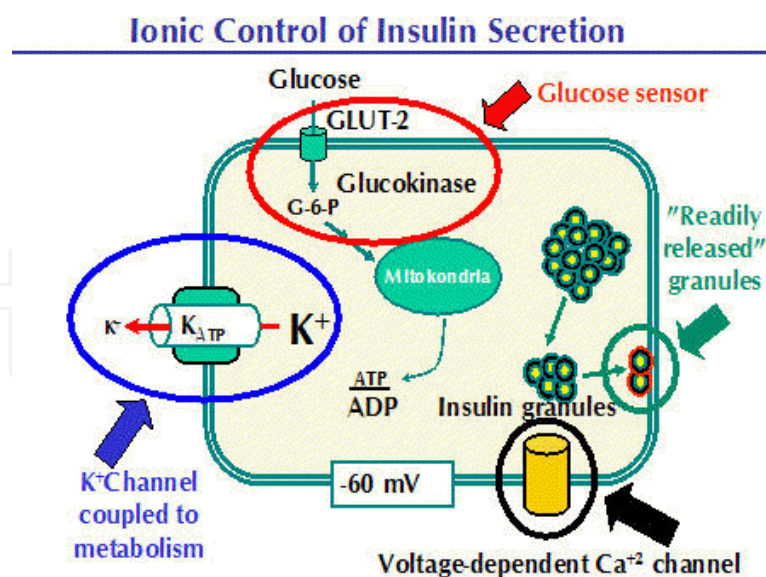
Zinc is highly concentrated in the insulin-secreting beta cells of our pancreas. Zinc can keep insulin molecules together in the beta cells. Beta cells must have zinc to function. In fact, beta cells

contain their own special zinc transporter called zinc transporter 8 that enables beta cells to take up zinc. Gene alterations in this zinc transporter are now known to cause type II diabetes while type I diabetes is associated with antibodies against this zinc transporter (meaning the immune system knocks out function of beta cells so they can't produce insulin).

Zinc directly influences how insulin is produced and secreted by our beta cells. So the people with zinc deficiency can't store and release insulin. Furthermore, zinc is self-protecting to the beta cells. It has now been shown that zinc directly reduces the inflammatory signals that damage the beta cells, a process that leads to type I diabetes.

### 3. Mechanisms of insulin secretion from beta cells

The secretion of insulin from pancreatic beta cells is a complex process involving the integration and interaction of multiple external and internal stimuli. Thus, nutrients, hormones, neurotransmitters, and drugs all activate or inhibit insulin secretion. The primary stimulus for insulin release is the beta-cell response to changes in glucose concentration. Normally, glucose induces a biphasic pattern of insulin release. First-phase insulin release occurs within the first few minutes after exposure to an elevated glucose level; this is followed by a more permanent second phase of insulin release. Of particular importance is the observation that first-phase insulin secretion is lost in patients with type 2 diabetes. Thus, molecular mechanisms involved in phasic insulin secretion are important. This processes discussed as follow (fig 2).



**Figure 2.** The beta cell structure

A widely accepted sequence of events involved in glucose-induced insulin secretion is as follows:

1. Glucose is transported into beta cells through facilitated diffusion of GLUT2 glucose transporters.
2. Intracellular glucose is metabolized to ATP.
3. Elevation in the ATP/ADP ratio induces closure of cell-surface ATP-sensitive K<sup>+</sup> (KATP) channels, leading to cell membrane depolarization.
4. Cell-surface voltage-dependent Ca<sup>2+</sup> channels (VDCC) are opened, facilitating extracellular Ca<sup>2+</sup> influx into the beta cell.
5. A rise in free cytosolic Ca<sup>2+</sup> triggers the exocytosis of insulin.

It is understood that glucose stimulates insulin secretion in the pancreatic beta cell by means of a synergistic interaction between at least two signaling pathways. In the K (ATP) channel-dependent pathway, glucose stimulation increases the entry of extrinsic Ca<sup>2+</sup> through voltage-gated channels by closure of the K (ATP) channels and depolarization of the beta cell membrane. The resulting increase in intracellular Ca<sup>2+</sup> stimulates insulin exocytosis. While in the GTP-dependent pathway, intracellular Ca<sup>2+</sup> is elevated by GTP-dependent proteins and augments the Ca<sup>2+</sup>-stimulated release. Secretagogues and insulin secretion inhibitors act at intermediate steps of these signaling pathways and influence the process of insulin exocytosis. Several researchers have investigated this intricate mode of known secretagogue action using isolated islets as an *in vitro* model. To quote a few; imidazoline antagonists of alpha 2-adrenoreceptors increase insulin release *in vitro* by inhibiting ATP-sensitive K<sup>+</sup> channels in pancreatic beta cells. Some researchers have evaluated the properties of sulphonylurea receptors (SUR) of human islets of Langerhans. They studied the binding affinity of various oral hypoglycaemic agents to the receptor and also tested insulinotropic action of the drugs on intact human islets. This binding potency order was parallel with the insulinotropic potency of the evaluated compounds. Some investigators have shown an insulinotropic effect of Triglitzone (CS-045) and have shown its mode of action to be distinct from glibenclamide (a sulphonylurea drug). A-4166, a derivative of D-phenylalanine, evokes a rapid and short-lived hypoglycaemic action *in vivo*. It has been shown to act via the tolbutamide binding sites<sup>14</sup>. Some studies showed S21403, a meglitinide analogue to be a novel insulinotropic tool in the treatment of type 2 diabetes, as it affected cationic fluxes and the drugs secretory responses displayed favourable time course of prompt, and not unduly prolonged, activation of beta cells. Some studies demonstrated that tetracaine (an anaesthetic) stimulates insulin secretion by release of intracellular calcium and for the first time elucidated the role of intracellular calcium stores in stimulus-secretion coupling in the pancreatic beta cells. JTT-608, is a nonsulphonylurea oral hypoglycaemic agent which stimulates insulin release at elevated but not low glucose concentrations by evoking PKA-mediated Ca<sup>2+</sup> influx.

#### 4. The importance of KATP channels

The KATP channels play an integral role in glucose-stimulated insulin secretion by serving as the transducer of a glucose-generated metabolic signal (ie, ATP) to cell electrical activity



(membrane depolarization). Thus, like neurons, beta cells are electrically excitable and capable of generating  $\text{Ca}^{2+}$  action potentials that are important in synchronizing islet cell activity and insulin release. In addition to being signal targets for glucose, KATP channels are the targets for sulfonylureas, which are commonly prescribed oral agents in the treatment of type 2 diabetes. The sulfonylureas, like glucose, induce closure of KATP channels and stimulate insulin secretion.

The beta-cell KATP channel is a complex octameric unit of 2 different proteins: the sulfonylurea receptor (SUR-1) and an inward rectifier (Kir6.2). The sulfonylurea receptor belongs to a superfamily of ATP-binding cassette proteins and contains the binding site for sulfonylurea drugs and nucleotides. The inward rectifier represents the  $\text{K}^{+}$  conducting pore and is also regulated by ATP. It is interesting that KATP channels are present in other tissues of the body, including heart (SUR-2A/Kir 6.2), smooth muscle (SUR-2B/Kir 6.2), and brain (SUR-1/Kir 6.2). Recently, Mark L. Evans, MD, Yale University Medical School, New Haven, Connecticut, and colleagues have suggested that glucose sensing in the brain during hypoglycemia may be mediated by KATP channels located in brain hypothalamic neurons. Thus, these molecules may also serve as new therapeutic targets for the restoration of impaired hypoglycemia awareness and glucose counterregulation in type 1 diabetes.

## 5. Voltage-dependent $\text{Ca}^{2+}$ channels: Novel regulators

Extracellular  $\text{Ca}^{2+}$  influx through L-type voltage-dependent  $\text{Ca}^{2+}$  channels (VDCC) raises free cytoplasmic  $\text{Ca}^{2+}$  levels and triggers insulin secretion. The structure of the VDCC is complex and consists of 5 subunits: alpha1, alpha2, beta, gamma, and delta units. The alpha subunit constitutes the ion-conducting pore, whereas the other units serve a regulatory role. Previous work has identified that isoforms of alpha1 subunits interact with exocytotic proteins. More recently, using the yeast hybrid screening method, a novel protein, Kir-GEM, interacting with the beta3 isoform of the VDCC, has been identified by Seino and colleagues. Furthermore, it has been determined that Kir-GEM inhibits alpha ionic activity and prevents cell-surface expression of alpha subunits. The investigators have proposed that in the presence of  $\text{Ca}^{2+}$ , Kir-GEM binds to the beta isoform, and this interaction interferes in the trafficking or translocation of alpha subunits to the plasma membrane. The relevance of Kir-GEM in insulin secretion was made evident by its attenuation of glucose-stimulated  $\text{Ca}^{2+}$  increases and C-peptide secretion in an insulin-secreting cell line.

The potential therapeutic role of Kir-GEM lies in the inhibitory effects on VDCC activity that may serve to protect beta cells from overstimulation and subsequent failure, which is part of the disease etiology of type 2 diabetes.

## 6. Novel cAMP signaling pathways of insulin release

The incretins are another set of factors that are important hormonal regulators of insulin secretion. The incretins are polypeptide hormones released in the gut after a meal that potentiate in-

ulin secretion in a glucose-dependent manner. Due to their dependence on ambient glucose for action, they are emerging as important new therapeutic agents to promote insulin secretion without accompanying hypoglycemia (a common complication of sulfonylurea treatment).

Unlike sulfonylureas, incretins act by activating Gs (a G-protein that activates adenylyl cyclase) to increase cAMP in beta cells. cAMP, like ATP, is an important signal that regulates insulin release. Typically, the main mechanism of action of cAMP is by activation of an enzyme called protein kinase A (PKA) that, in turn, phosphorylates other substrates to turn on (or off) vital cell functions. Using a biochemical assay called the yeast hybrid screening method to identify and isolate new proteins, some researchers identified a novel protein, cAMP-GEF II, a cAMP sensor (cAMPS) that forms a complex with other intracellular proteins (Rim2 and Rab3) to directly regulate insulin exocytosis. Then, using molecular reagents that antagonize the effects of cAMPS, they observed that incretin-potentiated insulin secretion is attenuated. These results provide a mechanism whereby cAMP can directly promote exocytosis of insulin granules without activation of PKA (ie, a PKA-independent pathway), and thereby provide additional molecular targets for therapeutic intervention.

## 7. Beta cell dysfunction and apoptosis

**Type one diabetes:** Islet beta-cells are almost completely destroyed when patients with type 1 diabetes are diagnosed. Type 1 diabetes occurs when the body's own immune system destroys the beta cells. Some people develop a type of diabetes – called secondary diabetes -- which is similar to type 1 diabetes, but the beta cells are not destroyed by the immune system but by some other factor, such as cystic fibrosis or pancreatic surgery.

**Type two diabetes:** Defects in insulin action and insulin secretion are both present in type 2 diabetes, and both are believed to be genetically predetermined. In the absence of a defect in beta-cell function, individuals can compensate indefinitely for insulin resistance with appropriate hyperinsulinemia, as observed even in obese populations. Both insulin secretion and insulin action are impaired in type 2 diabetes. However, when allowance is made for the hyperglycaemia and the fact that glucose stimulates insulin secretion, it becomes apparent that the insulin levels in diabetic patients are lower than in healthy controls and inadequate beta-cell function therefore represents a key feature of the disease. Theoretically, the insulin secretory defect could result from either defects of beta-cell function or a reduction in beta-cell mass. Most quantitative estimates indicate that type 2 diabetes associates with either no change or < 30% reduction in beta-cell mass. Moreover, the secretion defect is more severe than can be accounted for solely by the reduction in beta-cell mass. It therefore appears that the insulin secretory defect in type 2 diabetes does not primarily result from insufficient beta-cell mass but rather from an impairment of insulin secretion.

## 8. Prevention of beta cell dysfunction and apoptosis

Islet beta-cells are almost completely destroyed when patients with type 1 diabetes are diagnosed. To date, insulin substitute therapy is still one of the main treatments. The cure of

type 1 diabetes requires beta-cell regeneration from islet cell precursors and prevention of recurring autoimmunity. Therefore, beta-cell replacement, regeneration and proliferation emerge as a new research focus on therapy for type 1 diabetes; however, its application is limited by the shortage of pancreas donors. In-vitro expansion of human cadaveric islet beta cells represents an attractive strategy for generation of abundant beta-like cells. Human beta cells patent a very low proliferation capacity in vivo, and intact isolated islets cultured in suspension do not proliferate, although they remain functional for months. When islets are allowed to attach, limited replication of beta cells can be induced by growth factors or extracellular matrix components before the beta-cell phenotype is lost. Previous accepting of the determinants of tissue mass during adult life is still rudimentary. Insights into this problem may suggest novel approaches for the treatment of neoplastic as well as degenerative diseases. In the case of the pancreas, elucidating the mechanisms that govern  $\beta$  cell mass will be important for the design of regenerative therapy for both type 1 and type 2 diabetes, diseases characterized by an insufficient mass of  $\beta$  cells. It is clear that  $\beta$  cell mass increase during pregnancy and in insulin-resistant states, but evidence on the ability of  $\beta$  cells to regenerate from a severe, diabetogenic injury is conflicting. Whereas autoimmune diabetes is normally irreversible, recent evidence from both humans and rodents suggests that  $\beta$  cell function (i.e., insulin production and the maintenance of glucose homeostasis) can partly recover if autoimmunity is blocked.

Islet beta-cell regeneration and development are controlled by many growth factors, especially insulin-like growth factor-1 (IGF-1). Pancreatic islets produce Igf1 and Igf2, which bind to specific receptors on  $\beta$ -cells. Igf1 has been shown to influence  $\beta$ -cell apoptosis, and both Igf1 and Igf2 increase islet growth; Igf2 does so in a manner additive with fibroblast growth factor 2. Some study showed that IGF-1 can protect beta-cells from the destruction of apoptosis factors and promoting beta-cell survival and proliferation. Interleukin-1beta (IL-1 beta) is a potent pro-inflammatory cytokine that has been shown to inhibit islet beta cell function as well as to activate Fas-mediated apoptosis in a nitric oxide-dependent manner. Furthermore, this cytokine is effective in recruiting lymphocytes that mediate beta cell destruction in type one diabetes. IGF-I has been shown to block IL-1beta actions in vitro.

Glucagon like peptide 1 (GLP-1) is a potent insulin secretagogue released by L-cells of the distal large intestine in response to meal ingestion and, together with glucose-dependent insulinotropic polypeptide (GIP), account for 90% of the incretin effect. Type 2 diabetic patients are characterized by severely impaired  $\beta$ -cell function, reduced plasma GLP-1 response to meal/glucose ingestion that correlates with reduced insulin secretion, and severe  $\beta$ -cell resistance to the stimulatory effect of GLP-1 on insulin secretion. GLP-1 also inhibits glucagon secretion, delays gastric emptying, and promotes weight loss by its appetite-suppressant effect. GLP-1 analogs also stimulate islet neogenesis and  $\beta$ -cell replication and inhibit islet apoptosis. The gluco-incretin hormones GLP-1 and GIP can protect beta-cell against apoptosis induced by cytokines or glucose and free fatty acids. Both hormones bind to specific Gs-coupled receptors, which trigger cAMP formation. In beta-cells, basal cAMP levels controls glucose competence, i.e., the magnitude of the insulin secretion response to a given increase in extracellular glucose concentration. Increases in cAMP levels, for instance



as stimulated by GLP-1 or GIP action, potentiate glucose-stimulated insulin secretion by both protein kinase A (PKA)-dependent and independent mechanisms; they also stimulate gene transcription through PKA dependent phosphorylation of the transcription factor CREB. In beta-cells, increased cAMP levels also activate the MAP kinase cascade, leading to rapid phosphorylation of Erk1/2. An activation of the PI3Kinase/Akt pathway is also observed. PI3kinase may be directly activated by the  $\beta\gamma$  subunit of Gs, be secondary to transactivation of the EGF receptor by betacellulin, or may follow transcriptional induction of IRS-2 through the PKA/CREB pathway. The IRS-2/PI3kinase/Akt pathway is known to have anti-apoptotic effects; however, it is unclear why increased expression of IRS-2 leads to activation of its signaling pathway. IRS-2 may be downstream of the insulin (IR) or IGF-1 (IGF-1R) receptors. Studies of mice with beta-cell specific inactivation of either receptor indicated that the insulin receptor was important for compensatory growth of the beta-cells in response to insulin resistance whereas the IGF-1 receptor was involved in the control of glucose competence. Although these properties make GLP-1 an ideal antidiabetic agent, it is rapidly cleaved ( $T_{1/2} = 1-2$  min) by dipeptidyl peptidase-4. GLP-1 enhances beta cell function with an increase in the ability to secrete insulin and restore first phase insulin release. Our previous study showed that a novel GLP-1 analogue consisting of the fusion of active GLP-1 and IgG heavy chain constant regions (GLP-1/IgG-fc) therapy can enhance beta cell mass. It also could increase insulin secretion. Within the pancreas, GLP-1 expands  $\beta$ -cell mass via promotion of  $\beta$ -cell growth and reduction of  $\beta$ -cell death.

$\gamma$ -Aminobutyric acid (GABA), a prominent inhibitory neurotransmitter, is present in high concentrations in  $\beta$ -cells of islets of Langerhans. The GABA shunt enzymes, glutamate decarboxylase (GAD) and GABA transaminase (GABA-T) have also been localized in islet  $\beta$ -cells. With the recent demonstration that the 64,000-Mr antigen associated with insulin-dependent diabetes mellitus is GAD, there is increased interest in understanding the role of GABA in islet functions. Only a small component of  $\beta$ -cell GABA is contained in insulin secretory granules, making it unlikely that GABA, co-released with insulin, is physiologically significant. Our immunohistochemical study of GABA in  $\beta$ -cells of intact islets indicates that GABA is associated with a vesicular compartment distinctly different from insulin secretory granules. Whether this compartment represents a releasable pool of GABA has yet to be determined. GAD in  $\beta$ -cells is associated with a vesicular compartment, similar to the GABA vesicles. In addition, GAD is found in a unique extensive tubular cisternal complex (GAD complex). It is likely that the GABA-GAD vesicles are derived from this GAD-containing complex. Physiological studies on the effect of extracellular GABA on islet hormonal secretion have had variable results. Effects of GABA on insulin, glucagon, and somatostatin secretion have been proposed. The most compelling evidence for GABA regulation of islet hormone secretion comes from studies on somatostatin secretion, where it has an inhibitory effect. Some researchers present new evidence demonstrating the presence of GABAergic nerve cell bodies at the periphery of islets with numerous GABA-containing processes extending into the islet mantle. This close association between GABAergic neurons and islet  $\alpha$ - and  $\delta$ -cells strongly suggests that GABA inhibition of somatostatin and glucagon secretion is mediated by these neurons. Intracellular  $\beta$ -cell GABA and its metabolism may have a role in  $\beta$ -cell function. New evidence indicates that GABA shunt activity is involved in regula-

tion of insulin secretion. In addition, GABA or its metabolites may regulate proinsulin synthesis. These new observations provide insight into the complex nature of GABAergic neurons and  $\beta$ -cell GABA in regulation of islet function. Our study showed that GABA exerts has protective and regenerative effects on islet beta cells and reverses diabetes. GABA therapy increased beta cell proliferation and decreased beta cell apoptosis, which in turn increase beta cell mass and induced the reversal of hyperglycemia in the different kind of mice. Our data suggest that GABA exerts has anti-inflammatory effects, and is directly inhibitory to T cells and macrophages.

Magnesium deficiency has recently been proposed as a novel factor implicated in the pathogenesis of the diabetic complications. In our previous study we showed that oral chronic Mg administration could improve islet structure and decrease the blood glucose.

Another potential treatment is the combination of two growth factors called gastrin and epidermal growth factor (EGF), which has been shown to promote beta-cell regeneration in rats.

Many traditional treatments have been recommended in the alternative system of medicine for treatment of diabetes mellitus and regeneration of beta cells such as Garlic, *Teucrium polium*, Cinnamon and *Psidium guava* leaves. Photochemical analysis of those herbs have revealed the presence of flavonoids, which include quercetin and its derivatives. It is concluded that quercetin, a flavonoid with antioxidant properties brings about the regeneration of the pancreatic islets and probably increases insulin release in streptozocin-induced diabetic rats.

Connective tissue growth factor (CTGF), to induce adult  $\beta$  cell mass expansion. Some study showed that CTGF is required for embryonic  $\beta$  cell proliferation<sup>3</sup>, and that CTGF overexpression in embryonic cells increases  $\beta$  cell proliferation and  $\beta$  cell mass.

The mouse pancreas develops from ventral and dorsal evaginations of the posterior foregut endoderm at embryonic day, a process dependent on the transcription factors Pdx1 and Ptf1. Differentiation of all pancreatic endocrine cell types ( $\alpha$ ,  $\beta$ ,  $\Delta$  and PP) is dependent on the transcription factor, neurogenin 3 (Ngn3). *Ngn3* expression is controlled by a variety of factors, including the Notch signaling pathway and the transcriptional regulators pancreatic and duodenal homeobox 1 (Pdx1), SRY-box 9 (Sox9) and hepatic nuclear factor 6 (Hnf6). Although  $\beta$  cell neogenesis begins, these early insulin-positive cells do not contribute to mature islets. Instead, endocrine cells that will go on to contribute to the mature islets begin to differentiate period known as the secondary transition. Some transcription factors critically involved in  $\beta$  cell differentiation include NK2 homeobox 2 (Nkx2.2), Nkx6.1, islet 1 (Isl-1), neuronal differentiation 1 (NeuroD1), motor neuron and pancreas homeobox 1 (Mnx1), paired box gene 4 (Pax4) and Pdx1.

In adults, physiological stimuli can enhance  $\beta$  cell proliferation during development. Although several factors have been identified that play a role in the regulation of embryonic and neonatal  $\beta$  cell proliferation. One cell cycle regulator that does play a role in embryonic  $\beta$  cell proliferation is the cell cycle inhibitor, p27Kip1. Inactivation of *p27Kip1* during embryogenesis results in an increase in  $\beta$  cell proliferation and subsequently  $\beta$  cell mass. There was no change, however, in early postnatal  $\beta$  cell proliferation, suggesting that p27Kip1 is not crucial to postnatal proliferation.

As mentioned above *Pdx1* expressed in multipotent pancreatic progenitors in the early stages of pancreas development, but, *Pdx1* expression becomes enhanced in insulin-positive cells and is found at only low levels in exocrine cells. This expression pattern is maintained into adulthood and *Pdx1* plays a critical role in maintenance of the mature  $\beta$  cell phenotype. Inactivation of *Pdx1* in embryonic insulin-expressing cells results in a dramatic decrease in  $\beta$  cell proliferation at late gestation, leading to decreased  $\beta$  cell mass at birth and early onset diabetes. Two large Maf (musculoaponeurotic fibrosarcoma oncogene homolog) transcription factors that are closely related to one another, MafA and MafB, are critical for  $\beta$  cell differentiation and embryonic *Pdx1* expression<sup>22</sup> and therefore may have an indirect effect on embryonic  $\beta$  cell replication.

Inactivation of the eIF2 $\alpha$  endoplasmic reticulum resident kinase, PERK (protein kinase RNA-like endoplasmic reticulum kinase), specifically in embryonic  $\beta$  cells (PERK $\Delta$ beta) results in a 2-fold decrease in  $\beta$  cell proliferation, which persists through postnatal day (P).

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