18

Protein Kinases and Pancreatic Islet Function

Gabriela Da Silva Xavier
Imperial College London, Section of Cell Biology, Division of Diabetes, Endocrinology and Metabolism, London UK

1. Introduction

Intense research on pancreatic islet function is fuelled by its link to the disease diabetes mellitus. Diabetes is a chronic disease that is characterised by inappropriate regulation of blood glucose levels. This dysregulation of blood glucose homeostasis occurs when the pancreas produces insufficient amounts of the hormone, insulin, or when insulin sensitive organs lose sensitivity to insulin (insulin resistance). Increasingly there is evidence to support the idea that abnormal release of another pancreatic hormone, glucagon, may be involved in the dysregulation of blood glucose homeostasis.

There are two types of diabetes. Type 1 diabetes is characterised by the failure of the pancreas to produce insulin. In most cases, type 1 diabetes is caused by autoimmune destruction of the pancreatic β cells that produce insulin and release the hormone in response to changes in blood glucose levels. Type 2 diabetes is characterised by relative insulin insufficiency and insulin resistance. This is the more common form of diabetes, comprising of 90 % of people with diabetes worldwide. The prominence of this form of diabetes is associated with lifestyle choices: the obesity epidemic has led to an increase in the incidence of diseases associated with metabolic imbalance such as diabetes. Energy homeostasis and obesity are intimately linked. Between 45-80 % of our energy intake is in the form of carbohydrates (1;2), which are converted to glucose and transported in the blood stream (3). Thus, there has been much interest in the mechanisms that regulate glucose homeostasis, particularly those involving the endocrine pancreas. The pancreatic hormones glucagon and insulin, produced and released in the pancreatice α and β cells, repectively, are involved in maintaining blood glucose homeostasis.

Uncontrolled diabetes leads to hyperglycaemia and can lead to a number of diabetes related complications over time, such as increased risk of cardiovascular disease, diabetic retinopathy, kidney failure, and diabetic neuropathy. Current figures published by the World Health Organisation (WHO) indicate that 346 million people worldwide have diabetes. It is estimated that 5 % of all deaths worldwide each year are as a consequence of diabetes and its associated complications, with more than 80 % of these deaths occuring in low- and middle-income countries (WHO figures). It is projected that the number of diabetes related deaths will double between 2005 and 2030 (WHO figures), making diabetes a major burden on society and the health system. There is currently no cure for diabetes.

2. The pancreatic endocrine compartment

Blood glucose homeostasis is regulated by the pancreatic hormones, glucagon and insulin, which are secreted from the pancreatic islets of Langerhans. There are approximately one million islets in the adult human pancreas; this equates to about 2 % of total pancreatic mass. Pancreatic islets of Langerhans consist of four different cell types: glucagon producing α cells, insulin producing β cells, somatostatin producing δ cells and pancreatic polypeptide producing PP cells. The hormones insulin and glucagon are the principal islet hormones regulating blood glucose levels. Insulin is characteristic of the fed state and is released in response to hyperglycaemia. Glucagon is characteristic of the fasted state and is released in response to hypoglycaemia. Multiple other factors, including neural factors, regulate hormone release. The regulation of hormone release occurs at the level of the single hormone producing cell, the islet of Langerhans, the pancreas and the whole organism (Fig. 1).

Each islet of Langerhans is composed of about 2000 cells; typically, 60 % of these cells are insulin producing β cells. Insulin ensures that glucose is taken up and stored by peripheral tissues (4). Insulin secretion from islet β cells is regulated by nutrient availability,

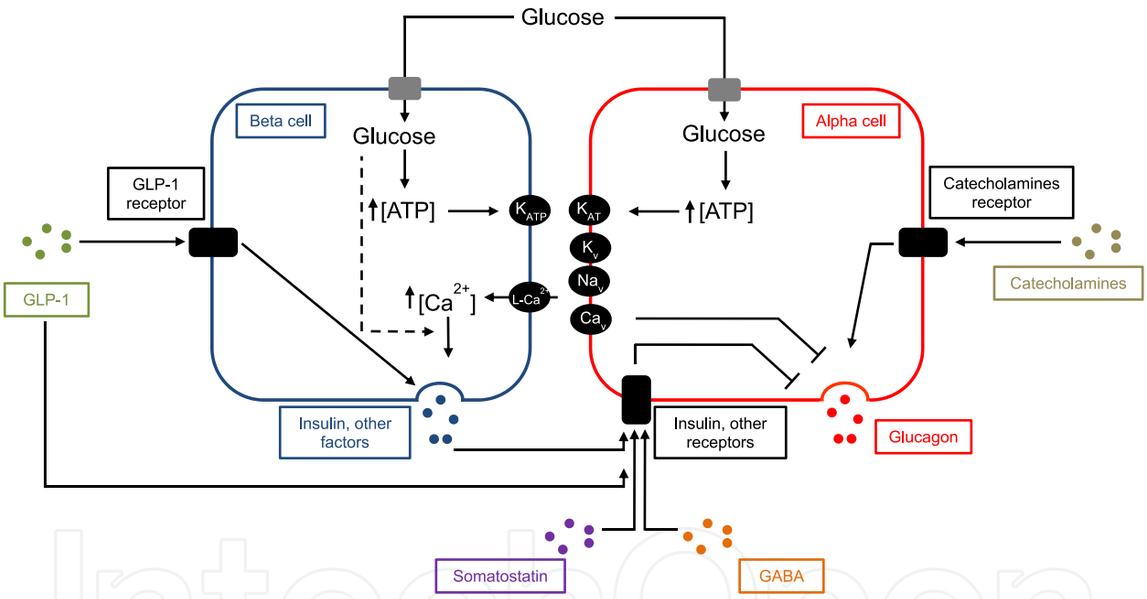


Fig. 1. **Insulin and glucagon release are regulated by nutrient availability, and a range of other factors.** Glucose entry in pancreatic α and β cells leads to increased ATP production, which in turn leads to closure of K-ATP (K_{ATP}) channels and membrane depolarisation. In the β cell this leads to opening of L-type voltage-gated calcium channels (L-Ca^{2+}) and subsequent release of insulin via the triggering pathway. Glucose metabolism augment the calcium signal to enhance insulin secretion through the amplification pathways (dashed line). The incretin, glucagon-like peptide 1 (GLP-1), which is secreted from L-cells in the gut, can enhance insulin secretion from pancreatic β cells. In the α cells the presence of voltage gated sodium (Na_v) and potassium (K_v) channels keep voltage-gated calcium (Ca_v) channels closed, and leads to inhibition of glucagon release when extracellular glucose concentrations are high. Insulin and other factors secreted by the pancreatic β cell, e.g. zinc ions and gamma aminobutyric acid (GABA), somatostatin (secreted by pancreatic δ cells), and catecholamines all play a part in the regulation of glucagon release (42;220-224).

neurotransmitters, and hormones. β cells are electrically excitable and transduce variations in circulating glucose concentrations into secretory signals through changes in their own metabolic state. β cells are equipped with a high capacity glucose transporter (5-7) and the high K_m type IV hexokinase (or glucokinase) (8;9). Thus, glucose phosphorylation is a rate limiting step in glucose metabolism in the β cell and glucokinase is generally known as the β cell glucose sensor (10). However, other steps in the lower glycolytic pathway are also important in regulating glucose metabolism (11-13; reviewed in 14). Ultimately, the resultant increase in cellular ATP leads to changes in the activity of the K_{ATP} and L-type voltage gated Ca^{2+} channels, influx of calcium into the cell and, subsequently, insulin secretion (15-19; Fig. 1).

2.1 Insulin release from the islet β cell

Glucose stimulated insulin secretion from islets of Langerhans is biphasic (20), with a rapid first phase and more sustained second phase. The first phase is activated by the triggering pathway- K_{ATP} channel closure following increased glucose influx into pancreatic β cells, as described above. The second phase involves the activation of amplification pathways, also called K_{ATP} channel independent mechanisms (18;21), whereby the increase in intracellular calcium concentrations following K_{ATP} channel closure leads to changes in the sensitivity of the secretory machinery (18;22). Protein kinase A and C (21), AMP activated protein kinase (AMPK; (23-27), and insulin sensitive protein kinases such as protein kinase B and p70S6 kinase (28-33), are involved in regulating the amplifying pathways. The phosphoinositide 3 kinases (PI3Ks) are also thought to be important in the regulation of insulin secretion and synthesis (34-40). The roles of some of these protein kinases will be discussed in section 3.

2.2 Glucagon release from the islet α cell

Glucagon is released from pancreatic α cells in response to low blood glucose concentration, amongst other stimuli, to maintain blood glucose levels in the fasted state (Fig. 1). Elevated glucose concentrations (> 3.5 mM) normally suppress the release of glucagon from pancreatic α cells and dysregulation of this process is a feature of both types 1 and 2 diabetes (41;42). The lack of a counter regulatory response leads to potential danger from episodes of hypoglycaemia and is a limiting factor for good glycaemic management in diabetes (43).

Many of the proteins that are involved in glucose sensing in the β cell, such as glucokinase (44), are also present in the α cell and glucose is able to raise intracellular ATP concentrations in the α cells (45). Both intrinsic (45;46) and extrinsic (42;47;48) mechanisms for the regulation of glucagon secretion have been proposed. Recent evidence suggest that two fuel sensitive protein kinase, PAS-domain containing protein kinase (PASK) and AMPK, may be involved in the regulation of glucagon release and may have a role in the pathophysiology of type 2 diabetes (49; see section 3.1 and 3.2).

3. Glucose sensing and hormone production/release

A number of protein kinases are known to play crucial roles in the regulation of islet α and β cell function. These protein kinases represent potential drug targets for the treatment of type 2 diabetes, as glucose sensitivity and secretory capacity of the pancreatic islets may be improved (or restored) through the manipulation of the action of these proteins.

3.1 AMP activated protein kinase (AMPK)

AMPK is an evolutionarily conserved fuel-sensitive protein kinase that plays a role in glucose homeostasis (23-25;50-53). It is a target of the glucose-lowering drugs, metformin and thiazolidinediones, which act to improve insulin sensitivity in insulin-sensitive tissues such as muscle and liver (54). However, the long term effects of these drugs on β cell survival and function are less clear (53).

AMPK is a heterotrimeric protein consisting of an α catalytic subunit (two isoforms, α1 and 2), a β (two isoforms, β1 and 2) scaffold subunit, and a gamma (three isoforms, gamma 1, 2, 3) regulatory subunit (55;56). It is activated by increased intracellular AMP concentrations, i.e. at times of fuel deprivation. Salt and colleagues (23) showed that both AMPK catalytic subunits are present in the clonal rat pancreatic β cell line, INS-1 (57), and that AMPK activity is regulated by extracellular glucose concentrations in this cell type (23). Moreover, they demonstrated that insulin secretion and AMPK activity were inversely related (23). AICA riboside (5-aminoimidazole-4-carboxamide riboside; AICAR) (23;25), an activator of AMPK, and metformin (58), inhibited glucose stimulated insulin secretion in both clonal β cell lines and primary rat islets. Similarly, overexpression of a constitutively active form of AMPK in clonal β cells (25) and primary islets (59) led to impaired β cell function, due in part to the inhibition of secretory granule transport to the cell surface (27). In contrast, overexpression of a dominant negative form of AMPK led to increased insulin secretion at non-premissive glucose concentrations (25) without affecting release at elevated glucose concentrations (60).

In support of the above findings, it was recently demonstrated that transgenic mice over-expressing constitutively active AMPK specifically in pancreatic β cells were glucose intolerant and displayed defective insulin secretion (26). Mice in which expression of both AMPK catalytic subunits was ablated selectively in pancreatic β cells displayed defective glucose homeostasis due to defective insulin secretion in response to hyperglycaemia *in vivo* (26). Ablation of the expression of AMPK catalytic subunits in the β cell was protective against the deleterious effects of exposure to a high fat diet on insulin secretion (26).

Aside from insulin secretion, data from work in clonal cell lines indicate that AMPK may also be involved in the regulation of insulin gene expression in response to changing glucose concentrations (24;25). Thus, inhibition of the AMPK α2 catalytic subunit (24), which displays substantial nuclear localisation (24;57), led to increased insulin gene expression, while inhibition of the AMPK α1 catalytic subunit, which is predominantly cytosolic (57), had no effect on insulin gene expression (24).

Recently, Leclerc and colleagues showed that AMPK activity is modulated by glucose in a mouse clonal α cell line, αTC1-9 cells (61). Overexpression of constitutively active AMPK in αTC1-9 cells and specifically in pancreatic α cells in primary mouse islets of Langerhans led to activation of glucagon release at inhibitory glucose concentrations (61). Activation of AMPK with metformin, phenformin (62) and a selective activator of AMPK, A-769662 (63-65), in αTC1-9 cells led to increased AMPK activity and stimulated glucagon secretion at both permissive and non-permissive glucose concentrations (61). In contrast, overexpression of dominant negative AMPK and/or the AMPK inhibitor, compound C (66), inhibited glucagon release (61).

Thus, AMPK is involved in the regulation of both the release and biosynthesis of insulin in pancreatic β cells, and glucagon release from pancreatic α cells, in response to glucose challenge. Drugs that specifically inhibit AMPK activity in the pancreatic islet are likely to be useful in the treatment of diabetes by performing the dual role of increasing insulin secretion and inhibiting glucagon secretion.

3.2 PAS domain containing protein kinase (PASK)

Whilst homologous genes are common in prokaryotes, there is only one known mammalian PASK (67;68). The enzyme has one well-defined ligand-binding domain with potential for drug-targeting (67). We (49;69) and others (70;71) have shown that PASK is important for energy-sensing and maintenance of normal cellular energy balance in mammalian systems. Thus, *PASK*/*Pask* is expressed in human and rodent pancreatic islets of Langerhans and its expression is regulated by glucose (49;69;71). *PASK* is expressed in both α and β cells in human pancreatic islets (49). Importantly, *PASK* expression is lower in the β cells of patients with type 2 diabetes in comparison to β cells of non-diabetic individuals (49). Very recently, an activating mutation in *PASK* was identified which is associated with non-autoimmune early-onset diabetes in humans (72). However, this mutant did not fully co-segregate with the disease and appears to serve as a modifier for a separate disease-causing mutation in another gene. Thus, the mutated PASK (G1117E) has ~25 % higher activity than wild-type PASK and overexpression of this kinase variant led to a left-shift in the glucose response in mouse pancreatic islets. As a result, glucose-stimulated insulin secretion and insulin gene expression were increased at normally non-permissive (3 mM) glucose concentrations (72).

Pask activity is regulated by glucose and the enzyme is involved in the regulation of glucose-induced preproinsulin and pancreatic duodenum *homeo*box-1 (PDX-1) gene expression in the mouse pancreatic β cell line, MIN6 (69;71). Recently, PASK was implicated in the regulation of lipogenic gene expression (70) and might, therefore, influence glucose signaling through lipid intermediates as proposed for glucose-induced insulin secretion (73). *Pask* null (*Pask*$^{-/-}$) mice (74) have normal glucose tolerance (49;70;74) and lower plasma insulin content than control littermates (49;70), but increased insulin sensitivity in peripheral tissues (70).

Glucose-stimulated insulin secretion from *Pask*$^{-/-}$ islets was variously shown to be not different (74) or lower (70) *vs* control islets. However, the lack of corresponding total islet insulin measurements in these studies made it difficult to evaluate islet secretory capacity (70). In our hands, *Pask*$^{-/-}$ islets were able to release insulin in response to glucose (49) but islet insulin content (49) and, thus, the amount of insulin released, was lower, in agreement with (70). Our data also indicate that the total pancreatic insulin content in *Pask*$^{-/-}$ is lower than control mice (49).

Pask$^{-/-}$ mice, when maintained on a high fat diet (HFD), develop glucose intolerance (70). Furthermore, inhibition of insulin gene expression by palmitate was reversed by *PASK* over-expression in MIN6 β cells (71), suggesting a role for PASK in protection against lipotoxicity. Thus, PASK appears to exert a protective effect in mature β cells and aberrant PASK expression and function may play a role in the development of diabetes.

Our recent data (49) indicate that PASK may regulate glucagon secretion in rodent and human pancreatic α cells. Eight-week old *Pask*$^{-/-}$ mice displayed higher plasma glucose after

16 h of fasting than wild-type littermate controls, but normal glucose tolerance after intraperitoneal glucose injection. After fasting, plasma glucagon was higher in *Pask*$^{-/-}$ mice than littermate controls. This increased glucagon concentration may account for the increased levels of blood glucose after the 16 h fast. This is physiologically relevant as long-term elevated plasma glucagon and glucose is a feature of type 2 diabetes (75).

The regulation of glucagon secretion by glucose was also impaired in *Pask*$^{-/-}$ islets (49). Interestingly, we observed a slight inhibitory effect of glucose on glucagon secretion, suggesting either a cell autonomous role for PASK in the α cell and/or reflecting altered secretion of regulatory factors from neighbouring β cells, e.g. insulin (49). Forced changes in PASK content affected the regulation of glucagon secretion by glucose in αTC1-9 cells (a mouse clonal α cell line) and human islets (49). RNAi-mediated silencing of *Pask* expression in αTC1-9 cells led to constitutive release of glucagon (49), while over-expression of PASK in αTC1-9 cells or in human islets led to inhibition of glucagon secretion, suggesting that PASK may be involved in glucose-sensing in pancreatic α cells (49). Inhibition of glucagon secretion by insulin was not affected in *Pask* silenced αTC1-9 cells indicating that the insulin signalling pathway was intact (49). Interestingly, there was still an apparent effect of glucose on glucagon secretion in human islets over-expressing PASK, possibly due to insulin release from β cells. Thus, the dysregulation of glucagon secretion in *Pask*$^{-/-}$ islets may be due, in part, to the decrease in insulin secretion.

To identify the mechanism(s) through which PASK may regulate glucagon secretion, we measured the expression of a number of potential target genes in *Pask*$^{-/-}$ islets (49) and αTC1-9 cells (49). The expression of both the insulin and *Pdx-1* genes was impaired in *Pask*$^{-/-}$ islets (49;69;71). Thus, the decrease in insulin release may be due to decreased insulin synthesis and/or islet number in *Pask*$^{-/-}$ pancreata (49). Preproglucagon gene expression was increased, although total glucagon protein content was unaltered (49), consistent with the relatively slow turnover of mature glucagon. AMPKα2, but not AMPKα1, gene expression was increased by loss of *Pask* expression (49). This is an interesting observation since AMPK activity is glucose-responsive in pancreatic α and β cells (24;61) and regulates insulin (25;27) and glucagon (61) release.

Interestingly, we also observed that E13.5 rat pancreatic epithelial explants (76) in which PASK gene expression was silenced also display similar gene expression changes following culture to allow the development of endocrine cells (49) indicating that loss of PASK gene expression may have effects on pancreatic development that lead to the dysregulation of glucagon release. These data, and those from pancreatic β cells (69;71;72), suggest that changes in PASK activity may be important for appropriate glucose signalling in both α and β cells.

3.3 Protein kinase A (PKA)

Glucose administered via the gastointestinal tract leads to a greater induction of glucose-stimulated insulin secretion than a comparable intravenous adminstration of glucose (77;78) due to stimulation of the release of the incretin hormones, glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), from intestinal L- and K-cells respectively (79;80). Potentiation of glucose stimulated insulin secretion only occurs at permissive glucose concentrations (81), making the use of incretins attractive in the treatment of diabetes (80). Both hormones potentiate glucose stimulated insulin secretion (82) via binding to their

cognate G-protein coupled receptors on pancreatic β cells, activating adenylyl cyclase and thereby increasing cytosolic cyclic AMP (cAMP) levels (83-85). cAMP regulates insulin secretion, in part, by inducing the phosphorylation of proteins involved in the secretory process by PKA (86-88). For example, there is evidence that PKA activation is involved in controlling vesicle exocytosis by regulating Munc 13-1 function (89;90).

3.4 Protein Kinase C (PKC)

There is evidence both for and against the involvement of PKC in stimulus secretion coupling in the β cell (reviewed in (91;92). Early studies using pharmacological modulation of PKC activity in β cells gave contradictory results (91;92). Conventional PKCs are recruited to the plasma membrane by calcium-dependent binding of the C2 domain to the phospholipids, which is potentiated by the binding of diacyglycerol to the C1 domains (93). Conventional, novel and atypical PKCs are found in pancreatic islet cells (94-97), and PKC activity is present in primary pancreatic islets (98) and clonal β cell lines (99;100). It was proposed that the increase in cytosolic calcium concentrations, following exposure of pancreatic β cells to high glucose concentrations, leads to increased diacyglycerol (DAG) production which leads to the activation of PKC, and the translocation of PKC to the plasma membrane leading to potentiation of insulin release (92;101). DAG is produced by activated phospholipase C (PLC) from phosphatidyl-4,5-bisphosphate, and PLC activity in pancreatic β cells has been shown to occur in a dose-dependent manner in parallel to physiologically relevant increases in glucose that lead to insulin secretion (102-104).

The use of PKC isoform and green fluorescent protein chimeras, coupled with the use of total internal reflection fluorescence (TIRF) microscopy, demonstrated that elevated glucose concentrations led to complex oscillatory translocation of the conventional PKC, PKCβ2, to the plasma membrane, in primary β cells and clonal β cell lines, in response to the formation of calcium microdomains following transient depolarisation of the plasma membrane (101). Moreover, PKCβ2 was shown to migrate to the surface of secretory vesicles, suggesting that the process of vesicle fusion may be regulated locally (101) by this kinase.

3.5 Phosphoinositide 3 Kinases (PI3Ks)

The autocrine feedback action of insulin on pancreatic β cell function is a subject of much debate. β cells secrete insulin at basal glucose concentrations and increase the level of secretion in response to a glucose challenge. Thus, much of the discussion has been on whether the insulin signalling pathway in β cells is desensitised as these cells are constantly exposed to the hormone. Recent studies, using approaches that circumvent some of the confounding factors in earlier studies, have provided evidence that insulin acts as a positive regulator of its own secretion and synthesis in pancreatic β cells, and of β cell mass and survival (30;32;34-36;38;39;105-130). Activation of the insulin and insulin-like growth factor 1 (IGF-1) receptor (IGF-1R), through insulin and/or IGF-1 binding to these receptors, leads to activation of downstream signalling cascades including, those involving the PI3Ks (35;36;110;111;116;126;130), resulting in the moderation of β cell function. There are three classes of mammalian PI3Ks, class I-III (131). Class Ia and II PI3Ks have been reported to be activated by insulin and will be reviewed in the following subsections. The class I PI3Ks generate phosphatidyl 3,4,5-trisphosphate (132), while the class II PI3Ks generate phosphatidyl 3-phosphate (PI3P) *in vivo* (133;134), both of which interact with distinct

molecules. Therefore, the activation of class I and II PI3Ks result in the activation of distinct signaling cascades.

3.5.1 PI3Ks and insulin gene expression

There is evidence in the literature suggesting that insulin regulates the expression of its own gene via activation of Class Ia PI3K (PI3K-1a) (35;36). Of a number of transcription factors that regulate the expression of the insulin gene, the action of the transcription factors pancreatic duodenal homeobox-1 (PDX-1) (110;135-141) and FoxO-1 (142) are thought to be regulated by insulin in a PI3K-1a dependent manner.

Insulin gene expression is upregulated in response to increasing glucose concentrations in a PI3K-1a-dependent manner (30;35;36;110). The increase in insulin gene expression in response to elevated glucose concentrations is due, at least in part, to the the activation of PI3K-1a by secreted insulin (35;36;107;143;144). Thus, PDX-1 translocates from the cytosol to the nucleus in response to an increase in circulating glucose concentrations (110;144;145) and binds to a region upstream of the insulin gene called the A3 box (139). This binding is upregulated as glucose concentrations are increased in the near physiological range (140;141), and in response to insulin (146), to activate insulin gene expression. The expression of the PDX-1 gene itself is regulated by insulin (147), further implicating insulin and PI3K-1a in the feed-forward regulation of insulin gene expression.

Activation of PI3K-1a by insulin also leads to enhanced expressionof glucose/insulin-responsive genes through the removal of transcriptional repressors. For example, the transcription factor, FoxO1, is phosphorylated at Ser-256 in response to activation of PI3Ks and PKB by insulin (142;148), translocates from the nucleus to the cytosol (149;150) and is degraded (151). The degradation of FoxO1 leads to enhanced expression of glucose/insulin-responsive genes (152) such as the L-type pyruvate kinase (36), insulin 2 (*Ins2*) and *Pdx-1* genes in pancreatic β cells (142).

3.5.2 PI3Ks and insulin secretion

Data is available in the published literature suggesting that insulin has an inhibitory, activatory or no role in the regulation of its own secretion (153-160). Whilst most studies have focussed on the action of the class I PI3Ks on insulin secretion, recent data implicated the class II PI3K, PI3K-C2α, in the regulation of insulin secretion (126;130).

PI3K-C2α gene expression was shown to be down-regulated in islets of Langerhans of patients with type 2 diabetes (130). Leibiger and colleagues showed that PI3K-C2α is able to enhance glucose-stimulated insulin release in a feed-forward (126) mechanism, in response to stimuli from insulin itself, via the activation of PKB by PI3P. Subsequently, it was shown that PI3K-C2α may have a role in the late stages of insulin granule release through its action on the synaptosomal-associated protein of 25 kDA (SNAP25), which is independent of nutrient control (130). Insulin granules dock at the plasma mebrane via the interaction of SNAP25 within a protein complex (161-163), with granule fusion and insulin release occuring post proteolysis of SNAP25 (164). PI3K-C2α was shown to regulate the degradation rate of SNAP2, thereby controlling insulin granule fusion with the plasma membrane (130).

3.6 Homeodomain interacting protein kinase 2 (HIPK2)

Homeodomain interacting protein kinase 2 (HIPK2) belongs to the family of homeodomain interacting protein kinases, which was originally identified as binding partners of the homeodomain protein neurokinin-3 (NK-3) (165). Studies have shown that members of the HIPK family interact with, phosphorylate and modulate the function of other homeodomain containing proteins and transcription factors (166-170), indicating that the HIPKs may have an important role in the control of transcription. Recently it was shown that HIPK2 is expressed in the developing pancreatic epithelium from E12 to E15 and that its expression is confined preferentially to pancreatic endocrine cells later in development (171). Phosphorylation of the transcription factor, PDX-1, in the C-terminus by HIPK2, possibly at Ser-214 (172), was reported to increase the stability and transcriptional activity of PDX-1 (171). Our own data indicate that HIPK2 posphorylates PDX-1 at Ser-269 in the C-terminal portion of PDX-1 in pancreatic β cells *in vivo* and that phosphorylation at this site leads to nuclear exclusion of PDX-1 and a decrease in PDX-1 target gene expression (172). As PDX-1 has been shown to directly bind to and regulate the promoter activity of various β cell genes, e.g. insulin (110;135;140;144-146), glucose transporter 2 (GLUT2;173), glucokinase (GCK)(174;175), and islet amyloid polypeptide (176;177), HIPK2 represents an important regulator of β cell gene expression during development and in adult β cells.

4. β cell survival, growth and proliferation

Maintenance of an adequate functional β cell mass is a potential therapeutic target for diabetes. In this section we will look at the evidence that indicate protein kinases such as AMPK, Serine/threonine protein kinase 11 (STK11/LKB1), mammalian target of rapamycin (mTOR), and protein kinases in the Wnt signalling pathway may be involved in the regulation of β cell proliferation.

4.1 AMPK and LKB1

In section 3.1, we discussed the role of AMPK in the regulation of pancreatic β cell function. Recent data indicate that AMPK may also have a role in the maintenance of adequate β cell mass. Activation of AMPK has been shown to lead to decreased β cell viability (178;179), potentially through its action on the cell cycle regulator, p53 (180). Mice in which the expression of both AMPK catalytic subunits was ablated selectively in pancreatic β cells have normal β cell mass but smaller β cells and pancreatic islets (26). Islets of Langerhans in which the expression of both AMPK catalytic subunits was ablated did not display apparent differences in the ratio of α to β cells or in islet architecture. β cell proliferation was enhanced in islets from mice in which the expression of both AMPK catalytic subunits was ablated selectively in pancreatic β cells (26). In contrast, islets of Langerhans from mice in which the expression of an AMPK upstream kinase liver kinase B1 (LKB1) was ablated, had increased islet and β cell size (181) and altered islet architecture (181-184). Thus, the number of large islets, which may account for as much as 50 % of the total pancreatic β cell mass in normal pancreata (185), was increased in pancreata from mice in which LKB1 expression was selectively ablated in the β cell (181). These data indicate that AMPK and LKB1 play distinct roles in the control of islet development and cell proliferation and may impact on the development of pharmacological reagents targetting these pathways for the treatment of diabetes. In particular, inhibition of LKB1, or its downstream targets, may be a means by which β cell mass may be increased for the treatment of diabetes.

4.2 mTOR

Activation of the PI3K-PKB pathway by growth factors such as insulin and IGF-1, and subsequent activation of mammalian target of rapamycin (mTOR), is involved in β cell compensation in animals with genetic or high-fat diet induced insulin resistance (122;186). mTOR is an important nutrient sensor that plays a central role in the regulation of cellular metabolism, growth, proliferation and apoptosis (187-190). Signalling by (mTOR) to eukaryotic initiation factor 4-binding protein-1 (4E-BP1) and ribosomal S6 kinase (S6K) was enhanced in islets of Langerhans from mice in which LKB1 expression was specifically ablated in the β cell (181). Likewise, there is evidence for crosstalk between mTOR and AMPK as a regulatory pathway that couples cellular fuel availability to β cell apoptosis (58;59;191). S6K1 knockout mice are glucose intolerant, despite increased insulin sensitivity, which is associated with depletion of pancreatic insulin content, hypoinsulinaemia and reduced β cell mass (192;193), indicating that S6K1 is required for β cell growth and function. In addition, crosstalk between the mTOR and JNK pathways (194) is thought to regulate β cell survival through action on FoxO1 (195;196), whereby activation of FoxO1 in β cells protects the cells from oxidative stress by reducing cellular metabolic activity and energy-consuming processes, e.g. proliferation, and cell-specific function, e.g. insulin secretion (195;196).

4.3 Wnt signalling

The Wnt proteins are a family of cysteine-rich glycoproteins involved in intracellular signalling during vertebrate development. Activation of Wnt signalling leads to the expression of genes that are involved in promoting stem cell fate and inhibiting cell differentiation (197). One of the prominent biological phenomena controlled by Wnt signaling is the expansion of cells with predefined fates (198;199). It has previously been shown to be involved in the regulation of pancreatic development at all stages during organogenesis from specification to maintenance of normal function (200-206;206-211). Thus, tight temporal regulation of the Wnt signalling pathway is required for normal development.

Activation of the Wnt signalling pathway was shown to upregulate β cell proliferation in mouse islets (208;212;213) with upregulation of cell cycle genes that have been shown to regulate β cell proliferation (214) such as cyclin D1 and D2, and cyclin-dependent kinase 4 (CDK4) (208;213). The Wnt signalling pathway was also shown to be involved in the neogenesis of human β cells *in vitro* (215).

It was recently demonstrated that the incretin, GLP-1, induced β cell proliferation via activation of the Wnt signaling pathway (216). GLP-1 has previously been shown to increase β cell proliferation and survival (217-219). Liu and colleagues showed that Wnt signaling can be activated by downstream events from GLP-1 receptor activation in a Protein kinase B (PKB) and PKA-dependent manner (216).

5. Prospects for the development of treatment

Type 2 diabetes is fast becoming a major global problem and understanding the signalling molecules that regulate the maintenance of glucose homeostasis, particularly those that regulate pancreatic islet function, could lead to better therapeutic intervention for the

disease. Increasing functional β cell mass is a particularly promising strategy: although islet transplantation is an effective means to restore glucose homeostasis, the lack of transplantable material makes this a non-viable treatment module for the masses. Thus, strategies that can lead to the generation and proliferation of β cells *in viv*o and/or *in vitro* may be important for the treatment of the disease.

6. Acknowledgements

Work in the author's laboratory is funded by the European Foundation for the Study of Diabetes, Diabetes U.K. and the Juvenile Diabetes Research Foundation.

7. References

[1] Henderson L, Gregory J, Irving K, and Swan G. The national diet and nutrition survey: adults aged 19 to 64 years. Volume 2. Energy, protein, carbohydrate , Fat and alcohol intake. HMSO: Norwich, 2003.

[2] Wright JD, Wang CY, Kennedy-Stephenson J, Ervin RB (2003) Dietary intake of ten key nutrients for public health, United States: 1999-2000. Adv.Data 1-4

[3] Burelle Y, Lamoureux MC, Peronnet F, Massicotte D, Lavoie C (2006) Comparison of exogenous glucose, fructose and galactose oxidation during exercise using 13C-labelling. Br.J.Nutr. 96: 56-61

[4] Ashcroft FM, Ashcroft SJM (1992) Insulin, Molecular Biology to Pathology. Oxford University Press, Oxford,

[5] Bell GI, Kayano T, Buse JB, et al (1990) Molecular biology of mammalian glucose transporters. Diabetes Care 13: 198-208

[6] Thorens B, Sarkar HK, Kaback HR, Lodish HF (1988) Cloning and functional expression in bacteria of a novel glucose transporter present in liver, intestine, kidney, and beta-pancreatic islet cells. Cell 55: 281-290

[7] Schuit FC (1997) Is GLUT2 required for glucose sensing? Diabetologia 40: 104-111

[8] Matschinsky FM, Meglasson M, Ghosh A, et al (1986) Biochemical design features of the pancreatic islet cell glucose-sensory system. Adv.Exp.Med.Biol. 211: 459-469

[9] Iynedjian PB (1993) Mammalian glucokinase and its gene. Biochem.J. 293 (Pt 1): 1-13

[10] Meglasson MD, Matschinsky FM (1986) Pancreatic islet glucose metabolism and regulation of insulin secretion. Diabetes Metab Rev. 2: 163-214

[11] Sekine N, Cirulli V, Regazzi R, et al (1994) Low lactate dehydrogenase and high mitochondrial glycerol phosphate dehydrogenase in pancreatic beta-cells. Potential role in nutrient sensing. J.Biol.Chem. 269: 4895-4902

[12] Schuit F, De VA, Farfari S, et al (1997) Metabolic fate of glucose in purified islet cells. Glucose-regulated anaplerosis in beta cells. J.Biol.Chem. 272: 18572-18579

[13] Berman HK, Newgard CB (1998) Fundamental metabolic differences between hepatocytes and islet beta-cells revealed by glucokinase overexpression. Biochemistry 37: 4543-4552

[14] Rutter GA (2001) Nutrient-secretion coupling in the pancreatic islet beta-cell: recent advances. Mol.Aspects Med. 22: 247-284

[15] Rorsman P (1997) The pancreatic beta-cell as a fuel sensor: an electrophysiologist's viewpoint. Diabetologia 40: 487-495

[16] Aguilar-Bryan L, Bryan J (1999) Molecular biology of adenosine triphosphate-sensitive potassium channels. Endocr.Rev. 20: 101-135
[17] Seino S, Iwanaga T, Nagashima K, Miki T (2000) Diverse roles of K(ATP) channels learned from Kir6.2 genetically engineered mice. Diabetes 49: 311-318
[18] Henquin JC (2000) Triggering and amplifying pathways of regulation of insulin secretion by glucose. Diabetes 49: 1751-1760
[19] Ashcroft FM (2007) The Walter B. Cannon Physiology in Perspective Lecture, 2007. ATP-sensitive K+ channels and disease: from molecule to malady. Am.J.Physiol Endocrinol.Metab 293: E880-E889
[20] Curry DL, Bennett LL, Grodsky GM (1968) Dynamics of insulin secretion by the perfused rat pancreas. Endocrinology 83: 572-584
[21] Aizawa T, Komatsu M, Asanuma N, Sato Y, Sharp GW (1998) Glucose action 'beyond ionic events' in the pancreatic beta cell. Trends Pharmacol.Sci. 19: 496-499
[22] Jonas JC, Gilon P, Henquin JC (1998) Temporal and quantitative correlations between insulin secretion and stably elevated or oscillatory cytoplasmic Ca2+ in mouse pancreatic beta-cells. Diabetes 47: 1266-1273
[23] Salt IP, Johnson G, Ashcroft SJ, Hardie DG (1998) AMP-activated protein kinase is activated by low glucose in cell lines derived from pancreatic beta cells, and may regulate insulin release. Biochem.J. 335 (Pt 3): 533-539
[24] da Silva Xavier G, Leclerc I, Salt IP, et al (2000) Role of AMP-activated protein kinase in the regulation by glucose of islet beta cell gene expression. Proc.Natl.Acad.Sci.U.S.A 97: 4023-4028
[25] da Silva Xavier G, Leclerc I, Varadi A, Tsuboi T, Moule SK, Rutter GA (2003) Role for AMP-activated protein kinase in glucose-stimulated insulin secretion and preproinsulin gene expression. Biochem.J. 371: 761-774
[26] Sun G, Tarasov AI, McGinty J, et al (2010) Ablation of AMP-activated protein kinase alpha1 and alpha2 from mouse pancreatic beta cells and RIP2.Cre neurons suppresses insulin release in vivo. Diabetologia 53: 924-936
[27] Tsuboi T, da Silva Xavier G, Leclerc I, Rutter GA (2003) 5'-AMP-activated protein kinase controls insulin-containing secretory vesicle dynamics. J.Biol.Chem. 278: 52042-52051
[28] Rutter GA (1999) Insulin secretion: feed-forward control of insulin biosynthesis? Curr.Biol. 9: R443-R445
[29] Leibiger B, Leibiger IB, Moede T, et al (2001) Selective insulin signaling through A and B insulin receptors regulates transcription of insulin and glucokinase genes in pancreatic beta cells. Mol.Cell 7: 559-570
[30] Leibiger B, Wahlander K, Berggren PO, Leibiger IB (2000) Glucose-stimulated insulin biosynthesis depends on insulin-stimulated insulin gene transcription. J.Biol.Chem. 275: 30153-30156
[31] Khan FA, Goforth PB, Zhang M, Satin LS (2001) Insulin activates ATP-sensitive K(+) channels in pancreatic beta-cells through a phosphatidylinositol 3-kinase-dependent pathway. Diabetes 50: 2192-2198
[32] Aspinwall CA, Lakey JR, Kennedy RT (1999) Insulin-stimulated insulin secretion in single pancreatic beta cells. J.Biol.Chem. 274: 6360-6365

[33] Kulkarni RN, Bruning JC, Winnay JN, Postic C, Magnuson MA, Kahn CR (1999) Tissue-specific knockout of the insulin receptor in pancreatic beta cells creates an insulin secretory defect similar to that in type 2 diabetes. Cell 96: 329-339

[34] Kulkarni RN, Bruning JC, Winnay JN, Postic C, Magnuson MA, Kahn CR (1999) Tissue-specific knockout of the insulin receptor in pancreatic beta cells creates an insulin secretory defect similar to that in type 2 diabetes. Cell 96: 329-339

[35] Leibiger IB, Leibiger B, Moede T, Berggren PO (1998) Exocytosis of insulin promotes insulin gene transcription via the insulin receptor/PI-3 kinase/p70 s6 kinase and CaM kinase pathways. Mol.Cell 1: 933-938

[36] da Silva Xavier G, Varadi A, Ainscow EK, Rutter GA (2000) Regulation of gene expression by glucose in pancreatic beta -cells (MIN6) via insulin secretion and activation of phosphatidylinositol 3'-kinase. J.Biol.Chem. 275: 36269-36277

[37] Andreolas C, da Silva Xavier G, Diraison F, et al (2002) Stimulation of acetyl-CoA carboxylase gene expression by glucose requires insulin release and sterol regulatory element binding protein 1c in pancreatic MIN6 beta-cells. Diabetes 51: 2536-2545

[38] da Silva Xavier G, Qian Q, Cullen PJ, Rutter GA (2004) Distinct roles for insulin and insulin-like growth factor-1 receptors in pancreatic beta-cell glucose sensing revealed by RNA silencing. Biochem.J. 377: 149-158

[39] Kulkarni RN (2002) Receptors for insulin and insulin-like growth factor-1 and insulin receptor substrate-1 mediate pathways that regulate islet function. Biochem.Soc.Trans. 30: 317-322

[40] Burks DJ, White MF (2001) IRS proteins and beta-cell function. Diabetes 50 Suppl 1: S140-S145

[41] Unger RH (1985) Glucagon physiology and pathophysiology in the light of new advances. Diabetologia 28: 574-578

[42] Gromada J, Franklin I, Wollheim CB (2007) Alpha-cells of the endocrine pancreas: 35 years of research but the enigma remains. Endocr.Rev. 28: 84-116

[43] Cryer PE (2002) Hypoglycaemia: the limiting factor in the glycaemic management of Type I and Type II diabetes. Diabetologia 45: 937-948

[44] Heimberg H, De VA, Moens K, et al (1996) The glucose sensor protein glucokinase is expressed in glucagon-producing alpha-cells. Proc.Natl.Acad.Sci.U.S.A 93: 7036-7041

[45] Ravier MA, Rutter GA (2005) Glucose or insulin, but not zinc ions, inhibit glucagon secretion from mouse pancreatic alpha-cells. Diabetes 54: 1789-1797

[46] Rorsman P, Salehi SA, Abdulkader F, Braun M, MacDonald PE (2008) K(ATP)-channels and glucose-regulated glucagon secretion. Trends Endocrinol.Metab 19: 277-284

[47] Ishihara H, Maechler P, Gjinovci A, Herrera PL, Wollheim CB (2003) Islet beta-cell secretion determines glucagon release from neighbouring alpha-cells. Nat.Cell Biol. 5: 330-335

[48] Zhou H, Zhang T, Harmon JS, Bryan J, Robertson RP (2007) Zinc, not insulin, regulates the rat alpha-cell response to hypoglycemia in vivo. Diabetes 56: 1107-1112

[49] da Silva Xavier G, Farhan H, Kim H, et al (2011) Per-arnt-sim (PAS) domain-containing protein kinase is downregulated in human islets in type 2 diabetes and regulates glucagon secretion. Diabetologia 54: 819-827

[50] Shaw RJ, Lamia KA, Vasquez D, et al (2005) The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science 310: 1642-1646
[51] Towler MC, Hardie DG (2007) AMP-activated protein kinase in metabolic control and insulin signaling. Circ.Res. 100: 328-341
[52] Kurth-Kraczek EJ, Hirshman MF, Goodyear LJ, Winder WW (1999) 5' AMP-activated protein kinase activation causes GLUT4 translocation in skeletal muscle. Diabetes 48: 1667-1671
[53] Rutter GA, Leclerc I (2009) The AMP-regulated kinase family: enigmatic targets for diabetes therapy. Mol.Cell Endocrinol. 297: 41-49
[54] Long YC, Zierath JR (2006) AMP-activated protein kinase signaling in metabolic regulation. J.Clin.Invest 116: 1776-1783
[55] Stapleton D, Woollatt E, Mitchelhill KI, et al (1997) AMP-activated protein kinase isoenzyme family: subunit structure and chromosomal location. FEBS Lett. 409: 452-456
[56] Hardie DG, Carling D (1997) The AMP-activated protein kinase--fuel gauge of the mammalian cell? Eur.J.Biochem. 246: 259-273
[57] Salt I, Celler JW, Hawley SA, et al (1998) AMP-activated protein kinase: greater AMP dependence, and preferential nuclear localization, of complexes containing the alpha2 isoform. Biochem.J. 334 (Pt 1): 177-187
[58] Leclerc I, Woltersdorf WW, da Silva Xavier G, et al (2004) Metformin, but not leptin, regulates AMP-activated protein kinase in pancreatic islets: impact on glucose-stimulated insulin secretion. Am.J.Physiol Endocrinol.Metab 286: E1023-E1031
[59] Richards SK, Parton LE, Leclerc I, Rutter GA, Smith RM (2005) Over-expression of AMP-activated protein kinase impairs pancreatic {beta}-cell function in vivo. J.Endocrinol. 187: 225-235
[60] Gleason CE, Lu D, Witters LA, Newgard CB, Birnbaum MJ (2007) The role of AMPK and mTOR in nutrient sensing in pancreatic beta-cells. J.Biol.Chem. 282: 10341-10351
[61] Leclerc I, Sun G, Morris C, Fernandez-Millan E, Nyirenda M, Rutter GA (2011) AMP-activated protein kinase regulates glucagon secretion from mouse pancreatic alpha cells. Diabetologia 54: 125-134
[62] Hardie DG (2006) Neither LKB1 nor AMPK are the direct targets of metformin. Gastroenterology 131: 973-975
[63] Hawley SA, Boudeau J, Reid JL, et al (2003) Complexes between the LKB1 tumor suppressor, STRAD alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. J.Biol. 2: 28
[64] Scott JW, van Denderen BJ, Jorgensen SB, et al (2008) Thienopyridone drugs are selective activators of AMP-activated protein kinase beta1-containing complexes. Chem.Biol. 15: 1220-1230
[65] Cool B, Zinker B, Chiou W, et al (2006) Identification and characterization of a small molecule AMPK activator that treats key components of type 2 diabetes and the metabolic syndrome. Cell Metab 3: 403-416
[66] Zhou G, Myers R, Li Y, et al (2001) Role of AMP-activated protein kinase in mechanism of metformin action. J.Clin.Invest 108: 1167-1174

[67] Rutter J, Michnoff CH, Harper SM, Gardner KH, McKnight SL (2001) PAS kinase: an evolutionarily conserved PAS domain-regulated serine/threonine kinase. Proc.Natl.Acad.Sci.U.S.A 98: 8991-8996

[68] Hofer T, Spielmann P, Stengel P, et al (2001) Mammalian PASKIN, a PAS-serine/threonine kinase related to bacterial oxygen sensors. Biochem.Biophys.Res.Commun. 288: 757-764

[69] da Silva Xavier G, Rutter J, Rutter GA (2004) Involvement of Per-Arnt-Sim (PAS) kinase in the stimulation of preproinsulin and pancreatic duodenum homeobox 1 gene expression by glucose. Proc.Natl.Acad.Sci.U.S.A 101: 8319-8324

[70] Hao HX, Cardon CM, Swiatek W, et al (2007) PAS kinase is required for normal cellular energy balance. Proc.Natl.Acad.Sci.U.S.A 104: 15466-15471

[71] Fontes G, Semache M, Hagman DK, et al (2009) Involvement of Per-Arnt-Sim Kinase and extracellular-regulated kinases-1/2 in palmitate inhibition of insulin gene expression in pancreatic beta-cells. Diabetes 58: 2048-2058

[72] Semplici F, Vaxillaire M, Fogarty S, et al (2011) A human mutation within the per-ARNT-sim (PAS) domain-containing protein kinase (PASK) causes basal insulin hypersecretion. J.Biol.Chem.

[73] Corkey BE, Deeney JT, Yaney GC, Tornheim K, Prentki M (2000) The role of long-chain fatty acyl-CoA esters in beta-cell signal transduction. J.Nutr. 130: 299S-304S

[74] Borter E, Niessen M, Zuellig R, et al (2007) Glucose-stimulated insulin production in mice deficient for the PAS kinase PASKIN. Diabetes 56: 113-117

[75] Li XC, Liao TD, Zhuo JL (2008) Long-term hyperglucagonaemia induces early metabolic and renal phenotypes of Type 2 diabetes in mice. Clin.Sci.(Lond) 114: 591-601

[76] Miralles F, Serup P, Cluzeaud F, Vandewalle A, Czernichow P, Scharfmann R (1999) Characterization of beta cells developed in vitro from rat embryonic pancreatic epithelium. Dev.Dyn. 214: 116-126

[77] Elrick H, Stimmler L, Hlad CJ, Rai Y (1964) Plasma insulin response to oral and intravenous glucose administration. J.Clin.Endocrinol.Metab 24: 1076-1082

[78] Perley MJ, Kipnis DM (1967) Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic sujbjects. J.Clin.Invest 46: 1954-1962

[79] Holst JJ, Gromada J (2004) Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. Am.J.Physiol Endocrinol.Metab 287: E199-E206

[80] Baggio LL, Drucker DJ (2007) Biology of incretins: GLP-1 and GIP. Gastroenterology 132: 2131-2157

[81] Weir GC, Mojsov S, Hendrick GK, Habener JF (1989) Glucagonlike peptide I (7-37) actions on endocrine pancreas. Diabetes 38: 338-342

[82] Dupre J, Ross SA, Watson D, Brown JC (1973) Stimulation of insulin secretion by gastric inhibitory polypeptide in man. J.Clin.Endocrinol.Metab 37: 826-828

[83] Thorens B (1992) Expression cloning of the pancreatic beta cell receptor for the gluco-incretin hormone glucagon-like peptide 1. Proc.Natl.Acad.Sci.U.S.A 89: 8641-8645

[84] Usdin TB, Mezey E, Button DC, Brownstein MJ, Bonner TI (1993) Gastric inhibitory polypeptide receptor, a member of the secretin-vasoactive intestinal peptide receptor family, is widely distributed in peripheral organs and the brain. Endocrinology 133: 2861-2870

[85] Yasuda K, Inagaki N, Yamada Y, Kubota A, Seino S, Seino Y (1994) Hamster gastric inhibitory polypeptide receptor expressed in pancreatic islets and clonal insulin-secreting cells: its structure and functional properties. Biochem.Biophys.Res.Commun. 205: 1556-1562

[86] Seino S, Shibasaki T (2005) PKA-dependent and PKA-independent pathways for cAMP-regulated exocytosis. Physiol Rev. 85: 1303-1342

[87] Malaisse WJ, Malaisse-Lagae F (1984) The role of cyclic AMP in insulin release. Experientia 40: 1068-1074

[88] Prentki M, Matschinsky FM (1987) Ca2+, cAMP, and phospholipid-derived messengers in coupling mechanisms of insulin secretion. Physiol Rev. 67: 1185-1248

[89] Kwan EP, Gao X, Leung YM, Gaisano HY (2007) Activation of exchange protein directly activated by cyclic adenosine monophosphate and protein kinase A regulate common and distinct steps in promoting plasma membrane exocytic and granule-to-granule fusions in rat islet beta cells. Pancreas 35: e45-e54

[90] Kwan EP, Xie L, Sheu L, Ohtsuka T, Gaisano HY (2007) Interaction between Munc13-1 and RIM is critical for glucagon-like peptide-1 mediated rescue of exocytotic defects in Munc13-1 deficient pancreatic beta-cells. Diabetes 56: 2579-2588

[91] Jones PM, Persaud SJ, Howell SL (1991) Protein kinase C and the regulation of insulin secretion from pancreatic B cells. J.Mol.Endocrinol. 6: 121-127

[92] Wollheim CB, Regazzi R (1990) Protein kinase C in insulin releasing cells. Putative role in stimulus secretion coupling. FEBS Lett. 268: 376-380

[93] Nishizuka Y (1988) The molecular heterogeneity of protein kinase C and its implications for cellular regulation. Nature 334: 661-665

[94] Tian YM, Urquidi V, Ashcroft SJ (1996) Protein kinase C in beta-cells: expression of multiple isoforms and involvement in cholinergic stimulation of insulin secretion. Mol.Cell Endocrinol. 119: 185-193

[95] Onoda K, Hagiwara M, Hachiya T, Usuda N, Nagata T, Hidaka H (1990) Different expression of protein kinase C isozymes in pancreatic islet cells. Endocrinology 126: 1235-1240

[96] Arkhammar P, Juntti-Berggren L, Larsson O, et al (1994) Protein kinase C modulates the insulin secretory process by maintaining a proper function of the beta-cell voltage-activated Ca2+ channels. J.Biol.Chem. 269: 2743-2749

[97] Kaneto H, Suzuma K, Sharma A, Bonner-Weir S, King GL, Weir GC (2002) Involvement of protein kinase C beta 2 in c-myc induction by high glucose in pancreatic beta-cells. J.Biol.Chem. 277: 3680-3685

[98] Tanigawa K, Kuzuya H, Imura H, et al (1982) Calcium-activated, phospholipid-dependent protein kinase in rat pancreas islets of langerhans. Its possible role in glucose-induced insulin release. FEBS Lett. 138: 183-186

[99] Lord JM, Ashcroft SJ (1984) Identification and characterization of Ca2+-phospholipid-dependent protein kinase in rat islets and hamster beta-cells. Biochem.J. 219: 547-551

[100] Zawalich W, Brown C, Rasmussen H (1983) Insulin secretion: combined effects of phorbol ester and A23187. Biochem.Biophys.Res.Commun. 117: 448-455

[101] Pinton P, Tsuboi T, Ainscow EK, Pozzan T, Rizzuto R, Rutter GA (2002) Dynamics of glucose-induced membrane recruitment of protein kinase C beta II in living pancreatic islet beta-cells. J.Biol.Chem. 277: 37702-37710

[102] Best L, Malaisse WJ (1984) Nutrient and hormone-neurotransmitter stimuli induce hydrolysis of polyphosphoinositides in rat pancreatic islets. Endocrinology 115: 1814-1820

[103] Zawalich W (1990) Multiple effects of increases in phosphoinositide hydrolysis on islets and their relationship to changing patterns of insulin secretion. Diabetes Res. 13: 101-111

[104] Zawalich WS, Zawalich KC (1996) Regulation of insulin secretion by phospholipase C. Am.J.Physiol 271: E409-E416

[105] Rothenberg PL, Willison LD, Simon J, Wolf BA (1995) Glucose-induced insulin receptor tyrosine phosphorylation in insulin-secreting beta-cells. Diabetes 44: 802-809

[106] Harbeck MC, Louie DC, Howland J, Wolf BA, Rothenberg PL (1996) Expression of insulin receptor mRNA and insulin receptor substrate 1 in pancreatic islet beta-cells. Diabetes 45: 711-717

[107] Xu GG, Rothenberg PL (1998) Insulin receptor signaling in the beta-cell influences insulin gene expression and insulin content: evidence for autocrine beta-cell regulation. Diabetes 47: 1243-1252

[108] Porzio O, Federici M, Hribal ML, et al (1999) The Gly972-->Arg amino acid polymorphism in IRS-1 impairs insulin secretion in pancreatic beta cells. J.Clin.Invest 104: 357-364

[109] Xu GG, Gao ZY, Borge PD, Jr., Jegier PA, Young RA, Wolf BA (2000) Insulin regulation of beta-cell function involves a feedback loop on SERCA gene expression, Ca(2+) homeostasis, and insulin expression and secretion. Biochemistry 39: 14912-14919

[110] Rafiq I, da Silva Xavier G, Hooper S, Rutter GA (2000) Glucose-stimulated preproinsulin gene expression and nuclear trans-location of pancreatic duodenum homeobox-1 require activation of phosphatidylinositol 3-kinase but not p38 MAPK/SAPK2. J.Biol.Chem. 275: 15977-15984

[111] Aspinwall CA, Qian WJ, Roper MG, Kulkarni RN, Kahn CR, Kennedy RT (2000) Roles of insulin receptor substrate-1, phosphatidylinositol 3-kinase, and release of intracellular Ca2+ stores in insulin-stimulated insulin secretion in beta -cells. J.Biol.Chem. 275: 22331-22338

[112] Assmann A, Ueki K, Winnay JN, Kadowaki T, Kulkarni RN (2009) Glucose effects on beta-cell growth and survival require activation of insulin receptors and insulin receptor substrate 2. Mol.Cell Biol. 29: 3219-3228

[113] Hennige AM, Ozcan U, Okada T, et al (2005) Alterations in growth and apoptosis of insulin receptor substrate-1-deficient beta-cells. Am.J.Physiol Endocrinol.Metab 289: E337-E346

[114] Hennige AM, Burks DJ, Ozcan U, et al (2003) Upregulation of insulin receptor substrate-2 in pancreatic beta cells prevents diabetes. J.Clin.Invest 112: 1521-1532

[115] Hisanaga E, Nagasawa M, Ueki K, Kulkarni RN, Mori M, Kojima I (2009) Regulation of calcium-permeable TRPV2 channel by insulin in pancreatic beta-cells. Diabetes 58: 174-184

[116] Kaneko K, Ueki K, Takahashi N, et al (2010) Class IA phosphatidylinositol 3-kinase in pancreatic beta cells controls insulin secretion by multiple mechanisms. Cell Metab 12: 619-632

[117] Kulkarni RN, Almind K, Goren HJ, et al (2003) Impact of genetic background on development of hyperinsulinemia and diabetes in insulin receptor/insulin receptor substrate-1 double heterozygous mice. Diabetes 52: 1528-1534

[118] Kulkarni RN, Holzenberger M, Shih DQ, et al (2002) beta-cell-specific deletion of the Igf1 receptor leads to hyperinsulinemia and glucose intolerance but does not alter beta-cell mass. Nat.Genet. 31: 111-115

[119] Kulkarni RN, Winnay JN, Daniels M, et al (1999) Altered function of insulin receptor substrate-1-deficient mouse islets and cultured beta-cell lines. J.Clin.Invest 104: R69-R75

[120] Leibiger B, Leibiger IB, Moede T, et al (2001) Selective insulin signaling through A and B insulin receptors regulates transcription of insulin and glucokinase genes in pancreatic beta cells. Mol.Cell 7: 559-570

[121] Liu S, Okada T, Assmann A, et al (2009) Insulin signaling regulates mitochondrial function in pancreatic beta-cells. PLoS.One. 4: e7983

[122] Okada T, Liew CW, Hu J, et al (2007) Insulin receptors in beta-cells are critical for islet compensatory growth response to insulin resistance. Proc.Natl.Acad.Sci.U.S.A 104: 8977-8982

[123] Otani K, Kulkarni RN, Baldwin AC, et al (2004) Reduced beta-cell mass and altered glucose sensing impair insulin-secretory function in betaIRKO mice. Am.J.Physiol Endocrinol.Metab 286: E41-E49

[124] Roper MG, Qian WJ, Zhang BB, Kulkarni RN, Kahn CR, Kennedy RT (2002) Effect of the insulin mimetic L-783,281 on intracellular Ca2+ and insulin secretion from pancreatic beta-cells. Diabetes 51 Suppl 1: S43-S49

[125] Ueki K, Okada T, Hu J, et al (2006) Total insulin and IGF-I resistance in pancreatic beta cells causes overt diabetes. Nat.Genet. 38: 583-588

[126] Leibiger B, Moede T, Uhles S, et al (2010) Insulin-feedback via PI3K-C2alpha activated PKBalpha/Akt1 is required for glucose-stimulated insulin secretion. FASEB J. 24: 1824-1837

[127] Leibiger B, Moede T, Uhles S, Berggren PO, Leibiger IB (2002) Short-term regulation of insulin gene transcription. Biochem.Soc.Trans. 30: 312-317

[128] Leibiger IB, Leibiger B, Berggren PO (2008) Insulin signaling in the pancreatic beta-cell. Annu.Rev.Nutr. 28: 233-251

[129] Leibiger IB, Leibiger B, Berggren PO (2002) Insulin feedback action on pancreatic beta-cell function. FEBS Lett. 532: 1-6

[130] Dominguez V, Raimondi C, Somanath S, et al (2011) Class II phosphoinositide 3-kinase regulates exocytosis of insulin granules in pancreatic beta cells. J.Biol.Chem. 286: 4216-4225

[131] Fruman DA, Meyers RE, Cantley LC (1998) Phosphoinositide kinases. Annu. Rev. Biochem. 67: 481-507

[132] Cantley LC (2002) The phosphoinositide 3-kinase pathway. Science 296: 1655-1657

[133] Maffucci T, Cooke FT, Foster FM, Traer CJ, Fry MJ, Falasca M (2005) Class II phosphoinositide 3-kinase defines a novel signaling pathway in cell migration. J.Cell Biol. 169: 789-799

[134] Falasca M, Hughes WE, Dominguez V, et al (2007) The role of phosphoinositide 3-kinase C2alpha in insulin signaling. J.Biol.Chem. 282: 28226-28236

[135] Ohlsson H, Karlsson K, Edlund T (1993) IPF1, a homeodomain-containing transactivator of the insulin gene. EMBO J. 12: 4251-4259

[136] Leonard J, Peers B, Johnson T, Ferreri K, Lee S, Montminy MR (1993) Characterization of somatostatin transactivating factor-1, a novel homeobox factor that stimulates somatostatin expression in pancreatic islet cells. Mol.Endocrinol. 7: 1275-1283

[137] Miller CP, McGehee RE, Jr., Habener JF (1994) IDX-1: a new homeodomain transcription factor expressed in rat pancreatic islets and duodenum that transactivates the somatostatin gene. EMBO J. 13: 1145-1156

[138] Boam DS, Clark AR, Docherty K (1990) Positive and negative regulation of the human insulin gene by multiple trans-acting factors. J.Biol.Chem. 265: 8285-8296

[139] Petersen HV, Serup P, Leonard J, Michelsen BK, Madsen OD (1994) Transcriptional regulation of the human insulin gene is dependent on the homeodomain protein STF1/IPF1 acting through the CT boxes. Proc.Natl.Acad.Sci.U.S.A 91: 10465-10469

[140] MacFarlane WM, Read ML, Gilligan M, Bujalska I, Docherty K (1994) Glucose modulates the binding activity of the beta-cell transcription factor IUF1 in a phosphorylation-dependent manner. Biochem.J. 303 (Pt 2): 625-631

[141] Marshak S, Totary H, Cerasi E, Melloul D (1996) Purification of the beta-cell glucose-sensitive factor that transactivates the insulin gene differentially in normal and transformed islet cells. Proc.Natl.Acad.Sci.U.S.A 93: 15057-15062

[142] Meur G, Qian Q, da Silva Xavier G, et al (2011) Nucleo-cytosolic shuttling of FoxO1 directly regulates mouse Ins2 but not Ins1 gene expression in pancreatic beta cells (MIN6). J.Biol.Chem. 286: 13647-13656

[143] Rutter GA (1999) Insulin secretion: feed-forward control of insulin biosynthesis? Curr.Biol. 9: R443-R445

[144] MacFarlane WM, McKinnon CM, Felton-Edkins ZA, Cragg H, James RF, Docherty K (1999) Glucose stimulates translocation of the homeodomain transcription factor PDX1 from the cytoplasm to the nucleus in pancreatic beta-cells. J.Biol.Chem. 274: 1011-1016

[145] Rafiq I, Kennedy HJ, Rutter GA (1998) Glucose-dependent translocation of insulin promoter factor-1 (IPF-1) between the nuclear periphery and the nucleoplasm of single MIN6 beta-cells. J.Biol.Chem. 273: 23241-23247

[146] Wu H, MacFarlane WM, Tadayyon M, Arch JR, James RF, Docherty K (1999) Insulin stimulates pancreatic-duodenal homoeobox factor-1 (PDX1) DNA-binding activity and insulin promoter activity in pancreatic beta cells. Biochem.J. 344 Pt 3: 813-818

[147] Campbell SC, MacFarlane WM (2002) Regulation of the pdx1 gene promoter in pancreatic beta-cells. Biochem.Biophys.Res.Commun. 299: 277-284

[148] Cahill CM, Tzivion G, Nasrin N, et al (2001) Phosphatidylinositol 3-kinase signaling inhibits DAF-16 DNA binding and function via 14-3-3-dependent and 14-3-3-independent pathways. J.Biol.Chem. 276: 13402-13410

[149] Trumper A, Trumper K, Trusheim H, Arnold R, Goke B, Horsch D (2001) Glucose-dependent insulinotropic polypeptide is a growth factor for beta (INS-1) cells by pleiotropic signaling. Mol.Endocrinol. 15: 1559-1570

[150] Rena G, Guo S, Cichy SC, Unterman TG, Cohen P (1999) Phosphorylation of the transcription factor forkhead family member FKHR by protein kinase B. J.Biol.Chem. 274: 17179-17183

[151] Matsuzaki H, Daitoku H, Hatta M, Tanaka K, Fukamizu A (2003) Insulin-induced phosphorylation of FKHR (Foxo1) targets to proteasomal degradation. Proc.Natl.Acad.Sci.U.S.A 100: 11285-11290

[152] Brunet A, Bonni A, Zigmond MJ, et al (1999) Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. Cell 96: 857-868

[153] Zawalich WS, Zawalich KC (2000) Glucose-induced insulin secretion from islets of fasted rats: modulation by alternate fuel and neurohumoral agonists. J.Endocrinol. 166: 111-120

[154] Zawalich WS, Tesz GJ, Zawalich KC (2002) Inhibitors of phosphatidylinositol 3-kinase amplify insulin release from islets of lean but not obese mice. J.Endocrinol. 174: 247-258

[155] Hagiwara S, Sakurai T, Tashiro F, et al (1995) An inhibitory role for phosphatidylinositol 3-kinase in insulin secretion from pancreatic B cell line MIN6. Biochem.Biophys.Res.Commun. 214: 51-59

[156] Turner MD, Arvan P (2000) Protein traffic from the secretory pathway to the endosomal system in pancreatic beta-cells. J.Biol.Chem. 275: 14025-14030

[157] Li LX, MacDonald PE, Ahn DS, Oudit GY, Backx PH, Brubaker PL (2006) Role of phosphatidylinositol 3-kinasegamma in the beta-cell: interactions with glucagon-like peptide-1. Endocrinology 147: 3318-3325

[158] MacDonald PE, Joseph JW, Yau D, et al (2004) Impaired glucose-stimulated insulin secretion, enhanced intraperitoneal insulin tolerance, and increased beta-cell mass in mice lacking the p110gamma isoform of phosphoinositide 3-kinase. Endocrinology 145: 4078-4083

[159] Pigeau GM, Kolic J, Ball BJ, et al (2009) Insulin granule recruitment and exocytosis is dependent on p110gamma in insulinoma and human beta-cells. Diabetes 58: 2084-2092

[160] Aoyagi K, Ohara-Imaizumi M, Nishiwaki C, Nakamichi Y, Nagamatsu S (2010) Insulin/phosphoinositide 3-kinase pathway accelerates the glucose-induced first-phase insulin secretion through TrpV2 recruitment in pancreatic beta-cells. Biochem.J. 432: 375-386

[161] Rorsman P, Renstrom E (2003) Insulin granule dynamics in pancreatic beta cells. Diabetologia 46: 1029-1045

[162] Iezzi M, Kouri G, Fukuda M, Wollheim CB (2004) Synaptotagmin V and IX isoforms control Ca2+ -dependent insulin exocytosis. J.Cell Sci. 117: 3119-3127

[163] Gauthier BR, Duhamel DL, Iezzi M, et al (2008) Synaptotagmin VII splice variants alpha, beta, and delta are expressed in pancreatic beta-cells and regulate insulin exocytosis. FASEB J. 22: 194-206

[164] Marshall C, Hitman GA, Partridge CJ, et al (2005) Evidence that an isoform of calpain-10 is a regulator of exocytosis in pancreatic beta-cells. Mol.Endocrinol. 19: 213-224

[165] Kim YH, Choi CY, Lee SJ, Conti MA, Kim Y (1998) Homeodomain-interacting protein kinases, a novel family of co-repressors for homeodomain transcription factors. J.Biol.Chem. 273: 25875-25879

[166] Kim EA, Noh YT, Ryu MJ, et al (2006) Phosphorylation and transactivation of Pax6 by homeodomain-interacting protein kinase 2. J.Biol.Chem. 281: 7489-7497

[167] D'Orazi G, Cecchinelli B, Bruno T, et al (2002) Homeodomain-interacting protein kinase-2 phosphorylates p53 at Ser 46 and mediates apoptosis. Nat.Cell Biol. 4: 11-19

[168] Hofmann TG, Moller A, Sirma H, et al (2002) Regulation of p53 activity by its interaction with homeodomain-interacting protein kinase-2. Nat.Cell Biol. 4: 1-10

[169] Zhang Q, Yoshimatsu Y, Hildebrand J, Frisch SM, Goodman RH (2003) Homeodomain interacting protein kinase 2 promotes apoptosis by downregulating the transcriptional corepressor CtBP. Cell 115: 177-186

[170] Kanei-Ishii C, Ninomiya-Tsuji J, Tanikawa J, et al (2004) Wnt-1 signal induces phosphorylation and degradation of c-Myb protein via TAK1, HIPK2, and NLK. Genes Dev. 18: 816-829

[171] Boucher MJ, Simoneau M, Edlund H (2009) The homeodomain-interacting protein kinase 2 regulates insulin promoter factor-1/pancreatic duodenal homeobox-1 transcriptional activity. Endocrinology 150: 87-97

[172] An R, da Silva Xavier G, Semplici F, et al (2010) Pancreatic and duodenal homeobox 1 (PDX1) phosphorylation at serine-269 is HIPK2-dependent and affects PDX1 subnuclear localization. Biochem.Biophys.Res.Commun. 399: 155-161

[173] Waeber G, Thompson N, Nicod P, Bonny C (1996) Transcriptional activation of the GLUT2 gene by the IPF-1/STF-1/IDX-1 homeobox factor. Mol.Endocrinol. 10: 1327-1334

[174] Watada H, Kajimoto Y, Miyagawa J, et al (1996) PDX-1 induces insulin and glucokinase gene expressions in alphaTC1 clone 6 cells in the presence of betacellulin. Diabetes 45: 1826-1831

[175] Watada H, Kajimoto Y, Umayahara Y, et al (1996) The human glucokinase gene beta-cell-type promoter: an essential role of insulin promoter factor 1/PDX-1 in its activation in HIT-T15 cells. Diabetes 45: 1478-1488

[176] Bretherton-Watt D, Gore N, Boam DS (1996) Insulin upstream factor 1 and a novel ubiquitous factor bind to the human islet amyloid polypeptide/amylin gene promoter. Biochem.J. 313 (Pt 2): 495-502

[177] Carty MD, Lillquist JS, Peshavaria M, Stein R, Soeller WC (1997) Identification of cis- and trans-active factors regulating human islet amyloid polypeptide gene expression in pancreatic beta-cells. J.Biol.Chem. 272: 11986-11993

[178] Kefas BA, Heimberg H, Vaulont S, et al (2003) AICA-riboside induces apoptosis of pancreatic beta cells through stimulation of AMP-activated protein kinase. Diabetologia 46: 250-254

[179] Riboulet-Chavey A, Diraison F, Siew LK, Wong FS, Rutter GA (2008) Inhibition of AMP-activated protein kinase protects pancreatic beta-cells from cytokine-mediated apoptosis and CD8+ T-cell-induced cytotoxicity. Diabetes 57: 415-423

[180] Jones RG, Plas DR, Kubek S, et al (2005) AMP-activated protein kinase induces a p53-dependent metabolic checkpoint. Mol.Cell 18: 283-293

[181] Sun G, Tarasov AI, McGinty JA, et al (2010) LKB1 deletion with the RIP2.Cre transgene modifies pancreatic beta-cell morphology and enhances insulin secretion in vivo. Am.J.Physiol Endocrinol.Metab 298: E1261-E1273
[182] Williams T, Brenman JE (2008) LKB1 and AMPK in cell polarity and division. Trends Cell Biol. 18: 193-198
[183] Fu A, Ng AC, Depatie C, et al (2009) Loss of Lkb1 in adult beta cells increases beta cell mass and enhances glucose tolerance in mice. Cell Metab 10: 285-295
[184] Granot Z, Swisa A, Magenheim J, et al (2009) LKB1 regulates pancreatic beta cell size, polarity, and function. Cell Metab 10: 296-308
[185] Alanentalo T, Asayesh A, Morrison H, et al (2007) Tomographic molecular imaging and 3D quantification within adult mouse organs. Nat.Methods 4: 31-33
[186] Jetton TL, Lausier J, LaRock K, et al (2005) Mechanisms of compensatory beta-cell growth in insulin-resistant rats: roles of Akt kinase. Diabetes 54: 2294-2304
[187] Montagne J, Stewart MJ, Stocker H, Hafen E, Kozma SC, Thomas G (1999) Drosophila S6 kinase: a regulator of cell size. Science 285: 2126-2129
[188] Shima H, Pende M, Chen Y, Fumagalli S, Thomas G, Kozma SC (1998) Disruption of the p70(s6k)/p85(s6k) gene reveals a small mouse phenotype and a new functional S6 kinase. EMBO J. 17: 6649-6659
[189] Kwon G, Marshall CA, Liu H, Pappan KL, Remedi MS, McDaniel ML (2006) Glucose-stimulated DNA synthesis through mammalian target of rapamycin (mTOR) is regulated by KATP channels: effects on cell cycle progression in rodent islets. J.Biol.Chem. 281: 3261-3267
[190] Rajasekhar VK, Viale A, Socci ND, Wiedmann M, Hu X, Holland EC (2003) Oncogenic Ras and Akt signaling contribute to glioblastoma formation by differential recruitment of existing mRNAs to polysomes. Mol.Cell 12: 889-901
[191] Eto K, Yamashita T, Matsui J, Terauchi Y, Noda M, Kadowaki T (2002) Genetic manipulations of fatty acid metabolism in beta-cells are associated with dysregulated insulin secretion. Diabetes 51 Suppl 3: S414-S420
[192] Ruvinsky I, Sharon N, Lerer T, et al (2005) Ribosomal protein S6 phosphorylation is a determinant of cell size and glucose homeostasis. Genes Dev. 19: 2199-2211
[193] Pende M, Kozma SC, Jaquet M, et al (2000) Hypoinsulinaemia, glucose intolerance and diminished beta-cell size in S6K1-deficient mice. Nature 408: 994-997
[194] Fraenkel M, Ketzinel-Gilad M, Ariav Y, et al (2008) mTOR inhibition by rapamycin prevents beta-cell adaptation to hyperglycemia and exacerbates the metabolic state in type 2 diabetes. Diabetes 57: 945-957
[195] Kawamori D, Kaneto H, Nakatani Y, et al (2006) The forkhead transcription factor Foxo1 bridges the JNK pathway and the transcription factor PDX-1 through its intracellular translocation. J.Biol.Chem. 281: 1091-1098
[196] Buteau J, Shlien A, Foisy S, Accili D (2007) Metabolic diapause in pancreatic beta-cells expressing a gain-of-function mutant of the forkhead protein Foxo1. J.Biol.Chem. 282: 287-293
[197] De BJ, Wang HJ, Van BC (2004) Effects of Wnt signaling on proliferation and differentiation of human mesenchymal stem cells. Tissue Eng 10: 393-401
[198] van de WM, Sancho E, Verweij C, et al (2002) The beta-catenin/TCF-4 complex imposes a crypt progenitor phenotype on colorectal cancer cells. Cell 111: 241-250

[199] Korinek V, Barker N, Moerer P, et al (1998) Depletion of epithelial stem-cell compartments in the small intestine of mice lacking Tcf-4. Nat.Genet. 19: 379-383
[200] Heller RS, Dichmann DS, Jensen J, et al (2002) Expression patterns of Wnts, Frizzleds, sFRPs, and misexpression in transgenic mice suggesting a role for Wnts in pancreas and foregut pattern formation. Dev.Dyn. 225: 260-270
[201] Papadopoulou S, Edlund H (2005) Attenuated Wnt signaling perturbs pancreatic growth but not pancreatic function. Diabetes 54: 2844-2851
[202] Heiser PW, Lau J, Taketo MM, Herrera PL, Hebrok M (2006) Stabilization of beta-catenin impacts pancreas growth. Development 133: 2023-2032
[203] McLin VA, Rankin SA, Zorn AM (2007) Repression of Wnt/beta-catenin signaling in the anterior endoderm is essential for liver and pancreas development. Development 134: 2207-2217
[204] Dessimoz J, Bonnard C, Huelsken J, Grapin-Botton A (2005) Pancreas-specific deletion of beta-catenin reveals Wnt-dependent and Wnt-independent functions during development. Curr.Biol. 15: 1677-1683
[205] Wells JM, Esni F, Boivin GP, et al (2007) Wnt/beta-catenin signaling is required for development of the exocrine pancreas. BMC.Dev.Biol. 7: 4
[206] Pedersen AH, Heller RS (2005) A possible role for the canonical Wnt pathway in endocrine cell development in chicks. Biochem.Biophys.Res.Commun. 333: 961-968
[207] Fujino T, Asaba H, Kang MJ, et al (2003) Low-density lipoprotein receptor-related protein 5 (LRP5) is essential for normal cholesterol metabolism and glucose-induced insulin secretion. Proc.Natl.Acad.Sci.U.S.A 100: 229-234
[208] Rulifson IC, Karnik SK, Heiser PW, et al (2007) Wnt signaling regulates pancreatic beta cell proliferation. Proc.Natl.Acad.Sci.U.S.A 104: 6247-6252
[209] Grant SF, Thorleifsson G, Reynisdottir I, et al (2006) Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat.Genet. 38: 320-323
[210] Florez JC (2007) The new type 2 diabetes gene TCF7L2. Curr.Opin.Clin.Nutr.Metab Care 10: 391-396
[211] Murtaugh LC, Law AC, Dor Y, Melton DA (2005) Beta-catenin is essential for pancreatic acinar but not islet development. Development 132: 4663-4674
[212] Welters HJ, Kulkarni RN (2008) Wnt signaling: relevance to beta-cell biology and diabetes. Trends Endocrinol.Metab 19: 349-355
[213] Schinner S, Ulgen F, Papewalis C, et al (2008) Regulation of insulin secretion, glucokinase gene transcription and beta cell proliferation by adipocyte-derived Wnt signalling molecules. Diabetologia 51: 147-154
[214] Cozar-Castellano I, Fiaschi-Taesch N, Bigatel TA, et al (2006) Molecular control of cell cycle progression in the pancreatic beta-cell. Endocr.Rev. 27: 356-370
[215] Dodge R, Loomans C, Sharma A, Bonner-Weir S (2009) Developmental pathways during in vitro progression of human islet neogenesis. Differentiation 77: 135-147
[216] Liu Z, Habener JF (2008) Glucagon-like peptide-1 activation of TCF7L2-dependent Wnt signaling enhances pancreatic beta cell proliferation. J.Biol.Chem. 283: 8723-8735
[217] Egan JM, Bulotta A, Hui H, Perfetti R (2003) GLP-1 receptor agonists are growth and differentiation factors for pancreatic islet beta cells. Diabetes Metab Res.Rev. 19: 115-123

[218] Xu G, Stoffers DA, Habener JF, Bonner-Weir S (1999) Exendin-4 stimulates both beta-cell replication and neogenesis, resulting in increased beta-cell mass and improved glucose tolerance in diabetic rats. Diabetes 48: 2270-2276

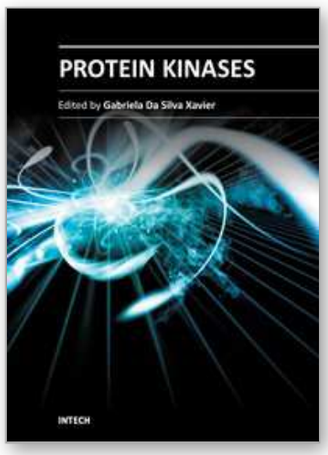
[219] List JF, Habener JF (2004) Glucagon-like peptide 1 agonists and the development and growth of pancreatic beta-cells. Am.J.Physiol Endocrinol.Metab 286: E875-E881

[220] Ashcroft FM (2006) K(ATP) channels and insulin secretion: a key role in health and disease. Biochem.Soc.Trans.34: 243-246.

[221] Braun M, Rorsman P (2006) The glucagon-producing alpha cell: an electrophysiologically exceptional cell. Diabetologia 53:1827-1830.

[222] Kawamori D, Kurpad AJ, Hu J, Liew CW, Shih JL, Ford EL, Herrera PL, Polonsky KS, McGuinness OP, Kulkarni RN (2009) Cell Metab 9:350-361.

[223] Henquin J.C, Nenquin M, Ravier M.A, Szollosi A (2009) Shortcomings of current models of glucose-induced insulin secretion. Diabetes Obes.Metab. 11 (Suppl 4): 168-179.



Protein Kinases

Edited by Dr. Gabriela Da Silva Xavier

ISBN 978-953-51-0640-1
Hard cover, 484 pages
Publisher InTech
Published online 05, June, 2012
Published in print edition June, 2012

Proteins are the work horses of the cell. As regulators of protein function, protein kinases are involved in the control of cellular functions via intricate signalling pathways, allowing for fine tuning of physiological functions. This book is a collaborative effort, with contribution from experts in their respective fields, reflecting the spirit of collaboration - across disciplines and borders - that exists in modern science. Here, we review the existing literature and, on occasions, provide novel data on the function of protein kinases in various systems. We also discuss the implications of these findings in the context of disease, treatment, and drug development.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Gabriela Da Silva Xavier (2012). Protein Kinases and Pancreatic Islet Function, Protein Kinases, Dr. Gabriela Da Silva Xavier (Ed.), ISBN: 978-953-51-0640-1, InTech, Available from: http://www.intechopen.com/books/protein-kinases/protein-kinases-and-pancreatic-islet-function

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen