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Review

Intracellular mechanism of nutrients and obesity induced pancreatic β-cell development and the implication of pancreatic cancer

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Abstract: Pancreatic β-cell is responsible for secreting insulin to decrease blood glucose, which is one of the most important cell type for both human and other mammals. Under condition of either peripheral insulin resistance or β-cell failure, β-cells are unable to release enough insulin, either by expansion of cell numbers or enhancement of insulin production, to fully compensate, resulting in hyperglycemia, which can lead to diabetes. Excessive nutrients intake and obesity are the major risk factors for β-cell mal-development and dysfunction. In this review, the intra-cellular signaling pathways that associated with pancreatic β-cells mass and insulin secretion has been reviewed. Furthermore, these pathways and potential mechanisms associated with the nutrients level, obesity and pancreatic cancer are also reviewed. The research will offer the means for potential early intervention and drug treatment in the future.

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1. Pancreatic development and function

In most mammals including rodents, and human, the pancreas is an elongated organ located across the back of the abdominal cavity and in closely associated with the duodenum, which includes both exocrine and endocrine functions. Pancreatic development starts from the formation of a ventral and dorsal bud [1, 2], and then fusion of the pancreatic ventral and dorsal buds to form the definitive pancreatic structure [3]. Pancreatic control of blood glucose concentrations is accomplished by two cell types located in the islets: the α-cell which is responsible for secreting glucagon to increase blood glucose and β-cell which is responsible for secreting insulin to decrease blood glucose. β-cell function can be estimated by measuring β-cell mass within the pancreas or cellular insulin synthesis and release [4, 5]. Under condition of either peripheral insulin resistance or β-cell failure, β-cells are unable to release enough insulin, either by expansion of cell numbers or enhancement of insulin production, to fully compensate, resulting in hyperglycemia, which can lead to diabetes [1, 5]. β-cell numbers are determined by cell neogenesis, proliferation, and apoptosis, which can be affected by either alterations in nutrition or hormonal production acting through specific second messenger pathways within the ß-cells themselves [6]. Quantitating insulin synthesis and/or release by β-cells is another way of determining β-cell function [6], which is mainly affected by alteration of nutrients including glucose, amino acids and fatty acids. If the β-cell mass is reduced, the activity of insulin biosynthesis and release by the remaining β-cell will be enhanced to try to compensate for this defect [5].

2. Pancreatic β-cell mass: neogenesis, proliferation and apoptosis

The insulin secreted by β-cells regulates glucose homeostasis in a very precise manner [5]. In order to maintain a normal blood glucose level, maintenance of optimal numbers of β-cells and adequate insulin secretion is crucial. These changes in pancreatic β-cell mass can significantly alter pancreatic and blood insulin levels. Numerous studies have shed light on the factors controlling β-cell mass and the intracellular signaling pathways involved [7-12] and these pathways are also widely associated with other organs and tissues [13-15]. The total β-cell mass is determined by changes in the cell neogenesis, proliferation and apoptosis [6]. Thus, the intracellular cellular pathways that control β-cell

neogenesis, proliferation and apoptosis are crucial in the development of insulin resistance and diabetes mellitus [6].

The process of pancreatic cell differentiation results from activation of one of two different pathways, which correspond to the endocrine and exocrine functions of the pancreas. Progenitor cells of the endocrine pancreas arise during the process of exocrine cell differentiation [3]. Furthermore, these progenitor cells differentiate to two lines of committed endocrine precursor cells dictated by transcriptional factors: 1) paired box gene 0 (Pax-0) and 2) Pax-6 [1-3]. The first line of endocrine precursor cells is influenced by Pax-0, to form α-cells and γ- cells, whereas the second line, directed by Pax-6, produces β-cells and δ-cells [1-3]. Insulin can be detected in the fetal pancreas as early as 70 days of gestation in humans but insulin in fetal plasma cannot be detected until 84 days in humans [2]. With increasing gestational age, the pancreatic content of insulin consistently increases in parallel with increased β-cell numbers in most species evaluated [16, 17].

Another source of β-cells is from the proliferation of already committed β-cells [4, 18]. Although the mitotic rate of β-cells is not high, the proliferation can continue for several years after birth in human offspring [18]. The rate of β-cell proliferation is associated with both nutritional level and hormone exposure in vivo and in vitro [2, 4, 8, 9, 19-23]. More specifically, glucose, amino acids, and other nutrients can mediate increases in β-cell mass [2, 23], whereas insulin-like growth factors (IGFs), insulin, growth hormone and other potential hormones mediate β-cells mass in an endocrine, paracrine, and autocrine fashion [2, 5, 8, 23].

Apoptosis negatively regulates β-cells mass, which can result in the type 1 diabetes and also plays a key role in the evolution of type 2 diabetes [5]. The incidence of programmed cell death in early fetal development is very low, and may not be the main regulator of β-cell mass at that time, however, β-cell apoptosis is significantly increased in late-gestation and neonates of both human and rats undergoes a wave of apoptosis, which is associated with pancreatic remodeling after birth [22, 24]. In humans, there is a wave of increased β-cell apoptosis occurring during the prenatal period, peaking at birth, and approaching a nadir by 6 months of age, with β-cell proliferation progressively declining from early gestation to extremely low levels by 6 months postnatal age [22]. These changes in β-cell proliferation and apoptosis may be responsible for the postnatal islet remodeling seen in these species. Although the β-cell apoptotic wave is a normal phenomenon in rats and humans, an increased rate of apoptosis may augment the chance of diabetes in their offspring [4, 25]. In 1995, Finegood *et al*. [4] constructed a well-accepted mathematical model of dynamics of the β-cell mass in the rodent. These researchers evaluated existing studies describing a variety of factors including β-cell proliferation and apoptosis thought to mediate pancreatic growth in the rat, and concluded that diabetes-prone strains may exhibit an exaggerated β-cell apoptotic wave.

3. β -cell insulin secretion and function

Insulin production and release is a very complicated process involving insulin granule biogenesis, sorting, and exocytosis, which is mainly modulated by nutritional factors and metabolic hormones. Dysregulation of this process can result in the developed of diabetes [26, 27]. Insulin biosynthesis starts with the synthesis of preproinsulin and conversion of preproinsulin to proinsulin in the rough endoplastic reticulum of β-cells, which is then packaged in the Golgi apparatus and sorted into immature secretory granules. These immature granules undergoes further proteolytic cleavage resulting in the formation of insulin and C-peptide [26, 27]. Glucose activates proinsulin gene expression through the phosphorylation of eukaryotic translation initiation factor 4E binding protein (eIF-4EBP), activates eIF-4E and forms eIF-4F which can recognize preproinsulin mRNA and recruits 40S ribosome to mRNA. eIF2 is another critical factor in insulin biosynthesis, which can be activated by glucose through converting GDP-bound eIF-2 to GTP-bound eIF-2 and further form eIF2-GTP•Met-tRNAi ternary complex, which then binds 40S ribosome and activates insulin gene expression [26-28]. In β-cells, insulin production is a cAMP dependent process and nutritionally-induced changes in adenyl cyclase can limit insulin production and further reduce insulin response to glucose [2, 29]. Thus, the changes of the developmental environment induced by nutritional and hormonal changes in utero may alter the translatability (capacity of DNA translation) of insulin mRNA with consequences for postnatal insulin deficiency [2].

Insulin secretion by β-cells can be stimulated by several factors including increased cellular glucose and amino acid metabolism, FFA signaling, and other

nutrients and hormones [5]. The rate of glucose metabolism in the β-cells is the key factor for determining the rate of insulin release. Glucose enters the β-cell through the glucose transporter 2 (GLUT2), and then enters glycolysis through glucokinase (GCK) and the respiratory cycle where multiple high-energy ATPs are produced [5]. The expressions of GLUT2 and GCK have been identified in islets of both humans and rats. In early human islets development when either GLUT2 or GCK expression was inhibited insulin release is reduced and led to growth retardation at birth [30]. Therefore, the ATP controlled potassium channels (K^+) closes which then leads to depolarization of the cell membranes. At depolarization, voltage-sensitive calcium channels (Ca^{2+}) activate and thus calcium flows into the β-cell, resulting in insulin granule exocytosis [5]. AMP-activated protein kinase (AMPK) has been demonstrated as an important component of the protein kinase cascade in intracellular sensing of energy balance and responds to AMP/ATP ratio [31] which suggests AMPK may play a major role in regulation of β-cell insulin secretion. However, Gleason *et al*. indicated that the inhibition of AMPK activity by glucose or other nutrients may play a very important role in nutrient-stimulated mTOR signaling pathway to regulate β-cells growth rather than the insulin secretion in the β-cells of rats [32]. So glucose may play a double role in terms of β-cell development and function: on one hand, it can stimulate β-cell growth and proliferation; on the other hand, it is involved in triggering insulin synthesis and secretion.

Free fatty acids (FFAs) are another crucial factor that influence insulin release and β-cell function. The mechanisms controlling this process involve two different pathways. The first signaling pathway is the binding of FFA to G-protein-coupled receptor 40 (GPR40), which is a G-protein-coupled receptor on the cell membrane, to increase intracellular calcium through activation of intracellular signaling and hence resulting in insulin granule exocytosis [33]. The other one involves generation of fatty acyl-CoA, which could increase insulin release either by directly stimulating secretion or by activation of PKC and increase intracellular calcium [34]. In a hyperthyroid rat model, Holness *et al*. [35] reported that higher circulating lipids improved β-cell function by increasing glucose stimulated insulin secretion. However, sustained exposure in fatty acids have been shown to induce lipotoxicity in β-cells through endoplasmic reticulum (ER) stress and lead to apoptosis [36-38].

Sensitivity to incretins is a third possible mechanism to regulate β-cells insulin secretion. Incretins are produced in the intestinal mucosa and are responsible for the regulation of the insulin secretion and β-cell mass [39]. Two main incretin candidate, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are secreted in a nutrient dependent way and regulate nutrient-dependent β-cell insulin secretion. This makes GLP-1 receptor (GLP-1R), which is expressed on β-cells, a very important factor to study [40]. Hardikar *et al*. [41] indicated that GLP-1 can stimulate maturation of glucose induced insulin secretion from β-cells in fetal pigs.

4. The compensatory effect of insulin secretion and pancreatic β-cell mass

In order to maintain the glucose levels in a normal physiological range, insulin secretion from β-cells must be tightly controlled by either altering β-cell number or insulin production and content per cell. If the β-cell mass is impaired, the activity of insulin biosynthesis and release will be enhanced to compensate for this defect [5, 42]. In non-diabetic obese humans, β-cells numbers increase by only 50% to correct for peripheral insulin resistance, whereas levels of insulin secretion increase fourfold to fivefold as a response to insulin resistance and elevated glucose concentrations in blood [5, 42], indicating significant reserve in the insulin secreting capacity of their β-cells. In human, the β-cells volume of obese people is significantly increased in respond to insulin resistance and this increase is largely dependent on hypertrophy of existing cells, which suggest, in abnormal circumstances, β-cells are able to increase cell size to generate more insulin to compensate for physiologic changes [43]. Limesand *et al*. [11, 44] indicate that heat-stress induced Intrauterine Growth Retardation (IUGR) resulted in decreased fetal β-cell mass, proliferation and insulin biosynthesis and/or storage in sheep, but the fraction of β-cell insulin released per unit insulin content was increased in IUGR, suggesting that a compensatory effect on β-cell insulin secretion exists when the cell mass is impaired (Fig. 1).

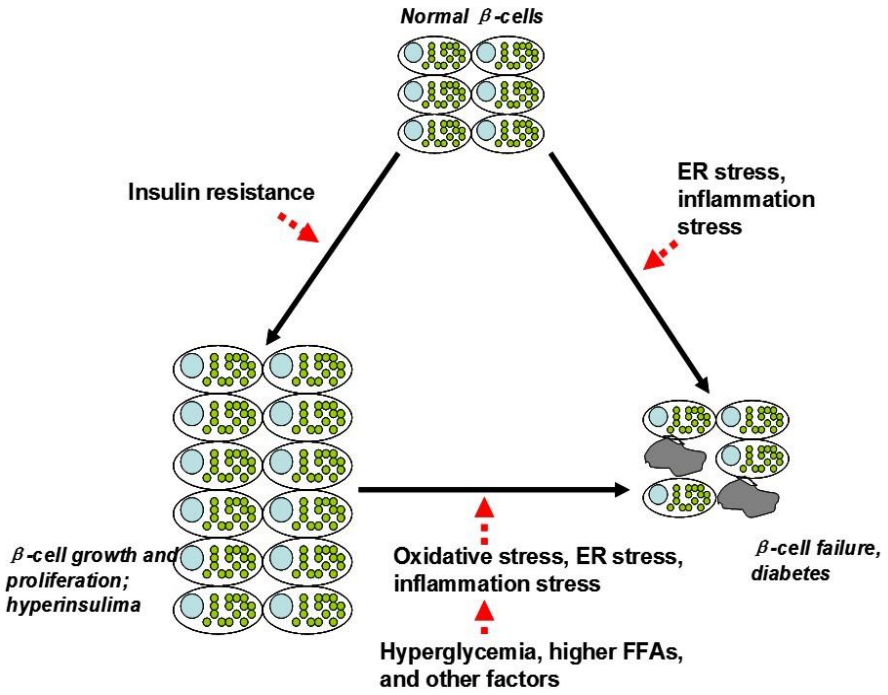

Fig.1. Process of β-cells failure and diabetes.

5. Obesity associated hormones signaling and insulin resistance

Obesity is associated with endocrine disorders, which are proposed to induce metabolic diseases such as diabetes [45-48]. Obesity is commonly associated with hyperglycemia, hyperinsulimia, as well as elevated free fatty acids, leptin, and adipocytokines [49]. The hyperglycemia and hyperinsulimia result from obesity induced peripheral insulin resistance, in which the pancreatic β-cells secret more insulin to compensate for the increased peripheral insulin resistance. As mentioned above, the effect of elevated glucose exposure on pancreatic β-cells mainly depends on glucose concentration and duration of exposure [36]. β-cells chronically exposed to elevated glucose concentrations initially have enhanced expression of glycolytic enzymes leading to increased β-cell numbers [36, 50]. However, on the second phase, β-cell mass decreases as a result of increased β-cell apoptosis with prolonged exposure to higher glucose concentrations, [36]. In both in *vivo* and *in vitro* rodent studies, chronically elevated glucose levels can cause increased β-cell apoptosis, resulting in insulin deficiency [36]. Impairment of normal mitochondrial function may also play a key role in hyperglycemia induced β-cell apoptosis [51]. Studies in both freshly isolated pancreatic β-cells and β-cell lines indicated that the alterations in the shape of mitochondria induced by hyperglycemia may lead to β-cell apoptosis and speculate that this may be involved in the pathophysiology of type 2 diabetes [51].

Pancreatic β-cells need fatty acids for normal cell function and metabolism, as well as insulin secretion. Deletion of fatty acid receptor (GPR40) genes in mice results in a marked decrease (~50%) in insulin secretion compared to normal mice, which illustrates the importance of fatty acids in normal insulin secretion. Further, over expression of GPR40 in pancreatic β-cells results in increased insulin secretion in response of glucose and fatty acids [52]. It is believed that in response to higher circulating fatty acids associated with obesity, the pancreatic β-cells mass and insulin secretion are enhanced to decrease fatty acids in blood stream [53]. However, similar to glucose, prolonged exposure of β-cell mass to elevated levels of fatty acids impairs their function [49]. Fatty acids have been shown to induce lipotoxicity in β-cells through either oxidative stress or endoplasmic reticulum (ER) stress via cytokine signaling pathways involving interleukin (IL)-1β and NF-κB *etc* [45-48]. On one hand, increased mitochondrial metabolism results in increased reactive oxygen species production leading to oxidative stress; on the other hand, increased insulin biosynthesis can

induce activation of unfolded protein response, which then leads to endoplasmic reticulum (ER) stress [49]. Both oxidative stress and ER stress result in β-cell dysfunction and lead to diabetes. There are several cohort pathways responsible for generating oxidative stress including glycosylation, glucose autoxidation, hexoamine biosynthesis, and glucose metabolism [49].

Exposing pancreatic β-cells to leptin and adipocytokines impairs β-cell mass and function as well. Generally, leptin impairs both pancreatic β-cell mass and function [54-57]. In vitro, chronic exposure of human pancreatic islet to excessive leptin impairs β-cell function and induces apoptosis through decreased production of interleukin-1 (IL-1) receptor antagonist and triggers IL-1β release [56]. Long term exposure of β-cells to leptin decreases both insulin biosynthesis [58] and secretion [57]. Park *et al*. [55] have demonstrated that central infusion of leptin can improve peripheral insulin resistance but suppresses β-cell function, without affecting β-cell mass in a type 2 diabetic rat model. However, Maedler *et al*. [54] reported that glucose and leptin induce apoptosis in human β-cells and impair glucose-stimulated insulin secretion through activation of c-Jun N-terminal kinases. Although differing concentrations and exposure lengths result in different impacts on β-cells, a reduction in β-cell function is the main result of leptin treatment. However, Islam *et al*. [59] have reported that functional leptin receptors are expressed in pancreatic islet cells, and the leptin stimulates proliferation of fetal islet cells in rats, which may play a role in determining final islet cell mass at birth, suggesting a necessary role of leptin for early fetal islet development and function .

In addition to the effects of leptin in β-cell growth and function, other adipocytokines also play a crucial role in β-cell development. The pancreatic β-cells express low level of TNF receptor type 1, which can bind to elevated levels of TNF-α to inhibit β-cell development. TNF-α along with IL-1β are generated by cells of the immune system and mainly act as inflammatory cytokines in type 1 diabetes, leading to apoptosis of β-cells [60]. Further, TNF-α potentiate the effects of IL-1β to inhibit glucose response and insulin secretion [61]. In both obese animals and human, there are higher concentrations of circulating TNF-α compared with lean subjects, which may directly or indirectly suppress insulin secretion leading to diabetes [62]. However, the specific mechanism is still unknown. Interluken-6 is another adipocytokine product of adipose tissue. Circulating IL-6 is positively associated with body mass index [63]. Southern *et al*. [64] reported that in contrast to IL-1β and TNF-α, IL-6 did not inhibit islet DNA synthesis, which suggests that the IL-6 is not inhibitory to β-cell function. In fact, Sandler *et al*. [65] reported that IL-6 increases insulin secretion of pancreatic islet but has no effect on insulin biosynthesis in rats. Choi *et al*. [66] have demonstrated that IL-6 can protect the pancreatic β-cells from apoptosis both in vitro and in vivo through a reduction in inflammatory cytokines, suggesting a positive role of IL-6 in maintaining functional islet mass. The protective mechanism of IL-6 pathway may function through activation of AMPK. Kelly *et al*. [67] reported that IL-6 knock out mice expressed less AMPK in adipose tissue, which suggests that IL-6 can increase AMPK level which may further inhibit lipid concentrations to protect β-cell function. IL-6 can also decrease adiponectin expression [68], which may influence β-cell function as well.

In contrast to leptin and TNF-α, adiponectin can protect β-cells from lipotoxicity and therefore maintain the normal development and function of the β-cell [62]. Adiponectin receptors including adipoR1 and adipoR2, both of which are expressed by pancreatic β-cells in both rat and human, and are regulated by circulating levels of FFAs [69]. In adiponectin knockout mice, Maeda *et al*. [70] have also reported that transgenic mice maintained on a normal diet showed unchanged blood FFAs and glucose levels but decreased insulin concentrations compared with wild type mice. Moreover, adiponectin knockout mice, exhibited elevated blood glucose levels and reduced insulin compared to wild type mice in response to an oral glucose tolerance test, suggesting impaired β-cell function [71]. The mechanism whereby adiponectin acts to protect β-cells is still unclear. One of the most recent studies reveals that adiponectin activates AMPK which inhibits formation of lipids in pancreatic β-cells suggesting one potential pathway [72].

Taking all these observations together, adipose tissue derived factors including FFAs, leptin, adiponectin, TNF-α, and IL-6 play important roles in mediating pancreatic β-cell mal-development and dysfunction (Fig. 2). As mentioned above, the maternal obesity induced elevation in fat mass and FFAs in the fetus could result in abnormal β-cell mass and insulin release, contributing to insulin insufficiency and diabetes in postnatal life.

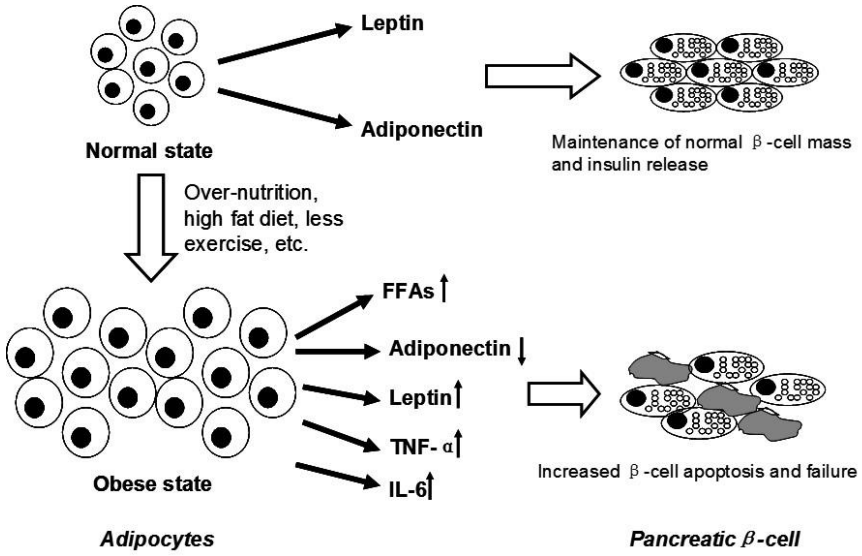

Fig. 2. Contributors of adipocyte derived factors to pancreatic β-cell development and function.

6. Pancreatic cancer induced changes on β-cells

Digestive zymogens activated prematurely result in generation of inflammatory mediators which further induces pancreatitis. The incidents progress from acute to chronic inflammation and then pancreatic cancer [73]. The specific mechanism was still unknown. Risk factors include alcohol, smoking, gall stone, certain medication and obesity may initiate the process with cathepsin-B prematurely converts trypsinogen to trypsin in acidic pH environment. Furthermore, the process combined with other factors leads to mutation of PRSS, SPINK1, CFTR and CTRC gene and activation of pancreatic stellate cells [73]. Fibrosis resulted from acute inflammation or other environment factors induced chronic pancreatitis and then pancreatic cancer when Kras gene mutation and loss of tumor suppressors P16 and P53 occur [74]. Patients with pancreatic cancer have an elevated incidence of insulin resistance, diabetes, and high circulating amylin concentrations. The mechanism of cancer induced changes on pancreatic β-cells is still unknown and both theories are proposed to illustrate the question: I. Pancreatic cancer induces β-cell changes, insulin resistance, and diabetes; II. Insulin resistance and diabetes result in pancreatic cancer [75]. Both of them have evidences to support and more investigations are needed to gradually unveil the mystery. However, one thing becomes clearer: pancreatic cancer leads to changes of pancreatic islet cell and insulin secretion which aggravates endocrine balance of patients [76] and may be one of the factors leading to poor prognosis of pancreatic cancer [77]. Ding *et al*. [78] demonstrated that a soluble factor from pancreatic cancer cells selectively stimulates amylin secretion from pancreatic islet cells which may further affect development of other pancreatic islet cells including β-cells. Li et *al*. [79] demonstrated that the association between hyperglycemia and poor prognosis in pancreatic cancer and the effect was attributed to the alterations of the invasive ability of the cells through the production of hydrogen peroxide.

7. Conclusion

All in all, as one of the most important cell types responsible for endocrine balance and insulin secreting, insulin secreting pancreatic β-cells modifies cell mass and insulin secretion pathway by altering intracellular signaling. Nutrients level, obesity and pancreatic cancer change pancreatic β-cell significantly by these intra-cellular signaling and further discovery of cellular/molecular mechanism will offer the means for potential early intervention and drug treatment in the future.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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