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 \( \beta \) 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 bloodstream (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 pancreatic \( \alpha \) and \( \beta \) cells, respectively, 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 occurring 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,

![Diagram of Insulin and glucagon release](https://www.intechopen.com)

**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 overexpressing 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 homeobox-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 overexpression 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 gastrointestinal tract leads to a greater induction of glucose-stimulated insulin secretion than a comparable intravenous administration 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 diacylglycerol 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 diacylglycerol (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 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 expression of 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 membrane via the interaction of SNAP25 within a protein complex (161-163), with granule fusion and insulin release occurring 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 phosphorylates PDX-1 at Ser-269 in the C-terminal portion of PDX-1 in pancreatic \( \beta \) 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 \( \beta \) 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 \( \beta \) cell gene expression during development and in adult \( \beta \) cells.

4. \( \beta \) cell survival, growth and proliferation

Maintenance of an adequate functional \( \beta \) 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 \( \beta \) cell proliferation.

4.1 AMPK and LKB1

In section 3.1, we discussed the role of AMPK in the regulation of pancreatic \( \beta \) cell function. Recent data indicate that AMPK may also have a role in the maintenance of adequate \( \beta \) cell mass. Activation of AMPK has been shown to lead to decreased \( \beta \) 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 \( \beta \) cells have normal \( \beta \) cell mass but smaller \( \beta \) 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 \( \alpha \) to \( \beta \) cells or in islet architecture. \( \beta \) cell proliferation was enhanced in islets from mice in which the expression of both AMPK catalytic subunits was ablated selectively in pancreatic \( \beta \) 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 \( \beta \) 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 \( \beta \) cell mass in normal pancreata (185), was increased in pancreata from mice in which LKB1 expression was selectively ablated in the \( \beta \) 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 targeting these pathways for the treatment of diabetes. In particular, inhibition of LKB1, or its downstream targets, may be a means by which \( \beta \) 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 vivo and/or in vitro may be important for the treatment of the disease.

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